The neurobiological basis of gait dysfunction in Parkinson's disease: A cross-sectional and longitudinal approach

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"He can keep up the motor movements that the rest of us perform automatically, by using his conscious mind… he still has Parkinson's; it's just that he has found a way to overcome it"

Norman Doidge, from "The Brain's Way of Healing", 2015

Abstract

Gait impairments are a cardinal feature of Parkinson's disease (PD) and significantly affect the well-being of patients. However, current therapies are not effective at improving specific aspects of gait in PD nor preventing them from worsening over time. This is largely due to poor understanding of the mechanisms that the brain uses to control discrete gait characteristics in PD. The aim of this thesis was, therefore, to investigate associations between the brain and gait characteristics in PD, using both cross-sectional and longitudinal analytical approaches.

Newly diagnosed PD participants (n=99) and age-matched controls (n=47) completed quantitative gait, structural magnetic resonance imaging and clinical assessments soon after diagnosis; additional gait assessments were completed every 18 months for up to six years. Partial correlations and linear regression analyses determined cross-sectional associations between regional brain volumes and gait. Linear mixed-effects models identified gait characteristics that changed over six years in PD, more so than in controls, and assessed the predictive nature of regional brain volumes on gait changes.

Original contributions to knowledge were that regional brain volumes selectively associated with discrete gait characteristics in PD; many associations were unique to PD, even in early disease. Brain regions which primarily relate to both motor and non-motor functions correlated with PD gait impairment. Associations with non-motor structures might be attributable to contributions from the cortical cholinergic system, given its role in maintaining gait in PD.

This thesis provides evidence for the reliance on alternative and compensatory neural mechanisms during PD gait. Additionally, this thesis demonstrates the first evidence for regional brain volumes predicting disease-specific changes in gait. This not only provides greater understanding of neural underpinnings of gait dysfunction in PD, but demonstrates the potential for regional brain volumes to be considered clinically as an indicator of those at greater risk of mobility loss and falls.

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Statement of work undertaken

Professor David Burn is the Chief Investigator for the Incidence of Cognitive Impairments in Cohorts with Longitudinal Evaluation in Parkinson's Disease (ICICLE-PD) study and was responsible for the study design and grant application. Professor Lynn Rochester is the Chief Investigator for the ICICLE-Gait study, a nested study within ICICLE-PD, and was responsible for the study design and grant application. Data collection from baseline to the 54-month assessment was collected prior to my PhD and was collected by the following at different times; Dr Sue Lord, Dr Brook Galna, Dadirayi Mhiripiri, Dr Tien K Khoo, Dr Alison Yarnall, Dr Gordon Duncan, Dr Rachael Lawson, Dr Rosie Morris, Dr Lisa Alcock Leanne Thompson, Victoria Foster & Phil Brown.

Dr Lisa Alcock, Dr Rosie Morris, Dr Rachael Lawson, Victoria Foster, Phil Brown and I contributed to 72-month data collection. Data checking and cleaning at various times in the study has been completed by myself, Dr Lawson, Dr Yarnall, Dr Duncan, Dr Fionnuala Johnston, Dr Khoo, Philip Brown and Heather Hunter.

As part of the ICICLE studies, I have completed over 50 participant assessments of gait. I also processed all imaging scans from the ICICLE-PD study and extracted volumetric data from them for use in this thesis, with advice from Dr Sean Colloby. Additional image processing and volume extraction was required for the analysis completed in chapter 7, which I completed in collaboration with Dr Nicola Ray and Dr Chesney Craig at Manchester Metropolitan University. I additionally coordinated, managed and submitted documentation for ethical approval and amendments for the Neurobiological basis of Gait dysfunction in Parkinson's disease (NeuroGait) study, through which I completed gait, imaging and questionnaire based data collection for 40 participants over multiple visits. I also assisted in cognitive data collection for over 25 participants in the Examination of Gait and Dementia and its subtypes (GaitDem) study; data from these studies are not included within this thesis.

I performed the statistical analysis and interpreted the results included in this thesis independently, with statistical advice from my supervisors, Dr Rachael Lawson, Dr Brook Galna and Calum Hamilton. I was responsible for the writing of this thesis.

Awards, publications and presentations stemming from this Thesis

Awards

- International Congress of Parkinson's disease and Movement Disorders 2018 Travel Grant ($1000 in 2018)
- Faculty of Medical Sciences PhD Travel Grant (£500 in 2019)
- Complimentary registration for the International Congress of Parkinson's disease and Movement Disorders 2019 (worth $350 in 2019)

Publications

- **Wilson J**, Allcock L, McArdle R, Taylor JP, Rochester L. The neural correlates of discrete gait characteristics in ageing: A structured review. 2019. *Neuroscience and Biobehavioural Reviews.*
- **Wilson J**, Alcock L, Yarnall A J, Lord S, Lawson R A, Morris R, Taylor JP, Burn D, Rochester L, Galna B. Gait progression over six years in Parkinson's disease: effects of age, medication and pathology. 2020. *Frontiers in Aging Neuroscience.*
- **Wilson J**, Yarnall A J, Craig C E, Galna B, Lord S, Morris R, Lawson R A, Alcock L, Duncan G W, Khoo T K, O'Brien J T, Burn D, Taylor JP, Ray N J, Rochester L. Cholinergic basal forebrain volumes predict gait decline in Parkinson's disease. 2021. *Movement Disorders.*

Other publications

- Mc Ardle R, Morris R, **Wilson J**, Galna B, Thomas A J, Rochester L. What can gait analysis tell us about dementia and its subtypes? A structured review. 2017. Journal of Alzheimer's Disease.

Oral Presentations

- Institute of Neuroscience lunchtime journal club (15th March 2017)
  The neural correlates of gait
- DemaNDs journal club (13th March 2017; 9th April 2018)
  The structural neural correlates of gait in healthy ageing and Parkinson's disease

- Wellcome Trust University site visit (21st February 2018, Henry Wellcome Building, Newcastle University). Invited speaker on behalf of Wellcome Trust funded students.
  The structural neural correlates of gait in healthy ageing and Parkinson's disease
- ICICLE-PD 10-year anniversary event for participants involved in the ICICLE-PD study (17th May 2019, Research Beehive, Newcastle University)
  What have we learnt from taking pictures of the brain?
- North East Postgraduate Conference (22nd November 2019, Newcastle Civic Centre)
  Regional subcortical volumes predict gait decline in early Parkinson's disease

Poster Presentations

- International Congress of Parkinson's disease and Movement Disorders (5th– 9th October 2018, Hong Kong)
  Structural neural correlates of independent gait domains in Parkinson's disease
- Parkinson's UK Research Conference (12th– 13th November 2018, York, UK)
  Structural neural correlates of independent gait characteristics in Parkinson's
- Institute of Neuroscience student symposium (6th June 2019, Newcastle, UK)
  The neural correlates of discrete gait characteristics in ageing: A structured review
  Organised and chaired this student symposium
- International Society for Gait and Posture Research (30th June – 4th July 2019, Edinburgh, UK)
  - *The neural correlates of discrete gait characteristics in ageing: A structured review*
  - *Structural neural correlates of independent gait characteristics in Parkinson's disease*
  - *Natural progression of gait impairment in early Parkinson's: A six-year longitudinal prospective incident cohort study*
- International Congress of Parkinson's disease and Movement Disorders (22nd– 26th September 2019, Nice, France)
  Regional subcortical volumes predict gait decline in early Parkinson's disease

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Abbreviations

3MS = Modified Mini Mental State Exam

Aβ = Amyloid beta

ACh = Acetylcholine

AchE = Acetylcholinesterase

AD = Alzheimer's disease

ANCOVA = Analysis of Covariance

Asy = Asymmetry

AxD = Axial Diffusivity

cBF = cholinergic Basal Forebrain

CDR = Cognitive Drug Research battery

CLR = Cerebellar Locomotor Region

CNS = Central Nervous System

CPG = Central Pattern Generators

CSF = Cerebrospinal Fluid

DARTEL = Diffeomorphic Anatomic Registration using Exponentiated Lie algebra

DAT = Dopamine Transporter

DBS = Deep Brain Stimulation

DKI = Diffusion Kurtosis Imaging

DLB = Dementia with Lewy Bodies

DSST = Digit Symbol Substitution Test

DTI = Diffusion Tensor Imaging

EEG = Electroencephalography

FA = Fractional anisotropy

FAB = Frontal Assessment Battery

FDG = Fluorodeoxyglucose

FDR = False Discovery Rate

FLAIR = Fluid-Attenuated Inversion Recovery

fNIRS = functional Near Infra-Red Spectroscopy

FOG = Freezing of Gait

fMRI = functional Magnetic Resonance Imaging

GDS-15 = Geriatric Depression Scale – 15

GLM = General Linear Model

GM = Grey Matter

GMV = Grey Matter Volume

H & Y = Hoehn and Yahr

HSV = High step Length Variability

ICICLE-PD = Incidence of Cognitive Impairments in Cohorts with Longitudinal Evaluation in Parkinson's Disease

INS = Implantable Neurostimulators

LEDD = Levodopa Equivalent Daily Dose

LMEM = Linear Mixed Effects Model

LSV = Low step Length Variability

MCI = Mild Cognitive Impairment

MD = Mean Diffusivity

MDS = Movement Disorders Society

MDS UPDRS III = Movement Disorders Society Unified Parkinson's Disease Rating Scale part three

MESH = Medical Subject Headings

MLR = Mesencephalic Locomotor Region

MMSE = Mini-Mental State Examination

MNI = Montreal Neurological Institute

MoCA = Montreal Cognitive Assessment

MP-RAGE = Magnetisation Prepared Rapid Acquisition Gradient Echo

MRI = Magnetic Resonance Imaging

MRS = Magnetic Resonance Spectroscopy

NART = National Adult Reading Test

NBM = nucleus basalis of Meynert

nVNS = Vagus Nerve Stimulation

PCA = Principle Component Analysis

PD = Parkinson's disease

PDD = Parkinson's disease dementia

PD-MCI = Parkinson's disease with Mild Cognitive Impairment

PET = Positron Emission Tomography

PiB = Pittsburgh Compound B

PIGD = Postural Instability and Gait Difficulty

PMRF = Pontomedullary Reticular Formation

PPN = Pedunculopontine Nucleus

RBD = REM sleep Behaviour Disorder

RD = Radial Diffusivity

REM = Rapid Eye Movement

SAI = Short Latency Afferent Inhibition

SCP = Superior Cerebellar Peduncle

SD = Standard Deviation

SLR = Subthalamic Locomotor Region

SMA = Supplementary Motor Area

SNpc = Substantia Nigra pars compacta

SPECT = Single Photon Emission Computed Tomography

SPM = Statistical Parametric Mapping

STN = Subthalamic Nucleus

TBSS = Tract-Based Spatial Statistics

TE = Echo Time

TIV = Total Intracranial Volume

TMS = Transcranial Magnetic Stimulation

TMT = Trail Making Task

TR = Repetition Time

VBM = Voxel Based Morphometry

WM = White Matter

WMH = White Matter Hyperintensity

χ^2 = Chi-squared

Chapter 1: Parkinson's disease: setting the scene

Impairments in gait, the way of walking, are common in Parkinson's disease (PD). There is, currently, poor clinical management of these gait impairments, in part due to limited understanding of the neural mechanisms which underpin gait and its progression throughout PD. This thesis aims to investigate the neural underpinnings of gait in early PD, through both cross-sectional and longitudinal evaluations of the associations between gait features and structural brain imaging parameters.

This chapter outlines gait and its impairment in PD, describes the pattern of neurodegeneration that occurs over the course of PD and summarises current theories of the neural mechanisms involved in PD gait.

1.1 Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disorder, second only to Alzheimer's disease (AD), which was initially described by James Parkinson in 1817 in his essay on the "shaking palsy" (Parkinson, 1817). A higher incidence of PD occurs in older adults and in males (Van Den Eeden *et al.*, 2003). There are over six million cases of PD worldwide; this number is set to almost double over the next twenty years, given that the average life expectancy is increasing (Feigin *et al.*, 2017; Dorsey and Bloem, 2018). It is therefore of growing importance to be able to manage PD effectively.

PD is typically classified as a movement disorder; this is reflected in the two-step process used to clinically diagnose PD as described in the most recent Movement Disorders Society (MDS) clinical diagnostic criteria for Parkinson's disease (Postuma *et al.*, 2015). Firstly, for a diagnosis of PD, parkinsonism should be present. This is defined as the presence of bradykinesia (an abnormal slowness of movement and reduction in speed or amplitude of continuous movements) as well as the presence of either muscular rigidity or resting tremor (Archibald and Burn, 2008). Secondly, no exclusion criteria can be met; this would define any observed parkinsonism as attributable to conditions other than PD, such as frontotemporal dementia. Many elements of these criteria originate from the Queen's Square Brain Bank clinical diagnostic criteria, traditionally the most common criteria used to diagnose PD (Hughes *et al.*, 1992). Non-motor symptoms, such as cognitive impairment and depression, are also common in PD (Hely *et al.*, 2008; Ziropadja *et al.*, 2012), and negatively impact on quality of life (Lawson *et al.*, 2017). Symptoms of PD typically become evident with a

reduction in dopaminergic neurotransmission throughout the brain, with loss of up to 80% of striatal dopaminergic neurons evident before symptom onset (Marsden, 1990; Dauer and Przedborski, 2003).

1.2 Gait in Parkinson's disease

Gait is defined as an individual's manner of walking. Gait is considered to be an important indicator of overall health; poor gait performance has been associated with greater morbidity, mortality, and fall risk in older adults (Hausdorff *et al.*, 2001; Verghese *et al.*, 2007; Studenski *et al.*, 2011). In the original essay from James Parkinson, patients were identified as being no longer able to walk in their usual manner, instead needing to take shorter and quicker steps (Parkinson, 1817), although this was observed only as the disorder progressed. Technological advancements over the last ten to fifteen years have enabled better understanding of gait and its impairments in neurological conditions, through quantitative gait measurement techniques. These have brought to light evidence suggesting that gait impairments are common even in early and prodromal stages of PD (Rochester *et al.*, 2014; Galna *et al.*, 2015; Del Din *et al.*, 2019a), and are associated with an increased falls risk (Lord *et al.*, 2016), cognitive impairment (Lord *et al.*, 2014; Morris *et al.*, 2017), poor quality of life (Curtze *et al.*, 2016) and low mood (Lord *et al.*, 2013a) in PD. This highlights the need to understand and ultimately remediate impaired gait early in PD.

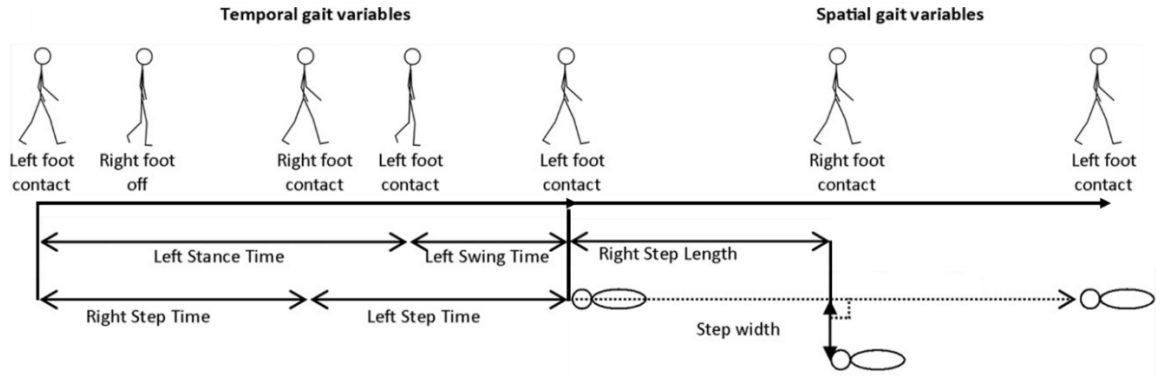
Although gait was traditionally thought of as an automatic motor task, this has been replaced with the idea that gait is a more complex skill, requiring additional input from sensory and cognitive mechanisms (Montero-Odasso *et al.*, 2012) and the integration of these mechanisms for safe and effective navigation (Takakusaki, 2013). Step velocity is typically used as a global measure of gait, due to its ease of measurement and reliability (Wade, 1992). However, this provides a limited approach to gait assessment, as it is not reflective of the complex and multifaceted nature of gait. Gait may instead be better represented by multiple discrete characteristics, as described below, which better encompass the different dimensions of gait, and which may differently reflect neural processes related to ageing and disease.

1.2.1 Spatiotemporal gait characteristics

Quantitative gait assessment enables gait to be measured through a variety of variables, or characteristics, relating to both spatial and temporal aspects of gait, measured in units of distance and time respectively as depicted in **Figure 1-1.** Previous work has identified 16

spatiotemporal gait characteristics that are of interest for assessment of ageing and neurodegenerative cohorts, due to their involvement in ageing and pathological processes and good reliability in their measurement (Lord *et al.*, 2013c). Spatial gait characteristics within this framework include step length and step width; temporal characteristics include step time, swing time and stance time. Additionally, the variability and asymmetry of these characteristics can be assessed where appropriate, to identify step-to-step variations in characteristics and differences between left and right steps respectively. These may have a particular relevance in PD, given that bradykinesia (slowing over the course of repetitive movements) is a fundamental feature of PD, and symptom onset typically begins unilaterally. Step velocity does not always reflect the subtle and selective gait alterations that occur in response to ageing and disease, which may signify discrete neurological changes (Stolze *et al.*, 2001; Verghese *et al.*, 2007; Lord *et al.*, 2014). It is therefore important to assess additional gait characteristics to step velocity. Careful selection of gait characteristics is needed to identify those of most relevance in PD, both in terms of characteristics most affected at a particular point in the disease course, and those which are most prone to longitudinal change due to disease progression. Several gait characteristics have been associated with fall risk, such as step velocity and stance time (Lord *et al.*, 2016), stride length variability (Schlenstedt *et al.*, 2016) and step width variability (Brach *et al.*, 2005), further emphasising the need to look beyond step velocity when assessing gait features of importance in PD.

Figure 1-1. Spatiotemporal gait characteristics, adapted from Lord *et al.*, 2013



There is high covariance between certain gait characteristics. To overcome this, several efforts have been made to group together characteristics into domains of gait, through using data reduction techniques (principle component analysis, PCA) to produce models of gait. Although these models have similarities, subtle differences differentiate them. Verghese et al. produced a model containing three gait domains; pace, rhythm and variability (Verghese *et al.*, 2008). Two additional domains were included within the model from Lord et al., asymmetry and postural control, through the inclusion of more gait characteristics (Lord *et al.*, 2013c). Other models, such as that from Verlinden et al., contain domains relating to more complex gait tasks such as turning (Verlinden *et al.*, 2013). Characteristics from the model conceived by Lord et al. have been considered throughout this thesis, as they form the most comprehensive model for simple, rather than complex, gait. This model has also been validated in PD (Lord *et al.*, 2013b) and will provide a framework for the interpretation and communication of study findings throughout this thesis.

1.2.2 Techniques to quantitatively measure gait

Quantitative measurement of gait enables objective and data rich spatiotemporal information to be obtained in comparison to observation alone. Quantitative gait assessments are typically completed in laboratory environments due to the nature of the equipment used to measure gait, as well as to ensure the safety of those being assessed and for ease of comparability between subjects. The most simplistic quantitative gait assessments have involved timed walks using stopwatches, which are prone to human errors. Clinically, measures such as the Timed Up and Go Test (Podsiadlo and Richardson, 1991) are used for assessment of gross motor features, but these cannot assess gait characteristics reflective of more subtle pathology. Many have assessed a range of spatiotemporal gait characteristics derived from instrumented walkways (McDonough *et al.*, 2001; Nelson, 2002; Webster *et al.*, 2005), infra-red motion capture systems (Springer and Yogev Seligmann, 2016) and footswitches (Pradeau *et al.*, 2017). Accelerometer based body worn monitors provide a novel method of gait data collection, allowing for gait to be assessed during day to day activities outside of the laboratory (Del Din *et al.*, 2016). In this thesis, gait characteristics derived from an instrumented walkway have been assessed, due to the widely regarded reliability of the gait measures derived (Menz *et al.*, 2004).

1.2.3 Gait impairments in Parkinson's disease

The motor symptoms required for a diagnosis of Parkinson's disease, namely bradykinesia and rigidity, concurrently affect gait. Gait impairments are common and debilitating for people with PD. As described by James Parkinson (Parkinson, 1817), steps are typically slow and shuffling, with variation from one step to the next, and posture is often flexed; this can lead to an increased risk of falling, as well as a cycle of reduced activity and muscular atrophy from disuse.

Gait decline is also a typical feature of the ageing process (Pirker and Katzenschlager, 2017); older adults demonstrate shorter step length (Ostrosky *et al.*, 1994) and increased variability (Kang and Dingwell, 2008) in comparison to younger adults, and demonstrate changes in variability measures over time (Jayakody *et al.*, 2018; Bogen *et al.*, 2019). These are associated not only with age-related neurological changes (Demnitz *et al.*, 2017) but the functioning of different organ systems which have a role in the physiology of gait (Cruz-Jimenez, 2017), including muscle strength (Kang and Dingwell, 2008) and cognition (Morris *et al.*, 2016). In spite of this, people with PD show greater gait impairments than age-matched controls, even when assessed whilst on optimal dopaminergic medication (Galna *et al.*, 2015; Pistacchi *et al.*, 2017).

Slow step velocity, and the closely associated shortening of step length, are well-known impairments in PD gait which have been identified in several research studies (Morris *et al.*, 1994b; Morris *et al.*, 1996; O'Shea *et al.*, 2002; Baltadjieva *et al.*, 2006; Carpinella *et al.*, 2007; Rochester *et al.*, 2012; Mak, 2013; Pistacchi *et al.*, 2017), even in early disease stages (Galna *et al.*, 2015). Gait characteristics relating to the rhythm or timing of walking, such as swing and step times, are often quicker in PD compared to healthy ageing (Baltadjieva *et al.*, 2006), which may be to compensate for shortened step length in an attempt to retain step velocity (Morris *et al.*, 1994a; Lewis *et al.*, 2000). Other discrete gait characteristics that show greater impairment in PD compared to age-matched controls include characteristics related to gait variability (Hausdorff *et al.*, 1998; Frenkel-Toledo *et al.*, 2005; Hausdorff, 2005; Mak, 2013; Lord *et al.*, 2014; Keloth *et al.*, 2019) and gait asymmetry (Baltadjieva *et al.*, 2006; Yogev, 2007; Galna *et al.*, 2015). Poor postural control is also evident in PD, both during movement and at rest (Adkin *et al.*, 2005; Peterson and Horak, 2016). Step width variability, a gait characteristic reflective of postural control, is also lower in PD than controls in early disease (Lord *et al.*, 2014; Rochester *et al.*, 2014; Galna *et al.*, 2015).

Additional features of gait disturbances in PD include delays in and poorer execution of steps during gait initiation (Roemmich *et al.*, 2012; Vallabhajosula *et al.*, 2013), difficulty

completing turns, as characterised by increased jerkiness and more steps required to complete a turn (Huxham *et al.*, 2008; Stack and Ashburn, 2008), and freezing of gait (FOG), a gait disturbance which can occur in later stages of PD described as a feeling that "feet are glued to the floor" (Giladi and Nieuwboer, 2008). These more complex features of PD gait will not be focussed on in this thesis, as the aim here is to understand the neural mechanisms underpinning features of simple continuous gait.

1.2.4 Progression of gait impairments in Parkinson's disease

There is limited understanding of the natural history of gait progression in PD, particularly of the changes in gait that are specifically due to disease progression rather than the ageing process per se. Although evidence suggests that step time variability increases over five years in PD in comparison to age-matched controls in both early (Hobert *et al.*, 2019) and moderate disease stages (Micó-Amigo *et al.*, 2019), there is limited precision in the interpretation of gait progression from these studies, as there was substantial variation in the number of years since diagnosis within the proposed disease stages. Previous work from the ICICLE-GAIT study (Rochester *et al.*, 2017) identified discrete gait impairments (variability of step time, step length and step width) that progress more rapidly over the first three years from diagnosis within an incident PD cohort compared to age-matched controls. However, to comprehensively determine changes in gait that are due specifically to PD progression, and to tease these apart from changes occurring as a result of an interaction between ageing and disease progression, gait change should be modelled over a longer timeframe in both PD and age-matched control cohorts.

Furthermore, there is little research that assesses the clinical predictors of longitudinal PD gait change, as there has been in cohorts of healthy older adults (Jayakody *et al.*, 2018; Pinter *et al.*, 2018). One study has linked the shortening of step length over time in PD to a worse "gait" score on the Movement Disorders Society Unified Parkinson's Disease Rating Scale part three (MDS-UPDRS III) (Schlachetzki *et al.*, 2017); overall change in motor disease severity (from the entire MDS-UPDRS III) has also been associated with change in gait parameters such as step velocity and step time variability (Hobert *et al.*, 2019). Knowledge of the clinical biomarkers of gait change is imperative for the identification of those at a higher risk of developing more severe gait impairments, and are therefore more likely to fall, who may benefit most from interventions.

1.2.5 Interventions to improve gait in Parkinson's disease

There is an increasing body of evidence for the use of both pharmacological and non-pharmacological interventions to improve gait in PD (Müller *et al.*, 2019).

Dopaminergic medications are most commonly used to treat motor symptoms in PD. Agents that restore dopamine, including levodopa, can be effective in improving several features of PD gait (Smulders *et al.*, 2016), particularly step velocity and spatial characteristics such as step length (Bryant *et al.*, 2011a; Bryant *et al.*, 2011b; Sterling *et al.*, 2015). There is, however, limited evidence of the effectiveness of dopaminergic therapies to improve gait variability (Bryant *et al.*, 2011a; Rochester *et al.*, 2011) and temporal gait characteristics remain unaffected by dopaminergic medication (Curtze *et al.*, 2015). Dopamine agonists augment the effects of levodopa, increasing step velocity (Brodsky *et al.*, 2010; Serrao, 2015), yet use of these may lead to an increased risk of falling or induce FOG (Serrao, 2015). Additionally, the effects of dopaminergic medications lessen with disease progression (Jenner, 2015) and long-term use of dopaminergic therapies typically leads to involuntary movements known as dyskinesia (Iravani, 2011). Several gait characteristics remain impaired in PD compared to age-matched controls despite assessment on optimal dopaminergic medication (Galna *et al.*, 2015). Furthermore, discrete characteristics continue to progress more quickly in PD than typical ageing despite increasing dopaminergic medication (Rochester *et al.*, 2017). These findings suggest that the neural mechanisms underpinning gait extend beyond dopaminergic substrates, and gait impairment may be improved with pharmacological interventions targeting other neurotransmitter systems.

Although the cholinergic system is traditionally viewed as having an involvement in cognitive processes (Klinkenberg *et al.*, 2011), there is increasing evidence of cholinergic involvement with PD gait (Müller and Bohnen, 2013). In addition to reduced cholinergic activity in fallers (Bohnen *et al.*, 2009; Karachi *et al.*, 2010; Yarnall *et al.*, 2011; Bohnen *et al.*, 2019) and those exhibiting FOG (Bohnen et al., 2014; Snijders et al., 2016), increases in short-latency afferent inhibition (SAI) (Rochester et al., 2012) and cholinergic denervation, as assessed through positron emission tomography (PET) (Bohnen *et al.*, 2013; Müller *et al.*, 2015; Sanchez-Catasus *et al.*, 2019), have been associated with slower walking speed. These associations may be due to shared neural pathways required for both gait and cognitive tasks (Leisman *et al.*, 2016), or reduced cortical cholinergic activity may be responsible for attentional loss during gait (Rochester *et al.*, 2014). There is preliminary evidence that acetylcholinesterase (AChE) inhibitors can reduce falls in PD (Chung *et al.*, 2010; Li *et al.*, 2015) and improve gait in AD (Montero-Odasso *et al.*, 2014) and PD (Henderson *et al.*, 2016).

Another neurotransmitter system of interest in PD is the serotoninergic system; serotoninergic degeneration has been linked to tremor (Pasquini *et al.*, 2018), depression, fatigue and visual hallucinations (Politis and Niccolini, 2015), and there is evidence of depression affecting gait (Lord *et al.*, 2013a). Noradrenergic medications may help to alleviate motor symptoms in PD, although further investigations are needed to fully understand their effects on gait (Auriel *et al.*, 2009). Glutamatergic agents improve gait in dementia (Beauchet *et al.*, 2013); however, initial evidence indicates that these may not improve aspects of gait pace in people with PD (Moreau *et al.*, 2013).

Non-pharmacological interventions such as exercise programmes and physical therapy typically improve spatiotemporal gait characteristics (Tomlinson *et al.*, 2012; Shen *et al.*, 2016; Rafferty *et al.*, 2017; Warlop *et al.*, 2017), although it is difficult to compare these different techniques due to substantial heterogeneity in the approaches taken.

Cueing techniques use external stimuli to facilitate repetitive movements; cues can improve gait and alleviate FOG (Nieuwboer *et al.*, 2007). Cueing can be facilitated by auditory, visual and tactile stimuli, through "open-loop" (fixed pattern of stimuli) or "closed-loop" (stimuli prompted by individual movement patterns in real-time) strategies (Muthukrishnan *et al.*, 2019). Again, there is heterogeneity in cueing strategies. Visual and auditory cues may have different effects on different spatiotemporal gait characteristics (Morris *et al.*, 1994b; Suteerawattananon *et al.*, 2004; Rochester *et al.*, 2007; De Icco *et al.*, 2015), although auditory cues may affect a larger number of gait characteristics than visual cues (Spaulding *et al.*, 2013) and may be preferred for use by people with PD (Nieuwboer *et al.*, 2007).

Long-term intervention techniques which stimulate the central nervous system (CNS), such as deep-brain stimulation (DBS) of the subthalamic nucleus (STN) or pedunculopontine nucleus (PPN) and mid-thoracic spinal cord stimulation, have been more recently developed to alleviate several motor impairments in PD. There is some evidence suggesting that these may also improve factors related to gait, such as scores from the MDS-UPDRS III which consider falls and the Postural Instability and Gait Difficulty (PIGD) phenotype (Wang *et al.*, 2017; Samotus *et al.*, 2018). However, the effect of CNS stimulation on different spatiotemporal characteristics of gait remains unclear; although DBS has been reported to improve parameters such as stride length, stride length variability and swing time asymmetry (Scholten *et al.*, 2017), there is also suggestion that DBS can worsen gait in some individuals (Bronstein *et al.*, 2011). Non-invasive stimulation techniques, such as vagus nerve stimulation (nVNS), may also improve gait, including measures of variability (Morris *et al.*, 2019b).

The effects of different intervention strategies on gait can aid in the interpretation of the neural underpinnings of gait impairment in PD. To fully understand the mechanisms which may relate to a worsening of gait over the disease course, neurological changes in PD should be considered.

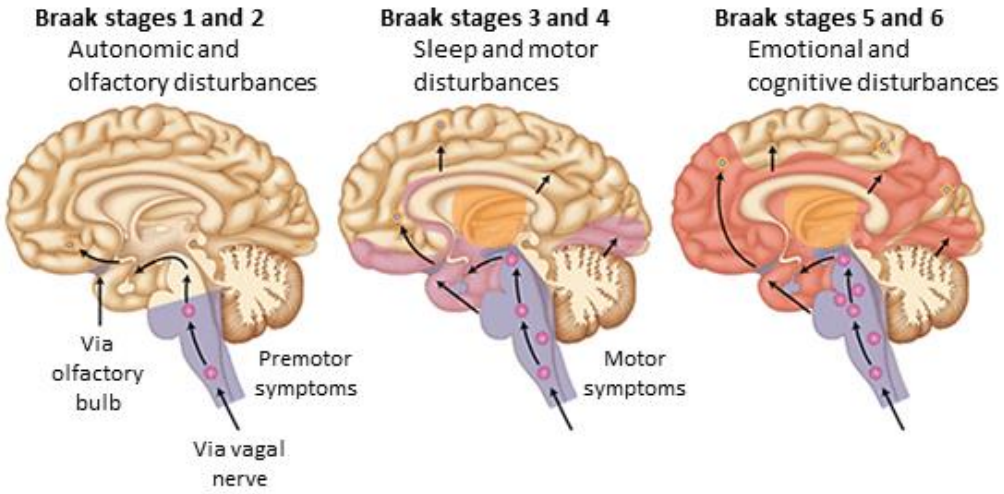
1.3 Neurodegeneration over the course of Parkinson's disease

Confirmation of a clinical diagnosis of PD can only be achieved post-mortem, through pathological evidence of neuronal loss from the substantia nigra pars compacta (SNpc) (Samii *et al.*, 2004), a portion of the basal ganglia and part of the dopaminergic nigrostriatal tract, in addition to a formation of Lewy bodies from the aggregation of α-synuclein (Jellinger, 2014). However, a wide range of neurodegenerative changes occur with disease progression. Knowledge of the progression of these pathologies is important for understanding the brain areas affected at different stages of disease. Additionally, assessments of neurological changes *in vivo* may be of greater clinical utility, as associations can be made with clinical phenotypes and used to inform intervention strategies. Advances in neuroimaging techniques have enabled such assessments to be completed, by evaluating changes in different aspects of brain structure and function.

1.3.1 Neuropathological progression of Parkinson's disease

Braak and colleagues (Braak, 2004) proposed a six-stage model of the progression of PD pathology, from prodromal disease stages to advanced disease, using staining techniques to identify α-synuclein in neurons, as shown in **Figure 1-2.** Within each stage, Braak's model states that pathology worsens in areas implicated in previous stages.

Figure 1-2. Braak staging for Parkinson's disease, adapted from Jellinger, 2014



This model describes initial pathological changes (stage 1) occurring in the medulla, the lowest brainstem portion (specifically in the dorsal motor nucleus of the vagal nerve) and in the anterior olfactory nucleus. Next, stage 2 demonstrates progression rostrally up the brainstem, so that Lewy pathology is observed in the raphe and locus coeruleus nuclei within the brainstem (located near the midline and within the pons respectively). Pathology at these stages implicates serotoninergic neurotransmission (Hornung, 2003), which may underpin symptoms of depression observed in early PD (Ishihara and Brayne, 2006), and explains rapid eye movement (REM) sleep behaviour disorder (RBD) as a manifestation of evolving PD (Boeve, 2013).

Braak's stage 3 describes pathology involving the SNpc, which coincides with the onset of motor symptoms. Disease progression occurring in the nucleus basalis of Meynert (NBM) and PPN, two of three origins of the cholinergic projection systems in the brain (Heckers *et al.*, 1992), occurs in the later parts of stage 3. Pathology spreads to the paralimbic cortex (consisting of piriform, entorhinal, parahippocampal and cingulate cortices located on the medial surface of the temporal lobe and rostrally adjacent to the corpus callosum), allocortex (consisting of the olfactory bulb and hippocampus) and thalamus in stage 4.

Pathological involvement of the neocortex (involved in higher-order function of the brain) occurs in stages 5 and 6 (Jellinger, 2014), with α-synuclein aggregates forming in the prefrontal cortex and high-order sensory association areas first, and then in primary motor and sensory areas to an extent. These final stages are thought to be associated with non-motor PD symptoms typically seen in later disease stages, such as visual hallucinations and dementia (Chaudhuri *et al.*, 2006).

It should be highlighted that Braak's staging is based on Lewy body distribution, and not neuronal degeneration, so may not fully encompass pathological changes in the brain that occur during PD. Furthermore, there is evidence suggesting that not everyone with PD experiences this pattern of spread of Lewy bodies (Burke *et al.*, 2008), as determined through pathology (Parkkinen *et al.*, 2005) and neuroimaging (Brooks, 2010) studies. However, it is still suggested that Braak's staging model is useful for understanding disease progression (Dickson *et al.*, 2010) and may accurately represent particular subgroups of PD patients, with more work required to understand any deviations from the model (Rietdijk *et al.*, 2017).

1.3.2 Neuroimaging techniques to assess neurodegeneration in Parkinson's disease

Many studies have utilised a wide range of neuroimaging techniques to develop a greater understanding of the neurological changes that occur over the course of PD *in vivo*, as outlined in recent reviews of PD imaging biomarkers (Sterling *et al.*, 2016; Saeed *et al.*, 2017; Helmich *et al.*, 2018; Yang, 2018). Some of the key outcomes from these studies are outlined below. A focus has been given to findings from volumetric structural imaging studies, as structural imaging offers a non-invasive, replicable and relatively cost-effective means for assessing the entirety of the brain. For these reasons, structural magnetic resonance imaging (MRI) has been utilised throughout this thesis.

Structural imaging – measures of grey matter atrophy

Structural three-dimensional MR images can be used to assess atrophy (tissue loss) over the whole brain, or a specific region or regions of interest. Volumetric analyses can be classified as region-of-interest based approaches (manual labelling or automatic segmentation of areas); voxel-based whole-brain morphometric analyses (VBM) or; surface based approaches, including cortical thickness (the distance between grey and white matter boundaries) and cortical gyrification (measures of the folding structure of the cortex).

Findings from studies utilising structural MRI to assess cortical atrophy are inconsistent (Sterling *et al.*, 2016). Cortical atrophy has been reported in PD compared to age-matched controls (Tinaz *et al.*, 2011) and in more severe disease stages of PD (Jubault *et al.*, 2011; Gao Y, 2018); this is reported to occur in relatively widespread regions yet is most commonly reported in frontal cortical regions (Ibarretxe-Bilbao *et al.*, 2012; Tessa *et al.*, 2014; Jia *et al.*, 2015; Lewis *et al.*, 2016; Mollenhauer *et al.*, 2016; Nürnberger *et al.*, 2016; Yau *et al.*, 2018; Uribe *et al.*, 2019). However, some evidence suggests few overall differences in cortical thickness between PD and control participants, particularly in early populations (Jubault *et*

al., 2011; Mak *et al.*, 2015), reflective of the late involvement of the cortex within Braak's staging of progression (Braak, 2004).

A similar inconsistency is reported in literature assessing subcortical atrophy. Volumetric studies of several subcortical structures have been completed. The main focus in PD has been imaging of the basal ganglia, as the dorsal striatum of the basal ganglia (consisting of the putamen and caudate) receive inputs from the SNpc that are used for movement control. Also, loss of nigrostriatal dopaminergic neurons is a pathological hallmark of PD (Dauer and Przedborski, 2003). Putamen atrophy has been widely reported at several stages of disease (Geng *et al.*, 2006; Ellmore *et al.*, 2010; Tinaz *et al.*, 2011; Pitcher *et al.*, 2012; Sterling *et al.*, 2013; Lewis *et al.*, 2016; Rosenberg-Katz *et al.*, 2016), but not in all studies (Lee *et al.*, 2011; Messina *et al.*, 2011; Mak *et al.*, 2015). Nigrostriatal projections to the putamen degenerate preferentially compared to caudate projections, which may explain several reports of a lack of caudate atrophy in PD compared to controls (Almeida *et al.*, 2003; Geng *et al.*, 2006; Lee *et al.*, 2011); again, though, findings are not consistent between studies (Pitcher *et al.*, 2012; Sterling *et al.*, 2013; Lewis *et al.*, 2016).

Fewer volumetric studies of the ventral striatum, globus pallidus and substantia nigra have been completed, which may be due to their small size and difficulty in precisely defining them and their sub-regions through MRI. Some evidence suggests atrophy in these regions in PD (Minati *et al.*, 2007; Tinaz *et al.*, 2011), although findings relating to the globus pallidus are not conclusive (Geng *et al.*, 2006; Lewis *et al.*, 2016). SNpc volume loss is thought to occur before volume loss of the cholinergic basal forebrain, again following the pattern of Lewy body progression outlined in the Braak progression staging (Ziegler *et al.*, 2013).

The thalamus is also of interest in PD, as it connects the basal ganglia to the cortex. Few of the investigations of thalamus atrophy have reported volumetric changes (Nagano-Saito *et al.*, 2005; Lee *et al.*, 2011) but changes in thalamus shape may occur (McKeown *et al.*, 2008). The hippocampus and amygdala are two structures thought to be implicated in non-motor PD symptoms, namely cognitive decline and depression (Solari *et al.*, 2013; van Mierlo *et al.*, 2015). Amygdala atrophy has been reported in several stages of PD (Ibarretxe-Bilbao *et al.*, 2012; Rosenberg-Katz *et al.*, 2016), although findings are inconsistent. Hippocampal atrophy is generally not evident in people with PD without any impairment in cognition (Apostolova *et al.*, 2010; Messina *et al.*, 2011).

Structural differences may, however, be more consistently observed when considering cognitively impaired PD populations. People with PD with cognitive impairment have been

reported to experience greater cortical thinning over frontal, parietal and temporal regions than PD without cognitive impairment, as well as greater atrophy of limbic structures and the NBM (Hanganu *et al.*, 2014; Mak *et al.*, 2015; Sterling *et al.*, 2016; Gee *et al.*, 2017; Ray *et al.*, 2017).

Structural imaging – measures of white matter health

Structural MRI has also been used to measure the extent of white matter hyperintensities (WMH) in people with PD, a pathology related to small vessel disease and commonly observed on brain scans of older adults. It is unclear whether WMH are more commonly observed in PD compared to age-matched controls due to conflicting evidence (Stern *et al.*, 1989; Piccini *et al.*, 1995; Dalaker *et al.*, 2009).

The integrity of white matter tracts can be assessed through Diffusion Tensor Imaging (DTI) and Diffusion Kurtosis Imaging (DKI), an extension of DTI. Poorer structural integrity is reported in PD compared to controls cross-sectionally, particularly within the substantia nigra (Cochrane and Ebmeier, 2013), corpus callosum (Fling *et al.*, 2016) and olfactory tracts (Scherfler *et al.*, 2005). Integrity also worsens over time in PD more so than in healthy ageing in areas connecting to the putamen (Surova *et al.*, 2018), SNpc (Ofori *et al.*, 2015; Loane *et al.*, 2016; Burciu *et al.*, 2017), thalamus (Zhang *et al.*, 2016) and widespread cortical regions (Taylor *et al.*, 2018).

Functional imaging

Several different functional imaging techniques have been used to assess neurological differences in PD; those with findings most relevant to this thesis are detailed below.

Functional molecular imaging techniques, such as PET and single photon emission computed tomography (SPECT), use radiolabelled molecules that interact with biological processes *in vivo*. A common application of these techniques in PD is to assess dysfunction of neurotransmitters. There is less dopamine transporter (DAT) binding in PD compared to age-matched controls (Im *et al.*, 2006), and reduced DAT binding occurs in the dorsal striatum longitudinally through early PD (Simuni *et al.*, 2018; Ikeda *et al.*, 2019). Additionally, serotoninergic and cholinergic dysfunction in PD has been assessed with targeting PET ligands (Bohnen *et al.*, 2018b; Liu *et al.*, 2018). There are few reports of longitudinal changes in these neurotransmitter systems as assessed with functional imaging, although evidence suggests reduced cholinergic binding in particular striatal regions (Bohnen *et al.*, 2018a) and a reduced pattern of cholinergic connections from a posterior portion of the NBM (Sanchez-Catasus *et al.*, 2019) over time.

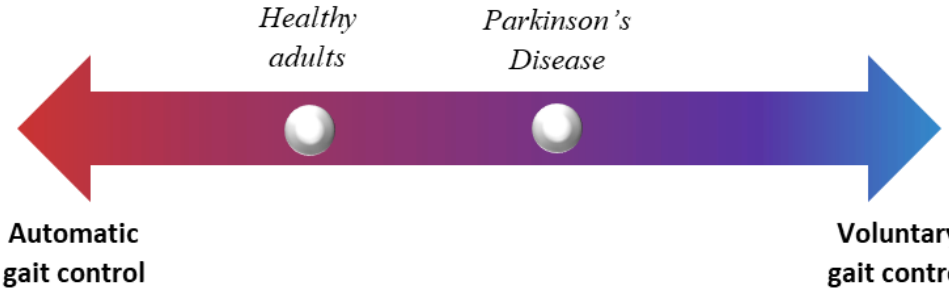
Functional MRI (fMRI) can assess the functional activation of different brain networks. Connectivity between the frontoparietal control network and the default mode and visual networks increases over time in PD compared to healthy ageing (Klobušiaková *et al.*, 2019), which may reflect alterations in networks required to maintain function.

Electroencephalography (EEG) can be used to record electrical activity within the brain, whereas functional near infra-red spectroscopy (fNIRS) measures brain activity through haemodynamic responses in relation to neuronal behaviour. Both modalities can provide real time information relating to brain activity at rest and during a task, including gait (Stuart *et al.*, 2018). Studies using these techniques, particularly fNIRS, have determined that prefrontal cortical activations play an important part in PD gait (Maidan, 2015; Maidan *et al.*, 2016; Maidan, 2017; Stuart *et al.*, 2018), implying that people with PD may require increased recruitment of cortical resources during gait.

1.4 Neural control of gait in Parkinson's disease

A large network of structures underpins human locomotion. Although walking was traditionally considered a purely automatic motor task, this notion has been replaced by a more encompassing sensory-cognitive-motor model which reflects a contemporary understanding of gait as a highly complex skill (Montero-Odasso *et al.*, 2012). Indeed, effective real-world gait is reliant on attending to the environment (Yogev-Seligmann *et al.*, 2008) and the integration of sensory signals (including visual, somatosensory and vestibular signals) to inform motor outputs (Takakusaki, 2017). In PD, it is thought that the neural structures relied upon for automatic movements are compromised, and so there is an increased reliance on these more compensatory mechanisms, including alternative pathways for motor signals to be relayed and voluntary movement control that is cortically driven (**Figure 1-3**). The brain regions and networks thought to be included within each of these processes are outlined in this section.

Figure 1-3. Proposed spectrum of the neural control of gait



[Gait is no longer considered a purely automatic motor task, as sensory and cognitive information is also required. In PD, it is proposed that there is increased reliance on these voluntary and compensatory mechanisms of gait control, thus mitigating impairments in the mechanisms required for automatic motor control.]

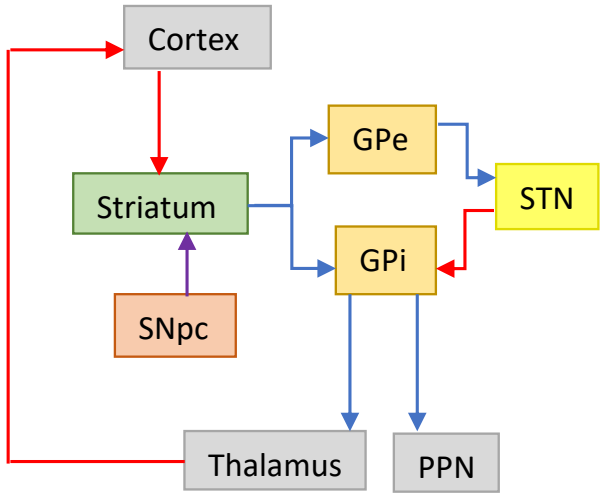
1.4.1 Automatic motor control of gait

A combination of animal models and human functional imaging approaches have informed understanding of the networks involved in locomotor control. The basic rhythm of stepping patterns is generated from a set of spinal inter-neuronal networks, known as central pattern generators (CPGs) (Takakusaki, 2013), which then interact with sensory feedback from the nervous system and brain structures to allow for adaptation of gait where necessary (Bohnen and Jahn, 2013). The automatic process of motor control is thought to be facilitated by the cerebellum and brainstem (Jahn *et al.*, 2008; Takakusaki, 2013). Three regions are of importance: the subthalamic locomotor region (SLR), located laterally to the hypothalamus; the mesencephalic locomotor region (MLR), located near to the PPN within the midbrain and; the cerebellar locomotor region (CLR) within the midline of the cerebellum. The MLR receives signals from the premotor cortices, limbic areas (including the SLR) and the basal ganglia, particularly the substantia nigra par reticulata as observed in felines (Takakusaki *et al.*, 2003). The MLR then projects these to the system that generates rhythm, which consists of the pontomedullary reticular formation (PMRF) within the brainstem. The CLR receives inputs from the cerebellum, particularly the vermis and paravermal cerebellar cortex which integrate proprioceptive, vestibular, and visual afferent information (Mori *et al.*, 2001); the CLR then also projects these inputs to the PMRF (Takakusaki, 2013). The PMRF then integrates signals from the MLR and CLR and transmits them to the CPGs (Bohnen and Jahn, 2013). This automatic movement control is thought to be impaired in PD, which may be linked to the MLR not receiving signals efficiently. The presence of Lewy pathology in these areas early in PD (Braak, 2004) may also affect locomotor control.

It is thought that projections from the frontal cortices are involved in the motor control of gait, particularly the premotor and supplementary motor areas (SMA), through projections to the

cerebellum via the thalamus and the basal ganglia as part of an "indirect" dopaminergic basal-ganglia-thalamocortical circuit (Silkis, 2001; Hashimoto, 2006). However, the precise involvement of the cortex during gait is not clear. In PD, movement problems are typically thought to originate from dysfunction of this indirect circuit, through a proposed "rate model" (**Figure 1-4**). Briefly, this is thought to occur by degeneration within the SNpc ensuring that fewer dopaminergic modulatory signals are sent to the dorsal striatum, causing both increased inhibition of the external portion of the globus pallidus and reduced inhibition of the internal globus pallidus. As the internal portion of the globus pallidus is responsible for inhibiting the thalamus and PPN, overall this causes increased inhibition of the thalamus and PPN, and therefore reduced excitation of cortical structures such as the SMA and primary motor cortex (Bohnen and Jahn, 2013; Peterson and Horak, 2016). The proposed diminished projections to these cortical structures may explain features of PD gait that reflect movement planning and amplitude, such as short step length. This is further supported by an initial improvement in these characteristics through dopaminergic medication use, as explained in section 1.2.5. Circuit dysfunction may be exacerbated by reduced functional connectivity in the basal ganglia in PD (Wu *et al.*, 2012), increased inhibitory output from the pons (part of the brainstem) suppressing output from the substantia nigra (Emir *et al.*, 2012) and abnormal firing patterns within the basal ganglia in PD (DeLong and Wichmann, 2009).

Figure 1-4. Indirect basal-ganglia-thalamocortical circuit

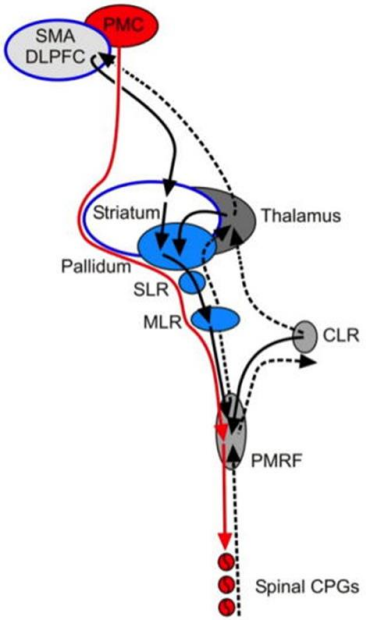


[Red arrows represent excitatory, blue arrows inhibitory and purple arrows modulatory projections. GPe, globus pallidus external portion; GPi, globas pallidus internal portion; SNpc, substantia nigra pars reticulate; STN, subthalamic nucleus.]

1.4.2 Compensatory mechanisms of gait control: alternative pathways

To compensate for the reduced activity of structures involved in automatic motor control of gait in PD, outlined in section 1.4.1, there is reasonable evidence that cerebellar activity increases (Wu and Hallett, 2013; Gilat *et al.*, 2017). This, in turn, encourages increased activity within a direct neural circuit involvement in movement, with signals projecting from the primary motor cortex straight to the spinal cord and rhythmic drive provided by the cerebellum (Bohnen and Jahn, 2013). This direct circuit bypasses the brainstem and basal ganglia (**Figure 1-5**) but might not allow for sufficient adaptation of gait to the environment.

Figure 1-5. Direct and indirect circuits of gait control, adapted from Bohnen, 2013



[The direct pathway (red) is thought to compensate for deficiencies in the indirect pathway (blue) in Parkinson's disease. CLR, cerebellar locomotor region; CPG, central pattern generator; DLPFC, dorsolateral prefrontal cortex; MLR, mesencephalic locomotor region; PMRF, pontomedullary reticular formation; PMC, primary motor cortex; SLR, subthalamic locomotor region; SMA: supplementary motor area.]

Similarly, there is a well-documented increase in activity in parietal-lateral motor pathways during movement in PD (Samuel *et al.*, 1997; Sabatini *et al.*, 2000), which is thought to compensate for underactive medial motor pathways. This again may be driven by increased cerebellar activity enabling greater integration of sensory information from the parietal cortex to inform motor outputs, whilst bypassing the ineffective basal-ganglia-thalamocortical circuit (Lewis *et al.*, 2013). Compensation through increased use of sensory information may begin to explain the effectiveness of cueing in PD (Spaulding *et al.*, 2013).

1.4.3 Compensatory mechanisms of gait control: increased cortical involvement

It has been hypothesised that impairment in the automatic control of gait in PD causes people with PD to rely more heavily on voluntary, conscious control of gait (Bohnen and Jahn, 2013; Wu *et al.*, 2015; Mc Ardle *et al.*, 2019). This implies increased reliance on cortical activity, particularly from the prefrontal cortex, as voluntary control of walking requires increased attention (Yogev-Seligmann *et al.*, 2008; Rossi *et al.*, 2009), a theory supported by recent neuroimaging studies using fNIRS (Stuart *et al.*, 2018).

There is a large body of evidence to support the role of cognition in gait that occurs in, but is not specific to, PD. This has been accumulated through correlational associations between gait and cognitive assessments in different clinical populations (Morris *et al.*, 2016), dual-task paradigms, which assess gait whilst a cognitive task is completed (Raffegeau *et al.*, 2019) and gait assessments in individuals with cognitive impairments (Mc Ardle *et al.*, 2017). In PD, attention and executive function have been most strongly related to gait pace; gait variability measures have been linked to global cognitive performance (Lord *et al.*, 2014; Morris *et al.*, 2016). Furthermore, early gait impairments in PD can be used as markers of cognitive decline over the first three years of disease (Morris *et al.*, 2017). These associations may be explained by gait and cognition sharing neural substrates (Leisman *et al.*, 2016).

The cortical cholinergic system is strongly related to cognitive ability (Muir, 1997; Müller and Bohnen, 2013; Bohnen *et al.*, 2015; Liu *et al.*, 2015; Ray *et al.*, 2017; Schulz *et al.*, 2018; Pereira *et al.*, 2020). Whilst most motor problems in PD are considered purely dopaminergic, gait is also thought to rely on cholinergic activity (Bohnen and Albin, 2011), as outlined in section 1.2.5. Although few studies have assessed the contribution of the cholinergic system to gait control in PD (Morris *et al.*, 2019a), there are several theories explaining its role in gait, including the increased attention required in PD gait, as outlined above, and the role of cholinergic interneurons within the striatum to modulate dopaminergic pathways (Lim *et al.*, 2014).

Section 1.3.1 discussed the aggregation of Lewy body pathology relatively early in PD within the NBM and PPN. The NBM and PPN innervate cortical and subcortical regions respectively, modulating neural activity via the neurotransmitter acetylcholine (ACh); the cholinergic system is therefore implicated in early PD. The PPN has been proposed to be more specifically involved in postural control during gait (Peterson and Horak, 2016; Morris *et al.*, 2019a), whereas the NBM may be associated with discrete gait measures, such as step velocity and characteristics of variability, as supported through neuroimaging (Bohnen *et al.*,

2013; Müller *et al.*, 2015). However, the more precise relationship between the cholinergic system and discrete characteristics of gait is yet to be thoroughly examined.

It is thought that PD gait requires additional cortical input in comparison to typical healthy gait, which may be achieved through cognitive and/or cortical cholinergic involvement in gait via one or several "non-motor networks" of gait control. However, it is unclear whether discrete gait characteristics are differently reliant on this cortical involvement. This is fundamental for us to understand so that the best therapeutic targets for discrete gait impairments can be discerned. It has been suggested that the compensatory mechanism of increased voluntary gait control may explain increases in gait variability in PD (Peterson and Horak, 2016), given that conscious control of tasks that are considered overlearned increases the variability in performance (Wulf, 2007). However, as associations have also been made between gait pace and cortical cholinergic activity (Rochester *et al.*, 2012; Bohnen *et al.*, 2013), it is expected that an increased cortical involvement in PD gait will affect several gait characteristics, not merely those related to gait variability.

In summary, the neural structures relied upon for automatic movements may be compromised in PD and so compensatory mechanisms may be more heavily relied upon. These may include wider "motor networks", utilising cerebellar inputs or the integration of sensory information for motor-related outputs. Additionally, "non-motor networks" may be more readily utilised in PD, which may include cognitive inputs (potentially through cholinergic activity). However, the relation of these compensatory mechanisms to discrete gait characteristics is not well understood.

1.5 The imaging techniques used to understand neural correlates of gait

To advance understanding of the neural control of discrete gait characteristics, associations between brain imaging parameters and these characteristics should be completed. A major challenge in understanding the neural underpinnings of gait in people with PD is that imaging the brain during gait in real-time is not easily achieved. Several approaches have been developed to address this limitation, such as fNIRS and EEG. However, these techniques can only measure superficial cortical activity, are indirect measures, can be subject to artefacts and lack spatial resolution, so cannot accurately measure responses at the neuronal or subcortical level.

Task-based fMRI protocols allow for functional imaging of cortical and subcortical structures during tasks designed to replicate gait. A variety of approaches have been taken, including

imagined gait (Peterson *et al.*, 2014a) and virtual reality stimuli motor tasks with the use of foot pedals (Gilat *et al.*, 2017). However, it has been recently highlighted that different methodologies and analyses likely cause different responses from neural networks, currently limiting overall interpretation from studies of this nature (Mirelman *et al.*, 2019).

An alternative approach to understanding the neural substrates of gait is to adopt study designs that indirectly explore the relationships between gait and different brain imaging parameters, typically assessed using a range of neuroimaging techniques including MRI, fMRI, DTI, PET and transcranial magnetic stimulation (TMS) coupled with nerve stimulation (Tokimura *et al.*, 2000). These techniques can be used to analyse the brain on global and regional levels, aiding understanding of the general imaging parameters associated with gait as well as the more specific brain areas and functions linked to different aspects of gait control. The neural underpinnings of discrete gait characteristics can be assessed through correlational analysis between gait characteristics and imaging parameters measured separately (Bohnen *et al.*, 2013; Verlinden *et al.*, 2016; Fling *et al.*, 2018). However, correlational analyses such as these are more commonly achieved through a comparison of brain images between groups of PD participants with and without an overall "clinical symptom" of gait impairment, such as people with PD with and without FOG (Gilat *et al.*, 2018) and those with the PIGD or tremor dominant PD subtypes (Rosenberg-Katz K, 2016), as highlighted in two recent reviews which discuss neural correlates of gait in PD (Allali *et al.*, 2018; Mirelman *et al.*, 2019). These analyses do not allow for the investigation of gait characteristics which may more sensitively reflect different pathologies.

Overall, the neural control of walking in PD is not well understood. It is still an emerging area of work, mainly due to recent advances in the understanding of gait as well as the development of a wide array of neuroimaging techniques. This thesis aims to provide a better understanding of this area of research, as detailed in section 1.6.

1.6 Thesis outline, aims and hypotheses

This thesis was designed to identify the neural correlates of gait in early PD, by exploring the cross-sectional and longitudinal associations between regional brain volumes and discrete gait characteristics. While cross-sectional studies provide interesting insights, longitudinal studies are needed to fully understand the neural mechanisms contributing to early gait decline, in turn identifying potential novel imaging markers that could be used to monitor and predict gait decline in PD. Structural magnetic resonance imaging has been utilised throughout as it offers a non-invasive, replicable and relatively cost-effective means for brain imaging. Also, thorough investigations of the discrete brain structures associated with discrete gait characteristics can be used to inform future network-based analyses, so that particular networks of interest may be identified and used to develop a more complete model of the neural control of gait. The significance of this body of work has been highlighted throughout this first chapter. This thesis is split into an additional seven chapters as outlined below. More specific hypotheses are included within each chapter as appropriate.

1.6.1 Chapter 2: The neural correlates of discrete gait characteristics in ageing and Parkinson's disease

This chapter provides a comprehensive summary of the work to date that has investigated associations between discrete gait characteristics and brain imaging parameters. This was completed so that a clear understanding of current associations in the literature could be used to further inform this thesis. The chapter is split into two sections, as described below.

Section 1: The neural correlates of discrete gait characteristics in ageing: A structured review

The first section of chapter 2 consists of a published structured review which examines the cross-sectional and longitudinal associations between gait characteristics and brain imaging parameters in healthy older adults. As this review provides a summary of the literature relating to healthy ageing, direct comparisons can be made between findings from this chapter and subsequent chapters, to help to tease apart the effects of disease, rather than the typical ageing process, on the neural underpinnings of PD gait.

Aims:

- Explore associations between discrete gait characteristics and brain structure and/or function in older adults, as identified through neuroimaging
- Explore the longitudinal relationship between changes in gait and anatomical or functional imaging correlates
- Identify recommendations for future areas of research

Hypothesis:

- Independent gait characteristics will reflect discrete regional brain structure and functional brain activity in older adults

Section 2: Associations between discrete gait characteristics and imaging parameters in PD

This second section of chapter 2 provides an overview of the literature concerning associations between gait characteristics and brain imaging parameters in Parkinson's disease. Compared to literature pertaining to healthy ageing, relatively less research has focussed on the neural correlates of gait in PD. Fewer restrictions on both neuroimaging parameters and methods of gait assessment were therefore implemented when assessing the literature in PD, to enable a broader understanding of neural underpinnings of PD gait. As this overview provides a summary of the literature relating to PD, direct comparisons can be made between findings from this chapter and subsequent chapters.

Aim:

- Explore associations between discrete gait characteristics and brain structure and/or function in PD, as identified through neuroimaging

Hypotheses:

- Independent gait characteristics will reflect discrete regional brain structure and functional brain activity in PD
- The pattern of associations will be different to those identified in healthy ageing

1.6.2 Chapter 3: General Methods – the ICICLE-PD and ICICLE-GAIT studies

This chapter gives an overview of the ICICLE-PD and ICICLE-GAIT studies which form the basis of this thesis. Descriptions of participant recruitment and the clinical, gait and imaging assessments completed through these studies are provided, and statistical analyses that are applicable to all subsequent chapters are detailed. Further methodology is provided in other chapters as appropriate.

1.6.3 Chapter 4: Gait progression over six years in Parkinson's disease: effects of age, medication and pathology

This chapter investigates the discrete gait characteristics that change over six years in early PD and determines whether changes are due to PD progression, ageing or a combination of both. This has been completed for the identification of gait characteristics that are most reflective of evolving PD pathology, so are of most interest when considering neural mechanisms contributing to early gait decline. Linear mixed effects analyses examine the gait characteristics which significantly change over time in PD and age-matched control cohorts, and the characteristics for which change is associated with dopaminergic medication change. This chapter concludes by comparing findings to established changes in gait over three years and highlighting the gait characteristics that will be used in subsequent longitudinal analyses.

Aims:

- Identify gait characteristics that significantly change over six years in newly diagnosed PD and healthy age-matched controls
- Evaluate gait changes in the PD cohort which related to ageing and/or disease progression, by comparing rates of gait change between PD and control groups
- Explore the relationship between gait changes and changes in dopaminergic medication dose in early PD

Hypotheses:

- The same characteristics that are known to change over the first three years of PD will also be identified as changing over this longer timeframe
- Additional characteristics will demonstrate significant change over six years that are specific to the PD cohort
- Change in selective gait characteristics will be associated with changes in dopaminergic medication

1.6.4 Chapter 5: The cortical grey matter volumes associated with PD gait: a global & regional perspective

This chapter examines the cross-sectional and longitudinal associations between discrete gait characteristics and cortical thickness. Vertex-wise general linear models assess differences in cortical thickness between PD and age-matched control participants. Two approaches have been adopted within cross-sectional and longitudinal analyses of correlations between imaging and gait parameters; data-driven approaches (utilising vertex-wise general linear models) allow for objective measures of the entire cortex whereas hypothesis driven approaches (using regression and linear mixed effect analyses) enable the investigation of specified cortical regions of interest without requiring the use of strict multiple comparison corrections. Findings are then related back to current knowledge of the associations between the cortex and gait in PD.

Aims:

- Determine differences in cortical thickness between early PD and age-matched control participants
- Explore the cross-sectional associations between cortical thickness and gait characteristics as assessed soon after PD diagnosis
- Assess cortical thickness as a predictor of changes in gait that occur as a result of PD progression

Hypotheses:

- Stronger cross-sectional associations between gait and cortical thickness will occur in PD compared to controls
- Cross-sectional associations between gait and cortical thickness of areas linked to sensory and cognitive functions will occur more commonly in PD, whereas associations with areas linked to motor areas will occur more commonly in controls
- Cortical thickness of areas linked to both motor and non-motor functions will predict PD-specific gait decline
- Characteristics from different gait domains will differently associate with the cortical thickness of areas linked to motor and non-motor functions

1.6.5 Chapter 6: The subcortical volumes associated with PD gait

This chapter examines the cross-sectional and longitudinal associations between discrete gait characteristics and subcortical volumes. Firstly, univariate analyses compare subcortical volumes between PD and healthy control participants. Next, correlation and regression analyses assess cross-sectional associations between gait characteristics and subcortical volumes soon after PD diagnosis. Subcortical volumes are then investigated as predictors of PD-specific gait change. Findings are then related back to current knowledge of the subcortical mechanisms underlying gait in PD.

Aims:

- Determine differences in subcortical and limbic volumes in early PD compared to healthy controls
- Explore the cross-sectional associations between subcortical volumes and gait characteristics as assessed soon after PD diagnosis
- Identify whether subcortical volumes are able to predict PD specific changes in gait

Hypotheses:

- Cross-sectional associations between gait and subcortical volumes of areas related to automatic motor functions will occur more commonly in controls compared to PD
- Cross-sectional associations between gait and subcortical volumes of areas involved in compensatory mechanisms and/or non-motor functions will occur more commonly in PD compared to controls
- Subcortical volumes linked to motor and non-motor networks will predict PD-specific gait decline
- Characteristics from different gait domains will differently associate with the volumes of subcortical areas linked to motor and non-motor functions

1.6.6 Chapter 7: Involvement of the cortical cholinergic system with gait: an assessment of cholinergic basal forebrain sub-regional volumes

This chapter examines the cross-sectional and longitudinal associations between discrete gait characteristics and volumes of substructures of the cholinergic basal forebrain (cBF). Firstly, group differences in basal forebrain sub-regional volumes are assessed univariately. Correlational analyses next assess cross-sectional associations between gait characteristics and sub-regional basal forebrain volumes. Regional basal forebrain volumes are then investigated as predictors of PD-specific gait change. Findings are finally related back to current knowledge of the involvement of the cholinergic system in PD gait.

Aims:

- Determine differences in sub-regional cholinergic basal forebrain volumes between PD and age-matched controls
- Explore the cross-sectional associations between cholinergic sub-regional basal forebrain volumes and gait
- Assess the ability of sub-regional basal forebrain volumes to predict Parkinson's disease specific progression of gait impairments

Hypotheses:

- Sub-regional cBF volumes will show stronger associations with gait in PD rather than controls
- NBM volume will be the sub-regional volume of the cholinergic basal forebrain most strongly related to gait function in PD
- Characteristics from the pace and variability domains of gait will most strongly relate to cholinergic basal forebrain volumes
- Step length will show a discrete association with the sub-regional volume of the cholinergic basal forebrain which provides cholinergic input to the hippocampus

1.6.7 Chapter 8: Discussion and thesis summary

Chapter 8, the final section of this thesis, provides an overall summary of findings from all chapters. This chapter also highlights the clinical implications of this thesis and provides an overview of limitations of the thesis and directions for future research.

Chapter 2: The neural correlates of discrete gait characteristics in ageing and Parkinson's disease

As outlined in chapter one, understanding the mechanisms of gait is crucial to ultimately improve the health status of people with PD, yet the precise nature of the neural control of gait is currently unclear. Recent literature has recognised associations between gait and the brain, through brain imaging, and have explored associations between the two through both cross-sectional and longitudinal study designs. To further understand the neural underpinnings of gait, and how these may differ in PD compared to typical ageing, an overview of the literature assessing neural correlates of gait has been completed in both healthy older adult (section 1) and PD (section 2) populations.

Section 1: The neural correlates of discrete gait characteristics in ageing: a structured review*

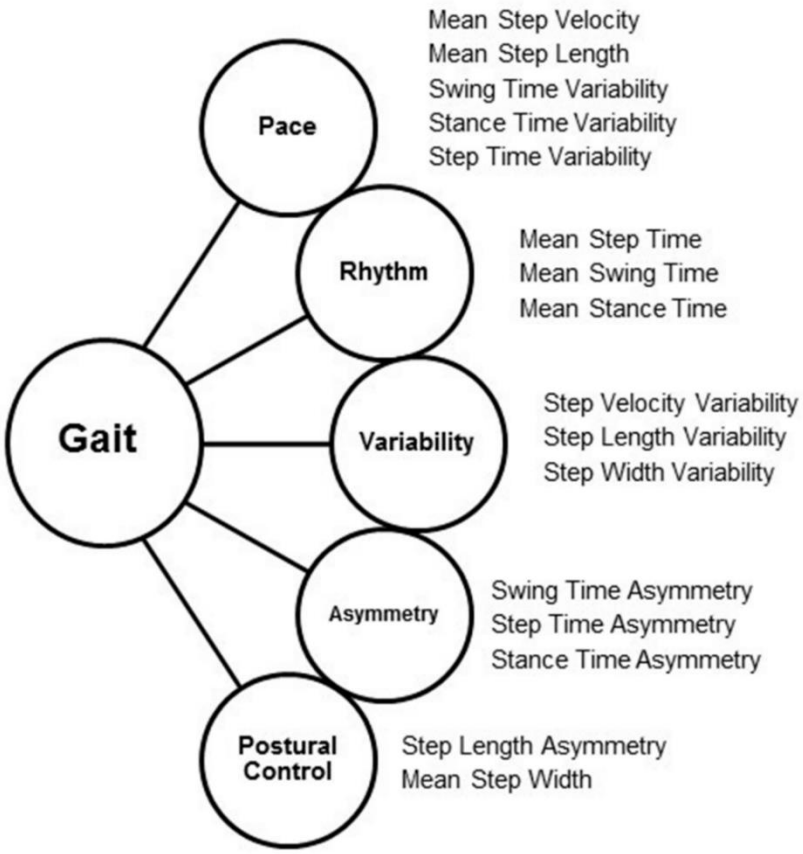
2.1 Introduction

The precise brain regions and neural processes or networks linked to discrete characteristics of gait control are not well defined. This lack of clarity causes difficulty in discerning whether individual neural regions or networks should be targeted in a different manner when aiming to improve gait impairments. To date, no group has taken a structured approach to comprehensively map the neural correlates of gait to a full robust gait model. The purpose of this review was to assess the global and regional neural correlates of gait in ageing, taking a detailed and complete approach. A matrix of associations between individual brain imaging parameters and gait characteristics was formed, so that the discrete nature of gait control may be better understood. The gait characteristics considered in this review are from the model of gait derived by Lord and colleagues in older adults (grouped into their appropriate gait domain (Lord *et al.*, 2013c)(**Figure 2-1**)), which has been adopted here as the most comprehensive model for simple gait, providing a framework for rationalising and interpreting study findings. In addition to cross-sectional studies, longitudinal study types which focus on healthy older adults are included, so that the effects of typical ageing on neural gait correlates may be identified. Additionally, the effects of cognitive test scores, which assess higher order brain functions such as attention and memory, on neural gait correlates identified in individual studies are outlined. This will help determine whether any neural pathways or regions are shared between gait and cognition, as suggested in Chapter 1.

The specific aims of this review are to: i) explore associations between discrete gait characteristics and brain structure and/or function in older adults, as identified through neuroimaging; ii) explore the longitudinal relationship between changes in gait and anatomical or functional imaging correlates, and; iii) identify recommendations for future areas of research. It is hypothesised that independent gait characteristics will reflect discrete regional brain structure and functional brain activity in older adults. This review will provide a clear representation of the current literature, provide a map of the neural correlates of gait control and highlight gaps for future research.

*This section has been published in Neuroscience and Biobehavioural Reviews

Figure 2-1. The model of gait developed by Lord et al. for older adults



[16 gait characteristics map to 5 gait domains; Pace, Rhythm, Variability, Asymmetry and Postural Control]

2.2 Methods

2.2.1 Search Strategy

Three databases were used for the search: Medline, PsycInfo and Scopus. Search terms relating to gait, neuroimaging and older adults were included within each search; where possible, age limits and medical subject headings (MESH) were used. The search was limited to full journal articles only, written in the English language between 1990 and April 2018. Boolean operators were utilised in the search; "OR" was included between search terms within each section, whereas "AND" was included between the sections within each database. **Table 2-1** includes the search terms used for each search.

Table 2-1. Search terms used for the searches performed within each of the databases

	Medline	PsycInfo	Scopus
Gait	**MESH headings**: Gait; Walking; Locomotion **Key words:** Speed*; Velocity*; Step*; Stride*; Rhythm; Pace; Variability; Symmetry; Asymmetry; Swing; Dual task*; Stance; Ambul*	**MESH headings**: Gait; Walking; Locomotion **Key words**: Speed; Velocity; Step*; Stride*; Rhythm; Pace; Variability; Symmetry; Asymmetry; Swing; Dual task*; Stance; Ambulation; Ambulate; Ambulatory; Ambulating	**Key words:** Gait OR; Walk* OR; Locomotion OR; Speed OR; Velocity OR; Step* OR; Stride* OR; Rhythm OR; Pace OR; Variability OR; Symmetry OR; Asymmetry OR; Swing OR; Dual task* OR; Single support* OR; Double support* OR; Double limb OR; Stance OR; Ambul*
Neuroimaging	**MESH headings**: Neuroimaging; Tomography; Electroencephalography; Evoked potentials; Spectroscopy, Near-Infrared **Key words:** SPECT; MRI; Magnetic resonance*; Neural network*; Resting state; DTI; Connectivity; fMRI; sMRI; PET; CT; VBM; Voxel based morphometry; EEG; fNIRS; FLAIR; Fluid-attenuated inversion recovery; DaTSCAN; Dopaminergic imaging	**MESH headings:** Spectroscopy; Neural networks; Brain Connectivity; Neuroimaging; Tomography; Electroencephalography; Evoked potentials **Key words:** fMRI; sMRI; MRI; Magnetic resonance*; Resting state; DTI; Functional Neuroimaging; Brain Mapping; Connectome; SPECT; PET; CT; VBM; Voxel based morphometry; EEG; fNIRS; functional near infra-red spectroscopy; FLAIR; Fluid-attenuated inversion recovery; DaTSCAN; Dopaminergic imaging	**Key words:** Magnetic Resonance* OR; MRI OR; Neural network* OR; Resting state OR; Diffusion tensor imaging OR; DTI OR; Connectivity OR; fMRI OR; sMRI OR; Neuroimaging OR; Neuroradiography OR; Functional Neuroimaging OR; Brain Mapping OR; Connectome OR; Tomography OR; Computed tomography OR; Single Photon Emission Computed Tomography OR; Positron Emission Tomography OR; SPECT OR; PET OR; CT OR; Susceptibility weighted imaging OR; Optical tomography OR; Diffuse optical tomography OR; VBM OR; Voxel based morphometry OR; EEG OR; Electroencephalography OR; Evoked potential OR; Event related potential OR; fNIRS OR; functional near infra-red OR; spectroscopy OR; FLAIR OR; Fluid-attenuated inversion recovery OR; DaTSCAN OR; Dopaminergic imaging OR; Arterial spin labelling
Old age	"All aged" limit set	"Aged" limit set	**Key words:** Old*; Aged; Ageing; Elderly; Senior*

[All searches contained terms from the imaging, gait and age categories.]

2.2.2 Inclusion and Exclusion Criteria

Articles were included if they assessed gait in healthy older adults under single task conditions and used at least one brain imaging technique. As the focus of this review was to look specifically at quantitative gait characteristics, complex paradigms which involved standing or turning, such as the Timed Up and Go task, were excluded, as were protocols which made use of imagined gait. Additionally, walks performed under dual-task conditions (which involve a secondary task being completed whilst walking) were not considered, as the methodologies of these dual-task paradigms greatly vary and may cause different impairments in gait (Beurskens *et al.*, 2014; Doi *et al.*, 2017), the details of which are not well explored and are beyond the scope of this review. Articles involving animal models, case studies, intervention studies, clinical trials or only nerve or brain stimulation were excluded, as were those that only assessed falls, freezing of gait or general physical activity.

2.2.3 Data Extraction

Once duplicates were removed, one reviewer (Joanna Wilson) screened the titles from the initial search, and two reviewers (Joanna Wilson and Liesl Allcock) independently screened the abstracts to identify potential articles. The full-text of articles was retrieved if reviewers were unable to determine the eligibility of the study from the title and abstract alone. All full-length articles were assessed by three reviewers (Joanna Wilson, Liesl Allcock and Ríona McArdle). Data extraction forms were completed, which included information about population characteristics, whether the study was cross-sectional or longitudinal, the study inclusion and exclusion criteria, the gait analysis technique and variables measured, the imaging technique and variables measured, the statistical tools used and the main study findings. A quality assessment was conducted separately by two reviewers (Joanna Wilson and Ríona McArdle) and overall quality scores were determined for each study.

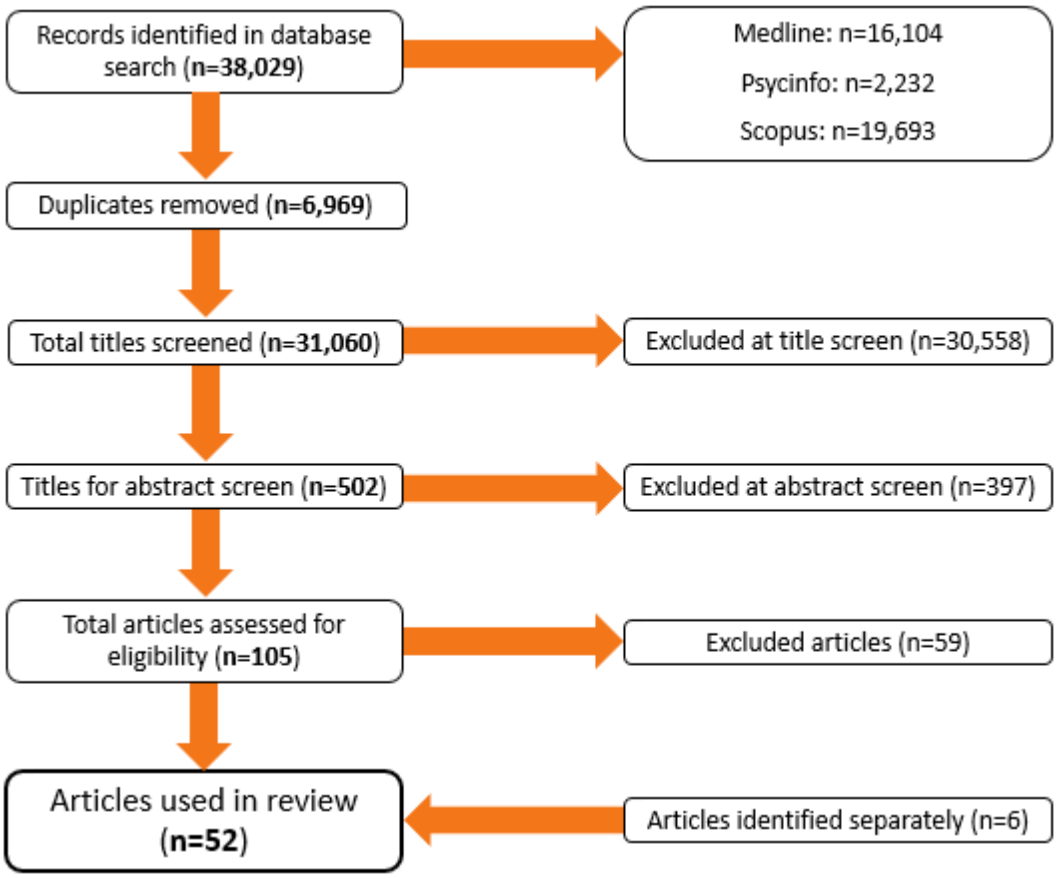
2.3 Results

2.3.1 Search Yield

The search yield is shown in **Figure 2-2**. The search, completed on 04.04.2018, generated a total of 38,029 studies after search limits were applied. Once duplicates were removed, a total of 31,060 studies were yielded from the search. After the initial title screen, 502 studies were identified as being of interest; 105 studies were then eligible for data extraction after abstract screening. 59 studies were excluded during data extraction, as only dual-task gait was assessed (n=4); only the timed up and go task was completed (n=2); the gait assessment involved a turn (n=3); the gait measurement tool was not described (n=1); derived gait

measures were unsuitable (n=21); the paper and data were inaccessible (n=2); the image analysis undertaken only involved brain or nerve stimulation (n=1); the age range investigated was inappropriate (n=3); the type of article was unsuitable (n=2); only results relating to disease cohorts were presented (n=11); only results representing group comparisons were presented (n=1); the direction of association between the variables was not specified (n=1) and there was no direct link between the two variables of interest (n=7). Six additional studies have been identified outside of the search strategy since the search closed. Therefore, 52 studies are included in this review. Publication dates range from 1997 to 2018.

Figure 2-2. Prisma diagram demonstrating the search yield for the structured review



2.3.2 Brain imaging and gait assessments - methodological comparisons

Six imaging modalities were described in the studies included in this review. The majority of studies used structural magnetic resonance imaging (MRI) for brain imaging; 33 studies used structural MRI as the only imaging technique (Rosano *et al.*, 2005a; Rosano *et al.*, 2005b; Wolfson *et al.*, 2005; Rosano *et al.*, 2007; Baezner *et al.*, 2008; Rosano *et al.*, 2008; Nadkarni

et al., 2009; Novak *et al.*, 2009; Soumaré *et al.*, 2009; Murray *et al.*, 2010; de Laat *et al.*, 2011b; Ryberg *et al.*, 2011; Sorond *et al.*, 2011; Choi *et al.*, 2012; de Laat *et al.*, 2012; Dumurgier *et al.*, 2012; Frederiksen *et al.*, 2012; Manor *et al.*, 2012; Moscufo *et al.*, 2012; Callisaya *et al.*, 2013; Willey *et al.*, 2013; Wolfson *et al.*, 2013; Annweiler *et al.*, 2014; Beauchet *et al.*, 2014; Bolandzadeh *et al.*, 2014; Callisaya *et al.*, 2014; Nadkarni *et al.*, 2014; Beauchet *et al.*, 2015; Ezzati *et al.*, 2015; Rosario *et al.*, 2016; Stijntjes *et al.*, 2016; Beauchet *et al.*, 2017), five studies used both structural MRI and diffusion tensor imaging (DTI) techniques (Della Nave *et al.*, 2007; de Laat *et al.*, 2011a; de Laat *et al.*, 2011c; Rosso *et al.*, 2014; van der Holst *et al.*, 2018) and one study combined the use of structural MRI with magnetic resonance spectroscopy (MRS) (Zimmerman *et al.*, 2009). Four studies used imaging parameters derived from DTI images only (Bruijn *et al.*, 2014; Fling *et al.*, 2016; Verlinden *et al.*, 2016; Fling *et al.*, 2018), one study used functional MRI (Yuan *et al.*, 2015), positron emission tomography (PET) was used in seven studies (Shimada *et al.*, 2013; Sakurai *et al.*, 2014; Del Campo *et al.*, 2016; Nadkarni *et al.*, 2017; Sakurai *et al.*, 2017; Tian *et al.*, 2017a; Wennberg *et al.*, 2017a) and functional near infrared spectroscopy (fNIRS) used in one study (Holtzer *et al.*, 2015).

Eight different quantitative gait measurement techniques were reported. Twenty-seven studies reported the use of gait walkway systems (Rosano *et al.*, 2005a; Rosano *et al.*, 2008; Nadkarni *et al.*, 2009; Zimmerman *et al.*, 2009; Murray *et al.*, 2010; de Laat *et al.*, 2011a; de Laat *et al.*, 2011b; de Laat *et al.*, 2011c; Choi *et al.*, 2012; de Laat *et al.*, 2012; Callisaya *et al.*, 2013; Annweiler *et al.*, 2014; Bolandzadeh *et al.*, 2014; Callisaya *et al.*, 2014; Nadkarni *et al.*, 2014; Rosso *et al.*, 2014; Beauchet *et al.*, 2015; Ezzati *et al.*, 2015; Holtzer *et al.*, 2015; Yuan *et al.*, 2015; Rosario *et al.*, 2016; Verlinden *et al.*, 2016; Beauchet *et al.*, 2017; Wennberg *et al.*, 2017a; Fling *et al.*, 2018; van der Holst *et al.*, 2018), one study used both a gait walkway and inertial sensors to measure different gait characteristics (Fling *et al.*, 2016), two studies utilised two photoelectric cells connected to a chronometer (Soumaré *et al.*, 2009; Dumurgier *et al.*, 2012), footswitches were used in two studies (Manor *et al.*, 2012; Beauchet *et al.*, 2014), an accelerometer was described in one study (Stijntjes *et al.*, 2016), one study made use of a treadmill (Shimada *et al.*, 2013), one study described the use of reflective markers with a motion analysis system during treadmill walking (Bruijn *et al.*, 2014) and 17 studies derived gait characteristics from timed walks (Rosano *et al.*, 2005b; Wolfson *et al.*, 2005; Della Nave *et al.*, 2007; Rosano *et al.*, 2007; Baezner *et al.*, 2008; Novak *et al.*, 2009; Ryberg *et al.*, 2011; Sorond *et al.*, 2011; Frederiksen *et al.*, 2012; Moscufo *et al.*, 2012; Willey *et al.*, 2013; Wolfson *et al.*, 2013; Sakurai *et al.*, 2014; Del Campo *et al.*, 2016;

Nadkarni *et al.*, 2017; Sakurai *et al.*, 2017; Tian *et al.*, 2017a). Gait characteristics relating to intraindividual variability were derived either as the standard deviation of the variability within the original measurement (Zimmerman *et al.*, 2009; Verlinden *et al.*, 2016) or as a coefficient of variance of the measurement (Rosano *et al.*, 2008; de Laat *et al.*, 2011c; Manor *et al.*, 2012; Shimada *et al.*, 2013; Annweiler *et al.*, 2014; Beauchet *et al.*, 2014; Rosso *et al.*, 2014; Beauchet *et al.*, 2015; Beauchet *et al.*, 2017; Wennberg *et al.*, 2017a).

2.3.3 Associations between brain structure and function and gait characteristics

Associations between quantitative gait characteristics and structural and functional imaging parameters were explored. In order to examine the wide variety of gait characteristics assessed, all gait characteristics included within studies were mapped onto the five domains of gait outlined in Lord et al.'s gait model (Lord *et al.*, 2013c). Studies assessing either steps or strides were considered and grouped together for the purposes of this review. Imaging parameters were also grouped by the imaging technique used for an effective interpretation of results. Imaging parameters derived from structural MRI were divided in to two groups, those assessing brain volumes and those investigating white matter changes that are common in ageing. Where possible, the specific brain regions in which associations were made have been reported, as well as any covariates included in statistical analyses.

47 studies described cross-sectional associations between gait and brain imaging parameters (Rosano *et al.*, 2005a; Rosano *et al.*, 2005b; Della Nave *et al.*, 2007; Rosano *et al.*, 2007; Baezner *et al.*, 2008; Rosano *et al.*, 2008; Nadkarni *et al.*, 2009; Novak *et al.*, 2009; Soumaré *et al.*, 2009; Zimmerman *et al.*, 2009; Murray *et al.*, 2010; de Laat *et al.*, 2011a; de Laat *et al.*, 2011b; de Laat *et al.*, 2011c; Sorond *et al.*, 2011; Choi *et al.*, 2012; de Laat *et al.*, 2012; Dumurgier *et al.*, 2012; Manor *et al.*, 2012; Moscufo *et al.*, 2012; Shimada *et al.*, 2013; Willey *et al.*, 2013; Wolfson *et al.*, 2013; Annweiler *et al.*, 2014; Beauchet *et al.*, 2014; Bolandzadeh *et al.*, 2014; Bruijn *et al.*, 2014; Callisaya *et al.*, 2014; Nadkarni *et al.*, 2014; Rosso *et al.*, 2014; Sakurai *et al.*, 2014; Beauchet *et al.*, 2015; Ezzati *et al.*, 2015; Holtzer *et al.*, 2015; Yuan *et al.*, 2015; Del Campo *et al.*, 2016; Fling *et al.*, 2016; Rosario *et al.*, 2016; Stijntjes *et al.*, 2016; Verlinden *et al.*, 2016; Beauchet *et al.*, 2017; Nadkarni *et al.*, 2017; Sakurai *et al.*, 2017; Tian *et al.*, 2017a; Wennberg *et al.*, 2017a; Fling *et al.*, 2018). **Figure 2-3** summarises the number of studies comparing each gait characteristic to each imaging parameter; detailed descriptions of each cross-sectional study are included in **Appendix A**.

Eleven studies described longitudinal associations between gait and brain imaging parameters (Rosano *et al.*, 2005b; Wolfson *et al.*, 2005; Soumaré *et al.*, 2009; Ryberg *et al.*, 2011; Frederiksen *et al.*, 2012; Moscufo *et al.*, 2012; Callisaya *et al.*, 2013; Willey *et al.*, 2013; Wolfson *et al.*, 2013; Tian *et al.*, 2017a; van der Holst *et al.*, 2018). **Figure 2-4** summarises the number of studies comparing each gait characteristic to each gait parameter; more detailed descriptions of each cross-sectional study are included in **Appendix B**.

As anticipated, gait velocity was the gait characteristic most commonly assessed. Several characteristics of gait are yet to be associated with any brain imaging parameters, including gait speed variability, swing time asymmetry and stance time asymmetry. Only four gait characteristics, from three gait domains, have been assessed longitudinally; gait velocity, step length, cadence and step width. Gait velocity was the only characteristic considered longitudinally in all studies. Step width, from the postural control domain, was assessed in only one study, and was not associated with any imaging parameter longitudinally (Callisaya *et al.*, 2013).

Figure 2-3. Heat map of the cross-sectional studies assessing each imaging and gait parameter

	Imaging technique	MRI - volumetric analysis				MRI – white matter changes			DTI				PET		fNIRS	MRS	fMRI
Gait domains	Parameters	Grey matter volume	White matter volume	Total brain volume	Ventricular volume	WMH presence	Infarct presence	MB presence	FA	MD	RD	AD	Aβ burden	Glucose uptake	HbO_2 change	NAA/ Cr ratio	Functional connectivity
Pace	Gait velocity	11	5	3	3	16	4	3	5	4	2	2	4	2	1	-	1
	Step length	4	1	1	1	3	2	2	2	3	1	1	1	2	1	1	-
	Step time variability	4	1	1	1	-	-	-	1	1	-	-	-	-	-	-	-
	Swing time variability	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Stance time variability	-	-	-	-	1	1	-	-	-	-	-	1	-	-	-	-
Rhythm	Double support time	2	-	1	1	1	2	2	1	1	-	-	1	-	-	-	-
	Cadence	2	1	1	-	2	1	2	2	2	1	1	1	2	-	-	-
	Swing time	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-
	Single support phase	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-
	Step time	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Variability	Step length variability	1	-	1	-	2	1	-	2	3	-	-	-	1	-	1	-
	Step width variability	1	-	1	-	1	1	-	1	1	-	-	-	-	-	-	-
	Gait speed variability	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Asymmetry	Swing time asymmetry	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Stance time asymmetry	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Step time asymmetry	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-
Postural control	Step width	3	-	1	-	2	1	2	4	2	1	1	-	-	-	-	-
	Step length asymmetry	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-

Figure 2-4. Heat map of the longitudinal studies assessing each imaging and gait parameter

	Imaging technique	MRI - volumetric analysis				MRI – white matter changes			DTI				PET
Gait domain	Parameters	Grey matter volume	White matter volume	CSF volume	Ventricle volume	WMH presence	Infarct presence	Microbleed presence	FA	MD	RD	AD	Aβ burden
Pace	Gait velocity	2	5	1	1	7	2	1	1	1	1	1	1
	Step length	2	2	-	-	2	1	1	1	1	1	1	-
Rhythm	Cadence	2	2	-	-	2	1	1	1	1	1	1	-
Postural Control	Step width	1	1	-	-	1	-	-	-	-	-	-	-

2.3.3.1 MRI – volumetric analysis

2.3.3.1.1 Cross-sectional associations from volumetric analysis

Measurements of brain volume were the most commonly derived brain imaging parameters; 21 studies evaluated associations between brain volumes and gait characteristics (Rosano *et al.*, 2005a; Rosano *et al.*, 2005b; Della Nave *et al.*, 2007; Rosano *et al.*, 2007; Rosano *et al.*, 2008; Novak *et al.*, 2009; Zimmerman *et al.*, 2009; de Laat *et al.*, 2011c; Sorond *et al.*, 2011; de Laat *et al.*, 2012; Dumurgier *et al.*, 2012; Manor *et al.*, 2012; Annweiler *et al.*, 2014; Beauchet *et al.*, 2014; Callisaya *et al.*, 2014; Nadkarni *et al.*, 2014; Rosso *et al.*, 2014; Beauchet *et al.*, 2015; Ezzati *et al.*, 2015; Stijntjes *et al.*, 2016; Beauchet *et al.*, 2017).

Grey matter volume

Grey matter (GM) volume was the most widely evaluated volume type, with 16 studies taking measures of grey matter atrophy (Rosso *et al.*, 2014), cortical thickness as a proxy for grey matter volume (de Laat *et al.*, 2012), or total (Della Nave *et al.*, 2007; Manor *et al.*, 2012; Callisaya *et al.*, 2014), cortical (Ezzati *et al.*, 2015; Stijntjes *et al.*, 2016) or regional (Rosano *et al.*, 2007; Rosano *et al.*, 2008; Novak *et al.*, 2009; Zimmerman *et al.*, 2009; Dumurgier *et al.*, 2012; Manor *et al.*, 2012; Beauchet *et al.*, 2014; Nadkarni *et al.*, 2014; Beauchet *et al.*, 2015; Ezzati *et al.*, 2015; Stijntjes *et al.*, 2016; Beauchet *et al.*, 2017) GM volumes. Grey matter regions were identified either through manual region of interest identification or automated processes.

Pace

Fifteen of these studies assessed characteristics within the pace domain of gait. Eight of eleven studies assessing gait velocity found that slower gait was associated with reduced GM volume (Rosano *et al.*, 2007; Novak *et al.*, 2009; de Laat *et al.*, 2012; Dumurgier *et al.*, 2012; Callisaya *et al.*, 2014; Nadkarni *et al.*, 2014; Ezzati *et al.*, 2015; Stijntjes *et al.*, 2016). This association was made across many brain regions. Slower gait was associated with reduced global GM volume (Callisaya *et al.*, 2014; Ezzati *et al.*, 2015), reduced frontal grey matter (Rosano *et al.*, 2007; Novak *et al.*, 2009; Callisaya *et al.*, 2014), reduced grey matter in the occipital cortex (Callisaya *et al.*, 2014), reduced hippocampal volume (Ezzati *et al.*, 2015; Stijntjes *et al.*, 2016) and, in the only study to assess cortical thickness, with cortical thinning in all regions except for the inferior temporal gyrus (de Laat *et al.*, 2012). Subcortically, slower gait was associated with cerebellar atrophy (Rosano *et al.*, 2007; Callisaya *et al.*, 2014; Nadkarni *et al.*, 2014) and reduced basal ganglia volume (Dumurgier *et al.*, 2012; Callisaya *et al.*, 2014). Reduced step length was also associated with reduced grey matter in all four studies assessing both parameters (Rosano *et al.*, 2008; Zimmerman *et al.*, 2009; de Laat *et al.*, 2012; Callisaya *et al.*, 2014). The association was again made with many brain regions, including global GM volume (Callisaya *et al.*, 2014), hippocampal volume (Zimmerman *et al.*, 2009) and prefrontal, parietal, supplementary motor, sensorimotor, occipital and limbic regional volumes (Rosano *et al.*, 2008; de Laat *et al.*, 2012). The relationship between step time variability and GM volume is less clear. Three of the four studies assessing this relationship used similar datasets; whilst greater step time variability was associated with increased hippocampal volume (Beauchet *et al.*, 2015) and reduced GM volume of the right parietal lobe (Beauchet *et al.*, 2014) in two papers, no association was made between step time variability and hippocampal or sensory cortex volume in the third (Beauchet *et al.*, 2017). Similarly, no association was made between stride duration variability and global GM volume or cerebellar, dorsolateral prefrontal cortex or basal ganglia volumes in one study (Manor *et al.*, 2012). Swing time variability was not associated with hippocampal volume in one study (Beauchet *et al.*, 2015); as no other studies have investigated swing time variability with grey matter volume, no firm conclusions can be drawn.

Rhythm

Five studies have investigated associations between GM volume and characteristics from the rhythm domain of gait. Two studies assessed double support time and had conflicting results; one found that longer double support time associated with a reduction of GM volume in areas

including dorsolateral prefrontal cortex, right parietal lobules, right motor cortex and sensorimotor cortex (Rosano *et al.*, 2008), the other found no association between double support time and global, cerebellar, dorsolateral prefrontal cortex or basal ganglia GM volumes (Manor *et al.*, 2012). Similarly, the three studies assessing step time and cadence – the inverse of step time – had conflicting results. Whilst no association was made between step time and hippocampal volume (Beauchet *et al.*, 2015), or between cadence and total GM volume (Callisaya *et al.*, 2014), one study found that decreased cadence was associated with cortical thinning in left cingulate and visual regions, the left fusiform gyrus and the primary and premotor cortices (de Laat *et al.*, 2012). Only one study assessed swing time; it was not associated with hippocampal volume (Beauchet *et al.*, 2015).

Variability, Asymmetry and Postural Control

Within the variability domain, one study investigated the association between each of step length variability and step width variability; these were not associated with total grey matter atrophy (Rosso *et al.*, 2014) or hippocampal volume (Beauchet *et al.*, 2015). No gait characteristics within the asymmetry domain have yet been assessed with GM volume. Three studies assessed GM volume with step width, the only characteristic assessed from the postural control domain. Two of three studies found that wider steps were associated with reduced GM volume in the inferior parietal lobe (Rosano *et al.*, 2008; de Laat *et al.*, 2012). Several other brain regions were related to step width in only one of these two studies, including the orbitofrontal and ventrolateral prefrontal cortices, temporal gyrus, left fusiform gyrus and the dorsal anterior cingulate cortex (de Laat *et al.*, 2012), as well as the pallidum and right dorsolateral prefrontal cortex (Rosano *et al.*, 2008).

White matter volume

Six studies assessed total, cortical and regional white matter (WM) volumes (Della Nave *et al.*, 2007; Sorond *et al.*, 2011; Beauchet *et al.*, 2014; Callisaya *et al.*, 2014; Ezzati *et al.*, 2015; Stijntjes *et al.*, 2016). All studies assessed characteristics from the pace domain of gait. Four of five studies found no association between WM volume and gait velocity (Della Nave *et al.*, 2007; Callisaya *et al.*, 2014; Ezzati *et al.*, 2015; Stijntjes *et al.*, 2016). Similarly, no association was identified between WM volume and step length (Callisaya *et al.*, 2014) or step time variability (Beauchet *et al.*, 2014) from the pace domain, or with cadence from the rhythm domain (Callisaya *et al.*, 2014). No other gait characteristics were assessed with WM volume.

Total brain volume

Total brain volume was assessed in three studies, either as an absolute value (Della Nave *et al.*, 2007; de Laat *et al.*, 2011c) or through assessment of brain parenchymal fraction (Sorond *et al.*, 2011). All assessed gait velocity; two of three studies found no association between gait velocity and total brain volume (Della Nave *et al.*, 2007; Sorond *et al.*, 2011). De Laat *et al.*, however, found associations between total brain volume and gait characteristics from all domains except asymmetry (de Laat *et al.*, 2011c) with increased total brain volume being associated with increased gait velocity, step length and cadence, and with reduced step time variability, double support time, step length variability and step width.

Ventricular volume

Four studies assessed ventricular volume (Rosano *et al.*, 2005a; Rosano *et al.*, 2005b; Annweiler *et al.*, 2014; Ezzati *et al.*, 2015). Again, all studies assessed gait characteristics within the pace domain of gait. Gait velocity was the only gait characteristic assessed in multiple studies; two of these three studies found no association between gait velocity and ventricular volume (Rosano *et al.*, 2005a; Ezzati *et al.*, 2015). For the other gait characteristics assessed, one study found that increased step time variability was associated with increased ventricular volume (Annweiler *et al.*, 2014), whereas another study found no association between ventricular volume and either step length or double support time (Rosano *et al.*, 2005a). No characteristics from the variability, asymmetry or postural control domains were assessed with ventricular volume.

2.3.3.1.2 Longitudinal associations from volumetric analysis

In contrast to the cross-sectional findings, only two studies assessed changes in GM volume with changes in gait (Callisaya *et al.*, 2013; van der Holst *et al.*, 2018), and their results conflicted. Van der Holst et al. found no association between GM volume change and a change in either gait velocity, step length or cadence (van der Holst *et al.*, 2018), whereas Callisaya et al. identified that a decrease in total GM volume over time was associated with a decrease in gait velocity and a decrease in cadence over time, and hippocampal volume reduction was associated with slowing of gait velocity and shortening of step length over time (Callisaya *et al.*, 2013).

Five studies assessed WM volume longitudinally with gait (Wolfson *et al.*, 2005; Ryberg *et al.*, 2011; Frederiksen *et al.*, 2012; Callisaya *et al.*, 2013; van der Holst *et al.*, 2018). Both studies that used baseline WM volumes to predict gait changes identified that smaller baseline WM volume were predictive of greater decline in gait velocity over time (Wolfson *et al.*, 2005; Ryberg *et al.*, 2011). However, of the three studies assessing a change in WM volume with a change in gait velocity (Frederiksen *et al.*, 2012; Callisaya *et al.*, 2013; van der Holst *et al.*, 2018), only one found that greater reductions in WM volume over time related to greater decline in gait velocity (Callisaya *et al.*, 2013). A reduction in step length over time was associated with a reduction in WM volume over time in both studies assessing it (Callisaya *et al.*, 2013; van der Holst *et al.*, 2018). Change in cadence, from the rhythm domain of gait, was assessed with WM volume change in two studies (Callisaya *et al.*, 2013; van der Holst *et al.*, 2018), yet results were conflicting. One study found that a reduction in total WM volume over time was associated with a reduction in cadence over time (Callisaya *et al.*, 2013), whereas another study found no association between the parameters (van der Holst *et al.*, 2018).

Two studies used baseline CSF volume (Wolfson *et al.*, 2005) and ventricular volume (Rosano *et al.*, 2005b) to predict gait changes; larger volumes of each of these at baseline were predictive of a greater decline in gait velocity over time.

2.3.3.2 MRI – white matter changes associated with age

2.3.3.2.1 Cross-sectional associations from analysis of white matter change

20 studies investigated cross-sectional associations between gait and white matter changes which are common in ageing, namely a combination of white matter hyperintensity (WMH) presence, which includes age-related white matter changes (Baezner *et al.*, 2008) leukoaraiosis (Della Nave *et al.*, 2007) and measures of WMH presence and severity (Rosano *et al.*, 2005a; Rosano *et al.*, 2005b; Baezner *et al.*, 2008; Rosano *et al.*, 2008; Nadkarni *et al.*, 2009; Novak *et al.*, 2009; Soumaré *et al.*, 2009; Murray *et al.*, 2010; de Laat *et al.*, 2011a; Sorond *et al.*, 2011; Moscufo *et al.*, 2012; Willey *et al.*, 2013; Wolfson *et al.*, 2013; Bolandzadeh *et al.*, 2014; Rosso *et al.*, 2014; Rosario *et al.*, 2016; Stijntjes *et al.*, 2016), a presence of infarcts (Rosano *et al.*, 2005a; Rosano *et al.*, 2005b; Rosano *et al.*, 2008; Choi *et al.*, 2012; Stijntjes *et al.*, 2016) and a presence of microbleeds (de Laat *et al.*, 2011b; Choi *et al.*, 2012; Stijntjes *et al.*, 2016).

WMH presence

WMH presence was commonly assessed; 18 studies evaluated it with gait (Rosano *et al.*, 2005a; Rosano *et al.*, 2005b; Della Nave *et al.*, 2007; Baezner *et al.*, 2008; Rosano *et al.*, 2008; Nadkarni *et al.*, 2009; Novak *et al.*, 2009; Soumaré *et al.*, 2009; Murray *et al.*, 2010; de Laat *et al.*, 2011a; Sorond *et al.*, 2011; Moscufo *et al.*, 2012; Willey *et al.*, 2013; Wolfson *et al.*, 2013; Bolandzadeh *et al.*, 2014; Rosso *et al.*, 2014; Rosario *et al.*, 2016; Stijntjes *et al.*, 2016).

Pace

Seventeen studies assessed WMH presence with gait characteristics from the pace domain; only one study did not assess gait velocity (Della Nave *et al.*, 2007). Findings within the domain were not consistent with each other; 13 of 16 studies found that slower gait velocity was associated with increased WMH presence (Rosano *et al.*, 2005a; Rosano *et al.*, 2005b; Baezner *et al.*, 2008; Nadkarni *et al.*, 2009; Soumaré *et al.*, 2009; Murray *et al.*, 2010; de Laat *et al.*, 2011a; Sorond *et al.*, 2011; Moscufo *et al.*, 2012; Willey *et al.*, 2013; Wolfson *et al.*, 2013; Bolandzadeh *et al.*, 2014; Rosario *et al.*, 2016), whereas two of three studies found no association between step length and WMH presence (Rosano *et al.*, 2005a; Nadkarni *et al.*, 2009). Regionally, reduced gait velocity was linked to more WMHs within the corpus callosum, both in anterior (Bolandzadeh *et al.*, 2014; Rosario *et al.*, 2016) and posterior (Moscufo *et al.*, 2012) regions, frontal brain regions (Nadkarni *et al.*, 2009; Murray *et al.*, 2010; Willey *et al.*, 2013), periventricular regions (Soumaré *et al.*, 2009; Murray *et al.*, 2010) and within the basal ganglia (Rosano *et al.*, 2005a; Nadkarni *et al.*, 2009). Other regions of WMH presence were associated with gait velocity, including the right centrum semiovale (de Laat *et al.*, 2011a), the anterior corona radiata, superior longitudinal and fronto-occipital fasciculus (Rosario *et al.*, 2016) the right anterior thalamic radiation (Bolandzadeh *et al.*, 2014) and temporal, parietal and occipital regions (Murray *et al.*, 2010). One study assessed stance time variability, and found that increased stance time variability was associated with increased presence of WMHs (Rosano *et al.*, 2008).

Rhythm

Three studies have assessed WMH presence with characteristics from the rhythm domain of gait. Again, findings within the domain were inconsistent with each other, although this relatively small number of studies ensures that no firm conclusions can yet be drawn. Whilst two studies found no association between WMH presence and cadence (Nadkarni *et al.*, 2009; de Laat *et al.*, 2011a), the other found that increased global WMH presence, and WMHs

within the brainstem, were associated with increased double support time (Rosano *et al.*, 2005a).

Variability, Asymmetry and Postural Control

Two studies have assessed WMH presence with gait characteristics from the variability domain. One study found that increased WMHs were associated with an increase in step length variability, but not with step width variability (Rosano *et al.*, 2008). The other study found no association between WMH presence and step length variability (Rosso *et al.*, 2014). No gait characteristics within the asymmetry domain have yet been assessed with WMH presence. Two studies assessed WMHs with step width, from the postural control domain of gait, and found conflicting results. Whilst one study found that increased WMH presence in several brain regions was associated with wider steps (de Laat *et al.*, 2011a), the other found that increased WMH presence specifically within the basal ganglia associated with narrower steps (Nadkarni *et al.*, 2009).

Infarcts

Five studies assessed the presence of infarcts with gait (Rosano *et al.*, 2005a; Rosano *et al.*, 2005b; Rosano *et al.*, 2008; Choi *et al.*, 2012; Stijntjes *et al.*, 2016). Each of these studies assessed gait characteristics from the pace domain; all four studies assessing gait velocity found that slower gait related to a higher number of infarcts (Rosano *et al.*, 2005a; Rosano *et al.*, 2005b; Choi *et al.*, 2012; Stijntjes *et al.*, 2016), one of which reported that infarcts in the basal ganglia were associated with gait velocity (Rosano *et al.*, 2005a). Both studies assessing step length associated shorter steps with an greater number of infarcts (Rosano *et al.*, 2005a; Choi *et al.*, 2012). One study assessed stance time variability, which was neither associated with the total number of infarcts nor the number of infarcts within the basal ganglia (Rosano *et al.*, 2008).

Associations made between the presence of infarcts and characteristics from the other gait domains are sparse and inconclusive. Two studies assessed whether double support time differed between participants grouped as either having or not having infarcts, yet only one found that double support time was increased in the group of participants with evidence of silent infarcts (Choi *et al.*, 2012). This study also found that those with evidence of infarcts had an increased step width compared to those with no infarcts evident; cadence did not differ between these groups of participants. The only study to investigate gait characteristics from the variability domain found that an increased number of infarcts, both globally and within the

basal ganglia, was associated with step length variability, but not step width variability (Rosano *et al.*, 2008).

Microbleeds

Three studies investigated the association between microbleeds and gait parameters (de Laat *et al.*, 2011b; Choi *et al.*, 2012; Stijntjes *et al.*, 2016). All three studies assessed gait velocity, yet only two found that a larger number of microbleeds was associated with reduced gait velocity (de Laat *et al.*, 2011b; Stijntjes *et al.*, 2016). De Laat et al. specified that this association was made not only with the number of microbleeds globally, but also with the number of microbleeds located specifically within the temporal lobe (de Laat *et al.*, 2011b). Two of the three studies assessed additional gait characteristics (de Laat *et al.*, 2011b; Choi *et al.*, 2012). Both found that a greater number of microbleeds was associated with increased double support time, but their results conflicted whilst assessing associations with step length, cadence and step width.

2.3.3.2.2 Longitudinal associations from analysis of white matter change

WMH presence was the most investigated imaging parameter longitudinally; seven studies longitudinally assessed WMHs with gait (Rosano *et al.*, 2005b; Soumaré *et al.*, 2009; Moscufo *et al.*, 2012; Callisaya *et al.*, 2013; Willey *et al.*, 2013; Wolfson *et al.*, 2013; van der Holst *et al.*, 2018). All seven studies assessed WMHs with gait velocity. In keeping with findings from cross-sectional evaluations, three of four studies that assessed baseline WMH presence with change in gait velocity found that increased WMH presence at baseline was associated with a greater decline in gait velocity over time (Rosano *et al.*, 2005b; Soumaré *et al.*, 2009; Willey *et al.*, 2013). However, only one of three studies assessing whether a change in the number of WMHs over time was associated with a longitudinal change in gait velocity found that a higher accumulation of WMHs over time was associated with a greater decline in gait velocity (Wolfson *et al.*, 2013). Two studies assessed a change in WMH presence with a change in step length; one found that increased WMH presence over time was associated with slowing of gait velocity over time (Callisaya *et al.*, 2013), whereas the other found no association (van der Holst *et al.*, 2018). Neither of these studies found an association between a change in the number of WMHs and a change in cadence.

Two studies assessed the longitudinal associations between gait and infarct and/or microbleed presence. One study found that a higher presence of infarcts at baseline was associated with a greater decline in gait velocity (Rosano *et al.*, 2005b), whereas the other found no association between a change in either infarct or microbleed presence and a change in gait velocity, step length or cadence (van der Holst *et al.*, 2018).

2.3.3.3 DTI

2.3.3.3.1 Cross-sectional associations with DTI parameters

Eight studies have utilised DTI imaging parameters in cross-sectional analyses (Della Nave *et al.*, 2007; de Laat *et al.*, 2011a; de Laat *et al.*, 2011c; Bruijn *et al.*, 2014; Rosso *et al.*, 2014; Fling *et al.*, 2016; Verlinden *et al.*, 2016; Fling *et al.*, 2018). A variety of methods were used to determine DTI parameters, including TBSS, Interhemispheric callosal tractography, Probabilistic tractography through ProbtrackX, SPM5 or in-house software.

Fractional Anisotropy

All studies utilizing DTI determined fractional anisotropy (FA); high values of FA indicated a good integrity of the tracts assessed. Five investigated gait characteristics from the pace domain; three of these five found that slower gait velocity was associated with reduced FA (de Laat *et al.*, 2011a; de Laat *et al.*, 2011c; Verlinden *et al.*, 2016) in most white matter tracts, except for the brainstem in one study (Verlinden *et al.*, 2016) and except for periventricular regions in another (de Laat *et al.*, 2011c). Both studies assessing step length found that shorter steps were associated with FA (de Laat *et al.*, 2011a; de Laat *et al.*, 2011c), and the one study that assessed step time variability found that increased variability was associated with reduced FA (de Laat *et al.*, 2011c). Two studies assessed gait characteristics from the rhythm domain (de Laat *et al.*, 2011a; de Laat *et al.*, 2011c); both found that reduced cadence was associated with reduced FA. Only one of these studies assessed double support time, and found that it was not associated with FA (de Laat *et al.*, 2011c). Two studies assessed characteristics from the variability domain. Whilst one found that increased step length variability was associated with reduced FA within grey matter (Rosso *et al.*, 2014), the other found no association between FA in white matter and either step length variability or step width variability (de Laat *et al.*, 2011c). The recent study from Fling et al. was the only one to assess step time asymmetry, from the asymmetry domain, or step length asymmetry

from the postural control domain (Fling *et al.*, 2018). Neither characteristic was associated with FA. Four studies assessed step width with FA, and their results conflicted. Two studies found that wider steps were associated with reduced FA (de Laat *et al.*, 2011a; de Laat *et al.*, 2011c); one found that narrower steps were associated with reduced FA (Bruijn *et al.*, 2014) and the other study found no association between the parameters (Fling *et al.*, 2016).

Mean, Radial and Axial Diffusivity

Four studies additionally used measures of mean diffusivity (MD) within white matter tracts, where high MD is a sign of poor white matter integrity (Della Nave *et al.*, 2007; de Laat *et al.*, 2011a; de Laat *et al.*, 2011c; Verlinden *et al.*, 2016). Three studies found that increased MD was associated with both slower gait velocity and shorter step length from the pace domain, and with increased step length variability from the variability domain (de Laat *et al.*, 2011a; de Laat *et al.*, 2011c; Verlinden *et al.*, 2016). Associations with MD were made in more regions than those with FA assessment; associations were additionally made in subcortical frontal and parietal regions in one study (de Laat *et al.*, 2011c), and within the brainstem in another study (Verlinden *et al.*, 2016). Two studies assessed additional gait characteristics (de Laat *et al.*, 2011a; de Laat *et al.*, 2011c); both found that increased MD was associated with reduced cadence from the rhythm domain and increased step width from the postural control domain. Additionally, one of these studies identified that increased MD was associated with increased step time variability (pace) and increased double support time (rhythm), but was not associated with step width variability (variability) (de Laat *et al.*, 2011c), and another study found that increased MD was associated with shorter stance times (rhythm) (Verlinden *et al.*, 2016). Two of the studies assessing MD additionally reported associations relating to radial diffusivity (RD) and axial diffusivity (AxD) (de Laat *et al.*, 2011a; Verlinden *et al.*, 2016), which related to gait in the same way as MD in both studies.

2.3.3.3.2 Longitudinal associations with DTI parameters

One study utilised DTI (van der Holst *et al.*, 2018) to determine longitudinal neural imaging correlates of gait. Van der Holst et al. found that changes in DTI parameters over time were not associated with decline in gait velocity or cadence, but that a decrease in FA over time was associated with a reduction in step length over time (van der Holst *et al.*, 2018). Similarly, reduced step length over time was associated with increased MD and RD over time, but not increased AxD.

2.3.3.4 PET

2.3.3.4.1 Cross-sectional associations with PET imaging

Four studies assessed amyloid beta, Aβ, burden through PET imaging (Del Campo *et al.*, 2016; Nadkarni *et al.*, 2017; Tian *et al.*, 2017a; Wennberg *et al.*, 2017a). Three of these utilised [^{11}C] Pittsburgh Compound B (PiB) PET scans (Nadkarni *et al.*, 2017; Tian *et al.*, 2017a; Wennberg *et al.*, 2017a), whereas del Campo et al. used [18F] Florbetapir PET scans (Del Campo *et al.*, 2016). Three of the studies found that an increased burden of Aβ was associated with reduced gait velocity (Del Campo *et al.*, 2016; Nadkarni *et al.*, 2017; Wennberg *et al.*, 2017a). Specifically, Aβ burden within basal ganglia regions, the precuneus, the temporal cortex and the anterior cingulate was negatively associated with gait velocity in more than one of these studies. No association was identified between gait velocity and Aβ burden within the hippocampus, pons, thalamus or parietal lobe. Additionally, Wennberg et al. (Wennberg *et al.*, 2017a) found that increased Aβ burden was associated with increased stance time variability, reduced cadence and increased double support time, in prefrontal, temporal and cingulate regions; no associations were made between step length and Aβ burden.

Three studies used fluorodeoxyglucose (FDG) PET imaging to determine cerebral glucose uptake (Shimada *et al.*, 2013; Sakurai *et al.*, 2014; Sakurai *et al.*, 2017). All three of these studies recruited only female participants from similar databases of elderly volunteers, limiting an overall interpretation of the associations between cerebral glucose uptake and gait in the general population. Both of the studies authored by Sakurai et al. (Sakurai *et al.*, 2014; Sakurai *et al.*, 2017) found that lower uptake of glucose was associated with reduced gait speed and reduced cadence, but not step length. Associations were made in the posterior cingulate and parietal cortex in both studies; other regions were investigated, but either no association was made or the associations was not consistent across both studies. These associations were made with gait characteristics assessed during fast walking only; no associations were made between glucose uptake and gait characteristics measured at a comfortable walking pace. In the study from Shimada et al. (Shimada *et al.*, 2013), participants were split in to two groups, those with low step length variability (LSV) and those with high step length variability (HSV). The LSV group had relatively increased glucose uptake in the primary sensorimotor area in comparison to the HSV group, and the HSV group had comparatively decreased uptake in the middle and superior temporal gyrus and hippocampus in relation to the LSV group; note that the direction of association is consistent in both sets of analyses. In this study, step length variability was assessed during

walking at a fixed pace of 2km/h, a relatively slow walking speed (Bohannon and Williams Andrews, 2011).

2.3.3.4.2 Longitudinal associations with PET imaging

One study utilised PET (Tian *et al.*, 2017a) imaging to determine longitudinal neural gait correlates. Gait velocity change was the only gait characteristic assessed alongside baseline PET imaging by Tian *et al*. longitudinally; they found that higher baseline Aβ burden was associated with a greater slowing of gait velocity over time (Tian *et al.*, 2017a).

2.3.3.5 fNIRS, MRS and fMRI

Only one study using each of fNIRS (Holtzer *et al.*, 2015), fMRI (Yuan *et al.*, 2015) and MRS (Zimmerman *et al.*, 2009) imaging techniques in relation to single-task gait characteristics were identified in this review. All studies were performed in cross-section, and assessed gait characteristics from the pace domain. These studies identified that gait velocity was associated with functional connectivity in sensorimotor, visual, vestibular, and left fronto-parietal cortical areas (Yuan *et al.*, 2015), but not with activation strength of the prefrontal cortex (Holtzer *et al.*, 2015), and stride length was not associated with either prefrontal cortex activation or N-acetylaspartate:creatine ratio within the hippocampus (Zimmerman *et al.*, 2009). However, the sparsity of studies focussed on these approaches and gait means that no firm conclusions can be drawn about associations between gait and parameters derived from these functional imaging techniques.

2.3.4 The effect of cognition on the relationship between gait and imaging correlates

The impact of cognition on the relationship between gait and imaging correlates was considered, through assessment of studies which assessed cognition and included cognitive test scores as covariates. Twelve studies within this review included a measure of cognition as a potential confounding factor (Rosano *et al.*, 2008; Dumurgier *et al.*, 2012; Annweiler *et al.*, 2014; Bolandzadeh *et al.*, 2014; Nadkarni *et al.*, 2014; Rosso *et al.*, 2014; Sakurai *et al.*, 2014; Ezzati *et al.*, 2015; Stijntjes *et al.*, 2016; Beauchet *et al.*, 2017; Nadkarni *et al.*, 2017; Tian *et al.*, 2017a). These cognitive measures included global and primarily executive outcomes: the mini mental state exam (MMSE), the modified mini mental state exam (3MS), trail making tasks A and B (TMT-A, TMT-B), the digit symbol substitution test (DSST), the frontal assessment battery (FAB) and the abbreviated Stroop test, although one study specifically included a free recall score task (Stijntjes *et al.*, 2016).

Gait velocity was frequently assessed as a measure in these studies. Adjusting for cognition caused gait velocity to no longer be associated with frontal and parietal lobe GM volume (Dumurgier *et al.*, 2012), hippocampal volume (Ezzati *et al.*, 2015), cerebellar volume (Nadkarni *et al.*, 2014), amyloid beta burden (Nadkarni *et al.*, 2017), WMHs in the anterior thalamic radiation and anterior corpus callosum (Bolandzadeh *et al.*, 2014) and almost all regional associations with baseline amyloid beta burden (Tian *et al.*, 2017a). In contrast, gait speed remained associated with some imaging parameters after the inclusion of cognition as a covariate, in particular, with basal ganglia and caudate volumes (Dumurgier *et al.*, 2012) as well as global microbleed and infarct presence (Stijntjes *et al.*, 2016).

The effect of cognition on the neural correlates of other gait characteristics were also considered. Associations between regional grey matter volume and step length, stance time and step width (Rosano *et al.*, 2008) were largely unaffected by the inclusion of cognition in statistical models, as were associations made between mean diffusivity in grey matter and step length variability (Rosso *et al.*, 2014) and the association between step time variability and ventricular volume (Annweiler *et al.*, 2014).

2.4 Discussion

This is the first structured review to comprehensively map many discrete gait characteristics, defined by a validated objective gait model, to their structural and functional imaging neural correlates. Many associations between gait characteristics and the brain were identified, however, findings demonstrate a limited understanding of the overall neural control of gait. This is as a result of studies mostly reporting associations with gait velocity, and the majority of studies focussing on structural, rather than functional, neuroimaging parameters. Additionally, network-based approaches were scarcely utilised within the neuroimaging methodologies, despite the importance of networks becoming increasingly evident (O'Sullivan *et al.*, 2001). There is emerging evidence linking other gait characteristics to a wider array of neuroimaging parameters, and of the effect of the ageing process on associations through longitudinal observations, although this remains limited.

2.4.1 Global neuroimaging correlates of discrete gait characteristics

The overarching findings from the studies included in this review is that a 'healthy brain' is associated with better gait. Larger volumes of healthy grey matter and WM integrity, determined through WMH presence in addition to FA and MD, were consistently associated

with quality of gait performance, as demonstrated by gait characteristics related to pace, rhythm, variability and postural control. Increased step width, from the postural control domain, was associated with both greater and less white matter integrity in different studies, consistent with the idea that optimal step width is neither too wide nor too narrow. Although wide steps provide greater stability (Gabell and Nayak, 1984), they could indicate compensation for poor balance control. Non-linear optimization of step width may also begin to explain why step width variability has not yet been associated with any imaging parameter.

The global presence of common white matter changes in ageing was associated with worse gait. Several of the studies in this review found that associations between gait and either brain volumes or DTI parameters were no longer significant once the presence of white matter changes such as WMH, infarct or microbleed presence were included as covariates, either in isolation or with a combination of other confounding factors. Some studies specified the presence of small vessel disease (through WMH or infarct presence) within their inclusion criteria (de Laat *et al.*, 2011a; de Laat *et al.*, 2011b; de Laat *et al.*, 2011c; de Laat *et al.*, 2012; van der Holst *et al.*, 2018), and none of the studies included assessments related to ageing factors such as frailty or muscle mass. Overall, this causes great difficulty in discerning whether global neural-gait correlates are due only to the presence of white matter artefacts, or if in fact these artefacts are an unrelated sign of ageing, and associations between ageing and gait are simply being identified. Clearer assessment of the direct effects of age-related white matter changes on associations between gait and the brain should be completed in future to resolve this issue. The global imaging correlates of gait presented here suggest that gait may not be controlled by discrete regions; instead, an efficient and effective gait might be a consequence of many different regions working in collaboration.

2.4.2 Regional neural correlates of gait

In addition to global associations between gait and the brain, this review aimed to identify regional neural structures and/or functions which related to specific gait characteristics. Studies which have attempted regional analyses were too disparate in approach to allow any firm conclusions to be drawn. A number of studies have focussed only on one region and most studies have each investigated different regions. Very few studies within this review assessed regions connected together through a network-based approach, either through the assessment of functional networks (Yuan *et al.*, 2015) or by assessing the specific structural tracts which connect different brain regions (Verlinden *et al.*, 2016). Several trends of gait domains relating to specific brain regions were identified; it is important to highlight,

however, that greater efforts should now be made to assess these regions together as one or several networks which may be responsible for gait control. Within the pace domain, the most consistent trends were towards an association of gait velocity with GM volume in frontal, basal ganglia, hippocampal and cerebellar regions, and with WMHs within frontal regions, the basal ganglia and the corpus callosum, although most brain regions have been associated with gait velocity in at least one study. Step length was consistently associated with several GM volumes, however, not all the regions associated with gait velocity also related to step length. This suggests specificity in findings; gait velocity, as the global measure of gait, may be associated with global brain features, whereas step length may be related more so to cortical, rather than subcortical brain regions. For gait characteristics from the other domains, few studies specified the regions in which associations were made, and most regions were identified in only one study. **Figure 2-5** shows maps of the regional associations between GM volume and all gait characteristics in which GM regions were specified; gait velocity, step length, step time variability, step width, cadence and double support time. The entirety of the gait velocity maps are in colour, to indicate that most brain regions have been associated with gait velocity in at least one study; regions in which several associations have been made have additionally been highlighted.

It is clear from **Figure 2-5** that some brain regional volumes have been associated with several gait characteristics. This may be due to the volumes assessed being too crude, which would not allow for the specificity of associations between smaller, better defined, regions and gait to be apparent. Alternatively, it may be that brain regions are responsible for several of the gait characteristics, which could be grouped into their own region-dependent domains in future. Before this can be clarified, however, further regional analyses assessing many of the gait characteristics through the same methodologies are required.

In studies assessing infarct and microbleed presence, the topographic location of these brain insults was rarely reported, although from the few studies that did detail regional associations it appears that insults within the basal ganglia have a negative impact on gait. Similarly, amyloid beta burden within the basal ganglia was associated with gait velocity. It is not yet clear whether these disturbances to the basal ganglia impact on all aspects of gait; it may be hypothesised that the basal ganglia are responsible for less complex gait characteristics, such as step length, as it is a lower level structure, although there is currently not enough literature to determine this with any certainty.

Two other reviews have recently been published which sought to determine neural-gait correlates. Tian *et al* focussed on associations made with variability characteristics of gait, and identified a particular association with temporal variability measures and the right hemisphere (Tian *et al.*, 2017a). Here, it was identified that the right hemisphere may also have a greater responsibility for double support time (Rosano *et al.*, 2008), whereas cadence may be more dependent on the left hemisphere (de Laat *et al.*, 2012); this asymmetry gives further evidence for specificity in the brain regions responsible for gait, and should be considered further. Wennberg *et al*. found that frontal and parietal regions of grey matter were most commonly associated with gait, as measured through more complex tests such as the timed up-and-go in addition to some of the gait characteristics identified here (Wennberg *et al.*, 2017b). This review additionally found that the involvement of subcortical areas such as the basal ganglia and limbic system, as well as the hippocampus, were related to several gait characteristics. Several of the gait characteristics appeared to rely on involvement from both types of brain area, strengthening the argument that brain areas associated with both motor tasks and cognition are heavily involved in coordinating gait.

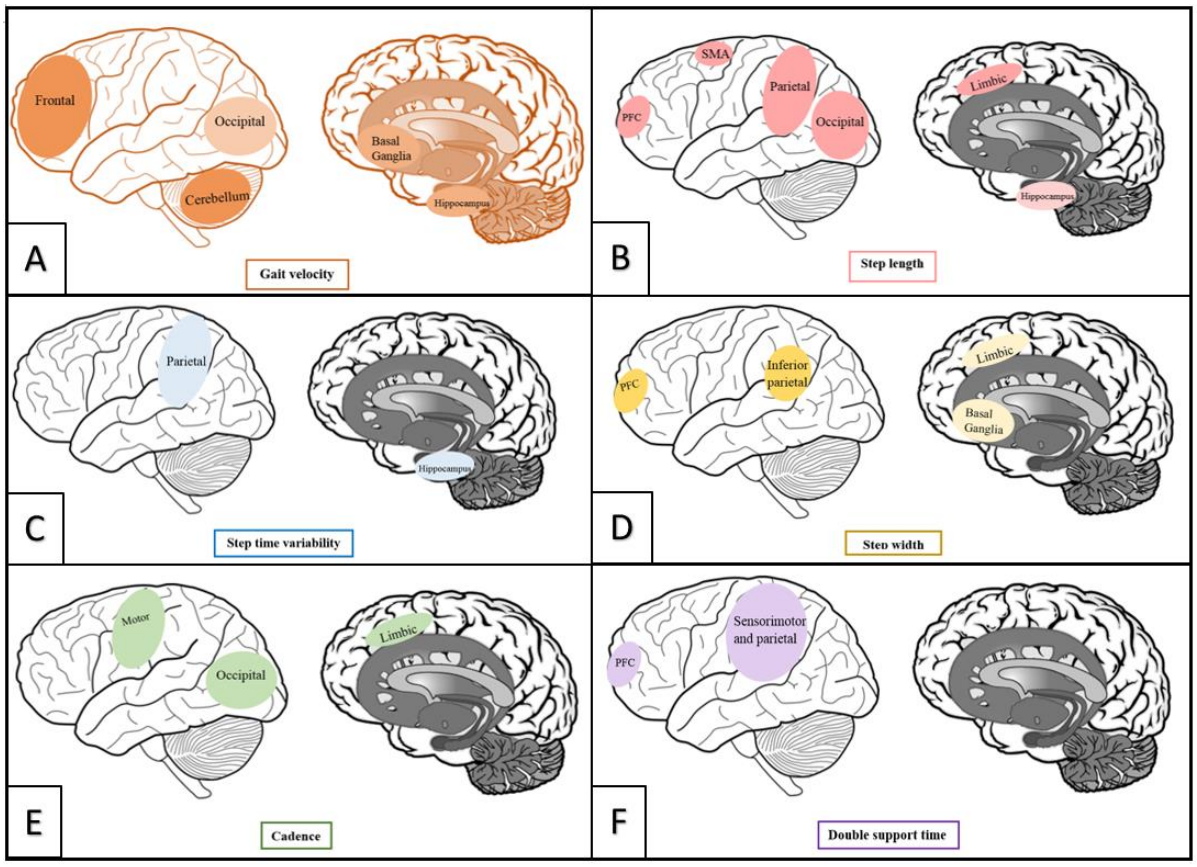
This review has demonstrated that, although many brain regions have been assessed with gait, there is a lack of cohesion between studies about the brain areas of most importance in gait. The non-specificity of findings between gait and structural volumes suggests that the impact of gait impairment on neural networks, connected either structurally or functionally, should be considered in future.

2.4.3 Longitudinal neural correlates of gait

A reduction in gait characteristics from the pace domain over time was not only associated with changes in WM volume over time, but also with baseline measures of WM volume. However, WM volume was not associated with gait during cross-sectional analyses. This highlights the importance of longitudinal study types when assessing associations between gait and the ageing brain, yet relatively few studies assessed the longitudinal neural correlates of gait. In general, this review identifies more associations between gait changes over time and imaging parameters when imaging was used as a *predictive* measure of gait decline, rather than where changes in imaging parameters were related to gait changes. This may indicate that predictive models utilizing only one set of brain imaging data should be considered more regularly in future, particularly given that gait assessment is relatively inexpensive and is more accessible to older adults than imaging. Clinically, improved

understanding of the brain changes associated with a poorer gait performance would allow us to utilise gait assessment more readily as a predictive measure for future neurodegeneration.

Figure 2-5. Map of the regional associations between grey matter volume and gait characteristics



[Gait velocity (A), step length (B), step time variability (C), step width (D), cadence (E) and double support time (F). Areas which are darker in colour indicate regions that were associated with the characteristic in multiple studies. Panel A shows the entire brain in an orange colour, to indicate that the volume of most brain regions have been associated with gait velocity.]

2.4.4 Methodological critiques

Most studies included in this review utilised structural MRI and/or diffusion tensor imaging, perhaps due to the major issue of cost surrounding functional imaging techniques such as PET and fNIRS and the intensity of task-based fMRI studies. Most studies that have utilised fMRI to assess associations between the brain and gait have done so through finding the neural correlates of imagined walking and leg movements whilst in an fMRI scanner. These were not considered in this review, as these protocols do not directly explore discrete gait

characteristics. The use of virtual reality and foot pedals within functional protocols may provide further insight into the functional networks utilised during walking, particularly as recent work has started to produce surrogate measures of gait characteristics such as step time variability (Gilat *et al.*, 2017). The recent development of new radiotracer elements and enhanced PET scanning techniques may contribute to current understanding of neural activity associated with gait. For example, in healthy adults aged 21-85 years, worsened gait velocity, cadence, and stance time are associated with lower striatal dopamine activity (Cham *et al.*, 2008). In PD, acetylcholinesterase ([11C]PMP) PET has been used to show that cholinergic deficits are associated with slow gait (Müller *et al.*, 2015). Additionally, nerve stimulation can be used to assess cholinergic activity through assessment of short-latency afferent inhibition (Rochester *et al.*, 2012); consideration of nerve or brain stimulation was beyond the scope of this review. No studies have utilised functional imaging of neurotransmitter activity in a group of healthy older adults to assess neural correlates of gait. Four of the seven studies which used PET imaging in this review assessed amyloid burden which, in effect, is a marker of structural rather than functional pathology and does not enhance understanding of the functional neurochemical correlates underlying gait impairments. Although the assessment of CSF biomarkers through lumbar puncture was not covered here, studies of this nature can provide us with additional information about the effects of an accumulation of pathologies such as amyloid and tau on motor performance (Rochester *et al.*, 2017).

Only one study within this review completed brain imaging in real time during the assessment of discrete gait characteristics. This is due to most fNIRS and EEG studies comparing differences in brain states between tasks, such as between single and dual task gait, rather than assessing single task gait characteristics (Hamacher *et al.*, 2015; Vitorio *et al.*, 2017). Electrophysiological responses, as measured through EEG, are consistent with haemodynamic responses assessed through both fNIRS and fMRI (Anwar *et al.*, 2016), demonstrating their reliability as promising technologies for future research in to the functional neural correlates of gait. Additionally, functional imaging both during real-time gait assessment and during the resting state can be used to assess neural networks; it is becoming increasingly evident that network analyses, particularly those of a dynamic rather than static nature, will be key to furthering understanding of the system-wide neural substrates which underpin dynamic gait control. There is evidence of an interaction between gait velocity and inter-network connectivity between the default mode network and supplementary motor as assessed through fMRI in older adults with mild cognitive impairment (Crockett *et al.*, 2017), yet no study has assessed this in a healthy ageing population; these areas could provide a starting point for the

neural networks to assess in association with gait. Decoupling between imaging and gait measurements introduces the potential for increased variance and noise, undermining potential correlation. Although structural imaging approaches are likely to be robust to this, functional imaging may be more sensitive due to its reliance on brain state and performance. To avoid this issue, further efforts should be made to develop strong protocols assessing real-time brain function with single task gait characteristics.

Several of the gait protocols within this review included use of a stopwatch during corridor walking. Although measures of gait velocity can be calculated through this technique, and its components in some instances, more subtle gait characteristics cannot be assessed. This limits understanding of the neural control of variability and asymmetry. Measures within the variability domain are of particular interest in gait research, as they can be used as markers of fall risk and cognitive decline (Montero-Odasso *et al.*, 2012; Tian *et al.*, 2017a); a greater understanding of the neural substrates of variability is therefore crucial to obtain. Additionally, non-linear approaches to analysis, such as the fractal analysis of stride-to-stride fluctuations in walking, are of increasing interest to human gait research as they take into consideration the structure and complexity of these large data sets (Hu *et al.*, 2009; Li *et al.*, 2018). Studies within this review varied not only by the gait measurement tools, but by the number, speed and type (continuous or intermittent) of walks performed, limiting interpretation of findings. If a standard robust single-task gait protocol were developed and used, findings would be more comparable between studies, and standardised reporting of characteristics other than gait velocity would be carried out more frequently.

2.4.5 Cognition as a covariate

Cognition had a mediating effect on some of the associations made between gait velocity and volumes of the frontal lobe and hippocampus. Executive function (the function of which is subsumed by frontal regions) and memory (controlled by the hippocampus as well as portions of the prefrontal cortex) have both been associated with gait velocity (Watson *et al.*, 2010; Morris *et al.*, 2016), therefore suggesting a broad three-way interplay between cognitive function, gait velocity and grey matter volume. It is currently unclear whether gait velocity is directly impacted by cognition, or whether impairments in both gait and cognition are as a result of changes within the brain. Understanding of the interaction between gait, cognition and the brain, and whether it applies to gait characteristics other than velocity, is limited due

to the relative scarcity of studies assessing cognition in addition to gait and neuroimaging parameters.

2.4.6 Current limitations and recommendations for future work

The literature is currently dominated by assessments of gait velocity, most likely due to its ease of measurement. Also, it is frequently assessed alongside other motor parameters in studies assessing "mobility" as opposed to pure gait. Gait velocity is a global measure of gait, which has been assessed through a wide range of techniques; its lack of specificity cannot reflect subtle gait changes that occur during ageing and disease, and its use increases the likelihood of chance findings and different clinical interpretations of results (Graham *et al.*, 2008). There is a relative scarcity of studies assessing gait characteristics other than gait velocity, therefore it cannot be concluded with any certainty whether characteristics within the same gait domain have similar neural underpinnings. Similarities in the grey matter regions associated with gait velocity and step length from the pace domain indicate that these may involve similar mechanisms, although it should be emphasised that this may be due to the high correlation between these characteristics. Until such a time that the neural correlates of several characteristics from each of the gait domains are well understood, to confirm whether characteristics within each domain are controlled in a similar manner, the number of gait characteristics to be associated with imaging parameters should not be reduced.

The literature mostly consists of assessments of neural structure rather than function, and the specific regions assessed differed across most studies, suggesting a high degree of heterogeneity. Associations between neuroimaging parameters and gait characteristics were typically conducted through correlational approaches. Correlations were not necessarily reflective of causation and can be affected more strongly by sample size; therefore any identified correlation should be interpreted with some degree of caution. It is justifiable to perform correlational analyses in the first instance, particularly given the limited understanding of the neural control of gait. However, correlations alone do not allow for a strong understanding of the neural control of gait; in the future, the development of methodologies that allow for the concurrent measurement of discrete gait characteristics and brain functionality, with high spatial resolution, should be a priority.

The MMSE was most commonly used as an assessment of cognition (where cognitive tests were completed); by using an assessment of global cognition, it is difficult to discern whether

the neural substrates associated with different cognitive domains, such as frontal regions with executive function, match those neural areas associated with gait. Confounding factors included in analyses generally differed between studies. Additionally, some papers highlighted results from unadjusted models whereas others only reported results from models including a full set of confounding factors. This may have caused some discrepancy when comparing studies. Also, gait assessed under dual-task conditions has not been considered, which may have moderated findings. A more robust understanding of the influence of cognition on neural-gait correlates is required before findings from dual-task protocols can be sufficiently interpreted. A limitation of this review is that the focus was on the neural correlates of gait in healthy older adults. A greater number of associations could have been identified if young or middle-aged adults were included, which may not have been confounded by age. Search criteria were restricted to older adults, to ensure that changes related to gait during normal ageing could be reviewed comprehensively. These age-related changes should better relate to the mechanisms underpinning gait dysfunction in disease. Nonetheless, it is important to highlight that the mechanisms of gait during earlier life stages may not be fully encompassed by the neural-gait correlates presented here. Overall, most of the studies considered within this review were only of average quality, as demonstrated in **Appendix C**. Some key recommendations for future studies within this field have therefore been summarised (**Figure 2-6**).

Figure 2-6. Key recommendations for future studies

Key recommendations for future studies:

- ✓ Functional imaging techniques should be utilized more frequently when assessing associations between the brain and gait, as they allow neural activity to be recorded during walking in real time, aiding interpretation of the role of different areas of the brain
- ✓ Protocols should include the assessment of gait characteristics other than gait velocity, to obtain better understanding of neural correlates of selective, rather than global, gait traits. Ideally, this should be based on a validated gait model, so that the selection of characteristics may be justified and data more clearly interpreted
- ✓ Studies should identify brain regions of interest which most strongly associate with discrete gait characteristics, so that brain maps of gait may be of higher quality. This could be achieved through specific, well designed studies that probe single neural areas, or through specific network approaches
- ✓ Cognition should be included as a covariate in analyses, ideally as a representative of clear cognitive domain(s), to increase our understanding of the mediating effect it has on any associations made
- ✓ More longitudinal studies should be completed, to determine whether baseline imaging can be used to predict future decline in different gait domains, and vice versa

In summary, this structured review has demonstrated that global imaging markers of a 'deteriorating brain', namely grey matter atrophy, high volume of white matter hyperintensity lesions and worsening of DTI measures of white matter integrity, are correlated with poor gait performance. Additionally, it was found that gait velocity decline over time can be predicted by an initial global assessment of imaging markers of white matter. Regionally, there was a predilection for both the volume of and white matter hyperintensity presence within frontal and basal ganglia regions to influence gait velocity, although many brain regions have been related to gait velocity in some capacity. Beyond this, conclusions are more limited, largely due to the small range of discrete gait characteristics included within each study design, as well as a lack of consistency in the brain regions investigated between studies. It was hypothesised that discrete gait characteristics may have more discrete neural correlates; although global associations have been more concretely assessed, there is an emerging specificity of associations between gait and the brain, evidenced by differences in the neural regions that have been associated with different gait characteristics thus far. This review has also demonstrated a relative scarcity of functional imaging correlates with formal gait measures; only one study utilised resting state functional networks in analyses, and only one

fNIRS study has identified neural-gait correlates through single task walking. This is somewhat surprising given the dynamic nature of gait, and given that the association between gait decline and a loss of generalised white matter integrity highlighted in this review points strongly towards an association between gait decline and reduced functional connectivity. Further work should take greater consideration of the covariates included within analyses, and particularly assess the influence of cognition on any associations found, so that a strong model of the three-way interplay between gait, cognition and the brain can be developed.

Section 2: Associations between discrete gait characteristics and imaging parameters in PD

2.5 Overview

The neural mechanisms sub-serving human locomotion, which ultimately fail in PD, are complex and remain poorly understood. Thanks to recent refinements and developments in neuroimaging, there has been increased interest in applying these technologies to better understand the pathophysiology of gait impairment in people with PD. The main aim of this section of chapter 2 was to explore associations between discrete gait characteristics and brain structure and/or function in PD, as identified through neuroimaging. It is hypothesised that, as with section 1, independent gait characteristics will reflect discrete regional brain structure and functional brain activity in PD. Furthermore, it is postulated that the pattern of associations will be different than those identified in healthy ageing; this would reflect the suggested disruption of automatic motor circuitry and consequent increased reliance on compensatory mechanisms in PD.

To enable a detailed and complete approach, as with section 1 of this chapter, the gait characteristics considered in this section are also from the gait model from Lord et al. (Lord *et al.*, 2013c)(**Figure 2-1**)), which has been validated in PD (Lord *et al.*, 2013b) and has been adopted as the most comprehensive model for simple gait. In contrast to section 1, however, the gait assessments used to measure discrete characteristics have not been limited to assessment during simple, single task gait. Assessment of gait characteristics under dual task, virtual reality and imagined gait have been considered here. This was, primarily, to be inclusive of the entirety of the literature evaluating the neural control of discrete gait characteristics in PD through neuroimaging, as relatively few assessments of this have been completed to date. Although this may cause more difficulty in comparing findings between different study designs, it enables a fuller understanding of the work completed. Assessments considering only freezing of gait (FOG) or the Postural Instability and Gait Difficulty (PIGD) subtype were not considered here. Again, both cross-sectional and longitudinal study types have been included. To be fully inclusive, studies in the PD literature utilising nerve or brain stimulation have also been reviewed in this section of chapter 2. A search strategy similar to that used in section 1 of this chapter was adopted, with additional inclusion of the term "Parkinson's disease" in all searches. Studies identified outside of the search strategy have also been included.

2.6 Findings

Studies that have used brain imaging to understand the neural mechanisms of discrete gait characteristics are summarised in **Table 2-2.** Regional associations have been mapped in **Figure 2-7**. An explanation of findings is provided below, grouped by imaging modality.

Structural MRI

Structural MRI has mostly been used to correlate measures of gait assessed under single and dual task conditions to the extent of WMH in people with PD (Acharya *et al.*, 2007; Sartor *et al.*, 2017; Toda *et al.*, 2019), as was the case in the healthy older adult literature (**Figure 2-3**). Increased WMH ratings, both globally and in frontal and occipital regions, have been linked to slower step velocity when assessed in single task, particularly in people with PD under the age of 70 (Sartor *et al.*, 2017; Toda *et al.*, 2019) but not in controls (Sartor *et al.*, 2017). However, whilst Toda et al. also found this association with step velocity measured under dual-task conditions, Sartour et al. did not; this may have been due to the extent of the effect of the cognitive dual-task on gait performance differing between studies. Toda et al. also identified that stride length (the addition of left and right step lengths) measured under single and dual-task conditions, but not step time variability, was associated with WMH in frontal regions. Acharya et al. found no association between cadence, the inverse of step time, and neither WMH rating, nor ventricular volume, a marker of global atrophy in PD (Acharya *et al.*, 2007); however, cadence was correlated with ventricular volume in controls. It should be highlighted that the gait assessment in this study included a turn, which may have affected the measure of cadence (particularly within the PD group).

One study has correlated step velocity measured under dual-task conditions with subcortical volumes of regions relating to the basal ganglia and limbic system (Rosenberg-Katz *et al.*, 2016); faster dual-task step velocity was associated with larger hippocampal volumes. Another study has identified a cross-sectional association with the structural integrity of cholinergic nucleus 4 (Ch4), which closely relates to the NBM, the source of cortical cholinergic innervation. Poorer Ch4 structural integrity was associated with slower walking speed approximately ten years after PD diagnosis, when assessed "on" dopaminergic medication (Dalrymple *et al.*, 2020).

Although these studies are correlational, which does not signify causation, they indicate associations between better gait and a healthy brain (i.e. free from WMH and with less atrophy) for areas linked to cognition (frontal, hippocampal and Ch4 areas). Tentatively, these findings may reflect the hypothesised increased cognitive control of gait in PD.

DTI

Several single-task gait characteristics have been correlated with FA within the corpus callosum, a measure of white matter tract integrity, by the same research group (Fling *et al.*, 2016; Fling *et al.*, 2018). Despite assessments of the association between FA and step velocity, stride width, step length asymmetry and step time asymmetry being completed, the only association to survive multiple comparison correction was between increased step length asymmetry and worse integrity of fibres connecting the pre-SMA in PD. No associations were identified in controls. This finding reflects the suggestion from Peterson and Horak that the neural control of gait asymmetry is related to asymmetric dopaminergic dysfunction specific to PD (Peterson and Horak, 2016), as there was reduced FA in the corpus callosum, the structure connecting the left and right brain areas. It also demonstrates the need to look at gait measures other than step velocity, as these can reflect different aspects of PD gait control. One other study has utilised DTI to assess neural correlates of PD gait (Peterson *et al.*, 2015), which identified that an inability to maintain stride length under dual task in PD is linked to more asymmetrical PPN connectivity; this may reflect the greater role of the cholinergic system in PD gait, particularly under dual-task (and therefore more attention-demanding) conditions.

Functional MRI (fMRI)

fMRI has been utilised through different methodologies. One study has assessed the connectivity between regions whilst participants were at rest and correlated these to step time and swing time measured under single and dual-task (Vervoort *et al.*, 2016). Reduced functional connectivity between the left caudate & superior temporal lobe, and increased functional connectivity between the left dorsal putamen & right precuneus (related to visuospatial function), were correlated to proportionally longer DT stance time & proportionally shorter DT swing time. These findings suggest that the balance of connections between cognitive and motor networks is altered in PD, where more reliance on cognitive areas corresponds to a worse gait performance.

fMRI has also been used in assessments of gait during virtual reality (Gilat *et al.*, 2017) and motor imagery (Peterson *et al.*, 2014b) tasks. From these studies, it is understood that faster step velocity can be achieved through: i) recruitment of the cerebellum, rather than cognitive, networks and; ii) increased recruitment of networks within the basal ganglia and between the basal ganglia and the cortex (specifically orbitofrontal and supplementary motor areas). This can be achieved with increased levels of dopamine, suggesting that the use of compensatory

neural mechanisms is required in PD where there is dopaminergic loss (and not in controls), but that step velocity appears to be maintained with increased dopaminergic intervention.

PET

Two studies have investigated the cholinergic system with PD gait characteristics through PET imaging which uses radioligands to target cholinergic activity (Bohnen *et al.*, 2013; Müller *et al.*, 2015). These both identified that increased cortical cholinergic activity in PD is associated with faster step velocity, and not cholinergic activity within the thalamus. This indicates that the NBM, the source of cholinergic projection to the cortex, may play a more important role than the PPN in PD gait.

DAT-SPECT

Recent studies have utilised DAT scans to assess dopaminergic activity within the striatum. This has been associated with step length variability (Hirata *et al.*, 2020) but no other gait characteristic, despite assessments of step velocity, step length, step timings (including step time, swing time, stance time), step width and variability of step velocity and step time being completed (Cabeleira *et al.*, 2019; Hirata *et al.*, 2020). The authors of these studies attribute the overall lack of associations to an involvement of additional neurotransmitter systems in PD gait. Given that dopaminergic medications can improve gait features such as step velocity and step length, but not measures of spatial variability, robustly (Smulders *et al.*, 2016), these findings may be considered unexpected.

SAI

Two studies have assessed cholinergic activity through SAI, and identified that lower SAI, indicating lower cholinergic activity within the primary motor cortex, is associated with slow step velocity and shorter step length in PD but not controls (Rochester *et al.*, 2012) and slowing of step velocity under dual task conditions in both PD and older adults (Pelosin *et al.*, 2016). These findings again highlight the importance of cortical cholinergic activity in gait, which may be specific to PD.

EEG

EEG has been incorporated into several study designs. Firstly, one study has identified that the longer it takes for electrical neural activity to reach peak amplitude in P300, i.e. worse neural function, the slower dual-task step velocity is (Maidan *et al.*, 2019). As P300 is associated with attention, this demonstrates a potential association between step velocity and attention. However, as the association was made in a combined sample of young and healthy

older adults as well as people with PD, it is unknown whether a stronger association between P300 and step velocity, indicative of increased demand of attentional activity in PD gait, is evident in PD.

Secondly, two studies have assessed gait performance in people with PD that have electrodes from DBS, in the PPN (Thevathasan *et al.*, 2012) or STN (Chen *et al.*, 2018). Faster step velocity was associated with increased power from the local field potentials from DBS electrodes in both cases, indicating brain areas that improve step velocity when there is increased activity and demonstrating roles for both dopaminergic and cholinergic control of step velocity in PD.

INS

Recently, implantable neurostimulators (INS) have been used to record electrophysiological data from the PPN and internal portion of the globus pallidus in PD participants with DBS whilst walking (Molina *et al.*, 2020). The PPN 1–8 Hz feature modulated in response to walking. Increased power in this feature was associated with slower step velocity within three participants who attended multiple assessments "off" dopaminergic medication. A similar association was only observed in one participant when assessed "on" medication. These findings relate to studies utilising EEG by tentatively demonstrating an association between the PPN and step velocity in PD that may be mediated by dopaminergic activity. However, the authors state that caution should be taken in interpretation of findings, as few subjects were assessed and the association was made in a direction opposing that which was expected.

Table 2-2 Associations made between discrete gait characteristics and brain imaging parameters in PD

Imaging modality	Imaging parameter	Author	Gait characteristics	Outcomes
Gait assessed during single task walking				
Structural MRI	WMH rating (global & within basal ganglia); ventricular volume	Acharya *et al.* 2007	Inverse of step time (cadence)	Cadence was not associated with either WMH rating or ventricular volume in PD. Cadence correlated with ventricular volume, but not WMH, in controls.
	Global WMH rating	Sartor *et al.* 2017	Step velocity	Faster step velocity was associated with higher WMH rating in young PD participants (50-69 years) but not old PD (70-89 years). Step velocity was not related to WMH rating in controls.
	Global WMH & periventricular hyperintensity rating	Toda *et al.* 2019	Step velocity Stride length Step time variability	Slower step velocity & shorter stride length were associated with increased periventricular hyperintensity rating in frontal (velocity) & occipital regions (length). Step time variability was not associated with periventricular hyperintensity rating. No gait characteristics were associated with WMH rating.
	Grey matter density of sub-regions of the cholinergic basal forebrain	Dalrymple *et al.* 2020	Step velocity (at participants' fastest pace)	Reduced grey matter density of cholinergic nucleus 4 (Ch4), but not cholinergic nucleus 1, 2, and 3 (Ch123), was associated with reduced fast walking speed when assessed "on" dopaminergic medication.
DTI	FA (measure of white matter integrity) of fibre tracts connecting prefrontal & sensorimotor cortical regions within the corpus callosum	Fling *et al.* 2016	Step velocity Stride width	Greater integrity of fibres connecting the primary motor & the primary somatosensory cortices was linked to faster step velocity in PD participants; this did not survive multiple comparison correction. There were no associations between fibre integrity & stride width in PD. No associations were made in controls.
	FA of fibre tracts connecting the primary & secondary sensorimotor cortices within the corpus callosum	Fling *et al.* 2018	Step length asymmetry Step time asymmetry	Worse integrity of fibres connecting the pre-SMAs & the primary somatosensory cortices was associated with greater step length asymmetry in PD participants; the second of these did not survive multiple comparison correction. There were no associations with step length asymmetry & the SMA or primary motor areas, nor between step time asymmetry & integrity of any fibres in PD. No associations were made in control subjects.
fMRI	Resting state functional connectivity between hypothesised regions-of-interest from the motor control & fronto-parietal network	Vervoot *et al.* 2016	Stance time Swing time	Increased functional connectivity between the left dorsal putamen & right precuneus was correlated to proportionally longer stance time & proportionally shorter swing time in PD participants.

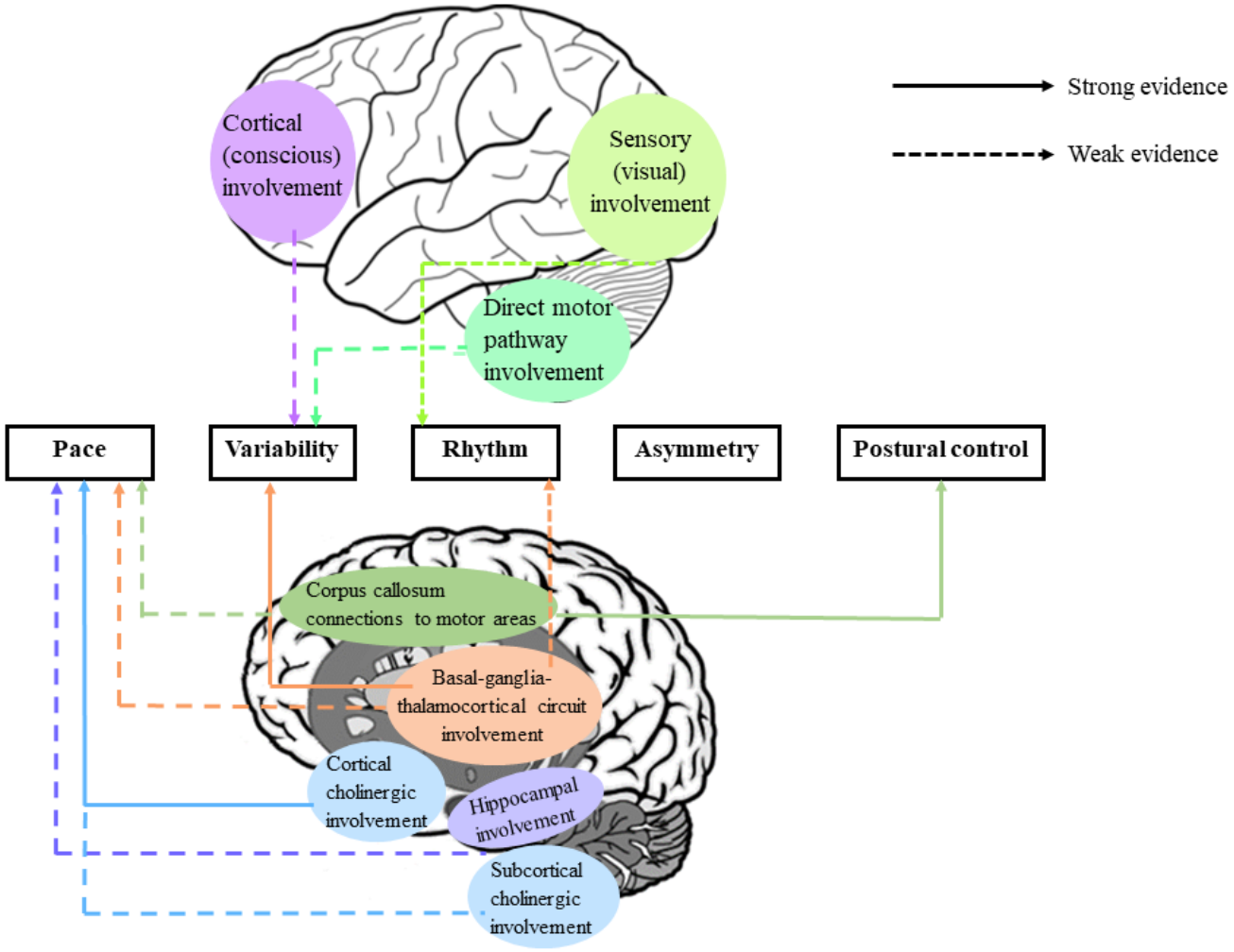
PET	Cortical & PPN-thalamic cholinergic activity; striatal dopaminergic activity	Bohnen *et al.* 2013	Step velocity	Slower step velocity in PD participants with less cortical cholinergic activity. No association between step velocity & PPN-thalamic cholinergic activity, nor striatal dopaminergic activity.
	Cortical & thalamic cholinergic activity	Müller *et al.* 2015	Step velocity	Slower step velocity was a risk factor for PD participants that had less cortical cholinergic activity, but not less combined cholinergic activity within the cortex & thalamus.
DAT-SPECT	DAT (dopamine) uptake in bilateral subregions of the striatum (sensorimotor, executive and limbic)	Hirata *et al.* 2020	Step velocity Step velocity variability Step length Step length variability Step time Step time variability	Larger step length variability was associated with less bilateral DAT uptake within executive and limbic subregions of the striatum (connected to executive and limbic areas of the frontal lobe respectively) in PD. No other associations were statistically significant.
	DAT (dopamine) uptake in the striatum (caudate, anterior and posterior putamen)	Cabeleria *et al.* 2019	Stance time (%) Swing time (%) Step velocity Inverse of step time (cadence) Step length Step width	No significant associations were evident between DAT uptake and any gait variable.
EEG	Peak alpha & beta power of the local field potential recorded from DBS electrodes within the PPN	Thevathasan *et al.* 2012	Step velocity	Faster step velocity was associated with increased peak alpha, but not beta, power.
	Peak alpha & beta power of the local field potential recorded	Chen *et al.* 2018	Step velocity	Faster step velocity was associated with increased peak beta power.

	from DBS electrodes within the STN			
Implantable neurostimulators (INS)	Average normalised power in 1-8Hz (low frequency) PPN	Molina *et al.* 2020	Step velocity Stride length Inverse of step time (cadence)	Step velocity increase was associated with a decrease in 1–8 Hz power (activity) in the PPN in 3 subjects; significant associations were identified "off" dopaminergic medication for all participants and "on" medication for one of these participants. Stride length and cadence were not associated with 1-8Hz power.
TMS	SAI, a surrogate measure of overall cholinergic activity	Rochester *et al.* 2012	Step velocity Stride length Stride time Step width	Slower step velocity and shorter step length correlated with reduced SAI in PD, signifying less inhibition & therefore less overall cortical cholinergic activity. No associations between gait and SAI were identified in controls.
Gait assessed during dual task walking				
Structural MRI	Subcortical regions; thalamus, caudate nucleus, putamen, globus pallidus, amygdala, nucleus accumbens and hippocampus	Rosenberg-Katz *et al.* 2016	DT Step velocity	Faster DT step velocity was associated with larger hippocampal volume. It is assumed that no correlations were evident between any other grey matter volume and DT (or ST) step velocity, although data is not presented.
	Global WMH rating	Sartor *et al.* 2017	DT Step velocity Dual task cost: Step velocity ((single task – dual task)/single task)	DT step velocity was not associated with WMH rating in young or old PD participants. Dual task cost i.e. relative change in step velocity during dual task correlated with WMH rating in old PD only. No correlations between WMH rating and dual task step velocity were made in controls.
	Global WMH & periventricular hyperintensity rating	Toda *et al.* 2019	DT Step velocity DT Stride length DT Step time variability	Slower DT step velocity & shorter DT stride length were associated with increased periventricular hyperintensity rating. DT step time variability was not associated with periventricular hyperintensity rating. No DT gait characteristics were associated with WMH rating.
DTI	Asymmetry of PPN structural connectivity	Peterson *et al.* 2015	Dual task interference (stride length): DT Stride length – ST Stride length	Greater dual task interference of stride length was associated with more asymmetrical PPN structural connectivity.

fMRI	Resting state functional connectivity between hypothesised regions-of-interest from the motor control & fronto-parietal network	Vervoot *et al.* 2016	DT Stance time DT Swing time	Reduced functional connectivity between the left caudate & superior temporal lobe, & increased functional connectivity between the left dorsal putamen & right precuneus were correlated to proportionally longer DT stance time & proportionally shorter DT swing time in PD participants (connectivity changes specific to those with freezing of gait).
EEG	Amplitude & latency of the event-related potential P300	Maidan *et al.* 2019	DT Step velocity	Slower DT step velocity was associated with increased P300 latency i.e. a longer time for electrical activity in the brain to reach its peak amplitude, a sign of worse neural function, in a combined sample of young adults, older adults and PD.
TMS	SAI, a surrogate measure of overall cholinergic activity	Pelosin *et al.* 2016	% change in step velocity from single task to dual task	Greater decrease in step velocity under dual task conditions correlated with reduced SAI, signifying less inhibition & therefore less overall cortical cholinergic activity. This was in a combined sample of PD and older adults (fallers and non-fallers).
Gait assessed during virtual reality or imagined walking				
fMRI	Global BOLD response Functional connectivity within the striatum	Gilat *et al.* 2017	Step time variability (surrogate measure)	Increased step time variability correlated with increased connectivity in the striatum (off medication only), driven by limbic-motor and limbic-cognitive circuits. Increased step time variability also correlated with increased connectivity between bilateral orbitofrontal cortex and inferior ventral striatum and dorsal putamen (off medication only), but not between the orbitofrontal cortex and dorsal caudate nucleus. There was greater BOLD response in the cerebellum for PD participants on dopaminergic medication, & in premotor & parietal cortical regions for participants off medication. Participants on medication had less variability than those off medication, signifying that cerebellar recruitment can occur with dopaminergic medication to maintain low step time variability.
	BOLD response in the SMA, putamen, globus pallidus, MLR & CLR due to performing an imagined walk	Peterson *et al.* 2014	Step velocity	Greater BOLD response within the left & right SMA, left putamen, left & right globus pallidus & right MLR due to imagined walking was associated with faster step velocity during usual walking, in PD but not controls.

[MRI=magnetic resonance imaging, WMH = white matter hyperintensity, DTI=diffusion tensor imaging, FA = fractional anisotropy, SMA = supplementary motor area, fMRI = function magnetic resonance imaging, PET = positron emission tomography, PPN = pedunculopontine nucleus, DAT = dopamine transporter, EEG = electroencephalography, DBS = deep brain stimulation, STN = subthalamic nucleus, TMS = transcranial magnetic stimulation, SAI = short-latency afferent inhibition, DT = dual-task, ST = single task, BOLD = blood oxygen level-dependent, MLR = mesencephalic locomotor region, CLR = cerebellar locomotor region.]

Figure 2-7 Map of regional associations made between imaging parameters and PD gait to date



[Strong evidence: association found in more than one study OR association survived stringent multiple comparison correction. Weak evidence: association identified in a single study or did not survive multiple comparison correction.]

2.7 Summary

As hypothesised, there was specificity in the associations made between discrete gait characteristics and imaging parameters in PD, within the few studies that assessed multiple gait characteristics. It was also postulated that the regional pattern of associations would differ between PD and healthy older adult populations. This was difficult to determine as i) not all studies assessed neural correlates of gait in both populations simultaneously and; ii) a number of studies within both populations identified associations with gait velocity, with many brain regions relating to velocity in some capacity. From the studies that did assess both PD and control cohorts, though, there is tentative evidence for different neural underpinnings of gait in age and disease, as findings differed between cohorts (Rochester *et al.*, 2012; Peterson *et al.*, 2014b; Fling *et al.*, 2016; Sartor *et al.*, 2017; Fling *et al.*, 2018). Future work must consider both PD and healthy control populations within the same study design, so that the neural control of PD gait (which may include an increased reliance on compensatory mechanisms) may be discerned from gait control mechanisms that occur as a result of the ageing process.

Overall, most associations between gait and neuroimaging parameters in PD have been with step velocity, the global measure of gait. This is reflective of the majority of literature assessing healthy older adults, identified in section 1 of this chapter. As explained in chapter 1, step velocity can be improved to an extent with dopaminergic medication in early disease, whereas some aspects of gait are unaffected; these other gait characteristics should therefore be assessed alongside imaging so that non-dopaminergic gait control can be better understood. Indeed, change in step velocity over the first three years of PD does not differ from change due to healthy ageing (Rochester *et al.*, 2017). The assessment of characteristics that demonstrate PD-specific change over time may better reflect PD pathology, so their assessment should be prioritised. It may be of particular interest to identify the gait characteristics associated most strongly with features of the cortical cholinergic system, as this system has been highlighted in the PD literature.

In the literature pertaining to healthy older adults, frontal and basal ganglia regions were highlighted as associating most frequently (and sometimes most strongly) with gait. Although these areas have been specified in the PD literature, particularly regions of the basal ganglia, they have not been the sole focus of investigations. Studies with PD populations have explored relatively widespread neural structures and functional networks, including the brainstem (including the PPN), occipital lobe, corpus callosum and cortical cholinergic activity. Findings from these studies may therefore indicate a reliance on compensatory

mechanisms of gait control, as outlined in chapter 1, although this cannot be stated definitively at present.

Longitudinal assessments of imaging associations with PD specific gait changes would enable a deeper understanding of the interplay between imaging parameters and gait, with the added utility of assessing the imaging features that could be used for identifying people with PD at a greater risk of future gait decline. Although imaging has been used to predict conversion to FOG or the PIGD subtype (Lenfeldt *et al.*, 2016; Moccia *et al.*, 2016; Kim *et al.*, 2018), no studies to date have assessed neural correlates of gait characteristics under a longitudinal study design in PD.

There is sufficient scope, therefore, to examine the neural correlates of discrete gait characteristics in PD with novelty. Assessments of longitudinal associations, and of associations with gait characteristics other than step velocity, have rarely been completed, yet would enrich our understanding of the neural mechanisms contributing to early gait decline. The majority of studies assessing healthy ageing cohorts have utilised structural imaging measures; these measures are of interest in PD cohorts, therefore, so that comparisons between associations made within each cohort can be readily completed and used to tease apart different control mechanisms in ageing and disease. This thesis, therefore, aims to provide increased understanding of the structural neural correlates of PD gait, particularly for gait characteristics which better reflect PD pathology, through both cross-sectional and longitudinal approaches.

Chapter 3: General Methods - the ICICLE-PD and ICICLE-GAIT studies

This chapter gives descriptions of participant recruitment and the demographic, clinical, neuropsychological, gait and imaging assessments completed through the ICICLE-PD and ICICLE-GAIT studies, which have been utilised in this thesis.

3.1 Methods

3.1.1 Study overview

This current project forms part of a large body of work completed through the Incidence of Cognitive Impairment with Longitudinal Evaluation in Parkinson's disease (ICICLE-PD) and ICICLE-GAIT studies (Khoo *et al.*, 2013; Lord *et al.*, 2014; Yarnall *et al.*, 2014). To date, there have been over sixty publications from the ICICLE studies.

ICICLE-PD is an incident, longitudinal, multicentre observational study, which includes two independent cohorts of newly diagnosed Parkinson's disease participants recruited from two defined regions in England; Newcastle-upon-Tyne/Gateshead and Cambridgeshire. The overall aim of the ICICLE-PD study is to increase knowledge of the anatomical, biochemical and genotypic mechanisms linked to cognitive decline in people with PD, with a particular focus on the clinical biomarkers predicting the transition from PD to dementia associated with PD (PDD). ICICLE-GAIT is a Newcastle-upon-Tyne/Gateshead based sub-study nested within ICICLE-PD, which aims more specifically to assess the predictive value of gait for cognitive decline and PDD conversion.

Participants completed an extensive assessment battery; assessments were completed at the initial baseline visit, soon after the diagnosis of PD in participants, and several clinical and neuropsychological evaluations were repeated every eighteen months up to and including ninety months after baseline. In addition to the clinical, neuropsychological, gait and imaging assessments described in this thesis, several participants were also involved in assessments of cerebrospinal fluid, genetics, neurophysiological responses, sleep, fMRI and fluorodeoxyglucose (FDG) PET. This thesis uses structural magnetic resonance imaging, clinical and neuropsychological data assessed at baseline, and gait data from every assessment up to and including seventy-two months after baseline. Further details of these assessments are presented later on in this chapter. As this project combines data from the ICICLE-PD and ICICLE-GAIT studies, the data and results within this thesis relate to participants recruited from the Newcastle-Gateshead region only.

3.1.2 Participants and recruitment

The study was approved by the Newcastle and North Tyneside research and ethics committee and all participants gave written informed consent with sufficient cognitive capacity.

Recruitment for the study was conducted between June 2009 and December 2011, with the aim of identifying every new case of PD within Newcastle-upon-Tyne/Gateshead. Outpatient care practices in Newcastle-upon-Tyne/Gateshead were encouraged to refer patients with suspected PD to members of the study team; patients that expressed an interest in participation were given a Patient Information Sheet for consideration. All patients had a confirmed diagnosis of PD as defined by the Queen Square Brain Bank criteria for idiopathic PD (Hughes *et al.*, 1992). Study exclusion criteria for ICICLE-PD comprised:

1. Patients suspected of Parkinsonism that were diagnosed prior to study onset.
2. Patients without sufficient working knowledge of the English language, defined as an inability to perform the neuropsychological assessments and questionnaires, in the opinion of the assessor.
3. Patients with significant memory impairment at presentation, defined as a score < 24 on the Mini-Mental State Examination, or meeting DSM IV criteria for dementia (APA American Psychiatric Association, 2000) or PDD (Emre *et al.*, 2007) at presentation.
4. Patients without the capacity to consent to be involved in the study, as assessed by criteria laid out in the Mental Health Act code of practice, section 4-3.
5. Patients with a diagnosis of Parkinsonian disorders other than PD, including:
    (i) Dementia with Lewy bodies (DLB), according to revised consensus criteria (McKeith *et al.*, 2005).
    (ii) Drug-induced Parkinsonism as a result of exposure to dopamine receptor blocking agents at symptom onset.
    (iii) Vascular Parkinsonism, defined as repeated strokes or the stepwise progression of symptoms.
    (iv) Atypical Parkinsonism, such as progressive supranuclear palsy, multiple system atrophy, or corticobasal degeneration, according to accepted diagnostic criteria (Litvan *et al.*, 2003).

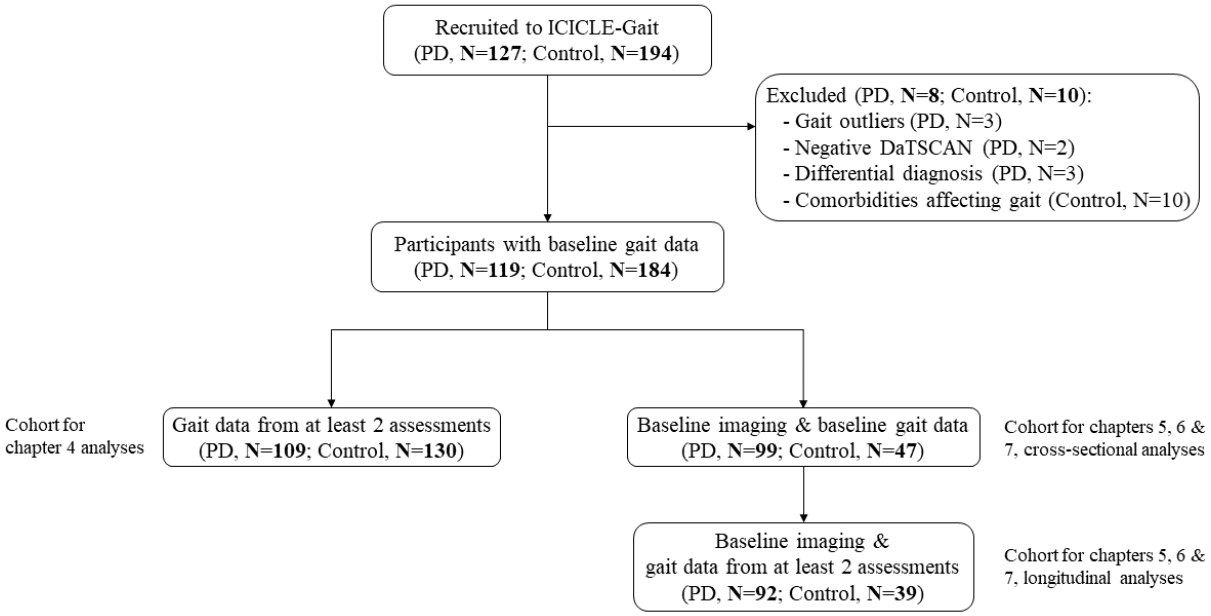
Healthy subjects were additionally recruited for this study, so that a comparison to typical ageing could be made. Recruitment was completed in the Newcastle-upon-Tyne/Gateshead area through local advertisements and community groups. They completed similar

assessments to the PD participants, with the exception of PD-specific rating scales and questionnaires. Control participants were not included in the study if they were under the age of forty-five; did not have sufficient command of the English language; were unable to walk independently without a mobility aid; demonstrated a history of significant neurological, movement or psychiatric disorders; could not give informed consent; or scored < 24 on the Mini-Mental State Examination or met DSM IV criteria for dementia. Neither spouses, relatives nor carers were used as control participants, so that there was no bias in their responses.

ICICLE-GAIT recruited a subset of the PD participants involved in ICICLE-PD. Two control cohorts were recruited into ICICLE-GAIT; one cohort was a subset of control participants that consented to ICICLE-PD (*N=100*), the other was recruited specifically for ICICLE-GAIT at the baseline and 36-month assessments only (*N=94*). Chapter 4 of this thesis investigates the gait characteristics that change over 72 months in PD and control participants. To increase the power of the analyses within this chapter, and therefore improve the accuracy of findings, participants that were involved in ICICLE-GAIT, but not necessarily ICICLE-PD, and that attended at least two gait assessments, were included in analysis within Chapter 4.

Chapters 5, 6 and 7 explore the associations between gait and volumetric parameters derived from structural MRI. Therefore, only participants that were involved in both ICICLE-PD and ICICLE-GAIT, with suitable baseline MRI scans and baseline gait assessments, were included in analyses for these chapters. All baseline assessments for each participant were completed within a median period of three weeks. For longitudinal analyses in chapters 5, 6 and 7, only participants that had gait assessed at more than one session were included. **Figure 3-1** displays an overview of the number of participants recruited into ICICLE-Gait and the number of these participants included in the analyses within each chapter of this thesis. This will be referenced in subsequent chapters of this thesis. A separate flowchart detailing participant attrition across the 72-month assessment period of ICICLE-GAIT is included within chapter 4.

Figure 3-1. Overview of the number of participants completing structural MRI and gait assessments through the ICICLE studies



3.1.3 Clinical assessments

Age, sex, height and mass were recorded; depression was also screened for (Geriatric Depression Scale [GDS-15], (Yesavage *et al.*, 1982), **Appendix D**). The National Adult Reading Test (NART, **Appendix E**) assessed premorbid intelligence at baseline (Mathias *et al.*, 2007). Global cognition was assessed through the Montreal Cognitive Assessment (MoCA, **Appendix F** (Nasreddine *et al.*, 2005)), developed as clinical tool to quickly identify mild cognitive impairment, as well as the Mini-Mental State Examination (MMSE, **Appendix G** (Folstein *et al.*, 1975)). Both measures of global cognition have been considered because, although the MoCA is thought to be a more sensitive measure to early cognitive decline in PD (Zadikoff *et al.*, 2008; Hoops *et al.*, 2009; Dalrymple-Alford *et al.*, 2010), not every participant completed the MoCA at baseline assessment.

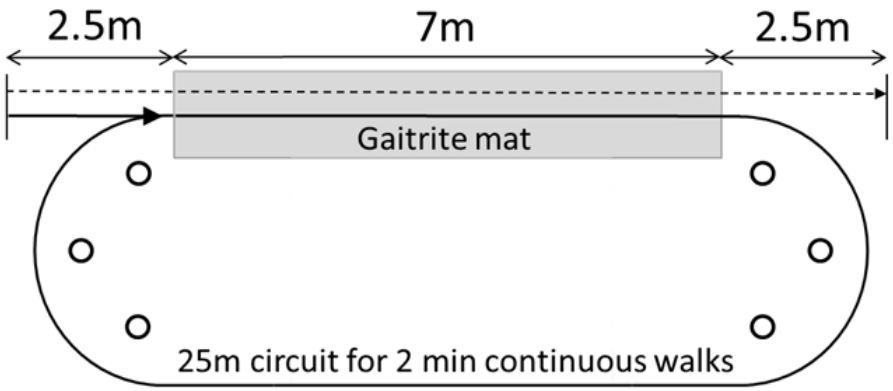
PD participants additionally completed specific PD clinical assessments. Within this thesis, PD specific motor disease severity was assessed through the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III, **Appendix H** (Goetz *et al.*, 2007)); higher scores on this assessment indicate greater disability. From this, the Hoehn and Yahr clinical rating scale (H&Y) was derived (**Appendix H**); again, larger scores represent more disability (Goetz *et al.*, 2004). The presence of freezing of gait (FOG) was assessed with the FOG questionnaire (Nieuwboer *et al.*, 2009). The intensity of dopamine dose of each participant was calculated using Levodopa equivalent daily dose as has been previously

described (Tomlinson *et al.*, 2010). All assessments were completed approximately one hour after dopaminergic medication, so that optimal performance was recorded.

3.1.4 Gait assessments

Gait was assessed at 18-month intervals for up to six years. Assessments were completed in the gait laboratory at the Clinical Ageing Research Unit, Newcastle University, one hour after dopaminergic medication for optimal performance. Gait was measured whilst participants walked at their self-selected pace for two minutes around a 25-metre oval circuit, demarcated by cones, which included a 7-metre long × 0.6-m-wide instrumented walkway (240Hz sampling frequency, Platinum model GAITRite, software version 4.5, CIR systems, United States of America, **Figure 3-2**). This method is reliable for measuring gait characteristics in older adults with and without pathology (Bilney *et al.*, 2003). Gait was repeatedly sampled as participants walked over the walkway and continued the circuit. At least 40 steps (5 passes) were completed over the walkway per participant to ensure robust measurement of gait variability (Galna *et al.*, 2013). Participants began to walk 2.5m ahead of the walkway so that acceleration did not affect walking.

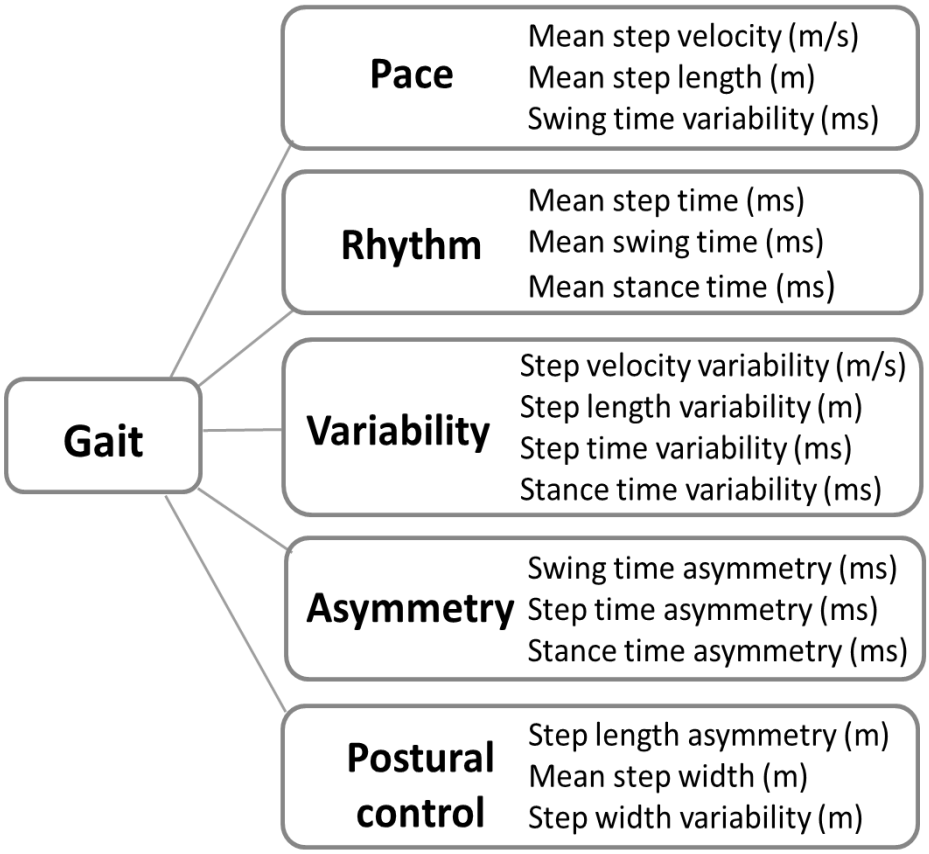
Figure 3-2. Set up of the laboratory for gait assessment



Sixteen discrete gait characteristics were derived and quantified from the GaitRite walkway according to an *a priori* model developed for older adults (Lord *et al.*, 2013c), and validated in PD (Lord *et al.*, 2013b), as shown in **Figure 3-3**. Both the domains (e.g. pace) and individual characteristics (e.g. step velocity) shown in **Figure 3-3** will be referenced throughout this thesis. Left and right steps were calculated separately and reported as mean values; gait characteristics were derived from both left and right steps. Gait characteristics

related to variability measures were calculated using the standard deviation (sd) of left and right steps calculated separately and then combined, to avoid confounding step-to-step variability with variability which originates from asymmetry (Galna *et al.*, 2013). Asymmetry characteristics were calculated as the absolute difference between the mean of the right and left steps (Galna *et al.*, 2015). An illustration of these characteristics can be found in chapter 1 (**Figure 1-1).**

Figure 3-3. The model of gait derived and validated by Lord et al. for PD



[16 gait characteristics map to 5 gait domains; Pace, Rhythm, Variability, Asymmetry and Postural Control]

3.1.5 Magnetic resonance imaging assessments

All MRI scans were completed at baseline assessment using a 3 Tesla Philips Intera Achieva scanner (Philips Medical Systems, Eindhoven, Netherlands) within the Newcastle University Magnetic Resonance Centre. An eight-channel receiver head coil was used, and head position and comfort were optimised through foam pads placed around the head. Participants were asked to try to minimise their body movements throughout the scan. Several sequences were performed using the scanner; scans resulting from the following sequences have been included in this thesis:

a) A sagittal T1-weighted volumetric sequence, which included the whole brain using a magnetisation prepared rapid acquisition gradient echo (MP-RAGE) sequence with the following parameters: Repetition Time (TR) = 9.6ms, Echo Time (TE) = 4.6ms, Flip Angle = 8°, SENSE factor = 2. 150 sagittal slices with a slice thickness of 1.2mm were taken, with a 240 x 240mm Field of View. This yielded a voxel size of 1.5 X 1.5 X 1.5mm^3. The acquisition time for this sequence was four minutes.

Descriptions of the MRI pre-processing techniques used in this thesis are presented in subsequent chapters, where applicable.

3.1.6 Data analysis

Statistical analyses were completed with Statistical Package for Social Sciences (SPSS v24.0, Chicago, IL) and R software (Version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria). The normality of each variable was assessed through the visual inspection of histograms; evaluation of skewness and kurtosis; and the Kolmogorov-Smirnov test. Group comparisons between normally distributed continuous variables were completed using Student's t-test or analysis of covariance (ANCOVA) correcting for age and sex as appropriate. The Mann-Whitney test was used for group comparisons of continuous variables that were not normally distributed. Group comparisons of categorical variables were assessed through Pearson's Chi-squared tests. Additional statistical analyses are outlined in each chapter as appropriate.

Chapter 4: Gait progression over six years in Parkinson's disease: effects of age, medication and pathology*

This chapter describes the progression of gait impairment over the first six years of PD. By delineating changes in gait associated with ageing, dopaminergic medication and disease progression, this chapter establishes the gait characteristics that are most reflective of evolving PD pathology. Therefore, this chapter identifies the gait characteristics that are of most interest when considering the neural mechanisms that may contribute to longitudinal gait decline in PD.

4.1 Introduction

As outlined in chapter 1, gait impairment is a common, debilitating feature of PD that manifests in early and prodromal disease stages (Galna *et al.*, 2015; Del Din *et al.*, 2019a; Del Din *et al.*, 2020) and is associated with an increased falls risk (Lord *et al.*, 2016) and reduced physical activity levels (Lord *et al.*, 2013d; Del Din *et al.*, 2019b). Although dopaminergic medications can provide immediate improvements of gait in PD (Bryant *et al.*, 2011a; Bryant *et al.*, 2011b; Sterling *et al.*, 2015), this is selective and some gait characteristics continue to worsen over time despite optimal dopaminergic treatment (Galna *et al.*, 2015). This suggests that additional interventions are required to minimise gait impairment and its progression (Lord, 2011), and so reduce falls and increase physical activity.

To develop appropriate interventions for the improvement of gait impairments, it is imperative that useful therapeutic targets are identified. However, as evidenced in chapter 2, the neuroanatomical and functional substrates which underpin discrete gait characteristics, and how these change in response to disease progression, remain poorly understood. To facilitate a comprehensive longitudinal investigation of the neural underpinnings of PD gait, the characteristics of gait that change as a result of disease progression must be identified.

The aetiology of gait impairment in PD is multifaceted. It is underpinned by a complex interaction of pathology, age-related changes, compensatory mechanisms and, eventually, secondary deconditioning due to restricted mobility (Lord *et al.*, 2013b). This explains, in part, the highly variable response to dopaminergic medication. Teasing apart changes in gait due to ageing, PD and medication will help to identify aspects of gait impairment that are most reflective of evolving PD pathology and are, therefore, of most interest when considering the neural mechanisms contributing to PD-specific gait decline. This is a fundamental step towards developing therapies which minimise gait progression in PD.

*This chapter has been published in Frontiers in Aging Neuroscience

Previous work, using gait data from the ICICLE-GAIT study (Rochester *et al.*, 2017), has shown that discrete gait characteristics (variability of step time, step length and step width) progress more rapidly over three years in a newly diagnosed, optimally medicated PD cohort than in age-matched controls. This provided the first evidence suggesting that the rate of progression of gait impairment is driven by several factors related to age and pathology. Others have identified a shortening of step length and swing time over 18 months from PD diagnosis (Galna *et al.*, 2015) and greater increases in step or stride time variability over five years in early and moderate stages of PD compared to healthy controls (Hobert *et al.*, 2019; Micó-Amigo *et al.*, 2019). However, relatively short study timeframes, inconsistent reporting of gait characteristics, lack of control cohorts, limited exploration of medication effects and wide variation in disease duration at inclusion has limited insights into gait progression, particularly with respect to background ageing and medication.

To comprehensively determine the discrete changes in gait which are specifically due to PD progression, gait change should be modelled over a longer timeframe with respect to an age-matched control cohort and with consideration of changes in dopaminergic medication. Additionally, modelling gait progression from diagnosis enables a more precise understanding of gait changes occurring prior to the onset of more severe motor symptoms and, therefore, during a time when interventions may be most beneficial.

Aims and hypotheses

The overall objective of this chapter is to describe the natural progression of gait impairment over the first six years of PD. Specific aims of this chapter are to: i) identify gait characteristics that significantly change over six years in newly diagnosed PD and healthy age-matched controls; ii) evaluate gait changes in the PD cohort which relate to ageing and/or disease progression by comparing rates of gait change between PD and control groups; and iii) explore the relationship between gait changes and changes in dopaminergic medication dose in early PD.

It is hypothesised that:

1. Variability of step time, step length and step width will significantly change over the first six years of PD, as they did over the first three years (Rochester *et al.*, 2017).
2. Additional characteristics will demonstrate significant change over six years that are specific to the PD cohort, to reflect the additional progression of PD pathology over a longer timeframe as well as any potential contributions of compensatory mechanisms and secondary deconditioning due to restricted mobility.

3. Changes in selective gait characteristics will be associated with changes in dopaminergic medication, as have been identified previously (Rochester *et al.*, 2017), to reflect the dopa-responsiveness (and therefore highlight dopa-resistance) of discrete gait characteristics.

4.2 Methods

4.2.1 Participants

Participants with newly diagnosed idiopathic PD were recruited into ICICLE-GAIT, a study nested within the incident cohort study ICICLE-PD. Recruitment was conducted between June 2009 and December 2011, as described fully in chapter 3. People with PD were tested 'on' medication, defined as one hour after PD medication. Healthy age-matched controls were recruited from the community in two cohorts so that progression due to typical ageing could be assessed; one cohort invited participants to assessments at the baseline and 36-month time points only (*N=94*), whereas the other cohort invited participants to all assessments (*N=100*). Gait was assessed at 18-month intervals for up to six years. **Figure 4-1** shows participant recruitment and attrition throughout ICICLE-GAIT.

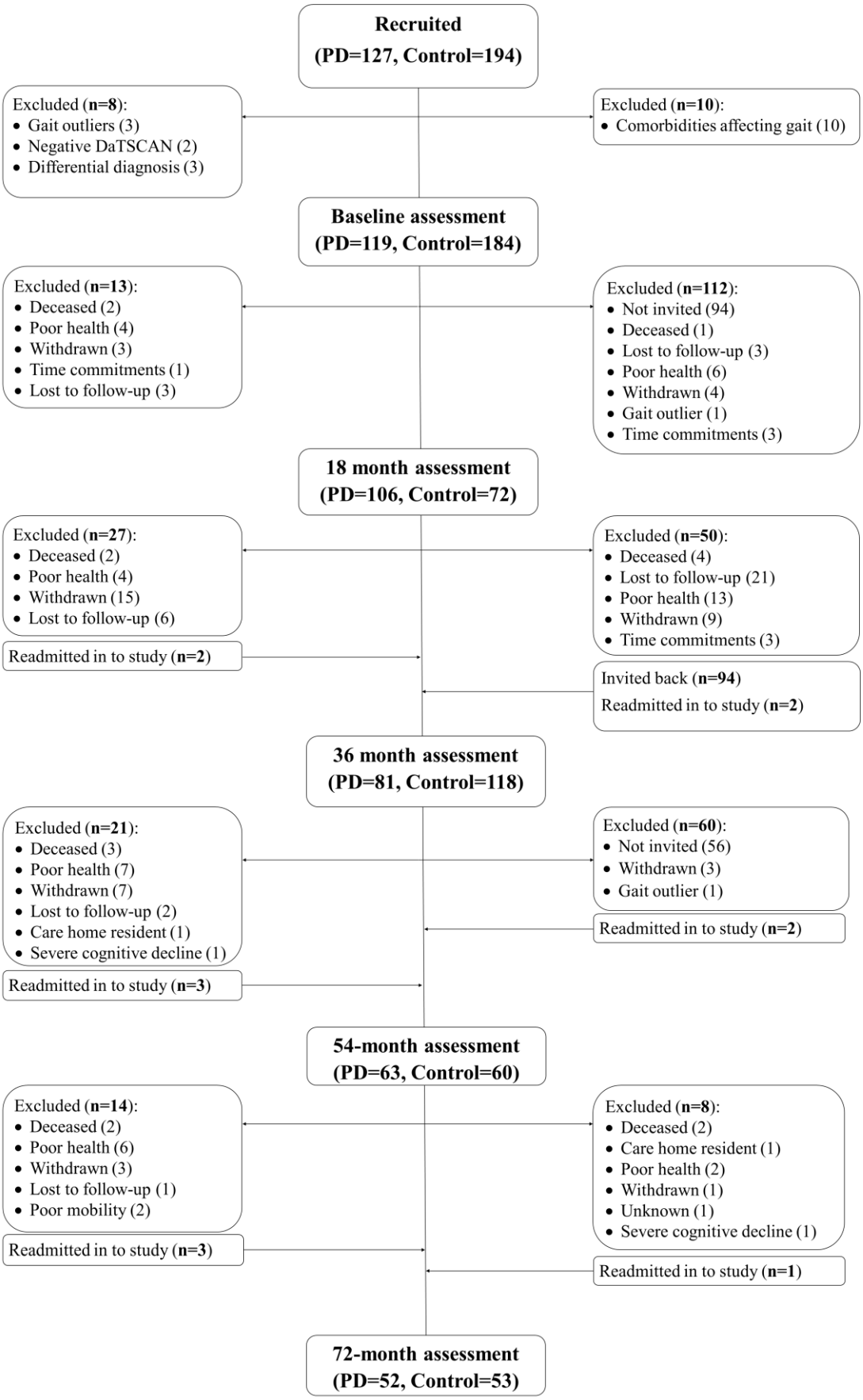
4.2.2 Clinical assessments

As outlined in chapter 3, age, sex, height and mass were recorded. Depression was also screened for using the GDS-15. Premorbid intelligence was assessed at baseline with the NART; global cognition was assessed through both the MMSE and MoCA. PD specific motor severity was assessed through the MDS-UPDRS III, from which Hoehn and Yahr Stage (H & Y) was derived. The presence of FOG was assessed with the FOG questionnaire. Levodopa equivalent daily dose (LEDD) was calculated at each session (Tomlinson *et al.*, 2010).

4.2.3. Gait assessment

As detailed in chapter 3, for gait assessment, participants walked at their self-selected pace for two minutes around a 25m oval circuit which included a 7m long instrumented walkway (Platinum model GAITRite, software version 4.5, CIR systems, United States of America, **Figure 3-2**). A minimum of five passes over the walkway were completed per participant to ensure robust measurement of gait variability (Galna *et al.*, 2013). Gait outcomes were derived and quantified according to an *a priori* model developed for older adults (Lord *et al.*, 2013c), and validated in PD (Lord *et al.*, 2013b), that describes 16 discrete gait characteristics (**Figure 3-3**). Methods to calculate the gait characteristics are described in chapter 3.

Figure 4-1. Flow chart of participant assessments for ICICLE-GAIT over 72 months



4.2.4 Statistical analyses

Analyses were completed using SPSS (IBM Corp. V.24, USA) and R (R Foundation for Statistical Computing, V3.5.2, Austria). The distribution of continuous variables was assessed through methods described in chapter 3.

Cross-sectional analyses

Firstly, univariate analyses described baseline demographic, clinical and gait data for both PD and control groups in cross-section. Student's t-test, Mann-Whitney U test and chi-square tests, as appropriate, assessed baseline differences between PD and control cohorts, and, within diagnostic groups, between participants who did ("completers") and did not ("non-completers") complete gait assessment at the 72-month time point. Due to high levels of skewness, gait asymmetry data were square root transformed and temporal variability data were natural log transformed for cross-sectional analysis; no outliers were removed.

Longitudinal analyses

Secondly, linear mixed effect models (LMEM; R, "lme4" (Bates *et al.*, 2015) and "lmerTest" (Kuznetsova *et al.*, 2017)) separately modelled change in each gait characteristic over 72 months. Due to the longitudinal nature of this study, some participants either withdrew or were lost to follow up across the 72-month study period. Linear mixed-effects models can give appropriate estimates of regression coefficients despite participant drop-out of this nature across the study period (Little, 1995). Random slope models gave each participant a unique intercept and slope, accounting for individual variability and allowing for correlation between intercept and slope. The *a priori* confounders baseline age and sex were included as fixed effects terms in all models; model fit was assessed by likelihood ratio tests. Preliminary analyses indicated that there is insufficient evidence for non-linear changes in gait over time (**Appendix I**). Linear models of change in gait over time were therefore deemed appropriate to use.

There were three stages to longitudinal analyses addressing each aim in turn: i) to quantify the progression of gait impairment over time within diagnostic groups, basic models independently assessed changes in gait for PD and control groups; ii) to compare the rate of gait change between the groups, each model included the interaction between group and time (Group x Time); and iii) to evaluate the association between change in gait and change in LEDD, PD models included the interaction between LEDD and time (LEDD x Time). In order to aid data interpretation with respect to the aims of this chapter, significant gait

changes in the PD cohort that were related to ageing and disease progression were discerned using the following criteria:

1. Gait change related only to disease progression: a significant gait change identified in the PD cohort but not in controls, where rate of change differed significantly between groups.
2. Gait change related to ageing: a significant gait change identified in both PD and control cohorts, where rate of change did *not* differ significantly between PD and control groups.
3. Gait change related to both ageing and disease progression: a significant gait change identified in both PD and control cohorts, where rate of change differed significantly between groups.

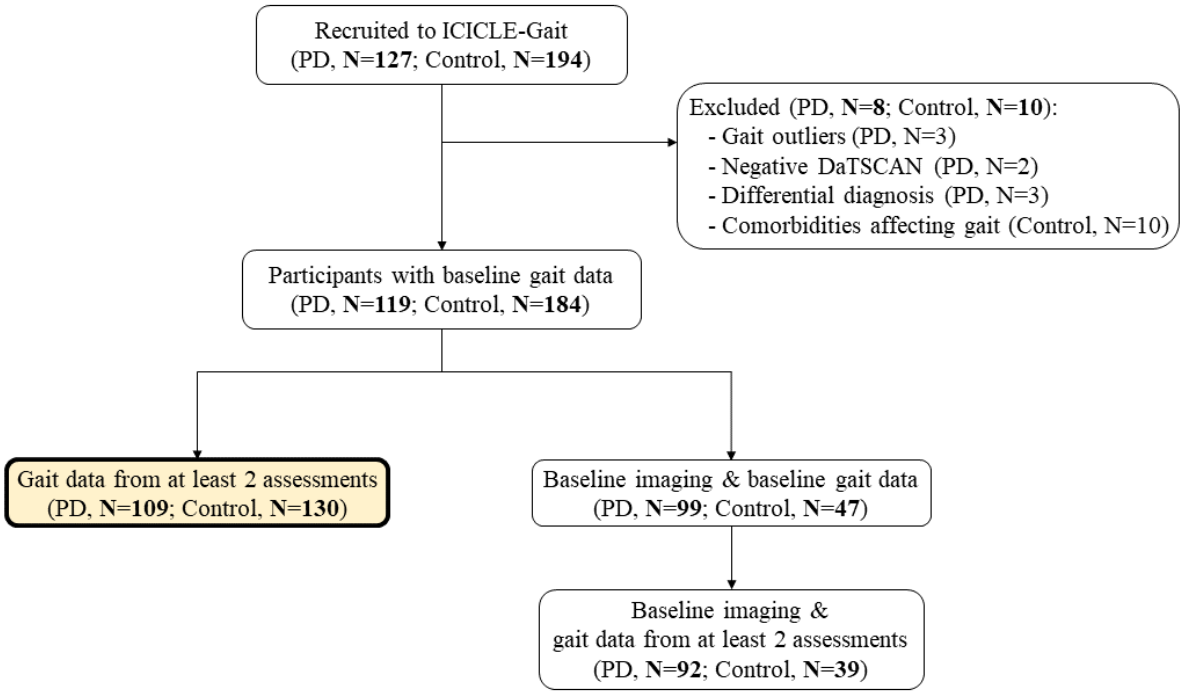
In addition, individual trajectories of gait change over time were plotted to illustrate variability within the cohorts. A threshold of $p < 0.05$ guided statistical interpretation. *p* values were not adjusted for multiple comparisons. This allowed for direct comparisons to be made with previous analyses from the ICICLE-GAIT cohort which quantified gait change over the first three years of PD (Rochester *et al.*, 2017). Additionally, this reduced the risk of type II statistical error (Rothman, 1990). As this chapter has been completed to determine the gait characteristics suitable for use in subsequent longitudinal analyses in this thesis, it was important to highlight all possible gait changes and avoid false negative findings. As the risk of type I error (false positives) may be increased, full *p* values are presented to allow for comparisons of the statistical robustness of findings.

4.3 Results

4.3.1 Study participants

130 control subjects and 109 PD patients completed at least two gait assessments and so have been included in this analysis (**Figure 4-2**). A detailed breakdown of the number of assessments completed by participants can be found in **Appendix J**.

Figure 4-2. Participants considered within chapter 4 analyses



At baseline, PD participants had a similar age, height, mass and NART score to controls, as shown in **Table 4-1**. The PD group had proportionately more males, poorer global cognition (MoCA & MMSE) and lower mood (GDS). The mean time from PD diagnosis to baseline assessment was six months. For PD participants, motor score severity at baseline was low (mean MDS-UPDRS III = 25); 10% had already experienced FOG and most (90%) were taking dopaminergic medication, in keeping with clinical practice. For both diagnostic groups, participants who completed the 72-month assessment ("completers") were younger and had better baseline performance on the MoCA compared to "non-completers" who did not attend the 72-month assessment. PD completers also had less severe motor disease (lower MDS-UPDRS III and Hoehn and Yahr stage) at baseline, compared to non-completers (**Table 4-2**).

Table 4-1. Baseline demographic and clinical characteristics

Characteristic	**Control (n = 130)**	**PD (n=109)**	**Group difference** ***(test statistic, p)***
Age (years)	69.5 (7.4)	67.4 (9.9)	t = 1.87, p = 0.063
Sex (f)	72f (55%)	37 f (34%)	**χ^2 = 11.0, p = 0.001***
Height (m)	1.68 (0.10)	1.70 (0.08)	t = -1.05, p = 0.294
Body mass (kg)	78.3 (14.9)	78.8 (15.4)	t = -0.28, p = 0.782
GDS	1 (2)	3 (2)	**U = 4077, p < 0.001***
Education (years)	14 (4)	13 (4)	U = 3723, p = 0.373
NART	117 (8)	115 (11)	U = 6650, p = 0.483
MoCA ⊦	27 (2)	25 (4)	**U = 2601, p < 0.001***
MMSE	29 (1)	29 (1)	**U = 5047, p <0.001***
MDS-UPDRS III (0-132)	-	25 (10)	-
H&Y stage n (%)	-	I 26 (24%); II 65 (60%); III 18 (17%)	-
n (%) who report FoG	-	11 (10%)	-
LEDD (mg/day)	-	175 (132)	-

[Results are presented as mean (sd), or number (%) where appropriate. BMI = Body Mass Index; GDS = Geriatric Depression Scale; NART = National Adult Reading Test; MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination; MDS-UPDRS III = Movement Disorders Society Unified Parkinson's Disease Rating Scale part III; H&Y = Hoehn and Yahr; FOG = Freezing of Gait; LEDD = Levodopa Equivalent Daily Dose. ⊦ demonstrates a smaller sample size; control n = 73, PD n = 104. Significant differences between groups are in bold and denoted by *.]

Table 4-2. Descriptive and clinical characteristics of PD and control completers and non-completers

Demographic or clinical characteristic	Control			PD		
	Completers (n = 53)	**Non-completers (n = 77)**	**Group difference *(test statistic, p)***	**Completers (n = 52)**	**Non-completers (n = 57)**	**Group difference *(test statistic, p)***
Age (years)	67.0 (6.3)	71.3 (7.6)	**t = 3.41, p = 0.001***	64.8 (9.8)	69.7 (9.5)	**t = 2.63, p = 0.010***
Sex	25f 28m	47f 30m	χ^2 = 2.44, p = 0.118	17f 35m	20f 37m	χ^2 = 0.07, p = 0.792
Height (m)	1.71 (0.09)	1.66 (0.10)	**t = -2.73, p = 0.007***	1.70 (0.08)	1.70 (0.08)	t = 0.05, p = 0.959
Body mass (kg)	82.7 (14.8)	75.3 (14.3)	**t = -2.84, p = 0.005***	77.5 (13.4)	80.0 (17.0)	t = 0.85, p = 0.396
GDS	1 (1)	2 (2)	U = 1825, p = 0.274	2 (2)	3 (2)	U = 1356, p = 0.436
Education (years)	14 (4)	12 (3)	U = 411, p = 0.077	14 (4)	13 (4)	U = 1265, p = 0.184
NART	117 (8)	117 (7)	U = 2024, p = 0.936	116 (11)	114 (11)	U = 1297, p = 0.333
MoCA	28 (2)	26 (2)	**U = 341, p = 0.012***	26 (3)	24 (4)	**U = 921, p = 0.005***
MMSE	29 (1)	29 (1)	U = 1184, p = 0.409	29 (1)	29 (1)	U = 1224, p = 0.103
MDS-UPDRS III (0-132)	-	-	-	22 (9)	28 (11)	**t = 2.96, p = 0.004***
Hoehn and Yahr stage n (%)	-	-	-	I 18 (35%); II 26 (50%); III 8 (15%)	I 8 (14%); II 39 (68%); III 10 (18%)	**χ^2 = 6.45, p = 0.040***
n (%) who report FoG	-	-	-	5 (10%)	6 (11%)	χ^2 = 0.03, p = 0.875
LEDD (mg/day)	-	-	-	160 (117)	190 (144)	t = 1.18, p = 0.241

[Results are presented as mean (sd), or number (%) where appropriate. Significant differences between completers and non-completers are in bold and denoted by *.]

4.3.2 Baseline gait assessment

Baseline gait characteristics for both PD and control groups are included in **Table 4-3**. There were impairments in 13 gait characteristics in PD compared to controls. PD participants walked slower with a shorter step length, longer step and stance time and greater asymmetry and variability (except for less step width variability) compared to controls. Within-group differences between PD and control completers and non-completers are presented in **Table 4-4**. PD completers walked significantly faster with a longer step at baseline compared to non-completers. Control completers were significantly less variable in stance time, step velocity and step length than non-completers.

Table 4-3. Differences in baseline gait between PD and control

Gait characteristic	Control (n = 130)	PD (n=109)	Group difference *(p)*
Step velocity (m/s)	1.29 (0.17)	1.13 (0.21)	**<0.001***
Step length (m)	0.69 (0.07)	0.62 (0.10)	**<0.001***
Swing time variability (ms)	14.3 (4.2)	17.3 (5.8)	**<0.001***
Step time variability (ms)	15.4 (4.5)	18.5 (6.4)	**<0.001***
Stance time variability (ms)	18.3 (6.1)	22.5 (9.3)	**<0.001***
Step velocity variability (m/s)	0.05 (0.01)	0.05 (0.02)	0.465
Step length variability (m)	0.02 (0.01)	0.02 (0.01)	**<0.001***
Step time (ms)	533 (45)	556 (45)	**<0.001***
Swing time (ms)	386 (31)	389 (32)	0.347
Stance time (ms)	683 (66)	723 (72)	**<0.001***
Step time asymmetry (ms)	9.8 (8.2)	20.6 (25.4)	**<0.001***
Swing time asymmetry (ms)	8.0 (7.8)	17.0 (20.0)	**<0.001***
Stance time asymmetry (ms)	8.0 (8.1)	16.6 (19.5)	**<0.001***
Step length asymmetry (m)	0.02 (0.02)	0.03 (0.02)	**0.007***
Step width (m)	0.09 (0.02)	0.09 (0.03)	0.279
Step width variability (m)	0.02 (0.01)	0.02 (0.01)	**<0.001***

[Descriptive data for untransformed variables are presented here as mean (sd). Significant differences between groups are in bold and denoted by *.]

Table 4-4. Baseline gait characteristics for PD and control completers and non-completers

Gait characteristic	Control			PD		
	Completers (n = 53)	**Non-completers (n=77)**	**Group difference *(p)***	**Completers (n = 52)**	**Non-completers (n=57)**	**Group difference *(p)***
Step velocity (m/s)	1.29 (0.14)	1.30 (0.18)	0.953	1.19 (0.20)	1.08 (0.20)	**0.006***
Step length (m)	0.69 (0.07)	0.68 (0.08)	0.319	0.65 (0.10)	0.59 (0.09)	**0.001***
Swing time variability (ms)	13.6 (3.8)	14.9 (4.3)	0.064	16.0 (4.3)	18.5 (6.7)	0.053
Step time variability (ms)	14.7 (4.2)	15.9 (4.6)	0.099	17.6 (5.9)	19.3 (6.7)	0.170
Stance time variability (ms)	17.1 (5.5)	19.2 (6.3)	**0.039***	21.5 (9.1)	23.5 (9.4)	0.209
Step velocity variability (m/s)	0.05 (0.01)	0.05 (0.01)	**0.002***	0.05 (0.02)	0.05 (0.02)	0.741
Step length variability (m)	0.02 (<0.01)	0.02 (0.01)	**0.015***	0.02 (0.01)	0.02 (0.01)	0.133
Step time (ms)	539 (44)	530 (46)	0.241	556 (45)	556 (46)	0.933
Swing time (ms)	385 (31)	386 (31)	0.947	395 (32)	384 (32)	0.091
Stance time (ms)	695 (64)	674 (67)	0.090	718 (71)	727 (73)	0.507
Step time asymmetry (ms)	11.1 (8.5)	8.9 (7.9)	0.084	22.9 (31.2)	18.5 (18.7)	0.419
Swing time asymmetry (ms)	8.2 (7.3)	7.9 (8.2)	0.723	17.5 (24.8)	16.4 (14.5)	0.717
Stance time asymmetry (ms)	8.1 (8.1)	7.9 (8.2)	0.946	17.7 (24.1)	15.7 (14.4)	0.941
Step length asymmetry (m)	0.02 (0.02)	0.02 (0.01)	0.976	0.03 (0.03)	0.02 (0.02)	0.791
Step width (m)	0.09 (0.02)	0.09 (0.03)	0.801	0.09 (0.03)	0.09 (0.03)	0.488
Step width variability (m)	0.02 (0.01)	0.02 (0.01)	0.331	0.02 (0.01)	0.02 (<0.01)	0.285

[Descriptive data for untransformed variables are presented here as mean (sd). Significant differences between completers and non-completers are in bold and denoted by *.]

4.3.3 Progression of gait impairment over 72 months

To address the first aim of this chapter, gait progression was modelled within each diagnostic group. In both groups, gait characteristics from all five domains of gait significantly progressed over 72 months. Progression was more extensive in the PD cohort. In basic change models, ten of sixteen characteristics significantly changed in PD compared to seven characteristics in controls (**Table 4-5**). In PD, gait became significantly slower, with a shorter step length, greater variability (swing and step time, step length, step width), reduced asymmetry (swing time), wider step width, and faster steps (step and swing time). Gait also became significantly slower in controls, with shorter steps, greater variability (step length), greater asymmetry (step length), wider step width and faster swing time. Variation was considerable between individuals in the trajectories of change for each gait characteristic (**Figure 4-3**). Descriptive data for gait performance at each session for both PD and control groups is presented in **Appendix K**.

4.3.4 Discerning PD-specific gait changes from ageing

In line with the second chapter aim, the ten significant gait changes identified within the PD cohort have been separated into those relating to ageing and/or disease progression, according to three criteria outlined in the methods (section 4.2). Four characteristics demonstrated change related only to disease progression, meeting criterion 1. Specifically, increasing variability (step and swing time), reducing asymmetry (swing time) and worsening postural control of gait (increasing step width variability) were significant changes in PD but not controls (**Figure 4-3**, panel A), and change differed significantly between the groups (significant Group x Time interaction, **Table 4-5**, **Figure 4-4**).

Three characteristics changed solely due to ageing, meeting criterion 2: slowing step velocity, quickening swing time and increasing step width were exhibited in PD and controls at similar rates (**Figure 4-4**). Step time changed in the PD group only; as this change was not significantly different from change in the control group, it does not meet any of the outlined criteria so has not been considered further.

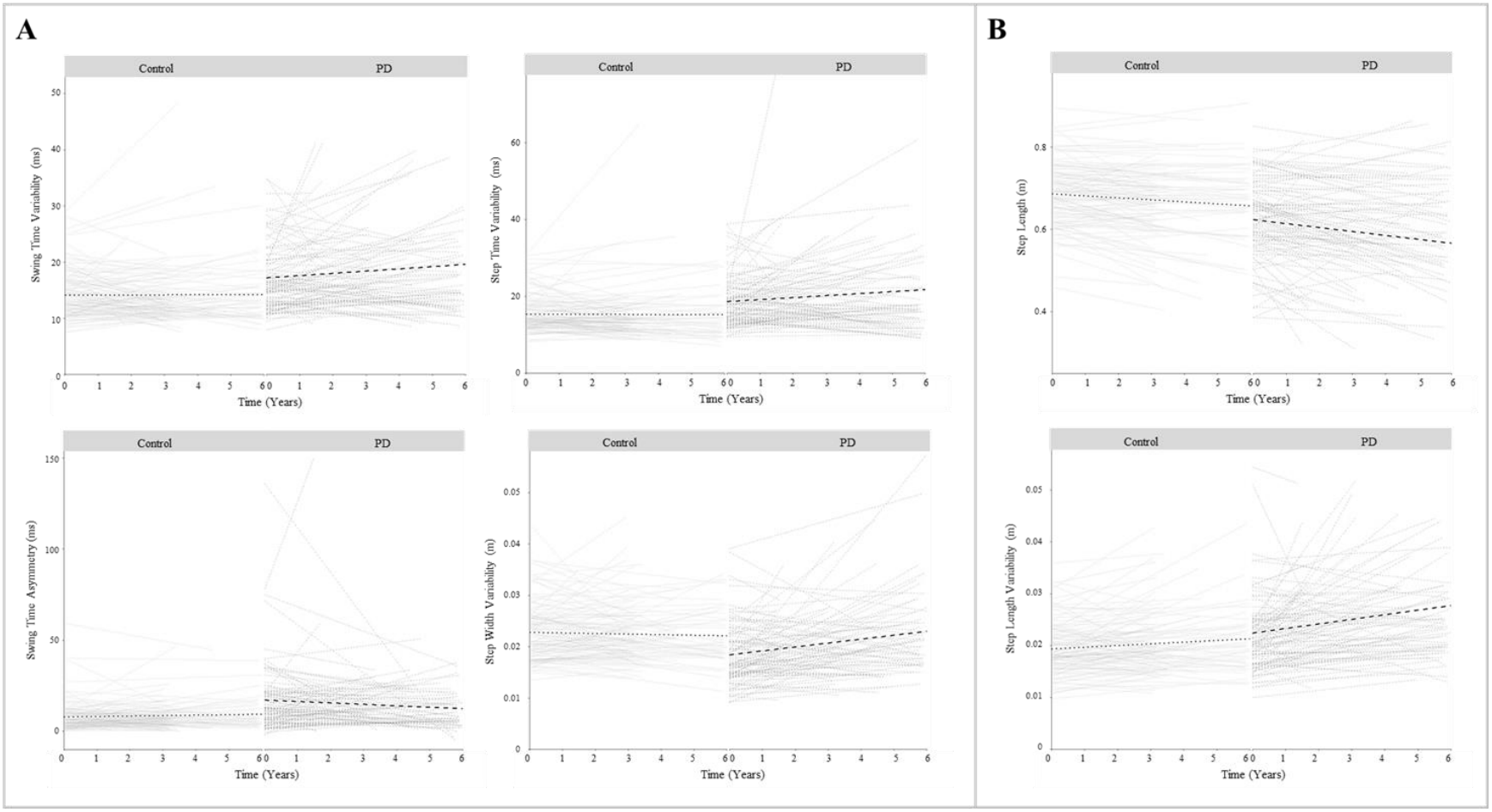
Finally, two characteristics demonstrated change related to both ageing and disease progression, meeting criterion 3. Step length shortened and step length variability increased significantly in both groups; however, the rate of change was significantly greater in PD than controls (**Figure 4-3**, panel B).

Table 4-5. Modelled change in gait characteristics over 72 months, in PD and control cohorts, and the Group*Time and LEDD*Time interactions for modelled gait change

	Controls			PD			Group x Time interaction			LEDD x Time interaction		
	Δ per year	**p-value**	**95% CI**	**Δ per year**	**p-value**	**95% CI**	**β**	**p-value**	**95% CI**	**β**	**p-value**	**95% CI**
Pace												
Step velocity	**-0.005**	**0.046***	**-0.011, -<0.001**	**-0.012**	**0.004***	**-0.021, 0.004**	-0.007	0.158	-0.016, 0.003	0.7×10^{-5}	0.415	-1.0×10^{-5}, 2.5×10^{-5}
Step length	**-0.005**	**<0.001***	**-0.007, -0.003**	**-0.009**	**<0.001***	**-0.013, -0.005**	**-0.004**	**0.035***	**-0.009, -<0.001**	-7.7×10^{-6}	0.855	-7.7×10^{-6}, 6.4×10^{-6}
Swing time sd	0.011	0.893	-0.158, 0.177	**0.397**	**0.016***	**0.075, 0.724**	**0.376**	**0.031***	**0.035, 0.719**	-5.7×10^{-4}	0.301	-16.5×10^{-4}, 5.1×10^{-4}
Variability												
Step time sd	-0.027	0.773	-0.207, 0.156	**0.513**	**0.007***	**0.149, 0.896**	**0.520**	**0.009***	**0.132, 0.913**	-3.3×10^{-4}	0.535	-13.8×10^{-4}, 7.2×10^{-4}
Stance time sd	-0.004	0.976	-0.270, 0.262	0.457	0.061	-0.020, 0.946	0.483	0.075	-0.049, 1.019	-8.6×10^{-4}	0.283	-24.2×10^{-4}, 7.1×10^{-4}
Step velocity sd	-<0.001	0.708	-0.001, <0.001	0.001	0.107	-<0.001, 0.002	0.001	0.060	-<0.001, 0.002	0.1×10^{-7}	0.993	-25.6×10^{-7}, 25.8×10^{-7}
Step length sd	**<0.001**	**0.002***	**<0.001, 0.001**	**0.001**	**<0.001***	**0.001, 0.001**	**0.001**	**0.004***	**<0.001, 0.001**	-1.9×10^{-7}	0.759	-14.3×10^{-7}, 10.5×10^{-7}
Rhythm												
Step time	-0.984	0.160	-2.369, 0.388	**-1.789**	**0.007**	**-3.049, -0.529**	-0.807	0.353	-2.503, 0.890	-2.1×10^{-3}	0.363	-6.6×10^{-3}, 2.5×10^{-3}
Swing time	**-0.928**	**0.006***	**-1.579, -0.287**	**-2.039**	**<0.001***	**-3.095, -0.992**	-1.10	0.068	-2.285, 0.083	-0.7×10^{-3}	0.669	-4.3×10^{-3}, 2.8×10^{-3}
Stance time	-0.938	0.418	-3.231, 1.342	-1.385	0.183	-3.418, 0.694	-.349	0.806	-3.131, 2.462	-4.0×10^{-3}	0.235	-10.7×10^{-3}, 2.7×10^{-3}
Asymmetry												
Step time asy	**0.444**	**0.020***	**0.073, 0.821**	-0.651	0.239	-1.736, 0.451	-1.080	0.054	-2.176, 0.024	-0.8×10^{-3}	0.556	-3.7×10^{-3}, 2.0×10^{-3}
Swing time asy	0.256	0.069	-0.020, 0.530	**-0.814**	**0.042***	**-1.594, -0.027**	**-1.014**	**0.012***	**-1.803, -0.221**	-0.4×10^{-3}	0.704	-2.4×10^{-3}, 1.6×10^{-3}
Stance time asy	0.221	0.145	-0.077, 0.519	-0.750	0.052	-1.505, 0.011	**-0.878**	**0.027***	**-1.653, -0.100**	-0.6×10^{-3}	0.564	-2.6×10^{-3}, 1.5×10^{-3}
Postural Control												
Step length asy	**0.001**	**0.025***	**-<0.001, -0.001**	0.001	0.125	-<0.001, -0.002	<0.001	0.813	-0.001, 0.001	0.8×10^{-7}	0.959	-30.1×10^{-7}, 31.3×10^{-7}
Step width	**0.001**	**0.027***	**<0.001, 0.001**	**0.001**	**0.014***	**<0.001, 0.002**	<0.001	0.650	-0.001, 0.001	0.6×10^{-6}	0.632	-1.8×10^{-6}, 2.9×10^{-6}
Step width sd	-<0.001	0.290	-<0.001, <0.001	**0.001**	**<0.001***	**<0.001, 0.001**	**0.001**	**<0.001***	**0.001, 0.001**	**1.6×10^{-6}**	**<0.001***	**0.7×10^{-6}, 2.5×10^{-6}**

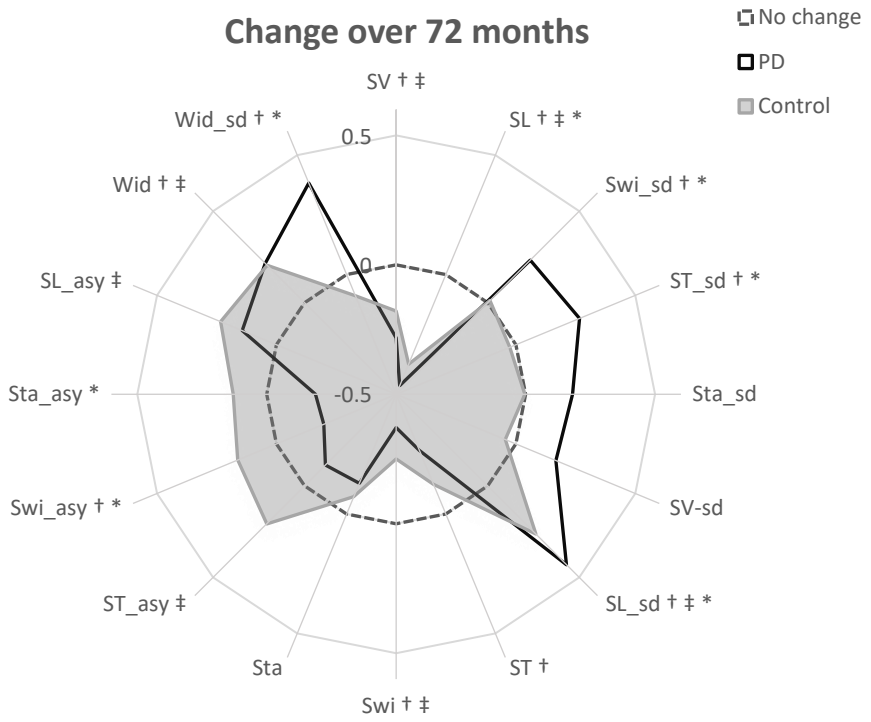
[All models were adjusted for baseline age and sex. Significant associations (p<0.05) are in bold and denoted by *. asy, asymmetry; sd, standard deviation (gait variability).]

Figure 4-3. Change in gait over six years for control and PD participants, for gait characteristics that demonstrated significant change in PD related to disease progression



[Panel A shows gait characteristics that significantly changed in PD but not controls, so demonstrated change related to disease progression only. Panel B shows gait characteristics that significantly changed in PD and control groups, but the rate of change was greater in PD, so demonstrated change related to both ageing and disease progression. Bold lines show overall change within groups; faint lines show change for individuals.]

Figure 4-4. Radar plot illustrating change in each gait characteristic over 72 months



[The central dotted line represents no change. Deviations from zero along the axes radiating from the centre of the plot represent the relative change in each gait characteristic over 72-months within each diagnostic group, calculated as the modelled change per year divided by the standard deviation of the modelled change. Gait characteristics are abbreviated as follows: SV, step velocity; SL, step length; Swi, swing time; ST, Step time; Sta, Stance time; Wid, Step width; sd, standard deviation (gait variability); asy, asymmetry. † indicates significant change in gait in the PD cohort over 72 months; ‡ indicates significant change in gait in controls over 72 months; * indicates a significantly different rate of change in PD gait compared to the rate of gait change in controls. †* denotes criterion 1 satisfied; †‡ denotes criterion 2 satisfied; †‡* denotes criterion 3 satisfied.]

4.3.5 Associations between gait changes and change in levodopa dose over time

LEDD increased by 106 mg/day each year. Only one gait characteristic was related to LEDD change; larger increases in step width variability related to greater increases in LEDD over time (**Table 4-5**). Inclusion of the LEDD x Time interaction resulted in no significant change in step width variability ($p>0.05$), indicating that step width variability change is at least partially explained by change in LEDD. All other gait characteristics meeting criteria 1 and 3 did not show associations between gait change and LEDD change and therefore exhibited disease-specific change that was not related to levodopa adjustments (**Figure 4-5**).

Figure 4-5. Summary of the longitudinal analyses completed in Chapter 4

	Significantly changed over time in typical ageing?	Significantly changed over time in PD?	Change over time different between PD and controls?	PD change related to LEDD change?
Step velocity	↘	↘	-	-
Step length	↘	↘	✓	-
Swing time variability	-	↗	✓	-
Step time variability	-	↗	✓	-
Stance time variability	-	-	-	-
Step velocity variability	-	-	-	-
Step length variability	↗	↗	✓	-
Step time	-	↘	-	-
Swing time	↘	↘	-	-
Stance time	-	-	-	-
Step time asymmetry	↗	-	-	-
Swing time asymmetry	-	↘	✓	-
Stance time asymmetry	-	-	✓	-
Step length asymmetry	↗	-	-	-
Step width	↗	↗	-	-
Step width variability	-	↗	✓	↗

[Arrows indicate the direction of association; more darkly shaded boxes indicate a stronger association (relative to associations made within each set of analysis).]

4.4 Discussion

This chapter forms the first study to objectively and quantitatively model progression of gait impairment over six years in an incident cohort of early PD and a well-matched control group. This allowed for changes associated with ageing to be discerned from those linked to PD progression. In the PD group, four gait characteristics showed disease-specific progression, three showed age-related progression and change in two characteristics could be explained through a combination of age and disease progression. Most gait changes occurred irrespective of increasing dopaminergic medication, highlighting limitations of dopaminergic therapies and indicating the involvement of other mechanisms of gait impairment. Novel therapies targeting non-dopaminergic mechanisms are therefore required to slow the rate of gait progression and reduce the associated consequences of falls and reduced physical activity. Ultimately, these findings improve current understanding of gait impairment in early PD. Findings also highlight the gait characteristics that are most reflective of evolving PD pathology, so should be considered in assessments concerning the neural mechanisms contributing to longitudinal gait decline in PD.

4.4.1 Changes in gait over six years

The first aim of this chapter was to describe gait changes in PD and controls over an extended period of six years. As expected, many gait characteristics changed in both PD and control cohorts; changes in gait occurred more frequently and at greater magnitudes in PD compared to changes in controls. Several changes were unique to each cohort, highlighting the specificity of gait change. Although not significant in all cases, it was interesting to see that, generally, asymmetry decreased in PD but increased in controls, indicating a potential use of asymmetry changes as a unique outcome measure for PD progression.

PD-specific changes in gait

To fulfil the second aim of this chapter, three criteria established gait changes specific to PD pathology (criterion 1), reflective of ageing (criterion 2) or indicative of a combination of PD progression and ageing (criterion 3). Four characteristics significantly changed in PD only (variability of swing and step time, swing time asymmetry and step width variability) and are argued to describe changes due specifically to disease progression, meeting criterion 1. These findings extend previous studies in this cohort that were completed over shorter time periods (Galna *et al.*, 2015; Rochester *et al.*, 2017) by revealing additional changes in asymmetry and

variability that are not evident over 18 or 36 months. Findings are also supported by a smaller study which showed step time variability increased more over five years in 22 people in the early stages of PD compared to a typically ageing cohort (Hobert *et al.*, 2019). The specific disease mechanisms underlying changes in variability (step, swing, step width) were not confirmed in this previous study. However, evidence suggests that increasing variability may be due to aggregation of disease pathologies over the first six years of PD, affecting the neural control of gait, including amyloid and tau (Kang *et al.*, 2013; Rochester *et al.*, 2017). Neurological changes exacerbated by PD may additionally influence changes in gait variability, as identified in chapter 2. This idea will be further investigated in subsequent chapters of this thesis. Greater gait asymmetry in people with PD at baseline is aligned with an asymmetrical pattern of neuronal loss (Wang *et al.*, 2015; Claassen *et al.*, 2016). Moreover, reduced asymmetry over time in PD may relate to bilateral neuronal loss with PD progression (Rousseaux *et al.*, 2012).

The role of levodopa in PD gait progression

To further understand the drivers of gait progression specific to PD, the relationship between change in gait and change in levodopa was explored, addressing the third chapter aim. Findings in this chapter, along with previous work (Rochester *et al.*, 2017), demonstrate that increasing step width variability is related to increasing levodopa medication. This increase could be interpreted in a number of ways; as a positive effect of levodopa on step width variability, or that levodopa is exacerbating difficulties with balance (Curtze *et al.*, 2015). It is also possible that changes in levodopa and step width variability both reflect a more progressive PD phenotype and are not causally linked. No other gait characteristics were related to levodopa change. Progression could therefore be argued to be resistant to levodopa medication (dopa-resistant) or, at least, dopaminergic medications are unable to keep pace with change in gait, highlighting the need for alternative therapies (Curtze *et al.*, 2015; Galna *et al.*, 2015). Although the precise mechanisms of non-dopaminergic gait control are unclear, emerging evidence suggests the importance of the cholinergic system (Morris *et al.*, 2019a). Cholinergic neurons in the pedunculopontine nucleus (PPN) influence gait and postural control (Karachi *et al.*, 2010) while slower walking speed in PD is associated with increases in short-latency afferent inhibition (Rochester *et al.*, 2012) and cortical cholinergic denervation (Bohnen *et al.*, 2013; Müller *et al.*, 2015). The benefits of drugs targeting the cholinergic system on PD gait are also being explored (Henderson *et al.*, 2016; Smulders *et al.*, 2016; Müller *et al.*, 2019). Overall, interpretation of the relationship between dopamine and gait progression is limited as gait was not assessed "off" medication, nor were biomarkers

of dopaminergic activity such as DAT imaging used. Nevertheless, findings indicate that discrete gait characteristics progress irrespective of levodopa, suggesting an importance of non-dopaminergic mechanisms in gait impairment.

The contribution of ageing to PD gait progression

Understanding how gait changes with normal ageing is important, as age-related changes cumulatively contribute to gait progression in people with PD alongside disease progression. Three characteristics changed in both PD and control cohorts over six years; change in these characteristics was therefore considered to be due primarily to ageing mechanisms rather than disease progression. These changes (slowing of gait, widening of steps and a quickening swing time) met criterion 2.

Slowing of gait is considered a typical feature of PD progression. However, it was found that walking speed (step velocity) slowed over time in both groups, suggesting this is a more general feature of ageing. Although the rate of change was greater in PD, this was not significant, replicating previous findings (Galna *et al.*, 2015; Hobert *et al.*, 2019). While walking speed may be a useful measure of change and response to therapy, interpreting change in walking speed is more complex and may be more likely to reflect a combination of ageing and disease. This may explain, in part, the large inter-individual variation in rates of gait change within each group (**Figure 4-3**). Walking speed provides an overall measure of gait performance, influenced by discrete characteristics such as step length, timings of steps and step width (Wade, 1992; Galna *et al.*, 2015). Further investigation into predictive factors for gait change in PD and healthy ageing cohorts may give better insight into the reasons behind individual differences in gait progression and aid better interpretation of reduced gait speed in PD and ageing cohorts. Small yet clinically meaningful changes in gait speed are reported as 0.03-0.06 m/s in older adults with mobility issues (Perera *et al.*, 2006) and in PD (Hass *et al.*, 2014). Work within this chapter therefore indicates that a clinically meaningful change in gait typically occurs within the first six years of PD (0.07 m/s over 6 years in people with PD; see **Table 4-5** for estimates of yearly change). Overall, given that change in step velocity does not significantly differ between PD and control groups, looking beyond walking speed is important in order to allow more nuanced interpretation of changes and their underlying mechanisms.

Age-related change contributes to gait impairments observed in PD, suggesting that therapies addressing features of ageing may be effective in reducing the burden of PD. It is therefore important to consider the mechanisms driving age-related gait change. Change may be due to

atrophy and loss of muscle strength (Abernethy, 2005; Song and Geyer, 2018), physical inactivity (Busch *et al.*, 2015) and development of age-related conditions, such as osteoarthritis (Zhang and Jordan, 2010), causing increased pain and stiffness during movement (Jayakody *et al.*, 2018). Age-related changes in the brain, such as atrophy and white matter abnormalities, also explain the slowing and increased variability of gait during ageing. Increasing evidence implies that specific neural regions or networks underpin discrete gait characteristics (Tian *et al.*, 2017b), which could be specifically targeted to prevent discrete components of age-related gait decline. On this point, gait performance in PD is improved by exercise-based interventions aiming to increase muscle strength and activity (van der Kolk and King, 2013; Shen *et al.*, 2016); speculatively these therapies may, at least partially, be targeting age-related changes which, in turn, positively impact PD gait.

Two gait characteristics, step length and step length variability, significantly worsened in both PD and control groups over six years, yet changes in PD occurred at a significantly greater rate. These characteristics therefore met criterion 3, suggesting that both PD and age-related mechanisms contributed to their progression. In previous work over a shorter time frame (36 months from diagnosis (Rochester *et al.*, 2017)), step length change was not significantly different in PD compared to controls. This may be due to shorter step length in PD strongly associating with dopaminergic dysfunction (Galna *et al.*, 2015) and the resultant hypokinesia (Morris *et al.*, 1996), so may decline as dopaminergic medications become less effective over time due to neuronal cell loss (Zahoor *et al.*, 2018). Alternatively, change may simply be due to loss of muscle mass and strength over time (sarcopenia), as a result of ageing, or as a secondary consequence of the reduced activity observed over the course of PD. Further investigation into the underlying mechanisms of these gait changes, such as direct measurement of muscle mass over time, may indicate whether these are purely age-related changes accelerated by disease progression, or whether ageing and disease mechanisms act independently of each other to cause change. Collectively, findings highlight the benefits of a longer follow-up duration, through identifying changes related specifically to disease progression and changes reflective of both disease progression and ageing over six years. These gait characteristics may act as new therapeutic targets for the prevention of gait progression in PD.

4.4.2 Study strengths and limitations

This chapter forms the largest study to document gait change in PD over the longest time period from diagnosis, in a relatively homogeneous cohort of incident PD participants. The main strength was that changes in gait could be attributed to disease separately from ageing,

as a well-matched control cohort was assessed alongside people with PD. Relatively precise modelling of gait change in early PD was achieved as PD participants were recruited close to diagnosis, enabling monitoring over the first six years of disease. Inter-individual variation was accounted for through the random effect term included in all models. The inclusion of LEDD in analyses enabled the investigation of gait changes that were related and, arguably more importantly, not related to changes in dopaminergic medication, to identify potential therapeutic targets for non-dopaminergic interventions. The effects of dopamine on gait progression could be further explored by comparing gait progression for characteristics measured "on" and "off" medication.

Some limitations should be noted. As with many longitudinal studies, attrition was substantial (57%), although comparable to similar studies (Micó-Amigo *et al.*, 2019). PD completers were younger, with less severe motor disease, better global cognition and less severe gait impairment at baseline, indicating a potential underestimation of overall progression rates. Mixed-effects modelling allowed the use of all data, reducing bias compared to traditional analytical approaches. PD misdiagnosis is unlikely to have affected findings, as diagnosis was reviewed at each assessment and the number of revised diagnoses was low (**Figure 4-1**). Multiple comparisons were not corrected for; this was justified as it allowed for direct comparison with gait changes over 36 months (Rochester *et al.*, 2017), and reduced the risk of type II error. However, a cautious approach to interpretation has been taken throughout. To account for the possibility of type I errors, *p* values for each comparison have been provided for transparency.

4.4.3 Conclusions

Discrete gait impairments progress over six years after a diagnosis of PD, due to a combination of disease-specific and age-related mechanisms. Gait changes are mostly unrelated to dopaminergic medication adjustments, highlighting limitations of current dopaminergic therapy and the need to improve interventions targeting gait decline in PD.

Importantly, a foundation has been laid to enable the completion of work identifying neuroimaging predictors of gait changes over the course of PD. Six gait characteristics were highlighted as changing over time as a result of disease progression; namely swing time variability, step time variability, swing time asymmetry, step width variability, step length and step length variability. The observed change in step width variability was associated with changing levodopa medication, with the inclusion of medication in models implying that this

change in gait may be explained by medication changes. These confounding effects of medication mean that it would be inappropriate to consider step width variability in the longitudinal investigations of the neural control of PD gait completed in subsequent chapters. The imaging correlates of step width variability change would be better investigated in a dedicated study that carefully considered variability measures longitudinally both "on" and "off" levodopa medication and utilised DAT imaging.

Therefore, longitudinal analyses of the structural neural correlates of gait throughout the rest of this thesis will consider only the five gait characteristics that significantly change due to PD progression over 72-months, where change is not explained by a change in dopaminergic medication.

Chapter 5: The areas of cortical grey matter associated with PD gait: a global and regional perspective

This chapter explores the associations between cortical thickness and discrete gait impairments and their progression in PD.

5.1 Introduction

This thesis has so far outlined the gait impairments that occur throughout early PD. Chapter 4 showed that dopaminergic medications in themselves do not sufficiently alleviate all aspects of gait impairment in PD, nor prevent them from worsening as a result of disease progression. These findings indicate that the neural mechanisms underpinning gait disturbance in PD may extend beyond dopaminergic substrates. However, the precise nature of gait control in PD, and the involvement of mechanisms other than dopaminergic control, is not well understood.

Previous chapters of this thesis have outlined that gait is a complex skill requiring input from sensory and cognitive mechanisms in addition to more automatic motor control (Montero-Odasso *et al.*, 2012). The neural structures typically relied upon for automatic motor control are thought to be compromised in PD due to degeneration of the SNpc causing dopaminergic loss (DeLong and Wichmann, 2009). It is therefore proposed that an increased reliance on more conscious input, potentially from cortical areas involved in sensory and cognitive functions, is required for effective gait in PD (Bohnen and Jahn, 2013; Wu *et al.*, 2015; Peterson and Horak, 2016).

Sensory information is thought to input to motor areas; cortical areas linked to sensory outputs may therefore be considered part of wider "motor networks" for locomotor control. Somatosensory, vestibular and visual sensory signals are proposed to be involved in typical locomotor control (Takakusaki, 2017). In PD, there may be increased reliance on these sensory signals during gait, which would explain the observed increased activity in parietal-lateral motor pathways during movement in PD (Sabatini *et al.*, 2000) to compensate for underactive medial motor pathways (Lewis *et al.*, 2013). Reliance on sensory systems may also explain why external cues are effective at improving gait in PD (Rochester *et al.*, 2009; Spaulding *et al.*, 2013).

Cueing is also dependent on attention (Peterson and Smulders, 2015). There is a known link between gait and cognition in PD, as described in chapter 1; pace and variability characteristics have been particularly associated with executive function and attention (Morris *et al.*, 2016). Although both executive function and attention are not easily attributable to distinct cortical areas, executive attention has been most strongly ascribed to the prefrontal cortex and anterior cingulate cortex (Collette *et al.*, 2006; Yogev-Seligmann *et al.*, 2008; Morris *et al.*, 2016) particularly when relied upon during gait (Koenraadt *et al.*, 2014; Pelicioni *et al.*, 2019). These areas may therefore form part of one or several "non-motor networks" involved in locomotor control. Overall, however, these proposed neural mechanisms of gait control in PD remain largely unsubstantiated (see chapter 2, **Table 2-2**).

As outlined in chapter 2, associations between neuroimaging and gait parameters can help to establish the neural substrates involved in locomotion. Furthermore, assessment of several discrete gait characteristics can help to determine whether there is specificity in the neural underpinnings of gait. This ultimately informs us as to whether specific impairments in gait should be differentially targeted by therapies. Chapter 2 also highlighted a paucity of studies conducted longitudinally to assess neural correlates of gait, particularly in PD, yet longitudinal study designs provide two key benefits: firstly, they allow for greater determination of a causal relationship between gait and imaging parameters, as the same participants are assessed multiple times; secondly, they can be used to stratify individuals at greater risk of gait decline who may benefit most from early interventions.

Although the presence of amyloid and white matter insults has been associated with impaired gait, current understanding of neural correlates of gait in healthy ageing has mostly stemmed from volumetric structural MRI. Structural MRI provides a relatively cost-effective, replicable and non-invasive tool to assess neural structures. Associations identified between gait and structural brain volumes in PD can be compared to those established in typical ageing, enabling a better understanding of the neural mechanisms of gait resulting specifically from PD and its progression rather than ageing. Assessment of both cortical and subcortical volumes facilitates a more complete understanding of the neural correlates of gait. Associations between gait and cortical volumes will be assessed in this chapter; chapter 6 will then use volumes of subcortical structures. Surface-based analysis of cortical thickness has been used to assess cortical volumes here, as it is a more sensitive measure of grey matter atrophy in PD than more traditional imaging analyses such as voxel based morphometry (Pereira *et al.*, 2012).

Aims and hypotheses

This chapter aims to identify associations between gait and cortical thickness in PD. More specific chapter aims are to i) determine differences in cortical thickness between early PD and age-matched controls; ii) explore cross-sectional associations between cortical thickness and gait characteristics as assessed soon after PD diagnosis, and; iii) assess cortical thickness as a predictor of gait changes occurring as a result of PD progression. It is hypothesised that:

1. Overall, stronger cross-sectional associations between gait and cortical thickness will occur in PD compared to controls, due to the increased reliance on cortical control of gait in PD. In this context, PD participants would be more sensitive from a gait perspective to loss of cortical brain tissue than controls.
2. Related to hypothesis one, cross-sectional associations between gait and cortical thickness of areas linked to sensory and cognitive functions (related to motor and non-motor networks respectively) will occur more commonly in PD compared to controls due to increased reliance on these functions.
3. Cross-sectional associations between gait and cortical thickness of motor areas will occur more commonly in controls compared to PD, as automatic motor control networks are less affected in controls (as they are unaffected by PD pathology although may still be influenced by age-related changes).
4. Cortical thickness of areas linked to both motor and non-motor networks will predict PD-specific gait decline, as non-motor cortical structures may be increasingly relied upon for gait as PD progresses (and thus more sensitive to atrophy in these structures) due to initial degeneration of subcortical structures.
5. Associations with gait characteristics from pace and variability domains will occur with cortical thickness of areas related to both motor and non-motor functions, given findings from the existing literature (**Table 2-2**).
6. Associations with characteristics from the rhythm domain will occur with cortical thickness of areas related to motor functions, as it is thought that the cerebellum links to motor cortices to adjust the timing of gait.
7. Associations with asymmetry characteristics will occur with cortical thickness of areas related to motor functions, given previous findings in PD (**Table 2-2**).
8. Associations with characteristics from the postural control domain will occur with cortical thickness of areas related to non-motor functions, as postural control of gait may be more driven by loss of cholinergic function.

5.2 Methods

For this study of cortical thickness and its associations with gait, the same demographic and clinical assessments were considered as in chapter 4. All sixteen gait characteristics from the model of gait produced by Lord et al. that has been validated in PD (**Figure 3-3** (Lord *et al.*, 2013b)) were considered in cross-sectional analyses. Longitudinal analyses considered only the five gait characteristics that significantly changed due to PD progression over 72-months, as identified in chapter 4, where change was not explained by a change in dopaminergic medication. PD participants were 'on' medication for all assessments, defined as one hour after PD medication.

5.2.1 Participants

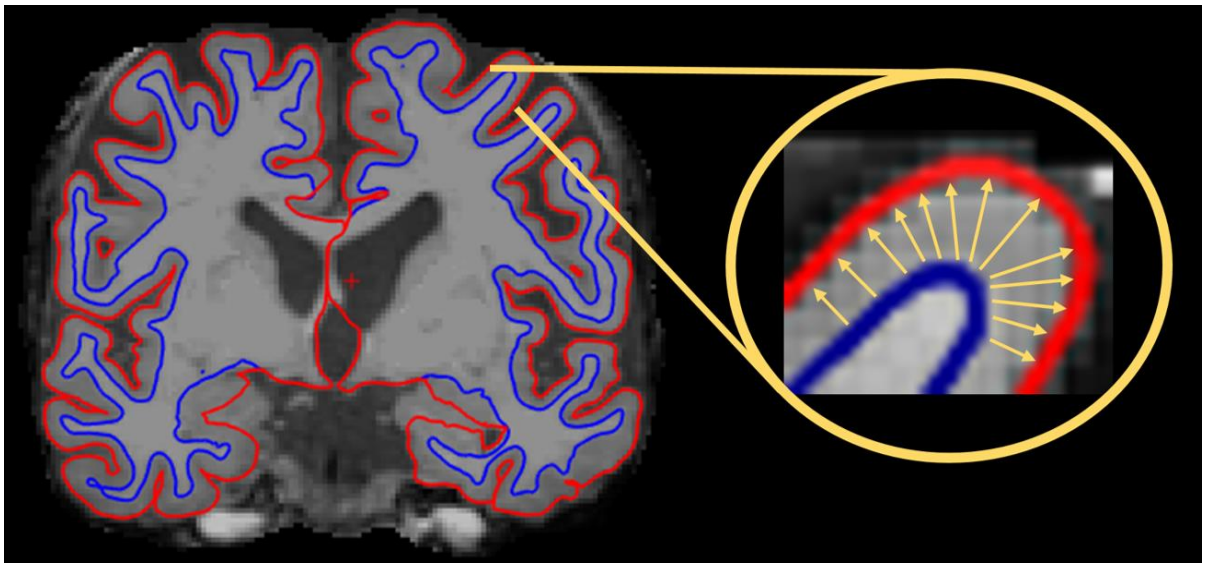
As described in chapter 3, participants considered in analyses within this chapter were recruited from both the ICICLE-PD and ICICLE-GAIT studies. Participants were required to have suitable baseline MRI scans and baseline gait assessments from these studies for inclusion in cross-sectional analyses, and to have completed at least two assessments of gait for inclusion in longitudinal analyses. The total number of gait assessments completed by this restricted cohort of PD and control participants across the 72-month assessment period are detailed in **Appendix L**.

5.2.2 Assessments of cortical thickness

Cortical thickness was estimated from cortical surface reconstructions computed from T1 images (described in chapter 3) using FreeSurfer v 6.0 (http://surfer.nmr.mgh.harvard.edu). The technical aspects of this methodology are described in greater detail from publications written by members and collaborators of the laboratory for computational neuroimaging, Athinoula A. Martinos Centre for Biomedical Imaging, Massachusetts, USA (Dale *et al.*, 1999; Fischl *et al.*, 1999; Fischl and Dale, 2000). To summarise, image processing involved intensity non-uniformity correction, Talairach registration, skull stripping to remove non-brain tissue, segmentation of white, limbic and subcortical grey matter, tessellation of the boundary between grey and white matter and surface deformation to optimally set borders between grey and white matter and between grey matter and CSF. Once cortical models were generated, surface inflation, transformation to a spherical atlas and parcellation of the cerebral cortex into gyral based regions of interest were completed (Desikan *et al.*, 2006), using both intensity and continuity information from the entire 3D MR volume in the

segmentation and deformation procedures to produce representations of cortical thickness. Cortical thickness was calculated as the closest distance between the grey matter-CSF and grey matter-white matter borders at each vertex on the tessellated surface (**Figure 5-1**). Cortical thickness measures were mapped to the inflated surface.

Figure 5-1. **A representation of the cortical thickness calculation process**



Images were then aligned to a common surface template and smoothed with a 15mm full width at half maximum surface-based Gaussian kernel in accordance with recent assessments of cortical thickness in PD (Mak *et al.*, 2015). Images were carefully visually inspected at each step of the FreeSurfer processing stream by a single operator (J. Wilson) and moderated by an independent observer (S. Colloby) to check the accuracy of the segmentations. Any images with segmentation errors that could not be corrected by further editing and processing were excluded.

5.2.3 Data analysis

Description of study participants

Distribution of continuous variables were tested as outlined in chapter 3. Baseline demographic and clinical data were described for the participants assessed in this chapter; group differences in demographics were assessed using the same tests described in chapter 3.

Baseline cortical thickness

Baseline comparisons were completed using vertex-wise general linear models (GLMs) as performed with QDEC software (http://surfer.nmr.mgh.harvard.edu/fswiki/Qdec). Firstly, models included cortical thickness as a dependent factor and individually included age, sex and education as independent factors, to assess the suitability of the inclusion of these factors as covariates in subsequent analyses involving cortical thickness. Secondly, regional differences in cortical thickness between PD and control groups were examined within each hemisphere; the model included cortical thickness as a dependent factor and group as an independent factor, with age and sex included as nuisance covariates. Finally, regional differences in cortical thickness between PD participants who would and would not go on to complete gait assessment at 72 months ("completers" and "non-completers") were examined within each hemisphere; the model included cortical thickness as a dependent factor and completion as an independent factor, with age and sex as nuisance covariates. A false discovery rate approach (FDR) corrected for multiple comparisons across all vertices.

Cross-sectional associations between gait and cortical thickness

Analyses were completed through both data-driven and regions-of-interest (hypothesis-driven) approaches. Data-driven approaches are widely utilised in investigations of cortical thickness, as analyses are objective and performed on a vertex-by-vertex basis, enabling precision in findings. Previous chapters of this thesis have outlined a clear rationale for selecting several regions-of-interest *a priori* which are anticipated to be associated with gait in PD. A hypothesis-driven approach has therefore also been adopted here with far fewer comparisons, reducing the likelihood of family-wise error.

Data-driven approach

Within-group GLMs, using QDEC software, assessed whether the correlation between cortical thickness and each gait characteristic significantly differed from zero within each hemisphere at each vertex. Models included cortical thickness as a dependent factor and each gait characteristic (untransformed) as independent factors in separate models, with age and sex as nuisance covariates. Analyses were corrected for multiple comparisons using the FDR approach (if significant, $p<0.05$ FDR). If no association was evident between cortical thickness and gait after FDR correction, cluster-wise analyses were used to report weakly significant clusters ($p<0.001$ uncorrected), so that trends could be identified.

Hypothesis-driven approach

Of the 68 gyral-based cortical regions segmented by FreeSurfer (34 within each hemisphere, (Desikan *et al.*, 2006), **Figure 5-2a**), 34 regions-of-interest that are involved in both motor and non-motor related functions (17 within each hemisphere) were selected *a priori* (**Figure 5-2b)**. **Appendix M** details the reasoning for the selection of these gyral regions. The average cortical thickness within each gyral based region of interest was derived for each individual (http://surfer.nmr.mgh.harvard.edu/fswiki/aparcstats2table). Pearson's partial correlations, controlling for age and sex, explored associations between gait and average regional cortical thickness. To further identify independent associations between gait and imaging parameters, multiple linear regression was then performed. Independent models were developed for each gait characteristic. For each model, the gait characteristic of interest was added in as the dependent variable. Independent variables were added in two stages; age and sex were entered in the first block for all models using the enter procedure, then regions of cortical thickness that reached significance in partial correlations between gait and imaging variables were entered in to the second block using the stepwise procedure. For cross-sectional hypothesis-driven analyses, gait variables were transformed as described in chapter 4 so that parametric statistical tests could be utilised. For these analyses, the Benjamini-Hochberg correction was applied across the combined 34 regions-of-interest within each gait characteristic to correct for multiple comparisons. For clarity, uncorrected p-values from these analyses are reported. Correlations that were not significant after multiple comparison correction, but where ($p<0.05$), were considered statistical trends.

Longitudinal associations between gait and cortical thickness

Longitudinal analyses were also completed through both data-driven and hypothesis-driven approaches, to determine whether baseline cortical thickness was associated with a change in gait over 72 months. Five gait characteristics were of interest longitudinally; step length, swing time asymmetry and variability of swing time, step time and step length.

Data-driven approach

For the five gait characteristics of interest, the rate of change in gait, as determined through linear mixed-effects models (LMEM; R, "lme4" (Bates *et al.*, 2015) and "lmerTest" (Kuznetsova *et al.*, 2017)) in chapter 4, was derived for each individual. Within-group GLMs, using QDEC software, then assessed whether the correlation between cortical thickness and the change in each gait characteristic of interest significantly differed from zero within each

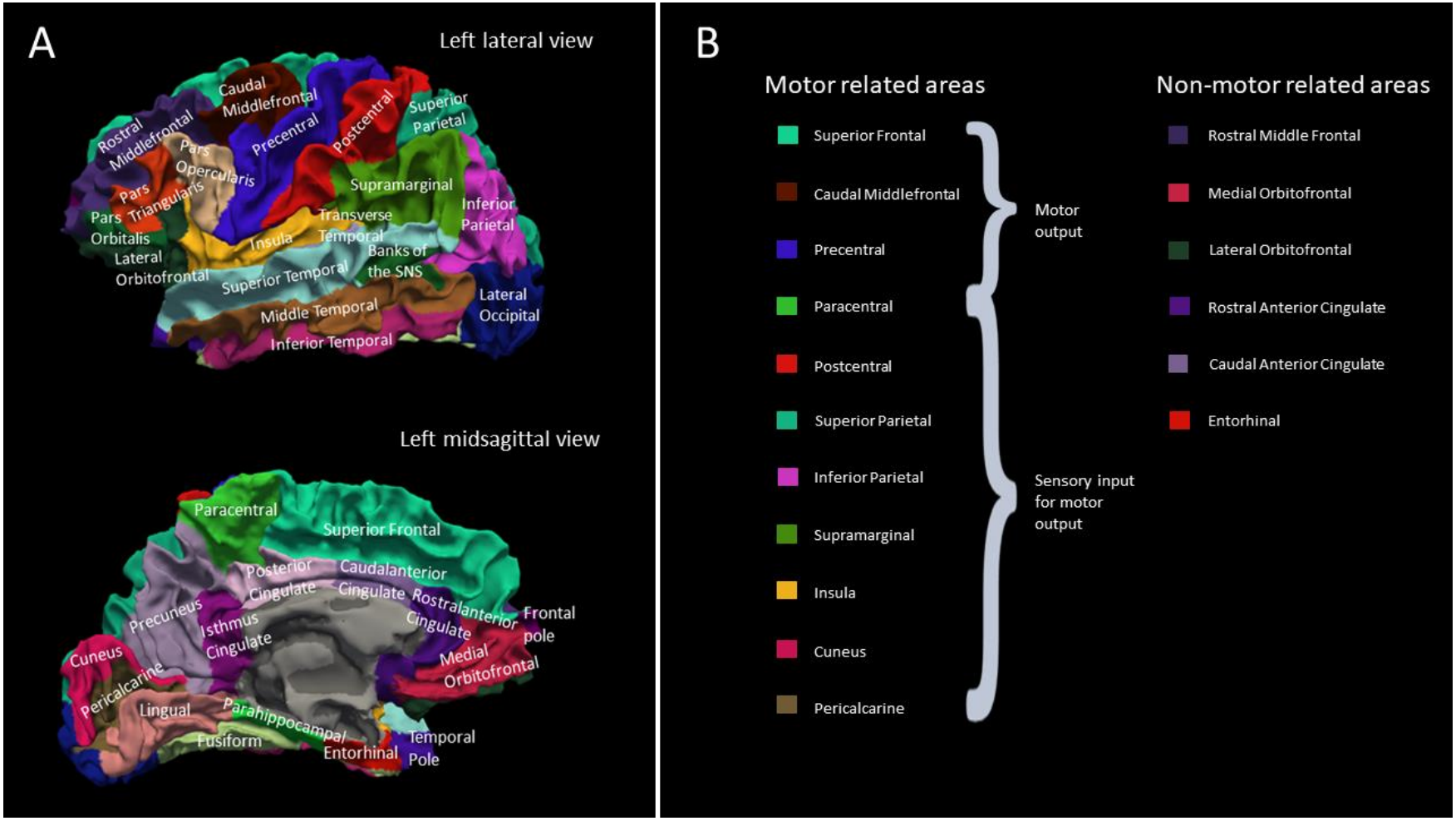
hemisphere at each vertex. Models included cortical thickness as a dependent factor and gait change slopes as independent factors in separate models. Age and sex were included in all models that individual change slopes were derived from, so were not included again as nuisance covariates. Analyses were FDR corrected; if no association was evident after FDR correction, cluster-wise analyses were used to report weakly significant clusters ($p<0.001$ uncorrected).

Hypothesis-driven approach

LMEM was used to determine whether specified regions of cortical thickness could predict gait decline. Basic models of gait change were constructed as described in chapter 4 for the PD group, again including baseline age and sex as fixed effects. Average regional cortical thickness for each of the 34 pre-defined regions-of-interest (17 for each hemisphere, **Figure 5-2b**) was separately entered as an interaction term with time (Thickness*Time) into basic models of gait change. Log-likelihood ratio tests assessed whether model fit was significantly improved with the inclusion of the (Thickness*Time) interaction term in basic models. As with the hypothesis-driven approach for cross-sectional analyses, the Benjamini-Hochberg correction was applied across the combined 34 regions-of-interest within each gait characteristic to correct for multiple comparisons. For clarity, uncorrected p-values from these analyses are reported. Cortical thickness measures that were not considered significant predictors after multiple comparison correction, but where ($p<0.05$), were considered statistical trends.

To visualise the effect of baseline cortical thickness on changes in gait over time, the PD group was split into quartiles of baseline cortical thickness; separate quartile splits were conducted for each gyral region-of-interest. Change over time in gait characteristics of interest were then plotted separately for each quartile of cortical thickness.

Figure 5-2. Gyral-based cortical regions, segmented from a representative participant



[Panel A shows the 68 regions (34 in each hemisphere) that associations between cortical thickness and gait may be identified in from data-driven analytical approaches. Panel B shows the 34 regions of interest (17 in each hemisphere), relating to motor and non-motor areas, used in hypothesis-driven analyses.]

5.3 Results

5.3.1 Study participants

Of all the participants that completed gait assessment at baseline (chapter 4), only 100 PD and 47 control subjects had MRI data available. One PD subject was excluded as their scan could not be properly processed (due to poor skull stripping), therefore 99 PD participants and 47 controls were included in cross-sectional analyses (**Figure 5-3**). **Table 5-1** shows the baseline clinical and demographic characteristics of the subset of PD and control participants included in the analyses of this chapter. These participants were representative of the whole ICICLE-GAIT cohort assessed within chapter 4. In contrast to the entire cohort, however, the proportion of males did not significantly differ between groups in this smaller sample.

Figure 5-3. Participants considered within cross-sectional analyses

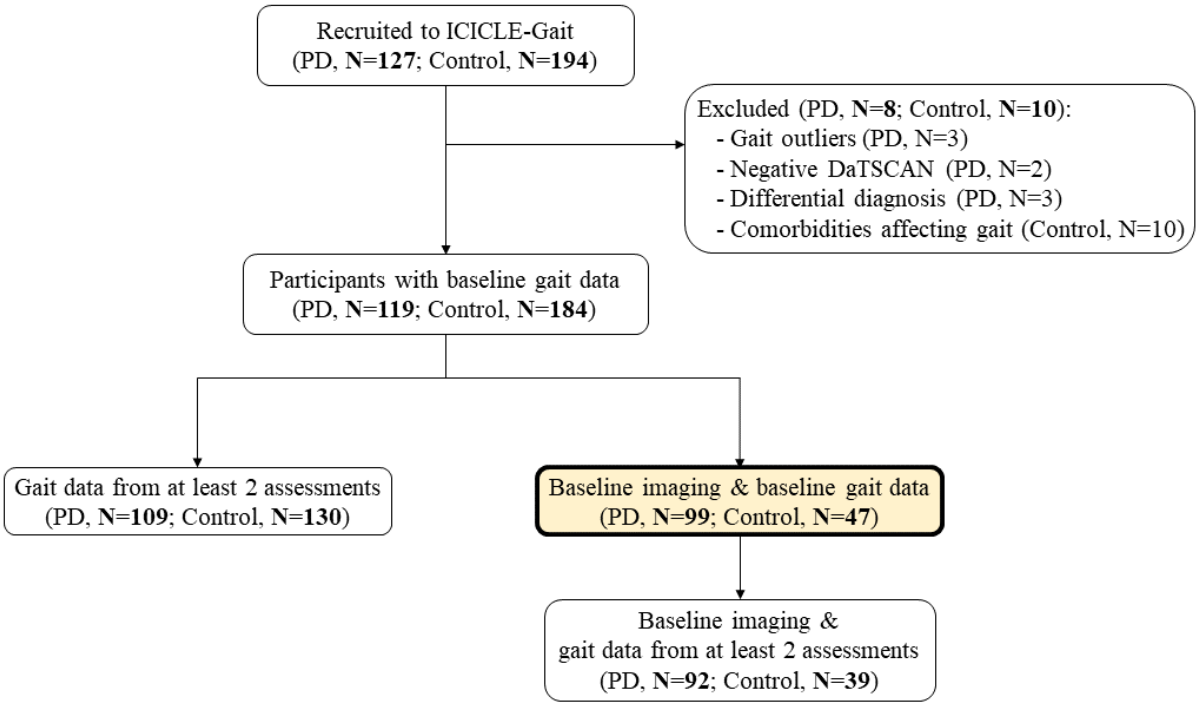


Table 5-1. Baseline demographic characteristics for participants with baseline gait and imaging data available

Characteristic	Control (n=47)	PD (n=99)	Group difference *(test statistic, p)*
Age (years)	65.8 (8.0)	66.5 (10.7)	t = -0.45, p = 0.683
Sex (f)	18 f (38%)	33 f (33%)	χ^2 = 0.35, p = 0.557
Height (m)	1.71 (0.10)	1.70 (0.08)	t = 0.87, p = 0.386
Body mass (kg)	79.5 (13.0)	78.9 (15.1)	t = 0.23, p = 0.817
GDS-15	1 (1)	3 (2)	**U = 1099, p < 0.001***
Education (years)	14 (4)	13 (4)	U = 2197, p = 0.584
NART	118 (8)	116 (10)	U = 2152, p = 0.586
MoCA ⊦	28 (2)	25 (4)	**U = 1234, p < 0.001***
MMSE	29 (1)	29 (1)	**U = 1673, p = 0.004***
MDS-UPDRS III (0-132)	-	25 (10)	-
H&Y stage n (%)[1]	-	I 23 (23%); II 58 (59%); III 18 (18%)	-
LEDD (mg/day)	-	171 (129)	-

[Results are presented as mean (sd), or number (%) where appropriate. GDS = Geriatric Depression Scale; NART = National Adult Reading Test; MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination; MDS-UPDRS III = Movement Disorders Society Unified Parkinson's Disease Rating Scale part III; H&Y = Hoehn and Yahr; LEDD = Levodopa Equivalent Daily Dose. ⊦ demonstrates a smaller sample size; control n = 38, PD n = 86.]

5.3.2 Baseline cortical thickness

Widespread cortical thinning was associated with increasing age for PD participants (**Appendix N**). In age-matched controls the relationship between cortical thinning and increasing age was more topographically selective and found mostly in the insula, frontal and temporal lobes and cingulate cortex. Cortical thinning was greater in males with PD in the temporal, frontal and parietal lobes. In contrast, sex was not associated with cortical thickness in controls. Education was not associated with cortical thickness in either group. Given these associations, age and sex were included as confounding factors for all subsequent work involving cortical thickness.

In keeping with previous findings from the ICICLE-PD study (Mak *et al.*, 2015), there was no difference in cortical thickness between PD and control groups after multiple comparison (FDR) correction. Before corrections were applied, increased cortical thinning was weakly identified in PD compared to controls in a small cluster within the right fusiform gyrus (n=146, df=140, area=47mm^2, p=0.0006, uncorrected). There were no differences in cortical thickness between PD completers and non-completers, neither before nor after corrections.

5.3.3 Cross-sectional associations between gait and cortical thickness

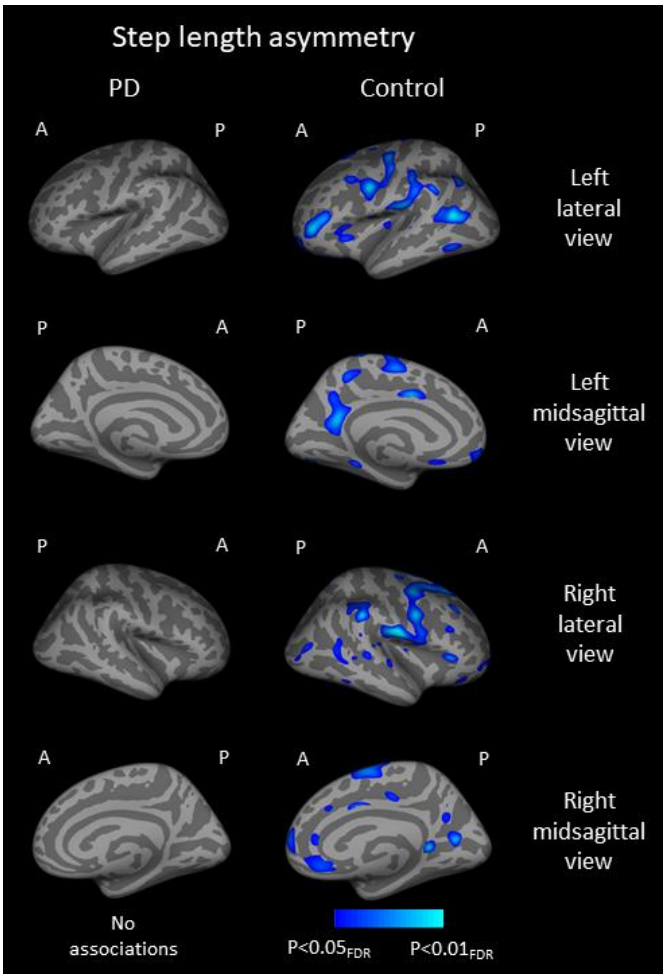
5.3.3a Data-driven approach

In PD, no cross-sectional associations between gait and cortical thinning were identified using the data-driven approach after FDR correction. Cluster-wise analysis, without FDR correction, revealed weak associations ($0.001 < p < 0.0001$) between baseline gait and the thickness of several regions. Most commonly, these associations were made within superior frontal and precentral regions, as well as the lateral occipital and inferior temporal gyri (**Appendix O**). For all associations, greater thinning was associated with poorer gait (*i.e.* slower gait with wider steps, greater variability, longer step and stance times and greater asymmetry), except that greater step width variability was associated with increased thickness.

Conversely, associations between cortical thickness and step length asymmetry survived multiple comparison correction in controls (**Figure 5-4**). Increased asymmetry was associated with greater thinning of several areas; associations were strongest within the parietal lobe (postcentral, inferior parietal and supramarginal regions) and the precentral gyrus. No other gait characteristic demonstrated a significant association with cortical thickness in controls after multiple comparison corrections were applied. Cluster-wise analyses identified weak associations ($0.001 < p < 0.0001$) between cortical thickness and each gait characteristic (**Appendix O**); these associations were made most frequently in superior frontal, rostral middle frontal, supramarginal and lateral orbitofrontal gyri, and most commonly with step length and step width (as well as step length asymmetry). For the most part, greater thinning was again linked to poorer gait.

Weak associations, from cluster-wise analyses, occurred more frequently in controls than PD (**Appendix P**). Associations between cortical thickness and characteristics from the pace and postural control domains of gait occurred more strongly in controls compared to PD. In contrast, weak associations were made between cortical thickness and characteristics from the rhythm domain in PD, whereas no weak associations were evident in controls.

Figure 5-4. Location of cross-sectional associations between cortical thickness and step length asymmetry, as identified through a data-driven approach



[A = Anterior, P = Posterior, FDR = False Discovery Rate. Results are multiple comparison corrected. Blue indicates a negative correlation between gait and cortical thickness. Brighter colours indicate stronger associations.]

5.3.3b Hypothesis-driven approach

Significant partial correlations (after multiple comparison correction) between gait characteristics and average cortical thickness of the pre-defined regions of interest (**Figure 5-2b**), corrected for age and sex, are displayed in **Table 5-2**. All correlations assessed within the PD group have been included in **Appendix Q**. Significant correlations occurred with different gait characteristics for PD and control groups. Few significant correlations were identified within the PD group. Greater cortical thinning of a cortical area linked to visual input significantly correlated with greater impairment in two gait characteristics; specifically, characteristics from the variability domain (variability of step time and stance time) correlated with average thickness of the left cuneus region ($|r| \geq 0.34$, $p \leq 0.001$ for both). Non-significant trends were also identified between greater impairments in gait characteristics from the pace and variability domains and greater thinning of the left cuneus region in PD ($|r| \geq 0.29$, $0.001 < p \leq 0.004$ for all, **Appendix Q**).

In controls, significant correlations were more abundant and occurred in more widespread regions than in PD. Significant correlations were identified with three different gait characteristics, which matched the characteristics that were associated with cortical thickness through the data-driven approach. In controls: greater cortical thinning of regions within the parietal lobe, linked to sensory inputs, correlated with shorter step length ($|r| \geq 0.36$, $p \leq 0.014$ for all); greater thinning in regions relating to both motor and non-motor functions related to increased step length asymmetry ($|r| \geq 0.36$, $p \leq 0.014$ for all) and; greater thinning of the left insula, as well as regions linked to non-motor functions, associated with increased step width ($|r| \geq 0.41$, $p \leq 0.005$ for all). All correlations assessed within the control group can be found in **Appendix R**.

Multiple linear regressions identified the strongest regional cortical thickness predictors of gait performance in cross-section (**Table 5-3**). In PD, thickness of the left cuneus region predicted variability characteristics ($|\beta| \geq 0.38$, $p \leq 0.001$), accounting for at least 11% of the total variance for each characteristic. In contrast, inferior parietal, rostral anterior cingulate and insula regional thicknesses predicted characteristics from pace and postural control domains in controls ($|\beta| \geq 0.42$, $p \leq 0.001$), accounting for at least 15% of the total variance for each characteristic.

Table 5-2. Age and sex controlled partial correlations between regional average cortical thickness and gait

Gait domain	Gait characteristic	Control	PD
Pace	Step length	0.49 (0.001) L Inferior Parietal 0.45 (0.002) R Inferior Parietal 0.42 (0.004) R Supramarginal 0.42 (0.005) R Superior Parietal 0.41 (0.005) L Rostral Middle Frontal 0.41 (0.005) L Superior Parietal 0.41 (0.005) L Insula 0.38 (0.011) L Lateral Orbitofrontal 0.37 (0.012) L Supramarginal 0.37 (0.014) R Superior Frontal	-
Variability	Step time sd	-	-0.35 (0.001) L Cuneus
	Stance time sd	-	-0.37 (<0.001) L Cuneus
Postural control	Step length asy	-.050 (<0.001) R Rostral Anterior Cingulate -0.50 (0.001) R Supramarginal -0.46 (0.001) L Medial Orbitofrontal -0.45 (0.002) R Precentral -0.44 (0.003) L Precentral -0.44 (0.003) L Paracentral -0.41 (0.005) L Supramarginal -0.39 (0.008) R Medial Orbitofrontal -0.38 (0.010) R Superior Frontal -0.36 (0.014) L Lateral Orbitofrontal	-
	Step width	-0.51 (<0.001) L Insula -0.48 (0.001) L Rostral Anterior Cingulate -0.48 (0.001) L Lateral Orbitofrontal -0.41 (0.005) R Superior Frontal	-

[Correlations are displayed as rho (p). L = Left, R = Right, sd = standard deviation (variability), asy = asymmetry.]

Table 5-3. Multiple regression analysis for independent associations between gait and regional average cortical thickness

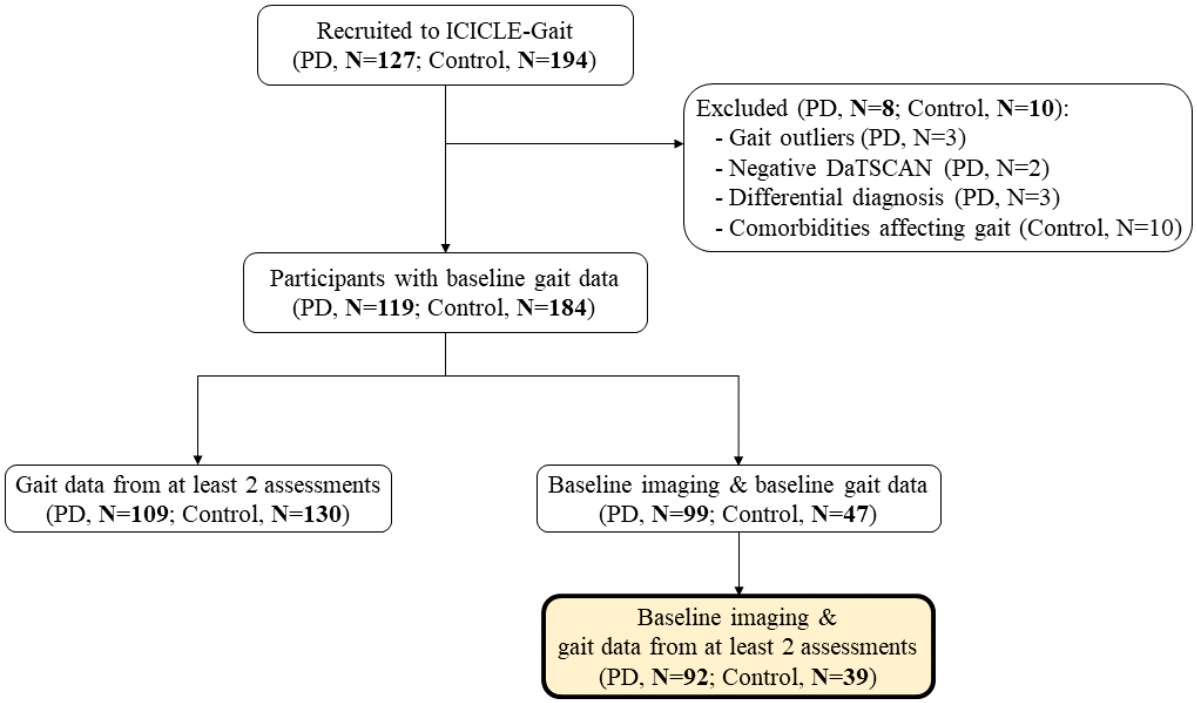
Group	Gait domain	Gait characteristic	Imaging predictors	β	t-statistic	p	95% CI for β		R	R^2	Adjusted R^2	Standard error	ΔR^2
Control	Pace	Step length	L Inferior Parietal	0.42	3.66	0.001	0.09	0.32	0.72	0.51	0.48	0.05	0.15
	Postural control	Step length asy	R Rostral Anterior Cingulate	-0.51	-3.83	<0.001	-0.16	-0.05	0.69	0.48	0.45	0.05	0.18
		Step width	L Insula	-0.54	-3.84	<0.001	-0.06	-0.02	0.57	0.33	0.28	0.02	0.23
PD	Variability	Step time sd	L Cuneus	-0.38	-3.59	0.001	-1.04	-0.30	0.37	0.14	0.11	0.30	0.12
		Stance time sd	L Cuneus	-0.41	-3.85	<0.001	-1.30	-0.41	0.39	0.15	0.13	0.36	0.13

[Age and sex were entered in the first step for all models, and all average thicknesses which had significant partial correlations with each gait characteristic were next enetered using the stepwise approach. L=Left, R=Right, sd=standard deviation, asy=asymmetry]

5.3.4 Longitudinal associations between gait and cortical thickness

92 Parkinson's disease subjects and 39 control participants had gait data available from at least one follow-up assessment (**Figure 5-5** and **Appendix L**) so were included in longitudinal analyses.

Figure 5-5. Participants considered within longitudinal analyses

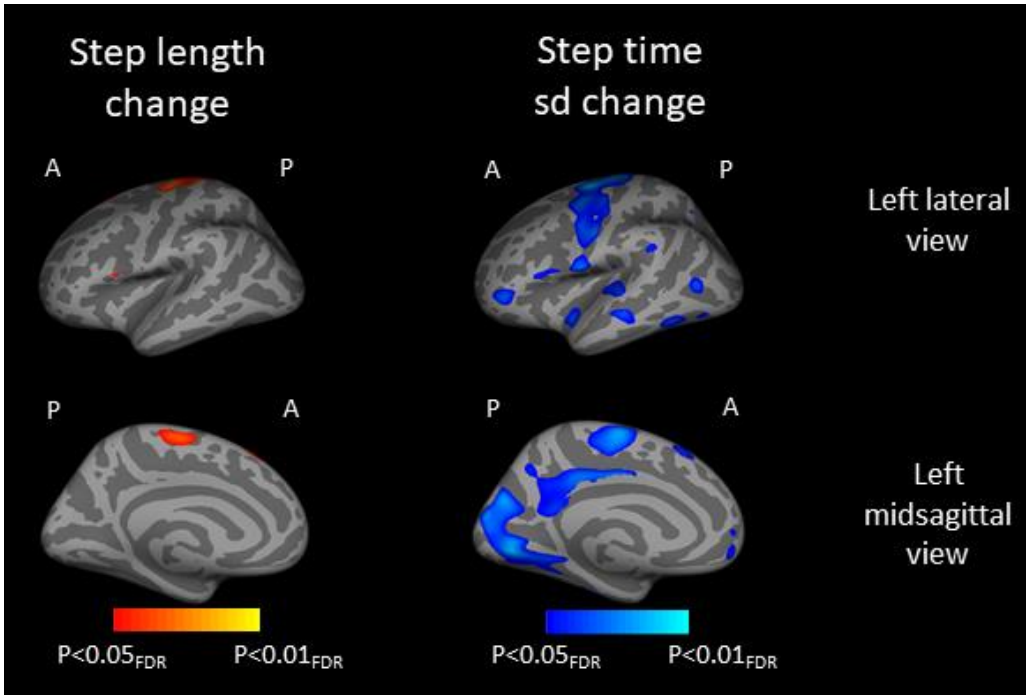


5.3.4a Data-driven approach

Using the data-driven approach, change slopes for both step length and step time variability (which accounted for baseline age and sex) were significantly associated with baseline cortical thickness of regions in the left hemisphere in PD ($p<0.05$ FDR corrected). Greater decline in step length over 72 months was associated with increased baseline thinning of left superior frontal, precentral & paracentral regions at baseline. Greater increase in step time variability over time also associated with greater thinning of left precentral and paracentral regions at baseline, as well as thinning in lingual, fusiform and posterior cingulate regions (**Figure 5-6**).

Cluster-wise analyses, without FDR correction, revealed additional weak associations (0.0001 <p< 0.001 uncorrected) between gait change and baseline cortical thickness. Cluster-wise analyses identified that: greater decline in step length over time was weakly associated with greater thinning of precentral and parietal lobe regions in the right hemisphere at baseline; greater increase in step time variability over 72 months associated with greater baseline thinning of right frontal and temporal regions; increasing swing time variability was associated with greater baseline thinning of superior frontal and inferior temporal regions and; greater increase in step length variability over time was associated with thinning of left lingual and right superior frontal regions at baseline. The location and peak vertex significance of all associations between gait change and baseline cortical thickness (as identified through both FDR corrected analyses and cluster-wise analyses) are listed in **Table 5-4** and depicted in **Appendix S**.

Figure 5-6. Location of longitudinal associations between cortical thickness and gait change



[A = Anterior, P = Posterior, sd = standard deviation, FDR = False Discover Rate. Associations made after multiple comparison correction. All associations indicate that greater gait impairment is linked to reduced cortical thickness: red indicates a positive correlation between gait change and cortical thickness (*i.e.* greater thinning linked to greater decline in step length (worsening step length over time)); blue indicates a negative correlation (*i.e.* greater thinning linked to greater increase in step time variability (worsening step time variability over time)). Brighter colours indicate stronger associations.]

Table 5-4. Location and peak vertex significance of all associations (p<0.001) between cortical thickness and gait change in PD

Group	Gait characteristic	Cluster location	x	y	z	NVtxs	Area (mm^2)	$-\log_{10}P$
PD	**Δ Step length (left hemisphere)***	Left Superior frontal	-13.5	23.3	54.7	489	303	4.18
		Left Precentral	-24.9	-21.0	69.7	1695	720	4.18
		Left Paracentral	-6.9	-19.2	61.3	665	275	3.81
		Left Pars opercularis	-52.6	13.5	9.4	66	33	3.26
	Δ Step length (right hemisphere)	Right Superior parietal	27.2	-49.7	62.4	414	209	4.12
		Right Precentral	12.6	-24.9	69.5	1124	478	3.73
		Right Supramarginal	60.2	-39.5	34.5	361	182	3.66
		Right Pars opercularis	53.7	14.5	13.5	136	86	3.44
	Δ Swing time sd	Right Superior frontal	10.5	51.7	7.7	72	58	-3.12
		Right Inferior temporal	44.0	-19.8	-22.8	58	28	-3.12
	Δ Step time sd (left hemisphere)*	Left Precentral	-20.3	-12.8	57.0	0 7137	3094	-4.05
		Left Lingual	-8.8	-76.4	-4.0	1 5066	3418	-3.89
		Left Paracentral	-7.0	-15.2	61.3	1637	661	-3.62
		Left Fusiform	-41.8	-19.2	-22.8	479	234	-3.36
		Left Posterior cingulate	-4.5	-15.1	38.0	8 2906	1250	-3.24
		Left Precentral	-57.9	-3.6	10.6	869	345	-3.18
		Left Pars triangularis	-41.7	38.5	-5.2	528	343	-2.98
		Left Lateral occipital	-41.6	-64.7	5.7	294	145	-2.91
		Left Superior temporal	-43.9	-9.0	-16.7	447	167	-2.87
		Left Middle temporal	-54.4	-26.8	-12.7	469	236	-2.86
		Left Inferior temporal	-49.8	-54.0	-13.2	435	292	-2.86
		Left Superior temporal	-59.5	-20.9	1.0	856	366	-2.77
		Left Superior frontal	-6.8	24.3	55.2	252	130	-2.60
		Left Pars opercularis	-52.6	20.0	12.3	340	192	-2.44
		Left Supramarginal	-54.5	-45.8	29.3	167	77	-2.44
		Left Medial orbitofrontal	-8.3	51.2	-9.0	147	133	-2.39
		Left Lateral occipital	-40.2	-71.8	-9.4	98	59	-2.33
		Left Superior parietal	-25.3	-62.8	48.1	32	16	-2.26
		Left Supramarginal	-42.3	-23.1	20.8	34	14	-2.25
		Left Superior frontal	-13.3	51.0	5.0	41	23	-2.20
	Δ Step time sd (right hemisphere)	Right Superior frontal	10.8	51.5	8.4	930	609	-4.26
		Right Inferior temporal	43.7	-24.5	-21.2	378	179	-3.79
		Right Medial orbitofrontal	6.9	55.0	-16.8	203	130	-3.38
		Right Insula	38.0	0.0	-12.3	87	33	-3.22
		Right Precentral	41.6	-12.0	30.3	167	48	-3.22
		Right Medial orbitofrontal	9.1	26.6	-20.6	85	51	-3.15
		Right Transverse temporal	48.5	-19.6	6.7	50	17	-3.11
	Δ Step length sd	Left Lingual	-5.5	-73.1	4.3	92	54	-3.39
		Right Superior frontal	11.0	51.4	9.1	424	307	-3.63
	Δ Swing time asy	N/A	-	-	-	-	-	-

[sd = standard deviation (variability), asy = asymmetry, Δ = change in. * signifies associations that survived multiple comparison correction. All other reported cluster-wise associations are uncorrected, p<0.001 ($-\log_{10}P > 3$)]

5.3.4b Hypothesis-driven approach

Table 5-5 summarises the hypothesised regions of cortical thickness that predicted PD specific gait change over 72 months in linear mixed-effects models, after multiple comparison corrections were applied. For all predictors, model fit was significantly improved with the individual inclusion of each region of average cortical thickness as an interaction with time (χ^2>6.0, p<0.05 for all predictors). Specifically: greater decline in step length over 72 months was predicted by smaller baseline thickness of areas relating to motor outputs (β>0.018, p≤0.005 for all); greater increase in step length variability was predicted from thinning of non-motor areas (β< -0.025, p≤0.005 for all) and; greater increase in step time variability over time was predicted from smaller baseline thickness of areas relating to both motor and non-motor functions (β< -0.025, p≤0.005 for all). All regions that predicted change in either step length or step length variability also predicted change in step time variability. Change in swing time variability and asymmetry was not significantly predicted from the thickness of any region.

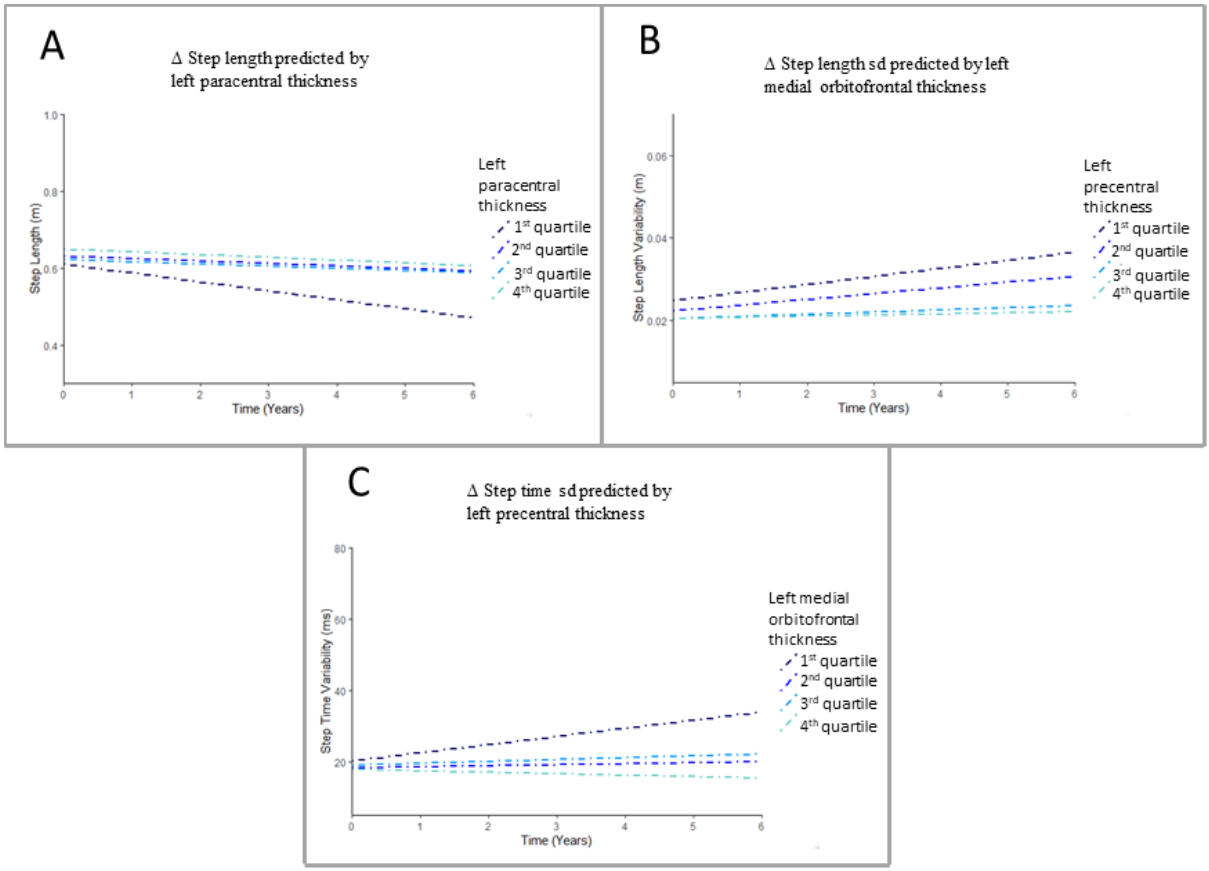
Table 5-5. Regions of average cortical thickness that predicted PD-specific gait change

Gait characteristic	Location of region	Predictor region	Regression coefficients			
			β	SE	t	p
Step length	Frontal	**L Paracentral**	0.020	0.006	3.44	**0.001***
		R Paracentral	0.020	0.006	3.16	**0.002***
		L Superior frontal	0.024	0.008	2.97	**0.004***
		R Precentral	0.018	0.006	2.90	**0.005***
Step time variability	Frontal	**L Precentral**	-2.416	0.663	-3.64	**<0.001***
		R Paracentral	-2.328	0.716	-3.25	**0.002***
		R Medial Orbitofrontal	-2.842	0.876	-3.24	**0.002***
		R Precentral	-2.177	0.688	-3.17	**0.002***
		L Paracentral	-2.102	0.694	-3.03	**0.003***
		R Superior Frontal	-2.572	0.938	-2.74	**0.007***
		L Medial Orbitofrontal	-2.356	0.863	-2.73	**0.008***
		R Lateral Orbitofrontal	-2.327	0.896	-2.60	**0.011***
		L Rostral Middle Frontal	-3.613	1.429	-2.53	**0.013***
		L Superior Frontal	-2.260	0.908	-2.49	**0.015***
	Parietal	**R Postcentral**	-3.057	1.276	-2.40	**0.019***
	Occipital	**R Pericalcarine**	-4.630	1.528	-3.03	**0.003***
		L Cuneus	-3.369	1.329	-2.54	**0.013***
		L Pericalcarine	-3.830	1.566	-2.45	**0.017***
	Cingulate	**L Rostral Anterior Cingulate**	-1.944	0.636	-3.06	**0.003***
		R Rostral Anterior Cingulate	-1.359	0.576	-2.36	**0.020***
	Insula	**R Insula**	-1.604	0.641	-2.50	**0.014***
Step length variability	Frontal	**L Medial Orbitofrontal**	-0.003	0.001	-3.22	**0.002***
		R Medial Orbitofrontal	-0.003	0.001	-3.09	**0.002***
		R Lateral Orbitofrontal	-0.003	0.001	-2.96	**0.004***
		L Rostral Middle Frontal	-0.004	0.001	-2.88	**0.005***

[All predictors of gait change survived multiple comparison correction. L = Left, R = Right.]

All regional predictors of gait change that were significant at $p<0.05$ (those that survived multiple comparison correction and those that were not significant but demonstrated a statistical trend) are included in **Appendix T**. To visualise the effect of cortical thickness on changes in gait over time, groups were split into quartiles of regional cortical thickness, for the strongest regional predictor of change for each gait characteristic (**Figure 5-7**).

Figure 5-7. Change in gait over 72 months in PD, for individuals within each quartile of regional cortical thickness



[Δ; change in. sd; standard deviation (variability). Darker colours represent lower quartiles *i.e.* smaller regional cortical thickness. Panel A shows change in step length when the PD group was split by quartiles of left paracentral thickness. Panel B shows change in step length variability when the group was split by quartiles of left medial orbitofrontal thickness. Panel C shows change in step time variability when the PD group was split by quartiles of left precentral thickness.]

5.4 Discussion

This chapter details the first study to assess the associations between cortical thickness and discrete gait characteristics in PD. This was a large study in an incident PD cohort followed from diagnosis, allowing for precise modelling to determine the cortical areas associated with PD gait in early disease. This study provides mechanistic evidence for a coupling of regional cortical volumetric changes with discrete impairments in PD gait. This coupling occurred with areas linked to both motor and non-motor related functions. Additionally, this is the first study to determine that regional cortical thickness measures quantified soon after PD diagnosis can predict future PD-specific changes in gait. This study therefore provides the first evidence of cortical thickness measures having the potential to be considered clinically for the determination of those most at risk of gait decline.

5.4.1 The neural correlates of gait unique to PD

Overall, data-driven cross-sectional analyses identified no strong associations between cortical thickness and any discrete gait characteristic in PD, yet strong cross-sectional associations that survived multiple comparison corrections were identified in controls. This result goes against hypothesis 1, which suggested overall stronger associations in PD due to an increased reliance on the cortex for effective gait to compensate for ineffective automatic motor control. However, findings did support hypothesis 3, as the strong associations evident in controls and not PD were with cortical thickness of areas linked to motor outputs. Results from this chapter therefore suggest that coupling between locomotor control and the structural integrity of cortical motor networks is retained in healthy older adults, whereas this coupling may be lost even in early PD. This reinforces the argument that dysfunction or pathology in other regions may be more salient for gait impairment in early PD. Speculatively, cross-sectional findings may further indicate that there is an overall breakdown of a consistent pattern of cortical control of gait in PD, and that any available resource from a diverse set of regions is instead relied upon for gait, which may explain the overall lack of correlations identified in PD. Alternatively, cortical thickness may simply not be a sensitive enough measure to assess with gait cross-sectionally, particularly when trying to compare associations across diagnostic groups, given the lack of difference in cortical thickness between PD and healthy control groups both here and in other assessments in early PD (Jubault *et al.*, 2011; Mak *et al.*, 2015).

Of the weak cross-sectional associations identified in PD (through data-driven, cluster-wise analyses as well as those identified through hypothesis-driven analyses only), greater cortical

thinning was associated with poorer gait *i.e.* slower gait with shorter step length, greater variability and greater asymmetry, as expected. In exception to this, greater thinnning was associated with reduced step width variability. It was proposed in chapter 4 that reduced step width variability may represent a maladaptation because it reflects an inability to maintain stability; findings in this study may support this notion as reduced step width variability reflected a "less healthy" brain.

Areas related to the visual system, particularly the cuneus, were most commonly associated with PD gait characteristics (from pace and variability domains) through both forms of cross-sectional analysis (**Appendix Q**). These areas were not, however, associated with gait in controls (**Appendix R**). Previous work has identified associations between structural integrity of the occipital cortex and step length and cadence in healthy older adults (**Figure 2-5**), but no investigations specifically targetting the occipital lobe have been conducted in PD (**Table 2-2**). Combined, these findings indicate that visual input is required for effective gait in both ageing and disease, but is more heavily relied upon to compensate for gait impairment in PD than in healthy ageing. This supports the use of external visual cues to mitigate gait impairment in PD; indeed, it has been identified that people with PD are more reliant on visual cues for gait control compared to controls (Azulay *et al.*, 2006). Visual dysfunction is associated with gait impairment (Swigler *et al.*, 2012; Shin *et al.*, 2015) and gait response to visual cues has been attributed to visual function in PD, although this association is thought to be modulated by attention (Stuart *et al.*, 2018). The interaction between attentional and visual processes and their influence on gait can be assessed in real-time by measuring saccades (fast eye movements between environmental areas of interest) during walking (Stuart *et al.*, 2015). It is thought that saccades allow the acquisition of visual information which is then integrated into motor networks involved in gait via attentional projections (Kravitz *et al.*, 2011; Stuart *et al.*, 2017). As gait characteristics from the pace and variability domains were associated with cortical thinning in visual areas in PD, this chapter further supports the notion that attentional networks may underpin these characteristics (Morris *et al.*, 2016). Future analyses could include saccadic impairment and/or measures of attention (e.g. through the cognitive drug research battery (CDR) (Nicholl *et al.*, 1995)) in models of gait and occipital cortex imaging to further understand the relationship between visual function and gait in PD.

It was expected that prefrontal areas would also exhibit links to PD gait, particularly given the numerous reports of increased prefrontal activity during gait in PD compared to controls (Stuart *et al.*, 2019) and the reliance on attention for visual exploration during gait (Peterson and Smulders, 2015). However, structural measures of the prefrontal cortex were not

associated with gait in PD in cross-section. This again may be due to structural imaging not reflecting PD-related gait impairments effectively in very early disease.

The only cross-sectional associations between cortical thinning and gait that were stronger in PD compared to age-matched controls were with characteristics from the rhythm domain of gait, although these were only identified through the data-driven analytical approach. Interestingly, greater stance and step times were associated with greater precentral thinning, corresponding to the primary motor cortex. This goes against hypothesis 2, as stronger associations in PD compared to controls were generally expected in non-motor regions. However, this finding does support hypothesis 6, as characteristics from the rhythm domain were associated with the cortical thickness of motor areas. Although poor gait rhythmicity in PD is typically linked to shorter step times, the associations identified here are thought to be as a result of compensations to preserve step velocity despite shorter step length (Morris *et al.*, 1994a). This compensation is thought to be driven by the cerebellum increasing its activity to the primary motor cortex (Bohnen and Jahn, 2013; Peterson and Horak, 2016). People with PD with less grey matter in the primary motor cortex may not be able to respond as effectively to this increased cerebellar compensatory activity, and may therefore not reduce their step time effectively to preserve step velocity. Associations between cerebellar volume and characteristics from the rhythm domain (as assessed in chapter 6 of this thesis) will give greater insight into this proposed compensatory mechanism.

Few studies have assessed associations between cortical thickness and gait in healthy older adults (de Laat *et al.*, 2012; Jayakody *et al.*, 2020). de Laat *et al.* identified associations between cortical thickness and step length and step width; these characteristics also demonstrated some of the strongest associations with cortical thickness of control participants in this chapter (**Table 5-2**). In both this chapter and the study from de Laat *et al.*, step length related to thinning in parietal regions and step width related to PFC thinning, suggesting that characteristics from the pace domain are mediated by motor-related networks whereas postural control characteristics are mediated (at least in part) through non-motor networks. These findings therefore support hypotheses 5 and 8. As has been described throughout this thesis, pace characteristics respond well to dopaminergic medication (Smulders *et al.*, 2016) whereas postural instability is thought to better relate to subcortical cholinergic innervation in PD (Müller *et al.*, 2013; Craig *et al.*, 2020). These neurotransmitters may therefore primarily underpin motor and non-motor networks respectively, although this speculation warrants further investigation. Jayakody *et al.* (Jayakody *et al.*, 2020) investigated measures of gait variability with cortical thickness and found associations with step time variability and step

width variability with widespread regions involved in both motor and non-motor networks. In this chapter, no associations were identified with step width variability in older adults; step time variability was weakly associated with areas related to sensory functions (**Apendix 5.5**). Differences in findings may arise from less stringent multiple comparison corrections used by Jayakody *et al.*, as vertex-wise analyses were not performed.

5.4.2 Areas linked to both motor and non-motor functions predict PD-specific gait decline

The strongest findings of this chapter demonstrated that cortical thickness in areas related to motor and non-motor functions predicted changes in gait pace and variability over time. These findings support hypotheses 4 and 5. Specifically, reduced cortical thickness of motor areas at baseline predicted shortening step length over 72 months, whereas reduced thickness of both motor and non-motor areas predicted increasing step time variability. An increase in step length variability was also related to non-motor areas, although these associations were only identified through hypothesis-driven analyses, so are arguably not as robust. Analyses therefore demonstrated specificity in the neural underpinnings of discrete gait characteristics in PD, as different areas predicted different gait changes.

Although chapter 2 identified that no longitudinal assessments of the neural correlates of PD gait have been completed, previous cross-sectional findings relate to longitudinal findings within this chapter. Change in step length variability was attributed to the structural integrity of non-motor cortical areas here; step length variability has previously been associated with dopaminergic activity in areas connecting the striatum to executive and limbic areas of the frontal lobe, which are also arguably non-motor cortical areas (Hirata *et al.*, 2020). Step time variability has previously related to increased functional connectivity, both within the striatum and between the putamen and orbitofrontal cortices (Gilat *et al.*, 2017). In this thesis, the striatum (including the putamen) has been considered part of motor networks involved in automatic locomotor control, and orbitofrontal cortices part of non-motor networks involved in higher-order cognitive tasks that may be utilised in PD gait control. Therefore, the prediction of step time variability change from the structural integrity of areas related to both motor and non-motor networks in this chapter relates well to previous work.

Changes in step time variability were predicted from cortical thinning of both motor and non-motor related areas, whereas step length changes were only predicted from thinning of motor related areas and step length variability changes from thinning of non-motor related areas only. Speculatively, these findings may present an explanation for the inclsuion of step time

variability in different domains of gait, depending on the population assessed. In the model of gait for healthy older adults, step time variability best fitted in the pace domain (**Figure 2-1**, (Lord *et al.*, 2013c)) whereas in the validated PD model it was best placed within the variability domain (**Figure 3-3** (Lord *et al.*, 2013b)). In healthy ageing, perhaps, step time variability may depend more on automatic motor related networks, as these are not affected by pathology, and so may better reflect the neural underpinnings of characteristics from the pace domain. Conversely, step time variability may become more reliant on non-motor network involvement in PD, to compensate for impaired motor networks, and therefore have more similar neural mechanisms to variability characteristics.

Changes in pace may be best targetted through interventions targetting the motor system, whereas variability may require interventions targetting non-motor areas. As described in chapter 1, dopaminergic medications are commonly prescribed to treat PD motor symptoms; pace characteristics such as step length are thought to improve with dopaminergic medications because they alleviate bradykinesia. Dopaminergic medications may also sufficiently prevent decline in step length in very early PD, which may explain why changes in step length are no different to those identified during typical ageing over the first three years of PD (Rochester *et al.*, 2017). However, as dopaminergic medications become less effective over time in PD due to nigostriatal cell loss (Zahoor *et al.*, 2018), the ability of dopaminergic medications to normalise step length may be compromised over time, explaining the significant difference in step length change between PD and control groups when assessed over a longer timeframe of 72 months (chapter 4).

Conversely, variability measures may require additional interventions targetting non-motor networks (thought to relate to the prefrontal cortex, as discussed in section 5.1) to prevent PD-specific decline. Both dopaminergic and cholinergic pathways have strong connections to the prefrontal cortex (Robbins and Roberts, 2007; Kehagia *et al.*, 2010). While there is limited evidence of the effectiveness of dopaminergic therapies to improve gait variability (Bryant *et al.*, 2011a; Rochester *et al.*, 2011), gait variability characteristics may be improved by cholinergic medications in PD (Henderson *et al.*, 2016). As sources of cholinergic innervation are affected in early Braak stages of PD, the cholinergic system may underpin changes in variability that occur in early PD. As cholinergic interventions are not common in the clinical treatment of PD, this may explain why changes in the variability of step time and step length are apparent even over 36 months (Rochester et al., 2017). Future investigations of the cholinergic system with gait variability may help further our understanding; this could be completed through functional imaging studies of the cholinergic system (Bohnen *et al.*, 2013),

assessments of SAI (Rochester *et al.*, 2012) or through structural imaging studies assessing areas that produce acetylcholine (Ray *et al.*, 2017). Findings from this chapter present a neural basis for the widely reported associations between gait variability in PD and cognitive deficits (Morris *et al.*, 2016; Mc Ardle *et al.*, 2019), which may be as a result of shared substrates between gait and cognitive processes.

Perhaps most strikingly, the cortical thickness predictors of change in step length and step length variability were also predictors of step time variability. This indicates that step time variability may be the best gait characteristic to use when assessing changes in PD gait, as it appears to be a fully-encompassing gait characteristic. In chapter 4, changes in step length and step length variability were identified as being due to both disease progression and ageing; step time variability, however, appeared more independent and reflected disease progression only. Step time variability progression is therefore not confounded as strongly by ageing, strengthening the argument for its use as a clinical marker of disease progression. People with PD with greater cortical thinning at baseline went on to develop greater impairments in gait. This was particularly true for those within the smallest quartile of cortical thickness (**Figure 5-7)**, who may therefore be most at risk of falling or developing PDD. The vulnerability of this particular group could be investigated in more detail in future.

Changes in the variability and asymmetry of swing time were not strongly predicted by the cortical thickness of any region. Weak associations between swing time variability and cortical thickness (identified through cluster-wise analyses in the data-driven approach, $p<0.001$) occurred in the right superior frontal and right inferior temporal regions. These areas match the areas within the right hemisphere that most strongly associated with change in step time variability in data-driven analyses (**Table 5-4**). Swing time variability is most likely controlled by the same neural pathways as step time variability, as it is a sub-component of step time (**Figure 1-1**). These pathways may be less identifiable for swing time variability as change in this characteristic is more subtle than change in step time variability, as identified in chapter 4 as well in analyses over 36 months (Rochester *et al.*, 2017). This speculation will be assessed further in chapters 6 and 7 through comparisons of the neural underpinnings of variability in step and swing time.

Change in swing time asymmetry was not associated with any baseline volumetric measurement. Although a weak cross-sectional association was identified between step time asymmetry and the left precentral region in PD (the location of the primary motor cortex, **Appendix P**), this is insufficient evidence to reasonably accept hypothesis 7 (that asymmetry measures would relate to cortical thickness of areas linked to motor functions). In chapter 4 a

conjecture was presented that asymmetry changes may reflect PD pathology becoming more bilateral over time; therefore asymmetry measurements of the brain (such as volumetric differences between left and right regions) may better predict change in gait asymmetry. Moreover, gait asymmetry may be most strongly underpinned by the integrity of connections between motor areas within the left and right hemispheres, through the corpus callosum (Fling *et al.*, 2018). These speculations require further in-depth analyses to fully understand and would be important follow-on studies from the work presented in this thesis.

5.4.3 Clinical implications

Primarily, this thesis aims to further current understanding of the neural underpinnings of gait impairment in PD from a mechanistic viewpoint. However, findings also have clinical utility. This chapter provides the first evidence that volumetric cortical measures can be used as predictors of gait change in early PD; these also have the potential, therefore, to be further investigated for clinical use as early warning markers of falls (Lord *et al.*, 2016) and cognitive decline (Morris *et al.*, 2017). Despite the negative impact of gait impairments, little work to date has assessed the clinical markers predictive of gait changes in PD (Rochester *et al.*, 2017; Hobert *et al.*, 2019). In healthy older adults, risk factors for more severe changes in gait include higher BMI, arthritis, slower processing speed and low quadricep strength (Jayakody *et al.*, 2018). Further exploration of predictors of gait decline in PD should be completed to enable the development of a powerful combinational battery of markers of gait progression that can be used to inform individualised therapuetic management plans.

Additionally, this study has provided tentative evidence for an associaton between non-motor brain structures and PD gait, further highlighting the need for novel therapies that target both motor and non-motor systems. Variability of both step time and step length, which exhibit early changes in PD that are dopa-resistant (Rochester *et al.*, 2017), were associated with cortical thinning in non-motor structures within the prefrontal cortex. Although function of the prefrontal cortex is influenced by a combination of neurotransmitter systems, including dopaminergic and cholinergic systems (Robbins and Roberts, 2007; Kehagia *et al.*, 2010), the dopa-resistance of these variability characteristics indicates that they may, at least in part, be more contingent upon cholinergic function. As cholinergic medications can improve gait variability in PD (Henderson *et al.*, 2016), findings from this study help strengthen the case for targetting the cholinergic system to limit gait progression in PD.

5.4.4 Study strengths and limitations

This study has several strengths and limitations; those that relate specifically to the ICICLE cohort and the longitudinal nature of this study are outlined in chapter 4.

This is the first study to utilise both data-driven and hypothesis-driven approaches to establish associations between cortical thickness and gait. Similar associations were made through the different analytical approaches, thereby strengthening confidence in the robustness and replicability of these findings. The use of multiple comparison corrections, and the consideration of age and sex in all analyses, also demonstrates the robustness of findings. The measures of cortical thickness used were considered reliable, as image processing was completed through reliable methods and suitable processing of images was verified at each stage. Cross-sectional associations were made in very early disease; this is crucial for furthering current understanding of the gait mechanisms involved in early PD, which may be indicative of novel intervention targets at a time where they would be most beneficial. In this chapter, associations between discrete gait characteristics and cortical volumes have been throuroughly assessed, laying a strong foundation for future work that may consider more network-based approaches.

This study also has some limitations. Gait and imaging assessments were dissociated in time so correlation-based analyses were relied upon, although baseline assessments were conducted a median of three weeks apart. Atrophic volumetric losses may not best represent early neural changes in PD (Mak *et al.*, 2015; Firbank *et al.*, 2017; Rektor *et al.*, 2018) so may not sufficiently reflect gait impairments soon after a diagnosis of PD. Further, the volumetric measures considered here do not reflect integrative brain networks that may better reflect the dynamic brain during gait. Approaches such as DTI (Verlinden *et al.*, 2016), resting-state fMRI (Yuan *et al.*, 2015) and assessment of spatial covariance patterns (Colloby *et al.*, 2015) may be useful next steps in this regard. Nonetheless, work presented here is indicative of the regions most involved in PD gait and provides a good foundation for future studies to lead more hypothesis-driven network based approaches when assessing the neural underpinnings of PD gait.

Cortical thickness measures were selected for investigation as they are sensitive to change in PD (Pereira *et al.*, 2012). Additional cortical measures, such as cortical surface area, may be independently affected in PD (Gerrits *et al.*, 2016), so their investigation may provide further insight into the structural neural underpinnings of PD gait. In hypothesis-driven approaches, cortical thickness was averaged across gyral regions of interest; therefore, the imaging

parameters used were not as precise as in data-driven approaches. However, the use of both data-driven and hypothesis-driven approaches enabled comparisons to be completed between them; associations identified through both methods were considered robust. Cognition was not considered here, despite strong associations between gait and cognition. Understanding the role of cognition in associations between gait and cortical thickness requires an in-depth investigation of the effects of different cognitive domains on both gait and imaging parameters, as well as how these interact over time. The complexity of this goes beyond the main aims of this thesis, although further insights from cognition may be useful to assess in future. Lastly, findings from this study should be replicated in an independent cohort.

5.4.5 Conclusions

To conclude, this chapter demonstrates the first evidence of associations between cortical thickness and discrete gait characteristics in a large incident PD cohort. Cross-sectional associations were weaker in PD than in age-matched controls, thought to indicate an overall breakdown of the neural networks typically used in gait control in PD. Furthermore, this is the first study to find that cortical areas related to both motor and non-motor outputs can predict future changes in gait that occurr as a result of PD progression rather than ageing. These novel findings indicate that structural MRI could be investigated in future for use as an indicator of those at greater risk of falling or developing cognitive impairment and are, therefore, in need of early targetted interventions. Findings from this chapter also signify a potential role of the cholinergic system in PD-specific changes in gait, which warrants further exploration. Future work should establish whether connectivity between the cortical regions identified here is also associated with disease-specific gait changes, to form greater understanding of the overall neural networks that most affect gait in PD. This will enable future therapies to be more targeted.

Chapter 6: The subcortical volumes associated with PD gait

Following on from chapter 5, this chapter investigates associations between volumes of subcortical structures and the progression of discrete gait impairments in PD.

6.1 Introduction

Thus far, this thesis has discussed the importance of understanding the mechanisms that underpin gait impairment in PD. Chapter 5 detailed the first study in PD to show a specificity in the cortical regions associated with discrete characteristics from a validated gait model. Whilst PD-specific changes in pace characteristics were predicted from volumetric measures of motor-related cortical structures, gait variability changes were predicted from the volumes of cortical structures involved in non-motor networks. As introduced in chapter 5, an assessment of associations between subcortical structures and gait is needed for a more complete picture of the neural regions associated with PD gait impairment, particularly of the involvement of motor and non-motor related structures. This is of importance when considering PD, as subcortical regions are affected by neuronal loss and pathology earlier than cortical regions (Marsden, 1990; Dauer and Przedborski, 2003; Braak, 2004). Subcortical structures may, therefore, influence PD-specific gait changes more strongly than cortical structures and cross-sectional associations in early disease may be more apparent.

Subcortical structures are thought to be involved in automatic motor control during gait (Bohnen and Jahn, 2013; Takakusaki, 2013). As outlined in chapter 1, section 1.4., problems with movement in PD are thought to stem from dysfunction of the basal-ganglia-thalamocortical circuit (**Figure 1-4**) due to SNpc degeneration. Overall, dysfunction of this circuit leads to reduced excitation of cortical structures. Poor structural integrity of subcortical structures involved in this motor-related circuit, including the dorsal striatum (putamen and caudate), internal and external portions of the globus pallidus and the thalamus, may have a compounding effect on gait impairment. Although few studies assessing neural correlates of gait in healthy older adults have specified these subcortical structures in analyses (Rosano *et al.*, 2008; Dumurgier *et al.*, 2012), more concentrated work in PD has detailed associations between better gait performance and increased functional connectivity (Vervoort *et al.*, 2016; Gilat *et al.*, 2017) and activity (Peterson *et al.*, 2014) within portions of the basal ganglia, particularly the putamen.

Chapter 1 also detailed that the brainstem and cerebellum facilitate the automatic process of motor control (Jahn *et al.*, 2008; Takakusaki, 2013). Although Lewy body pathology is present in the brainstem early in PD (Braak, 2004) and may therefore affect locomotor control, it is thought overall that these structures are involved in compensatory mechanisms to overcome deficiencies in the basal-ganglia-thalamocortical circuit (**Figure 1-5**). In particular, the cerebellum is believed to increase its activity to drive a direct motor-related circuit between the primary motor cortex and spinal cord (Wu and Hallett, 2013; Gilat *et al.*, 2017) and to increase the integration of sensory information to inform motor outputs (Lewis *et al.*, 2013). The structural integrity (or lack of) of both the brainstem and cerebellum may relate to discrete gait impairments in PD as part of wider motor networks, due to increased reliance on these structures for compensatory mechanisms for gait control. Findings from chapter 5 identified that characteristics from the rhythm domain of gait were associated with thinning in the primary motor cortex, speculated to be driven by the cerebellum via compensatory mechanisms (Bohnen and Jahn, 2013; Peterson and Horak, 2016). Worsened gait has been associated with cerebellar atrophy (Rosano *et al.*, 2007; Callisaya *et al.*, 2014; Nadkarni *et al.*, 2014) and poorer structural integrity of the brainstem (Rosano *et al.*, 2005a; Verlinden *et al.*, 2016) in healthy ageing; increased functional responses of the cerebellum and brainstem, but not structural integrity of these regions, have been associated with improved gait in PD (Peterson *et al.*, 2014; Gilat *et al.*, 2017). Overall, it is not currently known whether the cerebellum and brainstem are selectively associated with discrete gait impairments in PD.

Subcortical volumes of structures related to non-motor functions may also be related to PD gait. This may be particularly true for gait characteristics within variability and postural control domains, given that these characteristics were most strongly associated with cortical thinning in non-motor related areas in chapter 5. In PD, recent work has identified smaller volumes of the amygdala and globus pallidus in people with the PIGD subtype of PD compared to those with the tremor dominant subtype (Rosenberg-Katz K, 2016). This study also found an association between smaller hippocampal volume and slower dual task gait speed in PD; this relates to studies in older adult populations, as described in chapter 2, linking hippocampal volume to shorter step length both cross-sectionally and longitudinally (Zimmerman *et al.*, 2009; Callisaya *et al.*, 2013). Shorter stride length has also been associated with smaller nucleus accumbens volume, part of the ventral striatum, in a mixed cohort of healthy and cognitively impaired older adults (McGough *et al.*, 2018). Step time variability may be associated with hippocampal volume in older adults (Beauchet *et al.*, 2015), although evidence is conflicting (Beauchet *et al.*, 2017). The thalamus may

additionally be involved in non-motor functions that relate to PD gait, through cholinergic projections from the PPN, although evidence suggests that thalamic cholinergic activity does not relate to discrete gait characteristics as strongly as cortical cholinergic activity (Bohnen *et al.*, 2013; Müller *et al.*, 2015).

Volumetric imaging of subcortical structures can be performed with automated software, which is less sensitive to variations in anatomy between individuals and registration errors (Khan *et al.*, 2008). Although this technique has some limitations, it is considered a gold-standard approach for morphological MR analyses in older adults (Fischl *et al.*, 2002; Fischl *et al.*, 2004). The volumes of hypothesised structures of interest can be associated with discrete gait characteristics, both in cross-section and longitudinally, to increase current understanding of the subcortical mechanisms of gait control in PD.

Aims and hypotheses

This chapter aims to i) determine differences in subcortical volumes in PD compared to healthy controls in early disease; ii) explore the cross-sectional associations between subcortical volumes and gait characteristics as assessed soon after PD diagnosis and; iii) identify whether subcortical volumes are able to predict PD specific changes in gait.

Following on from chapter 5 findings, it is hypothesised that:

1. Cross-sectional associations between gait and subcortical volumes of areas related to automatic motor functions will be more evident in controls compared to PD, because automatic motor control networks remain intact.
2. Cross-sectional associations between gait and subcortical volumes of areas involved in compensatory mechanisms (brainstem and cerebellum) and/or non-motor functions (hippocampus, amygdala and nucleus accumbens) will be more evident in PD compared to controls, due to increased reliance on these functions in disease.
3. Subcortical volumes linked to motor and non-motor networks will predict PD-specific gait decline, as compensatory and non-motor subcortical structures are increasingly relied upon for gait control with PD progression (and thus more sensitive to atrophy in these structures).
4. Overall, gait characteristics from the pace domain will be associated with subcortical volumes related to motor functions, given findings from chapter 5 (**Table 5-5**). Pace characteristics will show a discrete association with the hippocampus, given the existing literature in ageing and PD cohorts.

5. Gait variability characteristics will be associated with both motor and non-motor related subcortical volumes, given findings from chapter 5 (**Table 5-5**).
6. Gait characteristics from the rhythm domain will be associated with cerebellum volume, as it is thought that the cerebellum links to the primary motor cortex to adjust the timing of gait.
7. Gait asymmetry characteristics will be associated with the volume of areas related to motor functions, given previous findings in PD (**Table 2-2**) and weak evidence presented in chapter 5 (**Appendix P**).
8. Gait characteristics from the postural control domain will be associated with the volume of areas related to non-motor functions, given cross-sectional findings in controls from chapter 5 (**Table 5-2**).

6.2 Methods

6.2.1 Participants

For this study utilising subcortical volumes, participants were again recruited from both the ICICLE-PD and ICICLE-GAIT studies, as outlined in chapters 3 and 5. Participants included in cross-sectional analyses completed both baseline gait and MRI assessments and those within longitudinal analyses completed at least two gait assessments. The same gait characteristics were analysed within cross-sectional and longitudinal analyses as in chapter 5; 16 characteristics from a validated model of gait were assessed in cross-section (**Figure 3-3** (Lord *et al.*, 2013b)) and the five characteristics that demonstrated disease-related change were assessed longitudinally. PD participants were 'on' medication for all assessments, defined as one hour after levodopa medication.

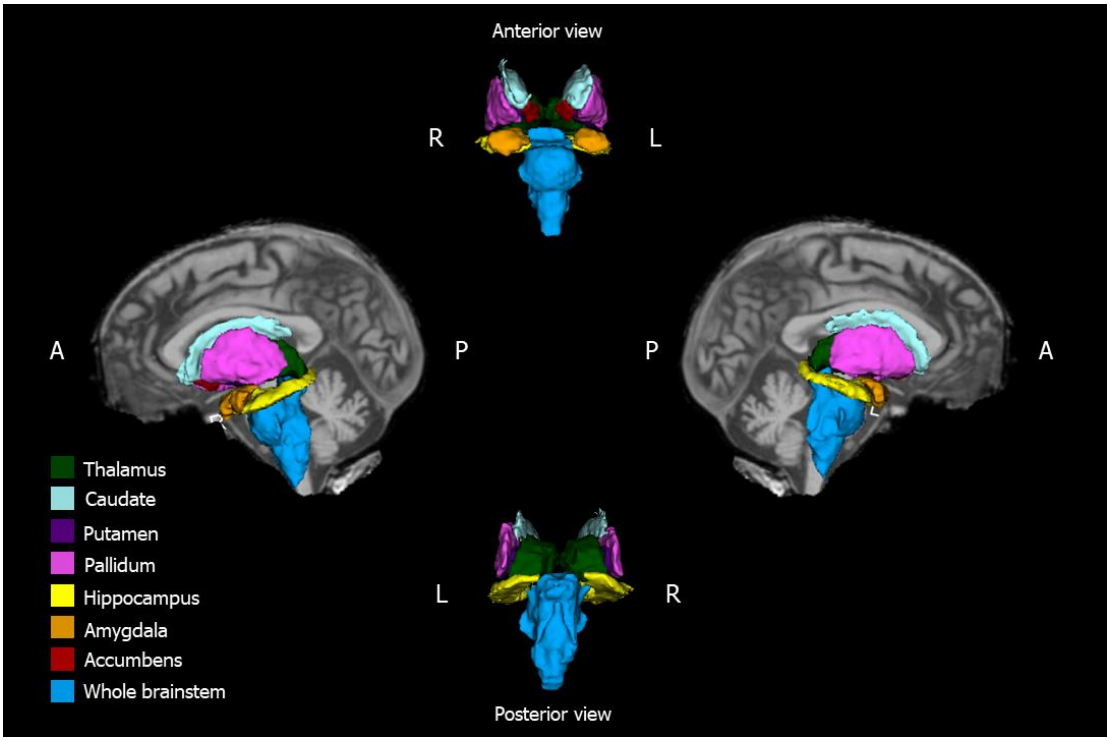
6.2.2 Subcortical volumetric assessments

Subcortical volumes were estimated from anatomical segmentations computed from T1 images (described in chapter 3) using FreeSurfer (v 6.0, http://surfer.nmr.mgh.harvard.edu/). Technical aspects of this segmentation process are detailed in publications from the laboratory for computational neuroimaging, Athinoula A. Martinos Centre for Biomedical Imaging, Massachusetts, USA (Dale *et al.*, 1999; Fischl *et al.*, 1999; Fischl and Dale, 2000). The image processing stream, briefly summarised in chapter 5, included automated labelling of subcortical regions in both cerebral hemispheres. As described in chapter 5, images were visually inspected at each step of the FreeSurfer processing stream to check the accuracy of

segmentations (J. Wilson); independent moderation of this process was also completed (S. Colloby). Images with segmentation errors that could not be corrected by further editing and processing were excluded.

The subcortical and selective limbic volumes selected for assessment were the brainstem and bilateral amygdala, caudate, cerebellum, globus pallidus (combined internal and external portions, referred to as "pallidum"), hippocampus, nucleus accumbens, putamen and thalamus. These selected regions of interest closely match volumes chosen in a similarly designed study in PD (Rosenberg-Katz K, 2016) and are thought to represent subcortical volumes that are involved in motor and/or non-motor neural networks for gait control. Reasons for the selection of these volumes are listed in **Appendix U**. Lateral volumes were considered to allow for possible differences in findings with left and right hemispheric structures to be identified, as considered in previous studies in PD (Peterson *et al.*, 2014; Gilat *et al.*, 2017). The total intracranial volume (TIV) of each participant was also estimated through FreeSurfer. Subcortical volume estimates for individuals were expressed as a percentage of their TIV, so that subcortical volumes were normalised for head size. **Figure 6-1** depicts the subcortical segmentations of interest, excluding cerebellum, of a representative participant in the anterior, posterior and lateral views by FreeSurfer.

Figure 6-1. Subcortical FreeSurfer segmentations from a representative participant



[Segmentations are displayed in anterior, posterior and lateral views. Segmentations are overlaid on brain T1 MRI images for anatomical reference. L= left, R = right, A = anterior, P = posterior]

Additionally, FreeSurfer was used to automatically segment four substructures of the brainstem (midbrain, pons, medulla oblongata and superior cerebellar peduncle (SCP)) from T1 scans. These substructures are structurally unique and are thought to support different functions (Maidich *et al.*, 2009). Sub-volumes of the brainstem were considered only in post-hoc analyses, in instances where significant associations with the whole brainstem occurred. This enabled consideration of the underlying reasons for associations occurring, without the need for additional multiple comparison corrections in all analyses. Brainstem segmentation was completed through a recently developed Bayesian segmentation algorithm; a probabilistic atlas of the brainstem and surrounding structures detected local variations in MRI contrast, from which brainstem substructures were delineated. The framework for this algorithm has been described in full by its creators (Iglesias *et al.*, 2015).

6.2.3. Data analysis

The distributions of subcortical volumes were tested using methods outlined in chapter 3. Demographic and clinical data have already been described for the participants assessed in this chapter (see **Table 5-1**).

Baseline subcortical volumes

Age, sex and education were correlated with subcortical volumes to assess the suitability of their inclusion as covariates in subsequent analyses involving subcortical volumes. Differences in subcortical volumes between PD and control groups, and between PD participants who did and did not complete gait assessment at 72 months, were assessed through ANCOVA, corrected for age and sex. Subcortical volumes were expressed as a percentage of TIV throughout analyses, to correct for differences in head size.

Cross-sectional associations between gait and subcortical volumes

Pearson's partial correlations, controlling for age and sex, explored associations between gait and TIV-corrected subcortical volumes. To further identify independent associations between gait and imaging parameters, multiple linear regression was then performed. As with the cross-sectional, hypothesis-driven approach adopted in chapter 5, independent models were developed for each gait characteristic. For each model, the gait characteristic of interest was added in as the dependent variable. Independent variables were added in two stages; age and sex were entered in the first block for all models using the enter procedure, then subcortical volumes that reached significance or trended towards significance in partial correlations between gait and imaging variables were entered in to the second block using the stepwise

procedure. Due to high levels of skewness, gait asymmetry data were square-root transformed and temporal variability data natural log transformed for cross-sectional analysis.

Longitudinal associations between gait and subcortical volumes

As in chapter 5, five gait characteristics were of interest longitudinally: step length, swing time asymmetry and variability of swing time, step time and step length. These characteristics were identified in chapter 4 as changing significantly in PD over 72 months, where change was not attributed solely to ageing nor increasing levodopa dose. For longitudinal analysis, linear mixed effects models (LMEM) were used to derive imaging predictors of gait decline, as in chapter 5. In short, random slope models gave each participant a unique intercept and slope, allowing for correlation between intercept and slope. Gait change over 72 months was modelled as in chapter 4, using LMEM to create a basic model for each gait characteristic, which was adjusted for age and sex. To identify the subcortical volumes that were predictors of gait change, volumes were separately entered into basic models of gait change as an interaction term with time, i.e. Volume*Time. Log-likelihood ratio tests compared model fit.

Multiple comparison corrections

All analyses that considered the subcortical volumes of interest (brainstem and bilateral nucleus accumbens, amygdala, caudate, cerebellum, hippocampus, pallidum, putamen and thalamus) were Benjamini-Hochberg corrected for multiple comparisons across the seventeen regions. To be in keeping with the stringent multiple comparison corrections applied via FDR correction in chapter 5, the Benjamini-Hochberg correction was applied across all brain regions for assessments within (and not across) each gait characteristic. This means that higher p-values may reach significance with gait characteristics for which several associations with imaging parameters were made. Associations that were not considered significant after multiple comparison corrections were applied, but where $p<0.05$ uncorrected, were considered statistical trends. In instances where the brainstem was associated with gait, analyses were repeated using substructures of the brainstem, without multiple comparison correction. For clarity, uncorrected p-values are displayed throughout.

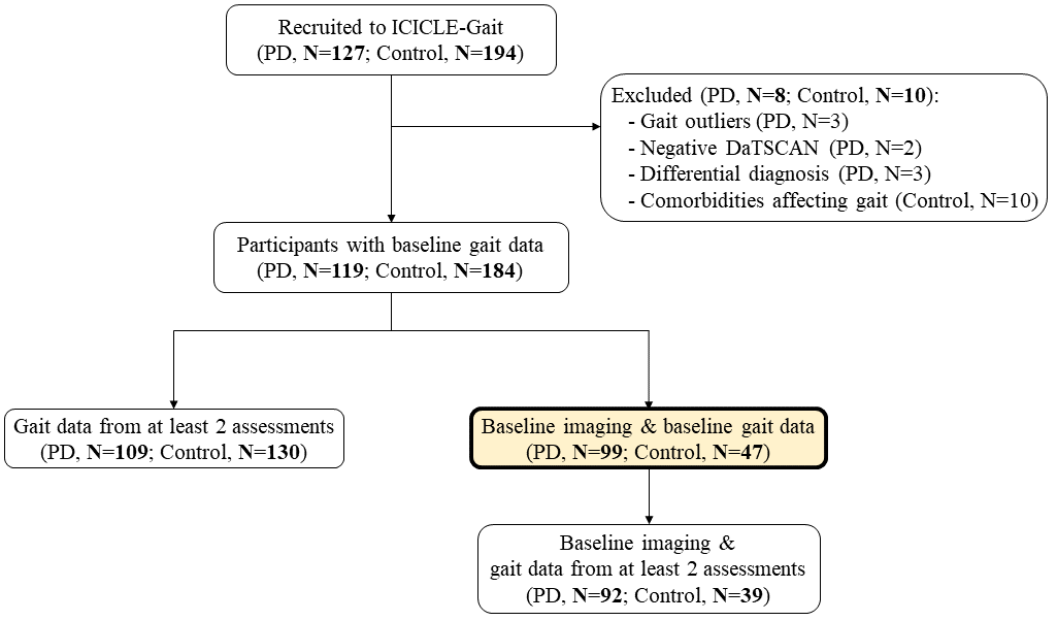
Data visualisation

To visualise the effect of baseline subcortical volumes on longitudinal gait changes, the PD group was split into quartiles of each regional volume. Changes in gait characteristics of interest over time were then separately plotted for each quartile of the strongest volumetric predictor.

6.3 Results

Participants considered within this chapter match those within chapter 5 (**Figure 6-2**); baseline clinical and demographic data for these participants can be found in **Table 5-1**.

Figure 6-2. Participants considered within cross-sectional analyses



6.3.1 Baseline subcortical volumes

Most normalised subcortical volumes were related to the age and sex of participants in both PD and control groups, whereas education was only associated with some subcortical volumes in the PD group only (**Appendix V)**. As associations with education were weak and did not occur bilaterally, age and sex, but not education, have been included as covariates in all subsequent analysis involving subcortical volumes. **Table 6-1** presents the subcortical volumes for PD and control groups. **Table 6-2** displays subcortical volumes for those in the PD group who completed ("completers") and did not complete ("non-completers") gait assessment at 72 months. Subcortical TIV-normalised volumes did not significantly differ between PD and control participants. When comparing TIV-normalised volumes between PD completers and non-completers, left cerebellum ($F_{1, 95}$=8.36, p=0.005) and right pallidum ($F_{1, 95}$=8.41, p=0.005) volumes were significantly larger in those that completed gait assessments at 72 months. There was also a statistical trend towards larger volumes of the right cerebellum in PD completers ($F_{1, 95}$=6.62, p=0.012).

Table 6-1. Subcortical and selective limbic volumes of PD and control participants

	Control (n=47)		PD (n=99)		Statistic	
Subcortical region	**Mean**	**SD**	**Mean**	**SD**	**$F_{1, 142}$**	**p-value**
L Cerebellum	3.30	0.31	3.27	0.37	0.11	0.736
R Cerebellum	3.35	0.30	3.30	0.40	0.29	0.593
L Thalamus	0.46	0.05	0.46	0.05	0.84	0.360
R Thalamus	0.42	0.05	0.42	0.05	0.24	0.625
L Caudate	0.19	0.03	0.19	0.03	0.03	0.856
R Caudate	0.21	0.02	0.21	0.03	0.26	0.614
L Putamen	0.27	0.03	0.27	0.03	0.16	0.691
R Putamen	0.28	0.04	0.27	0.04	0.22	0.640
L Pallidum	0.12	0.01	0.12	0.02	0.28	0.601
R Pallidum	0.12	0.01	0.12	0.02	1.45	0.230
L Hippocampus	0.25	0.03	0.24	0.03	0.01	0.934
R Hippocampus	0.25	0.03	0.25	0.03	0.26	0.612
L Amygdala	0.09	0.01	0.09	0.01	1.17	0.282
R Amygdala	0.11	0.01	0.11	0.01	1.69	0.195
L Accumbens	0.02	0.00	0.02	0.00	1.35	0.247
R Accumbens	0.03	0.01	0.03	0.00	0.11	0.739
Brainstem	1.32	0.12	1.33	0.14	0.23	0.632

[L=left, R=right.]

Table 6-2. Subcortical and selective limbic volumes of completers and non-completers

	PD					
	Completers (n=46)		**Non-completers (n=53)**		**Statistic**	
Subcortical region	**Mean**	**SD**	**Mean**	**SD**	**$F_{1, 95}$**	**p-value**
L Cerebellum	3.41	0.40	3.15	0.31	**8.36**	**0.005***
R Cerebellum	3.44	0.41	3.19	0.36	6.62	0.012
L Thalamus	0.48	0.06	0.45	0.04	2.94	0.090
R Thalamus	0.43	0.05	0.41	0.04	1.78	0.186
L Caudate	0.19	0.02	0.19	0.03	0.55	0.459
R Caudate	0.21	0.02	0.21	0.03	0.78	0.378
L Putamen	0.26	0.03	0.27	0.04	1.98	0.163
R Putamen	0.28	0.03	0.27	0.04	0.02	0.901
L Pallidum	0.12	0.02	0.11	0.02	3.80	0.054
R Pallidum	0.13	0.02	0.11	0.02	**8.41**	**0.005***
L Hippocampus	0.25	0.03	0.24	0.03	0.31	0.580
R Hippocampus	0.25	0.03	0.25	0.03	2.06	0.154
L Amygdala	0.09	0.01	0.09	0.01	0.44	0.509
R Amygdala	0.11	0.01	0.10	0.01	0.01	0.946
L Accumbens	0.02	0.01	0.02	0.00	0.76	0.387
R Accumbens	0.03	0.00	0.03	0.00	0.62	0.434
Brainstem	1.36	0.16	1.29	0.11	3.07	0.083

[L=left, R=right. Significant associations are in bold and denoted by *.]

6.3.2 Cross-sectional associations between gait and subcortical volumes

There were no significant cross-sectional associations between gait characteristics and subcortical volumes after multiple comparison corrections were applied. Statistical trends ($p<0.05$) are displayed in **Table 6-3**. All partial correlations can be found in **Appendix W** for controls and **Appendix X** for PD participants.

Partial correlations identified that, in controls: slower step velocity trended towards an association with smaller right caudate volume ($r = 0.31$, $p=0.037$) and; greater step time variability and stance time variability trended with smaller left thalamus volume ($r =-0.34$, $p=0.023$ and $r =-0.32$, $p=0.035$ respectively). Greater swing time variability trended with smaller left thalamus volume ($r =-0.34$, $p=0.028$), larger amygdala volume ($p=0.038$) and smaller brainstem volume ($r =-0.34$, $p=0.023$); post-hoc analyses with brainstem structures could not determine which portion of the brainstem drove this finding (**Appendix W)**.

In PD: reduced step length trended towards an association with smaller brainstem ($r =0.23$, $p=0.023$); increased step length variability trended with smaller volumes of the right pallidum ($r = -0.24$, $p=0.020$) and brainstem ($r =-0.21$, $p=0.036$); reduced swing time trended with smaller volumes of the left thalamus ($r =0.20$, $p=0.049$) and right cerebellum ($r =0.21$, $p=0.040$) and; greater step width trended with smaller volumes of the right pallidum ($r = -0.23$, $p=0.022$) and brainstem ($r =-0.23$, $p=0.025$). From post-hoc analyses, the pons region of the brainstem drove trends with step length ($r =0.22$, $p=0.033$), step length variability ($r =-0.26$, $p=0.009$) and step width ($r =-0.25$, $p=0.014$); the trend with step width was also driven by the SCP ($r =-0.23$, $p=0.027$) and medulla oblongata ($r =-0.22$, $p=0.029$) brainstem portions, although not as strongly (**Appendix X**).

Multiple linear regression identified the subcortical regions most strongly associated with gait (**Table 6-4)**. For control participants, slower step velocity trended towards an association with smaller right caudate volume ($\beta=0.32$, $p=0.037$), accounting for 9% of the total variance. Greater swing time variability was associated with both smaller brainstem volume ($\beta=-0.44$, $p=0.003$) and larger amygdala volume ($\beta=0.43$, $p=0.005$), which together accounted for 26% of the total variance. This finding was not altered with the additional inclusion of volumes of all brainstem substructures into regression models. Greater step time variability and stance time variability trended with smaller left thalamus volume ($\beta=-0.42$, $p=0.023$; $\beta=-0.38$, $p=0.035$ respectively), accounting for 11% and 9% of the total variance respectively.

In PD, reduced step length trended with smaller brainstem volume (β=0.23, p=0.023), accounting for 4% of the total variance; additional inclusion of volume of the pons brainstem subregion did not change this finding. Increased step length variability trended with smaller right pallidum volume (β=-0.28, p=0.020), accounting for 5% of the total variance. Similarly, increased step width trended with smaller right pallidum volume (β=-0.28, p=0.022), accounting for 5% of the total variance. Additionally, reduced swing time trended with smaller right cerebellum volume (β=0.23, p=0.040), accounting for 4% of the total variance.

Table 6-3. Age and sex controlled partial correlations between subcortical volumes and gait

Gait domain	Gait characteristic	Control	Parkinson's
Pace	Step velocity	0.31 (0.037) R Caudate	-
	Step length	-	0.23 (0.023) Brainstem
	Swing time sd	-0.34 (0.023) Brainstem -0.33 (0.028) L Thalamus 0.31 (0.038) L Amygdala	-
Variability	Step time sd	-0.34 (0.023) L Thalamus	-
	Stance time sd	-0.32 (0.035) L Thalamus	-
	Step length sd	-	-0.24 (0.020) R Pallidum -0.21 (0.036) Brainstem
Rhythm	Swing time	-	0.21 (0.040) R Cerebellum 0.20 (0.049) L Thalamus
Postural control	Step width	-	-0.23 (0.022) R Pallidum -0.23 (0.025) Brainstem

[Correlations are displayed as rho (p). L = Left, R = Right, sd = standard deviation. All correlations demonstrate statistical trends ($p<0.05$) that were not significant after multiple comparison correction.]

Table 6-4 Multiple regression analysis for independent associations between gait and subcortical volumes

Group	Gait domain	Gait characteristic	Imaging predictors	β	t-statistic	p	95% CI for β		R	R^2	Adjusted R^2	Standard error	ΔR^2
Control	Pace	Step velocity	R Caudate	0.32	2.15	0.037	0.11	3.49	0.36	0.13	0.07	0.14	0.09
		Swing time sd	Brainstem	-0.44	-3.13	0.003	-1.55	-0.33	0.53	0.28	0.22	0.23	0.26
			L Amygdala	0.43	2.96	0.005	2.85	15.10					
	Variability	Step time sd	L Thalamus	-0.42	-2.36	0.023	-4.37	-0.34	0.37	0.14	0.08	0.26	0.11
		Stance time sd	L Thalamus	-0.38	-2.18	0.035	-4.47	-0.17	0.38	0.15	0.09	0.28	0.09
PD	Pace	Step length	Brainstem	0.23	2.31	0.023	0.02	0.30	0.51	0.26	0.24	0.09	0.04
	Variability	Step length sd	R Pallidum	-0.28	-2.36	0.020	-0.22	-0.02	0.36	0.13	0.10	0.01	0.05
	Rhythm	Swing time	R Cerebellum	0.23	2.08	0.040	0.84	36.07	0.37	0.14	0.11	31.1	0.04
	Postural control	Step width	R Pallidum	-0.28	-2.33	0.022	-0.90	-0.07	0.32	0.10	0.07	0.03	0.05

[Age and sex were entered in the first step for all models, and all volumes which had trends for partial correlations with each gait characteristic were next enetered using the stepwise approach. L=Left, R=Right, sd=standard deviation.]

6.3.3 Longitudinal associations between gait and subcortical volumes

As in chapter 5, 92 PD and 39 control participants completed baseline imaging and multiple gait assessments through ICICLE-PD and ICICLE-GAIT, so were included in longitudinal analyses (**Figure 6-3**).

Figure 6-3. Participants considered within longitudinal analyses

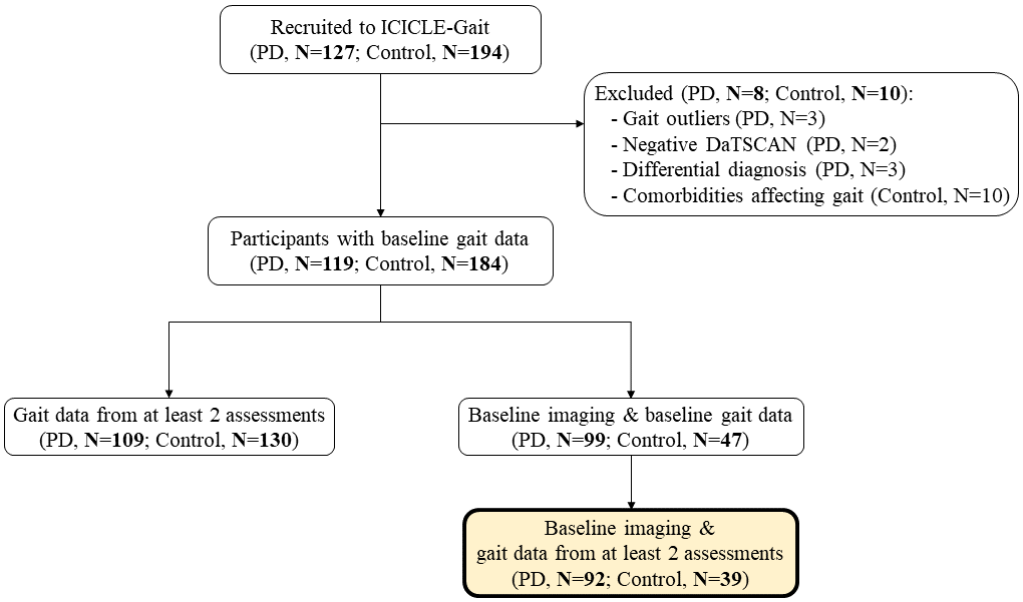


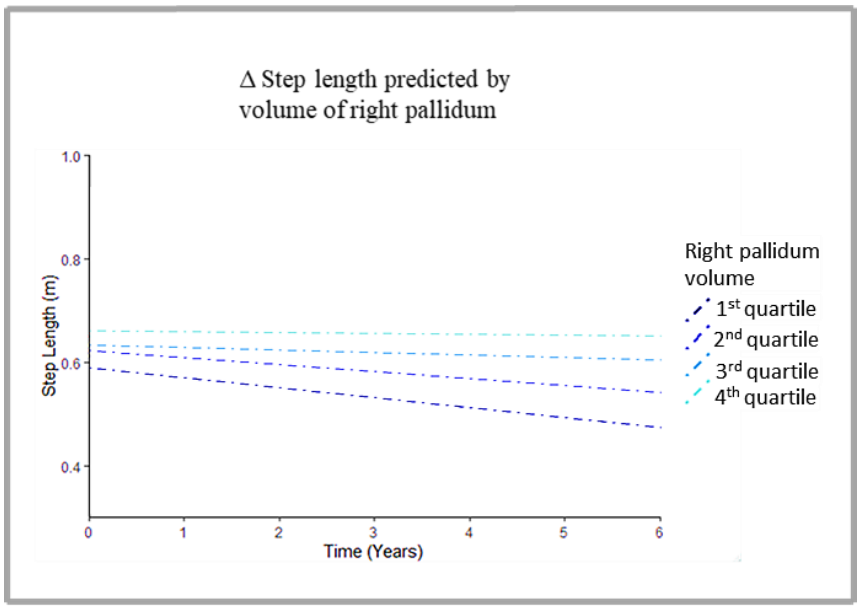
Table 6-5 summarises the baseline subcortical volumes which predicted PD specific gait change over 72 months, either with significance after multiple comparison correction or showing a trend towards significance ($p<0.05$). PD participants with larger baseline volumes of the left cerebellum ($\beta=0.012$, $p=0.011$), left and right thalamus ($\beta=0.123$, $p<0.001$; $\beta=0.129$, $p=0.001$ respectively), left and right putamen ($\beta=0.156$, $p=0.011$; $\beta=.151$, $p=0.012$ respectively), left and right pallidum ($\beta=0.273$, $p=0.017$; $\beta=0.394$, $p<0.001$ respectively) and left and right hippocampus ($\beta=0.186$, $p=0.003$; $\beta=0.166$, $p=0.012$ respectively) had a less steep decline in step length over 72 months. To visualise this, participants were split by quartiles of right pallidum volume, as the strongest regional predictor of change (**Figure 6-4**). The inclusion of most volumes significantly improved model fit, with the exception of left pallidum as a predictor of shortening step length ($\chi^2=5.88$, $p=0.053$). No subcortical volumes were significant predictors of change in variability of swing time, step time or step length, or change in swing time asymmetry, after Benjamini-Hochberg corrections were applied for multiple comparisons across the seventeen regions of interest within each gait characteristic. Full results of subcortical predictors of PD specific gait change are located in **Appendix Y**.

Table 6-5. Linear mixed effects models identifying subcortical and selective limbic volumes (expressed as a percentage of TIV) as predictors of PD specific gait change

Gait characteristic	Predictor region	Regression coefficients			
		β	SE	t-statistic	p-value
Step length (m)	**R Pallidum**	0.394	0.103	3.83	**<0.001***
	L Thalamus	0.123	0.032	3.85	**<0.001***
	R Thalamus	0.129	0.037	3.52	**0.001***
	L Hippocampus	0.186	0.060	3.11	**0.003***
	L Putamen	0.156	0.060	2.62	**0.011***
	L Cerebellum	0.012	0.005	2.62	**0.011***
	R Hippocampus	0.166	0.064	2.59	**0.012***
	R Putamen	0.151	0.059	2.57	**0.012***
	L Pallidum	0.273	0.111	2.45	**0.017***
	R Cerebellum	0.010	0.004	2.21	0.031
Swing time variability (ms)	**L Pallidum**	-26.412	11.027	-2.40	0.018
	R Pallidum	-23.946	10.623	-2.25	0.026
	L Putamen	-13.754	6.309	-2.18	0.031
	L Thalamus	-6.869	3.310	-2.08	0.040
Step time variability (ms)	**R Pallidum**	-32.110	11.686	-2.75	0.007
	L Pallidum	-30.503	12.081	-2.53	0.014
	L Putamen	-16.953	6.821	-2.49	0.015
	L Thalamus	-8.908	3.652	-2.44	0.017
	R Putamen	-15.184	6.695	-2.27	0.026
	R Cerebellum	-1.003	0.485	-2.07	0.042
Step length variability (ms)	**L Thalamus**	-0.009	0.004	-2.69	0.008
	R Cerebellum	-0.001	0.001	-2.45	0.015
	L Cerebellum	-0.001	0.001	-2.32	0.022
	L Pallidum	-0.026	0.012	-2.26	0.025
	R Thalamus	-0.009	0.004	-2.17	0.032
	R Pallidum	-0.023	0.011	-2.06	0.041
Swing time asymmetry (ms)	**R Cerebellum**	-1.557	0.765	-2.04	0.045

[This table contains all regions that predicted gait change at $p<0.05$; those which survived multiple comparison correction are in bold and denoted by *. L = left, R = right.]

Figure 6-4. Change in step length over 72 months in PD, for individuals within each quartile of right pallidum volume



[Δ; change in. Darker colours represent lower quartiles i.e. smaller right pallidum volume.]

6.4 Discussion

This chapter extends results from chapter 5 by being the first study to explore associations between gait and subcortical and selective limbic volumes in PD through both cross-sectional and longitudinal approaches. This study provides evidence for selective associations occurring between subcortical volumes and discrete gait impairments and, as with chapter 5, identifies an involvement of both motor and non-motor related structures in PD gait. This chapter also shows first evidence for the use of subcortical volumes as predictors of disease-specific changes in gait, which could be considered for clinical use in future.

6.4.1 Group differences in subcortical volumes

In this chapter, no volumetric differences were evident between PD and control groups. This was in keeping with findings from a larger population of ICICLE-PD participants (Mak *et al.*, 2015), which only identified smaller volumes of the left hippocampus and nucleus accumbens in PD participants with mild cogntive impairment (PD-MCI) at baseline. It may have been expected that participants who withdrew before the gait assessment at 72 months (non-completers) may have had volumetric differences similar to those previously identified in the PD-MCI cohort, as both groups demonstrated worse cognition at baseline (**Table 4-2**). However, baseline volumes of the brainstem and right globus pallidus were smaller in non-completers than completers, demonstrating that volumes of areas related to motor, rather than non-motor, functions were more indicative of completion status here. This suggests that motor impairments might be more relevant than cognitive impairments for non-completion, supported by higher MDS-UPDRS III score and Hoen and Yahr stage at baseline in non-completers (**Table 4-2**). Previous reports have identified smaller volumes of the amygdala and dorsal striatum (including the putamen and caudate nucleus) in PD compared to controls (Geng *et al.*, 2006; Ellmore *et al.*, 2010; Tinaz *et al.*, 2011; Ibarretxe-Bilbao *et al.*, 2012; Pitcher *et al.*, 2012; Sterling *et al.*, 2013; Lewis *et al.*, 2016; Rosenberg-Katz *et al.*, 2016); differences in this study are likely due to assessments being completed in very early disease.

6.4.2 The subcortical correlates of gait unique to PD

In cross-sectional analyses, no correlations reached statistical significance. Unlike chapter 5, which demonstrated several significant cross-sectional associations in controls, cross-sectional associations were weak in both PD and control groups. Primarily, these findings

suggest that volumetric measures of subcortical structures may not be the best to use when assessing the neural mechanisms of gait in cross-section. This was unexpected, given previous significant associations made between subcortical volumes and gait in healthy older adults (as described in chapter 2). This discrepency may be the result of previous associations being made in much larger cohorts (i.e. better powered to identify small volumetric differences) of adults who were older (where more atrophy may be expected) (Rosano *et al.*, 2007; Zimmerman *et al.*, 2009; Dumurgier *et al.*, 2012; Callisaya *et al.*, 2014; Nadkarni *et al.*, 2014).

This section will consider observations from the cross-sectional statistical trends idenitified in this chapter. It is important to note, however, that a lack of significant cross-sectional associations means that interpretation of trends is limited and so hypotheses 1 and 2 are not strongly supported.

Overall, correlations indicated that smaller volumes were associated with more impaired gait (i.e. slower gait with shorter step length and swing time and greater step width and temporal variability, **Table 6-3**). However, in controls, smaller volumes of the amygdala were associated with less variability of swing time (reflective of less impaired gait), an association that was independent of that between swing time variability and brainstem volume (**Table 6-4**). Previous work in PD has identified smaller amygdala volume with gait difficulties (through assessing people with the PIGD subtype (Rosenberg-Katz *et al.*, 2016)), going against the direction of association within this chapter, although increased functional connectivity with the amygdala has been associated with FOG (i.e. gait dysfunction) which may be due to a behavioural link between anxiety and FOG (Gilat *et al.*, 2018). Only one other study has specified the amygdala in investigations between gait and neuroimaging parameters in a mixed cohort of healthy and cognitively impaired older adults (and found no association between stride length and amygdala volume, (McGough *et al.*, 2018)). The correlation identified between the amygdala and swing time variability in controls was relatively weak in this study ($p=0.038$) and is therefore difficult to interpret. It should be noted that this finding may simply be spurious.

Direct comparisons between cross-sectional findings in PD and controls from this chapter are challenging, as different characteristics showed statistical trends with imaging parameters within each group. These characteristics also differ from those identified most strongly in cross-sectional analyses within chapter 5, limiting interpretation across the brain globally. **Table 6-3** shows that, overall, statistical trends between gait and imaging parameters were most common with the thalamus in controls, and with the brainstem in PD. These findings

show some support, although limited, for hypotheses 1 and 2, as it was postulated that cross-sectional associations would be most evident with structures linked to automatic motor control in control participants, and structures linked to compensatory mechanisms in PD (as increased reliance on alternative circuits implies that degeneration within these structures causes greater gait decompensation). Further analyses with substructures of the brainstem showed that the pons was the substructure most commonly implicated in PD gait. The pontomedullary reticular formation (PMRF), which directly recieves signals from the primary motor cortex in a proposed compsensatory mechanism in PD (**Figure 1-5**), is located among the pons and medulla oblongata substructures, as the name suggests. The cerebellum is also most strongly connected to the brainstem via connections with the pons. Therefore, this chapter may demonstrate tentative evidence for increased reliance on compensation from the brainstem and cerebellum, and less reliance on the basal ganglia-thalamic-cortical circuit, even in early PD. Few investigations have assessed involvement of the thalamus and brainstem specifically in PD gait (**Table 2-2**); those which have been completed have typically concentrated on the PPN and cholinergic activity within the thalamus, originating in the PPN (Thevathasan *et al.*, 2012; Bohnen *et al.*, 2013; Müller *et al.*, 2015; Peterson *et al.*, 2015; Molina *et al.*, 2020). To substantiate findings from this chapter, analyses should be repeated in a larger cohort in future.

This chapter found that swing time related most strongly to right cerebellum volume in PD (**Table 6-4**), but this was not a significant relationship. This association therefore gives some support to hypothesis 6, which postulated that characteristics from the rhythm domain would associate with cerebellar volume. Combined, findings from chapters 5 and 6 show that, in PD, rhythm characteristics relate to structures involved in a proposed "direct" compensatory circuit between the primary motor cortex and spinal cord which is driven by cerebellar activity (**Figure 1-5**). This compensatory strategy has been suggested to act to quicken steps (thereby reducing step timings) to improve step velocity overall (Morris *et al.*, 1994a) and is supported by the association in chapter 5 between step and stance times and thickness of the primary motor cortex. Chapter 2 found that few studies have targeted the cerebellum when identifying neuroimaging correlates of PD gait, with only one study finding an involvement of the cerebellum alongside dopaminergic medication in reducing step time variability (Gilat *et al.*, 2017). Assessments in PD participants of functional connectivity between (or activity within) the primary cortex and cerebellum, and how these relate to each gait characteristic from the rhythm domain, may help in interpreting the precise effects of this compensatory mechanism on PD gait. Overall, findings from this thesis tentatively support an association

with rhythm characteristics of gait and structures that contribute to a direct motor-related neural circuit which is relied upon during PD gait.

Combining findings from chapters 5 and 6, this thesis has shown overall that cross-sectional associations between volumes of the brain and discrete gait characteristics are relatively weak, particularly in PD. This may indicate that coupling between locomotor control and structural integrity of the brain globally is lost even in early PD, that there is a breakdown of consistent patterns of gait control in PD, or that structural imaging is simply not a sensitive enough measure to use when assessing neural correlates of PD gait. There is, however, tentative evidence arising from this thesis for selective relationships occuring between discrete gait characteristics and specific neural regions in cross-section. In PD, characteristics from pace and variability domains related most strongly to cortical areas involved in the visual system (thought to be modulated by attention, chapter 5), which may be involved in motor-related networks via the brainstem (chapter 6) to bypass ineffective basal-ganglia-thalamocortical circuitry (described in chapter 1, section 1.4.2, (Lewis *et al.*, 2013)). Rhythm characteristics, as described above, appear to be mediated by the cerebellum (in keeping with the temporal function of the cerebellum (Spencer and Ivry, 2013), chapter 6) encouraging activity within a direct circuit between the primary motor cortex (chapter 5) and spinal cord. These findings show some support for hypotheses 4, 5 and 6. Characteristics of gait asymmetry were not strongly associated with imaging parameters in either chapter 5 or 6 in PD; these characteristics may reflect asymmetries within the brain and/or impairments in connections between cerebral hemispheres (Fling *et al.*, 2016; Fling *et al.*, 2018). Additionally, findings with gait asymmetry characteristics may have been blunted by combining participants in to an overall PD group; PD is an asymmetrical disease and, although participants were all assessed in very early disease, bilateral pathology will have developed at different temporal rates in individuals. Gait characteristics from the postural control domain were significantly associated with cortical areas that are linked to non-motor functions in controls (chapter 5); in PD, however, statistical trends were evident between postural control characteristics and both cortical and subcortical areas related to motor functions only. These findings therefore do not support hypotheses 7 and 8. Cross-sectional analyses within this thesis have mostly demonstrated an involvement of structures within motor related networks, and not non-motor networks, in PD gait.

6.4.3 Subcortical volumes predict PD-specific gait decline

In contrast to cross-sectional findings, the volumes of subcortical structures involved in both motor and non-motor functions demonstrated associations with the development of greater impairments in PD gait over time. Specifically, shortening step length could be significantly predicted from smaller baseline left cerebellum volume and bilateral volumes of basal ganglia structures (putamen and globus pallidus), the thalamus and the hippocampus. These findings therefore support hypotheses 3 and 4. Findings were mostly bilateral, in keeping with previous reports that have found no difference in neuroimaging outcomes between those with worse motor symptom severity on the left and right hand sides (Peterson *et al.*, 2014). The cohort mostly had moderate bilateral disease (59% were assessed as Hoen and Yahr stage II, **Table 5-1**), which also agrees with the overall bilaterality of findings in this chapter.

Worsening step length may be associated with a reduced ability to utilise automatic motor control mechanisms during gait in PD (Morris *et al.*, 1996), supported by the predictive utility of structures involved in the basal-ganglia-thalamocortical circuit (i.e. putamen, globus pallidus and thalamus, **Figure 1-4**) on step length decline. Furthermore, associations with these volumes fit with speculations from chapter 5 that postulated the involvement of structures regulated by dopamine in the control of pace characteristics, as pace is responsive to dopaminergic medications (Bryant *et al.*, 2011a; Bryant *et al.*, 2011b; Sterling *et al.*, 2015). Cerebellar activity during PD gait may also be contingent on dopaminergic involvement (Gilat *et al.*, 2017); therefore, the predictive utility of cerebellum volume on step length change also fits with these speculations.

Greater change in step length could be predicted from thinning of the right precentral gyrus (primary motor cortex, chapter 5) and cerebellar volume (chapter 6). This supports the involvement of the cerebellum through the direct compensatory mechanism to mitigate gait impairment (i.e. cerebellar drive encouraging signals to be sent directly from the primary motor cortex to the spinal cord; less ability to utilise this resource (due to greater atrophy) causes step length to decline more rapidly). As cerebellar volumes did not predict changes in gait variability characteristics, this compensation appears to not affect variability measures.

Hippocampal volumes could additionally predict shortening step length in PD. Although the hippocampus is considered a non-motor structure, hippocampal atrophy has been associated with step length in healthy older adults, both cross-sectionally (Zimmerman *et al.*, 2009) and longitudinally (Callisaya *et al.*, 2013), due to gait being cognitively demanding even in healthy ageing (Montero-Odasso *et al.*, 2012). Hippocampal function during gait is proposed

to be related to spatial navigation (O'Keefe *et al.*, 1998; Maguire *et al.*, 2003; Jahn *et al.*, 2004) and its involvement in locomotion is supported by animal models (Vanderwolf, 1969; Sams-Dodd *et al.*, 1997; Paylor *et al.*, 2001; Bland, 2004). As the hippocampus is a shared neural substrate of both gait slowing and cognitive decline (Rosso *et al.*, 2017), and as hippocampal volume is predictive of step shortening in PD, this chapter provides neurological reasoning for the predictive power of step length on cognitive decline, including visual memory, in PD (Morris *et al.*, 2017). This chapter also supports findings of hippocampal volume predicting cognitive decline in PD (Foo *et al.*, 2017).

Step length shortening has been attributed to both disease progression and the ageing process (chapter 4). As hippocampal atrophy has been associated with shortening step length longitudinally in healhy older adults (Callisaya *et al.*, 2013), there is reason to suggest that hippocampal volumes predict shortening step length in PD due to ageing mechanisms. Further, smaller hippocampal volumes have been associated with impaired gait in MCI (Allali *et al.*, 2016; Beauchet *et al.*, 2020); since associations between the hippocampus and gait have been found in different diagnostic groups, PD pathology is unlikely to be the sole reason for the predicitive utility of hippocampus volume identified here. However, as lewy body pathology affects the hippocampus in stage 4 of the Braak stages (Braak, 2004), there may also be an element of disease progression driving the association. Additionally, the hippocampi are structures that are sensitive to amyloid deposition (Leal *et al.*, 2017); as amyloid pathology has been associated with worsening gait due specifically to PD progression (Rochester *et al.*, 2017), it may be that the association between hippocampal atrophy and poor gait performance is mediated by amyloid deposition.

Hippocampal atrophy appears to associate selectively with pace characteristics; across ageing, cognitively impaired and PD cohorts, dual-task gait speed has been associated with hippocampal volume (Rosenberg-Katz *et al.*, 2016) but no associations have been identified with cadence (the inverse of step time), swing time, step width or step width variability (Callisaya *et al.*, 2013; Beauchet *et al.*, 2015). Additionally, evidence for a hippocampal association with step time variability (included within the pace domain in healthy ageing and variability domain in PD) is contradictory (Beauchet *et al.*, 2015; Beauchet *et al.*, 2017) as are investigations of step length variability (Zimmerman *et al.*, 2009; Shimada *et al.*, 2013; Rosso *et al.*, 2014). This chapter is therefore largely in agreement with previous findings, as baseline hippocampus volume predicted change in pace (step length) only. It has previously been suggested that the hippocampus is involved in gait rhythmicity (Zimmerman *et al.*, 2009; Beauchet *et al.*, 2015) or in cognitively demanding environments (Shimada *et al.*, 2013).

Findings from this chapter support hippocampal involvement in simple gait in PD, and an association with spatial, rather than temporal, characteristics.

Hypothesis 5 was not well supported in longitudinal analyses, as variability measures (step time and step length variability) were not significantly predicted by any baseline subcortical volume. Indeed, statistical trends identified associations between variability characteristics and volumes of structures involved in motor networks only. Chapter 5 found that both motor and non-motor related cortical areas significantly predicted change in step time variability, yet only non-motor cortical areas significantly related to change in step length variability. Non-motor substrates of gait variability may therefore be cortically, and not subcortically, driven and underpinned by cholinergic involvement, as suggested in chapter 5. Chapter 7 will assess the cortical cholinergic underpinnings of gait variability in further detail. It is also possible that dopaminergic involvement in non-motor networks contributes to gait variability, as dopamine uptake in striatal regions connecting to executive and limbic areas of the frontal lobe has been associated with step length variability (Hirata *et al.*, 2020).

As with chapter 5, the imaging measures demonstrating trends with swing time variability matched those trending with step time variability; associations were weaker with swing time variability (**Table 6-5**). This gives further evidence for swing time variability being controlled by the same neural pathways as step time variability, as posited in chapter 5, as swing time contributes to step time. Change in swing time asymmetry was weakly predicted by right cerebellum volume; again, asymmetry measurements of the brain, or measures of connectivity across cerebral hemispheres, may better predict changes in gait asymmetry.

Overall, longitudinal study designs give greater insights to the neural mechanisms underpinning gait impairment in early PD than cross-sectional studies alone. The relationships observed with cortical thinning (chapter 5) were generally stronger than those with subcortical volumes in this chapter. Structures involving motor networks predict changes in pace, while the selective relationship between step length and hippocampal volume likely demonstrates an age-related mechanism. Change in step time variability (and to a lesser extent, swing time variability) is predicted from volumetric measures of both motor and non-motor structures, although the involvement of non-motor structures is cortical in nature. Change in step length variability is largely related to cortical non-motor structures.

6.4.4 Clinical implications

As with chapter 5, the clinical implications of findings from this chapter are twofold. Firstly, this chapter forms the first study to demonstrate the predictive value of subcortical volumes for gait decline in early PD. Subcortical volumes have the potential, therefore, to be considered as part of a combinational battery of clinical biomarkers of gait progression in future, for use when monitoring disease progression and for the identification of those that would most benefit from early interventions. As poor gait performance can predict cognitive decline (Morris *et al.*, 2017) and falls risk (Lord *et al.*, 2016), the ability of subcortical volumes to be used as an early warning marker for these warrants further investigation (Ray *et al.*, 2017). Given the relative cost effectiveness of 3T structural MRI, and the automatic procedure used to quantify volumetric measures, subcortical volumes may provide a measure of the brain that is more clinically useful than other imaging parameters. Subcortical volumes may, therefore, be preferential for use as clinical warning markers in future.

Secondly, work presented in this chapter builds on that from chapter 5 by demonstrating an association between step length and the hippocampus, a structure typically involved in non-motor functions. This finding highlights the need for novel therapies targeting both motor and non-motor systems to mitigate gait dysfunction in PD. The hippocampus is closely related to amyloid deposition (Leal *et al.*, 2017); this, combined with evidence that amyloid pathology is associated with change in step time variability in PD (Rochester *et al.*, 2017), suggests that clinically targeting amyloid deposition (for example, through use of inhibitors of amyloid aggregation (Davies and Koppel, 2009)) may lead to less severe gait decline. Further, as hippocampal function relies heavily on cholinergic innervation (Haam and Yakel, 2017), this finding may further implicate the cholinergic system as having an involvement in PD gait. Chapter 7 will explore the associations between gait and the cortical cholinergic system in greater detail.

6.4.5 Limitations

There are several strengths and limitations within this study, most of which have been described in chapters 4 and 5. However, some limitations are specific to work within this chapter. Left cerebellum and right globus pallidus volumes were significantly larger in PD participants that completed gait assessments at 72 months compared to non-completers; the effects of these volumes on longitudinal changes in gait may, therefore, have been underestimated. Most notably, this may have affected the labelling of right globus pallidus volume as a significant predictor of step time variability change, rather than a statistical trend. Automatic segmentations have been used here due to their robustness. A potential limitation could be in the accuracy of estimations of limbic and subcortical volumes. However, automatic segmentation considered a gold-standard approach for morphological MR analyses in older adults (Fischl *et al.*, 2002; Fischl *et al.*, 2004) and no discrepancies in segmentations performed by the algorithm were detected in manual verifications. Analyses should be replicated in an independent cohort to validate the overall findings from this chapter.

Automatic segmentations defined a global measure of the globus pallidus, made up of both the internal and external portions which have opposing roles within the automatic control of gait. Future work should aim to quantify the separate portions of the globus pallidus, potentially using methods similar to those derived for use on low resolution MRI (Iacono *et al.*, 2011), and explore whether associations with gait differ between the portions. Similarly, the cerebellum has been considered in its entirety here. Further investigations could use the foundational work presented in this chapter to delineate distinct lobules of the cerebellum (Diedrichsen *et al.*, 2009) and assess whether discrete regions are differently associated with PD gait (specifically characteristics from pace and rhythm domains), as they are with gait of healthy older adults (Nadkarni *et al.*, 2014) and the MDS-UPDRS III in PD (Solstrand Dahlberg *et al.*, 2020). In the main, the brainstem was considered as a whole volume in this chapter; however, the angle of head placement during an MRI scan can affect brainstem quantification. To negate the impact of this, subsections of the brainstem were delineated and used where associations with the brainstem were most apparent. Sub-sectional brainstem segmentations may not delineate the SCP as effectively as other substructures (Iglesias *et al.*, 2015) and so the influence of the SCP on associations made with the whole brainstem may not have been optimally considered. Finally, the substantia nigra could not be delineated through automatic segmentations; investigations of substantia nigra volume may support findings from this chapter suggesting an involvement of structures within the basal-ganglia-thalamocortical circuit with PD gait.

6.4.6 Conclusions

In conclusion, this chapter extends findings from chapter 5, again identifying selective associations between structural volumes and discrete gait characteristics. There is weak evidence for the involvement of a direct compensatory circuit between the primary motor cortex and spinal cord (driven by the cerebellum) in gait control, even in very early PD. This chapter presents the first evidence for subcortical volumes as predictors of gait change in PD. Shortening step length through early PD can be predicted from early volumetric measures of both motor and non-motor related subcortical structures; these novel findings indicate that structural MRI could be investigated in the future for clinical use to identify those at greater risk of falling or developing cognitive impairment. Future work should extend these findings by investigating overall networks associated with discrete gait impairments, by investigating discrete networks that involve regions-of-interest as identified in both chapters 5 and 6. Work presented here does, however, highlight that widespread neural networks are involved in gait control in PD, which relates to the suggestion that gait may be the sixth vital sign of brain health (Fritz and Lusardi, 2009).

Chapter 7: Involvement of the cortical cholinergic system with gait: an assessment of cholinergic basal forebrain sub-regional volumes

This chapter determines whether relationships between cholinergic basal forebrain degeneration and gait occur in early PD.

7.1 Introduction

Dopaminergic medications are used to treat motor symptoms in PD. Although these provide immediate improvements in some aspects of PD gait (Bryant *et al.*, 2011a; Bryant *et al.*, 2011b; Sterling *et al.*, 2015), this improvement is selective; some gait characteristics do not improve with dopaminergic medications (Curtze *et al.*, 2015) and continue to worsen over time despite optimal dopaminergic treatment (as evidenced in chapter 4). This is indicative of a non-dopaminergic contribution to PD gait impairment. Understanding the mechanisms of gait impairment, particularly from non-dopaminergic neurotransmitter systems, would ultimately enable the development of intervention strategies that more effectively target gait decline in early PD.

The hypothesised involvement of the cholinergic system in gait was first introduced in chapter 1 (Müller and Bohnen, 2013; Morris *et al.*, 2019a). The brain contains several cholinergic projection systems. Firstly, cholinergic basal forebrain (cBF) nuclei provide cholinergic input to cortical brain regions and the hippocampus, through topographical projections originating in the nucleus basalis of Meynert (NBM) (Mesulam *et al.*, 1983a; Bloem *et al.*, 2014; Ballinger *et al.*, 2016) and a combination of the medial septal nucleus and vertical diagonal band of Broca (Kondo and Zaborszky, 2016) respectively. Secondly, projections from the pedunculopontine nucleus-laterodorsal tegmental complex (PPN), located in the brainstem, provide cholinergic input to subsets of the striatum, thalamus, cerebellum and other brainstem regions (Mesulam *et al.*, 1983b; Heckers *et al.*, 1992). Finally, cholinergic interneurons in the striatum have a local origin (Mesulam *et al.*, 1992) and modulate dopaminergic pathways (Lim *et al.*, 2014). Cholinergic degeneration is evident in PD; people with PD have less acetylcholine (ACh) than age-matched controls (Bohnen *et al.*, 2012) and degeneration of the cBF, particularly the NBM, occurs in PD and results in less cortical cholinergic activity (Bohnen and Albin, 2009; Bohnen and Albin, 2011).

Several studies have made associations between the cholinergic system and gait in PD. Reduced thalamic cholinergic innervation, originating primarily from the PPN, has been associated with history of falls (Bohnen *et al.*, 2012), freezing of gait (Bohnen *et al.*, 2019) and balance disturbance (Müller *et al.*, 2013) in PD. Furthermore, poorer structural integrity of the PPN has been associated with postural instability and gait difficulty (PIGD) in primates (Karachi *et al.*, 2010; Grabli *et al.*, 2013) and people with PD (Craig *et al.*, 2020).

Cortical cholinergic denervation may also play a role in gait impairment in PD (Morris *et al.*, 2019a). The NBM, included within the cBF (Mesulam *et al.*, 1983a), provides the major cholinergic input to the cortex; the structural integrity of this region is therefore thought to closely relate to cortical cholinergic innervation. Slower walking speed and shorter step length have been linked to reduced short-latency afferent inhibition (SAI) (Rochester *et al.*, 2012), indicative of less cortical cholinergic activity (Di Lazzaro *et al.*, 2000). Slower walking speed is also associated with cortical cholinergic denervation, as assessed through PET imaging, whereas no association is evident with thalamic cholinergic denervation (Bohnen *et al.*, 2013; Müller *et al.*, 2015; Sanchez-Catasus *et al.*, 2019). Recent work has also identified a cross-sectional association between NBM integrity and fast walking speed approximately ten years after PD diagnosis (Dalrymple *et al.*, 2020). However, no studies have yet assessed the cholinergic system in relation to gait characteristics other than step velocity and step length; gait parameters which may give better insights into disease-specific mechanisms.

There is a well-established relationship between discrete gait impairments and cognitive impairment in PD, particularly for characteristics associated with the pace and variability of gait (Lord *et al.*, 2014; Morris *et al.*, 2016). Moreover, gait impairments predict early cognitive decline (Morris *et al.*, 2017); these findings collectively suggest shared neurological mechanisms. As the cortical cholinergic system is strongly related to cognitive ability (Muir, 1997; Müller and Bohnen, 2013; Bohnen *et al.*, 2015; Liu *et al.*, 2015; Ray *et al.*, 2017; Schulz *et al.*, 2018; Pereira *et al.*, 2020), it follows that discrete gait impairments may be closely aligned to a loss in cBF integrity. This is further supported by findings from chapters 5 and 6 of this thesis, which give evidence for the involvement of non-motor areas of the brain in PD gait control. Specifically, chapter 5 demonstrated associations between gait variability and cortical thinning in the prefrontal cortex, an area to which executive function and attention are strongly attributed (Collette *et al.*, 2006; Yogev-Seligmann *et al.*, 2008; Morris *et al.*, 2016). Chapter 6 identified a selective relationship between step length and the hippocampus, which is responsible for memory and spatial navigation (Stella *et al.*, 2012). As these areas are reliant

on cholinergic projections, worsened structural integrity of the source for these cholinergic projections (i.e. the cBF) may also relate to worsening gait.

As described throughout this thesis, longitudinal studies are needed to understand the neural mechanisms contributing to early gait decline. Previous work from the ICICLE-GAIT study has shown that cerebrospinal fluid (CSF) β-amyloid 1-42, traditionally a biomarker for dementia, predicts discrete gait decline in early PD (Rochester *et al.*, 2017). As impaired cortical cholinergic neurotransmission may contribute to β-amyloid burden (Schliebs and Arendt, 2006; Kerbler *et al.*, 2015), and as Lewy body aggregates and neuronal losses in the cBF occur early, volumetric measurements of the cBF may be able to predict gait decline in early disease.

Until recently, the cBF could only be delineated manually from structural images, into an area labelled the "substantia innominata" (George *et al.*, 2011) which did not encompass the entirety of the cBF nor define its distinct sub-regions. Now, stereotactic mapping of discrete cBF nuclei is feasible (Kilimann *et al.*, 2014) and recent work has identified that NBM volume can predict changes in cognition in early PD (Ray *et al.*, 2017). However, the ability of these volumetric measures to predict decline in discrete gait characteristics over time remains unclear.

Aims and hypotheses

This chapter aims to i) determine differences in sub-regional cBF volumes between PD and age-matched controls; ii) explore the cross-sectional associations between cBF regional volumes and gait characteristics in very early PD and; iii) assess the ability of sub-regional cBF volumes to predict PD specific progression of gait impairments.

It is hypothesised that:

1. Sub-regional cBF volumes will show stronger associations with gait in PD compared to control participants, given the theorised increased reliance on the cholinergic system during PD gait.
2. The NBM will be the sub-regional cBF volume most strongly related to gait function in PD, given the selective relationship between the NBM and cognitive decline.
3. Gait pace and variability characteristics will most strongly relate to cBF volumes, given that these gait features are most strongly associated with cognitive ability.
4. Step length will be associated with the volume of the medial septum and the vertical limb of the diagonal band of Broca, given that this sub-region provides cholinergic input to the hippocampus, a region which strongly related to step length in chapter 6.

7.2 Methods

In this study assessing sub-regional volumes of the cBF, participants were recruited from the ICICLE-PD and ICICLE-GAIT studies as described in chapters 3 and 5. As in chapters 5 and 6, sixteen gait characteristics were assessed with cBF volumes in cross-section, for participants with both baseline MRI and gait data available. The five gait characteristics which changed significantly over 72 months in PD, where change was not related to a change in levodopa medication dose, were used in longitudinal evaluations. PD participants were assessed 'on' dopaminergic medication for all assessments.

7.2.1 Stereotactic map of the cholinergic basal forebrain

Stereotactic mapping of cBF nuclei was used to create the cBF map, as described and used by Kilimann *et al.* (Kilimann *et al.*, 2014). In short, the map was derived from a brain specimen of a 56-year-old male who died from myocardial infarction. This underwent histological preparation and post-mortem MRI scans, both *in situ* and after the brain was dehydrated for histological preparation. Mesulam's nomenclature (Mesulam *et al.*, 1983b) was followed to identify cholinergic nuclei on digital pictures of the stained brain slices; these were manually transferred into the corresponding magnetic resonance slices of the dehydrated brain. The MRI scan of the dehydrated brain was then transformed into the space of the post-mortem *in situ* scan, using an initial 12-parameter affine transformation followed by a high-dimensional nonlinear registration between the two brain scans (Ashburner and Friston, 1999). This was transferred into Montreal Neurological Institute (MNI) standard space to enable the use of the high-dimensional DARTEL (Diffeomorphic Anatomic Registration using Exponentiated Lie algebra) registration method (Ashburner, 2007). The final stereotactic map distinguishes different subdivisions of the cBF, including clusters of cholinergic cells which correspond to the medial septum, vertical and horizontal limb of the diagonal band, and the NBM.

7.2.2. Pre-processing of the imaging data

The T1-weighted baseline MRI scans were automatically segmented into grey matter, white matter, and CSF partitions of 1.5 mm isotropic voxel size using the segmentation routine of the VBM8 toolbox (http://www.neuro.uni-jena.de/vbm/download/) running under SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Each participant's resultant grey and white matter partitions were then registered to MNI space using DARTEL (Ashburner, 2007).

Grey matter segments were warped using the individual flow fields resulting from the DARTEL registration, and voxel values were modulated for volumetric changes introduced by the high-dimensional normalisation, enabling for the total amount of grey matter volume present before warping to be preserved. All pre-processed grey matter maps were visually inspected by one of three operators (J. Wilson, C. Craig, N. Ray) for overall segmentation and registration accuracy. One PD participant did not pass this inspection (due to poor skull stripping, described in chapter 5); their data were therefore removed from further analysis.

Region-specific cBF grey matter volumes were calculated as means of the total modulated grey matter voxel values within the respective region of interest masks in template space. These volumes and global grey matter were normalised using regression by total intracranial volume (sum of total grey matter, white matter and CSF volumes, as a proxy for head size). In short, the sub-regional cBF volumes reported within the results section equate to the residuals of a regression between each sub-regional volume and TIV; TIV has been regressed out of the sub-regional volumes, in keeping with previous reports of the volumetric measures (Ray *et al.*, 2017). Negative volumetric measures may therefore occur, indicating that individual cBF volumes are smaller than would be expected, given the associated TIV. Following previous literature in PD using the same cBF mask (Ray *et al.*, 2017), regions of interest selected for analysis were: (i) a combination of the medial septum (Ch1) and the vertical limb of the diagonal band (Ch2), (ii) the NBM (Ch4), and (iii) a posterior NBM subdivision (Ch4p). These regions are shown in **Figure 7-1**. TIV-normalised whole brain grey matter volumes were additionally extracted and included as confounders in analyses to confirm that any associations with cBF volumes could not be explained by overall grey matter atrophy.

7.2.3. Data analysis

The distributions of sub-regional cBF volumes were tested as outlined in chapter 3. Demographic and clinical data have been described for the participants assessed in this chapter (**Table 5-1**).

Baseline cBF volumes

Age and sex were correlated with sub-regional cBF volumes to assess the suitability of their inclusion as covariates in subsequent analyses. Differences in cBF volumes between PD and control groups, and between PD participants who did and did not complete gait assessment at 72 months, were assessed through analysis of covariance, corrected for age.

Cross-sectional associations between gait and cBF volumes

Pearson's correlations and Pearson's partial correlations, controlling for age and sex, explored within-group associations between baseline gait and cBF volumes. Sex is included in these analyses due to its influence on gait. As in previous chapters, gait asymmetry data were square-root transformed and temporal variability data natural log transformed for cross-sectional analysis.

Longitudinal associations between gait and cBF volumes

As in chapters 5 and 6, five gait characteristics were of interest longitudinally: step length, swing time asymmetry and variability of swing time, step time and step length. Linear mixed effects models (LMEM) assessed imaging predictors of gait decline, as in chapters 5 and 6. In brief, changes in gait over 72 months were modelled using LMEM, to create basic models for linear change over time for each gait characteristic which adjusted for age and sex. To identify the cBF volumes that were predictors of gait change, sub-regional cBF volumes were separately entered as an interaction term with time (Volume*Time) into basic models. TIV-normalised whole brain grey matter volumes were additionally included as fixed effect terms, to confirm that any associations with cBF were not explained by global grey matter loss. Log-likelihood ratio tests compared model fit.

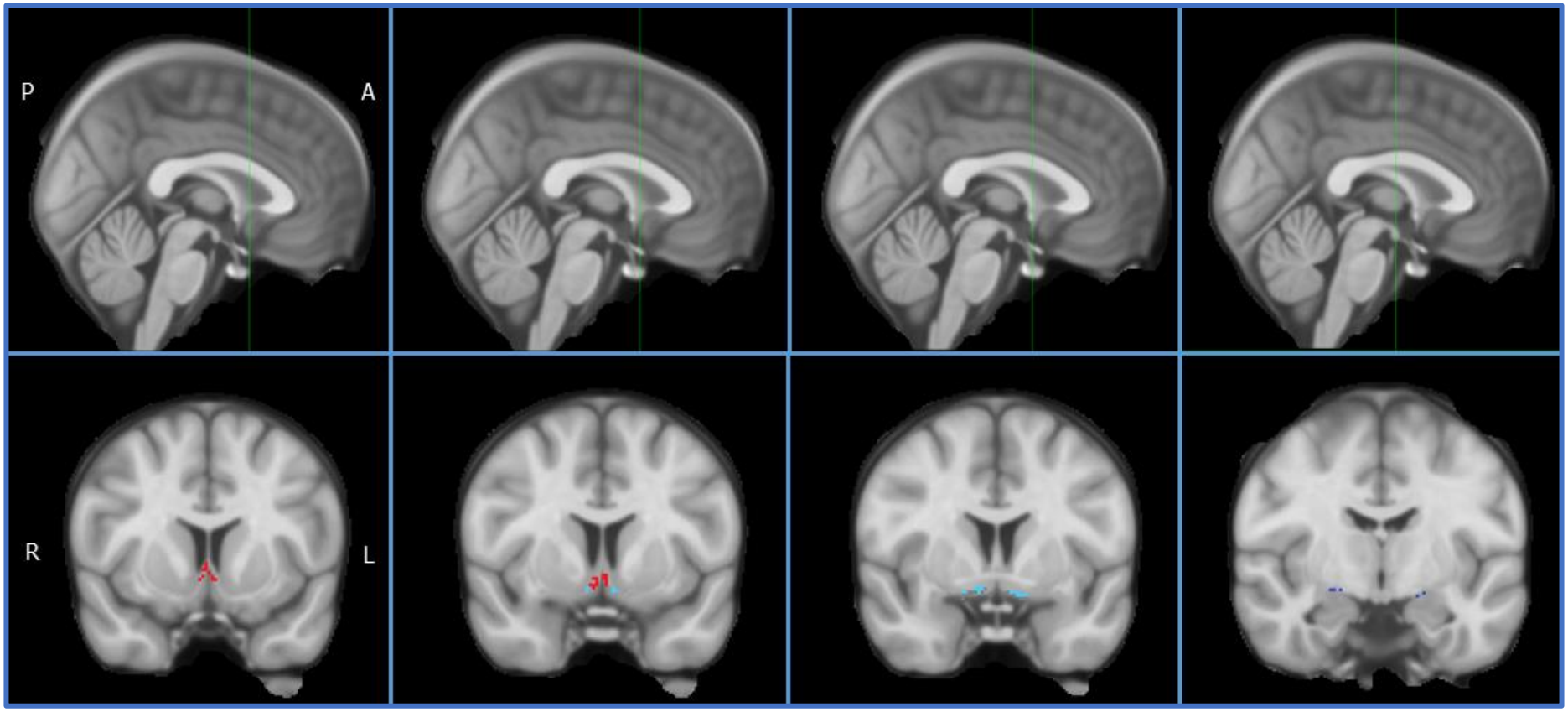
Multiple comparison corrections

The NBM (Ch4) has previously been implicated in degeneration in PD (Ray *et al.*, 2017); results for this hypothesised region-of-interest were considered significant at $p < 0.05$ (two-tailed) in PD. Posterior NBM (Ch4p) and the medial septum and vertical limb of the diagonal band (Ch1-2) regions of interest were Benjamini-Hochberg corrected for multiple comparisons across the two regions in PD. There were no region-specific predictions in control participants, therefore Benjamini-Hochberg corrections were applied for multiple comparisons across the three cBF regions of interest. For clarity, uncorrected p-values are displayed throughout. Statistical trends towards significance was defined as associations where $p<0.05$, but association does not survive multiple comparison correction.

Data visualisation

To visualise the effect of baseline sub-regional cBF volumes on changes in gait over time, the PD group was split into quartiles of each regional volume. Changes in gait over time were then separately plotted for each quartile of the strongest volumetric predictor.

Figure 7-1. Cholinergic basal forebrain regions of interest

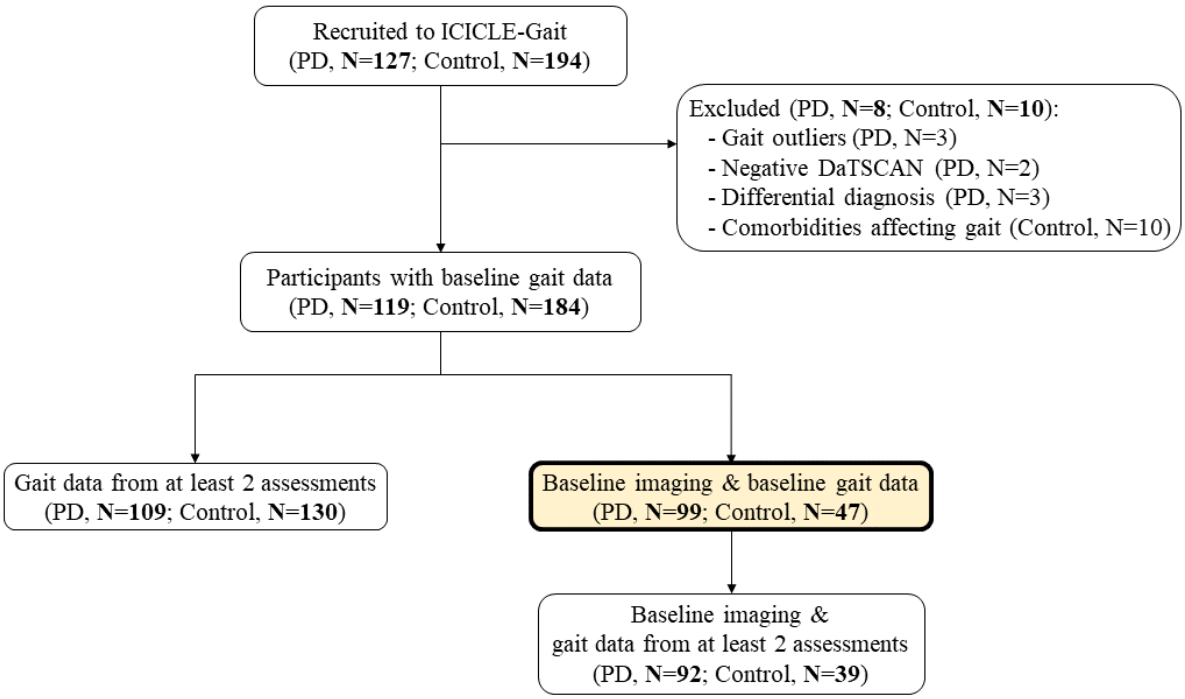


[Slices from left to right are coronal slices 9, 6, 3 and -8, as demonstrated in the top row. In the bottom row, red signifies the Ch1-2 region of interest, corresponding to the medial septum and vertical limb of the diagonal band; light blue and dark blue represent the Ch4 region of interest, corresponding to the NBM; dark blue signifies the Ch4p region of interest, corresponding to the posterior NBM.]

7.3 Results

Participants considered in this chapter are the same as those within chapters 5 and 6 (**Figure 7-2** and **Figure 7-3)**.

Figure 7-2. Participants considered within cross-sectional analyses



7.3.1 Baseline cholinergic basal forebrain volumes

Age, but not sex, was significantly correlated with all total intracranial volume-normalised cBF regional volumes in the PD group and with the Ch4 and Ch4p regions in the control group (**Appendix Z**). **Table 7-1** presents the cBF for PD and control groups and, within the PD group, for those who completed ("completers") and did not complete ("non-completers") gait assessment at 72 months respectively. Total intracranial volume-normalised cBF volumes did not significantly differ between PD and control participants, nor between PD completers and non-completers ($p \geq 0.05$ for all comparisons).

Table 7-1. Baseline TIV normalised cBF sub-regional volumes

cBF volume	Control (n=47)	PD (n=99)	Statistic		PD completers (n=46)	PD non-completers (n=53)	Statistic	
			$F_{1, 143}$	p-value			$F_{1, 96}$	p-value
TIV normalised Ch4p volume, mm^3	0.01 (0.06)	-<0.01 (0.07)	1.12	0.292	0.01 (0.06)	-0.02 (0.07)	0.78	0.379
TIV normalised Ch4 volume, mm^3	0.01 (0.04)	-0.01 (0.05)	3.33	0.070	0.01 (0.04)	-0.01 (0.05)	1.04	0.310
TIV normalised Ch1-2 volume, mm^3	0.01 (0.05)	-<0.01 (0.06)	0.83	0.363	0.01 (0.05)	-0.01 (0.06)	0.23	0.632

[Results are presented as mean (sd). cBF; cholinergic basal forebrain. TIV; total intracranial volume. Note; basal forebrain volumes have been TIV normalised using ANCOVA, as described fully in section 7.2.]

7.3.2 Cross-sectional associations between gait and cBF volumes

In the PD group, both greater step velocity and step length at baseline were bivariately correlated with larger volumes of all total intracranial volume-normalised cBF regions (step velocity: $r > 0.20$, $p \leq 0.045$ in all regions; step length: $r > 0.27$, $p \leq 0.006$ in all regions). However, these associations were no longer significant in age and sex adjusted partial correlations ($|r| < 0.07$, $p > 0.05$ in all regions). In the control group, no correlations reached statistical significance in either bivariate or partial correlations. All bivariate and partial correlations between cBF volumes and gait characteristics can be found in **Table 7-2**.

Table 7-2. Bivariate and partial correlations between cBF volumes and gait in PD and controls

Bivariate correlations: controls	**Step velocity (m/s)**	**Step length (m)**	**Swing time sd (ms)**	**Step time sd (ms)**	**Stance time sd (ms)**	**Step velocity sd (m/s)**	**Step length sd (m)**	**Step time (ms)**	**Swing time (ms)**	**Stance time (ms)**	**Step time asy (ms)**	**Swing time asy (ms)**	**Stance time asy (ms)**	**Step length asy (m)**	**Step width (m)**	**Step width sd (m)**
TIV normalised Ch4p volume	0.27 (0.062)	0.35 (0.017)	0.04 (0.813)	-0.21 (0.163)	-0.21 (0.148)	-0.21 (0.168)	-0.04 (0.772)	0.09 (0.568)	0.17 (0.260)	0.04 (0.817)	0.04 (0.805)	-0.03 (0.869)	-0.02 (0.893)	0.06 (0.672)	0.08 (0.595)	-0.05 (0.734)
TIV normalised Ch4 volume	0.20 (0.170)	0.17 (0.259)	0.07 (0.619)	-0.15 (0.309)	-0.17 (0.262)	-0.12 (0.406)	0.07 (0.620)	-0.03 (0.846)	0.06 (0.689)	-0.08 (0.616)	0.01 (0.949)	0.05 (0.752)	0.10 (0.512)	0.04 (0.789)	0.12 (0.419)	-0.09 (0.548)
TIV normalised Ch1-2 volume	0.20 (0.177)	0.23 (0.128)	0.03 (0.819)	-0.15 (0.326)	-0.22 (0.140)	-0.27 (0.066)	-0.02 (0.914)	0.02 (0.893)	0.12 (0.437)	-0.03 (0.828)	-0.07 (0.637)	0.04 (0.810)	0.06 (0.689)	0.15 (0.323)	0.31 (0.032)	0.09 (0.568)
Partial correlations: controls	**Step velocity (m/s)**	**Step length (m)**	**Swing time sd (ms)**	**Step time sd (ms)**	**Stance time sd (ms)**	**Step velocity sd (m/s)**	**Step length sd (m)**	**Step time (ms)**	**Swing time (ms)**	**Stance time (ms)**	**Step time asy (ms)**	**Swing time asy (ms)**	**Stance time asy (ms)**	**Step length asy (m)**	**Step width (m)**	**Step width sd (m)**
TIV normalised Ch4p volume	0.18 (0.235)	0.16 (0.284)	-<0.01 (0.993)	-0.18 (0.246)	-0.13 (0.407)	-0.12 (0.448)	-0.02 (0.910)	-0.08 (0.609)	-0.09 (0.539)	-0.06 (0.700)	-0.13 (0.401)	0.06 (0.677)	-0.08 (0.914)	0.02 (0.911)	-0.05 (0.731)	-0.01 (0.930)
TIV normalised Ch4 volume	0.09 (0.539)	-0.05 (0.749)	0.02 (0.876)	-0.12 (0.427)	-0.09 (0.569)	-0.05 (0.746)	0.10 (0.522)	-0.18 (0.238)	-0.18 (0.235)	-0.16 (0.298)	-0.13 (0.392)	0.15 (0.341)	0.13 (0.411)	-0.04 (0.803)	-<0.01 (0.982)	-0.07 (0.635)
TIV normalised Ch1-2 volume	0.11 (0.474)	-0.01 (0.941)	-0.12 (0.441)	-0.16 (0.289)	-0.18 (0.243)	-0.22 (0.142)	-0.15 (0.321)	-0.19 (0.201)	-0.14 (0.346)	-0.19 (0.205)	-0.24 (0.113)	0.11 (0.488)	0.08 (0.614)	-0.15 (0.330)	0.13 (0.410)	0.02 (0.901)
Bivariate correlations: PD	**Step velocity (m/s)**	**Step length (m)**	**Swing time sd (ms)**	**Step time sd (ms)**	**Stance time sd (ms)**	**Step velocity sd (m/s)**	**Step length sd (m)**	**Step time (ms)**	**Swing time (ms)**	**Stance time (ms)**	**Step time asy (ms)**	**Swing time asy (ms)**	**Stance time asy (ms)**	**Step length asy (m)**	**Step width (m)**	**Step width sd (m)**
TIV normalised Ch4p volume	***0.21 (0.038)***	***0.29 (0.003)***	-0.11 (0.301)	-0.04 (0.680)	-0.04 (0.724)	-0.02 (0.884)	-0.10 (0.309)	0.06 (0.550)	0.19 (0.056)	-<0.01 (0.977)	0.09 (0.354)	0.08 (0.429)	0.05 (0.655)	0.04 (0.728)	-0.06 (0.568)	-0.09 (0.367)
TIV normalised Ch4 volume	***0.23 (0.025)***	***0.33 (0.001)***	-0.07 (0.519)	<0.01 (0.985)	-0.02 (0.816)	0.01 (0.920)	-0.08 (0.453)	0.08 (0.410)	0.19 (0.055)	0.03 (0.794)	.004 (0.725)	0.07 (0.505)	<0.01 (0.972)	0.10 (0.338)	-0.01 (0.959)	0.03 (0.759)
TIV normalised Ch1-2 volume	***0.20 (0.045)***	***0.28 (0.006)***	-0.05 (0.655)	0.01 (0.957)	-0.05 (0.638)	-0.01 (0.948)	0.01 (0.935)	0.04 (0.690)	0.11 (0.271)	0.01 (0.948)	-0.05 (0.642)	<0.01 (0.969)	-0.06 (0.576)	0.21 (0.035)	0.07 (0.506)	-0.04 (0.685)
Partial correlations: PD	**Step velocity (m/s)**	**Step length (m)**	**Swing time sd (ms)**	**Step time sd (ms)**	**Stance time sd (ms)**	**Step velocity sd (m/s)**	**Step length sd (m)**	**Step time (ms)**	**Swing time (ms)**	**Stance time (ms)**	**Step time asy (ms)**	**Swing time asy (ms)**	**Stance time asy (ms)**	**Step length asy (m)**	**Step width (m)**	**Step width sd (m)**
TIV normalised Ch4p volume	0.02 (0.858)	0.01 (0.931)	0.04 (0.707)	0.06 (0.555)	0.07 (0.495)	0.04 (0.668)	0.02 (0.827)	-0.02 (0.846)	0.02 (0.832)	-0.04 (0.725)	-0.06 (0.534)	-0.01 (0.950)	-0.05 (0.654)	-0.05 (0.612)	-0.13 (0.215)	0.04 (0.701)
TIV normalised Ch4 volume	0.06 (0.572)	0.06 (0.573)	0.07 (0.489)	0.11 (0.270)	0.08 (0.431)	0.08 (0.423)	0.02 (0.852)	-0.02 (0.838)	0.02 (0.869)	-0.03 (0.738)	-0.12 (0.230)	-0.01 (0.962)	-0.08 (0.446)	-0.01 (0.894)	-0.06 (0.536)	0.17 (0.105)
TIV normalised Ch1-2 volume	0.07 (0.514)	0.02 (0.846)	0.06 (0.536)	0.10 (0.323)	0.03 (0.767)	0.06 (0.573)	0.09 (0.445)	-0.11 (0.295)	-0.09 (0.409)	-0.10 (0.323)	-0.20 (0.056)	-0.06 (0.559)	-0.12 (0.229)	0.11 (0.294)	0.04 (0.686)	-<0.01 (0.968)

[All results are listed as rho (p-value). Significant associations (after Benjamini-Hochberg multiple comparison correction where applicable) are highlighted in colour and are in bold. sd; standard deviation. asy; asymmetry. TIV; total intracranial volume.]

7.3.3 Longitudinal associations between gait and cBF volumes

Table 7-3 summarises the baseline sub-regional cBF volume predictors of gait change in the PD group. Smaller baseline posterior NBM (Ch4p) volume predicted a greater increase in step time variability (β=-9.077, p=0.006); the inclusion of posterior NBM volume improved the fit of the model of step time variability change over time (χ^2=7.75, p=.021). Smaller baseline posterior NBM also trended towards significance to predict greater shortening of step length (β=0.068, p=0.026) and greater increase in step length variability (β=-0.007, p=0.034). Smaller baseline NBM (Ch4) volumes predicted a greater increase in variability of both step time and swing time (β= -14.490, p=0.001; β=-8.156, p=0.045 respectively); the inclusion of NBM volume into models improved model fit for step time variability change (χ^2 = 13.18, p=0.001) but not change in swing time variability (χ^2=5.72, p=.057). Smaller volume of the medial septum and vertical limb of the diagonal band (Ch1-2) also predicted a greater increase in step time variability (β=-9.975, p=0.008); the inclusion of this volume improved the model fit (χ^2=8.74, p=.013). Smaller Ch1-2 volume trended towards significantly predicting greater increase in swing time variability (β=-7.327, p=0.031). To illustrate these findings, **Figure 7-4** shows overall trajectories of change in gait for PD participants, split by quartiles of cBF volumes.

Figure 7-3. Participants considered within longitudinal analyses

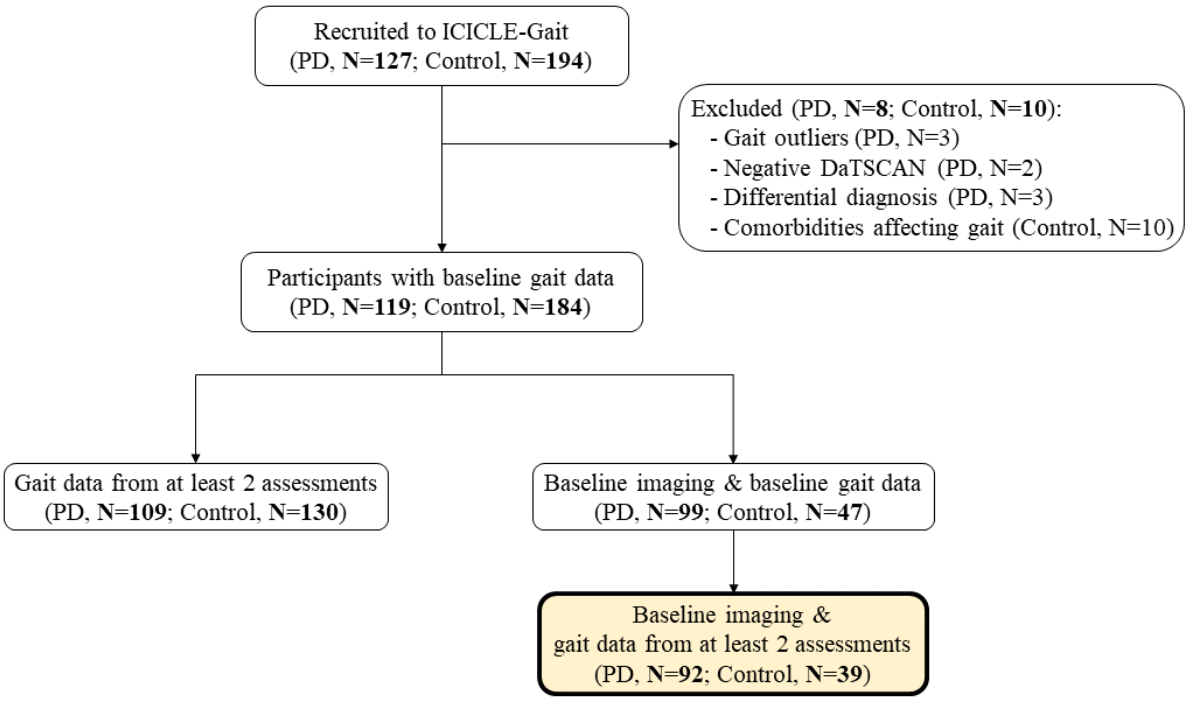
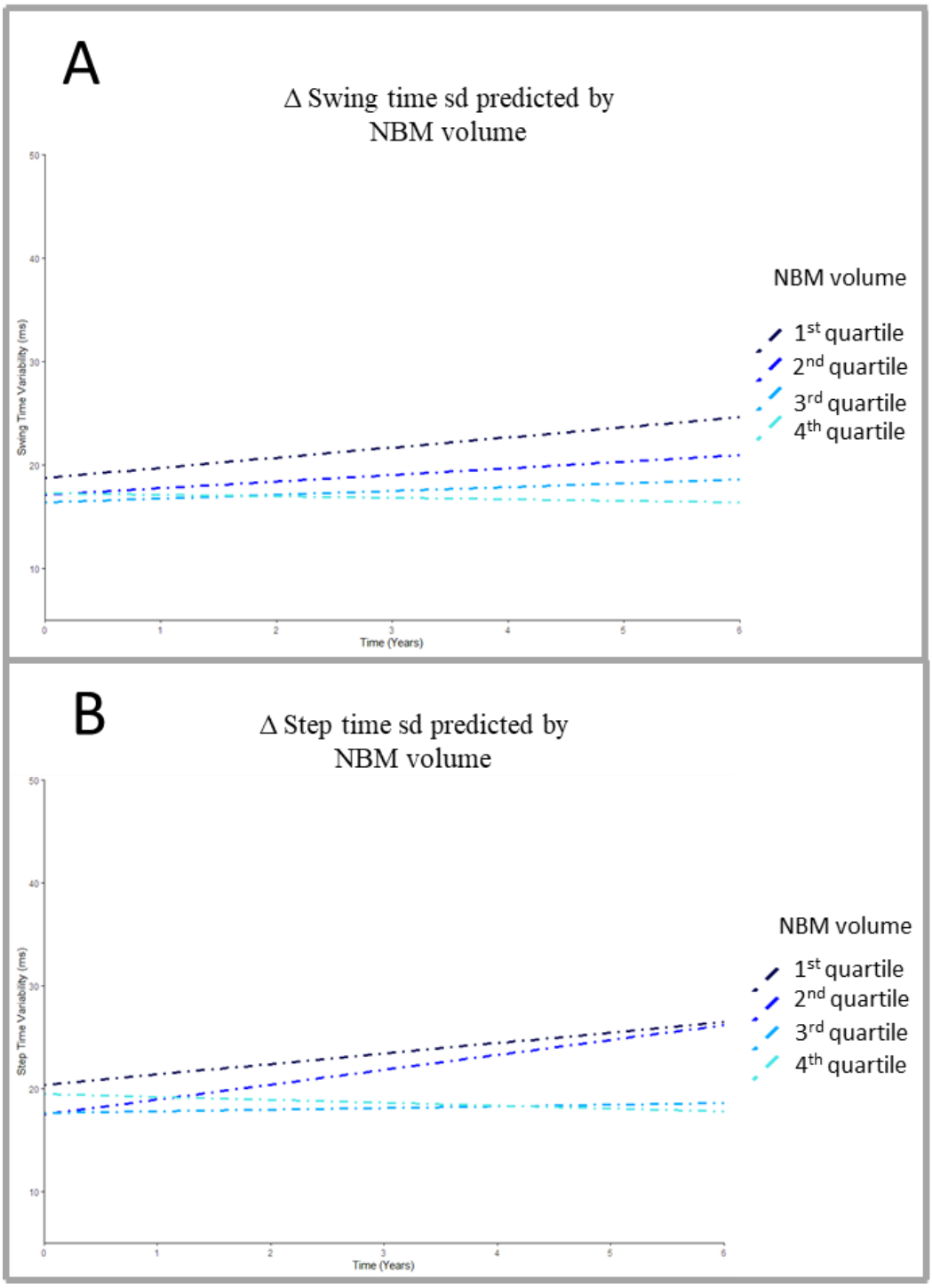


Table 7-3. Linear mixed effects models identifying cBF volumes as predictors of PD gait change

Gait characteristic	Predictor region	Regression coefficients			
		β	**SE**	**t-statistic**	**p-value**
Step length	**TIV normalised Ch4p volume**	0.068	0.030	2.27	0.026
	TIV normalised Ch4 volume	0.056	0.041	1.36	0.177
	TIV normalised Ch1-2 volume	0.027	0.034	0.79	0.430
Swing time variability	**TIV normalised Ch4p volume**	-5.270	3.011	-1.75	**0.**082
	TIV normalised Ch4 volume	-8.156	4.034	-2.02	**0.045***
	TIV normalised Ch1-2 volume	-7.327	3.365	-2.18	0.031
Step time variability	**TIV normalised Ch4p volume**	-9.077	3.249	-2.79	**0.006***
	TIV normalised Ch4 volume	-14.490	4.403	-3.29	**0.001***
	TIV normalised Ch1-2 volume	-9.975	3.650	-2.73	**0.008***
Step length variability	**TIV normalised Ch4p volume**	-0.007	0.003	-2.14	0.034
	TIV normalised Ch4 volume	-0.009	0.004	-1.96	0.052
	TIV normalised Ch1-2 volume	-0.006	0.004	-1.77	0.079
Swing time asymmetry	**TIV normalised Ch4p volume**	-2.239	5.322	-0.42	0.675
	TIV normalised Ch4 volume	-5.430	7.113	-0.76	0.447
	TIV normalised Ch1-2 volume	2.475	5.975	0.41	0.680

[Baseline age, sex and global grey matter volume were included as fixed effects in models. Significant associations (after a Benjamini-Hochberg multiple comparison correction was applied across the Ch4p and Ch1-2, but not Ch4, sub-regions) are in bold and denoted by *. TIV; total intracranial volume.]

Figure 7-4. Change in gait over 72 months in PD, for individuals within each quartile of cBF volume



[Δ; change in. sd; standard deviation (variability). Darker colours represent lower quartiles i.e. smaller volumes. Panel A shows change in swing time variability when the group was split by quartiles of NBM volume. Panel B shows change in step time variability when the PD group was split by quartiles of NBM volume.]

7.4 Discussion

This chapter forms the first study to assess the relationship between sub-regional cholinergic basal forebrain volumes and gait decline over time in PD. All assessments were conducted in very early disease; therefore, associations between the cortical cholinergic system and gait were made at a time where intervention strategies may be most effective. This chapter identified that, although relationships between cBF volumes and PD gait are mediated by age in cross-section, sub-regional cBF volumes can predict disease-specific gait decline whilst accounting for age. The NBM was the sub-regional cBF volume most strongly related to gait, and associations were made with characteristics relating to gait pace and variability; findings therefore supporting hypotheses 2 and 3. This chapter builds on our current understanding of cortical cholinergic underpinnings of gait impairment in early PD and highlights possible therapeutic targets (i.e. cholinergic) in early disease for the prevention of disease-specific gait progression and therefore future mobility loss and falls.

7.4.1 Cross-sectional associations are mediated by age

There was limited association between gait variables and sub-regional cBF volumes in both PD and control groups at baseline. Only step velocity and step length were identified in PD and, this was no longer the case after controlling for age and sex. To understand this further, post-hoc analyses identified that age, rather than sex, drove this finding (**Appendix AA**). The effects of ageing on cBF volumes have been explored previously, using stereotactic mapping similar to that used in the current study (Grothe *et al.*, 2012). Grothe *et al.* found that, whilst cBF atrophy was moderate throughout early and mid-adulthood, cBF volumes showed greater decline from approximately 65-70 years of age. The age range for the PD cohort in this chapter was substantial, with the mean and median age at baseline lying at this “tipping point” for more severe cBF atrophy. It was very likely, therefore, for age to have had a strong effect on all associations made with cBF volumes.

However, disease pathology may also be a contributing factor in associations between the cBF and gait, rather than age alone explaining correlations, as bivariate associations between cBF volumes and gait were evident in PD and not controls. It is known that the cBF is particularly affected by the progression of PD (Braak, 2004; Sanchez-Catasus *et al.*, 2019; Pereira *et al.*, 2020). Ray et al. (Ray *et al.*, 2017) also found no cross-sectional relationships between cBF volumes and cognitive scores after controlling for age in a separate early-disease cohort, whereas longitudinal associations were evident. Speculatively, the effects of ageing on

associations between the cBF and gait and cognition may initially outweigh the effects of PD in very early disease, whereas the effects of ageing may become secondary to disease pathology as the disease progresses. Repeating cross-sectional analyses at a later point in disease, or in a cohort of various stages of PD, may give valuable insight to this postulate.

It is also worth noting that there is likely substantial heterogeneity of cholinergic involvement in early PD (Bohnen *et al.*, 2012). This may explain why no group differences in sub-regional cBF volumes were observed in the ICICLE cohort and this is consistent with findings in another early PD cohort (Ray *et al.*, 2017; Schulz *et al.*, 2018). Degeneration of white matter projections is thought to occur before grey matter atrophy in PD (Rektor *et al.*, 2018) and this same pattern of deterioration may be reflected in the cBF. Indeed, the integrity of NBM white matter projections is more strongly associated with cognitive performance than NBM volume in cognitively normal individuals (Nemy *et al.*, 2020). It follows that NBM white matter tract degeneration may be more strongly associated with cognitive and gait impairments in PD than grey matter atrophy. Further analyses should be carried out to explore this in future. Given findings from chapter 6, which indicated trends towards cross-sectional associations between PD gait and brainstem volume, greater insights in to the involvement of the cholinergic system with gait in cross-section may be gained from assessing the structural properties of the PPN with discrete characteristics (Henssen *et al.*, 2019). Although there are challenges in taking volumetric measures of this structure, due to its location within the brainstem, recent efforts have enabled the development of a stereotactic map of the PPN to derive metrics of microstructural integrity via DTI (Alho *et al.*, 2017). As the PPN is thought to be involved in postural stability (Müller *et al.*, 2013; Craig *et al.*, 2020), characteristics from the postural control domain of gait may relate to structural integrity of the PPN.

7.4.2 The longitudinal associations between gait and cBF regions

Sub-regional volumes of the cBF predicted disease-specific gait changes. Analyses were controlled for both TIV and total grey matter volume, giving confidence in the precision of the relationship between cBF sub-regional volumes and gait. Specifically, smaller volumes of the NBM (Ch4) predicted worsening step time variability and swing time variability (indicated by greater increases in variability); smaller volumes of the posterior NBM (Ch4p) and the medial septum and vertical limb of the diagonal band (Ch1-2) also predicted worsening step time variability. As there was a trend towards the Ch1-2 sub-region predicting change in swing time variability, findings in this chapter further support the notion, presented

in chapter 5, that swing time variability may be controlled or influenced by the same neural pathways as step time variability. These pathways have been less identifiable in swing time variability than step time variability throughout chapters 5, 6 and 7, which may be due to changes in swing time variability over time being more subtle (chapter 4). As changes in the variability of swing and step times is attributed to disease progression and not age-related changes (chapter 4), findings in this chapter show some support for hypothesis 1.

Volumes of the posterior NBM significantly predicted change in step time variability. There is a close interplay between posterior NBM atrophy and β-amyloid in cognitively-stable older adults (Kerbler *et al.*, 2015). As ACh influences the production of β-amyloid (Schliebs and Arendt, 2006), findings from this chapter relate well to previous work from the ICICLE-GAIT study (Rochester *et al.*, 2017), which identified CSF β-amyloid 1-42 as a significant predictor of change in single-task step time variability. The current study adds to this by providing a neural basis for this previously reported finding, suggesting specifically the role of the posterior NBM. Furthermore, step time variability increase over time was predicted from all cBF sub-regional volumes assessed in this chapter; the structural integrity of the whole cortical cholinergic system origin, rather than just the NBM, may therefore influence PD gait. This fits with findings from chapter 5, which identified widespread cortical regions that could predict step time variability change. Step time variability has demonstrated disease-specific change not only in the ICICLE-GAIT cohort over three years (Rochester *et al.*, 2017) and six years (chapter 4), but also in other cohort studies of early (Hobert *et al.*, 2019) and moderate (Micó-Amigo *et al.*, 2019) stages of PD. This characteristic should therefore be considered a robust measure of gait change in PD, importantly, that reflects disease-specific change in contrast to age-related change. Step time variability could, therefore, be considered for use as a primary outcome measure when assessing the effectiveness of interventions targeting cholinergic dysfunction which aim to mitigate gait impairment in PD, as well as a possible marker of disease progression and falls risk (Henderson *et al.*, 2016).

Statistical trends were evident for posterior NBM also predicting changes in step length and step length variability. Chapter 4 identified changes in these characteristics as being attributed to both ageing and disease mechanisms. Speculatively, ageing effects may have mediated associations between cBF volumes and gait, as they did in cross-section, hence associations were weaker for characteristics demonstrating both disease-related and age-related change. Step length typically responds well to levodopa as it closely reflects hypokinesia, whereas gait variability measures are not always responsive to dopaminergic medication (Smulders *et al.*,

2016). It is noteworthy, therefore, that a trend towards an association between the cortical cholinergic system and step length was identified here, suggesting that step length may not be purely dependent upon the dopaminergic system. This supports previous work which identified an association between step length and SAI (Rochester *et al.*, 2012). As step length change over time has consistently been linked to volumes of the hippocampus in healthy older adults (Zimmerman *et al.*, 2009; Callisaya *et al.*, 2013) and in PD (chapter 6), it was thought that the medial septum and vertical limb of the diagonal band (Ch1-2), which projects to the hippocampus (Mesulam *et al.*, 1983a), may have been associated with step length. However, this was not the case; findings in this chapter did not support hypothesis 4. Questions remain about the precise contribution of the cholinergic system to step length in PD, which could be explored further through the consideration of mediation of this gait characteristic through higher cognitive processes (which in turn may depend on cholinergic function). This is discussed more in the next section.

7.4.3 The role of cognition

Cortical ACh is primarily associated with cognition, specifically executive function and attention (Bohnen *et al.*, 2006). Both executive function and attention, as well as global cognition, are strongly related to gait dysfunction in PD (Yogev *et al.*, 2005; Lord *et al.*, 2014; Xu *et al.*, 2014; Morris *et al.*, 2016). More specifically, discrete gait outcomes that represent independent domains of gait control (Lord *et al.*, 2013c) such as pace, including step length, have been linked to executive function and attention whereas global cognition has been linked to gait variability (Lord *et al.*, 2014). Additionally, changes in fluctuating attention in early PD are predicted by step length, step length variability and step time variability (Morris *et al.*, 2017). Work in this chapter provides tentative evidence for a shared neural underpinning of gait and cognition that may originate within the NBM. As structural integrity of the NBM has been particularly associated with cognitive impairment in PD (Ray *et al.*, 2017; Schulz *et al.*, 2018), findings from this chapter give further validation for NBM degeneration being a principal underlying factor for both changes in cognition and mobility in PD (Yarnall *et al.*, 2011). The effects of cognition on associations were not considered here, despite strong associations between cognition and both cholinergic activity and gait. Understanding the role of cognition in associations between gait and cBF volumes requires an in-depth investigation of the effects of different cognitive domains on both gait and imaging parameters, as well as how these interact over time. The complexity of this warrants its own independent investigation and would be a useful follow-on study to complete.

7.4.4 Clinical implications

Primarily, this chapter aimed to further current understanding of the cholinergic underpinnings of gait impairment in PD from a mechanistic viewpoint. As with chapters 5 and 6, however, findings may also have clinical utility. This chapter provides the first evidence that cBF volumes can be used as predictors of gait change in early PD. These volumes could therefore be investigated for clinical use in monitoring disease progression identifying those that would benefit most from early interventions. NBM volumes could be used as an early warning marker to determine those more likely to experience cognitive decline (Ray *et al.*, 2017); whether this is also the case for determining those at an increased falls risk (Lord *et al.*, 2016) warrants further investigation.

Additionally, this study has provided further evidence for an association between the cortical cholinergic system and gait impairment in PD, further highlighting the need for novel therapies that extend beyond the dopaminergic system to target gait decline. Interventional studies have shown that AChE inhibitors, which act to increase the overall amount of available ACh, can improve mobility measures in PD (Smulders *et al.*, 2016; Morris *et al.*, 2019a). Of particular relevance, AChE inhibitors have been shown to improve gait speed and step time variability in PD (Henderson *et al.*, 2016). In that study, step time variability was considered a proxy marker for falls risk, given the well-established association between the two measures (Hausdorff *et al.*, 1997; Hausdorff *et al.*, 2001; Callisaya *et al.*, 2011). Findings from this chapter strengthen and begin to explain the improvement in gait and subsequently falls risk in PD after treatment with AChE inhibitors. As an association between step time variability and the cortical cholinergic system has been identified in this chapter, it may be that AChE inhibitors do not act purely subcortically. AChE inhibitors also reduce total Aβ concentration (Sharma, 2019) so may facilitate an improvement in gait through this secondary mechanism. Further, AChE inhibitors may act to reduce the rate of atrophy of the NBM (Cavedo *et al.*, 2017). Overall, findings from this study help strengthen the case for therapeutically targetting the cholinergic system to limit gait progression in PD.

7.4.5 Limitations

Most of the limitations of work completed within this chapter have already been described in chapters 4 and 5. Specific to this chapter, an additional limitation is in the precision of the stereotactic map utilised. Although most of the NBM region-of-interest from the stereotactic atlas corresponds to cholinergic neurons, non-cholinergic portions of the NBM, including

GABAergic, NADPH-diaphorase-positive and peptidergic neurons (Smiley and Mesulam, 1999), may have also been included. Additionally, the stereotactic map was based on one post-mortem brain specimen, therefore inter-individual variability in cBF volumes may not be optimally considered. However, volumes derived from this map have been compared to those from a different map (Grothe *et al.*, 2013), and the highly efficient DARTEL algorithm was used to normalise cBF volumes in MNI space (Kilimann *et al.*, 2014), thereby improving the quality of the stereotactic map utilised here. As with all volumetric measures, cBF volumes may not directly reflect neuronal activity. Comparison of cBF volumes from this stereotactic mask with cholinergic activity within the same cohort, as assessed through molecular imaging specifically targeting the cortical cholinergic system (Bohnen *et al.*, 2013; Müller *et al.*, 2015), will give a more precise understanding of the effect of cBF volume loss on cholinergic activity. Finally, other regions responsible for cholinergic projection, such as the PPN, should be examined in future so that an overall understanding of the involvement of the cholinergic system on specific gait characteristics can be gained. The PPN, in particular, may relate to gait features responsible for postural control (Müller *et al.*, 2013; Craig *et al.*, 2020).

7.4.6 Conclusions

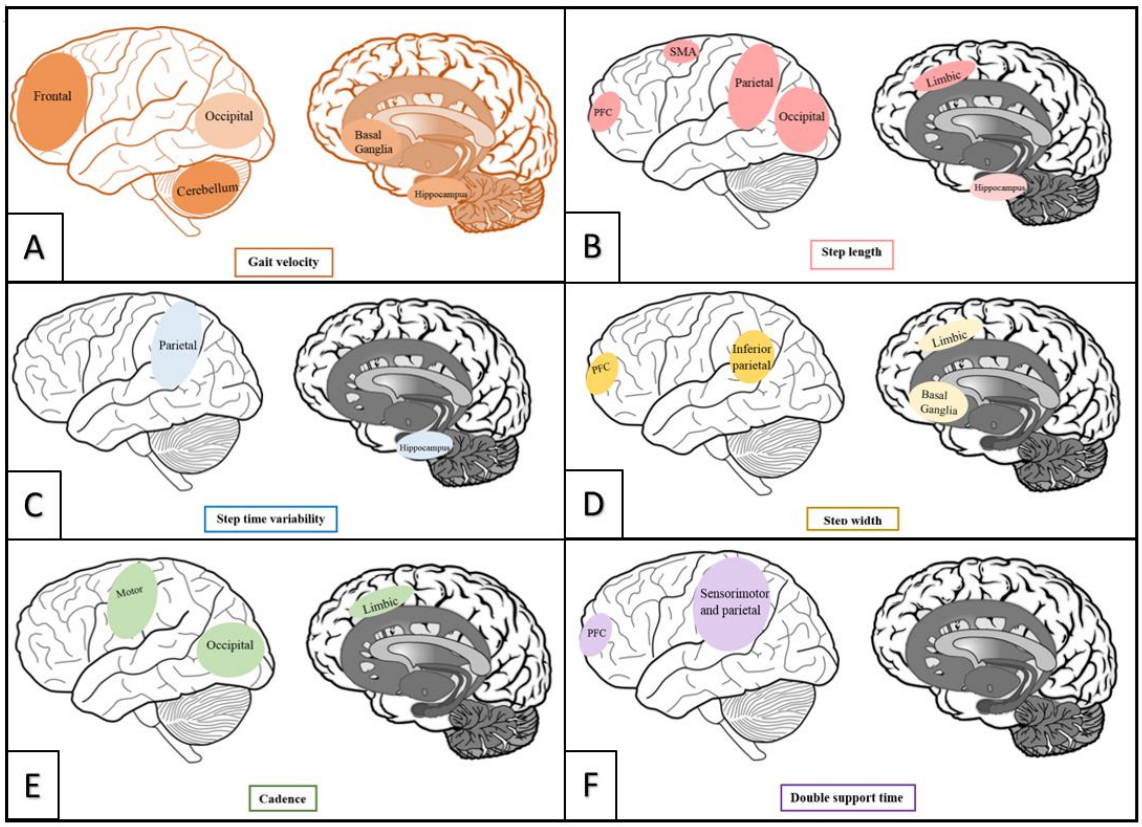
In summary, this chapter has demonstrated the first evidence that volumes of the cholinergic basal forebrain assessed in early PD can be used to predict changes in gait that are specific to disease progression. Findings reinforce the notion outlined throughout this thesis that gait control in PD involves the cortical cholinergic system. Cortical acetylcholine should therefore be considered as a therapeutic target to mitigate gait dysfunction in PD. Cross-sectional associations were mediated by age, highlighting the benefit of longitudinal study designs and the need to differentiate ageing and disease-related mechanisms of gait control in studies with PD populations. Future work should investigate whether measures of the structural integrity of the PPN differently associate with PD gait, and whether measures of connectivity within different cholinergic projection systems give further insights into the role of the cholinergic system in PD gait. As it is thought that atrophy of the NBM may underpin both motor and cognitive impairments; further investigations of the interplay between NBM volume, gait and cognition must be considered in future to understand this complex three-way interaction.

Chapter 8: Discussion and thesis summary

The aim of this thesis was to explore the neural mechanisms that underpin gait and its progression in early PD. Gait impairments are common and debilitating in PD, even in early stages. Dopaminergic therapies are unable to improve all aspects of gait nor prevent gait from declining over the course of PD, suggesting that the neural mechanisms involved in PD gait extend beyond dopaminergic substrates. Recent theories have hypothesised that compensatory and voluntary mechanisms are involved, through the recruitment of motor and non-motor related neural structures, to overcome the breakdown in systems involved in automatic gait control. However, there is limited empirical evidence to support these theories, as few have assessed the relationship between the brain and discrete gait characteristics in PD.

PD is a condition that typically affects older adults; there is, therefore, likely to be synergism between disease-related and age-related changes in the neural control of gait. In PD, there may also be a decompensation of the normal processes that help to minimise gait decline as part of healthy ageing. Consequently, to understand the neural underpinnings of PD gait, the impact of ageing must first be understood, thereby enabling the discrete effects of disease to be discerned. By doing so, therapies can be developed in future which target both of these aspects of gait decline, to ultimately maximise mobility. To establish the current understanding of the neural underpinnings of discrete characteristics in PD, an overview of the literature assessing neural correlates of gait characteristics was completed in **chapter 2**, in both healthy older adult and PD populations. Firstly, a structured review examined: i) cross-sectional associations between discrete gait characteristics and brain structure and function in healthy older adults, as identified through neuroimaging, and; ii) the longitudinal relationship between changes in gait and anatomical or functional imaging correlates in the same cohort. This review demonstrated that global imaging markers of a ‘deteriorating brain’, most commonly grey matter atrophy and a breakdown in white matter integrity, are correlated with poor gait performance in healthy older adults. Regionally, frontal and basal ganglia regions were most commonly associated with gait in healthy ageing cohorts. Importantly, this review highlighted that there is an emerging specificity of associations between gait and the brain, evidenced by differences in the neural regions associated with different gait characteristics thus far (**Figure 8-1**). Additionally, worsening gait over time could be predicted from imaging markers. This review highlighted that relatively few studies have been completed to assess imaging predictors of gait progression over time in older adults, nor to assess neural correlates of gait characteristics other than step velocity, a global measure of gait.

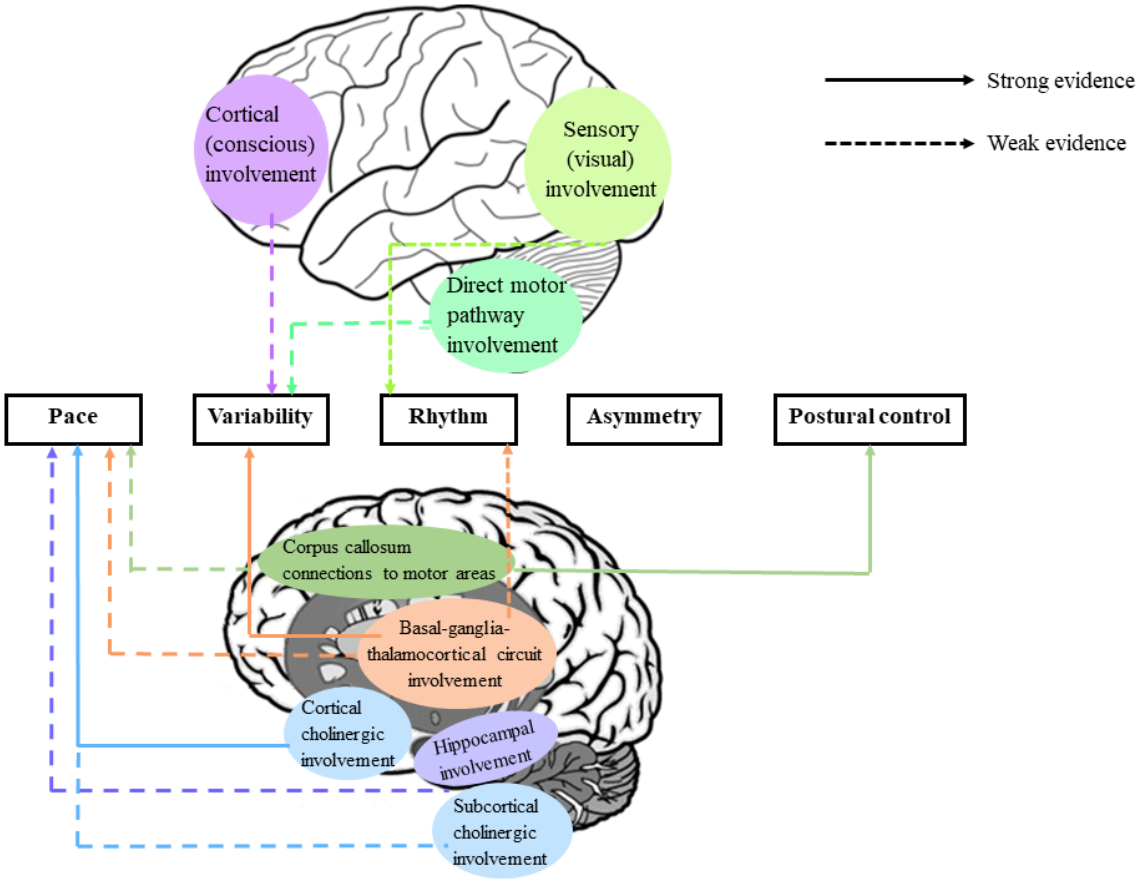
Figure 8-1. Map of associations between grey matter volumes and gait in older adults



[Gait velocity (A), step length (B), step time variability (C), step width (D), cadence (E) and double support time (F). Areas which are darker in colour indicate regions that were associated with the characteristic in multiple studies. Panel A shows the entire brain in an orange colour, to indicate that the volume of most brain regions have been associated with gait velocity.]

Secondly, associations between discrete gait characteristics and neuroimaging parameters were examined in PD. As with healthy ageing, in PD, i) there was specificity in the associations between discrete gait characteristics and imaging parameters, ii) most associations between gait and neuroimaging parameters in PD have been with step velocity and iii) no longitudinal study designs have been utilised in PD cohorts to date. There is tentative evidence for different neural substrates being involved in the gait of ageing and disease populations, as findings differed between cohorts in several studies. However, these are not well established. Studies in PD have explored relatively widespread neural structural and functional networks, including structures such as the brainstem, occipital lobe and corpus callosum as well as cholinergic activity. Findings from these studies therefore indicate a potential reliance on compensatory and non-motor mechanisms of gait control in PD, although the involvement of these mechanisms in the control of discrete gait characteristics remains relatively unsubstantiated. **Figure 8-2** summarises the regional associations made to date with gait characteristics from independent domains of gait in PD.

Figure 8-2. Map of regional associations made between imaging parameters and PD gait to date

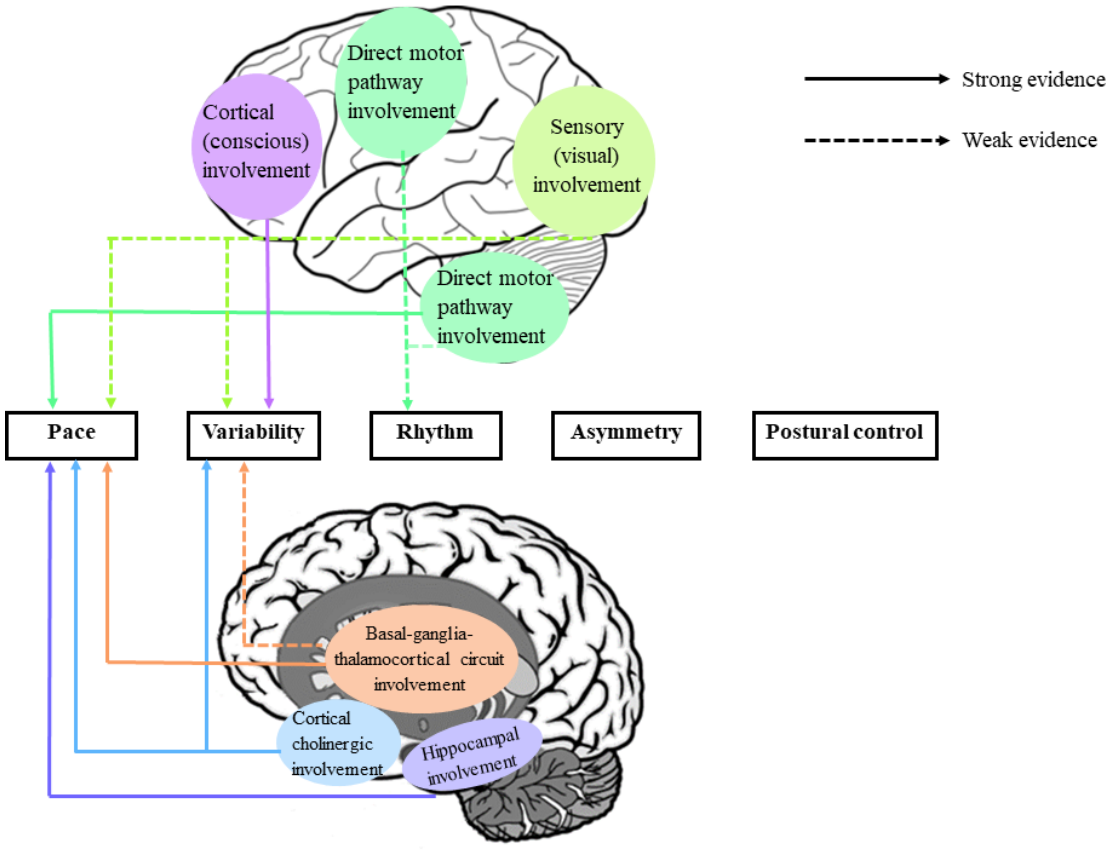


[Strong evidence: association found in more than one study OR association survived stringent multiple comparison correction. Weak evidence: association identified in a single study or did not survive multiple comparison correction.]

To aid in the interpretation of longitudinal associations made between gait and brain imaging parameters, **chapter 4** sought to determine the gait characteristics which change over time in early PD and delineate changes that occurred as a result of disease progression, ageing and changes in dopaminergic medications. In PD, four gait characteristics showed disease-specific progression, three showed age-related progression and change in two characteristics could be explained through a combination of ageing and disease progression. Change in one of the characteristics demonstrating disease-specific progression was explained by increasing dopaminergic medication over time. Overall, therefore, five gait characteristics (namely step length, swing time asymmetry and variability of step time, swing time and step length) were identified as being reflective of evolving PD pathology and were of interest in longitudinal evaluations of the neural correlates of PD gait.

Three chapters within this thesis (**chapters 5, 6 and 7**) demonstrate a robust approach to identify regional brain volumes associated with PD gait. Typically, smaller regional volumes were associated with poorer gait. Importantly, volumes of regions primarily related to both motor and non-motor functions were associated with gait. Furthermore, structures thought to be involved in compensatory mechanisms for PD gait control (both motor and non-motor related compensations) were associated with discrete gait characteristics. The strongest associations between gait and imaging parameters were made in longitudinal evaluations and therefore mostly pertain to characteristics from the pace and variability gait domains. Findings from these key chapters have been summarised in **Figure 8-3**. Through a comparison of **Figure 8-2** and **Figure 8-3**, it is evident that work within this thesis has contributed to new knowledge of the neural underpinnings of discrete gait characteristics. In particular, this thesis has identified: i) an involvement of visual processing in gait pace and variability control, ii) involvement of a "direct" motor pathway in the control of characteristics from the pace and rhythm domains of gait and, iii) cortical cholinergic involvement in gait variability.

Figure 8-3. Map of associations between regional volumes and gait in PD in this thesis



[Strong evidence: significant associations made between imaging and gait parameters. Weak evidence: trends towards associations made.]

Chapter 5 explored the associations between cortical volumes and gait in PD, through the evaluation of cortical thickness. This chapter provided evidence for a coupling of regional cortical volumetric changes with discrete impairments in PD gait. In the healthy older adult cohort only, cross-sectional associations were made between thinning in motor-related cortical areas and characteristics from the pace domain of gait, and between thinning in non-motor regions and gait characteristics from the postural control domain. These findings were in keeping with those identified within chapter 2. Cross-sectional associations between cortical thickness and gait were weak in PD, which may have related to an overall, widespread breakdown of motor networks in disease. There was, however, weak evidence for atrophy of cortical areas relating to the visual system in gait pace and variability that was unique to PD, indicating that visual processing may be more heavily relied upon in PD for effective gait. Weak associations were also made between thinning of the primary motor cortex and an apparent improvement (increase) in characteristics from the rhythm domain of gait. Since there is a supposed compensatory mechanism, involving the direct motor pathway, that is thought to negatively influence gait rhythm in order to preserve overall step velocity, it may be expected that pathologic changes in this cortical area may have a seemingly positive impact on this gait domain. Cortical thinning, soon after PD diagnosis, in both motor and non-motor related areas could predict changes in gait that occurred as a result of disease progression. There was specificity in these predictors: thinning of motor related areas predicted reduction in step length (gait pace), whereas thinning of non-motor areas, most notably the prefrontal cortex, predicted an increase in variability of both step time and step length. This chapter therefore indicates that PD gait, particularly measures of gait variability, may become increasingly reliant on cortical involvement over time and thus more sensitive to pathologic change in these areas.

Chapter 6 explored associations between subcortical volumes and gait in PD. Again, selective associations were made between discrete gait characteristics and both motor and non-motor related subcortical structures. In cross-section, weak associations with gait were mostly found with the brainstem in PD, and the thalamus in age-matched controls. There was, therefore, limited evidence for involvement of different subcortical structures in gait in PD compared to healthy ageing, which may relate to an increased reliance on the direct motor pathway in PD. The cerebellum was associated with the rhythm domain of gait, giving further evidence for a selective involvement of the direct motor pathway in the control of rhythm (i.e. step timing). Longitudinally, changes in gait pace were predicted from volumes of both motor and non-motor related structures, including structures within the basal-ganglia-

thalamocortical circuit as well as the cerebellum and hippocampus. Findings within this chapter therefore concur with those in chapter 5, as gait pace was primarily associated with motor related structures. However, the association between step length change and hippocampal volume provided additional insights into the role of non-motor structures in PD gait. As cholinergic neurons densely innervate the hippocampus, this association implies an involvement of the cortical cholinergic system in PD gait.

To further investigate the role of the cortical cholinergic system in PD gait, **chapter 7** explored associations between gait and sub-regional volumes of the cholinergic basal forebrain (cBF), which provides cholinergic innervation to the hippocampus and cortex. There were no associations between gait characteristics and cBF volumes in cross-section in PD nor ageing cohorts; this may have been because of ageing obscuring the effects of disease, given the well-established, age-related atrophy of the cBF. In contrast, cBF volumes were strong predictors of gait changes that were specific to PD. The NBM was the sub-regional cBF volume most strongly predictive of gait change, predicting a worsening of gait impairment via reductions in gait pace and increases in gait variability. Findings from this chapter therefore reinforce the notion that gait control in PD may involve the cortical cholinergic system.

8.1 Clinical implications

Primarily, this thesis aimed to further current understanding of the neural underpinnings of gait impairment in PD from a mechanistic viewpoint. However, thesis findings may also have clinical utility. This thesis has identified the first evidence that regional brain volumes, derived from structural MRI scans taken in very early disease, can predict changes in gait which occur specifically in PD. Regional volumes could therefore be investigated in future for use as novel markers to identify people with PD at a greater risk of developing more severe impairments in gait over time. It is important to identify those at a greater risk in early disease, before motor disease progresses too severely and resultant muscular atrophy develops. Furthermore, those at greater risk of gait decline are also at a greater risk of falling and experiencing cognitive decline; regional volumetric measures of the brain could therefore be further investigated as early warning markers of falls and cognitive decline. Additionally, this thesis has provided evidence for an association between the cortical cholinergic system and gait impairment in PD, further highlighting the need for novel therapies that extend beyond the dopaminergic system to target gait decline. Interventional studies have shown that AChE inhibitors can improve mobility measures, including step time variability, in PD;

findings from this thesis help to strengthen the case for therapeutically targeting the cholinergic system to limit gait progression in PD. As this thesis has shown that both age-related and disease-related changes in gait occur in early PD, findings indicate that combination therapies targeting both of these aspects of gait decline should perhaps be considered to minimise future mobility loss and falls in PD.

8.2 Strengths, limitations and future work

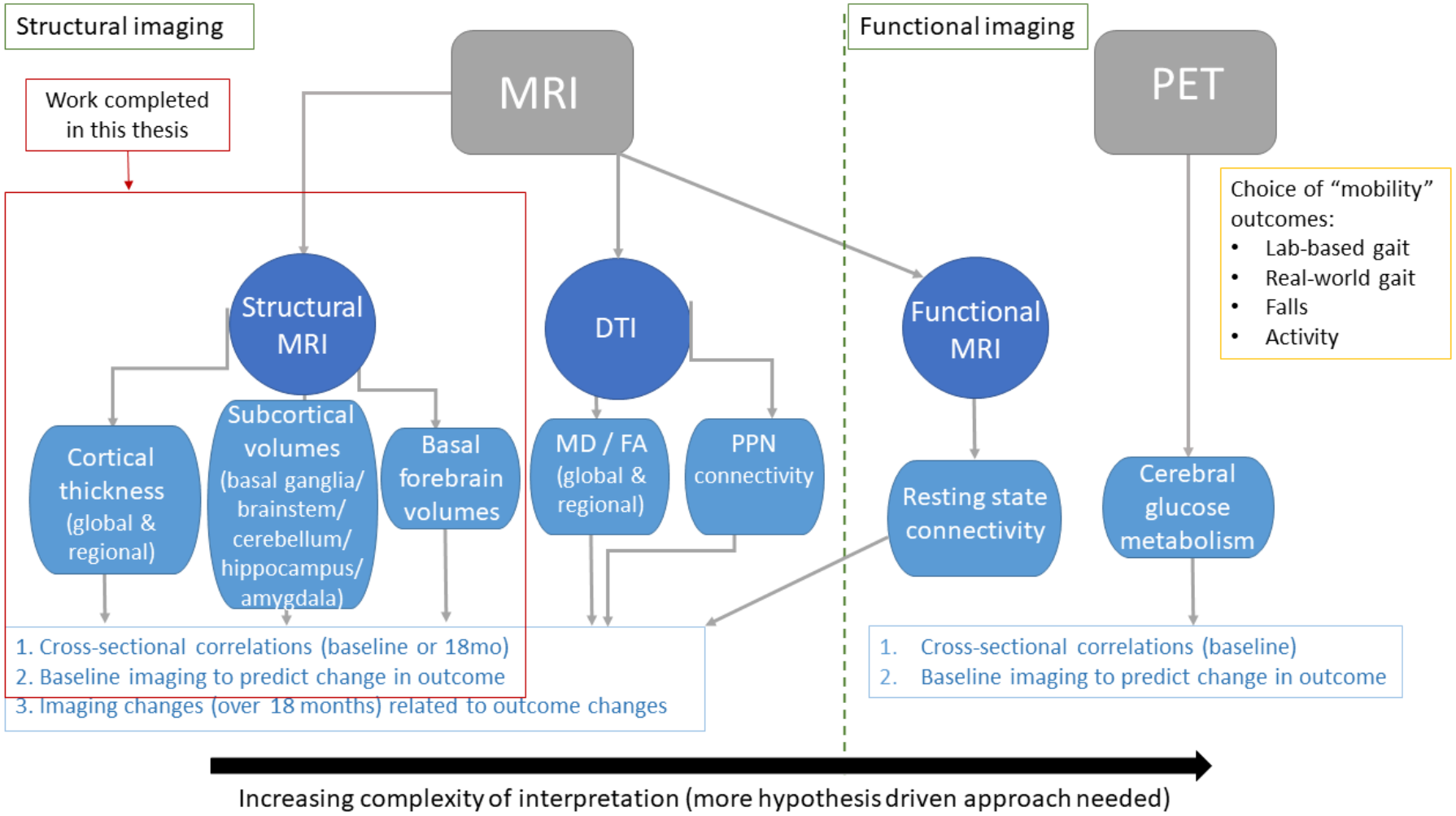
This thesis has identified novel evidence for a potential involvement of compensatory and non-motor neural mechanisms in PD gait. Detailed quantitative gait analysis was completed, with variable selection based on a validated model of gait containing characteristics sensitive to ageing and neurodegenerative disease. Additionally, high quality imaging data was obtained; both sets of data were collected within a very short time from each other. Cross-sectional associations were made in very early disease; this is crucial for furthering current understanding of the gait mechanisms involved in early PD, which may be indicative of novel intervention targets at a time where they would be most beneficial. Furthermore, substantial compensation comes into effect over time, as a result of increasing immobility, making it difficult to differentiate the primary neural substrates involved in gait control in later disease. Where possible, different analytical approaches were used to assess associations between imaging and gait parameters. Similar findings resulted from these different approaches; findings were therefore considered robust. Multiple comparison corrections were implemented in all analyses using regional volumes, again demonstrating the robustness of findings. A major strength of this work was the ability to assess longitudinal associations between neural structures and gait. Longitudinal study designs are needed to understand the neural mechanisms contributing to early gait decline; they also allow for the determination of a causal relationship between gait and imaging parameters, as the same participants are assessed multiple times. Changes in gait could be attributed to disease separately from ageing, as a well-matched control cohort was assessed alongside people with PD. Gait change was precisely modelled as all participants were recruited soon after PD diagnosis.

Some limitations with work presented in this thesis should also be acknowledged. Gait and imaging assessments were dissociated in time and so correlation-based analyses were relied upon; causation, therefore, cannot be assumed. However, assessments were completed in close succession and therefore any atrophic changes are likely to have been very small and would not have had a major effect on findings. Although regional volumes were considered, the assessment of sub-regions of structures that are thought to have different functions (for

example, the cerebellum) may give greater insights into the role of these structures during gait. Neuronal activity was not assessed, yet understanding the involvement of dopaminergic and cholinergic projection systems on PD gait may help in determining the most appropriate interventions (both pharmaceutical and non-pharmaceutical) to use for different gait impairments. Future comparisons of regional volumes with dopaminergic and cholinergic activity within the same cohort, as assessed through molecular imaging targeting these systems, may give a more precise understanding of the effect of volume loss on activity and thereby aid with interpretation of findings within this thesis. Gait characteristics measured "on" and "off" dopaminergic medication could also be associated with imaging parameters to give further insights into the role of dopaminergic networks in early PD gait.

Participant drop out was substantial over time, yet this was comparable to similarly designed studies and the study remains the largest longitudinal assessment of PD gait over the longest timeframe. Although this may have caused the overall rate of gait progression to have been underestimated; mixed-effects models were used to handle any missing data, thereby reducing potential bias in interpretations. Cognition was not considered in associations between imaging and gait parameters. Understanding the mediating role of cognition in these associations requires an in-depth investigation of the effects of different cognitive domains on both gait and imaging parameters, as well as how these interact over time. The complexity of this goes beyond the main aims of this thesis; further insights from cognition may be useful to assess in future, since it is clear that effective gait is dependent on the involvement of a broad network that involves both motor and non-motor related brain functions. Finally, studies within this thesis involved volumetric measures, which do not reflect the integrative brain networks that may better reflect the dynamic brain during gait. Approaches such as DTI, fMRI and assessment of spatial covariance patterns may be useful next steps in this regard; these assessments could be completed with data generated through the ICICLE studies, as displayed in **Figure 8-4**. Further studies, particularly utilising a multimodal imaging approach, are needed to validate the associations between the brain and PD gait identified here. Nevertheless, work within this thesis is strongly indicative of the regions most involved in PD gait, thereby providing a good foundation for future studies to lead more hypothesis-driven and network-based approaches when assessing associations between gait and neuroimaging parameters in PD.

Figure 8-4. An overview of the imaging data available through the ICICLE-PD study, and possible mobility outcomes to assess with imaging parameters



8.3 Conclusions

This thesis has used a comprehensive and robust approach to investigate the structural neural correlates of gait in early PD. Studies within this thesis provide evidence that both motor and non-motor structures may be relied upon for gait in PD, and the first evidence that regional brain volumes are predictive of PD specific gait changes. This not only provides a greater understanding of the specific regions of neuronal loss (reflected by volumetric reductions) that may contribute to gait dysfunction in PD, but demonstrates the potential of regional volumes to be further investigated for clinical use as early warning markers of falls and cognitive decline. Final conclusions from this thesis are as follows:

- A large and structured review identified that neural regions may selectively associate with discrete gait characteristics in ageing and disease populations, and that measurements of regional brain volumes have the potential to predict future changes in gait in older adults.
- Despite optimal medication, gait impairments progress more quickly in early PD than in a typically ageing cohort. Selective gait impairments are thought to progress because of disease progression and not the ageing process.
- Cortical thinning in areas linked to motor functions predicts shortening step length over the first six years of PD. Cortical thinning in areas linked to non-motor functions predicts increasing gait variability.
- Smaller subcortical volumes of both motor and non-motor regions predict shortening step length in PD, but not gait variability.
- Sub-regional cholinergic basal forebrain volumes predict changes in gait over the first six years of PD, demonstrating a role for the cholinergic system in PD gait and explaining associations made with non-motor structures.
- Longitudinal studies of discrete associations between imaging and gait parameters may be key to understanding the mechanisms relied upon during PD gait.

Chapter 9: Appendices

Appendix A. Descriptive information of all cross-sectional studies associating imaging and gait parameters in older adults

Study	Participant characteristics	Gait variables measured in pace domain	Gait analysis tool	Imaging parameters measured	Imaging modality and analytical technique utilised	Main Findings	Covariates	Effect of covariates on findings
1. Annweiler et al. (2014)	Older Adults (n=115), 43.5% F, age 70.4 ± 4.4	Stride time variability (%CV)	GAITRite (9.72m)	Ventricular sub-volumes (total, temporal horns and ventricular body volumes)	MRI: Brain Ventricle Quantification Suite (BVQ)	The highest tertile of stride time variability had larger temporal horns than the lowest and intermediate tertiles, and larger middle portions of ventricular bodies than the intermediate, but not lowest, tertile	CIRS-G, lower limb proprioception, visual acuity, Go-NoGo, MMSE, GDS, muscle strength, age, gender, BMI, gait speed, vascular burden in brain, psychoactive drugs	After adjusting for covariates, posterior body volume no longer associated with stride time variability
2. Baezner et al. (2008)	Older Adults (n=639), 53.9% F, age range 65-84	Gait velocity (ms^{-1})	Timed walk (8m; fastest of two trials)	Age-related white matter changes (ARWMC), ranked as mild, moderate or severe, using a modified version of the Fazekas visual scale	MRI: FLAIR	Slower gait velocity associated with more severe global age-related white matter changes, in mild vs moderate and mild vs severe conditions	age, sex, peripheral vascular disease, diabetes	When covariates included in analyses, associations remained in the mild vs. severe condition, but not in the mild vs. moderate condition
3. Beauchet et al. (2014)	Older Adults (n=71), 59.7% F, age 69 ± 0.8	Stride time variability (%CV)	SMTEC footswitches (20m, comfortable walking pace)	Regional grey and white matter volumes (Fazekas visual scale of ARWMC was assessed for exclusion criteria)	MRI: VBM	Increased stride time variability associated with reduced grey matter volume in the right parietal lobe. There was no association between stride time variability and white matter volume, perhaps as partipants with extreme ARWMC were excluded	age, gender, BMI, total brain matter	All associations were made with inclusion of covariates
4. Beauchet et al. (2015)	Older Adults (n=47), 49% F, age 69.7 ± 3.6	Stride time variability (%CV), Swing time	GAITRite Gold (9.72m)	Hippocampal volume: absolute hippocampal volume mm^3 and ratio of absolute	MRI: Freesurfer morphometric procedures	Increased stride time variability associated with a larger hippocampal volume. There were no associations between swing time variability, stride time, swing	age, gender, BMI, daily drugs taken, falls within last year, gait velocity, total white matter abnormalities,	When covariates were *not* adjusted for, associations were not significant

		variability (%CV), Stride time (ms), Swing time (ms), Stride width variability (%CV), stride width (cm)		hippocampal volume $mm^{3/}$ total brain volume mm^3		time stride width variability or stride width and hippocampal volume..	MMSE	
5. Beauchet et al. (2017)	Older Adults (n=77), 45.5% F, age 69.8 ± 3.5	Gait speed (ms^{-1}), Stride time variability (%CV)	GAITRite Gold (9.72m, comfortable walking pace)	Hippocampal and somatosensory cortex volumes	MRI: Freesurfer morphometric procedures	No associations were made between gait speed or stride time variability and hippocampal or somatosensory cortex volumes	Age, sex, body mass index, comorbidities, use of psychoactive drugs, far-distance visual acuity, lower-limb proprioception, depressive symptoms and cognitive scores (Mini-Mental State Examination, Frontal Assessment Battery)	Inclusion of all covariates in analyses had no significant effect on associations
6. Bolandzadeh (2014)	Older Adults (n=253), 58.0% F, age 82.7 ± 2.7	Gait speed (ms^{-1})	GaitMat II (3, 4 and 6m walks)	White matter hyperintensity volume. Selected regions of interest: global brain volume, right anterior thalamic radiation and frontal corpus callosum volume	MRI: Automated labelling pathway (ALP)	Slower gait speed associated with higher global white matter hyperintensity volume, and most strongly with white matter hyperintensities in the right anterior thalamic radiation and frontal corpus callosum	age, sex, BMI, quadriceps strength, education, standing height, chronic pain, Prevelant hypertension, 3MS (global cognition), DSST (executive function)	Associations reduced when 3MS or DSST were included in analyses – when adjusted, associations between gait speed and frontal corpus callosum lose significance.
7. Bruijn et al. (2014).	Older Adults (n=25), 40.0% F, age 70.9	Step width (m)	Vicon MX markers (300m at fixed pace on treadmill)	Fractional Anisotropy	DTI: TBSS	A narrower step width associated with reduced fractional anisotropy, in the left corticospinal tract, left anterior thalamic radiation and left longitudinal fasciculus.	age	This association was found in older adults; younger adults also demonstrated the relationship, but to a lesser extent

8. Callisaya et al. (2014)	Older Adults (n=305), 45.9% F, age 71.4 ± 6.9	Gait speed(cm/s), Step length (cm), cadence (steps per minute)	GAITRite (4.6m)	Total grey and normal appearing white matter volumes	MRI: VBM	Slower gait speed and shorter step length associated with reduced total grey matter volume, and with reduced grey matter within regions in all cortices (frontal, cingulate, insula, temporal, parietal, occipital) as well as the cerebellum, insula, parahippocampus, thalamus, caudate nucleus, putamen and claustrum. No associations were made with gait speed or step length and normal appearing white matter, or between cadence and total grey or white matter volumes	1. Age, sex, height 2. Vascular risk factors (weight, blood pressure, physical activity or self-reported vascular medical history), medication use 3. WMH volume, total grey or white matter volume (as appropriate)	All associations were made with inclusion of covariates 1 (age, sex and height.) When adding (2) there were no alterations. When adding (3) associations with grey matter were minimally altered – removing associations with gait speed and the right precuneus, left caudate nucleus, left thalamus, left inferior occipital and left inferior temporal lobes, right superior parietal and right inferior occipital lobes, right precuneus, right insula and left anterior cingulate areas. Associations with step length only minimally altered.
9. Choi et al. (2012)	Older Adults (n=377), age and gender characteristics grouped by presence of infarcts and microbleeds	Gait speed (cm/s), Step length (cm), Cadence (steps per minute), Double support time (s), Step width (cm)	GAITRite (4.6m)	Silent infarcts and cerebral microbleed presence	MRI: FLAIR	Slower gait speed, smaller step length and wider steps associated with increased global silent infarct presence, but not global microbleed presence. Longer double support time associated with increased presence of silent infarcts and microbleeds. Reduced cadence associated with increased microbleed, but not silent infarct, presence.	age, sex, total intracranial volume, white matter lesion volume, microbleeds or silent infarcts as appropriate	Inclusion of all covariates in analyses caused associations to no longer be statistically significant
10. De Laat et al. (2011a)	Older Adults (n=429), 45.2% F,	Gait velocity (ms^{-1}), Stride	GAITRite (5.6m)	White matter lesion (WML) presence, Fractional Anisotropy (FA),	MRI: FLAIR DTI: TBSS	Slower gait velocity, shorter stride length and wider stride width associated with WML presence in the right centrum	age, sex, height, WML total volume, number of lacunar	Most associations between gait velocity or stride length and white matter integrity

	age 65.2 ± 8.9	length (m), Cadence (steps per minute), Stride width (cm)		Mean Diffusivity (MD)		semiovale. Shorter stride length also associated with increased WML presence in periventricular frontal lobes. No significant associations were identified between WML presence and cadence. Slower gait velocity, shorter stride length and wider strides also associated with reduced FA and increased MD in most regions, including normal-appearing white matter and white matter lesion regions. Less cadence associated with reduced FA and increased MD in few voxels.	infarcts or total brain volume	parameters were no longer significant when white matter lesions and lacunar infarcts were included as covariates. Associations that remained were those between fractional anisotropy and stride length in the genu and splenium of the corpus callosum, and between mean diffusivity and stride length in the body of the corpus callosum
11. De Laat et al. (2011b)	Older Adults (n=485), 43.1% F, age 65.6± 8.8	Gait velocity (ms^{-1}), Stride length (m), Cadence (steps per minute), Double Support percentage (% of gait cycle), Stride width (cm)	GAITRite (5.6m)	Microbleeds: number and location	MRI: gradient-echo T2*-weighted sequences	Slower gait velocity and shorter stride length associated with an increased number of microbleeds, both globally and in the temporal lobe. Stride length was also associated with the number of microbleeds in the frontal lobes and basal ganglia. Cadence was not associated with the number of microbleeds. Increased double-support percentage and wider strides associated with an increased number of microbleeds (regional burden was not considered for these gait characteristics).	age, sex, height, total brain volume, number of territorial infarcts, WML total volume, number of lacunar infarcts	Inclusion of all covariates in analyses did not significantly alter associations with stride length, but caused associations with gait velocity to no longer be significant
12. De Laat et al. (2011c)	Older Adults (n=484), 43.4% F, age 65.6 ± 8.9	Gait velocity (ms^{-1}), Stride length (m), Stride time	GAITRite (5.6m)	Total brain volume, Fractional Anisotropy (FA), Mean Diffusivity (MD)	MRI: SPM unified segmentation routines DTI: SPM5	Slower gait velocity, shorter stride length, increased stride time variability, less cadence, greater double support percentage, increased stride length variability and larger stride width associated with a reduced total brain volume.	age, sex, height, total brain volume (where appropriate), white matter lesion total volume, number of lacunar infarcts	Including WML volume and number of lacunar infarcts as covariates caused relationship with fractional anisotropy, but not mean diffusion, disappear. Associations made with total brain

		variability (%CV), Cadence (steps per minute), Double Support percentage (% of gait cycle), Stride length variability (%CV), Stride width variability (%CV), Stride width (cm)				Reduced FA in normal appearing white matter associated with slower gait velocity, shorter step length, reduced cadence and larger stride width. Increased MD in both normal appearing white matter and white matter lesions was associated with slower gait velocity, shorter step length, reduced cadence, greater double support percentage, and larger stride width. Increased MD was associated with increased stride length variability in normal appearing white matter only, and with reduced stride width variability in white matter lesions only. The associations between FA and gait velocity were significant within periventricular frontal, occipital and temporal regions; associations between gait velocity and MD were additionally significant in subcortical frontal and parietal regions.		volume were made whilst including all covariates in analyses
13. De Laat et al. (2012)	Older Adults (n=415), 46.3% F, age 65.1 ± 8.8	Gait velocity (ms^{-1}), Cadence (steps per minute), Stride length (m), Stride	GAITRite (5.6m)	Cortical thickness	MRI: Civet Pipeline	Slower gait velocity, shorter stride length, reduced cadence and larger stride width associated with decreased cortical thickness. Associations with gait velocity were made in areas involving most of the cortex, associations with stride length were made in most frontal	age, sex, height, WML total volume, number of lacunar infarcts	Associations weakened after the inclusion of WML total volume as a covariate, but mostly remained significant

		width (cm)				regions except for the bilateral motor cortices, visual areas and anterior and posterior cingulate areas, associations with cadence were mostly within the left cingulate, bilateral visual areas and the left fusiform gyrus and stride width associations were made within the orbitofrontal and ventrolateral prefrontal cortex, the cortical areas adjacent to the posterior insula, inferior temporal gyrus, left fusiform gyrus and dorsal anterior cingulate cortex		
14. del Campo et al. (2016)	Older Adults (n=128), 60.2% F, age 76.1 ± 4.6	Gait speed (ms^{-1})	Timed walk (4m; fastest of two trials)	Amyloid beta burden assessed through standard uptake value ratios (SUVR's)	PET: [18F]	Slower gait speed associated with increased amyloid beta burden within the putamen, occipital cortex, precuneus, and anterior cingulate	age, sex, education, BMI, APOE genotype, days since baseline at PET, time between gait and PET assessments, regional 18F standard uptake value ratios (as appropriate)	Association was made with inclusion of covariates
15. Della Nave, et al (2007)	Older Adults (n=36), 58.0% F, age 77 ± 4.5	Gait velocity (ms^{-1})	Timed walk (4m)	Leukoaraiosis through the Fazekas scale (LA), Total brain volume, Grey matter volume, White matter volume, ractional Anisotropy (FA), Mean Diffusivity (MD)	MRI: SIENAX DTI: Philips in-house software	Results were unclear; It is interpreted that gait velocity was not associated with any of the imaging parameters investigated	Not reported	Unknown
16. Dumurgier et al. (2012)	Older Adults (n=1623), 60.5% F,	Walking speed (ms^{-1})	Chronometer connected to 2 photoelectri	Regional grey matter volume	MRI: VBM	Slower walking speed associated with reduced grey matter volume; regions that reached statistical	age, sex, BMI, education, WML volume, silent infarcts, total	Adjusting for cognitive test scores caused associations with frontal

	age 73.3 ± 4.1		c cells (6m; fast walking condition)			significance were the basal ganglia and caudate nucleus.	intracranial volume, MMSE or TMT-A, depression, hypertension, diabetes, hypercholesterolemia, smoking. P values were Bonferroni corrected	and parietal lobes to no longer be significant
17. Ezzati et al. (2015).	Older Adults (n=112) 59.8% F, age 79.3 ± 5.0	Gait velocity (cm/s)	GAITRite (4.6m; normal pace, two trials)	Cortical grey matter volume, Cerebral total white matter volume, hippocampal volume, ventricular volume	MRI: Freesurfer standard segmentation procedures and Freesurfer morphometric procedures	In unadjusted models, slower gait velocity was associated with reduced grey matter, white matter and hippocampal volumes. No association was made with gait velocity and ventricular volume	age, gender, education, total intracranial volume, memory performance. p-values were corrected for type one error	Associations with white matter and hippocampal volumes were not significant after adjusting for covariates
18. Fling et al. (2016)	Older Adults (n=10), 60% F, average age 75 (62-84 age range)	Gait velocity (ms^{-1}), stride width (cm)	GAITRite (8m)	Fractional anisotropy, Mean Diffusivity	DTI: Interhemispheric Callosal Tractography	No associations were made between gait velocity or stride width and fractional anisotropy or mean diffusivity.	Not reported	Unknown
19. Fling et al. (2018).	Older Adults (n=20), 65% F, age 71.4 ± 8.1	Step length asymmetry (%), Step time asymmetry (%)	GAITRite (8m)	Fractional anisotropy	DTI: Interhemispheric Callosal Tractography. Regions investigated: pre-supplementary motor area, supplementary motor area, primary motor and primary somatosensory	No associations were made between either step length asymmetry or step time asymmetry and fractional anisotropy in any of the regions of interest.	Not reported	Unknown
20. Holtzer et al. (2015)	Older Adults (n=348), 59.0% F, age 76.8 ± 6.8	Stride velocity (cm/s), Stride length (cm)	Zeno walkway (14 foot)	Activation strength (due to oxyHb levels)	fNIRS: 16-channel	No associations were made between gait velocity or stride length and activation strength of the prefrontal cortex	Disease comorbidity score, RBANS (cognition), age, sex, education	Association was made with inclusion of covariates

21. Manor et al. (2012)	Older Adults (n=89), 46.5%F, age 65.3 ± 8.2	Walking speed (ms^{-1}), Stride duration variability (%CV), Double support (% of stride time)	Timed 12 minute walk using Mega Electronics heel and Toe footswitches (75m course)	Global and regional grey matter volume. Specific regions of interest: right and left precentral gyri, basal ganglia and cerebellum, post central gyri and dorsolateral prefrontal cortex.	MRI: SPM segmentation routines	No associations were made between walking speed, stride duration variability or double support time and global, cerebellar dorsolateral prefrontal cortex or basal ganglia grey matter volumes.	Age, sex, body mass	Associations were made with inclusion of covariates
22. Moscufo et al. (2012)	Older Adults (n=77), 60% F, age 84 ± 3.9	Walk speed (ms^{-1}) (max velocity and usual velocity)	SPPB (2.5m)	WMH volume. Selected regions of interest – corpus collosum, corona radiate, superior longitudinal fasiculus.	MRI: FLAIR	At two separate time points, maximum and usual walk speeds associated with WMH burden in the splenium of the corpus callosum. At the earlier time point, both walking speeds were additionally associated with WMH burden in the corona radiata; at the later time point, both walking speeds were additionally associated with WMH burden in the body of the corpus callosum	age, gender, mini-mental state score (MMSE), and body mass index (BMI)	Inclusion of all covariates in analyses had no effect on associations
23. Murray et al. (2010)	Older Adults (n=148), 56.1% F, average age 79 (73-91 age range)	Gait velocity (cm/s), Stride length (cm)	GAITRite (4.9m)	WMH volume	MRI: FLAIR	Slower gait velocity and shorter stride length associated with an increased number of white matter hyperintensities in all regions (total, periventricular, subcortical, frontal temporal, parietal and occipital).	Not reported	Unknown
24. Nadkarni et al. (2009)	Older Adults (n=33), 47% F, age 73 ± 8	Gait velocity (cm/s), Stride length (cm), cadence (steps per minute),	GAITRite (12 foot)	WMH severity	MRI: Age related white matter change rating scale; results were reported through groups split by white matter burden	Slower gait velocity associated with increased severity of total white matter hyperintensities, as well as WMH severity in frontal and basal ganglia regions. No associations were made between stride length or cadence and WMH. Narrower steps associated with	age, UPDRS, MMSE, dementia rating scale	Not specified

		step width (cm)				increased WMH severity in basal ganglia regions.		
25. Nadkarni et al. (2014)	Older Adults (n=231), 58.4% F, age 82.9 ± 2.7	Gait speed (ms^{-1})	GaitMat II (4m)	Cerebellar grey matter volume	MRI: hidden Markov random field (HMRF) model	Slower gait speed associated with reduced total cerebellar volume, as well as cognitive and sensorimotor cerebellar regions.	age, gender, WMH, atrophy, DSST	After adjusting for DSST, the association between larger cerebellar volume and faster gait speed was no longer statistically significant
26. Nadkarni et al. (2017)	Older Adults (n=183), 41.5% F, age 85.5 ± 3	Gait speed (ms^{-1})	Timed walk (4.57m)	Amyloid beta burden through standard uptake volume ratios (SUVRs)	PET: [11C]PiB	Slower gait speed associated with global increased amyloid beta burden, and amyloid beta burden in anterior caudate and putamen, lateral temporal cortex, precuneus cortex and sensory-motor cortex	age, sex, race, education, weight, hypertension, coronary heart disease, stroke, cortical atrophy, SVD, MMSE, APOE ε4	When MMSE was included as a covariate, associations lessened but persisted. When APOE ε4 was included as a covariate, associations were no longer significant
27. Novak et al. (2009)	Older Adults (n=76), 52.6% F, age 64.7 ± 7.2	Gait speed (ms^{-1})	Timed walk (12 minutes)	Frontal grey and white matter volume, WMH volume	MRI: FLAIR	Slower gait speed associated with reduced frontal grey and white matter volumes. No association was made between gait speed and white matter hyperintensity volume.	age, BMI, posturographic measures	Associations were made with inclusion of covariates
28. Rosano et al. (2005a)	Older Adults (n=321), 60.7% F, age 78.3	Gait speed (ms^{-1}), Stride length (m), Double support time (s)	GaitMat II (4m)	WMH volume, infarcts, ventricular enlargement	MRI: comparison to an atlas of predefined visual standards	Slower gait speed associated with an increase in the number of subcortical and basal ganglia infarcts and WMH. Stride length did not associate with the number of WMH, but did associate with an increase in the number of subcortical and basal ganglia infarcts. Longer double support time associated with an increase in total WMH, but not infarct number. No gait characteristic was associated with ventricular enlargement.	age, sex, race, CVD risk factors	Adjusting for covariates had little effect on relationship identified
29. Rosano et al. (2005b)	Older Adults (n=2450), 57% F, age 74.4 ± 4.7	Gait speed (ms^{-1})	Timed walk (15 foot)	Ventricular enlargement, WMH volume, infarcts	MRI: comparison to an atlas of predefined visual standards	Slower gait speed associated with increased ventricular size, an increase in the severity of WMHs and infarct presence.	age, sex, race, education, cardiovascular risk factors, cardiovascular	Adjusting for covariates had little effect on relationship identified

							disease, 3ms, incident stroke, incident dementia	
30. Rosano et al. (2007a)	Older Adults (n=327), 56.5% F, age 78.2 ± 3.9	Gait speed (ms^{-1})	Timed walk (15 foot)	Regional grey matter volume	MRI: Automated labelling pathway (ALP)	Slower gait speed associated with a reduction in grey matter volume in the precuneus, left cerebellum and prefrontal regions.	gender, education, BMI, head size, osteoarthritis, peripheral arterial disease, WMH, infarcts, ventricular enlargement	Adjusting for covariates had little effect on relationships identified
31. Rosano et al. (2007b)	Older Adults (n=331), ?% F, age 78.3 ± 4.0	Stance Time variability (CV%), Step length variability (%CV), Step width variability (%CV)	GaitMat II (4m)	Total and basal ganglia infarcts and WMH severity	MRI: comparison to an atlas of predefined visual standards	Increased stance time variability associated with WMH severity, but not the number of total or basal ganglia infarcts. Increased step length variability associated with WMH severity and the number of total and basal ganglia infarcts. Step width variability did not correlate with any imaging parameter	age, gender, 3MSE, CV diseases, UPDRS, CES-D, BMI, hip/knee pain, joint arthritis	Associations were made with inclusion of covariates
32. Rosano et al. (2008)	Older Adults (n=220), 63.2% F, age 78 ± 3.9	Step length (m), Double support time (s), Step width (m)	GaitMat II (4m)	Regional grey matter volume	MRI: ROI	Shorter step length, longer double support time amd wider steps associated with reduced of grey matter volume. Regionally, step length associated with the dorsolateral prefrontal cortex, left supplementary motor cortex, right parietal lobules, motor cortex and sensorimotor cortex. Double support time associated the dorsolateral prefrontal cortex, right parietal lobules, right motor cortex and sensorimotor cortex. Wider steps associated the right dorsolateral prefrontal cortex pallidum and inferior parietal lobe.	age, gender, total brain volume, BMI, arthritis, sensory impairment, ankle arm ratio, infarct, WMH, stroke, 3MSE, DSST, CES-D, dementia	Adjusting for covariates had little effect on step length relationships identified; only the association between left motor cortex and step length was attenuated

33. Rosario et al. (2016)	Older Adults (n=265), 57% F, age 82.9 ± 2.7	Gait speed (ms^{-1})	GaitMat II (4m)	WMH volume	MRI: FLAIR (DTI imaging also completed, but for use as a covarying factor only)	Slower gait speed associated with an increased number of white matter hyperintensities, with stronger associations in the corona radiata, superior longitudinal and fronto-occipital fasciculus, uncinate fasciculus, anterior limb of internal capsule, posterior limb of internal capsule and left retrolenticular part of internal capsule, right posterior thalamic radiation, external capsule and corpus callosum. Associations were made in many regions in participants with low fractional anisotropy, but in few regions in participants with high fractional anisotropy.	age, sex, fractional anisotropy, muscle strength, body mass index, diabetes, hypertension, stroke	Associations held after adjustment for age and sex, and after adjustment for fractional anisotropy.
34. Rosso et al. (2014)	Older Adults (n=265), 57.4% F, age 82.9± 2.7	Step length variability (%CV)	GaitMat II (4m)	Grey matter atrophy, WMH volume, fractional anisotropy, mean diffusivity	MRI: Automated segmentation (FAST) and FLAIR DTI	Increased step length variability associated with increased mean diffusivity within the hippocampus and anterior cingulate cortex	age, gender, obesity, diabetes, muscle strength, gait speed, CES-D, DSST	Associations were made with inclusion of covariates.
35. Sakurai et al. (2014)	Older Adults (n=182), 100% F, age 69.4 ± 6.6	Gait speed (m/minute), Step length (cm), step frequency (steps per second)	Timed walk (unspecified) (5m) (comfortable speed and max speed)	normalised regional cerebral metabolic rates of glucose uptake	PET: 18F	Slower gait speed and lower step frequency during walking at maximum speed associated with a reduction in metabolic rates of glucose uptake in the prefrontal, posterior cingulate, and parietal cortices. There was no association between step length and metabolic rates of glucose uptake when assessed at maximum gait speed, or with any gait characteristics assessed at comfortable pace.	age, BMI, education, hypertension, cardiac disease, diabetes mellitus, blood pressure, days between assessment	Associations were made with inclusion of covariates

36. Sakurai et al. (2017)	Older Adults (n=149), 100% F, age 70.2 ± 6.2	Gait speed (ms^{-1}), Step length (cm), step frequency (steps per second)	Timed walk (unspecified) (5m) (comfortable and fast walk)	normalised regional cerebral metabolic rates of glucose	PET: 18F	During fast walking, slower gait speed and lower step frequency were associated with a reduction in metabolic rates of glucose in the posterior cingulate, occipital, parietal and primary sensorimotor cortices. There was no association between step length during fast walking and metabolic rates of glucose. No associations were made when walking parameters assessed at a comfortable pace	Age, education, comorbidities, blood glucose level, BMI,	Associations were made with inclusion of covariates
37. Shimada et al. (2013)	Older Adults (n=24), 100% F, age 78.0 ± 2.3	Step length variability (%CV), participants were split in to low or high step length variability groups	Treadmill walk with infrared step counter (25 minutes at 2km/h, so approx. 833m)	Metabolic rates of glucose	PET: 18F	The low step length variability (LSV) group had relatively increased glucose uptake in the primary sensorimotor area in comparison to the high step length variability (HSV) group. The HSV group had comparatively decreased uptake in the middle and superior temporal gyrus and hippocampus in relation to the LSV group	Not reported	Unknown
38. Sorond et al. (2011)	Older Adults (n=42), 54.8% F, age 76 ± 5 (fast gait), 82 ± 6 (slow gait)	Gait speed (ms^{-1})	Timed walk (4m) (fastest of 2 trials)	WMH volume, brain parenchymal volume	MRI: FLAIR	Slower gait speed associated with a higher burden in the total number of white matter hyperintensities. No significant associations were made between gait speed and brain parenchymal volume, although there was a trend towards this relationship	Not reported	Unknown
39. Soumaré et al. (2009)	Older Adults (n=1702), 60.6% F, age 72.4 ± 4.1	Walking speed (ms^{-1})	Chronometer connected to 2 photoelectric cells (6m)	WMH volume	MRI: Fully automated software	Slow walking speed was associated with the highest number of total, periventricular and deep WMH	age, gender, education, brain white matter volume, BMI, homocysteine level, psychotropic drugs, hypertension, physical	All associations were made after adjustment for age, gender, education, lacunar infarcts and brain white matter volume.

			(maximum speed)				activity, lacunar infarcts,	Additional adjustment for other covariates caused associations between only the highest number of total and periventricular white matter hyperintensities to remain significant; associations with deep white matter hyperintensities were no longer significant.
40. Stijntjes et al. (2016)	Older Adults (n=237), age and gender characteristics not specified for just those with imaging and gait data	Walking speed (ms^{-1})	Timed walk (4m and 25m)	Total grey and white matter volumes, hippocampal volume, basal ganglia volume, cerebral microbleed presence, lacunar infarct presence	MRI: automated segmentation (SIENAX, FIRST) and visualization (MIPAV)	Slower walking speed associated with the presence of microbleeds and infarcts, and with smaller hippocampal volume (during 4m walking only). No other associations between walking speed and total grey or white matter or basal ganglia volume was observed.	age, gender, whole brain volume, cognition through immediate and delayed recall	Associations were made with inclusion of age, gender and whole brain volume. Additional inclusion of cognition did not alter findings.
41. Tian et al. (2017)	Older Adults (n=59), 50.8%F, age 74.8 ± 7.8	Gait speed (ms^{-1})	Timed walks (6m)	Amyloid beta burden through distribution volume ratio (DVR)	PET: [11C]PiB	No cross-sectional association between gait speed and amyloid beta burden was observed.	Age, sex, BMI, cardiovascular risk, APOE ε4 status, California Verbal Learning Test score	Analyses included all covariates
42. Verlinden et al. (2016)	Older Adults (n=2330), 55.1% F, age 65.9 ± 9.2	Gait velocity (cm/s), Stride length (cm), Single support phase (%), Stride length SD (cm)	GAITRite walkway (4.88m)	Fractional Anisotropy (FA), Mean Diffusivity (MD), Axial Diffusivity (AxD), Radial Diffusivity (RD)	DTI: Probabilistic tractography (ProbtrackX)	Slower gait velocity associated with increased MD in brainstem, projection, association, limbic and callosal tracts. Associations with FA occurred in all but brainstem tracts, with MD in all but limbic tracts, with RD in all tracts and with AxD in association and projection tracts only. Shorter stride length associated with increased MD in brainstem,	age, age-squared, sex, height, weight, education, interval between gait and MRI, MMSE, intracranial volume, lacunar infarcts, tract specific WM volume, log transformed WML volume, other gait domains, direction of encoding on scan	Associations were made with inclusion of covariates.

						projection, association, limbic and callosal tracts. Reduced single support phase associated with MD in the anterior thalamic radiation (projection), inferior fronto-occipital fasiculus and superior longitudinal fasiculus (association). Increased stride length SD associated with increased MD in the superior longitudinal fasiculus (association) only		
43. Wennberg et al. (2017)	Older adults (n=611), 49.3% F, age 62.7 (age range 50-69)	Gait speed (ms^{-1}), Stride length (cm), Stance time variability (%CV), Cadence (steps per minute), Double Support time (s)	GAITRite (5.6m)	Amyloid beta burden through SUVR	PET: [11C]PiB	Slower gait speed associated with higher amyloid beta burden in orbitofrontal and temporal regions. Stride length did not associate with amyloid beta burden in any region of interest. Increased stance time variability associated with higher amyloid beta burden in prefrontal, orbitofrontal, temporal, anterior and posterior cingulate and motor regions. Less cadence associated with higher amyloid beta burden in all regions of interest (orbitofrontal, prefrontal, parietal, temporal, anterior and posterior cingulate and motor regions). Increased double support time associated with increased amyloid beta burden in all regions except motor	Age, sex, BMI, education, APOE e4 allele, Charlson comorbidity index, depression, AD-associated neurodegeneration (HVa, FDG PET SUVR, and cortical thickness)	Adjustment for AD-associated neurodegeneration caused gait speed to additionally associate with SUVR in prefrontal and anterior and posterior cingulate regions. Also, stride length associated with SUVR in temporal regions and stance time variability additionally associated with SUVR in parietal regions
44. Willey et al. (2013)	Older Adults (n=701), 67,2% F,	Gait speed (ms^{-1})	Straight line walking (4m)	WMH volume	MRI:FLAIR	Slow gait speed associated with large total WMH volume in cross-section, as well as WMH volume in the frontal lobe.	Age, ethnicity, gender, cardiovascular risk factors, MCI or	Associations were significant after adjusting for cardiovascular risk factors and silent brain

	age 80.3 ± 5.6						dementia, silent brain infarcts	infarcts, however adjustment for other covariates caused associations to be no longer significant
45. Wolfson et al. (2013)	Older Adults (n=67), 61% F, age 81.7 ± 3.9	Gait velocity (ms^{-1})	SPPB (2.5m)	WMH volume	MRI:FLAIR	Slower gait velocity associated with total WMH volume at the baseline time point. No association was made at the second time point.	age, gender, BMI (baseline where appropriate)	Inclusion of all covariates in analyses had no effect
46. Yuan et al. (2015)	Older Adults (n=30), 51.8% F, age 72.5 ± 5.2	Gait velocity (cm/s)	GAITRite (8 foot)	Functional connectivity	Resting-state fMRI: BOLD	Gait velocity associated with functional connectivity in sensorimotor, visual, vestibular, and left fronto-parietal cortical areas.	Not reported	Unknown
47. Zimmerman et al. (2009)	Older Adults (n=48), 47.9% F, age 81.2 ± 5.5	Stride length (cm), stride length variability (SD)	GAITRite walkway (9 foot)	Hippocampal volume and hippocampal N-acetylaspartate: creatine ratio	MRI: ROI Magnetic resonance spectroscopy: Gaussian broadening	Shorter stride length was associated with smaller hippocampal volume. There was no association between stride length or stride length variability and N-acetylaspartate: creatine ratio.	age, midsagittal area, gender, weight, gait velocity	Including gait velocity as a covariate caused the association to be no longer significant

Appendix B. Descriptive information of all longitudinal studies

Study	Participant characteristics	Gait variables measured longitudinally	Gait analysis tool	Imaging parameters measured	Imaging modality and analytical technique utilised	Time points at which gait and imaging parameters were assessed	Main Findings	Covariates	Effect of covariates on findings
1. Callisaya et al. (2013)	Older Adults (n=225), 43.6% F, age 71.4 ± 6.8	Gait velocity (cm/s), Step length (cm), Cadence (steps per minute), Step width (cm)	GAITRite (4.6m)	Total grey and white matter volume, WMH, hippocampal volume	MRI: automated segmentation, FLAIR	Gait and MRI assessments were completed at both baseline and follow-up (mean duration between assessments was 30.6 ± 4.9 months.)	Greater decline in gait velocity over time associated with reduced grey matter, white matter and hippocampal volumes over time, and increased WMH volume over time. Greater decline in stride length over time associated with reductions in white matter and hippocampal volumes over time, and increased WMH volume over time. Greater decline in cadence over time associated with reduced grey and white matter volumes over time. Change in stride width over time did not associate with change in any imaging parameter over time	age, sex, BMI, total intracranial volume, time between assessments, change in grey matter/change in white matter/change in WMH as appropriate	Gait velocity only associated with grey matter volume reductions when baseline imaging parameters were included as covariates. Including age as a covariate modified the association between stride length decline and change in WMH volume over time; older adults had more strong associations. Cadence only associated with grey matter volume reductions when the number of infarcts at baseline was included as a covariate
2. Frederiksen et al. (2011)	Older Adults (n=328), 53% F, age 73.8 ± 5.0	Gait velocity (ms^{-1})	Timed walk on unspecified walkway (8m)	Corpus Callosum volume	MRI: automatic segmentation	Gait and MRI assessments were completed at both baseline and follow-up (additional gait and imaging assessments were conducted	Change in gait velocity over time did not associate with change in total or regional corpus callosum volume over time	age, gender, Rotterdam progression scale score, MTA score, incident lacunes	Not reported

						4 years after baseline)			
3. Moscufo et al. (2012).	Older Adults (n=77), 60% F, age 84 ± 3.9	Walk speed (ms^{-1})	SPPB (2.5m)	WMH volume	MRI: FLAIR	Gait and MRI assessments were completed at both baseline and follow-up (mean duration between assessments was 1.9 ± 0.2 years.)	Change in gait velocity over time did not associate with change in total or regional WMH burden over time	age, gender, mini-mental state score (MMSE), and body mass index (BMI)	Inclusion of all covariates in analyses had no effect on associations
4. Rosano et al. (2005b)	Older Adults (n=2450), 57% F, age 74.4 ± 4.7	Gait velocity (ms^{-1})	Timed walk (15 foot)	Ventricular enlargement, WMH volume, infarcts	MRI: comparison to an atlas of predefined visual standards	Gait and MRI assessments were completed baseline. At follow-up, only gait was re-assessed (mean duration between baseline and follow-up assessments was 4.0 years.)	A greater decline in gait velocity over time associated with greater ventricular enlargement, WMH volume and brain infarcts at baseline	age, sex, race, education, cardiovascular ris factors, cardiovascular disease	Association was made with inclusion of covariates
5. Ryberg et al. (2011)	Older Adults (n=563), 55% F, age 74 ± 5	Gait velocity (ms^{-1})	Timed walk (8m)	Corpus Callosum volume	MRI: automatic segmentation	Gait and MRI assessments were completed baseline. At follow-up, only gait was re-assessed (3 additional assessments of gait were conducted; 1, 2 and 3 years after baseline)	A greater decline in gait velocity over time associated with the interaction between corpus callosum volume at baseline and time; both total corpus callosum volume and regions 2 (Rostral body), 3 (Midbody) and 5 (Splenium)	age, gender, handedness, general atrophy, ARWMC load	Association was made with inclusion of covariates
6. Soumaré et al. (2009)	Older Adults (n=1702), 60.6% F, age 72.4 ± 4.1	Walking speed (ms^{-1})	Chronometer connected to 2 photoelect	WMH volume	MRI: Fully automated software	Gait and MRI assessments were completed baseline. At follow-up, only gait was	A greater decline in gait velocity over time associated with a high number of total and periventricular white	age, gender, education, baseline walking speed, baseline white matter volume, baseline BMI,	Inclusion of all covariates in analyses had no effect on associations

			ric cells (6m)			re-assessed (additional assessments of gait were conducted 8 years after baseline)	matter hyperintensities at baseline.	diabetes, physical activity, psychoactive drug use, lacunar infarcts at baseline	
7. Tian et al. (2017)	Older Adults (n=59), 50.8% F, age 74.8 ± 7.8	Gait velocity (ms-1)	Course walks (6m)	Amyloid beta burden through distribution volume ratio	PET: [11C]PiB	Gait and MRI assessments were completed baseline. At follow-up, only gait was re-assessed (mean duration between baseline and follow-up assessments was 4.7 years.)	A greater decline in gait velocity over time associated with higher amyloid beta burden at baseline, both in the overall cortex and regionally in the dorsolateral prefrontal cortex, putamen and lateral temporal lobe	Age, sex, BMI, cardiovascular risk, APOE ε4 status, memory, depressive symptoms, peripheral arterial disease, processing speed, executive function, cerebrovascular disease ankle–arm index, DSST, TMT-B, and WMH/ICV, repeated measures of CVLT and CES-D.	Adjusting for TMT-B attenuated all associations except that with the putamen. Adjusting for DSST attenuated the association with dorsolateral prefrontal cortex
8. van der Holst et al. (2018)	Older adults (with SVD, n=275) 43.6% F, age 62.9 ± 8.2	Gait velocity (ms-1), Stride length (m), Cadence (steps per minute)	GAITRite (5.6m)	Change in following characteristics: WMH volume, white matter volume, grey matter volume, infarcts, microbleeds, fractional anisotropy, mean diffusivity, axial diffusivity,	MRI: FLAIR, SPM 12 DTI: TBSS	Gait and MRI assessments were completed at both baseline and follow-up (mean duration between assessments was 5.4 ± 0.2 years.)	A reduction in white matter volume was associated with a reduction in stride length. An increase in radial and mean diffusivity was associated with a decline in stride length; a decrease in mean fractional anisotropy related to increased decline of stride length. No other associations with stride length were made. No associations were made between gait velocity or cadence and	Age, sex, follow-up duration, height, and baseline gait characteristic. Additionally, changes in cerebral small vessel disease characteristics for associations related to DTI parameters	Association was made with inclusion of covariates

				radial diffusivity			any of the imaging parameters.		
9. Willey et al. (2013).	Older Adults (n=701), 67,2% F, age 80.3 ± 5.6	Gait velocity (ms^{-1})	Timed walk (4m)	WMH volume	MRI:FLAIR	Gait and MRI assessments were completed baseline. At follow-up, only gait was re-assessed (mean duration between baseline and follow-up assessments was 4.7 ± 0.5 years.)	A decline to slow gait velocity over time associated with large total WMH volume at baseline, as well as WMH volume in the frontal lobe	Age, ethnicity, gender, cardiovascular risk factors, MCI or dementia, silent brain infarcts, gait speed at enrollment, time between assessments	Associations were significant after adjusting for cardiovascular risk factors and silent brain infarcts, however adjustment for other covariates caused associations with WMH in the frontal lobe to be no longer significant
10. Wolfson et al. (2005)	Older Adults (n=14), 36% F, age 81 ± 1.7 (normal mobility), age 84 ± 3.4 (impaired mobility)	Gait velocity (ms^{-1})	SPPB (2.5m)	CSF volume, white matter volume	MRI: Fully automated software	Gait and MRI assessments were completed baseline. At follow-up, only gait was re-assessed (median duration between baseline and follow-up assessments was 20 months)	A change in gait velocity over time associated positively with total white matter volume and negatively with CSF volume at baseline	Age and gait	Not reported
11. Wolfson et al. (2013)	Older Adults (n=67), 61% F, age 81.7 ± 3.9	Gait velocity (ms^{-1})	SPPB (2.5m)	WMH volume	MRI:FLAIR	Gait and MRI assessments were completed at both baseline and follow-up (additional assessments of gait were conducted 4 years after baseline).	A change in gait velocity over time did not associate with either a change in WMH volume over time, or with baseline WMH volume	age, gender, BMI (baseline where appropriate)	Inclusion of all covariates in analyses had no effect

Appendix C. A quality assessment of all studies included in review from largest to smallest study size

Study	Was the research question or objective in this paper clearly stated?	Was the study population clearly specified and defined?	Were withdrawals reported and explained?	Were inclusion and exclusion criteria for participants defined and determined *prior* to the study onset?	Was a sample size justification, power description, or variance and effect estimates provided?	Were the gait measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Were the image analysis techniques utilised, and the associated imaging parameters, valid, reliable and described in sufficient detail?	Were brain regions of interest clearly defined?	Were key potential confounding variables measured and their impact on the outcome(s) statistically adjusted for?	Quality Assessment: Reviewer 1 (J.W.)	Quality Assessment: Reviewer 2 (R.M.A.)
[1] Rosano 2005 (b) (n=2450)	Yes	Yes	J.W. No R.M.A. Yes	Yes	No	No	No	No	Yes	Average (4/9)	Average (5/9)
[2] Verlinden 2016 (n=2330)	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Average (6/9)	Average (6/9)
[3] Soumaré 2009 (n=1702)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Good (7/9)	Good (7/9)
[4] Dumurgier 2012 (n=1623)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good (8/9)	Good (8/9)
[5] Willey 2013 (n=701)	Yes	Yes	No	No	No	No	Yes	J.W. Yes R.M.A. No	Yes	Average (5/9)	Average (4/9)
[6] Baezner 2008 (n=639)	Yes	J.W. Yes R.M.A. No	No	Yes	No	J.W. No R.M.A. Yes	No	No	Yes	Average (4/9)	Average (4/9)
[7] Wennberg 2017 (n=611)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Good (7/9)	Good (7/9)
[8] Ryberg 2011 (n=563)	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Average (6/9)	Average (6/9)
[9] De Laat 2011 (c) (n=485)	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Average (6/9)	Average (6/9)
[10] De Laat 2011 (a) (n=484)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good (8/9)	Good (8/9)
[11] De Laat 2011 (b) (n=429)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good (8/9)	Good (8/9)
[12] De Laat 2012 (n=415)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good (8/9)	Good (8/9)
[13] Choi 2012 (n=377)	Yes	Yes	J.W. No R.M.A. Yes	Yes	No	Yes	Yes	No	Yes	Average (6/9)	Good (7/9)

[14] Holtzer 2015 (n=348)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Good (7/9)	Good (7/9)
[15] Rosano 2007 (b) (n=331)	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Average (6/9)	Average (6/9)
[16] Fredriksen 2011 (n=328)	Yes	Yes	J.W. No R.M.A. Yes	Yes	No	No	Yes	Yes	No	Average (5/9)	Average (6/9)
[17] Rosano 2007 (a) (n=327)	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Average (5/9)	Average (5/9)
[18] Rosano 2005 (a) (n=321)	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Average (6/9)	Average (6/9)
[19] Callisaya 2014 (n=305)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Good (7/9)	Good (7/9)
[20] van der Holst 2018 (n=275)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good (8/9)	Good (8/9)
[21] Rosso 2014 (n=265)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Good (7/9)	Good (7/9)
[22] Rosario 2016 (n=265)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Good (7/9)	Good (7/9)
[23] Bolandzadeh 2014 (n=253)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Average (6/9)	Average (6/9)
[24] Stijntjes 2016 (n=237)	No	Yes	No	No	No	No	Yes	Yes	Yes	Average (4/9)	Average (4/9)
[25] Nadkarni 2014 (n=231)	Yes	Yes	J.W. No R.M.A. Yes	Yes	No	Yes	Yes	Yes	Yes	Good (7/9)	Good (8/9)
[26] Callisaya 2013 (n=225)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good (8/9)	Good (8/9)
[27] Rosano 2008 (n=220)	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Average (6/9)	Average (6/9)
[28] Nadkarni 2017 (n=183)	Yes	J.W. No R.M.A. Yes	Yes	No	No	Yes	Yes	Yes	Yes	Average (6/9)	Good (7/9)
[29] Sakurai 2014 (n=182)	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Average (5/9)	Average (6/9)
[30] Sakurai 2017 (n=149)	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Average (6/9)	Average (6/9)
[31] Murray 2010 (n=148)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Average (6/9)	Average (6/9)
[32] del Campo 2016 (n=128)	Yes	J.W. No R.M.A. Yes	Yes	Yes	No	No	Yes	Yes	Yes	Average (6/9)	Good (7/9)
[33] Annweiler 2014 (n=115)	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Good (7/9)	Good (7/9)
[34] Ezzati 2015 (n=112)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Good (8/9)	Good (8/9)

[35] Manor 2012 (n=89)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Good (7/9)	Good (7/9)
[36] Beauchet 2017 (n=77)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Good (7/9)	Good (7/9)
[37] Moscufo 2012 (n=77)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Good (7/9)	Good (7/9)
[38] Novak 2009 (n=76)	Yes	Yes	No	Yes	No	J.W. No R.M.A. Yes	Yes	Yes	Yes	Average (6/9)	Good (7/9)
[39] Beauchet 2014 (n=71)	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Average (6/9)	Average (6/9)
[40] Wolfson 2013 (n=67)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Average (6/9)	Average (6/9)
[41] Tian 2017 (n=59)	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Average (6/9)	Average (6/9)
[42] Zimmerman 2009 (n=48)	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Average (6/9)	Average (6/9)
[43] Beauchet 2015 (n=47)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Good (7/9)	Good (7/9)
[44] Sorond 2011 (n=42)	Yes	Yes	No	Yes	No	No	No	No	No	Poor (3/9)	Poor (3/9)
[45] Della Nave 2007 (n=36)	J.W. No R.M.A. Yes	Yes	No	No	No	No	Yes	Yes	No	Poor (3/9)	Average (4/9)
[46] Nadkarni 2009 (n=33)	Yes	No	No	Yes	No	Yes	No	Yes	No	Average (4/9)	Average (4/9)
[47] Yuan 2015 (n=30)	Yes	J.W. Yes R.M.A. No	No	Yes	No	Yes	Yes	Yes	No	Average (6/9)	Average (5/9)
[48] Bruijn 2014 (n=25)	Yes	No	No	No	No	Yes	Yes	Yes	No	Average (4/9)	Average (4/9)
[49] Shimada 2013 (n=24)	Yes	No	No	Yes	No	Yes	Yes	Yes	No	Average (5/9)	Average (5/9)
[50] Fling 2018 (n=20)	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Average (5/9)	Average (5/9)
[51] Wolfson 2005 (n=14)	Yes	No	No	Yes	No	No	Yes	No	No	Poor (3/9)	Poor (3/9)
[52] Fling 2016 (n=10)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Good (7/9)	Good (7/9)
TOTAL										20 Good 29 Average 3 Poor	24 Good 26 Average 2 Poor

Appendix D: Geriatric Depression Scale, GDS-15

Subject ID: _____ Date: _____

Choose the best answer for the way you have felt over the last week:

		Please circle:	
1.	Are you basically satisfied with your life?	YES	NO
2.	Have you dropped many of your interests and activities?	YES	NO
3.	Do you feel that your life is empty?	YES	NO
4.	Do you often get bored?	YES	NO
5.	Are you in good spirits most of the time?	YES	NO
6.	Are you afraid that something bad is going to happen to you?	YES	NO
7.	Do you feel happy most of the time?	YES	NO
8.	Do you often feel helpless?	YES	NO
9.	Do you prefer to stay at home, rather than going out and doing new things?	YES	NO
10.	Do you feel that you have more problems with your memory than most?	YES	NO
11.	Do you think that it is wonderful to be alive now?	YES	NO
12.	Do you feel pretty worthless the way you are now?	YES	NO
13.	Do you feel full of energy?	YES	NO
14.	Do you feel that your situation is hopeless?	YES	NO
15.	Do you feel that most people are better off than you are?	YES	NO

Total score:

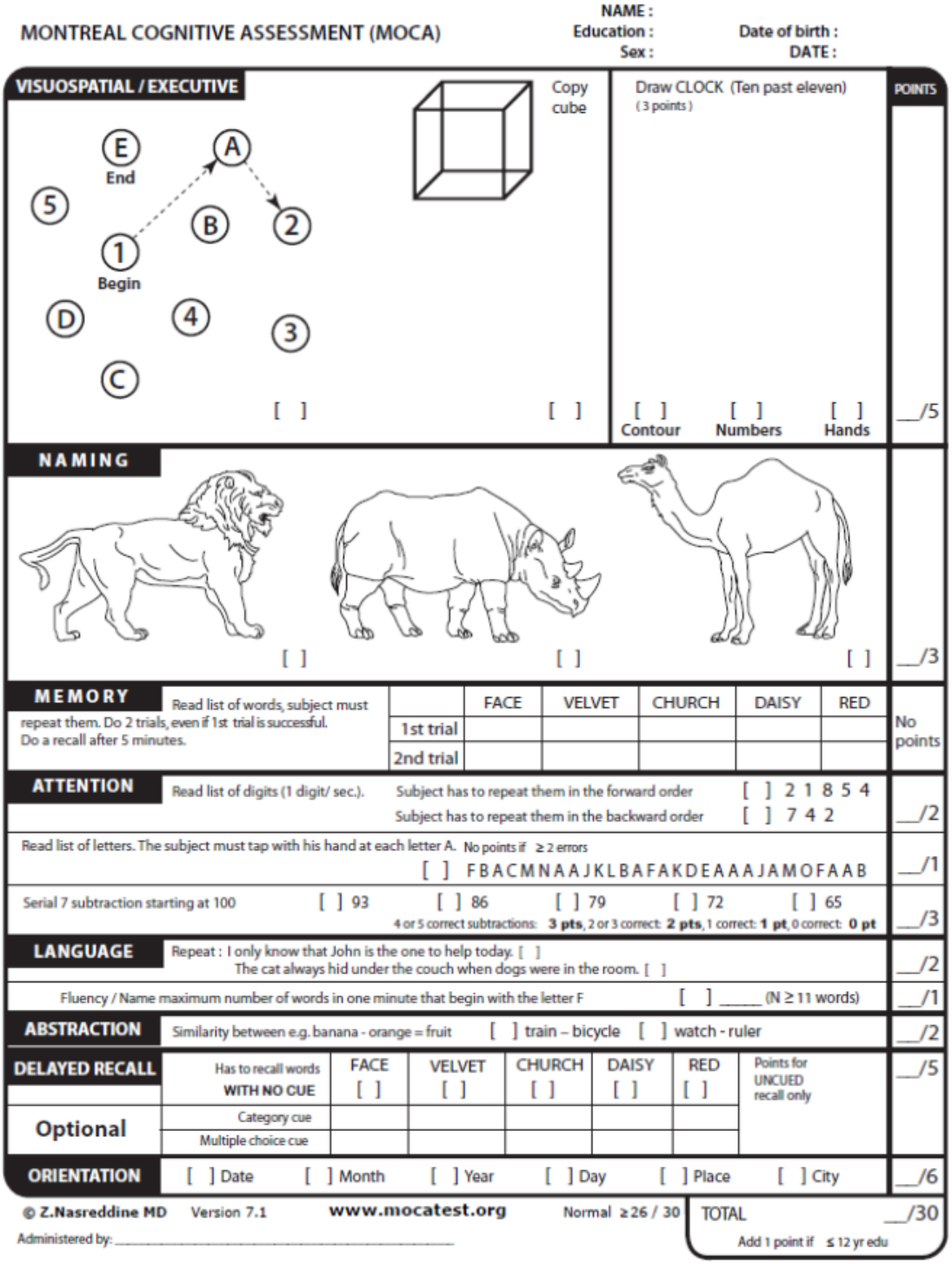
Appendix E: National Adult Reading Test (NART)

National Adult Reading Test (NART)

NAME..... STUDY I.D..... DATE.....

	ERRORS		ERRORS
CHORD	.....	SUPERFLUOUS	.....
ACHE	.....	SIMILE	.....
DEPOT	.....	BANAL	.....
AISLE	.....	QUADRUPED	.....
BOUQUET	.....	CELLIST	.....
PSALM	.....	FACADE	.....
CAPON	.....	ZEALOT	.....
DENY	.....	DRACHM	.....
NAUSEA	.....	AEON	.....
DEBT	.....	PLACEBO	.....
COURTEOUS	.....	ABSTEMIOUS	.....
RAREFY	.....	DETENTE	.....
EQUIVOCAL	.....	IDYLL	.....
NAIVE	.....	PUERPERAL	.....
CATACOMB	.....	AVER	.....
GAOLED	.....	GAUCHE	.....
THYME	.....	TOPIARY	.....
HEIR	.....	LEVIATHAN	.....
RADIX	.....	BEATIFY	.....
ASSIGNATE	.....	PRELATE	.....
HIATUS	.....	SIDEREAL	.....
SUBTLE	.....	DEMESNE	.....
PROCREATE	.....	SYNCOPE	.....
GIST	.....	LABILE	.....
GOUGE	.....	CAMPANILE	.....

Appendix F: Montreal Cognitive Assessment (MoCA)



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Appendix G: Mini Mental State Examination (MMSE)

Scripted MMSE and C.D.T.

Subject and test details

Name		
NHS Number		
Date of birth - Age	/ /	yrs
Assessed by		
Reason assessed		
Date assessed - Time	/ /	:

Introduce yourself and put the patient at ease, for example –

"Do you mind if we do a short memory test? I do one with everyone I see. Some of the questions are easy, some are harder. Everyone makes mistakes so don't worry if you can't answer some of them"

Score 1 for a correct response and 0 for an incorrect response.

1 Orientation

"What year are we in?" *(exact only)*

"What season is this?"

"What month are we in?"

"What is today's date?" *(allow error of one day)*

"What day of the week is it today?" *(exact only)*

"What country are we in?"

"What county are we in?"
(Accept Newcastle, Northumberland or Tyne & Wear)

"What city / town / village are we in?"

"What is this address / the name of this place?"

"Name 2 streets nearby" OR " What floor/ ward is this?"
(Ask the former if at home or the latter if in hospital)

2 Registration *(Allow 3 trials – score first only)*

"I'm going to give you the names of three objects. When I've finished I'd like you to repeat them and then remember them."

Apple (Ball)

Table (Car)

Penny (Man)

3 Attention – concentration

"I would like you to take 7 away from 100."
"Now keep taking 7 away until I tell you to stop."
Record each answer below, awarding one point for each answer which is 7 less than the previous.
(An alternative question for people who have never been able to calculate is - "Can you spell WORLD backwards?")

\- - - -

4 Recall

"What were the names of the three objects I asked you to repeat and remember a little while ago?"

Apple (Ball)

Table (Car)

Penny (Man)

5 Naming

"What is this called?" *(show pen or pencil)*

"What is this called?" *(show watch)*

6 Comprehension

"Can you repeat this phrase 'No ifs, ands or buts'?"

"Can you read and do this?" *(show close your eyes)*

7 Praxis

"Can you copy this drawing?" *(show pentagon)*

"Can you think up & write a complete sentence?"

"Take this paper in your right/left hand, fold it in half with both hands and put it down on your lap."

Takes paper in right /left hand

Folds paper

Lays paper on lap

MMSE Score

8 Clock Drawing Test *(not part of MMSE)*

"Imagine this circle is the face of a clock. Put in all the numbers." "Now set the hands to ten past eleven"

All numbers present

Numbers placed correctly

Hands placed correctly

Comment on any factors which could have influenced performance e.g. sensory deficits or behaviour / mental state / physical state at time of testing.

Appendix H: Movement Disorders Society Unified Parkinson's Disease Rating Scale part three (MDS-UPDRS III)

MDS-UPDRS

The Movement Disorder Society (MDS)-sponsored new version of the UDPRS is founded on the critique that was formulated by the Task Force for Rating Scales in Parkinson's disease (*Mov Disord* 2003;18:738-750). Thereafter, the MDS recruited a Chairperson to organize a program to provide the Movement Disorder community with a new version of the UDPRS that would maintain the overall format of the original UPDRS, but address issues identified in the critique as weaknesses and ambiguities. The Chairperson identified subcommittees with chairs and members. Each part was written by the appropriate subcommittee members and then reviewed and ratified by the entire group. These members are listed below.

The MDS UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living, Part III (motor examination) and Part IV (motor complications). Part I has two components: IA concerning a number of behaviors that are assessed by the investigator with all pertinent information from patients and caregivers and IB that is completed by the patient with or without the aid of the caregiver, but independently of the investigator. It can, however, be reviewed by the rater to ensure that all questions are answered clearly and the rater can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the investigator to ensure completeness and clarity. Of note, the official versions of Part1A, Part1B and Part2 of the MDS-UPDRS do not have separate on or off ratings. However, for individual programs or protocols the same questions can be used separately for on and off. Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater. Part IV has instructions for the rater and also instructions to be read to the patient. This part integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater.

The authors of this new version are:

Chairperson: Christopher G. Goetz
Part I: Werner Poewe (chair), Bruno Dubois, Anette Schrag
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Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

ON is the typical functional state when patients are receiving medication and have a good response.
OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see". Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's Disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on Levodopa ? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

	SCORE
3.1 SPEECH Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables) and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐
3.2 FACIAL EXPRESSION Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling and parting of lips. 0: Normal: Normal facial expression. 1: Slight: Minimal masked facies manifested only by decreased frequency of blinking. 2: Mild: In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted. 3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest. 4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.	☐

	SCORE
3.3 RIGIDITY Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity. 0: Normal: No rigidity. 1: Slight: Rigidity only detected with activation maneuver. 2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved. 3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort. 4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.	☐ Neck ☐ RUE ☐ LUE ☐ RLE ☐ LLE
3.4 FINGER TAPPING Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.5 HAND MOVEMENTS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing c) the amplitude decrements starting after the 1st supination-pronation sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.7 TOE TAPPING Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.8 LEG AGILITY Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.9 ARISING FROM CHAIR Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum up to two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13 0: Normal: No problems. Able to arise quickly without hesitation. 1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. 2: Mild: Pushes self up from arms of chair without difficulty. 3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help. 4: Severe: Unable to arise without help.	☐
3.10 GAIT Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13 0: Normal: No problems. 1: Slight: Independent walking with minor gait impairment. 2: Mild: Independent walking but with substantial gait impairment. 3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person. 4: Severe: Cannot walk at all or only with another person's assistance.	☐

	SCORE
3.11 FREEZING OF GAIT Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment. 0: Normal: No freezing. 1: Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. 2: Mild: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. 3: Moderate: Freezes once during straight walking. 4: Severe: Freezes multiple times during straight walking.	☐
3.12 POSTURAL STABILITY Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13 0: Normal: No problems: Recovers with one or two steps. 1: Slight: 3-5 steps, but subject recovers unaided. 2: Mild: More than 5 steps, but subject recovers unaided. 3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner. 4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	☐

	SCORE
3.13 POSTURE Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking , and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	☐
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA) Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements. 4: Severe: Severe global slowness and poverty of spontaneous movements.	☐
3.15 POSTURAL TREMOR OF THE HANDS Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L

	SCORE
3.16 KINETIC TREMOR OF THE HANDS Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L
3.17 REST TREMOR AMPLITUDE Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor. As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating. Extremity ratings 0: Normal: No tremor. 1: Slight.: < 1 cm in maximal amplitude. 2: Mild: > 1 cm but < 3 cm in maximal amplitude. 3: Moderate: 3 - 10 cm in maximal amplitude. 4: Severe: > 10 cm in maximal amplitude. Lip/Jaw ratings 0: Normal: No tremor. 1: Slight: < 1 cm in maximal amplitude. 2: Mild: > 1 cm but < 2 cm in maximal amplitude. 3: Moderate: > 2 cm but < 3 cm in maximal amplitude. 4: Severe: > 3 cm in maximal amplitude.	☐ RUE ☐ LUE ☐ RLE ☐ LLE ☐ Lip/Jaw

	SCORE
3.18 CONSTANCY OF REST TREMOR Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating. 0: Normal: No tremor. 1: Slight: Tremor at rest is present < 25% of the entire examination period. 2: Mild: Tremor at rest is present 26-50% of the entire examination period. 3: Moderate: Tremor at rest is present 51-75% of the entire examination period. 4: Severe: Tremor at rest is present > 75% of the entire examination period.	☐
DYSKINESIA IMPACT ON PART III RATINGS A. Were dyskinesias (chorea or dystonia) present during examination? ☐ No ☐ Yes B. If yes, did these movements interfere with your ratings? ☐ No ☐ Yes	
HOEHN AND YAHR STAGE 0: Asymptomatic. 1: Unilateral involvement only. 2: Bilateral involvement without impairment of balance. 3: Mile to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test. 4: Severe disability; still able to walk or stand unassisted. 5: Wheelchair bound or bedridden unless aided.	☐

Appendix I. Preliminary analysis of non-linear trajectories of gait change over 72 months

A non-linear term for "time" (quadratic) was included into models of change for each gait characteristic as both a fixed and random effect, thereby enabling trajectories of change to differ between individuals. The inclusion of these terms did not significantly improve model fit for all characteristics (see below); there was not consistent non-linearity.

Comparison of model fit with / without inclusion of non-linear terms:

Gait characteristic	χ^2	***p-value***
Step velocity (m/s)	5.21	0.267
Step length (m)	2.51	0.644
Swing time variability (ms)	**11.6**	**0.021**
Step time variability (ms)	8.43	0.077
Stance time variability (ms)	9.44	0.051
Step velocity variability (m/s)	0.84	0.934
Step length variability (m)	6.95	0.139
Step time (ms)	2.19	0.702
Swing time (ms)	3.18	0.528
Stance time (ms)	2.91	0.573
Step time asymmetry (ms)	**51.8**	**<0.001***
Swing time asymmetry (ms)	**31.8**	**<0.001***
Stance time asymmetry (ms)	**43.6**	**<0.001***
Step length asymmetry (m)	1.33	0.857
Step width (m)	1.08	0.897
Step width variability (m)	6.25	0.182

Notably, modelled change in gait velocity, the global measure of gait, was not improved by the inclusion of non-linear terms in either diagnostic group. Further, the gait characteristics for which non-linear terms did improve model fit (measures of variability and asymmetry) are those characteristics that demonstrate high levels of positive skewness and kurtosis in their distributions amongst study participants. It may be that non-linear terms better describe trajectories of change for participants with particularly large variability or asymmetry and not necessarily the majority; future investigations should explore this in more detail.

Appendix J. The number of participants that completed assessments up until 72 months

Total number of assessments	Time points at which assessments took place					PD frequency	Control frequency
	Baseline	18 months	36 months	54 months	72 months		
1	●					10	54
2	●	●				24	10
	●		●			1	56
	●			●		1	0
3	●	●	●			18	3
	●	●		●		0	1
	●	●			●	1	0
4	●	●	●	●		13	7
	●	●	●		●	2	1
	●	●		●	●	2	1
	●		●	●	●	1	2
5	●	●	●	●	●	46	49
						119	**184**

Appendix K. Descriptive data of gait assessments completed at baseline, 18, 36, 54 and 72 months for PD and control

Gait characteristic	Controls					PD				
	Baseline (n=130)	18 months (n=72)	36 months (n=118)	54 months (n=60)	72 months (n=53)	Baseline (n=109)	18 months (n=106)	36 months (n=81)	54 months (n=63)	72 months (n=52)
Step velocity (m/s)	1.29 (0.17)	1.28 (0.18)	1.28 (0.21)	1.26 (0.20)	1.29 (0.17)	1.13 (0.21)	1.13 (0.23)	1.12 (0.23)	1.13 (0.24)	1.15 (0.25)
Step length (m)	0.69 (0.07)	0.69 (0.08)	0.67 (0.09)	0.68 (0.09)	0.68 (0.08)	0.62 (0.10)	0.61 (0.10)	0.61 (0.11)	0.62 (0.11)	0.62 (0.12)
Swing time variability (ms)	14.3 (4.2)	13.6 (4.8)	13.7 (5.3)	14.1 (4.5)	13.8 (4.5)	17.3 (5.8)	17.4 (9.3)	18.4 (10.1)	17.9 (7.7)	17.5 (8.7)
Step time variability (ms)	15.4 (4.5)	15.1 (6.5)	14.9 (6.7)	15.0 (5.2)	14.2 (5.7)	18.5 (6.4)	19.3 (9.1)	19.8 (9.9)	18.9 (8.4)	19.0 (10.7)
Stance time variability (ms)	18.3 (6.1)	18.3 (8.8)	17.5 (9.5)	18.2 (7.5)	17.7 (8.4)	22.5 (9.3)	24.0 (15.5)	23.6 (11.8)	22.9 (10.7)	23.4 (14.4)
Step velocity variability (m/s)	0.05 (0.01)	0.05 (0.01)	0.05 (0.01)	0.05 (0.01)	0.05 (0.01)	0.05 (0.02)	0.05 (0.01)	0.06 (0.02)	0.06 (0.02)	0.06 (0.02)
Step length variability (m)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.03 (0.01)	0.02 (0.01)	0.02 (0.01)
Step time (ms)	533 (45)	538 (45)	530 (50)	540 (46)	532 (39)	556 (45)	551 (47)	550 (43)	553 (55)	542 (55)
Swing time (ms)	385 (31)	391 (30)	384 (31)	387 (30)	382 (29)	389 (32)	384 (32)	385 (34)	389 (39)	380 (36)
Stance time (ms)	683 (66)	686 (68)	677 (78)	694 (71)	683 (58)	723 (72)	718 (75)	715 (71)	718 (85)	705 (73)
Step time asymmetry (ms)	9.78 (8.17)	12.6 (10.6)	11.7 (10.4)	13.0 (11.3)	13.3 (12.0)	20.6 (25.4)	20.9 (25.8)	21.8 (19.4)	18.1 (17.3)	15.3 (12.8)
Swing time asymmetry (ms)	8.01 (7.84)	9.04 (10.31)	8.28 (8.15)	9.63 (9.04)	9.95 (8.82)	17.0 (20.0)	15.9 (19.6)	15.2 (14.0)	13.9 (12.0)	11.0 (8.7)
Stance time asymmetry (ms)	7.96 (8.12)	9.08 (10.83)	8.08 (8.46)	9.22 (8.70)	9.86 (8.68)	16.6 (19.5)	16.2 (20.0)	15.0 (13.8)	13.9 (11.2)	11.8 (8.0)
Step length asymmetry (m)	0.02 (0.02)	0.02 (0.02)	0.02 (0.02)	0.02 (0.02)	0.02 (0.02)	0.03 (0.02)	0.02 (0.02)	0.03 (0.02)	0.02 (0.02)	0.03 (0.03)
Step width (m)	0.09 (0.02)	0.09 (0.03)	0.09 (0.03)	0.09 (0.03)	0.09 (0.03)	0.09 (0.03)	0.09 (0.03)	0.09 (0.03)	0.09 (0.04)	0.09 (0.04)
Step width variability (m)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.00)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)

[All are displayed as mean (standard deviation).]

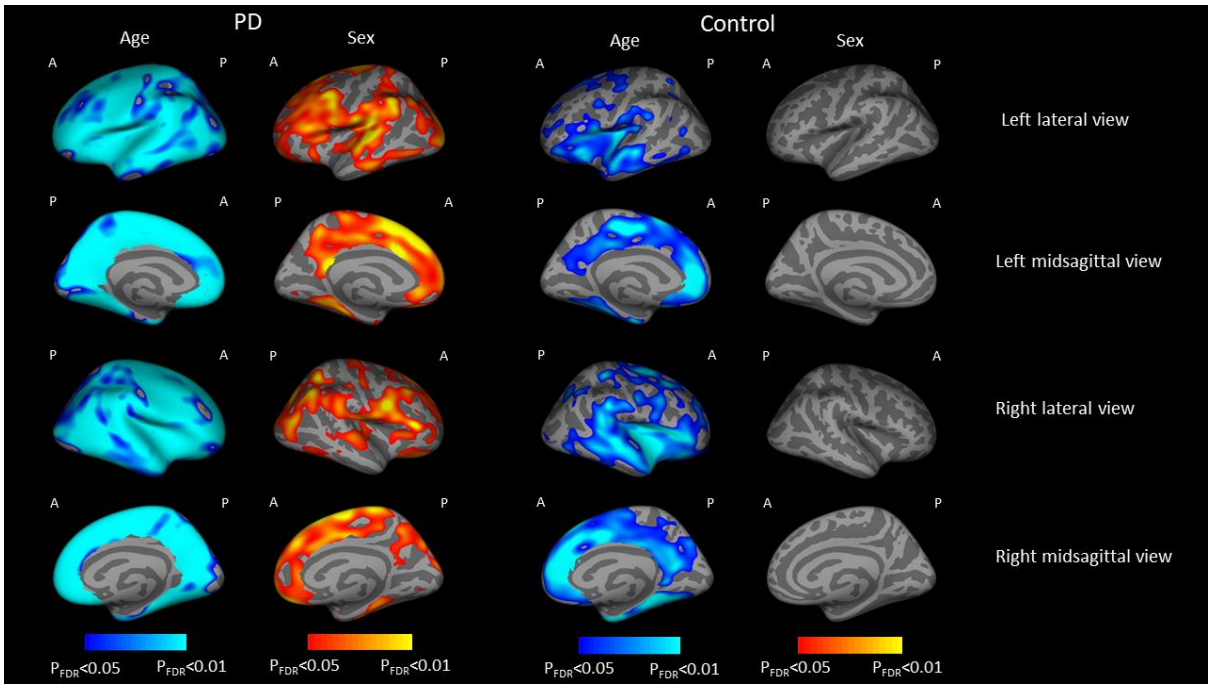
Appendix L. The total number of gait assessments completed by PD and control participants with baseline imaging and gait data available

Total number of assessments	Time points at which assessments took place					PD frequency	Control frequency
	Baseline	18 months	36 months	54 months	72 months		
1	●					7	8
2	●	●				20	3
	●		●			1	0
	●			●		1	0
3	●	●	●			13	1
	●	●		●		0	1
4	●	●	●	●		11	3
	●	●	●		●	2	0
	●	●		●	●	2	0
	●		●	●	●	1	2
5	●	●	●	●	●	41	29
						99	**47**

Appendix M. Gyral regions-of-interest selected *a priori*, with reasons for selection

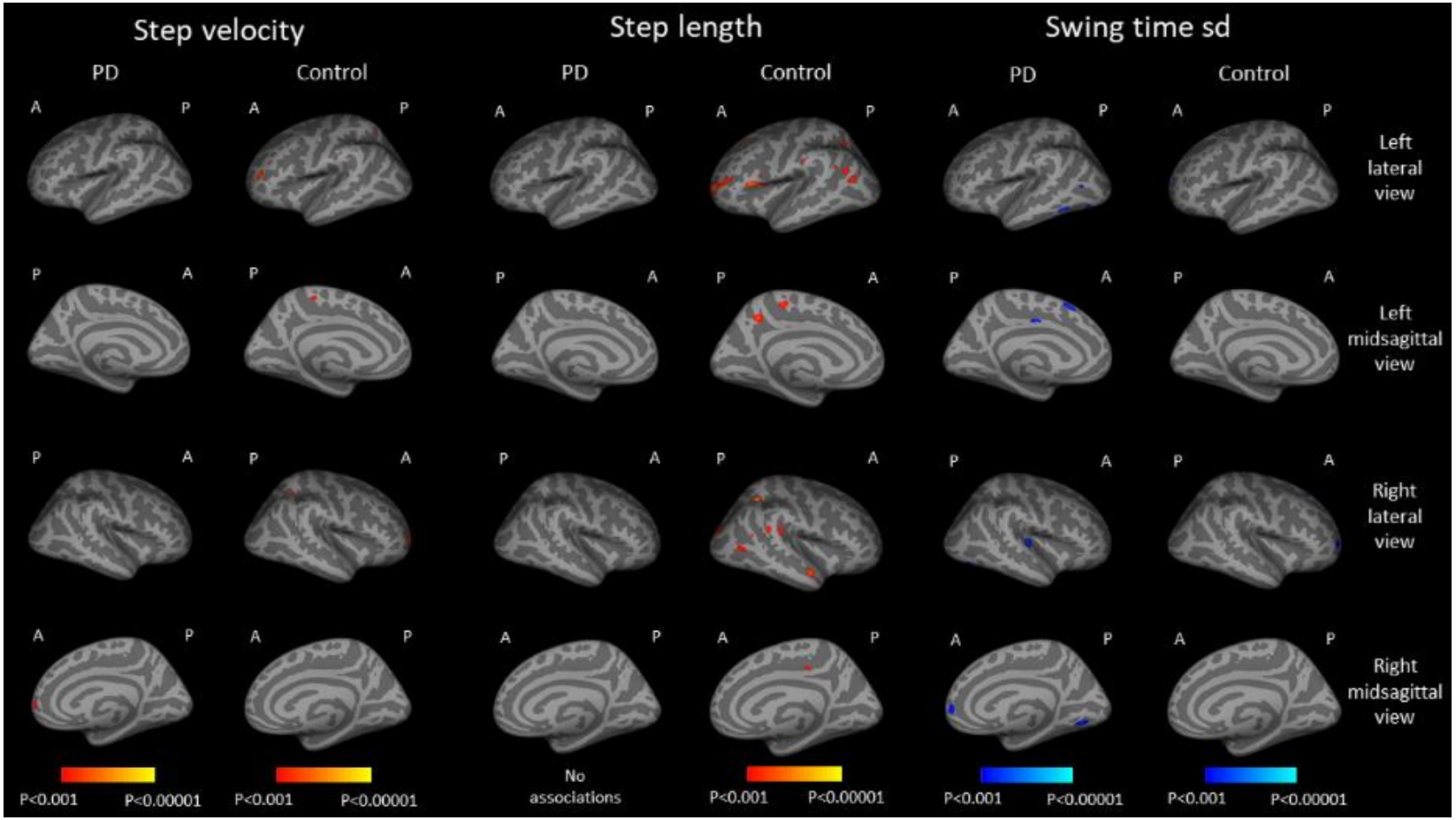
Gyral region	Reason for selection
Precentral	Location of primary motor cortex (Brodmann's area 4). **Motor** output.
Superior frontal	Posterior portion occupied by the supplementary motor area and premotor cortex (Brodmann's area 6). Anterior regions are involved in the planning of complex movements (Brodmann's area 9). **Motor** output.
Caudal middle frontal	Occupied by the supplementary motor area and premotor cortex (Brodmann's area 6). **Motor** output.
Paracentral	Continuation of the precentral and postcentral gyri. **Motor** output.
Postcentral	Location of primary somatosensory cortex (Brodmann's areas 1, 2, 3). Sensory input for **motor** output.
Superior parietal	Involved in many sensory and cognitive processes e.g. somatosensory, motor planning, mental imagery and visuospatial attention (Brodmann's area 5 and 7). Sensory input for **motor** output.
Inferior parietal	Involved in interpreting sensory information e.g. through visuospatial processing (Brodmann's area 39). Sensory input for **motor** output.
Supramarginal	Involved in interpreting sensory information e.g. through motor planning (Brodmann's area 40). Sensory input for **motor** output.
Cuneus	Location of primary visual cortex (Brodmann's area 17). Sensory input for **motor** output.
Pericalcarine	Location of primary visual cortex (Brodmann's area 17). Sensory input for **motor** output.
Insula	Involved in the vestibular system, and therefore self-awareness of body position in space. Sensory input for **motor** output.
Rostral middle frontal	Part of the dorsolateral prefrontal cortex, involved in executive function (Brodmann's area 9, 10). **Non-motor** output.
Medial orbitofrontal	Part of the ventromedial prefrontal cortex, involved in higher-order cognitive tasks (Brodmann's area 11). **Non-motor** output.
Lateral orbitofrontal	Part of the ventromedial prefrontal cortex, involved in higher-order cognitive tasks (Brodmann's area 11). **Non-motor** output.
Rostral anterior cingulate	Associated with higher-order cognitive tasks (Brodmann's area 32). **Non-motor** output.
Caudal anterior cingulate	Associated with higher-order cognitive tasks (Brodmann's area 24). **Non-motor** output.
Entorhinal	Involved in spatial navigation (Brodmann's areas 28, 34). **Non-motor** output.

Appendix N. Cortical thickness associations with age and sex, for PD and control groups

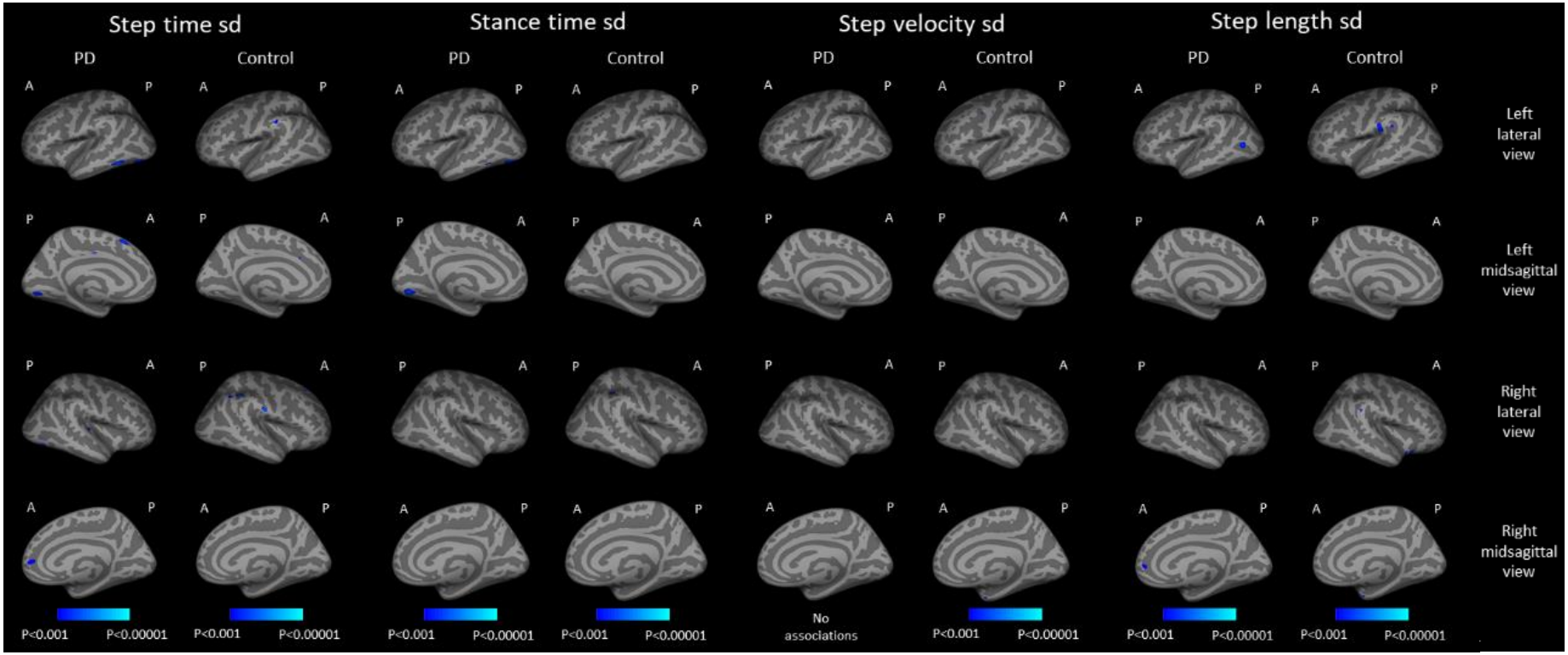


[A=anterior, P=posterior, FDR=False Discovery Rate. Brighter colours represent areas of stronger associations. Blue indicates a negative correlation between age and cortical thickness. Red indicates increased thinning in men compared to women.]

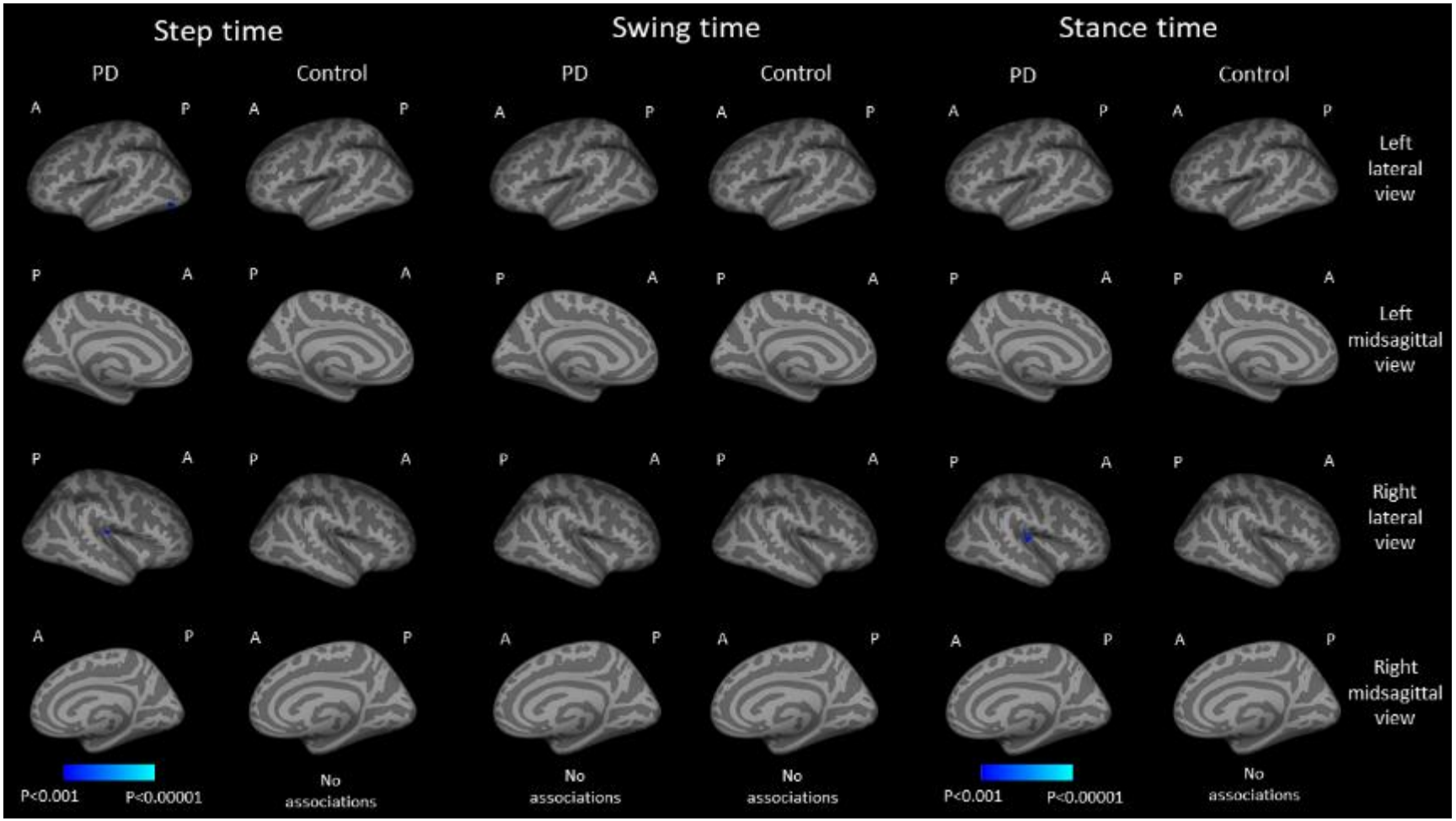
Appendix O. Location of cross-sectional associations between cortical thickness and discrete gait characteristics identified through a data-driven approach



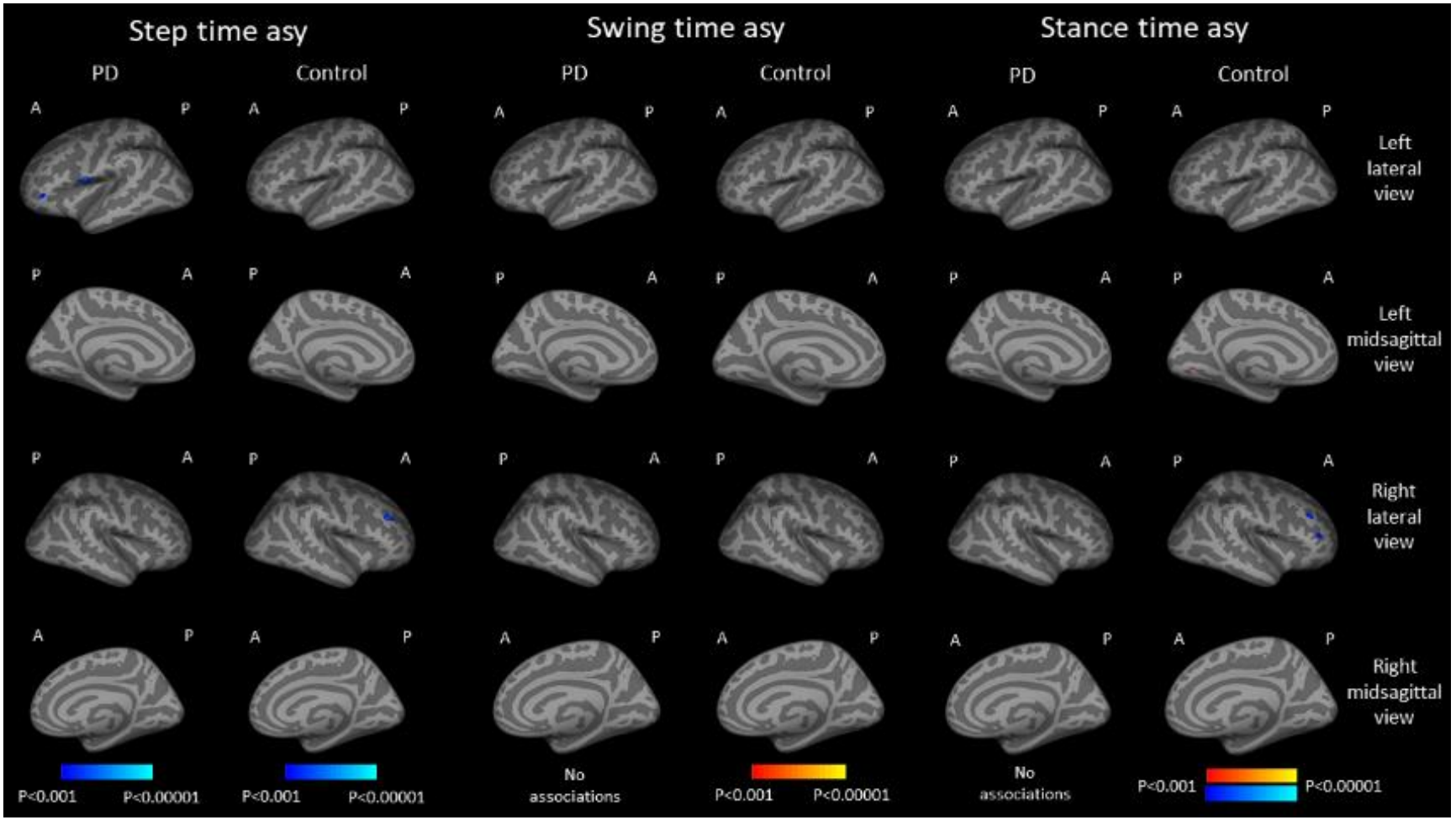
[a. Gait characteristics from the pace domain of gait. A = Anterior, P = Posterior, sd=standard deviation (variability). Results are uncorrected for multiple comparisons. Red indicates a positive correlation between gait and cortical thickness, blue indicates a negative correlation. Brighter colours indicate stronger associations.]



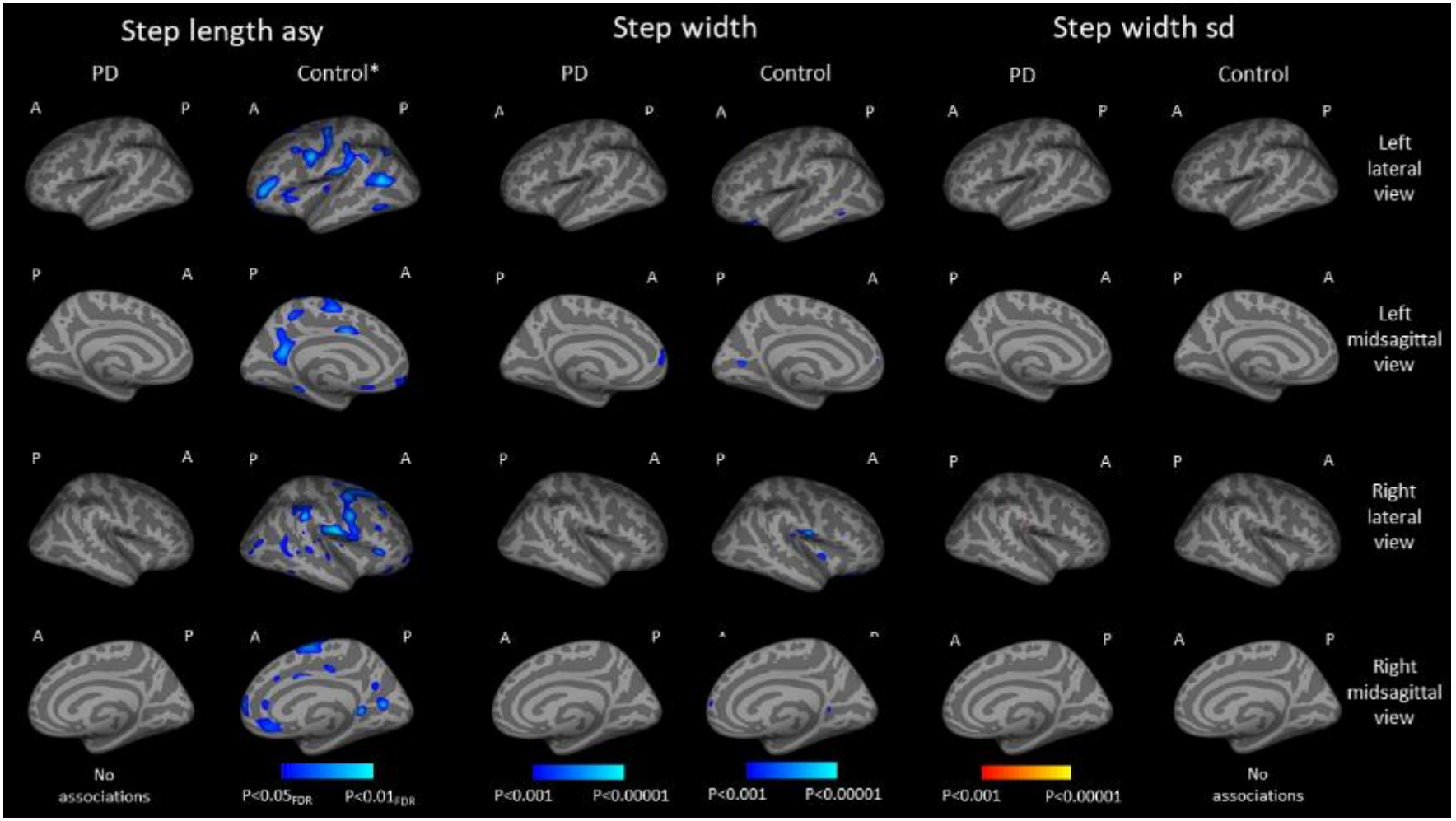
[b. Gait characteristics from the variability domain of gait. A = Anterior, P = Posterior, sd=standard deviation (variability). Results are uncorrected for multiple comparisons. Blue indicates a negative correlation between gait and cortical thickness. Brighter colours indicate stronger associations.]



[c. Gait characteristics from the rhythm domain of gait. A = Anterior, P = Posterior. Results are uncorrected for multiple comparisons. Blue indicates a negative correlation between gait and cortical thickness. Brighter colours indicate stronger associations.]



[d. Gait characteristics from the asymmetry domain of gait. A = Anterior, P = Posterior, asy=asymmetry. Results are uncorrected for multiple comparisons. Red indicates a positive correlation between gait and cortical thickness, blue indicates a negative correlation. Brighter colours indicate stronger associations.]



[e. Gait characteristics from the postural control domain of gait. A = Anterior, P = Posterior, asy=asymmetry, FDR = False Discover Rate. * indicates associations that survived FDR correction; all other results are uncorrected for multiple comparisons. Red indicates a positive correlation between gait and cortical thickness, blue indicates a negative correlation. Brighter colours indicate stronger associations.]

Appendix P. Location and peak vertex significance of all associations between cortical thickness and gait for each group

Group	Gait characteristic	Cluster location	x	y	z	NVtxs	Area (mm^2)	$-log_{10}P$
PD	**Step velocity**	Right Superior frontal	9.7	56.9	4.8	110	94	3.33
	Step length	N/A	-	-	-	-	-	-
	Swing time sd	Left Superior frontal	-7.0	19.8	55.9	201	109	-3.62
		Left Inferior temporal	-53.0	-54.1	-17.2	162	124	-3.57
		Left Posterior cingulate	-5.3	-11.0	39.6	114	45	-3.42
		Left Lateral occipital	-40.5	-75.0	-11.2	73	47	-3.23
		Left Inferior parietal	-42.0	-65.2	6.5	40	19	-3.13
		Left Precentral	-31.5	-6.4	43.7	20	8	-3.04
		Right Transverse temporal	48.0	-21.0	7.2	411	157	-3.83
		Right Fusiform	41.6	-72.6	-15.3	118	97	-3.45
		Right Lingual	16.2	-72.2	-6.1	251	241	-3.40
		Right Superior frontal	12.0	52.0	3.0	159	119	-3.28
	Step time sd	Left Lateral occipital	-40.1	-76.5	-12.8	313	218	-3.78
		Left Inferior temporal	-53.6	-55.0	-16.9	267	201	-3.73
		Left Superior frontal	-7.3	21.4	53.9	166	93	-3.54
		Left Lingual	-12.9	-81.1	-10.8	237	259	-3.47
		Left Posterior cingulate	-4.6	-11.4	38.8	39	15	-3.18
		Right Lateral occipital	42.8	-72.6	-15.4	131	111	-3.58
		Right Transverse temporal	48.7	-20.6	6.7	96	36	-3.21
		Right Superior frontal	14.7	46.4	4.8	131	73	-3.09
	Stance time sd	Left Lateral occipital	-39.9	-76.6	-13.1	393	279	-3.96
		Left Lingual	-14.0	-79.7	-9.4	380	392	-3.85
		Left Inferior temporal	-53.6	-55	-16.9	50	37	-3.11
	Step velocity sd	N/A	-	-	-	-	-	-
	Step length sd	Left Superior frontal	14.8	45.5	2.5	74	41	-3.07
		Right Lateral occipital	-40.8	-66.5	5.4	182	96	-3.52
	Step time	Left Lateral occipital	-43.2	-74.9	-9.6	141	100	-3.42
		Right Superior frontal	14.3	-8.0	64.9	242	121	-3.92
		Right Insula	32.2	-28.0	18.6	227	66	-3.28
	Swing time	N/A	-	-	-	-	-	-
	Stance time	Right Insula	32.1	-28.4	16.1	569	169	-3.68
		Right Superior frontal	14.0	-7.6	65.6	92	48	-3.36
		Right Precentral	49.2	5.1	12.8	6	3	-3.01
	Step time asy	Left Precentral	-56.7	1.6	6.7	671	265	-4.32
		Left Pars triangularis	-47.7	35.6	-4.4	97	51	-3.27
	Swing time asy	N/A	-	-	-	-	-	-
	Stance time asy	N/A	-	-	-	-	-	-
	Step length asy	N/A	-	-	-	-	-	-
	Step width	Left Superior frontal	-9.1	57.2	14.1	286	180	-3.31
		Right Inferior temporal	50.4	-20.0	-31.3	116	78	-3.39
	Step width sd	Right Supramarginal	59.4	-19.9	21.0	22	7	3.07
Control	**Step velocity**	Left Rostral middle frontal	-36.9	44.6	12.5	184	122	3.74
		Left Paracentral	-7.3	-33.4	52.5	75	30	3.23
		Left Superior parietal	-24.1	-59.8	50.5	68	27	3.22
		Left Superior frontal	-16.4	26.0	50.3	35	29	3.18
		Left Supramarginal	-57.0	-24.7	26.6	26	10	3.07
		Right Rostral middle frontal	22.7	53.3	2.2	300	208	3.97
		Right Superior parietal	30.2	-51.0	39.2	227	82	3.50
	Step length	Left Superior frontal	-17.2	25.8	50.8	278	193	4.43
		Left Rostral middle frontal	-26.0	48.1	2.9	567	344	4.32
		Left Pars opercularis	-47.9	20.1	9.9	542	277	4.07
		Left Precuneus	-9.9	-52.4	42.7	220	113	3.60
		Left Inferior parietal	-37.8	-60.2	20.7	167	78	3.46
		Left Paracentral	-8.6	-32.3	51.3	186	73	3.44
		Left Inferior parietal	-40.8	-67.7	12.4	182	78	3.42
		Left Superior parietal	-26.5	-60.4	45.7	151	57	3.30
		Left Superior parietal	-29.7	-57.3	37.6	70	27	3.29

Control	**Step length**	Left Temporal pole	-35.1	4.0	-37.4	71	48	3.20
		Left Supramarginal	-57.0	-25.4	27.2	55	22	3.18
		Left Supramarginal	-51.3	-54.3	23.3	51	21	3.14
		Left Pars opercularis	-46.6	10.2	15.9	41	22	3.08
		Left Inferior temporal	-46.7	-40.2	-22.2	10	6	3.01
		Left Rostral middle frontal	-23.1	45.8	18.5	2	1	3.01
		Left Superior parietal	30.2	-51.7	39.4	397	149	4.72
		Left Superior temporal	50.1	-3.7	-18.2	242	142	3.89
		Left Lateral occipital	24.3	-85.8	16.3	214	146	3.55
		Left Supramarginal	53.4	-36.6	18.1	237	109	3.48
		Right Supramarginal	57.1	-43.3	18.1	171	83	3.46
		Right Temporal pole	36.4	3.7	-28.2	52	24	3.25
		Right Lateral occipital	43.3	-63.5	4.3	152	74	3.21
		Right Posterior cingulate	13.9	-28.9	36.5	75	27	3.19
		Right Superior frontal	22.1	27.6	44.5	49	34	3.15
		Right Supramarginal	51.7	-36.4	31.7	39	13	3.14
		Right Inferior parietal	50.0	-57.1	15.6	36	17	3.07
		Right Supramarginal	47.7	-40.2	39.4	11	5	3.02
		Right Posterior cingulate	10.3	-4.0	42.6	1	<1	3.00
	Swing time sd	Left Rostral middle frontal	-23.6	49.6	13.3	32	23	-3.08
		Left Medial orbitofrontal	-8.3	52.2	-5.5	14	13	-3.05
		Left Supramarginal	-55.9	-33.2	39.2	15	6	-3.04
		Right Rostral middle frontal	24.4	49.4	4.1	167	101	-3.24
		Right Superior frontal	20.8	26.9	46.7	46	32	-3.18
	Step time sd	Left Supramarginal	-61.6	-31.3	33.6	104	40	-3.15
		Left Caudal anterior cingulate	-12.1	20.2	29.5	8	3	-3.03
		Right Supramarginal	42.3	-43.3	35.2	312	108	-3.98
		Right Postcentral	60.1	-18.1	24.1	173	65	-3.94
		Right Inferior parietal	47.7	-55.9	45.1	148	64	-3.29
		Right Superior frontal	21.8	27.3	45.2	44	30	-3.18
		Right Rostral middle frontal	23.7	50.7	2.1	18	11	-3.05
	Stance time sd	Left Superior parietal	-24.2	-59.6	49.6	22	9	-3.13
		Right Supramarginal	41.3	-43.0	34.9	161	55	-3.57
	Step velocity sd	Left Precentral	-40.5	1.1	39.9	21	12	-3.05
		Right Temporal pole	32.4	2.8	-28.9	33	16	-3.28
		Right Entorhinal	26.4	1.7	-34.3	64	32	-3.149
	Step length sd	Left Supramarginal	-53.8	-25.9	20.3	368	158	-3.41
		Left Supramarginal	-50.1	-40.1	29.0	68	32	-3.19
		Right Temporal pole	31.0	3.2	-30.1	137	71	-3.83
		Right Insula	28.2	13.7	-14.5	202	69	-3.74
		Right Insula	36.0	5.1	-15.7	107	42	-3.32
		Right Supramarginal	59.9	-40.4	26.9	34	18	-3.14
		Right Lateral orbitofrontal	19.3	12.0	-16.4	6	2	-3.03
	Step time	N/A	-	-	-	-	-	-
	Swing time	N/A	-	-	-	-	-	-
	Stance time	N/A	-	-	-	-	-	-
	Step time asy	Right Rostral middle frontal	41.9	31.3	30.6	290	178	-3.93
	Swing time asy	Left Paracentral	-5.3	-41.4	70.9	48	17	3.19
	Stance time asy	Left Lateral occipital	-26.0	-95.1	-16.0	34	24	-3.30
		Left Lingual	-5.7	-74.8	0.0	36	27	3.18
		Right Rostral middle frontal	42.5	29.7	30.9	168	105	-3.57
		Right Rostral middle frontal	36.2	37.5	8.7	112	55	-3.26
	Step length asymmetry*	Left Inferior parietal	-46.3	-60.0	11.1	1641	779	-4.40
		Left Precentral	-52.9	0.3	33.0	9 3482	1595	-4.34
		Left Rostral middle frontal	-37.3	41.2	0.6	1291	955	-4.21
		Left Lateral orbitofrontal	-15.2	54.1	-15.0	6 1583	1218	-3.92
		Left Precuneus	-5.1	-57.4	15.6	2036	931	-3.92
		Left Supramarginal	-51.0	-24.0	22.0	0 2820	1203	-3.82
		Left Posterior cingulate	-4.9	2.3	37.5	471	190	-3.74
		Left Inferior parietal	-39.3	-67.1	46.0	641	308	-3.70
		Left Postcentral	-8.6	-38.3	74.2	468	199	-3.49
		Left Superior frontal	-7.2	-14.8	55.9	1414	588	-3.36

Control	**Step length asymmetry***	Left Precuneus	-7.7	-46.7	50.3	458	190	-3.08
		Left Inferior temporal	-50.0	-59.4	-9.1	366	220	-3.08
		Left Parahippocampal	-28.9	-40.0	-11.1	318	152	-2.96
		Left Fusiform	-29.3	-79.8	-9.8	532	416	-2.88
		Left Superior frontal	-17.5	16.6	57.7	292	193	-2.88
		Left Lateral orbitofrontal	-28.3	23.5	1.5	807	286	-2.80
		Left Insula	-35.0	-24.7	0.3	218	93	-2.54
		Left Superior parietal	-12.6	-91.8	23.6	126	101	-2.52
		Left Precentral	-48.5	-0.6	8.1	151	67	-2.52
		Left Medial orbitofrontal	-6.9	23.3	-15.7	200	110	-2.51
		Left Lateral orbitofrontal	-24.9	14.5	-20.5	122	45	-2.43
		Left Superior frontal	-20.0	-5.4	57.9	70	34	-2.32
		Left Superior temporal	-64.1	-26	4.9	12	4	-2.24
		Right Postcentral	61.5	-11.5	16.0	5 8946	4354	-5.20
		Right Supramarginal	59.5	-38.1	36.3	1944	918	-4.15
		Right Isthmus cingulate	16.2	-49.8	4.7	519	193	-4.06
		Right Pericalcarine	19.9	-67.3	8.3	508	286	-3.87
		Right Pars triangularis	42.0	29.8	2.2	439	227	-3.61
		Right Posterior cingulate	4.6	3.8	37.8	180	81	-3.25
		Right Rostral middle frontal	31.4	29.8	38.4	257	131	-3.22
		Right Superior frontal	10.4	58.0	11.2	477	363	-3.08
		Right Precentral	25.9	-14.0	56.2	298	138	-2.93
		Right Medial orbitofrontal	9.7	31.1	-11.7	592	285	-2.92
		Right Posterior cingulate	12.4	-22.5	37.3	252	95	-2.83
		Right Superior parietal	15.5	-63.8	58.8	97	47	-2.77
		Right Lateral occipital	46.2	-75.6	9.5	292	218	-2.75
		Right Inferior temporal	45.3	-38.5	-18.8	167	76	-2.68
		Right Middle temporal	52.5	-58.6	5.7	613	325	-2.65
		Right Superior temporal	54.4	-31.8	1.8	290	123	-2.65
		Right Superior temporal	64.1	-12.0	-0.6	183	74	-2.61
		Right Precuneus	6.9	-63.8	25.9	219	111	-2.58
		Right Rostral middle frontal	20.1	57.7	-2.7	343	260	-2.58
		Right Rostral anterior cing.	7.5	37.5	8.0	135	83	-2.58
		Right Rostral middle frontal	42.9	26.6	24.6	160	86	-2.57
		Right Lateral orbitofrontal	27.9	34.1	-7.5	187	92	-2.53
		Right Superior frontal	13.8	24.5	31.8	145	57	-2.51
		Right Inferior temporal	54.7	-51.3	-18.7	83	58	-2.47
		Right Isthmus cingulate	8.7	-45.3	23.1	4	1	-2.45
		Right Lateral orbitofrontal	17.5	23.9	-22.1	55	35	-2.40
		Right Banks of the STS	52.9	-43.3	-1.5	80	36	-2.37
		Right Lateral occipital	25.4	-96.0	-13.7	39	29	-2.36
		Right Superior temporal	43.9	-30.7	8.1	69	30	-2.34
		Right Insula	33.9	-11.2	11.4	55	22	-2.34
		Right Supramarginal	63.0	-39.5	16.6	41	17	-2.32
		Right Superior temporal	60.5	-29.2	7.3	36	19	-2.30
		Right Precentral	16.8	-21.6	70.5	2	1	-2.27
	Step width	Left Inferior temporal	-39.7	-7.2	-39.2	369	230	-4.19
		Left Pericalcarine	-22.1	-73.8	4.7	278	110	-3.70
		Left Superior frontal	-19.3	34.8	48.0	161	99	-3.64
		Left Lateral orbitofrontal	-27.4	23.2	-19.8	379	185	-3.64
		Left Inferior temporal	-54.1	-58.2	-9.1	73	47	-3.29
		Left Superior frontal	-10.5	52.3	9.6	14	10	-3.05
		Right Postcentral	58.6	-10.8	13.1	622	243	-4.74
		Right Lateral orbitofrontal	21.0	28.4	-12.8	325	178	-4.04
		Right Insula	37.6	-3.9	-0.7	227	106	-3.44
		Right Supramarginal	37.1	-31.1	21.8	190	66	-3.40
		Right Isthmus cingulate	19.4	-51.7	6.0	94	40	-3.18
		Right Superior frontal	11.0	54.0	11.0	66	54	-3.13
		Right Superior frontal	14.7	23.7	53.2	3	2	-3.01
	Step width sd	N/A	-	-	-	-	-	-

[* signifies associations that survived multiple comparison correction. All other reported cluster-wise associations are uncorrected, $p<0.001$ ($-\log_{10}P > 3$). sd = standard deviation; asy = asymmetry.]

Appendix Q. Partial correlations (accounting for age and sex) between average regional cortical thickness and gait at baseline, in the PD group

	Step velocity (m/s)	**Step length** (m)	**Swing time sd** (ms)	**Step time sd** (ms)	**Stance time sd** (ms)	**Step velocity sd** (m/s)	**Step length sd** (m)	**Step time** (ms)	**Swing time** (ms)	**Stance time** (ms)	**Step time asy** (ms)	**Swing time asy** (ms)	**Stance time asy** (ms)	**Step length asy** (m)	**Step width** (m)	**Step width sd** (m)
L Superior Frontal	0.14 (0.171)	0.08 (0.458)	***-0.21 (0.039)***	-0.18 (0.072)	-0.18 (0.083)	-0.14 (0.167)	***-0.23 (0.023)***	-0.19 (0.067)	-0.11 (0.298)	-0.19 (0.060)	-0.17 (0.101)	-0.04 (0.709)	-0.07 (0.523)	-0.04 (0.699)	***-0.21 (0.037)***	0.04 (0.699)
L Rostral Middle Frontal	0.08 (0.451)	0.05 (0.617)	-0.12 (0.242)	-0.08 (0.411)	-0.08 (0.456)	-0.04 (0.679)	-0.12 (0.245)	-0.10 (0.348)	-0.05 (0.637)	-0.10 (0.327)	-0.12 (0.249)	0.01 (0.899)	<0.01 (<0.001)	0.03 (0.780)	***-0.20 (0.048)***	0.02 (0.870)
L Caudal Middle Frontal	0.15 (0.155)	0.08 (0.453)	***-0.21 (0.042)***	-0.19 (0.069)	***-0.21 (0.041)***	-0.19 (0.066)	***-0.21 (0.039)***	***-0.21 (0.042)***	***-0.21 (0.038)***	-0.17 (0.094)	***-0.20 (0.045)***	-0.11 (0.280)	-0.12 (0.226)	0.05 (0.639)	-0.05 (0.609)	0.08 (0.456)
L Lateral Orbitofrontal	0.18 (0.081)	0.14 (0.170)	-0.15 (0.154)	-0.11 (0.271)	-0.09 (0.375)	-0.02 (0.841)	-0.15 (0.154)	-0.15 (0.150)	-0.06 (0.542)	-0.16 (0.117)	-0.08 (0.467)	0.01 (0.961)	0.01 (0.942)	-0.02 (0.823)	***-0.21 (0.036)***	0.03 (0.740)
L Medial Orbitofrontal	***0.20 (0.048)***	0.13 (0.223)	-0.17 (0.092)	-0.18 (0.087)	-0.18 (0.086)	-0.03 (0.750)	-0.18 (0.079)	***-0.21 (0.040)***	-0.09 (0.392)	***-0.23 (0.025)***	-0.09 (0.393)	0.02 (0.854)	-0.01 (0.950)	<0.01 (0.980)	-0.16 (0.118)	-0.02 (0.822)
L Precentral	0.14 (0.164)	0.07 (0.507)	***-0.22 (0.029)***	***-0.21 (0.042)***	***-0.21 (0.038)***	-0.12 (0.234)	-0.18 (0.074)	***-0.21 (0.044)***	-0.17 (0.105)	-0.19 (0.064)	-0.15 (0.146)	-0.13 (0.200)	-0.15 (0.134)	-0.11 (0.298)	-0.09 (0.382)	-0.03 (0.779)
L Paracentral	0.11 (0.282)	0.09 (0.394)	-0.13 (0.215)	-0.15 (0.147)	-0.15 (0.148)	-0.08 (0.456)	-0.13 (0.196)	-0.11 (0.297)	-0.03 (0.753)	-0.12 (0.238)	-0.12 (0.231)	-0.13 (0.224)	-0.15 (0.157)	-0.12 (0.234)	-0.11 (0.305)	0.01 (0.898)
L Superior parietal	0.04 (0.701)	0.02 (0.880)	-0.13 (0.205)	-0.08 (0.436)	-0.08 (0.461)	-0.03 (0.805)	-0.08 (0.439)	-0.07 (0.488)	-0.08 (0.434)	-0.06 (0.587)	-0.10 (0.325)	-0.04 (0.682)	-0.08 (0.414)	0.07 (0.475)	-0.12 (0.255)	<0.01 (0.991)
L Inferior Parietal	0.15 (0.136)	0.13 (0.206)	-0.16 (0.108)	-0.11 (0.276)	-0.12 (0.248)	-0.10 (0.310)	-0.19 (0.070)	-0.12 (0.237)	-0.07 (0.473)	-0.12 (0.230)	-0.18 (0.078)	-0.05 (0.600)	-0.06 (0.541)	0.13 (0.222)	-0.18 (0.075)	0.14 (0.178)
L Supramarginal	0.11 (0.304)	0.07 (0.472)	-0.14 (0.175)	-0.12 (0.236)	-0.13 (0.215)	-0.11 (0.276)	-0.14 (0.168)	-0.12 (0.239)	-0.09 (0.372)	-0.11 (0.275)	***-0.22 (0.033)***	-0.04 (0.683)	-0.06 (0.564)	-<0.01 (0.967)	-0.09 (0.408)	0.13 (0.202)
L Postcentral	0.11 (0.291)	0.08 (0.419)	-0.18 (0.084)	-0.15 (0.134)	-0.15 (0.143)	-0.15 (0.134)	-0.10 (0.335)	-0.10 (0.335)	-0.08 (0.448)	-0.09 (0.367)	***-0.26 (0.009)***	-0.18 (0.083)	***-0.21 (0.040)***	0.06 (0.532)	-0.12 (0.234)	0.04 (0.702)
L Entorhinal	0.14 (0.184)	0.14 (0.188)	-0.10 (0.348)	-0.11 (0.291)	-0.11 (0.283)	-0.12 (0.251)	-0.19 (0.070)	-0.06 (0.539)	<0.01 (0.970)	-0.08 (0.436)	-0.04 (0.724)	-0.05 (0.663)	-0.04 (0.724)	-0.03 (0.795)	-0.10 (0.351)	-0.01 (0.915)
L cuneus	***0.31 (0.002)***	***0.29 (0.004)***	***-0.31 (0.002)***	***-0.35 (0.001)***	***-0.37 (<0.001)***	-0.17 (0.104)	***-0.30 (0.003)***	-0.18 (0.074)	0.01 (0.934)	***-0.23 (0.023)***	-0.11 (0.282)	-0.17 (0.101)	-0.20 (0.056)	-0.19 (0.064)	-0.12 (0.229)	0.05 (0.600)

L Pericalcarine	0.09 (0.379)	0.04 (0.693)	-0.16 (0.116)	***-0.22 (0.030)***	-0.18 (0.072)	-0.11 (0.294)	-0.20 (0.054)	-0.11 (0.280)	-0.02 (0.843)	-0.13 (0.198)	-0.14 (0.180)	-0.16 (0.130)	-0.16 (0.110)	***-0.22 (0.035)***	-0.11 (0.299)	-0.06 (0.545)
L Rostral Anterior Cingulate	0.08 (0.435)	0.02 (0.848)	-0.10 (0.318)	-0.09 (0.382)	-0.11 (0.288)	-0.05 (0.613)	-0.14 (0.186)	-0.13 (0.222)	-0.07 (0.492)	-0.13 (0.201)	-0.04 (0.737)	0.02 (0.858)	-0.01 (0.937)	-0.04 (0.731)	-0.13 (0.215)	0.04 (0.711)
L Caudal Anterior Cingulate	0.12 (0.249)	0.07 (0.508)	-0.08 (0.424)	-0.09 (0.371)	-0.13 (0.194)	-0.07 (0.487)	-0.14 (0.168)	-0.13 (0.198)	-0.06 (0.531)	-0.14 (0.171)	-0.01 (0.955)	0.09 (0.406)	0.06 (0.550)	-0.09 (0.392)	-0.11 (0.284)	0.1 (0.348)
L Insula	0.15 (0.155)	0.06 (0.544)	***-0.22 (0.034)***	-0.17 (0.092)	-0.15 (0.138)	-0.11 (0.306)	-0.16 (0.120)	***-0.21 (0.039)***	-0.16 (0.121)	***-0.20 (0.049)***	-0.14 (0.175)	-0.04 (0.677)	-0.06 (0.590)	-0.04 (0.693)	-0.15 (0.137)	0.09 (0.386)
R Superior Frontal	0.18 (0.084)	0.10 (0.340)	-0.18 (0.080)	-0.18 (0.081)	-0.18 (0.080)	-0.14 (0.163)	-0.20 (0.055)	***-0.22 (0.032)***	-0.14 (0.168)	***-0.22 (0.031)***	-0.19 (0.068)	-0.08 (0.459)	-0.09 (0.367)	-0.03 (0.779)	-0.11 (0.272)	0.12 (0.246)
R Rostral Middle Frontal	0.08 (0.419)	0.03 (0.763)	-0.12 (0.232)	-0.11 (0.299)	-0.09 (0.362)	-0.05 (0.655)	-0.12 (0.241)	-0.12 (0.234)	-0.04 (0.680)	-0.14 (0.176)	-0.13 (0.211)	-0.01 (0.926)	0.01 (0.959)	0.02 (0.868)	-0.15 (0.140)	<0.01 (0.983)
R Caudal Middle Frontal	0.17 (0.097)	0.09 (0.406)	***-0.24 (0.020)***	-0.19 (0.059)	-0.18 (0.076)	-0.09 (0.397)	-0.15 (0.154)	***-0.25 (0.014)***	***-0.21 (0.043)***	***-0.23 (0.023)***	***-0.26 (0.009)***	-0.16 (0.116)	-0.16 (0.112)	0.06 (0.570)	-0.13 (0.201)	0.10 (0.323)
R Lateral Orbitofrontal	***0.21 (0.043)***	0.14 (0.173)	-0.19 (0.060)	-0.20 (0.056)	-0.17 (0.098)	-0.04 (0.711)	-0.11 (0.272)	***-0.22 (0.032)***	-0.13 (0.208)	***-0.22 (0.029)***	-0.06 (0.549)	-0.01 (0.965)	<0.01 (0.987)	-0.04 (0.722)	***-0.22 (0.034)***	-0.01 (0.945)
R Medial Orbitofrontal	0.20 (0.055)	0.13 (0.218)	***-0.22 (0.032)***	***-0.20 (0.048)***	-0.18 (0.080)	-0.10 (0.337)	***-0.22 (0.032)***	***-0.21 (0.041)***	-0.09 (0.365)	***-0.23 (0.027)***	-0.14 (0.175)	-0.09 (0.385)	-0.10 (0.310)	-0.09 (0.404)	-0.19 (0.059)	0.02 (0.849)
R Precentral	0.13 (0.190)	0.07 (0.513)	***-0.22 (0.034)***	-0.17 (0.095)	-0.15 (0.145)	-0.03 (0.805)	-0.14 (0.172)	-0.20 (0.053)	-0.14 (0.187)	-0.19 (0.061)	***-0.22 (0.033)***	-0.17 (0.102)	-0.19 (0.062)	-0.11 (0.275)	-0.11 (0.292)	0.04 (0.679)
R Paracentral	0.12 (0.242)	0.05 (0.610)	-0.17 (0.091)	-0.18 (0.085)	-0.18 (0.079)	-0.12 (0.241)	-0.16 (0.117)	-0.19 (0.065)	-0.14 (0.187)	-0.18 (0.076)	-0.18 (0.077)	-0.15 (0.138)	-0.16 (0.110)	-0.04 (0.696)	-0.06 (0.566)	0.09 (0.373)
R Superior parietal	-<0.01 (0.993)	-0.04 (0.683)	-0.02 (0.831)	0.01 (0.941)	<0.01 (0.999)	-<0.01 (0.987)	<0.01 (0.999)	-0.08 (0.437)	-0.07 (0.528)	-0.08 (0.461)	-0.09 (0.372)	-0.04 (0.736)	-0.06 (0.543)	0.06 (0.567)	-0.11 (0.273)	0.04 (0.690)
R Inferior Parietal	0.16 (0.126)	0.10 (0.353)	-0.18 (0.077)	-0.12 (0.230)	-0.12 (0.233)	-0.05 (0.603)	-0.13 (0.224)	-0.18 (0.085)	-0.11 (0.265)	-0.18 (0.086)	-0.15 (0.158)	0.02 (0.846)	-<0.01 (0.975)	0.06 (0.548)	-0.16 (0.115)	0.13 (0.201)
R Supramarginal	0.19 (0.061)	0.16 (0.120)	-0.14 (0.169)	-0.14 (0.177)	-0.17 (0.107)	-0.10 (0.322)	-0.15 (0.134)	-0.15 (0.137)	-0.07 (0.494)	-0.16 (0.113)	-0.17 (0.088)	-0.01 (0.960)	-0.03 (0.790)	0.03 (0.754)	-0.14 (0.173)	0.20 (0.051)
R Postcentral	0.04 (0.732)	-0.02 (0.850)	-0.17 (0.103)	-0.11 (0.273)	-0.08 (0.425)	-0.08 (0.444)	-0.10 (0.341)	-0.12 (0.246)	-0.14 (0.182)	-0.09 (0.369)	-0.19 (0.060)	-0.12 (0.245)	-0.14 (0.175)	-0.02 (0.888)	-0.08 (0.434)	0.01 (0.943)

R Entorhinal	0.10 (0.318)	0.07 (0.505)	-0.12 (0.261)	-0.11 (0.268)	-0.08 (0.439)	-0.01 (0.919)	-0.05 (0.664)	-0.11 (0.282)	-0.08 (0.440)	-0.11 (0.299)	-0.09 (0.403)	0.01 (0.920)	-0.01 (0.898)	-0.13 (0.223)	-0.18 (0.077)	0.02 (0.834)
R cuneus	***0.20 (0.049)***	0.14 (0.167)	-0.20 (0.053)	***-0.23 (0.024)***	***-0.25 (0.014)***	-0.13 (0.192)	***-0.23 (0.021)***	-0.20 (0.052)	-0.05 (0.637)	***-0.23 (0.024)***	-0.12 (0.226)	-0.06 (0.574)	-0.10 (0.352)	-0.18 (0.076)	-0.18 (0.085)	0.05 (0.637)
R Pericalcarine	0.12 (0.231)	0.06 (0.572)	-0.19 (0.058)	***-0.20 (0.046)***	***-0.23 (0.024)***	-0.17 (0.093)	***-0.28 (0.006)***	-0.17 (0.092)	-0.10 (0.336)	-0.18 (0.085)	-0.04 (0.718)	-0.05 (0.651)	-0.09 (0.400)	-0.14 (0.187)	-0.11 (0.268)	-0.03 (0.750)
R Rostral Anterior Cingulate	0.12 (0.226)	0.03 (0.765)	-0.16 (0.124)	-0.17 (0.103)	-0.12 (0.251)	-0.03 (0.752)	-0.15 (0.150)	***-0.20 (0.047)***	-0.12 (0.238)	***-0.21 (0.042)***	-0.04 (0.716)	0.06 (0.587)	0.07 (0.489)	-0.15 (0.146)	-0.11 (0.306)	0.02 (0.816)
R Caudal Anterior Cingulate	0.10 (0.312)	0.06 (0.559)	-0.03 (0.743)	-0.04 (0.672)	-0.05 (0.648)	0.01 (0.956)	-0.03 (0.747)	-0.10 (0.314)	-0.04 (0.686)	-0.12 (0.259)	0.04 (0.667)	0.12 (0.250)	0.10 (0.354)	-0.06 (0.541)	-0.08 (0.464)	0.13 (0.205)
R Insula	0.15 (0.134)	0.07 (0.472)	-0.15 (0.155)	-0.17 (0.089)	-0.18 (0.085)	-0.09 (0.366)	-0.12 (0.256)	-0.20 (0.054)	-0.15 (0.137)	-0.19 (0.069)	-0.17 (0.102)	-0.05 (0.661)	-0.07 (0.524)	-0.02 (0.881)	-0.07 (0.501)	0.12 (0.249)

[Correlations are displayed as rho (p). L = Left, R = Right, sd = standard deviation (variability), asy = asymmetry. Bright colour indicates a significant association after multiple comparison corrections; faint colour indicates a statistical trend ($p<0.05$).]

Appendix R. Partial correlations (accounting for age and sex) between average regional cortical thickness and gait at baseline, in the control group

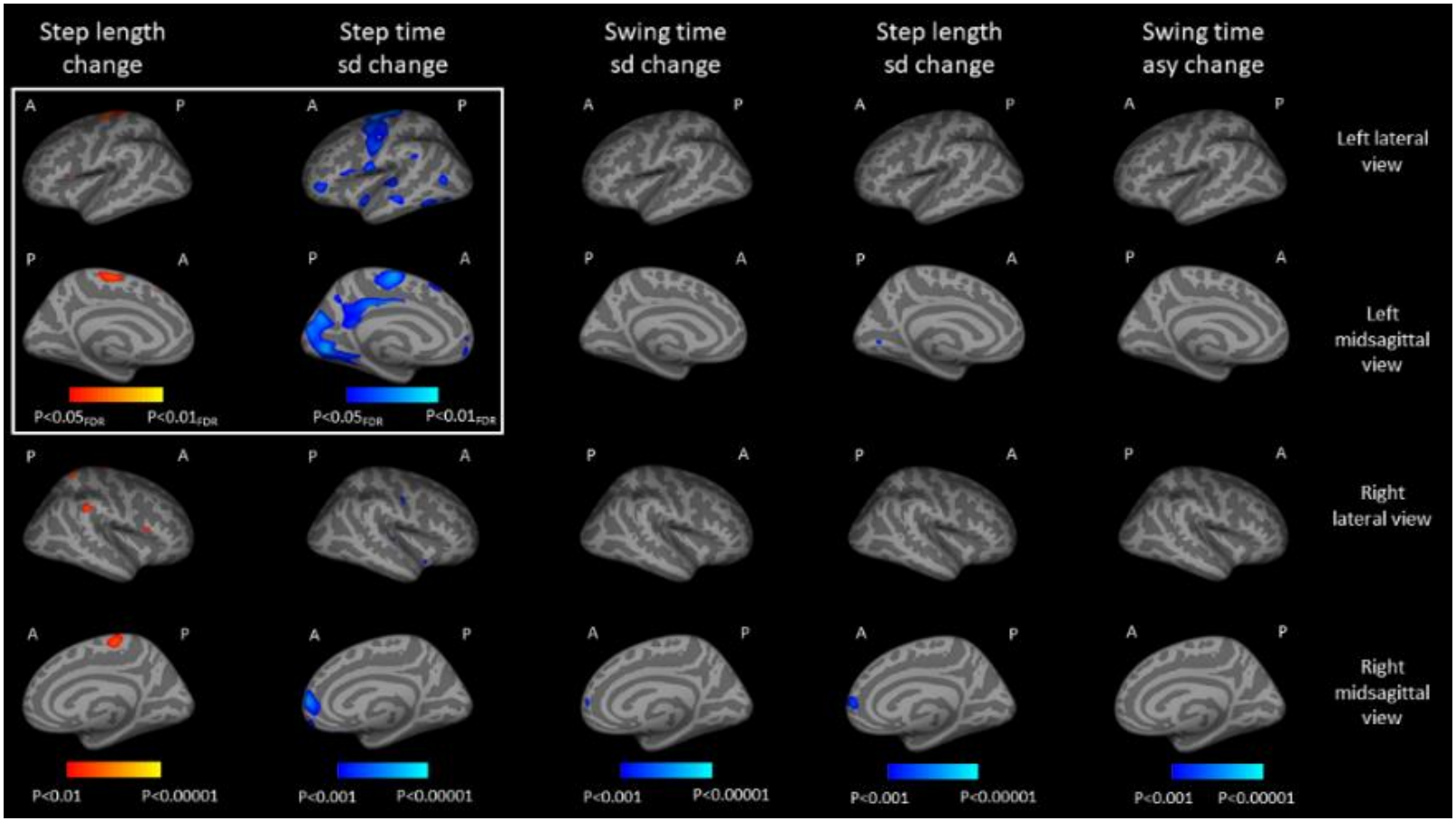
	Step velocity (m/s)	**Step length** (m)	**Swing time sd** (ms)	**Step time sd** (ms)	**Stance time sd** (ms)	**Step velocity sd** (m/s)	**Step length sd** (m)	**Step time** (ms)	**Swing time** (ms)	**Stance time** (ms)	**Step time asy** (ms)	**Swing time asy** (ms)	**Stance time asy** (ms)	**Step length asy** (m)	**Step width** (m)	**Step width sd** (m)
L Superior Frontal	***0.33 (0.027)***	***0.35 (0.018)***	***-0.36 (0.016)***	***-0.31 (0.042)***	***-0.30 (0.044)***	-0.15 (0.315)	-0.28 (0.060)	-0.09 (0.552)	0.02 (0.897)	-0.13 (0.405)	***-0.30 (0.045)***	-0.10 (0.516)	-0.09 (0.541)	***-0.31 (0.038)***	***-0.37 (0.010)***	-0.05 (0.731)
L Rostral Middle Frontal	***0.36 (0.014)***	***0.41 (0.005)***	***-0.34 (0.024)***	***-0.36 (0.015)***	***-0.31 (0.036)***	-0.17 (0.277)	-0.22 (0.145)	-0.08 (0.602)	0.04 (0.772)	-0.13 (0.412)	-0.25 (0.099)	-0.18 (0.243)	-0.22 (0.138)	-0.29 (0.053)	-0.26 (0.082)	-0.01 (0.932)
L Caudal Middle Frontal	0.20 (0.185)	***0.31 (0.039)***	-0.26 (0.086)	-0.22 (0.156)	-0.23 (0.133)	***-0.30 (0.048)***	***-0.35 (0.018)***	0.06 (0.688)	0.15 (0.313)	0.01 (0.943)	-0.14 (0.351)	-0.08 (0.587)	-0.09 (0.540)	-0.25 (0.093)	***-0.31 (0.038)***	-0.04 (0.780)
L Lateral Orbitofrontal	0.27 (0.073)	***0.38 (0.011)***	***-0.32 (0.030)***	-0.29 (0.055)	-0.28 (0.063)	-0.24 (0.115)	***-0.43 (0.004)***	0.03 (0.847)	0.12 (0.439)	-0.01 (0.935)	***-0.31 (0.041)***	-0.25 (0.099)	-0.20 (0.182)	***-0.36 (0.014)***	***-0.48 (0.001)***	-0.01 (0.952)
L Medial Orbitofrontal	***0.36 (0.015)***	***0.35 (0.018)***	-0.27 (0.070)	-0.29 (0.053)	-0.25 (0.095)	-0.14 (0.366)	-0.29 (0.051)	-0.15 (0.328)	-0.06 (0.681)	-0.17 (0.277)	-0.25 (0.093)	-0.15 (0.326)	-0.13 (0.379)	***-0.46 (0.001)***	***-0.37 (0.012)***	0.02 (0.907)
L Precentral	0.26 (0.080)	***0.30 (0.049)***	-0.15 (0.330)	-0.16 (0.311)	-0.13 (0.394)	-0.09 (0.565)	-0.22 (0.146)	-0.04 (0.812)	0.06 (0.720)	-0.07 (0.634)	-0.23 (0.136)	0.10 (0.512)	0.12 (0.441)	***-0.44 (0.003)***	-0.28 (0.062)	<0.01 (0.978)
L Paracentral	***0.32 (0.033)***	***0.30 (0.044)***	-0.22 (0.151)	-0.19 (0.223)	-0.20 (0.198)	-0.03 (0.850)	-0.05 (0.739)	-0.13 (0.387)	-0.12 (0.436)	-0.12 (0.428)	-0.20 (0.190)	0.12 (0.416)	0.14 (0.366)	***-0.44 (0.003)***	-0.15 (0.323)	0.10 (0.528)
L Superior parietal	***0.26 (0.034)***	***0.41 (0.005)***	-0.19 (0.206)	-0.23 (0.132)	-0.21 (0.163)	-0.14 (0.372)	-0.19 (0.224)	0.01 (0.927)	0.17 (0.273)	-0.05 (0.735)	-0.06 (0.718)	-0.03 (0.827)	0.01 (0.972)	***-0.31 (0.037)***	***-0.35 (0.020)***	-0.09 (0.569)
L Inferior Parietal	***0.32 (0.034)***	***0.49 (0.001)***	-0.28 (0.062)	***-0.31 (0.037)***	***-0.31 (0.038)***	-0.27 (0.068)	***-0.33 (0.027)***	0.11 (0.491)	0.26 (0.087)	0.03 (0.857)	-0.11 (0.488)	-0.19 (0.219)	-0.18 (0.247)	***-0.34 (0.022)***	-0.26 (0.087)	-0.08 (0.591)
L Supramarginal	***0.31 (0.037)***	***0.37 (0.012)***	***-0.31 (0.038)***	***-0.33 (0.025)***	-0.27 (0.078)	***-0.33 (0.029)***	***-0.48 (0.001)***	-0.04 (0.807)	0.09 (0.571)	-0.09 (0.574)	-0.10 (0.520)	-0.09 (0.570)	-0.08 (0.625)	***-0.41 (0.005)***	-0.29 (0.057)	-0.03 (0.824)
L Postcentral	0.24 (0.119)	***0.31 (0.038)***	-0.18 (0.250)	-0.09 (0.570)	-0.06 (0.690)	0.08 (0.611)	-0.03 (0.866)	0.02 (0.890)	0.03 (0.851)	0.02 (0.904)	-0.17 (0.266)	0.10 (0.532)	0.15 (0.339)	***-0.31 (0.040)***	-0.18 (0.230)	0.02 (0.914)
L Entorhinal	0.26 (0.080)	***0.32 (0.035)***	-0.19 (0.215)	-0.29 (0.055)	-0.29 (0.055)	***-0.41 (0.005)***	***-0.40 (0.007)***	-0.06 (0.722)	0.05 (0.753)	-0.10 (0.535)	-0.20 (0.189)	-0.14 (0.358)	-0.22 (0.145)	-0.24 (0.114)	-0.24 (0.113)	-0.09 (0.553)
L cuneus	0.19 (0.218)	0.25 (0.094)	-0.13 (0.385)	-0.16 (0.284)	-0.18 (0.250)	-0.16 (0.290)	-0.10 (0.514)	0.02 (0.910)	0.01 (0.937)	0.03 (0.865)	0.02 (0.916)	0.01 (0.930)	<0.01 (0.993)	-0.19 (0.212)	-0.11 (0.471)	-0.08 (0.611)

L Pericalcarine	-0.07 (0.672)	0.02 (0.902)	-0.11 (0.469)	0.05 (0.757)	-0.01 (0.972)	0.05 (0.767)	0.05 (0.740)	0.12 (0.454)	-0.06 (0.711)	0.19 (0.224)	-0.03 (0.859)	-0.07 (0.664)	0.02 (0.911)	-0.05 (0.738)	***-0.35 (0.017)***	-0.18 (0.242)
L Rostral Anterior Cingulate	0.21 (0.170)	0.22 (0.143)	-0.12 (0.422)	-0.12 (0.446)	-0.11 (0.458)	-0.15 (0.313)	***-0.33 (0.026)***	-0.06 (0.720)	0.02 (0.921)	-0.08 (0.606)	-0.26 (0.090)	-0.21 (0.166)	-0.21 (0.178)	-0.25 (0.105)	***-0.48 (0.001)***	-0.11 (0.472)
L Caudal Anterior Cingulate	0.07 (0.638)	0.18 (0.231)	-0.19 (0.209)	-0.18 (0.240)	-0.16 (0.285)	-0.24 (0.114)	-0.25 (0.099)	0.10 (0.501)	0.19 (0.206)	0.05 (0.756)	-0.19 (0.220)	-0.04 (0.778)	-0.09 (0.571)	-0.14 (0.371)	-0.25 (0.103)	-0.20 (0.193)
L Insula	***0.30 (0.043)***	***0.41 (0.005)***	-0.13 (0.406)	-0.15 (0.312)	-0.19 (0.220)	-0.16 (0.282)	***-0.30 (0.049)***	0.01 (0.926)	0.14 (0.356)	-0.04 (0.788)	***-0.32 (0.032)***	-0.22 (0.140)	-0.20 (0.189)	-0.29 (0.053)	***-0.51 (0<.001)***	-0.08 (0.608)
R Superior Frontal	0.27 (0.070)	***0.37 (0.014)***	-0.29 (0.052)	-0.28 (0.067)	-0.26 (0.091)	-0.15 (0.335)	-0.26 (0.081)	0.01 (0.931)	0.12 (0.438)	-0.03 (0.824)	-0.27 (0.073)	-0.12 (0.419)	-0.16 (0.305)	***-0.38 (0.010)***	***-0.41 (0.005)***	-0.09 (0.557)
R Rostral Middle Frontal	***0.35 (0.020)***	***0.32 (0.033)***	***-0.33 (0.025)***	***-0.35 (0.020)***	***-0.30 (0.048)***	-0.13 (0.391)	-0.24 (0.114)	-0.17 (0.252)	-0.08 (0.615)	-0.20 (0.188)	-0.28 (0.061)	-0.18 (0.239)	-0.29 (0.055)	-0.27 (0.073)	-0.24 (0.108)	-0.03 (0.859)
R Caudal Middle Frontal	0.22 (0.155)	***0.33 (0.028)***	-0.25 (0.093)	-0.28 (0.059)	-0.22 (0.157)	-0.22 (0.147)	-0.26 (0.081)	0.08 (0.617)	0.15 (0.319)	0.03 (0.834)	-0.17 (0.268)	-0.07 (0.649)	-0.11 (0.489)	***-0.33 (0.028)***	-0.26 (0.087)	-0.03 (0.836)
R Lateral Orbitofrontal	0.16 (0.284)	0.22 (0.146)	-0.27 (0.072)	-0.25 (0.104)	-0.22 (0.155)	-0.10 (0.521)	***-0.30 (0.043)***	0.02 (0.879)	0.13 (0.399)	-0.02 (0.876)	-0.21 (0.163)	-0.17 (0.258)	-0.17 (0.275)	***-0.35 (0.020)***	***-0.37 (0.013)***	-0.17 (0.253)
R Medial Orbitofrontal	0.26 (0.082)	***0.34 (0.024)***	-0.16 (0.306)	-0.18 (0.236)	-0.23 (0.132)	-0.09 (0.544)	-0.20 (0.196)	-0.01 (0.941)	0.06 (0.718)	-0.04 (0.808)	***-0.30 (0.044)***	-0.18 (0.236)	-0.23 (0.126)	***-0.39 (0.008)***	-0.29 (0.050)	-0.01 (0.975)
R Precentral	0.23 (0.123)	0.27 (0.070)	-0.16 (0.306)	-0.18 (0.227)	-0.12 (0.434)	-0.08 (0.624)	-0.16 (0.294)	-0.02 (0.879)	0.03 (0.862)	-0.04 (0.774)	-0.18 (0.241)	0.14 (0.364)	0.11 (0.494)	***-0.45 (0.002)***	-0.22 (0.156)	0.01 (0.941)
R Paracentral	***0.33 (0.027)***	***0.33 (0.029)***	-0.19 (0.221)	-0.19 (0.207)	-0.09 (0.563)	0.11 (0.482)	0.01 (0.965)	-0.12 (0.431)	-0.05 (0.726)	-0.13 (0.380)	-0.17 (0.268)	0.05 (0.731)	0.08 (0.626)	***-0.35 (0.018)***	-0.21 (0.162)	-<0.01 (0.982)
R Superior parietal	***0.35 (0.017)***	***0.42 (0.005)***	-0.25 (0.096)	-0.26 (0.088)	-0.21 (0.174)	-0.06 (0.676)	-0.10 (0.521)	-0.03 (0.859)	0.10 (0.531)	-0.08 (0.623)	-0.06 (0.698)	-<0.01 (0.990)	0.04 (0.806)	***-0.32 (0.033)***	-0.20 (0.185)	0.04 (0.773)
R Inferior Parietal	***0.35 (0.017)***	***0.45 (0.002)***	***-0.30 (0.046)***	***-0.36 (0.014)***	***-0.33 (0.028)***	-0.21 (0.169)	-0.26 (0.089)	0.01 (0.944)	0.15 (0.341)	-0.05 (0.762)	-0.18 (0.225)	-0.18 (0.231)	-0.20 (0.199)	***-0.34 (0.022)***	-0.26 (0.083)	-0.05 (0.755)
R Supramarginal	***0.38 (0.009)***	***0.42 (0.004)***	***-0.41 (0.005)***	***-0.42 (0.004)***	***-0.34 (0.021)***	-0.24 (0.109)	***-0.35 (0.019)***	-0.09 (0.572)	0.05 (0.765)	-0.13 (0.379)	-0.21 (0.177)	-0.13 (0.400)	-0.15 (0.333)	***-0.50 (0.001)***	***-0.31 (0.039)***	-0.01 (0.926)
R Postcentral	***0.32 (0.034)***	***0.30 (0.049)***	***-0.32 (0.031)***	-0.29 (0.052)	-0.19 (0.207)	0.06 (0.700)	-0.15 (0.328)	-0.11 (0.459)	-0.05 (0.740)	-0.12 (0.421)	-0.24 (0.115)	-0.04 (0.819)	-0.01 (0.976)	-0.28 (0.060)	-0.21 (0.167)	-0.11 (0.461)

R Entorhinal	0.05 (0.746)	0.04 (0.772)	***-0.32 (0.031)***	-0.20 (0.194)	-0.27 (0.069)	***-0.33 (0.025)***	***-0.32 (0.035)***	-0.04 (0.799)	-0.07 (0.670)	-0.02 (0.884)	-0.18 (0.249)	-0.17 (0.276)	-0.28 (0.059)	-0.23 (0.122)	-0.23 (0.132)	-0.20 (0.188)
R cuneus	0.26 (0.087)	***0.31 (0.037)***	-0.18 (0.242)	-0.14 (0.371)	-0.20 (0.178)	0.06 (0.703)	-<0.01 (0.979)	-0.04 (0.802)	-0.06 (0.709)	-0.02 (0.917)	-0.16 (0.282)	-0.07 (0.670)	-0.07 (0.632)	-0.24 (0.111)	-0.09 (0.543)	-0.02 (0.880)
R Pericalcarine	0.28 (0.060)	***0.34 (0.022)***	-0.10 (0.500)	-0.08 (0.614)	-0.01 (0.966)	0.18 (0.228)	0.02 (0.899)	-0.02 (0.909)	-0.09 (0.577)	0.02 (0.888)	-0.12 (0.417)	-0.15 (0.324)	-0.06 (0.690)	-0.26 (0.083)	***-0.33 (0.026)***	0.15 (0.319)
R Rostral Anterior Cingulate	0.18 (0.230)	0.23 (0.132)	-0.22 (0.157)	-0.14 (0.349)	-0.10 (0.516)	-<0.01 (0.987)	-0.24 (0.114)	<0.01 (0.993)	0.05 (0.736)	-0.02 (0.901)	***-0.34 (0.024)***	-0.06 (0.699)	-0.12 (0.449)	***-0.50 (<0.001)***	***-0.33 (0.027)***	-0.08 (0.617)
R Caudal Anterior Cingulate	0.08 (0.583)	0.08 (0.606)	-0.24 (0.108)	-0.29 (0.051)	-0.17 (0.256)	-0.29 (0.053)	***-0.35 (0.018)***	-0.04 (0.800)	-0.02 (0.899)	-0.04 (0.775)	-0.28 (0.060)	-0.12 (0.426)	-0.29 (0.056)	-0.28 (0.062)	-0.24 (0.107)	-0.26 (0.084)
R Insula	0.21 (0.171)	0.28 (0.065)	-0.26 (0.089)	-0.18 (.246)	-0.18 (0.238)	-0.12 (0.449)	***-0.32 (0.034)***	<0.01 (0.998)	0.05 (0.763)	-0.02 (0.895)	-0.28 (0.063)	-0.21 (0.165)	-0.25 (0.097)	***-0.32 (0.035)***	***-0.39 (0.008)***	-0.16 (0.281)

[Correlations are displayed as rho (p). L = Left, R = Right, sd = standard deviation (variability), asy = asymmetry. Bright colour indicates a significant association after multiple comparison corrections; faint colour indicates a statistical trend (p<0.05).]

Appendix S. Location of longitudinal associations between cortical thickness and change in all gait characteristics



[Gait characteristics that significantly change as a result of PD progression. A = Anterior, P = Posterior, sd = standard deviation, asy=asymmetry, FDR = False Discover Rate. Figures within the white box indicate associations that survived FDR correction; all other results are uncorrected for multiple comparisons. Red indicates a positive correlation between gait change and baseline cortical thickness (i.e. greater thinning linked to greater decline in gait characteristic), blue indicates a negative correlation (i.e. greater thinning linked to greater increase in gait characteristic). Brighter colours indicate stronger associations.]

Appendix T. All regional cortical thickness predictors of gait change, where p<0.05

Gait characteristic	Location of region	Predictor region	Regression coefficients			
			β	SE	t	p
Δ Step length	Frontal	**L Paracentral**	0.020	0.006	3.44	**0.001***
		R Paracentral	0.020	0.006	3.16	**0.002***
		L Superior frontal	0.024	0.008	2.97	**0.004***
		R Precentral	0.018	0.006	2.90	**0.005***
		R Superior frontal	0.022	0.008	2.66	0.010
		L Precentral	0.016	0.006	2.57	0.012
		R Medial Orbitofrontal	0.017	0.009	2.14	0.036
	Parietal	**R Supramarginal**	0.020	0.009	2.28	0.026
		L Postcentral	0.025	0.011	2.22	0.030
		R Superior Parietal	0.025	0.012	2.17	0.034
Δ Swing time variability	Frontal	**L Precentral**	-1.367	0.620	-2.21	0.029
		L Medial Orbitofrontal	-1.681	0792	-2.12	0.036
		R Precentral	-1.293	0.635	-2.04	0.043
Δ Step time variability	Frontal	**L Precentral**	-2.416	0.663	-3.64	**<0.001***
		R Paracentral	-2.328	0.716	-3.25	**0.002***
		R Medial Orbitofrontal	-2.842	0.876	-3.24	**0.002***
		R Precentral	-2.177	0.688	-3.17	**0.002***
		L Paracentral	-2.102	0.694	-3.03	**0.003***
		R Superior Frontal	-2.572	0.938	-2.74	**0.007***
		L Medial Orbitofrontal	-2.356	0.863	-2.73	**0.008***
		R Lateral Orbitofrontal	-2.327	0.896	-2.60	**0.011***
		L Rostral Middle Frontal	-3.613	1.429	-2.53	**0.013***
		L Superior Frontal	-2.260	0.908	-2.49	**0.015***
		L Lateral Orbitofrontal	-2.073	0.956	-2.17	0.033
		L Caudal Middle Frontal	-2.274	1.048	-2.17	0.033
	Parietal	**R Postcentral**	-3.057	1.276	-2.40	**0.019***
		L Postcentral	-2.690	1.259	-2.14	0.036
	Occipital	**R Pericalcarine**	-4.630	1.528	-3.03	**0.003***
		L Cuneus	-3.369	1.329	-2.54	**0.013***
		L Pericalcarine	-3.830	1.566	-2.45	**0.017***
	Cingulate	**L Rostral Anterior Cingulate**	-1.944	0.636	-3.06	**0.003***
		R Rostral Anterior Cingulate	-1.359	0.576	-2.36	**0.020***
	Insula	**R Insula**	-1.604	0.641	-2.50	**0.014***
		L Insula	-1.531	0.680	-2.25	0.027
Δ Step length variability	Frontal	**L Medial Orbitofrontal**	-0.003	0.001	-3.22	**0.002***
		R Medial Orbitofrontal	-0.003	0.001	-3.09	**0.002***
		R Lateral Orbitofrontal	-0.003	0.001	-2.96	**0.004***
		L Rostral Middle Frontal	-0.004	0.001	-2.88	**0.005***
		L Precentral	-0.002	0.001	-2.56	0.011
		R Paracentral	-0.002	0.001	-2.44	0.016
		L Lateral Orbitofrontal	-0.002	0.001	-2.44	0.016
		R Superior Frontal	-0.002	0.001	-2.40	0.018
		R Precentral	-0.002	0.001	-2.32	0.022
		R Rostral Middle Frontal	-0.003	0.001	-2.26	0.025
		L Superior Frontal	-0.002	0.001	-2.13	0.035
	Parietal	**L Superior Parietal**	-0.003	0.001	-2.33	0.021
		R Inferior Parietal	-0.002	0.001	-2.28	0.024
		R Superior Parietal	-0.003	0.001	-2.11	0.036
		R Supramarginal	-0.002	0.001	-2.08	0.039
	Temporal	**R Entorhinal**	-0.001	0.001	-2.11	0.036
	Occipital	**R Pericalcarine**	-0.003	0.002	-2.09	0.038
	Cingulate	**R Rostral Anterior Cingulate**	-0.001	0.001	-2.58	0.011
		L Rostral Anterior Cingulate	-0.001	0.001	-2.33	0.021
		R Caudal Anterior Cingulate	-0.001	0.001	-2.06	0.041
	Insula	**R Insula**	-0.002	0.001	-2.53	0.012

[L=left, R=right. * indicates significant predictors that survived multiple comparison correction.]

Appendix U. Subcortical regions-of-interest selected *a priori*, with reasons for selection

Region	Reason for selection
Amygdala	Part of the limbic system, abnormal connectivity associated with freezing of gait and smaller volumes linked to depression, which has been associated with impaired gait. **Non-motor** output.
Brainstem	Thought to control automatic gait, along with cerebellum, as outlined in chapter 1. **Motor** output.
Caudate	Part of the dorsal striatum of the basal ganglia, which may be more heavily involved in automatic motor control after preferential degeneration of the putamen. **Motor** output.
Cerebellum	Thought to control automatic gait, along with brainstem, as outlined in chapter 1. **Motor** output.
Globus Pallidus	Part of the basal ganglia, involved in automatic motor control through the basal-ganglia-thalamocortical circuit. **Motor** output.
Hippocampus	Part of the limbic system involved in spatial navigation and previously associated with gait characteristics in older adults as shown in chapter 2**. Non-motor** output.
Nucleus Accumbens	Part of the ventral striatum of the basal ganglia and of the mesolimbic pathway, linked to cognition & previously linked to gait in older adults. **Non-motor** output.
Putamen	Part of the dorsal striatum of the basal ganglia, involved in automatic motor control through the basal-ganglia-thalamocortical circuit. **Motor** output.
Thalamus	Relays motor and sensory signals and involved in the rate model, as explained in chapter 1. Also receives acetylcholine from PPN. **Motor** output (and **potential non-motor** output).

Appendix V. Bivariate correlations between subcortical volumes and age, sex and education

	Control			PD		
Subcortical volume	**Age**	**Sex**	**Education**	**Age**	**Sex**	**Education**
L Cerebellum	-0.19 (0.208)	0.13 (0.398)	0.07 (0.627)	***-0.40 (<0.001)***	***0.25 (.015)***	0.19 (0.064)
L Thalamus	***-0.48 (0.001)***	***0.38 (0.009)***	0.05 (0.739)	***-0.69 (<0.001)***	***0.46 (<0.001)***	0.19 (0.060)
L Caudate	***-0.38 (0.008)***	0.15 (0.329)	-0.01 (0.993)	-0.16 (0.117)	***0.41 (<0.001)***	0.02 (0.874)
L Putamen	***-0.42 (0.004)***	***0.31 (0.032)***	0.05 (0.756)	***-0.46 (<0.001)***	0.15 (0.135)	0.16 (0.113)
L Pallidum	***-0.47 (0.001)***	***0.33 (0.026)***	0.06 (0.710)	***-0.53 (<0.001)***	***0.24 (0.018)***	***0.25 (0.015)***
L Hippocampus	***-0.30 (0.044)***	***0.31 (0.036)***	-0.14 (0.342)	***-0.56 (<0.001)***	***0.40 (<0.001)***	***0.22 (0.026)***
L Amygdala	***-0.37 (0.011)***	0.16 (0.298)	-0.05 (0.742)	***-0.49 (<0.001)***	***0.25 (0.013)***	***0.29 (0.004)***
L Accumbens	-0.10 (0.508)	0.01 (0.953)	-0.04 (0.790)	***-0.28 (0.005)***	-0.09 (0.399)	-0.08 (0.422)
R Cerebellum	-0.14 (0.355)	0.13 (0.393)	0.03 (0.833)	***-0.46 (<0.001)***	***0.21 (0.035)***	0.16 (0.105)
R Thalamus	***-0.39 (0.006)***	***0.33 (0.024)***	0.05 (0.729)	***-0.66 (<0.001)***	***0.52 (<0.001)***	***0.27 (0.006)***
R Caudate	-0.21 (0.153)	0.19 (0.205)	-0.08 (0.609)	-0.05 (0.655)	***0.29 (0.004)***	-0.03 (0.781)
R Putamen	***-0.37 (0.011)***	***0.30 (0.038)***	0.07 (0.638)	***-0.43 (<0.001)***	0.15 (0.141)	0.10 (0.316)
R Pallidum	***-0.46 (0.001)***	0.28 (0.054)	0.06 (0.709)	***-0.57 (<0.001)***	***0.30 (0.002)***	***0.27 (0.007)***
R Hippocampus	***-0.38 (0.008)***	***0.40 (0.006)***	-0.13 (0.382)	***-0.51 (<0.001)***	***0.46 (<0.001)***	***0.23 (0.025)***
R Amygdala	***-0.40 (0.005)***	0.23 (0.118)	0.07 (0.648)	***-0.43 (<0.001)***	0.04 (0.692)	0.20 (0.050)
R Accumbens	***-0.51 (<0.001)***	0.28 (0.054)	0.04 (0.795)	***-0.35 (<0.001)***	0.03 (0.757)	0.10 (0.312)
Brainstem	-0.28 (.058)	0.01 (0.936)	0.19 (0.207)	***-0.41 (<0.001)***	***0.27 (0.008)***	***0.26 (0.011)***

[All results are listed as rho (p-value). L; left. R; right. Significant associations (p<0.05) are highlighted and are in bold.]

Appendix W. Partial correlations between subcortical volumes and gait characteristics in controls

	Step velocity	Step length	Swing time sd	Step time sd	Stance time sd	Step velocity sd	Step length sd	Step time	Swing time	Stance time	Step time a	Swing time a	Stance time a	Step length a	Step width	Step width sd
L Cerebellum	0.01 (0.936)	0.17 (0.263)	-0.12 (0.425)	-0.01 (0.938)	-0.02 (0.895)	-0.01 (.968)	-0.15 (0.338)	0.19 (0.224)	0.20 (0.188)	0.16 (0.302)	-0.06 (0.705)	-0.15 (0.314)	-0.18 (0.239)	-0.09 (0.550)	-0.22 (0.155)	-0.05 (0.724)
L Thalamus	0.21 (0.174)	0.26 (0.089)	***-0.33 (0.028)***	***-0.34 (0.023)***	***-0.32 (0.035)***	-0.18 (0.228)	-0.09 (0.537)	-0.03 (0.870)	0.02 (0.875)	-0.05 (0.770)	-0.04 (0.819)	-0.09 (0.574)	-0.15 (0.335)	-0.20 (0.178)	-0.16 (0.294)	0.16 (0.295)
L Caudate	0.28 (0.066)	0.26 (0.086)	0.03 (0.865)	-0.12 (0.444)	-0.02 (0.915)	0.03 (0.835)	0.05 (0.727)	-0.10 (0.526)	0.06 (0.692)	-0.16 (0.293)	0.02 (0.915)	0.28 (0.064)	0.21 (0.171)	-0.04 (0.805)	-0.09 (0.571)	0.08 (0.588)
L Putamen	0.01 (0.970)	0.04 (0.775)	<0.01 (0.990)	<0.01 (0.977)	-0.03 (0.840)	-0.05 (0.747)	-0.03 (0.824)	0.06 (0.712)	0.11 (0.488)	0.02 (0.874)	-0.12 (0.427)	-<0.01 (0.985)	-0.12 (0.426)	0.07 (0.657)	-0.17 (0.259)	0.07 (0.666)
L Pallidum	0.08 (0.607)	0.14 (0.372)	-0.19 (0.208)	-0.18 (0.244)	-0.15 (0.335)	-0.04 (0.804)	-0.04 (0.793)	0.04 (0.818)	0.07 (0.655)	0.01 (0.939)	0.06 (0.697)	0.03 (0.870)	-0.08 (0.616)	-0.02 (0.877)	-0.18 (0.239)	-0.03 (0.855)
L Hippocampus	-0.03 (0.866)	0.05 (0.744)	-0.04 (0.809)	-0.05 (0.761)	0.06 (0.710)	-0.13 (0.401)	-0.22 (0.152)	0.07 (0.652)	-0.03 (0.867)	0.11 (0.489)	-0.10 (0.515)	-0.12 (0.443)	-0.26 (0.091)	-0.25 (0.101)	-0.24 (0.111)	0.10 (0.518)
L Amygdala	-0.11 (0.468)	-0.15 (0.314)	***0.31 (0.038)***	0.09 (0.555)	0.22 (0.152)	0.02 (0.901)	-0.04 (0.776)	-0.03 (0.861)	-0.03 (0.831)	-0.02 (0.886)	-0.17 (0.273)	0.02 (0.921)	-0.16 (0.283)	-0.12 (0.441)	-0.15 (0.338)	-0.20 (0.184)
L Accumbens	0.16 (0.300)	0.10 (0.513)	-0.09 (0.559)	-0.05 (0.731)	-0.05 (0.724)	0.05 (0.748)	0.02 (0.888)	-0.13 (0.385)	-0.14 (0.373)	-0.12 (0.445)	-0.19 (0.208)	-0.09 (0.546)	-0.13 (0.386)	0.15 (0.336)	0.06 (0.683)	-0.08 (0.619)
R Cerebellum	0.05 (0.746)	0.24 (0.106)	-0.13 (0.386)	<0.01 (0.999)	-0.12 (0.450)	<0.01 (0.983)	-0.09 (0.577)	0.22 (0.151)	0.26 (0.085)	0.18 (0.250)	-0.02 (0.891)	-0.23 (0.131)	-0.19 (0.202)	0.07 (0.664)	-0.20 (0.199)	<0.01 (0.980)
R Thalamus	-0.07 (0.660)	0.01 (0.959)	-0.15 (0.312)	-0.15 (0.319)	-0.05 (0.747)	-0.15 (0.323)	-0.19 (0.202)	0.12 (0.451)	0.09 (0.551)	0.11 (0.470)	0.12 (0.443)	0.17 (0.278)	0.06 (0.691)	-0.24 (0.116)	-0.11 (0.484)	-0.07 (0.651)
R Caudate	***0.31 (0.037)***	0.22 (0.151)	-0.08 (0.623)	-0.27 (0.073)	-0.08 (0.597)	-0.05 (0.740)	-0.06 (0.708)	-0.19 (0.211)	-0.03 (0.867)	-0.24 (0.109)	0.08 (0.613)	0.29 (0.056)	0.24 (0.113)	-0.14 (0.358)	-0.16 (0.303)	0.03 (0.852)
R Putamen	0.08 (0.623)	0.13 (0.414)	-0.10 (0.512)	-0.09 (0.545)	-0.08 (0.615)	-0.10 (0.518)	-0.06 (0.721)	0.05 (0.771)	0.04 (0.783)	0.04 (0.800)	-0.11 (0.488)	0.09 (0.558)	-0.05 (0.768)	-0.07 (0.650)	-0.15 (0.315)	0.09 (0.543)
R Pallidum	0.14 (0.367)	0.14 (0.371)	-0.17 (0.271)	-0.16 (0.293)	-0.23 (0.122)	-0.04 (0.814)	0.11 (0.489)	-0.07 (0.665)	-0.02 (0.895)	-0.08 (0.592)	-0.05 (0.739)	<0.01 (0.989)	-0.15 (0.332)	0.04 (0.774)	-0.06 (0.710)	0.11 (0.490)
R Hippocampus	-0.09 (0.559)	0.02 (0.878)	0.09 (0.581)	0.07 (0.657)	0.17 (0.272)	<0.01 (0.989)	-0.12 (0.421)	0.15 (0.330)	-0.01 (0.981)	0.20 (0.180)	-0.04 (0.806)	-0.06 (0.688)	-0.19 (0.206)	-0.23 (0.122)	-0.15 (0.331)	0.05 (0.758)
R Amygdala	0.17 (0.256)	0.07 (0.669)	0.07 (0.646)	-0.08 (0.617)	-0.01 (0.972)	0.01 (0.941)	-0.13 (0.400)	-0.17 (0.262)	-0.17 (0.266)	-0.15 (0.340)	-0.08 (0.589)	0.12 (0.430)	-0.01 (0.954)	-0.06 (0.713)	-0.04 (0.810)	-0.14 (0.368)
R Accumbens	0.22 (0.139)	0.14 (0.359)	-0.14 (0.356)	-0.17 (0.272)	-0.19 (0.213)	-0.14 (0.351)	-0.12 (0.453)	-0.21 (0.167)	-0.15 (0.341)	-0.22 (0.151)	-0.13 (0.382)	0.05 (0.739)	-0.07 (0.641)	-0.04 (0.812)	-0.04 (0.773)	0.12 (0.440)
Whole Brainstem	0.16 (0.298)	0.25 (0.097)	***-0.34 (0.023)***	-0.27 (0.076)	-0.25 (0.093)	-0.12 (0.421)	-0.14 (0.363)	0.04 (0.810)	0.04 (0.789)	0.03 (0.850)	0.09 (0.569)	-<0.01 (0.980)	-0.11 (0.472)	-0.13 (0.390)	-0.16 (0.308)	0.05 (0.748)
Medulla oblongata	-	-	-0.25 (0.101)	-	-	-	-	-	-	-	-	-	-	-	-	-
Pons	-	-	-0.27 (0.073)	-	-	-	-	-	-	-	-	-	-	-	-	-
SCP	-	-	-0.03 (0.841)	-	-	-	-	-	-	-	-	-	-	-	-	-
Midbrain	-	-	-0.22 (0.145)	-	-	-	-	-	-	-	-	-	-	-	-	-

Appendix X. Partial correlations between subcortical volumes and gait characteristics in PD

	Step velocity	Step length	Swing time sd	Step time sd	Stance time sd	Step velocity sd	Step length sd	Step time	Swing time	Stance time	Step time a	Swing time a	Stance time a	Step length a	Step width	Step width sd
L Cerebellum	-0.01 (0.926)	0.03 (0.732)	0.01 (0.941)	0.01 (0.939)	<0.01 (0.974)	<0.01 (0.983)	-0.01 (0.946)	0.06 (0.594)	.015 (0.132)	<0.01 (0.997)	0.06 (0.560)	-0.06 (0.565)	-0.06 (0.571)	-0.08 (0.453)	-0.15 (0.149)	0.05 (0.611)
L Thalamus	0.02 (0.832)	0.05 (0.622)	0.06 (0.531)	0.09 (0.363)	0.06 (0.595)	0.08 (0.415)	0.02 (0.868)	0.06 (0.552)	***0.20 (0.049)***	-0.01 (0.908)	0.17 (0.091)	0.06 (0.580)	0.06 (0.544)	-0.02 (0.833)	-0.18 (0.084)	0.11 (0.304)
L Caudate	0.07 (0.479)	0.08 (0.451)	0.13 (0.213)	0.03 (0.792)	0.02 (0.826)	0.13 (0.213)	0.14 (0.169)	-0.01 (0.904)	0.06 (0.586)	-0.04 (0.683)	0.01 (0.921)	0.03 (0.760)	-0.02 (0.885)	-0.01 (0.888)	-0.05 (0.620)	-0.02 (0.878)
L Putamen	0.02 (0.869)	-0.03 (0.747)	0.12 (0.249)	-0.01 (0.935)	-0.05 (0.634)	-0.03 (0.801)	0.02 (0.879)	-0.08 (0.429)	-0.05 (0.610)	-0.08 (0.415)	<0.01 (0.968)	0.04 (0.723)	-0.02 (0.819)	-0.05 (0.643)	0.01 (0.936)	-0.07 (0.503)
L Pallidum	0.03 (0.785)	-0.05 (0.599)	0.01 (0.929)	-0.03 (0.779)	-0.08 (0.414)	-0.02 (0.865)	-0.07 (0.511)	-0.12 (0.231)	-0.13 (0.222)	-0.11 (0.288)	0.17 (0.099)	0.07 (0.510)	0.05 (0.653)	<0.01 (0.998)	-0.11 (0.285)	-0.07 (0.504)
L Hippocampus	-0.05 (0.603)	-0.09 (0.399)	0.02 (0.853)	0.05 (0.658)	0.07 (0.527)	-0.04 (0.725)	-0.05 (0.639)	0.01 (0.954)	-0.01 (0.891)	0.09 (0.936)	0.12 (0.233)	0.05 (0.622)	0.05 (0.663)	-0.01 (0.897)	-0.02 (0.872)	-0.06 (0.576)
L Amygdala	-0.10 (0.333)	-0.12 (0.226)	0.08 (0.468)	0.07 (0.510)	0.13 (0.220)	-0.01 (0.895)	0.04 (0.675)	0.03 (0.769)	-0.04 (0.669)	0.05 (0.601)	0.08 (0.430)	0.12 (0.257)	0.08 (0.446)	0.07 (0.506)	0.03 (0.753)	-0.08 (0.417)
L Accumbens	-0.06 (0.591)	-0.03 (0.775)	0.18 (0.076)	0.17 (0.089)	0.13 (0.209)	0.14 (0.179)	0.18 (0.086)	0.07 (0.470)	0.13 (0.207)	0.04 (0.698)	0.02 (0.874)	0.10 (0.329)	0.06 (0.572)	0.04 (0.675)	-0.12 (0.254)	0.02 (0.816)
R Cerebellum	<0.01 (0.970)	0.06 (0.541)	<0.01 (0.996)	-0.01 (0.940)	-0.02 (0.874)	-<0.01 (0.968)	<0.01 (0.996)	0.09 (0.400)	***0.21 (0.040)***	0.02 (0.865)	0.09 (0.395)	-0.05 (0.652)	-0.05 (0.614)	-0.14 (0.181)	-0.14 (0.168)	0.12 (0.246)
R Thalamus	0.03 (0.756)	0.03 (0.806)	0.08 (0.447)	0.07 (0.526)	0.01 (0.932)	-0.02 (0.869)	-0.07 (0.474)	-0.01 (0.943)	0.13 (0.190)	-0.07 (0.472)	0.13 (0.215)	0.05 (0.621)	0.05 (0.630)	0.04 (0.699)	-0.14 (0.179)	0.12 (0.252)
R Caudate	0.08 (0.430)	0.12 (0.247)	0.15 (0.148)	0.10 (0.354)	0.07 (0.483)	0.09 (0.410)	0.10 (0.329)	0.03 (0.771)	0.11 (0.298)	-0.01 (0.934)	0.07 (0.492)	0.07 (0.499)	0.06 (0.579)	0.03 (0.776)	<0.01 (0.988)	0.08 (0.450)
R Putamen	0.06 (0.550)	0.01 (0.919)	<0.01 (0.998)	-0.11 (0.274)	-0.13 (0.217)	-0.08 (0.433)	-0.06 (0.556)	-0.09 (0.410)	0.02 (0.857)	-0.12 (0.247)	-0.02 (0.877)	-0.07 (0.480)	-0.09 (0.364)	-0.09 (0.359)	-0.05 (0.632)	-0.09 (0.368)
R Pallidum	0.12 (0.225)	0.08 (0.458)	-0.15 (0.157)	-0.16 (0.112)	-0.18 (0.076)	-0.15 (0.154)	***-0.24 (0.020)***	-0.13 (0.222)	-0.05 (0.618)	-0.14 (0.160)	0.13 (0.208)	-0.03 (0.808)	-0.02 (0.877)	-0.04 (0.707)	***-0.23 (0.022)***	-0.04 (0.735)
R Hippocampus	-0.17 (0.101)	-0.20 (0.054)	0.10 (0.319)	0.09 (0.387)	0.11 (0.284)	-0.09 (0.395)	-0.04 (0.694)	0.06 (0.534)	-0.04 (0.696)	0.09 (0.361)	0.06 (0.579)	0.06 (0.583)	0.04 (0.712)	0.08 (0.463)	0.08 (0.420)	-0.01 (0.905)
R Amygdala	-0.09 (0.370)	-0.08 (0.422)	0.03 (0.808)	0.02 (0.874)	0.05 (0.606)	-0.06 (0.587)	-0.01 (0.932)	0.07 (0.502)	0.08 (0.416)	0.05 (0.625)	0.01 (0.926)	<0.01 (0.987)	-0.02 (0.854)	-0.06 (0.593)	<0.01 (0.999)	-0.02 (0.813)
R Accumbens	-0.01 (0.964)	-0.01 (0.943)	0.08 (0.457)	0.04 (0.700)	-0.01 (0.946)	0.07 (0.522)	0.13 (0.196)	0.04 (0.700)	0.10 (0.310)	0.01 (0.965)	0.07 (0.490)	0.15 (0.148)	0.06 (0.545)	0.04 (0.723)	-0.05 (0.664)	-0.11 (0.297)
Whole Brainstem	0.17 (0.102)	***0.23 (0.023)***	-0.07 (0.482)	-0.09 (0.374)	-0.12 (0.232)	-0.10 (0.339)	***-0.21 (0.036)***	<0.01 (0.988)	0.16 (0.111)	-0.07 (0.497)	0.04 (0.717)	-0.03 (0.764)	-0.03 (0.790)	-0.13 (0.221)	***-0.23 (0.025)***	0.07 (0.496)
Medulla oblongata	-	0.15 (0.132)	-	-	-	-	-0.14 (0.173)	-	-	-	-	-	-	-	***-0.22 (0.029)***	-
Pons	-	***0.22 (0.033)***	-	-	-	-	***-0.26 (0.009)***	-	-	-	-	-	-	-	***-0.25 (0.014)***	-
SCP	-	0.15 (0.138)	-	-	-	-	-0.16 (0.126)	-	-	-	-	-	-	-	***-0.23 (0.027)***	-
Midbrain	-	0.13 (0.200)	-	-	-	-	-0.17 (0.105)	-	-	-	-	-	-	-	-0.06 (0.542)	-

Appendix Y. All subcortical and limbic volumetric predictors of PD gait change

Predictor region	Step length (m)				Swing time variability (ms)				Step time variability (ms)				Step length variability (ms)				Swing time asymmetry (ms)			
	β	**SE**	**t**	***p***	**β**	**SE**	**t**	***p***	**β**	**SE**	**t**	***p***	**β**	**SE**	**t**	***p***	**β**	**SE**	**t**	***p***
L Cerebellum	**0.012**	**0.005**	**2.62**	**0.011***	-0.763	0.469	-1.63	0.105	-1.003	0.521	-1.92	0.058	-0.001	0.001	-2.32	0.022	-1.378	0.823	-1.68	0.098
R Cerebellum	0.010	0.004	2.21	0.031	-0.812	0.438	-1.85	0.066	-1.003	0.485	-2.07	0.042	-0.001	0.001	-2.45	0.015	-1.557	0.765	-2.04	0.045
L Thalamus	**0.123**	**0.032**	**3.85**	**<0.001***	-6.869	3.310	-2.08	0.040	-8.908	3.652	-2.44	0.017	-0.009	0.004	-2.69	0.008	-9.366	5.915	-1.58	0.117
R Thalamus	**0.129**	**0.037**	**3.52**	**0.001***	-5.973	3.793	-1.58	0.117	-7.325	4.219	-1.74	0.087	-0.009	0.004	-2.17	0.032	-9.052	6.718	-1.35	0.182
L Caudate	0.008	0.073	0.12	0.909	-4.881	7.277	-0.67	0.503	-7.597	8.076	-0.94	0.350	-0.006	0.008	-0.73	0.466	-17.108	12.294	-1.39	0.168
R Caudate	0.020	0.072	0.27	0.786	-6.323	7.309	-0.87	0.388	-4.827	8.046	-0.60	0.550	-0.009	0.008	-1.20	0.233	-11.921	12.162	-0.98	0.329
L Putamen	**0.156**	**0.060**	**2.62**	**0.011***	-13.753	6.309	-2.18	0.031	-16.953	6.821	-2.49	0.015	-0.010	0.007	-1.41	0.162	-19.331	10.760	-1.80	0.076
R Putamen	**0.151**	**0.059**	**2.57**	**0.012***	-10.182	6.177	-1.65	0.101	-15.184	6.695	-2.27	0.026	-0.007	0.007	-1.07	0.288	-14.727	10.510	-1.40	0.164
L Pallidum	**0.273**	**0.111**	**2.45**	**0.017***	-26.412	11.027	-2.40	0.018	-30.503	12.081	-2.53	0.014	-0.026	0.012	-2.26	0.025	-36.215	19.271	-1.88	0.064
R Pallidum	**0.394**	**0.103**	**3.83**	**<0.001***	-23.946	10.623	-2.25	0.026	-32.110	11.686	-2.75	0.007	-0.023	0.011	-2.06	0.041	-34.191	18.301	-1.87	0.065
L Hippocampus	**0.186**	**0.060**	**3.11**	**0.003***	-9.857	5.981	-1.65	0.102	-12.219	6.697	-1.83	0.072	-0.008	0.006	-1.20	0.232	-13.700	10.384	-1.32	0.191
R Hippocampus	**0.166**	**0.064**	**2.59**	**0.012***	-9.894	6.265	-1.58	0.117	-10.920	7.047	-1.55	0.126	-0.007	0.007	-1.07	0.285	-19.625	10.908	-1.80	0.076
L Amygdala	0.150	0.148	1.02	0.313	-7.445	14.129	-0.53	0.599	-8.925	15.939	-0.56	0.577	0.001	0.015	0.04	0.971	-38.640	25.057	-1.54	0.127
R Amygdala	0.115	0.162	0.71	0.482	-17.908	15.759	-1.14	0.258	-26.662	17.489	-1.52	0.132	-0.014	0.017	-0.84	0.405	-8.259	27.737	-0.30	0.767
L Accumbens	0.195	0.390	0.50	0.619	-12.850	37.378	-0.34	0.731	-36.153	42.041	-0.86	0.393	-0.050	0.040	-1.24	0.216	-31.139	67.641	-0.46	0.647
R Accumbens	0.032	0.412	0.08	0.939	-30.070	39.947	-0.75	0.453	-53.125	44.643	-1.19	0.238	-0.044	0.043	-1.02	0.309	-50.721	70.653	-0.72	0.475
Brainstem	0.022	0.013	1.69	0.096	-1.375	1.264	-1.09	0.279	-2.128	1.425	-1.49	0.140	-0.002	0.001	-1.16	0.250	-3.245	2.218	-1.46	0.147

[L; left. R; right. Significant associations (multiple comparison corrected) are in bold and denoted by*.]

Appendix Z. Bivariate correlations between age, sex and cBF volumes

	Control		PD	
cBF volume	**Age**	**Sex**	**Age**	**Sex**
Ch4p	***-0.51 (<0.001)***	-0.03 (0.838)	***-0.64 (<0.001)***	0.10 (0.352)
Ch4	***-0.46 (0.001)***	0.09 (0.564)	***-0.60 (<0.001)***	0.07 (0.518)
Ch1-2	-0.21 (0.160)	-0.05 (0.733)	***-0.53 (<0.001)***	0.06 (0.527)

[All results are listed as rho (p-value). Significant associations are in bold and highlighted in colour (red for controls and blue for PD.]

Appendix AA. Partial correlations between cBF volumes and gait in PD, correcting solely for age or sex

Partial correlations (age corrected): PD	Step velocity (m/s)	Step length (m)
TIV normalised Ch4p volume	0.02 (0.822)	0.02 (0.821)
TIV normalised Ch4 volume	0.07 (0.525)	0.08 (0.477)
TIV normalised Ch1-2 volume	0.07 (0.481)	0.04 (0.728)
Partial correlations (sex corrected): PD	**Step velocity (m/s)**	**Step length (m)**
TIV normalised Ch4p volume	***0.21 (0.038)***	***0.28 (0.005)***
TIV normalised Ch4 volume	***0.23 (0.021)***	***0.31 (0.002)***
TIV normalised Ch1-2 volume	***0.22 (0.030)***	***0.25 (0.013)***

[All values are presented as r (p). Significant correlations (under Benjamini-Hochberg correction) are highlighted in colour and are in bold.]

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