A NOVEL APPROACH TO STUDYING POSTURAL INSTABILITY IN PARKINSON’S DISEASE

by

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Abstract

Individuals with Parkinson’s disease (PD) often experience postural instability, a debilitating and largely treatment-resistant symptom. A better understanding of the neural substrates contributing to postural instability could lead to more effective treatments. However, investigating these neural substrates is made difficult by constraints of current functional neuroimaging techniques, such as the horizontal orientation of most MRI scanners. To address this constraint, we proposed to use a novel balance simulator that allows participants, while supine, to perform tasks that mimic free-standing balance. Overall, the general purpose of this thesis was to investigate the specific nature of balance deficits in PD, as well as the neural substrates contributing to postural instability in individuals with PD.

First, a narrative review of the literature was conducted to summarize the current evidence for the effect of PD, and the effect of antiparkinson treatment interventions, on static balance control. When focusing on studies that recorded quiet stance for at least 60 s, some consistent findings emerged that indicated individuals with PD display larger and faster sway compared to elderly controls, and that levodopa provides little improvement. Second, the MRI compatible balance simulator was validated in individuals with PD and elderly controls. Results indicated that the simulator was easy to use for all participants, balance behaviour during the simulated balance tasks was similar to that seen during upright standing balance, and both static and dynamic balance deficits could be detected in the individuals with PD using the simulator. Finally, the simulator was used in the MRI scanner to investigate the neural substrates of static and dynamic balance deficits in PD using both brain connectivity and brain activation amplitude analyses. The connectivity analysis suggested elderly controls show a preference of subcortical over motor cortical control networks during dynamic balancing, while dynamic balance control
in individuals with PD relies more on networks involving cortical (motor) areas. A similar pattern of results was seen for static balance during the brain activation amplitude analysis.

Overall, this thesis furthers our understanding of the specific nature of static balance deficits in individuals with PD, as well as the neural substrates underlying postural instability in PD.
Lay Summary

Balance problems experienced by individuals with Parkinson’s disease (PD) often result in falls. Unfortunately, currently available antiparkinson treatments do not provide improvement. A better understanding of the brain regions involved in the balance problems in PD could lead to more effective treatment interventions. However, to investigate these brain regions participants need to lie supine in an MRI scanner. This thesis validated a novel balance simulator that allowed participants to perform tasks that mimic free-standing balance while supine. The simulator was easy to use for participants and could detect static and dynamic balance deficits in individuals with PD. Subsequently, the simulator was used in the MRI scanner to investigate the activation within, and communication between, brain regions involved in the balance problems in PD. Results suggested balance control in individuals with PD is less automatic than in elderly controls. Future studies could use the simulator to identify new treatment targets in PD.
Preface

All data presented in this thesis were collected by Elizabeth Pasman, with assistance by others where noted below. All of the studies in this thesis were collected at the Vancouver-Point Grey campus of the University of British Columbia (UBC), Canada, in either the Neural Control of Posture and Movement Laboratory within the School of Kinesiology or the UBC MRI Research Centre within UBC Hospital. All methods used throughout this thesis were reviewed and approved by the UBC Clinical Research Ethics Board (ID: H14-02698; Title: Postural Instability in PD). Methodologies relating to MRI data collection were also reviewed and approved by the Vancouver Coastal Health Research Institute and the UBC MRI Research Centre.

A version of Chapter 2 is being prepared for submission to a peer-reviewed journal [Pasman, E.P., Johnson, K.J., McKeown, M.J., Inglis, J.T., Carpenter, M.G.]. Pasman EP was the lead investigator on the project and was responsible for conceptualizing the study, formulating and running the database search, screening the records found for inclusion/exclusion criteria, extracting data from the articles included in the review, summarizing and interpreting the results, and drafting and revising the manuscript, tables, and figures. Johnson KJ contributed to extracting data from the articles included in the review and providing critical review of the manuscript, tables, and figures. McKeown MJ and Inglis JT contributed by providing critical review of the manuscript, tables, and figures. Carpenter MG was the supervisory author and contributed to the project conception, formulation of the database search, interpretation of results, as well as providing critical review of the manuscript, tables, and figures.

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MRI Compatible Balance Simulator to Detect Postural Instability in Parkinson's Disease. 

*Frontiers in Neurology*, 10, 922. doi: 10.3389/fneur.2019.00922]. This chapter describes two different studies conducted to validate the use of a novel balance simulator in individuals with Parkinson’s disease and healthy older adults. Pasman EP was the lead investigator on the project and was responsible for conceptualizing the study, designing the experimental procedures, data collection and analysis, interpretation of results, and drafting and revising the manuscript, tables, and figures. McKeown MJ contributed to conception of the project, organizing data collection, and critical review of the manuscript, tables, and figures. Cleworth TW contributed to data collection, performing statistical analyses, and critical review of the manuscript, tables, and figures. Bloem BR and Inglis JT contributed to conception of the project and critical review of the manuscript, tables, and figures. Carpenter MG was the supervisory author and contributed to the project conception and design, data collection, interpretation of results, as well as providing critical review of the manuscript, tables, and figures.

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List of Abbreviations

ANOVA: Analysis of variance
AP: Anterior-posterior
BBS: Berg Balance Scale
BESTest: Balance Evaluation Systems Test
BOLD: Blood oxygenation level-dependent
COM: Centre of mass
COP: Centre of pressure
DB: Dynamic balancing
DBN: dynamic Bayesian network
DBS: Deep brain stimulation
Dynamic\textsubscript{Real}: Real dynamic balancing task performed by participants while standing upright
Dynamic\textsubscript{Sim}: Simulated dynamic balancing task performed by participants while supine
EEG: Electroencephalography
EMG: Electromyography
EC: Eyes closed
EO: Eyes open
FOG: Freezing of gait
fMRI: Functional magnetic resonance imaging
fNIRS: Functional near infrared spectroscopic imaging
GPi: Globus pallidus internus
H&Y: Hoehn and Yahr
LASSO: Least Absolute Shrinkage and Selection Operator
LDA: Linear discriminant analysis
LGAS: Lateral gastrocnemius
MGAS: Medial gastrocnemius
ML: Medial-lateral
MPF: Mean power of frequency
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
PCA: Principal component analysis
PCs: Principal components
PCfdr: Peter Spirtes and Clark Glymour, false discovery rate
PD: Parkinson’s disease
PD_{OFF}: Individual with Parkinson’s disease in the ‘off’ medication state
PD_{ON}: Individual with Parkinson’s disease in the ‘on’ medication state
PET: Positron emission tomography
PIGD: Postural instability and gait difficulty
PPN: Pedunculopontine nucleus
rCBF: Regional cerebral blood flow
RMS: Root mean square
ROI: Region of interest
SB: Static balancing
SD: Standard deviation
SE: Standard error of the mean
SMA: Supplementary motor area
SOL: Soleus
Static\textsubscript{Real}: Real static balancing task performed by participants while standing upright

Static\textsubscript{Sim}: Simulated static balancing task performed by participants while supine

STN: Subthalamic nucleus

TA: Tibialis anterior

UDPRS-ME: Unified Parkinson’s Disease Rating Scale motor examination
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Dedication

Ik draag dit proefschrift op aan papa, mama, JW, Kris, en mijn oma’s
Chapter 1: General introduction

1.1 Parkinson’s disease

1.1.1 Prevalence and impact on society of Parkinson’s disease

Parkinson’s disease (PD) is a progressive neurodegenerative disorder with great impact on the quality of life of affected individuals. It is one of the most prevalent neurodegenerative disorders in the world. In Canada the estimated prevalence of PD, reported by four different studies, ranges from 69 to 248.9 per 100,000 (Allyson Jones et al., 2012). Prevalence rates depend on the age group investigated, increasing steadily with advancing age. Worldwide prevalence rates range from 41 per 100,000 in individuals 40 to 49 years of age to 1,903 per 100,000 in individuals over the age of 80 (Pringsheim et al., 2014). It is estimated that by 2030 the number of individuals over the age of 50 with PD in developed countries will lie between 8.7 and 9.3 million, a doubling compared to 2005 when the number of individuals over the age of 50 with PD was between 4.1 and 4.6 million (Dorsey et al., 2007). It is expected that PD will put an increasing social and economic burden on societies as populations age (de Lau & Breteler, 2006).

1.1.2 Clinical features and pathophysiology of Parkinson’s disease

PD is a progressive disorder characterized by four cardinal symptoms: rest tremor, rigidity, bradykinesia, and postural instability (Jankovic, 2008). These symptoms are due to degeneration of neurons in the basal ganglia. The basal ganglia are nuclei located deep within the brain and consist of the substantia nigra, striatum (caudate nucleus and putamen), globus pallidus, and subthalamic nucleus. These nuclei have strong connections to the cerebral cortex as well as the thalamus, forming five parallel and functionally segregated basal ganglia-thalamo-
cortical circuits (Alexander et al., 1986). As a result, the basal ganglia are involved in various sensorimotor, cognitive, and behavioural processes that are closely associated with the executive and motor functions of the prefrontal and frontal cortex (Groenewegen, 2003). In addition to the thalamo-cortical projections, the basal ganglia also project to the brainstem and spinal cord. In the brainstem, the pedunculopontine nucleus (PPN) and other midbrain areas, including the superior colliculus, are important basal ganglia output targets (J. E. Visser & Bloem, 2005). In addition to the four cardinal motor symptoms, individuals with PD exhibit a wide range of non-motor symptoms that can be categorized into neuropsychiatric dysfunction, sleep disorders, autonomic dysfunction, and sensory dysfunction (Poewe, 2008; Ziemssen & Reichmann, 2007).

The symptoms of PD occur due to degeneration of the dopaminergic nigrostriatal system, i.e., degeneration of dopaminergic neurons in the substantia nigra pars compacta resulting in a shortage of dopamine in the striatum. The symptoms of PD emerge when about 80% of striatal dopamine and 50% of the dopaminergic neurons in the substantia nigra pars compacta are lost (Samii et al., 2004). The neuronal cell death in the substantia nigra is caused by neuronal inclusions composed of misfolded α-synuclein proteins. These inclusions are referred to as Lewy bodies, when located within neuronal cell bodies, and Lewy neurites, when located within neuronal cell processes (Braak et al., 2004; Dickson, 2012).

Although it is clear that PD is a hypodopaminergic syndrome (Grimbergen et al., 2009), there is evidence for involvement of non-dopaminergic systems in PD as well. For instance, Lewy bodies and Lewy neurites are found outside of the dopaminergic nigrostriatal system in individuals with PD (Dickson, 2012; Langston, 2006; Samii et al., 2004; Seidel et al., 2015; Surmeier & Sulzer, 2013). As such, certain motor symptoms and many non-motor symptoms do not respond well to dopaminergic medication (Sethi, 2008). Postural instability is one of the
motor symptoms that does not respond well to dopaminergic treatment. It is thought that postural instability is the result of abnormalities in both dopaminergic and non-dopaminergic systems (Bohnen & Albin, 2011; Grimbergen et al., 2009).

1.2 Parkinson’s disease and postural instability

Postural instability and resultant falls are very common in individuals with PD, and significant causes of disability, lost independence, and reduced quality of life (S. D. Kim et al., 2013). Several studies prospectively investigated the occurrence of falls in individuals with PD using follow up periods of different lengths. Between 32.8% and 90% of the individuals with PD reported falling at least once during monitoring periods ranging from 1 to 29 months, while between 25% and 86% of individuals experienced recurrent falls (Allen et al., 2013; Cheng et al., 2014; Gazibara et al., 2015; J.-S. Kim et al., 2013; Mak & Auyeung, 2013; Paul et al., 2014; Pickering et al., 2007; Rudzińska et al., 2013b; Smulders et al., 2014). The variability in fall rates reported is due to the specific inclusion criteria used in different studies and differences in methods of monitoring falls (Allen et al., 2013). The rates found in these prospective studies may differ from those found in retrospective studies but are more reliable as retrospective reporting of falls is specific (i.e., few false positive fall reports), although less sensitive (i.e., more false negative fall reports), compared to prospective reporting of falls (Ganz et al., 2005).

Three prospective studies, with monitoring periods ranging from 12 to 29 months, investigated the occurrence of falls in newly diagnosed individuals with PD (Hiorth et al., 2013; Mactier et al., 2015; Voss et al., 2012). Falls were reported by 17% of individuals with PD with an average disease duration of 2.3 years and who had not yet started with dopaminergic medication at the time of enrollment in the study. Of these individuals, 11.8% experienced more
than 1 fall (Hiorth et al., 2013). Falls were reported by 36.9% of individuals with PD recruited within 4 months of receiving their PD diagnosis. Of these individuals, 58.5% experienced more than 1 fall (Mactier et al., 2015). Finally, falls were reported by 23% of individuals with PD recruited within 5 years of receiving their PD diagnosis and who did not require symptomatic therapy. Of all fallers, 20% experienced a fall within 2 years of diagnosis, while 45% fell within 2 to 4 years of diagnosis (Voss et al., 2012). These studies provide evidence that falling is prevalent even in individuals with PD in the early stages of the disease. However, it should be noted that if individuals with PD fall early on in the disease then one should consider alternative diagnoses, such as one of the various forms of atypical parkinsonism (Wenning et al., 1999).

There have also been prospective studies with much longer follow up periods. Falls were reported in 72% of the remaining individuals with PD after a follow up period of 8 years (Hiorth et al., 2014) and in 87% of the remaining individuals with PD after a follow up period of 20 years (Hely et al., 2008).

Not only are postural instability and resultant falls very common in individuals with PD, they are also a major source of morbidity and mortality in this clinical population. It has been reported that 22% to 78% of falls result in injuries (Matinolli et al., 2011; Paul et al., 2013; Pickering et al., 2007; Rudzińska et al., 2013a), and injuries as a result of a fall occur in 24% to 38.9% of individuals with PD (Gazibara et al., 2014; Pickering et al., 2007). While the most common injuries are soft-tissue contusions, 4.6% to 12.7% of falls result in more serious consequences including fractures and the need for hospitalization (Gazibara et al., 2014; Matinolli et al., 2011; Paul et al., 2013; Rudzińska et al., 2013a). One study even found fall-related fractures in 32% of the individuals with PD investigated (Cheng et al., 2014). Not only do falls result in physical harm, fear of future falls is also very common in individuals with PD as
almost 50% of individuals express a fear of falling (Bloem, van Vugt, et al., 2001). Furthermore, in terms of mortality, postural instability/gait disorder subtype and postural instability that persisted during the ‘on’ medication state decrease survival in individuals with PD (Auyeung et al., 2012). Finally, individuals with PD were found to have a 51% greater risk for injury mortality than individuals without PD (Allyson Jones et al., 2012).

1.3 Balance control in individuals with Parkinson’s disease

Although it is well accepted that postural instability is a very common and debilitating symptom in individuals with PD, the pathophysiological processes that contribute to postural instability are largely unknown. Most likely these underlying processes are complex. Most of the clinical balance tests commonly used to assess postural instability in individuals with PD are crude and subjective. As such, they do not give insight into the complex underlying pathophysiological processes of postural instability (Grimbergen et al., 2009).

For instance, the retropulsion test, also known as the pull test, evaluates the ability of individuals with PD to recover from a backward pull on the shoulders. It is an integral component of the Unified Parkinson’s Disease Rating Scale motor examination (UPDRS-ME) and is widely used by clinicians to assess postural stability in individuals with PD. It is used to distinguish between milder PD, i.e., Hoehn and Yahr (H&Y) stages 1 and 2, and moderate to severe PD, i.e., H&Y stages 3 to 5 (Hunt & Sethi, 2006). However, the pull test has several limitations (Bloem, Beckley, et al., 1998; Munhoz et al., 2004; Nonnekes, Goselink, et al., 2015; M. Visser et al., 2003). First, there is disagreement as to how the pull test should be executed; different variants exist, and errors in execution of specific aspects of the test are common. To illustrate, there is disagreement regarding if (a) participants should have their eyes open or
closed; (b) participants should be instructed that taking corrective steps backward are allowed or not; (c) the first pull should be an instructional demonstration that is not rated or if the test should be executed several times to examine habituation effects; (d) prior warning should be given.

Second, it is difficult to standardize the pull test across individuals with different heights, weights and degrees of postural instability. The pull force may also vary between and within examiners. Lastly, it is unclear how the balance reaction should be scored, and inter-rater reliability depends on the specific rating scale used to score the outcome of the pull test. The lowest inter-rater reliability is seen when rating is done according to the UPDRS. In addition, there is disagreement about how well the pull test correlates with quantitative measures of balance control (Bloem, Beckley, et al., 1998; Ebersbach & Gunkel, 2011; Hagiwara et al., 2004; Horak et al., 2005; Johnson et al., 2013; Maurer et al., 2003; Ozinga et al., 2017, 2015; Rocchi et al., 2002; Viitasalo et al., 2002), and disagreement about how well it predicts falls, especially future falls (Bloem, Grimbergen, et al., 2001; Jacobs et al., 2006; Munhoz & Teive, 2014; Nonnekes, Goselink, et al., 2015). The ability of the pull test to predict falls depends on the medication state, with poorer predictive ability in the ‘on’ compared to the ‘off’ medication state (Valkovic et al., 2008).

The Push-and-Release test rates the postural response to a sudden release of a subject pressing backward on the examiner’s hands which are placed on the subject’s back (Jacobs et al., 2006). The Push-and-Release test is a more sensitive but less specific test of postural instability than the pull test, with higher inter-rater correlations and more consistently applied perturbation forces (Jacobs et al., 2006; Valkovic et al., 2008). Although overcoming some of the limitations of the pull test, the Push-and-Release test also shows variability in administration and inconsistency in response. Furthermore, there is disagreement regarding which trial (i.e., the first
or the third) should be rated (Nonnekes, Goselink, et al., 2015; B. A. Smith et al., 2016). The Push-and-Release test correlates better with retrospectively reported falls than the pull test (Jacobs et al., 2006; Valkovic et al., 2008), however, it has yet to be determined if the Push-and-Release test is also more sensitive in predicting future falls (Nonnekes, Goselink, et al., 2015).

In addition to the clinical balance tests mentioned above, there are several rating scales used to assess postural instability in individuals with PD, including the Berg Balance Scale (BBS) (Berg et al., 1992), the Balance Evaluation Systems Test (BESTest) (Horak et al., 2009), and the mini-BESTest (Franchignoni et al., 2010). All three rating scales have been validated in individuals with PD (Leddy et al., 2011a, 2011b; Qutubuddin et al., 2005). While the BBS is simple and safe to administer, dynamic balance control is not assessed as all items involve either quiet stance or sitting. The BBS may therefore not be challenging enough, resulting in a ceiling effect, and lacks the ability to identify early postural instability in individuals with PD (la Porta et al., 2015; Leddy et al., 2011a). Both static and dynamic balance control are assessed by the BESTest. Compared to the BBS, the BESTest is more sensitive for identifying individuals with PD that fell during the previous 6 months (Leddy et al., 2011a). However, a major drawback of the BESTest, a 36-item test, is that it takes about 35-45 minutes to administer. The mini-BESTest, a shortened version of the BESTest including 16 of the 36 original items, only takes about 15 minutes to administer and is also able to identify individuals with PD who have a history of falls (Duncan et al., 2013; Leddy et al., 2011b). When all three clinical rating scales are compared to each other with regard to their utility to detect balance decline over a 12 month period, it becomes clear only the BESTest and mini-BESTest are able to do so (Duncan et al., 2015). Despite this, a recent study concluded that both the BBS and the mini-BESTest only have moderate capacity to predict future falls in individuals with PD (Schlenstedt et al., 2016).
In contrast to the clinical balance tests and rating scales described above, posturography provides a more objective and quantitative measure of balance and postural instability (Bloem et al., 2003; J. E. Visser, Carpenter, et al., 2008). Balance performance during posturography can be quantified using electromyography (EMG), kinetics (i.e., analysis of forces and joint moments), and kinematics (i.e., analysis of how body parts move) (Bloem et al., 2003). In posturography there are two major categories: static posturography and dynamic posturography. During static posturography participants are assessed while standing quietly on a stationary support surface (Grimbergen et al., 2009; J. E. Visser, Carpenter, et al., 2008). During dynamic posturography participants are assessed while experiencing balance perturbations. These perturbations can either be self-induced, such as during voluntary movement, or experimentally induced, such as experienced when standing on an unstable and/or moving support surface or when an external force is applied to the body (Grimbergen et al., 2009; J. E. Visser, Carpenter, et al., 2008). Balance control has been extensively investigated in individuals with PD using either static or dynamic posturography. Differences between individuals with PD and healthy participants have been found in the postural control of quiet standing, when performing voluntary movements, and when experiencing unexpected movements of the support surface the participants were standing on.

1.3.1 Static balance control in individuals with Parkinson’s disease

Static balance control can be assessed by recording kinetic and/or kinematic data while participants are standing quietly. Kinetic data can be collected by having participants stand on a force plate, which records ground reaction forces and moments that can be used to calculate the centre of pressure (COP). COP is a weighted average of all forces acting beneath the feet (Winter
et al., 1996). Usually the characteristics of the COP signal are quantified in terms of its mean position, amplitude, and velocity and/or frequency of displacements in the anterior-posterior (AP) and medial-lateral (ML) directions. COP descriptive measures can provide indirect insight into the movement of the trunk, assuming the body acts as an inverted pendulum (Winter et al., 1996). However, movements of the trunk or centre of mass (COM), both examples of kinematic data, can also be measured directly to quantify the characteristics of postural sway. The COM is the point where the net effect of gravity on the body acts through. The vertical projection of the body’s COM needs to be maintained within the base of support for stable quiet stance to be achieved (Maki & McIlroy, 1997). This means that depending on the size of the base of support, more or less postural sway can be tolerated. The base of support is bound by the points of contact between body segments and the support surface.

A number of studies have recorded kinetic and/or kinematic data during quiet standing to investigate static balance control in individuals with PD. However, there is a wide variability among these studies in methodology used and characteristics of the individuals with PD investigated. Data collection protocols and methods mostly varied with respect to (a) measurement equipment used, (b) dependent measures used, (c) trial length, (d) number of trials, (e) sampling frequency, (f) filtering, (g) stance width participants were asked to adopt. In addition, characteristics of the individuals with PD included mostly varied with respect to (a) medication status, (b) disease duration, (c) disease severity.

The vast majority of studies recording kinetic data during quiet standing in individuals with PD used either one (e.g., Pasman et al., 2011) or two force plates (e.g., Rocchi et al., 2002). However, a handful of studies used alternative devices such as force-sensitive resistors attached to the bottom of removable insoles (Bamberg et al., 2006), a photoelastic system (Kitamura et
al., 1993), or foot pressure measurement systems (e.g., Na et al., 2019). The measurement equipment used in studies collecting kinematic data was more variable. Frequently used measurement systems included optical motion analysis systems (e.g., Ozinga et al., 2015) or lightweight sensors that recorded the position, velocity, and/or acceleration of the body segments they were attached to, such as angular velocity sensors (Vrancken et al., 2005) or inertial measurement units (e.g., Mancini et al., 2011), including accelerometers and gyroscopes within tablets (e.g., Ozinga et al., 2017) or a cellphone (Lipsmeier et al., 2018). However, a variety of other devices were used to record kinematic data as well, including: an inclinometric device attached at the level of iliac crest (Viitasalo et al., 2002); a light rod attached at waist level which was connected to a linear transducer (Waterston et al., 1993); a 3D ultrasound motion analysis system (Kammermeier et al., 2018); a magnetic tracking system (e.g., Bonnet et al., 2017); a platform-mounted potentiometer attached to a rod fastened at the hips (Horak et al., 1992); a swaymeter extending posteriorly onto an adjustable height table measuring displacement of body at level of waist (Menant et al., 2011); and potentiometers attached to the participants’ hip and shoulder levels (Chong, Horak, et al., 1999). When interpreting, and especially when comparing, results from studies using different measurement equipment it is important to consider the type of signal recorded (i.e., displacement, velocity, acceleration, etc.). In addition, if available, the equipment specifications (e.g., measurement errors and range, sensitivity, etc.) should be taken into account as well.

Many different dependent measures have been calculated by the various studies recording kinetic and/or kinematic data during static balance in individuals with PD. These measures can be roughly divided into two categories: traditional measures and non-traditional measures. The traditional descriptive measures determined by static balance studies in PD included (a) mean
position; (b) root mean square error (RMS) and standard deviation (SD), both reflecting variability of the signal; (c) range, defined as the difference between the minimum and maximum values in the signal in one direction; (d) sway area, often defined as an elliptical area containing 90% or 95% of the sampled data points; (e) total excursion or sway path length, reflecting the total distance travelled by the signal and affected by both amplitude and velocity/frequency components of the signal; (f) velocity, mostly measured as mean velocity; (g) mean, median, centroid, and 95% power frequency (i.e., the frequency below which 95% of the power of the signal lies), providing insight into the frequency content of the signal. In some studies, mostly those recording acceleration, jerk was determined as well, which is the rate of change of acceleration and a measure of smoothness of sway (e.g., Mancini et al., 2011). Non-traditional analysis measures are less commonly used but represent information that is complementary to traditional descriptive measures (Schubert et al., 2012). The non-traditional measures used in studies that investigated static balance control in PD included: fractal dimension (Manabe et al., 2001), sample entropy (Pantall et al., 2018), approximate entropy (Mirahmadi et al., 2018), stabilogram diffusion measures (study of random walks) (Maurer et al., 2004), and detrended fluctuation measures (High et al., 2018). Comparing among studies is made difficult by the diversity of the descriptive measures that have been used, as some measures quantify the COP and kinematic recordings in the time-domain (e.g., RMS, SD, range, sway area, sway path length, mean velocity), while others do so in the frequency domain (e.g., mean, median, centroid, and 95% power frequency). In addition, some dependent measures are two-dimensional and characterize the COP and kinematic signals as a whole, therefore representing information from both AP and ML directions simultaneously (e.g., sway area). Other measures are one-dimensional, allowing balance control to be assessed in the AP and ML directions separately.
(e.g., AP and ML RMS, AP and ML range, etc.). Furthermore, the interpretation of the values of the descriptive measures also depends on the type of data recorded. For example, the range and RMS values of COP displacements should be interpreted differently to the range and RMS values of trunk acceleration.

Trial lengths varied from 3 s (Burleigh et al., 1995) to 180 s (Workman & Thrasher, 2019), with the majority of studies recording quiet stance for 30 s or less. In addition, the number of trial repetitions ranged from 1 (e.g., Adkin et al., 2003) to 10 (e.g., Mitchell et al., 1995), with most studies requiring participants to perform 1 to 3 trials. Sampling duration significantly influences the magnitude and reliability of various COP descriptive measures in the time and frequency domains (Carpenter, Frank, et al., 2001; van der Kooij et al., 2011). For instance, longer sample durations result in increased reliability of traditional COP measures, such as 95% confidence ellipse area, range, RMS, and mean power of frequency (MPF) (Carpenter, Frank, et al., 2001; Doyle et al., 2007; Lafond et al., 2004), as well as non-linear measures, including stabilogram diffusion measures (Doyle et al., 2008). In addition, reliability of descriptive measures is also increased when averaging over multiple trials (Doyle et al., 2007). Overall, to optimize the stability and reliability of COP descriptive measures, trial lengths of at least 60 s should be used when vision is available, and longer trial lengths when participants are asked to keep their eyes closed (Carpenter, Frank, et al., 2001; Doyle et al, 2007; Lafond et al., 2004; van der Kooij et al., 2011).

The majority of studies, whether collecting kinetic and/or kinematic data, failed to report the sampling frequency used to record the data as well as whether or not the data were filtered. Studies that did report this information, reported widely varying values. For force plate data, sampling frequency ranged from 10 Hz (e.g., Marchese et al., 2003) to 3000 Hz (Bekkers et al.,
and the cut-off frequencies of applied low-pass filters ranged from 3.5 Hz (e.g., Mancini et al., 2011) to 50 Hz (e.g., Bekkers, Dockx, et al., 2018). For kinematic studies the sampling frequency chosen depended on the measurement equipment used, but still varied between studies using similar equipment. For instance, the frequency used to sample accelerometer data ranged from 30 Hz (Marchesi et al., 2019) to 128 Hz (Hasegawa et al., 2019). The cut-off frequency for low-pass filters applied was more consistent among kinematic studies, with most studies reporting the use of a 3.5 Hz low-pass filter cut-off (e.g., Mancini et al., 2011). For COP data it is recommended that sampling frequency is at least 50 Hz (Scoppa et al., 2013), and while the majority of studies used a sampling frequency above the recommended minimum, not all studies did (e.g., Marchese et al., 2003). Filter characteristics are important as over 90% of the total power in COP and COM recordings is found in frequencies below 0.5 Hz (Carpenter, Frank, et al., 2001; Gage et al., 2004), while rest and postural tremors in individuals with PD have a typical frequency between 4 to 7 Hz (Kerr et al., 2008). Low pass filtering the data with a cut-off frequency of less than 7 Hz may remove (part) of the tremor from the data in individuals with PD. Filter characteristics can therefore affect dependent measures related to frequency, such as MPF and 95% power frequency, but also sway path length, and filter cut-off frequencies should be considered when comparing results between studies.

The foot position participants were asked to adopt varied among studies from feet together (e.g., Adkin et al., 2003) to feet shoulder width apart (e.g., Pasman et al., 2011), with many different variations in between. Stance width has been shown to influence COP and trunk/COM sway, with increasing stance width resulting in increased frequency of sway and decreased amplitude and velocity of sway, mainly in the ML direction (Bonnet, 2012; Day et al., 1993; Gatev et al, 1999; J.-W. Kim et al., 2014).
Another source of variability between studies was whether the individuals with PD investigated were currently treated with dopaminergic medication, and if so, if they were tested while ‘off’ or ‘on’ their medication. This is important to know as in individuals with PD who are drug-naïve or ‘off’ their medication, both dopaminergic and non-dopaminergic lesions may influence their quiet standing performance during testing. In contrast, when individuals are tested in their optimal ‘on’ state following intake of their dopaminergic medication (i.e., levodopa, dopamine-agonists), quiet standing performance will generally reflect the effect of any non-dopaminergic lesions plus potential side-effects arising from the dopaminergic medication.

Unfortunately, medication state was not always reported by studies investigating static balance control in individuals with PD. Additionally, some studies included individuals with PD who received deep brain stimulation (DBS) in the subthalamic nucleus (STN) (e.g., Maurer et al., 2003), globus pallidus internus (GPi) (e.g., Johnson et al., 2015), or the PPN (e.g., Yousif et al., 2016). DBS is often used as a therapeutic option for individuals with PD in whom the effectiveness of medication is limited by motor response complications (i.e., levodopa-induced dyskinesia and motor fluctuations; Maurer et al., 2003). It is currently still largely unclear what the effect of DBS is on the kinetic and kinematic characteristics of quiet stance in PD.

Finally, disease duration and severity of individuals with PD investigated varied widely. For instance, one study investigated drug-naïve individuals with PD with a mean disease duration of 1.3 years (Nardone et al., 2012), while another study tested individuals with PD who received STN DBS and had a mean disease duration of 16.9 years (Crenna et al., 2006). Disease severity was most commonly assessed using the H&Y scale and/or the UPDRS-ME, and the scores reported depended heavily on the medication and DBS state the individuals with PD were tested in. Although most studies reported on clinical characteristics of the individuals with PD
that were investigated, reports were often incomplete, and, in a few cases, even missing altogether.

Overall, the diversity in static posturography protocols used, and clinical characteristics of the individuals with PD investigated, most likely contributed to the dissimilar, and sometimes even contradictory, findings between studies (Hubble et al., 2015; Kamieniarz et al., 2018). Therefore, it is currently unclear what the specific deficits in static balance control are that individuals with PD exhibit compared to healthy older adults.

1.3.2 Dynamic balance control in individuals with Parkinson’s disease

Dynamic balance control can be investigated by having participants undergo balance perturbations, either self-induced or experimentally induced, and recording their postural responses. Sudden movements of the support surface on which the participants stand are a common method for experimentally inducing balance perturbations (Bloem et al., 2003; J. E. Visser, Carpenter, et al., 2008). The unexpected movements of the support surface are often rotations, translations, or a combination of both. Postural responses induced by these perturbations involve stereotypical muscle activation patterns. The exact pattern of muscle activation in the response depends on the type and the direction of support surface perturbation used. In addition, the magnitude of the postural responses needs to be appropriately scaled to the velocity and amplitude of the perturbations experienced. The muscle responses can be divided into stretch reflexes (including short-latency reflexes and medium-latency reflexes), balance correcting, secondary balance correcting, and stabilizing reaction responses (Allum et al., 2002). To illustrate, during sudden toe-up support surface rotations the ankle joint is rapidly dorsiflexed resulting in stretch reflexes in the stretched medial and lateral gastrocnemius (MGAS and LGAS
respectively) and soleus (SOL), and a balance correcting response in the shortened tibialis anterior (TA). The short-latency reflex is considered to be too small to significantly contribute to body sway induced by the toe-up rotation. The medium-latency reflex is functionally destabilizing as it aggravates the posterior body sway induced by the toe-up rotation. The balance correcting response on the other hand is functionally stabilizing as it results in anterior body sway thus counteracting the posterior body sway induced by the support surface tilt perturbation (Bloem et al., 1996). During sudden toe-down support surface rotations the ankle joint is rapidly plantarflexed resulting in stretch reflexes in TA, and balance correcting responses in plantar flexor muscles.

Several studies investigated dynamic balance control in individuals with PD using support surface perturbations. When responding to transient support surface perturbations a distinction can be made between fixed-support (i.e., feet in place) and change-in-support (i.e., stepping or grasping movements of the limbs) balance recovery strategies (Maki & McIlroy, 1997). While most studies used perturbations that occurred in the AP plane only, a few studies investigated dynamic balance control in individuals with PD using multidirectional support surface translations or rotations. A major advantage of the use of multidirectional perturbations is that the perturbations are less predictable, preventing habituation of postural responses and anticipatory strategies such as leaning. In addition, when using multidirectional perturbations it is possible to investigate the directional sensitivity of postural instability in individuals with PD.
1.3.2.1 Dynamic balance control in individuals with Parkinson’s disease compared to healthy control participants

Postural responses to multidirectional translations have mostly been investigated in individuals with PD in the ‘off’ medication state (PD$_{OFF}$), and it should be noted that each of the four studies that will be discussed reported on subsets of data collected from the same group of individuals with PD during the same experiment (Dimitrova, Horak, & Nutt, 2004; Dimitrova, Nutt, & Horak, 2004; Horak et al., 2005; Jacobs et al., 2005). Postural responses in individuals with PD during multidirectional rotations have been investigated in individuals in both the ‘off’ and ‘on’ medication state (Carpenter et al., 2004; J. E. Visser, Allum, Carpenter, Esselink, Limousin-Dowsey, et al., 2008; J. E. Visser, Allum, Carpenter, Esselink, Speelman, et al., 2008). One study investigated individuals with PD in the ‘on’ medication state (PD$_{ON}$), and a subset of these individuals also in the ‘off’ medication state (Carpenter et al., 2004), while the other studies investigated individuals, with their bilateral STN DBS turned ‘off’, after intake of a suprathreshold levodopa dose (i.e., 150% of each patient’s regular levodopa equivalent dose) (J. E. Visser, Allum, Carpenter, Esselink, Limousin-Dowsey, et al., 2008; J. E. Visser, Allum, Carpenter, Esselink, Speelman, et al., 2008). It should be noted that the latter two reports studied data collected in the same patient group during the same experiment.

In individuals with PD$_{OFF}$, during multidirectional translations, similar timing of muscle activation is seen compared to healthy participants (Table 1.1). In terms of the amplitude of muscle activation, increased background muscle activity is seen in individuals with PD$_{OFF}$. In addition, while the amplitude of agonist muscle activity is similar, the amplitude of antagonist muscle activity is larger in individuals with PD$_{OFF}$ compared to healthy participants, leading to co-contraction. Biomechanical consequences include increased passive ground reactive forces,
decreased and abnormally directed active ground reactive forces, decreased hip and knee joint angle displacements, and increased COM displacement (Dimitrova, Horak, & Nutt, 2004; Dimitrova, Nutt, & Horak, 2004; Horak et al., 2005; Jacobs et al., 2005). The postural instability seen in individuals with PD\textsubscript{OFF} during multidirectional translations is directionally specific, as individuals are most unstable during translations that induce backward and lateral body sway (Horak et al., 2005).

In individuals with PD\textsubscript{ON}, during multidirectional rotations, timing of muscle activation is similar compared to healthy participants (Table 1.1). In terms of the amplitude of muscle activation, increased background activity in lower leg, hip and trunk muscles is present in individuals with PD\textsubscript{ON}. While the amplitude of short-latency reflexes is similar in individuals with PD\textsubscript{ON} compared to healthy participants, larger amplitude of balance correcting responses in agonistic muscles and larger amplitude of both medium-latency reflexes and balance correcting responses in antagonistic (stretched) muscles are seen, leading to co-contraction. Biomechanical consequences include reduced ankle torque changes, abnormal trunk and pelvis movements, and larger COM displacements (Carpenter et al., 2004; J. E. Visser, Allum, Carpenter, Esselink, Limousin-Dowsey, et al., 2008; J. E. Visser, Allum, Carpenter, Esselink, Speelman, et al., 2008). It should be noted that one study found the amplitude of trunk pitch rotation to be decreased and the amplitude of trunk roll to be similar between individuals with PD\textsubscript{ON} and healthy participants (Carpenter et al., 2004), while another study found trunk pitch to be normal but trunk roll to be abnormal in the individuals with PD\textsubscript{ON} (J. E. Visser, Allum, Carpenter, Esselink, Limousin-Dowsey, et al., 2008). The discrepancy between the findings of the two studies was attributed to clinical factors as most of the individuals included in the more recent study had young-onset PD, were 13.5 years younger and had 2.5 years longer disease duration (J. E. Visser, Allum,
Carpenter, Esselink, Limousin-Dowsey, et al., 2008). Finally, earlier and abnormally directed protective arm movements are seen in individuals with PD_{ON} (Carpenter et al., 2004).

The normal timing, but abnormal amplitude of postural responses, and increased background muscle activity and co-contraction, resulting in stiffness, found in individuals with PD by studies using multidirectional perturbations (Table 1.1) are in agreement with the findings reported by uniplanar dynamic posturography studies (Beckley et al., 1991; Benninger et al., 2010; Bloem et al., 1995, 1994, 1996, 1992; Bloem, van Vugt, et al., 1998; Diener et al., 1991; Horak et al. 1996, 1992; Schieppati & Nardone, 1991; St George et al., 2012).

1.3.2.2 Adaptation of postural responses in individuals with Parkinson’s disease

Healthy participants adapt postural responses based on expectation, prior experience, or context. This is known as postural set. Individuals with PD are unable to adapt their postural responses in response to changes in postural set. The inability to adapt postural responses to changes in postural set seems general, rather than task dependent, in individuals with PD as the difficulty to quickly adapt postural responses is evident in different types of postural set tasks (Chong, Jones, & Horak, 1999).

The pattern of postural responses depends on the perturbation type. Some postural responses that are stabilizing during one perturbation type, are destabilizing during another. For instance, the medium-latency reflexes seen in MGAS is stabilizing in backward translations but destabilizing in toe-up rotations. Healthy participants suppress MGAS activity during the first toe-up rotation experienced after a series of backward translations. In contrast, individuals with PD ‘off’ and ‘on’ medication show little change in MGAS activity during the first toe-up rotation but do show suppressed activity during subsequent rotations (Chong et al., 2000).
Individuals with PD ‘off’ and ‘on’ medication are able to scale the magnitude of surface reactive torques to displacement velocities and amplitudes during support surface translations, although they have more difficulty scaling their postural responses in anticipation of larger perturbation amplitudes than healthy participants (Horak et al., 1996). Furthermore, while both healthy participants and individuals with PD ON gradually transition their postural strategy from an ankle strategy to a hip strategy when perturbation amplitude increases, individuals with PD ON show inappropriate scaling of hip and ankle responses and inflexible adjustments of these responses as perturbation amplitudes increase (S. Kim et al., 2009).

Individuals with PD have difficulty with quickly changing postural set in response to new environmental conditions when experiencing external balance perturbations (Bloem et al., 1995; Chong, Jones, & Horak, 1999; Horak et al., 1992; Schieppati & Nardone, 1991). First, when holding on to a stable frame, healthy participants show a reduction in TA activity during toe-up rotations and a reduction in SOL activity during backward translations. In contrast, individuals with PD fail to reduce the activity in these muscles during toe-up rotations and backward translations when holding on to a stable frame (Chong, Jones, & Horak, 1999; Schieppati & Nardone, 1991). Second, when healthy participants experience backward translations they use an ankle strategy to recover balance while standing on a wide surface and switch to a hip strategy when experiencing these perturbations while standing on a narrow beam. However, in addition to activating proximal leg and trunk muscles, congruent with a hip strategy, individuals with PD simultaneously display a muscle synergy congruent with an ankle strategy when standing on a narrow beam (Horak et al., 1992). Third, in contrast to healthy participants, who increase activity in all muscles, individuals with PD do not increase muscle activity when standing with a narrow stance as opposed to a wide stance (Dimitrova, Horak, & Nutt, 2004). Fourth, healthy
participants decrease the balance correcting responses in TA and increase the medium-latency reflexes in MGAS when told to ‘yield’ in response to toe-up rotations, individuals with PD on the other hand decrease TA activity to a lesser extent and do not modify the amplitude of MGAS activity (Bloem et al., 1995; Chong et al., 2000). Individuals with PD also have difficulty increasing their response when told to ‘resist’ either toe-up rotations or backward translations (Chong et al., 2000). Finally, individuals with PD do not suppress irrelevant leg muscle activity in response to support surface translations when sitting (Chong, Jones, & Horak, 1999; Horak et al., 1992).

1.3.2.3 The effect of treatment on dynamic balance control in individuals with Parkinson’s disease

Dopaminergic treatment results in little improvement of dynamic balance control abnormalities in individuals with PD (Bloem et al., 1996; Carpenter et al., 2004; Horak et al., 1992). During multidirectional support surface rotations abnormal trunk movement in the AP direction is not improved by medication, but some improvements in trunk roll stability and arm responses are seen in individuals with PD when ‘on’ medication compared to ‘off’ medication (Carpenter et al., 2004). However, medication does not improve the ability of individuals with PD to adapt postural responses when postural set is manipulated, which is one of the prominent dynamic balance control deficits seen in this patient population (Chong et al., 2000; Horak et al., 1992). Not only does dopaminergic medication provide little improvement of dynamic balance control, it might even worsen some of the abnormalities seen. For instance, it reduces the magnitude of torque and muscle responses, in addition to lowering background muscle activity. The combined effect of decreased passive stiffness and decreased magnitude of corrective
responses makes it harder for individuals with PD\textsubscript{ON} to resist support surface perturbations (Horak et al., 1996). Furthermore, while dopaminergic medication does not affect the ability of individuals with PD to scale postural responses to perturbation velocity, it worsens their ability to scale postural responses to perturbation amplitude (Horak et al., 1996).

Only two studies, both investigating the same cohort of participants, examined the effect of bilateral STN DBS on dynamic balance control in individuals with PD using multidirectional perturbations (J. E. Visser, Allum, Carpenter, Esselink, Limousin-Dowsey, et al., 2008; J. E. Visser, Allum, Carpenter, Esselink, Speelman, et al., 2008). STN DBS does not alleviate levodopa-resistant postural instability in individuals with PD. The increased backward COM displacement during backward directed rotations seen in individuals with PD after intake of a suprathreshold levodopa dose was not reduced when STN DBS was turned ‘on’. In fact, in some individuals backward COM displacement even further increased when STN DBS was turned ‘on’, indicating that increased postural instability can occur as a side effect of STN DBS (J. E. Visser, Allum, Carpenter, Esselink, Speelman, et al., 2008). STN DBS also did not improve levodopa-resistant abnormal trunk and pelvis movement, although it did improve directional sensitivity. In addition, STN DBS failed to improve paraspinal EMG asymmetry, but overall muscle activity was decreased (J. E. Visser, Allum, Carpenter, Esselink, Limousin-Dowsey, et al., 2008). These findings were corroborated by findings of a study investigating the effect of STN and GPi DBS in individuals with PD using uniplanar dynamic posturography (St George et al., 2012). The individuals in this study had undergone bilateral DBS, where electrode placement site (STN or GPi) was randomized and blinded to the individuals and experimenters. The stability margin (i.e., difference between peak COP displacement and peak COM displacement) improved in individuals with both STN and GPi DBS when the DBS ‘off’ and DBS ‘on’ state
were compared after surgery, but no improvement of co-activation of antagonistic muscles was seen. However, when the best treatment state before and after surgery (i.e., ‘on’ medication before surgery and ‘on’ medication with DBS turned ‘on’ after surgery) were compared, the individuals with STN DBS showed lower stability margins after surgery while no differences were seen in the individuals with GPi DBS. This change in the STN patient group was attributed to microlesions created by the surgical procedure. As the detrimental effects of the microlesions created during surgery were larger than the benefit of the DBS stimulation itself, a worsening of postural instability was seen in individuals with STN DBS after surgery (St George et al., 2012).

1.4 The neural substrates of postural instability in Parkinson’s disease

Investigating balance control in individuals with PD using static and dynamic posturography has provided much insight in the differences at a neurophysiological level between individuals with PD and healthy older adults. However, there is a need for a better understanding of the neural substrates contributing to postural instability in individuals with PD. Postural instability is one of the motor symptoms that does not respond well to dopaminergic medication (Sethi, 2008). The theory that non-dopaminergic systems are involved in postural instability in PD is based on findings from studies which included individuals with pure dopaminergic syndromes (i.e., neuroleptic induced parkinsonism, neurotoxin induced parkinsonism, young-onset PD) and studies that investigated individuals with PD both ‘off’ and ‘on’ medication. Some of the postural abnormalities found in individuals with PD were absent in the individuals with pure dopaminergic syndromes and/or persisted after intake of dopaminergic medication (Bloem et al., 1994; Carpenter et al., 2004; Grimbergen et al., 2009). For instance, the amplitude of medium-latency reflexes did not differ between healthy participants and
individuals with parkinsonism due to exposure to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a heroin analogue that selectively destroys nigrostriatal neurons in the substantia nigra (Bloem et al., 1994). As opposed to individuals with idiopathic PD, individuals with parkinsonism due to MPTP exposure are thought to have a more pure dopaminergic syndrome (i.e., with minimal involvement of non-dopaminergic pathways). The amplitude of medium-latency reflexes therefore does not seem to be primarily regulated by supraspinal dopaminergic control, and the larger medium-latency reflexes seen in individuals with PD are most likely due to lesions in non-dopaminergic pathways (Bloem et al., 1994). The adrenergic system is one non-dopaminergic system possibly involved in postural instability in individuals with PD. Individuals with PD exhibit cell loss in the locus coeruleus, a nucleus in the pontine tegmentum which uses norepinephrine as its main neurotransmitter (Grimbergen et al., 2009). The cell loss in the locus coeruleus is thought to contribute to postural instability as it occurs particularly in the caudal part of the nucleus. This part of the nucleus projects to the spinal cord and cerebellum, neural structures important for normal balance control (Grimbergen et al., 2009). The cholinergic system is another non-dopaminergic system possibly involved in postural instability in individuals with PD. A small placebo controlled clinical trial showed that treatment with donepezil, a central cholinesterase inhibitor, for 6 weeks reduced the frequency of falls about 50% in individuals with PD who reported falling, or nearly falling, 2 or more times per week (Chung et al., 2010). Furthermore, decreased thalamic cholinergic innervation was found in individuals with PD with a history of falls compared to individuals without a history of falls, a result consistent with PPN degeneration (Bohnen et al., 2009). The PPN has gained attention as a new DBS target for alleviating postural instability and gait dysfunction in individuals with PD. The PPN is a cholinergic nucleus located in the dorsolateral part of the ponto-mesencephalic
tegmentum that provides inputs to the basal ganglia, thalamus, cerebellum, several brainstem nuclei and the spinal cord (Bohnen et al., 2009; Lee et al., 2000). It is part of the mesencephalic locomotor region, a functionally defined area involved in controlling locomotion (J. E. Visser & Bloem, 2005). Degeneration of the PPN in individuals with PD is thought to cause postural instability and gait dysfunction (Bohnen & Albin, 2011; Lee et al., 2000) and some studies have demonstrated that freezing of gait, postural instability, and falls can be improved by low frequency stimulation of the PPN (Collomb-Clerc & Welter, 2015; Ferraye et al., 2010; Moro et al., 2010; Plaha & Gill, 2005; Stefani et al., 2007; Thevathasan et al., 2011). However, larger controlled trials are needed to further evaluate the benefit of PPN DBS (Ferraye et al., 2010).

1.4.1 Investigating the neural substrates of balance control using functional neuroimaging

Not only is there a need for a better understanding of the neural substrates contributing to postural instability in PD, but the neural substrates, and their functional interactions, involved in controlling healthy balance are also still relatively poorly understood. These neural substrates can be investigated using functional neuroimaging. Functional neuroimaging is used to determine brain function in real time by measuring neural activity while participants are either at rest or engaged in a specific task. Neural activity can be recorded using hemodynamic techniques that measure changes in regional cerebral blood flow (rCBF), i.e., functional magnetic resonance imaging (fMRI), positron emission tomography (PET), or functional near infrared spectroscopic imaging (fNIRS). Neural activity can also be determined using electro-magnetic techniques that record electrical currents, i.e., electroencephalography (EEG), or magnetic fields, i.e., magnetoencephalography. The spatial and temporal resolutions of functional neuroimaging
depend on the technique used to record neural activity. In general, hemodynamic techniques have better spatial resolution, i.e., they are better at measuring the location of the neural activity, while electro-magnetic techniques have better temporal resolution, i.e., they are better at determining the time-course of the neural activity. fMRI and PET are able to record neural activity in both cortical and subcortical structures, while fNIRS, EEG, and magnetoencephalography are able to record cortical activity, but are limited in their ability to record subcortical activity. In healthy individuals balance control likely involves an integrated network of both cortical and subcortical structures (Takakusaki, 2017), fMRI and PET are the functional neuroimaging techniques of choice to investigate all possible neural substrates involved in balance control simultaneously, including subcortical substrates. One advantage of investigating all possible neural substrates involved in balance control simultaneously is that, in addition to identifying the individual areas that show neural activity, the connectivity between cortical and subcortical structures can be determined.

Both fMRI (Bhatt et al., 2018; de Lima-Pardini et al., 2017; Ferraye et al., 2014; Jahn et al., 2008, 2004, 2009; Karim et al., 2014; Mouthon et al., 2018; Taube et al., 2015; Zwergal et al., 2012) and PET (Malouin et al., 2003; Ouchi et al., 2001, 1999) have been used to investigate the neural substrates of balance control in healthy participants. Most of these studies were conducted in healthy young participants (Bhatt et al., 2018; de Lima-Pardini et al., 2017; Ferraye et al., 2014; Jahn et al., 2008, 2004, 2009; Mouthon et al., 2018; Ouchi et al., 1999; Taube et al., 2015; Zwergal et al., 2012), although a few studies included older adults as participants (Karim et al., 2014; Malouin et al., 2003; Mouthon et al., 2018; Ouchi et al., 2001; Zwergal et al., 2012).

Investigating the neural substrates of balance control using fMRI and PET is complicated by the fact that most standard scanners require participants to lie horizontally, and movement of
the head must be strictly minimized to get adequate signal quality. Therefore, most studies have been limited to participants performing motor imagery of standing under static or dynamic conditions (Bhatt et al., 2018; Ferraye et al., 2014; Jahn et al., 2008, 2004, 2009; Malouin et al., 2003; Mouthon et al., 2018; Taube et al., 2015; Zwergal et al., 2012), although two studies used upright PET scanners, and were able to investigate the neural substrates of balance control in participants standing upright (Ouchi et al., 2001, 1999). In addition, two studies had participants perform balance-related tasks while lying supine (de Lima-Pardini et al., 2017; Karim et al., 2014). The first study had participants perform an active tracking task with their feet during fMRI scanning (Karim et al., 2014), while the second had participants perform single leg raises to simulate step initiation (de Lima-Pardini et al., 2017).

1.4.2 The neural substrates of balance control investigated using motor imagery

Most studies investigating the neural substrates of balance control using motor imagery investigated static balance control (Jahn et al., 2008, 2004, 2009; Malouin et al., 2003; Mouthon et al., 2018; Taube et al., 2015; Zwergal et al., 2012), while four studies investigated dynamic balance control (Bhatt et al., 2018; Ferraye et al., 2014; Mouthon et al., 2018; Taube et al., 2015) (Table 1.2). In all studies the brain activation pattern seen during the motor imagery task was compared to a control task to determine which areas showed statistically significant changes in activation. While some studies used a control task that involved mental imagery (Bhatt et al., 2018; Ferraye et al., 2014; Jahn et al., 2008, 2004, 2009; Zwergal et al., 2012), others used resting state scans (Malouin et al., 2003; Mouthon et al., 2018; Taube et al., 2015). As the changes in activation seen during the motor imagery task in the three studies comparing to resting state would also include general changes in brain activation related to the mental
representation of motor actions (Malouin et al., 2003), the changes in activations seen in the studies comparing to a mental imagery control task are a better representation of the activity of neural substrates involved in balance control. This should be taken into account when interpreting the results of studies investigating the neural substrates of balance control in motor imagery. Therefore, the following discussion will focus on studies that used a mental imagery control task.

In order to study the neural substrates of static balance, participants were asked to imagine standing upright for 20 s at a time during the task trials and to imaging lying during the mental imagery control task (Jahn et al., 2008, 2004, 2009; Zwergal et al., 2012) (Table 1.2). Subcortically, increased rCBF was seen in the basal ganglia and thalamus with a left-sided predominance (Jahn et al., 2008, 2004; Zwergal et al., 2012). In addition, cerebellar activation was found, located in the vermis and both hemispheres (Jahn et al., 2008, 2004; Zwergal et al., 2012). Motor imagery of upright standing was also associated with increased rCBF in the left midbrain and bilaterally in the dorsal pontine tegmentum, corresponding to the vestibular nuclei and lateral reticular formation (Jahn et al., 2008, 2004; Zwergal et al., 2012). At the level of the cortex, bilateral activation of the supplementary motor area (SMA) in the frontal lobe was found (Jahn et al., 2008), although one study did not find changes in rCBF in frontal lobe cortical motor areas (Jahn et al., 2004). In addition, activation was seen in the dorsolateral prefrontal cortex with a left-sided predominance; in the anterior prefrontal cortex; and in the pars opercularis, triangularis and orbitalis of the inferior frontal gyrus (Jahn et al., 2008, 2004; Zwergal et al., 2012). In the parietal lobe increased rCBF was found in the primary somatosensory cortex with a right-sided predominance, the precuneus, supramarginal gyrus, and angular gyrus bilaterally, and the subcentral area (Jahn et al., 2008; Zwergal et al., 2012). Furthermore, activation has been
observed in the temporal and occipital lobes in: the hippocampus in the right hemisphere; the superior and middle temporal gyrus; the primary auditory cortex; the primary and secondary visual cortex; and the visual association cortex (Jahn et al., 2008, 2004, 2009; Zwergal et al., 2012). Finally, bilateral activation of the insular and cingulate cortex was seen (Jahn et al., 2008; Zwergal et al., 2012). Of note, no cortical deactivations were found during motor imagery of upright standing (Jahn et al., 2004).

One study included both healthy young and healthy older participants in order to investigate age-dependent changes in the supraspinal locomotor and postural networks. The pattern of activation of the basic postural network during motor imagery of upright standing was preserved in the older participants. However, relatively enhanced activation of the visual, vestibular and somatosensory cortical areas was also seen in the older participants. This increased activation was suggested to be due to a reduced reciprocal inhibitory sensory interaction and could be considered a compensatory strategy for age-related peripheral sensory decline (Zwergal et al., 2012).

Two studies investigated the neural substrates underlying dynamic balance control using motor imagery (Bhatt et al., 2018; Ferraye et al., 2014) (Table 1.2). During the task trials, the first study asked participants to imagine themselves slipping on a treadmill while walking (Bhatt et al., 2018), while in the second study participants were asked to imagine swaying forward and backward on a balance board (Ferraye et al., 2014). The mental imagery control task consisted of imagining walking on a treadmill for the first study (Bhatt et al., 2018), a visual imagery task where participants imagined seeing a laser dot move up and down was used for the second study (Ferraye et al., 2014). Both studies observed subcortical activation of the cerebellum, thalamus (ventral lateral nucleus and pulvinar nucleus), and pons (Bhatt et al., 2018; Ferraye et al., 2014).
Activation of the left globus pallidus externus, bilaterally the putamen, and the right anterior part of the mesencephalic locomotor region were also found (Ferraye et al., 2014). Cortically, in the motor and parietal regions, the right SMA and left dorsal premotor cortex, as well as the left precentral gyrus, were activated, together with the precuneus, and superior and inferior parietal lobules (Bhatt et al., 2018; Ferraye et al., 2014). Increased rCBF was also present bilaterally in the cingulate and insular cortices (Bhatt et al., 2018; Ferraye et al., 2014). Further cortical activation was seen the superior, middle, and transverse temporal gyri, the parahippocampal gyrus, and the middle frontal gyrus (Bhatt et al., 2018). Compared to the brain activity seen in studies of motor imagery of upright standing, a few differences were noted. First, stronger activation of both the basal ganglia and SMA were seen during motor imagery of dynamic balance. Second, dynamic balance preferentially recruited the median cerebellum, while activation of both the median cerebellum and cerebral hemispheres was seen during motor imagery of upright standing (Ferraye et al., 2014).

Only one study to date used motor imagery of a balance task in individuals with PD (Peterson et al., 2014b). This study investigated brain activation amplitudes during motor imagery of static balance in individuals with PD_{OFF} with and without freezing of gait but did not include any healthy older participants. During motor imagery of static balance, compared to rest, decreased activation of the right globus pallidus and cerebellar locomotor region were found in individuals without freezing of gait, while decreased activation of the left mesencephalic locomotor region was seen in both individuals with and without freezing of gait (Peterson et al., 2014b).

Nevertheless, there are significant limitations for using motor imagery as a paradigm to investigate the neural substrates of balance control. The ability to perform motor imagery varies
greatly among individuals (Saimpont et al., 2015; Zabicki et al., 2019), with older participants showing decreased or qualitatively different motor imagery ability compared to young participants (Saimpont et al., 2013; Zapparoli et al., 2013), especially for complex movements (Kalicsinski et al., 2015). This is problematic as brain activation patterns differ depending on motor imagery ability (Guillot et al., 2008; van der Meulen et al., 2014; Zabicki et al., 2019). Although previous work has shown individuals with PD can perform motor imagery (Abbruzzese et al., 2015; McInnes et al., 2016), compared to healthy older participants, they tend to rely on different motor imagery strategies (Poliakoff, 2013), which are known to involve different brain activation patterns (Guillot et al., 2009; Jiang et al., 2015). Furthermore, while certain neural substrates are shared between motor imagery and motor execution of the same task, the overlap is incomplete; some brain areas are more strongly, or selectively, activated during motor execution of a task compared to motor imagery of the same task, and vice versa (Guillot et al., 2012; O’Shea & Moran, 2017). While motor imagery of balance control may therefore be a useful tool for investigating the neural substrates of balance control in healthy young participants, it may be less suitable for investigating these neural substrates in healthy older participants, especially individuals with PD.

1.4.3 The neural substrates of balance control investigated using real balance tasks

A few studies have investigated the neural substrates involved in balance control while participants were standing upright (Ouchi et al., 2001, 1999) (Table 1.2) or were engaged in either an active tracking task with their feet (Karim et al., 2014) or single leg raises to simulate step initiation (de Lima-Pardini et al., 2017).
One study used a PET system with a mobile gantry, enabling vertical movement, to measure rCBF while participants performed five different tasks. The control task was adopting a supine posture. The other four tasks were standing with feet together with eyes open, standing on one foot with eyes open, standing in tandem with eyes open and standing with feet together with eyes closed. The authors listed several methodological limitations to their study. First, fixation of the head might have interfered with a free and natural standing style and impaired the participant’s ability to correct for imbalance during standing. Although magnitude of sway did not differ significantly from that measured during a preliminary study. Second, removal of head fixation between scans might have caused positional errors. This was countered by the use of a face mask, head holder, and a three-dimensional laser marker. Thirdly, the PET scanner’s axial field of view was insufficient to cover the whole brain; therefore, the brain region covering the primary somatosensory foot area was excluded. Finally, brain hemodynamics might alter when changing position from supine to standing. However, systemic blood pressure and pulse rate were found not to be significantly different in standing during this study. The findings of this study showed activation during upright standing in the cerebellum and the primary and secondary visual cortex. No activation of the lower brainstem (i.e., vestibular nuclei) was found, which might be due to the head and gaze fixation used (Ouchi et al., 1999). Another study using PET also found increase in rCBF in the cerebellum and the primary and secondary visual cortex in standing when compared to passively sitting or a supine position. No significant activations in the basal ganglia or thalamus were found. However, a decrease in activation was seen in the premotor cortex/SMA, anterior prefrontal, and orbitofrontal cortex. Limitations pointed out by the authors for this study were related to the effects of fixation of the head, the short axial view
of the PET scanner, and the inability of this study to measure rapid hemodynamic changes on a real-time basis in response to an orthostatic behavioural shift (Ouchi et al., 2001).

An active tracking task was used in one study to investigate the neural substrates of balance control using fMRI (Karim et al., 2014). During the active tracking task participants lay supine and used visual feedback to control AP COP movements, calculated from ground reaction forces and moments recorded by an MRI compatible force plate. As COP movements were generated by ankle dorsi- and plantarflexor activity, an ankle dorsi- and plantarflexor activation task was used to control for activation of the primary motor areas. A visual stimulation control task was used to control for activation of the visual system by the visual feedback provided. When brain activation patterns were compared between the active tracking task and the ankle muscle activation task, subcortically, increased rCBF was seen in the right caudate nucleus. Cortically, activation was found in the right hemispheric corpus callosum and insular cortex. In addition, activation of the left premotor cortex/SMA, medial, middle, and inferior frontal gyri was seen. Finally, bilateral activation of the middle temporal gyrus and activation of the superior temporal gyrus and anterior cingulate cortex were seen in the left hemisphere. The authors noted that a limitation of the task used (regarded as a simulated balance task by the authors) was that the task, which is performed supine, may not completely represent the activation of standing upright (Karim et al., 2014). During the task a stationary circle was placed at the midpoint of a vertical bar on a monitor in front of the participants. When the participants did not apply any force with their feet on the MRI compatible force plate, a cross would pseudorandomly move up and down the vertical bar according to a sum of sines displacement that had the frequency characteristics of postural sway. When participants applied force, the movement of the cross represented a summation of the pseudorandom displacement and the location of the COP in the...
AP direction. The participants were instructed to keep the cross within the stationary circle by applying force with their heels or toes (Karim et al., 2014). Although the authors considered the task a simulated balance task, the participants were not required to balance an unstable object, such as an inverted pendulum, during testing and used feed-forward volitional control to complete the task.

To investigate the neural substrates of anticipatory postural adjustments, another study had both healthy young adults and individuals with PD perform single leg raises to simulate step initiation with and without external support at the knee in a supine position (de Lima-Pardini et al., 2017). When participants raised their leg from the hip with a straight knee an anticipatory postural adjustment was elicited, this was not the case when they raised their leg while their knee was supported. An MRI compatible force measurement system was used to record the level of force applied by both feet. When brain activation was compared between the unsupported and supported conditions, increased activation in the right SMA, and medial regions of the pre- and post-central gyri was seen in healthy young participants. In contrast, individuals with PD_{ON} lacked a focused brain activation pattern (de Lima-Pardini et al., 2017). While anticipatory postural adjustments have an important role in maintaining balance, they are elicited only when the postural outcome of a movement or event is known in advance. Consequently, they may involve postural control mechanisms that are distinct from those involved in the control of static or reactive dynamic balance.

Even though none of these studies relied on the motor imagery of a balance task to investigate the neural substrates of balance control, given the limitations described above, there is a need to further investigate the neural substrates, and their functional interactions, involved in controlling healthy balance using functional neuroimaging. In addition, functional neuroimaging
could be used to investigate the neural substrates contributing to postural instability in individuals with PD.

### 1.4.4 A novel approach to investigating the neural substrates of postural instability in Parkinson’s disease

A novel approach to investigate the neural substrates contributing to postural instability in individuals with PD using functional neuroimaging, without having to rely on motor imagery or the use of an upright PET scanner, is to mimic actual balance performance using a balance simulator. A few balance simulator designs have been developed and tested in the lab (Buettner et al., 2017; Fitzpatrick et al., 1992; Loram et al., 2001)

Recently, a moveable balance board producing torque resembling gravity, inertia and damping effects of free standing was developed (Buettner et al., 2017). While using it participants were asked to continuously balance the board by moving their feet in the ankle joint. While the balance board system took into account the characteristics of an inverted pendulum body, participants did not balance a physical weight but instead a torque was generated using an electric motor with the potential effect of electromechanical delays limiting the use of this balance simulator design. In addition, it is unclear if the balance board system is MRI compatible and would allow participants to perform the balance-related task while supine.

A different balance simulator design allowed participants to balance an external weight as a substitute for their own body (Fitzpatrick et al., 1992; Loram et al., 2001). To use the balance simulator, the participant was fixed to a stable, vertical support surface and instructed to control an inverted pendulum by activation of postural muscles around the ankle joint (Figure 1.1) (Fitzpatrick et al., 1992; Loram et al., 2001). While such a setup has been used effectively to
study sensorimotor contributions to healthy balance control, it has not been adapted for use within an fMRI scanner. In this thesis, a novel adaptation of the balance simulator paradigm – essentially rotating the apparatus 90° with the participant lying horizontally – is used so that it can be realistically performed within an fMRI scanner (Figure 1.2).

1.5 General purpose

The general purpose of this thesis was to investigate the pathophysiological processes that contribute to postural instability in individuals with PD. Specifically, a narrative review of the literature was conducted to gain better insight into the specific deficits in static balance control that individuals with PD exhibit. In addition, the neural substrates contributing to postural instability in individuals with PD were investigated using a modified balance simulator paradigm in an fMRI scanner.

The first aim of this thesis was to gain better insight into the specific deficits in static balance control that individuals with PD exhibit compared to healthy older participants as well as between different pharmacological and/or neurosurgical treatment conditions. To address this aim, a narrative review of the literature on static balance control in individuals with PD was conducted (Chapter 2).

The second aim of this thesis was to validate the use of the modified balance simulator that was designed specifically by our research group for the purpose of studying balance control in individuals with PD and healthy older participants within an fMRI scanner. To address the second aim, two separate experiments were completed in which kinematic data was recorded to compare balance performance between individuals with PD_{ON} and healthy older participants.
while they performed both real upright standing and simulated static and dynamic balance tasks (Chapter 3).

The third aim of this thesis was to investigate the neural substrates contributing to static and dynamic balance deficits in individuals with PD using the novel balance simulator in an fMRI scanner. To address this aim, individuals with PD\textsubscript{ON} and healthy older participants performed both simulated static and dynamic balance tasks as part of two separate fMRI experimental protocols collected within the same fMRI session. The first protocol (Chapter 4) allowed for effective brain connectivity to be determined during both static and dynamic simulated balancing tasks in both individuals with PD and healthy older participants. The second protocol (Chapter 5) allowed for changes in brain activation amplitude during static and dynamic simulated balancing tasks to be determined between individuals with PD and healthy older participants.
<table>
<thead>
<tr>
<th><strong>DYNAMIC BALANCE</strong></th>
<th><strong>MULTIDIRECTIONAL TRANSLATIONS</strong></th>
<th><strong>MULTIDIRECTIONAL ROTATIONS</strong></th>
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</thead>
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<tr>
<td>Reference</td>
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<td>R2</td>
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<tr>
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<td>8</td>
</tr>
<tr>
<td>Sample CS</td>
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<tr>
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<td>Trials per direction/total</td>
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<td>5/40</td>
</tr>
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</table>

**RESULTS**

**EMG**

- **Onset latency**: Normal
- **Amplitude**: Trunk, Hip, Normal, Normal SLR, BCR
- **Direction max activation**: Normal
- **Tuning curves**: BD in RA
- **BGR EMG/co-contraction**: ↑/Yes, -/Yes, ↑/Yes

**KINETIC**

- **QS forces**: -
- **Passive reactive forces**: -
- **Active reactive forces**: -
- **COP responses**: -
- **Ankle torque change**: -

**KINEMATIC**

- **COM displacement**: -
- **Trunk rotation**: -
- **Pelvis rotation**: -
- **Joint angle displacement**: -

| **Table 1.1 Overview of studies comparing postural responses between individuals with Parkinson’s disease and healthy older adults during multidirectional support surface perturbations** |

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R1 = (Dimitrova, Horak, & Nutt, 2004); R2 (Dimitrova, Nutt, & Horak, 2004); R3 (Horak et al., 2005), R4 (Jacobs et al., 2005), R5 = (Carpenter et al., 2004), R6 = (Visser, Allum, Carpenter, Esselink, Speelman, et al., 2008), R7 = (Visser, Allum, Carpenter, Esselink, Limousin-Dowsey, et al., 2008); Sample PD = sample size individuals with PD; Sample CS = sample size control subjects; Age PD and CS: mean ± SD, in years; Disease duration: mean ± SD, in years; H&Y stage: mean ± SD; UPDRS-ME: mean ± SD; Perturbations parameters = amplitude, velocity and/or acceleration of perturbations: PA = peak acceleration; Trials per direction/total = number of perturbation trials per direction/total number of perturbation trials; Results: ↑ = statistically significant increase in PD compared to CS, ↓ = statistically significant decrease in PD compared to CS, normal = no statistically significant difference in PD compared to CS; EMG amplitude: SLR = short-latency reflex, MLR = medium-latency reflex, BCR = balance correcting response; EMG tuning curves: BD = bidirectional, RA = rectus abdominis; EMG BGR EMG/co-contraction = background EMG/co-contraction; Kinetic data: QS forces = forces during quiet stance; Note: all comparisons between individuals with PD and healthy participants regard trials where vision was available; darkened columns regard studies using multidirectional translations.
## Neuroimaging

<table>
<thead>
<tr>
<th>Neuroimaging</th>
<th>Upright standing</th>
<th>Motor imagery of static balance</th>
<th>Motor imagery of dynamic balance</th>
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### SUBCORTICAL

#### Basal ganglia

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### Brainstem

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### CORTICAL

#### Frontal lobe

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#### Temporal lobe

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<tr>
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<td>↑B</td>
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#### Occipital lobe

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#### Other cortical areas

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40
Table 1.2 Overview of studies investigating the neural substrates of balance control in healthy participants using functional neuroimaging

R# (#) = reference (sample size); R1 = (Ouchi et al., 1999), R2 = (Ouchi et al., 2001), R3 = (Malouin et al., 2003), R4 = (Jahn et al., 2004), R5 = (Jahn et al., 2008), R6 = (Zwergal et al., 2012), R7 = (Taube et al., 2015), R8 = (Mouthon et al., 2018), R9 = (Ferraye et al., 2014); R10 = (Bhatt et al., 2018); Imagery control task: n/a = not applicable; Age participants: mean ± SD or range, in years; Subcortical and cortical structures: ↑ = activation, ↓ deactivation, ns = no statistically significant difference in activation, R = right, L = left, B = bilateral. Note: darkened columns regard motor imagery studies that did use a mental imagery control task.
Figure 1.1 Illustration of the original balance simulator

Illustration of the original balance simulator (inverted pendulum apparatus) used by Loram et al. (2001) to examine sensorimotor control of healthy participants standing in a vertical position.
Figure 1.2 Illustration of the modified balance simulator

Illustration of the modified balance simulator, designed to be used while lying supine within an fMRI scanner.
Chapter 2: The effect of Parkinson’s disease on the kinetic and kinematic characteristics of static balance control: a narrative review

2.1 Introduction

PD is one of the most prevalent neurodegenerative disorders in the world (Pringsheim et al., 2014). It is characterized by four hallmark symptoms: rest tremor, rigidity, bradykinesia, and postural instability (Jankovic, 2008). Postural instability is a particularly disabling symptom of PD as it often leads to falls, which are a major source of morbidity and mortality in this clinical population (Auyeung et al., 2012; Fasano et al., 2017; Gazibara et al., 2014; Pickering et al., 2007). Therefore, investigating the underlying pathophysiology of balance deficits in PD has been a major focus of research studies over the years.

One aspect of balance control that has been extensively studied in individuals with PD is quiet standing (static balance). Spontaneous sway occurs during quiet stance, irrespective of whether individuals attempt to consciously focus on standing as still as possible, or direct attention to other tasks (Bonnet, 2016). Large visible deviations in sway or a loss of balance are often used in clinical settings as subjective measures of static balance to identify gross balance abnormalities. However, these observations are not sensitive enough to detect subtle changes in balance control that may occur in earlier stages of a balance disorder such as PD (Mancini et al., 2011; Mancini, Salarian, et al., 2012).

Static balance control can be rigorously assessed using posturography during which biomechanical outcome measures are recorded (Bloem et al., 2003; J.E. Visser, Carpenter, et al., 2008). Several biomechanical outcome measures can be used to quantify balance, including kinetics, the analysis of forces and joint moments, and kinematics, the analysis of how body parts...
move (Bloem et al., 2003). Kinetic data can be collected by having participants stand on a force plate that records ground reaction forces and moments, which are then used to calculate COP. When quantifying balance control using COP displacements, the movement of the weighted average of all forces acting beneath the feet is measured (Winter et al., 1996). Kinematic measures of standing balance have become more frequent as body-worn sensors become more accurate, portable, and readily accessible (Mancini, Salarian, et al., 2012). When quantifying static balance control using kinematics, the absolute or relative position, velocity, or acceleration of the trunk, hip, or legs are often used to estimate sway of the body’s COM. In healthy participants, during quiet standing, the body above the ankle is generally assumed to act as a single rigid segment which rotates around the ankle joint, analogous to an inverted pendulum (Gage et al., 2004). Assuming the body acts as an inverted pendulum, the low frequency components of COP displacements would represent the low frequency components of the COM movement (Winter et al., 1996). Therefore, one would expect kinetic and kinematic measures of balance control that are influenced primarily by the lower end of the frequency spectrum to be congruent (Gage et al., 2004; Winter et al., 1998). However, if the inverted pendulum control of balance is affected by a particular task constraint, or disease state, then discrepancies between kinetic and kinematic measures of static balance control may occur. Therefore, valuable information about static balance control can be gathered from both kinematic and kinetic measures, although the two are rarely measured simultaneously in studies examining neurological deficits such as PD.

Two systematic reviews have previously examined static balance literature in PD (Hubble et al., 2015; Kamieniarz et al., 2018), although neither review specifically focused on static balance, and their search queries may not have been able to locate all relevant studies on
this topic. Hubble et al. (2015) limited the scope of their review to studies using wearable sensors to assess standing balance and walking stability in individuals with PD. In contrast, the review by Kamieniarz et al. (2018) considered studies that used a force plate, video camera, and/or clinical tests to assess balance in individuals in PD. Hubble et al. (2015) included nine studies that investigated standing balance in individuals with PD, and reported contradictory findings among these studies. Methodological differences across studies, such as the use of different tasks to assess standing balance (e.g., semi-tandem stance, sensory organization test, Romberg test, etc.), were offered as a possible explanation for the discrepancies. In addition, it was noted that three of the nine studies appeared to have investigated the same patient cohort, limiting the overall interpretation of the literature (Hubble et al., 2015). Kamieniarz et al. (2018) included 20 studies that investigated quiet stance in individuals with PD using a force plate. Again, findings among studies were reported to often be dissimilar and contradictory. Several possible explanations were offered for the mixed results, including methodological differences across studies (e.g., duration and number of repetitions of quiet standing trials, differences in equipment and sampling frequencies used), limited statistical power in studies with relatively small sample sizes, and differences in the disease stage of the included individuals with PD (Kamieniarz et al., 2018).

Prior reviews highlighted the difficulty in comparing findings across studies due to the wide disparity in descriptive measures used to quantify sway characteristics (Hubble et al., 2015; Kamieniarz et al., 2018). Comparing across different descriptive measures can be difficult as some measures quantify the COP and kinematic recordings in the time-domain (e.g., RMS, SD, range, sway area, sway path length, mean velocity), while others do so in the frequency-domain (e.g., mean, median, centroid, and 95% power frequency). Descriptive measures can also be
separated into traditional measures, such as those mentioned above, and non-traditional measures, which include fractal dimension, sample and approximate entropy, stabilogram diffusion measures (study of random walks), and detrended fluctuation measures. Finally, some descriptive measures are two-dimensional and characterize the COP and kinematic signals as a whole, therefore representing information from both AP and ML directions simultaneously (e.g., sway area). Other measures are one-dimensional, allowing balance control to be assessed in the AP and ML directions separately (e.g., AP and ML RMS, AP and ML range, etc.).

Prior systematic reviews have also highlighted differences in sampling duration as an obstacle for meaningful comparisons across balance control studies in individuals with PD, although this was not used as a factor in their interpretation of the literature (Hubble et al., 2015; Kamieniarz et al., 2018). Sampling duration has long been recognized as a potentially confounding variable for balance control research that should be carefully considered and standardized (LeClair & Riach, 1992). It deserves particular attention when designing and interpreting static balance research as it has been shown to significantly influence the magnitude and reliability of many time- and frequency-domain descriptive measures that are commonly used to quantify COP and COM recordings during quiet stance (Carpenter, Frank, et al., 2001; van der Kooij et al., 2011). Longer sampling durations also result in increased reliability of traditional COP measures, such as sway area, range, RMS, and MPF (Carpenter, Frank, et al., 2001; Doyle et al., 2007; Lafond et al., 2004), as well as non-traditional measures, including stabilogram diffusion measures (Doyle et al., 2008). In addition, it was recently shown that differences in amplitude of COP displacements between individuals with PD and healthy older adults were greater during longer trials (Jehu et al., 2018). To optimize the stability and reliability of COP descriptive measures, trial lengths of at least 60 s should be used when vision
is available, and longer trial lengths when participants are asked to keep their eyes closed (Carpenter, Frank, et al., 2001; Doyle et al, 2007; Lafond et al., 2004; van der Kooij et al., 2011).

Prior reviews have highlighted the importance of considering antiparkinson medication as a factor for balance control changes in individuals with PD but did not strictly separate studies based on medication status when summarizing and interpreting results (Hubble et al., 2015; Kamieniarz et al., 2018). It is important to note whether individuals with PD were drug-naïve (i.e., they had never been treated with dopaminergic or other antiparkinson medication), or ‘off’ or ‘on’ their normal antiparkinson medication when their balance was investigated. When individuals with PD who are drug-naïve or ‘off’ their medication are tested, both dopaminergic and non-dopaminergic lesions may influence their quiet standing performance. In contrast, when individuals with PD are tested in their optimal ‘on’ state following intake of their antiparkinson medication (i.e., levodopa, dopamine-agonists), quiet standing performance will generally reflect the effect of any non-dopaminergic lesions plus potential side-effects arising from the dopaminergic medication. In addition to antiparkinson medication, several neurosurgical treatments are available as therapeutic options for individuals with PD in whom the effectiveness of medication is limited by motor response complications (i.e., levodopa-induced dyskinesia and motor fluctuations; Maurer et al., 2003). However, there is currently no review that has examined the specific effects of neurosurgical procedures on static balance control in individuals with PD.

Given the limitations of the prior reviews, as outlined above, there is a need for a review of the literature which focuses solely on static balance control in individuals with PD. Therefore, the primary objective of this narrative review was to summarize the current evidence for the effect of PD on the kinetic and kinematic characteristics of quiet, bipedal standing. A secondary objective was to summarize the current evidence for the effect of antiparkinson treatment
interventions (pharmacological and/or neurosurgical) on the kinetic and kinematic characteristics of quiet, bipedal standing in individuals with PD. In addition, the evidence for a change in visual dependency during static balance control in individuals with PD compared to healthy older adults, and evidence for any correlations between postural sway measures and clinical characteristics of individuals with PD, will also be examined.

2.2 Methods

2.2.1 Data sources and search strategy

A literature search was conducted in the following electronic databases: MEDLINE (OVID), EMBASE (OVID), and CINAHL in accordance with the PRISMA statement (Liberati et al., 2009; Moher et al., 2009). The search queries were constructed using three themes: (1) PD, (2) static balance, and (3) kinetic and kinematic outcome measures. Both subject headings (MEDLINE and CINAHL: MeSH terms; EMBASE: Emtree) and free search terms were used. The Boolean operator “OR” was used to combine related terms for each theme. The Boolean operator “AND” was subsequently used to combine all the themes. Table 2.1 reports the final search queries for the MEDLINE, EMBASE, and CINAHL databases. No language or publication date restrictions were applied. The final search was performed in August 2019. Reference lists of articles meeting the inclusion/exclusion criteria were manually searched for additional records not covered by the databases search. All results were imported into RefWorks for screening.
2.2.2 Eligibility criteria

All original research articles comparing kinetic and/or kinematic characteristics of static balance control in individuals with PD to those in healthy age-matched controls, or between antiparkinson treatment interventions (dopaminergic medication and/or neurosurgical), were considered for inclusion. Articles that met the following criteria were included: (a) involving individuals with idiopathic PD; (b) assessing quiet, bipedal standing; and (c) measuring biomechanical (kinetic or kinematic) outcomes. Articles meeting the following criteria were excluded: (a) individuals with atypical parkinsonism were included; (b) published in languages other than English; (c) case studies, review articles, and conference abstracts; (d) no healthy age-matched controls and no comparison between antiparkinson treatment interventions; (e) treatment interventions other than dopaminergic medication and/or neurosurgical procedures were investigated; (f) insufficient information was provided about study design and results; and (g) only non-traditional descriptive measures were used.

2.2.3 Data extraction and synthesis

First, duplicates and conference abstracts were removed, then the remaining records were screened for title and/or abstract against the inclusion/exclusion criteria. The full-text of studies that reported on kinetic and/or kinematic characteristics of static balance control in individuals with idiopathic PD were subsequently screened and assessed for eligibility. Data extraction from included articles was performed using a predefined table. The following data were extracted from articles that met the inclusion criteria: author, sample size, demographic and clinical characteristics of participants, data acquisition methods, outcome measures, and reported findings.
2.3 Narrative review search results

2.3.1 Article selection

The database searches identified 2349 records (MEDLINE: n = 753; EMBASE: n = 1287; CINAHL: n = 309) and two additional records were identified through other sources (Figure 2.1 and Table 2.1). After removal of duplicates and conference abstracts 1012 records remained. Of these, an additional 803 records were excluded because after reviewing the title and/or abstract it appeared that these articles did not meet the inclusion/exclusion criteria. After screening the full-text of the remaining 209 records, another 38 articles were excluded for the following reasons: there was no full-text in English available (n = 20); the articles did not compare individuals with PD to healthy older participants, or between treatment conditions (n = 7); sensory information was manipulated, other than vision removal, during all quiet standing trials (n = 4); a dual-task was performed during all quiet standing trials (n = 4); the articles were case studies (n = 2); the study focused on feature selection only (n = 1). In the end, 171 full-text articles met the inclusion criteria.

As a trial length of at least 60 s is recommended in order to optimize the stability and reliability of COP descriptive measures (Carpenter, Frank, et al., 2001; Doyle et al, 2007; Lafond et al., 2004; van der Kooij et al., 2011), the 171 articles meeting the inclusion criteria were further screened for trial length. Of the 171 studies screened, 152 investigated the effect of PD on static balance by quantifying the kinetic and/or kinematic characteristics of quiet, bipedal standing in both individuals with PD and healthy older participants. However, only 42 of these studies recorded quiet standing performance for longer than 60 s (Figure 2.2). Both kinetic and kinematic outcomes measures were reported in three studies, while 29 and 10 studies reported on
kinetic or kinematic outcome measures only, respectively. Of the 171 studies screened, 54 investigated the effect of dopaminergic medication and/or neurosurgical procedures on static balance by quantifying the kinetic and/or kinematic characteristics of quiet, bipedal standing in the same individuals with PD under different treatment conditions (Figure 2.3). However, only 13 of these studies recorded quiet standing performance for longer than 60 s. Both kinetic and kinematic outcomes measures were reported in one study, while 12 studies reported on kinetic outcome measures only. Overall, data was extracted only from the 42 articles that measured the kinetic and/or kinematic characteristics of quiet, bipedal standing in both individuals with PD and healthy older participants, and the 13 articles that measured the kinetic and/or kinematic characteristics of quiet, bipedal standing in the same individuals with PD under different treatment conditions.

During data extraction, several additional articles were excluded for the following reasons: no statistics were reported (PD versus healthy: n = 2; PD treatment effect: n = 2); only non-traditional outcome measures were reported (PD versus healthy: n = 2); there was no direct comparison between PD and healthy participants (PD versus healthy: n = 4); data came from force-sensitive resistors in shoes (PD versus healthy: n = 1); STN DBS was always on in individuals with PD (PD versus healthy: n = 1; PD treatment effect: n = 1); data was analyzed from 2 s bout windows (PD versus healthy: n = 1); there was no direct comparison between treatment conditions (PD treatment effect: n = 2); results were only reported for PD_{OFF} (PD treatment effect: n = 1) (Figure 2.2 and 2.3). Therefore, to address the primary objective of this narrative review, which was to summarize the current evidence for the effect of PD on the kinetic and kinematic characteristics of quiet, bipedal standing, a total of 31 articles were included in the review (Figure 2.4). In addition, to address the secondary objective of this
review, which was to summarize the current evidence for the effect of antiparkinson treatment interventions (pharmacological and/or neurosurgical) on the kinetic and kinematic characteristics of quiet, bipedal standing in individuals with PD, a total of eight articles were included in the review (Figure 2.5).

2.3.2 Treatment status of individuals with Parkinson’s disease

Of the 31 studies reporting on the effect of PD on static balance control, 18 studies compared quiet standing performance between healthy older participants and individuals with PD when they were in the ‘on’ medication state (i.e., approximately one to two hours after levodopa administration; Barbosa et al., 2015; Benninger et al., 2010; Cruz et al., 2018; Ebersbach & Gunkel, 2011; Halmi et al., 2019; Hill et al., 2016; Johnson et al., 2013, 2015; Kitamura et al., 1993; Maurer et al., 2004; Mirahmadi et al., 2018; Ozinga et al., 2017, 2015; Papapetropoulos et al., 2010; Pasman et al., 2011; Rocchi et al., 2002; Scidas et al., 2016; Viitasalo et al., 2002), while 14 studies compared healthy older participants to individuals with PD when they were in the ‘off’ medication state (i.e., after individuals withdrew from dopaminergic medication for a minimum of 12 hours; Azulay et al., 2002; Feller et al., 2019; Hagiwara et al., 2004; Jazaeri et al., 2018; Johnson et al., 2015; Mancini, Carlson-Kuhta, et al., 2012; Maurer et al., 2003, 2004; Rocchi et al., 2002) or to individuals that had never been treated with dopaminergic medication (Ellingsen et al., 2019; Mancini, Carlson-Kuhta, et al., 2012; Mancini et al., 2011; Mancini, Salarian, et al., 2012; Na et al., 2019) (Figure 2.4). One study was unclear about whether the individuals with PD were tested when ‘off’ or ‘on’ their medication and reported that individuals were instructed to withhold their antiparkinson medication, but not if this produced disabling motor symptoms (Waterston et al., 1993). Two other studies did not
report whether the individuals with PD were tested in the ‘off’ or ‘on’ medication state (Bronstein et al., 1990; Pascolo & Marini, 2006).

Of the eight studies reporting on the effect of dopaminergic medication and/or neurosurgical procedures on static balance control in PD, six studies tested individuals with PD both when they were ‘off’ and ‘on’ their dopaminergic medication, and were therefore able to report on the effect of medication on quiet standing performance directly (D'Andrea Greve et al., 2014; Feller et al., 2019; Johnson et al., 2015; Maurer et al., 2003; Rocchi et al., 2002; Workman & Thrasher, 2019) (Figure 2.5). Four studies included individuals with PD who had undergone implantation of bilateral DBS electrodes in either the STN or GPi and tested these individuals with the DBS turned ‘off’ and ‘on’ (Johnson et al., 2015; Maurer et al., 2003; Rocchi et al., 2002; Vallabhajosula et al., 2015) (Figure 2.5). One study tested individuals before and after undergoing unilateral pallidotomy (Hagiwara et al., 2004). These studies were therefore able to report on the effect of neurosurgical treatments on quiet standing performance in individuals with PD.

2.3.3 Static balance control in individuals with Parkinson’s disease compared to healthy older adults

The methods and results from the studies that investigated static balance control in both individuals with PD and healthy older participants are summarized in Table 2.2 and 2.3 for studies that collected kinetic data, and Table 2.4 and 2.5 for studies that collected kinematic data. The results discussed below first focus on studies that compared static balance control between healthy older participants and individuals with PD that were drug-naïve or in the ‘off’ medication
state, and subsequently focus on the studies investigating individuals with PD while in the ‘on’ medications state.

Only a handful of studies compared quiet standing performance between drug-naïve individuals with PD and healthy older participants (Ellingsen et al., 2019; Mancini, Carlson-Kuhta, et al., 2012; Mancini et al., 2011; Mancini, Salarian, et al., 2012; Na et al., 2019), and it should be noted that for three out of five studies it seems results are reported on data collected in the same cohort of participants (Mancini, Carlson-Kuhta, et al., 2012; Mancini et al., 2011; Mancini, Salarian, et al., 2012). Perhaps unsurprisingly, the findings related to COP displacements in drug-naïve individuals with PD are mostly inconclusive (Table 2.2). While some evidence for larger amplitude of COP displacements was found in one cohort of drug-naïve individuals with PD when compared to healthy older participants (Mancini et al., 2011; Mancini, Salarian, et al., 2012), other studies reported no difference in amplitude of COP displacement (Ellingsen et al., 2019, Na et al., 2019). Descriptive measures representing frequency of COP displacements were only determined in one cohort of participants and found to be lower in drug-naïve individuals with PD compared to healthy older adults (Mancini et al., 2011; Mancini, Salarian, et al., 2012). Velocity of COP displacements did not differ between drug-naïve individuals with PD and healthy older participants (Ellingsen et al., 2019; Mancini et al., 2011; Mancini, Salarian, et al., 2012). Trunk acceleration during quiet, bipedal standing was only recorded in one cohort of participants (Mancini, Carlson-Kuhta, et al., 2012; Mancini et al., 2011; Mancini, Salarian, et al., 2012) (Table 2.4). Larger variability and jerkiness, and lower frequency, of trunk acceleration were found, while velocity of trunk movements was generally not different, in drug-naïve individuals with PD compared to healthy older adults (Mancini, Carlson-Kuhta, et al., 2012; Mancini et al., 2011; Mancini, Salarian, et al., 2012).
As shown in Table 2.2 and 2.4, when comparing quiet standing performance between individuals with PD_{OFF} and healthy older adults some consistent findings emerge. In general, individuals with PD show higher velocity and higher frequency COP displacements, while mean position of COP is not different (Hagiwara et al., 2004; Jazaeri et al., 2018; Johnson et al., 2015; Maurer et al., 2003, 2004; Rocchi et al., 2002). Although larger amplitude of COP displacement was found by some studies (Hagiwara et al., 2004; Johnson et al., 2015; Maurer et al., 2003, 2004), other studies found no difference in amplitude of COP displacements between individuals with PD_{OFF} and healthy older participants (Feller et al., 2019; Rocchi et al., 2002). In studies recording kinematic data, larger amplitude and velocity trunk movements were seen in individuals with PD_{OFF} (Mancini, Carlson-Kuhta, et al., 2012; Maurer et al., 2003; Waterston et al., 1993). In addition, larger variability and jerkiness of trunk acceleration were observed, and these differences were more pronounced in the ML than AP direction (Mancini, Carlson-Kuhta, et al., 2012).

The results regarding quiet standing performance comparisons between individuals with PD_{ON} and healthy older participants, shown in Table 2.3 and 2.5, are also fairly consistent. In general, individuals with PD_{ON} displayed larger amplitude and velocity of COP displacements, while their COP mean position and frequency of COP displacements showed no differences, when compared to healthy older adults (Barbosa et al., 2015; Halmi et al., 2019; Johnson et al., 2013, 2015; Kitamura et al., 1993; Maurer et al., 2004; Mirahmadi et al., 2018; Papapetropoulos et al., 2010; Pasman et al., 2011; Rocchi et al., 2002). However, a few studies reported different findings, including no difference in amplitude or velocity of COP displacements in individuals with PD_{ON} compared to healthy older adults (Benninger et al., 2010; Johnson et al., 2015; Maurer et al., 2004; Pasman et al., 2011; Sciadas et al., 2016). Studies that investigated trunk
movements, found larger amplitude and velocity trunk movements in individuals with PD\textsubscript{ON} (Cruz et al., 2018; Ozinga et al., 2015; Viitasalo et al., 2002), especially in the ML direction (Viitasalo et al., 2002). Additionally, increased variability of trunk acceleration was also observed, while both frequency and jerkiness of trunk acceleration were not found to be different, in the individuals with PD\textsubscript{ON} (Hill et al., 2016; Ozinga et al., 2017).

The two studies that did not report whether the individuals with PD were tested in the ‘off’ or ‘on’ medication state both showed no difference in amplitude of COP displacements between the groups (Bronstein et al., 1990; Pascolo & Marini, 2006), while one reported increased mean velocity of COP displacements in individuals with PD compared to healthy older participants (Pascolo & Marini, 2006).

2.3.4 Visual dependency in individuals with Parkinson’s disease

Seventeen out of the 31 studies that investigated the kinetic and/or kinematic characteristics of quiet stance in individuals with PD and healthy older adults had participants perform the quiet standing trials both with eyes open and eyes closed (Azulay et al., 2002; Barbosa et al., 2015; Bronstein et al., 1990; Ellingsen et al., 2019; Hagiwara et al., 2004; Halmi et al., 2019; Johnson et al., 2013, 2015; Kitamura et al., 1993; Mancini et al., 2011; Maurer et al., 2003, 2004; Mirahmadi et al., 2018; Ozinga et al., 2017, 2015; Viitasalo et al., 2002; Waterston et al., 1993). However, only six studies specifically investigated or discussed whether individuals with PD were more dependent on vision during quiet stance than healthy older adults (Azulay et al., 2002; Barbosa et al., 2015; Bronstein et al., 1990; Mancini et al., 2011; Mirahmadi et al., 2018; Waterston et al., 1993). None of the studies found evidence for increased visual dependence in individuals with PD, irrespective of whether they were drug-naïve (Mancini et al.,
2011), ‘off’ medication (Azulay et al., 2002; Waterston et al., 1993), or ‘on’ medication (Barbosa et al., 2015; Mirahmadi et al., 2018). For instance, Azulay et al. (2002) did not find a difference in the Romberg quotient (i.e., total COP displacement with eyes closed divided by the total COP displacement with eyes open) between individuals with PD_{OFF} and healthy older adults. Bronstein et al. (1990) also found no difference in the Romberg quotient between individuals with PD and healthy older adults, although the medication state was not reported. Two other studies found no group by vision interactions for the descriptive measures they calculated in individuals with PD_{ON} (Barbosa et al., 2015; Mirahmadi et al., 2018).

### 2.3.5 Correlations between kinetic and/or kinematic characteristics of quiet stance and clinical characteristics in individuals with Parkinson’s disease

Of the 31 studies reporting on the effect of PD on static balance control, nine studies correlated one or more kinetic or kinematic descriptive measure(s) to clinical characteristics of the individuals with PD tested, including disease duration, H\&Y stage, total UPDRS-ME score, and different UPDRS-ME subscores (Ebersbach & Gunkel, 2011; Hagiwara et al., 2004; Johnson et al., 2013; Mancini et al., 2011; Maurer et al., 2003; Ozinga et al., 2017, 2015; Rocchi et al., 2002; Viitasalo et al., 2002). Of these studies, five had a sample size of individuals with PD of more than 20 (Ebersbach & Gunkel, 2011; Hagiwara et al., 2004, Johnson et al., 2013; Ozinga et al., 2017; Viitasalo et al., 2002), while the remaining studies ran the correlations on data from less than 20 individuals with PD (Mancini et al., 2011; Ozinga et al., 2015) or less than 10 individuals with PD (Maurer et al., 2003; Rocchi et al., 2002).

In the only study that correlated sway measures with clinical characteristics in drug-naïve individuals with PD, no significant correlations were found between any of the COP or trunk
acceleration descriptive measures (e.g., RMS, mean velocity, 95% power frequency, jerk) and total UPDRS-ME score or UPDRS-ME subscores (Mancini et al., 2011).

Only one study looked at correlations between sway measures and clinical characteristics in individuals with PD_{OFF} (Hagiwara et al., 2004). Significant negative correlations between rigidity and COP sway area and ML COP mean position, but not total sway path length or AP COP mean position, were observed. A negative correlation was also seen between AP COP mean position and total UPDRS-ME score, with mildly affected individuals with PD (UPDRS-ME ≤ 40) tending to lean forward and severely affected individuals with PD (UPDRS-ME > 40) tending to lean backward. A significant positive correlation was reported between tremor and total sway path length, but not COP sway area, AP COP mean position, or ML COP mean position. No significant correlations were found between COP sway area, total sway path length, or ML COP mean position, and total UPDRS-ME score, akinesia, or gait and instability (Hagiwara et al., 2004).

Five studies correlated sway measures with clinical characteristics in individuals with PD_{ON}. The two studies correlating COP measures with clinical characteristics in individuals with PD, both with sample sizes larger than 20, saw conflicting results for the correlations involving the pull-test (Ebersbach & Gunkel, 2011; Johnson et al., 2013). Ebersbach and Gunkel (2011) found a low positive correlation between COP sway path length and the pull-test. However, it was unclear if this correlation was statistically significant. In contrast, Johnson et al. (2013) did not find a significant correlation between the pull test or disease duration and COP sway area but did see a significant positive correlation between COP sway area and total UPDRS-ME and UPDRS-ME axial scores. Similarly, the three studies that correlated kinematic measures with clinical characteristics in individuals with PD_{ON} observed conflicting results for correlations
involving the pull-test as well (Ozinga et al., 2017, 2015; Viitasalo et al., 2002). Viitasalo et al. (2002) determined that in their sample of 28 individuals with PD, trunk movement velocity, length, and area positively correlated with H&Y stage and several subscores of the UPDRS-ME, including leg agility, arising from a chair, posture, postural instability, body bradykinesia, and gait (sway area only). No correlation was found between trunk movement velocity, length, and area and the tremor, rigidity, finger taps, hand movements, and rapid alternating movements of the hand scores of the UPDRS-ME. Similarly, Ozinga et al. (2017), using a sample size of 27 individuals with PD, found trunk movement to be positively correlated with the postural instability and gait subscore of the UPDRS-ME, but not the total UPDRS-ME score. In contrast, Ozinga et al. (2015), using a sample size of 17 individuals with PD to run the correlations, did not find a correlation between trunk movement and total UPDRS-ME score or the postural instability and gait subscore.

The correlation results from Rocchi et al. (2002) should be interpreted with a degree of caution given the small sample size of six individuals with PD. The COP-based 95% power frequency, which represents the frequency below which 95% of the power of the signal lies, was the only measure to show a significant positive correlation with the total UPDRS-ME score, overall severity of posture and gait impairments, gait, bradykinesia, and tremor. Overall, poor performance on axial motor tasks seemed to be associated with increased frequency of COP displacements. In contrast, the postural component and pull test were not correlated with 95% power frequency, or any of the other COP descriptive measures. While the correlations between COP measures and UPDRS-ME total score and subscores were done across all four treatment conditions (‘off’, ‘on’, DBS, and ‘on’ with DBS), it was unclear which of the treatments conditions the reported correlation results applied to (Rocchi et al., 2002).
The correlation results from Maurer et al. (2003) were also based on a small sample size of eight individuals with PD. Velocity and frequency of COP displacements correlated significantly with improvement of the total UPDRS-ME score under treatment as well as several UPDRS-ME subscores, including tremor, rigidity, finger tapping, hand movements, rapid alternating movements, leg agility, arising from a chair, and body bradykinesia. However, velocity and frequency of COP displacements did not correlate significantly with improvement of the posture, gait, and postural instability subscores under treatment (Maurer et al., 2003).

2.4 The effect of antiparkinson treatment interventions on static balance control in individuals with Parkinson’s disease

The methods and results from the studies that investigated kinetic behaviour during quiet, bipedal stance in individuals with PD in different treatment conditions are summarized in Table 2.6. The results discussed below first focus on studies that compared static balance control between individuals with PD in the ‘off’ and ‘on’ medication state, and subsequently focus on the studies investigating the effect of neurosurgical treatment interventions in individuals with PD.

Dopaminergic medication provides little improvement to quiet standing performance. Individuals with PD ‘on’ medication compared to ‘off’ medication had larger amplitude COP displacements, while a decrease or no difference in the velocity and frequency of COP displacements was seen (D’Andrea Greve et al., 2014; Feller et al., 2019; Johnson et al., 2015; Maurer et al., 2003; Workman & Thrasher, 2019). There was also no difference in mean position of COP between individuals with PD ‘off’ and ‘on’ medication (D’Andrea Greve et al., 2014).
Unilateral pallidotomy did not appear to affect quiet standing performance (Hagiwara et al., 2004). However, as shown in Table 2.6, the effect of DBS on quiet standing performance is inconsistent (Johnson et al., 2015; Maurer et al., 2003; Rocchi et al., 2002; Vallabhajosula et al., 2015). For example, two studies reported no difference in amplitude and velocity of COP displacements in individuals with PD OFF when DBS was turned ‘on’ compared to turned ‘off’ (Johnson et al., 2015; Vallabhajosula et al., 2015), although a non-significant reduction in sway area was seen in one of those studies (Johnson et al., 2015). Another study reported that both the amplitude and frequency of COP displacements were decreased, while no difference was found in the velocity, in individuals with PD OFF when DBS was turned ‘on’ compared to turned ‘off’ (Rocchi et al., 2002). In contrast, a different study found larger amplitude COP displacements in conditions where DBS was turned ‘on’ compared to turned ‘off’, while both velocity and frequency of COP displacements were decreased by DBS (Maurer et al., 2003). In terms of the amplitude of COP displacements, one study found that the effect of DBS and dopaminergic medication combined reflected the sum of the individual treatments, and the amplitude was increased more in the ML than AP direction (Maurer et al., 2003). This was in contrast to the study by Johnson et al. (2015) who observed that an increase in sway area due to the dopaminergic medication did no longer occur in the treatment condition where dopaminergic medication and DBS were combined.

2.5 Discussion

The purpose of this narrative review was to summarize the current evidence for the effect of PD, as well as the current evidence for the effect of antiparkinson treatment interventions (pharmacological and/or neurosurgical) in individuals with PD, on the kinetic and kinematic
characteristics of quiet, bipedal standing. By carefully considering both the methodological differences among studies and the clinical characteristics of the individuals with PD included, the following findings and novel insights emerged from this review (a) individuals with PD\textsubscript{OFF} display increased amplitude, velocity, and frequency of COP displacements and trunk sway compared to healthy older adults; (b) individuals with PD\textsubscript{ON} display larger amplitude and velocity, but no difference in frequency, of COP displacements and trunk sway compared to healthy older adults; (c) findings in drug-naïve individuals with PD were inconsistent; (d) individuals with PD\textsubscript{ON} display larger amplitude, but no difference in velocity or frequency, of COP displacements compared to individuals with PD\textsubscript{OFF}, confirming that levodopa provides little improvement to quiet standing performance; (e) findings regarding the effect of DBS on static balance control were inconsistent; (f) visual dependency during static balance does not differ between individuals with PD and healthy older adults.

2.5.1 Visual dependence during static balance and clinical characteristics of individuals with Parkinson’s disease

Although 17 out of 31 studies had individuals with PD and healthy older participants perform quiet stance both with eyes open and eyes closed, only six specifically reported whether visual dependency differed between the groups (Azulay et al., 2002; Barbosa et al., 2015; Bronstein et al., 1990; Mancini et al., 2011; Mirahmadi et al., 2018; Waterston et al., 1993). As none of these studies found evidence for increased visual dependence in individuals with PD, regardless of medication state, results from studies with eyes open and/or eyes closed trials will be compared directly for the remainder of the discussion section of this narrative review.
The clinical characteristics (e.g., disease duration, mean H&Y stage, mean UPDRS-ME score) of individuals with PD varied widely across studies, as expected. When possible, these clinical characteristics were considered when comparing and interpreting findings. However, this was made difficult as some studies reported none or only some of these clinical characteristics. Similarly, signal processing and/or experimental protocol details were not always reported but taken into account when available.

2.5.2 Static balance control in drug-naïve individuals with Parkinson’s disease compared to healthy older adults

Findings were inconsistent in drug-naïve individuals with PD, although there was some evidence for larger amplitude and variability, as well as lower frequency, of COP displacements and trunk acceleration in these individuals when compared to healthy older participants. However, the number of studies specifically investigating static balance control in drug-naïve, early stage individuals with PD was limited, and three of the five studies appeared to report results coming from the same cohort of participants (Mancini, Carlson-Kuhta, et al., 2012; Mancini et al., 2011; Mancini, Salarian, et al., 2012). In addition, the findings on kinematic characteristics of quiet stance in drug-naïve individuals with PD came solely from this one participant cohort (Mancini, Carlson-Kuhta, et al., 2012; Mancini et al., 2011; Mancini, Salarian, et al., 2012).

While the findings on the kinetic characteristics of quiet stance from one cohort of participants suggested that static balance control is impaired in untreated individuals with PD (Mancini, Carlson-Kuhta, et al., 2012; Mancini et al., 2011; Mancini, Salarian, et al., 2012), the results from other studies did not support this (Ellingsen et al., 2019; Na et al., 2019). This
discrepancy could be due to several factors. First, the three studies reporting on the same participant cohort investigated static balance in individuals with PD only, while the two other studies were mainly interested in investigating individuals diagnosed with manganism (Ellingsen et al., 2019) and individuals with multiple system atrophy with predominant parkinsonism (Na et al., 2019), but also tested individuals with PD and healthy older adults. Additionally, the static posturography protocols for the two studies investigating other clinical populations differed from the protocol used in the three studies that only included individuals with PD with regard to force measurement equipment used, number of trial repetitions, as well as the descriptive measures calculated (Ellingsen et al., 2019; Mancini, Carlson-Kuhta, et al., 2012; Mancini et al., 2011; Mancini, Salarian, et al., 2012; Na et al., 2019). Whether differences in signal processing could account for the discrepancy is unclear as these details were only reported for the studies investigating the same participant cohort (Mancini, Carlson-Kuhta, et al., 2012; Mancini et al., 2011; Mancini, Salarian, et al., 2012). Finally, while the mean disease duration, H&Y stage, and UPDRS-ME scores reported by Na et al. (2019) were comparable to those reported for the individuals with PD included in the three studies by Mancini et al., the mean H&Y stage reported by Ellingsen et al. (2019) was 2.8 compared to a mean H&Y stage of 1.9 reported by the other studies. It would be expected that differences between groups are more easily found in individuals with more advanced PD, however, Ellingsen et al. (2019) did not find differences. Individuals with PD included in the study by Mancini, Carlson-Kuhta, et al. (2012) were followed for 12 months. During this follow-up period eight out of 13 untreated PD participants started low-dose antiparkinson medication. Interestingly, sway measures progressively worsened over time only in the PD subgroup that continued to be untreated during the 12-month follow-up (Mancini, Carlson-Kuhta, et al., 2012). One possible explanation given for this finding was that
an increase in daily activity and exercise due to the antiparkinson medication may have resulted in improved central control of balance (Mancini, Carlson-Kuhta, et al., 2012).

2.5.3 Static balance control in individuals with Parkinson’s disease ‘off’ medication compared to healthy older adults

Results were more consistent in individuals with PD_{OFF}, with increased amplitude, velocity, and frequency of COP and trunk sway observed in these individuals compared to healthy older adults.

The findings of larger velocity COP displacements were observed in four out of five studies that calculated mean velocity (Jazaeri et al., 2018; Maurer et al., 2003, 2004; Rocchi et al., 2002), although two studies reported on results from the same participant cohort (Maurer et al., 2003, 2004). Mean disease duration and mean H&Y stage of individuals with PD_{OFF} reported by these studies were comparable to those reported by Johnson et al. (2015), who found no difference in velocity of COP displacements. Jazaeri et al. (2018) divided their cohort of individuals with PD into a low anxiety and high anxiety subgroup, with high anxiety being defined by a score of more than 11 on the anxiety subscale of the hospital anxiety and depression scale (maximum score 21). Interestingly, higher mean velocity in individuals with PD_{OFF} compared to healthy older adults was found only for the subgroup with high anxiety (Jazaeri et al., 2018).

Three studies reported descriptive measures characterizing frequency of COP displacements, and all found higher COP frequency in individuals with PD_{OFF} compared to healthy older participants (Maurer et al., 2003, 2004; Rocchi et al., 2002). Postural tremor could potentially account for some of the observed increases in frequency of COP displacements. One
study noted that power spectral density plots showed increased power around 4-5 Hz in individuals with PD_{OFF} and the 95% power frequency measure was significantly correlated with resting tremor (Rocchi et al., 2002). Postural tremors in individuals with PD have a typical frequency between 4-7 Hz (Kerr et al., 2008). The COP data from Rocchi et al. (2002) were low-pass filtered using a 10 Hz cut-off frequency, therefore not removing the tremor from the data (Rocchi et al., 2002).

Four out of six studies reporting descriptive measures related to amplitude found evidence for larger amplitude COP displacements in individuals with PD_{OFF} compared to healthy older adults (Hagiwara et al., 2004; Johnson et al., 2015; Maurer et al., 2003, 2004). Mean disease duration among the six studies ranged from 9.9 (Hagiwara et al., 2004) to 14.8 years (Rocchi et al., 2002), and mean UPDRS-ME from 36.5 (Hagiwara et al., 2004) to 56.8 (Rocchi et al., 2002). Interestingly, the study reporting the longest mean disease duration and highest mean UPDRS-ME score did not find a difference in amplitude of COP displacements compared to healthy older participants (Rocchi et al., 2002), while the study reporting the lowest mean disease duration and mean UPDRS-ME score did (Hagiwara et al., 2004). Feller et al. (2019) also found no difference in amplitude of COP displacements between individuals with PD_{OFF} and healthy older adults. While the clinical characteristics they reported did not seem to differ much from those reported by the other studies, this may have been influenced by the heterogeneity of their sample of individuals with PD, as indicated by the SD value of 9.7 for a mean disease duration of 11.4 years. Disease duration among the eight individuals with PD appeared to range from 1 to 34 years, and the ‘off’ medication UPDRS-ME score of the individual with PD with disease duration of one year was not available (Feller et al., 2019).
The three studies investigating kinematic characteristics of quiet stance in individuals with PD\textsuperscript{OFF} suggested larger amplitude and velocity of trunk movements (Mancini, Carlson-Kuhta, et al., 2012; Maurer et al. 2003; Waterston et al., 1993), as well as increased variability and jerk of trunk acceleration (Mancini, Carlson-Kuhta, et al., 2012). However, for two studies not all individuals with PD may have been ‘off’ medication, as in one study PD participants were instructed to withhold their antiparkinson medication, but not if this produced disabling motor symptoms (Waterston et al., 1993), while for the other study five out of 13 PD participants were untreated instead of ‘off’ medication (Mancini, Carlson-Kuhta, et al., 2012). Despite the relatively consistent findings, the baseline and clinical characteristics of the participants described in these studies varied noticeably. First, the mean age of the individuals with PD as well as the healthy participants included in the study by Maurer et al. (2003) was almost 10 years younger than the mean age of participants in the other two studies. It was explained that their group of individuals with PD included had a mean age of onset of 34.8 years (Maurer et al., 2003). Additionally, while the individuals with PD included in the study by Mancini, Carlson-Kuhta, et al. (2012) were all in the early stage of the disease with a mean disease duration of about two years, mean H\&Y stage of 1.7, and mean UPDRS-ME of 29.4, those included in the two other studies were more severely affected with a mean H\&Y stage of 2.6 reported by Waterston et al. (1993) and a mean disease duration of 13.2 years, H\&Y stage range of 3 to 5, and mean UPDRS-ME of 49.4 reported by Maurer et al. (2003).
2.5.4 Static balance control in individuals with Parkinson’s disease ‘on’ medication compared to healthy older adults

The observations in individuals with PDON (i.e., approximately one to two hours after levodopa administration) were fairly consistent as well, with, in general, larger amplitude and velocity, but no difference in frequency, of COP and trunk movements compared to healthy older participants.

Although larger amplitude COP displacements were found in individuals with PDON compared to healthy older participants (Barbosa et al., 2015; Johnson et al., 2013, 2015; Maurer et al., 2004; Mirahmadi et al., 2018; Papapetropoulos et al., 2010; Rocchi et al., 2002), some studies found no difference in amplitude (Benninger et al., 2010; Pasman et al., 2011; Sciadas et al., 2016). One possible explanation for this discrepancy is a difference in clinical characteristics of included individuals with PD. Although a few studies that found higher amplitude did not report mean disease duration (Barbosa et al., 2015; Mirahmadi et al., 2018; Papapetropoulos et al., 2010), for the ones that did (Johnson et al., 2013, 2015; Maurer et al., 2004; Rocchi et al., 2002), mean disease was generally higher than in studies that did not find a difference in amplitude of COP displacements (Benninger et al., 2010; Pasman et al., 2011; Sciadas et al., 2016). This did not translate to mean UPDRS-ME scores, which varied more amongst studies finding the same result. Another possible explanation is a difference in testing protocol between studies. For instance, the study from Pasman et al. (2011) was aimed at investigating whether individuals with PD and healthy older adults would respond similarly to increases in postural threat. Therefore, participants were tested in three different experimental conditions with varying levels of postural threat. The group differences would have been determined by collapsing the data from all three experimental conditions (Pasman et al., 2011). One study subdivided the
individuals with PD in non-fallers and fallers, defined as having a history of one or more falls during the previous two years (Johnson et al., 2013). Larger amplitude COP displacements were only found in the fall subgroup compared to healthy older adults, and no differences were found between the non-faller and faller subgroups (Johnson et al., 2013).

Similar to amplitude of COP displacements, larger velocity COP displacements were found in individuals with PD compared to healthy older participants by the majority of studies (Barbosa et al., 2015; Halmi et al., 2019; Mirahmadi et al., 2018; Papapetropoulos et al., 2010; Rocchi et al., 2002), although others found no difference (Johnson et al., 2015; Maurer et al., 2004; Sciadas et al., 2016). One noticeable difference between the studies reporting these conflicting results was that a low-pass filter cut-off of 5.5 Hz or lower was used in three out of four studies that did not find a difference in velocity of COP displacements between groups (Johnson et al., 2015; Maurer et al., 2004; Sciadas et al., 2016) while the cut-off frequency was 10 Hz in two studies that found larger velocity (Mirahmadi et al., 2018; Rocchi et al., 2002). The other studies finding either no difference or larger velocity did not report whether any filtering was applied (Barbosa et al., 2015; Halmi et al., 2019; Johnson et al., 2015; Papapetropoulos et al., 2010). Clinical characteristics between individuals with PD differed among all studies that determined velocity of COP displacements, but a noticeable pattern related to COP velocity could not be detected.

All three studies reporting on frequency of COP displacements showed no difference between individuals with PD compared to healthy older adults, despite showing differences in clinical characteristics of included individuals with PD (Maurer et al., 2004; Pasman et al., 2011; Rocchi et al., 2002). It should be noted that two of these three studies in individuals with PD used low-pass filters with a cut-off frequency below 5.5 Hz (Maurer et al., 2004; Pasman et al.,
2011), while the third study used a 10 Hz cut-off (Rocchi et al., 2002). As postural tremors in individuals with PD have a typical frequency between 4-7 Hz (Kerr et al., 2008), in the studies using a cut-off frequency of 5 to 5.5 Hz, part of the frequency content associated with the postural tremor may have been removed.

A total of five studies reported on kinematic characteristics of static balance control in individuals with PD\textsubscript{ON} compared to healthy older adults. All found increased amplitude and variability of trunk sway and acceleration (Cruz et al., 2018; Hill et al., 2016; Ozinga et al., 2017, 2015; Viitasalo et al., 2002), with one study also observing larger velocity of trunk sway (Viitasalo et al., 2002). The clinical characteristics of the individuals included in each study were generally similar. In addition, differences in methodology were mainly due to a difference in equipment used, which included optic motion capture systems (Cruz et al., 2018; Ozinga et al., 2015), an inclinometer sensor attached with a rod to the participants hips (Viitasalo et al., 2002), and accelerometers attached to the lower back (Hill et al., 2016; Ozinga et al., 2017, 2015). The fact that there were no real conflicting results is most likely due to both the limited number of studies that looked at the kinematic characteristics of quiet stance in individuals with PD\textsubscript{ON}, as well as the limited number of descriptive measures determined by these studies.

2.5.5 Static balance control in different treatment conditions in individuals with Parkinson’s disease

Dopaminergic medication was found to provide little improvement in quiet standing performance. In individuals with PD ‘on’ compared to ‘off’ medication, larger amplitude COP displacements, together with a decrease or no difference in the velocity and frequency of COP displacements, were seen. The increase in amplitude of COP displacements after intake of
dopaminergic medication was observed in all six studies that were designed to investigate medication effects (D’Andrea Greve et al., 2014; Feller et al., 2019; Johnson et al., 2015; Maurer et al., 2003; Workman & Thrasher, 2019), although in one study the results were only a statistical trend (Rocchi et al., 2002). Similarly, the lack of change in velocity of COP displacements after medication intake was found by four out of six studies (D’Andrea Greve et al., 2014; Johnson et al., 2015; Rocchi et al., 2002; Workman & Thrasher, 2019), although one study found lower velocity in ‘on’ compared to ‘off’ states (Mauer et al., 2003). Frequency of COP displacements was only investigated by one study and while there was no statistical significance difference, there was a trend for lower frequency in ‘on’ compared to ‘off’ states (Rocchi et al., 2002). Although larger amplitude and no difference in velocity of COP displacements were found by most of the six studies, the results should be interpreted with some caution as four out of six studies had a sample size of less than 10 individuals with PD (Feller et al., 2019; Johnson et al., 2015; Maurer et al., 2003; Rocchi et al., 2002).

Of the neurosurgical treatments, unilateral pallidotomy seems to have no effect on static balance performance in individuals with PD (Hagiwara et al., 2004), but this was only investigated in one study and the results are therefore anecdotal. The effect of DBS was inconsistent, with different studies reporting no effect (Johnson et al., 2015; Vallabhajosula et al., 2015), as well as increased (Maurer et al., 2003) and decreased (Rocchi et al., 2002) amplitude COP displacements when DBS is turned ‘on’ compared to turned ‘off’ in the absence of dopaminergic medication. The lack of agreement across studies may be due to variability in patient characteristics. For instance, while mean disease duration was about 13 to 14 years in all four studies, the mean UPDRS-ME scores for the DBS and ‘on’ with DBS condition varied noticeably across studies, with the lowest scores in the DBS and ‘on’ with DBS conditions...
reported by Maurer et al. (2003), which were 7.4 and 4.1 respectively, and the highest scores by Rocchi et al., 2002, which were 37.5 and 19.5 respectively. Therefore, the largest differences in mean UPDRS-ME scores in the DBS and ‘on’ with DBS conditions were seen between the two studies that reported opposite (i.e., increase vs decrease of amplitude in DBS ‘on’ versus ‘off’) results (Maurer et al., 2003; Rocchi et al., 2002). In addition, the lack of agreement could also be due to (a) location of the bilateral DBS electrodes (i.e., STN vs GPi); (b) surgical procedure; (c) electrode localization within the STN; (d) time elapsed between implantation surgery and testing. For instance, two studies included only individuals with PD receiving bilateral STN DBS (Maurer et al., 2003; Vallabhajosula et al., 2015), one study included only individuals with PD receiving bilateral GPi DBS (Johnson et al., 2015), while the last study included individuals with PD receiving STN as well as individuals receiving GPi DBS (Rocchi et al., 2002). Of the studies showing opposite effects of DBS on amplitude of COP displacement, one included individuals with PD receiving bilateral GPi DBS (Rocchi et al., 2002), but the other did not (Maurer et al., 2003). However, of the two studies that did not find significant differences in amplitude or velocity of COP displacements in individuals with PD on when DBS was turned ‘on’ compared to turned ‘off’, only one included individuals with bilateral STN DBS (Vallabhajosula et al., 2015), while the other only included individuals with bilateral GPi DBS (Johnson et al., 2015). Interestingly enough the latter study found a non-significant reduction in sway area during bilateral GPi DBS (Johnson et al., 2015), similar to the other study that included individuals with GPi DBS and found decreased amplitude (Rocchi et al., 2002).
2.6 Conclusion

Overall, by carefully considering both the methodological differences among studies and
the clinical characteristics of the individuals with PD included, some consistent findings and
novel insights have emerged from this narrative review that focused on studies investigating
static balance control in individuals with PD using trial lengths of more than 60 s. First,
individuals with PD_{OFF} show increased amplitude, velocity, frequency of COP and trunk sway
when compared to healthy older adults. Second, individuals with PD_{ON} exhibit larger amplitude
and velocity, but no difference in frequency, of COP and trunk movements when compared to
healthy older adults. Third, dopaminergic medication, as well as, STN and GPi DBS appear to be
unable to alleviate, and may even aggravate some aspects of, static balance deficits in individuals
with PD.

While consistent findings have emerged from this narrative review, there are still some
important gaps in the literature on static balance control in individuals with PD, as well as
recommendations to be made: (a) posturography protocols, including trial duration and signal
processing details, need to be standardized for easier comparison and interpretation of future
studies; (b) clinical characteristics of individuals with PD included need to be reported
consistently and fully; (c) results from the studies included in the current review need to be
confirmed in larger sample sizes, including medication and DBS treatment effects; (d) future
studies should record both kinetic and kinematic data in the same individuals with PD during the
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Table 2.1 Search queries used for the MEDLINE, EMBASE, and CINAHL databases

mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word; Bolded row represent the final search for each database
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Table 2.2 Overview of studies comparing kinetic behaviour between individuals with Parkinson’s disease who are drug-naïve or in the ‘off’ medication state and healthy older participants during quiet standing

DN = individuals with PD were drug naïve, OFF = individuals with PD were in the ‘off’ medication state; R1 = (Mancini et al., 2011), R2 = (Mancini, Salarian et al., 2012), R3 = (Ellingsen et al., 2019), R4 = (Na et al., 2019), R5 = (Azulay et al., 2002), R6 = (Rocchi et al., 2002), R7 = (Maurer et al., 2003), R8 = (Maurer et al., 2004), R9 = (Hagiwara et al., 2004), R10 = (Johnson et al., 2015), R11 = (Jazaeri et al., 2018), R12 = (Feller et al., 2019); Sample PD: sample size individuals with PD, P1 = PD patients with low-anxiety, P2 = PD patients with high-anxiety; Sample CS = sample size control subjects; Age PD and CS: mean ± SD or range, in years; Disease duration: mean ± SD, in years; H&Y stage: mean ± SD or range; UPDRS-ME score: mean ± SD; Trials = number of trials/length of trials, in seconds; Fs = sampling frequency, in Hz; Filter = low pass filter cut-off frequency, in Hz; Stance: FAC10 = feet abducted comfortable amount and heels 10 cm apart, FT = feet together, F4 = feet 4 cm apart, FS = feet shoulder width apart, F7 = feet 7 cm apart, FAC5 = feet abducted comfortable amount and heels 5 cm apart; Vision: EO = eyes open, EC = eyes closed; Results: ↑ = statistically significant increase in PD compared to CS, ↓ = statistically significant decrease in PD compared to CS, 1 = AP direction only, 2 = ML direction only, 3 = AP and ML direction, O = eyes open, C = eyes closed, O/C = eyes open and eyes closed; Amplitude: RMS = root mean square, MD = mean distance, SA = sway area, RNG = range, TM = total movement, SD = standard deviation; Velocity: MV = mean velocity, SD-MV = standard deviation of mean velocity; Frequency: F95 = 95% power frequency, MF = median frequency, CF = centroidal frequency, FD = frequency dispersion, TP = total power, PR = PSD ratio (ratio of the power in the 0.7±1.1 Hz frequency range to the overall power in the 0.0125±1.1 Hz range); Position: MOV = movement of COP; Other: AF = mean (average) frequency, SPL = sway path length, SI = sway intensity, RQ = Romberg quotient, ASI = absolute symmetry index; Note: only comparisons for which the results of inferential statistical analysis were reported are included and bolded dependent measures represent statistically significant differences between individuals with PD and healthy older adults, darkened columns regard studies investigating drug-naïve individuals with PD.
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Table 2.3 Overview of studies comparing kinetic behaviour between individuals with Parkinson’s disease in the ‘on’ medication state and healthy older participants during quiet standing

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Table 2.4 Overview of studies comparing kinematic behaviour between individuals with Parkinson’s disease who are drug-naïve or in the ‘off’ medication state and healthy older participants during quiet standing

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RESULTS

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Table 2.4 Overview of studies comparing kinematic behaviour between individuals with Parkinson’s disease who are drug-naïve or in the ‘off’ medication state and healthy older participants during quiet standing

DN = individuals with PD were drug naïve, OFF = individuals with PD were in the ‘off’ medication state; R1 = (Mancini et al., 2011); R2 = (Mancini, Salarian, et al., 2012); R3 = (Mancini, Carlson-Kuhta, et al., 2012); R4 = (Waterston et al., 1993); R5 = (Maurer et al., 2003); 3-6M = testing session 3-6 months after baseline session, results from testing at baseline session reported under R1; Sample PD: sample size individuals with PD; Sample CS = sample size control subjects; Age PD and CS: mean ± SD or range, in years; Disease duration: mean ± SD, in years; H&Y stage: mean ± SD or range; UPDRS-ME score: mean ± SD; Trials = number of trials/length of trials, in seconds; Fs = sampling frequency: in Hz; Filter = low pass filter cut-off frequency, in Hz; Stance: FAC10 = feet abducted comfortable amount and heels 10 cm apart, PS = preferred (comfortable) stance, F7 = feet 7 cm apart; Vision: EO = eyes open, EC = eyes closed; Data = equipment used to record kinematic data: Acc-L5 = sensor with accelerometers attached to low back at L5, LT-waist = linear transducer attached with rod at waist level recording sway angle, KM-SH = kinematic markers (on a rigid triangle) attached to shoulder and hip used to calculate upper body (UB) and lower body (LB) excursions; Results: ↑ = statistically significant increase in PD compared to CS, ↓ = statistically significant decrease in PD compared to CS, ^1 = AP direction only, ^2 = ML direction only, ^3 = AP and ML direction, ^o = eyes open, ^c = eyes closed, ^o/c = eyes open
and eyes closed; Displacement and acceleration: RMS = root mean square, MD = mean distance, RNG = range, SA = sway area, SD = standard deviation; Velocity: MV = mean velocity; Frequency: FD = frequency dispersion, F95 = 95% power frequency, TP = total power, MF = median frequency, CF = centroidal frequency; Other = JERK = jerkiness of sway, AF = mean (average) frequency, SPL = sway path length, ISC = inter-segmental UB-LB coupling; Note: only comparisons for which the results of inferential statistical analysis were reported are included and bolded dependent measures represent statistically significant differences between individuals with PD and healthy older adults, darkened columns regard studies investigating drug-naive individuals with PD.
Table 2.5 Overview of studies comparing kinematic behaviour between individuals with Parkinson’s disease in the ‘on’ medication state and healthy older participants during quiet standing

ON = individuals with PD were in the ‘on’ medication state; R1 = (Viitasalo et al., 2002); R2 = (Ozinga et al., 2015); R3 = (Hill et al., 2016); R4 = (Ozinga et al., 2017); R5 = (Cruz et al., 2018); Sample PD: sample size individuals with PD; Sample CS = sample size control subjects; Age PD and CS: median or mean ± SD or range, in years; Disease duration: mean ± SD or range, in years; H&Y stage: mean ± SD or range; UPDRS-ME score: median or mean ± SD; Trials = number of trials/length of trials, in seconds; Fs = sampling frequency: in Hz; Filter = low pass filter cut-off frequency, in Hz; Stance: FT = feet together, FH = feet hip width apart, SO = shoes on; Vision: EO = eyes open, EC = eyes closed; Data = equipment used to record kinematic data: Incl-IC = inclinometer sensor attached with a rod to iliac crest level used to calculate deviating movement, KM-24 = kinematic markers attached to 24 anatomical landmarks to calculate center of mass linear and angular acceleration, Acc-S2 = tablet with accelerometers attached as close as possible to S2 vertebra, Acc-L5 = sensor with accelerometers attached to low back at L5, Acc-W = tablet with accelerometers attached around waist, KM-T8 = kinematic marker attached to the 8th thoracic vertebra; Results: ↑ = statistically significant increase in PD compared to CS, ↓ = statistically significant decrease in PD compared to CS, 1 = AP direction only, 2 = ML direction only, 3 = AP and ML direction, O = eyes open, C = eyes closed; Displacement and acceleration: SD = standard deviation, MX = maximum deflection, 90S = 90% of sway, SA = sway area, EV = ellipsoid volume, RMS = root mean square, P2P = peak to peak; Velocity: MV = mean velocity; Frequency: F95 = 95% power frequency; Other: SPL = sway path length, JERK = jerkiness of sway. Note: only comparisons for which the results of inferential statistical analysis were reported are included and bolded dependent measures represent statistically significant differences between individuals with PD and healthy older adults.
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<td>R2</td>
<td>R3</td>
<td>R4</td>
<td>R5</td>
<td>R6</td>
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<td>6</td>
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<td>Age PD</td>
<td>58.4 ± 11.1</td>
<td>64.0 ± 7.2</td>
<td>67.1 ± 7.5</td>
<td>61.2 ± 9.9</td>
<td>48.1, 36-60</td>
<td>58.8 ± 5.6</td>
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<td>Disease duration</td>
<td>17.8 ± 5.0</td>
<td>11.4 ± 9.7</td>
<td>6.7 ± 5.8</td>
<td>14.8 ± 5.2</td>
<td>13.2 ± 2.4</td>
<td>13.4 ± 5.8</td>
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<td>DBS site</td>
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<td>-</td>
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<td>Bilateral GPi</td>
<td>Bilateral STN</td>
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<td>DBS setting</td>
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<tr>
<td>UPDRS-ME score</td>
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<td>OFF: 40.5 ± 16.9</td>
<td>ON: 19.4 ± 14.3</td>
<td>OFF: 44.4 ± 13.3</td>
<td>ON: 24.5 ± 7.6</td>
<td>DBS: 37.5 ± 17.5</td>
<td>DBS+ON: 19.5 ± 8.9</td>
<td>OFF: 56.8 ± 25.9</td>
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<td>4/80</td>
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<td>Amplitude</td>
<td>SA³⁰⁵⁰c</td>
<td>RMS²⁰⁵⁰c</td>
<td>SA³⁰⁵⁰c</td>
<td>RMS DBS&lt;OFF</td>
<td>SD³⁰⁵⁰c</td>
<td>SA³⁰⁵⁰c</td>
<td>Exp 1 and Exp 2: RNG², RMS³, SA³⁰⁵⁰c</td>
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<td></td>
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<td>ON&gt;OFF</td>
<td>ON&gt;OFF</td>
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<td>SA ON&gt;DBS</td>
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<td></td>
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<td>RMS ON&gt;DBS</td>
<td>SA ON&gt;DBS</td>
<td>SD³⁰⁵⁰c DBS&lt;OFF</td>
<td>SD³⁰⁵⁰c DBS&lt;OFF</td>
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<td></td>
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<td>ON&lt;OFF</td>
<td>MV³⁰⁵⁰c</td>
<td>ON&lt;OFF</td>
<td>MV³⁰⁵⁰c</td>
<td>ON&lt;OFF</td>
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<tr>
<td></td>
<td>MV³⁰⁵⁰c</td>
<td>DBS&lt;OFF</td>
<td>MV³⁰⁵⁰c</td>
<td>DBS&lt;OFF</td>
<td>MV³⁰⁵⁰c</td>
<td>DBS&lt;OFF</td>
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<tr>
<td>Frequency</td>
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<td>-</td>
<td>-</td>
<td>F95 DBS&lt;OFF</td>
<td>PR³ ON&lt;OFF</td>
<td>-</td>
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<tr>
<td></td>
<td>F95 DBS+ON&lt;OFF</td>
<td>F95 DBS+ON&lt;OFF</td>
<td></td>
<td>PR³ DBS+ON&lt;OFF</td>
<td>PR³ DBS+ON&lt;OFF</td>
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<tr>
<td>Position</td>
<td>MA³⁰⁵⁰c</td>
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<td>-</td>
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<td>Other</td>
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<td>-</td>
<td>-</td>
<td>SPL³⁰⁵⁰c</td>
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84
Table 2.6 Overview of studies comparing kinetic behaviour between treatment conditions within a group of individuals with Parkinson’s disease during quiet standing

OFF/ON = individuals with PD were in the ‘off’ and ‘on’ medication state, DBS = DBS was turned on individuals with PD, UP = unilateral pallidotomy; R1 = (D’Andrea Greve et al., 2014), R2 = (Feller et al., 2019), R3 = (Workman & Thrasher, 2019), R4 = (Rocchi et al., 2002), R5 = (Maurer et al., 2003), R6 = (Johnson, et al., 2015), R7 = (Vallabhajosula et al., 2015), R8 = (Hagiwara et al., 2004); Sample size PD: sample individuals with PD, Exp 1 = experiment 1, Exp 2 = experiment 2; Age PD: mean ± SD or range, in years; Disease duration: mean ± SD, in years; DBS site = location of bilateral DBS electrodes, STN = subthalamic nucleus, GPi = internal globus pallidus; DBS setting = DBS parameters used during testing: 60 = stimulation at 60 Hz, BV = baseline voltage, BF = stimulation at baseline frequency (≥ 130 Hz), 30 = stimulation at 30 Hz, MTV = maximum tolerable voltage; UPDRS-ME score: mean ± SD, B-UP = before UP, A-UP = after UP; Trials = number of trials/length of trials, in seconds; Fs = sampling frequency, in Hz; Filter = low pass filter cut-off frequency, in Hz; Stance: FP = feet pelvic width apart, FS = feet shoulder width apart, F7 = feet 7 cm apart, FAC5 = feet abducted comfortable amount and heels 5 cm apart, F10 = feet 10 cm apart, FT = feet together; Vision: EO = eyes open, EC = eyes closed; Results: > = statistically significant increase, < = statistically significant decrease, 1 = AP direction only, 2 = ML direction only, 3 = AP and ML direction, O = eyes open, C = eyes closed, O/C = eyes open and eyes closed; Amplitude: SA = sway area, RMS = root mean square, SD = standard deviation, RNG = range; Velocity: MV = mean velocity; Frequency of COP displacements: F95 = 95% power frequency, PR = PSD ratio (ratio of the power in the 0.7±1.1 Hz frequency range to the overall power in the 0.0125±1.1 Hz range); Position: MA = mean amplitude, MOV = movement of COP; Other: iTTB = integrated time to boundary, SPL = sway path length; Note: only comparisons for which the results of inferential statistical analysis were reported are included and bolded dependent measures represent statistically significant differences between treatment conditions individuals with PD.
Figure 2.1 Selection process for eligible articles

- Records identified through database searching
  - MEDLINE (OVID): 753
  - EMBASE (OVID): 1287
  - CINAHL: 309
  - Total: 2349

- Additional records identified through other sources
  - Total: 2

- Records after removal of duplicates and conference abstracts
  - Total: 1012

- Records excluded after reading title and abstract
  - Total: 803

- Full-text assessed for eligibility
  - Total: 209

- Records excluded after assessing full-text
  - No full-text in English: 20
  - No comparison PD versus healthy or between treatments: 7
  - Sensory information manipulated during standing: 4
  - Only dual-task standing trials: 4
  - Case studies: 2
  - Feature selection only: 1
  - Total: 38

- Full-text articles meeting eligibility criteria
  - Total: 171
Figure 2.2 Flow chart of the selection of relevant studies comparing static balance performance between individuals with Parkinson’s disease and healthy older adults
Figure 2.3 Flow chart of the selection of relevant studies comparing between treatment conditions in individuals with Parkinson’s disease
Figure 2.4 Medication status of individuals with Parkinson’s disease investigated in studies comparing static balance performance between individuals with Parkinson’s disease and healthy older adults
Figure 2.5 Medication/neurosurgical status of individuals with Parkinson’s disease investigated in studies comparing between treatment conditions in individuals with Parkinson’s disease
Chapter 3: A novel MRI compatible balance simulator to detect postural instability in Parkinson’s disease

3.1 Introduction

Postural instability and falls are common in PD patients, resulting in significant disability, loss of independence, and reduced quality of life (S. D. Kim et al., 2013). Pharmacological and neurosurgical treatments currently used for PD are unable to alleviate, and may in some cases even aggravate, postural instability (Boonstra et al., 2008; Crouse et al., 2016; Grimbergen et al., 2009). In addition, since the pathophysiology underlying postural instability is insufficiently understood (Crouse et al., 2016; Grimbergen et al., 2009; S. D. Kim et al., 2013), a better understanding of the neural substrates contributing to postural instability in PD could lead to new targets for improved pharmacological and neurosurgical interventions.

PD patients have unique balance deficits. Current evidence suggests PD patients exhibit larger angular and linear displacement and velocity of the trunk during static balance compared to elderly controls (Cruz et al., 2018; Viitasalo et al., 2002). While vision affects sway amplitude and frequency (Gill et al., 2001; van der Kooij et al., 2011), the effects of PD on static balance performance are independent of visual condition (Marchese et al., 2003; Mirahmadi et al., 2019; Schieppati & Nardone, 1991). Additionally, in response to dynamic perturbations delivered to the trunk, PD patients show increased trunk displacement compared to elderly controls (Di Giulio et al., 2016).

There would be tremendous benefit in being able to investigate the network of cortical and subcortical structures contributing to postural control normally and in PD. However, this necessitates the use of fMRI scanners, which are almost exclusively horizontally-based. While
some studies have had participants perform balance-related tasks while lying down, none of the tasks involved participants actively maintaining equilibrium of a free-standing balance system (Buettner et al., 2017; de Lima-Pardini et al., 2017; Karim et al., 2014). Motor imagery may offer an alternative for complex upright tasks such as walking (Bakker et al., 2008; Snijders et al., 2011), but may be limited when studying non-volitional sensorimotor tasks such as static and reactive dynamic balance. Also, although motor imagery and motor execution of the same task share neural substrates, subtle but important differences exist (O’Shea & Moran, 2017).

The aim of the current study was to develop, and validate the effectiveness of using, an MRI compatible balance simulator to investigate static and dynamic balance control in PD patients and elderly controls, in tasks commonly used to identify balance deficits (Bloem et al., 2016). For the balance simulator to be effective, it should be relatively easy for both healthy participants and PD patients to control the simulator after only a few minutes of practice. Moreover, the simulator should elicit balance behaviours comparable to those observed during upright balancing tasks and be sensitive to PD changes seen in both static and dynamic balance performance.

We hypothesized that PD patients, compared to elderly controls, would show larger amplitude and higher frequency of sway during static balancing, independent of vision, and increased peak sway during dynamic balancing, when standing upright, as well as when actively controlling the balance simulator. To test these hypotheses, we performed two independent studies: the first investigated only static balancing; and the second investigated both static and dynamic balancing. These studies serve to validate the novel balance simulator for future use in fMRI experiments.
3.2 Materials and methods

3.2.1 Participants

Eighty-five participants (38 PD patients, 47 elderly controls) participated across two independent studies. Exclusion criteria for PD patients were any of the following medical issues (self-reported during initial screening): any prior neurosurgical procedures such as deep brain stimulation; excessive levodopa-induced dyskinesia that impaired their balance; botulinum toxin injections in lower leg muscles within the last 3 months; documented proprioceptive loss (e.g., abnormal vibratory sense, altered joint position sense, etc.); dementia precluding informed consent; history of other neurological disease (e.g., stroke, seizures); and medical issues (other than PD) that influenced their balance. Exclusion criteria for controls were any medical issues (self-reported during initial screening) that influenced their balance, including ankle injuries/surgery, stroke, conditions affecting vestibular function, diabetes, and conditions resulting in a loss of sensation in the feet and/or lower legs. All participants were fluent in English, provided written informed consent prior to testing, and followed experimental procedures that were approved by the UBC Clinical Research Ethics Board. Nine participants were excluded due to: technical issues (n = 5), inability to complete the protocol (n = 3), or withdrawal of consent due to anxiety (n = 1). As a result, study 1 included 34 participants (14 PD patients; 20 controls) and study 2 included 42 participants (20 PD patients; 22 controls) (see Table 3.1 for details).

All PD patients were examined approximately one hour after intake of their regular antiparkinson medication to coincide with their subjectively best clinical ‘on’ condition. We purposely opted for this condition for two reasons: first, balance control is usually not altered much by dopaminergic medication; and second, testing PD_{ON} patients avoids any potential
confounds of fatigue, anxiety and cumbersome bradykinesia/rigidity that may accompany the ‘off’ phase. All participants completed a brief medical history survey. PDON patients were clinically assessed using the H&Y scale (Goetz et al., 2004) and UPDRS-ME (Goetz et al., 2008) (Table 3.2).

### 3.2.2 Apparatus

Simulated stance trials were performed using a customized balance simulator (“simulator”) made completely from non-ferrous MRI compatible material (wood, glue and plastic/glass bearings). In the simulator, the participant lay supine with their feet placed at a width equal to their foot length against a footplate that rotated about an axis aligned with the ankle joints that controlled a free-standing inverted pendulum (Figure 3.1A, 3.1B, and 3.1C). The COM of the balance-arm of the simulator was located approximately 1m above the axis of rotation. For each participant individually, the ankle load stiffness seen during normal upright quiet stance was calculated using the formula:

\[ S = m \cdot g \cdot h, \]

where \( S \) = load stiffness, \( m \) = body mass (kg), \( g \) = gravitational acceleration constant (9.81 m/s\(^2\)) and \( h \) = height of the participant’s estimated COM (m) (Fitzpatrick et al., 1992). The mass on the simulator was adjusted to achieve ~75% of the ankle load stiffness estimated during upright quiet stance for study 1 (range 54-87%, mean ± SD 76 ± 8.1%); and 60% for study 2 (38-81%, 60 ± 8.4%). The current studies served to validate the simulator for future use in functional MRI experiments. MRI-scanning tables typically have a table weight limit; which was 300 lbs. for the
MRI-scanner available at our research institution at UBC. Therefore, the weight that could be added to the simulator to increase load stiffness was limited by the total weight of the participant and simulator combined. To prevent participants from being pushed away from the footplate when balancing the simulator, and eliminate corresponding movements of the trunk and head, tightly-fastened adjustable straps wrapped around the waist and shoulders were attached to the base of the simulator and tightened to maximum level tolerated by the participant. Mechanical stops were used to limit the simulator to a range of $\pm 17^\circ$ to ensure participant safety (Figure 3.1C).

3.2.3 Experimental protocol for study 1

Participants performed a series of real static balancing tasks ($\text{Static}_{\text{Real}}$) while standing upright and simulated static balancing tasks ($\text{Static}_{\text{Sim}}$) while lying down using the simulator (Figure 3.1A). In both conditions, two practice trials of at least 60 s (1 eyes open (EO) and 1 eyes closed (EC)) were performed first to allow participants to become familiar with the procedures, visual feedback, and to remove any potential first trial effects (Adkin et al., 2000). Participants then performed two additional EO and EC trials in alternating order with a total duration of 120 s each (Carpenter, Frank, et al., 2001; van der Kooij et al., 2011). Trials were separated by a few minutes of rest. The order of the balance and visual conditions were counterbalanced across participants. A spotter stood next to the participants to assist them in case there was a loss of balance in both balance conditions.

During EO $\text{Static}_{\text{Sim}}$ trials, participants were provided with real-time visual feedback of the simulator. A potentiometer, attached to one side of the axis about which the simulator rotated, was calibrated and used to determine the angular position of the simulator. The angular
position was then used to render a visual scene (Vizard, WorldViz, USA) displayed on a monitor located 0.4 m in front of the participant.

In the Static\textsubscript{Real} condition, participants stood quietly with their arms hanging loosely by their sides, and feet placed at a width equal to their foot length during each trial. Foot position was marked to ensure that participants returned to the same foot position in every trial. Participants were instructed to stand as still as possible.

At the start of each Static\textsubscript{Sim} trial, the experimenter positioned the simulator approximately 3° from vertical, leaning towards the participant, to mimic upright stance (Loram et al., 2001). Participants were given verbal feedback by the experimenter until they fully controlled the simulator and were then required to keep the simulator as still as possible for the duration of the trial.

3.2.4 Experimental protocol for study 2

Participants performed two Static\textsubscript{Real} and Static\textsubscript{Sim} trials using a similar protocol to study 1. Trials were 80 s in duration, and performed only with EC, as PD effects on Static\textsubscript{Sim} performance were found to be independent of vision in study 1 (see results). Participants also performed dynamic balancing tasks, in which they were required to maintain balance while responding to repetitive perturbations applied to the COM (a sudden push delivered to the participant’s lower back or the simulator by the experimenter), when standing upright (Dyn\textsubscript{Real}) and in the simulator (Dyn\textsubscript{Sim}) (Figure 3.1B). Specifically, participants were instructed to respond to perturbations with corrections about the ankle joint without moving their feet. In both Dyn\textsubscript{Real} and Dyn\textsubscript{Sim}, perturbations were delivered in the AP plane by the experimenter using a hand-held bar, instrumented with a load transducer (sampled at 1 kHz) to control perturbation force. In
addition, online calculation of waist or simulator angular displacement provided monitoring of the perturbation magnitude. Most perturbations were in the forward direction, with some backward perturbations (a sudden backward pull to the lower back or simulator) serving as catch trials to prevent anticipatory leaning (percentage of catch trials for Dyn\textsubscript{Real}: range 8-23%, mean ± SD 15 ± 3.8%; Dyn\textsubscript{Sim}: 6-22%, 12 ± 4.2%). The inter-perturbation interval ranged from 2.0 to 8.4 s for Dyn\textsubscript{Real} and from 2.5 to 28.2 s for Dyn\textsubscript{Sim}. The order of the balance condition and task were counterbalanced across participants.

### 3.2.5 Measurements for study 1

Postural sway in the AP direction was measured using an angular velocity sensor (SwayStar\textsuperscript{TM}, Balance Int. Innovations GmbH, Switzerland), mounted on the participants’ trunk at the level of the lower back (L1-L3) near the body’s COM (Static\textsubscript{Real}) or on the crossbeam of the simulator (Static\textsubscript{Sim}). Angular velocity signals were sampled at 100 Hz and used to calculate angular displacement via trapezoidal integration. The angular displacement signals were low-pass filtered offline using a fourth-order, 3.5 Hz cutoff dual-pass Butterworth filter, to remove rest and postural tremors in PD patients which have a typical frequency between 4 to 7 Hz (Kerr et al., 2008). Data were clipped at 80 s to coincide with the longest duration that all participants could balance the simulator across trials, and still meet the recommended minimum of 60 s for stance trials (Carpenter, Frank, et al., 2001; van der Kooij et al., 2011). The mean was removed from the signal prior to calculating RMS and MPF, which were averaged over the 2 trials for EO and EC conditions.
3.2.6  Measurements for study 2

Postural sway was measured using an OPTOTRAK (NDI, Waterloo, Canada) motion capture system (sampled at 125 Hz). The placement of infrared markers and rigid bodies are illustrated in Figure 3.1D and 3.1E. Missing data (< 40 ms) was interpolated using cubic spline. Kinematic data were low-pass filtered offline using a fourth order dual-pass Butterworth filter with either a 3.5 Hz (Static) or 5 Hz (Dyn) cutoff. Total body COM displacement was calculated for Static\textsubscript{Real} and Dyn\textsubscript{Real} trials using a four-segment model from 2-dimensional filtered coordinates defining the foot, shank, thigh and head/arms/trunk segments (Brown & Frank, 1997) in conjunction with anthropometric data (Winter, 2005). For both Static\textsubscript{Real} and Dyn\textsubscript{Real} trials, AP angular COM displacement was calculated using the inverse tangent function.

For Static\textsubscript{Real} and Static\textsubscript{Sim} trials, the mean was removed from the COM signal prior to calculating the RMS and MPF, which were averaged over both trials. Static\textsubscript{Real} total body COM data were unavailable for one participant due to technical difficulties during collection.

For Dyn\textsubscript{Real} and Dyn\textsubscript{Sim} trials, mean force + 4 SD was calculated offline from 500 ms pre-perturbation and used as a threshold to detect perturbation onset. The area under the curve from perturbation onset to the first zero crossing was calculated. Individual perturbations were excluded if the perturbation force exceeded the mean ± 1 SD range of the perturbation force calculated across all perturbations and participants within the Dyn\textsubscript{Real} and Dyn\textsubscript{Sim} conditions. Remaining trials were used to calculate peak and time-to-peak AP angular COM displacement and velocity within each condition and participant. A minimum of 5 perturbations was required for the participant’s data to be included in the final analysis. Data from 5 participants were removed due to: an inability to successfully complete the Dyn\textsubscript{Sim} trials (n = 2), or technical difficulties during collection (n = 3).
3.2.7 Statistical analysis

Assumptions of normality were validated using Shapiro-Wilk’s test and inspection of histograms and quantile-quantile plots. Baseline characteristics between P Donovan patients and controls were compared using independent t-tests, Mann-Whitney tests, or Chi-square tests where appropriate.

For study 1, all dependent measures were analyzed using a 2 x 2 mixed design analysis of variance (ANOVA) with group (P Donovan, controls) and vision (EO, EC) as independent variables for StaticReal and StaticSim separately. Non-normal data were log-transformed prior to analysis. For all dependent measures, Levene’s tests demonstrated equality of variances across groups, and Box M’s tests demonstrated equality of covariance matrices. Partial eta-squared was used to assess effect size.

For study 2, all dependent measures were compared between P Donovan patients and controls for Static and Dyn tasks separately using independent t-tests and Mann-Whitney tests where appropriate. Cohen’s $d$ and eta-squared were used to assess effect size where appropriate.

An overall $\alpha < 0.05$ was used for all statistical comparisons. Unless otherwise stated, results are means ± standard error of the mean (SE).

3.3 Results

3.3.1 Static balancing tasks

During both studies, differences in upright quiet standing performance were observed between P Donovan patients and controls (Figure 3.2A, 3.2B, and 3.3, and Table 3.3). During study 1, there was a significant main effect of group on trunk AP RMS ($F_{(1,32)} = 4.725, p = .037$) with
significantly larger displacements in PD\textsubscript{ON} patients (0.557 ± 0.043°) than controls (0.445 ± 0.036°). There was a significant main effect of vision on trunk AP RMS ($F_{(1,32)} = 11.674, p = .002$) with significantly larger displacements in EC trials (0.539 ± 0.032°) than EO trials (0.462 ± 0.030°). No significant main effects for trunk AP MPF, or interactions for trunk AP RMS or MPF, were found. During study 2, there was a significant main effect of group on COM AP RMS ($U = 132.0, z = -2.034, p = .042$) with significantly larger displacements in PD\textsubscript{ON} patients (median = 0.438°) than controls (median = 0.331°). There was no significant main effect of group on COM AP MPF.

During both studies, differences in simulated static balance performance were observed between PD\textsubscript{ON} patients and controls (Figure 3.2A, 3.2B, and 3.3, and Table 3.3). Similar to upright quiet standing, during study 1 there was a significant main effect of group on simulator AP RMS ($F_{(1,32)} = 7.205, p = .011$) with significantly larger displacements in PD\textsubscript{ON} patients (0.676 ± 0.044°) than controls (0.521 ± 0.037°). There was also a significant main effect of vision on simulator AP MPF ($F_{(1,32)} = 5.143, p = .030$) with significantly higher MPF in EC trials (0.121 ± 0.008°) than EO trials (0.107 ± 0.010°). No significant interactions were found for simulator AP RMS or MPF. During study 2, there was a significant main effect of group on simulator AP RMS ($U = 108.0, z = -2.660, p = .007$) with significantly larger displacements in PD\textsubscript{ON} patients (median = 0.738°) than controls (median = 0.500°). There was no significant main effect of group on simulator AP MPF.
3.3.2 Dynamic balancing tasks

Perturbation force was not significantly different between the PD_{ON} patients (Dyn_{Real}: 15.491 ± 0.537 N; Dyn_{Sim}: 4.310 ± 0.107 N) and controls (Dyn_{Real}: 16.244 ± 0.528 N; Dyn_{Sim}: 4.025 ± 0.151 N).

During Dyn_{Real}, there were no significant main effects of group on COM peak angular displacement or velocity and COM time-to-peak angular displacement or velocity (Figure 3.2C and 3.4, and Table 3.3). In contrast, differences were observed between PD_{ON} patients and controls for Dyn_{Sim} (Figure 3.2C and 3.4, and Table 3.3). There was a significant main effect of group on simulator peak angular displacement ($U = 55.0, z = -2.182, p = .029$) with significantly larger displacement in PD_{ON} patients (median = 3.954°) than controls (median = 3.046°). There was a significant main effect of group on simulator time-to-peak angular displacement ($t_{(19.789)} = -2.344, p = .030$) with significantly longer time-to-peak in PD_{ON} patients (0.843 ± 0.046 s) than controls (0.721 ± 0.024 s). There was a significant main effect of group on simulator time-to-peak velocity ($U = 34.0, z = -3.099, p = .001$) with significantly longer time-to-peak velocity in PD_{ON} patients (median = 0.330 s) than in controls (median = 0.308 s). There was no significant main effect of group on simulator peak velocity.

3.4 Discussion

The aim of this study was to develop, and validate the effectiveness of using, a novel MRI compatible balance simulator for investigating static and dynamic balance control in PD_{ON} patients and elderly controls. In order for the balance simulator to be effective, it should be relatively easy for both healthy participants and PD patients to control the simulator after only a few minutes of practice. Moreover, the simulator should elicit balance behaviours comparable to
those observed during upright balancing tasks and be sensitive to PD changes seen in both static
and dynamic balance performance.

The majority of participants that performed the protocol without technical issues were
successful in completing the simulated balancing tasks with minimal practice (76/79
participants). The three participants unable to successfully complete the simulated balancing
tasks failed to control the simulator for at least 80 s.

Sway characteristics recorded during simulated static balancing tasks were comparable to
those observed during upright quiet standing (Figure 3.2A and 3.3). This suggests that a similar
balance behaviour is exhibited when maintaining balance using the simulator and when
maintaining balance of the body during upright quiet standing.

During the StaticReal trials, PD\textsubscript{ON} patients showed larger amplitude but no difference in
frequency of AP sway compared to controls. These findings are consistent with previous work
that investigated static balance control in PD\textsubscript{ON} patients with similar disease severity and
comparable sample durations and dependent measures (Cruz et al., 2018). Congruent PD-related
changes in sway were observed in the balance simulator, with significantly larger amplitude of
AP sway compared to controls. Therefore, not only is the simulator able to elicit static balance
behaviour similar to that seen during upright quiet standing in the same participants, but
differences in balance behaviour between controls and PD\textsubscript{ON} patients seen during real static
balancing tasks can also be detected using the simulator.

During the DynReal trials, no differences were found in peak and time-to-peak AP sway
amplitude and velocity between PD\textsubscript{ON} patients and controls. This conflicts with previous work
reporting larger peak AP sway in response to a forward pull of the body at shoulder level in
PD\textsubscript{ON} patients with similar disease severity (H&Y stage of 1 or 2), albeit longer mean disease
duration (8.3 ± 1.7 years vs 5.5 ± 0.79 years in current study) (Di Giulio et al., 2016). Although perturbation forces were similar across studies, there were several methodological differences such as the point of application of the perturbation on the torso, perturbation delivery method, and method of measuring peak sway. While no group differences were detected during DynReal trials, larger peak amplitude, and longer time-to-peak amplitude and velocity were observed in the PDON patients compared to controls, despite similar perturbation forces, during the DynSim trials. Therefore, the simulator may be able to detect subtle differences in dynamic balance behaviour between controls and PDON patients that are not observable during real dynamic balancing tasks.

While other studies have tried to develop systems allowing participants to perform balance-related tasks while lying down (Buettner et al., 2017; de Lima-Pardini et al., 2017; Karim et al., 2014), none truly simulated free-standing balance. Karim et al. (2014) developed an MRI compatible force platform and had participants use visual feedback to control AP centre of pressure movements generated by ankle dorsiflexor and plantarflexor activation. Participants used feed-forward volitional control to complete the task. De Lima-Pardini et al. (2017) developed an MRI compatible force measurement system designed to investigate anticipatory postural adjustments during single leg raises in order to simulate step initiation. Lastly, Buettner et al. (2017) developed a moveable balance board producing torque resembling gravity, inertia and damping effects of free standing and asked participants to continuously balance the board by moving their feet in the ankle joint. While the balance board system took into account the characteristics of an inverted pendulum body, participants did not balance a physical weight but instead a torque was generated using an electric motor with the potential effect of
electromechanical delays limiting the results of the study. While all three studies investigated balance-related tasks, none truly simulated free-standing balance in a supine condition.

The free-standing inverted pendulum model used in our simulator design distinguishes it from the previously developed systems. It allows for the tasks performed in the simulator to closely mimic free-standing balance with sensory feedback of relevant joints and muscle receptors, and motor pathways controlling tonic and reflexive muscle responses. In addition, the simulator load stiffness levels approached those seen during normal upright standing. Therefore, our fully MRI compatible simulator allows for functional neuroimaging to be combined with balance-relevant tasks to investigate the neural substrates of free-standing static and dynamic balance control.

Currently severely affected PD patients, and other clinical populations, in whom upright standing trials can no longer be safely carried out and/or that cannot stand unassisted for long enough periods of time are usually excluded from participating in postural instability research. The simulator could provide an opportunity to include these more severely-affected individuals as it would not require upright stance. The inclusion of these individuals would lead to postural instability research results that are more generalizable to the entire PD population.

There are a few limitations of the proposed simulator. First, as participants are supine, loading of the body and vestibular input is different compared to upright standing. Tightly fastened straps wrapped around the waist and shoulders were used to mimic, as much as possible, gravitational pull on the body, and resultant input from joint, Golgi tendon organ, and foot sole cutaneous receptors. While vestibular input was different, the fact that similar balance deficits with PD were seen between real and simulated balance tasks suggests a non-vestibular origin of the balance deficits. Second, it is not possible to assess balance behaviour in the ML
direction using the simulator in its current form. Prior studies have found ML sway to also be affected in PD patients (Cruz et al., 2018; Viitasalo et al., 2002), with larger ML sway amplitude in PD patients. However, ML instability is generally much less pronounced, as reflected by the normally narrow-based gait and intact tandem gait test in even advanced PD stages (Abdo et al., 2006; Nonnekes et al., 2014). Additionally, although different muscle/joints are involved in controlling AP and ML sway, there is no evidence to suggest they are controlled using different cortical or subcortical structures. Third, dyskinesia may prevent proper placement of the feet on the footplate of the simulator in PD patients. Therefore, further testing is needed to determine the feasibility of using the simulator in PD patients suffering from dyskinesia and other symptoms not apparent in this study.

In conclusion, the results of this study indicate that deficits in both static and dynamic balance control in PD_{ON} patients can be detected in recumbent individuals using a novel MRI compatible balance simulator. The simulator provides a unique opportunity to combine functional neuroimaging with balance-relevant tasks, and a new means to create insights into the cortical and subcortical structures contributing to postural instability in PD.
### Table 3.1 Baseline participant characteristics for study 1 and study 2

Data are displayed as mean (SE) or number of persons (percentage between parentheses); PDON, Parkinson’s disease patients.

<table>
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<th>PDON</th>
<th>Controls</th>
<th>p-value</th>
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Range: 57-78 | 1-17 | 14-46 | 1-3 | 100-1638

Mean (SE): 69.0 (1.6) | 6.0 (1.2) | 29.4 (2.7) | - | 704.6 (121.7)

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Range: 59-75 | 1-14 | 7-46 | 1-3 | 150-1450

Mean (SE): 67.6 (1.0) | 5.6 (0.8) | 27.0 (2.4) | - | 698.7 (85.9)

Table 3.2 Clinical characteristics Parkinson’s disease patients for study 1 and study 2

PDON, Parkinson’s disease patients; Maximum Unified Parkinson’s Disease Rating Scale motor examination (UPDRS-ME) score is 108; Maximum Hoehn & Yahr (H&Y) score is 5.
### Table 3.3 Results static and dynamic balancing tasks for study 1 and study 2

Data are displayed as mean (SE) for analysis of variance (study 1), and mean (SE) and median for independent t-tests and Mann-Whitney tests (study 2). PD<sub>ON</sub>, Parkinson’s disease patients; AP, anterior-posterior; RMS, root mean square; MPF, mean power of frequency; F<sub>(x,x)</sub>, F-value (degrees of freedom); η<sup>2</sup>, partial eta-squared; U, Mann-Whitney U statistic; z, z-score; t(x), t-statistic (degrees of freedom); d, Cohen’s d; η<sup>2</sup>, eta-squared; * Data were log-transformed, for ease of interpretation mean (SE) values of the non-log-transformed data are shown; p < 0.05 shown in bold.
Figure 3.1 Experimental set-up

Experimental set-up for (A) StaticReal and StaticSim (Note: spotter was present but is not shown here), and (B) DynReal and DynSim. (C) Close-up of the balance simulator with black arrows indicating mechanical stops. Kinematic marker set-up for (D) real and (E) simulated balance.
Figure 3.2 Representative anterior-posterior angular displacement traces and power spectral density plots

Representative anterior-posterior angular displacement traces and power spectral density plots of an elderly control and PD patient during real and simulated (A and B) static and (C) dynamic balance. Dashed line indicates perturbation onset for dynamic balance.
Figure 3.3 Group means of root mean square and mean power of frequency of angular displacements during static balance

Group means and standard errors of (A and C) root mean square (RMS) and (B and D) mean power of frequency (MPF) of angular displacements during real and simulated static balance. Study 1: eyes open and eyes closed data were combined. *p < 0.05
Figure 3.4 Group means of peak and time-to-peak amplitude and velocity of angular displacements during dynamic balance

Group means and standard errors of peak and time-to-peak (A and B) amplitude and (C and D) velocity of angular displacements during real and simulated dynamic balance. *p < 0.05
Chapter 4: Brain connectivity during simulated balance in older adults with and without Parkinson’s disease

4.1 Introduction

Postural instability is a debilitating symptom of PD, often treatment-resistant and leading to falls (Boonstra et al., 2008; Crouse et al., 2016; Fasano et al., 2017; Grimbergen et al., 2009). Effective treatment of postural instability in PD is significantly impeded by a relatively poor understanding of both the neural networks involved in healthy balance and the pathophysiology underlying balance deficits in individuals with PD (Crouse et al., 2016; Grimbergen et al., 2009; S. D. Kim et al., 2013). Balance control in healthy individuals likely involves an integrated network of cortical and subcortical structures (Takakusaki, 2017), however, the specific networks involved remain unresolved. Moreover, the extent to which changes in the activation of, and connection between, cortical and subcortical structures contribute to balance deficits in PD has not been established.

Investigating neural activation patterns and connectivity networks contributing to healthy and abnormal balance control is hindered by the constraints of current functional neuroimaging options. Although portable neuroimaging techniques, such as EEG and fNIRS, allow for functional neuroimaging in participants standing upright (albeit frequently with unacceptable levels of movement artifact), their ability to record from subcortical structures is limited. Both cortical and subcortical activity can be measured using PET and fMRI scanners, however, these scanners are almost exclusively horizontal, requiring the participant to be lying supine. Wearable PET scanners have recently been developed (Bauer et al., 2016; Melroy et al., 2017), but are
limited by poor temporal resolution and the weight of the wearable PET device, potentially interfering with balance control.

Motor imagery of static and dynamic balance tasks offers a less-than-ideal approach to probing balance networks but has been successfully employed in healthy participants (Bhatt et al., 2018; Ferraye et al., 2014; Gilat et al., 2019; Jahn et al., 2008, 2004; Malouin et al., 2003; Mouthon et al., 2018; Taube et al., 2015; Zwergal et al., 2012) and individuals with PD (Gilat et al., 2019; Peterson et al., 2014b). Unsurprisingly, some brain areas are more strongly, or selectively, activated during actual motor execution of a task compared to motor imagery of the same task, and *vice versa* (Guillot et al., 2012; O’Shea & Moran, 2017). The ability to perform motor imagery varies greatly among individuals (Saimpont et al., 2015) and declines with age for complex movements (Kalicinski et al., 2015; Saimpont et al., 2013), making it less suitable for investigating balance networks in healthy older participants and individuals with PD.

A few studies have attempted performance of balance-related tasks while recording fMRI data in participants lying supine (de Lima-Pardini et al., 2017; Karim et al., 2014). Karim et al. (2014) constructed an MRI compatible force platform and had participants use visual feedback to generate anterior-posterior ankle torque using feed-forward volitional control. Likewise, de Lima-Pardini et al. (2017) developed an MRI compatible force measurement system to investigate anticipatory postural adjustments during single leg raises to simulate step initiation. Although these prior studies had participants perform balance-related tasks while lying down, neither truly simulated free-standing balance.

Recently, we developed and validated a novel MRI compatible balance simulator able to detect postural instability in individuals with PD (Pasman et al., 2019). The balance simulator was shown to be relatively easy to control for both healthy participants and individuals with PD.
after only a few minutes of practice outside the scanner. During validation, lab studies verified that qualitatively similar balance behaviour was seen in participants when maintaining balance of their body during upright standing and when maintaining balance using the balance simulator while supine. The balance simulator was also sensitive enough to detect deficits in both static and dynamic balance control in individuals with PD (Pasman et al., 2019).

Here we use this newly-validated balance simulator during fMRI scanning to investigate effective connectivity during static and dynamic balance control tasks in individuals with PD and healthy older adults. As abnormal brain connectivity patterns have previously been found in individuals with PD at rest and during a variety of motor and non-motor tasks (Filippi et al., 2018), we hypothesized differences in brain connectivity networks between individuals with PD and healthy older adults during performance of simulated free-standing static and dynamic balance tasks.

4.2 Materials and methods

4.2.1 Participants

Eighteen individuals with PD and 19 age-matched elderly controls participated in this study (Table 4.1). All participants provided written informed consent prior to testing and followed experimental procedures that were approved by the UBC Clinical Research Ethics Board, the Vancouver Coastal Health Research Institute, and the UBC MRI Research Centre. Three participants were excluded due to: inability to complete the protocol in the MRI scanner (n = 2) and finding of an incidental abnormality on their anatomical MRI scan (n = 1). Therefore, 17 individuals with PD and 17 controls were included in the final data set (Table 4.1).
Individuals with PD were examined approximately one hour after intake of their regular antiparkinson medication to coincide with their subjectively best clinical ‘on’ condition and for dopa-unresponsive balance effects to be assessed specifically. All participants completed a brief balance-oriented medical history survey, including the occurrence of prior falls within the past 6 months. The H&Y scale (Goetz et al., 2004) and UPDRS-ME (Goetz et al., 2008) were administered to individuals with PD on a separate day prior to MRI scanning (range 0-31 days, mean ± SD 9 ± 8 days) when participants became familiar with the experimental tasks outside of the MRI scanner (Table 4.2). Balance behaviour was quantified during the lab-based familiarization session for all participants, and deficits in both static and dynamic balance control were seen in individuals with PDON compared to controls (Pasman et al., 2019).

### 4.2.2 Apparatus

During the simulated stance trials participants were asked to control a customized balance simulator (“simulator”) (Pasman et al., 2019). Briefly, in the simulator the participant lay supine with their feet placed against a footplate that controlled a free-standing inverted pendulum in the anterior-posterior direction about an axis aligned with the ankle joints (Figure 4.1). The mass on the simulator was adjusted such that the estimated load stiffness was about 60% of the ankle load stiffness seen during upright quiet stance (range 38-81%, mean ± SD 60 ± 8.7%). At the start of each simulated stance trial, the experimenter positioned the simulator approximately 3° from vertical, leaning towards the participant. To prevent participants from being pushed away from the footplate when balancing the simulator, and eliminate corresponding movements of the trunk and head, tightly-fastened adjustable straps wrapped around the waist and shoulders were attached to the base of the simulator. Mechanical stops were used to limit the simulator to a...
range of ± 17° to ensure participant safety. In addition, the experimenter stood beside the simulator at all times throughout the testing to assist if needed.

4.2.3 Experimental tasks

Participants performed 4 different tasks: resting, proprioceptive, static balancing (SB), and dynamic balancing (DB). Since PD effects on simulated SB performance were previously found to be independent of vision (Pasman et al., 2019), all tasks were performed with eyes closed to prevent the activation of cortical regions associated with processing of visual information. The resting and proprioceptive tasks were used as reference tasks. During the resting task participants were instructed to remain awake and lay still. During the proprioceptive task the simulator was moved by the experimenter and participants were instructed to continuously track the passive movement of the ankle joints by moving their left index finger. Using the proprioceptive task as one of the reference tasks ensured brain connectivity seen during the balancing tasks was due to balance related activation, not solely proprioception. During the SB task participants were instructed to keep the simulator as still as possible. During the DB task participants were instructed to keep the simulator balanced while responding to transient, random, anterior-posterior perturbations applied to the simulator by the experimenter using a hand-held bar. The resting task was performed first. While the order of the SB and DB tasks was counterbalance across participants, the proprioceptive task was always presented in between the balancing tasks to minimize fatigue. In addition, we allowed 2 minutes of rest between each task.
4.2.4 MRI scanning

MRI data were collected on a 3 Tesla scanner (Philips Achieva 3.0T R3.2; Philips Medical Systems, The Netherlands) equipped with a head-coil. Head motion was minimized by a strap placed around the participants’ head within the head coil, and foam wedged between the participants’ head and the head coil. Participants wore ear plugs and earmuffs to minimize scanner noise. An MRI safe sandbag was placed on top of the participants’ pelvic area to further stabilize the hips during the balancing tasks.

During fMRI scanning echo-planar T2*-weighted images with blood oxygenation level-dependent (BOLD) contrast were taken. Scanning parameters were: repetition time 2000 ms, echo time 30 ms, flip angle 90°, field of view 240 x 240 x 143 mm, matrix size 80 x 80, pixel size 3.0 x 3.0 mm. Thirty-six axial slices of 3.97 mm thickness were collected in each volume, with a gap thickness of 1 mm. A high resolution, 3-dimensional T1-weighted image of the whole brain was acquired to facilitate anatomical localization of activation for each participant. The duration of each functional run was 8 minutes for the resting task and 2 minutes for the other three tasks.

4.2.5 Functional MRI preprocessing

The fMRI data collected were preprocessed using the AFNI software package. Preprocessing steps performed on the whole brain included despiking, slice time correction, and 3-D isotropic reslicing (3 mm in each dimension). Motion correction using rigid body alignment was performed to correct for any major head motion during scanning. As the brainstem can move independently from the rest of the brain, a separate motion correction of the brainstem was performed. The amount of head motion was assessed using mean volume-to-volume framewise
displacement (Power et al., 2012). Fifty-seven regions of interest (ROIs) were extracted using FreeSurfer software (Harvard, MA, USA), and HMAT atlas for motor areas (Mayka et al., 2006), from the T1-weighted scans (Table 4.3). The choice for the ROIs was mostly based on prior evidence of the brain regions involved in balance (Bhatt et al., 2018; Ferraye et al., 2014; Jacobs & Horak, 2007; Jahn et al., 2008, 2004; Malouin et al., 2003; MacKinnon, 2018; Mouthon et al., 2018; Takakusaki, 2017; Taube et al., 2015; Visser & Bloem, 2005; Zwergal et al., 2012). Each of the participants’ structural scans was then co-registered to the fMRI scan using rigid registration.

All analyses were done in the individual’s native space rather than transforming all data to a common template, to prevent excessive error (Nieto-Castanon et al., 2003; Ozcan et al., 2005), particularly in small subcortical regions such as the basal ganglia, as we have specifically shown in individuals with PD (Chen et al., 2009; Ng et al., 2009). Nuisance regression was then used to remove several sources of variance such as head motion parameters, their temporal derivatives and their squares, white-matter signal, and cerebrospinal fluid signal. The fMRI signal was then detrended and iteratively smoothed until it reached 6 full width at half maximum of smoothness. Finally, the fMRI signal was high-pass filtered using a 0.01 Hz filter cut-off. The preprocessed time courses of the voxels within each ROI were averaged as the overall activity of the ROI.

### 4.2.6 Effective brain connectivity analysis

Effective connectivity, which captures the causal and dynamic influence brain regions exert over one another and reveals the strength and directionality of information flow between brain regions (Appel-Cresswell et al., 2010; Friston, 2011), was computed between the 57
FreeSurfer-derived ROIs using the PCfdr (Peter Spirtes and Clark Glymour, false discovery rate) algorithm (J. Li, Wang, & McKeown, 2008; J. Li & Wang, 2009). This algorithm is specifically designed to assess connectivity when a relatively large number of ROIs and relatively few time points are available. It explores the dependence/independence between pairs of ROIs conditional on an exhaustive search of all other ROI combinations. The false discovery rate threshold was set to 5%. We pooled the PD and control groups together and computed the significant connections amongst ROIs for all tasks. The strength and direction of significant connections between ROIs were determined using a dynamic Bayesian network (DBN) group analysis approach (J. Li et al., 2006; J. Li et al., 2007; J. Li, Wang, Palmer, & McKeown, 2008).

Four separate statistical models were created utilizing a binomial logistic regression: contrasting SB vs {rest, proprioception} and DB vs {rest, proprioception} for both individual with PD and control groups. Principal component analysis (PCA) was employed to achieve dimensionality reduction for the significant connections detected by the PCfdr/DBN method. PCA was performed separately for controls and individuals with PD. The first 12 principal components (PCs), explaining at least 75% of the variance in both groups, were selected. Overall model fits were determined by comparing the full model to an intercept only model using the log-likelihood test.

Only the DB vs {rest, proprioception} models for controls and individuals with PD were significant (see results), and thus these models were investigated further. The $\beta$ regression coefficients and their Wald $\chi^2$ statistic were examined to determine which PCs were making a significant contribution to the prediction of the task. Connections with the largest effect on each significant PC were identified by converting the PCA loadings into Z-scores and selecting all connections with an absolute Z-score $\geq 1.96$. To evaluate the ability of the logistic regression
models to correctly predict the task category of observed cases, contingency tables and leave-one-out cross validation were used, followed by two-tailed Fisher’s Exact Tests of independence to examine the relationship between performed and predicted tasks.

In order to directly compare relevant connections between controls and individuals with PD, we first took the union of the connections significant in the DB task in either individuals with PD or controls. We then performed a logistic regression with Least Absolute Shrinkage and Selection Operator (LASSO) regularization to identify connections predicting group membership. An $\alpha < 0.05$ was used for all statistical comparisons.

### 4.2.7 Participant baseline characteristics and head motion parameters

For both participant baseline characteristics and head motion parameters, assumptions of normality were validated using Shapiro-Wilk’s test and inspection of histograms and quantile-quantile plots. Baseline characteristics between controls and individuals with PD were compared using independent $t$-tests or Fisher’s Exact Tests where appropriate. Mean volume-to-volume framewise displacements, used to assess head motion, were log-transformed due to non-normality and subsequently analyzed using a $2 \times 4$ mixed design ANOVA with group (PD, controls) and task (rest, proprioception, SB, DB) as independent variables. In the case where Mauchly’s tests of sphericity ($p < 0.05$) was significant, the Greenhouse-Geisser $\varepsilon$ statistic was used. An $\alpha < 0.05$ was used for all statistical comparisons. In case of significant main and interaction effects, post hoc comparisons were performed after adjusting for multiple comparisons using a Bonferroni correction.
4.3 Results

4.3.1 Head motion

Minimal head motion occurred during the MRI scans and all participants were included in the fMRI analysis. For both groups mean volume-to-volume framewise displacement was less than 0.3 mm in all tasks (Table 4.4). This is comparable to head motion reported previously during resting-state fMRI in older adults (H. Li et al., 2017) and fMRI during a foot-pedalling task in individuals with PD (Matar et al., 2019). No significant main effects of task or group, or interaction effects, were found for mean framewise displacement.

4.3.2 Effective connectivity

The PCfdr/DBN method detected 164 significant connections between ROIs, which represent ~5.1% of all possible (57 x 56 = 3,192) directional connections. PCA of these 164 significant connections showed that the first 12 PCs contained 76% and 90% of the total variability for controls and individuals with PD respectively.

4.3.2.1 Static balancing task

In both controls and individuals with PD, the full model with 12 predictors was not significantly better at predicting the tasks compared to the constant only model (controls: $\chi^2[12, N = 51] = 18.632, p = 0.098$; individuals with PD: $\chi^2[12, N = 51] = 10.706, p = 0.554$).

4.3.2.2 Dynamic balancing task

In controls, the log-likelihood test indicated that the full model with 12 predictors was significantly better at predicting the tasks compared to the constant only model ($\chi^2[12, N = 51] =$
43.286, p = 2e^{-5}). The full model was able to correctly classify 97% of the resting/proprioceptive tasks and 94% of the DB tasks, for an overall success rate of 96%. Fisher’s Exact Test indicated there was a statistically significant relationship between the performed and predicted tasks (p<0.0001, odds ratio [95% asymptotic confidence interval] = 528.000 [30.991, 8995.500]). During leave-one-out cross validation, the full model was able to correctly classify 88% of the resting/proprioceptive tasks and 47% of the DB tasks, for an overall success rate of 75%. There was a statistically significant relationship between the performed and predicted tasks (p = 0.012, 6.667 [1.623, 27.377]). Examination of the β coefficients and their Wald χ² statistic showed 4 PCs making a significant contribution to the prediction of the DB task (Table 4.5). In general, the connections with the largest effect on the significantly contributing PCs connect the following areas (number of corresponding connections in brackets): brainstem to either cerebellum (2), limbic (1), thalamus (1), or other brainstem structures (1); limbic to other limbic (2) or basal ganglia structures (2); motor to other motor areas (4); frontal to other frontal (2) or basal ganglia structures (1); temporal to frontal (4) or limbic areas (3); and parietal to frontal (1) or temporal areas (1) (Figure 4.2A and 4.2B, and Table 4.6).

In individuals with PD, the log-likelihood test showed that the full model was significantly better at predicting the outcomes compared to the constant only model (χ²[12, N = 51] = 46.982, p = 5e^{-6}). The full model correctly classified 97% of the resting/proprioceptive tasks and 88% of the DB tasks, for an overall success rate of 94%. Fisher’s Exact Test indicated there was a statistically significant relationship between the performed and predicted tasks (p < 1e^{-4}, 247.500 [20.792, 2946.100]). During leave-one-out cross validation, the full model was able to correctly classify 88% of the resting/proprioceptive tasks and 71% of the DB tasks, for an overall success rate of 82%. There was a statistically significant relationship between the
performed and predicted tasks ($p = 4e^{-5}$, 18.000 [4.116, 78.711]). Examination of the $\beta$ coefficients and their Wald $\chi^2$ statistic showed 5 PCs making a significant contribution to the prediction of the DB task (Table 4.5). In general, the connections with the largest effect on the significantly contributing PCs connect the following areas (number of corresponding connections in brackets): brainstem to either cerebellum (2), limbic (2), thalamus (1), or basal ganglia structures (2); limbic to other limbic (2) or basal ganglia structures (1); motor to other motor (2) or frontal areas (1); frontal to other frontal (2) or basal ganglia structures (1); temporal to either frontal (2), limbic (2), or other temporal areas (1); and parietal to other parietal areas (1) (Figure 4.3A and 4.3B, and Table 4.7).

To directly compare between groups, 34 connections, making a significant contribution to predicting the DB task in controls and/or individuals with PD, were entered in the logistic LASSO regression. Five connections survived, indicating that they are important to predicting group membership (control or individual with PD) during the DB task (Table 4.8). The connections predicting group membership involve the following areas: midbrain to left nucleus accumbens, left anterior cingulate cortex to left caudate, right insular cortex to left insular cortex, left dorsal premotor area to left pre-SMA, and right middle temporal cortex to right lateral orbitofrontal cortex.

### 4.4 Discussion

We used a novel MRI compatible balance simulator (Pasman et al., 2019) to investigate effective brain connectivity patterns related to static and dynamic balance-related tasks in individuals with PD and healthy older adults. We showed that a network of cortical and subcortical neural structures, including frontal, parietal, and temporal cortices as well as basal
ganglia, cerebellum, and brainstem, was active during dynamic balancing in healthy older adults. In individuals with PD, a similar network of cortical and subcortical neural structures was active during dynamic balancing, however, the strength and direction of connections between certain areas were different.

4.4.1 Effective connectivity network for dynamic balancing in healthy older adults

We observed decreased connectivity between different motor areas and increased connectivity from the brainstem to several cortical and subcortical areas in healthy older adults during dynamic balancing compared to the rest/proprioception conditions. Taken together, this indicates a preference of subcortical over motor cortical control of dynamic balancing in healthy older adults. Our results are generally consistent with prior results from motor imagery studies that identified several subcortical (e.g., mesencephalic locomotor region, thalamus, cerebellum, and basal ganglia) and cortical (e.g., frontal, temporal, parietal, and cingulate cortices) areas as part of a distributed dynamic balance network (Bhatt et al., 2018; Ferraye et al., 2014; Mouthon et al., 2018; Taube et al., 2015). Additionally, our results provide novel insight into the directionality of the connections between these areas and highlighting the potential context- and task-specificity of SMA activity during dynamic balance tasks.

4.4.2 Connectivity involving subcortical and brainstem regions increases in healthy older adults during dynamic balancing

As shown in Figure 4.2B, connectivity increased from the dorsolateral prefrontal and anterior cingulate cortices to the basal ganglia, more specifically the caudate nucleus, in healthy elderly during dynamic balancing. This finding is consistent with fMRI evidence of increased
activation in the prefrontal and anterior cingulate cortices, as well as in the basal ganglia (putamen and globus pallidus), during motor imagery of dynamic balance tasks (Bhatt et al., 2018; Ferraye et al., 2014; Mouthon et al., 2018; Taube et al., 2015). Increased activity in prefrontal and anterior cingulate cortices during dynamic balance responses has also been implicated with EEG and fNIRS (Bogost et al., 2016; Mihara et al., 2008; Sipp et al., 2013; Solis-Escalante et al., 2019).

The involvement of the prefrontal cortex during dynamic balancing that we observed is consistent with its role in error detection (Bogost et al., 2016) and monitoring postural stability (Solis-Escalante et al., 2019) through sensory integration and allocation of attentional resources (Mihara et al., 2008; Teo et al., 2018). The anterior cingulate also plays an important role in monitoring motor error which is critical for detecting loss of balance during challenging posture and gait tasks (Bhatt et al., 2018; Goel et al., 2019; Marlin et al., 2014; Sipp et al., 2013). The basal ganglia have long been linked to balance control, particularly in terms of sensorimotor integration, gain control of balance correcting responses, and proper selection and execution of context-specific balance correcting responses (Ferraye et al., 2014; Jacobs & Horak, 2007; Taube et al., 2015; J. E. Visser & Bloem, 2005). Therefore, the observed increase in connectivity from the prefrontal and anterior cingulate cortices to the basal ganglia during our simulated dynamic balance task adds further evidence for the critical role of these areas in maintaining balance control.

We also found increased connectivity from pons to cerebellum, and midbrain to thalamus and insular cortex (Figure 4.2B). These results are consistent with prior findings from motor imagery of dynamic balance tasks that have demonstrated increased activation of the pons and mesencephalic locomotor region of the midbrain (Ferraye et al., 2014), and increased activation
of the cerebellum, thalamus, and insula (Bhatt et al., 2018; Ferraye et al., 2014; Taube et al., 2015). Increased connectivity between brainstem structures, the thalamus, and cerebellum supports growing evidence for the importance of the corticopontocerebellar-thalamocortical loop in integrating feedforward commands with sensory information to shape and modulate subsequent motor commands (MacKinnon, 2018) and allows for postural responses to be modified by prior experience and changes in central set (Bhatt et al., 2018; Jacobs & Horak, 2007).

Several areas in the pons are thought to be involved in balance control, including the pontomedullary reticular formation, locus coeruleus, and vestibular nuclei (MacKinnon, 2018; Takakusaki, 2017). The vestibular nuclei contribute to the modulation of dynamic balance responses through descending vestibular-spinal pathways, ascending projections to the thalamus and insula, and bidirectional connections to the vermis and flocculonodular nuclei of the cerebellum (MacKinnon, 2018; Takakusaki, 2017). The increased connectivity observed during dynamic balancing from pons to cerebellum, supports extensive evidence for the vestibulo-cerebellar networks crucial role in maintaining postural control (Carpenter, Allum, & Honegger, 2001; Morton & Bastian, 2004; Schniepp et al., 2017), allowing for efferent and afferent proprioceptive and vestibular inputs to be compared in order to rapidly identify and correct movement error associated with a balance disturbance (Peterka, 2018). Nuclei within the midbrain have also been linked to postural control, including the mesencephalic locomotor region (composed of the cuneiform nucleus and PPN) and caudal raphe nuclei (MacKinnon, 2018; Takakusaki, 2017). The PPN has connections with the basal ganglia and limbic areas, thalamus, cerebellum, brainstem, spinal cord, and cerebral cortex (Alam et al., 2011). The observed connection from midbrain to thalamus makes sense given the role of the posterolateral
thalamus in maintaining upright posture (Masdeu & Gorelick, 1988), and verticality perception (Barra et al., 2010; Jacobs & Horak, 2007). The parieto-insular vestibular cortex, which includes part of the posterior insula and parietal operculum, as well as part of the temporo-peri-sylvian cortex in the superior temporal gyrus, has strong connections with other vestibular-related cortical areas, and receives converging sensory inputs (Indovina et al., 2015; Takakusaki, 2017). This region is thought to be essential for sensory integration during postural tasks (Jacobs & Horak, 2007), contributing to perception of visual and perceived gravitational vertical (Jacobs & Horak, 2007; Takakusaki, 2017) and spatial orientation and self-motion perception (Bhatt et al., 2018; Taube et al., 2015).

Healthy older adults also showed increased connectivity from temporal cortices to both subcortical and other cortical areas (Figure 4.2A and 4.2B). Connectivity increased from the superior temporal cortex to the amygdala, as well as middle temporal cortex and inferior temporal cortex to the lateral and medial orbitofrontal cortices. The superior temporal gyrus was found to be activated in previous studies during motor imagery of dynamic balancing (Taube et al., 2015), and its temporo-peri-sylvian cortex is part of the parieto-insular vestibular cortex (Indovina et al., 2015).

4.4.3 Connectivity involving motor and parietal regions decreases in healthy older adults during dynamic balancing

Our results indicate that healthy older adults, when performing simulated dynamic balance, had decreased connectivity from the dorsal premotor area to SMA and pre-SMA, as well as the right to left pre-SMA (Figure 4.2A). Our observation of reduced connectivity between and within motor cortical areas contrasts with evidence of increased premotor and SMA
activity recorded with MRI during motor imagery of dynamic balance tasks (Bhatt et al., 2018; Ferraye et al., 2014; Mouthon et al., 2018; Taube et al., 2015). This discrepancy between the current study and prior motor imagery studies could be due to differences in the level of automaticity associated with the dynamic balance tasks. Reduced activation of pre-SMA, premotor areas, and superior and inferior parietal areas has been reported in healthy older adults as tasks become more automatic (Wu & Hallett, 2005a). In contrast to the dynamic balance-simulator task used in the current study that required rapid ankle responses to transient, unpredictable perturbations in random directions, in order to minimize anticipatory control, Ferraye et al. (2014) used a voluntary sway task which requires feedforward coordination of postural adjustments to the voluntary sway movements. In addition, internally and externally triggered movements are associated with different brain activation patterns, with increased activation in SMA during internally driven compared to externally triggered movements (Filyushkina et al., 2019). The dynamic balance task used in the current study resembles an externally triggered movement, as opposed to the imagined dynamic balancing tasks where the disturbances to balance are anticipated because they have to be self-generated. The SMA and premotor areas are most critical in preparing planned or complex motor programs (MacKinnon, 2018; Takakusaki, 2017) and thus more likely to contribute to balance tasks that require more feedforward, less automatic balance control (Ferraye et al., 2014; Mierau et al., 2015; Takakura et al., 2015), and/or later phases of the compensatory balance reactions such as stepping or reaching responses (Marlin et al., 2014; Mihara et al., 2008).
4.4.4 Dynamic balancing relies more on cortical than subcortical control in individuals with Parkinson’s disease

When individuals with PD were asked to perform a dynamic balancing task, compared to the rest/proprioception tasks, they showed an effective connectivity pattern largely similar to healthy older adults. However, there were some notable differences. Qualitatively, individuals with PD had increased connectivity associated with motor control and parietal areas, and decreased connectivity from brainstem to other subcortical areas, suggesting that dynamic balance control in individuals with PD relies relatively more on cortical motor areas. The increased cortical involvement we observed in individuals with PD during dynamic balancing compared to healthy older adults is consistent with the ‘posture second strategy’ observed in individuals with PD, whereby engagement in a mental task (e.g., mental arithmetic) results in disproportionate decreases in postural control (Bloem et al., 2006).

4.4.5 Cortical connectivity was generally increased in individuals with Parkinson’s disease during dynamic balancing

When comparing the effective connectivity networks qualitatively, in contrast to healthy older adults who showed decreased connectivity associated with motor control areas and the inferior parietal cortex (Figure 4.2A), individuals with PD had increased connectivity from the SMA and premotor areas to the pre-SMA, and from the superior parietal cortex to precuneus (Figure 4.3A). Increased activation in the pre-SMA and SMA was previously found in individuals with PDON, compared to healthy older adults, during active, but not passive, ankle movements (Katschnig et al., 2011). Our findings are also in line with previous observations of reduced activation in motor control and parietal areas in healthy older adults (Wu and Hallett,
2005a), but increased activation in the cerebellum, motor, parietal, and prefrontal areas in individuals with PD_{OFF} (Wu and Hallett, 2005b), during automatic movements. Therefore, it seems as if individuals with PD_{OFF} compensate for their inefficient brain activity with increased premotor-parietal region activation during execution of automatic movements (Wu and Hallett, 2005b). The qualitative differences in connectivity associated with motor control areas were supported with direct statistical comparison between the groups. In particular, individuals with PD were best discriminated from the healthy older adults by an abnormal increase in connectivity from the dorsal premotor area to the pre-SMA.

While cortical connectivity increased in motor and parietal areas, connectivity from the dorsal prefrontal and anterior cingulate cortices to the caudate nucleus were reduced in individuals with PD when qualitatively compared to healthy older adults. Reduced activity in the superior parietal and anterior cingulate cortices was found previously during motor imagery of gait in individuals with PD_{OFF} compared to healthy older adults (Snijders et al., 2011). Direct statistical comparison between the groups confirmed that a lack of normal increase in connectivity strength from the anterior cingulate cortex to the caudate nucleus was important in discriminating individuals with PD from healthy older adults. In addition, an abnormal increase in connectivity from the middle temporal cortex to lateral orbitofrontal cortex, and lack of normal increase between the bilateral insular cortices were also important in best discriminating individuals with PD from health older adults during dynamic balancing.
4.4.6  **Subcortical connectivity was altered in individuals with Parkinson’s disease during dynamic balancing**

Reduced connectivity was seen in individuals with PD from the midbrain to thalamus, cerebellum, nucleus accumbens, and amygdala (Figure 4.2B). These findings corroborate previous work which found that the tendency to shift execution of automatic movements to subcortical areas is less clear in individuals with PD_{OFF} compared to healthy older adults (Wu et al., 2010). Some of the subcortical connections identified in predicting the dynamic balancing task in individuals with PD, such as the connections from the midbrain to thalamus and cerebellum, were common to both groups when comparing them qualitatively. However, unique connections in individuals with PD included reduced connectivity from midbrain to nucleus accumbens and amygdala, and increased connectivity from midbrain to the pallidum and pons to insular cortex. Direct statistical comparison between the groups confirmed an abnormal decrease in connectivity from the midbrain to nucleus accumbens was important in discriminating individuals with PD from health older adults.

4.4.7  **Effective connectivity network for static balancing**

In both healthy older adults and individuals with PD we were unable to determine an effective connectivity network associated with static balancing. During the proprioceptive task, the simulator was moved by the experimenter, and participants were instructed to passively undergo these simulator movements while tracking them using their left index finger. During the static balancing task participants were instructed to keep the simulator as still as possible. They would have mostly relied on somatosensory information from muscle spindle, joint, Golgi tendon organ, and foot sole cutaneous receptors as vestibular and visual inputs were limited by
lying supine and having their eyes closed respectively. The brain connectivity network associated with the simulated static balancing tasks might not have been distinct enough from that associated with the proprioception task despite the fact that tightly fastened straps wrapped around the waist and shoulders were used to mimic, as much as possible, gravitational pull on the body, and resultant input from somatosensory receptors. The addition of visual input, through real-time visual feedback of the simulator’s angular position provided by an MRI compatible potentiometer, was previously proven to be feasible, but not used in the current study as PD effects on static balance performance were previously found to be independent of vision during both real and simulated static balancing tasks (Pasman et al., 2019). Vestibular input was different given the supine position participants were in, however, the fact that similar balance deficits with PD were previously seen between real and simulated balance tasks suggests a non-vestibular origin of the balance deficits (Pasman et al., 2019). Future studies might be able to use electrical vestibular stimulation in order to add artificial vestibular input during the simulated balancing tasks to further investigate vestibular control during these tasks.

4.4.8 Limitations and future directions

Using the simulator in its current form, it is not possible to assess ML balance control. However, while different muscle/joints are involved in controlling AP and ML postural sway, there is no evidence to suggest they are controlled using different cortical or subcortical structures.

The risk of head movements was increased due to the clinical population investigated and the tasks with lower leg motion used. During data collection, head motion was minimized by immobilizing the participants’ head using straps and foam, as well as stabilizing participants’
hips using weights (see methods). Head motion, as assessed by mean volume-to-volume
framewise displacement, was comparable to head motion reported previously (H. Li et al., 2017;
Matar et al., 2019).

The individuals with PD included in this study consisted mostly of individuals with
moderate disease (Table 4.2). Future work is needed to investigate whether the neural substrates
associated with postural instability in individuals with PD change with disease severity. In
addition, included individuals with PD also had relatively good cognition, which was required to
comply with the task requirements. However, cognitive decline contributes to balance deficits in
individuals with PD, and excluding cognitively impaired individuals – as we and many others
have done (Domingos et al., 2015) – may create an incorrect perspective of the severest balance
deficits in PD.

Future work is needed to correlate the neural substrates of balance control with the
balance behaviour exhibited by participants when maintaining balance using the simulator or
during upright standing. This provides the opportunity to investigate whether the neural
substrates associated with postural instability in individuals with PD change with the severity of
their balance deficits as measured using either clinical balance or posturographic measures.

All individuals with PD were tested during their subjectively best clinical ‘on’ condition
as postural instability is often unaltered by dopaminergic medication (Grimbergen et al., 2009).
Future work is needed to investigate the effect of dopaminergic medication on the brain
connectivity patterns associated with balance control by testing individuals with PD during both
the ‘on’ and ‘off’ condition, as previous studies have shown levodopa reduces the utilization of
motor reserve for compensation in individuals with PD (Palmer et al., 2009)
4.5 Conclusion

In conclusion, the results of this study indicate that a network of cortical and subcortical neural structures, including frontal, parietal, and temporal cortices as well as basal ganglia, thalamus, cerebellum, and brainstem, was active during dynamic balancing in healthy older adults. In individuals with PD a qualitatively similar network of cortical and subcortical neural structures was found. However, dynamic balancing was more reliant on motor cortical control in individuals with PD compared to healthy older adults. The increased understanding of the neural substrates contributing to postural instability in PD provided by the novel MRI compatible balance simulator could lead to new targets for improved pharmacological and neurosurgical interventions.
<table>
<thead>
<tr>
<th>General information</th>
<th>Parkinson</th>
<th>Control</th>
<th>Statistics</th>
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<tbody>
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<td>Sample size</td>
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<tr>
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<td>Number of women (%)</td>
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<tr>
<td>Weight (kg)</td>
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<td>65.8 (3.7)</td>
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<td>Fallers (≤ 6 months)</td>
<td>4 (24%)</td>
<td>1 (6%)</td>
<td>$p = 0.335$</td>
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</tbody>
</table>

Table 4.1 Baseline participant characteristics

Data are displayed as mean (SE) or number of persons (percentage between parentheses); Exclusion criteria for individuals with Parkinson’s disease were any of the following medical issues (self-reported during initial telephone screening): presence of atypical parkinsonism; any prior neurosurgical procedures such as deep brain stimulation; excessive levodopa-induced dyskinesias that impaired their balance; botulinum toxin injections in lower leg muscles within the last 3 months; documented proprioceptive loss (e.g., abnormal vibratory sense, altered joint position sense, etc.); dementia precluding informed consent; history of other neurological disease (e.g., stroke, seizures); and medical issues (other than Parkinson’s disease) that influenced their balance. Controls were excluded if during initial phone screening they self-reported any medical conditions that influenced their balance. Participants in both groups were also excluded if they exceeded the height (max height: 182 cm) and weight (max weight participant and balance simulator combined: 136 kg) restrictions of the MRI scanner, and if they had any contraindications precluding them from undergoing MRI scanning. All participants were fluent in English.
<table>
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<th>Age (years)</th>
<th>Disease duration (years)</th>
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<th>Hoehn &amp; Yahr score</th>
<th>Levodopa equivalent dose</th>
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<td>20</td>
<td>2</td>
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<td>16</td>
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**Range** 59-75 1-14 7-46 1-3 150-1450

**Mean** (SE) 67.6 (1.1) 5.8 (0.9) 26.6 (2.8) 664.0 (92.5)

Table 4.2 Clinical characteristics individuals with Parkinson’s disease

PDON, Individuals with Parkinson’s disease; Maximum Unified Parkinson’s Disease Rating Scale motor examination (UPDRS-ME) score is 108; Maximum Hoehn & Yahr (H&Y) score is 5.
<table>
<thead>
<tr>
<th>Cortical</th>
<th>Region of interest</th>
<th>Bilateral</th>
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<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>Primary motor cortex</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Supplementary motor area</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Pre-supplementary motor area</td>
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</tr>
<tr>
<td></td>
<td>Dorsal premotor cortex</td>
<td>Yes</td>
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<tr>
<td></td>
<td>Ventral premotor cortex</td>
<td>Yes</td>
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<tr>
<td><strong>Parietal</strong></td>
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<td>Primary somatosensory cortex</td>
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<td></td>
<td>Superior parietal cortex</td>
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</tr>
<tr>
<td></td>
<td>Inferior parietal cortex</td>
<td>Yes</td>
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<tr>
<td></td>
<td>Precuneus</td>
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<tr>
<td><strong>Frontal</strong></td>
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<tr>
<td></td>
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<tr>
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<tr>
<td></td>
<td>Inferior temporal cortex</td>
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<td>Anterior cingulate cortex</td>
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<td>Posterior cingulate cortex</td>
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<td>Insular cortex</td>
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<td>Pons</td>
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<td>Medulla</td>
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Table 4.3 Regions of interest
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<th>Task</th>
<th>Parkinson</th>
<th>Control</th>
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<tr>
<td>Rest</td>
<td>0.16 (0.01)</td>
<td>0.19 (0.02)</td>
</tr>
<tr>
<td>Proprioception</td>
<td>0.26 (0.05)</td>
<td>0.17 (0.02)</td>
</tr>
<tr>
<td>Static balancing</td>
<td>0.16 (0.02)</td>
<td>0.17 (0.02)</td>
</tr>
<tr>
<td>Dynamic balancing</td>
<td>0.27 (0.03)</td>
<td>0.23 (0.02)</td>
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</tbody>
</table>

Table 4.4 Mean volume-to-volume framewise displacement

Data are displayed as mean (SE)
<table>
<thead>
<tr>
<th>Predictor</th>
<th>$\beta$</th>
<th>SE $\beta$</th>
<th>Wald's $\chi^2$</th>
<th>df</th>
<th>p</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elderly controls – DB task (H-DB)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>5.765</td>
<td>1</td>
<td>0.016</td>
<td>0.049</td>
</tr>
<tr>
<td>H-DB PC-1</td>
<td>0.236</td>
<td>0.277</td>
<td>0.723</td>
<td>1</td>
<td>0.395</td>
<td>1.266</td>
</tr>
<tr>
<td>H-DB PC-2</td>
<td>0.457</td>
<td>0.531</td>
<td>0.740</td>
<td>1</td>
<td>0.390</td>
<td>1.579</td>
</tr>
<tr>
<td>H-DB PC-3</td>
<td>0.814</td>
<td>0.565</td>
<td>2.078</td>
<td>1</td>
<td>0.149</td>
<td>2.258</td>
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<tr>
<td>H-DB PC-4</td>
<td>-0.078</td>
<td>0.622</td>
<td>0.016</td>
<td>1</td>
<td>0.901</td>
<td>0.925</td>
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<td>H-DB PC-5</td>
<td>-0.452</td>
<td>0.709</td>
<td>0.405</td>
<td>1</td>
<td>0.524</td>
<td>0.637</td>
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<tr>
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<td>1.061</td>
<td>3.390</td>
<td>1</td>
<td>0.066</td>
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<td><strong>0.016</strong></td>
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<td>1.383</td>
<td>2.189</td>
<td>1</td>
<td>0.139</td>
<td>7.735</td>
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<td>2.719</td>
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<td>0.019</td>
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<td><strong>0.549</strong></td>
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<td>-1.545</td>
<td><strong>0.504</strong></td>
<td><strong>9.383</strong></td>
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<td><strong>0.002</strong></td>
<td><strong>0.213</strong></td>
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<td>0.185</td>
<td>0.494</td>
<td>0.141</td>
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<td>0.708</td>
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<td>0.860</td>
<td>3.097</td>
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<td>0.078</td>
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<td><strong>2.834</strong></td>
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<td><strong>0.050</strong></td>
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<td>3.606</td>
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<td>0.058</td>
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</tr>
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</table>

Table 4.5 Multiple binomial logistic regression models

$\beta =$ beta coefficient, SE $\beta =$ standard error of beta coefficient, Wald’s $\chi^2 =$ Wald’s chi-square statistic, df = degrees of freedom, p = significance Wald’s $\chi^2$, OR = odds ratio (equal to $\exp(\beta)$). Bolded predictors made a significant contribution to the prediction of the task.
<table>
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<tr>
<th>PC</th>
<th>Connection from</th>
<th>Connection to</th>
<th>From area</th>
<th>To area</th>
<th>Loading</th>
<th>Z-score</th>
<th>Strength RL/PL</th>
<th>Strength DL</th>
<th>Δ Strength</th>
<th>Direction</th>
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</thead>
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<tr>
<td>PC-7</td>
<td>Pons</td>
<td>L cerebellum</td>
<td>BS</td>
<td>CER</td>
<td>0.455</td>
<td>5.810</td>
<td>0.376</td>
<td>0.453</td>
<td>-0.077</td>
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<tr>
<td></td>
<td>R superior frontal ctx</td>
<td>R dorsolateral prefrontal ctx</td>
<td>FRON</td>
<td>FRON</td>
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<td>BS</td>
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<td>L pre-SMA</td>
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<td>R lateral orbitofrontal ctx</td>
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<td>BS</td>
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<td>0.265</td>
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<td>LIMB</td>
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<td>Hemisphere 2</td>
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<td>PC 2</td>
<td>PC 3</td>
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<td>Sign</td>
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Table 4.6 Connections with largest effect on the significant principal components predicting dynamic balance task in elderly controls

PC = principle component, R = right, L = left, ctx = cortex, SMA = supplementary motor area, BS = brainstem, BG = basal ganglia, CER = cerebellum, TEMP = temporal, LIMB = limbic, FRON = frontal, MOT = motor, THAL = thalamus, PAR = parietal
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<th>Connection to</th>
<th>From area</th>
<th>To area</th>
<th>Loading</th>
<th>Z-score</th>
<th>Strength RL/PL</th>
<th>Strength DL</th>
<th>Δ Strength</th>
<th>Direction</th>
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<td>↓</td>
</tr>
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<td>PC-2</td>
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<td>R pallidum</td>
<td>BS</td>
<td>BG</td>
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<td>-2.269</td>
<td>1.147</td>
<td>2.194</td>
<td>-1.047</td>
<td>↑</td>
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<tr>
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<td>BS</td>
<td>BG</td>
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<td>12.051</td>
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</tr>
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<td>R pallidum</td>
<td>BS</td>
<td>BG</td>
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Table 4.7 Connections with largest effect on the significant principal components predicting dynamic balance task in individuals with Parkinson’s disease
PC = principle component, R = right, L = left, ctx = cortex, SMA = supplementary motor area, BS = brainstem, BG = basal ganglia, CER = cerebellum, TEMP = temporal, LIMB = limbic, FRON = frontal, MOT = motor, THAL = thalamus, PAR = parietal
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Table 4.8 Multiple binomial logistic LASSO regression model predicting group membership in the dynamic balance task

DB = dynamic balance, R = right, L = left, ctx = cortex, SMA = supplementary motor area, BS = brainstem, BG = basal ganglia, TEMP = temporal, LIMB = limbic, MOT = motor, β = beta coefficient
Figure 4.1 Experimental set-up of the balance simulator in the MRI environment
Figure 4.2 Effective connectivity network found in healthy older adults during the dynamic balancing task.
Figure 4.3 Effective connectivity network found in individuals with Parkinson’s disease during the dynamic balancing task
Chapter 5: Neural substrates of static and dynamic balance deficits in individuals with Parkinson’s disease

5.1 Introduction

Deficits in static and dynamic balance control are prominent, disabling features of PD (Debû et al., 2018; S. D. Kim et al., 2013), and are associated with an increased risk of falls (Fasano et al., 2017). Unfortunately, treatment interventions currently available for PD, such as levodopa and deep brain stimulation, result in limited improvement, and sometimes even worsening, of static and dynamic balance deficits (Carpenter et al., 2004; D’Andrea Greve et al., 2014; Feller et al., 2019; Johnson et al., 2015; Maurer et al., 2003; J. E. Visser, Allum, Carpenter, Esselink, Limousin-Dowsey, et al., 2008; J. E. Visser, Allum, Carpenter, Esselink, Speelman, et al., 2008; Workman & Thrasher, 2019). The unresponsiveness of balance deficits to dopaminergic treatment, coupled with the relatively late onset of severe postural instability and falls compared to other hallmark symptoms, supports a potential non-dopaminergic contribution to postural deficits in PD (Grimbergen et al., 2009; Morris et al., 2019). However, direct evidence for the neural substrates contributing to postural instability in PD is currently lacking.

Healthy balance control likely involves an integrated network of both cortical and subcortical structures (Takakusaki, 2017). Investigating this integrated network, whether in healthy individuals or clinical populations, is made difficult by the limitations of available functional neuroimaging options. Portable neuroimaging techniques, such as EEG and more recently fNIRS, have been extensively used to record brain activation patterns during a variety of balance tasks in both healthy participants and individuals with PD (Stuart et al., 2018; Wittenberg et al., 2017). While these studies have increased our knowledge of the cortical
control of balance, they have been unable to provide insight into the subcortical regions involved in balance control, including the basal ganglia and brainstem. PET or fMRI scanners allow recording from both cortical and subcortical areas but are limited by the fact that they are almost exclusively horizontally based. Wearable PET scanners have been recently developed (Bauer et al., 2016; Melroy et al., 2017), but are hindered by their poor temporal resolution and interference of the weight of the device with balance control.

Motor imagery of static and dynamic balance tasks has been widely used to address the need for participants to lie supine in the PET or MRI scanner. Several studies have used the motor imagery paradigm to investigate the neural substrates of balance control in healthy young and elderly participants (Bhatt et al., 2018; Ferraye et al., 2014; Gilat et al., 2019; Jahn et al., 2008, 2004; Malouin et al., 2003; Mouthon et al., 2018; Taube et al., 2015; Zwergal et al., 2012), as well as individuals with PD (Gilat et al., 2019; Peterson et al., 2014b). For static balance, in healthy participants, subcortical activation in basal ganglia, thalamus, cerebellum, midbrain and pons was reported, as well as cortical activation in the premotor areas, prefrontal cortex, parietal and limbic areas, and temporal and occipital lobes (Jahn et al., 2008, 2004; Malouin et al., 2003; Mmouthon et al., 2018; Taube et al., 2015; Zwergal et al., 2012). For dynamic balance, subcortical activation in basal ganglia, thalamus, cerebellum, and pons were found, as well as cortical activation in premotor, prefrontal, parietal, limbic, and temporal areas (Bhatt et al., 2018; Ferraye et al., 2014; Mmouthon et al., 2018; Taube et al., 2015). Only one study to date has investigated brain activation during motor imagery of static balance in individuals with PD and found decreased activation in the globus pallidus, the cerebellar locomotor region, and the mesencephalic locomotor region compared to rest (Peterson et al., 2014b).
Using motor imagery to study balance deficits in PD has limitations as the capacity for motor imagery varies greatly among individuals (Saimpont et al., 2015; Zabicki et al., 2019) and declines with age for complex movements (Kalicinski et al., 2015; Saimpont et al., 2013). This is problematic as brain activation amplitudes and patterns differ depending on motor imagery ability (Guillot et al., 2008; van der Meulen et al., 2014; Zabicki et al., 2019). In addition, while individuals with PD can perform motor imagery (Abbruzzese et al., 2015; McInnes et al., 2016), they tend to rely on different motor imagery strategies compared to controls (Poliakoff, 2013), which results in different brain activation patterns (Guillot et al., 2009; Jiang et al., 2015). Finally, although motor imagery and motor execution of the same task share neural substrates; some brain areas are more strongly, or selectively, activated during motor execution of a task compared to motor imagery of the same task, and vice versa (Guillot et al., 2012; O’Shea & Moran, 2017). While motor imagery of balance control may therefore be a useful tool to investigate the neural substrates of balance control in healthy young participants, it may be less suitable for investigating these neural substrates in healthy older participants and individuals with PD.

Recently, we developed and validated a novel MRI compatible balance simulator that can elicit balance behaviour qualitatively similar to that observed during upright standing and detect postural instability in individuals with PD during both static and dynamic balance performance (Pasman et al., 2019). Subsequently, the balance simulator was successfully used in the MRI environment to investigate brain connectivity during simulated balance in healthy older adults and individuals with PD (Pasman et al., 2020 submitted). When participants were asked to maintain equilibrium of the balance simulator during transient perturbations applied to the simulator, effective connectivity analyses revealed a network of cortical and subcortical brain
regions in both the healthy older adults and individuals with PD. However, whereas healthy older adults showed a preference for subcortical over motor cortical control, individuals with PD relied more on cortical motor areas during dynamic balancing (Pasman et al., 2020 submitted). In contrast to dynamic balance, for static balance we were unable to find significant effective connectivity networks in both healthy older adults and individuals with PD.

While brain connectivity analyses identify statistical dependencies or causal interactions between different brain regions, brain amplitude analyses allow insight into hypo- and hyperactivation of discrete brain regions (Appel-Cresswell et al., 2010). Changes in connectivity between healthy older adults and individuals with PD have been found to be independent from changes in brain activation during different motor control tasks (Palmer et al., 2010; Wu et al., 2010; Wu & Hallett, 2005b). Therefore, the assessment of changes in brain activation amplitude during balance-relevant tasks may provide unique insights into the neural substrates involved in postural instability in PD that complement prior evidence based on measures of connectivity (Pasman et al., 2020 submitted) and motor imagery (Bhatt et al., 2018; Ferraye et al., 2014; Jahn et al., 2008, 2004; Malouin et al., 2003; Mountho et al., 2018; Peterson et al., 2014; Taube et al., 2015; Zwergal et al., 2012).

Only one study, to date, has compared brain amplitude activation between healthy participants and individuals with PD during a balance-related task in an MRI scanner (de Lima-Pardini et al., 2017). In this study the neural substrates of anticipatory postural adjustments were investigated in participants performing single leg raises to simulate step initiation. Whereas young healthy participants showed activation of the SMA and sensorimotor cortex during the anticipatory postural adjustments, the individuals with PD lacked a focussed pattern of brain activation (de Lima-Pardini et al., 2017). While anticipatory postural adjustments have an
important role in maintaining balance, they are elicited only when the postural outcome of a movement or event is known in advance, and thus, might involve postural control mechanisms distinct from those involved in the control of static or reactive dynamic balance.

Amplitude analyses in fMRI are typically performed using an event-related or “box-car” design, while prolonged tasks are more amenable to connectivity analyses. We elected to use a “box-car” design, with the assumption that the hemodynamic response would be saturated after many stimuli within a given block, as this is relatively efficient in terms of time required for the task, as we were particularly interested in which regions of the brain were associated with balance control in individuals with PD and healthy older adults.

The aim of the current study was to investigate the neural substrates underlying deficits in static and dynamic balance control in individuals with PD using the newly-validated MRI compatible balance simulator. We applied linear discriminant analysis (LDA) to identify the pattern of brain regions in which activation amplitude best discriminated between healthy older adults and individuals with PD. We hypothesized that increased activation amplitude in motor and parietal cortical regions as well as the cerebellum, and decreased activation amplitude in the basal ganglia and brainstem regions would be found in individuals with PD compared to healthy older adults. Our hypothesis was based on evidence of decreased basal ganglia and brainstem activity during motor imagery of static balance in individuals with PD (Peterson et al., 2014b), and increased premotor-parietal region and cerebellar activation during execution of automatic movements observed in individuals with PD compared to healthy older adults (Wu & Hallett, 2005b).
5.2 Materials and methods

5.2.1 Participants

Eighteen individuals with PD and 19 age-matched elderly controls participated in this study. The participants have been described previously (please refer to Pasman et al., 2020 submitted), as within the same MRI scanning session they performed two separate experimental protocols, one specific for brain connectivity analysis and one specific for brain amplitude analysis. Controls and individuals with PD were excluded if they: had other causes of balance impairment (i.e., ankle injuries/surgery, stroke, conditions affecting vestibular function, diabetes, and conditions resulting in a loss of sensation in the feet and/or lower legs), exceeded the height (max height: 182 cm) and weight (max weight participant and balance simulator combined: 136 kg) restrictions of the MRI scanner, had any contraindications precluding them from undergoing MRI scanning, or were not fluent in English. Additional exclusion criteria for individuals with PD were: atypical parkinsonism, any prior neurosurgical procedures (i.e., DBS), excessive levodopa-induces dyskinesia, botulinium toxin injections in lower leg muscles within the last 3 months, and dementia precluding informed consent. All participants provided written informed consent prior to testing. Experimental procedures were approved by the University of British Columbia’s Clinical Research Ethics Board, the Vancouver Coastal Health Research Institute, and the UBC MRI Research Centre. Three participants were excluded due to: inability to complete the protocol in the MRI scanner (n = 2), or abnormality on their anatomical MRI scan (n = 1). Therefore, 17 individuals with PD and 17 controls were included in the final data set (see Table 5.1 for participant details).

Individuals with PD were examined approximately one hour after intake of their regular antiparkinson medication to coincide with their subjectively best clinical ‘on’ condition. We
purposely opted for this for two reasons: first, balance control is usually not altered much by dopaminergic medication; and second, testing individuals with PD_{ON} avoids any potential confounds of fatigue, anxiety, and cumbersome bradykinesia/rigidity that may accompany the ‘off’ phase. All participants completed a brief balance-oriented medical history survey, including the occurrence of prior falls within the past 6 months. The severity of motor symptoms in individuals with PD was assessed using the H&Y scale (Goetz et al., 2004) and UPDRS-ME (Goetz et al., 2008). All individuals with PD had mild to moderate PD (H&Y stage 1-3) with a disease duration of (mean ± SD) 5.8 ± 3.7 years and UPDRS-ME score of 26.6 ± 11.5 (Table 5.1). The clinical assessment took place on a separate day prior to MRI scanning (range 0-31 days, mean ± SD 9 ± 8 days) when participants got familiar with the experimental tasks outside of the MRI scanner. Balance behaviour was quantified during the lab-based familiarization session for all participants, and deficits in both static and dynamic balance control were seen in individuals with PD_{ON} compared to controls (Pasman et al., 2019).

5.2.2 Apparatus

During the simulated stance trials participants were asked to control a customized balance simulator (“simulator”) (Pasman et al., 2019). Briefly, in the simulator the participant lay supine with their feet placed against a footplate that controlled a free-standing inverted pendulum. The footplate rotated in the anterior-posterior direction about an axis aligned with the ankle joints (Figure 5.1). For each participant individually, ankle stiffness during normal upright quiet stance was estimated using the formula:

\[ S = m \cdot g \cdot h, \]
where \( S = \) load stiffness, \( m = \) body mass (kg), \( g = \) gravitational acceleration constant (9.81 m/s\(^2\)) and \( h = \) height of the participant’s estimated centre of mass (m) (Fitzpatrick et al., 1992). The mass on the simulator was adjusted such that the load stiffness was about 60% of the ankle load stiffness seen during upright quiet stance (range 38-81%, mean ± SD 60 ± 8.7%). At the start of each simulated stance trial the experimenter positioned the simulator approximately 3° from vertical, leaning towards the participant, similar to the position of the body during quiet stance (Loram et al., 2001). Both healthy participants and individuals with PD were able to control the balance simulator after only a few minutes of practice. Tightly-fastened adjustable straps wrapped around the participants’ waist and shoulders were attached to the base of the simulator to prevent participants from being pushed away from the footplate when balancing the simulator and eliminate corresponding movements of the trunk and head. Mechanical stops were used to limit the simulator to a range of ± 17° to ensure participant safety. In addition, the experimenter stood beside the simulator at all times throughout the testing to assist if needed.

5.2.3 Experimental tasks

Participants performed 3 different tasks: SB, DB, and proprioceptive tasks. We utilized a “box-car” design experiment during which participants performed 6 repetitions of a single task and rest block (Figure 5.2A). All tasks and rest periods were performed with eyes closed to prevent the activation of brain areas associated with processing of visual information. In addition, PD effects on simulated SB performance were previously found to be independent of vision (Pasman et al., 2019). During the SB task participants were instructed to keep the simulator as still as possible. During the DB task participants were instructed to keep the
simulator balanced while responding to transient, random, anterior-posterior perturbations applied to the simulator by the experimenter using a hand-held bar. During the proprioceptive task the simulator was moved by the experimenter and participants were instructed to continuously track the passive movement of the ankle joints by moving their left index finger.

Both the rest periods and proprioceptive task were used as reference tasks. Using the proprioceptive task as a reference task ensured brain activation amplitudes seen during the balancing tasks were due to balance related activation, not solely proprioception. While the order of the SB and DB tasks was counterbalance across participants, the proprioceptive task was always presented second to minimize fatigue (Figure 5.2A). In addition, we allowed 2 minutes of rest between each task.

5.2.4 MRI data collection and preprocessing

Collection and pre-processing of the MRI data have been described previously (Pasman et al., 2020 submitted). MRI data were collected on a 3 Tesla scanner (Philips Achieva 3.0T R3.2; Philips Medical Systems, The Netherlands). BOLD sensitive functional images were acquired using an echo-planar T2* sequence (repetition/echo time 2000/30 ms, flip angle 90°, field of view 240 x 240 x 143 mm, matrix size 80 x 80, pixel size 3.0 x 3.0 mm, 36 axial slices of 3.97 mm thickness, 1 mm gap thickness). Whole brain, high resolution, 3-dimensional T1-weighted images were collected to facilitate anatomical localization of activation for each participant. Head motion was minimized using foam wedged between the participants’ head and the head coil, as well as a strap placed around the participants’ head. An MRI safe sandbag, placed on top of the pelvic area, further stabilized participants’ hips during the balancing tasks. Participants were provided with ear plugs and earmuffs to minimize scanner noise. For all three
tasks, each participant performed 6 functional runs. Each run lasted 40 s and consisted of single 20 s task and 20 s rest blocks. For the simulated balance tasks, the run was started as soon as the participant had the simulator in a stable position. After 20 s (i.e., halfway through the run) the experimenter grabbed the simulator to hold it in a neutral position while the participant rested for 20 s until the functional run ended. These brief runs of 40 s were specifically designed so that adequate stabilization of the balance simulator could take place between runs (Figure 5.2A).

The first three volumes from each functional run were discarded for all trials. Preprocessing of the fMRI data included despiking, slice time correction, 3-D isotropic reslicing (3 mm in each dimension), motion correction using rigid body alignment to correct for any major head motion during scanning, and separate motion correction of the brainstem. Head motion was assessed using mean volume-to-volume framewise displacement (Power et al., 2012). As our study is one of the first to investigate the neural substrates underlying deficits in static and dynamic balance control in individuals with PD using fMRI, we chose an exploratory approach and a priori specified 57 ROIs to be included in our analysis (Table 5.2). The choice for the ROIs was mostly based on prior evidence of the brain regions involved in balance control (Bhatt et al., 2018; Ferraye et al., 2014; Jacobs & Horak, 2007; Jahn et al., 2008, 2004; Malouin et al., 2003; MacKinnon, 2018; Mouton et al., 2018; Takakusaki, 2017; Taube et al., 2015; Visser & Bloem, 2005; Zwergal et al., 2012). The 57 ROIs were defined using FreeSurfer software (Harvard, MA, USA), and HMAT atlas for motor areas (Mayka et al., 2006), on the T1-weighted scans. Each of the participants’ anatomical scans was co-registered to the fMRI scan. As spatial normalization of fMRI data to a common space has been demonstrated to result in excessive error (Chen et al., 2009; Ng, Abu-Gharbieh, & McKeown, 2009; Nieto-Castanon et al., 2003; Ozcan et al., 2005), all analysis was done in the individual fMRI space. Next steps included nuisance regression to
remove several sources of variance (e.g., head motion parameters, their temporal derivatives and their squares, white-matter signal, and cerebro-spinal fluid signal), detrending, iterative smoothing, and high-pass filtering of the fMRI signal.

5.2.5 **Brain activation amplitude analysis**

Whole brain statistical parametric maps of t-statistics were constructed using the fmridesign.m and fmrilm.m MATLAB functions from fmristat (Worsley et al., 2002) for the following contrasts: SB vs \{rest, proprioception\} and DB vs \{rest, proprioception\} for each participant (Figure 5.2B). The analysis was restricted to t-statistics of voxels belonging to the 57 preselected ROIs. Many of the selected ROIs were relatively large and activation may only have occurred in a small proportion of voxels in these ROIs. Noise from non-activated voxels could overwhelm the signal from the small proportion of activated voxels when averaging across the entire ROI (Poldrack, 2007). Therefore, we selected a voxel cluster from each ROI that represented the largest change in activation amplitude between different tasks. To accomplish this, for all participants we subdivided each of the 57 ROIs into an optimal number of clusters using a custom written k-medoids clustering algorithm with a geodesic distance parameter. The optimal number of clusters was defined as the number of cluster where the average silhouette value for all voxels, determine by the silhouette.m MATLAB function, was highest. A maximum of 10 clusters were used for ROIs greater than 250 voxels. For smaller ROIs, the maximum number of clusters allowed were scaled from 1 (<20 voxels), 2 (21-30 voxels), 3 (31-40 voxels), 4 (41-50 voxels), to 5 (50-250 voxels). The optimal number of clusters could fall anywhere between 1 and the maximum for each ROI. For ROIs greater than 20 voxels, the representative cluster was defined as the cluster with the largest medoid value and a minimum size of 10
voxels. For SB and DB separately, LDA models were created to determine the brain regions in which activation amplitude best discriminated between healthy older adults and individuals with PD. Since LDA results become more unstable as the number of independent variables increases relative to the sample size, we chose to include 7 predictor ROIs in each LDA model to ensure a 5:1 ratio of samples to independent variables (Ho, 2014). Mann Whitney U statistics were used to select the 7 ROIs that statistically showed the largest group differences (Table 5.3). Given the exploratory nature of the study, and relatively small sample size, we also constructed LDA models with 15 predictor ROIs to ensure that ROIs potentially important for discriminating between individuals with PD and healthy older adults during static balancing were not missed by a more stringent model design. These models were included as supplemental data (see ‘exploratory models’ in results, Figure 5.5 and 5.6, and Table 5.5). By including 15 ROIs we made sure the number of predictors did not exceed the sample size of each group (Sarma & Vardhan, 2018). Assumptions of univariate normality for each predictor ROI were validated using Shapiro-Wilk’s test and inspection of histograms and quantile-quantile plots. Inspection of scatterplots showed no serious nonlinearity between the pairs of independent variables. Examination of Mahalanobis distances showed no indication of multivariate outliers. Box M’s tests demonstrated equality of covariance matrices. Tolerance values were all greater than 0.10, indicating multicollinearity was not an issue. Wilks’ lambda was used to determine if the LDA model significantly differentiated between participant groups and the canonical correlation was used to compute the effect size for the discriminant function. The contributions of each ROI to the discrimination between groups were investigated using both the standardized canonical discriminant function coefficients and the structure matrix (i.e., pooled within-groups correlation between discriminating variables and standardized canonical discriminant functions). To
evaluate the ability of the LDA models to correctly predict the group membership of observed cases, contingency tables and leave-one-out cross validation were used, followed by calculation of the Press Q statistic to examine if the discriminatory power of the classification was statistically better than chance.

5.2.6 Participant baseline characteristics and head motion parameters

For both participant baseline characteristics and head motion parameters, assumptions of normality were validated using Shapiro-Wilk’s test and inspection of histograms and quantile-quantile plots. Baseline characteristics between controls and individuals with PD were compared using independent $t$-tests or Fisher’s Exact Tests where appropriate. Mean volume-to-volume framewise displacements, used to assess head motion, were log-transformed due to non-normality and subsequently analyzed using a 2 x 3 mixed design ANOVA with group (PD, controls) and task (proprioception, SB, DB) as independent variables. For all tasks, Levene’s tests demonstrated equality of variances across groups. In the case where Mauchly’s tests of sphericity ($p < 0.05$) was significant, the Greenhouse-Geisser $\epsilon$ statistic was used. An $\alpha < 0.05$ was used for all statistical comparisons. In case of significant main and interaction effects, post hoc comparisons were performed after adjusting for multiple comparisons using a Bonferroni correction.

5.3 Results

5.3.1 Head motion

For both groups mean volume-to-volume framewise displacement was less than 0.34 mm in all tasks (Table 5.4), and all participants were included in the analysis. Statistical comparison
found no significant main effect of group, or interaction effect between group and task, for mean framewise displacement. However, there was a significant main effect of task on mean framewise displacement ($F_{(2,64)} = 47.022, p < 0.001$) with significantly higher mean framewise displacement in DB (median = 0.331) than SB (median = 0.240) and proprioception trials (median = 0.182), as well as higher mean framewise displacement in SB than proprioception trials.

### 5.3.2 Brain activation during static balancing

The Mann-Whitney U tests indicated statistically significant group differences existed for all 7 ROIs that were entered into the LDA for SB: right amygdala, right pallidum, left caudate, right anterior and posterior cingulate cortices, right primary somatosensory cortex, and right middle temporal cortex (Figure 5.3 and Table 5.3). The conservative LDA model with 7 predictor ROIs significantly differentiated the participant groups ($\chi^2(7) = 21.577, p = 0.003, \text{partial } \eta^2 = 0.223$). The canonical correlation of 0.729 showed that 53% of the variance in the discriminant scores is explained by differences between the two groups. The conservative LDA model correctly classified 76% of the controls and 88% of the individuals with PD_{ON}, for an overall success rate of 82%. Classification results exceeded the classification accuracy expected by chance (Press’ Q = 14.235, p < 0.001). During leave-one-out cross validation, the conservative LDA model correctly classified 76% of the controls and 76% of the individuals with PD_{ON}, for an overall success rate of 76%. Cross validation classification results also exceeded the classification accuracy expected by chance (Press’ Q = 9.529, p < 0.01). The standardized canonical discriminant function coefficients indicate that the predictor ROIs contributing the most to differentiating between individuals with PD_{ON} and healthy older adults
while performing a static balancing task were, in descending order, the: right amygdala, right pallidum, right middle temporal cortex, right anterior cingulate cortex, and right primary somatosensory cortex (Table 5.3). The structure matrix suggests the right amygdala was correlated the strongest with the overall discriminant function (Table 5.3). Of the predictor ROIs contributing the most to the discriminant function, the right amygdala showed higher brain activation amplitudes individuals with PD\textsubscript{ON} compared to controls while the right pallidum, right middle temporal cortex, right anterior cingulate cortex, and primary somatosensory cortex all showed lower activation in individuals with PD\textsubscript{ON} compared to controls (Figure 5.3B).

5.3.3 **Brain activation during dynamic balancing**

The Mann-Whitney U tests indicated there were no statistically significant group differences for any of the ROIs for DB. Irrespective, the 7 ROIs with the lowest Mann-Whitney U statistic values were entered in the conservative LDA for DB: right caudate, left putamen, right anterior and posterior cingulate cortices, right SMA, right superior parietal cortex, and left middle temporal cortex (Figure 5.4 and Table 5.3). The LDA model with 7 ROIs did not significantly differentiate the participant groups ($\lambda = 0.738$, $\chi^2(7) = 8.667$, $p = 0.277$, partial $\eta^2 = 0.096$). The canonical correlation of 0.512 showed that 26% of the variance in the discriminant scores is explained by differences between the two groups. The conservative LDA model with the 7 ROIs correctly classified 59% of the controls and 82% of the individuals with PD\textsubscript{ON}, for an overall success rate of 71%. Classification results exceeded the classification accuracy expected by chance ($\text{Press’ } Q = 5.765$, $p < 0.05$). During leave-one-out cross validation, the conservative LDA model correctly classified 47% of the controls and 59% of the individuals with PD\textsubscript{ON}, for
an overall success rate of 53%. Cross validation classification results did not exceed the classification accuracy expected by chance (Press’ Q = 0.118, p > 0.05).

5.3.4 Exploratory models

For SB, in addition to the original 7 ROIs described above, the following brain regions were also included in the exploratory LDA model with 15 predictor ROIs: right caudate, left accumbens, left cerebellum cortex, right insular cortex, left SMA, as well as the right inferior parietal, inferior temporal, and superior frontal cortices (Figure 5.5 and Table 5.5). The exploratory LDA model with 15 predictor ROIs significantly differentiated the participant groups ($\lambda = 0.285$, $\chi^2(15) = 30.731$, $p = 0.010$, partial $\eta^2 = 0.342$). During leave-one-out cross validation, the exploratory LDA model correctly classified 71% of the controls and 71% of the individuals with PD$_{ON}$, for an overall success rate of 71%, and exceeded the classification accuracy expected by chance (Press’ Q = 5.765, $p < 0.05$).

For DB, the exploratory LDA model with 15 predictor ROIs included the following brain regions in addition to those described above: pons, left caudate, right pallidum, right putamen, left thalamus, left insular cortex, and left superior parietal and lateral orbitofrontal cortices (Figure 5.6 and Table 5.5). The exploratory LDA model with 15 predictor ROIs was also unable to significantly differentiate the participant groups ($\lambda = 0.448$, $\chi^2(15) = 19.693$, $p = 0.184$, partial $\eta^2 = 0.235$).

5.4 Discussion

In the present study we used a novel MRI compatible balance simulator (Pasman et al., 2019) to investigate the neural substrates underlying deficits in static and dynamic balance
control in individuals with PD. Brain regions in which activation amplitude best discriminated between healthy older adults and individuals with PD\textsubscript{ON} while performing a static balance task were the right amygdala, right pallidum, right middle temporal cortex, right anterior cingulate cortex, and right primary somatosensory cortex. Additional areas identified by the exploratory model included the right caudate, left accumbens, left cerebellum cortex, right insular cortex, left SMA, and the right inferior parietal cortex. For the dynamic balance task, no significant LDA models were found that could significantly discriminate between the two groups using either the conservative or exploratory model approach.

In the following sections we will first outline the novel aspects of our experimental design and analysis methods compared to previous work investigating the neural substrates of balance control. Next, we will discuss the neural substrates underlying static balance deficits in individuals with PD\textsubscript{ON}, and possible explanations for the lack of a significant LDA model for dynamic balance. Finally, we will compare our current brain activation amplitude findings to our previous effective connectivity findings, and discuss limitations of the current study.

5.4.1 Novel approaches to investigating the neural substrates of balance deficits in Parkinson’s disease

The balance simulator used in this study is the first of its kind to allow participants to perform static and dynamic balance-related tasks while lying supine in the MRI scanner (Pasman et al., 2019; Pasman et al., 2020 submitted). This represents a significant technical advancement for research aimed at understanding the neural substrates of balance control in healthy and diseased states. Most prior studies used a motor imagery paradigm to investigate the neural substrates of balance control, whether in healthy participants or individuals with Parkinson’s
disease (Bhatt et al., 2018; Ferraye et al., 2014; Jahn et al., 2008, 2004; Malouin et al., 2003; Mouthon et al., 2018; Peterson et al., 2014; Taube et al., 2015; Zwergal et al., 2012). However, motor imagery of automatically controlled tasks, including postural control, is limited as, for instance, the balance disturbances during imagined dynamic balancing tasks are self-generated, and therefore anticipated and no longer truly automatic. In addition, the use of motor imagery is also limited in older adults (Kalicinski et al., 2015; Saimpont et al., 2013; Zapparoli et al., 2013) and individuals with PD (Poliakoff, 2013). Other studies investigating the neural correlates of balance control had participants perform balance-related tasks while supine (de Lima-Pardini et al., 2017; Karim et al., 2014). However, neither of the tasks used by the latter two studies truly simulated free-standing balance. Using the novel MRI compatible balance simulator, we were able to overcome the limitations described above, and, for the first time, investigate, simultaneously, the subcortical and cortical substrates contributing to balance deficits in individuals with PD.

The proprioceptive task was included as part of the reference task for our brain activation amplitude analysis to ensure amplitude changes observed were specific to the more automatic control of balance. Upright standing balance control relies on multiple sensory modalities, including visual, vestibular, and proprioceptive information (Horak, 2006). During the current study, participants were supine and had their eyes closed while performing the balance tasks, limiting both visual and balance-relevant vestibular information, but not somatosensory information from muscle spindle, joint, Golgi tendon organ, and foot sole cutaneous receptors. Participants would likely have mostly relied on proprioceptive information, coming from the muscle spindles in the ankle joint muscles. Given that proprioceptive deficits have been observed in individuals with PD and that dopaminergic medication appears to worsen these deficits
(Carpenter & Bloem, 2011), we tried to control for this potential confounding effect in order to be able to specifically examine brain regions involved in the control of balance. During the proprioceptive task the simulator was moved by the experimenter and participants were instructed to continuously track the passive movement of the ankle joints by moving their left index finger. By including the proprioceptive task as part of the reference task, changes seen in brain activation amplitude during the balancing tasks reflected balance related activation differences.

The fMRI analysis for this study was done in each participant’s native space. This is in contrast to most previous studies investigating the neural substrates of static or dynamic balance control that used univariate whole-brain amplitude analyses and transformed the data to a common template (Bhatt et al., 2018; de Lima-Pardini et al., 2017; Ferraye et al., 2014; Jahn et al., 2008, 2004; Karim et al., 2014; Malouin et al., 2003; Mouthon et al., 2018; Ouchi et al., 1999; Taube et al., 2015; Zwergal et al., 2012). Across functional neuroimaging studies it is customary to transform the images for each participant to match a template brain, such as the brain described by Talairach and Tournoux or the structural template provided by the Montreal Neurological Institute (Brett et al., 2002). However, the more a participant’s brain differs from the template, the more likely the transformation will result in errors (Samanez-Larkin & D'Esposito, 2008). This is especially problematic in populations with increased anatomical variability, such as older adults and individuals with neurological disease (Ng, Abu-Gharbieh, & McKeown, 2009; Samanez-Larkin & D'Esposito, 2008). The spatial normalization of fMRI data has indeed been demonstrated to result in excessive error (Nieto-Castanon et al., 2003; Ozcan et al., 2005), particularly in small subcortical areas such as the basal ganglia and brainstem regions, as we have specifically shown in individuals with PD (Chen et al., 2009; Ng, Abu-Gharbieh, &
Correctly identifying basal ganglia and brainstem regions is important as they are thought to play crucial roles in balance control (Jacobs & Horak, 2007; MacKinnon, 2018; Takakusaki, 2017; Visser & Bloem, 2005). Therefore, we did not spatially normalize each participant’s data to a common space. Instead, the ROIs used were defined for each participant individually using their high-resolution, 3-dimensional T1-weighted anatomical scan in order to account for inter-individual anatomical variability.

Another relatively unique technique used in the current study was the application of cluster analysis to determine the subsection of each ROI that represented the largest change in activation amplitude between the balance and reference tasks. Different methods exist to extract a single-value summary measure from each ROI, with simply taking the ROI mean or median being the most commonly used methods (Poldrack, 2007). However, especially in larger ROIs, inactive or deactivated voxels can greatly affect the ROI mean or median values (Poldrack, 2007). As many of our pre-selected ROIs were relatively large, we used a custom written k-medoids clustering algorithm with a geodesic distance parameter to select a voxel cluster from each ROI that represented the largest change in activation amplitude between different tasks.

Finally, we constructed LDA models to identify the brain regions in which activation amplitude best discriminated between healthy older adults and individuals with PD while performing a static and dynamic balance task. Most commonly, brain activation amplitude analyses are univariate, where each voxel or ROI is analyzed in isolation, and the information provided by spatial patterns of activation is thus not considered (Haynes & Rees, 2006; Ng, Abu-Gharbieh, & McKeown, 2009). This information may be important during our tasks as balance control is thought to involve an integrated network of both cortical and subcortical structures (Takakusaki, 2017). The LDA models aimed to find a linear combination of ROIs that
discriminated between the two groups. Therefore, all included ROIs were taken into account simultaneously which allowed us to identify the combination of ROIs whose activation amplitude best discriminated between the healthy older adults and individuals with PD during the balance tasks.

Overall, the approaches outlined above aimed to increase the validity of our results as they ensured we were able to investigate, simultaneously, the cortical and subcortical structures involved in static and dynamic balance deficits in individuals with PD.

5.4.2 Differences in brain activation amplitude between individuals with Parkinson’s disease and healthy older adults during static and dynamic balancing

For static balance, our conservative LDA model showed that brain activation amplitude is increased in the right amygdala, and decreased in the right pallidum, right middle temporal cortex, right anterior cingulate cortex, and right primary somatosensory cortex in individuals with PD compared to healthy older adults (Figure 5.3 and Table 5.3). We initially limited the number of predictor ROIs entered into the LDA due to our relatively small sample size. However, using our exploratory LDA model we tried to identify additional potentially important predictor ROIs (Figure 5.5 and Table 5.5). The exploratory model indicated that in addition to the increased activation in the right amygdala and decreased activation in the right pallidum and right primary somatosensory cortex, individuals with PD, compared to healthy older adults, showed decreased activation in the left caudate and left cerebellum cortex, as well as increased activation in the left nucleus accumbens, left SMA, right inferior parietal cortex, and right insular cortex during static balancing.
For dynamic balance, both our conservative and exploratory LDA models were unable to discriminate between individuals with PD and healthy older adults (Figure 5.4 and 5.6, and Table 5.3 and 5.5). Of the predictor ROIs entered into the model, the activation amplitude in the left putamen, left middle temporal cortex, right anterior cingulate cortex, and right superior parietal cortex differed the most between group, although none reached univariate statistical significance. Activation amplitude in all four of these ROIs was lower in individuals with PD than healthy older participants.

Our hypothesis was that decreased activation in the basal ganglia and brainstem, as well as increased cortical activation, would be found in individuals with PD compared to healthy older adults during the static and dynamic balance tasks. For static balance, our findings of decreased activation in the right pallidum and left caudate, and increased activation in the left SMA, right inferior parietal cortex, and right insular cortex were consistent with our hypothesis. Observations not predicated by our hypotheses were the decreased activation in the left cerebellum cortex, right primary somatosensory cortex, right anterior cingulate cortex, and right middle temporal cortex, as well as the increased activation in the right amygdala and left nucleus accumbens.

5.4.3 Neural substrates underlying static balance deficits in individuals with Parkinson’s disease

The decrease in activation of the pallidum and caudate we observed in individuals with PDON compared to healthy older participants reflects basal ganglia dysfunction, one of the main features of PD (Grimbergen et al., 2009; Samii et al., 2004). Decreased activation of the right globus pallidus was previously found in individuals with PD during motor imagery of standing
compared to rest (Peterson et al., 2014b). There is widespread recognition that the basal ganglia, which include the pallidum and caudate, play a role in balance control (Jahn et al., 2004; Jacobs & Horak, 2007; Visser & Bloem, 2005). Basal ganglia involvement in static balance has been previously attributed to sensorimotor integration (Visser & Bloem, 2005). During the simulated balance tasks participants had their eyes closed (i.e., no visual information) and balance-relevant vestibular information was limited. Participants would thus have mostly relied on proprioceptive information, the central processing of which by the basal ganglia is thought to be impaired in PD (Konczak et al., 2009), which could explain the lower activation in the basal ganglia during the static balance task. However, due to the incorporation of the proprioceptive task as part of the reference task, it would be unlikely for the decreased basal ganglia activation to only be due to differences in central processing of proprioceptive information between individuals with PD_ON and healthy older adults. Instead, we argue that the lower activation of the basal ganglia also reflects a difference in balance related involvement of these nuclei between the two groups.

The increased activation seen in the left SMA, right inferior parietal cortex, and right insular cortex could be compensatory in nature. In PD, basal ganglia dysfunction may be compensated for by increased activity in other brain areas, including prefrontal, premotor, and parietal areas, as well as the cerebellum (Wu & Hallett, 2005b). This compensatory activity has been suggested to occur during a variety of motor tasks in individuals with PD, including upper limb automatic movements and gait (Gilat et al., 2019; Palmer et al., 2010; Peterson & Horak, 2016; Wu & Hallett, 2005b). Although the majority of these studies investigated individuals with PD ‘off’ medication (Gilat et al., 2019; Palmer et al., 2010; Peterson & Horak, 2016; Wu & Hallett, 2005b), and levodopa may partially normalize the activation (Maillet et al., 2015; Palmer et al., 2009). However, for activity to be considered compensatory it should serve to maintain
optimal behavioural performance (Appel-Cresswell et al., 2010). We did not measure behavioural performance in the MRI-scanner, but quantitative measures of upright standing and simulated static balance performance were collected in all participants in the lab (Pasman et al., 2019) and deficits in static balance performance were observed in the individuals with PD_{ON}. Therefore, compensation from the stronger activation of the SMA, inferior parietal cortex, and insular cortex seems to be incomplete. This could potentially explain the observed decreased activation in the cerebellum and several cortical areas, such as the right primary somatosensory cortex, right anterior cingulate cortex, and right middle temporal cortex in individuals with PD compared to healthy older adults. Alternatively, the decreased activation in the cerebellum and primary somatosensory cortex might be explained by the inclusion of the proprioceptive task as one of the reference tasks in this study. Both the cerebellum and primary somatosensory cortex were previously found to be activated during passive ankle movement in healthy participants, and therefore seems to play a role in the processing of proprioceptive information (Ciccarelli et al., 2005; Francis et al., 2009). Proprioceptive function is impaired in individuals with PD (Carpenter & Bloem, 2011), and the decreased activation of the cerebellum and primary somatosensory cortex may reflect this.

Several of the areas that were found to have lower activation in the individuals with PD_{ON} compared to the healthy older adults have previously been linked to static balance control and impaired functioning of these areas may therefore contribute to the static balance deficits observed. For instance, evidence for involvement of the cerebellum in balance control comes from the observation that cerebellar lesions result in balance disturbances, including increased postural sway during quiet standing (Morton & Bastian, 2004). In addition, increased activation of the cerebellum was found during actual upright standing using a mobile PET system as well as
during static balance motor imagery in both healthy young and older adults (Jahn et al., 2008, 2004; Ouchi et al., 2001, 1999; Zwergal et al., 2012). Furthermore, the anterior cingulate cortex serves to monitor task execution and motor error in order to detect a loss of balance (Bhatt et al., 2018; Goel et al., 2019; Marlin et al., 2014; Sipp et al., 2013; Zwergal et al., 2012).

Unexpectedly, we found increased activation of the amygdala in individuals with PD compared to healthy older adults. The amygdala is important for emotional processing and plays an integral role in fear and anxiety (Janak & Tye, 2015). Fear of falling has been shown to alter balance performance in healthy older adults and individuals with PD (Pasman et al., 2011), and is common in individuals with PD (Bloem, Grimbergen, et al., 2001). Reciprocal connections exist between areas of the brain controlling emotion, including the amygdala, and brain regions involved in postural control, including the vestibular nuclei, the reticular formation, and the basal ganglia (Balaban & Thayer, 2001; Cardinal et al., 2002; Staab et al., 2013). Therefore, the increased activation seen in the amygdala has the potential to affect static balance performance in individuals with PD.

The importance of several non-dopaminergic areas, such as cortical regions, the cerebellum, and amygdala, in the discrimination between individuals with PD_{ON} and healthy older adults during static balance controls supports the idea that postural instability in PD is not just a dopaminergic problem (Grimbergen et al., 2009; Morris et al., 2019). This aligns with prior studies that have found deficits in static balance control individuals with PD_{ON}, when the availability of dopamine is highest, compared healthy older adults, as well as the persistence of static balance deficits in individuals with PD ‘on’ medication compared to ‘off’ medication (e.g., Barbosa et al., 2015; Maurer et al., 2003; Rocchi et al., 2002; Viitasalo et al., 2002) Overall, the
current and previous results emphasize the need for development of other treatment options for postural instability in PD that target non-dopaminergic pathways.

5.4.4 Neural substrates underlying dynamic balance deficits in individuals with Parkinson’s disease

We did not find a significant LDA model able to successfully discriminate between individuals with PD and healthy older participants during the dynamic balance task. One possible explanation could be that none of the predictor ROIs entered in the conservative or exploratory LDA model were relevant for balance. However, previous studies showed increased activation of the pons, putamen, pallidum, thalamus, SMA, superior parietal cortex, anterior and posterior cingulate cortices, and insular cortex during motor imagery of dynamic balance control in healthy participants (Bhatt et al., 2018; Ferraye et al., 2014; Mouthon et al., 2018; Taube et al., 2015). This aligns with evidence that the basal ganglia, which include the putamen and pallidum, play an important role in the gain control of balance correcting responses, as well as proper selection and execution of context-specific balance correcting responses (Jacobs & Horak, 2007; Visser & Bloem, 2005). Additionally, several areas in the pons, including the pontomedullary reticular formation, locus coeruleus, and vestibular nuclei, have previously been linked to balance control (MacKinnon, 2018; Takakusaki, 2017). This is also the case for the thalamus, anterior cingulate, and insular cortex (Goel et al., 2019; Jacobs & Horak, 2007; Marlin et al., 2014; Sipp et al., 2013; Takakusaki, 2017). Therefore, the lack of result cannot be attributed to the predictor ROIs entered into the LDA models not being related to dynamic balance control.

Secondly, the individuals with PD included in this study were all moderately affected (Table 5.1), with most showing no clinical signs of postural instability as indicated by their
scores on the pull test (item 12 on the UPDRS-ME). However, using quantitative measures of balance performance in the lab we were able to detect deficits in these individuals with PD compared to the healthy older adults during simulated dynamic balance (Pasman et al., 2019). Future studies should include more severely affected individuals with PD, especially with more pronounced signs of postural instability.

Another potential explanation is the increased amount of head motion seen during the dynamic balance task compared to the other tasks. Some head motion occurred despite our efforts to minimize head motion as much as possible by immobilizing the participants’ head using straps and foam, as well as stabilizing participants’ hips using weight (see methods). Movement artifacts can result in signal changes and influence study outcomes and interpretation (Havsteen et al., 2017). We are unable to rule out that the larger head motion seen in the dynamic task is a contributing factor to the lack of discriminatory ability of the LDA models in this condition.

Finally, our “box-car” experiment might have been less ideal to investigate the dynamic balance task. During the dynamic balance task participants were instructed to keep the simulator balanced while responding to transient, random, anterior-posterior perturbations applied to the simulator by the experimenter using a hand-held bar. Postural responses typically occur within 80-200 ms of a perturbation of the body for both healthy older adults and individuals with PD (Carpenter et al., 2004). A cortical response, with a maximum over the fronto-central areas, occurs at about 100-200 ms after the perturbation (Adkin et al., 2006). The number of perturbations presented during the functional run was limited with a new perturbation presented every few seconds. Therefore, it was possible that not enough stimuli were presented during the task time to be able to detect a difference in activation from the reference tasks. In contrast,
during static balancing the participants were continuously engaged in the task throughout the functional run. Given the intermittent character of the dynamic task, using an event-related design might have been more suitable.

5.4.5 Brain activation amplitude versus brain connectivity during static and dynamic balance control

While a significant LDA model was found to discriminate between individuals with PD and healthy older adults for static balance, no significant models were found for dynamic balance. In contrast, significant effective connectivity models have been identified for dynamic balance, but not for static balance using the same balance simulator as the current study (Pasman et al., 2020 submitted). One possible explanation for these discrepancies is that although the brain activation amplitude analysis and effective connectivity analysis were performed on data collected from the same participants and during the same MRI scanning session, the data entered into each analysis came from different functional runs. In addition, as pointed out in the introduction, changes in connectivity between healthy older adults and individuals with PD have been found to be independent from changes in brain activation during different motor control tasks (Palmer et al., 2010; Wu et al., 2010; Wu & Hallett, 2005b). Our observations therefore reiterate that the assessment of changes in brain activation amplitude provide unique insights that complements evidence gained based on measures of connectivity.

Results from the current static balance amplitude analysis suggest decreased involvement of subcortical areas, particularly basal ganglia and cerebellum, and increased involvement of certain cortical areas, including the SMA, right inferior parietal, and right insular cortex, in individuals with PD_{ON} compared to healthy older adults. Similarly, our previous effective
connectivity results suggest healthy older adults show a preference of subcortical over motor corticale control networks during dynamic balancing, while dynamic balance control in individuals with PD relies more on networks involving cortical (motor) areas (Pasman et al., 2020 submitted). Thus, during both the static and dynamic balancing tasks, we observed increased involvement of cortical motor and parietal areas, and decreased involvement of subcortical regions, in individuals with PDON compared to healthy older adults.

5.4.6 Limitations

Participants lying supine and having their eyes closed resulted in both balance-relevant vestibular and visual inputs being limited during the simulated balance tasks. However, the effect of PD on simulated static balance performance was previously found to be independent of vision and a non-vestibular origin of balance deficits in PD was suggested by the observation of similar balance deficits during both real and simulated balance tasks (Pasman et al., 2019).

Due to our relatively small sample size only a limited number of predictors could be entered in our LDA models. We tried to partially overcome this by also creating exploratory LDA models with more predictor ROIs entered. While for nearly all the predictor ROIs included in either the static or dynamic balance LDA models previous evidence existed that ROI played a role in postural control, additional areas not included in our models have also been linked balance control. These areas include the midbrain, including the mesencephalic locomotor area, and prefrontal cortex (Bogost et al., 2016; Ferraye et al., 2014; MacKinnon, 2018; Mihara et al., 2008; Sipp et al., 2013; Solis-Escalante et al., 2019; Takakusaki, 2017). Future studies, with larger sample size, would be able to include more balance relevant areas, and have more power to detect differences in activation amplitudes for individual ROIs.
While we recorded balance behaviour in all our participants in the lab prior to MRI scanning, we did not measure their balance behaviour during MRI scanning directly. This would be possible using an MRI compatible potentiometer or accelerometer. Direct recording of balance behaviour during MRI scanning would allow balance performance to be correlated with the brain amplitude and/or connectivity measures determined. This would make it possible to determine whether the increased activation of the cortical areas seen in individuals with PD compared to healthy older adults is indeed due to (partial) compensation, as the increased, compensatory activation would be expected to positively correlate with better balance performance.

5.5 Conclusion

In conclusion, during static balance control a pattern of decreased basal ganglia and cerebellum activation, as well as increased amygdala, premotor, parietal, and insular cortical activation was found to discriminate between individuals with PD\textsubscript{ON} compared to healthy older adults. This suggests static balance control may be more cortically controlled and influenced by fear and anxiety in individuals with PD\textsubscript{ON}. Further studies are needed to verify these findings, as well as further investigate brain activation patterns that may discriminate between individuals with PD and healthy older adults during dynamic balance control.
<table>
<thead>
<tr>
<th>General information</th>
<th>Parkinson</th>
<th>Control</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.6 (1.1)</td>
<td>68.1 (1.3)</td>
<td>p = 0.288</td>
</tr>
<tr>
<td>Number of women (%)</td>
<td>8 (47%)</td>
<td>10 (59%)</td>
<td>p = 0.732</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.7 (1.5)</td>
<td>166.2 (2.2)</td>
<td>p = 0.104</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.2 (3.2)</td>
<td>65.8 (3.7)</td>
<td>p = 0.106</td>
</tr>
<tr>
<td>Fallers (≤ 6 months)</td>
<td>4 (24%)</td>
<td>1 (6%)</td>
<td>p = 0.335</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>5.8 (0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS-ME score</td>
<td>26.6 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&amp;Y score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&amp;Y 1</td>
<td>3 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&amp;Y 2</td>
<td>12 (70%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&amp;Y 3</td>
<td>2 (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiparkinson medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levodopa equivalent dose</td>
<td>664.0 (92.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levodopa/carbidopa</td>
<td>17 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasagiline</td>
<td>6 (35%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pramipexole</td>
<td>2 (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ropinirol</td>
<td>1 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>1 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entacapone</td>
<td>1 (6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.1 Baseline participant characteristics

Data are displayed as mean (SE) or number of persons (percentage between parentheses); Maximum Unified Parkinson’s Disease Rating Scale motor examination (UPDRS-ME) score is 108, maximum Hoehn & Yahr (H&Y) score is 5.
<table>
<thead>
<tr>
<th>Cortical Region of interest</th>
<th>Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>Primary motor cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>Yes</td>
</tr>
<tr>
<td>Pre-supplementary motor area</td>
<td>Yes</td>
</tr>
<tr>
<td>Dorsal premotor cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Ventral premotor cortex</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Parietal</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>Primary somatosensory cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Superior parietal cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Inferior parietal cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Precuneus</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Frontal</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>Superior frontal cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Ventrolateral prefrontal cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Medial orbitofrontal cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Lateral orbitofrontal cortex</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Temporal</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>Superior temporal cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Middle temporal cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Inferior temporal cortex</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Limbic</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Posterior cingulate cortex</td>
<td>Yes</td>
</tr>
<tr>
<td>Insular cortex</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Subcortical</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>Yes</td>
</tr>
<tr>
<td>Caudate</td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>Yes</td>
</tr>
<tr>
<td>Pallidum</td>
<td>Yes</td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Limbic</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>Amygdala</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Yes</td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
</tr>
<tr>
<td>Brainsstem</td>
<td>No</td>
</tr>
<tr>
<td>Midbrain</td>
<td>No</td>
</tr>
<tr>
<td>Pons</td>
<td>No</td>
</tr>
<tr>
<td>Medulla</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 5.2 Regions of interest
Table 5.3 Mann Whitney U test results and linear discriminant analysis models for static and dynamic balancing with 7 ROIs included

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>MW U</th>
<th>MW p</th>
<th>LDA standardized coefficients</th>
<th>LDA rank SC</th>
<th>LDA structure matrix</th>
<th>LDA rank SM</th>
<th>LDA unstandardized coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Static balance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-1.329</td>
</tr>
<tr>
<td>R amygdala</td>
<td>74</td>
<td><strong>0.014</strong></td>
<td>-0.770</td>
<td>1</td>
<td>-0.490</td>
<td>1</td>
<td>-5.709</td>
</tr>
<tr>
<td>R pallidum</td>
<td>85</td>
<td><strong>0.041</strong></td>
<td>0.574</td>
<td>2</td>
<td>0.355</td>
<td>3</td>
<td>5.254</td>
</tr>
<tr>
<td>R middle temporal ctx</td>
<td>77</td>
<td><strong>0.020</strong></td>
<td>0.463</td>
<td>3</td>
<td>0.390</td>
<td>2</td>
<td>6.004</td>
</tr>
<tr>
<td>R primary sensory ctx</td>
<td>71</td>
<td><strong>0.011</strong></td>
<td>0.371</td>
<td>5</td>
<td>0.267</td>
<td>7</td>
<td>2.674</td>
</tr>
<tr>
<td>L caudate</td>
<td>87</td>
<td><strong>0.049</strong></td>
<td>0.114</td>
<td>6</td>
<td>0.280</td>
<td>6</td>
<td>0.771</td>
</tr>
<tr>
<td>R posterior cingulate ctx</td>
<td>83</td>
<td><strong>0.034</strong></td>
<td>-0.091</td>
<td>7</td>
<td>0.302</td>
<td>5</td>
<td>-0.486</td>
</tr>
<tr>
<td><strong>Dynamic balance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-1.885</td>
</tr>
<tr>
<td>R anterior cingulate ctx</td>
<td>92</td>
<td>0.073</td>
<td>0.714</td>
<td>1</td>
<td>0.649</td>
<td>2</td>
<td>3.604</td>
</tr>
<tr>
<td>R superior parietal ctx</td>
<td>92</td>
<td>0.073</td>
<td>0.600</td>
<td>2</td>
<td>0.556</td>
<td>3</td>
<td>5.006</td>
</tr>
<tr>
<td>L putamen</td>
<td>88</td>
<td>0.053</td>
<td>0.301</td>
<td>3</td>
<td>0.652</td>
<td>1</td>
<td>1.996</td>
</tr>
<tr>
<td>R SMA</td>
<td>110</td>
<td>0.245</td>
<td>0.266</td>
<td>4</td>
<td>0.352</td>
<td>6</td>
<td>1.920</td>
</tr>
<tr>
<td>R posterior cingulate ctx</td>
<td>110</td>
<td>0.245</td>
<td>-0.212</td>
<td>5</td>
<td>0.293</td>
<td>7</td>
<td>-1.021</td>
</tr>
<tr>
<td>R caudate</td>
<td>103</td>
<td>0.160</td>
<td>-0.150</td>
<td>6</td>
<td>0.464</td>
<td>5</td>
<td>-0.803</td>
</tr>
<tr>
<td>L middle temporal ctx</td>
<td>89</td>
<td>0.056</td>
<td>0.092</td>
<td>7</td>
<td>0.490</td>
<td>4</td>
<td>0.637</td>
</tr>
</tbody>
</table>

L = left, R = right, ctx = cortex, SMA = supplementary motor area; MW U and MW p = Mann Whitney U statistic and corresponding p-value, bolded when statistically significant with p < 0.05; LDA standardized coefficients = standardized canonical discriminant functions coefficients; LDA rank SC = rank of absolute values of LDA standardized coefficients when sorted in descending order; Structure matrix = pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions; LDA rank SM = rank of absolute values of LDA structure matrix correlations when sorted in descending order; LDA unstandardized coefficients = canonical discriminant function coefficients.
<table>
<thead>
<tr>
<th>Task</th>
<th>Parkinson</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprioception</td>
<td>0.19 (0.16, 0.25)</td>
<td>0.16 (0.13, 0.23)</td>
</tr>
<tr>
<td>Static balancing</td>
<td>0.28 (0.17, 0.38)</td>
<td>0.20 (0.16, 0.25)</td>
</tr>
<tr>
<td>Dynamic balancing</td>
<td>0.33 (0.24, 0.47)</td>
<td>0.32 (0.20, 0.39)</td>
</tr>
</tbody>
</table>

Table 5.4 Volume-to-volume framewise displacement

Data are displayed as median (first quartile, third quartile)
### Table 5.5 Mann Whitney U test results and linear discriminant analysis models for static and dynamic balancing with 15 ROIs included

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>MW U</th>
<th>MW p</th>
<th>LDA standardized coefficients</th>
<th>LDA rank SC</th>
<th>LDA structure matrix</th>
<th>LDA rank SM</th>
<th>LDA unstandardized coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Static balance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Constant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R primary sensory ctx</td>
<td>71</td>
<td>0.011</td>
<td>0.744</td>
<td>1</td>
<td>0.180</td>
<td>10</td>
<td>-0.818</td>
</tr>
<tr>
<td>R insular ctx</td>
<td>105</td>
<td>0.182</td>
<td>0.654</td>
<td>2</td>
<td>-0.210</td>
<td>13</td>
<td>3.504</td>
</tr>
<tr>
<td>L accumbens</td>
<td>103</td>
<td>0.160</td>
<td>-0.594</td>
<td>3</td>
<td>-0.140</td>
<td>5</td>
<td>-6.246</td>
</tr>
<tr>
<td>R inferior parietal ctx</td>
<td>92</td>
<td>0.073</td>
<td>-0.573</td>
<td>4</td>
<td>-0.239</td>
<td>4</td>
<td>-3.838</td>
</tr>
<tr>
<td>R pallidum</td>
<td>85</td>
<td>0.041</td>
<td>0.520</td>
<td>5</td>
<td>0.239</td>
<td>3</td>
<td>4.767</td>
</tr>
<tr>
<td>R amygdala</td>
<td>74</td>
<td>0.014</td>
<td>-0.505</td>
<td>6</td>
<td>-0.329</td>
<td>1</td>
<td>-3.746</td>
</tr>
<tr>
<td>L caudate</td>
<td>87</td>
<td>0.049</td>
<td>0.486</td>
<td>7</td>
<td>0.188</td>
<td>9</td>
<td>3.285</td>
</tr>
<tr>
<td>R posterior cingulate ctx</td>
<td>100</td>
<td>0.131</td>
<td>-0.478</td>
<td>8</td>
<td>-0.206</td>
<td>7</td>
<td>-2.885</td>
</tr>
<tr>
<td>R anterior cingulate ctx</td>
<td>73</td>
<td>0.034</td>
<td>0.344</td>
<td>10</td>
<td>0.203</td>
<td>8</td>
<td>1.834</td>
</tr>
<tr>
<td>R superior frontal ctx</td>
<td>101</td>
<td>0.140</td>
<td>-0.212</td>
<td>12</td>
<td>0.056</td>
<td>15</td>
<td>-1.655</td>
</tr>
<tr>
<td>R caudate</td>
<td>88</td>
<td>0.053</td>
<td>0.146</td>
<td>13</td>
<td>0.160</td>
<td>11</td>
<td>0.897</td>
</tr>
<tr>
<td>R inferior temporal ctx</td>
<td>99</td>
<td>0.112</td>
<td>-0.052</td>
<td>14</td>
<td>0.130</td>
<td>14</td>
<td>-0.629</td>
</tr>
<tr>
<td>R middle temporal ctx</td>
<td>77</td>
<td>0.020</td>
<td>-0.017</td>
<td>15</td>
<td>0.262</td>
<td>2</td>
<td>-0.227</td>
</tr>
<tr>
<td><strong>Dynamic balance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Constant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R anterior cingulate ctx</td>
<td>92</td>
<td>0.073</td>
<td>1.077</td>
<td>1</td>
<td>0.349</td>
<td>2</td>
<td>5.434</td>
</tr>
<tr>
<td>R putamen</td>
<td>115</td>
<td>0.322</td>
<td>-0.931</td>
<td>2</td>
<td>-0.165</td>
<td>12</td>
<td>-5.302</td>
</tr>
<tr>
<td>L thalamus</td>
<td>113</td>
<td>0.290</td>
<td>0.916</td>
<td>3</td>
<td>0.191</td>
<td>9</td>
<td>5.276</td>
</tr>
<tr>
<td>L insular ctx</td>
<td>118</td>
<td>0.375</td>
<td>-0.800</td>
<td>4</td>
<td>0.178</td>
<td>11</td>
<td>-5.127</td>
</tr>
<tr>
<td>R superior parietal ctx</td>
<td>92</td>
<td>0.073</td>
<td>-0.559</td>
<td>5</td>
<td>0.298</td>
<td>3</td>
<td>4.667</td>
</tr>
<tr>
<td>R caudate</td>
<td>103</td>
<td>0.160</td>
<td>-0.551</td>
<td>6</td>
<td>0.249</td>
<td>5</td>
<td>-2.943</td>
</tr>
<tr>
<td>R SMA</td>
<td>110</td>
<td>0.245</td>
<td>0.510</td>
<td>7</td>
<td>0.189</td>
<td>10</td>
<td>3.676</td>
</tr>
<tr>
<td>L middle temporal ctx</td>
<td>89</td>
<td>0.056</td>
<td>0.484</td>
<td>8</td>
<td>0.263</td>
<td>4</td>
<td>3.338</td>
</tr>
<tr>
<td>L caudate</td>
<td>116</td>
<td>0.339</td>
<td>-0.364</td>
<td>9</td>
<td>-0.221</td>
<td>7</td>
<td>-1.616</td>
</tr>
<tr>
<td>L superior parietal ctx</td>
<td>115</td>
<td>0.322</td>
<td>-0.319</td>
<td>10</td>
<td>-0.092</td>
<td>15</td>
<td>-2.603</td>
</tr>
<tr>
<td>R pallidum</td>
<td>113</td>
<td>0.290</td>
<td>0.314</td>
<td>11</td>
<td>0.162</td>
<td>13</td>
<td>2.230</td>
</tr>
<tr>
<td>Pons</td>
<td>113</td>
<td>0.290</td>
<td>0.285</td>
<td>12</td>
<td>-0.193</td>
<td>8</td>
<td>1.798</td>
</tr>
<tr>
<td>L putamen</td>
<td>88</td>
<td>0.053</td>
<td>0.182</td>
<td>13</td>
<td>0.350</td>
<td>1</td>
<td>1.210</td>
</tr>
<tr>
<td>L lateral orbitofrontal ctx</td>
<td>113</td>
<td>0.290</td>
<td>0.102</td>
<td>14</td>
<td>0.249</td>
<td>6</td>
<td>0.497</td>
</tr>
<tr>
<td>R posterior cingulate ctx</td>
<td>110</td>
<td>0.245</td>
<td>-0.060</td>
<td>15</td>
<td>0.157</td>
<td>14</td>
<td>-0.290</td>
</tr>
</tbody>
</table>

L = left, R = right, ctx = cortex, SMA = supplementary motor area; MW U and MW p = Mann Whitney U statistic and corresponding p-value, bolded when statistically significant with p < 0.05; LDA standardized coefficients = standardized canonical discriminant functions coefficients; LDA rank SC = rank of absolute values of LDA standardized coefficients when sorted in descending order; Structure matrix = pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions; LDA rank SM = rank of absolute values of LDA structure matrix correlations when sorted in descending order; LDA unstandardized coefficients = canonical discriminant function coefficients.
Figure 5.1 Experimental set-up of the balance simulator in the MRI environment
Figure 5.2 Functional MRI scanning protocol and analysis steps

Functional MRI scanning (A) experimental protocol with a block design and (B) brain activation amplitude analysis steps.
Figure 5.3 Mean medoid values of the regions of interest entered in the conservative linear discriminant analysis with 7 ROIs for static balancing

Group means and standard errors of (A) and differences in (B) t-statistic medoid values for 7 regions of interest selected to be entered in the linear discriminant analysis for static balancing. Regions of interest are presented from left to right in descending order of the absolute value of their corresponding standardized canonical discriminant functions coefficients. For (A), white bars indicate healthy older adults and black bars indicate individuals with PD.
Figure 5.4 Mean medoid values of the regions of interest entered in the conservative linear discriminant analysis with 7 ROIs for dynamic balancing

Group means and standard errors of (A) and differences in (B) t-statistic medoid values for 7 regions of interest selected to be entered in the linear discriminant analysis for dynamic balancing. Regions of interest are presented from left to right in descending order of the absolute value of their corresponding standardized canonical discriminant functions coefficients. For (A), white bars indicate healthy older adults and black bars indicate individuals with PD.
Figure 5.5 Mean medoid values of the regions of interest entered in the exploratory linear discriminant analysis with 15 ROIs for static balancing

Group means and standard errors of (A) and differences in (B) t-statistic medoid values for 15 regions of interest selected to be entered in the linear discriminant analysis for static balancing. Regions of interest are presented from left to right in descending order of the absolute value of their corresponding standardized canonical discriminant functions coefficients. For (A), white bars indicate healthy older adults and black bars indicate individuals with PD.
Figure 5.6 Mean medoid values of the regions of interest entered in the exploratory linear discriminant analysis with 15 ROIs for dynamic balancing

Group means and standard errors of (A) and differences in (B) t-statistic medoid values for 15 regions of interest selected to be entered in the linear discriminant analysis for dynamic balancing. Regions of interest are presented from left to right in descending order of the absolute value of their corresponding standardized canonical discriminant functions coefficients. For (A), white bars indicate healthy older adults and black bars indicate individuals with PD.
Chapter 6: Conclusions and general discussion

6.1 Overall background and aim

PD is one of the most prevalent neurodegenerative disorders in the world (Pringsheim et al., 2014), with the number of individuals with PD estimated to be between 69 and 248.9 per 100,000 in Canada (Allyson Jones et al., 2012). It is characterized by four hallmark symptoms: rest tremor, rigidity, bradykinesia, and postural instability (Jankovic, 2008). These symptoms are due to degeneration of neurons in the basal ganglia, which include the substantia nigra, striatum (caudate nucleus and putamen), globus pallidus, and subthalamic nucleus. It is well recognized that PD is a hypodopaminergic syndrome (Grimbergen et al., 2009), however, there is evidence for involvement of non-dopaminergic systems in PD as well (Surmeier & Sulzer, 2013). Postural instability and resultant falls are very common in individuals with PD (Fasano et al., 2017; Pickering et al., 2007), even in the early stages of the disease (Hiorth et al., 2013; Mactier et al., 2015; Voss et al., 2012), and they are a major source of morbidity and mortality (Auyeung et al., 2012; Gazibara et al., 2014; Matinolli et al., 2011; Paul et al., 2013; Pickering et al., 2007; Rudzińska et al., 2013a). The pathophysiological processes contributing to postural instability in PD are still largely unknown. Commonly used clinical balance tests, such as the retropulsion test (Nonnekes, Goselink, et al., 2015), the Push-and-Release test (Jacobs et al., 2006), the BBS (Berg et al., 1992), the BESTest (Horak et al., 2009), and the mini-BESTest (Franchignoni et al., 2010), are crude and subjective, and do not give insight into the complex underlying pathophysiological processes of postural instability in PD (Grimbergen et al., 2009). In contrast, static and dynamic posturography provide more objective and quantitative measures of balance and postural instability (Bloem et al., 2003; J. E. Visser, Carpenter, et al., 2008). Many studies have previously investigated static balance deficits in individuals with PD by recording kinetic
and/or kinematic data while participants stood quietly. However, due to the wide variety of static posturography protocols used, and clinical characteristics of individuals with PD investigated, findings across studies have been inconsistent (Hubble et al., 2015; Kamieniarz et al., 2018). Using posturography, deficits in dynamic balance control have also been observed in individuals with PD, including abnormal gain of balance correcting responses, as well as improper selection and execution of context-specific balance correcting responses (Carpenter et al., 2004; Chong, Jones, & Horak, 1999; Dimitrova, Horak, & Nutt, 2004; Dimitrova, Nutt, & Horak, 2004; Horak et al., 2005; Jacobs et al., 2005). Unfortunately, dopaminergic medication and neurosurgical treatments currently used for PD do not alleviate, and may even worsen, the static and dynamic balance deficits (Carpenter et al., 2004; D’Andrea Greve et al., 2014; Johnson et al., 2015; Maurer et al., 2003; J. E. Visser, Allum, Carpenter, Esselink, Limousin-Dowsey, et al., 2008; J. E. Visser, Allum, Carpenter, Esselink, Speelman, et al., 2008; Workman & Thrasher, 2019). Therefore, non-dopaminergic systems are thought to be involved in postural instability in PD (Bohnen & Albin, 2011; Grimbergen et al., 2009; Morris et al., 2019), although direct evidence in humans to substantiate the actual neural mechanisms underlying postural instability in PD is limited.

It is possible to investigate the neural substrates of postural instability in PD using functional neuroimaging. However, the functional neuroimaging technique of choice, fMRI, requires participants to lie supine as MRI scanners are almost exclusively horizontally based. The requirement for participants to lie supine during MRI scanning has been addressed using experimental paradigms such as balance-relevant tasks or motor imagery of static and dynamic balance control. However, these methods have limitations, especially when used with older adults and individuals with PD (de Lima-Pardini et al., Karim et al., 2014; Polliakoff, 2013;
Saimpont et al., 2013). A novel approach to investigating the neural substrates of postural instability in PD is to mimic actual balance performance using a balance simulator. In this thesis, a novel adaptation of the balance simulator paradigm previously utilized by Fitzpatrick et al. (1992) and Loram et al. (2001) is used so that it can be realistically performed within an fMRI scanner. Overall, the general purpose of this thesis was to investigate the pathophysiological processes that contribute to postural instability in individuals with PD by conducting a narrative review of the literature on static balance control in PD, and by investigating the neural substrates contributing to postural instability in individuals with PD using the modified balance simulator in an fMRI scanner.

6.2 Summary of results

6.2.1 Narrative review of static balance in individuals with Parkinson’s disease

The first aim of this thesis was to gain better insight into the current state of knowledge on the specific nature of static balance deficits associated with PD. To address this aim, a review of the literature was conducted to summarize the current evidence for the effect of PD, and the effect of the most common antiparkinson treatment interventions (pharmacological and/or neurosurgical), on the kinetic and kinematic characteristics of quiet, bipedal standing (Chapter 2). The electronic databases MEDLINE (OVID), EMBASE (OVID), and CINAHL were searched for relevant articles in accordance with the PRISMA statement (Liberati et al., 2009; Moher et al., 2009). After screening a total of 2351 records that were identified across all three databases and additional resources, 31 articles were found that quantified static balance for at least 60 s in both individuals with PD and healthy older participants, as well as 8 articles that quantified static balance for at least 60 s in individuals with PD under different pharmacological
and/or neurosurgical treatment conditions. There was a wide variance across studies with respect to the static posturography protocols used, and clinical characteristics of individuals with PD investigated, which made comparing and interpreting results difficult. However, a few consistent findings emerged from the narrative review (a) individuals with PD\textsubscript{OFF} display increased amplitude, velocity, and frequency of COP displacements and trunk sway compared to healthy older adults; (b) individuals with PD\textsubscript{ON} display larger amplitude and velocity, but no difference in frequency, of COP displacements and trunk sway compared to healthy older adults; (c) individuals with PD\textsubscript{ON} display larger amplitude, but no difference in velocity or frequency, of COP displacements compared to individuals with PD\textsubscript{OFF}, confirming that levodopa provides little improvement to quiet standing performance.

6.2.2 Design and validation of a novel balance simulator to investigate postural instability in Parkinson’s disease

The second aim of this thesis was to validate the use of the modified balance simulator (“simulator”) that was designed specifically by our research group for the purpose of studying balance control in individuals with PD and healthy older participants within an fMRI scanner. The simulator was developed to address limitations from experimental protocols previously used to investigate the neural substrates of balance control, including the limitations associated with motor imagery of static and dynamic balance tasks. Chapter 3 described two studies that were completed to validate the use of the simulator. During study 1, individuals with PD\textsubscript{ON} and healthy older adults performed Static\textsubscript{Real} and Static\textsubscript{Sim} trials both with eyes open and eyes closed. AP trunk and simulator angular displacements were recorded using a SwayStar\textsuperscript{TM} device. Individuals with PD\textsubscript{ON} showed larger amplitude, but no difference in frequency, of sway during
both the Static\textsubscript{Real} and Static\textsubscript{Sim} trials compared to the elderly controls. There was no difference in visual dependency during Static\textsubscript{Real} and Static\textsubscript{Sim} between individuals with PD\textsubscript{ON} and the elderly controls, which was consistent with findings from previous studies (Azulay et al., 2002; Barbosa et al., 2015; Bronstein et al., 1990; Mancini et al., 2011; Mirahmadi et al., 2018; Waterston et al., 1993).

Study 2 was designed to try and replicate the static balance results from study 1 and to validate the use of the simulator during dynamic balancing tasks. In study 2, individuals with PD\textsubscript{ON} and healthy older adults performed Static\textsubscript{Real} and Static\textsubscript{Sim} trials, as well as Dyn\textsubscript{Real} and Dyn\textsubscript{Sim} trials, with eyes closed. AP COM and simulator angular displacements were recorded using an OPTOTRAK motion capture system. The Static\textsubscript{Real} and Static\textsubscript{Sim} results from study 1 were replicated in study 2 with similar PD-related changes in static balance observed in real and simulated trials. For dynamic balance, larger peak amplitude, and longer time-to-peak amplitude and velocity of simulator angular displacements were observed during the Dyn\textsubscript{Sim} trials in the individuals with PD\textsubscript{ON} compared to the elderly controls, while no group differences were detected during Dyn\textsubscript{Real} trials. Both studies confirmed that for all participants the simulator was easy to use after only a few minutes of practice and in both groups balance behavior was qualitatively similar when participants were maintaining balance of their body during upright standing and when they were maintaining balance using the simulator while supine. Overall, it was found that the simulator was sensitive enough to detect static and dynamic balance deficits in individuals with PD\textsubscript{ON} compared to healthy older adults. In the case of dynamic balance, the simulator even revealed differences between the individuals with PD\textsubscript{ON} and elderly controls that were not found significant during the real stance condition. Together these findings are important as they demonstrate that the simulator can be used effectively to investigate elements of static
and dynamic balance control, and provides a novel tool for studying the neural substrates of postural instability in PD in combination with fMRI.

6.2.3 Insight into the neural substrates underlying static and dynamic balance deficits in Parkinson’s disease

The third aim of this thesis was to investigate the neural substrates contributing to static and dynamic balance deficits in individuals with PD. To address this aim, individuals with PDON and healthy older participants actively performed simulated static and dynamic balancing tasks while lying supine in an fMRI scanner as part of two separate fMRI experimental protocols. Chapters 4 and 5 covered the fMRI experimental protocol aimed at investigating effective connectivity and brain activation amplitude changes, respectively, during balance control in individuals with PDON compared to healthy older adults.

6.2.3.1 Brain effective connectivity changes during static and dynamic balance in Parkinson’s disease

Balance control is thought to involve an integrated network of both cortical and subcortical brain regions (Takakusaki, 2017). However, to date, analysis of brain connectivity networks has not yet been used to investigate the neural substrates of static and dynamic balance control in individuals with PD compared to healthy older adults. Therefore, in Chapter 4 of this thesis, the effective connectivity networks in individuals with PDON and elderly controls during static and dynamic balancing tasks were determined. Effective connectivity was used as it captures the causal and dynamic influence brain regions exert over one another and reveals the strength and directionality of information flow between regions of the brain (Appel-Cresswell et
Connectivity during the balance tasks was contrasted with connectivity during rest and a passive ankle proprioceptive task to try and identify unique substrates related to the active and automatic control of balance, that are independent and distinct from conscious monitoring of movements about the ankle joints. For static balancing, no significant effective connectivity networks were found in either group. In contrast, for dynamic balancing, a significant effective connectivity network, involving subcortical as well as cortical brain regions, was found for both individuals with PDON and healthy older adults. Decreased connectivity between different cortical motor areas and increased connectivity from the brainstem to several cortical and subcortical areas was observed in healthy older adults during dynamic balance, while individuals with PDON showed increased connectivity associated with cortical motor and parietal areas, and decreased connectivity from brainstem to other subcortical areas.

6.2.3.2 Brain activation amplitude changes during static and dynamic balance in Parkinson’s disease

Previously only two studies investigated brain activation amplitude during balance-related tasks in individuals with PD (de Lima-Pardini et al., 2017; Peterson et al., 2014b). Peterson et al. (2014b) used motor imagery of standing balance in individuals with PD with and without FOG but did not compare individuals with PD to healthy older adults. In contrast, de Lima-Pardini et al. (2017) compared brain activity associated with anticipatory postural adjustments that occur prior to voluntary leg raises between individuals with PD and healthy young adults. It should be noted that anticipatory postural adjustments are thought to be distinct, and have different control mechanisms, from static balance or postural reactions, as they are organized as part of the overall motor control strategy prior to movement initiation (Mackinnon...
et al., 2007). These studies both used univariate brain activation amplitude analyses, as have most other studies investigating the neural substrates of balance control in healthy participants (Bhatt et al., 2018; de Lima-Pardini et al., 2017; Ferraye et al., 2014; Jahn et al., 2008, 2004, 2009; Karim et al., 2014; Malouin et al., 2003; Mouthon et al., 2018; Ouchi et al., 2001, 1999; Peterson et al., 2014b; Taube et al., 2015; Zwergal et al., 2012). However, relying on univariate brain activation does not take into account information provided by spatial patterns of activation (Haynes & Rees, 2006; Ng, Abu-Gharbieh, & McKeown, 2009), which may be important when investigating the integrated network of brain regions involved in balance control (Takakusaki, 2017). Therefore, the study described in Chapter 5 utilized LDA models to determine the combination of brain regions whose activation amplitude best discriminated between the healthy older adults and individuals with PD\(_{ON}\) during static and dynamic balance. With this approach, we found evidence for a significant LDA model for static balance that distinguished individuals with PD\(_{ON}\) from healthy elderly controls. The model was characterized by a pattern of decreased activation in the basal ganglia, cerebellum, primary somatosensory cortex, anterior cingulate cortex, middle temporal cortex, and increased activation in the SMA, inferior parietal cortex, insular cortex, amygdala, and nucleus accumbens. For dynamic balancing, no statistically significant LDA model was found that was able to discriminate between the groups.

6.3 New insights into balance deficits in individuals with Parkinson’s disease

The findings from the narrative review (Chapter 2) as well as the two simulator validation studies (Chapter 3) extended our understanding of the balance deficits in individuals with mild to moderate PD. During both validation studies, we observed larger amplitude of trunk sway in the individuals with PD\(_{ON}\) compared to the elderly controls, while there was no difference in
frequency of trunk sway between the two groups (Pasman et al., 2019). These observations are consistent with evidence from the narrative review that individuals with PD\textsuperscript{ON} display larger amplitude trunk movements compared to healthy older adults (Cruz et al., 2018; Ozinga et al., 2015; Viitasalo et al., 2002). The larger amplitude of postural sway seen in individuals with PD\textsuperscript{ON} may have been due to levodopa-induced dyskinesias, which are involuntary movements that usually occur in individuals with PD after prolonged treatment with levodopa (T. N. Tran et al., 2018). At least one study has shown a significant correlation between mild dyskinesia symptoms, assessed using a clinical dyskinesia rating scale, and sway area during quiet stance in PD\textsuperscript{ON} (Johnson et al., 2015), although this was based on limited data, and has not been a universal finding (Rocchi et al. 2002). Since our validation studies excluded individuals with PD experiencing excessive levodopa-induced dyskinesias that impaired balance it is unlikely that dyskinesias contributed to the larger amplitude of trunk angular displacements observed.

Alternatively, the larger amplitude of postural sway seen in individuals with PD\textsuperscript{ON} may be related to deficits in proprioceptive function in PD. Upright standing balance control relies on multiple sensory modalities, including proprioceptive information (Horak, 2006). Several studies have observed deficits in proprioceptive function in individuals with PD\textsuperscript{OFF}, as well as individuals with PD\textsuperscript{ON} (Carpenter & Bloem, 2011). In addition, dopaminergic medication appears to worsen proprioceptive deficits seen in PD (Carpenter & Bloem, 2011). The proprioceptive impairments found in individuals with PD are most likely due to deficits in the central processing of afferent proprioceptive information (Konczak et al., 2009). First, individuals with PD show normal timing and increased amplitudes of postural responses (Carpenter et al., 2004), while individuals with diabetic polyneuropathy show severely decreased amplitudes of postural responses (Bloem et al., 2000). Second, muscle spindle responses,
recorded using microneurography, are normal in individuals with PD (Proske & Gandevia, 2012). Furthermore, impaired cortical and subcortical processing of proprioceptive information has been demonstrated in individuals with PD using proprioception-related evoked potentials (Seiss et al., 2003), transcranial magnetic stimulation during muscle vibration (Schrader et al., 2008), and PET scanning during muscle vibration (Boecker et al., 1999). Finally, neurons in the (pre)SMA and basal ganglia in primates rendered parkinsonian by MPTP show increased sensitivity and decreased specificity in response to passive limb movements (Escola et al., 2002; Filion et al., 1988). While individuals with PD with self-reported proprioceptive loss (e.g., abnormal vibratory sense, altered joint position sense, etc.) were excluded from participation in the validation studies, proprioceptive function was not objectively verified as part of our experimental protocol (Pasman et al., 2019). Therefore, proprioceptive impairment may have contributed to the larger amplitude of trunk sway we observed in our sample of individuals with PD_{ON} when compared to healthy older adults.

The lack of difference found in frequency of trunk movements between the groups during both validation studies (Pasman et al., 2019) was also in line with evidence from the narrative review which suggested increased velocity of trunk movements (Viitasalo et al., 2002), but no difference in frequency of trunk movements, between individuals with PD_{ON} and healthy older adults (Hill et al., 2016). Increased frequency of postural sway in individuals with PD_{OFF} has previously been linked to rest and postural tremors (Hagiwara et al., 2004; Rocchi et al., 2002), which have a typical frequency between 4 to 7 Hz in PD (Kerr et al., 2008). We applied a 3.5 Hz low-pass filter to the recorded trunk angular displacements specifically to eliminate possible contributions of rest or postural tremors, this could explain the lack of difference in frequency of trunk movements seen between the individuals with PD_{ON} and healthy older adults. Also, since
over 90% of the total power in COP and COM data is found in frequencies below 0.5 Hz (Carpenter, Frank, et al., 2001; Gage et al., 2004), the measure of MPF we used is likely less sensitive to residual high-frequency artefacts due to tremor than measures of mean velocity or 95% power frequency.

During the first validation study, participants performed the StaticSim trials both with and without visual feedback (i.e., with eyes open and eyes closed). Removal of vision during bipedal, quiet stance results in increase amplitude and velocity of trunk sway in healthy older adults (Gill et al., 2001). Previous studies have reported that balance changes following the removal of vision are similar in individuals with PD and healthy older participants (Azulay et al., 2002; Barbosa et al., 2015; Bronstein et al., 1990; Mancini et al., 2011; Mirahmadi et al., 2018; Waterston et al., 1993). Consistent with this prior evidence, the results of the first validation study showed no significant group by vision interactions for quiet stance for individuals with PD_ON compared to elderly controls (Pasman et al., 2019). Given the lack of evidence for increased visual dependency in individuals with PD_ON, and to prevent the activation of cortical areas associated with visual information processing, participants performed tasks only with eyes closed during the second simulator study and subsequent fMRI experiments.

The vestibular system, located in the inner ear, detects both linear and angular accelerations of the head. Balance-relevant vestibular information was therefore limited during the simulated balance tasks as participants were lying down, and, any head movement was decoupled from movement of the simulator. Evidence has shown that individuals can rapidly adjust for incongruent vestibular information by down-weighting the contributions of vestibular input to the control of balance (Fitzpatrick et al., 1994; Luu et al., 2012). While there is some evidence for vestibulo-spinal reflex abnormalities in individuals with PD (P. F. Smith, 2018), the
fact that similar balance deficits with PD were seen between the Static Real and Static Sim conditions suggests a non-vestibular origin for the observed static balance deficits in our sample of individuals with PD ON. In addition, recent, preliminary work from our research group suggests there is no difference in vestibular control of static balance in individuals with PD ON compared to healthy older adults (Tisserand et al., 2020), and that stochastic vestibular stimulation has little effect on improving static balance deficits in individuals with PD ON (S. Tran et al, 2018).

With both visual and vestibular inputs being limited during the simulated balance trials, participants would have mostly relied on somatosensory information, including proprioception, to perform the tasks. As outlined above, individuals with PD exhibit impairments of proprioceptive function which are thought to worsen under levodopa treatment (Carpenter & Bloem, 2011). While we excluded individuals with PD self-reporting proprioceptive loss, we did not objectively test proprioceptive function during our experiment. Any existing proprioceptive deficits in our participants could have influenced performance during both Static Real and Static Sim and contribute to the observed differences between the individuals with PD ON and the elderly controls during both static balance conditions.

Other findings from the narrative review add to our current understanding of static balance deficits in PD as well. First, there is converging evidence that individuals with PD OFF show increased amplitude, velocity, and frequency COP displacements and trunk movements compared to healthy older adults. Second, levodopa does not improve, and may even aggravate, static balance deficits in individuals with PD ON. This supports the hypothesis that impairments in non-dopaminergic pathways are part of the pathophysiology underlying postural instability in PD (Bohnen & Albin, 2011; Grimbergen et al., 2009; Morris et al., 2019). This confirmation emphasizes that in order to successfully treat postural instability in PD new non-dopaminergic
targets need to be investigated. The simulator developed and validated in this thesis could contribute to future identification of these potential new treatment targets. Third, the narrative review of this thesis was the first to summarize the evidence for the effect of neurosurgical treatments on static balance control in PD from studies using a trial duration of at least 60 s. Due to the limited number of studies available, and wide disparities in methods and findings, the results should be considered largely inconclusive (Hagiwara et al., 2004; Johnson et al., 2015; Maurer et al., 2003; Rocchi et al., 2002; Vallabhajosula et al., 2015). There was only anecdotal evidence that unilateral pallidotomy does not affect static balance control (Hagiwara et al., 2004). In addition, the results for the effect of STN and Gpi DBS on static balance control were inconsistent. Some studies found no difference (Johnson et al., 2015; Vallabhajosula et al., 2015), one found increased sway (Maurer et al., 2003), and another found decreased sway (Rocchi et al., 2002). The discrepancies in findings may have been due to differences in electrode localization (i.e., STN vs Gpi). However, STN and Gpi DBS have also been shown to provide no improvement, and sometimes even aggravation, of dynamic balance control in individuals with PD (St George et al., 2012; J. E. Visser, Allum, Carpenter, Esselink, Limousin-Dowsey, et al., 2008; J. E. Visser, Allum, Carpenter, Esselink, Speelman, et al., 2008). Given the evidence for impairments in non-dopaminergic pathways contributing to postural instability in PD, other DBS targets should be investigated. One such target is the PPN, which has connections with the basal ganglia and limbic areas, thalamus, cerebellum, brainstem, spinal cord, and cerebral cortex (Alam et al., 2011). The effect of unilateral or bilateral PPN DBS on neurophysiological parameters of gait and gait initiation has been investigated in several studies, although findings have generally been inconclusive (Collomb-Clerc & Welter, 2015; Snijders et al., 2016). In contrast, studies investigating the effect of PPN DBS on balance control have
mostly used the pull test as an outcome measure (Golestanirad et al., 2016; Wang et al., 2017), which may not be sensitive or reliable enough to detect a clinically meaningful change (Munhoz et al., 2004). During the narrative review search only two studies were identified that investigated the effect of PPN DBS on static balance control in PD (Perera et al., 2018; Yousif et al., 2016), one of which reported using a trial duration of at least 60 s (Yousif et al., 2016). However, this study was excluded from the review as the four individuals with PD investigated had both bilateral PPN and STN DBS electrodes implanted, and STN DBS was turned ‘on’ during all trials. Interestingly, when PPN DBS was turned ‘on’ in addition to the STN DBS, during eyes closed trials, sway path length increased (Yousif et al., 2016). Overall, further work is needed to investigate, using posturography, whether PPN DBS can improve static and/or dynamic balance deficits in individuals with PD (Thevathasan et al., 2018).

There is extensive evidence that individuals with PD display impaired feet-in-place postural responses to multi-directional support surface perturbations (Carpenter et al., 2004; Dimitrova, Horak, & Nutt, 2004; Dimitrova, Nutt, & Horak, 2004; Horak et al., 2005; Jacobs et al., 2005; J. E. Visser, Allum, Carpenter, Esselink, Limousin-Dowsey, et al., 2008; J. E. Visser, Allum, Carpenter, Esselink, Speelman, et al., 2008), or perturbations are applied to the trunk (Di Giulio et al., 2016). In addition, levodopa does not alleviate these deficits and may even worsen some of the postural control changes in individuals with PD (Carpenter et al., 2004; Di Giulio et al. 2016; Horak et al., 1996). During the second validation study, we observed larger peak amplitude, and longer time-to-peak amplitude and velocity of simulator angular displacements during the Dyn\textsuperscript{Sim} trials in the individuals with PD\textsubscript{ON} compared to the elderly controls, while no group differences were detected during Dyn\textsubscript{Real} trials (Pasman et al., 2019). The lack of group differences seen for Dyn\textsubscript{Real} conflicted with previous observations of larger peak AP sway in
response to a forward pull of the body at shoulder level in individuals with PD\textsubscript{ON} (Di Giulio et al., 2016). Although the studies by Pasman et al. (2019) and Di Giulio et al. (2016) used similar perturbation forces and included individuals with PD with similar disease severity and duration, there were some notable methodological differences. First, Di Giulio et al. (2016) applied the perturbation to the shoulder while we applied it at waist level. Second, Di Giulio et al. (2016) delivered the perturbation using two force-feedback-controlled motors, in contrast, during the second validation study the perturbations were applied manually, although under online monitoring of perturbation force and magnitude. Third, peak sway was calculated differently in each study. Finally, Di Giulio et al. (2016) did not report whether participants had their eyes open or closed during testing. During the simulator validation study, participants had their eyes closed. However, previous work showed no effect of vision on postural responses (Carpenter et al., 1999). Irrespective, it is important to have shown that differences in dynamic balance control between individuals with PD and elderly controls could be detected with the simulator, and this approach may be more sensitive to certain balance control changes with PD than during real balance because during the simulated dynamic balance task participants are mostly relying on proprioceptive information, which is impaired in individuals with PD, while during upright standing balance-relevant vestibular information is also available.

### 6.4 Neural substrates of postural instability in individuals with Parkinson’s disease

Direct comparison between the connectivity results (Chapter 4) and the brain activation amplitude results (Chapter 5) is difficult as we found significant effective connectivity models only for dynamic balance, and a pattern of brain activation amplitude differences discriminating between individuals with PD\textsubscript{ON} and healthy older adults only for static balance. These
discrepancies between the connectivity and amplitude analyses may be surprising but not completely unexpected, considering connectivity differences between healthy older adults and individuals with PD have been found to be independent from changes in brain activation during different motor control tasks (Palmer et al., 2010; Wu et al., 2010; Wu & Hallett, 2005b). Our observations therefore reiterate that the assessment of changes in brain activation amplitude provide unique insights that complements evidence gained based on measures of connectivity. Irrespective, there were some common features of the results of our connectivity and amplitude studies that help to improve our understanding of the neural substrates of postural instability in PD.

The effective connectivity analysis described in Chapter 4 showed that for both individuals with PD\textsubscript{ON} and healthy older adults a network consisting of cortical and subcortical brain regions was involved in dynamic balance control. These findings align with the current view that balance control involves an integrated network of cortical and subcortical areas (Jacobs & Horak et al., 2007; MacKinnon, 2018; Takakusaki, 2017). We observed qualitative differences between the dynamic balance effective connectivity networks for healthy older adults and individuals with PD\textsubscript{ON}. In healthy older adults there was decreased connectivity between different cortical motor areas and increased connectivity from the brainstem to several cortical and subcortical areas. In contrast, individuals with PD\textsubscript{ON} showed increased connectivity associated with cortical motor and parietal areas, and decreased connectivity from brainstem to other subcortical areas. The qualitative observations were supported by the results from a quantitative analysis that showed which connections relevant for dynamic balance best discriminated between groups. Individuals with PD\textsubscript{ON} had unique decreased connectivity from the midbrain to left nucleus accumbens, absent connections from the left anterior cingulate
cortex to left caudate and from the right to the left insular cortex, and increased instead of decreased connectivity from the left dorsal premotor area to the left pre-SMA and right middle temporal cortex to right lateral orbitofrontal cortex compared to the elderly controls. Overall, the effective connectivity results suggest healthy older adults show a preference of subcortical over motor cortical control networks during dynamic balancing, while dynamic balance control in individuals with PD relies more on networks involving cortical (motor) areas.

Results from the static balance amplitude analysis also suggest decreased involvement of subcortical areas, particularly basal ganglia and cerebellum, and increased involvement of certain cortical areas, including the SMA, right inferior parietal, and right insular cortex, in individuals with PD_{ON} compared to healthy older adults. Thus, during both the static and dynamic balancing tasks, we observed increased involvement of cortical motor and parietal areas in individuals with PD_{ON} compared to healthy older adults. Increased cortical involvement has previously been observed in individuals with PD during various other motor tasks, including upper limb automatic movements and gait (Gilat et al., 2019; Palmer et al., 2010; Peterson & Horak, 2016; Wu & Hallett, 2005b). However, the majority of these studies investigated individuals with PD_{OFF} (Gilat et al., 2019; Palmer et al., 2010; Peterson & Horak, 2016; Wu & Hallett, 2005b), and levodopa may partially normalize the activation (Maillet et al., 2015; Palmer et al., 2009). The increased involvement of cortical brain regions is often thought to compensate for impaired function of the basal ganglia (Palmer et al., 2009; Wu & Hallett, 2005b). However, for activity to be considered compensatory it should serve to maintain optimal behavioural performance (Appel-Cresswell et al., 2010). We did not measure behavioural performance in the MRI-scanner, but quantitative measures of upright standing and simulated static balance performance were collected in all participants in the lab (Pasman et al., 2019) and deficits in static balance
performance were observed in the individuals with PD. Therefore, compensation from the stronger activation of the SMA, inferior parietal cortex, and insular cortex seems to be incomplete. This could potentially explain the observed decreased activation in the cerebellum and several cortical areas, such as the right primary somatosensory cortex, right anterior cingulate cortex, and right middle temporal cortex in individuals with PD compared to healthy older adults. The increased cortical involvement is consistent with the ‘posture second strategy’ observed in individuals with Parkinson’s disease, whereby engagement in a mental task (e.g., mental arithmetic) results in disproportionate decreases in balance performance (Bloem et al., 2006).

For both static and dynamic balance control, the basal ganglia contributed to the discrimination between the individuals with PD\textsubscript{ON} and elderly controls. During static balance the activation of the caudate and pallidum was decreased. During dynamic balancing a connection from the left anterior cingulate to the left caudate was absent in individuals with PD\textsubscript{ON}, while it was present in healthy older adults. One of the neuropathological hallmarks of PD is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to a shortage of dopamine in the striatum (caudate nucleus and putamen) (Grimbergen et al., 2009; Samii et al., 2004). The basal ganglia are thought to play a role in balance control through sensorimotor integration, which is important for both static and dynamic balance control, as well as gain control of balance correcting responses, which is important for dynamic balance control (Jacobs & Horak, 2007; Visser & Bloem, 2005). With little sensory-integration required during the simulator tasks (which were performed with eyes closed and the head fixed while lying supine), the altered basal ganglia involvement between groups was more likely to be associated with impairments in the central processing of proprioceptive information in PD (Konczak et al.,
However, by including a proprioceptive task as part of the reference task for both our connectivity and brain activation amplitude analyses we tried to account for this potential confounding effect. Therefore, the contribution of the basal ganglia to discriminate between the individuals with PD\textsubscript{ON} and elderly controls was unlikely to only be due to differences in central processing of proprioceptive information, but also reflects a difference in balance related involvement between the groups, and/or integration with other functions such as emotion.

The amygdala plays an integral role in emotional processing including fear and anxiety (Janak & Tye, 2015). Reciprocal connections exist between areas of the brain controlling emotion, including the amygdala, and brain regions involved in postural control, including the vestibular nuclei, the reticular formation, and the basal ganglia (Balaban & Thayer, 2001; Cardinal et al., 2002; Staab et al., 2013). The amygdala was the most important contributor to group discrimination between individuals with PD\textsubscript{ON} and healthy older adults during static balance control, with increased activation seen in the individuals with PD\textsubscript{ON}. While not contributing to group discrimination during the dynamic balance task, qualitative comparison of the effective connectivity networks indicated connections received by the amygdala differed between healthy older adults and individuals with PD\textsubscript{ON}. These observations are relevant as fear of falling is common in individuals with PD (Bloem, Grimbergen, et al., 2001) and fear and anxiety have been shown to alter balance performance in healthy older adults and individuals with PD (Pasman et al., 2011).

The anterior cingulate cortex, insular cortex, middle temporal cortex, and nucleus accumbens were all involved, to some degree, in discriminating between groups during both static and dynamic balance control. The anterior cingulate cortex plays a role in monitoring task execution and motor error in order to detect a loss of balance (Bhatt et al., 2018; Goel et al.,
2019; Marlin et al., 2014; Sipp et al., 2013; Zwergal et al., 2012). Both the insular cortex and temporal cortex are thought to belong to the parieto-insular vestibular cortex, an area with strong connections with other vestibular-related cortical areas and receiving converging sensory inputs (Indovina et al., 2015; Takakusaki, 2017), that has a role in sensory integration during postural tasks (Jacobs & Horak, 2007).

6.5 Overlap between neural substrates of postural instability and gait difficulty in individuals with Parkinson’s disease

Postural instability and gait impairments are both prominent features of PD and frequently lead to falls (Fasano et al., 2017; Morris et al., 2019). They are often considered together under the broader term of “postural instability and gait difficulty”, or PIGD for short (Debû et al., 2018), and PIGD-dominant PD is recognized as one of several distinct subtypes of PD (Thenganatt & Jankovic, 2014). There are various reasons why combining postural instability and gait impairments together may be inappropriate. First, while postural instability and gait impairments often co-occur, this is not always the case, i.e., some individuals with PD may experience gait impairments without significant balance deficits, while others may experience balance deficits without significant gait impairments (Debû et al., 2018). Second, using the overarching term PIGD implies that postural instability and gait impairments share common underlying mechanisms and will thus respond to the same treatment (Debû et al., 2018).

However, in a cohort of 104 individuals with PD, levodopa was found to worsen static balance control, while it did not impair or change balance control during walking (Curtze et al., 2015). Additionally, measures of postural sway could not predict spatial or temporal measures of gait in individuals with PD_{OFF}, which suggests a relative independence of the neural control of static
balance and gait (Horak et al., 2016). One type of gait impairment in PD that is common and particularly disabling is freezing of gait (FOG), which is described by individuals with PD as their feet feeling “glued to the floor” (Snijders et al., 2016). The frequent co-occurrence of postural instability and FOG has raised the question whether these two phenomena have a shared pathophysiology (Nonnekes, de Kam, et al., 2015). Bekkers, Dijkstra, et al. (2018) suggested three possible relationships between postural instability and FOG: (1) they are two independent phenomena, with no shared common neural mechanisms and no causal relationship; (2) they are two independent phenomena, but there could be behavioural interference, i.e., postural instability may be a consequence of FOG, and vice versa; (3) they are overlapping phenomena, with a shared underlying pathophysiology.

A review of the literature that compared individuals with and without FOG across different domains of balance control (i.e., quiet stance, reactive postural control, anticipatory postural adjustments, dynamic balance that included turning, self-initiated stepping, and voluntary alternating weight-shifting during stepping in place) showed that the largest differences between the two groups were seen for dynamic balance tasks and anticipatory postural adjustments, while there was less evidence for deficits in static balance or reactive postural control in FOG (Bekkers, Dijkstra, et al., 2018). Overall, evidence did not point to one of the three proposed models being highly favored over the others. Instead, there was some evidence for postural instability and FOG to be independent, but also evidence for components of each phenomenon to mutually reinforce each other, as well as evidence for at least some shared underlying pathophysiology (Bekkers, Dijkstra, et al., 2018).

While the review from Bekkers, Dijkstra, et al. (2018) provided valuable insight into whether there is evidence for a shared pathophysiology between FOG and postural instability,
most of the evidence provided was based on studies investigating the differences between individuals with and without FOG at a neurophysiological level. However, several previous studies have looked at the neural substrates underlying FOG (Bharti et al., 2019; Bluett et al., 2019; Gilat et al., 2019) and comparing the findings from these studies with the results from the brain effective connectivity and brain activation amplitude analyses described in this thesis (Chapters 4 and 5) could shed more light on whether there is overlap in the neural substrates underlying both postural instability and FOG. Widespread structural and functional impairments in cortical as well as subcortical brain regions have been found in individuals with PD that experience FOG (Bharti et al., 2019). Studies investigating the neural substrates underlying FOG during task-based fMRI have frequently used motor imagery of gait to do so (Gilat et al., 2019).

During motor imagery of gait, individuals with PDoFF that experience FOG showed altered activation of the mesencephalic locomotor region, cerebellum, basal ganglia, as well as prefrontal, motor, premotor, sensory cortices, and anterior cingulate compared to healthy older adults (Maillet et al., 2015; Peterson et al., 2014a; Snijders et al., 2011). One study found the reduced activation in the primary motor cortex, basal ganglia, thalamus, and cerebellum in individuals with PDoFF with FOG to be restored by levodopa (Maillet et al., 2015). In addition, in individuals with PDoFF who experience FOG increased activation in the mesencephalic locomotor region and decreased activation of the putamen were observed compared to individuals without FOG (Peterson et al., 2014b; Snijders et al., 2011). Recently, instead of motor imagery of gait, a virtual reality paradigm has been used where participants navigate a virtual course with triggers that commonly induce FOG (e.g., narrow doorways) from a first-person perspective using foot-pedals to control their ‘walking’ (Naismith & Lewis, 2010; Shine et al., 2013). This task is more comparable to the simulated balance tasks used throughout this
thesis as the virtual reality paradigm does not rely on motor imagery and participants perform stepping motions that require direct involvement of sensorimotor regions and result in at least some afferent information. Shine et al. (2013) used the virtual reality paradigm to compare cortical and subcortical activation amplitudes observed during periods of motor arrests with those observed during effective walking within the same individuals with PD off in the fMRI scanner. The motor arrests were associated with increased activation of bilateral dorsolateral prefrontal cortices, posterior parietal cortices, and anterior insular cortices, together with decreased activation in bilateral sensorimotor cortices, caudate head, anterior thalamus, globus pallidus internus, subthalamic nucleus, and mesencephalic locomotor region (Shine et al., 2013).

While the differences in methodology (i.e., motor imagery of gait vs virtual reality with foot tapping vs simulated balance) and participants investigated (i.e., PD with FOG vs PD without FOG vs healthy controls, medication status, other clinical characteristics) should be taken into account, there seems to be some overlap in brain regions involved in FOG and postural instability. First, this thesis found evidence for decreased activation of the basal ganglia in individuals with PD on during balance control. Similarly, the studies investigating FOG also observed decreased activation of the basal ganglia (Maillet et al., 2015; Peterson et al., 2014a; Shine et al., 2013), although activation may have been in part restored by levodopa (Maillet et al., 2015). As we did not investigate individuals with PD off in this thesis, we cannot confirm if the decrease in activation of the basal ganglia would have been more prominent between individuals with PD off and healthy older adults. Second, altered activation of several cortical areas was observed in individuals with PD in studies investigating FOG as well as during the static and dynamic balance tasks performed in this thesis (Maillet et al., 2015; Shine et al., 2013; Snijders et al., 2011). A recent meta-analysis that combined brain activation data from several
studies investigating gait in PD noted that lower activation of the SMA in individuals with PD during gait compared to healthy older adults was one of the most consistent findings (Gilat et al., 2019). Interestingly, we observed increased activation amplitude in the SMA in individuals with PD_ON compared to healthy older adults during static balance and increased effective connectivity between motor cortical areas during dynamic balance. However, as pointed out above, the discrepancy in results could be due to a variety of differences between our studies and the studies investigating FOG. Similarly, we observed lower activity in the cerebellum during static balance control in individuals with PD, in contrast, the recent meta-analysis found that gait in PD was consistently associated with increased cerebellum activation, specifically in the cerebellar locomotor region (Gilat et al., 2019). Finally, the mesencephalic locomotor region was an area found to be differentially activated in individuals with FOG, although the direction of change varied among studies. Snijders et al. (2011) were the first to observe an increase in this region in individuals with FOG compared to those without FOG. However, Shine et al. (2013) found the mesencephalic locomotor region to show decreased activation when motor arrests are compared to effective walking in individuals with PD_OFF. While we did not see increased or decreased activation in the midbrain during static balance control, we did observe a decrease in strength in several connections coming from the midbrain going to other subcortical areas in individuals with PD_ON during the dynamic balancing task. It should be noted that these connections were not part of the dynamic effective connectivity network for healthy older adults and were not found to contribute to discrimination between the two groups during the quantitative group comparison. In addition, the mesencephalic locomotor region is only one smaller region, composed of the cuneiform nucleus and PPN, in the midbrain. Therefore, we cannot be certain if the changed connections in individuals with PD coming from the midbrain, were related to this particular
subregion. Interestingly, previous work observed that dynamic balance control and gait activate different parts within the mesencephalic locomotor region, with the activation during dynamic balance located anterior, lateral, and rostral compared to the gait-related activation (Ferraye et al., 2014; Snijders et al., 2011). Future studies, using the balance simulator, should further investigate the involvement of the mesencephalic locomotor regions during balance control.

6.6 Limitations

The sample sizes in the studies of this thesis were relatively small, especially the sample sizes for the MRI studies (17 participants in each group). The small sample sizes were in part due to difficulty in recruiting participants that would meet the height and weight restrictions that had to be imposed due to the maximum total weight of 300 lbs. the MRI table would allow. The results of the studies presented in this thesis should be confirmed using larger group sizes. This may require, especially for MRI studies, a multi-center approach. This will in turn result in additional challenges, such as the need for multiple identical versions of the simulator that will fit each center’s MRI table dimensions, as well as performing data analysis on fMRI signals recorded by different MRI scanners.

The individuals with PD that volunteered to participate in the studies for this thesis generally had mild to moderate symptoms (H&Y stage 1 to 3), although a few suffered from severe postural instability. Despite this, we were able to detect differences in static and dynamic balance control between these moderately affected individuals with PD and the elderly controls. Future work is needed to investigate whether the neural substrates associated with postural instability in individuals with PD change with disease severity. In addition, our studies excluded participants with poor cognition, to ensure they would be able to comply with the task
requirements. However, cognitive decline contributes to balance deficits in individuals with PD, and excluding cognitively impaired individuals may limit the generalizability of our results to include those that experience the most severe balance deficits in PD.

Individuals with PD were only tested while in the ‘on’ medication state during this thesis. This was purposefully done in order to investigate levodopa-unresponsive balance deficits. However, balance deficits are also present in individuals with PD\textsubscript{OFF} and levodopa does not improve, and may even aggravate, balance deficits in PD (Carpenter et al., 2004; D’Andrea Greve et al., 2014; Feller et al., 2019; Johnson et al., 2015; Maurer et al., 2003; J. E. Visser, Allum, Carpenter, Esselink, Limousin-Dowsey, et al., 2008; J. E. Visser, Allum, Carpenter, Esselink, Speelman, et al., 2008; Workman et al., 2019). It would therefore be interesting to see how brain connectivity as well as brain activation amplitude change between the ‘off’ and ‘on’ medication state during simulated balance tasks.

A few studies noted that the increase in amplitude of postural sway in individuals with PD\textsubscript{ON} was more pronounced in the ML compared to the AP direction (Rocchi et al., 2002; Viitasalo et al., 2002). Using the simulator in its current form, it is not possible to assess ML balance control. However, while ML sway is mainly regulated by hip abductors/adductors and AP sway is mainly regulated by the muscles around the ankle joint (Winter et al., 1996), there is no evidence to suggest AP and ML sway are controlled using different cortical or subcortical structures.

Dynamic balance perturbations were delivered manually in both the validation and fMRI studies. As outlined above, the lack of statistical differences seen between the individuals with PD\textsubscript{ON} and healthy older adult during the Dyn\textsubscript{Real} trials of the second validation study may have in part been due to the manual presentation of the perturbations, although perturbation force and
magnitude were monitored online (Pasman et al., 2019). It would therefore be recommended that in future studies a mechanical or motorized system is used to apply perturbations to the participants when standing upright as well as the simulator during DynSim trials that is also MRI compatible.

Several precautions were taken during fMRI scanning to minimize head motion, including wedging foam between the participants’ head and the head coil, as well as placing a strap around the participants’ head and an MRI safe sandbag on top of the pelvic area to further stabilized participants’ hips during the balancing tasks. Despite the precautions, head motion still occurred and may have contributed to our inability to find a significant LDA model that could discriminate between individuals with PDON and elderly controls during dynamic balancing.

We did not quantify balance performance in the fMRI scanner. This would be possible using an MRI compatible accelerometer or potentiometer and allow balance behaviour to be directly correlated with brain activation and connectivity. In addition, it may allow for an event related design to be utilized for the dynamic balance control condition when a mechanical or motorized method of perturbation delivery is used. This may then subsequently allow for the effect of perturbation amplitude and/or direction on brain activation and connectivity to be investigated.

6.7 Future directions

For most studies in this thesis vision was absent and balance-relevant vestibular information was limited due to head fixation during the simulated balance tasks in the MRI scanner. Given the involvement of the basal ganglia in sensorimotor integration during balance control, it would be interesting to see how the addition of other sensory modalities changes the
brain connectivity and brain activation amplitude results during simulated balance. The first simulator validation study of this thesis already provided evidence that it is feasible to have participants perform the simulated static balancing tasks using real-time visual feedback from a virtual reality scene driven by the output from a potentiometer attached to the axis of the simulator. Using an MRI compatible potentiometer, a similar set-up would be possible in the MRI scanner. In addition, vestibular information could be added using electrical vestibular stimulation, which has already previously been used in the fMRI environment (Cai et al., 2018).

As most studies investigating the neural substrates of balance control have used motor imagery of a static or dynamic balance task, future studies should directly compare these paradigms in the same participants to see if and where differences in brain connectivity and brain activation amplitude exist. This would inform if and to what extent the results obtained using the simulator paradigm can be directly compared with the many studies performed using motor imagery in the past.

For this thesis we were only able to separate the brainstem into three segments (i.e., midbrain, pons, medulla) using FreeSurfer software (Harvard, MA, USA). However, given the evidence that smaller subregions of the brainstem, such as the mesencephalic locomotor region/PPN, locus coeruleus, vestibular nuclei, and reticular formation, are likely involved in balance control (MacKinnon, 2018; Takakusaki, 2017), future studies should use more sophisticated techniques to be able to analyze these brainstem nuclei independently from each other.

The brain activation amplitude analysis used in the current thesis did not allow us to detect compensation in individuals with PD due to increased spatial activation of brain regions involved in balance control. This can be done using three-dimensional moment invariants (Ng,
Abugharbieh, Huang, & McKeown, 2009). This technique was used previously comparing brain activation in individuals with PD and healthy older adults during a motor task, and in addition to recruiting new brain regions individuals with PD also increase the spatial extent of activation in brain regions known to be involved in the motor task (Palmer et al., 2009).

Future studies should improve on our study design by measuring balance behavior in the MRI scanner directly. In addition, it would then be interesting to follow the individuals with PD prospectively and periodically collect data on clinical characteristics (i.e., UPDRS-ME, anxiety, medication), falls, balance performance using posturography, and functional MRI data during simulated balance tasks. This would allow for the neural substrates of postural instability to be tracked over time and could potentially lead to the identification of postural instability and/or fall specific brain connectivity and/or brain activation amplitude patterns that could then hopefully be used to identify individuals with PD most at risk for falling before they actually experience any falls.

It is difficult to draw meaningful interpretation from the current body of literature on postural control in PD due to a lack of consistent methods and measures (see Chapter 2, and Hubble et al., 2015; Kamieniarz et al., 2018). Therefore, further technical studies are needed to determine how factors such as trial duration and filter settings can impact the accurate measurement of PD-related balance deficits. This information is crucial for the development of standardized static posturography protocols to be used in future investigations on the effect of PD, and the effect of current and novel treatments, on the kinetic and kinematic characteristics of quiet stance.
6.8 Conclusion

In conclusion, the collective results from this thesis have increased our understanding of the specific nature of static balance deficits in individuals with PD, as well as the neural substrates underlying postural instability in PD. Firstly, converging evidence from a narrative literature review indicated individuals with PD display larger and faster sway compared to healthy older adults during quiet, bipedal standing, and that levodopa provides little improvement. Secondly, a novel MRI compatible balance simulator was developed and validated in individuals with PD and healthy older adults that was subsequently used in the MRI scanner to investigate the neural substrates of postural instability in PD. Results from both brain connectivity and brain activation amplitude analyses suggested there is increased involvement of cortical motor and parietal areas, and decreased involvement of subcortical regions, in individuals with PDON compared to healthy older adults during static and dynamic balance control.
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