

**BRAIN STRUCTURAL AND FUNCTIONAL CORRELATES
WITH BALANCE/GAIT IN PARKINSON'S DISEASE**

By

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A DISSERTATION

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List of Abbreviations

AC-PC	Anterior Commissure - Posterior Commissure
ANTs	Advanced Normalization Tools
AP	Anteroposterior
APA	Anticipatory Postural Adjustments
APR	Automatic Postural Responses
Aud	Auditory Network
BOLD	Blood Oxygen Level Dependent signal
CiO	Cingulo-Opercular Network
CPG	Central Pattern Generator
DAN	Dorsal Attention Network
DBS	Deep Brain Stimulation
Def	Default mode Network
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalogram
ES	Effect Size
fMRI	Functional Magnetic Resonance Imaging
FPn	Frontoparietal Network
FSL	FMRIB Software Library
HCP	Human Connectome Project
INs	Interneurons
Lan/VeA	Language/Ventral Attention Network
M1	Primary Motor Cortex
MAE	Mean Absolute Error
MDS-UPDRS	Movement Disorders Society - Unified Parkinson's Disease Rating Scale
ML	Mediolateral
MLR	Mesencephalic Locomotor Region
MNs	Motoneurons
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic Resonance Imaging
OHSU	Oregon Health & Science University
OrA	Orbito-Affective Network
PD	Parkinson's Disease
PDRP	Parkinson's Disease Related Pattern
PET	Positron Emission Tomography
PIC	Posterior Insular Cortex

PIGD	Postural Instability and Gait Disorders
PIVC	Parieto-Insular Vestibulo Cortex
PLSR	Partial Least Square Regression
PM	Premotor Cortex
PMm	Posterior Multi-Modal Network
PMRF	Ponto Medullary Reticular Formation
PPC	Posterior Parietal Cortex
PPN	Pedunculopontine Nucleus
PwPD	People with Parkinson's Disease
ROI	Region of Interest
rs-fMRI	Resting State Functional Magnetic Resonance Imaging
S1	Primary Sensory Cortex
SBG	Subcortical-Basal Ganglia Network
SCb	Subcortical-Cerebellar Network
SMA	Supplementary Motor Cortex
Smn	Somatomotor Network
SNR	Signal to Noise Ratio
T1	T1-weighted image
T2	T2-weighted image
TE	Echo Time
TI	Inversion Time
TR	Repetition Time
Vis	Visual
VMm	Ventral Multi-modal Network
VN	Vestibular Nucleus

Table of Contents

Acknowledgments.....	iii
List of Abbreviations.....	vi
Table of Contents.....	xi
List of Tables.....	xv
List of Figures	xvii
Abstract.....	xix
Chapter I: Introduction.....	1
1.1 What We Know About Parkinson's Disease	1
1.1.1 Prevalence and History	1
1.1.2 Clinical Features	2
1.1.3 Pathophysiology of PD.....	3
1.2 Balance and Gait Control in Humans.....	4
1.2.1 Domains of Gait and Balance	4
1.3 Neural Mechanisms of Balance and Gait.....	11
1.3.1 Subcortical – Brainstem	13
1.3.2 Subcortical – Cerebellum.....	15
1.3.3 Subcortical – Basal Ganglia	16
1.3.4 Cortical Systems	17
1.3.5 Impairments of Balance and Gait in PD	19
1.4 Balance and Gait Assessment.....	19
1.5 Role of Magnetic Resonance Imaging in PD Research	21
1.6 Challenges in Imaging.....	23
1.7 Goal of the Dissertation.....	24
Chapter II: Relationship Between Brain Volumes and Objective Balance and Gait Measures in Parkinson's Disease	27
2.1 Abstract	27
2.2 Introduction.....	28

2.3	Materials and Methods.....	30
2.3.1	Study Sample	30
2.3.2	MRI Acquisition and processing.....	32
2.3.3	Balance and Gait Assessment Outcome Measures	33
2.3.4	Statistical Analysis	35
2.4	Results	36
2.4.1	Sample Characteristics	36
2.4.2	Brain Volumes and Balance and Gait Metrics in PD and Control Groups	37
2.4.3	Brain Volumes Related to Balance and Gait.....	39
2.4.4	Brain Volumes Related to Clinical Scores	42
2.4.5	Relationship Between the Brain Volumes and Age:	43
2.5	Discussion	43
2.5.1	Summary of Results.....	43
2.5.2	Brain volumes related to postural sway	44
2.5.3	Brain volumes related to anticipatory postural adjustments.....	45
2.5.4	Brain volumes related to gait	46
2.5.5	Brain volumes related to postural stepping responses	47
2.5.6	Brain volumes related to clinical scores	48
2.5.7	Limitations	48
2.5.8	Conclusion	49
2.6	Supplementary Materials	50
2.6.1	Supplementary Tables	50
2.6.2	Supplementary Figures	53

Chapter III: Resting State Functional Connectivity Networks Predict

Motor Signs in Parkinson's Disease.....	57
3.1 Abstract	57
3.2 Introduction.....	58
3.3 Methods.....	61
3.3.1 Participants	61

3.3.2	Standard Protocol Approvals, Registrations, and Patient Consents	61
3.3.3	Clinical data.....	61
3.3.4	Neuroimaging.....	62
3.3.5	Statistical Analysis	66
3.4	Results	67
3.5	Discussion	71
3.5.1	Summary of results	71
3.5.2	Somatomotor – Subcortical-Basal Ganglia network connectivity predicts PD motor severity	72
3.5.3	Somatomotor – Visual network connectivity predicts PD motor severity	73
3.5.4	Cingulo-Opercular – Language/Ventral Attention network connectivity predicts PD motor severity.....	74
3.5.5	Strengths and Limitations	75
3.6	Conclusions.....	77
3.7	Supplementary materials	78

Chapter IV: Resting State Functional Networks Predict Different Aspects of Balance Control in Parkinson’s Disease 81

4.1	Abstract	81
4.2	Introduction.....	82
4.3	Methods.....	84
4.3.1	Participants	84
4.3.2	Posture outcome measures	85
4.3.3	Neuroimaging.....	86
4.3.4	Statistical Analysis	89
4.4	Results	89
4.5	Discussion	93
4.5.1	Anticipatory Postural Adjustments (APAs).....	93
4.5.2	Automatic Postural Responses (APRs)	94
4.5.3	Postural Sway	95

4.5.4	Clinical Postural Instability	96
4.6	Conclusions.....	97
4.7	Supplementary materials	98
Chapter V: Discussion and Future Directions		105
5.1	Summary of Findings	105
5.1.1	Subcortical Volumes Relate to Postural Control	106
5.1.2	Motor and Attention Functional Networks Relate to Motor Signs	108
5.1.3	Higher-Order Functional Networks Involved in Postural Control	108
5.2	General Discussion	110
5.2.1	How Do Clinical Assessments Relate to Objective Assessment of Mobility?	111
5.2.2	Role of Subcortical Regions in Balance and Gait Control.....	112
5.2.3	Role of the Cortex in Balance and Gait Control	116
5.2.4	Imaging Considerations for Studying Balance and Gait in PD.....	121
5.3	Limitations and Future Directions.....	122
5.4	Conclusion.....	124
Appendix A.....		129
Bibliography.....		131

List of Tables

Table 2.1. Demographics and clinical characteristics.....	31
Table 2.2. Mean (SD) of the brain volumes and balance and gait metrics in Control and PD groups with group difference test significance values.....	37
Table 2.3. Significant standardized beta coefficients with p-values from ANCOVA for main and interaction effects between brain volumes and balance/gait metrics in people with PD and healthy controls.....	40
Table 2.S1. Significant standardized beta coefficients with p-values for interaction and main effects between brain volumes and balance/gait metrics in freezers and non-freezers	50
Table 2.S2. Significant correlations between age, disease duration and brain ICV with brain volumes or balance/gait metrics.....	51
Table 3.1 Sample Characteristics.....	67
Table 3.2. Significant functional connectivity network pairs predicting clinical motor scores in PD	69
Table 4.1 Sample Characteristics.....	85
Table 4.2. Significant functional connectivity network pairs predicting objective and clinical balance domains in older adults and PD	90
Table 4.S1. List of subcortical ROIs from PD25 and FreeSurfer Atlases	101
Table 5.1. Summary of results from three projects.....	Error! Bookmark not defined.
Table A.1. Correlation between Clinical motor scores and instrumented balance and gait metrics used in this thesis.....	129

List of Figures

Figure 1.1. Four Balance Domains	5
Figure 1.2. Anticipatory postural adjustments for a voluntary step	6
Figure 1.3. Automatic postural responses using push and release test	8
Figure 1.4. Postural sway in quiet stance	9
Figure 1.5. Neural control system of posture and locomotion	12
Figure 1.6. Cortical and subcortical mechanisms in PD movement control	13
Figure 2.1. Scatterplot of significant main effects of the relationship between brain volumes with balance and gait metrics for older adults.	41
Figure 2.2. Scatterplots of significant interaction effects between PD and control group for the relationship of brain volumes with instrumented balance and gait metrics.	41
Figure 2.S1. Scatterplot of significant main effects of the relationship between brain volumes with balance and gait metrics for non-freezers.	53
Figure 2.S2. Scatterplots of significant interaction effects between freezers and non-freezers group for the relationship of brain volumes with instrumented balance and gait metrics (in PD).	54
Figure 3.1. HCP Cortical functional networks and subcortical networks with PD25 and FreeSurfer combined ROIs.....	65
Figure 3.2. Functional connectivity network pairs that predict the MDS-UPDRS motor scores.....	70
Figure 3.S1. Plots showing the beta weights and FC of the training and the test dataset for the 3 network pairs that predict MDS-UPDRS-III.	78
Figure 3.S2. Scatter plots showing the correlation between age and residuals of PLSR models of functional connectivity network pairs that predicted MDS- UPDRS III scores	79

Figure 3.S3. Scatter plots showing the correlation between disease duration and residuals of PLSR models of functional connectivity network pairs that predicted MDS-UPDRS III scores	79
Figure 4.1. HCP Cortical functional networks and subcortical networks with PD25 and FreeSurfer combined ROIs.....	88
Figure 4.2. Functional connectivity network pairs predicting APAs in OAs.	91
Figure 4.3. Functional connectivity network pairs predicting APAs, APRs and postural sway in PD.....	92
Figure 4.S1. Plots showing the beta weights and functional connectivity of the training and the test dataset for the significant network pairs that predict balance measures.	99
Figure 4.S2. Scatter plots showing the correlation between age and residuals of PLSR models of functional connectivity network pairs that predicted balance measures.....	100
Figure 4.S3. Scatter plots showing the correlation between disease duration of the PD subjects and residuals of PLSR models of functional connectivity network pairs that predicted balance measures	100

Abstract

Parkinson's disease (PD) is a neurodegenerative disorder with major clinical sensorimotor signs, including bradykinesia (slowed movements), rigidity, tremor and postural instability with gait disability. It affects multiple aspects (domains) of balance and gait, namely, anticipatory postural adjustments prior to voluntary movements, automatic postural responses to external perturbations, postural sway in stance and dynamic stability during gait. However, motor disorders in people with PD are heterogeneous. For instance, some people have more postural dysfunctions and others have more tremor. The response of different motor signs to antiparkinsonian medication also varies, as gait speed usually improves, but postural stability often gets worse.

Multiple brain regions are involved in control of balance and gait; however, it is still unknown which brain networks control specific domains of balance and gait and how these brain networks are impaired in people with PD. The goal of the present work is to improve our understanding of brain networks involved in balance and gait disorders by studying the associations between structural/functional characteristics of the brain with motor behaviors in people with PD and older adults. In Study 1, we investigated how brain volumes are related to instrumented domains of balance and gait and clinical motor signs. We hypothesized that impairments of different domains of balance and gait in PD will be associated with atrophy in different brain areas. In Study 2, we used a predictive modelling approach to identify the functional connectivity of brain networks related to severity of motor signs in PD. We hypothesized that, along with sensorimotor networks, higher-order, non-motor networks are also associated with motor signs in PD. In Study 3, we focused on how functional connectivity of brain networks were associated with different, instrumented domains of balance control. We hypothesized that functional

connectivity of different brain networks will be associated with each domain of balance and that people with PD will have more brain networks associated with balance control than older adults.

The results of our studies demonstrate that balance and gait are controlled, not only by motor networks, but also by higher-order networks. The structural imaging study showed that postural control measures are more sensitive to structural volume atrophy than gait measures. We found that cerebellar, parietal and frontal regions integrity is associated with different aspects of balance and gait. The functional connectivity studies showed that attention-related networks were also impacted by PD, as well as the sensorimotor network. We also learned that different domains of balance are related to different brain network functional connectivities. Involvement of higher-order brain networks in motor signs of PD, clinically assessed, suggests that the brain finds alternative network strategies to control critical behaviors, such as balance and gait. These novel findings contribute to a better understanding of the complex relationships between the brain and balance/gait will be helpful to design individualized treatment therapies specific to each individual's impairments.

Chapter I: Introduction

1.1 What We Know About Parkinson's Disease

1.1.1 Prevalence and History

Parkinson's disease (PD) is the most common neurodegenerative movement disorder affecting about 10 million people worldwide and about one million in the US alone. Approximately 60,000 Americans are diagnosed with PD every year according to the Parkinson's disease foundation. Older adults and men are at a higher risk of PD. Prevalence increases with age, with average age for diagnosis being 70.5 (Van Den Eeden et al. 2003).

PD has been known since historical times. Ancient Greek, Chinese and Indian texts mention conditions characteristic of PD. Indian Ayurvedic texts describe of a disease called "Kampavata/Vepathu", (Kampa – Shaking/tremor, Vata roga – Neurological disease) a progressive condition with tremor and deterioration of movement (Manyam 1990; Ovallath and Deepa 2013). The *Mucuna pruriens* plant was used in ancient times to treat the symptoms, and was later discovered to contain about 4-6% of levodopa (Katzenschlager et al. 2004).

In the past 200 years, it was James Parkinson who gave the first clinical description of the disease in his 1817 *Essay on the Shaking Palsy* (Parkinson 1817). However, it was Jean-Martin Charcot, a 19th century clinical neurologist who brought attention to James Parkinson's contribution and named it *Parkinson's disease*. Even though the disease has been known for a long time, we still do not know the causal mechanisms of PD. Nonetheless, remarkable advancements have been made in understanding the pathophysiology of the

disease, such as the discovery of Lewy pathologies by Frederick Lewy in 1912, the link between dopamine deficiency and PD by Arvid Carlsson and Oleh Hornykiewicz in 1957, identification of toxins (MPTP) inducing parkinsonism by William Langston in 1982 and discovery of gene mutations by Polymeropoulos and colleagues in 1996 (Joseph Jankovic and Tan 2020). Nevertheless, the brain networks affected by PD attributable to specific parkinsonian disorders, such as aspects of balance and gait motor disorders, are not understood.

1.1.2 Clinical Features

PD is a heterogeneous disease characterized by motor and non-motor signs. There is no biomarker established for PD so diagnosis is made primarily by the physician in the clinic after a neurological examination. Clinical criteria for diagnosis of PD requires the presence of bradykinesia and any of the following cardinal signs: rigidity, resting tremor and postural instability (J. Jankovic 2008).

Bradykinesia is the slowness of movement and impairs planning, initiating and executing movements. Some of the manifestations of bradykinesia are loss of spontaneity of movements and gestures, reduced arm swing while walking and slowed walking. Bradykinesia is hypothesized to be related to disrupted motor cortical activity, in part due to reduced dopaminergic inputs from the key subcortical structures that are connected to it (Alexander 2004). Rigidity, characterized by increased resistance to passive movement, causes stiffness and inflexibility of limbs, trunk and neck, contributing to decreased range of motion and pain. Resting tremor is a common observed symptom of PD and prominent in the limb extremities and rarely involves head/neck in PD. Most cases, tremor begins on one side and as the disease progresses it is observed bilaterally. Postural instability occurs at the later stages of the disease and one of

the most common reasons for falls and injury in PD. It is tested by a “pull-test” where the patient is given a backward tug and rate of recovery is observed. Taking more than two steps backwards or the absence of any postural response is considered an abnormal postural response (J. Jankovic 2008).

Non-motor signs like depression, anxiety, constipation, loss of sense of smell, orthostatic hypotension, rapid-eye-movement sleep disorders and cognitive decline are often present along with the motor signs (Gelb, Oliver, and Gilman 1999; J. Jankovic 2008). In many cases, non-motor signs precede the motor signs. The work presented in this thesis will primarily focus on the motor signs and the brain areas and networks underlying the motor signs with specific focus on balance and gait disorders.

1.1.3 Pathophysiology of PD

The defining pathologic characteristic of PD is the progressive loss of dopamine-generating neurons in a subcortical region of the basal ganglia, called the substantia nigra, pars compacta (Greenfield and Bosanquet 1953; Takahashi et al. 2018). The dopaminergic dysfunction leads to downstream changes in other nuclei of the basal ganglia, thalamus, cerebellar, brainstem and cortical areas. More than half the substantia nigra cells are lost before the onset of symptoms. Multiple, compensatory circuits are thought to mask the effects of dopamine depletion on motor behavior, especially in the pre-symptomatic phase. The following section will review neural mechanisms underlying control of balance and gait and how balance and gait is impaired by PD.

1.2 Balance and Gait Control in Humans

Balance is the ability to maintain the body center of mass within the limits of stability, defined as base of support, while performing variety of tasks (Horak, F B, Earhart, G M 2021). Orientation is the alignment of body segments with respect to each other and to the environment. Balance control requires control of orientation and equilibrium. Gait is the sequence of movements that occurs during ambulation and is the integration of locomotor control and dynamic equilibrium control. Normal balance and gait require intact musculoskeletal and neurological systems, integration of multiple sensory inputs and neuromuscular execution, internal models, antigravity tone, coupling between movement and postural goals, and ability to improve control via motor learning (Mancini, Nutt, and Horak 2020a).

1.2.1 Domains of Gait and Balance

We hypothesize that the postural control mechanisms underlying control of different balance tasks actually represent different, independent domains of balance control that likely involve different brain areas and networks. This thesis focuses on 4 balance domains summarized in Figure 1.1: (1) *Anticipatory postural adjustments* (postural changes anticipating the effects of voluntary movements on the center of mass), (2) *Automatic postural responses* (reacting to external perturbations to recover equilibrium), (3) *postural sway in stance posture* and (4) *dynamic stability during gait* (walking).

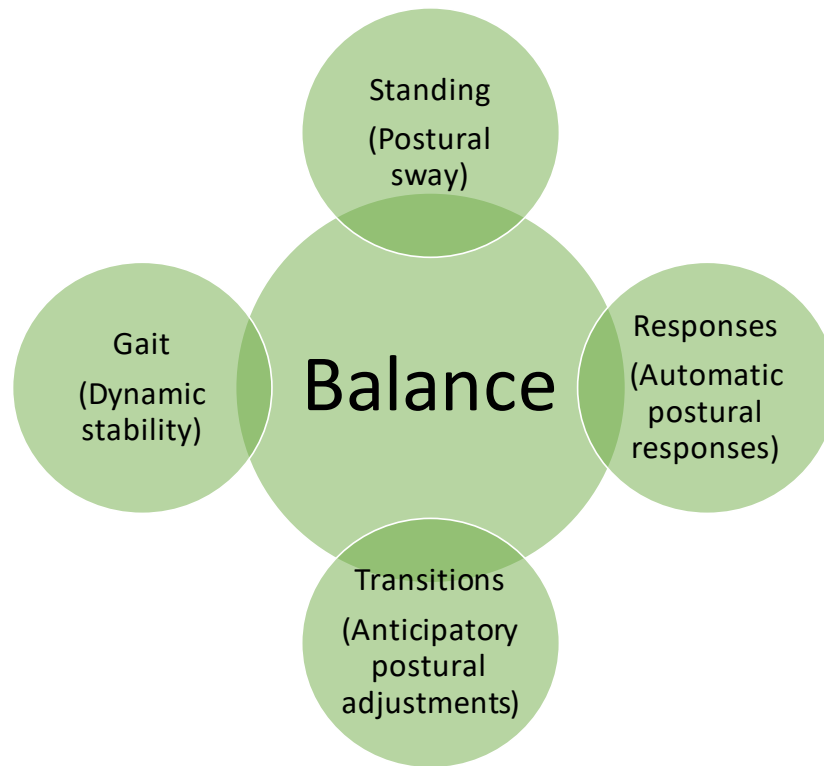


Figure 1.1. Four Balance Domains

Four balance (postural) domains for control of standing, postural responses, postural transitions, and dynamic gait during walking.

1.2.1.1 Balance Domains

This thesis uses characteristics of movement within the following domains of balance control with body-worn inertial sensors and relates these characteristic behaviors to brain structure and function:

Anticipatory Postural Adjustments (APAs): In this thesis, we examine APAs based on the forward and lateral weight shift towards the stance leg, prior to gait initiation and the range of motion of first step (Massion 1992; MacKinnon et al. 2007). We measure the size of the APAs as backward and lateral acceleration of the pelvis toward the stepping leg with an inertial sensor on the lumbar level (Fay B. Horak and Mancini 2013; Schlenstedt et al. 2017).

APAs prior to voluntary limb movement, serve to maintain postural stability by compensating for destabilizing forces associated with moving a limb (Massion 1992). APAs are a form of feedforward postural control which are a part of a planned action and are task-specific. Examples of APAs include forward and lateral weight shift prior to gait initiation, forward weight shift prior to raising on toes, activation of leg muscles prior to rapid arm elevation when standing and forward trunk motion prior to raising from chair (Jian et al. 1993; Aruin and Latash 1995; MacKinnon et al. 2007). APAs also adapt to the changes in the postural stability requirements. For instance, posterior leg muscles are activated for arm raising whereas anterior leg muscle are activated for arm descent. APAs are absent when externally supported and postural stability is not threatened (Mancini, Nutt, and Horak 2020a). Figure 1.2 shows lateral APAs in preparation for a voluntary step as measured by inertial sensors.

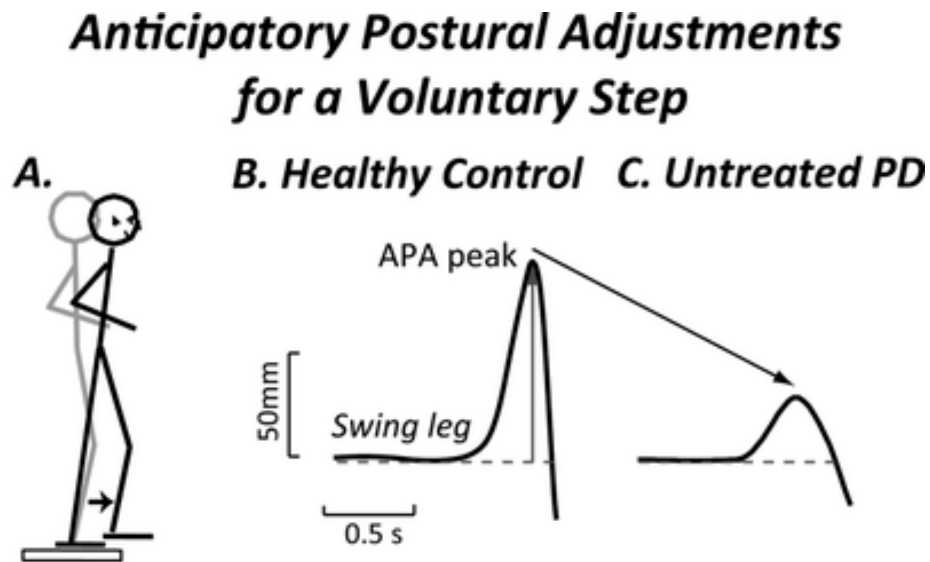


Figure 1.2. Anticipatory postural adjustments for a voluntary step

A. Subject standing on a force plate stepping forward, B. APA of a control subject, C. Early, untreated PD shows smaller APA and longer latency before stepping foot. Figure from (Schoneburg et al. 2013)

Cortical regions are thought to be involved in postural adjustment tasks. While decerebrate cats can perform basic tasks like sitting, standing and walking, postural preparations are not possible. Premotor cortex, in particular, the supplementary motor area (SMA), is involved in the planning and preparatory phase of voluntary movement (Deecke 1987).

Automatic Postural Responses (APRs): This thesis measures APRs as stepping responses after an external perturbation induced by asking participants to lean backward on the examiner's hands, followed by a release of force, requiring a backward step to recover equilibrium (Jesse V. Jacobs et al. 2006). We measure of size of the APR (in vertical and anteroposterior directions) as the first step length to recover equilibrium as calculated from inertial sensors on the feet (El-Gohary et al. 2017).

Postural responses are required to return the body back to equilibrium and orientation after an external perturbation. It can be achieved either through short- or long-latency responses. Short-latency responses, around 50-100 ms long, keep the feet in-place, whereas long-latency responses, which are over 100 ms but faster than a voluntary reaction time (about 180 ms), are elicited through stepping responses. During postural responses, arm movements can also occur, if required, to recover/maintain equilibrium (F. B. Horak and Nashner 1986; J. V. Jacobs and Horak 2007). APRs are reactive in nature and are due to feedback mechanisms driven primarily by the somatosensory inputs from the limbs, although they can be elicited by moving visual stimuli and auditory startle stimuli. Figure 1.3 is an illustration of APR when a subject is going through the push and release test.

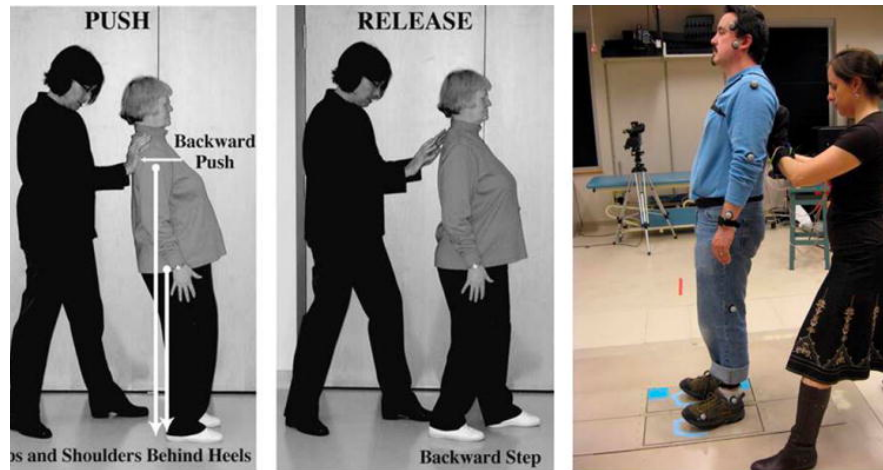


Figure 1.3. Automatic postural responses using push and release test

Panel on the left shows the backward lean/push by the subject, middle panel shows the release part by the clinician and right panel shows the instrumented testing of push and release test with wearable sensors.

Figure from (El-Gohary et al. 2017).

Typically, long-latency postural responses involve cortical control (J. V. Jacobs and Horak 2007). Involvement of cortical regions would mean that postural responses are adaptable to changes in sensory inputs, cognitive state, prior experience or warning of an upcoming perturbation (F. B. Horak, Diener, and Nashner 1989). Sensory inputs to APRs are provided through visual and vestibular systems in the head and somatosensory receptors, spread across the body. Interaction across these sensory inputs is essential for proper interpretation of the sensory signals and response adequacy. It is suggested that the cerebello-cortical loop controls experience-based adaptation of postural response and basal-ganglia-cortical loop performs context-based preselecting and optimizing of postural responses (J. V. Jacobs and Horak 2007; Mancini, Nutt, and Horak 2020a; Jahn and Wühr 2020).

Postural Sway: We quantified postural sway with 3-dimensional accelerometers placed on the lumbar spine at the level of L5 during 30 seconds

of quiet standing on compliant foam surface with eyes open, a condition previously shown to be especially sensitive to PD (Hasegawa et al. 2019a). Human posture while standing is unstable because of the narrow base of support and high position of center of body mass. Standing without any external perturbation requires continuous corrections to posture, since the body center of pressure is in front of the ankles and the body needs to be actively pulled backward (by calf muscles) to avoid falling forward. This continuous correction is characterized by postural oscillations, termed postural sway (F. B. Horak, Diener, and Nashner 1989; Mancini, Nutt, and Horak 2020a). Figure 1.4 shows the postural sway area measured by the force plate in anteroposterior and mediolateral directions.

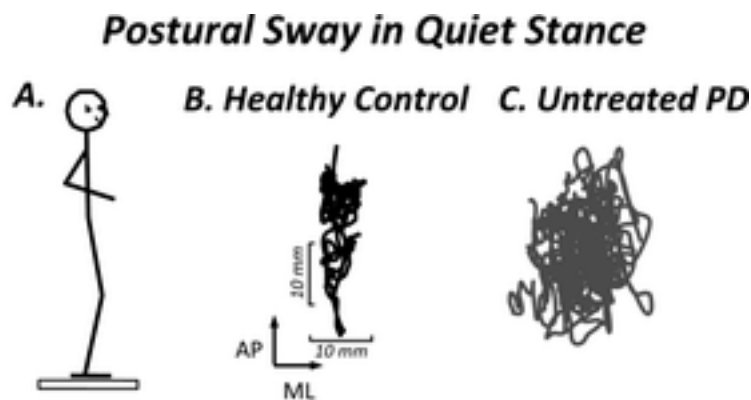


Figure 1.4. Postural sway in quiet stance

A shows subject standing on a force plate that measures the center of pressure (CoP). B and C show the postural sway area in healthy control and untreated PD subject. Figure from (Schoneburg et al. 2013)

Control of posture relies on integration of multi-sensory (somatosensory, visual and vestibular) information. The contribution of the sensory inputs can be quantified by measuring postural sway under different sensory conditions, such as changing the support surface (stable versus unstable), eyes open versus closed and compromising both surface and visual inputs. For instance, when the

support surface is not stable (as when standing on compliant foam in this thesis), compromising somatosensory inputs, reliance on visual and vestibular systems increases and postural sway is larger (Mancini, Nutt, and Horak 2020a).

Dynamic Stability During Gait: This thesis utilizes several characteristics of gait, including pace, rhythm, variability, turning and upper body stability during walking (via inertial sensors on the feet and lumbar spine) to relate to brain volumes. Walking is a continuous state of dynamic imbalance in humans as the center of mass is not within the feet and passes in front of, and medial to, the supporting foot. Altering foot placement and tilting the trunk provides various strategies to maintain postural stability during walking. Turning while walking is even more complex dynamic balance task than straight walking and is performed very slowly in people with PD (Mancini, Nutt, and Horak 2020a). Gait contains multiple, discrete characteristics, including variability, pace, rhythm, etc. that likely represent different features of neural control (Lord et al. 2013; Wilson et al. 2019). For example, gait and standing balance disorders have been shown to be uncorrelated in people with PD, consistent with separate neural controllers (Fay B. Horak et al. 2016).

Control of locomotor stepping movements involves spinal pattern generators, whereas control of dynamic balance while walking likely occurs in higher subcortical and cortical networks. The integration of locomotor and postural information is thought to happen in the brainstem (pontomedullary reticular formation). The cerebellum is involved in the rhythmicity of gait, multisensory integration, multi-joint coordination, dynamic balance control, and adaption of gait based on prior experience, important for motor learning (MacKinnon 2018a). Modifying gait for turning is thought to involve premotor regions for advance sensorimotor planning (Mancini, Nutt, and Horak 2020a).

Although it is clear that control of balance and gait involve many networks from the brainstem to the prefrontal cortex, the specific networks involved in specific aspects of postural control are yet to be determined.

1.3 Neural Mechanisms of Balance and Gait

Understanding the neural mechanisms underlying balance and gait motor behavior will help develop a theoretical framework to target interventions. Human balance and gait control is highly complex and achieved through both feedforward and feedback mechanisms, and not just a result of automatic, stereotyped reflexes. The nervous system provides the basic motor patterns via pattern generators in the spinal cord, but quickly adapts to changes in the movement intention or environmental factors via supraspinal networks. Figure 1.5 shows a simplified schema of neural mechanisms contributing to control of balance and gait with sensory feedback in red and feedforward control in green. Figure 1.6 shows the cortical mechanisms that are thought to be related to different domains of balance and gait impairments observed in PD.

Neurodegenerative disorders, like PD, help us to understand the normal motor control of balance and gait and how the nervous system maintains behavior by redistributing neural control to less involved areas. This section will summarize what is known about neural systems (from subcortical to cortical) involved in balance and gait control.

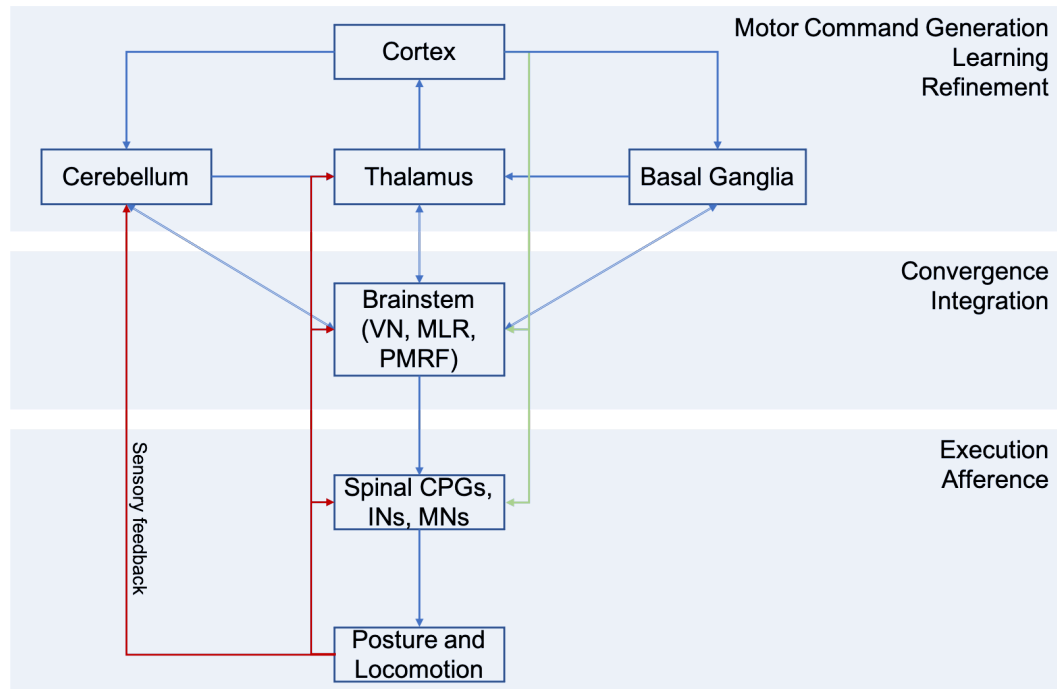


Figure 1.5. Neural control system of posture and locomotion

VN – vestibular nucleus, MLR – mesencephalic locomotor region, PMRF – pontomedullary reticular formation, CPGs – central pattern generators, INs – interneurons, MNs – Motoneurons. Green line represents cortical connections sending feedforward information at various levels through corticospinal tract, red line represents sensory feedback mechanisms. Adapted from (MacKinnon 2018a)

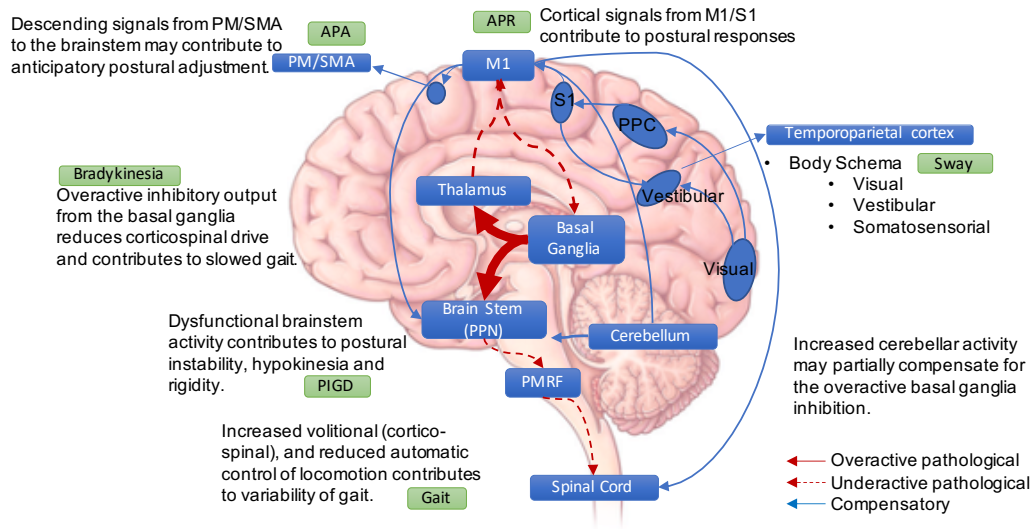


Figure 1.6. Cortical and subcortical mechanisms in PD movement control

Alterations in basal ganglia lead to brain-wide systematic changes to compensate for underactive excitatory or overactive inhibitory systems leading to observed motor signs like bradykinesia and postural instability with gait disorders (PIGD). We hypothesize that APAs, APRs, sway and gait are associated with different brain networks. The cerebellum is thought to play an important compensatory role for loss of basal ganglia control. APA – anticipatory postural adjustments, APR – automatic postural responses, M1 – primary motor cortex, PIGD – postural instability and gait disorders, PMRF – pontomedullary reticular formation, PPC – posterior parietal cortex, PPN – pedunculo-pontine nucleus, S1 – primary sensory cortex. Adapted from (Takakusaki 2013; Mancini, Nutt, and Horak 2020a)

1.3.1 Subcortical – Brainstem

In later Chapters (2 and 5) of this thesis, we illustrate how brainstem structures and networks are related to multiple domains of balance and gait. Here we will briefly review the role of brainstem in balance control and its neural connection to other subcortical and cortical regions.

The brainstem contains important nuclei for balance control, such as the mesencephalic locomotor region (MLR), pontomedullary reticular formation (PMRF) and vestibular nuclei. They are, in turn, connected to other subcortical structures, such as the basal ganglia and cerebellum as well as cortical areas (Figures 1.5 and 1.6). The brainstem plays a crucial role in multiple aspects of balance and gait control including postural tone, postural sway, muscle synergies for APAs, APRs and integration of planning and execution phases of gait (Mancini, Nutt, and Horak 2020a). The MLR, in the reticular formation of the brainstem, contributes to postural tone control and, in conjunction with cerebellum, controls locomotor rhythm generation. It consists of pedunculopontine nucleus (PPN) and cuneiform nucleus. PPN is considered to be one of the primary regions for postural adjustments and locomotor control. PPN contributes to postural control and locomotion through tight communication with the basal ganglia and cuneiform nucleus. It is also responsible for modulation of brain state and muscle tone (Takakusaki 2017; MacKinnon 2018a).

From animal studies, it is thought that PMRF is likely a hub for sensorimotor integration required for APAs, APRs, control of locomotor speed and muscle tone regulation (Takakusaki 2017; MacKinnon 2018a). The cortical inputs to PMRF helps to couple voluntary movement commands with postural adjustments in accordance with changes in sensory feedback. The vestibular nuclei in the brainstem are a point of convergence for multisensory systems and supraspinal centers, enabling it to modulate APAs and APRs (MacKinnon 2018a). Neither the basal ganglia nor the cerebellum project directly to the spinal cord and all their communication is mediated through brainstem nuclei (PPN for brainstem and vestibular (among others) for cerebellum) (MacKinnon 2018a). In people with PD, the PPN has been shown to have reduced cell count and a PPN

DBS helps improve freezing of gait and postural instability in some people with PD (Thevathasan et al. 2011).

1.3.2 Subcortical – Cerebellum

This thesis will show that cerebellar volume is related to multiple aspects of postural control and cerebellar connectivity with sensory systems is related to APRs in people with PD (Chapter 4).

The cerebellum plays a supervised motor learning role, critical for error detection, correction and refinement of motor activity. The cerebellum receives sensory inputs from the spinal cord and brainstem, and influences via subcortical and cortical projections (figures 1.5 and 1.6). It has three zones, namely, medial vermis (projecting to fastigial nucleus and considered to have cerebellar locomotor and postural regions), intermedial paravermis (projecting to interposed nuclei and considered involved in APRs) and lateral neocerebellum (projecting to dentate nucleus and the largest part of cerebellum related to voluntary movement initiation). The cerebellar vermis, located medially in the cerebellum, has projections to the (fastigial nucleus and) vestibular nuclei and is considered primary for balance control in response to vestibular and visual stimuli. The intermediate paravermal zone, projecting to the interposed nuclei, activate after movement onset and are considered to be involved in reactive postural control. The lateral neocerebellum, projecting to the somatomotor and premotor areas through dentate nucleus, is thought to help in movement preparation and initiation, such as step initiation (MacKinnon 2018a). The cerebellum controls the timing and intensity of the descending signals through pontomedullary reticular formation (PMRF) in the brainstem.

In PD, the cerebellum is one of the important structures identified with both balance and gait impairments. It is thought to partially play a compensatory role, but may be impacted by PD also. In summary, the cerebellar locomotor region is implicated in dynamic balance control in gait (Gilat et al. 2019) and also impacted in freezing of gait (Fasano, Laganieri, et al. 2017), the paravermis in APRs, the cerebellar vermis for control of postural sway, and the hemispheres in control of APAs prior to step initiation (Dijkstra et al. 2020). The cerebellar projections to the striatum are thought to influence the indirect pathway in the basal ganglia (Bostan and Strick 2018).

1.3.3 Subcortical – Basal Ganglia

This thesis will discuss the involvement of basal ganglia regions and subcortical networks in motor signs of PD (Chapters 2, 3 and 5). The basal ganglia mediate and modify cortical and brainstem circuits for balance and locomotion. The basal ganglia control the scaling (vigor) of motor activity, automaticity, posture-movement coupling and adaptation of balance control based on the context (Mancini, Nutt, and Horak 2020a). The basal ganglia region exerts its control by modulating the activity of two primary output structures, namely the internal segment of globus pallidus and substantia nigra pars reticulata. These output nuclei have inhibitory projections to the thalamus and brainstem (PPN) which, in turn, have excitatory projections to the cortex. So, movement is facilitated by reduced firing of basal ganglia output and suppressed by increased firing which is impaired in PD (Figure 1.6). The subthalamic nucleus also projects to the cerebellum via pontine nucleus. The degree to which the basal ganglia influences movement is modulated by the dopaminergic projections from the substantia nigra, pars compacta to the putamen and caudate nuclei,

which is degenerated in PD. Bradykinesia, the most important motor sign in PD, is thought to be related to increased inhibitory output of basal ganglia (due to dopamine loss) to sensorimotor cortex via the thalamus (Lozza, Marié, and Baron 2002).

The basal ganglia likely control balance and gait via their brainstem and thalamocortical projections. The brainstem projections from the basal ganglia are thought to be involved in more automatic control of balance and gait whereas the frontal cortex projections from the basal ganglia to the SMA (in turn, to primary motor cortex) via the thalamus are thought to be involved in more voluntary, and less automatic, movements (Mancini, Nutt, and Horak 2020a).

While the basal ganglia are the most affected region by PD, many brain areas are eventually involved. Parkinsonian motor signs become apparent only after loss of over 50% of dopaminergic neurons in the basal ganglia. Redundant neural networks compensate for the loss of dopaminergic neurons to maintain critical behaviors, like balance and walking.

1.3.4 Cortical Systems

In this thesis, we demonstrate that, along with the brainstem and motor cortex, multiple cortical regions are involved in balance and gait control.

Frontal regions of the cortex, including the sensorimotor, prefrontal and premotor cortices are essential for selection, planning, initiation, execution, transition and modifying movement. The motor cortex projects directly to the brainstem and spinal cord via the corticospinal tract for precise control of muscle activation (Figure 1.5) (MacKinnon 2018a). Premotor activity, particularly SMA, is thought to be involved in anticipatory modulation of postural control and gait initiation (APAs) (Deecke 1990). SMA is one of the consistent regions that is

involved in motor planning and activated during gait and gait initiation (however, hypo-activated in PD) (Figure 1.6). Recently, functional MRI studies of mental imagery, action observation or actual movement through EEG and fNIRS systems have been used to study the cortical control of balance and gait (Jahn et al. 2008; Jahn and Zwergal 2010; Zwergal et al. 2012; Stuart et al. 2018).

The frontal cortex is involved in APRs, because, M1-S1 regions and the prefrontal cortex are activated 50 ms after an external perturbation and 50 ms prior to muscle activation (J. V. Jacobs and Horak 2007). Moreover, cortical activations (that are task-dependent) are seen across regions like dorsolateral prefrontal cortex (DLPFC), superior and inferior frontal gyri, cingulate regions, parieto-vestibular insular cortex (considered the vestibular cortical center), superior and inferior temporal gyri and posterior and inferior parietal lobe (Wittenberg et al. 2017; Gilat et al. 2019; Surgent et al. 2019; Dijkstra et al. 2020), Visual, vestibular and somatosensory signals are integrated at the temporoparietal-posterior parietal cortices, where the body schema is generated and updated. This body information is transmitted to the premotor/SMA via sensory cortex and is utilized to generate motor programs (Takakusaki 2013).

People with PD have cognitive impairments and non-motor symptoms, along with the balance and gait impairments. These nonmotor symptoms have a huge impact on their quality of life and aggravate their mobility impairments, increasing the impact of the disease (Gilat et al. 2018). Also, people with postural instability and gait disorders (PIGD) subtype show more cognitive decline compared to the tremor-dominant subtype (Arie et al. 2017). People with dementia also show mobility impairments as their disease progresses (Van Ooteghem et al. 2019). Only recently studies of cortical involvement outside the motor cortical regions are being undertaken in balance and gait control in PD.

This thesis attempts to improve our understanding of how the higher-order cortical systems are associated with different aspects of balance and gait.

1.3.5 Impairments of Balance and Gait in PD

PD impairs all domains of balance, as well as gait. That is, APAs are small and weak, and sometimes repetitive (in freezing of gait); APRs are weak with short steps; postural sway is large and jerky, especially when somatosensory inputs are disrupted by standing on compliant foam; and dynamic stability of the trunk while walking is impaired, resulting in slow gait (short strides), increased variability in gait and slow turns (Hasegawa et al. 2019a). However, balance and gait impairments are heterogeneous in individuals with PD and not all motor balance and gait impairments improve with treatment, consistent with independence of neural control (Curtze et al. 2015; Fay B. Horak et al. 2016).

1.4 Balance and Gait Assessment

This thesis examines the functional brain networks associated with both clinical and instrumented measures of balance and gait. We use the MDS-UPDRS Part III to clinically assess severity of motor signs and its PIGD sub-score to assess balance/gait impairments in people with PD (See Chapters 3 and 4).

The most widely used clinical rating scale for severity of PD is the Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS). MDS-UPDRS consists of four parts of evaluation: Part I consists of question pertaining to nonmotor experiences of daily living, Part II concerns

motor experiences of daily living, Part III is the motor examination, and Part IV concerns motor complications (Goetz et al. 2008). Part III motor examination is widely used in clinical and research settings to evaluate motor signs, including the balance and gait impairments in PD. The PIGD sub-score of Part III is often used to evaluate the balance impairments. Unfortunately, the clinical rating scales that are used currently suffer from rater bias, limited interrater reliability and poor resolution of mobility (balance and gait) disorders. Objective measures of mobility can add unbiased, quantitative and simple measurements to evaluate the disease and disease progression.

In addition to relating clinical assessments of motor signs, balance and gait with the structural and functional characteristics of the brain, this thesis also relates objective measures of balance and gait (See Chapters 2 and 4). With technological advancements, wearable inertial sensors (that include a tri-axial gyroscope, accelerometer, and magnetometer) have made it possible to develop quick, objective measures of balance and gait impairments in both research and clinical settings (Mancini, King, et al. 2011). Synchronized data from sensors placed on body can quantify change in orientation of the limbs and axial trunk (sternum and lumbar areas, for example) to quantify postural movements. An inertial sensor on the lumbar segment is close to the body center of mass and thereby can quantify body sway to maintain equilibrium while standing still as well as the size of the APA prior to the first step before walking. Inertial sensors on the feet can be used to accurately measure stride length during gait or the size of a step to recover equilibrium when perturbed.

1.5 Role of Magnetic Resonance Imaging in PD Research

This thesis focuses on both structural volume measures and rs-fMRI network connectivity of the whole brain and how they relate to different aspects of balance and gait in people with PD and similar aged, healthy adults.

The major advantage of MRI is that it enables the study of morphological and functional changes in the subcortical and cortical brain regions noninvasively. MRI findings were considered normal in PD for a long time. With progress in MR techniques and image processing methods, now there are structural, functional and connectivity changes that can be detected. We can use MRI to determine brain correlates of behavioral features observed in PD using various techniques like structural volume and thickness measurements, diffusion imaging, functional imaging, etc. With improvements in surface-based registration methods we can better the registration compared to the volume-based registration methods. With surface-based method, we can treat the cortical gray matter as a 2D plane and cortical measures and functional data can be evaluated in this plane. We can measure more accurate information about the cortical features, as the convoluted cortical sheet is geometrically better manipulated as a 2D surface than a 3D volume. The ROI delineations are also more accurate as the convoluted brain is flattened in 2D surface plane. Also, surface-based registration methods are better at eliminating noise signals from CSF or white matter. Computationally, surface based registration methods are relatively easier problem to handle (Glasser et al. 2013).

Functionally, MRI has enabled us to investigate patterns of brain connectivity, large-scale functional network organization and how these interact

with behavior. Resting state functional MRI (rs-fMRI) has enabled us to measure spontaneous synchronized neuronal activity between spatially diverse regions across the brain through spatiotemporal correlations of the blood oxygen level dependency (BOLD) signal (Fox and Raichle 2007). One of the advantages of rs-fMRI is the ability to quickly characterize whole brain, wide ranging networks and how different networks interact. Rs-fMRI identifies spatially distinct brain regions that demonstrate repeated patterns of activity in the absence of a task or external stimulus. Using these rs-fMRI networks, we can identify functionally distinct regions, such as motor regions, visual regions, etc. Large bodies of work have characterized these patterns in synchronized neuronal activity that make up different resting-state networks (Power et al. 2011; Gordon et al. 2016; Grayson and Fair 2017; Ji et al. 2019). More importantly, these rs-fMRI networks have been identified to be altered with various disorders of the brain.

Rs-fMRI studies in PD showed that sensorimotor network and cortico-striatal network is one of the most altered in PD (Tessitore et al. 2014; Tahmasian et al. 2015). Dopamine depletion leads to a decreased coupling in the cortico-striatal sensorimotor network and between the striatum and the brainstem and increased coupling in the associative network probably as a compensatory network and were modulated by medication (Sharman et al. 2013; J. A. Obeso et al. 2017). In PD, it is not only the dopaminergic systems, but other non-motor systems are also impacted and widespread functional abnormalities are observed that cannot be limited to basal ganglia. We further do not have an understanding of how these functional abnormalities impact balance and gait. While there are many rs-fMRI studies looking at differences between PD and healthy adults, there are very few that have looked at the functional connectivity

that correspond to balance and gait impairments in PD (Tahmasian et al. 2015, 2017; de Lima-Pardini et al. 2020).

1.6 Challenges in Imaging

Applications of MRI to study the neuronal firing patterns however, require methodological considerations specific to the population being studied. PD is a geriatric illness with changes in the brain that are accompanied by the changes due to aging as well as neurodegenerative disorder. So, we need to take measures that account for the aging-related changes during the MRI processing steps. Typically, in order to make group comparisons, individual subject brains are registered to a standard template brain. The most common used template brain is the standard MNI template made from young adults (average age about 25 years). However, using this atlas in older population is problematic due to the age-related morphological changes (for example, slightly larger ventricles) in the older population that are unaccounted in the MNI template. One way we addressed the issue right at the registration step was by using a study-specific, intermediary template to co-register along with the standard MNI template. In order to account for age-related changes, we created an intermediate template from the age-matched neurotypical, older adults in our cohort. We also performed analyses for both PD and older adults (whenever data was available for both cohorts) to see the alterations in people with PD, compared to the age-matched, older adults.

We also modified the atlas that is used to delineate regions of interests (for functional analysis). PD affects basal ganglia regions that consists of striatum and smaller regions like substantia nigra and subthalamic nucleus. However,

most automated segmentation tools do not offer segmentations for the smaller regions. We found it necessary to delineate regions of interest that are specifically impacted by PD. So, we created a subcortical atlas which has a combination of subcortical regions implicated in PD (named Subcortical-Basal ganglia network in this thesis) and the rest that are standardly used in FreeSurfer (named Subcortical-Cerebellar network in this thesis) (Dale, Fischl, and Sereno 1999; Fischl et al. 2004) (See Chapter 3 and 4).

One of the primary requirements for accurate MRI is to not move in the scanner. However, PD is a motor neurodegenerative disease affecting the ability to lie still. People with PD have poor postural alignment with rigid necks that makes it difficult to position the head comfortably in supine position as well as having resting tremor, especially when measured in the Off-levodopa state, as in this thesis. These abnormal postures and involuntary movements are exaggerated during their time without medication. So, we implemented stringent processing steps to avoid motion-related artefacts. We implemented the best processing pipeline measures to account for and minimize motion artefacts.

1.7 Goal of the Dissertation

The goal of this dissertation is to improve our understanding of brain networks involved in motor disorders, specifically balance and gait disorders, through associations between structural/functional characteristics of the brain and the motor behaviors in people with PD and older adults. This research work used two neuroimaging measures (1. brain volumes and 2. Resting state functional connectivity) to be associated with objective and clinical measures of balance and gait. Neurological diseases, like PD, that specifically impairs

balance and gait, help us understand the role of brain regions and networks in control of mobility and how brain disorders are related to quantitative measures of balance and gait.

Structural MRI is increasingly being investigated as a marker for disease progression. However, there are not many studies that have used objective measures, beyond gait speed, and to relate to brain volume measures and motor performance. The aim of **Project 1** (Chapter 2) was to relate brain structure with balance and gait. We examined the global and regional brain volumes and objective measures of four domains of balance and gait in people with PD and OAs. We hypothesized that impairments of different domains of balance and gait in PD will be associated with atrophy in different brain areas.

Little is known about the inherent functional network changes in the brain with PD that may be related to motor severity and balance and gait impairments. Projects 2 and 3 were focused on identifying the resting state function network interactions that are related to clinical and objective mobility measures in people with PD and OAs. The aim of **Project 2** (Chapter 3) was to identify the most significant resting state functional networks that are associated with motor signs in people with PD. We hypothesized that parkinsonian motor signs would be associated with higher order cognitive networks, as well as sensorimotor and basal ganglia networks.

The aim of **Project 3** (Chapter 4) was to identify specific resting state functional brain network connectivities that are associated with three domains of balance control (APAs, APRs and postural sway in stance) in people with PD and older adults. We hypothesized that different functional networks are involved in different domains of balance control and the people with PD will involve more cortical networks for postural control compared to older adults.

Chapter II: Relationship Between Brain Volumes and Objective Balance and Gait Measures in Parkinson's Disease

This chapter has been reformatted for inclusion in this dissertation from:

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2.1 Abstract

Background: Instrumented measures of balance and gait measure more specific balance and gait impairments than clinical rating scales. No prior studies have used objective balance/gait measures to examine associations with ventricular and brain volumes in people with Parkinson's disease (PD).

Objective: To test the hypothesis that larger ventricular and smaller cortical and subcortical volumes are associated with impaired balance and gait in people with PD.

Methods: Regional volumes from structural brain images were included from 96 PD and 50 control subjects. Wearable inertial sensors quantified gait, anticipatory postural adjustments prior to step initiation (APAs), postural responses to a manual push (APR), and standing postural sway on a foam surface. Multiple linear regression models assessed the relationship between brain volumes and balance/gait and their interactions in PD and controls, controlling for sex, age and corrected for multiple comparisons.

Results: Smaller brainstem and subcortical gray matter volumes were associated with larger sway area in people with PD, but not older adults. In contrast, larger ventricle volume was associated with smaller APAs in older adults, but not in people with PD. A sub-analysis in PD showed significant interactions between freezers and non-freezers, in several subcortical areas with stride time variability, gait speed and step initiation.

Conclusions: Our models indicate that smaller subcortical and brainstem volumes may be indicators of standing balance dysfunction in people with PD whereas enlarged ventricles may be related to step initiation difficulties in normal aging. Also, multiple subcortical region atrophy may be associated with freezing of gait in PD.

2.2 Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by a multitude of balance and gait disturbances (José A. Obeso et al. 2000). In fact, gait in PD is characterized by short, shuffling steps, freezing of gait and difficulty initiating gait. Standing postural sway is also affected by PD, even early in the disease (Chastan et al. 2008; Mancini, Horak, et al. 2011). These disturbances, together with impaired postural responses, lead to impaired balance and gait, falls and poor quality of life (Debû et al. 2018; Fasano, Canning, et al. 2017). Patterns and severity of balance and gait dysfunction vary among patients with PD, as well as among the older adults without neurological disease.

In older adults without overt neurologic disease, slow gait has been associated with ventricular dilation, generalized brain atrophy, and white matter disease (Wilson et al. 2019). Although ventricular enlargement has not been associated with PD in general, ventricular dilatation has been associated with dementia in people with PD (Apostolova et al. 2010) and increased motor impairments in PD as measured by the

MDS-UPDRS Part-III scores (M. M. Lewis et al. 2009; Mak et al. 2017). However, the relationship between structural changes in the brain and balance and gait dysfunction in PD remains poorly characterized. To our knowledge, no prior studies have used instrumented measures of balance and gait to examine specific aspects of mobility that relate to ventricular dilation or global and regional cortical and subcortical volume atrophy in people with PD.

Balance and gait control depend on both cortical and subcortical structures (Mancini, Nutt, and Horak 2020b). However, balance and gait are likely independent functions that may be controlled by different brain regions (Fay B. Horak et al. 2016; Lord et al. 2013). Functional MRI studies have shown activations in cortical motor regions, brainstem and cerebellum while performing mental imagery of locomotion both in older adults and in people with PD (Jahn et al. 2008; Karachi et al. 2010). Instead, for balance control, a PET study has shown decreased thalamic cholinergic innervation associated with increased sway measured on a balance platform in people with PD (Müller et al. 2013). Freezing of gait in PD has been related to atrophy of subcortical structures, cortical motor areas as well as cortical non-motor areas, including the inferior parietal lobe (Mirelman et al. 2019). Despite the fact that neuroimaging studies show that subcortical and cortical regions are both impacted in PD, either by volumetric changes, loss of neurotransmitters or change in functional connectivity, the relationship between loss of cortical and subcortical gray matter volumes and specific types of balance and gait impairments is unknown. Since gray matter loss in many cortical and subcortical regions is associated with freezing of gait (Bharti et al. 2019), the relationship between brain volumes and balance and gait impairments may differ in freezers and non-freezers. There has been no previous comparison of brain structural changes related to specific aspects of balance and gait in freezers versus non-freezers.

Here, we hypothesize that larger ventricular volume and reduced cortical and subcortical volumes are associated with impaired balance and gait measures in people with PD. Specifically, we predict that impairments of different domains of balance and gait in PD will be associated with atrophy in different brain areas. We also hypothesize that atrophy in different cortical and subcortical regions are associated with different domains of balance and gait in freezing of gait. To objectively characterize multiple domains of balance and gait we used wearable inertial sensors (Hasegawa et al. 2020) and according to a common clinical test, characterize four domains of balance and gait: gait, anticipatory postural adjustments (APA) prior to gait initiation, automatic postural responses (APR) to external perturbations and postural sway in stance (Fay B. Horak, Wrisley, and Frank 2009).

This study examines the relationship between ventricular size, global and regional brain volumes and objective measures of four domains of balance and gait.

2.3 Materials and Methods

2.3.1 Study Sample

Data were collected from 100 people with Parkinson's disease (PD) and 58 older adult subjects. Subjects with PD had idiopathic PD clinically diagnosed by a movement disorders specialist using UK Brain Bank Criteria (Hughes et al. 1992). *Inclusion criteria* for subjects were: (1) between 50 and 90 years old, (2) no major musculoskeletal or peripheral disorders (other than PD) that could significantly affect their balance and gait, and (3) ability to stand, walk unassisted for 20 feet and to follow instructions. Older adults within the same age range with no neurological and mobility issues were recruited from the community. Exclusion criteria for all groups were: metal implants or any other

contraindications for brain imaging. In addition, people with PD and severe tremor were excluded to ensure good quality MRI. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Oregon Health & Science University, OHSU (#4131) and the OHSU/VAPORHCS joint IRB (#8979). These participants were a subset of subjects in a larger interventional study (Clinical Trials NCT02231073 and NCT02236286) and these MRI scans were acquired on average 6 (± 13) days before or after the baseline balance and gait testing (median: 2 days, range: 0-105 days).

Out of 158 subjects (older adults and people with PD), 12 subjects (4 PD and 8 control subjects) were removed from the imaging data due to issues with registration of native brain to the atlas resulting in poor segmentation of white and gray matter caused by motion artifacts. Out of these 12 subjects, 3 PD and 2 control subjects had larger ventricles, characterized as 1.5 standard deviation from the control mean. Our final sample sizes were 96 people with PD and 50 control subjects (see **Table 2.1** for more details). Of the 96 with PD, 40 had freezing of gait as indicated by the New Freezing of Gait Questionnaire (NFogQ) (Nieuwboer et al. 2009).

Table 2.1. Demographics and clinical characteristics

	Control	PD	Range (min-max)	t/χ^2 /KS-value, p-value
N	50	96		
Age (mean (SD))	69 (8.1)	68.4 (7.9)	50-88	0.46, p = 0.7
Sex (F/M)	21/29	32/57	-	0.27, p=0.6
MDS-UPDRS Part-III	NA	39.6 (11.7)	17-72	
PIGD	NA	4.94 (3.0)	0-15	
Disease duration	NA	6.3 (5.1)	0.3-24.6	

LEDD	NA	743.5 (101)	0-8680	
MDS-UPDRS total	NA	66.5 (20.3)	29-123	
H&Y	NA	2.27 (0.6)	2-4	
MoCA	26.8 (2.2)	25.4 (3.7)	21-30 (OA)	0.19, p=0.3
			15-30 (PD)	
MiniBESTest	24.0 (2.5)	18.5 (5.0)	4-28	0.5, p<0.001
ABC*	97 (4)	85 (25)	25-100	0.57; p < 0.001

* median and inter quartile range was computed instead of mean/SD; PIGD – 4-items of Postural instability and gait dysfunctions; For group comparisons, t-test/ Kolmogorov–Smirnov/chi-square were performed to test significant differences between groups

2.3.2 MRI Acquisition and processing

T1 weighted images were acquired using MPRAGE sequence using a 3 Tesla Siemens Trio scanner with a 12-channel head coil. T1-weighted image protocol is as follows: TR=2300 ms, TE=3.58 ms, voxel size=1mm x 1mm x 1.1mm, slices=160, FoV=256 mm, flip angle=10 degrees. T2-weighted images were acquired using SPC sequence using the following parameters: TR=3200 ms, TE=497 ms, resolution=1 mm isotropic, slices=160, FoV=256 mm. Due to an upgrade of MRI scanner during the phase of data collection, part of subjects were scanned with a 3 Tesla Siemens Prisma scanner with a 32-channel head coil. T1-weighted image acquisition protocol: TR=2500 ms, TE=2.88 ms, voxel size=1 mm x 1 mm x 1 mm, slices= 176, FoV = 256 mm, flip angle=8 degrees. T2-weighted images were acquired using SPC sequence using the following parameters: TR=3200 ms, TE=565 ms, resolution=1 mm isotropic, slices=176, FoV=256 mm.

Data was processed using an adapted version of the workflow pipelines from the human connectome project (HCP), as reported previously (Glasser et al. 2013; Miranda-Domínguez et al. 2020; Silva-Batista et al. 2021; Dsturge, Earl, and Kathy-snider 2019). Briefly, denoised T1-weighted and T2-weighted volumes were first aligned to the MNI atlas' AC-PC axis and then non-linearly registered to the MNI atlas (Jenkinson et al. 2012; Klein et al. 2009; Dale, Fischl, and Sereno 1999). Then, optimally aligned T1-weighted images were segmented using recon-all from FreeSurfer. Segmentations were improved by using the enhanced white matter-pial surface contrast of the T2-weighted image. All volume measures were divided by intracranial volume (ICV) to control for differences in head size. Total ventricular volume was computed as the sum of the lateral (including the inferior lateral), third and fourth ventricular volumes from the FreeSurfer outputs. Subjects were classified as normal or large size ventricle based on mean ventricle volume of older adults to select subjects to check for evidence of normal pressure hydrocephalus as accounted by the callosal angle.

The following brain volumes were extracted from FreeSurfer: Total cortical, subcortical and cerebellar volumes. Right and left cerebellar gray matter volumes from the FreeSurfer outputs were combined to get the total cerebellar gray matter volume. Total subcortical volumes outputs from FreeSurfer consisted of the following regions: sum of right and left putamen, pallidum, caudate, thalamus, hippocampus, accumbens, and amygdala. Bilateral cortical parcellations (Desikan-Killiany) were mapped into four lobes: frontal, parietal, temporal and occipital lobes using the FreeSurfer lobe mapping (Klein and Tourville 2012).

2.3.3 Balance and Gait Assessment Outcome Measures

Participants underwent instrumented assessment of balance and gait in the laboratory. All data in people with PD were collected in the practical "off" levodopa state,

withholding medication for at least 12 hours. People with PD were clinically rated by a trained examiner on the Motor Section (III) of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Postural instability and gait dysfunction components were estimated using the sum of 4 posture and gait items (sit-to-stand, standing posture, walking and pull test) of the MDS-UPDRS Part-III. Each participant was outfitted with 8 inertial sensors (APDM wearable technologies, Portland, OR, USA), worn on the sternum, lumbar spine, bilaterally on the wrists, shins, and feet. Each inertial sensor recorded tri-axial accelerations, tri-axial angular velocities, and magnetic field at 128 Hz. Subjects from both cohorts were sometimes unable to complete the balance or gait tasks due to various reasons, including postural instability, fatigue or limited time, or data quality was compromised. Those data were marked as missing.

We chose the balance and gait metrics for the analysis based on our previous study identifying the most reliable, discriminative, nonredundant measures most sensitive to PD compared to age matched control subjects (Hasegawa et al. 2019a). Best performing metrics from each of the four different domains of balance and gait were chosen: 1) Anticipatory postural Adjustments (APA) prior to gait initiation: first step Range of Motion of the leg (N=127), 2) Automatic postural responses (APR) to a backward external perturbation: step height in vertical direction (N=114) 3) Postural Sway during quiet stance: root mean square of acceleration time series in anteroposterior direction (Sway RMS AP standing on foam) when standing 30 seconds with eyes open on a foam surface (N=122) and 4) Dynamic Balance during walking (Spatiotemporal gait measures; N=134). We previously showed that standing on foam with eyes open was the most sensitive and specific metric to PD compared to standing on firm surface or with eyes closed on firm/foam surface (Hasegawa et al. 2019a). Since gait is considered to have multiple sub-domains (Wilson et al. 2019), the following gait

metrics were chosen for pace and turning, rhythm, upper body stability and variability: gait speed, turn velocity, stance time, arm range of motion and gait cycle duration variability (SD), respectively. This study was performed on a subset of subjects from our previous publications (N=236; (Jung et al. 2020; Hasegawa et al. 2019a)) who had high quality brain MR images at baseline (N=146). For detailed definitions of the metrics and how the metrics were selected, refer to Hasegawa et al. (2019) (Hasegawa et al. 2019a).

2.3.4 Statistical Analysis

Using a general linear model (GLM), analysis of covariance (ANCOVA) was used to assess the relationship between PD status (PD/Control) and brain volumes (ventricular volumes, global and regional subcortical and cortical brain volumes) with balance and gait metrics, while controlling for covariates. The ANCOVA model was run with group and normalized brain volumes as main effects, in addition to, the interaction between group and brain volumes as independent variables. The reported main effects use older adults as the reference group and PD as the indicator group. Balance and gait metrics were dependent variables. We controlled for the covariates age and sex as both are known to affect brain volumes (Scahill et al. 2003; Lotze et al. 2019) and age is known to affect balance and gait metrics (Park et al. 2016). ICV was not included as an additional covariate in the model because the brain volumes were used as a proportion of ICV. A sub-analysis was performed on people with PD. ANCOVA was used to assess whether the relationships between brain volumes with balance and gait metrics differed for freezers versus non-freezers (controlling for age, sex and disease duration). The reported main effects use non-freezers as the reference group and freezers as the indicator group. Regression analysis between balance and gait metrics and clinical scores (MDS-UPDRS Part-III and PIGD components) were performed for the PD group, controlling for sex and age. Multiple comparisons correction was performed at the model

level for all the outcome metrics and clinical scores, as well as brain volumes, with a False Discovery Rate (FDR) threshold of 0.05. The reported model p-values are FDR corrected. Seven subjects had Cook's distance more than $4/n$ while checking for potential outliers but removing these 7 subjects did not change the results, so they were kept in the cohort. All continuous variables were standardized to Z-scores in the regression analysis.

We assessed the group differences on following variables: T-tests were performed to check for PD versus control group differences for age, MoCA, MiniBESTest score, Activity Specific Balance Confidence (ABC) Scale and brain volumes for normally distributed data or Kolmogorov-Smirnov-test otherwise. A chi-square test was performed to test differences between sex in PD and control groups. We used Pearson's correlation to assess the relationship between the following variables: (1) Brain volumes were correlated with age and (2) Subcortical brain volumes were correlated with ventricle volume. All the data analyses were performed using R, version 3.4.3.

2.4 Results

2.4.1 Sample Characteristics

Average ages did not differ between the older adults and people with PD. 71 people with PD in the cohort were H&Y stage 2, 7 subjects were stage 3 and 8 subjects were stage 4. The demographic and clinical features of the participants are in **Table 2.1**.

2.4.2 Brain Volumes and Balance and Gait Metrics in PD and Control Groups

Group average ventricular volumes were similar between people with PD and older adults. Mean ventricular volume for people with PD was 1.9% of ICV (SD: 0.9% of ICV) and for the older adults was 2.1% of ICV (SD: 1% of ICV) (**Table 3.2**). When controlled for age and sex, bilateral cortical gray matter volume, occipital, parietal and temporal lobe volumes and putamen volumes were smaller in the PD group (Table 2). When classified as larger ventricle size based on the control mean plus 1 SD threshold, 8 older adult subjects and in 15 PD subjects showed larger ventricles. A neurologist (A.G.) reviewed the brain images and videos of the MDS-UPDRS of subjects with larger ventricles and did not see evidence of normal pressure hydrocephalus (NPH), as accounted by either callosal angle or wide-based gait. The callosal angle was greater than 90 degrees in all subjects with enlarged ventricles indicating absence of NPH.

As observed in our larger, parent study (n=223) (Hasegawa et al. 2019a), the balance and gait metrics in our sub-cohort (n=146) were worse in people with PD compared to older adults (**Table 2.2**). However, this study is a subset (N=146/223) of those previously reported results, limited to those with high quality brain imaging data.

Table 2.2. Mean (SD) of the brain volumes and balance and gait metrics in Control and PD groups with group difference test significance values

Brain region		Control	PD	t-, p- values
Global region (x10 ⁻²)	Ventricle	2.1 (1.0)	2.0 (0.8)	-0.3, 0.79
	Subcortical gray matter	3.3 (0.3)	3.2 (0.3)	1.5, 0.16

	Cerebellum	8.2 (0.8)	7.9 (0.9)	1.7, 0.12
	Cortical gray matter	29.8 (2.7)	29.2 (2.2)	2.5, 0.03
Sub-regions - cortical (x10 ⁻²)	Frontal lobe	11.3 (1.1)	11.2 (0.9)	1.9, 0.12
	Occipital lobe	3.1 (0.2)	2.9 (0.3)	2.5, 0.03
	Parietal lobe	7.9 (0.7)	7.7 (0.6)	2.7, 0.03
	Temporal lobe	6.8 (0.7)	6.7 (0.6)	2.6, 0.03
Sub-regions - subcortical (x10 ⁻³)	Caudate	4.4 (0.6)	4.2 (0.67)	1.0, 0.35
	Pallidum	1.7 (0.21)	1.7 (0.23)	-0.04, 0.96
	Putamen	5.7 (0.74)	5.3 (0.73)	2.9, 0.03
	Thalamus	8.5 (0.95)	8.3 (1.1)	1.0, 0.79
	Accumbens	0.58 (0.13)	0.55 (0.12)	1.7, 0.13
	Hippocampus	4.9 (0.7)	4.8 (0.66)	1.7, 0.13
	Amygdala	1.8 (0.28)	1.7 (0.25)	1.8, 0.13
	Brainstem	14.0 (1.3)	13.6 (1.5)	1.5, 0.17
Balance and gait Domain				
	Metric	Control	PD	t- & p-values
APA	1st step RoM (deg)	39 (7)	35 (5)	5.3, <0.001
APR	Step height (cm)	6.5 (3)	4.7 (2.5)	3.7, <0.001
Sway	RMS AP, on foam	0.099 (0.035)	0.12 (0.034)	-3.6, <0.001
Gait	Gait speed (m/s)	1.14 (0.1)	0.96 (0.1)	6.5, <0.001
	Turn velocity (deg/s)	191 (28)	148 (30)	10.0, <0.001
	Stance time (s)	60.1(1.7)	61.2 (2.2)	-3.16, 0.002
	Arm RoM (deg)	50.4 (18)	29 (12)	7.4, <0.001
	Stride Time Variability (SD)*	0.02 (0.01)	0.03 (0.01)	0.23, 0.06

* median and inter quartile range was computed instead of mean/SD and KS test significant value computed instead of t-test; var – variability; SD – standard deviation; deg – degree; s – seconds; cm – centimeter; m – meter; t-values and p-values have been corrected for age and sex

2.4.3 Brain Volumes Related to Balance and Gait

Using a GLM, ANCOVA was performed to determine how normalized brain volume was associated with balance/gait metrics in PD and older adult groups (controlling for age and sex). The main effect for group status was statistically significant for all balance and gait metrics, with the exception of stride time variability. The group with PD showed worse balance and gait. The models that also had statistically significant brain volume main effects or interaction effects are summarized in **Table 2.3**. The following main effects relating brain volumes with balance or gait metrics were found to be significant in older adults (reference group): (1) smaller brainstem volumes, smaller cerebellar volumes, and smaller parietal lobe volumes were associated with smaller (APR) reactive step height (Figures 2.1A, B, and C), (2) smaller amygdala volumes and smaller frontal lobe volumes were associated with larger stride time variability (Figures 2.1D and E) and (3) larger ventricular volumes and smaller occipital lobe volumes were associated with larger postural sway (root mean square in anteroposterior direction (RMS AP)) standing on foam (Figures 2.1F and G).

The significant interactions reflecting how the groups differed in their relationships between brain volumes and balance/gait metrics were: (1) people with PD, but not older adults, with smaller brainstem volumes and smaller total subcortical volumes showed larger (more abnormal) postural sway standing on foam (RMS AP; Figures 2.2A and B) and (2) older adults, but not people with PD, with larger ventricular volume was associated with smaller (APA) first step of gait initiation (Figure 2.2C).

Table 2.3. Significant standardized beta coefficients with p-values from ANCOVA for main and interaction effects between brain volumes and balance/gait metrics in people with PD and older adults

Balance & Gait Metrics	Brain Volumes	Model		Group Main Effects		BrainVol. Main Effects†		Interaction Effects*	
		F	p	β	p	β	p	β	p
APR step height	Brainstem	7.68	<0.01	-0.57	<0.01	0.37	0.01	-0.23	0.19
	Cerebellum	7.69	<0.01	-0.58	<0.01	0.35	0.01	-0.14	0.44
	Parietal lobe	7.87	<0.01	-0.54	<0.01	0.26	0.04	0.04	0.82
Stride time variability	Amygdala	4.84	<0.01	0.29	0.08	-0.34	0.01	0.22	0.20
	Frontal lobe	4.45	<0.01	0.31	0.07	-0.28	0.03	0.15	0.38
Sway RMS	Total ventricle	6.64	<0.01	0.60	<0.01	0.25	0.04	0.17	0.30
AP standing on foam	Occipital lobe	4.30	<0.01	0.52	<0.01	-0.31	0.03	0.29	0.11
	Brainstem	5.62	<0.01	0.58	<0.01	0.07	0.63	-0.40	0.02
	Subcortical	8.31	<0.01	0.53	<0.01	-0.15	0.26	-0.39	0.02
APA 1st step RoM	Total ventricle	8.53	<0.01	-0.86	<0.01	-0.24	0.05	0.33	0.04

†Main effects coefficients are reported for older adults (reference group)

*To get the beta coefficient of the PD group sum the interaction effects coefficients and the brain volume main effects in HC. Model $p < 0.05$ FDR corrected, uncorrected $p < 0.05$ for each predictor. HC – Older adults; RMS – Root mean square; AP – Anteroposterior; APA – Anticipatory postural adjustments; RoM – Range of motion; GM – gray matter; β – standardized beta coefficient

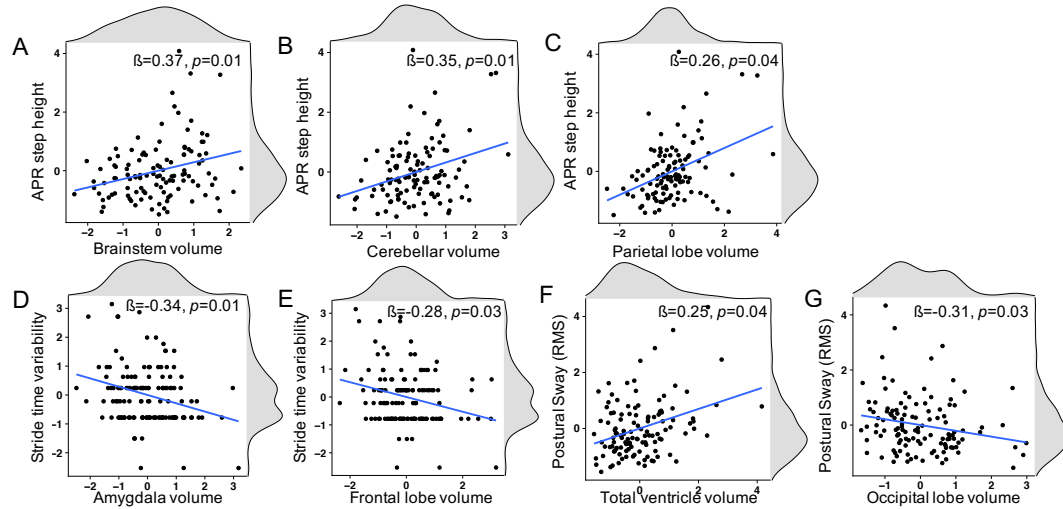


Figure 2.1. Scatterplot of significant main effects of the relationship between brain volumes with balance and gait metrics for older adults.

Distribution plots of brain volumes and balance and gait metrics are shown on the top and right margins. Standardized beta coefficients are shown at the top. X and y axis are Z-score of the brain volumes and balance and gait metrics. APA – anticipatory postural adjustments, RMS – root mean square, RoM – range of motion.

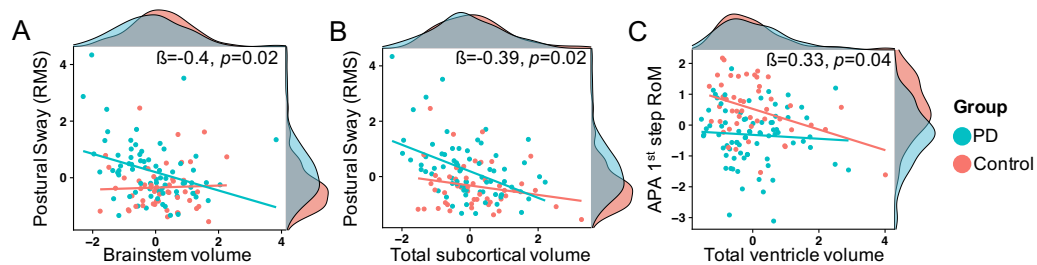


Figure 2.2. Scatterplots of significant interaction effects between PD and control group for the relationship of brain volumes with instrumented balance and gait metrics.

PD are represented in blue/cyan and control in red. Distribution plots of brain volumes and balance and gait metrics are shown on the top and right margins. Standardized beta coefficients are shown at the top. X and y axis are Z-score of the brain volumes and balance and gait metrics. RMS – root mean square, APA – anticipatory postural adjustments, RoM – range of motion.

Sub-analysis for freezers and non-freezers in PD: ANCOVA was used to determine how normalized brain volume was associated with balance/gait metrics in

freezers versus non-freezers (controlling for age, sex and disease duration). The main effect for group (freezer/non-freezer) was statistically significant for (APA) first step of gait initiation and for gait speed with worse balance and gait in freezers. The main effect for brain volume for non-freezers (reference group) was significant for subcortical areas associated with sway standing on foam and for several cortical areas associated with (APA) first step of gait initiation and (APR) reactive step height (See supplementary **Table 2.S1** for all results). We found several significant interactions between group (freezers/non-freezers) and how brain volumes associated with balance/gait metrics. Freezers with larger ventricle volume ($\beta=0.47$, $p=0.02$) and smaller cerebellum ($\beta=-0.49$, $p=0.02$), smaller brainstem ($\beta=-0.49$, $p=0.01$) and hippocampal ($\beta=-0.45$, $p=0.03$) volumes showed larger stride time variability. Freezers with smaller cerebellar volumes ($\beta=0.41$, $p=0.04$) showed slower gait speed. Non-freezers with smaller cerebellar volumes ($\beta=0.44$, $p=0.04$) showed shorter first step of gait initiation (APAs) while freezers showed larger APAs (For main and interaction effects plots see figures 2.S1 and 2.S2).

2.4.4 Brain Volumes Related to Clinical Scores

Significant associations between brain volumes and gait/posture were found only with the 4-item, PIGD component of the MDS-UPDRS Part-III and not the total score. Smaller brain volumes were associated with larger PIGD. Smaller total subcortical volumes ($\beta = -0.24$, $p = 0.04$), smaller putamen volumes ($\beta = -0.25$, $p = 0.017$), smaller accumbens volumes ($\beta = -0.26$, $p = 0.03$), smaller hippocampus volumes ($\beta = -0.33$, $p < 0.01$), smaller amygdala volumes ($\beta = -0.25$, $p = 0.02$) and smaller temporal lobe volumes ($\beta = -0.39$, $p < 0.01$) were associated with larger PIGD.

2.4.5 Relationship Between the Brain Volumes and Age:

Correlation of brain volumes with age showed that thalamus ($r = -0.42$, $p < 0.01$), brainstem ($r = -0.26$, $p = 0.03$) and occipital lobe ($r = -0.25$, $p = 0.03$) were correlated with age in the PD group alone, but not in the control group. The rest of the brain volumes were correlated with age in both the control and PD groups.

The normalized total ventricle volume correlated with volumes of normalized total subcortical volume ($r = -0.58$, $p < 0.01$), putamen ($r = -0.36$, $p < 0.01$), thalamus ($r = -0.63$, $p < 0.01$), accumbens ($r = -0.52$, $p < 0.01$), hippocampus ($r = -0.68$, $p < 0.01$), amygdala ($r = -0.57$, $p < 0.01$) and brainstem ($r = -0.47$, $p < 0.01$). However, the volumes of normalized pallidum and caudate had no significant correlation with ventricle volume. (for all significant correlation values, see supplementary **Table 3.S2**).

2.5 Discussion

2.5.1 Summary of Results

This study demonstrated that brain ventricular and gray matter volumes are significantly associated with instrumented measures of balance and gait, albeit with different patterns, in people with PD and age-matched older adults. In the primary analysis that consisted of both older adults and people with PD, the following associations were significant in older adults: enlarged ventricle and smaller occipital lobe volumes were associated with larger postural sway; smaller brainstem, cerebellar and parietal lobe volumes were associated with smaller reactive step height; and smaller amygdala and frontal lobe volumes were associated with larger stride time variability. Smaller brainstem and subcortical volumes were predictive of increased postural sway (while standing on foam causing disrupted surface somatosensory inputs) in people with

PD, but not the older adults. Larger ventricular volume in older adults, but not in people with PD, were associated with impaired gait initiation. A sub-analysis in people with PD, alone, showed that subcortical volumes associated with postural sway whereas cortical areas associated with APAs and APRs in non-freezers. Freezers, but not non-freezers showed associations between atrophy in several brain areas with larger stride time variability and showed the opposite relationship between cerebellar volume and APA size than non-freezers. People with PD with smaller total subcortical, putamen, accumbens, hippocampus, amygdala and temporal lobe volumes also showed worse PIGD (4 items from the MDS-UPDRS Part-III). As shown previously, putamen volume was significantly smaller in PD than in the control group when controlled for age and sex (Pitcher et al. 2012). Although ventricular volume was not larger in people with PD, total cortical GM volume and occipital, parietal and temporal lobe volumes were smaller in people with PD than in older adults, consistent with the literature (Mechelle M. Lewis et al. 2016).

2.5.2 Brain volumes related to postural sway

We found that ventricular enlargement and occipital lobe volumes were related to postural sway standing on foam with eyes open in older adults. Postural sway, especially when standing on foam, is known to be larger than normal in people with PD, older people without PD, and is related to fall risk (Schoneburg et al. 2013; Hasegawa et al. 2019a). Ventricular volume is an indirect measure of brain atrophy and could be used as a surrogate marker of neuronal loss. Our results are consistent with a previous study showing that larger volumes of supratentorial CSF and the ventricular system are associated with increased postural sway in older adults (Sullivan et al. 2009). Since there is a correlation between many subcortical volumes and ventricular volume, loss of gray matter in the subcortical volumes maybe an important contributor to ventricular

enlargement and increased standing postural sway. The occipital lobe may be involved in visual feedback for control of postural sway, especially when surface somatosensory inputs are disrupted and in older people, who rely on vision for postural control more than younger people (Peterka and Black 1990). Subjects with smaller occipital lobe volumes due to right-sided stroke showed greater sway eyes open, consistent with a role of the occipital lobe in visual control of postural sway (Manor et al. 2010).

People with PD show an association between brainstem volume and total subcortical volumes with postural sway when standing on foam with eyes open. We previously showed that standing on foam with eyes open, which compromises use of somatosensory information for balance, was the most sensitive and specific standing condition for PD (Hasegawa et al. 2019a). The brainstem is known to be one of the critical regions involved in both static (Jahn et al. 2008) and dynamic (Ferraye et al. 2014) posture control. Brainstem, along with other subcortical regions like basal ganglia, thalamus and cerebellum play a key role in human balance control and are most affected in people with balance disorders like PD (Surgent et al. 2019; De Micco, Russo, and Tessitore 2018). Also, functional imaging studies suggest that postural sway is primarily controlled by subcortical regions including the thalamus, globus pallidus and subthalamic nucleus (Jahn and Zwergal 2010).

2.5.3 Brain volumes related to anticipatory postural adjustments

We found that ventricle volume is associated with gait initiation, specifically the APA measure, first step range of motion, in older adult subjects, but not in people with PD. While we did not find significant associations between the APA measures and the subcortical or cortical volumes in the primary analysis, we did see parietal, frontal and

total cortical gray matter related to APAs in the PD-only cohort (see **Table S1**). The parietal and frontal cortex have been implicated in control of APAs for step initiation since transcutaneous magnetic stimulation over the posterior parietal cortex or over the SMA disrupts APAs in older subjects, and even more in subjects with PD (Hiraoka, Gonno, and Inomoto 2020; Richard et al. 2017; Chiou et al. 2018) and APAs can be absent in humans with lesions/tumors in the SMA (Gurfinkel' and Él'ner 1988).

Surprisingly, we found the opposite relationship between cerebellum volume and APA size in freezers versus non-freezers. That is, the smaller the cerebellum, the larger the APAs in freezers but the smaller the APAs in non-freezers. This is surprising because small APAs and steps are a hallmark of PD progression. It is also surprising because smaller APAs and smaller first steps are found in freezers than non-freezers. However, APAs are only small in freezers when they are not actively freezing when they become much larger than normal, suggesting that small APAs are a compensatory mechanism to avoid actual freezing events (Schlenstedt et al. 2018). Thus, APAs may become smaller and smaller as the disease progresses (as a cerebellar compensation strategy) until the compensation fails and smaller cerebellar volume is associated with larger and larger APAs associated with actual freezing events. The cerebellum is considered one of the locomotor hubs and implicated in freezing of gait (Fling et al. 2014).

2.5.4 Brain volumes related to gait

We found that amygdala and frontal lobe volumes were related to stride time variability in older adults. Greater variability in gait is often associated with fall risk and future mobility disabilities (Jeffrey M. Hausdorff 2005). Although impairments in amygdala are typically related to anxiety and cognitive decline, smaller amygdala, along with smaller frontal regions like medial prefrontal and inferior frontal gyrus have been

associated with slow gait in the elderly (Nishita et al. 2019; Liu et al. 2020). In general, structural imaging studies in people with PD have demonstrated neuroanatomical correlates of gait related to both cortical (frontal, dorsolateral and medial frontal cortical thickness) and subcortical (basal ganglia volume reduction and increased diffusivity in the substantia nigra and pedunculo pontine nucleus) regions (Mirelman et al. 2019). While we did not find any brain regions significantly associated with gait metrics for people with PD, we did find stride time variability and gait speed associated with cortical volumes in freezers, more than non-freezers with PD (**Table S1**). Stride time variability has been related to severity of freezing, even when measured during gait without any freezing episodes (J. M. Hausdorff et al. 2003). Perhaps, combining freezers and non-freezers as one group reduced associations between brain volumes and gait in the PD cohort.

2.5.5 Brain volumes related to postural stepping responses

We found brainstem, cerebellum and parietal lobe volumes to be associated with (APR) reactive step height in response to a backward perturbation in older adults. Although the brainstem and cerebellum play a substantial role in control of automatic postural responses, the cortex is also involved, especially for stepping responses (Dijkstra et al. 2020). The cortex is activated at 50 ms after a postural perturbation with leg muscle responses occurring a latency longer than 100 ms (Keck et al. 1998; Busel' and Moldavan 1984). Stepping response latencies are much longer and more variable and more dependent on instruction/intention/environmental conditions than feet-in-place postural responses, consistent with involvement of parietal, motor planning areas (MacKinnon 2018a; J. V. Jacobs and Horak 2007; Dietz, Quintern, and Berger 1984).

2.5.6 Brain volumes related to clinical scores

The clinical judgement about standing balance, walking, sit to stand and postural responses (pull test) reflected in the (4-items) MDS-UPDRS PIGD scores were inversely related to total subcortical, putamen, accumbens, hippocampus, amygdala and temporal lobe gray matter volumes. Thus, subcortical volumes were associated with both the clinical and objective measures of postural control. Putamen volume was inversely related to postural sway and larger temporal lobe volume was associated with larger (better) APRs (similar to the pull test) in the PD sub-analysis.

Putamen atrophy is known to be responsible for poor motor function and we found reduced putamen volume and cortical regions in our PD group, compared to the control group (Kish, Shannak, and Hornykiewicz 1988; Mechelle M. Lewis et al. 2016). However, the ventricular and other subcortical GM volumes were not significantly different between the 96 people with PD and the 50 older adult subjects, although we cannot rule out age-related atrophy in both groups. While some brain regions like thalamus and brainstem show atrophy due to PD, most regions show atrophy in both PD and control groups related to aging effects.

2.5.7 Limitations

One limitation of our study is inherent in examining brain volume measures. Structural thickness or surface area changes may be missed with total volume measurements. It is not possible to capture all the complex neuronal changes with volume measures, alone. It is also important to note that segmentation of subcortical structures is tricky and is prone to partial volume effects. In order to minimize such issues, manual quality checks were performed to ensure good segmentation. Additionally, our study is cross-sectional and does not examine longitudinal volumetric

changes, so, we cannot infer causality. Another limitation is that subjects with the worst balance and gait could not be included if they could not stand and walk independently (Hasegawa et al. 2019a). We did not perform lateralized brain region analysis, since it would increase the number of regression models and reduce the statistical power. We also did not account for cognitive issues such as Lewy body dementia or mild cognitive impairments. White matter hyperintensity is also another factor which affects both the brain volumes and the cognitive status. Future studies should consider the effects of those. Finally, the PD group consisted of both freezers and non-freezers, who we showed had different relationships between brain volumes and gait/balance. Nevertheless, this is the first study to examine the associations between instrumented balance and gait metrics and brain volumes.

2.5.8 Conclusion

In conclusion, we found several significant models relate brain volumes and balance and gait in people with and without PD. Smaller subcortical and brainstem volumes may indicate standing balance dysfunction in people with PD. Smaller total ventricular volume may indicate smaller step initiation lateral movements (APAs) in older adults. Finally, atrophy of multiple subcortical regions seems to be associated with freezing of gait in PD. Thus, clinicians may expect to see balance dysfunction and freezing in people with PD who have reduced subcortical volumes.

2.6 Supplementary Materials

2.6.1 Supplementary Tables

Table 2.S1. Significant standardized beta coefficients with p-values for interaction and main effects between brain volumes and balance/gait metrics in freezers and non-freezers

Balance & Gait Metrics	Brain Volumes	Model		Group Main Effect		BrainVol. Main Effect†		Interaction Effect*	
		F	p	B	p	B	p	B	p
Sway	Subcortical	3.5	0.01	0.15	0.55	-0.41	0.01	-0.2	0.42
RMS AP standing on foam	Putamen	3.0	0.03	0.21	0.39	-0.37	0.02	-0.1	0.76
APR step height	Parietal lobe	2.9	0.04	0.01	0.95	0.32	0.03	-0.1	0.87
	Temporal lobe	3.0	0.03	0.01	0.96	0.37	0.02	-0.1	0.73
APA 1st step RoM	Parietal	5.1	<0.01	-0.5	0.01	0.37	<0.01	-0.2	0.29
	Frontal lobe	4.3	<0.01	-0.6	0.01	0.30	0.04	-0.2	0.29
	Total cortical	4.5	<0.01	-0.6	0.01	0.33	0.02	-0.3	0.16
	Cerebellum	4.3	<0.01	-0.6	0.01	0.22	0.15	-0.4	0.04
Gait speed	Cerebellum	4.9	<0.01	-0.5	0.01	-0.15	0.32	0.41	0.04
Stride time variability	Cerebellum	3.0	0.03	0.18	0.44	0.18	0.27	-0.5	0.02
	Brainstem	3.1	0.03	0.17	0.45	0.27	0.07	-0.5	0.01
	Total ventricle	3.7	0.01	0.14	0.52	0.07	0.64	0.47	0.02
	Hippocampus	3.5	0.01	0.13	0.57	-0.03	0.83	-0.5	0.03

†Main effects coefficients are reported for non-freezers (reference group)

*To get the beta coefficient of the freezers group sum the interaction effects coefficients and the brain volume main effects in NF. Model $p < 0.05$ FDR corrected, uncorrected $p < 0.05$ for each predictor. NF

– Non-freezers; RMS – Root mean square; AP – Anteroposterior; APA – Anticipatory postural adjustments; RoM – Range of motion; GM – gray matter; β – standardized beta coefficient

Table 2.S2. Significant correlations between age, disease duration and brain ICV with brain volumes or balance/gait metrics

Covariate	X and Y variables	Correlation	
			P_fdr
Age	Putamen	-0.28	0.002
Age	Thalamus	-0.38	<0.001
Age	Accumbens	-0.48	<0.001
Age	Hippocampus	-0.46	<0.001
Age	Amygdala	-0.40	<0.001
Age	Frontal lobe	-0.45	<0.001
Age	Parietal lobe	-0.43	<0.001
Age	Temporal lobe	-0.45	<0.001
Age	Total ventricles	0.51	<0.001
Age	Cortical GM	-0.47	<0.001
Age	Subcortical GM	-0.37	<0.001
Age	Cerebellum	-0.31	0.001
Age	APA 1 st step RoM	-0.18	0.030
Age	APR vertical step height	-0.24	0.020
Age	Sway RMS AP	0.19	0.030
Age	Gait variability	0.20	0.039
Disease duration	APA 1st step RoM	-0.28	0.023
ICV	Putamen	-0.46	<0.001
ICV	Pallidum	-0.26	0.005
ICV	Caudate	-0.44	<0.001

ICV	Thalamus	-0.50	<0.001
ICV	Accumbens	-0.37	<0.001
ICV	Hippocampus	-0.53	<0.001
ICV	Amygdala	-0.46	<0.001
ICV	Frontal lobe	-0.39	<0.001
ICV	Parietal lobe	-0.45	<0.001
ICV	Temporal lobe	-0.47	<0.001
ICV	Occipital lobe	-0.33	<0.001
ICV	Brainstem	-0.40	<0.001
ICV	Total ventricles	0.29	0.002
ICV	Cortical GM	-0.47	<0.001
ICV	Subcortical GM	-0.58	<0.001
ICV	Cerebellum	-0.54	<0.001
ICV	Gait turn velocity	-0.28	0.003

2.6.2 Supplementary Figures

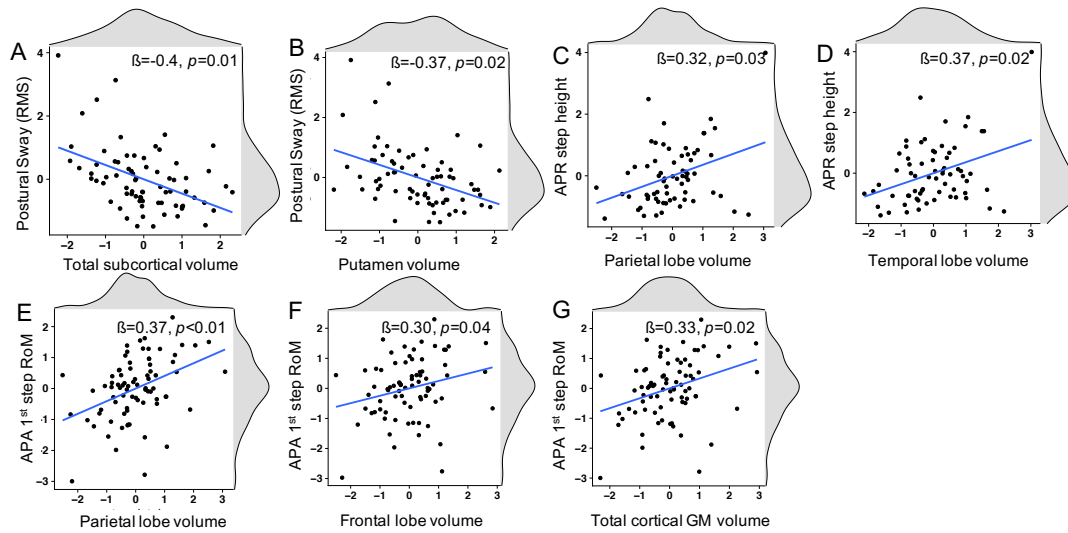


Figure 2.S1. Scatterplot of significant main effects of the relationship between brain volumes with balance and gait metrics for non-freezers.

Distribution plots of brain volumes and balance and gait metrics are shown on the top and right margins. Beta coefficients are shown at the top. APR – automatic postural responses, APA – anticipatory postural adjustments, RMS – root mean square, RoM – range of motion, GM – gray matter.

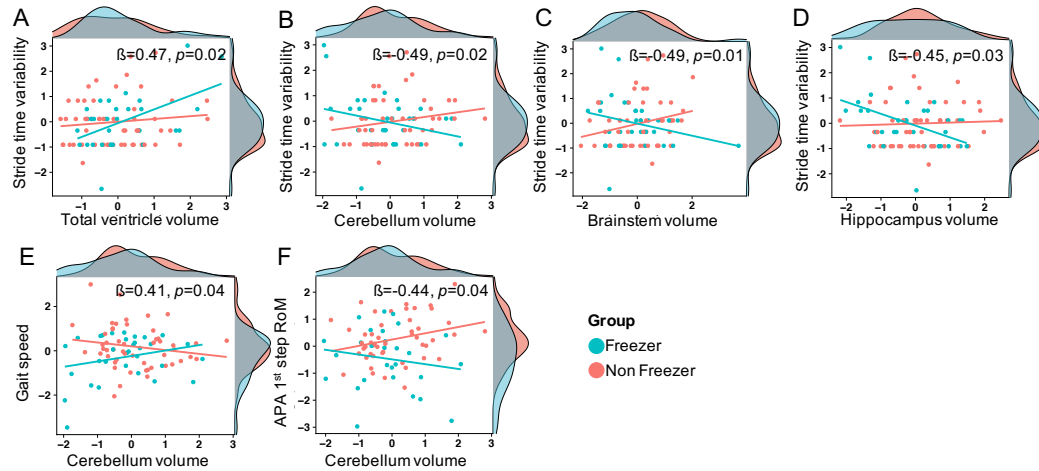


Figure 2.S2. Scatterplots of significant interaction effects between freezers and non-freezers group for the relationship of brain volumes with instrumented balance and gait metrics (in PD).

Freezers are represented in blue/cyan and non-freezers in red. Distribution plots of brain volumes and balance and gait metrics are shown on the top and right margins. Beta coefficients are shown at the top. APA – anticipatory postural adjustments, RMS – root mean square, RoM – range of motion

Chapter III: Resting State Functional Connectivity Networks Predict Motor Signs in Parkinson's Disease

This chapter is a manuscript in preparation: Ragothaman, A., Mancini, M., Nutt, J.G., Fair, D.A., Horak, F.B. and Miranda-Dominguez, O., *Resting State Functional Connectivity Networks Predict Motor Signs in Parkinson's Disease*. Neurology.

3.1 Abstract

Objective: Investigate the functional connectivity network pairs associated with the motor signs in people with Parkinson's disease (PD).

Background: PD is a neurodegenerative disorder primarily diagnosed and characterized by motor dysfunction. Functional MRI offers a unique opportunity to non-invasively characterize brain function. In this study, we hypothesized that the motor dysfunction observed in PD may involve connectivity in higher-level attention networks, as well as cortical motor networks. Understanding the resting state functional networks that correlate with the severity of the motor symptoms would be valuable to understand the disease physiology.

Methods: Our sample consisted of 88 PD subjects (mean age: 68.2(SD:10), 55M/33F). Motor severity of people with PD was assessed in practical OFF medication state, using MDS-UPDRS Part-III scores (mean: 49 (SD:10)). Atlas-based whole brain 91 cortical and subcortical functional connectivity network pairs were created for each subject. For subcortical network, we included the regions that are likely involved in motor

symptoms in PD as Subcortical-PD network. We used independent training (N=64) and test (N=24) data for predictive modelling. Partial least square regression (PLSR) model was used to predict MDS-UPDRS-III scores based on functional connectivity using the training dataset and optimized by leave-3-out cross validation. The most predictive modes were then used to predict MDS-UPDRS-III in the test dataset.

Results: The top 5% PLSR models that predicted the MDS-UPDRS-III scores with effect size > 0.5 were the connectivity between the somatomotor (SMN) and Subcortical-Basal-ganglia network pair, SMN and Visual network pair and CinguloOpercular (CiO) and language/Ventral attention (Lan/VeA) network pair.

Discussions: Our finding suggests that along with motor networks, visual- and attention-related cortical networks are also impacted in the motor symptoms of PD. SMN has been consistently observed in the PD literature and visual cueing is known to help some people with PD. CiO-Lan/VeA networks may play a compensatory role to overcome motor deficits. When people with PD have deficits in motor networks, probably more attention is required to carry out motor functions. Characterization of functional network during evolution of motor symptoms could be helpful in understanding the contribution of non-motor cortical regions in parkinsonian movement disorders and/or compensatory mechanisms.

3.2 Introduction

Parkinson's disease (PD) affects multiple systems in the brain as observed by the cardinal symptoms like bradykinesia, tremor, rigidity and postural dysfunctions (J. Jankovic 2008). Primary impairment in the brain happens in the basal ganglia system caused by loss of dopaminergic neurons. However, basal ganglia regions are highly interconnected through corticostriatal loop (Kemp and Powell 1971). While we know the

involvement of basal ganglia and associated subcortical regions and sensorimotor cortical regions (Baudrexel et al. 2011; Tessitore et al. 2014), the impact of PD on other functional networks across the whole brain is not well understood.

Using functional MRI, we can noninvasively measure brain function and characterize co-activation patterns across brain areas and also identify unique brain areas and networks (Power et al. 2011; Gordon et al. 2016). Resting state fMRI (rs-fMRI) offers a unique opportunity to examine how PD impacts the whole brain. Previous Functional imaging studies have shown that motor signs of PD are associated with reduced blood flow in sensorimotor cortical regions, putamen and globus pallidus and increased cerebral blood flow to premotor areas (Wu et al. 2009; Turner et al. 2003). However, they have primarily focused on specific brain regions (Filippi, Sarasso, and Agosta 2019). While there are many seed-based analysis studies that examine connectivity patterns from prior hypotheses, it is important to study whole brain network reorganization to identify lesser-studied brain regions/functions that might be affected by PD. Elucidating the functional network changes across the whole brain could help to understand the overall pathophysiology of the disease.

The few whole brain rs-fMRI network connectivity studies in PD in the literature have looked in the ON medication state (Tahmasian et al. 2015). However, levodopa is thought to partially normalize brain network changes due to PD so the impact of PD on brain network connectivity can best be understood when we examine the rs-fMRI networks in the OFF medication state (Tahmasian et al. 2015; Zhong et al. 2019). One study looked at whole brain rs-fMRI connectivity Off-medication (Hou et al. 2016), but they implemented a voxel-wise analysis that is less accurate than surface-based methods (Glasser et al. 2013) and used less stringent movement correction methods.

Sample size is becoming an increasingly important factor in replication of the results in neuroimaging studies (Marek et al. 2020). Most of the functional connectivity

studies in PD have focused on specific brain regions on very small sample sizes that do not stand the reproducibility test (Badea et al. 2017). We use a more reliable, novel approach that is not prone to over-fitting (McIntosh and Lobaugh 2004; Miranda-Domínguez et al. 2020; Silva-Batista et al. 2021). We performed a partial least square regression (PLSR) model with a training dataset on one scanner and an independent test dataset on another scanner to see if we could predict disease severity, based on the MDS-UPDRS Motor Part III score in both datasets. We have also employed stringent head motion corrections since the PD patients were Off medication (Tahmasian et al. 2015). While we know that the somatomotor and the basal ganglia networks are involved in PD, we do not know what other networks are impacted.

The motor impairments in PD are likely impacted not only by the motor circuits, but also by non-motor networks as well. For example, attention networks might be involved in control of balance and gait because people with PD show loss of automaticity of well learned motor tasks like walking (Wu, Hallett, and Chan 2015). Normally, the sensorimotor network becomes disassociated from the attention network while healthy people perform automated tasks (Bassett et al. 2015). However, people with PD continue to activate their attention systems even for automated tasks like natural walking (Stuart et al. 2020).

The objective of this study was to identify the brain networks that are associated with disease severity, as measured by MDS-UPDRS III motor scores. We hypothesized that parkinsonian motor signs would be associated with higher order cognitive networks, as well as sensorimotor and basal ganglia networks.

3.3 Methods

3.3.1 Participants

Data were collected from people who had idiopathic PD clinically diagnosed by a movement disorders specialist using UK Brain Bank Criteria. Inclusion criteria for subjects were: (1) between 50 and 90 years old, (2) no major musculoskeletal or peripheral disorders (other than PD) that could significantly affect their balance and gait, (3) ability to stand and to walk unassisted for 20 feet, and (4) without claustrophobia, severe tremor, or any health history that would interfere or put the subject at risk near the powerful magnetic field of the MRI scanner (implanted devices and deep brain stimulation). Exclusion criteria for PD subjects were: any other neurological disorders or musculoskeletal impairments that interfere with gait or balance, inability to follow instructions, and metal implants or any other contraindications for brain imaging. In addition, people with PD and severe tremor were excluded to ensure good quality MRI.

3.3.2 Standard Protocol Approvals, Registrations, and Patient Consents

All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Oregon Health & Science University, OHSU (#4131) and the OHSU/VAPORHCS joint IRB (#8979). These participants were part of a larger interventional study (Clinical Trials NCT02231073 and NCT02236286).

3.3.3 Clinical data

People with PD were assessed in the practical OFF levodopa state (12 hours overnight withdrawal of antiparkinsonian medication). Motor severity was assessed by a

trained/certified researcher using Movement Disorders Society Unified Parkinson's Disease Rating Scale motor subscale scores (MDS-UPDRS-III). The motor subscale is a composite score with evaluations of the following sections that range from 0-4: speech, facial expression, rigidity of neck and 4 extremities, finger taps, hand movements, pronation/supination, toe tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, posture, global spontaneity of movement, postural tremor of hands, kinetic tremor of hands, rest tremor amplitude and constancy of rest tremor.

3.3.4 Neuroimaging

Neuroimaging data were obtained within a week of motor assessment. Imaging data were acquired in practical OFF levodopa state using two different scanners, a 3T Siemens Trio scanner and later a 3T Siemens Prisma scanner, due to a scanner upgrade at Advanced Imaging Research Center during the phase of the study at OHSU. Data were collected by a trained and certified scanning technician and images were reviewed by a neurologist in the team if suspected anatomical abnormalities were found. Subjects were instructed to lie still and keep their eyes open. Head padding was provided to keep their heads still, earplugs were used to protect against scanner noise, and a leg bolster was provided to assist with back comfort. High resolution structural T1- and T2-weighted images and resting state functional images were obtained using following parameters: *Siemens Trio scanner*: T1-weighted images were acquired using a sagittal magnetization prepared rapid gradient echo (MPRAGE) sequence (TR=2300 ms, TE=3.58 ms, voxel size=1mm x 1mm x 1.1mm, slices=160). T2-weighted images were acquired using the following parameters: TR=3200 ms, TE=497 ms, resolution=1 mm isotropic, slices=160. Resting state functional BOLD images were acquired in 2 scans of 10 minutes each with the following parameters: TR/TE=2000/30 ms, resolution=3.8 mm isotropic, flip angle=90°, leading to a total of 600 frames. *Siemens*

Prisma scanner. T1-weighted images were acquired using a sagittal MPRAGE sequence (TR = 2500 ms, TE = 2.88 ms, TI = 1060 ms, resolution = 1 mm isotropic). T2-weighted images were acquired using the following parameters: TR = 3200 ms, TE = 565 ms, resolution = 1 mm isotropic, slices = 176. Resting state functional BOLD images were acquired in 2 scans of 10 minutes each with the following parameters: TR/TE=2500/30 ms, resolution=3.8x3.8x3.8 mm, flip angle=90°, leading to a total of 480 frames. Diffusion field maps were also acquired to correct for geometric distortions caused by susceptibility artefact.

3.3.4.1 Processing of imaging data

Data were processed using modified version of Human Connectome Project (available in github at <https://github.com/DCAN-Labs/abcd-hcp-pipeline>) which uses FSL, FreeSurfer and ANTs. Following sections describe the processing steps.

3.3.4.1.1 Structural image preprocessing

To give a brief overview of the structural data processing, T1 and T2 images were intensity normalized, brain images were extracted, then they were aligned to MNI's AC-PC axis and transformed to MNI atlas space using nonlinear registration. The transformation involved calculation of a single matrix for each individual to facilitate registration both to an intermediary study template (created using high quality MRI images from the age matched older adults of the study group) and to the MNI atlas. This original alignment was refined using boundary-based registration. T1-weighted images were then segmented using recon-all from FreeSurfer. Segmentations were improved by using the enhanced white matter-pial surface contrast of the T2-weighted sequence. The final standard space created the CIFTI file format and the associated grayordinate

spatial coordinate system (91282 anchor points) which combined cortical surface and subcortical volume analyses.

3.3.4.1.2 Resting state functional MRI preprocessing

The resting state functional data processing steps involved regression of (1) 6 degrees of freedom obtained by rigid-body head motion correction, (2) whole brain signal, (3) ventricular signal averaged from ventricular ROIs, (4) white matter signal averaged from white matter ROI, (5) first-order derivative terms and the squares for whole brain, ventricular and white matter signals to account for variance between regressors. Finally, time courses were filtered using a first-order Butterworth band pass filter with frequency range from 9 mHz to 80 mHz.

We used stringent measures for controlling for movement in the PD cohort. BOLD data was examined for movement by checking for framewise displacement (movement of a frame relative to its previous frame) of greater than 0.5 mm. Subjects with mean framewise displacement greater than 0.5 mm were eliminated. In this study we included participants with minimum of 5 minutes of surviving BOLD data. Connectivity matrices were calculated using randomly selected 5 minutes of data.

3.3.4.1.3 Functional connectivity and subcortical volume atlases

BOLD data was reported using regions of interest (ROIs) from two parcellation schemas. We used a modified version of a cortical functional connectivity atlas that defined 360 surface based cortical parcellation system from the Human Connectome Project (Glasser et al. 2016) into 12 networks (Ji et al. 2019). For subcortical areas, we combined 16 ROIs from the MNI PD25 atlas (Xiao et al. 2017) and 8 ROIs from the FreeSurfer ROIs (Fischl et al. 2004) (Table S1). Together, these 384 cortical and subcortical ROIs were grouped into 12 cortical and 2 subcortical functional networks

(see details below). **Figure 3.1** shows the cortical networks and subcortical combined PD25 and FreeSurfer subcortical ROIs and networks.

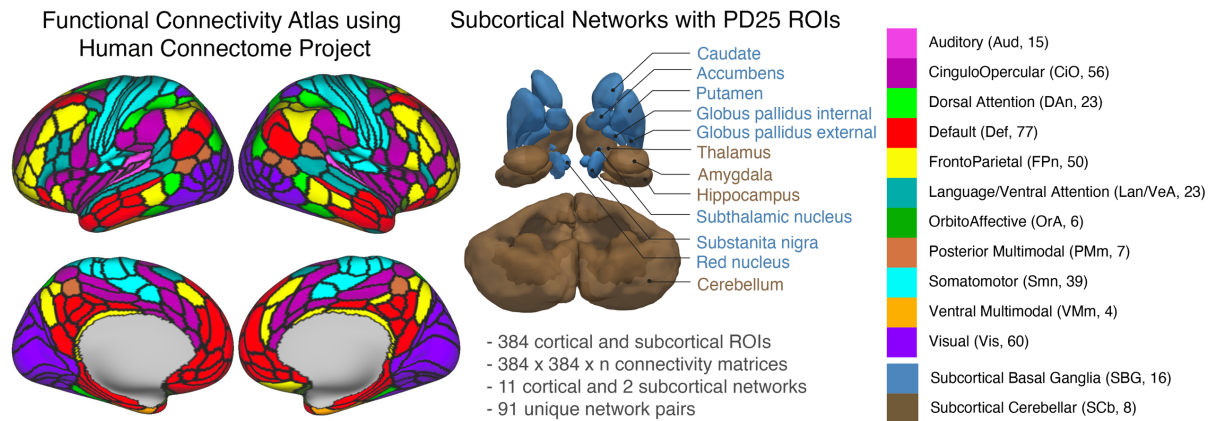


Figure 3.1. HCP Cortical functional networks and subcortical networks with PD25 and FreeSurfer combined ROIs.

The cortical ROIs were grouped into functional networks. The included cortical networks are, Auditory, Cingulo-Opercular, Dorsal attention, Default, Frontoparietal, Language, Orbito-Affective, Posterior Multi-modal, Somatomotor, Ventral-Multimodal and Visual. This network definition originally has 13 networks including primary (Visual1) and secondary (Visual2) visual networks. Since we were not focusing on primary versus secondary visual networks, we combined them as one Visual network. So, we had 12 cortical networks. It is worth noting that the so-called language network in the cortical functional atlas is a reorganization of a traditionally used Ventral attention network from previous works (Power et al. 2011; Gordon et al. 2016) and encompasses regions involved in language processing and attention. For the purpose of this study, the language network would be referred to as Language/Ventral-Attention network.

The subcortical regions consisted of 24 ROIs combined into 2 subcortical networks, Subcortical-Basal ganglia and Subcortical-Cerebellar. It is necessary to study

the ROIs and networks specifically implicated in PD. The standard FreeSurfer subcortical segmentation does not provide segmentations for substantia nigra, subthalamic nucleus, internal and external pallidum and red nucleus. So, we created a subcortical atlas which has a combination of subcortical ROIs implicated in PD and those that are standardly used in FreeSurfer(Fischl et al. 2004). We used the ROIs from the above mentioned PD25 MNI atlas to segment subthalamic nucleus, substantia nigra, red nucleus, pallidum internal and external, caudate, putamen and thalamus. We used FreeSurfer(Fischl et al. 2004) to segment the rest of subcortical ROIs, namely, accumbens, amygdala, hippocampus and cerebellum. Having the PD25 atlas ROIs along with other standard FreeSurfer ROIs helped in extracting functional information from subcortical regions known to be implicated in PD while having access to rest of the regions.

The PD25 MNI ROIs were in 1 mm space. So, we registered PD25 MNI atlas to a 2 mm MNI atlas and brought it to 2 mm space using ANTs(Klein et al. 2009). The FreeSurfer ROIs and PD25 ROIs were combined using FSL's `fslmaths` command(Jenkinson et al. 2012). There was an overlap of caudate and accumbens when the two atlases were combined. So, we performed manual corrections using ITKsnap(Yushkevich et al. 2006) under the guidance of a radiologist (JPW).

3.3.5 Statistical Analysis

In order to have reliability and reproducibility, we implemented a predictive modelling approach with partial least square regression (PLSR) model using independent training and test samples(McIntosh and Lobaugh 2004; Rudolph et al. 2018; Miranda-Domínguez et al. 2020; Silva-Batista et al. 2021). PLSR model predicted the associations between resting state functional connectivity data as independent variable and standardized MDS-UPDRS motor scores as dependent variable. PLSR

transforms the dependent and independent variables into smaller set of components that maximizes the outcome prediction. Associations were considered significant if models predicted out-of-sample data beyond chance. Mean absolute error (MAE) was used to estimate the accuracy of the predictions. Training data were used to optimize the PLSR model and choose the optimal number of components; goodness of the fit was quantified using hold-3-out cross validation and the significance of the results were determined using null data obtained using 10000 permutations. To determine the threshold of the significance, we compared the real data against the cumulative distribution of the MAE predicting the null-hypothesis data. We selected the optimal number of components that maximized the significance of the prediction in the permutation stage. Finally, we estimated the model performance on the independent test dataset. The optimal models learned from the training dataset were used to predict the motor scores in the independent test dataset and significant functional connectivity pairs were again selected comparing test data to the permuted null-data. PLSR implementations were done using MATLAB (Rosipal and Krämer 2006). To quantify the effect of age and disease duration, Pearson correlations of age and disease durations with the residuals of the prediction models were computed.

3.4 Results

Data were collected from 96 people with idiopathic PD. Out of a total of 96 subjects, 8 subjects were removed because of poor quality MR imaging data. Our final sample sizes consisted of 88 PD subjects (see **Table 3.1** for more details).

Table 3.1 Sample Characteristics

Feature	Training-Test data	Training vs Test
---------	--------------------	------------------

	Training dataset	Test dataset	Kstest2-, <i>p</i> -values
Original sample (n=96)	71	25	
High quality imaging data (n=88)			
Count	64	24	
Sex (F/M)	19/45	14/10	
Freezing status (F/nF)	28/36	10/14	
Age	69.0 (10)	67.5 (17.75)	0.27, 0.31
Disease duration	5.9 (7.6)	3.0 (3.0)	0.34, 0.09
H&Y	2 (0)	2 (0.25)	0.05, 0.9
LEDD	678.5	450	0.37, 0.09
MoCA	25.1 (3.8)	25.9 (3.6)	0.15, 0.9
MDS-UPDRS III	39.7 (14.2)	39.5 (9.4)	0.19, 0.77
MDS-UPDRS total	67.5 (22.3)	63.1 (17.7)	0.18, 0.86

Three functional network pairs predicted the MDS-UPDRS III score in both the training dataset and the independent test dataset, representing the top 5% of the 91 network pairs examined using the partial least square regression (PLSR) model. These 3 functional network pairs had an effect size (d) > 0.5 while predicting motor scores in the training dataset. These trained models when predicting the MDS-UPDRS III scores in the test dataset had mean absolute error (MAE) < 0.5.

Connectivity between (1) Somatomotor with Subcortical-Basal ganglia network pair (11 components, $d = 0.62$, MAE = 0.48 ($p=0.01$); Fig. 2A), (2) Somatomotor with Visual network pair (3 components, $d = 0.55$, MAE = 0.46 ($p=0.02$); Fig. 2B) and (3) Cingulo-Opercular with Language/Ventral-Attention network pair (1 component, $d = 0.49$, MAE 0.50 ($p=0.02$); Fig. 2C) predicted MDS-UPDRS III score. See **Table 3.2** for summary of results. The correlations between the observed and predicted MDS-UPDRS

III scores were $r > 0.43$. See **Figure 3.2** for visualization of the network pairs, correlation coefficients and MAE distributions.

Table 3.2. Significant functional connectivity network pairs predicting clinical motor scores in PD

HCP Functional system pair	Within training		Test data predictions using training dataset				Optimal # of Components
	MAE	ES	MAE	p	R	p	
Smn and SBG	0.73	0.62	0.48	0.01	0.53	<0.01	11
Smn and Vis	0.71	0.55	0.46	0.02	0.53	0.01	3
CiO and Lan/VeA	0.72	0.49	0.50	0.02	0.43	0.02	1

MAE – Mean absolute error, ES – Cohen's Effect size (d), p – p-value, R – correlation between observed and predicted MDS-UPDRS III score. Smn – Somatomotor, SBG – Subcortical-basal ganglia, Vis – Visual, CiO – Cinguloopercular, Lan/VeA – Language/Ventral attention

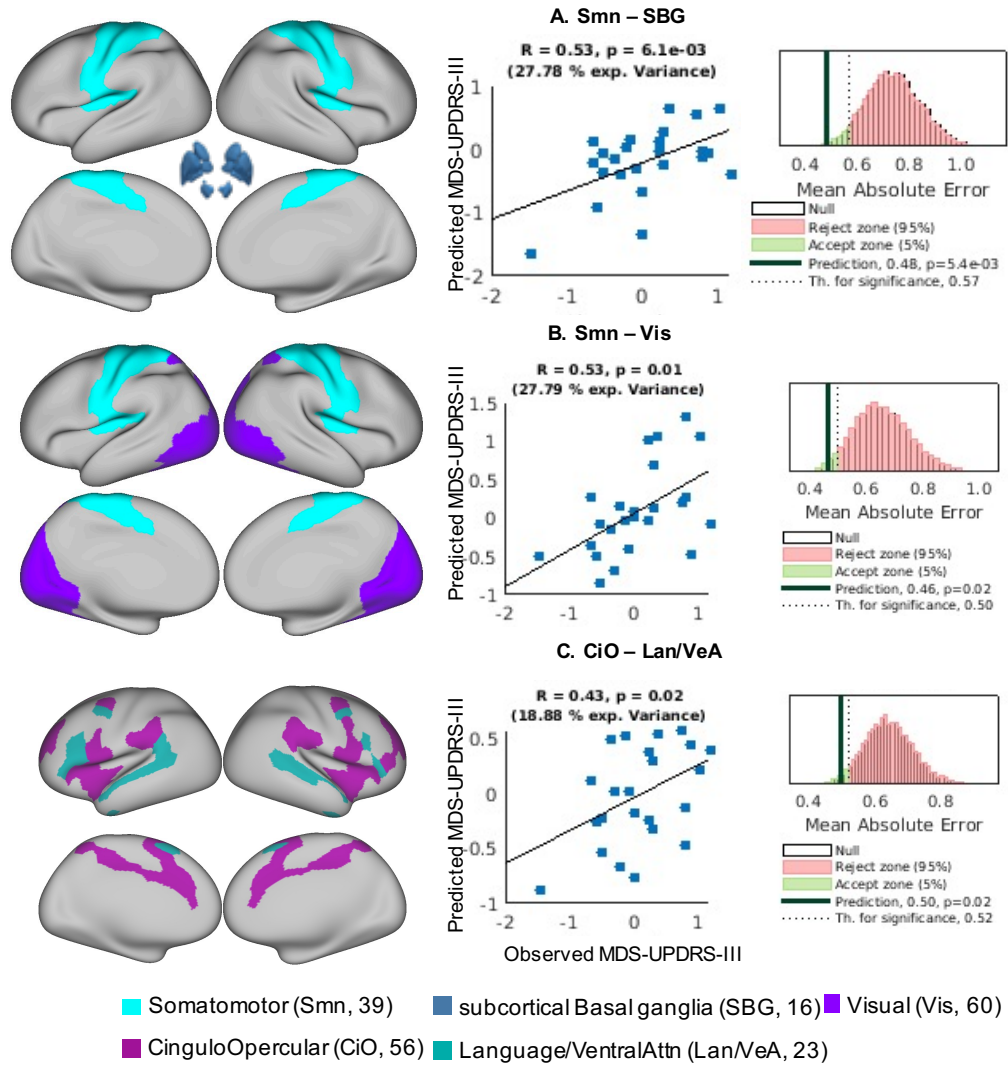


Figure 3.2. Functional connectivity network pairs that predict the MDS-UPDRS motor scores.

The column in the left shows the spatial representation of the functional networks on a very inflated brain; middle column shows the scatter plot of correlation between the observed and predicted MDS-UPDRS motor scores; column on the right shows the null distribution of the MAE, dotted line represents the threshold for significant prediction and dark black line shows the MAE for the actual prediction made. MAE - mean absolute error.

The linear combination of the beta-weights of the ROI-ROI connectivity within the 3 network pairs predicted the MDS-UPDRS III scores. The beta weights of the trained

models for each ROI-ROI connection and distribution of the functional connectivity values for the training and test datasets for the 3 network pairs are shown in supplementary Figure 3.S1.

No significant associations were found between age and the residuals of the PLSR models for the network pairs. The correlation coefficient (r) and p -values (corrected for multiple comparisons) of age with network pairs were: Somatomotor and Subcortical-Basal ganglia network pair ($r=0.32$, $p=0.13$), Somatomotor and Visual network pair ($r=0.19$, $p=0.36$), and Cingulo-Opercular and Language/Ventral-Attention network pair ($r=0.23$, $p=0.29$). The scatterplots are shown in supplementary Figure 3.S2.

Similarly, no significant associations were found between disease duration and the residuals of the PLSR models for the network pairs. The correlation coefficient (r) and p -values of disease duration and network pairs were: Somatomotor and Subcortical-PD network pair ($r=0.27$, $p=0.21$), Somatomotor and Visual network pair ($r=0.13$, $p=0.55$), and Cingulo-Opercular and Language/Ventral-Attention network pair ($r=0.23$, $p=0.29$). The scatterplots are shown in supplementary Figures 3.S3.

3.5 Discussion

3.5.1 Summary of results

Whole brain functional network connectivity in the resting state in people with PD Off medication identified higher-order cognitive and visual networks that are associated with severity of motor dysfunction in people with PD. Connectivity between Somatomotor and Subcortical-Basal ganglia networks, Somatomotor and Visual networks and Cingulo-Opercular and Language/Ventral-Attention network pairs predicted MDS-UPDRS III

motor score. We demonstrate that we can predict motor severity using functional connectivity network pairs using two independent datasets on two different scanners.

3.5.2 Somatomotor – Subcortical-Basal Ganglia network connectivity predicts PD motor severity

Consistent with the literature, we showed that the strength of connectivity between the Somatomotor and Subcortical-Basal ganglia networks were predictive of motor dysfunction in PD. Alterations within the somatomotor network is among the most identified networks in PD across different stages of the disease and different analysis methods as summarized by reviews(Tessitore et al. 2014; Strafella et al. 2018). In addition to alterations within somatomotor network, most ROI based studies have shown reduced connectivity between Somatomotor and striatal networks in people with PD(Helmich et al. 2010; Sharman et al. 2013; Agosta et al. 2014; Wang et al. 2021). In particular, connectivity between the SMA and putamen has been shown to be negatively correlated with the MDS-UPDRS III motor score(Wu et al. 2009). Another study by the same group showed decreased connectivity between premotor cortex, pre-SMA and putamen in people with PD compared to healthy adults(Wu et al. 2011). The Somatomotor network identified in our study includes not only motor execution ROIs like M1/S1, but also motor planning ROIs like SMA and pre-SMA. Involvement of motor planning regions like SMA, pre-SMA, premotor cortex along with the somatomotor regions like M1/S1 may suggest network level changes at the motor planning level disrupting motor execution.

3.5.3 Somatomotor – Visual network connectivity predicts PD motor severity

We found that connectivity between somatomotor and visual networks predicted motor severity in people with PD. The connectivity between somatomotor and visual networks related to motor severity identified in our study in PD maybe due to reduced connectivity responsible for impairments in spatial orientation or increased connectivity acting as a compensatory system in people with PD. In a recent Rs-fMRI study, Somatomotor-Visual network connectivity was reported to be the most different between PD and healthy adults with PD group showing reduced functional connectivity(Gratton et al. 2019). Reduced functional connectivity between somatomotor and sensory networks have been attributed to impaired sensory processing, integration leading to the issues with perception of forward-motion and observed motor impairments like freezing of gait(Patel, Jankovic, and Hallett 2014). For example, freezing often triggered during visual contexts such as narrow doorways(Cohen et al. 2011).

The association of PD motor severity with Somatomotor-Visual network connectivity in this study could also represent a compensatory mechanism for the impaired subcortical control of movement. People with PD are known to benefit from visual cueing and this benefit particularly for people with freezing(Schlick et al. 2016; Barthel et al. 2018; Gilat et al. 2021). A recent EEG study on visual cueing in people with PD has shown activations in the visual regions correlated with cueing and gait improvements and attention processing and those with worse attention seem to recruit more visual regions(Stuart et al. 2021).

Hemodynamic alterations in the visual network has shown a propensity for visual hallucination in people with PD(Yao et al. 2015). However, only 16 out of 88 people had

reported hallucinations in our cohort in the MDS-UPDRS question 1.2 and most of them had a mild score of one.

3.5.4 Cingulo-Opercular – Language/Ventral Attention network connectivity predicts PD motor severity

This is the first study to find that connectivity between Cingulo-Opercular and Language/Ventral attention networks predicted motor severity in people with PD.

Cingulo-Opercular and Language/Ventral attention are considered to be part of higher-order cortical network. Cingulo-Opercular network is generally attributed to maintaining tonic attention(Sadaghiani and D'Esposito 2015) while Language/Ventral attention is related to language processing and involve detecting unattended or unexpected stimuli and triggering shifts of attention(Corbetta and Shulman 2002; Menon and Uddin 2010). In relation to PD, studies have shown that motor performance recruit brain networks involved in more complex tasks like anterior cingulate cortex and dorsal anterior insula among other regions(Carbon et al. 2007; Tinaz et al. 2016). A recent dynamic functional connectivity study showed that people with PD (on medication) show more inter-network connectivity than intra-network connectivity with increased connectivity between central executive network and somatomotor network(Kim et al. 2017). Increased connectivity was observed between Ventral attention network and cognitive control network in people with PD while breaking motor arrest in virtual reality motor tasks(Shine et al. 2013). People with PD show persistent activation of attention networks for motor tasks (Wu, Hallett, and Chan 2015).

While the language/Ventral Attention network used in this study contains regions responsible for language processing and attention switching(Ji et al. 2019) interestingly, they also include parts of cortical vestibular network(Frank and Greenlee 2018). Recent

study on cortical vestibular network has identified distributed cortical systems to be involved in control of balance that comprise of regions in the parietal, somatosensory, cingulate, frontal, and insular cortices. The regions parieto-insular vestibular cortex (PIVC) and posterior insular cortex (PIC) are considered to be part of core vestibular system and they seem to share networks with the Cingulo-Opercular and Language/Ventral Attention networks. PIVC is known to encode head and full body movements and is involved in estimating heading direction by means of such movements while PIC is attributed to coordination of visual and vestibular cues (Frank and Greenlee 2018). Diffusion imaging study shows that PIVC and PIC are strongly interconnected and that both areas have connections with the insula, other portions of the Sylvian fissure, the parietal cortex, the superior temporal cortex, and the inferior frontal gyrus (Wirth et al. 2018). The regions superior temporal sulcus and temporo-parieto-occipital junction, although part of Language/Ventral Attention networks, they are also considered to contribute to the vestibular control.

3.5.5 Strengths and Limitations

Our predictive modelling method uses cross-validation, null-hypothesis test and comprises independent training and test datasets increasing chances for reproducibility of our results. We also used whole brain analysis approach and not selected brain networks/ROIs that enabled us to identify non-motor networks involved in motor symptoms in people with PD and OFF-medication. We also created a unique subcortical network consisting of regions specifically implicated in PD to identify if other subcortical regions played a role in motor symptoms. Our study is one of the few to include large cohort of people with PD and OFF-medication. We have implemented stringent correction methods for motion artifacts, particularly important in studying movement disorders like PD (Tahmasian et al. 2015; Gratton et al. 2019). During our registration

process, we also registered our PD subjects to an intermediary age-matched atlas to account for structural changes related to aging. Together, these methodological rigors address the confounding factors and aims to further the understanding of functional network connectivity associated with motor symptoms in PD.

Although our original sample consisted of 96 people with PD, we lost few subjects due to increased movement in the scanner and they predominantly belonged to the training sample. The subjects we lost were also observed to have moderately increased motor severity and disease duration compared to the group average. As the disease progresses, the neck posture tends to deteriorate, that could be a reason for the increased head motion. However, the number of subjects in our study are larger than most PD studies. The training and test dataset had differences in the disease duration and levodopa dosage, although they were not statistically significant. The functional connectivity atlas we used was created from HCP dataset which comprised of individuals with average age of 25. However, during registration process we registered our PD subjects to age matched intermediary atlas created from our age matched control cohort to control for the age-related anatomical changes. Future studies could use functional connectivity atlases made from older adults(Doucet et al. 2021) or implement individualized connectivity-based analysis that can be used for personalized prediction(Cui et al. 2020). Also, we implemented a predictive modeling approach using training and test dataset. However, that implied we could not explain the directionality of the relationships. Our interpretations of the results are based on available literature. Future studies should be conducted to validate if our interpretations hold true. We focused on motor impairments of PD and not on cognitive impairments, but majority of our subjects had a MoCA score of above 25. Our PD cohort included freezers and non-freezers as well as tremor dominant and PIGD dominant groups, but underpowered to

look at differences between sub-groups. Future studies could look for specific changes caused due to freezing or PIGD impairments.

3.6 Conclusions

We demonstrate that along with motor networks, higher-order non-motor networks also predicted motor severity of PD. Visual and motor network connectivity were also predictive of motor signs. Involvement of higher-order cognitive networks may explain the attention deficits experienced by people with PD and involvement of visual network may explain why some people with PD benefit from visual cueing. Characterization of these functional connectivity network during evolution of motor signs could help us understand the compensatory role played by non-motor regions and play a role to modulate the medication and improve PD symptoms.

3.7 Supplementary materials

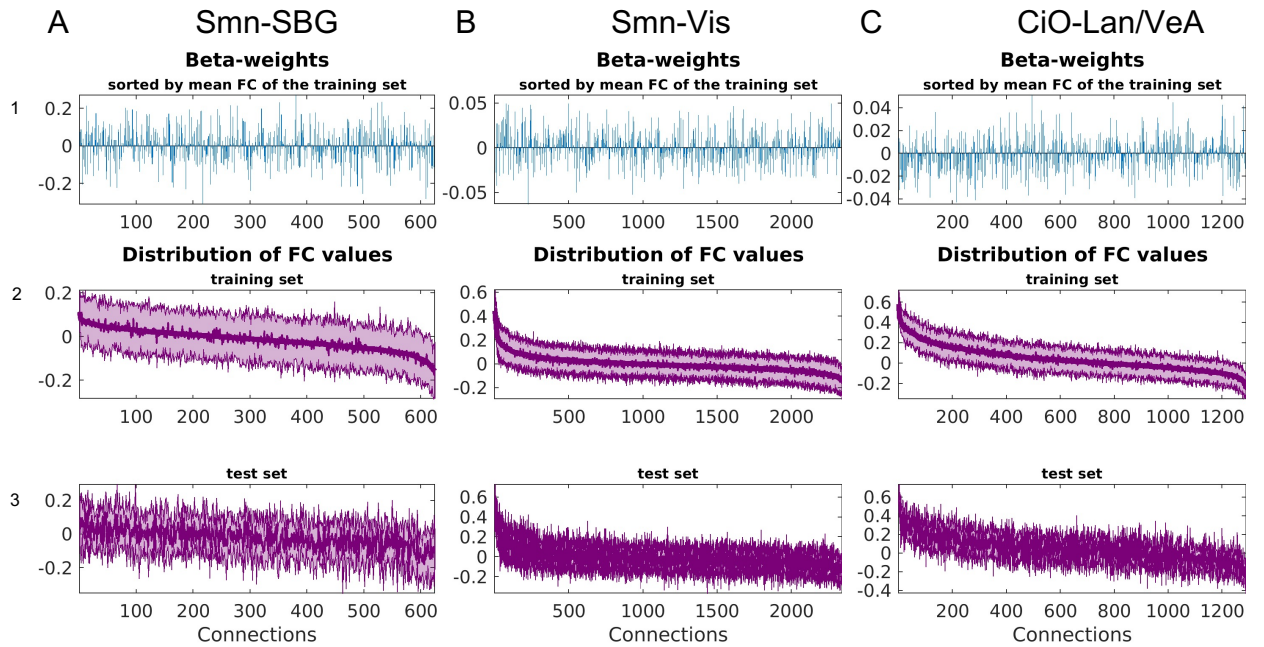


Figure 3.S1. Plots showing the beta weights and FC of the training and the test dataset for the 3 network pairs that predict MDS-UPDRS-III.

Panel 1 shows the beta weights sorted by mean FC of the training dataset. Panel 2 shows the distribution of FC for the training dataset, sorted by the mean FC. Panel 3 shows the distribution of FC for the test dataset, sorted by the mean FC of the training dataset. X-axis shows the number of ROI-ROI connections in a network pair.

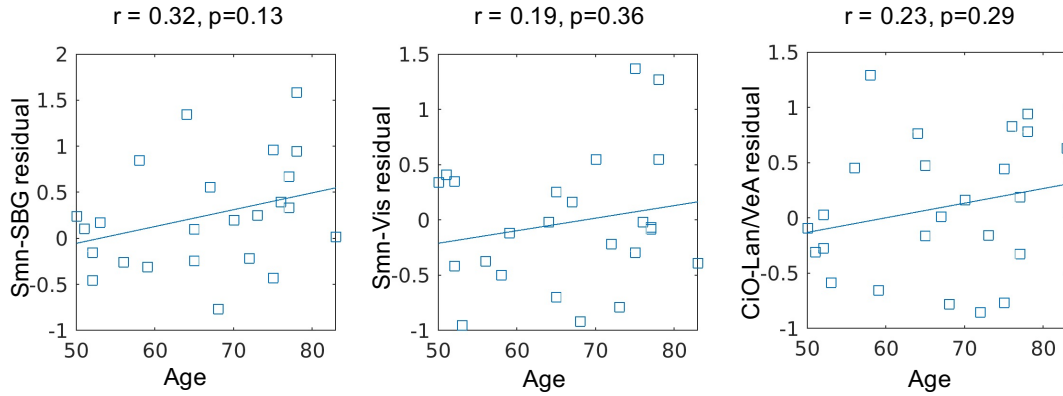


Figure 3.S2. Scatter plots showing the correlation between age and residuals of PLSR models of functional connectivity network pairs that predicted MDS-UPDRS III scores

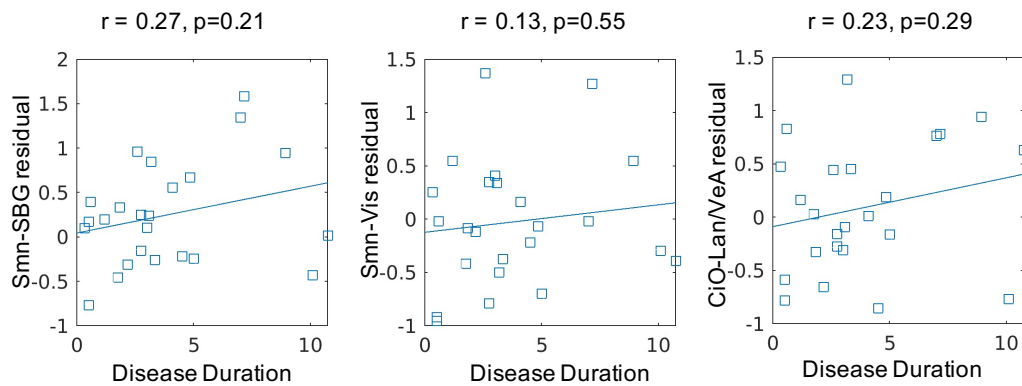


Figure 3.S3. Scatter plots showing the correlation between disease duration and residuals of PLSR models of functional connectivity network pairs that predicted MDS-UPDRS III scores

Chapter IV: Resting State Functional Networks Predict Different Aspects of Balance Control in Parkinson's Disease

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4.1 Abstract

Background: Parkinson's disease (PD) is a neurodegenerative disorder causing postural control impairments. Postural control involves multiple domains, such as control of postural sway in stance, automatic postural responses (APRs) and anticipatory postural adjustments (APAs). We hypothesize that impairments in each domain is associated with different atypical brain functional connectivity and that more brain networks are associated with postural control in people with PD (PwPD) than in older adults (OA).

Objective: To determine how connectivities between brain networks were related to three domains of postural control in people with PwPD and OA.

Methods: The cohort consisted of 65 PwPD (67.7 ± 8.1 years old) tested in their OFF state and 42 OA (69.7 ± 8.2 years old). Six body-worn, inertial sensors measured postural sway area while standing on foam, step length of APRs to a backward push-and-release perturbation, and magnitude of lateral APAs prior to voluntary gait initiation.

Resting state-fMRI data was reported on 352 regions of interest that were grouped into 13 functional brain networks. Associations between functional connectivity (FC) and postural metrics were characterized using predictive modeling, with an independent training (n=67) and test (n=40) dataset. Models were trained in the training sample and performance of the best model was validated in the independent test dataset.

Results: FC of different brain networks predicted each domain of postural control in PD: Frontoparietal and Ventral Attention FC for APAs; Cerebellar-Subcortical and Visual FC and Auditory and Cerebellar-Subcortical FC for APRs; Ventral Attention and Ventral Multimodal FC for postural sway. In OA, CinguloOpercular and Somatomotor FC predicted APAs.

Conclusions: Our findings suggest that PwPD have more cortical networks associated with posture control than OA and there is no overlap in brain networks associated with different domains of postural control. PwPD use more cortical frontal and attention networks for postural control than OAs.

4.2 Introduction

Age-related changes to neural processing and musculoskeletal systems impair postural control (Maki and McIlroy 1996). Neurodegenerative diseases, like Parkinson's disease (PD), further impair the neural control of posture (Mancini, Nutt, and Horak 2020a). For instance, people with PD (PwPD) show more impaired anticipatory postural adjustments (APAs), weaker postural responses (APRs) and increased postural sway area compared to OAs (Schoneburg et al. 2013; Mancini, Nutt, and Horak 2020a). Impaired postural control is the primary reason for the 5 fold increased fall risk in PD compared to age related OAs (Morris et al. 2000).

Postural control requires keeping the body upright while performing functional tasks, such as standing, transitioning between postures, responding to external perturbations or maintaining dynamic stability during gait (Mancini, Nutt, and Horak 2020a). Postural control during these different tasks is considered to represent independent aspects (domains) of balance because impairments across these aspects are not correlated with each other across subjects and are often affected differently by diseases or interventions (Mancini, Nutt, and Horak 2020a).

However, It is unclear whether different aspects of postural control are controlled by different brain networks (MacKinnon 2018b). It is also unclear if the postural control networks differ between OA and PwPD (Mancini, Nutt, and Horak 2020a). Resting state fMRI (Rs-fMRI) signal represents spatiotemporal brain activity captured by spontaneous fluctuations in oxygen level in the brain through BOLD signal that can be used noninvasively to measure brain function and characterize co-activation patterns across brain areas, representative of connectivity between brain networks (Snyder and Raichle 2012). These network-network interactions can be associated with behavior measures to study disease specific alterations. Studies that looked at brain areas involved in various postural tasks in older adults have reported involvement of regions like prefrontal (dorsolateral prefrontal cortex), premotor (supplementary motor area), somatomotor, posterior parietal cortices, cerebellar vermis, PPN in the brain stem, thalamus and visual cortex (see (Wittenberg et al. 2017; Dijkstra et al. 2020) for review) (Y. Mori et al. 2020; Bosch et al. 2021; Pasman et al. 2021). The involvement of cognitive and attention-related networks is even more evident in neurological disease like PD than in OAs, as they show more postural instability while multi-tasking (Morris et al. 2000). PwPD also rely more on vision and auditory feedback because of impaired central proprioceptive processing for postural control (Schlenstedt et al. 2017). However, most of the functional connectivity studies of brain networks on postural control looked only at healthy young

and OAs (Dijkstra et al. 2020), but not PwPD and have not compared brain connectivity across different types of postural control.

The aim of our study was to identify which specific network-to-network brain connectivities are associated with three domains of postural control (APAs, APRs and postural sway in stance) in PwPD and OAs. We hypothesized that different functional networks are involved in different domains of postural control and the PwPD will involve more cortical networks for postural control compared to OAs.

4.3 Methods

4.3.1 Participants

Data were collected from 150 subjects, with 103 people who had idiopathic PD clinically diagnosed by a movement disorders specialists using UK Brain Bank Criteria and 47 OAs. Inclusion criteria for subjects were: (1) 50 - 90 years old, (2) no major musculoskeletal or peripheral disorders (other than PD) that could significantly affect their posture and gait, (3) ability to stand and walk unassisted for 20 feet, and (4) without claustrophobia, severe tremor, severe dystonia, or other conditions that would prevent good quality MRI. Elderly adults within the same age range with no neurological and mobility issues were recruited from the community. Exclusion criteria for all groups were: (1) any other neurological disorders or musculoskeletal impairments that interfere with gait or postural control, (2) inability to follow instructions, and (3) metal implants at risk near the MRI scanner.

Out of 150 subjects, 43 subjects were removed during quality check of imaging data due to excessive head movement or lack of full-brain coverage. Our final sample size consisted of 107 subjects, with 42 OAs and 65 PwPD (**Table 4.1**). All subjects gave

written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Oregon Health & Science University, (#4131) and the OHSU/VAPORHCS joint IRB (#8979). These participants were part of a larger interventional study (Clinical Trials NCT02231073 and NCT02236286).

Table 4.1 Sample Characteristics

Feature	Training dataset		Test dataset	
	PD	OA	PD	OA
Original sample (n=150)	68	35	29	18
Imaging data after T1 structural QC (n=142)	66	34	26	15
Imaging data after Cerebellum QC (n=112)	45	27	25	15
Imaging data after removing high movers (n=107)	40	27	25	15
Sex (M/F)	15/25	14/13	15/10	4/11
Age	68.5 (6.5)	70.4 (7.6)	66.4 (10.1)	68.5 (9.3)
Disease duration	6.24 (5.3)	NA	3.81 (2.9)	NA
UPDRS III	39.8 (13.6)	NA	39.2 (9.5)	NA
PIGD	4.38 (2.7)	NA	4.96 (2.4)	NA
Total LEDD	871 (1338)	NA	486 (415)	NA
H&Y Score	2.17 (0.5)	NA	2.32 (0.7)	NA
ABC score	77.1 (15.5)	96.1 (3.9)	84.5 (16.7)	93 (8.68)
APA Peak ML**	0.035 (0.02)	0.047 (0.02)	0.031 (0.01)	0.045 (0.02)
APR First step length	0.198 (0.14)	0.254 (0.18)	0.196 (0.09)	0.168 (0.11)
Sway RMS AP EO foam**	0.136 (0.04)	0.105 (0.04)	0.113 (0.04)	0.094 (0.03)
Number of missing data per outcome metric				
APA Peak ML	2	0	2	0
APR First step length	3	0	5	0
Sway RMS AP EO foam	6	0	3	0

** significantly different between PD and OA, but not between training and test datasets. OA – Older adults, values in parenthesis represent standard deviation.

4.3.2 Posture outcome measures

PwPD were assessed in the practical OFF levodopa state, at least 12 hours withdrawal of antiparkinsonian medication. Motor severity was assessed by trained and

certified researchers using Movement Disorders Society Unified Parkinson's Disease Rating Scale motor subscale scores (MDS-UPDRS-III). Postural instability and gait dysfunction (PIGD) scores were estimated using Stebbins recommendations (Stebbins et al. 2013).

Each participant was outfitted with 6 inertial sensors (APDM Wearable Technologies, Portland, OR, USA), worn on the sternum, lumbar spine, bilaterally on the wrists and feet. Each inertial sensor recorded tri-axial accelerations, tri-axial angular velocities, and magnetic field at 128 Hz to calculate orientation in space. We chose the following postural measures for the analysis based on our previous studies that identified postural measures most sensitive to differentiate PD and OAs (Hasegawa et al. 2019b): 1) the magnitude of lateral APAs prior to voluntary gait initiation from the lumbar sensor (APA Peak ML) (Hasegawa et al. 2019b), 2) the length of the first postural correction step backwards in response to a push-and-release perturbation calculated from the foot sensors (APR first step length) (Hasegawa et al. 2019b); 3) the root mean square of the antero-posterior acceleration sensed at the lumbar level during sway task while standing on foam surface with eyes open (Sway RMS AP) recorded from the lumbar sensors because it was more sensitive/specific to PD than other standing conditions (Hasegawa et al. 2019b).

4.3.3 Neuroimaging

Neuroimaging data were obtained within a week of postural assessment. High resolution structural T1- and T2-weighted images and resting state functional images were obtained for all participants. Data were processed using modified version of Human Connectome Project (available in github at <https://github.com/DCAN-Labs/abcd-hcp-pipeline>) which uses FSL, FreeSurfer and ANTs. The image acquisition parameters and structural image processing steps are described in the supplementary section.

4.3.3.1 Resting state functional MRI preprocessing

The resting state functional data processing steps involved regression of (1) 6 degrees of freedom obtained by rigid-body head motion correction, (2) whole brain signal, (3) ventricular signal averaged from ventricular ROIs, (4) white matter signal averaged from white matter ROI, (5) first-order derivative terms and the squares for whole brain, ventricular and white matter signals to account for variance between regressors. Finally, time courses were filtered using a first-order Butterworth band-pass filter with frequency range from 9 mHz to 80 mHz.

BOLD data was examined for movement by checking for framewise displacement (movement of a frame relative to its previous frame) of greater than 0.5 mm. In this study we included participants with minimum of 5 minutes of surviving BOLD data. Connectivity matrices were calculated using randomly selected 5 minutes of data.

4.3.3.2 Functional connectivity and subcortical volume atlases

BOLD data was reported using regions of interest (ROIs) from two parcellation schemas. For cortical areas, we used the ROI set from the Human Connectome Project (Glasser et al. 2016) that reports 360 ROIs. For subcortical areas, we combined 16 ROIs from the MNI PD25 atlas (Xiao et al. 2017) and 8 ROIs from the FreeSurfer ROIs (Fischl et al. 2004) (Table S1). Together, these 384 cortical and subcortical ROIs were grouped into 12 cortical and 2 subcortical functional networks (see details below).

To provide further details about the networks, the cortical ROIs were grouped into functional networks as reported by Ji et al (Ji et al. 2019). The included cortical networks are, Auditory, Cingulo-Opercular, Dorsal attention, Default, Frontoparietal, Language, Orbito-Affective, Posterior Multi-modal, Somatomotor, Ventral-Multimodal and Visual. This network definition originally has 13 networks including primary (Visual1)

and secondary (Visual2) visual networks. Since we were not focusing on primary versus secondary visual networks, we combined them as one Visual network. So, we had 12 cortical networks.

As for the subcortical networks, we delineated 24 ROIs that were grouped into 2 subcortical networks, Subcortical-Basal ganglia and Subcortical-Cerebellar. It is necessary to study the ROIs and networks specifically implicated in PD (details of subcortical networks creation is in the supplementary materials). **Figure 4.1** shows the cortical networks and subcortical PD25 and FreeSurfer combined subcortical ROIs and networks.

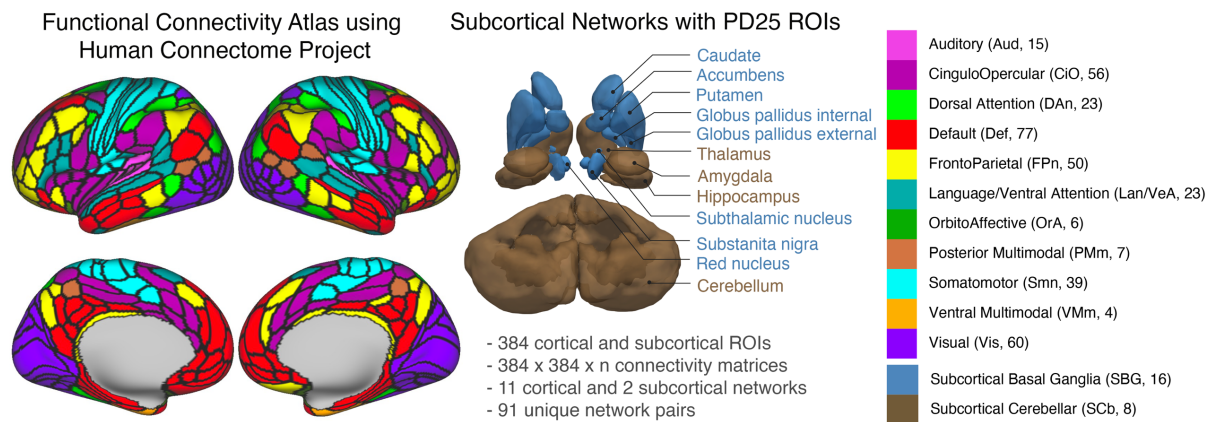


Figure 4.1. HCP Cortical functional networks and subcortical networks with PD25 and FreeSurfer combined ROIs.

It is worth noting that the so-called language network in the cortical functional HCP atlas (Ji et al. 2019) is a reorganization of a traditionally used Ventral attention network from previous works (see mentioned in (Ji et al. 2019)) and encompasses regions involved in language processing and attention. For the purpose of this study, the language network would be referred to as Language/Ventral Attention network.

4.3.4 Statistical Analysis

In order to ensure reliability and reproducibility, we implemented a predictive modelling approach with partial least square regression (PLSR) model using independent training and test samples (Rosipal and Krämer 2006). PLSR model predicted the associations between resting state functional connectivity data as independent variable and 3 postural metrics as the dependent variables, with independent runs for each postural aspect. Associations were considered significant if models predicted out-of-sample data beyond chance. Mean absolute error (MAE) was used to estimate the accuracy of the predictions. Training data were used to optimize the PLSR model and choose the optimal number of components; goodness of the fit was quantified using hold-3-out cross validation and significance was determined after comparing results (see supplementary for details) against null data obtained using 10000 permutations. Finally, we estimated the model performance on the independent test dataset. Lastly, to quantify the effect of age and disease duration, Pearson correlations of age and disease durations with the residuals of the prediction models were computed. PLSR implementations were done using MATLAB.

4.4 Results

The functional network pairs that predicted the postural control measures in both the training dataset and the independent test dataset represented the top 10% of the 91 network pairs examined using the PLSR model. The functional network pairs had an effect size (d) > 0.45 in predicting the postural measures in the training dataset. These trained models when predicting the postural measures in the test dataset had MAE < 0.7 .

In OA, connectivity between CinguloOpercular and Somatomotor networks (Figure 4.2) predicted APA Peak ML. No functional network connectivity significantly predicted APR or sway measures in OAs.

In PwPD, connectivity between Frontoparietal and Language/Ventral-Attention networks predicted APA Peak ML (Figure 4.3A). Connectivity between Subcortical-Cerebellar and Visual networks (Figure 4.3B) and connectivity between Subcortical-Cerebellar and Auditory networks predicted APR first step length in PwPD (Figure 4.3B). Connectivity between Language/Ventral-Attention and Ventral multimodal networks predicted Sway RMS AP in PwPD (Figure 4.3C). The clinical PIGD score, in PwPD, was predicted by the connectivity between the Auditory and CinguloOpercular networks (Figure 4.3D). See **Table 4.2** for summary of results. The beta weights of the trained models for each ROI-ROI connection and distribution of the functional connectivity values for the training and test datasets for the significant network pairs that predicted the postural control outcomes are shown in supplementary Figure 4.S1.

No significant associations were found between age and the residuals of the PLSR models for the network pairs. Similarly, no significant associations were found between disease duration and the residuals of the PLSR models for the network pairs. The scatterplots and correlation results are presented in supplementary section (Figures 4.S2 and 4.S3).

Table 4.2. Significant functional connectivity network pairs predicting objective and clinical balance domains in older adults and PD

Group	# of subjects	Balance domain	Functional system pair	# Comp	Out-of-sample predictions							
					Within Training			Training to Test				
					MAE	ES	MAE rank	MAE	<i>p</i>	R	<i>p</i>	MAE rank
OA	N=42	APA	CiO - Smn	4	0.72	0.48	4	0.62	0.03	0.30	0.11	7
PD	N=65	APA	FPn - Lan/VeA	3	0.67	0.51	2	0.63	0.04	0.11	0.31	2

APR	Snp - Vis	6	0.76	0.54	5	0.49	0.03	0.45	0.03	3
	Aud - Snp	2	0.79	0.45	10	0.50	0.02	0.56	<0.01	6
Sway	Lan/VeA - VMm	2	0.74	0.58	9	0.68	0.02	0.52	0.02	10
PIGD	Aud - CiO	5	0.63	0.47	2	0.71	0.02	0.42	0.02	5

OA – Older adults, # Comp – Number of components in PLSR model, MAE – Mean absolute error, ES – Cohen's Effect size (d), p – p-value, R – correlation between observed and predicted balance measures

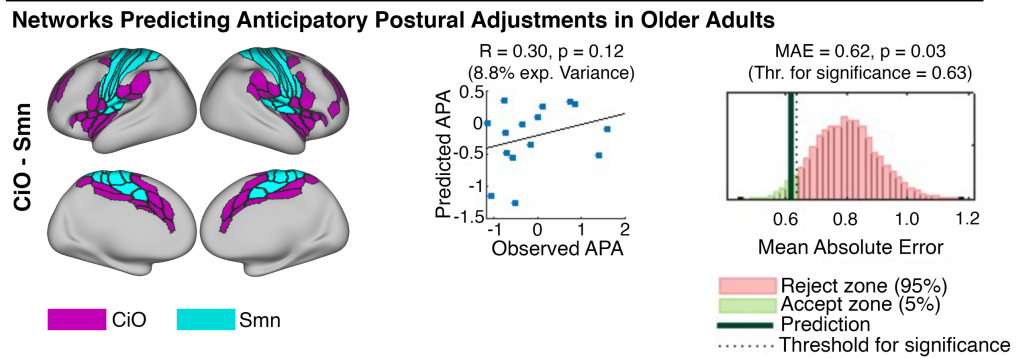


Figure 4.2. Functional connectivity network pairs predicting APAs in OAs.

The column to the left shows the spatial representation of the functional networks on a very inflated brain; middle column shows the scatter plot of correlation between the observed and predicted balance measure; column to the right shows the null distribution of the MAE, dotted line represents the threshold for significant prediction and dark black line shows the MAE for the actual prediction made. MAE - mean absolute error, APA – anticipatory postural adjustments, OA – Older Adults, CiO – CinguloOpercular, Smn – Somatomotor

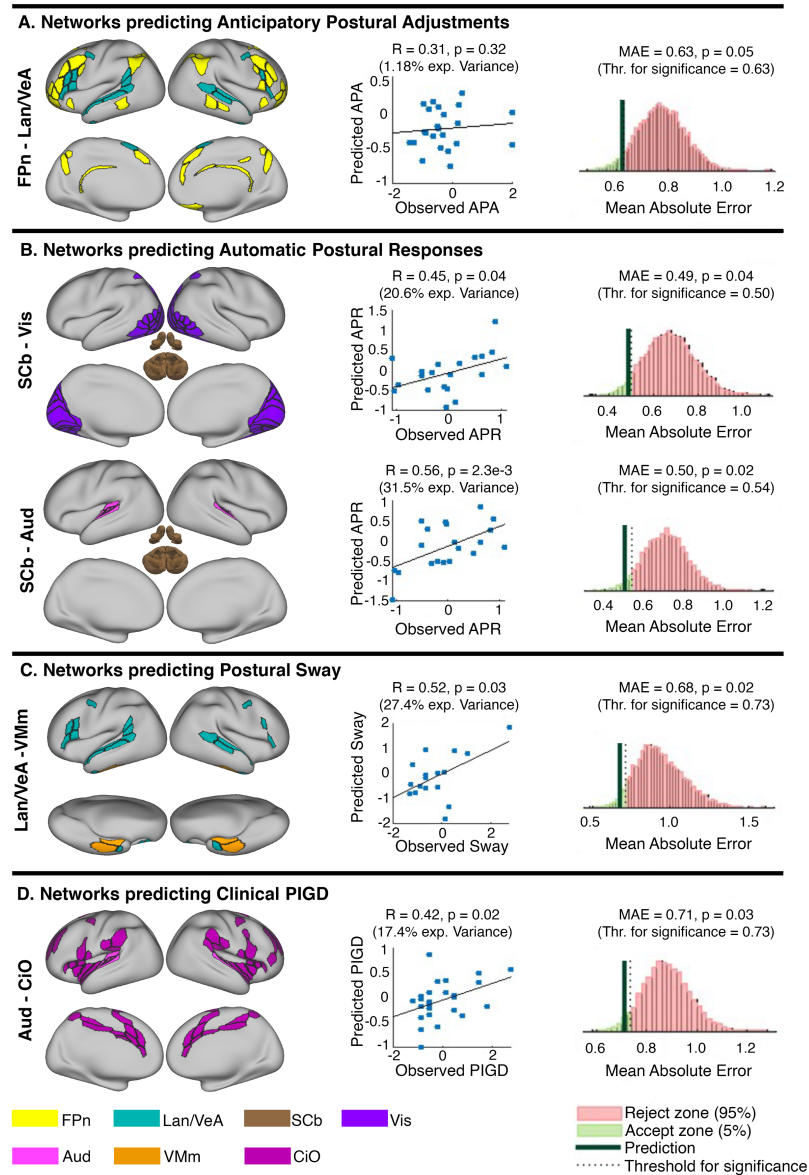


Figure 4.3. Functional connectivity network pairs predicting APAs, APRs and postural sway in PD.

The column to the left shows the spatial representation of the functional networks on a very inflated brain; middle column shows the scatter plot of correlation between the observed and predicted balance measures; column to the right shows the null distribution of the MAE, dotted line represents the threshold for significant prediction and dark black line shows the MAE for the actual prediction made. MAE - mean absolute error, APA – anticipatory postural adjustments, APR – automatic postural responses, FPn – frontoparietal, Lan/VeA – Language/Ventral Attention, SCb – subcortical-Cerebellar, Vis – Visual, Aud – Auditory, VMm – Ventral Multimodal, CiO - CinguloOpercular

4.5 Discussion

Our findings showed that multiple brain functional connectivity (FC) network pairs are related to 3 different domains of postural control (APA, APR, sway) in PwPD. In addition, a different brain network pair was related to APAs in OAs than in PwPD. We employed rigorous modeling and validation methods using independent training and test samples to ensure reliability and reproducibility in 65 PD and 42 OAs. This is the first study to identify FC network pairs predicting, APRs and postural sway in PwPD.

4.5.1 Anticipatory Postural Adjustments (APAs)

FC between CinguloOpercular and Somatomotor networks predicted APAs in OAs. In contrast, FC between Frontoparietal and Language/Ventral-Attention networks predicted APAs in PwPD. As expected, OAs showed involvement of somatomotor network for movement initiation which includes brain regions responsible for motor planning/step initiation like SMA (Deecke 1990), along with motor execution regions like M1 (Deecke 1987). APAs require a strong connectivity between Somatomotor and CinguloOpercular networks that are observed in healthy adults, but not in young children (Cignetti et al. 2018), supporting our findings.

Unlike OAs, Frontoparietal and Ventral-Attention systems were predictive of APAs in PwPD. PwPD show more persistent activation of frontoparietal regions for automated tasks like walking compared to OAs. When postural control becomes difficult with challenging tasks, EEG studies show increased parietal contribution in healthy adults (Edwards et al. 2018). Regions which are normally activated in OAs while multi-tasking, like prefrontal, superior parietal lobule and posterior parietal cortices, are activated in PwPD even without any multi-tasking (Wittenberg et al. 2017). It shows that PwPD have higher cognitive demands while performing simple postural control tasks like

step initiation. But, PwPD have smaller APAs than OAs and this could be due to incomplete, or poor, compensation as it has been hypothesized that deficiency in the information processing frontoparietal network may cause impairments of APAs and gait (Takakusaki 2017).

4.5.2 Automatic Postural Responses (APRs)

FC between Subcortical-Cerebellar and Visual networks and FC between Subcortical-Cerebellar and Auditory networks predicted APRs in PwPD. Subcortical-Cerebellar network contains ROIs in the cerebellum and the thalamus (among others) that are highly involved in postural control. Cerebellar control of movement, triggered by external sensory drive, is thought to compensate for loss of basal ganglia driven, self-initiated control of movement in PD. The cerebellar vermis, in particular, integrates proprioceptive, vestibular, auditory and visual information for postural control (S. Mori et al. 2001; Takakusaki 2017). The VA and VL nuclei in the thalamus merge inputs from both the basal ganglia and the cerebellum and deep brain stimulation in the right VIM nucleus has shown to improve postural responses in a patient with PD (Burleigh et al. 1993).

Postural responses are normally triggered by proprioceptive stimulation, specifically type II sensory afferents (MacKinnon 2018b). However, PwPD have been shown to have impaired central proprioceptive processing, which may result in over-dependence upon visual and auditory cues for triggering postural responses (Gawel et al. 1981).

Poor proprioceptive processing in PwPD results in visual over-dependence for control of voluntary movements, as well as postural control. For example, PwPD show higher visual dependence for postural control compared to healthy adults and are more affected by visual perturbations (provided by virtual reality) on both stable and unstable

surfaces (Hawkins et al. 2021). PwPD show impaired visual self-motion perception compared with age-matched controls and overweight visual cues during multisensory integration (Yakubovich et al. 2020). Even healthy adults depend more on vision when learning new postural skills and balance training increases cortical thickness in visual association areas (Rogge et al. 2018).

Poor proprioceptive processing in PwPD may result in auditory, as well as visual, over-dependence for triggering postural responses. Postural responses to perturbations are accelerated when accompanied by a startling auditory stimulus in PwPD (Nonnekes et al. 2015). On the contrary, PwPD who have freezing of gait show absent startle reflexes and longer postural response latencies and smaller postural response amplitudes (Thevathasan et al. 2011). Neurons in the cochlear nucleus communicate with the pontomedullary reticular formation in the brainstem in response to a startling auditory stimulus (Yeomans and Frankland 1995). The pontomedullary reticular formation is thought to be responsible for eliciting automatic postural responses to external perturbations (J. V. Jacobs and Horak 2007). Adding auditory stimulation during balance training results in sustained improvements in postural control (Capato et al. 2020).

4.5.3 Postural Sway

FC between the Ventral-attention and Ventral-Multimodal networks predicted postural sway while standing on foam in PwPD. This observation is consistent with the hypothesis that standing postural control is more cognitively (less automatically) controlled in PwPD than in OAs.

The ventral-attention network includes the posterior Insula, considered one of the hubs of the vestibular cortex for integration of proprioceptive and visual information (Frank and Greenlee 2018). The primary function of the Ventral-attention network is to

reorient attention to unexpected stimuli. It is shown to be deactivated during tasks requiring focused attention and activated when an unexpected event occurs (Corbetta and Shulman 2002). Disruption to the ventral attention network may result in inability to deactivate the network resulting in greater distraction and thus, poor postural control. Moreover, white matter hyperintensity disruptions to the ventral attention and somatomotor networks have been associated with increased postural sway when standing on an uneven surface and increased fall risk in OAs (Crockett et al. 2021).

The Ventral Multimodal network in the Inferior Temporal cortex, predominantly consists of the Fusiform gyrus, which has been associated with perception and categorization of visual stimuli (Rouw and Scholte 2007). PwPD are known to have difficulty visually judging the width and size of objects, such as the width of doorways. PwPD may be more dependent on central visual orientation information for control of postural sway compared to OAs, especially when standing on foam if they have difficulty in using vestibular information for postural control. The Fusiform gyrus of the inferior temporal cortex has been shown to be especially hypometabolic in postural instability-dominant PD compared to tremor-dominant PD in a FDG-PET study (Zhang et al. 2016).

4.5.4 Clinical Postural Instability

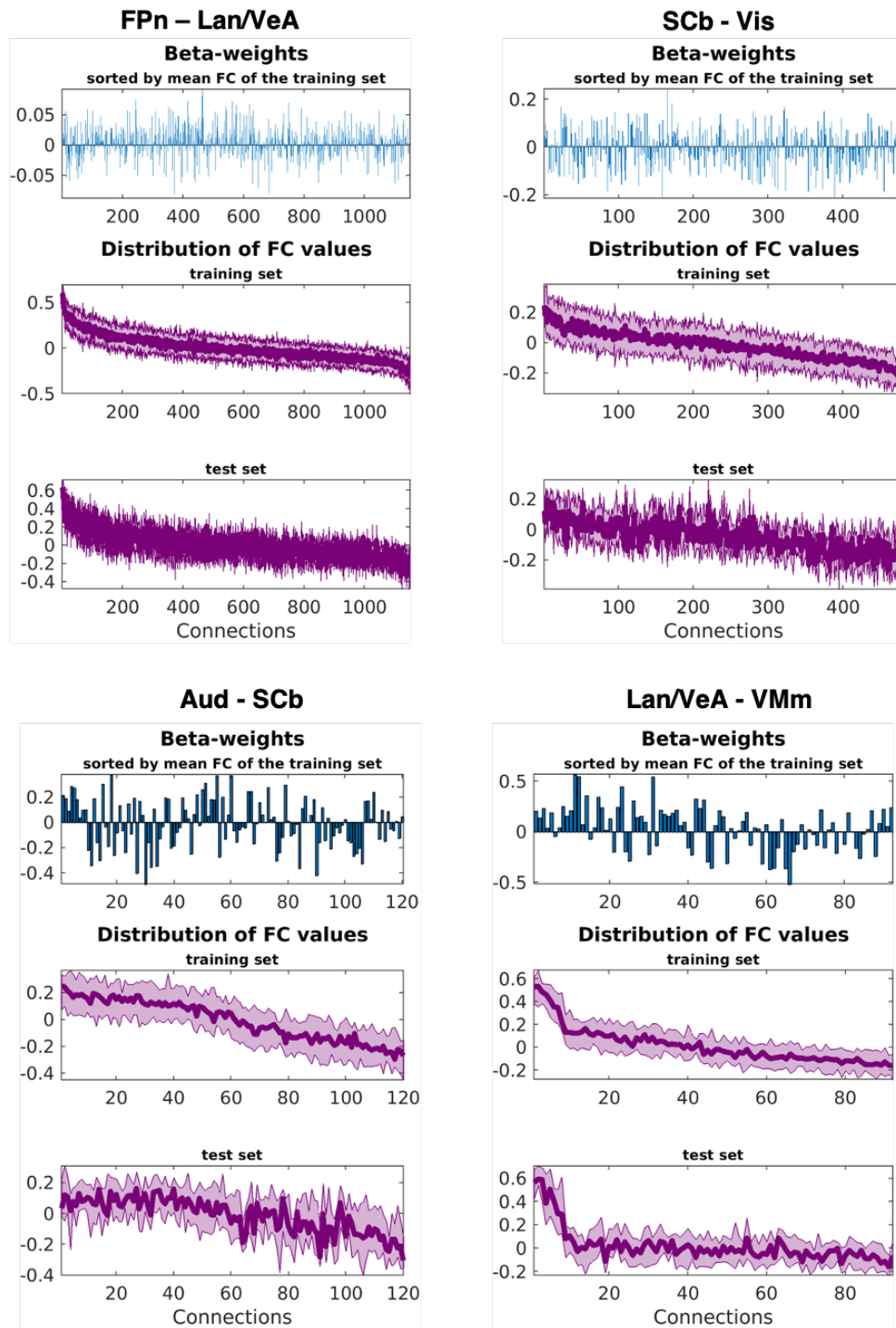
We identified FC between Auditory and CinguloOpercular networks predicting clinical PIGD score. The motivation behind doing this analysis was to see if there were similarities in FC between clinical PIGD and the objective postural measures and to better understand how clinical rating of postural control relates to objective measures. PIGD is a composite score representing a combined aspects of posture and gait dysfunctions. This could be a reason why we did not see exact network pairs observed in objective postural measures predictions. However, we saw a combination of Auditory network from the APR and CiO from the APA in OAs predicting PIGD.

There are few limitations in our study. Although our original sample consisted of 150 subjects, we lost few subjects due to the cerebellum being out of field of view and increased movement in the scanner and were predominantly PD subjects in the training sample. As the disease progresses, the neck posture tends to deteriorate, that could be a reason for the increased head motion and cerebellum going out of field of view. However, the number of subjects in our study are larger than most imaging studies in PD. The functional connectivity atlas we used was created from HCP dataset which comprised of individuals with average age of 25. However, during registration process we registered our PD subjects to age matched intermediary atlas created from our age matched control cohort to control for the age-related anatomical changes. Future studies could develop detailed functional connectivity atlases for OAs. We focused on balance impairments of PD. Functional brain network connectivity related to different gait domains could be performed in the future.

4.6 Conclusions

In summary, our findings suggest that PwPD have more cortical networks associated with posture control than OAs. Also, there is no overlap in brain networks associated with 3 different domains of postural control. APAs show involvement of central motor planning areas whereas APRs show involvement of the cerebellum and sensory areas. In contrast, postural sway is influenced by attention-related networks. Concurrent with the literature findings, we found that PwPD use more frontal and attention networks for postural control than OAs, a possible compensatory mechanism.

4.7 Supplementary materials



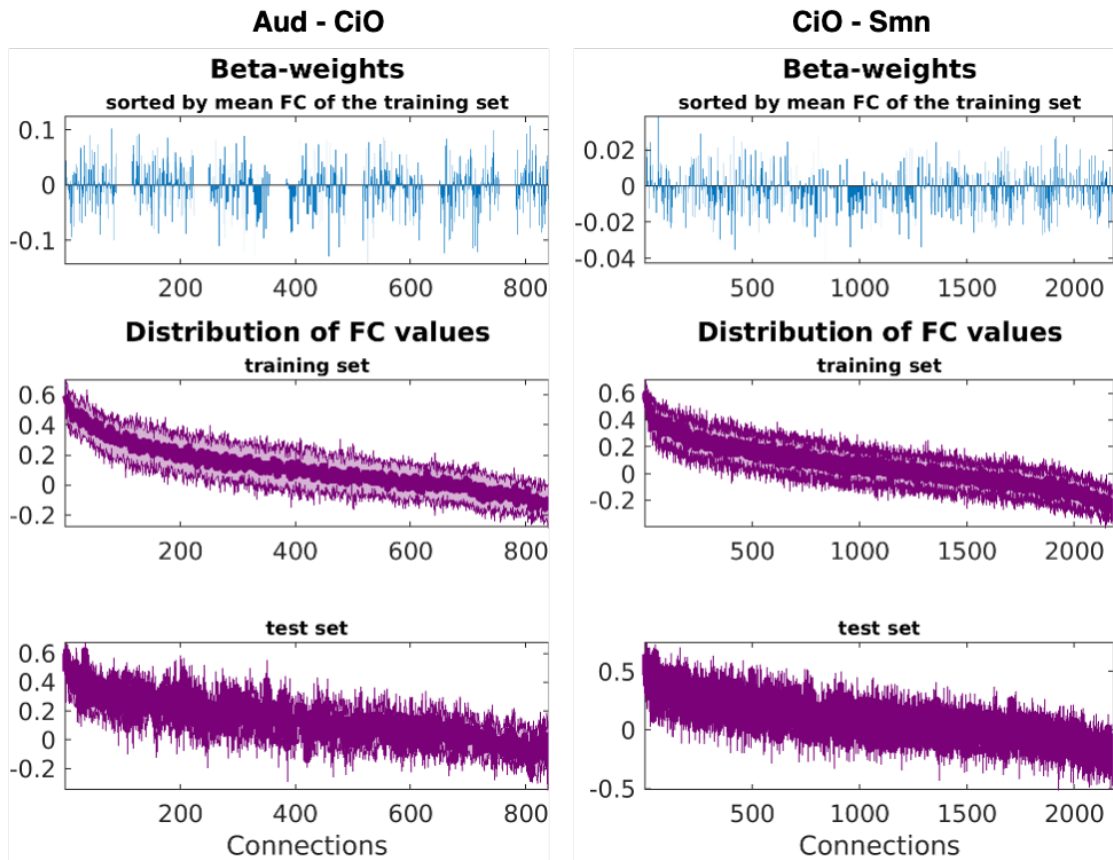


Figure 4.S1. Plots showing the beta weights and functional connectivity of the training and the test dataset for the significant network pairs that predict balance measures.

Row 1 shows the beta weights sorted by mean FC of the training dataset. Row 2 shows the distribution of FC for the training dataset, sorted by the mean FC. Row 3 shows the distribution of FC for the test dataset, sorted by the mean FC of the training dataset. X-axis shows the number of ROI-ROI connections in a network pair.

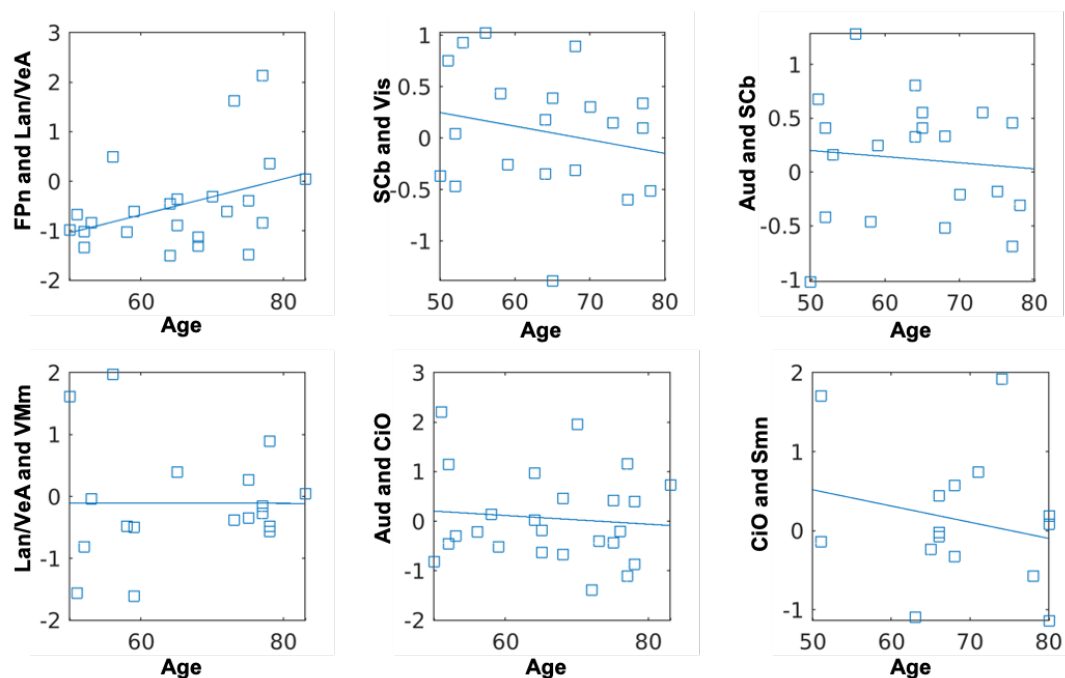


Figure 4.S2. Scatter plots showing the correlation between age and residuals of PLSR models of functional connectivity network pairs that predicted balance measures

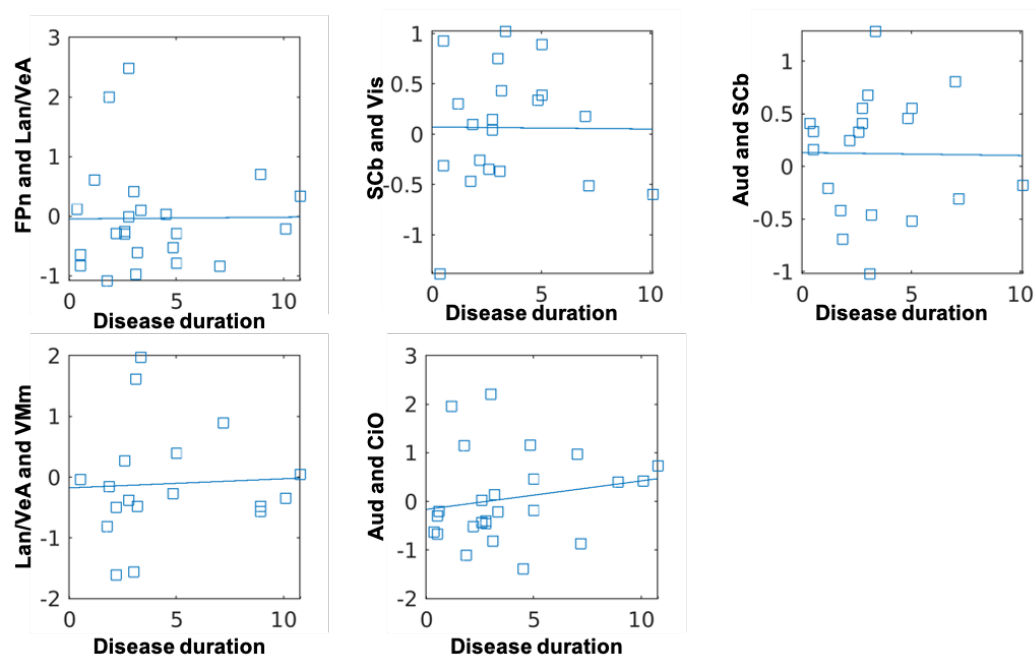


Figure 4.S3. Scatter plots showing the correlation between disease duration of the PD subjects and residuals of PLSR models of functional connectivity network pairs that predicted balance measures

Supplementary Tables

Table 4.S1. List of subcortical ROIs from PD25 and FreeSurfer Atlases

Subcortical ROIs from PD25 atlas	Subcortical ROIs from FreeSurfer atlas
Left Caudate	Left Thalamus
Right Caudate	Right Thalamus
Left Putamen	Left Amygdala
Right Putamen	Right Amygdala
Left Accumbens	Left Hippocampus
Right Accumbens	Right Hippocampus
Left Globus pallidus internal	Left Cerebellum
Right Globus pallidus internal	Right Cerebellum
Left Globus pallidus external	
Right Globus pallidus external	
Left Subthalamic nucleus	
Right Subthalamic nucleus	
Left Substantia nigra	
Right Substantia nigra	
Left Red nucleus	
Right Red nucleus	

Supplementary Methods:

Neuroimage acquisition parameters:

Imaging data were acquired using two different scanners, a 3T Siemens Trio scanner and later a 3T Siemens Prisma scanner, due to a scanner upgrade. Data were collected by a certified scanning technician and images were reviewed by a neurologist if anatomical abnormalities were suspected. Subjects were instructed to lie still and keep their eyes open. Head padding was provided to keep their heads still, earplugs were used to protect against scanner noise, and a leg bolster was provided to assist with back comfort.

High resolution structural T1- and T2-weighted images and resting state functional images were obtained using following parameters: Siemens Trio scanner: T1-weighted images were acquired using a sagittal magnetization prepared rapid gradient echo (MPRAGE) sequence (TR=2300 ms, TE=3.58 ms, voxel size=1mm x 1mm x 1.1mm, slices=160). T2-weighted images were acquired using the following parameters: TR=3200 ms, TE=497 ms, resolution=1 mm isotropic, slices=160. Resting state functional BOLD images were acquired in 2 scans of 10 minutes each with the following parameters: TR/TE=2000/30 ms, resolution=3.8 mm isotropic, flip angle=90°, leading to a total of 600 frames. Siemens Prisma scanner: T1-weighted images were acquired using a sagittal MPRAGE sequence (TR = 2500 ms, TE = 2.88 ms, TI = 1060 ms, resolution = 1 mm isotropic). T2-weighted images were acquired using the following parameters: TR = 3200 ms, TE = 565 ms, resolution = 1 mm isotropic, slices = 176. Resting state functional BOLD images were acquired in 2 scans of 10 minutes each with the following parameters: TR/TE=2500/30 ms, resolution=3.8x3.8x3.8 mm, flip angle=90°, leading to a total of 480 frames. Diffusion field maps were also acquired to correct for geometric distortions caused by susceptibility artefact.

Structural data registration process:

To give a brief overview of the structural data processing, T1 and T2 images were intensity normalized, brain images were extracted, then they were aligned to MNI's AC-PC axis and transformed to MNI atlas space using nonlinear registration. The transformation involved calculation of a single matrix for each individual to facilitate registration of both to an intermediary study template (created using high quality MRI images from the age matched older adults of the study group) and to the MNI atlas. This original alignment was refined using boundary-based registration. T1-weighted images were then segmented using recon-all from FreeSurfer. Segmentations were improved by

using the enhanced white matter-pial surface contrast of the T2-weighted sequence. The final standard space created the CIFTI file format and the associated grayordinate spatial coordinate system (91282 anchor points) which combined cortical surface and subcortical volume analyses.

Subcortical ROIs network creation and registration process:

The standard FreeSurfer subcortical segmentation does not provide segmentations for substantia nigra, subthalamic nucleus, internal and external pallidum and red nucleus. So, we created a subcortical atlas which has a combination of subcortical ROIs implicated in PD and those that are standardly used in FreeSurfer. We used the ROIs from the above mentioned PD25 MNI atlas to segment subthalamic nucleus, substantia nigra, red nucleus, pallidum internal and external, caudate, putamen and thalamus. We used FreeSurfer to segment the rest of subcortical ROIs, namely, accumbens, amygdala, hippocampus and cerebellum. Having the PD25 atlas ROIs along with other standard FreeSurfer ROIs helped in extracting functional information from subcortical regions known to be implicated in PD while having access to rest of the regions.

The PD25 MNI ROIs were in 1 mm space. So, we registered PD25 MNI atlas to a 2 mm MNI atlas and brought it to 2 mm space using ANT. The FreeSurfer ROIs and PD25 ROIs were combined using FSL's `fslmaths` command. There was an overlap of caudate and accumbens when the two atlases were combined. So, we performed manual corrections using ITKsnap.

Statistical Analysis – PLSR details:

To determine the threshold of the significance, we compared predictions with proper assignment against the cumulative distribution of the MAE predicting the null-hypothesis data. We selected the optimal number of components that maximized the significance of the prediction in the modeling stage. Finally, we estimated the model

performance on the independent test dataset. The optimal models learned from the training dataset were used to predict the motor scores in the independent test dataset and significant functional connectivity pairs were again selected comparing test data to the permuted null-data.

Supplementary Results:

The correlation coefficient (r) and p -values (corrected for multiple comparisons) of age with the significant network pairs were: CinguloOpercular and Somatomotor networks ($r=-0.22$, $p=0.43$), Frontoparietal and Language/Ventral Attention networks ($r=0.39$, $p=0.35$), Subcortical-Cerebellar and Visual networks ($r=-0.20$, $p=0.38$), Subcortical-Cerebellar and Auditory networks ($r=-0.09$, $p=0.69$), Language/Ventral Attention and Ventral multimodal networks ($r=-0.002$, $p=0.99$), and Auditory and CinguloOpercular networks ($r=-0.09$, $p=0.64$). The scatterplots are shown in Supplementary Figure S2.

The correlation coefficient (r) and p -values of disease duration and network pairs were: Frontoparietal and Language/Ventral Attention networks ($r=0.009$, $p=0.96$), Subcortical-Cerebellar and Visual networks ($r=-0.008$, $p=0.97$), Subcortical-Cerebellar and Auditory networks ($r=-0.01$, $p=0.96$), Language/Ventral Attention and Ventral multimodal networks ($r=0.05$, $p=0.83$), and Auditory and CinguloOpercular networks ($r=0.19$, $p=0.36$). The scatterplots are shown in supplementary Figures S3.

Chapter V: Discussion and Future Directions

5.1 Summary of Findings

This dissertation presents work from three research studies that investigate the associations between mobility impairments in people with PD and how they relate to brain characteristics. Specifically, the goal of these projects was to better understand the relationships between (objective and clinical) mobility metrics and brain structural and functional features and differences in these relationships between people with PD and age-related, older adults. Our goal was achieved by: 1) examining the brain structural volumes associated with objective and clinical balance and gait metrics; 2) investigating resting state functional connectivity of networks associated with clinical motor signs of PD; and 3) studying the resting state functional connectivity of networks associated with independent domains of balance control. **Table 5.1** summarizes the results of all 3 studies in this thesis.

Table 5.1. Summary of results from three projects.

Projects	Mobility Measures		Neural Correlates			
			Structural (Project 1)		Functional (Projects 2 & 3)	
			Subcortical	Cortical	Subcortical-cortical	Cortical
1, 2	Clinical mobility scores (Only PD)	MDS-UPDRS III	NS		SBG-Smn	Smn-Vis
1, 3		PIGD				CiO-VeA
			Tot. subcrotical	Temporal lobe		Aud-CiO
			Putamen			
			Accumbens			
			Hippocampus			
1, 3	Objective Balance measures (PD and OA)	APA	Cerebellum (Fr)	Parietal (nFr)		CiO - Smn (OA)
			Ventricle (OA)	Frontal (nFr)		FPn - VeA (PD)
			Tot. cortical (nFr)			
		APR	Brainstem (OA)	Parietal (nFr, OA)	SCb - Vis (PD)	
			Cerebellum (OA)	Temporal (nFr)	SCb - Aud (PD)	
		Sway	Brainstem (PD)	Occipital (OA)		VeA - VMm (PD)
			Tot. subcortical (PD, nFr)			
			Ventricle (OA)			
1	Objective Gait measures (PD and OA)	Gait Variability	Cerebellum (Fr)	Frontal (OA)		
			Brainstem (Fr)			
			Ventricle (Fr)			
			Hippocampus (Fr)			
			Amygdala (OA)			
		Gait Speed	Cerebellum (Fr)			
		Turn velocity	NS			
		Stance time				
		Arm RoM				

Project 1 investigated the structural correlates of clinical and objective mobility measures. Project 2 focused on the functional correlates of clinical MDS-UPDRS motor signs. Project 3 examined the functional correlates of objective balance measures.

5.1.1 Subcortical Volumes Relate to Postural Control

In **Project 1 (Chapter 2)**, we characterized the association between structural brain volumes and instrumented measures of balance and gait in people with PD (off-medication) and older adults (OA). We also investigated the brain volumes related to the clinical motor signs. While there is lot of research on grey matter volume in people with PD, most previous studies have focused on differences between PD and OA. Previous studies of the relationship between brain structure severity of balance and gait disorders have been mostly limited to clinical measures of balance and gait, albeit with inconsistent results. Instrumented measures of balance and gait provide more sensitive

and specific measures of balance and gait impairments than clinical rating scales.

Studies that looked at instrumented measure primarily focused on gait aspects like gait speed and step length (Chastan et al. 2009; Herman et al. 2014). No previous study has related instrumented measures of both balance and gait with brain volumes to determine the relationships between different domains of balance and gait with different brain areas in the same cohorts, either PD or OA.

We identified multiple, gray matter volumes associated with instrumented measures of balance and gait, both in PD and OA. Smaller brainstem and subcortical volumes were reflective of increased postural sway in PD whereas increased ventricle volume was related to impaired postural transitions (APAs) for gait initiation in OA. In OA, smaller brainstem, cerebellar and parietal lobe volumes were related to postural responses to external perturbations (APRs) and enlarged ventricle and smaller occipital lobe volumes were associated with larger postural sway. In addition, smaller amygdala and frontal lobe volumes were associated with larger variability in gait in OAs. A sub-analysis in PD revealed atrophy of multiple subcortical regions related to gait variability in patients with freezing of gait. Smaller volumes of temporal lobe and multiple subcortical regions, including parts of striatum (putamen and accumbens), hippocampus and amygdala were associated with clinical postural instability and gait disorders (PIGD) in PD.

In contrast to objective balance and gait measures, no brain volume associations were found for clinical motor scores. The associations between gray matter volume and clinical motor signs have been inconsistent in the literature. Our study shows that postural control measures are more sensitive than clinical motor signs to brain volume measures. Studies have attempted to develop an imaging biomarker for Parkinson disease progression (De Micco, Russo, and Tessitore 2018; Khan et al. 2019). Results from project 1 suggests that structural MRI may be considered for structural changes in

the brain impacting certain aspects of disease progression like postural sway. Perhaps, structural MRI, in combination with instrumented measures of mobility, could be used as a quantitative measure of disease progression.

5.1.2 Motor and Attention Functional Networks Relate to Motor Signs

In **Projects 2 and 3 (Chapters 3 and 4)**, we employed resting state functional connectivity to understand the brain networks involved in motor impairments in PD. To ensure reliability and reproducibility and to take advantage of a change in imaging technology mid-study, we implemented a predictive modelling approach with a training dataset and an independent, validation dataset.

In **Project 2 (Chapter 3)**, we used functional brain networks to predict clinical motor signs in people with PD. Consistent with previous studies, we identified functional connectivity between somatomotor and subcortical-basal ganglia networks, that are related to the motor functions to be predictive of the motor signs (MDS-UPDRS III). However, we also found connectivity between somatomotor and visual network and connectivity between cinguloopercular and ventral attention network to be predictive of motor signs. These results indicate that not only motor systems, but higher-order networks are also involved in motor dysfunctions in PD.

5.1.3 Higher-Order Functional Networks Involved in Postural Control

In **Project 3 (Chapter 4)**, we focused on brain networks to predict specific, objective balance measures. Unlike Project 2 (Chapter 4) in which PD clinical motor signs came from a general composite score, in Project 3 (Chapter 5), we sought to

investigate brain networks associated with more granular aspects of mobility than Project 2 (Chapter 3), by focusing several different aspects (domains) of balance control. We demonstrated that more brain networks are associated with balance control in our PD than OA cohorts. Moreover, we learned that different networks are involved in different aspects of balance control. Both the clinical signs (Project 2) and instrumented measures of balance (Project 3), were related to higher-order, cortical networks, in addition to sensorimotor networks in PD.

However, we also note that some brain regions that were implicated in posture control structurally were not implicated in functional network connectivity. First, anticipatory postural adjustments (APAs) were not significantly associated with any structural brain volumes in the PD cohort and APAs were correlated with ventricle volume in OA. In contrast, APAs were associated with connectivity between the frontoparietal and ventral attention networks in the PD cohort APAs and with functional connectivity between the somatomotor and cinguloopercular networks in OA. One potential reason for differences in results between studies is that different characteristics of APAs were used in each study. We chose APA first step range of motion for structural analysis based on our previous study that best differentiated PD and OA (Hasegawa et al. 2019a). However, we chose peak ML APA range for functional analysis as it is a more common measure used in the literature. While APA first step range and Peak ML are highly correlated APA measures, they represent slightly different aspects of APAs (peak ML is the trunk acceleration in the ML direction, whereas first step range is the range of motion of the leg during the compensatory step).

Second, automatic postural responses (APRs) were significantly associated with volumes of the brainstem, cerebellum and parietal lobe in the OA, but not the PD cohort. In contrast, APRs were associated with connectivity between the Subcortical-Cerebellar networks and sensory networks in the PD cohort. Again, differences in results between

studies (projects 1 and 3) may be that different characteristics of APRs were used in each study. We chose APR first step vertical height (for project 1), based on our previous results that best differentiated PD and OA (Hasegawa et al. 2019a). However, we chose APR first step horizontal length (for project 3) as it is a more common measure used in the literature.

Finally, for postural sway, the root mean square of acceleration in the AP direction was used for both structural and functional analysis. Structurally, we found total subcortical and brainstem volumes related to postural sway but functionally we found cortical region connectivity and no subcortical networks involved. There could be multiple reasons for this difference in results: (a) cortical volume measures may not be a sensitive measure to detect associations, since cortical volumes were calculated for large lobes, (b) BOLD signals at the subcortical levels may have lower SNR (higher noise) and not be sufficient to identify significant functional associations and (c) statistical methodological differences in the analyses performed. Most importantly, functional network connectivities do not necessarily translate to structural changes since networks are widely distributed across brain regions.

5.2 General Discussion

The aim of this thesis was to better understand the neural control of balance and gait and how it is affected in PD. This thesis adds more evidence to the existing literature that balance and gait control in humans involves widespread, complex interactions between subcortical and cortical regions (J. V. Jacobs and Horak 2007; Bohnen and Jahn 2013; Peterson and Horak 2016; Takakusaki 2017). Unlike earlier studies that assumed balance and gait was always automatically controlled by subcortical areas (Sherrington 1910), our studies consistently confirm involvement of higher level, cortical

areas, especially in people with PD who have lost some subcortical (automatic) control. Nevertheless, certain brain regions, such as the basal ganglia, brainstem, cerebellum, frontal, ventral attention and visual regions may be specifically involved in balance and gait control whereas other higher-level cortical networks become recruited as compensatory mechanisms in people with PD. Below, I show how our clinical mobility scores related to instrumented measures of balance and gait and then discuss how different aspects of balance and gait are impacted by changes in the subcortical and cortical systems due to PD.

5.2.1 How Do Clinical Assessments Relate to Objective Assessment of Mobility?

Two projects in this thesis (Projects 1 and 3) related instrumented measures of balance and gait to brain structure and function, whereas Project 2 focused on the clinical motor score (MDS-UPDRS III), which included clinical ratings of bradykinesia, rigidity, tremor, as well as the PIGD (sit to stand, stance postural alignment, gait and the pull test (eg; APRs)). To better understand differences (or similarities) in brain network connectivity related to clinical versus instrumented balance and gait measures, we explored correlations between these two types of mobility outcomes in this thesis.

While the instrumented measures relate to clinical measures, they also capture finer aspects of mobility impairments in PD which are not captured in clinical scores. In our cohort, the clinical motor scores correlated with multiple gait measures, more so than balance measures (see **Table A.1** in Appendix). MDS-UPDRS III was correlated with one aspect of APAs (first step range), but not with APR or postural sway. Postural instability and gait impairments score (PIGD) was correlated with APA and APR, but not sway. This result was expected, as postural sway is known to be an independent

measure from gait measures, even in people with PD (Mancini et al. 2012; Fay B. Horak et al. 2016).

In terms of associations with brain features, the clinical motor score (MDS-UPDRS, Part III) did not relate to *structural* brain measures (**Project 1**) although it did relate to multiple, higher order *functional network interactions* (**Project 2**). Unlike the MDS-UPDRS III total score, the PIGD score was associated with both structural (**Project 1**) and functional measures (**Project 3**) of the brain. The Subcortical-Basal ganglia network was associated with the Part III clinical motor score and putamen volume was related to PIGD. Part III clinical scores associated with the expected somatomotor and basal ganglia networks, but also to sensory and attention network. In contrast, instrumented measures of balance and gait were associated with cerebellar, multi-sensory and attention networks.

5.2.2 Role of Subcortical Regions in Balance and Gait Control

The findings in this thesis suggest that balance and gait control is a whole-brain phenomenon, involving multiple subcortical and cortical regions. The subcortical regions are particularly impaired by PD but are challenging to investigate due to their small size. In this thesis, we limit study of subcortical structural volume to the Subcortical Gray matter, Brainstem, Cerebellum, Caudate, Pallidum, Putamen, Thalamus, Accumbens, Hippocampus, Amygdala. In this thesis, we divided subcortical networks into those more directly affect by PD, called the Basal Ganglia-Subcortical Network versus those less directly affected by PD, call the Cerebellar-Subcortical Network. Here, the Discussion will summarize how our results about how each aspect of balance and gait were related to specific subcortical networks in people with PD and OAs relates to the literature.

Anticipatory Postural Adjustments (APAs): We found smaller cerebellar volume related to smaller size of lateral APAs prior to the first step in people with PD without freezing issues. The cerebellum is the most commonly reported subcortical structure related to balance control, especially in clinical populations with balance impairments, such as PD (Surgent et al. 2019). Also, an increase in cerebellar gray matter volume has been observed after dynamic balance training for 6 weeks in people with PD (Sehm et al. 2014).

Our results likely are due to the fact that the largest cerebellar volume we measured consists of the hemispheres, or lateral cerebellum. The lateral cerebellum, which is the neo-cerebrum (also called cerebro-cerebellum and developed the latest in humans), connects to primary and premotor cortical areas like the SMA, via pontine fibers. The cortico-ponto-cerebellar pathway carries information about movement preparation and initiation, such as APAs prior to step initiation (MacKinnon 2018a). Lesions to the lateral part of the cerebellum can result in delays in initiation of movement due to smaller APAs (Javalkar, Khan, and Davis 2014). Adding external load during simulated stepping movements in a fMRI study showed activation of the cerebellum, likely because added loads may require larger APAs (Jaeger et al. 2016).

Automatic Postural Adjustments (APRs): Smaller brainstem and cerebellum volumes were related to impaired postural responses in OAs. The Subcortical-cerebellar network, which consists of the cerebellum, thalamus, hippocampus and amygdala, predicted APR performance in PD. We found the cerebellum to be involved with APRs in both our structural and functional analyses.

A subset of cells from the medial vermal zone of cerebellum project to the vestibular nucleus directly suggesting that vermis contributes to reactive postural control by modulating the brainstem vestibulospinal and reticulospinal motor outputs in response to vestibular and visual stimuli (MacKinnon 2018a). Animal studies also show

that the cerebellum connects to PPN and PMRF in the brainstem through the fastigial nucleus (one of the cerebellar nuclei) that are involved in postural control (Takakusaki 2017; MacKinnon 2018a). The vermis is also thought to have connections to the locomotor central pattern generators in the spinal cord for step initiation (Takakusaki 2017). The cerebellum and basal ganglia are interconnected to each other through the subthalamic nucleus and brainstem (pontine nucleus) which explains the involvement of the cerebellum in a compensatory role in people with PD (Bostan and Strick 2018).

The brainstem is thought to be involved in the initial phase of postural responses to external perturbations and the cerebellum (through cortico-brainstem circuit) for modifying postural responses based on practice/experience (J. V. Jacobs and Horak 2007). Our results are consistent with task fMRI studies looking at reactive balance control in young adults using motor imagery (through visual field motion) that identified activation in the cerebellum, thalamus and putamen (Slobounov et al. 2006; Taube et al. 2015; Mouthon et al. 2018).

Postural Sway in Stance: Consistent with a prior study, we found smaller brainstem volume related to increased postural sway in people with PD (Müller et al. 2013). We also found that smaller total subcortical volume was also associated with increased postural sway. Our postural sway condition was on a foam surface which increases sway by impairing use of somatosensory inputs and was the condition most sensitive to PD (Hasegawa, 2020). A prior study found cholinergic activation in the brainstem (PPN) was directly related to postural sway (Müller et al. 2013). Motor imagery studies, in which people imagine they are balancing in standing, have also shown fMRI activations in the brainstem (vestibular nuclei), pontomesencephalic junction and left midbrain subcortical areas (Jahn et al. 2004, 2008; Zwergal et al. 2012). Motor imagery of postural sway in fMRI (when lying people push on a rotating platform to balance a weight) show activations in the following subcortical regions: right putamen,

left pallidum, mesencephalic locomotor region and vermis (Ferraye et al. 2014). Basal ganglia nuclei (caudate, putamen, pallidum), thalamus and right hippocampus have also been found to be activated during motor imagery of standing balance in older adults (Jahn et al. 2004, 2008, 2009; Zwergal et al. 2012; Karim et al. 2014).

While we did not find any structural or functional cerebellar involvement related to our postural sway condition, that cerebellar vermis has been reported to be involved (most of the time) with static postural control in healthy adults during motor imagery of stance tasks in fMRI or actual stance with a mobile PET system (Ouchi et al. 1999; Dijkstra et al. 2020). However, when stance simulation (through dorsiflexor and plantarflexor activation) was tested in fMRI in healthy adults, the cerebellum was not involved (Karim et al. 2014). The lack of relationship between the cerebellum and sway in our study may be because we did not divide the cerebellum into different parts and the vermis represents a much smaller volume (network) than the hemispheres.

Interestingly, we found hippocampal volume to be associated with PIGD in people with PD. Hippocampus has been associated with spatial orientation. Right anterior hippocampus has been reported to be active during motor imagery of quiet stance in young adults (Jahn et al. 2009).

Gait: We found multiple, subcortical volumes associated with variability of gait in people with PD who had freezing of gait issues. Gait variability is larger in people with PD than controls and even larger in people with freezing of gait. Specifically, cerebellum, brainstem, hippocampus, amygdala and ventricular volumes related to variability of gait. Cerebellar volume was also related to gait speed in freezers. Activations in the cerebellar locomotor region has been consistently related to walking in people with PD and controls (Surgent et al. 2019; Gilat et al. 2019; Dijkstra et al. 2020). The cerebellar vermal inputs to brainstem regions (MLR) are responsible for controlling the rhythmicity of gait (Armstrong 1988; Jahn and Zwergal 2010). This explains the increased gait

variability related to cerebellar and brainstem volume that we observed in PD freezers. Expert dancers also have increased cerebellar volume compared to non-dancers (Hüfner et al. 2011).

While we do not understand the exact role of the hippocampus related to gait variability in PD, the hippocampus is thought to be involved in visually-guided locomotion (Jahn et al. 2009). Consistent with our findings, hypo-activation has been observed within the left hippocampus and midline/lateral cerebellum in PD patients during mental imagery of gait (Crémers et al. 2012). OA who have increased variability in stride length also show lower levels of hippocampal neuronal metabolism (but not hippocampal volume) observed through proton MRS of (N-acetylaspartate to creatine ratios) (Zimmerman et al. 2009). Hippocampus and parahippocampal gyrus have been shown to be activated during mental imagery of walking in young adults (less activated during imagery of running) (Jahn et al. 2004).

While we analyzed different domains of gait and related structural volumes, we found only subcortical volumes related to gait speed and variability in PD. We did not find any significant structural associations for turn velocity, stance time or arm range of motion. Future studies should investigate whether different brain network functional connectivities are associated with different domains of gait.

5.2.3 Role of the Cortex in Balance and Gait Control

With loss of subcortical control and thereby reduced balance and gait automaticity in people with PD, motor actions that are normally controlled automatically become voluntary in PD and thus, we see more involvement of high-level, cortical systems. In this section, I will summarize our results related to the cortical structural and functional relationships to different aspects of balance and gait and relevance to the literature.

APAs: We found larger volumes of frontal, parietal and total cortical regions to be associated with better gait initiation in PD (non-freezers). In addition, functional connectivity between frontoparietal and ventral attention networks in people with PD and connectivity between cinguloopercular and somatomotor networks in OA predicted APAs.

Consistent with our results, frontal regions of the cortex, including prefrontal (DLPFC and preSMA), premotor (SMA and cingulate motor areas) and primary motor cortex are highly involved in voluntary movement planning and initiation (Deecke 1987; MacKinnon 2018a). When young adults were tested for weight shifting or lateral stepping (tasks requiring APAs), EEG recorded, movement-related potentials started 50–100 ms prior to the movement onset in the fronto-central cortex, which includes the SMA and primary motor cortex (Varghese et al. 2016). Although we did not find (structural or functional network) involvement of the brainstem or basal ganglia in APAs, connectivity between brainstem regions (VN, MLR, PMRF) and motor and premotor cortical areas enable preparation for movement (MacKinnon 2018a). Cortical regions like medial frontal gyrus (SMA), premotor cortex, superior parietal lobe, cingulate cortex, insula and occipital cortex have also been related to motor imagery of dynamic postural control (e.g.; voluntary swaying).

Consistent with our results, more involvement of frontal regions is observed during APAs in people with PD with increased disease severity, like freezing of gait (de Lima-Pardini et al. 2020). We also observed other higher-order networks like ventral attention and cinguloopercular to be predictive of APAs. These networks were also related to clinical MDS-UPDRS motor severity. Since the subcortical function is impaired due to dopaminergic loss, more cortical involvement could be a compensatory strategy to control APAs.

APRs: We found larger volumes of temporal lobe and parietal lobe related to better APRs in PD non-freezers and OA. Consistent with these results, the clinical PIGD score (which consists of pull-test, representing the APR component) was also related to temporal lobe volume. We also found that functional connectivity between subcortical-cerebellar and cortical visual networks and connectivity between subcortical-cerebellar and cortical auditory networks associated with quality of APRs (size of protective stepping response).

Consistent with our results, task fMRI studies looking at reactive balance control in young and older adults using motor imagery (through visual field motion), identified activations in the temporal visual area, superior temporal gyrus and sulcus, parietal and middle and inferior occipital gyrus (Slobounov et al. 2006; Taube et al. 2015; Mouthon et al. 2018). The middle occipital gyrus is critical for visual information processing for postural control (MacKinnon 2018a). Involvement of temporal and visual areas in postural reactive control could be for sensory processing of self-perceived motion to trigger postural responses. Although we did not find frontal cortical regions involved in APRs, frontal, prefrontal, premotor (SMA), inferior frontal, cingulate and insular regions were activated during simulated reactive postural control (Slobounov et al. 2006; Taube et al. 2015; Mouthon et al. 2018).

One reason we did not find frontal related to APRs could be that the APR metric we used was step length and not the time to achieve equilibrium measure. We did not choose time to equilibrium because it was significantly different between the training and validation dataset we used. The involvement of cortical centers mean that people with PD can train to respond better to externally-triggered perturbations and perhaps avoid falls and injury, for, repetitive training of compensatory steps are also shown to improve and sustain voluntary gait in PD with balance impairments (Jöbges et al. 2004).

Sway: We found larger occipital lobe volume associated with reduced postural sway in OA and functional connectivity between the Ventral Attention and Ventral Multimodal networks (inferior temporal cortex) related to postural sway in PD. Our studies were consistent with previous studies showing activation of more cortical areas related to postural sway in people with more compromised balance, such as the elderly (Wittenberg et al. 2017; Dijkstra et al. 2020). The only study to look at actual stance using a mobile gantry PET (although with its limitations in measuring sway and in imaging methods) also showed cortical activations in inferior occipital lobe (visual association occipital cortex) in healthy adults when standing compared to supine position (Ouchi et al. 1999). Another study showed deactivation of middle occipital gyrus in the older adults when examining stance followed by PET imaging (Schöberl et al. 2017).

Associations between connectivities of attention-related areas and postural sway in people with PD may be because they require more attention to stand on a compliant foam surface compared to OAs. Static balance with sensory challenges, like standing on an unstable support surface and eyes closed, recruit more attention regions in the elderly than younger subjects; (Karim et al. 2014; Ozdemir, Contreras-Vidal, and Paloski 2018; Dijkstra et al. 2020). Temporal regions, including the temporoparietal junction and inferior temporal cortex, which are part of the ventral attention network, are considered to be responsible for vestibular and multisensory processing, have also been identified in postural simulation tasks (Jahn et al. 2009; Frank and Greenlee 2018). Multiple studies which examined simulated static balance using motor imagery also found middle frontal gyrus (part of ventral attention network that we found) (Dijkstra et al. 2020), but the motor imagery could represent an attention-related aspect and our study also examined sway on unstable surface which requires more attention to stay upright. So, the role of attention-related cortical regions in stance could be when conscious effort is made to maintain upright stance. Postural control can be trained in people with PD and can show

lasting structural changes as balance training has shown to increase grey matter volume in the inferior temporal gyrus (Sehm et al. 2014) and professional expert dancers have increased inferior temporal gyrus volumes (Hüfner et al. 2011).

Gait: Consistent with previous studies, we found that the frontal lobe volume was associated with gait variability in OA. We also found the PD clinical motor score related to multiple functional network connectivities. Consistent with the literature, we identified functional connectivity between the cortical somatomotor and subcortical-basal ganglia networks associated with motor severity in PD (Tessitore et al. 2014; Strafella et al. 2018). The somatomotor region consists of areas required for motor execution (M1) and also planning (premotor). SMA, in the premotor area, is responsible for motor planning, and is consistently activated in OA and hypo-activated during motor imagery or foot-tapping during task-fMRI in people with PD (Gilat et al. 2019). In fact, hypoactivation of the somatomotor area due to loss of subcortical-basal ganglia drive, is thought to be the mechanism underlying bradykinesia of PD, including bradykinetic posture and gait. Ambulatory neuroimaging tools like EEG and fNIRS also show activation of frontal regions while walking in people with PD (Stuart et al. 2020).

Our results are consistent with the PD-related pattern (PDRP), the most recognized metabolic brain pattern associated with PD which includes increased activity in pallidothalamic and pontine areas and reduced activity in frontal, premotor and parieto-occipital association areas (Schindlbeck and Eidelberg 2018). SMA is highly connected to the basal ganglia through the mesial frontal loop (Akkal, Dum, and Strick 2007). SMA is hypo-activated in people with PD likely due to dopaminergic loss and sub-functional striatum, with SMA not receiving enough striatal input, they rely more on cerebellar locomotor loop as a compensatory system that we alluded to in the previous (6.2.2) section.

We also identified connectivities between somatomotor and visual network and cingulo-opercular and ventral attention networks associated with the clinical motor score. The right-sided parietal-lateral ventral attention network, which includes the temporoparietal junction incorporates sensory information into the control of gait (Takakusaki 2013). Impaired sensory processing and integration leads to issues with perception of motion (Patel, Jankovic, and Hallett 2014). Further, higher brain centers become progressively engaged as a compensatory system when demands of locomotor tasks require increasing cognitive and sensory information processing (Malouin et al. 2003).

5.2.4 Imaging Considerations for Studying Balance and Gait in PD

This thesis uses a whole brain approach to relate brain to behavior. Most previous functional MRI studies looking at balance and gait have used specific ROI-based analysis, which is good for hypothesis-driven studies and small sample sizes, but limit the understanding of how other brain regions not studied may be involved.

We also implemented a predictive modeling approach using independent training and validation dataset. Small sample size is also increasingly being recognized as a problem for replication and reliability of rs-fMRI results (Marek et al. 2020). Nevertheless, if the methods utilize cross-validation or independent datasets to validate results, as we did, it increases the chances of replication. This study is one of the largest in sample size, so far, to investigate the role of brain networks in different aspects of balance and gait control.

The methods implemented for registration and segmentation of the brain, controlling for head movement, accounting for physiological noise like respiration either

while scanning or during data-processing are crucial to identify the real associations between brain and behavior. However, controlling for head movement in people with movement disorders, like PD, is challenging as uncontrollable movement (rigidity, tremor) defines the disease. We tested PD subjects in the Off-levodopa state when these movement disorders would be most overt. Although testing in the Off state may have resulted in eliminating more data with movement artifacts, it provides a more sensitive state to identify PD-related network changes.

Subcortical and brainstem segmentations are particularly problematic due to lower SNR issues. Interpretation of results must be made cautiously.

5.3 Limitations and Future Directions

Limitations

There are several limitations to this thesis. Our sample size was smaller than we like due to elimination of brain data with movement artifact (albeit larger than most), which is an important consideration when working with high-dimensional data. We also examined more people with PD than age-matched OAs. However, predicting behavior in an independent dataset (in different scanners) improves the reproducibility of our studies. We had a large number of potential outcome measures in this dataset (Hasegawa et al. 2019b). But we apriori limited our study to only a very few outcomes based on sensitivity to PD, due to the multiple comparison and power limitations issues.

Another limitation was heterogeneity in the structure and function of brain regions. The way we segmented the structures and functional atlases limits the extent to which we can identify relationships. When we average the data across the ROIs for both structure and function, we lose the granular data that the small, sub-region (for instance, multiple nuclei within an ROI) might contain. Also, we were limited to only 5 minutes of

rsfMRI data collected after ensuring the quality of the rs-fMRI data collected across subjects. This limits our ability to infer group-level tendencies. At least 20 minutes of BOLD data are required for reliable subject-specific inferences (Gordon et al. 2017). Another limitation was cross-subject heterogeneity in the function characteristics of brain regions. While the community structure of functional networks show great overlap across atlases, there are also variabilities across individual subjects for the same functional networks (Grayson and Fair 2017).

Another limitation is that this study focused only on general motor and balance and gait characteristics but people with PD also exhibit many non-motor symptoms. Thus cognitive, emotional, autonomic heterogeneity among our subjects was not taken into consideration so future studies should examine brain networks associated with these PD signs.

Our study included ambulatory people with moderate to severe PD who were taking levodopa. The newly diagnosed and most severe PD patients were excluded and results cannot be generalized to them.

Future Directions:

Using low-cost, wearable technology to quantify balance and gait impairments holds a great promise in disease evaluation and treatment. Real-world daily monitoring in non-laboratory settings is the next phase of research and hopefully will give clinicians more insight into the disease patterns.

This thesis focused on cross-sectional analysis. The next step would be to look at the impact of exercise interventions (to improve balance) on brain networks. Also, another step would be investigating longitudinal changes in the brain networks for balance and gait as the disease progresses. Interestingly, certain aspects of balance improves while other worsen with levodopa medication. Looking at the effects of

levodopa on brain connectivity as well as balance and gait, is actively being studied (Gilat et al. 2017).

Higher-order, cortical systems are involved in control of balance and gait. The interrelationships between cognition and gait could mean that we could use mobility metrics as a potential marker to inform about cognitive decline. It requires further validation of the underlying mechanisms and identifying specific mobility measures that are impacted and related most to cognitive systems. A better understanding of comment brain networks involved in cognition and balance/gait could help in disease management and treatment.

Currently, the ability to compare across imaging studies is littered with issues like differences in scanning protocols, focusing on specific brain regions, variability in atlases and segmentations, etc. Bringing a standard across the measures will foster reproducibility and reliability. It can also help to perform large-scale data analysis compiling data across studies, when such standards are established. This would, in turn, help to reduce the sample size issues in the field.

5.4 Conclusion

Walking and standing are the most important functional behaviors across the animal kingdom, and yet, PD impairs this basic movement ability. Improved understanding of brain alterations related to balance and gait would enable better prognosis of mobility disability and more accurate tracking of disease progression and enhanced clinical care. Understanding the heterogeneity of the balance and gait impairments in PD and how they are impacted by different brain structures and networks is critical to provide better clinical management. Studying the network level changes are helpful even to understand the molecular nature of the disease as the prion-like progression of the disease can be

mapped by inter- and intra-network interaction changes (Warren et al. 2013). Thus, imaging may help to identify the underlying mechanisms. Finally, learning from research on balance and gait on PD could help improve symptomatic treatment and care in other neurodegenerative diseases like dementia, Alzheimer's and multiple sclerosis that share common features like interactions between cognitive and mobility disability.

Appendix A

Table A.1. Correlation between Clinical motor scores and instrumented balance and gait metrics used in this thesis

	Objective metric	MDS- UPDRS- III	PIGD	Individual MDS-UPDRS Part III components related to
APA	Peak ML	-0.05	-0.17	None
	1st step RoM	-0.3*	-0.44*	speech, facial expression, rigidity lower, finger tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, global spontaneity of movement
APR	1st step length	-0.24	-0.44*	speech, facial expression, finger tapping, hand movements, pronation supination, arising from chair, gait, postural stability, posture
	Step height	-0.19	-0.40*	finger tapping, toe tapping, arising from chair, gait, postural stability, kinetic tremor hand
Sway	RMS AP	0.2	0.12	finger tapping, hand movements
Gait	Speed	-0.39*		facial expression, finger tapping, hand movements, pronation supination, toe tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, global spontaneity of movement

Turn Velocity	-0.43*	speech, rigidity neck, rigidity upper, rigidity lower, finger tapping, hand movements, pronation supination, toe tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, global spontaneity of movement
Stance Time	0.12	None
Arm RoM	-0.22	gait, global spontaneity of movement
Variability	0.34*	finger tapping, hand movements, pronation supination, toe tapping, leg agility, gait, postural stability, global spontaneity of movement

* Significant correlations after correcting for multiple comparisons. Spearman correlations were calculated.

Bibliography

- Agosta, Federica, Francesca Caso, Iva Stankovic, Alberto Inuggi, Igor Petrovic, Marina Svetel, Vladimir S. Kostic, and Massimo Filippi. 2014. "Cortico-Striatal-Thalamic Network Functional Connectivity in Hemiparkinsonism." *Neurobiology of Aging* 35 (11): 2592–2602.
- Akkal, Dalila, Richard P. Dum, and Peter L. Strick. 2007. "Supplementary Motor Area and Presupplementary Motor Area: Targets of Basal Ganglia and Cerebellar Output." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 27 (40): 10659–73.
- Alexander, Garrett E. 2004. "Biology of Parkinson's Disease: Pathogenesis and Pathophysiology of a Multisystem Neurodegenerative Disorder." *Dialogues in Clinical Neuroscience* 6 (3): 259–80.
- Apostolova, Liana G., Mona Beyer, Amity E. Green, Kristy S. Hwang, Jonathan H. Morra, Yi Yu Chou, Christina Avedissian, et al. 2010. "Hippocampal, Caudate, and Ventricular Changes in Parkinson's Disease with and without Dementia." *Movement Disorders* 25 (6): 687–95.
- Arie, L., Talia Herman, S. Shema-Shiratzky, N. Giladi, and J. M. Hausdorff. 2017. "Do Cognition and Other Non-Motor Symptoms Decline Similarly among Patients with Parkinson's Disease Motor Subtypes? Findings from a 5-Year Prospective Study." *Journal of Neurology* 264 (10): 2149–57.
- Armstrong, D. M. 1988. "The Supraspinal Control of Mammalian Locomotion." *The Journal of Physiology* 405 (1): 1–37.
- Aruin, A. S., and M. L. Latash. 1995. "The Role of Motor Action in Anticipatory Postural Adjustments Studied with Self-Induced and Externally Triggered Perturbations." *Experimental Brain Research* 106 (2): 291–300.
- Badea, Liviu, Mihaela Onu, Tao Wu, Adina Roceanu, and Ovidiu Bajenaru. 2017. "Exploring the Reproducibility of Functional Connectivity Alterations in Parkinson's Disease." *PloS One* 12 (11): e0188196.
- Barthel, Claudia, Jorik Nonnekkes, Milou van Helvert, Renée Haan, Arno Janssen, Arnaud Delval, Vivian Weerdesteijn, et al. 2018. "The Laser Shoes." *Neurology* 90 (2): e164–71.
- Bassett, Danielle S., Muzhi Yang, Nicholas F. Wymbs, and Scott T. Grafton. 2015. "Learning-Induced Autonomy of Sensorimotor Systems." *Nature Neuroscience* 18 (5): 744–51.
- Baudrexel, Simon, Torsten Witte, Carola Seifried, Frederic von Wegner, Florian Beissner, Johannes C. Klein, Helmuth Steinmetz, Ralf Deichmann, Jochen Roeper, and Rüdiger Hilker. 2011. "Resting State FMRI Reveals Increased Subthalamic Nucleus–Motor Cortex Connectivity in Parkinson's Disease." *NeuroImage* 55 (4): 1728–38.
- Bharti, Komal, Antonio Suppa, Silvia Tommasin, Alessandro Zampogna, Sara Pietracupa, Alfredo Berardelli, and Patrizia Pantano. 2019. "Neuroimaging Advances in Parkinson's Disease with Freezing of Gait: A Systematic Review." *NeuroImage: Clinical* 24 (January): 102059.
- Bohnen, Nicolaas I., and Klaus Jahn. 2013. "Imaging: What Can It Tell Us about Parkinsonian Gait?" *Movement Disorders: Official Journal of the Movement Disorder Society* 28 (11): 1492–1500.

- Bosch, Taylor J., Stefan Kammermeier, Christopher Groth, Matt Leedom, Elizabeth K. Hanson, Patti Berg-Poppe, and Arun Singh. 2021. "Cortical and Cerebellar Oscillatory Responses to Postural Instability in Parkinson's Disease." *Frontiers in Neurology* 12 (November): 752271.
- Bostan, Andreea C., and Peter L. Strick. 2018. "The Basal Ganglia and the Cerebellum: Nodes in an Integrated Network." *Nature Reviews. Neuroscience* 19 (6): 338–50.
- Burleigh, A. L., F. B. Horak, K. J. Burchiel, and J. G. Nutt. 1993. "Effects of Thalamic Stimulation on Tremor, Balance, and Step Initiation: A Single Subject Study." *Movement Disorders: Official Journal of the Movement Disorder Society* 8 (4): 519–24.
- Busel', B. I., and M. G. Moldavan. 1984. "Activity of Motor Cortex Neurons in the Cat during a Conditioned Postural Change Reflex." *Neirofiziologija* 16 (6): 745–74553.
- Capato, Tamine T. C., Nienke M. de Vries, Joanna Int'Hout, Egberto R. Barbosa, Jorik Nonnekkes, and Bastiaan R. Bloem. 2020. "Multimodal Balance Training Supported by Rhythmical Auditory Stimuli in Parkinson's Disease: A Randomized Clinical Trial." *Journal of Parkinson's Disease* 10 (1): 333–46.
- Carbon, Maren, M. Felice Ghilardi, Vijay Dhawan, and David Eidelberg. 2007. "Correlates of Movement Initiation and Velocity in Parkinson's Disease: A Longitudinal PET Study." *NeuroImage* 34 (1): 361–70.
- Chastan, Nathalie, Bertrand Debono, David Maltête, and Jacques Weber. 2008. "Discordance between Measured Postural Instability and Absence of Clinical Symptoms in Parkinson's Disease Patients in the Early Stages of the Disease." *Movement Disorders* 23 (3): 366–72.
- Chastan, Nathalie, Manh Cuong Do, Fabrice Bonneville, Frédéric Torny, Frédéric Bloch, G. W. Max Westby, Didier Dormont, Yves Agid, and Marie-Laure Welter. 2009. "Gait and Balance Disorders in Parkinson's Disease: Impaired Active Braking of the Fall of Centre of Gravity." *Movement Disorders: Official Journal of the Movement Disorder Society* 24 (2): 188–95.
- Chiou, Shin-Yi, Madeleine Hurry, Thomas Reed, Jing Xiao Quek, and Paul H. Strutton. 2018. "Cortical Contributions to Anticipatory Postural Adjustments in the Trunk." *The Journal of Physiology* 596 (7): 1295–1306.
- Cignetti, Fabien, Marianne Vaugoyeau, Leslie M. Decker, Marie-Hélène Grosbras, Nadine Girard, Yves Chaix, Patrice Péran, and Christine Assaiante. 2018. "Brain Network Connectivity Associated with Anticipatory Postural Control in Children and Adults." *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* 108 (November): 210–21.
- Cohen, Rajal G., Amanda Chao, John G. Nutt, and Fay B. Horak. 2011. "Freezing of Gait Is Associated with a Mismatch between Motor Imagery and Motor Execution in Narrow Doorways, Not with Failure to Judge Doorway Passability." *Neuropsychologia* 49 (14): 3981–88.
- Corbetta, Maurizio, and Gordon L. Shulman. 2002. "Control of Goal-Directed and Stimulus-Driven Attention in the Brain." *Nature Reviews. Neuroscience* 3 (3): 201–15.
- Crémers, Julien, Kevin D'Ostilio, Julien Stamatakis, Valérie Delvaux, and Gaëtan Garraux. 2012. "Brain Activation Pattern Related to Gait Disturbances in Parkinson's Disease." *Movement Disorders: Official Journal of the Movement Disorder Society* 27 (12): 1498–1505.
- Crockett, Rachel A., Chun Liang Hsu, Elizabeth Dao, Roger Tam, Walid Alkeridy, Janice J. Eng, Todd C. Handy, and Teresa Liu-Ambrose. 2021. "Mind the Gaps:

- Functional Networks Disrupted by White Matter Hyperintensities Are Associated with Greater Falls Risk." *Neurobiology of Aging* 109 (October): 166–75.
- Cui, Zaixu, Hongming Li, Cedric H. Xia, Bart Larsen, Azeez Adebimpe, Graham L. Baum, Matt Cieslak, et al. 2020. "Individual Variation in Functional Topography of Association Networks in Youth." *Neuron* 106 (2): 340-353.e8.
- Curtze, Carolin, John G. Nutt, Patricia Carlson-Kuhta, Martina Mancini, and Fay B. Horak. 2015. "Levodopa Is a Double-Edged Sword for Balance and Gait in People With Parkinson's Disease." *Movement Disorders: Official Journal of the Movement Disorder Society* 30 (10): 1361–70.
- Dale, Anders M., Bruce Fischl, and Martin I. Sereno. 1999. "Cortical Surface-Based Analysis: I. Segmentation and Surface Reconstruction." *NeuroImage* 9 (2): 179–94.
- De Micco, Rosa, Antonio Russo, and Alessandro Tessitore. 2018. *Structural MRI in Idiopathic Parkinson's Disease*. 1st ed. Vol. 141. Elsevier Inc.
- Debû, Bettina, Clecio De Oliveira Godeiro, Jarbas Correa Lino, and Elena Moro. 2018. "Managing Gait, Balance, and Posture in Parkinson's Disease."
- Deecke, L. 1987. "Bereitschaftspotential as an Indicator of Movement Preparation in Supplementary Motor Area and Motor Cortex." *Ciba Foundation Symposium* 132: 231–50.
- . 1990. "Electrophysiological Correlates of Movement Initiation." *Revue Neurologique* 146 (10): 612–19.
- Dietz, V., J. Quintern, and W. Berger. 1984. "Corrective Reactions to Stumbling in Man: Functional Significance of Spinal and Transcortical Reflexes." *Neuroscience Letters* 44 (2): 131–35.
- Dijkstra, Bauke W., Esther M. J. Bekkers, Moran Gilat, Veerle de Rond, Robert M. Hardwick, and Alice Nieuwboer. 2020. "Functional Neuroimaging of Human Postural Control: A Systematic Review with Meta-Analysis." *Neuroscience and Biobehavioral Reviews* 115 (August): 351–62.
- Doucet, Gaelle E., Loic Labache, Paul M. Thompson, Marc Joliot, Sophia Frangou, and Alzheimer's Disease Neuroimaging Initiative. 2021. "Atlas55+: Brain Functional Atlas of Resting-State Networks for Late Adulthood." *Cerebral Cortex* 31 (3): 1719–31.
- Dsturge, Eric Earl, and Kathy-snider. 2019. "DCAN-Labs/Abcd-Hcp-Pipeline: V0.0.1: Singularity Hotfix," March. <https://doi.org/10.5281/ZENODO.2605698>.
- Edwards, Amy E., Onur Guven, Michael D. Furman, Qadeer Arshad, and Adolfo M. Bronstein. 2018. "Electroencephalographic Correlates of Continuous Postural Tasks of Increasing Difficulty." *Neuroscience* 395 (December): 35–48.
- El-Gohary, Mahmoud, Daniel Peterson, Geetanjali Gera, Fay B. Horak, and Jessie M. Huisinga. 2017. "Validity of the Instrumented Push and Release Test to Quantify Postural Responses in Persons with Multiple Sclerosis." *Archives of Physical Medicine and Rehabilitation* 98 (7): 1325–31.
- Fasano, Alfonso, Colleen G. Canning, Jeffrey M. Hausdorff, Sue Lord, and Lynn Rochester. 2017. "Falls in Parkinson's Disease: A Complex and Evolving Picture." *Movement Disorders* 32 (11): 1524–36.
- Fasano, Alfonso, Simon E. Laganieri, Susy Lam, and Michael D. Fox. 2017. "Lesions Causing Freezing of Gait Localize to a Cerebellar Functional Network." *Annals of Neurology* 81 (1): 129–41.
- Ferraye, Murielle Ursulla, Bettina Debû, Lieke Heil, Mark Carpenter, Bastiaan Roelof Bloem, and Ivan Toni. 2014. "Using Motor Imagery to Study the Neural Substrates of Dynamic Balance." *PloS One* 9 (3): e91183.

- Filippi, Massimo, Elisabetta Sarasso, and Federica Agosta. 2019. "Resting-State Functional MRI in Parkinsonian Syndromes." *Movement Disorders Clinical Practice* 6 (2): 104–17.
- Fischl, Bruce, David H. Salat, André J. W. van der Kouwe, Nikos Makris, Florent Ségonne, Brian T. Quinn, and Anders M. Dale. 2004. "Sequence-Independent Segmentation of Magnetic Resonance Images." *NeuroImage* 23 Suppl 1: S69–84.
- Fling, Brett W., Rajal G. Cohen, Martina Mancini, Samuel D. Carpenter, Damien A. Fair, John G. Nutt, and Fay B. Horak. 2014. "Functional Reorganization of the Locomotor Network in Parkinson Patients with Freezing of Gait." *PLoS ONE* 9 (6). <https://doi.org/10.1371/journal.pone.0100291>.
- Fox, Michael D., and Marcus E. Raichle. 2007. "Spontaneous Fluctuations in Brain Activity Observed with Functional Magnetic Resonance Imaging." *Nature Reviews. Neuroscience* 8 (9): 700–711.
- Frank, Sebastian M., and Mark W. Greenlee. 2018. "The Parieto-Insular Vestibular Cortex in Humans: More than a Single Area?" *Journal of Neurophysiology* 120 (3): 1438–50.
- Gawel, M. J., P. Das, S. Vincent, and F. C. Rose. 1981. "Visual and Auditory Evoked Responses in Patients with Parkinson's Disease." *Journal of Neurology, Neurosurgery, and Psychiatry* 44 (3): 227–32.
- Gelb, D. J., E. Oliver, and S. Gilman. 1999. "Diagnostic Criteria for Parkinson Disease." *Archives of Neurology* 56 (1): 33–39.
- Gilat, Moran, Peter T. Bell, Kaylena A. Ehgoetz Martens, Matthew J. Georgiades, Julie M. Hall, Courtney C. Walton, Simon J. G. Lewis, and James M. Shine. 2017. "Dopamine Depletion Impairs Gait Automaticity by Altering Cortico-Striatal and Cerebellar Processing in Parkinson's Disease." *NeuroImage* 152 (May): 207–20.
- Gilat, Moran, Bauke W. Dijkstra, Nicholas D'Cruz, Alice Nieuwboer, and Simon J. G. Lewis. 2019. "Functional MRI to Study Gait Impairment in Parkinson's Disease: A Systematic Review and Exploratory ALE Meta-Analysis." *Current Neurology and Neuroscience Reports* 19 (8): 49.
- Gilat, Moran, Kaylena A. Ehgoetz Martens, Oscar Miranda-Domínguez, Ishu Arpan, James M. Shine, Martina Mancini, Damien A. Fair, Simon J. G. Lewis, and Fay B. Horak. 2018. "Dysfunctional Limbic Circuitry Underlying Freezing of Gait in Parkinson's Disease." *Neuroscience* 374 (March): 119–32.
- Gilat, Moran, Pieter Ginis, Demi Zoetewei, Joni De Vleeschhauwer, Femke Hulzinga, Nicholas D'Cruz, and Alice Nieuwboer. 2021. "A Systematic Review on Exercise and Training-Based Interventions for Freezing of Gait in Parkinson's Disease." *NPJ Parkinson's Disease* 7 (1): 81.
- Glasser, Matthew F., Timothy S. Coalson, Emma C. Robinson, Carl D. Hacker, John Harwell, Essa Yacoub, Kamil Ugurbil, et al. 2016. "A Multi-Modal Parcellation of Human Cerebral Cortex." *Nature* 536 (7615): 171–78.
- Glasser, Matthew F., Stamatis N. Sotiropoulos, J. Anthony Wilson, Timothy S. Coalson, Bruce Fischl, Jesper L. Andersson, Junqian Xu, et al. 2013. "The Minimal Preprocessing Pipelines for the Human Connectome Project." *NeuroImage* 80: 105–24.
- Goetz, Christopher G., Barbara C. Tilley, Stephanie R. Shaftman, Glenn T. Stebbins, Stanley Fahn, Pablo Martinez-Martin, Werner Poewe, et al. 2008. "Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results." *Movement Disorders: Official Journal of the Movement Disorder Society* 23 (15): 2129–70.

- Gordon, Evan M., Timothy O. Laumann, Babatunde Adeyemo, Jeremy F. Huckins, William M. Kelley, and Steven E. Petersen. 2016. "Generation and Evaluation of a Cortical Area Parcellation from Resting-State Correlations." *Cerebral Cortex* 26 (1): 288–303.
- Gordon, Evan M., Timothy O. Laumann, Adrian W. Gilmore, Dillan J. Newbold, Deanna J. Greene, Jeffrey J. Berg, Mario Ortega, et al. 2017. "Precision Functional Mapping of Individual Human Brains." *Neuron* 95 (4): 791–807.e7.
- Gratton, Caterina, Jonathan M. Koller, William Shannon, Deanna J. Greene, Baijayanta Maiti, Abraham Z. Snyder, Steven E. Petersen, Joel S. Perlmutter, and Meghan C. Campbell. 2019. "Emergent Functional Network Effects in Parkinson Disease." *Cerebral Cortex* 29 (6): 2509–23.
- Grayson, David S., and Damien A. Fair. 2017. "Development of Large-Scale Functional Networks from Birth to Adulthood: A Guide to the Neuroimaging Literature." *NeuroImage* 160 (October): 15–31.
- Greenfield, J. G., and F. D. Bosanquet. 1953. "The Brain-Stem Lesions in Parkinsonism." *Journal of Neurology, Neurosurgery, and Psychiatry* 16 (4): 213–26.
- Gurfinkel, V. S., and A. M. Élnér. 1988. "Contribution of the Frontal Lobe Secondary Motor Area to Organization of Postural Components in Human Voluntary Movement." *Neurophysiology* 20 (1): 5–11.
- Hasegawa, Naoya, Vrutangkumar V. Shah, Patricia Carlson-Kuhta, John G. Nutt, Fay B. Horak, and Martina Mancini. 2019a. "How to Select Balance Measures Sensitive to Parkinson's Disease from Body-Worn Inertial Sensors—Separating the Trees from the Forest." *Sensors* 19 (15): 3320.
- . 2019b. "How to Select Balance Measures Sensitive to Parkinson's Disease from Body-Worn Inertial Sensors—Separating the Trees from the Forest." *Sensors (Basel, Switzerland)* 19 (15): 3320.
- Hasegawa, Naoya, Vrutangkumar V. Shah, Graham Harker, Patricia Carlson-Kuhta, John G. Nutt, Jodi A. Lapidus, Se Hee Jung, et al. 2020. "Responsiveness of Objective vs. Clinical Balance Domain Outcomes for Exercise Intervention in Parkinson's Disease." *Frontiers in Neurology* 11 (September): 940.
- Hausdorff, J. M., J. D. Schaafsma, Y. Balash, A. L. Bartels, T. Gurevich, and N. Giladi. 2003. "Impaired Regulation of Stride Variability in Parkinson's Disease Subjects with Freezing of Gait." *Experimental Brain Research. Experimentelle Hirnforschung. Experimentation Cerebrale* 149 (2): 187–94.
- Hausdorff, Jeffrey M. 2005. "Gait Variability: Methods, Modeling and Meaning."
- Hawkins, Kim E., Serene S. Paul, Elodie Chiarovano, and Ian S. Curthoys. 2021. "Using Virtual Reality to Assess Vestibulo-Visual Interaction in People with Parkinson's Disease Compared to Healthy Controls." *Experimental Brain Research. Experimentelle Hirnforschung. Experimentation Cerebrale* 239 (12): 3553–64.
- Helmich, Rick C., Loes C. Derikx, Maaïke Bakker, René Scheeringa, Bastiaan R. Bloem, and Ivan Toni. 2010. "Spatial Remapping of Cortico-Striatal Connectivity in Parkinson's Disease." *Cerebral Cortex* 20 (5): 1175–86.
- Herman, Talia, Keren Rosenberg-Katz, Yael Jacob, Nir Giladi, and Jeffrey M. Hausdorff. 2014. "Gray Matter Atrophy and Freezing of Gait in Parkinson's Disease: Is the Evidence Black-on-White?" *Movement Disorders: Official Journal of the Movement Disorder Society* 29 (1): 134–39.
- Hiraoka, Koichi, Shintaro Gonno, and Ryota Inomoto. 2020. "The Left Posterior Parietal Cortex Contributes to the Selection Process for the Initial Swing Leg in Gait Initiation." *Brain Sciences* 10 (5): 317.

- Horak, F. B., H. C. Diener, and L. M. Nashner. 1989. "Influence of Central Set on Human Postural Responses." *Journal of Neurophysiology* 62 (4): 841–53.
- Horak, F. B., Earhart, G. M. 2021. "Posture." In *Principles of Neural Science*, edited by Kandel E.R., & Koester J.D., & Mack S.H., & Siegelbaum S.A. 6e. McGraw Hill.
- Horak, F. B., and L. M. Nashner. 1986. "Central Programming of Postural Movements: Adaptation to Altered Support-Surface Configurations." *Journal of Neurophysiology* 55 (6): 1369–81.
- Horak, Fay B., and Martina Mancini. 2013. "Objective Biomarkers of Balance and Gait for Parkinson's Disease Using Body-Worn Sensors." *Movement Disorders: Official Journal of the Movement Disorder Society* 28 (11): 1544–51.
- Horak, Fay B., Martina Mancini, Patricia Carlson-Kuhta, John G. Nutt, and Arash Salarián. 2016. "Balance and Gait Represent Independent Domains of Mobility in Parkinson Disease." *Physical Therapy* 96 (9): 1364–71.
- Horak, Fay B., Diane M. Wrisley, and James Frank. 2009. "The Balance Evaluation Systems Test (BESTest) to Differentiate Balance Deficits." *Physical Therapy* 89 (5): 484–98.
- Hou, Yanbing, Chunyan Luo, Jing Yang, Ruwei Ou, Wei Song, Qianqian Wei, Bei Cao, et al. 2016. "Prediction of Individual Clinical Scores in Patients with Parkinson's Disease Using Resting-State Functional Magnetic Resonance Imaging." *Journal of the Neurological Sciences* 366 (July): 27–32.
- Hüfner, Katharina, Carolina Binetti, Derek A. Hamilton, Thomas Stephan, Virginia L. Flanagan, Jennifer Linn, Kirsten Labudda, et al. 2011. "Structural and Functional Plasticity of the Hippocampal Formation in Professional Dancers and Slackliners." *Hippocampus* 21 (8): 855–65.
- Hughes, A. J., S. E. Daniel, L. Kilford, and A. J. Lees. 1992. "Accuracy of Clinical Diagnosis of Idiopathic Parkinson's Disease: A Clinico-Pathological Study of 100 Cases." *Journal of Neurology Neurosurgery and Psychiatry* 55 (3): 181–84.
- Jacobs, J. V., and F. B. Horak. 2007. "Cortical Control of Postural Responses." *Journal of Neural Transmission* 114 (10): 1339–48.
- Jacobs, Jesse V., Fay B. Horak, K. Van Tran, and John G. Nutt. 2006. "An Alternative Clinical Postural Stability Test for Patients with Parkinson's Disease." *Journal of Neurology* 253 (11): 1404–13.
- Jaeger, Lukas, Laura Marchal-Crespo, Peter Wolf, Andreas R. Luft, Robert Riener, Lars Michels, and Spyros Kollias. 2016. "On the Modulation of Brain Activation during Simulated Weight Bearing in Supine Gait-like Stepping." *Brain Topography* 29 (1): 193–205.
- Jahn, Klaus, Angela Deutschländer, Thomas Stephan, Roger Kalla, Martin Wiesmann, Michael Strupp, and Thomas Brandt. 2008. "Imaging Human Supraspinal Locomotor Centers in Brainstem and Cerebellum." *NeuroImage* 39 (2): 786–92.
- Jahn, Klaus, Angela Deutschländer, Thomas Stephan, Michael Strupp, Martin Wiesmann, and Thomas Brandt. 2004. "Brain Activation Patterns during Imagined Stance and Locomotion in Functional Magnetic Resonance Imaging." *NeuroImage* 22 (4): 1722–31.
- Jahn, Klaus, Judith Wagner, Angela Deutschländer, Roger Kalla, Katharina Hüfner, Thomas Stephan, Michael Strupp, and Thomas Brandt. 2009. "Human Hippocampal Activation during Stance and Locomotion: fMRI Study on Healthy, Blind, and Vestibular-Loss Subjects." *Annals of the New York Academy of Sciences* 1164 (1): 229–35.
- Jahn, Klaus, and Max Wühr. 2020. "Postural Control Mechanisms in Mammals, Including Humans." In *The Senses: A Comprehensive Reference*, 344–70. Elsevier.

- Jahn, Klaus, and Andreas Zwergal. 2010. "Imaging Supraspinal Locomotor Control in Balance Disorders."
- Jankovic, J. 2008. "Parkinson's Disease: Clinical Features and Diagnosis." *Journal of Neurology, Neurosurgery, and Psychiatry* 79 (4): 368–76.
- Jankovic, Joseph, and Eng King Tan. 2020. "Parkinson's Disease: Etiopathogenesis and Treatment." *Journal of Neurology, Neurosurgery, and Psychiatry* 91 (8): 795–808.
- Javalkar, Vijayakumar, Misbba Khan, and Debra E. Davis. 2014. "Clinical Manifestations of Cerebellar Disease." *Neurologic Clinics* 32 (4): 871–79.
- Jenkinson, Mark, Christian F. Beckmann, Timothy E. J. Behrens, Mark W. Woolrich, and Stephen M. Smith. 2012. "FSL." *NeuroImage* 62 (2): 782–90.
- Ji, Jie Lisa, Marjolein Spronk, Kaustubh Kulkarni, Grega Repovš, Alan Anticevic, and Michael W. Cole. 2019. "Mapping the Human Brain's Cortical-Subcortical Functional Network Organization." *NeuroImage* 185 (January): 35–57.
- Jian, Yuancheng, D. A. Winter, M. G. Ishac, and L. Gilchrist. 1993. "Trajectory of the Body COG and COP during Initiation and Termination of Gait." *Gait & Posture* 1 (1): 9–22.
- Jöbges, M., G. Heuschkel, C. Pretzel, C. Illhardt, C. Renner, and H. Hummelsheim. 2004. "Repetitive Training of Compensatory Steps: A Therapeutic Approach for Postural Instability in Parkinson's Disease." *Journal of Neurology, Neurosurgery, and Psychiatry* 75 (12): 1682–87.
- Jung, Se Hee, Naoya Hasegawa, Martina Mancini, Laurie A. King, Patricia Carlson-Kuhta, Katrijn Smulders, Daniel S. Peterson, et al. 2020. "Effects of the Agility Boot Camp with Cognitive Challenge (ABC-C) Exercise Program for Parkinson's Disease." *Npj Parkinson's Disease* 6 (1): 31.
- Karachi, Carine, David Grabli, Frédéric A. Bernard, Dominique Tandé, Nicolas Wattiez, Hayat Belaid, Eric Bardinet, et al. 2010. "Cholinergic Mesencephalic Neurons Are Involved in Gait and Postural Disorders in Parkinson Disease." *Journal of Clinical Investigation* 120 (8): 2745–54.
- Karim, Helmet T., Patrick J. Sparto, Howard J. Aizenstein, Joseph M. Furman, Theodore J. Huppert, Kirk I. Erickson, and Patrick J. Loughlin. 2014. "Functional MR Imaging of a Simulated Balance Task." *Brain Research* 1555 (March): 20–27.
- Katzenschlager, R., A. Evans, A. Manson, P. N. Patsalos, N. Ratnaraj, H. Watt, L. Timmermann, R. Van der Giessen, and A. J. Lees. 2004. "Mucuna Pruriens in Parkinson's Disease: A Double Blind Clinical and Pharmacological Study." *Journal of Neurology, Neurosurgery, and Psychiatry* 75 (12): 1672–77.
- Keck, Martin E., Mirjam Pijnappels, Martin Schubert, Gery Colombo, Armin Curt, and Volker Dietz. 1998. "Stumbling Reactions in Man: Influence of Corticospinal Input." *Electroencephalography and Clinical Neurophysiology - Electromyography and Motor Control* 109 (3): 215–23.
- Kemp, J. M., and T. P. Powell. 1971. "The Connexions of the Striatum and Globus Pallidus: Synthesis and Speculation." *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 262 (845): 441–57.
- Khan, Ali R., Nole M. Hiebert, Andrew Vo, Brian T. Wang, Adrian M. Owen, Ken N. Seergobin, and Penny A. MacDonald. 2019. "Biomarkers of Parkinson's Disease: Striatal Sub-Regional Structural Morphometry and Diffusion MRI." *NeuroImage. Clinical* 21 (101597): 101597.
- Kim, Jinhee, Marion Criaud, Sang Soo Cho, María Díez-Cirarda, Alexander Mihaescu, Sarah Coakeley, Christine Ghadery, et al. 2017. "Abnormal Intrinsic Brain Functional Network Dynamics in Parkinson's Disease." *Brain: A Journal of Neurology* 140 (11): 2955–67.

- Kish, Stephen J., Kathleen Shannak, and Oleh Hornykiewicz. 1988. "Uneven Pattern of Dopamine Loss in the Striatum of Patients with Idiopathic Parkinson's Disease." *New England Journal of Medicine* 318 (14): 876–80.
- Klein, Arno, Jesper Andersson, Babak A. Ardekani, John Ashburner, Brian Avants, Ming-Chang Chiang, Gary E. Christensen, et al. 2009. "Evaluation of 14 Nonlinear Deformation Algorithms Applied to Human Brain MRI Registration." *NeuroImage* 46 (3): 786–802.
- Klein, Arno, and Jason Tourville. 2012. "101 Labeled Brain Images and a Consistent Human Cortical Labeling Protocol." *Frontiers in Neuroscience* 6 (DEC): 171.
- Lewis, M. M., A. B. Smith, M. Styner, H. Gu, R. Poole, H. Zhu, Y. Li, et al. 2009. "Asymmetrical Lateral Ventricular Enlargement in Parkinson's Disease." *European Journal of Neurology* 16 (4): 475–81.
- Lewis, Mechelle M., Guangwei Du, Eun Young Lee, Zeinab Nasrallah, Nicholas W. Sterling, Lijun Zhang, Daymond Wagner, et al. 2016. "The Pattern of Gray Matter Atrophy in Parkinson's Disease Differs in Cortical and Subcortical Regions." *Journal of Neurology* 263 (1): 68–75.
- Lima-Pardini, Andrea C. de, Daniel B. Coelho, Mariana P. Nucci, Catarina C. Boffino, Alana X. Batista, Raymundo M. de Azevedo Neto, Carla Silva-Batista, et al. 2020. "Brain Networks Associated with Anticipatory Postural Adjustments in Parkinson's Disease Patients with Freezing of Gait." *NeuroImage. Clinical* 28 (October): 102461.
- Liu, Li Kuo, Kun Hsien Chou, Chih Chin Heather Hsu, Li Ning Peng, Wei Ju Lee, Wei Ta Chen, Ching Po Lin, Chih Ping Chung, Pei Ning Wang, and Liang Kung Chen. 2020. "Cerebellar-Limbic Neurocircuit Is the Novel Biosignature of Physiocognitive Decline Syndrome." *Aging* 12 (24): 25319–36.
- Lord, Sue, Brook Galna, Joe Verghese, Shirley Coleman, David Burn, and Lynn Rochester. 2013. "Independent Domains of Gait in Older Adults and Associated Motor and Nonmotor Attributes: Validation of a Factor Analysis Approach." *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 68 (7): 820–27.
- Lotze, Martin, Martin Domin, Florian H. Gerlach, Christian Gaser, Eileen Lueders, Carsten O. Schmidt, and Nicola Neumann. 2019. "Novel Findings from 2,838 Adult Brains on Sex Differences in Gray Matter Brain Volume." *Scientific Reports* 9 (1): 1–7.
- Lozza, C., R-M Marié, and J-C Baron. 2002. "The Metabolic Substrates of Bradykinesia and Tremor in Uncomplicated Parkinson's Disease." *NeuroImage* 17 (2): 688–99.
- MacKinnon, Colum D. 2018a. "Sensorimotor Anatomy of Gait, Balance, and Falls." In *Handbook of Clinical Neurology*, 1st ed., 159:3–26. Elsevier B.V.
- . 2018b. "Sensorimotor Anatomy of Gait, Balance, and Falls." *Handbook of Clinical Neurology* 159: 3–26.
- MacKinnon, Colum D., Dennis Bissig, Julie Chiusano, Emily Miller, Laura Rudnick, Candice Jager, Yunhui Zhang, Marie-Laure Mille, and Mark W. Rogers. 2007. "Preparation of Anticipatory Postural Adjustments Prior to Stepping." *Journal of Neurophysiology* 97 (6): 4368–79.
- Mak, Elijah, Li Su, Guy B. Williams, Michael J. Firbank, Rachael A. Lawson, Alison J. Yarnall, Gordon W. Duncan, et al. 2017. "Longitudinal Whole-Brain Atrophy and Ventricular Enlargement in Nondemented Parkinson's Disease." *Neurobiology of Aging* 55: 78–90.
- Maki, B. E., and W. E. McIlroy. 1996. "Postural Control in the Older Adult." *Clinics in Geriatric Medicine* 12 (4): 635–58.

- Malouin, Francine, Carol L. Richards, Philip L. Jackson, Francine Dumas, and Julien Doyon. 2003. "Brain Activations during Motor Imagery of Locomotor-Related Tasks: A PET Study." *Human Brain Mapping* 19 (1): 47–62.
- Mancini, Martina, Patricia Carlson-Kuhta, Cris Zampieri, John G. Nutt, Lorenzo Chiari, and Fay B. Horak. 2012. "Postural Sway as a Marker of Progression in Parkinson's Disease: A Pilot Longitudinal Study." *Gait & Posture* 36 (3): 471–76.
- Mancini, Martina, Fay B. Horak, Cris Zampieri, Patricia Carlson-Kuhta, John G. Nutt, and Lorenzo Chiari. 2011. "Trunk Accelerometry Reveals Postural Instability in Untreated Parkinson's Disease." *Parkinsonism and Related Disorders* 17 (7): 557–62.
- Mancini, Martina, Laurie King, Arash Salarian, Lars Holmstrom, James McNames, and Fay B. Horak. 2011. "Mobility Lab to Assess Balance and Gait with Synchronized Body-Worn Sensors." *Journal of Bioengineering & Biomedical Science* Suppl 1 (December): 007.
- Mancini, Martina, John G. Nutt, and Fay B. Horak. 2020a. "How Is Balance Controlled by the Nervous System?" In *Balance Dysfunction in Parkinson's Disease*, 1–24. Elsevier.
- . 2020b. "How Is Balance Controlled by the Nervous System?" In *Balance Dysfunction in Parkinson's Disease*, 1–24. Elsevier.
- Manor, B., K. Hu, P. Zhao, M. Selim, D. Alsop, P. Novak, L. Lipsitz, and V. Novak. 2010. "Altered Control of Postural Sway Following Cerebral Infarction: A Cross-Sectional Analysis." *Neurology* 74 (6): 458–64.
- Manyam, B. V. 1990. "Paralysis Agitans and Levodopa in 'Ayurveda': Ancient Indian Medical Treatise." *Movement Disorders: Official Journal of the Movement Disorder Society* 5 (1): 47–48.
- Marek, Scott, Brenden Tervo-Clemmens, Finnegan J. Calabro, David F. Montez, Benjamin P. Kay, Alexander S. Hatoum, Meghan Rose Donohue, et al. 2020. "Towards Reproducible Brain-Wide Association Studies." *BioRxiv*. bioRxiv. <https://doi.org/10.1101/2020.08.21.257758>.
- Massion, J. 1992. "Movement, Posture and Equilibrium: Interaction and Coordination." *Progress in Neurobiology* 38 (1): 35–56.
- McIntosh, Anthony Randal, and Nancy J. Lobaugh. 2004. "Partial Least Squares Analysis of Neuroimaging Data: Applications and Advances." *NeuroImage* 23 Suppl 1: S250–63.
- Menon, Vinod, and Lucina Q. Uddin. 2010. "Saliency, Switching, Attention and Control: A Network Model of Insula Function." *Brain Structure & Function* 214 (5–6): 655–67.
- Miranda-Domínguez, Óscar, Anjanibhargavi Ragothaman, Robert Hermosillo, Eric Feczko, Rosie Morris, Patricia Carlson-Kuhta, John G. Nutt, Martina Mancini, Damien Fair, and Fay B. Horak. 2020. "Lateralized Connectivity between Globus Pallidus and Motor Cortex Is Associated with Freezing of Gait in Parkinson's Disease." *Neuroscience* 443 (September): 44–58.
- Mirelman, Anat, Paolo Bonato, Richard Camicioli, Terry D. Ellis, Nir Giladi, Jamie L. Hamilton, Chris J. Hass, Jeffrey M. Hausdorff, Elisa Pelosin, and Quincy J. Almeida. 2019. "Gait Impairments in Parkinson's Disease." *Lancet Neurology* 18 (7): 697–708.
- Mori, S., K. Matsuyama, F. Mori, and K. Nakajima. 2001. "Supraspinal Sites That Induce Locomotion in the Vertebrate Central Nervous System." *Advances in Neurology* 87: 25–40.

- Mori, Yutaro, Etsuji Yoshikawa, Masami Futatsubashi, and Yasuomi Ouchi. 2020. "Neural Correlates of Standing Imagery and Execution in Parkinsonian Patients: The Relevance to Striatal Dopamine Dysfunction." *PloS One* 15 (10): e0240998.
- Morris, M., R. Iansek, F. Smithson, and F. Huxham. 2000. "Postural Instability in Parkinson's Disease: A Comparison with and without a Concurrent Task." *Gait & Posture* 12 (3): 205–16.
- Mouthon, A., J. Ruffieux, M. Mouthon, H-M Hoogewoud, J-M Annoni, and W. Taube. 2018. "Age-Related Differences in Cortical and Subcortical Activities during Observation and Motor Imagery of Dynamic Postural Tasks: An FMRI Study." *Neural Plasticity* 2018: 1–12.
- Müller, Martijn L. T. M., Roger L. Albin, Vikas Kotagal, Robert A. Koeppe, Peter J. H. Scott, Kirk A. Frey, and Nicolaas I. Bohnen. 2013. "Thalamic Cholinergic Innervation and Postural Sensory Integration Function in Parkinson's Disease." *Brain* 136 (11): 3282–89.
- Nieuwboer, Alice, Lynn Rochester, Talia Herman, Wim Vandenberghe, George Ehab Emil, Tom Thomaes, and Nir Giladi. 2009. "Reliability of the New Freezing of Gait Questionnaire: Agreement between Patients with Parkinson's Disease and Their Carers." *Gait & Posture* 30 (4): 459–63.
- Nishita, Yukiko, Akinori Nakamura, Takashi Kato, Rei Otsuka, Kaori Iwata, Chikako Tange, Fujiko Ando, Kengo Ito, Hiroshi Shimokata, and Hidenori Arai. 2019. "Links Between Physical Frailty and Regional Gray Matter Volumes in Older Adults: A Voxel-Based Morphometry Study." *Journal of the American Medical Directors Association* 20 (12): 1587-1592.e7.
- Nonnekes, Jorik, Digna de Kam, Lars B. Oude Nijhuis, Karin van Geel, Bastiaan R. Bloem, Alexander Geurts, and Vivian Weerdesteijn. 2015. "StartReact Effects Support Different Pathophysiological Mechanisms Underlying Freezing of Gait and Postural Instability in Parkinson's Disease." *PloS One* 10 (3): e0122064.
- Obeso, J. A., M. Stamelou, C. G. Goetz, W. Poewe, A. E. Lang, D. Weintraub, D. Burn, et al. 2017. "Past, Present, and Future of Parkinson's Disease: A Special Essay on the 200th Anniversary of the Shaking Palsy." *Movement Disorders: Official Journal of the Movement Disorder Society* 32 (9): 1264–1310.
- Obeso, José A., Maria C. Rodriguez-Oroz, Manuel Rodriguez, José L. Lanciego, Julio Artieda, Nancy Gonzalo, and C. Warren Olanow. 2000. "Pathophysiology of the Basal Ganglia in Parkinson's Disease."
- Ouchi, Y., H. Okada, E. Yoshikawa, S. Nobezawa, and M. Futatsubashi. 1999. "Brain Activation during Maintenance of Standing Postures in Humans." *Brain: A Journal of Neurology* 122 (Pt 2) (February): 329–38.
- Ovallath, Sujith, and P. Deepa. 2013. "The History of Parkinsonism: Descriptions in Ancient Indian Medical Literature." *Movement Disorders: Official Journal of the Movement Disorder Society* 28 (5): 566–68.
- Ozdemir, Recep A., Jose L. Contreras-Vidal, and William H. Paloski. 2018. "Cortical Control of Upright Stance in Elderly." *Mechanisms of Ageing and Development* 169 (January): 19–31.
- Park, Jeong Ho, Martina Mancini, Patricia Carlson-Kuhta, John G. Nutt, and Fay B. Horak. 2016. "Quantifying Effects of Age on Balance and Gait with Inertial Sensors in Community-Dwelling Healthy Adults." *Experimental Gerontology* 85 (December): 48–58.
- Parkinson, James. 1817. "An Essay on the Shaking Palsy." *The Journal of Neuropsychiatry and Clinical Neurosciences* 14 (2): 223–36; discussion 222.
- Pasman, Elizabeth P., Martin J. McKeown, Saurabh Garg, Taylor W. Cleworth, Bastiaan R. Bloem, J. Timothy Inglis, and Mark G. Carpenter. 2021. "Brain Connectivity

- during Simulated Balance in Older Adults with and without Parkinson's Disease." *NeuroImage. Clinical* 30 (April): 102676.
- Patel, Neepa, Joseph Jankovic, and Mark Hallett. 2014. "Sensory Aspects of Movement Disorders." *Lancet Neurology* 13 (1): 100–112.
- Peterka, R. J., and F. O. Black. 1990. "Age-Related Changes in Human Posture Control: Sensory Organization Tests." *Journal of Vestibular Research: Equilibrium & Orientation* 1 (1): 73–85.
- Peterson, D. S., and F. B. Horak. 2016. "Neural Control of Walking in People with Parkinsonism." *Physiology (Bethesda, Md.)* 31 (2): 95–107.
- Pitcher, Toni L., Tracy R. Melzer, Michael R. MacAskill, Charlotte F. Graham, Leslie Livingston, Ross J. Keenan, Richard Watts, John C. Dalrymple-Alford, and Tim J. Anderson. 2012. "Reduced Striatal Volumes in Parkinson's Disease: A Magnetic Resonance Imaging Study." *Translational Neurodegeneration* 1 (1): 17.
- Power, Jonathan D., Alexander L. Cohen, Steven M. Nelson, Gagan S. Wig, Kelly Anne Barnes, Jessica A. Church, Alecia C. Vogel, et al. 2011. "Functional Network Organization of the Human Brain." *Neuron* 72 (4): 665–78.
- Richard, Aliénor, Angèle Van Hamme, Xavier Drevelle, Jean-Louis Golmard, Sabine Meunier, and Marie-Laure Welter. 2017. "Contribution of the Supplementary Motor Area and the Cerebellum to the Anticipatory Postural Adjustments and Execution Phases of Human Gait Initiation." *Neuroscience* 358 (September): 181–89.
- Rogge, Ann-Kathrin, Brigitte Röder, Astrid Zech, and Kirsten Hötting. 2018. "Exercise-Induced Neuroplasticity: Balance Training Increases Cortical Thickness in Visual and Vestibular Cortical Regions." *NeuroImage* 179 (October): 471–79.
- Rosipal, Roman, and Nicole Krämer. 2006. "Overview and Recent Advances in Partial Least Squares." In *Subspace, Latent Structure and Feature Selection*, 34–51. Springer Berlin Heidelberg.
- Rouw, Romke, and H. Steven Scholte. 2007. "Increased Structural Connectivity in Grapheme-Color Synesthesia." *Nature Neuroscience* 10 (6): 792–97.
- Rudolph, Marc D., Alice M. Graham, Eric Feczko, Oscar Miranda-Dominguez, Jerod M. Rasmussen, Rahel Nardos, Sonja Entringer, Pathik D. Wadhwa, Claudia Buss, and Damien A. Fair. 2018. "Maternal IL-6 during Pregnancy Can Be Estimated from Newborn Brain Connectivity and Predicts Future Working Memory in Offspring." *Nature Neuroscience* 21 (5): 765–72.
- Sadaghiani, Sepideh, and Mark D'Esposito. 2015. "Functional Characterization of the Cingulo-Opercular Network in the Maintenance of Tonic Alertness." *Cerebral Cortex* 25 (9): 2763–73.
- Scahill, Rachael I., Chris Frost, Rhian Jenkins, Jennifer L. Whitwell, Martin N. Rossor, and Nick C. Fox. 2003. "A Longitudinal Study of Brain Volume Changes in Normal Aging Using Serial Registered Magnetic Resonance Imaging." *Archives of Neurology* 60 (7): 989–94.
- Schindlbeck, Katharina A., and David Eidelberg. 2018. "Network Imaging Biomarkers: Insights and Clinical Applications in Parkinson's Disease." *Lancet Neurology* 17 (7): 629–40.
- Schlenstedt, Christian, Martina Mancini, Fay Horak, and Daniel Peterson. 2017. "Anticipatory Postural Adjustment During Self-Initiated, Cued, and Compensatory Stepping in Healthy Older Adults and Patients With Parkinson Disease." *Archives of Physical Medicine and Rehabilitation* 98 (7): 1316–1324.e1.
- Schlenstedt, Christian, Martina Mancini, Jay Nutt, Amie P. Hiller, Walter Maetzler, Günther Deuschl, and Fay Horak. 2018. "Are Hypometric Anticipatory Postural

- Adjustments Contributing to Freezing of Gait in Parkinson's Disease?" *Frontiers in Aging Neuroscience* 10 (FEB): 36.
- Schlick, Cornelia, Alina Ernst, Kai Bötzel, Annika Plate, Olena Pelykh, and Josef Ilmberger. 2016. "Visual Cues Combined with Treadmill Training to Improve Gait Performance in Parkinson's Disease: A Pilot Randomized Controlled Trial." *Clinical Rehabilitation* 30 (5): 463–71.
- Schöberl, Florian, Katharina Feil, Guoming Xiong, Peter Bartenstein, Christian la Fougère, Klaus Jahn, Thomas Brandt, Michael Strupp, Marianne Dieterich, and Andreas Zwergal. 2017. "Pathological Ponto-Cerebello-Thalamo-Cortical Activations in Primary Orthostatic Tremor during Lying and Stance." *Brain: A Journal of Neurology* 140 (1): 83–97.
- Schoneburg, Bernadette, Martina Mancini, Fay Horak, and John G. Nutt. 2013. "Framework for Understanding Balance Dysfunction in Parkinson's Disease." *Movement Disorders: Official Journal of the Movement Disorder Society* 28 (11): 1474–82.
- Sehm, Bernhard, Marco Taubert, Virginia Conde, David Weise, Joseph Classen, Juergen Dukart, Bogdan Draganski, Arno Villringer, and Patrick Ragert. 2014. "Structural Brain Plasticity in Parkinson's Disease Induced by Balance Training." *Neurobiology of Aging* 35 (1): 232–39.
- Sharman, Michael, Romain Valabregue, Vincent Perlberg, Linda Marrakchi-Kacem, Marie Vidailhet, Habib Benali, Alexis Brice, and Stephane Lehericy. 2013. "Parkinson's Disease Patients Show Reduced Cortical-Subcortical Sensorimotor Connectivity." *Movement Disorders: Official Journal of the Movement Disorder Society* 28 (4): 447–54.
- Sherrington, C. S. 1910. "Flexion-Reflex of the Limb, Crossed Extension-Reflex, and Reflex Stepping and Standing." *The Journal of Physiology* 40 (1–2): 28–121.
- Shine, James M., Elie Matar, Philip B. Ward, Michael J. Frank, Ahmed A. Moustafa, Mark Pearson, Sharon L. Naismith, and Simon J. G. Lewis. 2013. "Freezing of Gait in Parkinson's Disease Is Associated with Functional Decoupling between the Cognitive Control Network and the Basal Ganglia." *Brain: A Journal of Neurology* 136 (Pt 12): 3671–81.
- Silva-Batista, Carla, Anjanibhargavi Ragothaman, Martina Mancini, Patricia Carlson-Kuhta, Graham Harker, Se Hee Jung, John G. Nutt, Damien A. Fair, Fay B. Horak, and Oscar Miranda-Domínguez. 2021. "Cortical Thickness as Predictor of Response to Exercise in People with Parkinson's Disease." *Human Brain Mapping* 42 (1): 139–53.
- Silva-Batista, Carla, Anjanibhargavi Ragothaman, Martina Mancini, Patricia Carlson-Kuhta, Graham Harker, Se Hee Jung, John G. Nutt, Damien A. Fair, Fay B. Horak, and Oscar Miranda-Domínguez. 2021. "Cortical Thickness as Predictor of Response to Exercise in People with Parkinson's Disease." *Human Brain Mapping* 42 (1): 139–53.
- Slobounov, Semyon, Tao Wu, Mark Hallett, Hiroshi Shibasaki, Elena Slobounov, and Karl Newell. 2006. "Neural Underpinning of Postural Responses to Visual Field Motion." *Biological Psychology* 72 (2): 188–97.
- Snyder, Abraham Z., and Marcus E. Raichle. 2012. "A Brief History of the Resting State: The Washington University Perspective." *NeuroImage* 62 (2): 902–10.
- Stebbins, Glenn T., Christopher G. Goetz, David J. Burn, Joseph Jankovic, Tien K. Khoo, and Barbara C. Tilley. 2013. "How to Identify Tremor Dominant and Postural Instability/Gait Difficulty Groups with the Movement Disorder Society Unified Parkinson's Disease Rating Scale: Comparison with the Unified

- Parkinson's Disease Rating Scale." *Movement Disorders: Official Journal of the Movement Disorder Society* 28 (5): 668–70.
- Strafella, Antonio P., Nico I. Bohnen, Nicola Pavese, David E. Vaillancourt, Thilo van Eimeren, Marios Politis, Alessandro Tessitore, Christine Ghadery, Simon Lewis, and IPMDS-Neuroimaging Study Group. 2018. "Imaging Markers of Progression in Parkinson's Disease." *Movement Disorders Clinical Practice* 5 (6): 586–96.
- Stuart, Samuel, Rosie Morris, Andrew Giritharan, Joseph Quinn, John G. Nutt, and Martina Mancini. 2020. "Prefrontal Cortex Activity and Gait in Parkinson's Disease with Cholinergic and Dopaminergic Therapy." *Movement Disorders: Official Journal of the Movement Disorder Society* 35 (11): 2019–27.
- Stuart, Samuel, Rodrigo Vitorio, Rosie Morris, Douglas N. Martini, Peter C. Fino, and Martina Mancini. 2018. "Cortical Activity during Walking and Balance Tasks in Older Adults and in People with Parkinson's Disease: A Structured Review." *Maturitas* 113 (July): 53–72.
- Stuart, Samuel, Johanna Wagner, Scott Makeig, and Martina Mancini. 2021. "Brain Activity Response to Visual Cues for Gait Impairment in Parkinson's Disease: An EEG Study." *Neurorehabilitation and Neural Repair*, September, 15459683211041316.
- Sullivan, Edith, Jessica Rose, Torsten Rohlfing, and Adolf Pfefferbaum. 2009. "Postural Sway Reduction in Aging Men and Women: Relation to Brain Structure, Cognitive Status, and Stabilizing Factors." *Neurobiology of Aging* 30 (5): 793–807.
- Surgent, Olivia J., Olga I. Dadalko, Kristen A. Pickett, and Brittany G. Travers. 2019. "Balance and the Brain: A Review of Structural Brain Correlates of Postural Balance and Balance Training in Humans." *Gait and Posture* 71 (vember 2018): 245–52.
- Tahmasian, Masoud, Lisa M. Bettray, Thilo van Eimeren, Alexander Drzezga, Lars Timmermann, Claudia R. Eickhoff, Simon B. Eickhoff, and Carsten Eggers. 2015. "A Systematic Review on the Applications of Resting-State FMRI in Parkinson's Disease: Does Dopamine Replacement Therapy Play a Role?" *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* 73 (December): 80–105.
- Tahmasian, Masoud, Simon B. Eickhoff, Kathrin Giehl, Frank Schwartz, Damian M. Herz, Alexander Drzezga, Thilo van Eimeren, et al. 2017. "Resting-State Functional Reorganization in Parkinson's Disease: An Activation Likelihood Estimation Meta-Analysis." *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* 92 (July): 119–38.
- Takahashi, H., Y. Watanabe, H. Tanaka, M. Mihara, H. Mochizuki, K. Takahashi, K. Yamamoto, T. Liu, Y. Wang, and N. Tomiyama. 2018. "Comprehensive MRI Quantification of the Substantia Nigra Pars Compacta in Parkinson's Disease." *European Journal of Radiology* 109 (December): 48–56.
- Takakusaki, Kaoru. 2013. "Neurophysiology of Gait: From the Spinal Cord to the Frontal Lobe." *Movement Disorders: Official Journal of the Movement Disorder Society* 28 (11): 1483–91.
- . 2017. "Functional Neuroanatomy for Posture and Gait Control." *Journal of Movement Disorders* 10 (1): 1–17.
- Taube, Wolfgang, Michael Mouthon, Christian Leukel, Henri-Marcel Hoogewoud, Jean-Marie Annoni, and Martin Keller. 2015. "Brain Activity during Observation and Motor Imagery of Different Balance Tasks: An FMRI Study." *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* 64 (March): 102–14.

- Tessitore, Alessandro, Alfonso Giordano, Rosa De Micco, Antonio Russo, and Gioacchino Tedeschi. 2014. "Sensorimotor Connectivity in Parkinson's Disease: The Role of Functional Neuroimaging." *Frontiers in Neurology* 5 (September): 180.
- Thevathasan, Wesley, Alek Pogosyan, Jonathan A. Hyam, Ned Jenkinson, Marko Bogdanovic, Terry J. Coyne, Peter A. Silburn, Tipu Z. Aziz, and Peter Brown. 2011. "A Block to Pre-Prepared Movement in Gait Freezing, Relieved by Pedunculopontine Nucleus Stimulation." *Brain: A Journal of Neurology* 134 (Pt 7): 2085–95.
- Tinaz, Sule, Peter Lauro, Mark Hallett, and Silvina G. Horovitz. 2016. "Deficits in Task-Set Maintenance and Execution Networks in Parkinson's Disease." *Brain Structure & Function* 221 (3): 1413–25.
- Turner, Robert S., Scott T. Grafton, Anthony R. McIntosh, Mahlon R. DeLong, and John M. Hoffman. 2003. "The Functional Anatomy of Parkinsonian Bradykinesia." *NeuroImage* 19 (1): 163–79.
- Van Den Eeden, Stephen K., Caroline M. Tanner, Allan L. Bernstein, Robin D. Fross, Amethyst Leimpeter, Daniel A. Bloch, and Lorene M. Nelson. 2003. "Incidence of Parkinson's Disease: Variation by Age, Gender, and Race/Ethnicity." *American Journal of Epidemiology* 157 (11): 1015–22.
- Van Ooteghem, Karen, Kristin E. Musselman, Avril Mansfield, David Gold, Meghan N. Marcil, Ron Keren, Maria Carmela Tartaglia, Alastair J. Flint, and Andrea Iaboni. 2019. "Key Factors for the Assessment of Mobility in Advanced Dementia: A Consensus Approach." *Alzheimer's & Dementia (New York, N. Y.)* 5 (1): 409–19.
- Varghese, J. P., D. M. Merino, K. B. Beyer, and W. E. McIlroy. 2016. "Cortical Control of Anticipatory Postural Adjustments Prior to Stepping." *Neuroscience* 313 (January): 99–109.
- Wang, Shuaiwen, Yanli Zhang, Junqiang Lei, and Shunlin Guo. 2021. "Investigation of Sensorimotor Dysfunction in Parkinson Disease by Resting-State fMRI." *Neuroscience Letters* 742 (January): 135512.
- Warren, Jason D., Jonathan D. Rohrer, Jonathan M. Schott, Nick C. Fox, John Hardy, and Martin N. Rossor. 2013. "Molecular Nexopathies: A New Paradigm of Neurodegenerative Disease." *Trends in Neurosciences* 36 (10): 561–69.
- Wilson, Joanna, Liesl Allcock, Róna Mc Ardle, John Paul Taylor, and Lynn Rochester. 2019. "The Neural Correlates of Discrete Gait Characteristics in Ageing: A Structured Review."
- Wirth, Anna M., Sebastian M. Frank, Mark W. Greenlee, and Anton L. Beer. 2018. "White Matter Connectivity of the Visual-Vestibular Cortex Examined by Diffusion-Weighted Imaging." *Brain Connectivity* 8 (4): 235–44.
- Wittenberg, Ellen, Jessica Thompson, Chang S. Nam, and Jason R. Franz. 2017. "Neuroimaging of Human Balance Control: A Systematic Review." *Frontiers in Human Neuroscience* 11 (April): 170.
- Wu, Tao, Mark Hallett, and Piu Chan. 2015. "Motor Automaticity in Parkinson's Disease." *Neurobiology of Disease* 82 (October): 226–34.
- Wu, Tao, Xiangyu Long, Liang Wang, Mark Hallett, Yufeng Zang, Kuncheng Li, and Piu Chan. 2011. "Functional Connectivity of Cortical Motor Areas in the Resting State in Parkinson's Disease." *Human Brain Mapping* 32 (9): 1443–57.
- Wu, Tao, Liang Wang, Yi Chen, Cheng Zhao, Kuncheng Li, and Piu Chan. 2009. "Changes of Functional Connectivity of the Motor Network in the Resting State in Parkinson's Disease." *Neuroscience Letters* 460 (1): 6–10.
- Xiao, Yiming, Vladimir Fonov, M. Mallar Chakravarty, Silvain Beriault, Fahd Al Subaie, Abbas Sadikot, G. Bruce Pike, Gilles Bertrand, and D. Louis Collins. 2017. "A

- Dataset of Multi-Contrast Population-Averaged Brain MRI Atlases of a Parkinson's Disease Cohort." *Data in Brief* 12 (June): 370–79.
- Yakubovich, Sol, Simon Israeli-Korn, Orly Halperin, Gilad Yahalom, Sharon Hassin-Baer, and Adam Zaidel. 2020. "Visual Self-Motion Cues Are Impaired yet Overweighted during Visual-Vestibular Integration in Parkinson's Disease." *Brain Communications* 2 (1): fcaa035.
- Yao, Nailin, Shirley Pang, Charlton Cheung, Richard Shek-Kwan Chang, Kui Kai Lau, John Suckling, Kevin Yu, et al. 2015. "Resting Activity in Visual and Corticostriatal Pathways in Parkinson's Disease with Hallucinations." *Parkinsonism & Related Disorders* 21 (2): 131–37.
- Yeomans, J. S., and P. W. Frankland. 1995. "The Acoustic Startle Reflex: Neurons and Connections." *Brain Research. Brain Research Reviews* 21 (3): 301–14.
- Yushkevich, Paul A., Joseph Piven, Heather Cody Hazlett, Rachel Gimpel Smith, Sean Ho, James C. Gee, and Guido Gerig. 2006. "User-Guided 3D Active Contour Segmentation of Anatomical Structures: Significantly Improved Efficiency and Reliability." *NeuroImage* 31 (3): 1116–28.
- Zhang, Li, Tian-Nv Li, Yong-Sheng Yuan, Si-Ming Jiang, Qing Tong, Min Wang, Jian-Wei Wang, et al. 2016. "The Neural Basis of Postural Instability Gait Disorder Subtype of Parkinson's Disease: A PET and FMRI Study." *CNS Neuroscience & Therapeutics* 22 (5): 360–67.
- Zhong, Jianguo, Xiaojun Guan, Xia Zhong, Fang Cao, Quanquan Gu, Tao Guo, Cheng Zhou, et al. 2019. "Levodopa Imparts a Normalizing Effect on Default-Mode Network Connectivity in Non-Demented Parkinson's Disease." *Neuroscience Letters* 705 (July): 159–66.
- Zimmerman, Molly E., Richard B. Lipton, Jullie W. Pan, Hoby P. Hetherington, and Joe Verghese. 2009. "MRI- and MRS-Derived Hippocampal Correlates of Quantitative Locomotor Function in Older Adults." *Brain Research* 1291 (September): 73–81.
- Zwergal, Andreas, Jennifer Linn, Guoming Xiong, Thomas Brandt, Michael Strupp, and Klaus Jahn. 2012. "Aging of Human Supraspinal Locomotor and Postural Control in FMRI." *Neurobiology of Aging* 33 (6): 1073–84.