What can gait analysis tell us about dementia and its subtypes? An integrated study of brain and behaviour

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December 2018

A thesis submitted to Newcastle University for the Degree of Doctor of Philosophy

Abstract

Discrete gait characteristics are associated with select cognitive functions, potentially reflecting underlying neural processes. Therefore, different dementia subtypes may have unique signatures of gait impairment, reflecting their different underlying disease pathologies. As such, gait may be a useful tool to aid differential diagnosis of dementia disease subtypes, such as Alzheimer's disease (AD) and Lewy body disease (LBD), which includes dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). A large structured review undertaken as part of this thesis highlighted a lack of studies investigating a comprehensive range of gait characteristics in well-classified dementia subtypes. Thus, the primary aim of this thesis was to investigate the potential of discrete gait characteristics to differentiate dementia disease subtypes in both laboratory and free-living environments. There was a particular emphasis on discriminating AD and DLB, as clinical similarities between these subtypes can lead to misdiagnosis and incorrect management and treatment of disease.

110 people participated in this observational cross sectional study. Participants with mild cognitive impairment and dementia related to AD (n = 36), DLB (n = 30) and PDD (n = 15), and controls (n = 29) underwent gait assessment in controlled laboratory environments. Additionally, body-worn monitors continuously collected gait data over seven days in free-living environments, providing information about spatiotemporal gait characteristics, and the quantity, variability and pattern of habitual walking activity. Participants completed a battery of cognitive tests and, associations between gait and cognitive variables were examined across all testing environments.

Selective patterns of gait impairment differentiated AD and LBD subtypes in the laboratory, while PDD could be discriminated from all disease subtypes in free-living environments. When considering patterns of gait impairment across different walking bout lengths, there was promising evidence that gait could also differentiate AD and LBD in free-living environments. Gait-cognition associations appeared dependent on disease subtype, potentially reflecting underlying pathology. Additionally, differences in habitual walking behaviour between controls and dementia subtypes was found and associated with motor disease severity, balance confidence and executive dysfunction.

This thesis is the first to describe gait in well-characterised dementia disease subtypes in both laboratory and free-living conditions. It provides novel evidence to support a role for quantitative gait analysis and discrete characteristics as clinical biomarkers to aid differential diagnosis and further enhance understanding of the complex relationship between gait and cognition.

Acknowledgements

I would like to acknowledge the many people who have supported me throughout the last three years of my PhD. First and foremost, I would like to thank my supervisors, Professor Lynn Rochester, Professor Alan Thomas and Dr. Brook Galna, who gave me this opportunity and whose support and expertise have been invaluable over the last three years. I am particularly grateful for their encouragement in pursuing career development opportunities outside of my PhD project, allowing me to have a rich and diverse PhD experience.

I would also like to acknowledge the members of the Brain and Movement Research group, and the Clinical Ageing Research Unit who have helped me develop new skills, supported me throughout and provided a multi-disciplinary environment to conduct research. A special thanks to all those who worked on the GaitDem project with me: Dr. Lisa Alcock, Dr. Silvia Del Din, Dr. Sam Stuart, Philip Brown, Aodhán Hickey, Dr. Brook Galna, Dr. Chris Buckley, Heather Hunter, Ellen Lirani-Silva, Leanne Kapa and Joanna Wilson. I am particularly grateful to all the past and present members of the Brain and Movement Research Group, alongside Dr. Rachael Lawson, for facilitating open-minded discussions and instilling a passion for research within me.

I wish to thank the many people who helped me recruit participants to the GaitDem study, particularly Vicki Hetherington and the rest of the North-East DeNDRoN team. I also acknowledges the support of the National Institute for Health Research Clinical Research Network (NIHR CRN). Thanks are also due to the Alzheimer's Society for funding this study.

I am very grateful to my parents for acting as the voice of encouragement throughout my time in university and for teaching me that education is never a heavy burden. I am also thankful to my friends, family, and partner Gerhardt, for their unwavering support in this endeavour.

Finally, I would like to dedicate this thesis to the participants of the GaitDem Study, without whom this research would not have been possible.

Statement of work undertaken

Professor Lynn Rochester is the Principal Investigator for the GaitDem study and was responsible for the study design. Professor Alan Thomas is the Lead Investigator for the Newcastle University Alzheimer's Society Doctoral Training Centre, and is responsible for the grant application.

All gait data was collected by myself, with help from Dr. Lisa Alcock, Dr. Sam Stuart, Philip Brown, Heather Hunter, Ellen Lirani-Silva and Aodhán Hickey. All cognitive data was collected by myself, with help from Ellen-Lirani-Silva and Joanna Wilson, with the exception of ten participants recruited from the SUPERB study, a longitudinal study examining biomarkers for distinguishing mild cognitive impairment due Alzheimer's disease and Lewy body disease. Data checking and cleaning was completed by myself, Joanna Wilson, Philip Brown and Leanne Kapa. Body-worn monitor data was processed by Aodhán Hickey, Dr. Sam Stuart, Dr. Silvia Del Din and Dr. Chris Buckley, and the Matlab code was developed by Dr. Alan Godfrey and Dr. Silvia Del Din.

Throughout the three years of my PhD, I managed the GaitDem study at Newcastle University. I wrote and submitted the project's ethics application and submitted ethical amendments when needed. I wrote the study protocol, recruited and assessed participants, checked and analysed the data and disseminated the results.

I conducted statistical analysis independently with statistical support and advice from Dr. Brook Galna and Dr. Rachael Lawson. I am responsible for writing this thesis.

Awards, publications and presentations arising from this thesis

Awards

September 2018 *Newcastle University's Academic Development Scholarship, £3750-* full award covering maintenance stipend for three months.

June 2018 *Guarantors of Brain Travel Grant award, £1000* – supporting attendance at the Alzheimer's Association International Conference 2018, Chicago

June 2018 *Institute of Ageing, Newcastle University Travel Grant award, £214* – supporting attendance at the Alzheimer's Association International Conference 2018, Chicago

June 2018 *Faculty of Medical Sciences, Newcastle University Travel Grant award,* £1000 – supporting attendance at the Alzheimer's Association International Conference 2018, Chicago

May 2018 Winner of the *Insights Public Lecture Prize*, also known as *Newcastle University Faculty of Medical Sciences Public Speaking Award.*

March 2018 Nominated for the *Alzheimer's Society Rising Star in Dementia Research Award 2018*

March 2018 Shortlisted for the *INSIGHTS Public Lecture Prize 2018 (The Newcastle University Faculty of Medical Sciences' Public Speaking Prize)*

February 2018 *Alzheimer's Research UK Travel Grant award, £800* – supporting attendance at the Alzheimer's Research UK Annual Conference 2018, London

June 2017 *Alzheimer's Research UK Travel Grant award, £800* – supporting attendance at the International Society of Posture and Gait Research World Congress 2017, Florida

October 2015 *Alzheimer's Society Doctoral Training Centre Studentship* – full award covering tuition fees, research funding and annual stipend of £16,000

Publications

1. **Mc Ardle, R.,** Morris, R., Wilson, J., Galna, B., Thomas, A.J. and Rochester, L., 2017. **What Can Quantitative Gait Analysis Tell Us about Dementia and Its Subtypes? A Structured Review.** Journal of Alzheimer's Disease, 60(4), pp.1295-1312.

Oral Presentations

1. **Mc Ardle R,** Galna B, Thomas A, Rochester L (2018) Continuous monitoring of gait: what can it tell us about dementia and its subtypes? Oral presentation at Alzheimer's Association Internal Conference 2018, Chicago
2. **Mc Ardle R.** (2018). What can walking tell us about dementia? Invited speaker as part of the Insights Public Lecture Series, as winner of the Faculty of Medical Sciences Public Speaking Prize
3. **Mc Ardle R.** What can walking tell us about dementia and its subtypes? Speaker as part of the "Newcastle University Doctoral Training Centre" at the Alzheimer's Society Meeting, York 2018.
4. **Mc Ardle R.** Gait and dementia: A step in the right direction? Speaker and panel member for the "What type of dementia? Getting a differential diagnosis" workshop at the Alzheimer's Society Annual Conference 2017, London

Poster Presentations

1. **Mc Ardle R,** Galna B, Thomas A, Rochester L (2018) Continuous monitoring of gait: what can it tell us about dementia and its subtypes? Poster presentation at Alzheimer's Association Internal Conference 2018, Chicago
2. **Mc Ardle R,** Galna B, Thomas A, Rochester L (2018) Can gait analysis aid differential diagnosis of dementia? Poster presentation at Alzheimer's Association International Conference 2018, Chicago
3. **Mc Ardle R**, Galna B, Thomas A, Rochester L. (2018) What can every day walking tell us about dementia and its subtypes? Poster presentation at the Alzheimer's Society Annual Conference 2018, London
4. **Mc Ardle R**, Galna B, Thomas A, Rochester L. (2018) Can gait and walking patterns measured continuously during everyday life differentiate dementia subtypes? Poster presentation at the National Institute of Health Research Infrastructure Training Camp 2018, Hertfordshire
5. **Mc Ardle R,** Galna B, Thomas A, Rochester L. (2018) What factors contribute to physical activity in dementia subtypes? Poster presentation at the Alzheimer's Research UK Annual Conference 2018, London

6. **Mc Ardle R,** Galna B, Thomas A, Rochester L. (2018) What factors contribute to physical activity in dementia subtypes? Poster presentation at the Alzheimer's Research UK Early Careers Day 2018, London
7. **Mc Ardle R,** Galna B, Thomas A, Rochester L. (2017) Gait impairment in dementia with Lewy bodies: A useful biomarker? Poster presentation at the International Society of Posture and Gait Research World Congress 2017, Florida
8. **Mc Ardle R,** Galna B, Thomas A, Rochester L. (2017) Is everyday physical activity different in dementia compared to older adult controls? Poster presentation at the International Society of Posture and Gait Research World Congress 201, Florida
9. **Mc Ardle R,** Morris R, Wilson J, Galna B, Thomas A, Rochester L. (2017) Gait and dementia: A step in the right direction? Poster presentation at the International Society of Posture and Gait Research World Congress 2017, Florida
10. **Mc Ardle R**, Galna B, Thomas A, Rochester L. (2016) Gait in dementia subtypes: A step in the right direction? Poster presentation at the Alzheimer's Society Annual Conference 2016, Bristol

Public engagement

1. **Mc Ardle R.** (2018) What can walking tell us about dementia? Invited speaker as part of the British Science Association's Scibar.
2. **Mc Ardle R.** (2018) "What can gait analysis tell us about dementia and it subtypes?" Invited speaker for the Parkinson's Interest Group, Local Education and Training (PIGLET) Annual Meeting, 2018.
3. **Mc Ardle R.** (2018) "What can walking tell us about the brain?" Hosting speaker of an Alzheimer's Society tour of the Biomedical Research Centre, Newcastle University's facilities.
4. **Mc Ardle R.** (2018). What can walking tell us about dementia? Invited speaker as part of the Insights Public Lecture Series, as winner of the Faculty of Medical Sciences Public Speaking Prize
5. **Mc Ardle R. "**Walking and the brain" Invited lecture for The Brilliant Club Graduation, Newcastle University, 2018
6. **Mc Ardle R. "**What can walking tell us about the brain?" Invited speaker for Pint of Science, Durham, 2017

7. **Mc Ardle, R.** "What can gait analysis tell us about dementia and its subtypes?", Invited speaker for Demands Journal Club, Newcastle University, 2016
8. Designing and developing several 6 week courses about my PhD topic for the Brilliant Club to deliver to high school students from disadvantaged backgrounds

Awards, publications and presentations arising from other work

Publications

1. Joanna Wilson, Liesl Allcock, **Ríona Mc Ardle,** John-Paul Taylor, Lynn Rochester, **The neural correlates of discrete gait characteristics in ageing: A Structured Review**, Neuroscience & Biobehavioral Reviews, 2018,
2. **Mc Ardle, R**., Morris, R., Hickey, A., Del Din, S., Koychev, I., Gunn, R.N., Lawson, J., Zamboni, G., Ridha, B., Sahakian, B.J., Rowe, J.B., Thomas, A., Zetterberg, H., McKay, C., Lovestone, S. and Rochester, L., 2018. **Gait in mild Alzheimer's disease: Feasibility of multi-centre measurement in the clinic and home with body-worn sensors – a pilot study.** Journal of Alzheimer's disease, 63 (1)

Public Engagement

1. Invited speaker as part of the NIHR Dementia Researcher's podcast (2018; https://www.dementiaresearcher.nihr.ac.uk/podcast-aaic-day-one/)
2. Invited panel member for the workshop "Making the most out of your PhD experience", Newcastle University, 2018
3. Invited host for the workshop "How to write for the general public", Newcastle University, 2017 and 2016

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List of Abbreviations

ABC	=	Activities Balance Confidence Scale
ACE-III	=	Addenbrookes Cognitive Examination III
AD	=	Alzheimer's disease
ADL	=	Activities of daily living
AD-MCI	=	Mild cognitive impairment due to Alzheimer's disease
a-MCI	=	Amnestic Mild Cognitive Impairment
Asy	=	Asymmetry
BADLS	=	Bristol Activities of Daily Living Scale
BMI	=	Body mass index
CDR	=	Clinical Dementia Rating Scale
CI	=	Confidence Intervals
CIRS-G	=	Cumulative Illness Rating Scale-Geriatrics
CSF	=	Cerebrospinal Fluid
CV	=	Coefficient of Variance
DAT	=	Dopamine Transporter
DeNDRoN	=	Dementia and Neurodegenerative Diseases
DLB	=	Dementia with Lewy bodies
DLS	=	Double Limb Support
DSM	=	Diagnostic and Statistical Manuel
ESS	=	Epworth Sleepiness Scale
FAS	=	FAS Verbal Fluency Test
FAST	=	Functional Assessment Staging Test
GDS	=	Geriatric Depression Scale
LBD	=	Lewy Body disease

MCI	=	Mild cognitive impairment
MDS	=	Movement disorders society
MMSE	=	Mini Mental State Examination
na-MCI	=	Non-amnestic Mild Cognitive Impairment
NART	=	National Adult Reading Test
NHS	=	National Health Service
OD	=	Other dementia
PD	=	Parkinson's disease
PDD	=	Parkinson's disease dementia
PD-MCI	=	Mild cognitive impairment due to Parkinson's disease
PET	=	Positron Emission Tomography
RBD	=	Rapid Eye Movement Sleep Behaviour Disorder
REM	=	Rapid Eye Movement
RT	=	Reaction Time
SD	=	Standard Deviation
SLS	=	Single Limb Support
SPECT	=	Single-photon emission computed tomography
SUPERB	=	123I-MIBG Scintigraphy Utility as a biomarker for Prodromal Dementia with Lewy Bodies
TMT-A	=	Trail Making Task A
TUG	=	Timed Up and Go
UPDRS	=	Unified Parkinson's disease rating scale
VaD	=	Vascular dementia
Va-MCI	=	Mild cognitive impairment due to cerebrovascular disease
VS	=	Visuospatial
η^2	=	Partial Eta Squared

Chapter 1 Dementia and gait: setting the context

1.1 Dementia

Dementia is a clinical syndrome, defined by impairments across multiple cognitive domains, such as memory, language or attention, which affect an individual's abilities of daily living (American Psychiatric Association, 2013; Alzheimer's Association, 2017). Dementia is a global issue with 46.8 million people worldwide affected by the disease in 2015 and is strongly correlated with increasing age; with an ageing population, numbers of people living with dementia are set to rise to 131.5 million by 2050 (Prince *et al.*, 2015). The estimated economic global cost of dementia was $818 billion in 2015. In addition to economic costs, dementia has personal and societal costs. It is associated with physical and psychological comorbidities, loss of independence and functional abilities, high caregiver and family burden and institutionalisation (Werner *et al.*, 2016).

Table 1-1 Diagnostic criteria for major neurocognitive disorder (or dementia) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual–motor, or social cognition) based on:
1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B. The cognitive deficits interfere with independence in everyday activities (that is, at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).
C. The cognitive deficits do not occur exclusively in the context of a delirium.
D. The cognitive deficits are not better explained by another mental disorder.

Adapted from American Psychiatric Association (2013)

Early diagnosis of dementia is important to provide individuals and their families time to consider their legal and financial choices, implement appropriate care and treatment, and prevent harm caused by lack of knowledge or understanding (Kenigsberg *et al.*, 2016). It can also provide better understanding of the underlying causes of the condition, which may aid future prevention and treatment.

A prodromal stage of dementia is identified as mild cognitive impairment (Gauthier *et al.*, 2006). MCI can be characterised by symptoms reflecting dementia subtypes, such as Alzheimer's disease (AD), Lewy body dementia (LBD) and vascular dementia (VaD). These common dementia subtypes and their prodromal stages will now be discussed.

1.2 **Alzheimer's disease**

Alzheimer's disease is the most common form of dementia, accounting for approximately 60% of all dementia diagnoses (Alzheimer's Association, 2017). In 2017, approximately 5.5 million people were living with AD in the U.S. This number is predicted to increase to 7.1 million people by 2025.

According to revised guidelines in 2011 (McKhann *et al.*, 2011), AD refers to a spectrum of impairment from the initial pathological changes in the brain prior to symptom onset through to recognised and diagnosed dementia. This means the term AD represents individuals living with dementia, mild cognitive impairment and those who have verified biomarkers indicating risk of these future clinical conditions. The characteristic primary initial symptom of AD is gradual memory loss, observed by difficulty to remember new or recall recent information (Alzheimer's Association, 2017). However, clinical presentation of AD is heterogeneous and may include symptoms such as executive and attentional difficulties, disorientation to time and place, problems with language, visuospatial skills and decision-making, social withdrawal and changes in mood and personality, and these can be presenting features.

Alzheimer's disease is associated with two molecular pathologies; beta-amyloid plaques and tau tangles (Alzheimer's Association, 2017). Beta-amyloid plaques are aggregations of protein outside neurons, which are thought to interfere with communication of neurons via synapses; thus contributing to cell death. Tau tangles are abnormal forms of the protein tau inside neurons, which prevents transportation of nutrients and essential molecules inside cells. Neurodegeneration occurs in AD 20 or more years before onset of symptoms and initially affects the hippocampal regions in AD, an area important for the consolidation of new memories. As the condition advances, widespread neurodegeneration occurs throughout the brain – reflected by worsening cognitive and functional abilities.

Alzheimer's disease can be diagnosed as probable, possible or probable/possible AD with evidence of AD pathology (McKhann *et al.*, 2011). Diagnosis of probable AD requires presentation of dementia with a gradual onset and objectively worsening cognition, memory impairment along with either language, visuospatial or executive dysfunction and no evidence of prominent cerebrovascular disease, dementia with Lewy bodies, frontotemporal dementia, aphasia or another comorbidity that may substantially affect cognition. Possible AD diagnosis may be given when onset of the condition is sudden, or when a comorbid condition may be contributing to the cognitive decline.

The use of possible/probable AD with evidence of AD pathology is used within research rather than clinical use. This uses evidence from biomarkers –biological measures that identify aspects of the disease process – to strengthen certainty of diagnosis. Examples of biomarkers include evidence of elevated cerebrospinal fluid tau, decreased fluordodeoxyglucose uptake in the temporo-parietal lobe on positron emission tomography (PET) scans and imaging evidence of atrophy in the medial, basal and lateral temporal cortex, and the medial parietal lobe (McKhann *et al.*, 2011).

1.3 **Lewy body dementia**

Lewy body dementia is an umbrella term incorporating Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB). Both syndromes occur due to the same underlying disease process - Lewy body disease - and are separated clinically by an arbitrary one-year rule used to classify the conditions (McKeith, 2017). This proposes that if dementia occurs within 12 months of motor symptom onset, the diagnosis is DLB; however if the clinical history of parkinsonism is longer than 12 months, PDD is the appropriate diagnosis (McKeith, 2017). Although age of onset, response to levodopa and temporal course differentiate the disorders, no differences have been found in clinical, cognitive, neuropsychiatric and autonomic features (McKeith, 2007). This makes differential diagnosis difficult and questions the appropriateness of separating these conditions (Asada, 2017). It has been suggested that viewing PDD and DLB as different expressions of the same underlying disease may be useful for research purposes.

Pathologically, both PDD and DLB are associated with the presence of Lewy bodies, aggregates of abnormal α-synuclein protein deposits, in the brain at post-mortem (McKeith *et al.*, 2004). It is yet to be determined if these are a cause or an effect of the disorder, but they are associated with neuronal loss. The density and dispersion of this pathology varies between individuals, likely contributing to the heterogeneous nature of LBD. For example, increased numbers of Lewy bodies in the anterior and inferior temporal lobes are related to visual hallucinations, while parkinsonism is associated with neurodegeneration of the nigrostriatal dopaminergic pathways.

Pathology pertaining to AD, such as beta-amyloid plaques and tau tangles, may occur alongside LBD pathology (McKeith *et al.*, 2004) and alter clinical presentation; individuals with LBD and less AD pathology show more core features of LBD, while more AD pathology creates a more amnestic presentation. This contributes to difficulties in accurate diagnosis and highlights the necessity for establishing valid efficient biomarkers.

1.3.1 Dementia with Lewy bodies

Previous epidemiological reports have suggested that DLB accounts for approximately 4% of all dementia cases (Asada, 2017). However, with newly revised diagnostic guidelines and increasing recognition of the condition, prevalence and incidence rates are expected to increase (McKeith *et al.*, 2017). Recent findings report 4.6% of all dementia diagnoses as DLB in the United Kingdom, but noted regional variations – this may reflect differences in clinical diagnostic practices (Kane *et al.*, 2018).

Cognitively speaking, impairments in attention, visuospatial and executive function are prominent in DLB compared to AD, but diagnosis requires evidence of core clinical and neuropsychiatric features. Core features include presence of cognitive fluctuations, visual hallucinations, Rapid Eye Movement Sleep Behaviour Disorder (RBD) and parkinsonism. Cognitive fluctuations refer to spontaneous changes in cognition and attention, observed as incoherent speech, staring into space, zoning out and variable attention. These present differently amongst individuals and can occur in later stages of other dementias. Complex visual hallucinations, involving well-formed images of people or animals, occur in up to 80% of DLB cases (McKeith *et al.*, 2017). RBD is reported in 76% of individuals diagnosed with DLB and is recognised as the recurring enactment of vivid dreams with the absence of normal REM sleep paralysis. Dreams often depict being chased or attacked with injuries occurring to the individual or their bed partner due to limb movements (McKeith *et al.*, 2004). Parkinsonism in DLB can be characterised as bradykinesia (slowness of movement), rigidity or a resting tremor.

Supportive clinical features also increase diagnostic certainty, although they lack specificity. These include sensitivity to anti-psychotic medications, autonomic dysfunction, repeated falls, simple hallucinations, anxiety, depression, delusions, apathy, hypersomnia and hypersomnia (McKeith, 2017). Biomarkers, such as reduced dopamine transporter (DAT) uptake in the basal ganglia as assessed by single-photon emission computed tomography (SPECT) imaging, are also useful, but not sufficient evidence to base a diagnosis on (McKeith *et al.*, 2017). DLB can be diagnosed as probable, where the there are two or more core symptoms or one core symptom with one or more indicative biomarkers, or as possible, where there is only one core feature or one indicative biomarker.

1.3.2 Parkinson's disease with dementia

Parkinson's disease (PD) is a common neurodegenerative disorder, characterised by the cardinal motor symptom, bradykinesia, and one of the following: rigidity, postural instability

and a resting tremor (Postuma *et al.*, 2015). Additionally it has been associated with cognitive impairments such as visuospatial, attentional and executive dysfunction (Bartels and Leenders, 2009). Prevalence rates of dementia in PD have varied, with figures reported from 16-48% of people living with PD (Emre *et al.*, 2007). Due to the progressive nature of PD, prevalence of dementia becomes more likely throughout the disease course, with reports of up to 80% of individuals living with either dementia 20 years after disease onset (Hely *et al.*, 2008). Recent figures in the United Kingdom reported dementia in 9.7% of all PD cases (Kane *et al.*, 2018). This was a lower rate than expected, and may be due to insufficient detection of dementia in PDD, highlighting a need for validated and stringent diagnostic criteria.

Efforts have been made to define clinical diagnostic criteria for PDD (Emre *et al.*, 2007). These require a diagnosis of PD and evidence of dementia as according to DSM 5 criteria for major neurocognitive disorder (American Psychiatric Association, 2013). Probable PDD is characterised by both the presence of PD and dementia, along with cognitive impairment in two domains and the presence of at least one behavioural symptom, such as depression, apathy, hallucinations, anxiety, delusions or daytime sleepiness. There must be no evidence of comorbidities that may attribute to cognitive impairment, such as depression or vascular dementia. Possible PDD requires the presence of both PD and dementia, along with atypical impairment of one or more cognitive domain and no features suggestive of other disorders as the cause of impairments (Emre *et al.*, 2007).

1.4 **Vascular dementia**

Vascular dementia is the second most common type of dementia reported, accounting for approximately 15% of all cases (O'Brien and Thomas, 2015). It is a highly variable condition, largely due to the lack of consensus on its underlying pathology. This has led to classifying VaD into multiple subtypes with commonalities in the presence of infarcts and ischaemic changes in the brain substantially contributing to cognitive impairments (O'Brien *et al.*, 2003).

Clinical presentation depends on the underlying vascular pathology; subcortical vascular pathology is common and affects frontostriatal circuits – this leads to prominent impairments in attention, information processing and executive function compared to AD. Probable VaD is diagnosed when there is the presence of impairments in memory and two or more cognitive domains, cerebrovascular disease via neurological examination and imaging evidence, and a relationship between the two, e.g. cognitive problems arise post-stroke (Roman *et al.*, 1993). Gait impairments, frequent falls, urinary problems, changes in personality and mood and

pseudobulbar palsy all support the diagnosis of probable VaD. Possible VaD can be diagnosed when there is a lack of evidence surrounding the temporal connection between dementia and cerebrovascular disease, or when the onset of dementia is gradual with evidence of vascular pathology.

Vascular dementia is diagnostically difficult for three main reasons. Firstly, there has yet to be satisfactorily validated criteria for vascular dementia; better understanding of clinical and imaging markers is required along with characterisation of subtypes (O'Brien *et al.*, 2003). Secondly, the presence of memory impairment in VaD is variable in degree of impairment due to heterogeneous pathology (O'Brien and Thomas, 2015). Therefore, the term vascular cognitive impairment may be more appropriate as this incorporates the various subtypes. As the DSM-5 no longer requires a specific memory impairment to diagnose dementia, the term VaD will still be used when discussing vascular cognitive impairment (American Psychiatric Association, 2013). In line with this, only around 10% of all VaD cases have sufficient levels of cerebrovascular burden to fully account for their cognitive deficits – vascular pathology mixed with pathology pertaining to other dementias is considered a norm, not an exception (O'Brien and Thomas, 2015). As such, it may be more appropriate to assume vascular pathology contributes to clinical presentation in VaD cases, but does not account for it fully.

1.5 Mild cognitive impairment

Mild cognitive impairment refers to cognitive impairment that does not affect an individuals' independence (Gauthier *et al.*, 2006; American Psychiatric Association, 2013). Diagnostic criteria for MCI include subjective reporting of cognitive change via personal accounts of the individual, an informant or clinician, objective evidence of impairment of one or more cognitive domains, functional independence and no impairments in societal or occupational functions (Albert *et al.*, 2011). Incidence of MCI has been reported as 10-20% in the over 65 population (Langa and Levine, 2014). While a distinct syndrome from dementia, progression to dementia is likely – rates of up to 33% of individuals diagnosed with MCI have developed dementia within two years (Gauthier *et al.*, 2006). Therefore, MCI may be viewed a transitional period between normal ageing and the onset of dementia.

Table 1-2 Diagnostic criteria for mild neurocognitive disorder (or mild cognitive impairment) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

A .Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual–motor, or social cognition) based on:
1.Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B. The cognitive deficits do not interfere with capacity for independence in everyday activities (that is, complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).
C. The cognitive deficits do not occur exclusively in the context of a delirium.
D. The cognitive deficits are not better explained by another mental disorder (for example, major depressive disorder or schizophrenia

Adapted from American Psychiatric Association (2013)

Historically, MCI is classified into two broad categories: amnestic and non-amnestic MCI, based on neuropsychological patterns (Kondo *et al.*, 2016) - further classified in single- or multiple-domain impaired subtypes. Evidence has demonstrated amnestic-MCI (a-MCI) is like to progress into AD, while non-amnestic MCI (na-MCI) converts to DLB. The ability to predict the type of dementia early in the disease course has benefits in terms of information-giving, treatment and patient quality of life (Kondo *et al.*, 2016). Investigations into disease modifying drugs targeting pre-dementia stages has led to increased interest in classifying MCI based on the underlying disease, rather than a-MCI and na-MCI. As such, this thesis will focus on MCI pertaining to AD, DLB, PDD and VaD.

1.5.1 Mild cognitive impairment due to Alzheimer's disease

Mild cognitive impairment due to AD (AD-MCI), previously described as a-MCI, is characterised by a prominent memory impairment (Albert *et al.*, 2011). Other cognitive domains may also be impaired, such as language. Different studies report rates of 17- 48% of a-MCI cases developing into AD (Fischer *et al.*, 2007; Ferman *et al.*, 2013c). In order to identify MCI as AD-MCI or prodromal AD, other disorders that may affect cognitive or brain function must be ruled out. Therefore, evidence of parkinsonism, visual hallucinations, RBD, cerebrovascular disease or multiple vascular risk factors, decline in language or behaviour indicative of frontotemporal lobar degeneration or rapid cognitive decline reflective of metabolic disorders, neoplasm or prion disease, must be ruled out (Albert *et al.*, 2011).

Diagnostic certainty of AD-MCI has been improved by the development of biomarkers, and has equally contributed to said developments (Albert *et al.*, 2011). Presence of recognised biomarkers, such as amyloid plaques in cerebrospinal fluid, improve the accuracy of diagnosis and likelihood of conversion to Alzheimer's disease, while inversely negative findings may provide an alternative diagnosis (Albert *et al.*, 2011). Researchers may establish biomarkers in individuals with MCI, which in the future may allow identification of cognitive impairment prior to onset. While knowledge is limited, evidence of amyloid plaques or tau proteins using imaging methods strengthens diagnosis of AD-MCI for research purposes.

1.5.2 Mild cognitive impairment due to Lewy body disease

Reported rates of MCI cases transitioning to DLB range from 5-25% (Fischer *et al.*, 2007; Bombois *et al.*, 2008; Palmqvist *et al.*, 2012; Kondo *et al.*, 2016). Useful clinical biomarkers for prodromal DLB include RBD, visual hallucinations, and reduced dopamine transporters on SPECT or PET imaging (Donaghy and McKeith, 2014a; Donaghy *et al.*, 2015). The latter requires further evaluation as striatal dopamine innervation does not occur in all DLB cases.

On the other end of the LBD spectrum, MCI in PD (PD-MCI) is becoming a well-recognised stage between PD and PDD with 15-20% of individuals classified as MCI at time of PD diagnosis (Aarsland, 2016). Although PD-MCI is a heterogeneous clinical profile, it is distinct from AD-MCI with prominent visuospatial and executive function deficits and a lesser amnestic component. Criteria for diagnosis of PD-MCI includes a diagnosis of PD, gradual decline in cognitive function with objectively measured impairments, and subtle functional problems that do not affect abilities to carry out activities of daily living (Litvan *et al.*, 2012). Biomarkers do not yet aid diagnostic certainty, but there will be revisions to diagnostic criteria with developments of easy-to-use and accessible diagnostic markers. To date, there has been no validation of the current diagnostic criteria and any biomarkers for PD-MCI.

1.5.3 Mild cognitive impairment due to vascular impairment

To a lesser extent, mild cognitive impairment due to cerebrovascular disease (Va-MCI), or vascular cognitive impairment – no dementia, is recognised. However, due to its heterogeneity and variable amnestic presentation, it is difficult to differentiate Va-MCI from normal cerebrovascular changes with ageing (O'Brien and Thomas, 2015). As with VaD, diagnosis of Va-MCI is difficult due to overlap in pathology with AD. This leads to a mixed clinical presentation and uncertainty as to which subtype is predominant. Va-MCI is not described in the current diagnostic criteria for VaD (Roman *et al.*, 1993); recommendations surrounding this are in early stages (Hachinski *et al.*, 2006). Equally, the benefits of

establishing biomarkers for Va-MCI is recognised, but limited by heterogeneous nature and mixed pathology. More work needs to be done in order to understand and identify both VaD and Va-MCI.

1.6 Importance of accurate early diagnosis

Accurate identification and diagnosis of dementia disease subtypes is imperative for provision of appropriate care and support. Studies suggest that regional variations in diagnosis, under detection and misdiagnosis of subtypes may affect clinical care and service delivery (Kane *et al.*, 2018). Misdiagnosis occurs due to similarities in cognitive presentation, mixed pathology, and inconsistent application of diagnostic criteria. Diagnosis is particularly problematic between AD and DLB where it is reported that between 34-65% of cases are misdiagnosed (Tiraboschi, Salmon et al. 2006). Misdiagnosis of subtypes influences appropriate care and treatment, and is therefore it is important to improve abilities to distinguish subtypes.

Accurate diagnosis is important to sufficiently identify and treat co-current symptoms, such as motor symptoms, cognitive fluctuations, dysautonomia, high rates of falls and other non-psychiatric symptoms in DLB. It is also important for provision of correct treatment; for example, DLB comes with a high sensitivity to certain antipsychotics, which therefore should not be prescribed (National Institute for Health and Excellence, 2006). Subtypes also have different prognoses; with people with DLB having a more rapid decline, with more frequent hospital admissions, higher need for inpatient care and entering earlier entry into nursing care (Mueller *et al.*, 2018). The advent of disease modifying treatments will also necessitate subtype identification and dementia stratification for the optimal use of such therapies. Recognition of prodromal stages of dementias, such as MCI subtypes, strengthen understanding of the conditions in the early stages and provide foundations for biomarker research. Developing biomarkers for improving diagnostic accuracy of dementia, and to distinguish subtypes is vital (Korolev, Symonds et al. 2016).

As previously discussed, several biomarkers are under development, such as cerebrospinal fluid, blood samples, brain imaging and cognitive markers. With high costs and invasiveness associated with such biomarkers, there is a need for identification of inexpensive non-invasive clinical biomarkers for dementia. Such biomarkers should be easily implementable prognostic and diagnostic tools for clinical settings. Quantitative gait analysis holds potential as a clinical biomarker for dementia.

1.7 **Gait**

Safe and effective gait requires complex cognitive processes and interactions between different neural networks (Yogev-Seligmann *et al.*, 2008). Associative relationships between features of gait and cognition have been suggested (Morris *et al.*, 2016; MacAulay *et al.*, 2017; Verghese *et al.*, 2017) and gait impairments have been observed up to 12 years prior to onset of cognitive symptoms (Montero-Odasso *et al.*, 2012; Beauchet *et al.*, 2016). Therefore, evidence suggests quantitative gait analysis as a plausible diagnostic marker for early diagnosis of dementia.

Gait refers to an individual's pattern of walking. Gait has generally been considered an automatic motor function but safe gait engages complex cognitive processes (Yogev-Seligmann *et al.*, 2008; Montero-Odasso *et al.*, 2012; Amboni *et al.*, 2013; Lord *et al.*, 2013b; Morris *et al.*, 2016; Beauchet *et al.*, 2018). While unimpaired gait is associated with longevity and independence, gait impairments such as a slower gait speed, predict fall risk and cognitive decline (Atkinson *et al.*, 2007; Verghese *et al.*, 2007; Fritz and Lusardi, 2009; Verghese *et al.*, 2009; Studenski *et al.*, 2011; Weiss *et al.*, 2014; Beauchet *et al.*, 2016). Gait is a complex skill requiring involvement from widespread brain regions, including those related to different cognitive functions, such as the frontal cortex and hippocampus (Rosano *et al.*, 2007; Rosano *et al.*, 2012; Beauchet *et al.*, 2015a; Wilson *et al.*, 2018). Structural alterations in the brain could therefore lead to subtle changes in distinct gait characteristics, and provide information regarding underlying pathologies.

1.7.1 Spatiotemporal gait characteristics

Quantitative gait analysis provides us with information about aspects of walking not visible during casual observation (Tao *et al.*, 2012). It involves assessing spatial and temporal aspects of gait. Different features of the gait cycle reflect these spatiotemporal characteristics. The gait cycle (a stride) is comprised of time spent in stance - the period when the foot is on the ground - and swing - the period when the foot is off the ground (Kirtley, 2006). Other key components of the gait cycle are steps - referring to each time a single leg goes forward - and stride - referring to when a right and left step have been taken. Figure 1-1 illustrates these aforementioned characteristics.

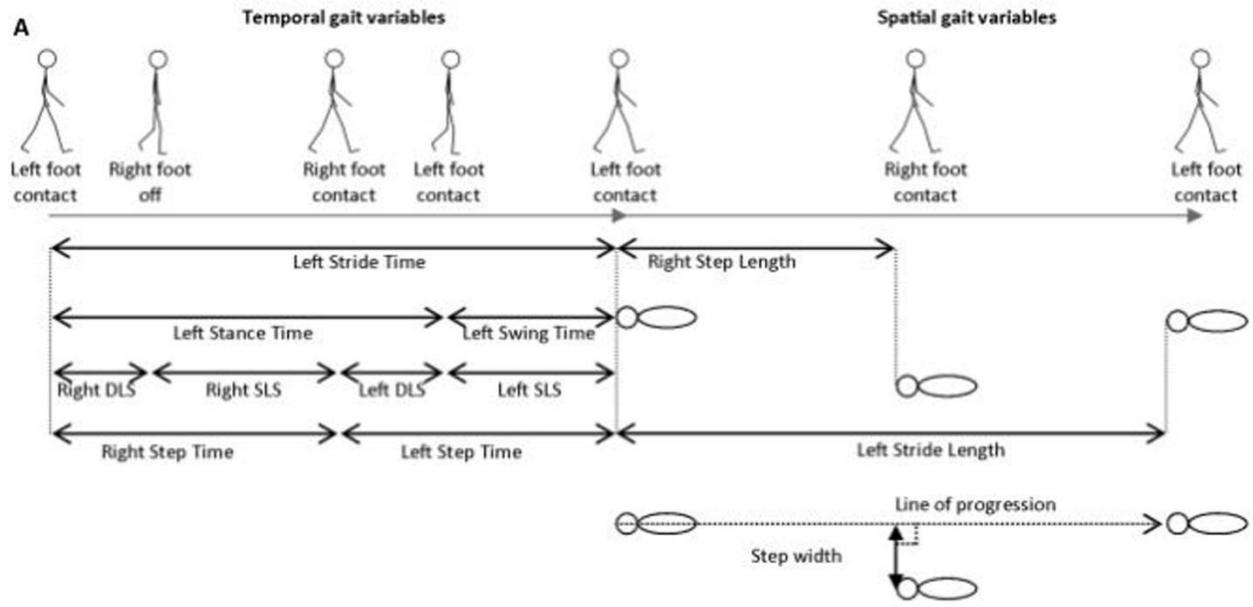

Figure 1-1 Spatiotemporal features of gait, adapted from Lord et al., 2013

DLS = double limb support, SLS = single limb support

Gait speed is the most commonly measured gait characteristic, as it is a reliable, valid and sensitive marker of global gait (Cesari *et al.*, 2005; Fritz and Lusardi, 2009; Van Kan *et al.*, 2009). It can reflect overall health and has been proposed as a useful clinical tool (Studenski *et al.*, 2011). However while a primary measure of gait assessment; gait speed does not have the sensitivity or specificity to discriminate subtle alterations in gait reflecting neuropathological alterations (Verghese *et al.*, 2007). Therefore, it is important to collect information on a range of spatiotemporal gait characteristics to allow for the complex relationship between the brain, cognition and gait (Lord *et al.*, 2013a; Weiss *et al.*, 2015a; Morris *et al.*, 2016; Wilson *et al.*, 2018).

Within the literature, there is a vast range of gait characteristics reported (see Table 1-3 for some of the most commonly described gait characteristics). While large numbers of gait outcomes can be useful, high co-variance between characteristics leads to redundancy, inconsistencies in interpretation and knowledge synthesis. To accommodate for this, conceptual models of gait have been proposed to define spatiotemporal gait characteristics in a structured manner (Verghese *et al.*, 2007; Hollman *et al.*, 2011; Lord *et al.*, 2013b; Verlinden *et al.*, 2013). These models use data reduction techniques to categorize gait characteristics by domain, such as pace and variability. Although comparable, there is no standardized model - different models emphasize different characteristics and domains. Both gait domains and independent gait characteristics should be reported to aid interpretation and strengthen research findings. This thesis will use Lord *et al.* (2013b)'s conceptual model of

gait, informed by principle component analysis and validated in older adults and PD, in order to structure data presentation and results throughout (see Figure 1-2, characteristics are hypothesized to represent different neural networks involved in gait).

Table 1-3 Definitions for commonly described characteristics of gait.

Gait Terms:	Definition:
Step	Every time a leg goes forward during walking
Step Length	Distance between the heel of a trailing foot and the heel of the leading foot.
Stride	When both a left and right footstep have been taken
Stride time	The time it takes to make a stride – also referred to as gait cycle duration.
Stance	When the foot is on the ground during walking – also referred to as single support duration.
Swing	When the foot is not on the ground during walking
Double Support	When both feet are on the ground during walking.
Velocity	Refers to the speed of walking – calculated as distance/time
Cadence	Number of steps per defined time measure (e.g. steps per minute)
Step width	Mediolateral distance between heels during double support
Pace	How fast or slow someone walks
Rhythm	Refers to temporal characteristics of walking, such as swing, stance and step time.
Variability	Changes in spatiotemporal parameters of gait, usually regarding step-to-step fluctuations. E.g., how much step length changes from one step to the next.
Asymmetry	The ratio between right and left steps
Postural control	Referring to characteristics contributing to keeping individuals upright during walking.

1.7.2 Gait factor domains

Lord *et al.* (2013b)'s model of gait includes domains pertaining to pace, rhythm, variability, asymmetry and postural control, which will now be described. Pace incorporates step velocity, step length and swing time variability and contributes to measures of gait speed. Rhythm refers to the temporal parameters of gait, such as swing time, step time and stance time. Gait variability describes the manner in which spatiotemporal characteristics of gait change across steps (Kirtley, 2006) and may have more discriminatory properties than other spatiotemporal measures such as gait velocity (Galna *et al.*, 2013). Asymmetry is a measure of the ratio between step time, swing time and stance time of each foot (Lord *et al.*, 2013b). Postural control is an important measure of balance ability during walking and is crucial for stable gait. Together, these five domains comprise key components of gait. Investigating changes across these characteristics could identify fall risk, improve knowledge of disease pathologies, map disease progression and guide interventions (Lord *et al.*, 2013b). Therefore, it is important to measure such a comprehensive battery of gait characteristics.

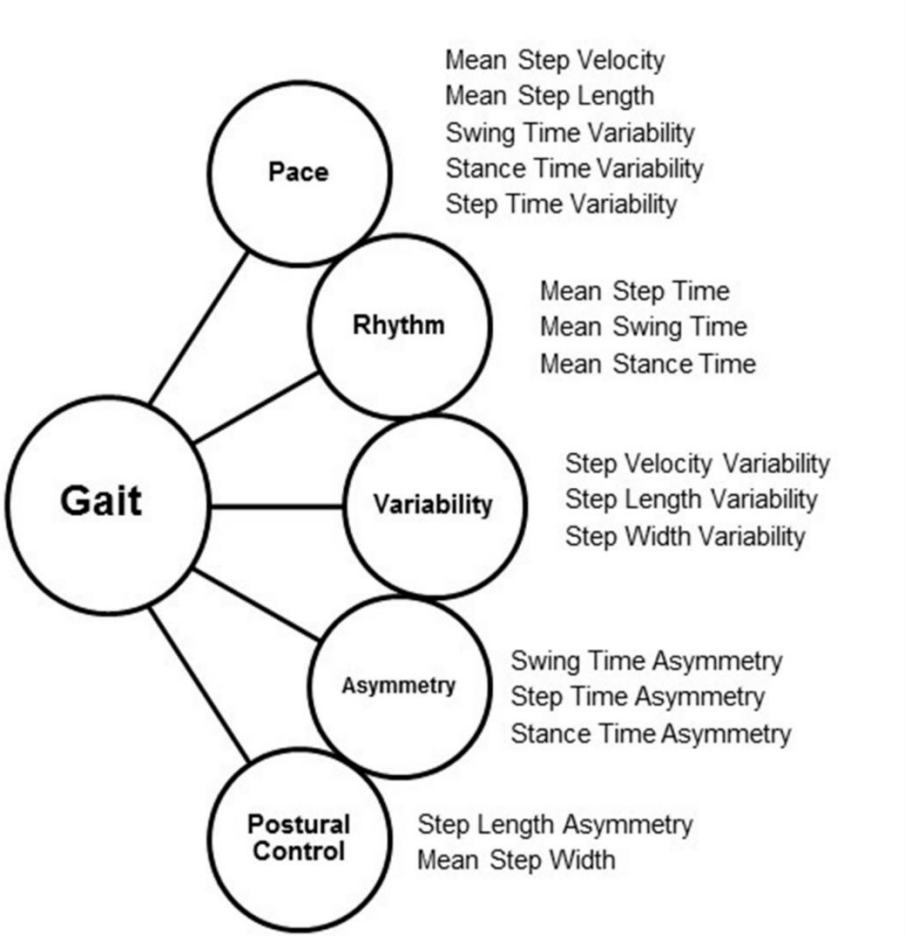

Figure 1-2 Lord et al., (2013b)'s conceptual model of gait for older adults. Gait domains include pace, rhythm, variability, asymmetry and postural control

1.8 Measuring gait

1.8.1 Lab-based gait analysis

Most gait assessments occur in controlled gait laboratories. This generally involves specialised validated equipment, such as multi-camera motion capture systems (Barker *et al.*, 2006) and instrumented walkways with pressure sensors (Nelson *et al.*, 2002; Tao *et al.*, 2012). These allow researchers to comprehensively characterise, detect, and monitor gait impairments in controlled environments. However, these systems can be expensive, require specialist research staff and have a limited area to walk within (Kosse *et al.*, 2015). Developments in technology have led to the advent of accelerometer based body-worn monitors, which provide an inexpensive method to conduct gait analysis (Tao *et al.*, 2012). Gait data collected from body-worn monitors are comparable to that provided by "gold-standard" instrumented walkways, due to the development of validated algorithms, which calculate a comprehensive battery of gait characteristics (Del Din *et al.*, 2016b; Del Din *et al.*,

2016c). Body-worn monitors have allowed researchers to take gait assessment outside of laboratory settings, and into the real world – also known as "free-living".

1.8.2 Free-living Gait Analysis

Body-worn sensors are an unobtrusive way of monitoring type, duration, intensity and quality of activity (Lord *et al.*, 2013c; Steins *et al.*, 2014; Del Din *et al.*, 2016a; Del Din *et al.*, 2016b). They can offer an objective measure of continuous unsupervised walking, which may provide a more accurate picture of an individual's gait profiles. Performing walking tasks in a laboratory is different in context and behaviour to that in real life (Awais *et al.*, 2015). In free-living, people engage within different functional domains, such as occupational, transportation, domestic and leisure, which change gait patterns. Gait is also influenced by environmental factors and requires more attention than a controlled laboratory in order to maintain postural control (Montero-Odasso *et al.*, 2012).

Research investigating the clinical utility of body-worn monitors is growing and has shown promising results. Free-living gait data identified fall risk in healthy older adults and PD, differentiated neurological populations from controls, such as PD and AD, and discriminated people with freezing of gait in PD from non-freezers, (Weiss *et al.*, 2013; Schwenk *et al.*, 2014; Weiss *et al.*, 2014; Weiss *et al.*, 2015b; Weiss *et al.*, 2015a; Del Din *et al.*, 2016b; Del Din *et al.*, 2017; Mancini *et al.*, 2018). Additionally, gait analysis in free-living conditions may provide a more sensitive measure of the relationship between gait and cognition as subjects undergo a heavier cognitive load while carrying out day-to-day tasks.

1.9 **Gait and cognition**

As previously stated, the overall relationship between gait and cognition have been established (Hausdorff *et al.*, 2005; Yogev-Seligmann *et al.*, 2008; Montero-Odasso *et al.*, 2012; Amboni *et al.*, 2013; Morris *et al.*, 2016). However, associations between cognitive domains and discrete gait characteristics are only emerging. Using Lord *et al.* (2013b)'s model of gait, associations between cognitive and gait domains can be mapped. Characteristics pertaining to pace are associated with global cognitive impairment, attention and executive dysfunction; slower pace is associated with global cognitive impairment (Morris *et al.*, 2016; Morris *et al.*, 2017; Mc Ardle *et al.*, 2018). Links between gait variability and attention have emerged, with patients with attentional difficulties and fluctuations demonstrating greater gait variability (Sheridan *et al.*, 2003; Morris *et al.*, 2017). A tentative relationship between aspects of rhythm and memory domains has been suggested, with changes in rhythm predicting memory decline (Verghese *et al.*, 2007). PD studies have

alluded that visuospatial abilities may be integral to postural stability, with associations between impairments and balance problems (Morris *et al.*, 2016). Currently, evidence of a relationship between cognition and gait asymmetry is very limited (Yogev *et al.*, 2007). Additionally, knowledge of the underlying pathological relationship between gait and cognition is still limited.

1.9.1 Gait and identification of cognitive impairment

Stage and type of cognitive impairment influences gait, as demonstrated in both MCI and dementia (Allali *et al.*, 2016). For example, MCI demonstrates more gait impairments than in healthy ageing but better gait performance than that in dementia (de Melo Borges *et al.*, 2015). Type of MCI also contributes to understanding this progression; gait deficits in amnestic-MCI (e.g. MCI due to AD) are significantly different from those in AD. However, gait in non-amnestic-MCI (e.g. MCI due to LBD or VaD) – specifically with executive function problems – was not distinguishable from AD (Persad *et al.*, 2008). This suggests neural pathways associated with mediating gait are affected similarly across dementia disease subtypes, but gait patterns may reflect different stages of disease. However, limited research surrounding gait differences across dementia disease subtypes makes it hard to extrapolate if different pathologies in dementia contribute to distinguishable signatures of gait. This will be discussed further in Chapter 2. Future research should investigate if different dementia disease subtypes have unique patterns of gait impairment, as this may provide a useful clinical tool for differential diagnosis (Montero-Odasso, 2016). Specifically, the potential for gait analysis to discriminate AD and DLB subtypes is of particular importance, due to their high rates of diagnosis and potential adverse effects of incorrect treatment, along with improving the accuracy of diagnosis when recruiting to clinical trials.

1.10 Thesis outline

This thesis aims to describe what gait impairment looks like in dementia disease subtypes compared to normal ageing, and investigate if gait can differentiate disease subtypes, with a particular focus on AD and DLB. This chapter has highlighted the importance of establishing unique patterns of gait impairment in different disease subtypes. The thesis breakdown will be outlined below.

Chapter 2: What can gait analysis tell us about dementia and its subtypes: A structured review

This chapter is adapted from a published structured review, exploring the current state of research into gait impairments across dementia subtypes. This review was undertaken to enhance understanding of current research and highlight gaps in the literature.

Aims

- Establish quantitatively assessed gait differences between dementia and non-cognitively impaired older adults.
- Review evidence for distinct gait profiles across dementia subtypes.
- Identify recommendations for future research.

Hypotheses

2.1. Gait will be more impaired across multiple domains in dementia compared to controls.

2.2. LBD and VaD will have slower pace and greater variability when walking compared to AD.

2.3. AD will have more pronounced impairments in temporal characteristics of gait.

Chapter 3: General Methods

This chapter will provide an overview of the GaitDem study, which formed the basis of this thesis. This will include details such as participant recruitment, clinical, cognitive and gait assessments, and statistical analysis applicable to all chapters. Further methodology will be described in relevant chapters.

Chapter 4: Gait impairments in dementia disease subtypes under laboratory conditions

This chapter investigates differences in gait impairments under single-task conditions across the spectrum of cognitive impairment and between dementia disease subtypes, and explain why gait impairments may occur.

Aims

- Investigate if gait impairment distinguishes normal ageing and in cognitive impairment due to AD, LBD and VaD.
- Investigate if gait impairment distinguishes the aforementioned disease subtypes from each other.
- Explore associations between discrete gait characteristics with cognitive domains across disease subtypes. It is important to also consider the role of motor disease

severity in gait impairment, to explore if cognition facilitates gait independent of motor control.

Hypotheses

4.1. Slower pace, greater variability and impaired characteristics of rhythm will distinguish AD from controls.

4.2. Slower gait velocity, shorter step length, greater variability and asymmetry of gait and a larger step width will distinguish LBD from controls and AD.

4.3. Patterns of gait impairment will be similar between DLB and PDD, but impairments will be more pronounced in PDD.

4.4. Slower pace and shorter steps will distinguish VaD from controls.

4.5. Characteristics of pace, variability and timing will be associated with cognitive functions associated with the prefrontal cortex, such as executive function, attention and visuospatial abilities. Characteristics of pace and timing will also be associated with motor disease.

4.6. The role of cognition in gait will be different between Alzheimer's disease and Lewy body disease due to different cognitive profiles inherent to the subtypes. Greater gait impairments in Lewy body disease will be explained by impairments in attention, visuospatial and executive functions.

Chapter 5: Spatiotemporal characteristics of gait in free-living environments in dementia disease subtypes

This chapter investigates differences in gait impairments under free-living conditions between dementia disease subtypes. It will consider explanations for gait impairment by considering cognition and motor disease.

Aims

- To investigate differences in patterns of gait impairment between dementia disease subtypes.
- To investigate the relationship between cognitive impairment, motor disease severity and discrete gait impairments in free-living conditions.

Hypotheses

5.1. All disease subtypes will walk slower with shorter steps, greater variability and asymmetry and longer stance time compared to controls.

5.2. The LBD groups will be distinguishable from the AD group by demonstrating greater variability and asymmetry of gait.
5.3. Characteristics of pace and variability will be associated with executive function and attention, while rhythm will be associated with memory.
5.4. Based on findings in Chapter 4, gait impairment in the LBD group will be predominately associated with cognition, while AD will show greater associations with motor disease severity.

Chapter 6: Setting the context: what does habitual walking behaviour look like in disease subtypes?

This chapter examines habitual walking behaviours between different disease subtypes and normal ageing. This allows an objective understanding of how much disease subtype affects walking behaviours, while providing a context for their spatiotemporal gait characteristics described in Chapter 5. This chapter also examines the factors that are associated with the amount, variability and pattern of everyday walking.

Aims

- Improve our understanding of habitual walking behaviours in people with cognitive impairment due to AD and LBD.
- Identify factors contributing to habitual walking behaviours in normal ageing and cognitively impaired populations.

Hypotheses

6.1. People with cognitive impairment will spend less time walking, with fewer steps and walking bouts, and demonstrate less variability in bout lengths and higher alpha scores compared to normal ageing. These differences will be amplified in DLB and PDD compared to AD.
6.2. People with cognitive impairment will spend less time in medium and sustained bouts compared to controls and similarly this will be more prominent in LBD compared to AD.
6.3. More severe motor symptoms and lower balance confidence will explain lower amounts of walking activity.
6.4. Cognitive impairment will be associated with less variability of bout length and higher alpha scores.

Chapter 7: Within the context: Patterns of gait impairment depend on length of walking bout in free-living environments

This chapter considers spatiotemporal gait characteristics in the context supplied by Chapter 6, examining how the length of a walking bout influences patterns of gait impairment across disease subtypes. It will consider explanations for gait impairment by considering cognition and motor disease.

Aims

- Investigate the impact of bout length on spatiotemporal gait characteristics and patterns of gait impairment.
- Explore associations between cognitive impairment, motor disease and gait impairments across bout length.

Hypotheses

7.1. Gait is faster with larger steps, less variability and asymmetry and quicker timing of the gait cycle as walking bout length increases. As such, patterns of gait impairment will differ dependent on bout length.

7.2. Medium bouts (30-60 seconds) and sustained bouts of walking (>60 seconds) will be the most useful for distinguishing patterns of gait impairment between disease subtypes.

7.3. The role of cognition in gait will vary depending on length of walking bout. Gait impairment in longer walking bouts will require greater cognitive contributions from attentional, executive and visuospatial functions, while gait impairment in shorter walking bouts will be associated with greater motor disease severity.

7.4. The role of cognition in gait will be different between disease subtypes. Gait impairments in AD will be predominately associated with motor disease severity, while in PDD and DLB they will be more greatly associated with impairments in attention, executive and visuospatial function and information processing.

Chapter 8: Thesis overview and conclusions

This chapter will provide a final overall summary of all chapters. It will outline key findings and the clinical implications of the thesis, along with discussion of limitations and recommendations for future research.

Chapter 2 What can gait analysis tell us about dementia and its subtypes? A structured review

As discussed in the first chapter, there is an intrinsic relationship between gait and cognition. As such, gait impairments often predict cognitive impairment and dementia. However, little is known regarding the presentation of gait impairment across dementia subtypes. This chapter is adapted and updated from a structured review undertaken to establish the current state of the literature surrounding gait impairments in dementia and its subtypes (Mc Ardle *et al.*, 2017).

2.1 Introduction

To date, there has not been a comprehensive review of gait impairments across dementia subtypes. The purpose of this review was to investigate the role of gait in differentiating dementia subtypes. This review will focus on the most common subtypes of dementia: Alzheimer's Disease (AD), vascular dementia (VaD) and Lewy body dementia (LBD; referring to dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD). This review will focus solely on single-task gait analysis as dual-task protocols (which involve walking while engaging in another task) vary widely in both methodology and type of secondary task (i.e. tests to assess different cognitive domains or manual function). Different tasks may produce different gait impairments and is therefore a subject for further detailed investigation beyond the scope of this review. Assessing differences in gait impairment during single-task walking is clinically useful, as it is a simple task to carry out and easy to understand – an important consideration for populations with cognitive impairment. For the purposes of this review, we will adopt a model of gait - Lord et al. [16] as a framework to provide structure to the synthesis of literature and aid interpretation of data (see Figure 1-2).

2.2 Aims and hypotheses

In consideration of this, the aims of this review are to:

- Establish quantitatively assessed gait differences between dementia and non-cognitively impaired older adults.
- Review evidence for distinct gait profiles across dementia subtypes.
- Identify recommendations for future research.

Hypotheses

2.1. Gait will be more impaired across multiple domains in dementia compared to controls.

2.2. LBD and VaD will have slower pace and greater variability when walking compared to AD.

2.3.AD will have more pronounced impairments in temporal characteristics of gait.

2.3 Methods

2.3.1 Search Strategy

Six databases were used for the search: Scopus, Embase, Web of Science, Psych Articles, Medline and Psychinfo. Key terms for the search strategy are detailed in Figure 2-1. The search was limited to papers published from 1946 to February 2018. Other eligible papers brought to the reviewers' attention were also considered. Articles were included if they: i) included at least one dementia subtype and control/other clinical cohort (i.e. Parkinson's disease; PD) or two dementia subtypes or at least one dementia subtype at different stages of disease severity; ii) included quantitative gait characteristics, obtained from electronic gait analysis, wearable technology, motion capture analysis or other suitable means; iii) were original articles; and iv) were written in English. Where an article included another clinical cohort (e.g. Parkinson's disease or mild cognitive impairment) or other clinical characteristics (e.g. urinary symptoms), only the data relating to dementia and gait was reviewed.

2.3.2 Data Extraction

One reviewer (R.M.A.) screened the titles from the initial search and two reviewers (R.M.A. and B.G.) independently screened the abstracts to identify potential articles. Full-text articles were retrieved when reviewers could not determine the eligibility of the study from the title and abstract. All full-length articles were reviewed by three reviewers (R.M.A, R.M and J.W).

Data were extracted from eligible articles. The key characteristics of interest were: (i) dementia subtypes included, (ii) gait parameters assessed, (iii) method of gait analysis, (iv) main findings of the study with respect to gait. A quality assessment was conducted separately by two reviewers (R.M.A and J.W) and overall quality scores were determined for each study (see Appendix A).

2.3.3 Interpretation of data

Due to the wide and varying range of gait characteristics, several groups have proposed models of gait that categorize gait characteristics by domain using data reduction techniques (Verghese *et al.*, 2007; Hollman *et al.*, 2011; Lord *et al.*, 2013b; Verlinden *et al.*, 2013). Although comparable, there is no standardized model - different models emphasize different

characteristics and domains. The model chosen for this review was validated in older adults and PD (see Figure 1-2). Gait characteristics across studies were broadly mapped onto five core domains pertaining to pace, variability, rhythm, asymmetry and postural control, and hypothesized to represent different neural networks involved in locomotor control in order to structure data presentation and interpretation of results for within this review (Morris *et al.*, 2016).

2.4 **Results**

2.4.1 Search Yield

The search strategy in October 2016 generated 11,515 papers after exclusion criteria were applied. After removing duplicates, 5211 papers remained from the search (see Figure 2-1). The initial title search yielded 376 papers with an abstract screening leaving 55 papers eligible for data extraction. Fourteen studies were excluded as they did not specify the subtype of dementia (n=10), were not relevant to the review (n=3) or had previously reported results in a paper included in the review (n=1). Data were extracted from 42 papers. After data extraction, a further 16 papers were removed as they only reported timed gait speed or used functional tasks which required additional tasks, such as the Timed Up and Go test. All papers were published between 1983 and 2016.

An updated search in February 2018 generated a further 1752 papers. After removing duplicates 1034 papers remained (see Figure 2-1). The title search resulted in 23 papers, with four papers remaining after an abstract screening. Three studies were excluded as they did not specify the subtype of dementia (n=2) or report comparison data between groups (n=1).

Out of the remaining 27 articles, the majority of studies investigated AD (n=26; 96%), followed by DLB (n=2; 7%), Parkinson's disease dementia (PDD; n=2; 7%), Lewy body dementia (LBD; n=1; 4%), VaD (n=1; 4%) and unspecified non-AD dementia (n=2; 7%). Two studies used Parkinson's disease (PD) for comparison, five used mild cognitive impairment (MCI) and 22 used older adult control groups.

2.4.2 Measurement of gait in dementia

Table 2-1 details the specific characteristics and findings for each of the reviewed papers. Quantitative gait analysis included the use of gait walkway systems (Visser, 1983; Webster *et al.*, 2006; Merory *et al.*, 2007; Nadkarni *et al.*, 2009a; Nadkarni *et al.*, 2009b; Ries *et al.*, 2009; Muir *et al.*, 2012; Gras *et al.*, 2015; Allali *et al.*, 2016), accelerometers (Gillain *et al.*,

2009; Maquet *et al.*, 2010; Choi *et al.*, 2011; Lamoth *et al.*, 2011; Hsu *et al.*, 2014; Konig *et al.*, 2017), motion capture analysis systems (Nakamura *et al.*, 1996; Nakamura *et al.*, 1997; Barbieri *et al.*, 2015; Simieli *et al.*, 2015; Lin *et al.*, 2016), pressurized foot-sensors (Goldman *et al.*, 1998; Goldman *et al.*, 1999; Nadkarni *et al.*, 2009a; Nadkarni *et al.*, 2012; Fritz *et al.*, 2016) and combinations of these and other methods such as forceplates (Suttanon *et al.*, 2012) and digital cameras (Coelho *et al.*, 2012). One study did not define the instruments they used (Tanaka *et al.*, 1995).

To examine the wide range of reported gait parameters, all gait characteristics were mapped to one of the five domains of gait (Lord *et al.*, 2013b). Commonly described gait parameters have been described in Supplementary Table 2. All 27 papers investigated pace (Visser, 1983; Tanaka *et al.*, 1995; Nakamura *et al.*, 1996; Nakamura *et al.*, 1997; Goldman *et al.*, 1998; Goldman *et al.*, 1999; Webster *et al.*, 2006; Merory *et al.*, 2007; Gillain *et al.*, 2009; Nadkarni *et al.*, 2009a; Nadkarni *et al.*, 2009b; Ries *et al.*, 2009; Maquet *et al.*, 2010; Choi *et al.*, 2011; Lamoth *et al.*, 2011; Coelho *et al.*, 2012; Muir *et al.*, 2012; Nadkarni *et al.*, 2012; Suttanon *et al.*, 2012; Hsu *et al.*, 2014; Barbieri *et al.*, 2015; Gras *et al.*, 2015; Simieli *et al.*, 2015; Allali *et al.*, 2016; Fritz *et al.*, 2016; Lin *et al.*, 2016; Konig *et al.*, 2017), 18 studies described characteristics relating to rhythm (Visser, 1983; Nakamura *et al.*, 1997; Merory *et al.*, 2007; Gillain *et al.*, 2009; Nadkarni *et al.*, 2009a; Nadkarni *et al.*, 2009b; Maquet *et al.*, 2010; Lamoth *et al.*, 2011; Coelho *et al.*, 2012; Nadkarni *et al.*, 2012; Hsu *et al.*, 2014; Barbieri *et al.*, 2015; Gras *et al.*, 2015; Simieli *et al.*, 2015; Allali *et al.*, 2016; Fritz *et al.*, 2016; Lin *et al.*, 2016; Konig *et al.*, 2017), 13 studies reported gait variability (Visser, 1983; Nakamura *et al.*, 1996; Nakamura *et al.*, 1997; Webster *et al.*, 2006; Gillain *et al.*, 2009; Nadkarni *et al.*, 2009a; Maquet *et al.*, 2010; Choi *et al.*, 2011; Lamoth *et al.*, 2011; Barbieri *et al.*, 2015; Allali *et al.*, 2016; Fritz *et al.*, 2016; Lin *et al.*, 2016), two studies described characteristics of gait asymmetry (Gillain *et al.*, 2009; Maquet *et al.*, 2010) and nine reported parameters relating to postural control (Tanaka *et al.*, 1995; Webster *et al.*, 2006; Merory *et al.*, 2007; Nadkarni *et al.*, 2009a; Nadkarni *et al.*, 2009b; Suttanon *et al.*, 2012; Barbieri *et al.*, 2015; Simieli *et al.*, 2015; Allali *et al.*, 2016; Fritz *et al.*, 2016).

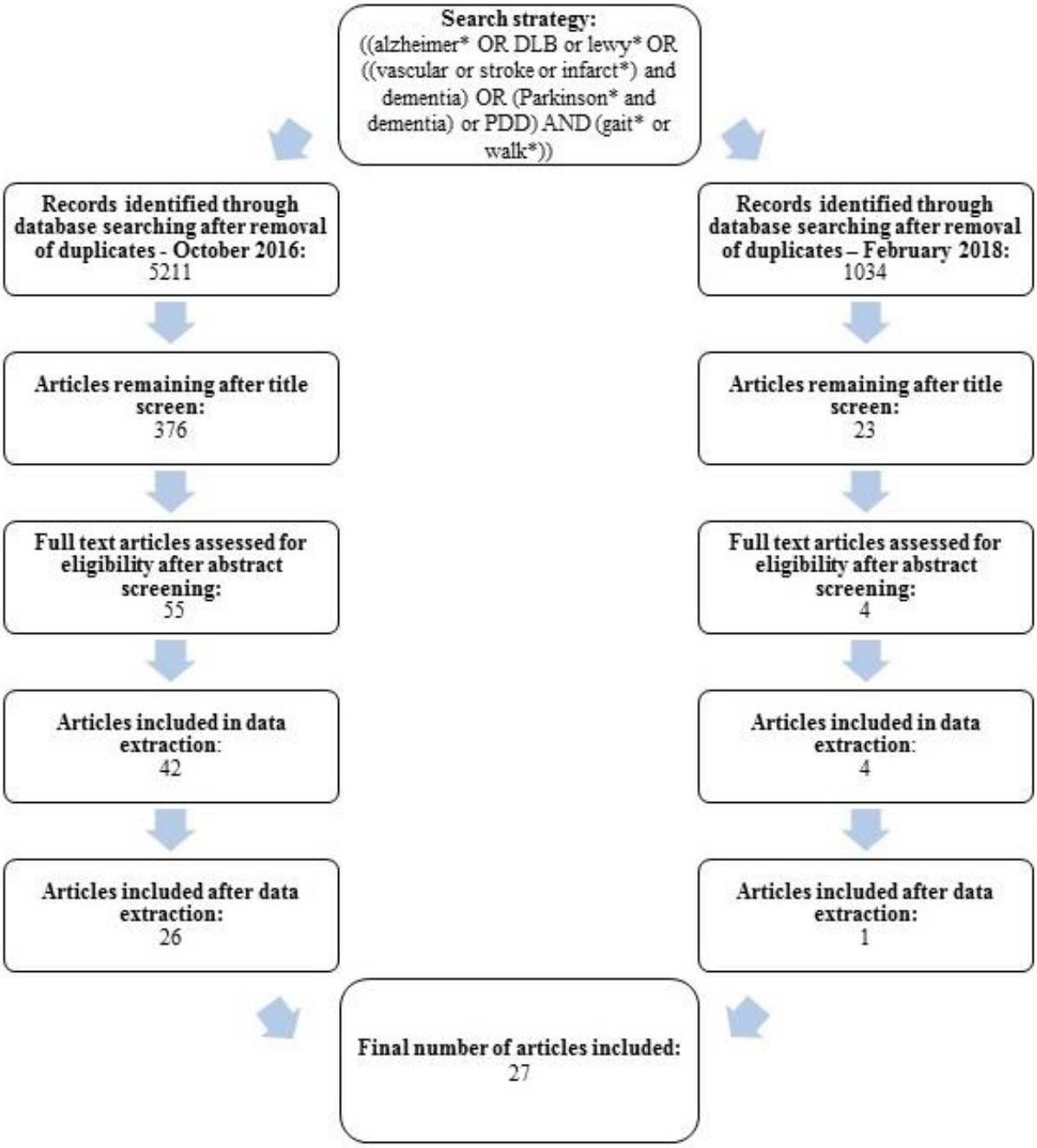

Figure 2-1 Flowchart of search strategy and extraction of eligible studies

2.4.3 Gait impairments in Alzheimer's Disease

27 studies assessed gait in AD (Visser, 1983; Tanaka *et al.*, 1995; Nakamura *et al.*, 1996; Nakamura *et al.*, 1997; Goldman *et al.*, 1999; Webster *et al.*, 2006; Merory *et al.*, 2007; Gillain *et al.*, 2009; Nadkarni *et al.*, 2009a; Nadkarni *et al.*, 2009b; Ries *et al.*, 2009; Maquet *et al.*, 2010; Choi *et al.*, 2011; Lamoth *et al.*, 2011; Coelho *et al.*, 2012; Muir *et al.*, 2012; Nadkarni *et al.*, 2012; Suttanon *et al.*, 2012; Hsu *et al.*, 2014; Barbieri *et al.*, 2015; Gras *et al.*, 2015; Simieli *et al.*, 2015; Fritz *et al.*, 2016; Lin *et al.*, 2016; Konig *et al.*, 2017); 22 of these

studies compared AD to controls (Visser, 1983; Tanaka *et al.*, 1995; Nakamura *et al.*, 1997; Goldman *et al.*, 1999; Webster *et al.*, 2006; Merory *et al.*, 2007; Gillain *et al.*, 2009; Nadkarni *et al.*, 2009a; Nadkarni *et al.*, 2009b; Maquet *et al.*, 2010; Choi *et al.*, 2011; Lamoth *et al.*, 2011; Muir *et al.*, 2012; Nadkarni *et al.*, 2012; Suttanon *et al.*, 2012; Hsu *et al.*, 2014; Barbieri *et al.*, 2015; Gras *et al.*, 2015; Simieli *et al.*, 2015; Allali *et al.*, 2016; Lin *et al.*, 2016; Konig *et al.*, 2017), four studies compared AD to other dementia subtypes (Tanaka *et al.*, 1995; Merory *et al.*, 2007; Allali *et al.*, 2016; Fritz *et al.*, 2016), five compared AD to MCI (Gillain *et al.*, 2009; Maquet *et al.*, 2010; Choi *et al.*, 2011; Muir *et al.*, 2012; Konig *et al.*, 2017) and four studies compared AD severity levels (Nakamura *et al.*, 1996; Goldman *et al.*, 1999; Ries *et al.*, 2009; Coelho *et al.*, 2012).

In AD, all 26 studies assessed characteristics of pace, such as step velocity, step length, step, stance and swing time variability (Visser, 1983; Tanaka *et al.*, 1995; Nakamura *et al.*, 1996; Nakamura *et al.*, 1997; Goldman *et al.*, 1999; Webster *et al.*, 2006; Merory *et al.*, 2007; Gillain *et al.*, 2009; Nadkarni *et al.*, 2009a; Nadkarni *et al.*, 2009b; Ries *et al.*, 2009; Maquet *et al.*, 2010; Choi *et al.*, 2011; Lamoth *et al.*, 2011; Coelho *et al.*, 2012; Muir *et al.*, 2012; Nadkarni *et al.*, 2012; Suttanon *et al.*, 2012; Hsu *et al.*, 2014; Barbieri *et al.*, 2015; Gras *et al.*, 2015; Simieli *et al.*, 2015; Allali *et al.*, 2016; Fritz *et al.*, 2016; Lin *et al.*, 2016; Konig *et al.*, 2017) (See table 2 for specific study details). People with AD typically walked with slower pace (Visser, 1983; Tanaka *et al.*, 1995; Nakamura *et al.*, 1997; Goldman *et al.*, 1999; Webster *et al.*, 2006; Merory *et al.*, 2007; Gillain *et al.*, 2009; Nadkarni *et al.*, 2009a; Nadkarni *et al.*, 2009b; Maquet *et al.*, 2010; Choi *et al.*, 2011; Lamoth *et al.*, 2011; Muir *et al.*, 2012; Nadkarni *et al.*, 2012; Suttanon *et al.*, 2012; Hsu *et al.*, 2014; Barbieri *et al.*, 2015; Gras *et al.*, 2015; Simieli *et al.*, 2015; Allali *et al.*, 2016; Lin *et al.*, 2016; Konig *et al.*, 2017) compared to controls, and were more impaired in severe AD (Nakamura *et al.*, 1997; Goldman *et al.*, 1999). Slower pace was also reported in AD compared to controls with low levels of white matter subcortical hyperintensities but not compared to controls with high levels of subcortical hyperintensities (Nadkarni *et al.*, 2009b).

In AD, 19 studies assessed characteristics of rhythm, such as step, swing and stance time (Visser, 1983; Nakamura *et al.*, 1997; Merory *et al.*, 2007; Gillain *et al.*, 2009; Nadkarni *et al.*, 2009a; Nadkarni *et al.*, 2009b; Maquet *et al.*, 2010; Lamoth *et al.*, 2011; Coelho *et al.*, 2012; Nadkarni *et al.*, 2012; Hsu *et al.*, 2014; Barbieri *et al.*, 2015; Gras *et al.*, 2015; Simieli *et al.*, 2015; Allali *et al.*, 2016; Fritz *et al.*, 2016; Lin *et al.*, 2016; Konig *et al.*, 2017). The majority found impaired rhythm in AD compared to controls (Visser, 1983; Merory *et al.*, 2007; Nadkarni *et al.*, 2009a; Maquet *et al.*, 2010; Hsu *et al.*, 2014; Barbieri *et al.*, 2015; Gras

et al., 2015; Simieli *et al.*, 2015; Allali *et al.*, 2016; Lin *et al.*, 2016; Konig *et al.*, 2017). One study found impaired rhythm with increased dementia severity (Nakamura *et al.*, 1997). One study found impaired rhythm in AD compared to controls with low levels of subcortical hyperintensities but not high levels (Nadkarni *et al.*, 2009b).

In AD, 12 studies assessed features of variability, such as step velocity, step length and step width variability (Visser, 1983; Nakamura *et al.*, 1996; Nakamura *et al.*, 1997; Webster *et al.*, 2006; Gillain *et al.*, 2009; Maquet *et al.*, 2010; Choi *et al.*, 2011; Lamoth *et al.*, 2011; Barbieri *et al.*, 2015; Allali *et al.*, 2016; Fritz *et al.*, 2016; Lin *et al.*, 2016). Results were inconsistent between AD and controls; five studies found greater variability in AD (Nakamura *et al.*, 1996; Webster *et al.*, 2006; Maquet *et al.*, 2010; Barbieri *et al.*, 2015; Allali *et al.*, 2016) while four did not (Visser, 1983; Gillain *et al.*, 2009; Choi *et al.*, 2011; Lin *et al.*, 2016).

In AD, only two studies assessed features of asymmetry such as step time, swing and stance asymmetry (Gillain *et al.*, 2009; Maquet *et al.*, 2010). Both compared AD to controls and MCI cohorts; no significant differences were found between any groups. In AD, nine studies assessed postural control of gait such as step width and step length asymmetry (Tanaka et al., 1995; Webster et al., 2006; Merory et al., 2007; Nadkarni et al., 2009a; Suttanon et al., 2012; Barbieri et al., 2015; Simieli et al., 2015; Allali et al., 2016). Typically, there were no significant differences between AD and controls for postural control characteristics of gait (Tanaka *et al.*, 1995; Webster *et al.*, 2006; Merory *et al.*, 2007; Nadkarni *et al.*, 2009a; Nadkarni *et al.*, 2009b; Suttanon *et al.*, 2012; Barbieri *et al.*, 2015; Simieli *et al.*, 2015).

Table 2-1 Descriptive information, methodology and main study findings of all studies

Study	Participant Characteristics	Diagnostic Criteria	Severity Rating	Gait analysis tool (distance)	Gait parameters measured (units)	Main study findings
Merory *et al.* (2007)	10 AD; 8M/2F, age: 76±6, MMSE: 28.7±1.2, UPDRS: 2.7±4.2 10 DLB; 8M/2F; age: 73±5, MMSE: 23.5±4, UPDRS: 27.1±9.4 10 Controls; 8M/2F, age: 72±7, MMSE: 28.7±1.2 Groups split by subcortical hyperintensity severity: (+) high severity, (-) low severity	AD: NINCDS-ADRDA DLB: McKeith	Not specified	GAITRite (8.3m x 0.89m)	Velocity (not specified) Cadence (not specified) Stride length (not specified) Step width (not specified) Double support time (not specified)	AD and DLB: slower velocity, shorter stride length and longer double support time compared to controls. No significant differences between AD and DLB
(Webster *et al.*, 2006)	42 AD; 60%F, age: 74±8, MMSE: 25±3, UPDRS: 7±7. 21 AD -; 68%F, age: 71±9, MMSE: 24±3, UPDRS ±3±3 21 AD+; 52%F, age: 77±6, MMSE: 25±2, UPDRS: 11±9 33 Controls; 47%, age: 73±8, MMSE: 29±1, UPDRS, 3±4 18 Controls -; 44%F, age: 69±7, MMSE: 29±1, UPDRS: 1±3 15 Controls +; 53%F, 76±7, MMSE: 28±1.3, UPDRS: 3±3	NINCDS-ADRDA – probable AD	MMSE ≥ 20. Dementia Rating Scale FAST 4/5: mild – moderate AD	GAITRite (2 x 12ft)	Velocity (cm/s) Stride Length (cm) Cadence (Steps/min) Step width (cm)	Controls -: faster velocity compared to controls +, AD – and AD +. Stride length longer and cadence higher compared to AD – and AD +
Ries *et al.* (2009)	20 mild-moderate AD; 60%F, age: 81.05±9.48, MMSE: 17.4±4.5 31 moderate-severe AD; 70.7%F, age: 80.48±8.43, MMSE: 10.20±8.83	Not specified	FAST 6/7: moderate – severe AD	GAITRite (15ft)	Gait speed (cm/s)	Moderate-severe AD had a slower gait speed on the GAITRite.
Gras *et al.* (2015)	13 AD; 10M/3F, age: 72.9±4.7, MMSE: 24.8±2.6	NINCDS-ADRDA	CDR 0.5: very mild AD	GAITRite (4.88m)	Velocity (m/s) Stance time (s)	AD: slower velocity, longer stance time, shorter step length compared to controls.

	13 Controls; 10M/3F, age: 72.6±4.6, MMSE: 29±1				Step length (m)	
Visser (1983)	11 AD; 2M/9F, age: 78.8±2.5. 11 Controls; 2M/9F, age: 78.3±2.6	Not specified	Set Test (Isaacs & Akhtar): severe dementia - < 10, moderate dementia – 10-20	Specially designed walkway with sensors (6m)	Speed (m/s) Step frequency (steps/sec) Step length (cm) Double support ratio (%) CV step length (%)	AD: slower walking speed, shorter step length, lower step frequency and longer double support ratio compared to controls
Gillain *et al.* (2009)	6 AD; 9%M, 9%F (overall sample), age: 73.66, MMSE: 22.83±2.14, education: 9.33±3.78 14 MCI; 21%M, 21%F, age: 72.85, MMSE: 26.71±1.68, education: 13.64±3.3 14 Controls; 19%M, 21%F, age: 75.53, MMSE: 28.21±1.58, education: 13.71±3.73	AD: NINCDS-ADRDA MCI: Confirmed isolated cognitive disorder that doesn't affect activities of daily living	CDR 0.5: MCI CDR 1: AD MMSE ≥ 24 – MCI MMSE ≥ 20 - AD	Tri-axial accelerometer (40m x 2 times)	Gait speed (m/s) Stride frequency (hz) Stride length (m) Regularity (dimensionless) Symmetry (dimensionless) Stops	AD: Slower speed and shorter stride length compared to controls. AD had less regularity compared to MCI. MCI had less stride frequency compared to controls.
Maquet *et al.* (2010)	6 AD; 3M/3F, age: 74±4 14 MCI; 7M/7F, age: 73±4 14 Controls; 7M/7F, age: 74±5	AD: NINCDS-ADRDA a-MCI: Pearson et al, 2001 na-MCI: Winblad et al, 2004	CDR 0.5: MCI CDR 1: AD MMSE 24≥ - MCI MMSE 20≥ - AD	Accelerometer (45m x 2times)	Walking speed (m/s) Stride frequency (hz) Stride length (m) Symmetry (au) Regularity (au) Stops (au)	AD: slower walking speed, lower stride frequency, shorter stride length and less regularity compared to controls. AD: slower walking speed, lower stride frequency, shorter stride length and less regularity compared to MCI. MCI: less stride frequency compared to controls.
Choi *et al.* (2011)	10 AD; 4M/6F, age: 77.2±6.84 7 MCI; 4M/3F, age: 72.9±6.28 6 Controls; 4M/2F, age: 71.6±5.78	Not specified	Not specified	Tri-axial accelerometer (100m)	Stride time (not defined) CV stride time Detrended fluctuation analysis Spectral analysis (LF/HF ratio)	AD: greater CV stride time compared to controls. AD: greater CV stride time compared to MCI. MCI: slower stride time, greater CV stride time and greater LF/HF ratio compared to controls.

Lamoth *et al.* (2011)	13 AD; 4M/9F, age: 82.62±4.29, MMSE: 18±3.54 13 Controls; 6M/7F, age: 79.38±5.55, MMSE: 28.23±1.09 10 mild AD fallers; 2M/8F, age: 75.4±2.5, MMSE: 17.8±2.1, disease duration: 2.9±0.7 40 mild AD non-fallers; 9M/31F, age: 74.6±2.7, MMSE: 18±1.8, disease duration: 3.1±0.5	Criteria of Alzheimer's Association	MMSE < 23	Tri-axial accelerometer	Speed (m/sec) Stride frequency (stride/sec) Stride time (sec) CV stride time (%) Phase variability index (%) Stride-to-stride variability (%)	No significant differences found between groups
Nakamura *et al.* (1996)	18 moderate AD fallers; 5M/13F, age: 74.8±2.3, MMSE: 11.3±2.6, disease duration: 6.0±0.8 29 moderate AD non-fallers: 8M/21F, age: 76±3, MMSE: 12.2±2.1, disease duration: 5.8±1 45 AD; 13M/32F, age: 76.8 (73-82) – Split by severity levels. 15 CDR1; 5M/10F, age: 75.9±3.6, MMSE: 18.6±1.7, disease duration: 2.2±1.8 15 CDR2; 4M/11F, age: 77.5±4.0, MMSE: 11.4±2.6, disease duration: 4.3±1.6 15 CDR3; 4M/11F, age: 78.1±3.2, MMSE: 6.8±2.4, disease duration: 7.0±2.1	NINCDS-ADRDA – probable AD DSM-III-R	MMSE CDR 1: Mild A CDR 2: Moderate AD	Motion capture analysis system (10 strides)	Speed Stride length CV stride length (%)	Moderate AD had a slower walking speed, shorter stride length and greater CV stride length compared to mild AD. AD -Moderate and severe: slower walking speed, shorter stride length, longer double support time, greater CV stride length compared to controls. AD – mild: did not differ from controls.
Nakamura *et al.* (1997)	15 Controls; 5M/10F, age: 77.1±3.4, MMSE: 27.4±1.3	DSM-III-R criteria for probable AD. NINCDS-ADRDA	MMSE CDR1: Mild CDR2: Moderate CDR3: Severe	Motion capture analysis system (10m)	Walking speed (m/s) Stride length (m) Double support time (s) CV stride length (%) Stride length (cm) Step width (cm)	Statistical comparisons between dementia severity groups not reported but trend implies that gait impairments worsen with progression of dementia. AD: shorter stride length, double-support duration, longer stride duration, slower stride velocity, greater CV stride length, greater CV double support time and greater CV stride duration compared to controls.
Barbieri *et al.* (2015)	15 AD; age: 78.33±5.23, MMSE: 17.73±3.93. 15 Controls: age: 77.44± 6.19, MMSE: 27.4±2.38.	Not specified	CDR Neuropsychiatric inventory	Motion capture analysis system (8m)	Stride duration (s) Stride velocity (cm/s) Double support duration (%) CV stride length (%)	

Simieli *et al.* (2015)	18 AD; 4M/15F, age: 78.33±5.23 15 Controls; age: 77.44±6.19	DSM-IV-TR and International Disease Code	CDR 1 and CDR 2 Neuropsychiatric inventory	Motion capture analysis system (8m)	CV step width (%) CV stride duration (%) CV stride velocity (%) CV double support duration (%) Stride length (cm) Step width (cm) Single support duration (s) Double support time (s) Stride duration (s) Stride velocity (cm/s) Velocity (leg length/sec) Cadence (steps/min)	AD: shorter stride length, shorter stride width, slower stride velocity, longer single support duration, longer double support time and longer stride duration compared to controls
Lin *et al.* (2016)	10 AD; 2M/8F, age: 74±8.6, MMSE: 17.7±4.1. 10 Controls, 2M/8F, age: 73.8±6.1, MMSE: 29.4±0.7	Criteria not specified.	CDR: 0.8±0.3 - mild	Motion capture analysis system (8m)	Stride length (leg length) CV stride length (%) Stride time (s) CV stride time (%)	AD: slower velocity, less cadence and longer stride time compared to controls.
Goldman *et al.* (1999)	40 very mild AD; 19M/21F, age: 71.98±7.51, education: 13.72±3.36 20 mild AD; 9M/11F, age: 73.68±7.82, education: 12.05±3.63 43 Controls; 21M/22F, age: 73.22±7.70, education: 14.44±3.26	NINCDS-ADRDA	CDR 0.5: very mild CDR 1: mild	Electric contact footpads with pressure-activated foot-switches (10m)	Velocity (distance/time)	Mild AD: slower velocity compared to controls. Very mild AD: did not differ from controls Mild AD: slower velocity compared to very mild AD.
Goldman *et al.* (1998)	22 PDD; 19M/3F, age: 71.6±7.8, education: 13.7±3.7 58 PD; 42M/16F, age: 69.7±6.0, education: 14.8±3.1 43 Controls; 21M/22F, age: 73.2±7.7, education: 14.4±3.3	Not specified	CDR 0.5: Questionable dementia	Electric contact footpads with pressure-activated foot-switches (10m)	Velocity (cm/s)	PDD: slower velocity compared to controls but did not differ from PD.

Nadkarni *et al.* (2009a)	40 AD; 55%F, age: 74±8, MMSE: 25±3, UPDRS: 7±8. 34 Controls; 45F, age: 73±8, MMSE: 29±1, UPDRS: 2±4	NINCDS-ADRDA	MMSE Dementia Rating Scale	GAITRite (2 x 12ft). Footswitches with motorised treadmill.	GAITRite: Velocity (cm/s) Cadence (steps/min) Stride length (cm) Cycle time (s) Stride width (cm) Double support time (s) Treadmill: Belt speed (cm/s) Cadence (steps/min) Cycle time (s) Double support time (s) CV cycle time (%) CV double support time (%) Overground gait speed (m/s) Self-selected treadmill walking speed (m/s)	GAITRite: AD had a slower velocity, less cadence, shorter stride length, longer cycle time and longer double support time than controls. Treadmill: AD had a slower belt speed and less cadence than controls compared to controls.
Nadkarni *et al.* (2009b)	24 AD; 60%F, age: 75±9, MMSE: 25±3, UPDRS: 6±7 20 Controls; 47%F, age: 72±8, MMSE: 29±1, UPDRS: 3±4	NINCDS-ADRDA – probable AD	MMSE Mattis Dementia Rating Scale	Footswitches on a motorised treadmill.	Cadence (not defined) Cycle time (not defined) Double support time (not defined)	AD: slower overground gait and slower self-selected treadmill walking speed compared to controls.
Fritz *et al.* (2016)	21 AD; 13M/8F, age: 75.05±4.96, MMSE: 22.43±4.25, education: 14.67±2.13, UPDRS: 3.9±3.62 21 LBD; 13M/8F, age: 73.95±4.78, MMSE: 22.57±3.57, education: 15.57±2.58, UPDRS: 25.95±5.82 LBD group split into subtypes DLB and PDD. 11 DLB; 6M/5F, age: 73.7±4.59, MMSE: 24.45±4.46, education: 15.54±2.38, UPDRS: 24.45±6.3 10 PDD; 7M/3F, age: 74.2±5.16, MMSE: 27.6±2.51, education: 15.6±2.91, UPDRS: 27.6±5.04 21 PD; 13M/8F, age: 72.38±4.72,	AD: NINCDS-ADRDA – probable DLB: McKeith PDD: Emre	Not defined	GAITRite	Velocity (m/s) Stride length (m) Swing (%) Swing time (s) Stance(%) Double support (%) CV step time (%) CV step length (%) CV stride length (%) CV swing time (%) CV stance time (%) CV double support time (%)	LBD: slower velocity, shorter stride length, longer stance time, longer double support time, decreased CV double support time compared to PD. AD: No differences found between AD and PD. CV measures were not investigated between AD and PD. LBD vs AD: slower velocity, shorter stride length, decreased swing, longer stance time, longer double support time, greater CV step time, greater CV step length, greater stride length, CV swing time and took longer to complete

	MMSE: 27.81±1.36, education: 14.86±2.31, UPDRS: 25.52±5.89					TUG compared to AD. DLB vs PDD: No significant differences between groups – CV differences not reported between groups.
Suttanon *et al.* (2012)	25 AD; 9M/16F, age: 81 (78.4-83.5), MMSE: 21.1 (19.2-23) 25 Controls; 9M/16F, age: 80.4 (78-82.7), MMSE: 29.2 (28.5-29.8)	Not specified	MMSE ≥ 10 – mild-moderate dementia	Forceplate (360cm)	Step width (cm) Step length (cm) Walking speed (m/s)	AD: slower walking speed and shorter step length compared to controls.
Coelho *et al.* (2012)	12 Mild AD; age: 75.7±6.8, MMSE: 22±2.2, education: 5.5±3.0. 11 Moderate AD; age: 80.1±7.5, MMSE: 16.2±2.2, education: 3.5±1.1	DSM IV - TR	CDR 1: Mild CDR 2: Moderate	Digital camera with passive marker (8m x 1.4m).	Stride length (m) Stride speed (m/s) Cadence (strides/sec)	Moderate AD had a shorter stride length and slower stride speed compared to mild AD.
Tanaka *et al.* (1995)	15 AD; 15F, age: 79.8±4.6 15 VaD; 15F, age: 80.3±4.4 15 Controls; 15F, age: 78.3±6.9	DSM IIIR	MMSE, CDR	10m walkway 3 times. Measurement of gait parameters not specified.	Walking velocity (m/s) Step length (mm) Step width (mm) Speed (m/s)	VaD and AD: slower velocity and shorter step length compared to controls VaD: slower velocity and shorter step length compared to AD.
Allali *et al.* (2016)	10 AD; 7M/3F, age: 77.6±5.5, MMSE: 18.9±3.9 10 Controls; 7M/3F, age: 72.4±6.5, MMSE: 28.4±1.7 196 mild AD; 134F, age: 82.5±5.1 177 moderate AD; 121F, age: 83.9±5.6 126 mild non-AD; 71F, age: 81.9±5.1 91 moderate non-AD; 52F, age: 83.3±5.2 108 a-MCI; 40F, age: 76.7±7.9 286 na-MCI; 134F, age: 75.5±6.6 735 Controls; 374F, age: 73.9±6.3	NINCDS-ADRDA Dementia subtypes: DSM-IV apart from TASCOG cohort (self-report, medical review, cognitive testing, clinical interview)	Not specified Mild dementia: CDR 1, MMSE ≥20 Moderate: CDR 2, MMSE 19-10	GAITRite (8m) GAITRite (ranging from 4.6m to 7.9m)	Stride length (m) CV stride length (%) Step width (cm) CV step width (%) Walking speed (cm/s) Stride length (cm) Stride time (ms) Swing time (ms) Stance time (ms) Single support time (ms) Double support time (ms) Stride width (cm) Stride velocity (m/s) CV stride length (%) CV stride time (%)	AD: slower speed, shorter stride length and greater CV stride length compared to controls. All dementia groups (mild/moderate AD and non-AD) had slower walking speed, shorter stride length, greater CV stride length, longer stride time, greater CV stride time, longer stance time, greater CV stance time, greater CV single support time, longer double support time, greater CV double support time, slower stride velocity and greater CV stride velocity compared to controls. All dementia groups except mild

		MCI subtypes: spontaneous cognitive complaints and objective impairment in memory/multiple domains			CV swing time (%) CV stance time (%) CV single support time (%) CV double support time (%) CV stride width (%) CV stride velocity (%)	AD demonstrated larger stride width and less CV stride width variability compared to controls. Only mild AD showed longer single support time compared to controls. Mild dementia: OD had greater CV stride length, larger stride width, less CV stride width and greater CV stride velocity compared to AD. Moderate dementia: OD had slower walking speed, shorter stride length, longer stance time, greater CV stance time, larger stride width, and slower stride velocity compared to AD. a-MCI: slower walking speed, greater CV stance time, slower stride velocity and greater CV stride velocity compared to controls. na-MCI: slower walking speed, shorter stride length, greater CV stride length, slower stride time, greater CV stride time, longer stance time, greater CV stance time, greater CV single support time, longer double support time, greater CV double support time, slower stride velocity and greater CV stride velocity compared to controls.
Muir *et al.* (2012)	23 AD; 14F, age: 77.5±5, MMSE: 24.2±2.3, education: 12.3±3.4 29 MCI; 17F, age: 73.6±6.2, MMSE: 27.5±1.9 22 Controls; 19F, age: 71±5, MMSE: 29.5±0.6, education: 13.4±3.1	AD: NINCDS-ADRDA MCI: Subjective memory complaint, report of	CDR 0.5: MCI MMSE 20≥ - AD	GAITRite (600cm x 64cm)	Gait velocity (cm/s) Stride time (ms) CV stride time (%)	No significant differences between groups

		cognitive deterioration, objective memory impairment in cognitive tests with lack of functional impairment and absence of clinical dementia				
Hsu *et al.* (2014)	21 AD; 10M/11F, age: 61.48±4.85, MMSE: 23±3.23 50 Controls; 20M/30F, age: 59.86±4.62, MMSE: 28.38±1.55	Not specified	Not specified	Wearable device with tri-axial accelerometer, bi-axial gyroscope, uni-axial gyroscope, microcontroller and micro SD flash card	No. of strides (count) Walking time (s) Stride length (m) Stride frequency (hz) Stride speed (m/s) Stride cadence (stride/min) Stride time (s) Stance time (s) CV stride time (%) CV stance time (%) CV swing time (%) Stance period (%) Swing time (%) CV stance period (%) CV swing period (%)	AD: higher number of strides, slower walking time, shorter stride length, slower stride speed, longer stance time, longer stance period, shorter swing period, greater CV stance period and greater CV swing period compared to controls.
(Konig *et al.*, 2017)	23 AD; 12M/11F, age: 77±9, MMSE 17±4.62 24 MCI; 8M/16F, age: 75±9, MMSE: 24.75±3.18 22 controls; 5M/15F, age:73±7, MMSE: 28.35±1.5	AD: Dubois *et al.* (2014) MCI: Peterson et al., 1999	MCI: MMSE ≥ 24	CE-marked accelerometer research prototype (Philips Research Labratories Europe) – wristworn.	Walking speed (s) Cadence (steps/min) Step variance (s)	AD: Trends indicate AD were slower with decreased cadence and greater step variance compared to MCI and controls. MCI: Trends indicate MCI slower, with decreased cadence and greater step variance compared to AD.

MMSE = Mini Mental State Examination; UPDRS = Unified Parkinson's Disease Rating Scale; FAST = Functional Assessment Staging Test; CDR = Clinical Dementia Rating scale

2.4.4 Gait impairments in Lewy Body Dementia

In LBD, three studies assessed gait. All studies assessed characteristics of pace (Goldman *et al.*, 1998; Merory *et al.*, 2007; Fritz *et al.*, 2016) and generally found slower pace compared to controls (Goldman *et al.*, 1998; Merory *et al.*, 2007). Findings were also inconsistent between LBD and PD, with one study reporting slower pace in LBD (Fritz *et al.*, 2016) and another study showing no group differences between PDD and PD (Goldman *et al.*, 1998). No significant differences were found between subtypes of LBD (Fritz *et al.*, 2016). In LBD, two studies assessed features of rhythm (Merory *et al.*, 2007; Fritz *et al.*, 2016) and found rhythm was impaired compared to controls (Merory *et al.*, 2007). One study reported impaired rhythm in LBD compared to PD but no significant differences between LBD subtypes (Fritz *et al.*, 2016). In LBD, only one study assessed characteristics of variability (Fritz *et al.*, 2016). It found no group differences between LBD and PD. The same study assessed postural control characteristics of gait in LBD and found no significant differences between controls and DLB. Asymmetry was not assessed in LBD.

2.4.5 Gait impairments in Vascular Dementia

One study assessed pace and postural control characteristics of gait in VaD (Tanaka *et al.*, 1995). It found slower pace but no differences in postural control in VaD compared to both controls. Rhythm, variability and asymmetry were not assessed in VaD.

2.4.6 Differences in gait between dementia subtypes and disease severity.

People with AD demonstrated better pace compared to VaD (Tanaka *et al.*, 1995). In contrast, comparisons with LBD are inconsistent; one study found no difference in pace or rhythm between AD and DLB (Merory *et al.*, 2007) whilst another reported slower pace, impaired rhythm and greater variability in LBD compared to AD (Fritz *et al.*, 2016). One study compared mild and moderate severity AD to mild and moderate severity unspecified non-AD dementia (Allali *et al.*, 2016); for both severity levels, non-AD dementia had slower pace and a larger stride width (a feature of postural control). However, impaired rhythm was only found in the non-AD group in the moderate cohort and impaired variability only in the non-AD group in the mild cohort. No significant differences for postural control characteristics were found between AD and VaD or AD and DLB (Tanaka *et al.*, 1995; Merory *et al.*, 2007). Surprisingly, no significant differences were found in pace or rhythm between AD and PD (Fritz *et al.*, 2016).

Slower pace was reported with increasing dementia severity. All four studies comparing dementia severity found reductions in pace in the moderate-to-severe AD groups compared to the milder groups (Nakamura *et al.*, 1996; Goldman *et al.*, 1999; Ries *et al.*, 2009; Coelho *et al.*, 2012). Results were inconsistent between AD and MCI; two studies reported slower pace in AD compared to MCI (Maquet *et al.*, 2010; Choi *et al.*, 2011) whilst two studies found no significant differences between these groups (Gillain *et al.*, 2009; Muir *et al.*, 2012). Trends in one study indicated AD were slower compared to MCI (Konig *et al.*, 2017). No differences in characteristics of rhythm were found across dementia severity (Gillain *et al.*, 2009; Coelho *et al.*, 2012; Muir *et al.*, 2012) and only one study reported impaired rhythm in AD compared to MCI (Maquet *et al.*, 2010). One study demonstrated trends of decreased rhythm in AD compared to MCI (Konig *et al.*, 2017). Inconsistent results for variability were found between AD and MCI, with two studies showing greater variability in AD (Gillain *et al.*, 2009; Maquet *et al.*, 2010) and two reporting no differences (Choi *et al.*, 2011; Muir *et al.*, 2012). One study found greater variability in moderate AD compared to mild AD (Coelho *et al.*, 2012) while another found greater variability in moderate and severe AD compared to controls; this was not found in mild AD (Nakamura *et al.*, 1997). Only one study found moderate AD had a larger stride width, a feature of postural control, compared to controls whereas mild AD did not (Allali *et al.*, 2016). No studies investigated asymmetry across dementia severity.

2.5 Discussion

This review aimed to summarize available data on gait differences in people with dementia compared to controls and identify distinct gait profiles in dementia subtypes. This review clarifies previous findings of gait impairment in dementia compared to controls, specifically attributing impairments to pace and rhythm domains. However, we extend previous literature by identifying that dementia subtypes differ from each other in characteristics of pace, rhythm and variability, although the number of studies comparing subtypes (Figure 2-2) and the range of gait characteristics described are limited.

2.5.1 Is gait in dementia distinct from normal aging?

Our findings provide insight into significant gait impairments in AD, VaD and LBD compared to non-cognitively impaired older adults that are consistent with our hypothesis. The majority of studies reported slower pace; however, it was also the most commonly assessed characteristic. Measuring other spatiotemporal gait characteristics may have been useful to identify unique signatures of gait in different dementia subtypes (Morris *et al.*, 2016). Temporal gait characteristics (i.e. those in the rhythm domain) appeared more impaired

in dementia and were dependent on disease stage. Impairments in variability are inconclusive, largely due to inconsistencies in the variables measured.

	AD	VaD	DLB	PDD	LBD	OD	MCI
AD	4						
VaD	1	0					
DLB	1	0	0				
PDD	0	0	1	0			
LBD	1	0	0	0	0		
OD	1	0	0	0	0	0	
MCI	5	0	0	0	0	0	1
PD	1	0	0	1	1	0	0
Controls	22	1	1	1	0	1	6

Figure 2-2 Heat map detailing number of studies comparing cohorts

AD = Alzheimer's disease, VaD = Vascular dementia, DLB = dementia with Lewy bodies, PDD=Parkinson's disease dementia, OD = Other dementia (non-AD), MCI = Mild cognitive impairment, PD = Parkinson's disease

2.5.2 Are gait impairments distinctive between dementia subtypes?

The findings of this review support the qualitative literature reporting that gait is more impaired in non-AD dementia subtypes compared to AD and emphasizes differences across pace, rhythm and variability domains, which is somewhat consistent with our hypothesis (Allan *et al.*, 2005). Figure 2-3 provides a synopsis of the findings described. Only four studies compared gait across subtypes, highlighting a significant gap in the literature. Interestingly, no differences were found between PD and AD in one study – however, trends indicated that PD walked slower with a mean velocity of 1.13 metres per second and mean stride length of 115.82 centimetres compared to 1.2 and 125.33 respectively (Fritz *et al.*, 2016). One study reported differences across MCI subtypes, which may relate to different dementia subtypes. For example, when compared to controls, amnestic-MCI had slower pace, while non-amnestic-MCI had slower pace and impaired rhythm (Allali *et al.*, 2016). This may be due to pathological differences with important implications, as a-MCI usually develops into AD, while na-MCI progresses into non-AD dementias, such as DLB or VaD (Ferman *et al.*, 2013a). Therefore, gait could act as an early marker to differentiate between dementia subtypes, however further work is needed to determine this.

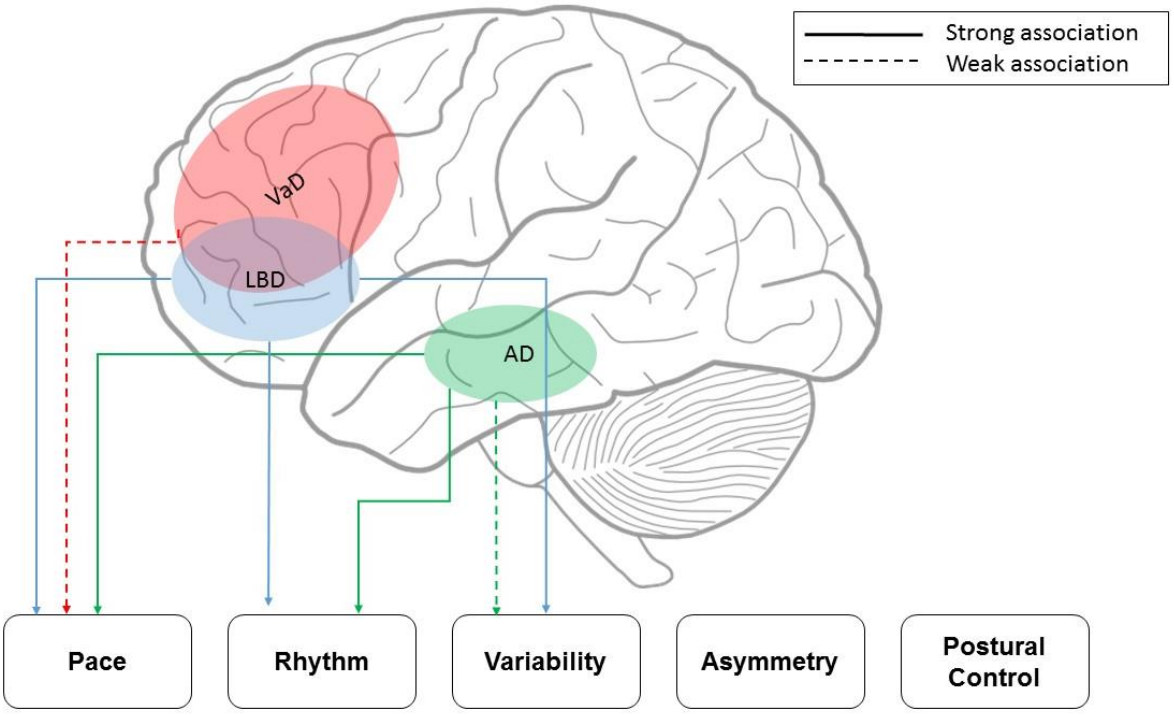

Figure 2-3 Associations between dementia subtypes and gait implied by the current literature, using Lord et al., (2013)'s mode as a framework to interpret results.

2.5.3 Do gait impairments across dementia subtypes relate to cognitive impairments and their underlying neural correlates?

This review provides evidence for gait impairment in dementia subtypes reflecting cognitive impairments. Selective cognitive domains have been associated with discrete gait impairments which may reflect underlying pathology (Verghese *et al.*, 2007). For example, characteristics of rhythm have been associated with memory, affected early in AD, while slower pace and greater variability have been associated with impaired attention and executive function, affected early in LBD and VaD (Morris *et al.*, 2016). These cognitive impairments relate to the underlying neural correlates and pathological changes in different dementia subtypes. Our findings suggest that gait impairments may similarly reflect these differences. Dementias such as LBD have associated motor impairments due to disease pathology, such as neurodegeneration of the substantia nigra, which is associated with key motor impairments, of which gait asymmetry and postural control may be a feature. It is worth noting however, that despite these impairments, diagnosis in the early disease stages is still difficult. Therefore while the differences in gait may not all be mediated by cognitive deficits and associated neural correlates, additional motor impairments may contribute to early differentiation.

An interesting question to ask is; do gait impairments reflect shared cognitive and pathological correlates consistent with different dementia subtypes? Alzheimer's disease is associated with amnestic memory deficits predominantly due to amyloid deposition in the entorhinal cortex and hippocampus (Braak and Braak, 1995). Atrophy of the hippocampus (involved in navigation and memory) is associated with decreased pace and variability (Annweiler *et al.*, 2012), with speculative links between rhythm and the hippocampus; temporal aspects of gait have been associated with memory (Verghese *et al.*, 2007). Slower pace and greater variability are associated with frontal lobe atrophy and white matter hyper-intensities affecting frontal subcortical circuits in both dementia and older adults – areas that mediate attention and executive function (Annweiler *et al.*, 2012; Suire *et al.*, 2017). Frontal white matter lesions are key characteristics of VaD (O'Brien and Thomas, 2015) and frontal neuronal loss is associated with Lewy body disease, lending explanation to pace and variability deficits. There are also correlations between increases in gait impairment with dementia severity and reduced frontal cerebral blood flow becoming more widespread (Nakamura *et al.*, 1997), suggesting gait impairment is reflective of ongoing neural changes in dementia. However, the majority of research associating gait with specific brain regions focuses on gait speed – further research needs to be completed before drawing robust conclusions in this area.

2.5.4 Limitations of current research and recommendations for the future

There are a number of discrepancies with the current research regarding quantitative gait assessment in dementia. Several additional studies using functional tasks (i.e. timed up and go) were identified but not included in this review, as they did not provide standardized measures of gait. This prevents comparison across studies and may be subject to confounding variables, such as impaired movement initiation. Of the studies that were included, distance walked, number of strides and steps, type of walk (i.e. continuous or intermittent) and gait analysis technique used (i.e. instrumented walkways, body worn sensors) varied. This limited interpretation when collating the results. Development of a standardized single-task gait protocol suitable for use in any clinic would be beneficial to aid generalizability of findings. This should include measuring at least 30 steps to assess variability characteristics (Galna *et al.*, 2013). Intermittent walks may be more suitable for dementia populations, particularly as the disease progresses – allowing for rest breaks as needed. Gait characteristics across studies also varied, with some studies limited to velocity and others assessing a wider range, such as stance time, step width, etc. Only two studies assessed features of asymmetry; this may be an oversight when considering dementias with notable asymmetric pathology, such as PDD, as

asymmetric pathology may be reflected in gait outcomes. Studies should strive to assess a large range of spatial and temporal aspects of gait, to establish distinct gait profiles across dementia subtypes.

There was also a limited number of studies comparing dementia subtypes, as seen in Figure 2-2. The majority focused on differences between AD and controls, with only five studies investigating non-AD dementias. Although non-AD dementias such as LBD and VaD have notable gait impairments as described in the qualitative literature (Allan *et al.*, 2005), quantitative gait assessment is needed to tease out subtle differences that may support diagnosis. More studies comparing subtypes are necessary. There were also discrepancies across studies regarding severity measures – a number of rating scales, such as the MMSE or the CDR, were used to establish stage of disease with inconsistent ratings determining disease stage. Studies were also restricted by small sample sizes and may not have provided a true picture of gait in dementia due to influence of outliers – studies should be adequately powered. Overall, the majority of studies were only of mediocre quality (see Appendix A). Therefore, we have provided key recommendations in Table 2-2 to guide future research.

Table 2-2 Recommendations for future research

Key recommendations for future research
• Development of a standardized single-task gait protocol. • Adopting a standardized framework to inform selection of gait characteristics – such as models suggested by Verghese *et al.* (2008); Hollman *et al.* (2011); Lord *et al.* (2013b) • More studies are needed to compare gait across the most common subtypes, i.e. AD, DLB, PDD and VaD. • Follow recommended diagnostic criteria for dementia to ensure accuracy of diagnosis in order to compare dementia sub-types (McKhann *et al.* (1984); Dubois *et al.* (2007b); Emre *et al.* (2007); Donaghy *et al.* (2017)). • Adherence to guidelines regarding measures for assessing stage of dementia (Hughes et al., 1982; Perneczky et al., 2006)

2.5.5 Clinical implications

While gait impairments are recognisably present and often early markers of dementia subtypes such as VaD, PDD or DLB (Allan *et al.*, 2005), clinical recognition of gait deficits in AD is an emergent area of research. The National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) includes gait disturbances in their exclusion criteria for a diagnosis of AD (McKhann *et al.*, 1984; Dubois *et al.*, 2007b). However the findings from this review and previous qualitative studies show that gait impairments are more common in AD compared to

controls (Allan *et al.*, 2005). Qualitative literature suggests that gait impairments are not present in mild AD; however, quantitative gait analysis reveals subtle discrete deficits in mild AD that progressively worsen. Equally, while parkinsonism is a core feature of DLB according to the latest diagnostic criteria (Donaghy *et al.*, 2017), specific gait impairments have not been described, and the revised DLB criteria suggests that at least one clinical marker and a biomarker suggestive of Lewy body disease are necessary for early diagnosis. Although limited, the current evidence suggests that dementia subtypes have distinctive patterns of gait impairment. While more research is necessary in order to establish unique gait profiles in dementia subtypes, the end-result could complement current diagnostic criteria and show potential utility as a biomarker. Similar to acknowledging the specific cognitive domains impaired early in disease onset (e.g. episodic memory in AD), specific gait domains may also be impaired early (e.g. rhythm in AD). Changes in gait are also found prior to onset of cognitive decline; therefore, gait analysis at early intervals could contribute to early diagnosis of dementia. With advancing technology, quantitative gait analysis techniques are becoming smaller, portable and more cost-effective and could prove a useful addition to a clinician's toolbox.

2.5.6 Conclusion

Gait is impaired in dementia compared to cognitively intact older adults. Dementia subtypes may have discrete gait profiles but more research is necessary to establish these. Use of standardized protocols and assessment of a comprehensive range of spatiotemporal gait characteristics are necessary when studying gait in dementia and its subtypes. Future research should endeavour to establish quantitative gait analysis as a cost-effective and easily applicable clinical biomarker for dementia.

Chapter 3 General Methods

The NHS Local Research Ethics Committee, Newcastle and North Tyneside 1 approved this study. All participants had capacity to consent to participation in the study and provided written informed consent.

3.1 Participants and Recruitment

This study involved a cross-sectional comparison of cognitively intact older adults (controls) and four dementia disease groups; Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease with dementia (PDD), and vascular dementia (VaD). Individuals in the dementia disease groups ranged from mild cognitive impairment (reflecting dementia disease subtypes) to mild-moderate dementia. This allowed us to view dementia groups across the spectrum of disease. Relatives, carers and friends answered questionnaires about the cognitively impaired participants. Table 3-1 outlines criteria for participant recruitment.

Table 3-1 Exclusion and inclusion criteria for participant recruitment

Exclusion Criteria	Inclusion Criteria
Drug-induced parkinsonism	**Common Criteria**
'Vascular' parkinsonism	Able to walk independently for two minutes
Progressive supranuclear palsy	(ascertained through self-report)
Multiple system atrophy	Individuals with walking aids for home and
Corticobasal degeneration	community were verified by a clinician.
Severe orthopaedic problems that will adversely	Must be over 60 years old
affect gait	**Controls**
Possible or probable frontotemporal dementia	No diagnosis of dementia, MCI or neurological
Any other co-existing movement disorder or	disorders
neurological condition	Not on anti-dementia medication
Severe mental illness (major depression (current	Must have no signs of cognitive impairment
episode), bipolar disorder, schizophrenia)	(sMMSE $\geq$ 25)
Poor command of English.	**Clinical Populations**
Evidence of a stroke which affects their motor	Diagnosis of probable AD, DLB, PDD, or probable
functioning.	or possible diagnosis of VaD, or a diagnosis of MCI.
	Aged over 60 with MMSE $\geq$15.
	Must have mental capacity to consent to the study.
	They must have provided written informed consent
	for participation in the study prior to any study
	specific procedures.

3.1.1 Dementia cohorts

There were a number of methods employed for recruitment of individuals with dementia. The main method was through Old Age Psychiatric, Geriatric Medicine or Neurology services after routine diagnostic assessments according to usual NHS practice. We recruited through a number of NHS trusts, including Newcastle upon Tyne Hospitals NHS Foundation Trust, Gateshead Health NHS Foundation Trust, Tees, Esk and Wear Valley NHS Trust, Northumbria Health Care NHS Foundation Trust and Northumberland, Tyne and Wear NHS Foundation Trust. Generally, participants were initially identified by the local treating clinical team or by experienced Clinical Research Officers in the Local Clinical Research Network for Dementia and Neurodegenerative Diseases (North East DeNDRoN). A member of the treating clinical team would then outline the study, and with the consent of the subject refer them to the research team or experienced Clinical Research Officers in North East DeNDRoN if they were potentially willing to consider taking part in the study and appeared to fulfil the study criteria. Patients who had already indicated their willingness to be approached about clinical studies were held on the North East DeNDRoN Case Register, and this register was checked for potential participants fulfilling the study criteria

Other methods to recruit into the study included liaising with other studies, such as the "Structural Retinal Changes: A biomarker for dementia in Parkinson's disease?" study, the "Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation – Parkinson's Disease" (ICICLE-PD) study, the "123I-MIBG in Dementia with Lewy bodies as a marker for sympathetic denervation" (MIDAS), "Sensitivity of people with Parkinson's to different intensities of emotion" (SPIES) study and the DIAMOND-Lewy study to identify and approach potential suitable participants. These studies were ongoing and recruited DLB, PDD and AD participants also.

3.1.2 Mild cognitive impairment cohorts

Mild cognitive impairment cohorts were also identified through NHS services and North East DeNDRoN. Participants in the ongoing "123I-MIBG Scintigraphy Utility as a biomarker for Prodromal Dementia with Lewy Bodies" (SUPERB) study were approached during their follow-up assessments. These participants had been identified as individuals with prodromal DLB or AD. As this study had adopted a similar cognitive protocol, an ethical amendment was submitted on behalf of SUPERB and approved, which allowed data-sharing between studies. This reduced participant burden by reducing repeated cognitive testing and allowed participants to partake in an optional gait assessment.

3.1.3 Control cohort

For comparison purposes, a control cohort of older adults with no reported cognitive problems were recruited. The control cohort comprised of volunteers already known to North East DeNDRoN, along with relatives or friends of participants.

3.2 Clinical Assessment

Age, height, weight and prescribed medication were recorded for all participants. The National Adult Reading Test (Nelson and Willison, 1991) measured participants' premorbid intelligence. All participants were asked had they had any falls in the last 12 months. Responses were recorded as "yes" or "no". The Cumulative Illness Rating Scale – Geriatrics (Linn *et al.*, 1968) was used to collect information regarding participants' overall health. Higher scores reflects higher numbers of co-morbidities.

Cognitively-impaired participants had received a clinical diagnosis prior to participating in the study. Further information was collected to confirm and rate severity of the disease through a diagnostic interview and validated tests. The Clinical Dementia Rating scale (Morris, 1993) provided participants' with a score of dementia severity. This scale ranges from 0-3; approximately cognitively intact individuals score zero, MCI rated as 0.5, and 1, 2 and 3 represent mild, moderate and severe dementia respectively. The Unified Parkinson's Disease Rating Scale (UPDRS) Part III (Movement Disorder Society Task Force on Rating Scales for Parkinson's, 2003) was used to assess patients' motor disease severity. Although specifically validated in Parkinson's disease, the UPDRS was used on all participants for comparative purposes. Higher scores represent worse motor disability. Overall PD severity was rated using Hoehn and Yahr clinical scale. This ranges from 0-5, with higher scores representing worsening disease severity.

Two clinicians (A.T. and P.D.) reviewed patients' clinical notes and study assessments in order to verify the diagnosis for the study. A third clinician (J.P.T.) reviewed disagreements regarding diagnosis in order to reach a consensus. Diagnostic criteria for dementia used were as follows: NINCDS-ADRDA for AD (McKhann *et al.*, 1984), McKeith (2017) for DLB, Dubois *et al.* (2007a) for PDD and NINDS-AIREN for VaD (Roman *et al.*, 1993). Diagnosis of MCI was made using the NIA-AA Criteria (Albert *et al.*, 2011) and AD and LB subtypes were identified as described in Donaghy *et al.* (2018), Thomas *et al.* (2019) and King *et al.* (2017). Diagnosis of PD-MCI was made using Litvan *et al.* (2012) criteria. Briefly, subjects with two core symptoms of DLB or one core symptom and an abnormal biomarker who met

NIA-AA MCI criteria were classified at probable MCI-LB (McKeith, 2017). Those who had no such symptoms or positive biomarkers were classified as probable MCI-AD.

3.3 Neuropsychological Assessment

The participants underwent a comprehensive battery of neuropsychological tests and questionnaires. These were used to assess their overall cognitive abilities, including attention, executive function, memory, language, fluency and visuospatial skills. Table 3-2 describes all neuropsychological tests used in the study.

Table 3-2 Neuropsychological tests employed during the study.

Assessment	Cognitive domain	Description
Standardised Mini-Mental State Examination (MMSE)	Global cognition	The MMSE involves 19 tests assessing 11 cognitive domains through a 30-point questionnaire which assesses global cognitive function (Molloy and Standish, 1997). It is the most commonly used method to rate cognitive decline.
Addenbrookes Cognitive Examination (ACE-III)	Global cognition	The ACE-III is a brief and specific test battery used to detect early cognitive dysfunction (Noone, 2015) (Mioshi *et al.*, 2006). It contains 5 subsets which evaluate attention, fluency, language, visuospatial and memory function
Trail Making Test (TMT) – Part A	Information processing/Executive function	The trail making test assesses set shifting ability and visual attention (Reitan, 1992). It consists of two parts: A and B. In A, 25 circles numbered between 1 and 25 are presented on a piece of paper and individuals must connect them in numerical order without taking the pencil off the page. Individuals are instructed to do the tasks as quickly as possible.
FAS	Fluency	The FAS test measures verbal fluency by giving individuals the letters "F", "A" and "S" and asking them to produce as many unique English words (excluding proper nouns) as possible beginning with those letters in a minute for each letter (Benton, 1967).

Several computer tasks were employed; including attentional tasks, the Angle discrimination task from the Newcastle visual perception prototype battery and the Stroop tests (Golden and Freshwater, 1978; Wood *et al.*, 2011). The Stroop test involves executive skills such as inhibition and set-shifting. Computer tasks were programmed in Matlab (The Mathworks Inc). Outcomes for all included mean reaction time (ms), error rates and number of correct trials. Further details of all computer tests are provided in Figure 3-1 and Table 3-3.

Table 3-3 Instructions and outcomes for computer tests used in the study

Test	Instructions	Cognitive domain
Simple Reaction Time Task	'An X will appear in the centre of the screen. As soon as this appears, I need you to press the button as quickly as you can. Don't worry if you miss one, it will automatically move on. We will have a try at a practice trial first. Is that clear? If you are ready to start please press the button.'	Attention
NEVIP-B Angle Discrimination Test	'A box will appear on the top of the screen, it will contain a line tipped at an angle. At the bottom of the screen, there are two boxes, both containing a line tipped at different angles. One of these boxes will be a match for the box at the top of the screen. If you think it is the left hand box that matches, press the left button, if you think it is the right hand box, press the right button. Speed is not important on this task, but do try to be accurate. If you are not sure which box matches, take your best guess. Some trials will be easier than others and as the trial goes on, it may become more difficult. We will have a try at a practice trial first. Is that clear? If you are ready to start please press the button.'	Visual Perception
Stroop Test	'A box will appear on the top of the screen, it will contain a word describing a colour. At the bottom of the screen, there are two boxes, both containing the name of a colour. One of these boxes will be the word describing the colour of the font in the box at the top of the screen. If you think it is the left hand box that matches, press the left button, if you think it is the right hand box, press the right button. Speed is not important on this task, but do try to be accurate. If you are not sure which box matches, take your best guess. Some trials will be easier than others and as the trial goes on, it may become more difficult. We will have a try at a practice trial first. Is that clear? If you are ready to start please press the button'	Executive function

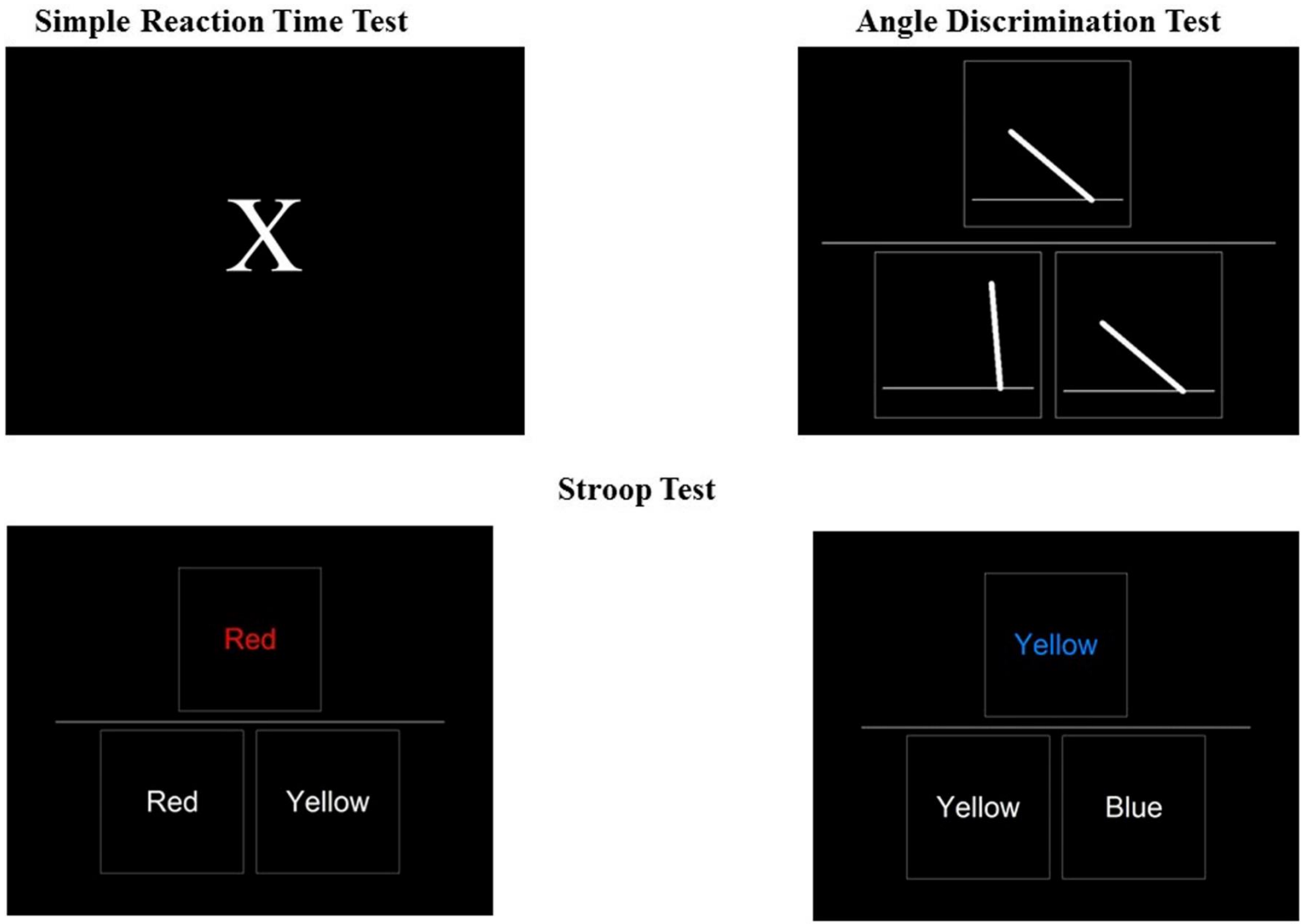

Figure 3-1 Examples of computer tests used during the study

3.4 Questionnaires

Both participants with dementia/MCI and carers answered questionnaires pertaining to neuropsychiatric symptoms, activities of daily living and balance confidence. Participants who did not have a carer, friend or relative attending the study session were asked to answer relevant questionnaires themselves to the best of their ability. These are outlined and described in Table 3-4.

Table 3-4 Questionnaires used within the study

Questionnaire	Informant	Description
Bristol Activities of Daily Living Scale (BADLS)	Carer	The Bristol Activities of Daily Living Scale is used to assess how able individuals with memory problems are to engage in activities of everyday living (Fish, 2011). It consists of 20 items (e.g. eating or preparing food) and asks informants to rate the individual's ability to carry out the task.
Epworth sleepiness scale (ESS)	Participant	The Epworth Sleepiness Scale is used to assess daytime sleepiness (Johns, 1993). It asks patients to rate between 0-3 the likelihood that they would doze in eight real-life situations.
Geriatric Depression Scale (GDS)	Participant	The Geriatric Depression scale is a 30-item questionnaire in which individuals are asked to say "yes" or "no" to questions about how they've felt over the last week (Brink *et al.*, 2013). It is used to detect depression in the older generation.
Activities Balance Confidence (ABC) Scale	Participant	The Activities-specific Balance Confidence (ABC) scale assesses balance confidence (Powell and Myers, 1995).

3.5 Gait Assessment

Gait assessments were completed in one session. Control participants completed gait assessment in the same session as neuropsychological tests and questionnaires. Cognitively-impaired groups completed gait in a separate session in order to alleviate cognitive burden and fatigue.

3.5.1 Laboratory Gait Assessment

Gait assessments were completed in the gait laboratory at the Clinical Ageing Research Unit, Campus for Ageing and Vitality, Newcastle University. Gait measures were recorded using a 7 x 0.6 metre (length x width) instrumented walkway (GaitRite, software version 4.5, CIR Systems Inc., United States of America). This method of gait analysis had been shown valid and reliable across ageing and pathology (Bilney *et al.*, 2003). Participants began walking 2.5 metres in front of the walkway. Gait was repeatedly sampled during each walk across the walkway.

The gait assessment in the laboratory involved walking six times across an instrumented walkway (Figure 3-3 depicts lab set up). This was designed to collect >40 steps, which allows a more reliable estimation of gait variability (Galna *et al.*, 2013). Participants were asked to walk at their comfortable pace.

3.5.2 Gait outcomes

The GaitRite walkway captured 16 spatiotemporal gait characteristics across five gait domains, derived from a theoretical model of gait and validated in older adults and PD (Lord *et al.*, 2013b). This thesis will use this model as a framework throughout, in order to aid interpretation of findings, and communication of results. Both the domains of gait and specific characteristics representing those domains were reported. Left and right footsteps were calculated separately and reported as mean values; gait characteristics were derived from these. Characteristics representative of variability were calculated using the standard deviation of left and right footsteps, calculated separately and then combined. Asymmetry characteristics show the absolute mean difference of the left and right footsteps (Galna *et al.*, 2015).

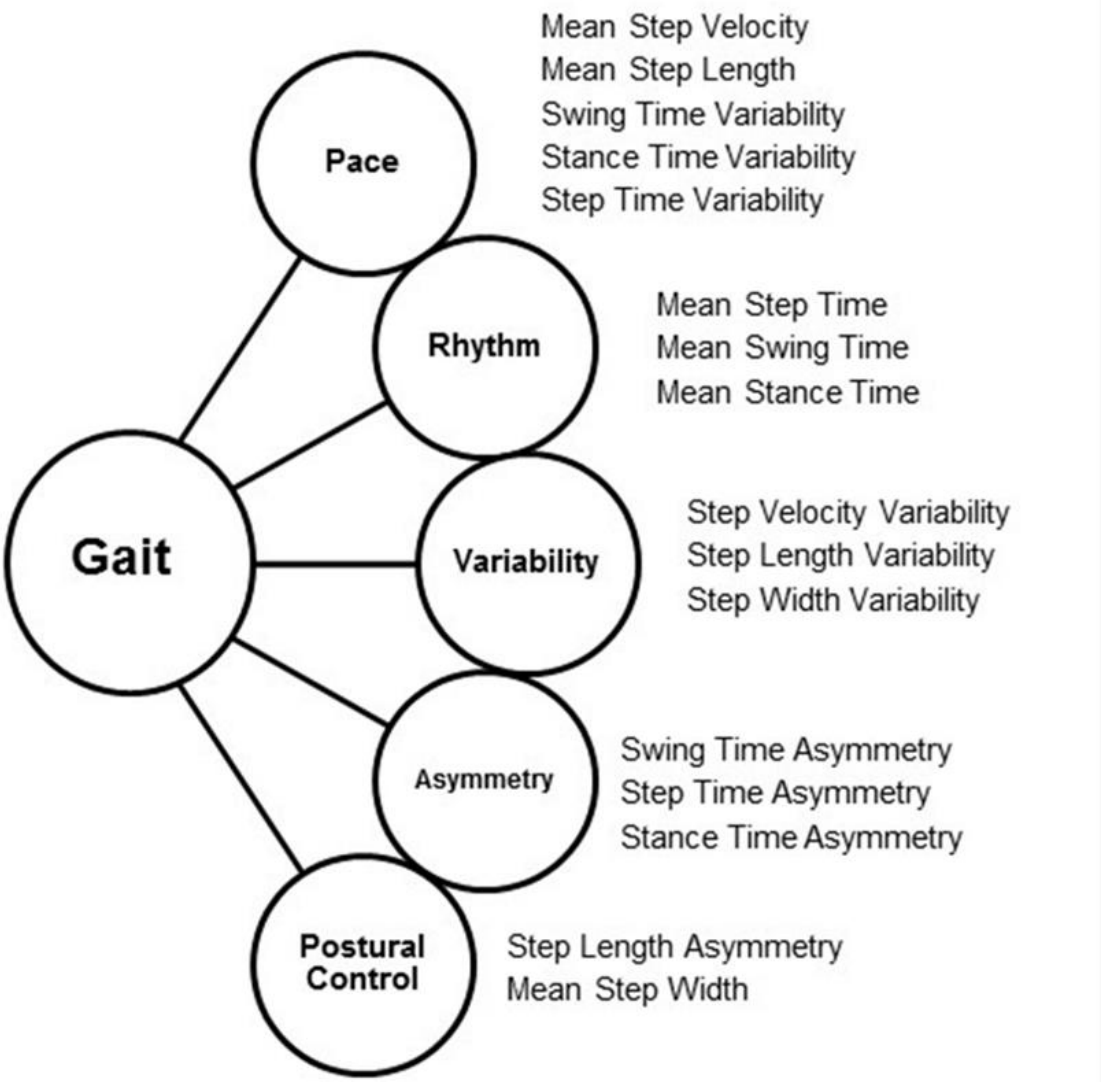

Figure 3-2 Theoretical model of gait validated in older adults and Parkinson's disease (Lord et al., 2013).

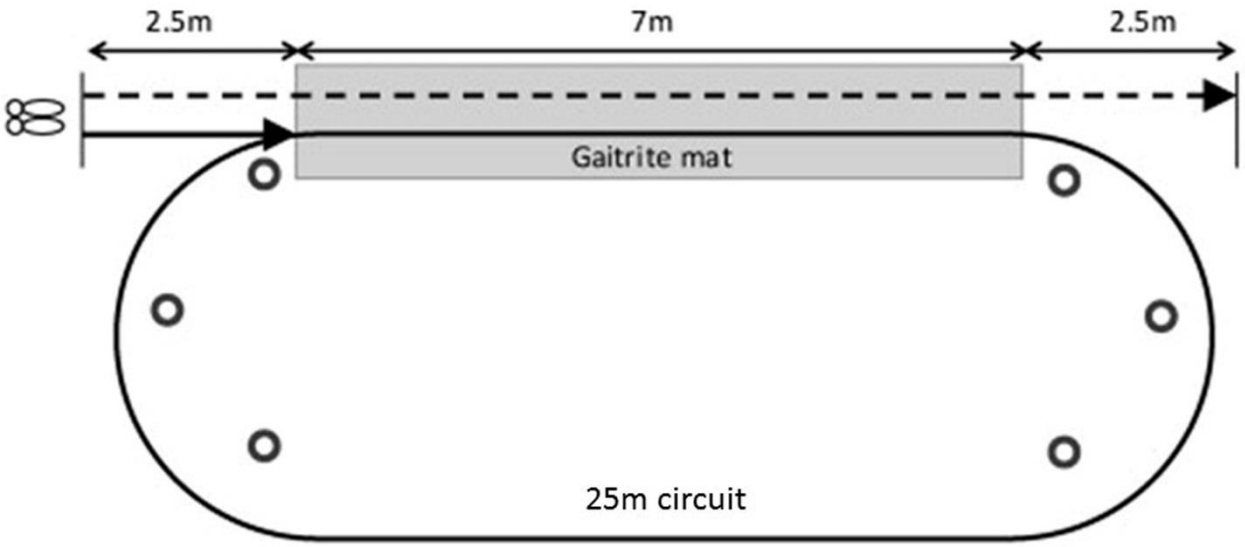

Figure 3-3 Laboratory layout for gait assessments

3.6 Gait assessment in free-living

All participants were asked to wear a body worn sensor for seven days in order to collect free-living gait data. Participants wore a tri-axial accelerometer-based wearable (Axivity AX3; Axivity, York, UK; Dimensions: 23.0mm x32.5mm x7.6mm, weight 9g) located on the fifth lumbar vertebra (L5; see Figure 3-4). The wearable was attached using PALStickies (PALStickies, PAL Technologies, Glasgow, UK) and Hypafix (BSN Medical Limited, Hull, UK) and was programmed to capture with a sampling frequency of 100Hz (16-bit resolution, range ±8g). Recorded signals were stored locally on the sensor's internal memory (512MB) as a raw binary file and then downloaded upon the completion of testing. Participants were provided with additional adhesives and attachment instructions for the duration of the 7-day free-living assessment. Participants were informed that the wearable was shower-resistant but could not be submerged in water (i.e. in a bath/swimming), and that it should remain in place throughout the duration of the week. Changes in orientation (i.e. misplacement of sensor) were accounted for by transforming accelerometer signals to a horizontal-vertical co-ordinate system for realignment(Moe-Nilssen, 1998).

Once data collection was finished, participants sent the sensors back in a prepaid envelope and data was downloaded. Fourteen of the 16 characteristics outlined in Figure 3-2 were measured. Information about amount, pattern and variability of walking activity was also collected. Further information pertaining to methodology for free-living gait assessment can be found in Chapter 5 and Chapter 6.

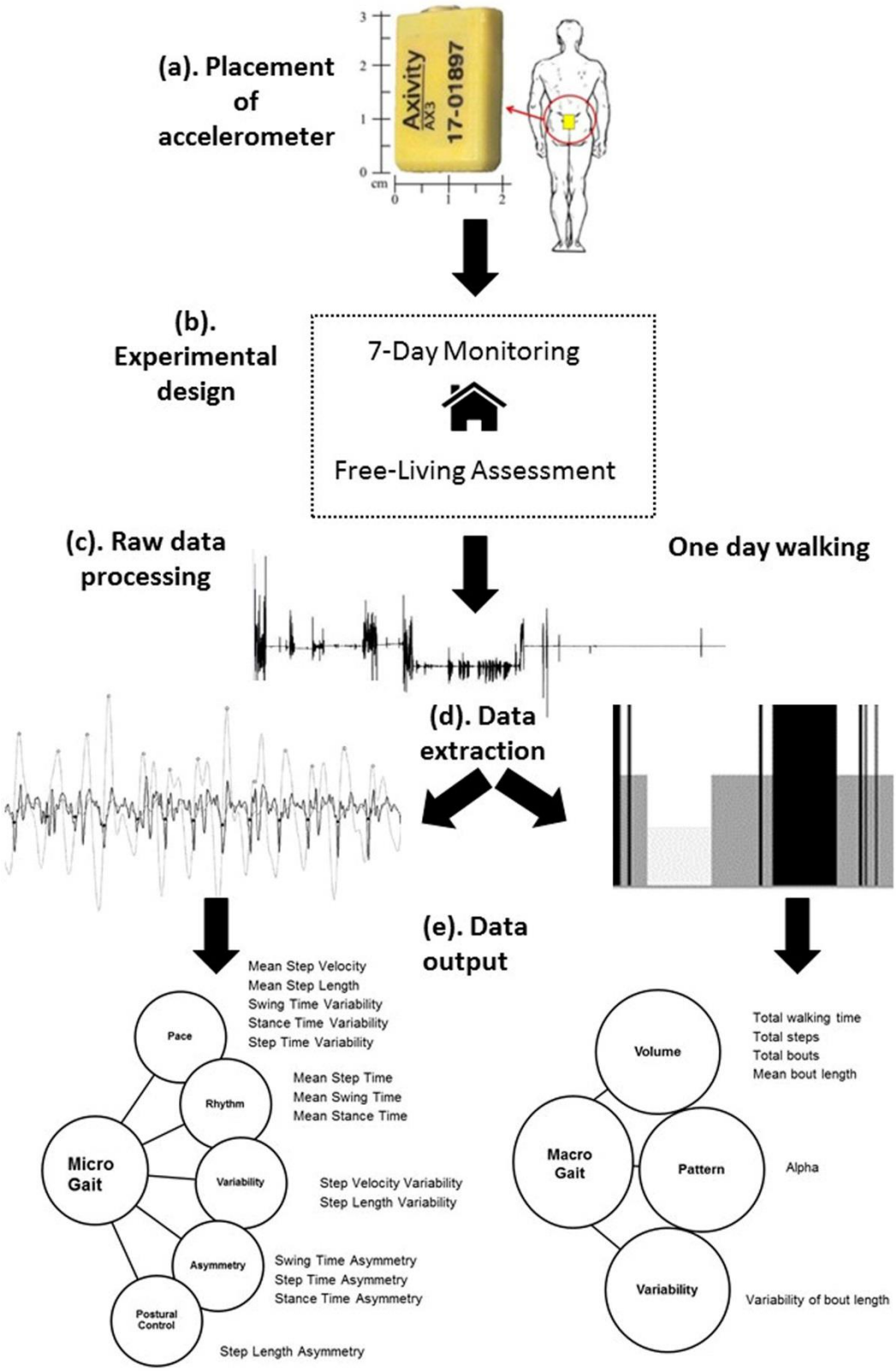

Figure 3-4: Demonstration of sensor placement, data collection, data processing and gait outcomes with the body-worn monitors

(a) Example of body worn monitor placement for both the clinic based and free-living data collection on L5 centrally located on the lower back; (b) Gait protocols for clinic and home based assessments for the D&FP feasibility study; (c) The raw vertical acceleration signal segmented into walking bouts (d) Left; Example of gait characteristic extraction from walking bouts: detecting initial contacts (black stars) and final contacts (white circles). Right: Identification of walking bouts (black bars) from free-living data from which gait characteristics are extracted; (e) Left: Conceptual model of gait representing domains and 14 gait micro characteristics. Right: Macro characteristics of gait described by domains of volume, pattern and variability.

3.7 **Data analysis**

Gait and cognitive data were described using descriptive output (e.g. mean, median, standard deviation) from SPSS V.24 and illustrated by scatterplots and boxplots. Distributions of continuous variables were assessed for normality by inspection of histograms and boxplots, and using the Shapiro-Wilk test. One-way analysis of variance (ANOVA) and Kruskal Wallis tests were used to examine differences between groups for demographic and clinical information; Fisher's LSD post-hoc and Mann Whitney U tests were used to establish where these differences lay ($p \leq .05$). Chi-square tests were used to determine differences between groups for sex and faller status (participants with and without falls during the previous year).

Specific statistical analysis techniques will be detailed in each chapter where relevant.

Chapter 4 Gait impairments in dementia disease subtypes under laboratory conditions

This chapter investigates differences in gait impairments under laboratory conditions across the spectrum of cognitive impairment and between dementia disease subtypes.

4.1 Introduction

Traditional diagnostic methods for dementia, such as recognition of clinical and cognitive symptoms, are limited by their lack of sensitivity and specificity to neuropathological changes associated with diseases which cause dementia, especially in the pre-dementia stages (Jack *et al.*, 2018). Despite specific diagnostic criteria for different dementia subtypes such as Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD) and vascular dementia (VaD), similarities in clinical symptoms can disguise subtle differences between these dementia subtypes and misdiagnosis may occur (Roman *et al.*, 1993; Emre *et al.*, 2007; McKhann *et al.*, 2011; McKeith, 2017).

Alzheimer's disease is the most common clinical diagnosis as a cause of dementia at 50-70% (Jack *et al.*, 2018); however, autopsy-verified cases have reported pure AD in only 13.6% of thoroughly assessed cases (Toledo *et al.*, 2013). Other pathologies present included Lewy body disease (LBD; 45.5%), medial temporal lobe pathology (40.9%) and vascular infarcts (22.7%). Kane *et al.* (2018) found that within a representative population in NHS services, 4.6% of all dementia diagnoses were considered DLB - lower than suggested from a previous meta-analysis (Jones and O'brien, 2014). This suggests that DLB is under-diagnosed clinically, with variation of clinical practice resulting in regional differences. In contrast, VaD appears to be over-diagnosed clinically. For example, Niemantsverdriet *et al.* (2015) only found 19% of clinically diagnosed cases of VaD to have sufficient neuropathological evidence – the other cases met neuropathological criteria for probable AD (48%), frontotemporal dementia (19%) and possible DLB (15%). Clinical misdiagnosis leads to inappropriate treatment of conditions and patient care, and leads to inclusion of wrongly diagnosed participants in disease-specific therapy studies.

Improved understanding of dementia as a biological construct is now a key research agenda. The emergence of biomarkers, such as amyloid positron emission tomography (PET) and cerebrospinal fluid Aβ42 for AD and dopamine active transporter (DAT) scans for Lewy body disease (LBD), have allowed researchers greater confidence in diagnostic accuracy and

identification of dementia prior to cognitive decline and dementia (Jack *et al.*, 2018). Lower-cost biomarkers, such as blood and saliva biomarkers, are being developed.

The use of biomarkers for early identification of dementia is essential for improving and utilising future treatments – with early initiation likely to be vital for effectiveness. However, current biomarkers are expensive and require specialist expertise, making it costly to acquire and analyse data on a wide scale. Lower-cost unobtrusive biomarkers need to be established as a screening technique for interventional clinical trials and further diagnostic investigations. With the emergence and validation of inexpensive wearable technologies for gait analysis (Del Din *et al.*, 2016c), gait has potential as a low-cost minimally invasive clinical biomarker.

Discrete gait impairments have been associated with specific cognitive domains (Morris *et al.*, 2016), potentially reflecting underlying neuropathological changes. Gait impairments such as reduced gait speed and greater stride time variability, are predictive markers of dementia (Beauchet *et al.*, 2016; Gillain *et al.*, 2016), occurring up to twelve years prior to dementia diagnosis (Buracchio *et al.*, 2010). However, research into gait analysis between different disease subtypes is limited (Bahureksa *et al.*, 2017; Mc Ardle *et al.*, 2017). Identifying discrete gait patterns in different dementia subtypes could be useful for differentiating subtypes in preclinical and established cases of dementia. This must first be carried out in valid and reliable lab-based gait assessments to establish the potential for gait to identify cognitive impairment and distinguishing dementia disease subtypes, before exploring the use of low-cost wearable technology in free-living environments for this purpose.

Furthermore, the role of cognition in the facilitation of gait should be considered; AD and LBD have differential profiles of cognitive impairment, demonstrating prominent memory impairments, and attentional and executive dysfunction respectively (Calderon *et al.*, 2001; Fuster, 2001; Buschman and Miller, 2007). These disease-specific differences in cognition reflect underlying pathology, as gait is proposed to do; thus by examining the associations between cognition and gait in different disease subtypes, we may improve our understanding of why gait is impaired in dementia, and why disease subtypes may have unique patterns of gait impairment. This could be strengthened by also exploring the relationship between motor disease severity and gait impairment amongst AD and LBD, questioning if motor disease and cognitive impairment play separate or interlinked processes with gait impairment in cognitively impaired populations.

4.2 Aims and hypotheses

Building on the current literature, this chapter addresses two key aims and their respective hypotheses for single-task gait.

- Investigate if gait impairment distinguishes normal ageing and in cognitive impairment due to AD, LBD and VaD.
- Investigate if gait impairment distinguishes the aforementioned disease subtypes from each other.
- Explore associations between discrete gait characteristics with cognitive domains across disease subtypes. It is important to also consider the role of motor disease severity in gait impairment, to explore if cognition facilitates gait independent of motor control.

Hypotheses

Based on findings from Chapter 2 and the current literature in this area, the following predictions were made:

4.1. Slower pace, greater variability and impaired characteristics of rhythm will distinguish AD from controls.

4.2. Slower gait velocity, shorter step length, greater variability and asymmetry of gait and a larger step width will distinguish LBD from controls and AD.

4.3. Patterns of gait impairment will be similar between DLB and PDD, but impairments will be more pronounced in PDD.

4.4. Slower pace and shorter steps will distinguish VaD from controls.

4.5. Characteristics of pace, variability and timing will be associated with cognitive functions associated with the prefrontal cortex, such as executive function, attention and visuospatial abilities. Characteristics of pace and timing will also be associated with motor disease.

4.6. The role of cognition in gait will be different between Alzheimer's disease and Lewy body disease due to different cognitive profiles inherent to the subtypes. Greater gait impairments in Lewy body disease will be explained by impairments in attention, visuospatial and executive functions.

4.3 Methods

4.3.1 Participants

Participants with mild cognitive impairment and dementia were recruited to four groups: AD, DLB, PDD and VaD. The diagnostic criteria and inclusion criteria used for these cohorts are outlined in chapter 3. Control participants of a similar age were recruited to account for effects of ageing on gait. All participants were assessed between April 2016 and April 2018. Dementia and MCI participants were assessed over two sessions, one focusing on gait and the other focusing on cognitive assessment to minimise fatigue and testing burden. In control participants gait and cognition were assessed in one session.

4.3.2 Clinical assessment

Age, sex, height and weight were recorded in the first session. The National Adult Reading Test (NART) assessed premorbid intelligence (Nelson and Willison, 1991). The Cumulative Illness Rating Scale – Geriatrics (CIRS-G) scored participants' comorbidities (Linn *et al.*, 1968). The Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III (UPDRS-III (Movement Disorder Society Task Force on Rating Scales for Parkinson's, 2003)) was used to provide measures of motor disease severity. Although this is a PD-specific assessment, all participants were assessed to provide comparison scores. The Clinical Dementia Rating Scale (CDR; (Morris, 1993) was used to rate severity of cognitive impairment. The Geriatric Depression Scale was used to detect depression (Brink *et al.*, 2013). Sleepiness ratings were collected using the Epworth Sleepiness Scale. Impairments in activities of daily living were assessed using the Bristol Activities of Daily Living Scale (BADLS; (Fish, 2011), while balance confidence was measured via the Activities of Balance Confidence (ABC) scale (Powell and Myers, 1995). Full details of all measures can be found in Chapter 3.

4.3.3 Cognitive assessment

Global cognition was measured using the Mini Mental State Examination (MMSE; (Molloy and Standish, 1997) and Addenbrookes Cognitive Examination III (ACE-III). The ACE-III subscales measured attention, memory, language, fluency and visuospatial function. Trail Making Task A (TMT A; (Reitan, 1992) measured information processing speed. The FAS test (Benton, 1967) measured verbal fluency and executive function. The Simple Reaction Time computerised test measured attention. The Stroop computerised test measured aspects of executive functions such as cognitive flexibility and inhibition.

4.3.4 Gait assessment

Participants performed six 10 metre walks, across a 7 metre x 0.6 metre (length x width) instrumented walkway (GaitRite, software version 4.5, CIR Systems Inc., United States of America). Participants were asked to walk at their comfortable pace. As previously mentioned in Chapter 3, 16 gait characteristics were selected pertaining to characteristics representing pace, variability, rhythm, asymmetry and postural control domains of gait. These were derived from Lord *et al.* (2013b)'s model of gait (Figure 3-2), developed in older adults and validated in Parkinson's disease (Lord *et al.*, 2013b).

4.3.5 Data analysis

Statistical analysis for demographic and clinical information is described in Chapter 3.

The first step of the analysis investigated differences in gait impairments between controls, mild cognitive impairment (MCI) and dementia groups, and between controls, AD, DLB and PDD. Variables that did not fit a normal distribution were transformed using logarithmic or square root transformations. One-way ANOVAs assessed group differences in gait outcomes. Fisher's LSD post-hocs were used to identify which groups were different as this was an exploratory analysis. A more conservative threshold of $p \leq .01$ was used for the robust interpretation of findings as this accounts for multiple comparisons.

As the overall key aim of this thesis questions if gait analysis can distinguish AD and LBD, independent t-tests were also conducted to verify significant differences between the disease groups, and effect sizes (partial eta squared; η^2) were calculated for key significant differences between these disease groups. Effect sizes were interpreted according to guidelines (Richardson, 2011); small (.01-.06), medium (.06-.14) and large (>.14).

Stepwise analysis of covariance (ANCOVA) assessed group differences for gait outcomes while controlling for effects of age, height and sex on gait outcomes. A further ANCOVA controlling for effects of cognitive impairment (ACE-III scores) and motor severity (UPDRS scores) was used to aid interpretation of results as the underlying mechanisms of gait are believed to rely on the co-ordination of cognitive and motor neural processes.

In order to examine potential explanatory variables for gait impairment within disease groups, Spearman's Rho correlations were used to identify associations between motor disease, cognition and gait impairment in AD and LBD subtypes. Variables demonstrating significant correlations were considered in univariate regressions to identify which variables should be

placed into backwards stepwise regression models. These models were used to identify which factors had the strongest contribution to gait.

Univariate regressions were employed on variables that showed significant associations between cognitive and gait variables. Significant variables reported by univariate regressions were placed into backwards stepwise regression models in order to identify which factors had the strongest contribution to gait. Backwards stepwise regression was chosen as forwards stepwise regression may highlight explanatory variables only significant due to another variable being held constant.

4.4 **Results**

4.4.1 Study participants and demographics

125 participants were recruited to this study. The flowchart in Figure 4-1 demonstrates number of participants approached, recruited, withdrawn and excluded from each stage of this study. Gait assessments were conducted for 119 suitable participants for this part of the study, with two further participants excluded due to festination (episodic gait interruption) occurring during assessment (n=1) and requirement of a walking stick (n=1). This left 29 controls, 36 people with AD, 30 with DLB, 15 with PDD and 7 with VaD. Results pertaining to laboratory gait assessment will be discussed in relation to previously described key aims.

4.4.2 Gait across dementia disease subtypes

Initially, differences in gait characteristics between the MCI and dementia groups were considered. There were no between group differences found for any of the sixteen gait characteristics and as such, participants with MCI and dementia pertaining to AD, DLB and PDD were included in their relevant disease subtypes (see Appendix B). This allowed larger sample sizes in each group, thus adding more power to the analysis. Due to small numbers (n=7), VaD were excluded from this analysis.

This left 110 participants across our four groups; AD, DLB, PDD and controls. Mild cognitively impaired participants made up 42% of AD (15 MCI; 21 dementia), 40% of DLB (12 MCI; 18 dementia) and 53% of PDD (8 MCI; 7 dementia) groups. Table 4-1 describes clinical and demographic information for each group.

As demonstrated in Table 4-1, there were no differences between groups for age ($p = .18$), height ($p = .5$) or body mass index ($p = .54$). Controls had higher scores for premorbid IQ (NART; $p \leq .05$), cognition (MMSE and ACE-III; $p \leq .001$) and balance confidence (ABC; $p \leq$

.001) compared to all dementia groups. Controls also had lower scores for comorbidities (CIRS-G; $p \leq .001$), motor severity (UPDRS-III; $p \leq .05$), depression (GDS; $p \leq .001$), and impairments in activities of daily living (BADLS; $p \leq .001$) compared to dementia groups. The control group also had a lower percentage of fallers compared to the dementia groups ($p \leq .05$).

Both the control and AD group had a higher percentage of females ($p \leq .01$) and lower scores for sleepiness ($p \leq .001$) compared to DLB and PDD groups. Participants with AD had less impairments in activities of daily living compared to DLB (BADLS; $p = .026$), lower scores for motor severity compared to DLB and PDD (UPDRS-III; $p \leq .001$), and higher scores for balance confidence compared to PDD ($p = .023$). PDD had higher scores for motor severity compared to DLB (UPDRS-III; $p = .028$).

There were no differences for scores relating to cognition, comorbidities, intelligence, depression or faller status between disease subtypes ($p \geq .05$ for all).

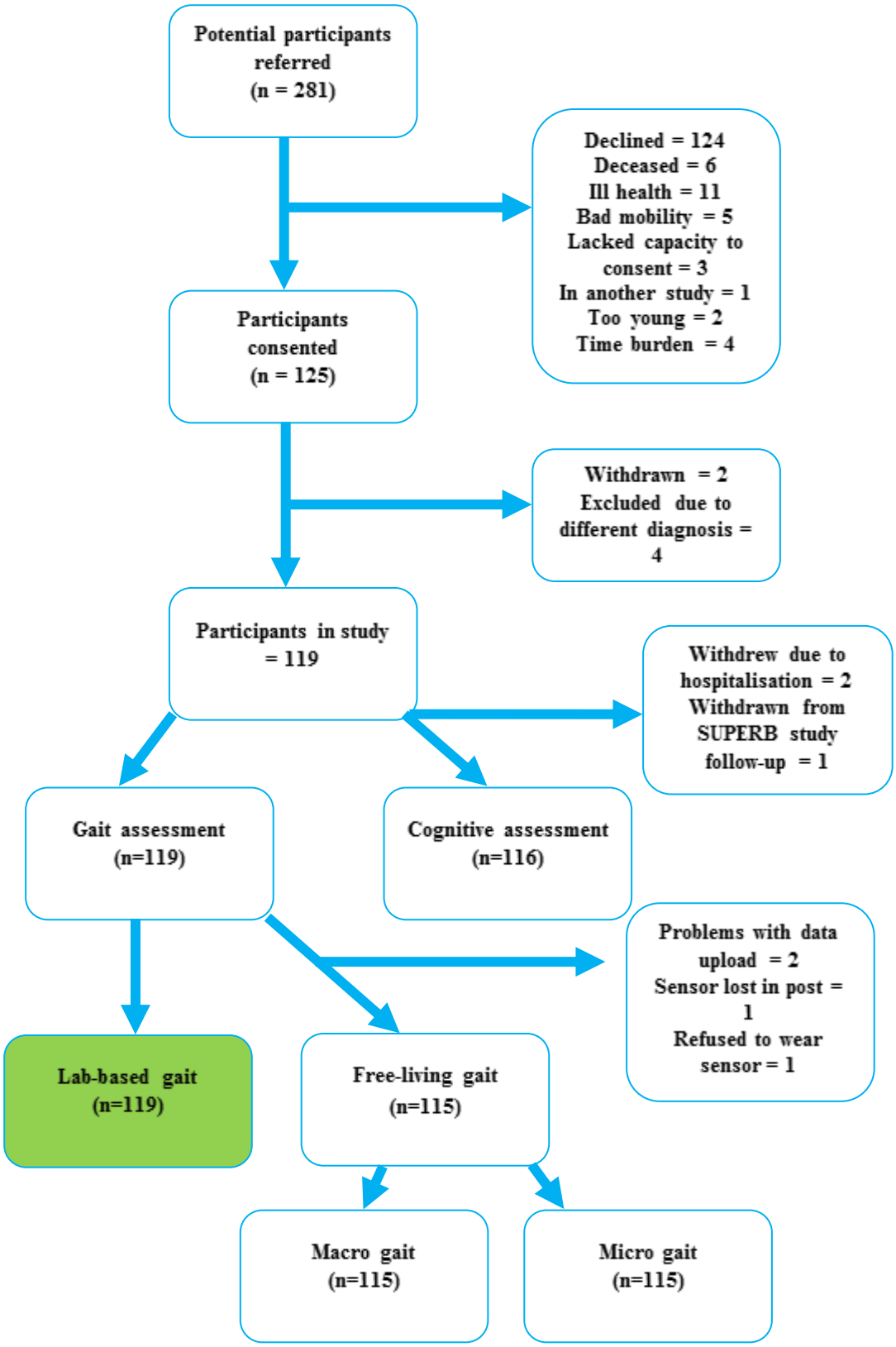

Figure 4-1 Participant approach, recruitment and assessment.

Table 4-1 Demographic and clinical information for controls and dementia disease subtypes

			Lewy body disease subtypes			Statistically significant differences between controls, AD, DLB and PDD	
	Controls	**AD**	**DLB**	**PDD**	**LBD**	**F/ χ 2**	**(p)**
N	29	36	30	15	45		
Age	74 ± 9	77 ± 6	76 ± 6	78 ± 6	77 ± 6	1.7	.180
Sex (% F)	59%[D,P]	58% [D,P]	20%[C,A]	7%[C,A]	16%	21	**≤.001**
CDR (0-3)	0 ± 0[A,D,P]	.8 ± .3 [C]	.9 ± .3 [C]	1 ± .6 [C]	.9 ± .4	120.7	**≤.001**
NART	123 (114-126) [A,D,P]	117 (101-125)	116 (101-124) [C]	120 (105-124) [C]	116 (101-124)	25	**≤.001**
% Faller	19% [A,D,P]	44%[C]	60% [C]	73% [C]	64%	14.4	**.002**
Height (m)	1.67 ± .096	1.66 ± .105	1.70 ± .099	1.67 ± .074	1.69 ± .09	0.8	.500
BMI	26 (21-35)	26 (18-42)	26 (18-43)	25 (20-35)	26 (18-43)	2.2	.535
CIRS-G (0 - 56)	4 (0-11) [A,D,P]	8 (3-19) [C]	10 (4-18) [C]	10 (3-17) [C]	10 (3-18)	30.7	**≤.001**
UPDRS III	1 (0-11) [A,D,P]	7 (0-19) [C,D,P]	23 (0-73) [C,A,P]	41 (20-78) [C,A,D]	31(0-78)	67	**≤.001**
MMSE (0-30)	30 (25-30) [A,D,P]	23 (14-29) [C]	24 (16-30) [C]	24 (12-30) [C]	24 (12-30)	53.2	**≤.001**
ACE-III (0-100)	97 (87-100) [A,D,P]	74 (28-90) [C]	77 (15-95) [C]	78 (49-95) [C]	77 (15-95)	60	**≤.001**
GDS (0 -15)	1 (0-5) [A,D,P]	4 (0-10) [C]	4 (0-13)	6 (0-12)	5 (0-13)	38.2	**≤.001**
ESS (0 - 24)	4 ± 3 [D,P]	6 ± 4[D,P]	9 ± 5 [C,A]	11 ± 3 [C,A]	10 ± 4	14.7	**≤.001**
ABC (0 - 100)	94 (52-100) [A,D,P]	89 (37-100) [C,P]	86 (42-100) [C]	71 (21-94) [C,A]	78 (21-100)	26.9	**≤.001**
BADLS (0 - 60)	0 (0-1) [A,D,P]	6 (0-31) [C,D]	13 (3-30) [C,A]	11 (1-31) [C]	13 (1-31)	55.8	**≤.001**

Data displayed as (mean ± standard deviation) were assessed using one-way ANOVAs and Students T-tests, while data displayed as (median (minimum-maximum)) were assessed using Kruskal Wallis and Mann Whitney U tests. C= different to controls, A = different to AD, D = different to DLB, P = different to PDD. CDR = Clinical Dementia Rating scale, NART = National Adult Reading Test, BMI = Body Mass Index, CIRS-G = Cumulative Illness Rating Scale –Geriatric, UPDRS-III = Unified Parkinson's Disease Rating Scale III, MMSE = Mini Mental State Examination, ACE-III = Addenbrookes Cognitive Examination III, GDS = Geriatric Depression Scale, ESS = Epworth Sleepiness Scale, ABC = Activities Balance Confidence Scale, BADLS = Bristol's Activities of Daily Living.

Differences in gait characteristics between controls and Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia

As shown in Table -4-2, thirteen of the sixteen characteristics were significantly different between controls, AD, DLB and PDD ($p \leq .05$). In order to use parametric tests, non-normally distributed variables were logarithmic and square root transformed.

All dementia groups walked slower ($p \leq .001$) with shorter steps ($p \leq .001$), and greater swing ($p \leq .001$), step ($p \leq .001$), and stance time ($p \leq .001$), step velocity ($p \leq .01$) and step length variability ($p \leq .001$), and a wider step width ($p \leq .01$) compared to controls (see Figure 4-2).

Differences in gait characteristics between Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia

Participants with AD demonstrated less swing ($p = .009$; partial $\eta^2 = .099$) and step time ($p = .008$; partial $\eta^2 = .118$), and step length variability ($p \leq .001$; partial $\eta^2 = .110$), and stance asymmetry ($p = .030$; partial $\eta^2 = .078$) compared to PDD. When considering these groups in an independent t-test, no differences were significant at $p \leq .01$.

Participants with AD were less variable for step velocity ($p = .036$) and step length ($p = .015$), and less asymmetric for step ($p = .033$) and swing time ($p = .018$) compared to DLB. When compared independently, DLB remained more variable for step length ($p = .002$; partial $\eta^2 = .144$) and more asymmetric for step ($p = .019$; partial $\eta^2 = .082$) and swing time ($p = .014$; partial $\eta^2 = .091$). Considering $p \leq .01$, only step length variability remained significant between groups.

There were no significant differences in gait outcomes between DLB and PDD (see Figure 4-2), and these results held when the groups were considered independently. With consideration of these results and as similar neurobiology has been demonstrated in DLB and PDD (Jellinger and Korczyn, 2018), the DLB and PDD group were merged into a LBD group for subsequent analysis (see Table 4-1 for clinical and demographic information).

Differences between controls and Alzheimer's disease and Lewy body disease

Significant differences between all disease groups and controls will first be discussed. Both AD and LBD walked slower ($p \leq .001$) with shorter steps ($p \leq .001$), longer stance ($p \leq .001$), and greater stance ($p \leq .001$), step ($p \leq .001$), swing time ($p \leq .001$), step velocity ($p \leq .01$) and step length variability ($p \leq .001$) compared to controls.

Participants with LBD also had a longer step time ($p \leq .001$), greater step time ($p = .006$) and stance time asymmetry ($p = .014$) and wider steps ($p \leq .001$) compared to controls. AD had a longer step time ($p = .041$), greater step velocity variability ($p = .013$) and a larger step width

(p = .026) compared to controls. When considering p ≤ .01, only significant differences between LBD and controls for step time, step time asymmetry and step width remained.

Controlling for age, sex and height

Controls, AD and LBD were compared in an adjusted model, controlling for age, sex and height as these are known covariates of gait. As demonstrated in Table -4-2, both disease subtypes had shorter steps, greater stance, step and swing time, step velocity and length variability and longer stance compared to controls. The LBD also walked slower, had longer step times, greater step, stance and swing time asymmetry (p = .003) and wider steps compared to controls (p≤ .01).

Controlling for age, sex, height and cognitive impairment

The model was adjusted to control for global cognitive impairment, age, sex and height with statistical significance set as (p≤.01). Both subtypes walked significantly slower (p≤.01) with shorter steps (p≤.01) and greater swing (p≤.01) and step length variability (p≤.01) and a larger step width (p≤.01) compared to controls.

LBD were significantly more variable for step (p≤.001) and stance time (p≤.001), and step velocity variability (p = .014) with longer stance time (p≤.01) and greater step (p = .003) and swing time asymmetry (p = .004) compared to controls. The AD group demonstrate more variability for step (p = .018) and stance variability (p = .024), and longer stance time (p = .045) compared to controls. When considering p ≤ .01, step and stance time variability, stance time and step and swing asymmetry remained significantly different between LBD and AD.

Controlling for age, sex, height and motor disease severity

When controlling for motor scores, age, sex and height, disease subtypes demonstrated greater variability for swing (p≤.001), step (p≤.001), stance (p≤.001) step velocity (p≤.05) and step length (p≤.001) with longer stance time (p≤.05) compared to controls. When considering p ≤ .01, between-group differences remained for step, swing, stance time, and step length variability.

The AD group also walked slower (p = .003) with shorter steps (p = .005), while the LBD group walked slower (p = .011), with greater step width variability (p = .035) and greater step (p = .027), swing (p≤.001) and stance time asymmetry (p = .004) and wider steps (p = .002) compared to controls. Considering p ≤ .01, people with AD walked slower than controls, and people with LBD had greater swing and stance time asymmetry and wider steps than controls.

Controlling for age, sex, height, motor disease severity and cognitive impairment

When the model was adjusted to control for both global cognitive impairment and motor disease severity, both dementia disease subtypes walked slower ($p \leq .05$), greater step time ($p \leq .01$) and step width variability ($p \leq .05$) and a wider step ($p \leq .01$) compared to controls. Participants with LBD also demonstrated greater step length variability ($p \leq .001$) and stance ($p = .003$) and swing time asymmetry ($p = .003$) compared to controls. Participants with AD also demonstrated greater step length variability ($p = .020$). When considering $p \leq .01$, people with AD and LBD both had greater step time variability and wider steps compared to controls, and people with LBD also had greater step length variability and swing time asymmetry.

Differences between Alzheimer's disease and Lewy body disease

Compared to AD, the LBD group demonstrated greater step ($p = .010$) and swing time ($p = .016$), step velocity ($p = .037$) and step length variability ($p \leq .001$), and step ($p = .022$), stance time ($p = .019$) and swing time asymmetry ($p = .009$) compared to AD. When applying the more stringent $p \leq .01$, only step time and length variability and swing time asymmetry remained significant.

When considered in an independent t-test, only step length variability remained significantly different between groups ($p \leq .01$). Participants with LBD showed greater variability for step ($p = .017$, $\eta^2 = .070$) and swing time ($p = .027$, $\eta^2 = .061$), and step length variability ($p \leq .001$, $\eta^2 = .135$) and greater swing ($p = .013$, $\eta^2 = .075$), step ($p = .020$; $\eta^2 = .066$) and stance time asymmetry ($p = .027$; $\eta^2 = .060$).

Controlling for age, sex and height

In an adjusted model controlling for age, sex and height, people with LBD walked slower ($p = .016$; $\eta^2 = .061$) with shorter steps ($p = .011$; $\eta^2 = .066$) and greater step ($p \leq .001$; $\eta^2 = .151$), swing ($p = .020$; $\eta^2 = .057$) and stance time ($p = .015$; $\eta^2 = .069$) and step length variability ($p \leq .001$; $\eta^2 = .126$), with greater step ($p \leq .001$; $\eta^2 = .151$), swing ($p \leq .001$; $\eta^2 = .145$) and stance time asymmetry ($p = .008$; $\eta^2 = .083$) compared to AD. When considering the more stringent $p \leq .01$, only step time and step length variability, and step, swing and stance time asymmetry remained significantly different between groups.

Controlling for age, sex, height and cognitive impairment

In an adjusted model controlling for global cognitive impairment, age, sex and height, participants with LBD walked slower ($p = .013$), with shorter steps ($p = .008$) and greater step ($p = .002$) and stance ($p = .008$) and swing time ($p = .014$), step velocity ($p = .037$), and step length variability ($p \leq .001$) and step ($p \leq .001$) and stance time asymmetry ($p = .014$) compared

to AD. When considering $p \leq .01$, only step length, step and stance time and step length variability, and step time asymmetry remained significant.

Controlling for age, sex, height and motor disease severity

When controlling for motor scores, age, sex and height, participants with LBD demonstrated greater step length variability ($p = .021$) and step ($p = .012$), swing ($p \leq .001$) and stance time ($p = .003$) asymmetry compared to LBD. When considering $p \leq .01$, only swing and stance time remained significantly different between groups.

Controlling for age, sex, height, motor disease severity and cognitive impairment

When the model was adjusted to control for both global cognitive impairment and motor disease, LBD participants were more variable for step length ($p = .014$), and asymmetrical for stance ($p = .006$) and swing time ($p \leq .001$) compared to AD. When considering a more stringent $p \leq .01$, only differences for stance and swing time asymmetry remained.

Summary of key findings

All dementia disease subtypes walked slower with shorter wider steps and greater variability compared to controls. Participants with LBD also had longer and more asymmetrical step times compared to controls.

Participants with DLB and PDD were more variable and asymmetric compared to AD. There were no significant differences between DLB and PDD. As such, they were combined to form a LBD group, and demonstrated greater variability for step time and step length and greater asymmetry for swing time compared to AD. When controlling for age, sex and height, they also demonstrated greater asymmetry for stance and step time. When additionally controlling for cognitive function, the LBD group also demonstrated shorter steps, greater variability and asymmetry compared to AD. When controlling for motor disease severity, and motor disease severity in addition to cognitive function, LBD only showed greater asymmetry compared to AD.

Table -4-2 Comparison of gait characteristics between controls and disease subtypes

						Statistically significant differences between controls, Alzheimer's disease and Lewy body disease									
						Unadjusted Model		Controlling for age, sex and height		Controlling for age, sex, height and ACE-III		Controlling for age, sex, height, and UPDRS-III		Controlling for age, sex, height, ACE-III and UPDRS-III	
	Control	**AD**	**DLB**	**PDD**	**LBD**	**F**	**(p)**	**F**	**(p)**	**F**	**(p)**	**F**	**(p)**	**F**	**(p)**
Pace															
Step Velocity (m/s)	1.26 ± .19[A,L]	1.03 ± .24[C]	.98 ± .23	.90 ± .24	.95 ± .24 [C]	16.5	**≤.001**	16	**≤.001**	11.5	**≤.001**	5.4	**.006**	3.3	.040
Step Length (m)	.70 ±.09 [A,L]	.57 ± .11 [C,L]	.57 ± .11	.51 ± .12	.55 ± .12 [C,A]	11.5	**≤.001**	15.9	**≤.001**	12	**≤.001**	4.5	.014	2.8	.067
Swing SD (ms)[ln]	14 (7-21) [A,L]	20 (9-45) [C]	23 (11-49)	29 (11-87)	25 (11-87) [C]	24.1	**≤.001**	18	**≤.001**	12	**≤.001**	9	**≤.001**	5.3	**.007**
Step Time SD (ms)[ln]	15 (9-23) [A,L]	21 (9-48) [C,L]	26 (13-80)	32 (13-60)	29 (13-80) [C,A]	25.1	**≤.001**	20.7	**≤.001**	12.3	**≤.001**	8.6	**≤.001**	3.7	.028
Stance SD (ms)[ln]	17 (12-31) [A,L]	29 (12-69) [C]	34 (16-118)	37 (14-76)	35 (14-118) [C]	22.5	**≤.001**	19.8	**≤.001**	9.9	**≤.001**	8.3	**≤.001**	2.5	.086
Variability (SD)															
Step Velocity SD (m/s)[ln]	.052 (.04-.11) [A,L]	.066 (.03-.11) [C]	.074 (.05-.15)	.068 (.05-.14)	.073 (.05-.15) [C]	12.1	**≤.001**	8.7	**≤.001**	3.6	.031	3.9	.024	1.2	.300
Step Length SD (m)[ln]	.021 (.01-.04) [A,L]	.030 (.01-.04) [C,L]	.034 (.02-.08)	.035 (.02-.06)	.035 (.02-.08) [C,A]	32.4	**≤.001**	22.8	**≤.001**	15.3	**≤.001**	12.4	**≤.001**	7.8	**≤.001**
Step Width SD (m)[ln]	.021 (.01-.03)	.022 (.01-.04)	.022 (.01-.04)	.022 (.01-.05)	.022 (.01-.05)	.6	.536	.2	.812	1.4	.253	2.3	.106	3.6	.033
Rhythm															
Step Time (ms)	536 ±48 [L]	565 ± 57	587 ± 70	577 ± 73	584 ± 70 [C]	5.3	**.006**	3.9	.024	2.4	.095	2.5	.090	1.5	.240
Swing (ms)	391±32	391 ± 37	400 ± 51	380 ± 53	393 ± 52	.04	.961	.6	.537	.771	.465	.2	.816	.1	.895
Stance (ms)[ln]	681 (571-787) [A,L]	722 (615-902) [C]	779 (599-981)	777 (627-1029)	777 (599-1029) [C]	9.2	**≤.001**	7.5	**≤.001**	5	**.009**	3.6	.033	2.1	.128
Asymmetry															
Step Time Asy (ms)[sqrt]	9 (.31-43) [A,L]	12 (.44-34) [C,L]	17 (2-49)	15 (2-65)	16 (2-65) [C,A]	4.8	.011	7.8	**≤.001**	6.8	**.002**	3.5	.034	2.6	.082
Swing Asy (ms)[sqrt]	6 (2-24) [A,L]	6 (.34-31) [C,L]	14 (3-38)	12 (.57-44)	14 (.57-44) [C,A]	4.9	**.010**	7.3	**≤.001**	7	**≤.001**	7.1	**≤.001**	6.5	**.002**
Stance Asy (ms)[sqrt]	7 (.58-24)	8 (.20-33)	14 (.13-36)	12 (1-47)	14 (.13-47)	4.4	.014	4.3	.017	4.1	.019	5.3	**.007**	4.8	**.011**
Postural Control															
Step Length Asy (m)[sqrt]	.018 (0-.06)	.019 (0-.13)	.02 (0-.07)	.021 (0-.06)	.02 (0-.07)	.3	.741	.9	.400	1.2	.304	.8	.438	.4	.667
Step Width (m)	.081 ± .023[L]	.099 ± .029	.106 ± .025	.103 ± .024	.105 ± .024 [C]	8.1	**≤.001**	6.2	**.003**	7.3	**≤.001**	5.6	**.005**	6.7	**.002**

Normally distributed data displayed as (mean ± standard deviation). Data for transformed variables are displayed as (median (minimum-maximum)) and refer to the non -transformed values. Significant values refer to differences between controls, AD and LBD in the adjusted model controlling for age, sex and height. C = different to controls, A = different to AD, L = different to LBD. SD = variability, asy = asymmetry, ln = log transformed, sqrt = square root transformed.

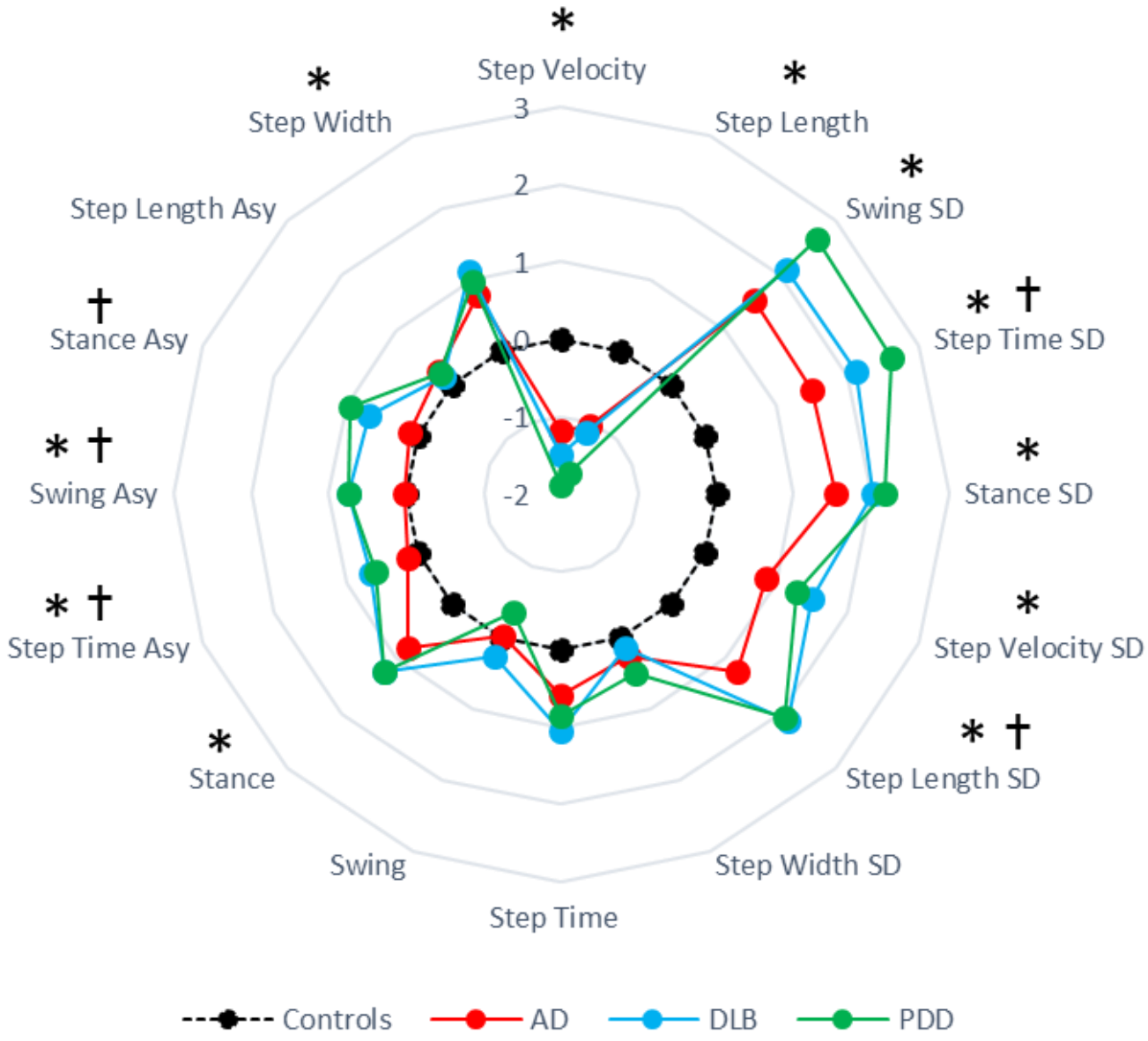

Figure 4-2 Radar plots illustrating patterns of impairment across 16 gait characteristics in controls, Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia groups.

*The central black line represents control data, and the lines representing AD, DLB and PDD demonstrate how many standard deviations from zero (z scores based on control means and standard deviations). Transformed data used from non-normally distributed variables previously described. * = controls different to disease group, † = differences between AD and LBD, when controlling for age, sex and height*

4.4.3 Is cognitive impairment and motor disease severity associated with gait impairment in disease subtypes?

Only gait characteristics that were significantly impaired in disease subtypes compared to controls were considered for this analysis in order to aid interpretation of the above findings.

Cognitive profiles between controls and disease subtypes

As demonstrated in Table 4-3, all disease groups were significantly impaired in global cognition (MMSE and ACE-III; $p \leq .001$ for both), attention (ACE-III attention subscale; $p \leq .001$; RT simple; $p \leq .001$ for LBD, $p = .023$ for AD), memory (ACE-III memory subscale; $p \leq .001$) verbal fluency (FAS and ACE-III fluency subscale; $p \leq .001$ for both), language (ACE-III language subscale; $p \leq .001$), visuospatial abilities (ACE-III visuospatial subscale; $p \leq .01$), information processing (TMT A; $p \leq .001$) and executive function (Stroop congruent; $p \leq .01$; Stroop incongruent; $p \leq .001$) compared to controls.

The LBD group were significantly more impaired in verbal fluency (FAS; $p = .038$), visuospatial abilities ($p = .008$), information processing ($p = .003$), attention (RT simple; $p = .046$) and executive function (Stroop congruent; $p = .033$) compared to AD participants. The AD group had greater impairments for memory ($p=.003$) compared to LBD participants.

Correlates of labratory gait performance in Alzheimer's disease.

For disease-specific correlations, cognitive variables were reduced to those that differentiated AD and LBD groups. In participants with AD, slower gait and greater step and swing time variability were moderately associated with greater motor disease severity, while shorter steps were moderately associated with older age and motor disease severity (see Table 4-4 for rho and p values). Greater stance time variability was moderately associated with greater motor disease severity and visuospatial impairments. Greater step velocity variability was moderately associated with greater impairment of global cognition. Longer stance time was moderately associated with taller height and greater motor disease severity. Greater swing time asymmetry was moderately associated with older age, while greater stance time asymmetry was moderately associated with greater visuospatial impairments.

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Table 4-3 Comparison of cognitive function between controls, Alzheimer's disease and Lewy body disease

	Controls	AD	LBD	F/χ	p
N	29	36	45		
MMSE (0-30)	30 (25-30)[A,L]	23 (14-29)[C]	24 (12-30)[C]	53.2	**≤.001**
ACE-III Attention (0-18)	18 (17-18)[A,L]	14 (6-18)[C]	15 (7-18)[C]	46.7	**≤.001**
ACE-III Memory (0-26)	25 (19-26) [A,L]	13 (3-23)[C,L]	20 (0-26)[C,A]	54.3	**≤.001**
ACE-III Fluency (0-14)	13 (5-14) [A,L]	9 (0-13)[C]	8 (2-13)[C]	45.2	**≤.001**
ACE-III Language (0-26)	26 (24-26) [A,L]	23 (11-26)[C]	24 (0-26)[C]	37.5	**≤.001**
ACE-III Visuospatial (0-16)	16 (13-16) [A,L]	14 (6-16)[C,L]	12 (0-16) [C,A]	33.1	**≤.001**
ACE-III Total (0-100)	97 (87-100) [A,L]	74 (29-90)[C]	77 (15-95)[C]	59.9	**≤.001**
TMT A (secs)	31 (19 - 65) [A,L]	049 (29-306) [C,L]	105 (24 - 955) [C,A]	47.6	**≤.001**
FAS	48 ± 12 [A,L]	35 ± 15 [C,L]	28 ± 14 [C,A]	18.1	**≤.001**
Simple RT (ms)	373 (291-493) [A,L]	415 (287-773) [C,L]	455 (287 - 3792) [C,A]	17.9	**≤.001**
Simple RT CV (secs)	.18 (.10-.97)	.21 (.13 - .91)	.28 (.13 - 1.12)	3.9	0.141
Angle Test (secs)	2.3 (1.1-5.3)	2.0 (1.0-7.0)	2.4 (.8 - 19.4)	5.0	0.081
Stroop RT Congruent (secs)	1.7 (1.0 -3.6) [A,L]	2.1 (1.3 - 10.6) [C,L]	2.9 (1.2 - 10.5) [C,A]	22.6	**≤.001**
Stroop RT Incongruent (secs)	1.8 (1.1 -4.5) [A,L]	2.7 (1.4 - 9.4)[C]	3.6 (1.2 - 11.9)[C]	23.9	**≤.001**

Data displayed as (median (minimum – maximum) analysed using Kruskal Wallis and Mann Whitney U tests. Data displayed as (mean ± standard deviation) analysed using one way ANOVAs and Student's t-test. Numbers of missing data can be found in Appendix C. A = different to Alzheimer's disease, L = different to Lewy body disease, C = different to controls. MMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time, Simple RT CV= Coefficient of variance for Simple Reaction Time Test Time, Stroop RT Congruent = Stroop Reaction Time Congruent Trials Mean Time, Stroop RT incongruent = Stroop Reaction Time incongruent Trials Mean Time.

.

Table 4-4 Spearman's correlations between cognitive impairment, motor disease and lab-based gait characteristics in Alzheimer's disease

Rho (p)	Step Velocity	Step Length	Swing SD	Step Time SD	Stance SD	Step Velocity SD	Step Length SD	Stance Time	Step Time Asy	Swing Asy	Stance Asy	Step Width
Age	-.187 (.274)	**-.353 (.035)**	.156 (.364)	.061 (.722)	.092 (.594)	-.048 (.780)	.107 (.536)	-.011 (.947)	-.004 (.982)	**.357 (.033)**	.321 (.057)	-.024 (.889)
Height	-.121 (.483)	.186 (.277)	.235 (.167)	.078 (.652)	.046 (.788)	-.243 (.154)	.275 (.104)	**.460 (.005)**	.022 (.900)	-.107 (.536)	-.014 (.935)	.067 (.698)
UPDRS-III	**-.452 (.006)**	**-.355 (.036)**	**.355 (.037)**	**.370 (.029)**	**.406 (.016)**	.056 (.750)	.258 (.134)	**.388 (.021)**	.180 (.301)	.232 (.181)	.104 (.551)	.075 (.668)
MMSE	.038 (.824)	.153 (.372)	-.083 (.631)	-.173 (.312)	-.234 (.169)	**-.448 (.006)**	-.068 (.694)	.175 (.307)	.022 (.897)	-.032 (.853)	-.198 (.247)	.188 (.271)
ACE-III Mem	.118 (.492)	.067 (.697)	-.078 (.649)	-.199 (.246)	-.231 (.175)	-.254 (.134)	-.176 (.305)	-.168 (.328)	-.025 (.883)	-.110 (.524)	-.032 (.851)	.153 (.372)
ACE-III VS	.239 (.160)	.305 (.070)	-.289 (.087)	-.321 (.056)	**-.342 (.041)**	-.264 (.120)	-.194 (.258)	.012 (.946)	-.207 (.227)	-.285 (.092)	**-.483 (.003)**	.065 (.708)
TMT A	-.076 (.662)	.013 (.941)	-.039 (.823)	.115 (.509)	.145 (.406)	.112 (.521)	.086 (.622)	.163 (.350)	.162 (.352)	.084 (.631)	.087 (.620)	.117 (.504)
FAS	.199 (.252)	.085 (.627)	-.169 (.332)	-.047 (.786)	-.156 (.371)	.221 (.201)	-.023 (.894)	-.286 (.096)	-.127 (.468)	-.108 (.537)	-.127 (.467)	-.258 (.134)
RT Simple	-.148 (.396)	-.080 (.646)	.134 (.443)	.169 (.332)	.203 (.241)	.189 (.276)	.120 (.492)	.097 (.581)	.163 (.350)	.069 (.695)	.101 (.565)	-.050 (.775)
Stroop RT Con	.026 (.887)	.164 (.361)	-.092 (.610)	.128 (.479)	.114 (.529)	.057 (.751)	-.148 (.410)	.093 (.607)	.121 (.502)	.064 (.724)	-.009 (.962)	-.188 (.295)

Data displayed as (rho (p)). Dark blue represents significant values, light blue represents rho values > .200. Numbers of missing data for each variable can be found in Appendix C . MMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time, Stroop RT Con = Stroop Reaction Time Congruent Trials Mean Time

Univariate regressions were carried out, investigating how significantly associated variables associated to age, sex, height, motor disease and cognition explained impaired gait characteristics (see Appendix D and Appendix E). Significant explanatory variables were entered into a backwards stepwise regression and the results are demonstrated in Table 4-5 and Table 4-7.

Only step velocity variability was significantly explained by a cognitive variable in AD, with greater global cognitive impairment (MMSE) contributing to greater step velocity, explaining 13.5% of the variance. Greater motor disease severity significantly explained slower step velocity (16.6% of the variance), shorter steps (11% of the variance), greater variability for step (16% of the variance) and stance time (20.4% of the variance). Table 4-5 illustrates all significant predictors of gait variables in AD; Appendix D provides information on all explanatory variables.

Table 4-5 Significant explanatory variables of lab-based gait impairment in Alzheimer's disease

	β	SE	t	p	F	R	R^2	Adjust R^2	95% CI Lower Bound	95% CI Upper Bound
Step Velocity										
UPDRS-III	.019	.000	-2.8	**.009**	7.8	.436	.190	.166	-.031	-.005
Step Length (m)										
UPDRS-III	-.007	.003	-2.3	**.029**	5.2	.369	.136	.110	-.013	-.001
Step Time SD										
UPDRS-III	.630	.230	2.7	**.010**	7.5	.430	.185	.160	.162	1.098
Stance Time SD										
UPDRS-III	.987	.317	3.1	**.004**	9.7	.477	.228	.204	.343	1.631
Step Velocity SD										
MMSE	-.002	.001	-2.5	**.016**	6.5	.400	.160	.135	-.003	.000
Stance Time Asy										
Age	.598	.233	2.6	**.015**	6.6	.403	.163	.138	.125	1.071

Numbers of missing data for each variable can be found in Appendix C. MMSE= Mini Mental State Exam, UPDRS-III = Unified Parkinson's disease rating scale III, SD = variability, Asy = asymmetry

Correlates of labratory gait performance in Lewy body disease

For LBD, slower gait speed was moderately associated with greater motor disease severity and verbal fluency impairment (see Table 4-6 for rho and p values). Shorter steps were moderately associated with shorter height, greater motor disease severity, slower information processing and greater impairments in verbal fluency and attention. Greater step time variability was moderately associated with slower information processing and greater verbal fluency impairments, and greater stance time variability was moderately associated with greater visuospatial, information processing and verbal fluency impairments. Greater step

velocity variability was also moderately associated with slower information processing. Longer stance time was moderately associated with taller height and greater step width was moderately associated with older age.

Slower step velocity was explained by greater motor disease severity and trends indicated greater impairments in verbal fluency also contributed, explaining 17.5% of the variance (see Table 4-7). Shorter steps were also explained by greater motor disease severity and shorter height, accounting for 37.6% of the variance. Greater step and stance time variability were predicted by greater impairment in verbal fluency, accounting for 10.8% and 11.3% respectively. Cognition did not predict any other gait variables in the LBD group.

Summary of key findings

Key findings of this analysis suggest that greater motor disease severity is a stronger explanatory variable of gait impairment in AD, with global cognition only significantly explaining 13.5% of the variance in step velocity variability. In comparison, greater variability of gait was significantly explained by verbal fluency impairment in LBD; greater motor disease severity was a significant explanatory variable for slower gait and shorter steps.

Table 4-6 Spearman's correlations between lab-based gait characteristics and motor disease severity and cognitive function in the Lewy body disease group

Rho (p)	Step Velocity	Step Length	Swing SD	Step Time SD	Stance SD	Step Velocity SD	Step Length SD	Stance	Step Time Asy	Swing Asy	Stance Asy	Step Width
Age	-.149 (.329)	-.116 (.446)	.122 (.425)	.171 (.262)	.106 (.488)	.079 (.607)	.118 (.441)	.088 (.564)	-.082 (.591)	.113 (.460)	.168 (.270)	**.312 (.037)**
Height	.184 (.227)	**.455 (.002)**	-.202 (.183)	-.148 (.333)	-.099 (.519)	-.139 (.362)	-.054 (.722)	**.404 (.006)**	-.276 (.066)	-.224 (.139)	-.195 (.198)	.062 (.688)
UPDRS-III	.115 (.453)	.152 (.317)	-.111 (.468)	-.160 (.294)	-.247 (.102)	-.138 (.364)	-.016 (.917)	-.019 (.903)	-.056 (.717)	.100 (.511)	.100 (.512)	.129 (.397)
MMSE	**-.339 (.023)**	**-.484 (.001)**	.165 (.278)	.209 (.169)	.209 (.168)	.018 (.907)	.005 (.973)	-.055 (.719)	.042 (.785)	-.277 (.066)	-.279 (.064)	-.057 (.711)
ACE-III Mem	-.021 (.896)	.003 (.985)	-.067 (.668)	-.124 (.429)	-.180 (.247)	-.223 (.150)	-.158 (.311)	.024 (.879)	-.007 (.963)	.134 (.390)	.070 (.655)	.180 (.247)
ACE-III VS	.234 (.131)	.268 (.082)	-.176 (.260)	-.270 (.080)	**-.303 (.049)**	-.129 (.411)	-.123 (.433)	-.060 (.703)	.003 (.983)	.032 (.836)	.079 (.613)	-.098 (.533)
TMT A	-.258 (.134)	**-.428 (.010)**	.299 (.081)	**.387 (.022)**	**.412 (.014)**	**.335 (.049)**	.301 (.079)	.039 (.824)	-.092 (.601)	-.113 (.520)	-.104 (.550)	-.155 (.374)
FAS	**.310 (.046)**	**.378 (.014)**	-.303 (.051)	**-.374 (.015)**	**-.373 (.015)**	-.138 (.382)	-.184 (.245)	-.118 (.455)	-.124 (.436)	-.033 (.836)	.011 (.946)	-.106 (.502)
RT Simple	-.302 (.062)	**-.450 (.004)**	.197 (.230)	.229 (.161)	.223 (.172)	-.077 (.642)	.077 (.640)	.044 (.789)	-.019 (.907)	-.170 (.301)	-.270 (.097)	-.183 (.266)
Stroop RT Con	.080 (.665)	-.084 (.646)	-.111 (.546)	-.040 (.830)	-.112 (.541)	-.105 (.567)	-.111 (.546)	-.180 (.325)	.005 (.976)	-.071 (.700)	-.157 (.390)	-.048 (.794)

Data displayed as (rho (p)). Dark blue represents significant values, light blue represents rho values > .200. Numbers of missing data for each variable can be found in Appendix C. MMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time, Stroop RT Con = Stroop Reaction Time Congruent Trials Mean Time

Table 4-7 Significant explanatory variables of lab-based gait impairment in Lewy body disease

	β	SE	t	p	F	R	R^2	Adjust R^2	95% CI Lower Bound	95% CI Upper Bound
Step Velocity										
UPDRS-III	-.005	.002	-2.9	**.005**	8.7	.410	.168	.149	-.008	-.002
FAS	.005	.003	2.1	**.040**	4.5	.318	.101	.078	.000	.011
Total Model				**.009**	5.4	.464	.215	.175		
FAS	.004	.003	1.7	.097					-.001	.009
UPDRS-III	-.004	.002	-2.4	**.022**					-.008	-.001
Step Length (m)										
Sex (male)	.120	.045	2.6	**.012**	7.0	.373	.139	.119	.028	.211
Height (m)	.667	.169	4.0	**.000**	15.6	.516	.267	.250	.327	1.007
UPDRS-III	-.003	.001	-4.2	**.000**	17.4	.537	.288	.272	-.005	-.002
FAS	.003	.001	2.4	**.020**	5.8	.357	.127	.105	.000	.006
Total Model				**.001**	13.3	.637	.406	.376		
UPDRS-III	-.003	.001	-3.5	**.001**					-.004	-.001
Height (m)	.543	.167	3.3	**.002**					.206	.880
Step Time SD										
FAS	-.375	.154	-2.4	**.019**	5.9	.360	.129	.108	-.686	-.064
Stance Time SD										
FAS	-.533	.214	-2.5	**.017**	6.2	.366	.134	.113	-.966	-.100

Numbers of missing data for each variable can be found in Appendix C FAS= FAS Test, UPDRS-III = Unified Parkinson's disease rating scale III, SD = variability

4.5 Discussion

The aim of this chapter was to investigate and explain patterns of gait impairment between different disease subtypes. This is the first study to look at gait in AD, DLB and PDD with a comprehensive model of spatiotemporal gait characteristics. Gait could differentiate all subtypes from normal ageing, and discrete gait characteristics appear to distinguish AD from LBD. The cohort included in this study consisted mainly of MCI and early dementia cases; no statistically significant differences in gait impairments between MCI and dementia were found. Therefore, this study has provided evidence that gait analysis can distinguish early cognitive impairment from normal ageing and can differentiate between AD and LBD in early stages of the disease.

4.5.1 Do different dementia disease subtypes have unique signatures of gait?

Results demonstrate that both AD and LBD demonstrated slower pace, greater variability and timing of gait and wider steps compared to controls, supporting Hypothesis 4.1 and 4.2. This supports the wealth of literature demonstrating that gait is impaired in neurodegenerative disorders, and may be a useful hallmark of cognitive decline (Nakamura *et al.*, 1996; Nakamura *et al.*, 1997; Gillain *et al.*, 2009; Ries *et al.*, 2009; Maquet *et al.*, 2010; Wittwer *et al.*, 2010; Choi *et al.*, 2011; Coelho *et al.*, 2012; Cedervall *et al.*, 2014; Allali *et al.*, 2016; Beauchet *et al.*, 2018; Montero-Odasso *et al.*, 2018). Due to difficulties recruiting participants with VaD, they were not included in this analysis; therefore, Hypothesis 4.4 could not be answered.

This study is novel as it is the first to consider a model of gait (Lord *et al.*, 2013b) between clinician-verified cohorts of AD and LBD. Five gait characteristics distinguished disease subtypes; participants with LBD demonstrated greater step time and step length variability and swing, stance and step time asymmetry compared to AD, with trends indicating they walked slower with shorter steps and greater overall variability. This supported Hypothesis 4.2. Effect sizes indicated a large magnitude of difference between groups for step length variability and step and swing time asymmetry, potentially highlighting such characteristics to be clinically useful – these should therefore be considered in a larger study.

There were also weaker significant differences between DLB and AD, which may be strengthened with a larger sample size – this is an important finding as these subtypes are commonly misdiagnosed (Toledo *et al.*, 2013). In particular, participants with DLB demonstrated greater variability for step length with a large effect size, highlighting the

potential clinical value of this gait characteristic for distinguishing AD and DLB. These results support and expand on Fritz *et al.* (2016)'s previous findings, the only other study to look at AD and LBD.

Interestingly, this study demonstrated greater severity of motor impairment as assessed by the MDS-UPDRS-III in PDD compared to DLB but gait performance is not reflective of this result, disputing Hypothesis 4.3. This may due to small sample size and lack of statistical power. However, Fritz *et al.* (2016) also found no differences between the two LBD groups, and it could be argued that this is due to dementia onset occurring in different stages of these subtypes; cognitive impairment occurs in early stages of DLB, while recognisable motor symptoms may not, while the inverse is true for PD, possibly reflecting the increased degeneration of dopaminergic nigrastriatal cells in PDD compared to DLB (McKeith *et al.*, 2017; Jellinger and Korczyn, 2018). Therefore, participants with PDD may have more observable motor problems, and gait analysis may be identifying subtle impairments undetectable through subjective measures. This is supported by the reported low rates of identifying gait impairment in AD through qualitative measures (Allan *et al.*, 2005) – this study clearly demonstrates significant gait impairments in AD compared to similarly aged controls. This highlights the importance of quantitative gait analysis in the detection and recognition of gait impairment in early dementia, as impaired gait has increases risk of falling.

Similarities in gait impairments between DLB and PDD supports the suggestion that LBD is a spectrum of overlapping motor and cognitive impairments (Aarsland *et al.*, 2004; McKeith, 2007; Gross *et al.*, 2008; Aarsland, 2016; Jellinger and Korczyn, 2018). Both diseases are associated with prominent attention, visuospatial and executive dysfunctions, as well as REM sleep behaviour disorder, cognitive fluctuations, visual hallucinations and parkinsonism (Emre *et al.*, 2007; McKeith, 2017). Imaging and neuropathology studies have demonstrated little differences between the subtypes (Gross *et al.*, 2008). Greater Lewy body pathology in the temporal lobes and cholinergic dysfunction in the striatum has been reported in DLB, possibly attributing to more prominent cognitive impairments in early stages of the disease (Aarsland *et al.*, 2004). Cerebral neurofibrillary tangles and amyloid-beta plaques, pathology associated with AD, have been found in both subtypes and are regarded as the strongest predictors for a short interval between motor impairments and dementia onset (Jellinger and Korczyn, 2018). The presence of this pathology may account for some similarities in gait impairments between AD and LBD, and greater presence of cross-pathology may explain cognitive, motor and neuropsychiatric similarities between LBD and AD as the diseases progress.

The finding of greater asymmetry of LBD may support the proposal that gait function may reveal underlying changes in the brain (Fritz and Lusardi, 2009), as it may be reflecting the asymmetric origins of pathology in LBD. Unilateral onset of motor symptoms is a cardinal characteristics of PD, attributed to asymmetric neurodegeneration in both striata (Scherfler *et al.*, 2012). Similarly, asymmetrical uptake of dopamine has been shown in the posterior putamen in PDD (Jellinger and Korczyn, 2018). Similar alterations in the basal ganglia and subcortical areas have been observed in DLB and PDD, with non-significant trends suggesting changes in DLB are less asymmetrical (Walter *et al.*, 2006). Individuals with PD are initially more asymmetric in their motor impairments but as the disease progresses along the spectrum of cognitive decline, their impairments become increasingly bilateral. This is supported by Hoehn and Yahr staging (Goetz *et al.*, 2004) and by studies demonstrating greater symmetry in LBD compared to PD (Gnanalingham *et al.*, 1997). Although limited, evidence therefore suggests that overall LBD may demonstrate greater gait asymmetry compared to AD due to this asymmetrical neurodegeneration. To our knowledge, this is the first study investigating gait asymmetry in AD and LBD. Future research should investigate the discriminatory potential of asymmetry across the LBD spectrum and strengthen current findings between AD and LBD.

4.5.2 What role does cognition and motor disease play in gait impairment?

Cognition appears to play a greater role in maintenance of gait in LBD compared to AD, as demonstrated by the associations between cognitive functions with discrete gait characteristics (see Table 4-4, Table 4-5, Table 4-6, and Table 4-7), supporting Hypothesis 4.6. Greater motor disease severity and greater impairments in verbal fluency, considered a measure of executive function (Litvan *et al.*, 2012), partially explained shorter steps in LBD, while verbal fluency impairment partially explained greater step and stance time variability. Associations were also found between attentional impairment and shorter step length, and slower information processing with shorter steps and greater variability. This supported Hypotheses 4.5 and 4.6, highlighting the role of attention, information processing and executive function in maintenance of gait in LBD, supported by previous literature and indicating the possible role of the prefrontal cortex in facilitation of gait (Fuster, 2001). This is supported by findings in older adults, cognitive impairment and PD populations (Verlinden *et al.*, 2014; Weiss *et al.*, 2015a; Morris *et al.*, 2016); however this is the first study to explore the gait-cognition relationship between AD and LBD subtypes.

Motor disease severity did not appear greatly associated with gait impairment in LBD, only contributing to slower gait and shorter steps, somewhat supporting Hypothesis 4.5. In

contrast, greater motor disease severity was explained slower gait, shorter steps, and greater variability in AD, while global cognition only significantly contributed to step velocity variability. Interestingly, there were no associations between gait and memory, contradicting previous findings (Verghese *et al.*, 2007) but as memory is associated with hippocampal function, this finding perhaps strengthens the suggestion that the prefrontal cortex is a key neural region involved in gait (Blumen *et al.*, 2018). This may also explain why cognition did not play a greater role in the facilitation of gait in AD; the most prominent impairment in early AD is episodic memory impairment, as demonstrated by results in Table 4-3. It must be noted that while cognition did not appear to play a strong role in gait for the AD cohort, trends suggest that more gait-cognition associations would have been apparent had this study had greater statistical power.

These results could be considered with regards to the proposed relationship between motor and cognitive function, in which common neural processes are responsible for gait (Montero-Odasso *et al.*, 2012; Morris *et al.*, 2016). This suggests that gait engages two distinct but interacting neural pathways; motor and cognitive (Leisman *et al.*, 2016). Both pathways are mediated by the frontal lobes, basal ganglia and cerebellum and their interaction is best understood with consideration of the perception-action cycle i.e. transforming perceived patterns of intended movement to coordinated patterns of actual movement (Fuster, 2001). For example, engaging in gait requires sensory interpretation, object recognition, and guidance and feedback for our movements (perception informing action) and feedback from the movement to inform future motor planning (action informing perception). Therefore, this relationship between cognitive and motor networks is bidirectional and if the function of one is affected, the function of the other will be affected.

The cognitive abilities associated with gait impairment in this study are often considered to require input from the prefrontal cortex (Verghese *et al.*, 2007; Montero-Odasso *et al.*, 2012; Morris *et al.*, 2016), and similar to gait, require co-ordination of the prefrontal networks with the brain stem, basal ganglia, limbic system and thalamus to carry out their functions (Fuster, 2001). The prefrontal cortex and associated networks are affected at different disease stages in AD and LBD and may contribute to differing cognitive presentation, and in turn, the differing degree of gait impairment for cognitively mediated characteristics, e.g. gait variability.

The basal ganglia is an important brain area involved in initiation and facilitation of movement, and affected by Lewy body pathology and dopaminergic loss in LBD (Middleton and Strick, 2000; Braak *et al.*, 2004). It projects to the anterior cingulate, premotor and prefrontal cortices, and considered part of the frontostriatal network. Disruption of

frontostriatal circuits due to dopaminergic dysfunction in the basal ganglia has been associated with impairments in executive function (Gratwicke *et al.*, 2015). Atrophy, white matter hyperintensities burden, infarcts and amyloid-beta burden in the basal ganglia have been associated with impaired spatial characteristics of gait, such as slower step velocity, shorter step length, wider steps and greater step length variability in older adults and AD (Rosano *et al.*, 2006; Nadkarni *et al.*, 2009b; Choi *et al.*, 2012; Dumurgier *et al.*, 2012; Lee *et al.*, 2014; Tian *et al.*, 2017; Wennberg *et al.*, 2017). These gait impairments are amplified in LBD compared to AD. Speculatively, this may suggest that prominent gait impairments occur early in LBD due to the dysfunction in motor networks. As such, the cognitive network may take greater control of gait facilitation – transforming gait from an automatic motor function to a cognitive task. This may be why the gait-cognition relationship appears stronger in LBD compared to AD in this study.

In contrast, key regions in the temporal lobe and their associated networks are affected in the earliest stages of AD. The temporal lobe integrates sensory and motor information and communicates with the prefrontal cortex through the entorhinal cortex and nigrostriatal systems – which is part of the basal ganglia motor loop (Schroeter *et al.*, 2009). Slower gait velocity, shorter step length and greater temporal gait variability have been associated with atrophy and greater amyloid-beta burden in the temporal lobe (Tian *et al.*, 2017; Wennberg *et al.*, 2017; Wilson *et al.*, 2018), and the anterior cingulate cortex, connecting the limbic system to the prefrontal cortex, has been associated with gait variability (Tian *et al.*, 2017). The spread of AD pathology to the basal ganglia occurs in later disease stages (Thal *et al.*, 2002), while the described networks associated with the prefrontal cortex may be affected in the mild AD group recruited to this study. Speculatively, cognitive control of gait may diminish earlier in AD and result in greater reliance on the motor network to facilitate and modulate gait – hence why greater gait impairments are associated with greater motor disease severity in AD.

Future research should examine gait-cognitive associations with imaging techniques to establish neural correlates of gait, and allow a better understanding of the interaction about cognitive and motor neural pathways in the facilitation of gait. This will provide greater insight into the potential of gait as a surrogate marker for cognition and brain function.

4.5.3 Conclusions

In conclusion, this is the largest study to examine differences in the pattern of gait impairment between LBD and AD. It has provided evidence for gait's potential as a non-invasive clinical tool for differential diagnosis of dementia, and for the utility of gait as a clinical biomarker for

overall cognitive impairment. This study found a relationship between cognitive functions associated with the prefrontal cortex (e.g. attention, executive function, verbal fluency, information processing and visuospatial ability) with discrete gait impairments, particularly in LBD groups. Cognition appeared to be differentially associated with gait across disease subtypes, and this may reflect the breakdown of motor-cognitive neural pathways. Unique signatures of gait in dementia disease subtypes may reflect both overlapping and discrete neurodegenerative pathologies and their effect on motor and cognitive functions. Future work will explore gait's potential as a cost-effective, easily accessible clinical tool by assessing gait impairments in everyday environments using body-worn monitors.

Chapter 5 Spatiotemporal characteristics of gait in free-living environments in dementia disease subtypes

This chapter investigates differences in gait impairments under free-living conditions between dementia disease subtypes, and explores their relationship with cognitive impairment and motor disease severity.

5.1 Introduction

Quantitative gait analysis in laboratory conditions may be a useful clinical tool for differential diagnosis as shown in Chapter 4. However, traditional methods of gait assessment are costly and only provide only a snapshot of an individual's best gait performance. Convenient clinical measures such as walking in a straight 10 metre line do not represent habitual walking activities or reflect the challenges of real-world environments (Orendurff *et al.*, 2008). As such, there is an increasing interest in analysing free-living gait in neurological populations, which provides objective measures of a person's day-to-day gait in their home and community environments (Del Din *et al.*, 2016b). Previous research has demonstrated the feasibility of using a body-worn sensor to continuously monitor gait over seven days in a cognitively impaired population (Mc Ardle *et al.*, 2018). This method captured both microstructural (micro) and macrostructural (macro) gait characteristics.

Micro gait characteristics refer to spatiotemporal gait characteristics derived from each bout of walking, such as those collected in laboratory environments and described in Chapter 4. Macro gait characteristics describe habitual walking behaviour, (Del Din *et al.*, 2016a; Del Din *et al.*, 2016c; Del Din *et al.*, 2017; Hickey *et al.*, 2017) and will be further described in Chapter 6. Micro gait characteristics are clinically relevant due to their sensitivity to changes in cognition, and potential to identify specific neurodegenerative disorders (Morris *et al.*, 2016; Mc Ardle *et al.*, 2017). Research in this area has focused on Parkinson's disease (PD) to explore potential use of free-living data (Maetzler *et al.*, 2013; Del Din *et al.*, 2016b) and this research is only beginning to translate to other neurological populations (Moore *et al.*, 2017; Mc Ardle *et al.*, 2018; Storm *et al.*, 2018).

Wearable technology shows considerable promise for the augmentation of clinical information concerning PD (Mirelman *et al.*, 2015). Gait in free-living conditions may better discriminate between PD and normal ageing compared to laboratory conditions (Del Din *et al.*, 2016a) and may reveal concurrent clinical problems in PD, such as fall risk and freezing of gait. Discrete characteristics of gait differentiate fallers and non-fallers in both PD and

normal ageing (Weiss *et al.*, 2013; Weiss *et al.*, 2014; Del Din *et al.*, 2017) and predict future falls (Weiss *et al.*, 2014). Identifying fall risk is important for the implementation of interventions and negotiating environmental hazards (e.g. introducing ambulatory aids or reducing potential obstacles in home environments). Potential use for the detection of freezing of gait has also been demonstrated (Weiss *et al.*, 2015b; Mancini *et al.*, 2018), and shows clinical utility as freezing may be difficult to detect in PD as episodes may rarely occur during clinical appointments. Therefore, the clinical use of wearable technology is evident and could be interest to populations beyond PD.

Continuous unobtrusive monitoring of behavioural activities in people with cognitive impairment is an area of growing interest (Hayes *et al.*, 2008; Kaye *et al.*, 2012; Nieto-Reyes *et al.*, 2017; Teipel *et al.*, 2018); however the application of wearable technology in cognitively impaired populations is still relatively novel. Continuously monitoring gait in people with cognitive impairment is feasible (Mc Ardle *et al.*, 2018), can distinguish dementia from normal ageing (Gietzelt *et al.*, 2013) and identify fall risk (Gietzelt *et al.*, 2014; Schwenk *et al.*, 2014). While these findings show potential clinical utility of wearable technology in cognitively impaired populations, more research is needed within dementia disease subtypes. As such, this chapter poses the question; can gait impairments in free-living conditions differentiate dementia disease subtypes? In order to answer this we must consider a similar range of spatiotemporal gait characteristics described in our previous work in laboratory settings (see Chapter 4).

As described in Chapter 4, cognition may play a greater role in the facilitation and maintenance of gait in LBD, and this may become more apparent in free-living environments, as these involve greater obstacle recognition and adaptive behaviours to navigate complex surroundings and therefore require greater attentional input (Montero-Odasso *et al.*, 2012). Associations between attention and executive function and free-living gait performance in PD have been found, (Weiss *et al.*, 2015a), while greater impairments in global cognition has been associated with slower gait velocity, shorter steps and greater variability of step velocity in AD (Mc Ardle *et al.*, 2018). Similarly, Higuma *et al.* (2017) found associations with attentional impairment and gait impairments in people with Alzheimer's Disease (AD), suggesting people with attentional impairment may struggle to adapt their gait patterns to their environments. These findings highlight the interplay between cognitive and motor function in gait. By exploring the associations between gait impairments in free-living conditions with cognitive function and motor disease severity, we may gain insight into the

different motor and cognitive mechanisms disease subtypes potentially utilise during their usual everyday gait.

5.2 Aims and hypotheses

Based on the current literature and the results described in Chapter 4, this chapter addresses two key aims and their respective hypotheses with regard to gait in free-living environments.

- To investigate differences in patterns of gait impairment between dementia disease subtypes.
- To investigate the relationship between cognitive impairment, motor disease severity and discrete gait impairments in free-living conditions.

Hypotheses

5.1. All disease subtypes will walk slower with shorter steps, greater variability and asymmetry and longer stance time compared to controls.

5.2. The LBD groups will be distinguishable from the AD group by demonstrating greater variability and asymmetry of gait.

5.3. Characteristics of pace and variability will be associated with executive function and attention, while rhythm will be associated with memory.

5.4. Based on findings in Chapter 4, gait impairment in the LBD group will be predominately associated with cognition, while AD will show greater associations with motor disease severity.

5.3 Methods

5.3.1 Study participants

Participants in this analysis were recruited as part of the GaitDem study and all completed the single-task gait protocol detailed in Chapter 4. Participants included individuals with mild cognitive impairment or dementia pertaining to Alzheimer's disease, dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD) and vascular dementia (VaD), and control participants of a similar age. Relevant information regarding the recruitment process and inclusion/exclusion criteria are detailed in Chapter 3.

5.3.2 Protocol

Clinical and cognitive assessments are detailed in Chapter 3 and Chapter 4. Key assessments for this aspect of the study examined the following; dementia disease severity (Clinical

Dementia Rating scale; CDR), co-morbidities (Cumulative Illness Rating Scale – Geriatrics; CIRSG), motor disease severity (Unified Parkinson's Disease Rating Scale – III; UPDRS-III), global cognition (Mini Mental State Exam and Addenbrookes Cognitive Examination III; MMSE and ACE-III), information processing (Trail Making Task Part A; TMT A), verbal fluency (FAS test), attention (Simple Reaction Time Task; RT Simple), Stroop Test (Congruent and incongruent trials), depression (Geriatric Depression Scale, GDS), sleepiness (Epworth Sleepiness Scale; ESS), balance confidence (Activities Balance Confidence scale; ABC) and activities of daily living (ADLs; Bristol Activities of Daily Living Scale; BADLS). Information pertaining to age, faller status, height and weight was also collected and body mass index (BMI) was calculated. 105 clinical and cognitive assessments were conducted by this doctoral candidate; 10 assessments were carried out as part of the SUPERB study, an ongoing longitudinal research study investigating biomarkers for AD and LBD.

5.3.3 Free-living gait assessment

Following the laboratory gait assessment detailed in Chapter 4, study participants were asked to wear a single tri-axial accelerometer-based body-worn monitor as detailed in Chapter 3.

5.3.4 Data processing and analysis

Data from the body-worn monitors was downloaded to a computer and segmented by day. Analysis was carried out using a Matlab programme. The full process from initial placement of the body-worn sensor through to data extraction and output is depicted in Figure 5-2. The development of the algorithm used to derive macro and micro gait characteristics was developed by Dr. Silvia Del Din and Dr. Alan Godfrey and processing of the data in this project was undertaken by members of the Wearables team within the Brain and Movement Research Group.

Accelerometer signals were transformed to a horizontal-vertical coordinate system and filtered with a 4th order Butterworth filter at 20Hz in order to remove "noise" from the signal.

For each day, ABs are identified by applying selective thresholds on the magnitude of vector and the standard deviation of tri-axial acceleration signals (further detailed in Hickey *et al.* (2017). An AB is defined as any continuous period of walking. In order to enhance robustness and remain consistent with previous published findings (Del Din *et al.*, 2016a; Mc Ardle *et al.*, 2018), a minimum bout length of three consecutive steps was applied and a resting time threshold of 2.5 seconds – if an individual stopped for longer than 2.5 seconds, their next three steps would be considered a new AB.

The Gaussian continuous wavelet transform of vertical acceleration was applied to smooth the data and filter out potential errors (Hickey *et al.*, 2017). Initial contact (heel strike) and final contact (toe-off) event of the gait cycle were identified, representing a step.

Micro gait charactistics

Fourteen gait characteristics were calculated from the free-living data. These have previously been described in Chapter 4. Step width and step width variability are not calculated due to limitations measuring such variables with tri-axial accelerometers. As described in Chapter 5, the identification of initial contact (heel strike) and final contact (toe off) events of the gait cycle represent a step. From this, the mean time it takes to make a step can be calculated, subsequently allowing the calculation of mean stance and swing time (Del Din *et al.*, 2016c). Step length is calculated using the inverted pendulum model (Zijlstra and Hof, 2003; Godfrey *et al.*, 2015). This uses the vertical motion of the trunk and monitor height (as a proxy for leg length) to estimate mean step length by assuming movement in the sagittal plane follows a sinusoidal motion during each single-leg stance phase.

Step velocity was calculated from the ratio of step length and step time (Godfrey *et al.*, 2015). Variability of step, stance and swing time, step velocity and step length were determined by the standard deviations of all steps. Asymmetry was calculated using the absolute difference of consecutive steps (i.e. odd and even). These characteristics have been validated in the lab with measures obtained from the GaitRite Mat (Del Din *et al.*, 2016c); however, there was poor-moderate agreement with asymmetry and variability characteristics, which should be noted when interpreting results.

5.3.5 Data analysis

Statistical analysis for demographic and clinical information is described in Chapter 3.

The first part of the analysis investigated differences in micro gait characteristics between controls and disease subtypes: AD, dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). The analysis considered differences between controls and disease subtypes by employing one-way ANOVA tests to identify between-group differences in gait. Fisher's LSD post-hocs were used to identify which groups were different as this was an exploratory analysis; however, statistical significance was considered at ($p \leq .01$) to account for multiple comparisons. One-way stepwise ANCOVA controlled for age, sex, height, motor disease severity and cognitive impairment.

As the overall key aim of this thesis questions if gait analysis can distinguish AD and DLB, independent t-tests were also conducted to verify significant differences between the disease

groups, and effect sizes (partial eta squared; η^2) were calculated for key significant differences between these disease groups. Effect sizes were interpreted in accordance to guidelines (Richardson, 2011); small (.01-.06), medium (.06-.14) and large (> .14).

One-way analysis of variance (ANOVA) and Kruskal Wallis tests were used to examine differences between groups for cognitive functions; Fischer's LSD posthoc and Mann Whitney U tests were used to establish where these differences lay. As this was an exploratory analysis with small sample sizes, we set the statistical significance to ($p \leq .05$) in order to avoid Type II error – however, results should be considered with caution.

Spearman's Rho correlations were used to identify associations between motor disease severity, cognitive impairment and gait impairment of gait variables in each disease subtype. Due to small sample sizes, regression models were inappropriate for this analysis.

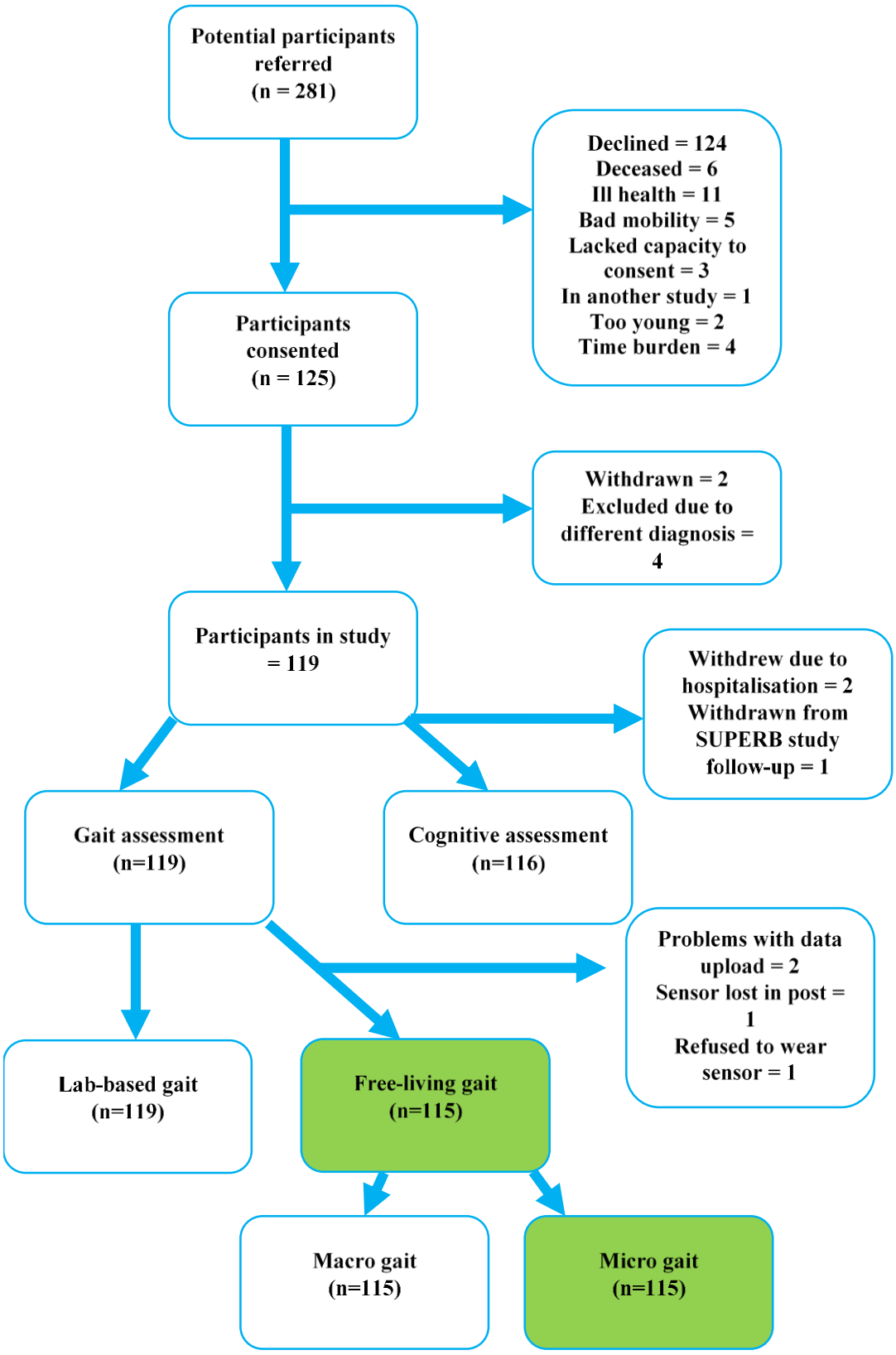

Figure 5-1 Participant approach, recruitment and assessment.

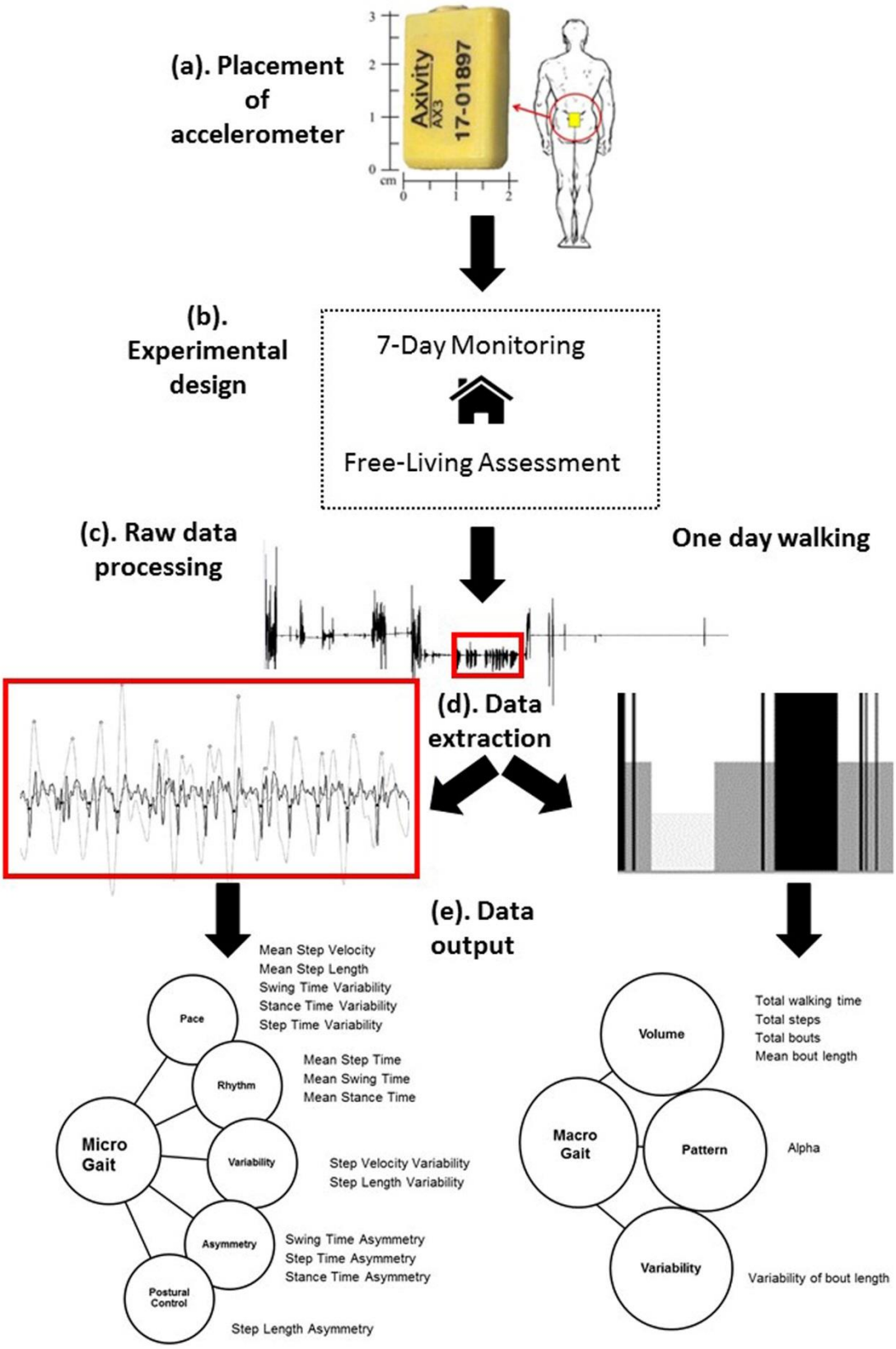

Figure 5-2 Illustration of gait protocol from initial body-worn monitor placement to data output.

(a) Example of body worn monitor placement for both the clinic based and free-living data collection on L5 centrally located on the lower back; (b) Gait protocols for free-living assessment; (c) The raw vertical acceleration signal segmented into walking bouts (d) Left; Example of gait characteristic extraction from walking bouts: detecting initial contacts (black stars) and final contacts (white circles). Right: Identification of walking bouts (black bars) from free-living data from which gait characteristics are extracted; (e) Left: Conceptual model of gait representing domains and 14 gait micro characteristics. Right: Macro characteristics of gait described by domains of volume, pattern and variability. Figure adapted from Mc Ardle et al., (2018).

5.4 Results

5.4.1 Participants

118 participants were assessed for this part of the study. The flowchart in Figure 5-1 demonstrates the number of participants approached, recruited, withdrawn and excluded from each stage of the study. 115 suitable participants remained; however, participants with VaD were excluded from this analysis, leaving 108 people in the study (26 controls, 36 people with AD, 30 with dementia with Lewy bodies, 16 with Parkinson's disease dementia). Five participants had less than seven days data collected due to hospitalisation (n = 1), discomfort (n = 1) and quality checks (n = 3). Participants were still included as data is reported as measures per day and all participants had over three days data collected; 3-7 days data collection is the current standard of free-living gait analysis (Del Din *et al.*, 2016b).

5.4.2 Differences in gait patterns between dementia disease subtypes

An initial analysis explored differences for gait impairment between the MCI and dementia cohorts; as no significant differences were found between MCI and dementia groups combined or within each subtype (see Appendix F), MCI and dementia cohorts were combined in their respective disease subtypes. As such, the groups were split as follows: 15 AD-MCI, 21 AD-dementia; 11 DLB-MCI; 19 DLB-dementia and 8 PD-MCI; 8 PDD.

As this cohort is a slightly different sample due to not all participants having free-living data (reasons outlined in Figure 5-1), group differences for clinical and cognitive measures was reanalysed, as demonstrated in Table 5-1 and Table 5-3.

Controls, AD, DLB and PDD groups were not significantly different for age ($p = .200$), height ($p = .570$), and body mass index ($p = .478$). Controls had significantly higher scores for cognition (MMSE and ACE-III; $p \leq .001$), intelligence (NART; $p \leq .05$), and balance confidence (ABC; $p \leq .001$). Controls had significantly more females ($p \leq .001$) and higher number of fallers compared to DLB and PDD ($p \leq .001$). Controls had significantly lower scores for sleepiness (ESS; $p \leq .05$), co-morbidities (CIRS-G; $p \leq .001$), motor disease severity (UPDRS-III; $p \leq .05$), depression (GDS; $p \leq .001$), dementia severity (CDR; $p \leq .001$), and impairments in ADLs (BADLS; $p \leq .001$) compared to all dementia disease subtypes.

AD had significantly lower scores for sleepiness (ESS; $p \leq .001$), motor disease severity (UPDRS-III; $p \leq .001$) and impairments in ADLs (BADLS; $p \leq .05$), and significantly more females ($p \leq .001$) compared to both DLB and PDD groups, and significantly higher scores for balance confidence ($p = .012$) compared to PDD.

Table 5-1 Demographic and clinical information for controls and dementia disease subtypes

						Significant differences between controls, AD, DLB and PDD	
	Controls	**AD**	**DLB**	**PDD**	**LBD**	**F/χ2**	**(p)**
N	26	36	30	16	46		
Age	74 ± 9	77 ± 6	76 ± 6	79 ± 6	77 ± 6	1.6	.200
Sex (% F)	58% [D,P]	58% [C,D,P]	20% [C,A]	13% [C,A]	17%	**18.3**	**.000**
CDR (0-3)	0 ± 0A,D,P	.8 ± .3C	.8 ± .3C,P	1 ± .6C,D	.9 ± .4	**121.6**	**.000**
NART	123 (114-126) [A,D,P]	117 (101-125) [C]	116 (101-124) [C]	119 (105-124)	116 (101-124)	**24.8**	**.000**
% Faller	21% [D,P]	44%	60% [C]	69% [C]	63%	**11.8**	**.008**
Height (m)	1.67 ± .095	1.66 ± .105	1.70 ± .098	1.67 ± .096	1.69 ± .091	.7	.570
BMI	25 (21-35)	26 (18-42)	27 (18-43)	25 (20-35)	26 (18-43)	2.1	.548
CIRS-G (0 - 56)	4 (0-11) [A,D,P]	8 (3-19) [C]	10 (4-18) [C]	10 (3-17) [C]	10 (3-18)	**27.0**	**.000**
UPDRS III	1 (0-11) [A,D,P]	7 (0-19) [C,D,P]	26 (5-57) [C,A,P]	41 (20-78) [C,A,D]	31 (5-78)	**68.9**	**.000**
MMSE (0-30)	30 (25-30) [A,D,P]	23 (14-29) [C]	24 (16-30) [C]	24 (12-30) [C]	24 (12-30)	**49.9**	**.000**
ACE-III (0-100)	97 (88-100) [A,D,P]	74 (28-90) [C]	77 (15-95) [C]	77 (49-95) [C]	77 (15-95)	**56.2**	**.000**
GDS (0 -15)	1 (0-5) [A,D,P]	4 (0-10) [C]	4 (0-13) [C]	5 (0-12) [C]	5 (0-13)	**35.1**	**.000**
ESS (0 - 24)	4 ± 3 [A,D,P]	6 ± 4 [C,D,P]	10 ± 5C,A	11 ± 3C,A	10 ± 4	**14.6**	**.000**
ABC (0 - 100)	94 (52-100) [A,D,P]	89 (37-100) [C,P]	86 (42-100) [C,P]	68 (21-94) [C,A,D]	78 (21-100)	**27.2**	**.000**
BADLS (0 - 60)	0 (0-1) [A,D,P]	6 (0-31) [C,D,P]	13 (3-24) [C,A]	11 (1-31) [C,A]	12 (1-31)	**52.6**	**.000**

Data displayed as (mean ± standard deviation) were assessed using one-way ANOVAs and Students T-tests, while data displayed as (median (minimum-maximum)) were assessed using Kruskal Wallis and Mann Whitney U tests. C= different to controls, A = different to AD, D = different to DLB, P = different to PDD. CDR = Clinical Dementia Rating scale, NART = National Adult Reading Test, BMI = Body Mass Index, CIRS-G = Cumulative Illness Rating Scale –Geriatric, UPDRS-III = Unified Parkinson's Disease Rating Scale III, MMSE = Mini Mental State Examination, ACE-III = Addenbrookes Cognitive Examination III, GDS = Geriatric Depression Scale, ESS = Epworth Sleepiness Scale, ABC = Activities Balance Confidence Scale, BADLS = Bristol's Activities of Daily Living.

DLB had lower scores for motor disease severity ($p = .042$) and dementia severity (CDR; $p = .030$) and significantly higher balance confidence scores ($p = .030$) compared to PDD. There were no significant differences between dementia groups for faller status, cognitive scores, intelligence, comorbidities, balance confidence or depression ($p \geq .05$).

Differences in gait characteristics between controls and Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia

All disease subtypes walked slower ($p \leq .01$) with shorter steps ($p \leq .01$) compared to controls. Participants with DLB and PDD were more variable for step ($p \leq .001$), stance ($p \leq .001$) and swing time ($p \leq .001$) compared to controls. The PDD group had greater step velocity variability ($p = .009$), and were more asymmetric for step ($p \leq .001$), swing ($p \leq .001$) and stance time ($p= .002$) compared to controls ($p \leq .001$). The AD group demonstrated greater step ($p = .025$), stance ($p = .026$), and swing time variability ($p = .030$), and less asymmetry for step ($p = .025$) and stance time ($p = .029$) compared to controls.

When considering the more stringent $p \leq .01$, the differences between AD and controls for variability and asymmetry characteristics, and between PDD and controls for step velocity variability no longer remained significant.

Controlling for age, sex and height

When compared in an adjusted model controlling for age, sex and height, both the AD and PDD groups walked slower ($p \leq .05$) compared to controls. The DLB and PDD groups took shorter steps ($p \leq .001$) with greater variability for swing ($p \leq .01$), step ($p \leq .01$) and stance ($p \leq .01$) time compared to controls. Participants with DLB walked more slowly ($p \leq .001$), while the PDD group demonstrated greater asymmetry for stance ($p \leq .01$), step ($p \leq .01$) and swing time ($p \leq .01$) compared to controls. The AD group also took smaller steps ($p = .023$) and had greater variability for step ($p = .043$), swing ($p = .048$) and stance time ($p = .048$) and greater asymmetry for step ($p =.036$) and stance time ($p = .047$) compared to controls.

When only considering a more conservative $p \leq .01$, the differences between controls and disease groups for step velocity, and between controls and AD for step length, variability and asymmetry measures no longer remained significant.

Controlling for age, sex, height and cognitive impairment

When controlling for cognitive impairment (ACE-III), the DLB and PDD groups walked slower ($p \leq .05$) and took shorter steps compared to controls ($p \leq .01$). Participants with DLB were more variable for swing time ($p = .037$) while the PDD group demonstrated greater

variability and asymmetry for swing ($p \leq .001$), step ($p \leq .001$) and stance ($p \leq .001$) compared to controls.

When only considering a more stringent $p \leq .01$, differences between PDD and controls for step velocity, and between DLB and controls for swing time variability no longer remained.

Controlling for age, sex, height, and motor disease severity

When additionally adjusting for motor disease severity scores (UPDRS-III), the PDD group were more asymmetric for step length compared to controls ($p = .022$). When applying a threshold of $p \leq .01$, no significant differences remained.

Controlling for age, sex, height, cognitive impairment and motor disease severity

When additionally adjusting for motor disease severity scores and cognitive impairment, the PDD group demonstrated greater asymmetry for step length ($p = .012$) compared to controls. No significant differences remained when applying a more stringent threshold of $p \leq .01$.

Differences in gait characteristics between Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia

The PDD group demonstrated shorter steps ($p = .005$) and greater variability for step ($p \leq .001$), stance ($p \leq .001$) and swing time ($p = .002$) compared to AD (see Table 5-2), and greater variability for stance time ($p = .009$) compared to DLB. They also had shorter step and stance times ($p \leq .05$) compared to AD and DLB participants. Participants with DLB had shorter steps ($p = .044$), were more variable for step length ($p = .031$) and more asymmetric for step length ($p = .002$) compared to AD.

When applying a more stringent threshold of $p \leq .01$, step length, step, stance and swing time variability remained significantly different between PDD and AD, and stance time variability between PDD and DLB. People with DLB also remained more asymmetric for step length compared to AD.

Controlling for age, sex and height

In an adjusted model controlling for age, sex and height (see Table 5-2 and Figure 5-3), participants with PDD demonstrated greater stance ($p = .003$) and step time ($p = .005$) variability compared to AD, and greater asymmetry for step ($p \leq .01$), stance ($p \leq .01$), and swing time ($p \leq .01$) compared to both DLB and AD. Both the DLB and PDD groups took shorter steps ($p \leq .05$) compared to AD participants. The PDD group also demonstrated greater variability for swing time ($p = .011$) compared to AD participants, and for step ($p =$

.039) and stance time (p = .035) compared to DLB participants. Both the AD and PDD groups were more asymmetric for step length ($p \leq .05$) compared to DLB participants.

When only considering $p \leq .01$, stance and step time variability remained significantly different between PDD and AD, and PDD had greater asymmetry for step, stance and swing time compared to AD and DLB.

Controlling for age, sex, height and cognitive impairment

When adjusting for age, sex, height and cognitive impairment (ACE-III scores), both DLB and PDD groups took shorter steps ($p \leq .05$) compared to the AD group. Participants with PDD were also more variable for swing (p= .009), step (p = .004) and stance time (p = .002) compared to the AD group. The PDD group were also more asymmetrical for step ($p \leq .01$), swing ($p \leq .01$) and stance ($p \leq .01$) compared to both DLB and AD, and more variable for step (p = .024) and stance time (p = .019) compared to the DLB group. Both the AD and PDD groups were more asymmetric for step length ($p \leq .05$) compared to the DLB group.

When applying the more stringent $p \leq .01$, differences between DLB, PDD and AD for step length and step length asymmetry and between PDD and DLB for variability characteristics were no longer significant.

Controlling for age, sex, height, and motor disease severity

When additionally adjusting for motor disease severity scores (UPDRS-III), the PDD group were more asymmetric for step length compared to DLB participants (p = .015). No differences remained when only considering values at the $p \leq .01$ threshold.

Controlling for age, sex, height, cognitive impairment and motor disease severity

When additionally adjusting for motor disease severity scores and cognitive impairment, both PDD and AD participants were more asymmetric for step length ($p \leq .05$) compared to the DLB group. This did not remain when considering values at the $p \leq .01$ threshold.

Differences in gait characteristics between Alzheimer's disease and dementia with Lewy bodies

As the key aim of this thesis was to question if gait analysis could differentiate AD and DLB, these subtypes were compared independently and effect sizes were calculated to demonstrate clinical significance.

In an unadjusted model, participants with DLB demonstrated greater variability (p = .018; partial η^2= .084) and less asymmetry (p = .003; partial η^2= .126) for step length compared to

AD. When controlling for age, sex and height, the DLB group demonstrated less step length asymmetry ($p = .014$; partial $\eta^2 = .096$) and shorter steps ($p = .027$; partial $\eta^2 = .079$). None of these differences remained significant when applying a more conservative threshold of $p \leq .01$.

When additionally controlling for cognition, DLB only demonstrated shorter steps ($p = .029$) and less step length asymmetry ($p = .016$) compared to AD. When controlling additionally for motor disease severity, and for both motor disease severity and cognitive impairment, no significant differences remained.

Summary of key findings

In comparison to controls, all disease subtypes walked slower with shorter steps, while both LBD groups demonstrated greater variability, and PDD also showed greater asymmetry for timing characteristics. These differences weakened when controlling for age, sex and height but DLB and PDD groups could still be distinguished from controls at ($p \leq .01$) significance threshold; the AD group could not. Similar findings occurred when controlling for cognitive impairment, but all group differences at ($p \leq .01$) disappeared when controlling for motor disease severity.

The PDD group could be distinguished from AD by shorter steps and greater variability, and also demonstrated greater stance time variability compared to DLB. The AD group could be differentiated from DLB participants by less variability, with a medium effect size, and greater asymmetry for step length, which demonstrated a strong effect size. When controlling for age, sex and height, participants with PDD remained more variable than those with AD, and showed greater asymmetry compared to both DLB and AD. Participants with AD remained more asymmetric for step length and took larger steps than the DLB group, both demonstrating medium effect sizes. When controlling for cognitive impairment, similar between-group differences remained; when controlling for motor disease severity, all differences at ($p \leq .01$) disappeared.

Table 5-2 Comparison of micro gait characteristics across controls, Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia groups in total bouts

					Unadjusted Model		Controlling for age, sex and height		Controlling for age, sex, height and UPDRS-III		Controlling for age, sex, height and ACE-III		Controlling for age, sex, height, ACE-III and UPDRS-III	
	Controls	**AD**	**DLB**	**PDD**	**F**	**(p)**	**F**	**(p)**	**F**	**(p)**	**F**	**(p)**	**F**	**(p)**
Pace														
Step Velocity (m/s)	1.09±.08^{A,D,P}	1.02±.08^{C}	.983±.10^{C}	.980±.08^{C}	6.7	**≤.001**	5.4	**.002**	1.5	.225	3.4	.020	0.8	.506
Step Length (m)	.61±.04 ^{A,D,P}	.58±.05^{C,P}	.55±.05^{C}	.53±.05^{C}	12.7	**≤.001**	8.3	**≤.001**	1.3	.294	5.1	**.003**	0.3	.845
Swing SD (s)	.139±.012^{D,P}	.147±.015^{P}	.152±.014^{C}	.161±017^{C,A}	8.5	**≤.001**	5.7	**≤.001**	1.8	.158	4.1	**.009**	1.1	.343
Step Time SD (s)	.166±.015 ^{D,P}	.176±.017^{P}	.181±.016^{C}	.194±.023^{C,A}	9.4	**≤.001**	6.1	**≤.001**	1.5	.225	4.4	**.006**	0.8	.499
Stance SD (s)	.176±.016 ^{D,P}	.187±.019^{P}	.194±.018^{C,P}	.209±.026^{C,A,D}	10.5	**≤.001**	6.6	**≤.001**	1.5	.227	5.0	**.003**	0.8	.484
Variability (SD)														
Step Velocity SD (m/s)	.359±.032	.359±.032	.370±.038	.388±.035	3.3	.024	.60	.615	0.2	.905	0.5	.653	0.2	.905
Step Length SD (m)	.149±.016	.147±.012	.154±.009	.157±.026	3.6	.016	2.4	.073	0.5	.679	2.4	.073	0.5	.653
Rhythm														
Step Time (ms)	594±30	606±24	601±31	578±35	3.7	.014	1.0	.383	1.2	.316	1.5	.223	1.8	.154
Swing (ms)	445±28	459±26	456±29	578±35	3.1	.031	1.3	.273	1.2	.297	1.1	.360	1.1	.369
Stance (ms)	743±34	755±25	750±36	723±45	3.5	.017	.8	.474	1.4	.247	1.6	.197	2.5	.068
Asymmetry														
Step Time Asy (ms)	.092±.009^{P}	.099±.013	.095±.008	.105±.015^{C}	4.7	**.004**	6.5	**≤.001**	2.3	.082	5.7	**≤.001**	2.0	.118
Swing Asy (ms)	.085±.008^{P}	.090±.011	.089±009	.096±.013^{C}	4.0	**.009**	5.3	**.002**	1.4	.256	4.9	**.003**	1.4	.256
Stance Asy (ms)	.094±.008^{P}	.100±.013	.096±010	.105±.014^{C}	4.0	**.009**	5.1	**.003**	1.8	.153	4.7	**.004**	1.7	.168
Postural Control														
Step Length Asy (m)	.086±.007	.089±.0121^{D}	.081±.101^{A}	.081±.014	4.0	**.010**	3.2	.027	2.9	.039	3.6	.017	3.5	.019

Significant values refer to differences between controls, Alzheimer's disease and Lewy body disease groups in unadjusted model. Normally distributed data and data analysed using one-way ANOVAs displayed as (mean ± standard deviation). C = different to controls, A = different to AD, D = different to DLB, P = different to PDD,. SD = variability, asy = asymmetry

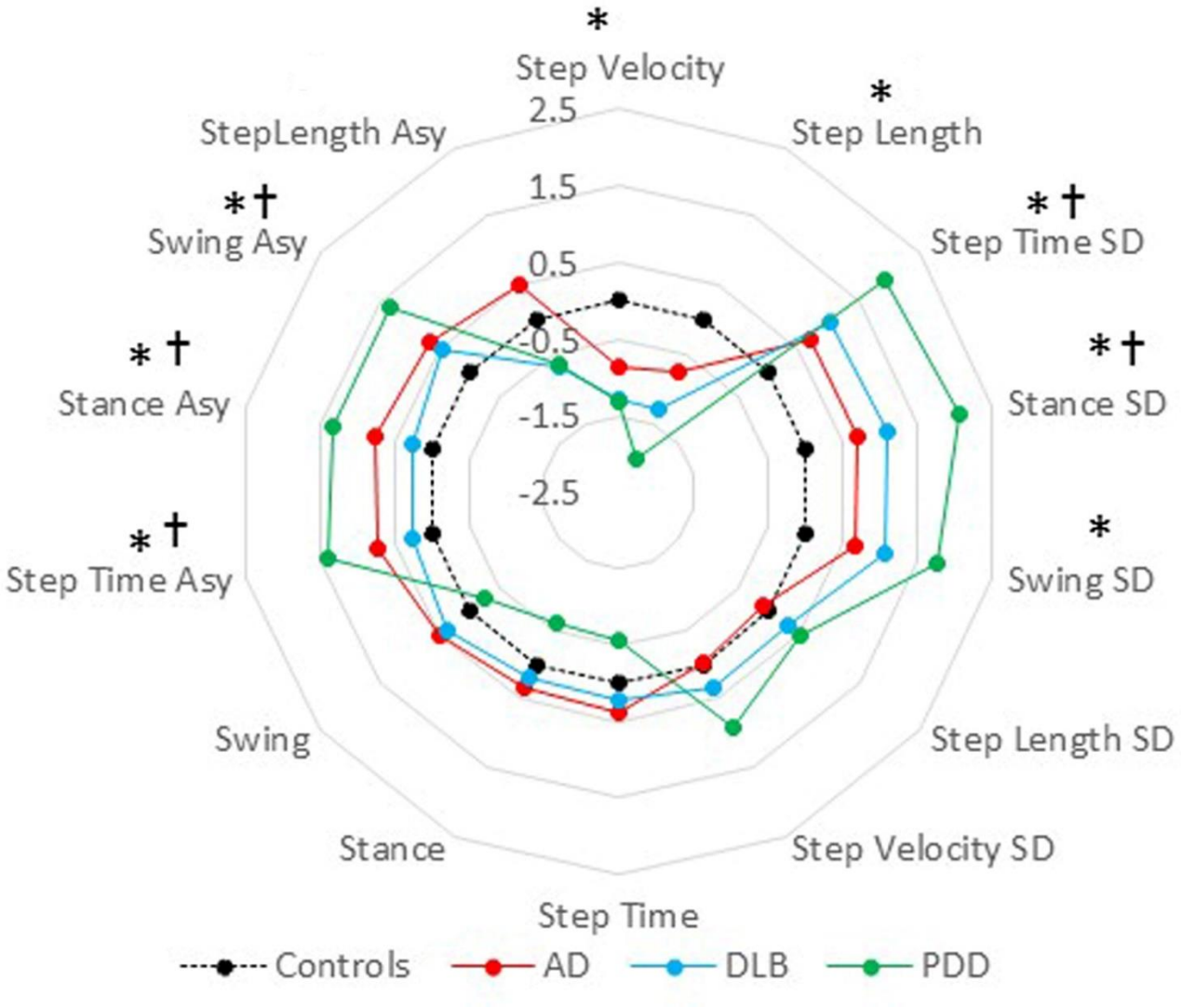

Figure 5-3 Radar plots illustrating patterns of impairment across 14 gait characteristics in controls, Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia groups.

*The central black line represents control data, and the lines representing AD, DLB and PDD demonstrate how many standard deviations from zero (z scores based on control means and standard deviations).. * = controls significantly different to disease subtypes, † = PDD different to AD and DLB, when controlling for age, sex and height.*

5.4.3 Cognitive profiles between controls, Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia groups

As demonstrated in Table 5-3, all disease groups were significantly more impaired for global cognition (MMSE and ACE-III; $p \leq .001$ for both), attention (ACE-III attention subscale; $p \leq .001$; Simple RT; $p \leq .05$), memory (ACE-III memory subscale; $p \leq .001$), fluency (ACE-III fluency subscale; $p \leq .001$), language (ACE-III language subscale; $p \leq .01$), visuospatial abilities (ACE-III visuospatial subscale; $p \leq .001$), information processing (TMT A; $p \leq .001$), verbal fluency (FAS; $p \leq .01$) and executive function (Stroop Congruent, $p \leq .05$; Stroop incongruent; $p \leq .001$) compared to controls.

The AD group were more impaired for memory compared to DLB ($p = .022$) and PDD ($p = .041$). Both PDD and DLB groups were more impaired for visuospatial abilities ($p \leq .05$) and information processing ($p \leq .05$) compared to AD participants. The PDD group had greater verbal fluency impairment ($p = .019$) compared to AD participants. They also had greater attentional impairment compared to AD ($p = .003$) and DLB groups ($p = .028$).

5.4.4 Associations between cognitive impairment, motor disease and gait impairment

Alzheimer's disease.

For disease-specific correlations, cognitive variables that differentiated disease groups were chosen. In AD, slower step velocity was moderately associated with greater memory impairment and motor disease severity, while shorter steps were moderately associated with greater motor disease severity (see Table 5-4 for rho and p values).

Dementia with Lewy bodies

In DLB, there were no significant associations between gait and cognition. Greater step length asymmetry was associated with less motor disease severity (see Table 5-5 for rho and p values).

Parkinson's disease dementia

In PDD, slower pace was strongly associated with greater impairments in visuospatial abilities (see Table 5-6 for rho and p values). Shorter steps were strongly associated with greater impairments in global cognition, visuospatial function and verbal fluency, slower information processing and greater motor disease severity. Shorter step time was strongly associated with greater impairment of global cognition and attention. Shorter stance time was strongly associated with greater impairment of global cognition, attention, and visuospatial skills, slower information processing and greater motor disease severity. Greater step length asymmetry was strongly associated with less attentional impairment.

Table 5-3 Comparison of cognitive function between controls, Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia

	Controls	AD	DLB	PDD	F/χ	p
N	26	36	30	16		
MMSE (0-30)	30 (25-30)[A,D,P]	23 (14-29)[C]	24 (16-30)[C]	24 (12-30) [C]	49.9	**≤.001**
ACE-III Attention (0-18)	18 (17-18) [A,D,P]	14 (6-18)[C]	16 (8-18) [C]	14 (7-18) [C]	44.6	**≤.001**
ACE-III Memory (0-26)	25 (21-26) [A,D,P]	13 (3-23)[C,D,P]	17 (0-26) [C,A]	20 (9-26) [C,A]	50.9	**≤.001**
ACE-III Fluency (0-14)	13 (5-14) [A,D,P]	9 (0-13)[C]	8 (3-13) [C]	7 (2-12) [C]	45.1	**≤.001**
ACE-III Language (0-26)	26 (24-26) [A,D,P]	23 (11-26)[C]	23 (0-26) [C]	25 (17-26) [C]	38.2	**≤.001**
ACE-III Visuospatial (0-16)	16 (13-16) [A,D,P]	14 (6-16)[C,D,P]	12 (0-16) [C,A]	11 (9-16) [C,A]	30.2	**≤.001**
ACE-III Total (0-100)	97 (88-100) [A,D,P]	74 (29-90)[C]	77 (15-95) [C]	77 (49-95) [C]	56.2	**≤.001**
TMT A (secs)	30 (19 - 49) [A,D,P]	49 (29-306) [C,D,P]	105 (28-835) [C,A]	95 (24-955) [C,A]	46.5	**≤.001**
FAS	46 (29-75) [A,D,P]	35 (3-61)[C,P]	30 (7-58) [C]	19 (11-48) [C,A]	27.3	**≤.001**
Simple RT (ms)	323 (291-493) [A,D,P]	415 (287-773) [C,P]	430 (287-1071) [C,A,P]	522 (387-3792) [C,A,D]	21.2	**≤.001**
Simple RT CV (secs)	.18 (.10-.97)	.21 (.13 - .91)	.28 (.14-1.12)	.25 (.13-.82)	4.8	0.184
Angle Test (secs)	2.3 (1.1-5.3)	2.0 (1.0-7.0)	2.3 (.80-19.35)	2.6 (1.2-6.8)	3.9	0.274
Stroop RT Congruent (secs)	1.7 (1.0 -3.6) [A,D,P]	2.1 (1.3 - 10.6) [C]	2.8 (1.2-10.5) [C]	3.5 (1.2-7.8) [C]	20	**≤.001**
Stroop RT Incongruent (secs)	1.9 (1.1 -4.5) [A,D,P]	2.7 (1.4 - 9.4)[C]	2.8 (1.2-11.9) [C]	3.8 (1.5-8.1) [C]	21.1	**≤.001**

Data displayed as (median (minimum – maximum) analysed using Kruskal Wallis and Mann Whitney U tests. Numbers of missing data can be found in Appendix G. A = different to Alzheimer's disease, D = different to dementia with Lewy bodies; P = different to Parkinson's disease dementia, C = different to controls. MMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time, Simple RT CV= Coefficient of variance for Simple Reaction Time Test Time, Stroop RT Congruent = Stroop Reaction Time Congruent Trials Mean Time, Stroop RT incongruent = Stroop Reaction Time incongruent Trials Mean Time.

Table 5-4 Spearman's correlations between free-living gait characteristics and motor disease severity and cognitive function in the Alzheimer's disease group

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
Age	-.223 (.190)	-.344 (.040)	.247 (.147)	.220 (.196)	.246 (.148)	.183 (.286)	.252 (.138)	-.156 (.363)	-.166 (.334)	-.020 (.906)	.121 (.481)	.104 (.546)	.194 (.258)	.022 (.897)
Height (m)	.010 (.955)	.213 (.213)	.108 (.532)	.055 (.749)	.175 (.308)	-.029 (.866)	-.047 (.786)	.366 (.028)	.390 (.019)	.271 (.110)	-.048 (.781)	-.056 (.744)	.075 (.662)	-.102 (.554)
UPDRS	-.421 (.012)	-.393 (.019)	.294 (.086)	.283 (.099)	.294 (.086)	.201 (.246)	.120 (.491)	.167 (.337)	.163 (.350)	.194 (.265)	.136 (.437)	.145 (.405)	.166 (.340)	.002 (.990)
sMMSE	.097 (.573)	.097 (.574)	-.161 (.348)	-.137 (.424)	-.118 (.495)	-.168 (.328)	-.191 (.265)	.022 (.897)	.189 (.271)	-.188 (.272)	-.067 (.700)	-.015 (.930)	.008 (.962)	.033 (.848)
ACE-III Mem	.333 (.047)	.293 (.083)	-.315 (.062)	-.289 (.087)	-.296 (.080)	-.194 (.258)	-.237 (.163)	-.229 (.179)	-.156 (.363)	-.301 (.075)	-.098 (.568)	-.102 (.555)	-.196 (.252)	-.046 (.791)
ACE-III VS	.282 (.096)	.271 (.110)	-.059 (.733)	-.022 (.898)	-.139 (.418)	-.011 (.951)	.009 (.957)	-.111 (.520)	.104 (.548)	-.250 (.142)	.130 (.449)	.152 (.375)	.183 (.286)	.253 (.136)
ACE-III Total	.284 (.094)	.263 (.121)	-.209 (.220)	-.162 (.344)	-.228 (.182)	-.146 (.397)	-.134 (.437)	-.115 (.506)	.044 (.801)	-.285 (.091)	-.024 (.887)	-.048 (.780)	-.098 (.569)	.070 (.684)
TMT A	.073 (.678)	.041 (.814)	.131 (.453)	.104 (.552)	.184 (.289)	.244 (.158)	.189 (.276)	.009 (.961)	-.050 (.776)	.131 (.454)	.048 (.785)	.008 (.962)	.127 (.468)	-.012 (.947)
FAS	.108 (.538)	.073 (.679)	-.159 (.362)	-.089 (.611)	-.203 (.243)	.060 (.731)	.008 (.965)	-.053 (.762)	.042 (.812)	-.226 (.191)	.233 (.179)	.161 (.356)	.135 (.440)	.174 (.316)
Simple RT	-.090 (.607)	-.028 (.872)	.154 (.376)	.097 (.579)	.227 (.189)	.054 (.759)	.096 (.585)	.075 (.667)	-.064 (.717)	.195 (.262)	-.223 (.198)	-.240 (.165)	-.176 (.313)	-.148 (.397)

Data displayed as (rho (p)). Dark blue is significant associations, light blue is rho values > .200. Numbers of missing data for each variable can be found in Appendix G. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

Table 5-5 Spearman's correlations between free-living gait characteristics and motor disease severity and cognitive function in the dementia with Lewy bodies group

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
Age	-.438 (.016)	-.283 (.129)	.150 (.430)	.138 (.469)	.152 (.423)	-.202 (.285)	-.273 (.145)	.237 (.207)	.160 (.397)	.278 (.137)	.172 (.362)	.203 (.283)	.191 (.313)	-.168 (.376)
Height (m)	-.146 (.442)	.190 (.313)	.371 (.044)	.229 (.224)	.370 (.044)	.184 (.332)	-.087 (.647)	.475 (.008)	.363 (.048)	.553 (.002)	.161 (.396)	.149 (.431)	.218 (.247)	.160 (.398)
UPDRS	-.258 (.177)	-.355 (.059)	-.114 (.557)	-.096 (.621)	-.156 (.420)	-.026 (.895)	-.093 (.632)	-.262 (.169)	-.261 (.171)	-.265 (.164)	-.248 (.195)	-.216 (.260)	-.248 (.196)	-.452 (.014)
sMMSE	.177 (.349)	.335 (.070)	-.044 (.816)	-.102 (.592)	-.008 (.967)	.103 (.590)	.018 (.924)	.141 (.458)	.174 (.358)	.077 (.687)	-.009 (.962)	.036 (.851)	-.012 (.949)	.239 (.203)
ACE-III Mem	-.101 (.602)	.085 (.662)	.012 (.951)	.003 (.987)	.042 (.830)	.056 (.775)	-.058 (.766)	.126 (.516)	.234 (.221)	.038 (.844)	-.064 (.743)	-.018 (.925)	.016 (.934)	.110 (.569)
ACE-III VS	.157 (.415)	.294 (.121)	.159 (.410)	.132 (.493)	.184 (.340)	.291 (.126)	.277 (.146)	.045 (.818)	.119 (.538)	-.058 (.765)	.098 (.612)	.122 (.528)	.196 (.308)	.302 (.112)
ACE-III Total	.054 (.783)	.254 (.184)	-.043 (.824)	-.055 (.776)	-.008 (.968)	.065 (.739)	-.041 (.831)	.125 (.519)	.248 (.194)	.017 (.930)	-.054 (.783)	.006 (.977)	.038 (.846)	.280 (.141)
TMT A	-.103 (.658)	-.334 (.139)	-.073 (.754)	-.112 (.630)	-.165 (.475)	-.222 (.333)	-.158 (.493)	-.217 (.345)	-.316 (.163)	-.091 (.695)	-.091 (.695)	-.232 (.311)	-.255 (.265)	-.175 (.447)
FAS	.128 (.516)	.268 (.167)	.097 (.622)	.073 (.713)	-.027 (.892)	.078 (.693)	.029 (.882)	.163 (.408)	.265 (.172)	.068 (.731)	-.092 (.641)	-.102 (.607)	-.066 (.738)	.187 (.341)
Simple RT	.005 (.980)	-.204 (.328)	.213 (.306)	.200 (.338)	.198 (.342)	-.034 (.872)	-.013 (.951)	-.106 (.614)	-.165 (.429)	-.043 (.838)	-.060 (.776)	-.188 (.367)	-.199 (.340)	-.072 (.734)

Data displayed as (rho (p)). Dark blue is significant associations, light blue is rho values > .200. Numbers of missing data for each variable can be found in Appendix G. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

Table 5-6 Spearman's correlations between free-living gait characteristics and motor disease severity and cognitive function in the Parkinson's disease dementia group

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
Age	-.652 (.006)	-.764 (.001)	-.153 (.571)	-.088 (.745)	-.172 (.524)	-.169 (.531)	-.362 (.168)	-.405 (.120)	-.384 (.142)	-.380 (.147)	-.074 (.787)	-.103 (.704)	-.028 (.918)	-.389 (.137)
Height (m)	.059 (.829)	.121 (.656)	.338 (.200)	.259 (.333)	.341 (.196)	.253 (.345)	-.038 (.888)	.144 (.594)	.153 (.572)	.203 (.451)	.068 (.803)	.088 (.745)	.318 (.231)	-.015 (.957)
UPDRS	-.343 (.211)	-.718 (.003)	.079 (.781)	.086 (.761)	.096 (.732)	.232 (.405)	.082 (.771)	-.500 (.058)	-.514 (.050)	-.321 (.243)	.096 (.732)	.057 (.840)	.086 (.761)	-.500 (.058)
sMMSE	.110 (.686)	.589 (.016)	-.150 (.580)	-.239 (.373)	-.086 (.752)	-.276 (.301)	-.254 (.343)	.431 (.095)	.374 (.154)	.449 (.081)	.006 (.983)	.058 (.832)	-.074 (.785)	.163 (.546)
ACE-III Mem	.182 (.516)	.431 (.108)	.080 (.777)	-.007 (.979)	.147 (.600)	-.082 (.772)	-.093 (.742)	.311 (.259)	.257 (.356)	.344 (.209)	.007 (.979)	.089 (.752)	.064 (.822)	.116 (.679)
ACE-III VS	.565 (.028)	.700 (.004)	.304 (.271)	.321 (.244)	.246 (.376)	.221 (.430)	.341 (.214)	.441 (.100)	.543 (.036)	.211 (.450)	-.013 (.963)	.091 (.748)	.102 (.718)	.347 (.206)
ACE-III Total	.316 (.251)	.700 (.004)	.115 (.683)	.059 (.834)	.093 (.741)	-.131 (.642)	-.163 (.561)	.564 (.029)	.515 (.049)	.503 (.056)	.036 (.899)	.149 (.596)	.101 (.721)	.300 (.278)
TMT A	-.357 (.191)	-.536 (.040)	.029 (.919)	.086 (.761)	.025 (.930)	-.064 (.820)	.079 (.781)	-.464 (.081)	-.521 (.046)	-.168 (.550)	.046 (.869)	-.057 (.840)	.104 (.713)	-.411 (.128)
FAS	.206 (.462)	.517 (.048)	.063 (.824)	.081 (.775)	-.048 (.864)	-.059 (.834)	-.107 (.703)	.460 (.084)	.449 (.093)	.292 (.291)	-.088 (.756)	.041 (.884)	-.077 (.785)	.172 (.540)
Simple RT	-.086 (.761)	-.425 (.114)	-.204 (.467)	-.154 (.585)	-.161 (.567)	-.007 (.980)	.307 (.265)	-.611 (.016)	-.607 (.016)	-.439 (.101)	-.261 (.348)	-.318 (.248)	-.207 (.459)	-.546 (.035)

Data displayed as (rho (p)). Dark blue is significant associations, light blue is rho values > .200. Numbers of missing data for each variable can be found in Appendix G. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

5.5 **Discussion**

The aim of this chapter was to compare gait impairment in dementia disease subtypes to controls and each other, with the key focus investigating distinguishable differences in gait impairment between AD and DLB subtypes. It also aimed to explore the relationship between motor disease severity, cognitive impairment and discrete gait impairment in disease subtypes to further aid interpretation of results. Key findings demonstrate that gait impairment differentiates dementia disease subtypes in free-living conditions, and that people with PDD demonstrate stronger gait-cognition associations compared to other subtypes.

5.5.1 What can free-living gait analysis tell us about disease subtypes?

Free-living gait analysis was able to distinguish participants with DLB and PDD from controls as they walked with greater variability, and differentiate PDD from controls as they had a more asymmetrical gait. This somewhat supports Hypothesis 5.1; however, this analysis appeared less sensitive to differences in gait impairment between AD participants and controls. These findings contrast results found in controlled settings, as described in Chapter 4, whereby people with AD walk slower with shorter steps and greater gait variability compared to controls. A possible explanation for this is laboratory conditions may influence performance due to greater awareness of the gait task. In laboratory conditions, participants are asked to attend to the task and walk in unfamiliar obstacle-free environments, and as a result, may improve their gait performance from that in the home. In free-living conditions, participants are monitored continuously over a prolonged time-period in constrained and complex environments, and as such, they are demonstrating their habitual gait performance – a more ecologically valid measure. As laboratory and free-living gait assessment are in different contexts and may induce different strategies, they are assessing different aspects of gait performance – what we *can* do and what we *do* (i.e. functional capacity versus habitual behaviour).

For example, control participants may have a greater capacity of gait compared to AD participants, and therefore their "best" gait performance in lab conditions underlies the significant differences in gait performance between these groups. In free-living environments, they are demonstrating their habitual walking behaviours without obtrusive observation; therefore, their gait performance may wane and as a result, differences between controls and AD participants may weaken. Greater gait impairments in free-living environments compared to laboratory settings in PD has previously been reported (Zampieri *et al.*, 2011; Del Din *et al.*, 2016a), supporting this interpretation. Assessing both gait capacity in the lab and habitual

gait in free-living environments allows a comprehensive understanding of individual function, but laboratory and free-living gait should be considered as separate measures.

Additionally, free-living gait analysis also appears less sensitive to differences between AD and DLB groups, demonstrating no significant differences in a model controlling for known covariates of gait, and these results differ from the laboratory-based findings presented in Chapter 4. In contrast to the lab environment, individuals with PDD demonstrated significantly greater gait variability compared to people with DLB. Another possible explanation for these discrepancies between laboratory and free-living analysis are due to different instruments employed; the accelerometer used in this study (Axivity AX3) has previously been validated against the GaitRite (as used in Chapter 4) and has shown poor agreement with characteristics of variability and asymmetry (Del Din *et al.*, 2016c). It has also been suggested that free-living gait analysis shows greater sensitivity to gait impairment in PD populations (Del Din *et al.*, 2016a). Future research should consider use of a gyroscope sensor to improve identification and allocation of left and right footsteps, which may improve quantification of variability and asymmetry measures.

Larger samples of well-characterised disease subtypes may enhance findings from the current study, and consideration of complementary metrics obtained by body-worn monitors, such as habitual walking, sleep activities and additional gait variables associated with cognition, such as frequency-based acceleration measures and turning (Weiss *et al.*, 2011; Mancini *et al.*, 2018), may improve the potential for wearable technology to serve as a digital biomarker. Longitudinal work is required to establish free-living gait's ability to identify changes in spatiotemporal gait characteristics and monitor disease progression.

5.5.2 Why is free-living gait analysis sensitive to gait impairment in Parkinson's disease dementia?

As previously discussed, this study found free-living gait analysis particularly sensitive to gait impairments in PDD, supporting prior studies. (Del Din *et al.*, 2016a). This study's results support Del Din *et al.* (2016a)'s findings that people with PD walk slower with shorter steps compared to controls, while also demonstrating greater variability and asymmetry in PDD compared to controls and AD participants. This is somewhat consistent with hypothesis 5.2. Slower timing of gait has also previously been reported in PD (Del Din *et al.*, 2016a). Trends in this study indicate that people with PDD have quicker step, stance and swing times compared to all other groups across all bout lengths. Del Din *et al.* (2017) demonstrated faster timing in PD fallers compared to non-fallers, and as such, these findings may reflect higher fall risk, with 69% of the PDD group reporting at least one fall in the last year. An alternate

explanation is that this is capturing patterns of festination. Capturing these temporal characteristics in a cohort of established PD freezers would allow further interpretation of such findings and give insight into a potential clinical measure of freezing of gait.

Fluctuating responses to PD medication (Moore *et al.*, 2007), such as dopamine replacement therapies, is also important to consider when interpreting these findings. Within this study, all PDD participants took medication for their motor symptoms, while only 20% of people with DLB and no people with AD took dopaminergic medication. While it is important to consider how the effects of drug therapies influences these results, assessing people with PDD during their "off" states over long time periods would be unfeasible and unethical. It must be acknowledged that many factors contribute to our daily behaviour and function and it is not possible to control for everything (Schwenk *et al.*, 2014). Understanding the context in which gait is assessed may improve how we interpret such findings. As such, Chapter 6 will examine and describe the context of habitual walking behaviour by considering the amount, variability and pattern of walking.

5.5.3 What role does cognition and motor disease play in gait impairment?

Another consideration when interpreting these findings is the different profiles between disease subtypes for associations between motor disease, cognition and gait impairments. Gait-cognitive associations were the least apparent in the DLB group and the most prominent in the PDD group, which contradicted Hypothesis 5.4. The numerous strong associations between cognitive and gait impairment in PDD, in conjunction with findings that gait is significantly more impaired in this group compared to other subtypes, strengthens the suggestion that cognitive input is required to maintain gait and may indicate increased requirement of cognition with greater neurodegeneration. Both the gait characteristics and cognitive domains considered were more impaired in PDD (see Table 5-2 and Table 5-3) which may reflect greater degeneration of shared motor-cognitive neural resources.

In contrast, the DLB group demonstrated no gait-cognition associations, only demonstrating greater motor disease severity was associated with less step length asymmetry. This may suggest that gait is still mediated by motor function in DLB and may require less cognitive input from PDD. As DLB and PDD are defined by their onset of cognitive impairment in relation to their motor disease (Jellinger and Korczyn, 2018), neural regions involved in motor processes may not be as affected in DLB during the mild dementia stage as that found in PDD. The relationship between motor disease severity, cognitive and gait impairment in AD was similar to that found in Chapter 4, demonstrating greater gait impairments were predominately associated with greater motor disease, as predicted by Hypothesis 5.4.

However, it must be noted that a number of trends indicate gait-cognition associations may have been significant with greater statistical power, and this should be considered in future studies with larger sample sizes.

Free-living gait impairments pertaining to step velocity and length, and timing characteristics of gait were associated with impairments in visuospatial abilities, attention, verbal fluency (a measure of executive function) and information processing in PDD: cognitive domains considered to be mediated by the prefrontal cortex (Fuster, 2001). A wealth of literature supports these findings in older adults, cognitive impairment and PD populations (Verlinden *et al.*, 2014; Weiss *et al.*, 2015a; Morris *et al.*, 2016); however this is the first study to consider it between AD and LBD subtypes. These findings may therefore indicate that gait impairments occur due to different disease-specific processes, and may reflect the differing stages pathology occurs in the prefrontal and motor cortices in these disease subtypes - brain regions previously linked to impaired gait in older adults and AD (Rosano *et al.*, 2008; de Laat *et al.*, 2012; Rosano *et al.*, 2012; Wennberg *et al.*, 2017; Blumen *et al.*, 2018).

5.5.4 Conclusions

This is the first study to compare free-living gait in AD, DLB and PDD disease subtypes. It has demonstrated the ability of body-worn monitors to describe gait impairments in dementia disease subtypes, but did not demonstrate evidence that free-living gait analysis could effectively discriminate AD and DLB subtypes. Future research should examine gait analysis in free-living conditions in greater depth, and consider how the context of walking activities may inform such findings. Key results also indicated that people with PDD require greater cognitive input for gait in free-living environments compared to other disease subtypes, and future research should explore if cognitive impairment influences their habitual walking behaviours, i.e. their macro gait.

Chapter 6 Considering the context: what does habitual walking behaviour look like in disease subtypes?

This chapter examines habitual walking behaviours in disease subtypes and controls. This allows an objective understanding of how much people with different dementia disease subtypes walk and the patterns of walking activity they engage in, while providing a context for their spatiotemporal gait characteristics described in Chapter 5. This chapter also examines the factors that are associated with the amount, variability and pattern of everyday walking.

6.1 Introduction

As described in Chapter 5, micro gait characteristics can distinguish cognitive impairment from normal ageing, and differentiate disease subtypes – demonstrating particular sensitivity to Parkinson's disease dementia (PDD). In order to further interpret these findings, they should be considered in the context of macro gait. Macro gait characteristics allow us to understand the amount and type of walking in which gait impairments occur in an individual, while providing a detailed picture of a person's functional abilities (Lord *et al.*, 2013c; Weiss *et al.*, 2013; Schwenk *et al.*, 2014; Mc Ardle *et al.*, 2018).

With the advent of inexpensive wearable technology, there has been increasing interest in the relationship between quantifiable activity and cognitive decline. Information previously garnered in this area was reliant on self-report measures, which lack reliability and accuracy, particularly when considering a cognitively impaired population. Using actigraphy, total daily activity (measured by sum of activity counts) have been related to global cognitive performance (Buchman *et al.*, 2008), development of Alzheimer's disease and rate of global cognitive decline (Buchman *et al.*, 2012). However, total daily activity is a broad measure and lacks specificity. By describing the amount, variability and pattern of habitual walking activity, we can provide a more detailed picture of day-to-day activity and investigate factors that may influence it (Lord *et al.*, 2013c).

Novel metrics described in previously published work (Lord *et al.*, 2013c; Schwenk *et al.*, 2014; Del Din *et al.*, 2016a; Mc Ardle *et al.*, 2018) allow a more detailed analysis of the patterns (alpha) and the variability of habitual walking behaviours. These variables, paired with further exploration into the amount of time people spend walking in short, medium and sustained bouts, may allow for a more holistic approach to examining daily walking behaviours (Del Din *et al.*, 2016a). As of yet, the amount, pattern and variability of habitual walking behaviours have not been examined in well-defined dementia disease subtypes.

6.2 Aims and hypotheses

This chapter aims to:

- Improve our understanding of habitual walking behaviours in people with cognitive impairment due to Alzheimer's disease (AD) and Lewy body disease (LBD).
- Identify factors contributing factors in normal ageing and cognitively impaired populations.

Hypotheses

6.1. People with cognitive impairment will spend less time walking, with fewer steps and walking bouts, and demonstrate less variability in bout lengths and higher alpha scores compared to normal ageing. These differences will be amplified in dementia with Lewy body disease (DLB) and PDD compared to AD.

6.2. People with cognitive impairment will spend less time in medium and sustained bouts compared to controls and similarly this will be more prominent in LBD compared to AD.

6.3. More severe motor symptoms and lower balance confidence will explain lower amounts of walking activity.

6.4. Cognitive impairment will be associated with less variability of bout length and higher alpha scores.

6.3 Methods

6.3.1 Study participants

Participants in this analysis were recruited as part of the GaitDem study and all completed the gait protocol detailed in Chapter 4. Participants included individuals with mild cognitive impairment or dementia pertaining to AD, DLB and PDD and control participants of a similar age. Relevant information regarding the recruitment process and inclusion/exclusion criteria are detailed in Chapter 3.

6.3.2 Protocol

Clinical and cognitive assessments are detailed in Chapter 3 and Chapter 4. Key assessments for this aspect of the study examined the following; dementia disease severity (Clinical Dementia Rating scale; CDR), co-morbidities (Cumulative Illness Rating Scale – Geriatrics; CIRSG), motor disease severity (Unified Parkinson's Disease Rating Scale – III; UPDRS-III), global cognition (Mini Mental State Exam and Addenbrookes Cognitive Examination III;

MMSE and ACE-III), information processing (Trail Making Task Part A; TMT A), verbal fluency (FAS test), attention (Simple Reaction Time Task; RT Simple), depression (Geriatric Depression Scale, GDS), sleepiness (Epworth Sleepiness Scale; ESS), balance confidence (Activities Balance Confidence scale; ABC) and activities of daily living (ADLs; Bristol Activities of Daily Living Scale; BADLS). Information pertaining to age, faller status, height and weight was also collected and body mass index (BMI) was calculated. This doctoral candidate conducted 105 clinical and cognitive assessments; 10 assessments were carried out as part of the SUPERB study, an ongoing longitudinal research study investigating biomarkers for AD and LBD.

Free-living gait assessment

As described in Chapter 3, participants were asked to wear a body-worn monitor (Axivity AX3, York, UK; dimensions 23.0 x 32.5 x 7.6 mm; weight: 11g; accuracy 20 parts per million) on their lower backs continuously for seven days.

6.3.3 Data processing and analysis

Data from the body-worn monitors was downloaded to a computer and segmented by day. Analysis was carried out using a Matlab programme. The full process from initial placement of the body-worn sensor through to data extraction and output is depicted in Figure 6-1. The development of the algorithm used to derive macro and micro gait characteristics was developed by Dr. Silvia Del Din and Dr. Alan Godfrey and processing of the data in this project was undertaken by members of the Wearables team within the Brain and Movement Research Group.

Macro gait characteristics

Accelerometer signals were transformed to a horizontal-vertical coordinate system and filtered with a 4th order Butterworth filter at 20Hz in order to remove "noise" from the signal.

For each day, walking bouts are identified by applying selective thresholds on the magnitude of vector and the standard deviation of tri-axial acceleration signals (further detailed in Hickey *et al.* (2017). A bout is defined as any continuous period of walking. In order to enhance robustness and remain consistent with previous published findings (Del Din *et al.*, 2016a; Mc Ardle *et al.*, 2018), a minimum bout length of three consecutive steps was applied and there was a resting time threshold of 2.5 seconds.

The Gaussian continuous wavelet transform of vertical acceleration was applied to smooth the data and filter out potential errors (Hickey *et al.*, 2017). Initial contact (heel strike) and final contact (toe-off) event of the gait cycle were identified, representing a step. Total steps per

bout and bout length could be calculated for each bout. Total number of bouts was calculated through identification of bouts. Total walking time, steps, bouts, and mean bout length were calculated by gathering information across all identified bouts. These were divided by number of days collected to provide average values per day.

Non-linear descriptors pertaining to the variability and pattern of habitual walking activity (alpha) were also derived. Variability (S_2) refers to variability of bout length between walking bouts and was estimated using maximum likelihood technique (previously described (Del Din *et al.,* 2016a; Mc Ardle *et al.,* 2018).This provided an estimation of how much an individual's bout length changed across the time period. High values indicate high amounts of variability, while low values indicate behaviour that is more consistent.

Alpha refers to the distribution of walking bouts, describing the ratio of short to long walking bouts. For example, a high alpha score means total walking time is made up of proportionally shorter walking bouts compared to long walking bouts. Alpha is derived by logarithmic transformation of bout density and length and is based on shape and power-law distribution.

6.3.4 Data analysis

Statistical analysis for demographic and clinical information is described in Chapter 3.

The first part of the analysis investigated differences in gait impairments between controls, AD, DLB and PDD. One-way ANOVAs assessed group differences for macro gait outcomes for normally distributed variables. For this analysis, logarithmic and square root transformations did not allow for normal distribution of any non-normally distributed variables. Results from both parametric and non-parametric tests were compared for non-normally distributed variables; where results did not change interpretation, results from one-way ANOVAs were reported. A more stringent statistical threshold of $p \leq .01$ was applied to account for multiple comparisons.

Fischer's LSD post hoc tests determined where group differences lay. Results from Kruskal Wallis tests were reported for variables that demonstrated conflicting results. Mann Whitney U tests demonstrated where between-group differences occurred. Stepwise analysis of covariance (ANCOVA) assessed group differences for normally distributed macro gait outcomes while controlling for age and sex. Further ANCOVAs additionally controlling for effects of motor disease severity (UPDRS-III), cognitive impairment (ACE-III) and both motor disease severity and cognitive impairment were used to aid interpretation of results.

In order to compare habitual walking behaviours in different bouts, bout lengths of <10 seconds (very short), 10-30 seconds (short), 30-60 seconds (medium) and >60 seconds (sustained) were derived from the data. For each bout length, total walk time, steps and bouts per day and mean bout length were compared between controls and the combined cognitive impairment group, and between controls and disease subtypes using Student's t-tests and one-way ANOVAs for normally distributed data, and Kruskal Wallis' and Mann Whitney U tests for non-normally distributed data.

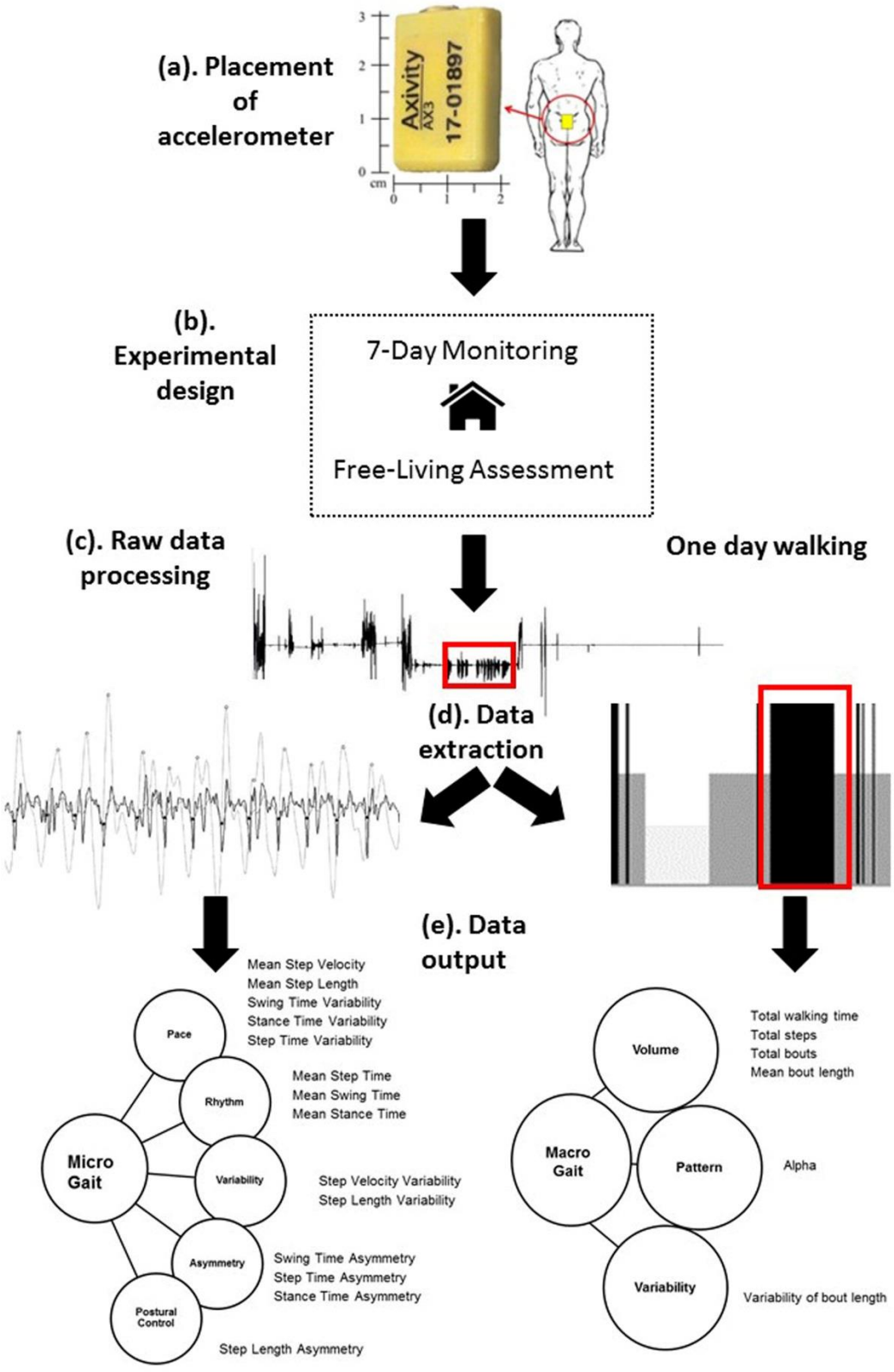

Figure 6-1 Illustration of gait protocol from initial body-worn sensor placement to data output

a) Example of body worn monitor placement for both the clinic based and free-living data collection on L5 centrally located on the lower back; ***(b)*** *Gait protocols for free-living assessment;* ***(c)*** *The raw vertical acceleration signal segmented into walking bouts* ***(d) Left;*** *Example of gait characteristic extraction from walking bouts: detecting initial contacts (black stars) and final contacts (white circles).* ***Right:*** *Identification of walking bouts (black bars) from free-living data from which gait characteristics are extracted;* ***(e) Left:*** *Conceptual model of gait representing domains and 14 gait micro characteristics.* ***Right:*** *Macro characteristics of gait described by domains of volume, pattern and variability. Figure adapted from Mc Ardle et al., (2018).*

The relationships between habitual walking behaviours and variables pertaining to cognition, motor disease severity, balance confidence, mood, age and sex were explored in both controls and the combined cognitive impairment group using Spearman's Rho correlations and univariate regression. Significant explanatory variables in the univariate regression further explored in the cognitively impaired group through multivariate backwards stepwise regression. This was not repeated in the control group as the sample size for this group was limited, making it inappropriate to examine more than one explanatory variable in a model. Backwards stepwise regression was chosen as forwards stepwise regression may highlight explanatory variables only significant due to another variable being held constant.

Associations between cognition, motor disease severity, balance confidence, and age were also examined in disease subgroups pertaining to AD, DLB and PDD using Spearman Rho correlations. Differences in sex were explored visually by box plots and tested using Mann Whitney U tests for each group.

6.4 Results

6.4.1 Participants

Participants included in this analysis are detailed in 5.4.1. Demographic information for this cohort can be found in Table 5-1. As there were no differences found between the MCI and dementia groups for walking behaviours (see Appendix H), these groups were combined in each subtype as detailed in previous chapters.

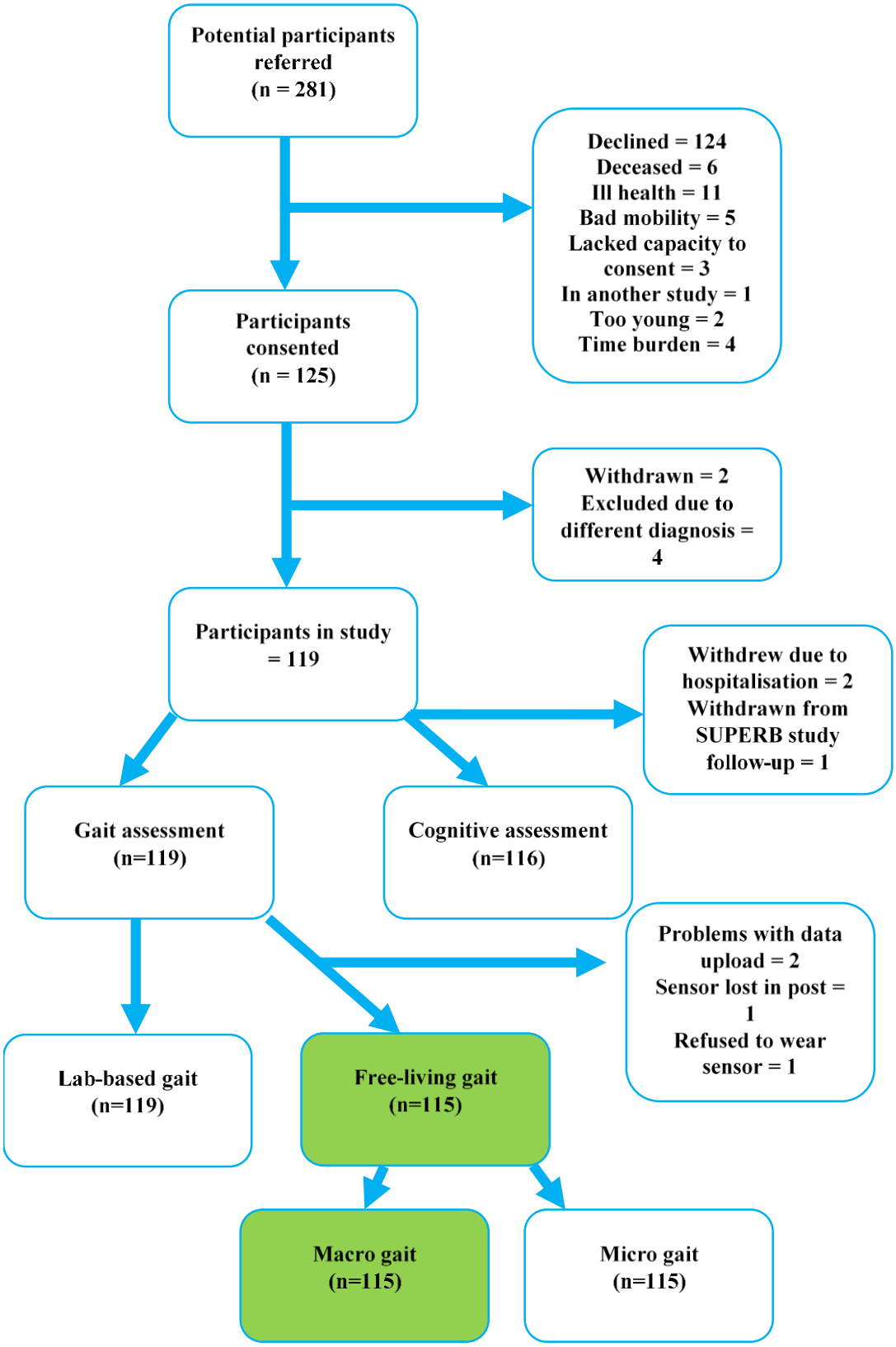

Figure 6-2 Participant approach, recruitment and assessment

6.4.2 What does habitual walking behaviour look like in dementia and its subtypes?

Macro gait characteristics between controls, Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia

Both DLB and PDD participants spent less time walking ($p \leq .01$), took less steps per day ($p \leq .001$), with shorter mean bout lengths ($p \leq .001$) and less variability of bout lengths ($p \leq .01$) compared to controls (see Table 6-1 and Figure 6-3). Participants with PDD also spent less time walking ($p \leq .001$), took less steps ($p \leq .001$), shorter bout lengths ($p = .003$) and higher alpha scores ($p = .002$) compared to the AD group, and had higher alpha scores ($p \leq .001$) compared to controls. These findings were considered significant at the threshold $p \leq .01$.

Participants with AD were less variable in their bout lengths ($p = .023$) compared to controls. People with PDD took less bouts ($p \leq .05$) per day compared to controls and AD, and had higher alpha scores ($p = .040$) compared to the DLB group. These findings did not remain significant when applying a more stringent threshold of $p \leq .01$.

As there were differences found between DLB and PDD groups at the ($p \leq .05$) threshold, the data were not combined to form a Lewy body disease (LBD) group. Only data appropriate for parametric analyses (bouts per day and alpha) were considered in the adjusted models (see Table 6-1).

Controlling for age and sex

When controlling for age and sex, only alpha remained significantly higher in people with PDD compared to controls, AD and DLB groups ($p \leq .001$ for all; see Table 6-1). Participants with DLB also had significantly higher alpha scores ($p = .040$) compared to controls, but this was not considered significant at $p \leq .01$.

Controlling for age, sex and motor disease severity

When controlling for age, sex and motor disease severity (UPDRS-III), there were no significant differences between groups for number of bouts per day or alpha scores at the threshold ($p \leq .05$; see Table 6-1).

Controlling for age, sex and cognitive impairment

When controlling for cognitive performance (ACE-III), only alpha was significantly higher in PDD participants compared to all other groups ($p \leq .001$ for all; see Table 6-1).

Controlling for age, sex, motor disease severity and cognitive impairment

When controlling for age, sex and both motor disease severity and cognitive impairment, there were no significant differences between groups (see Table 6-1).

Summary of findings between controls and disease groups

Both the DLB and PDD groups spent less time walking and took fewer steps per day compared to controls. They also had shorter, less variable walking bout lengths. The PDD groups also spent less time walking, took fewer steps per day, and had shorter less variable walking bout lengths compared to AD participants. They also spent proportionally more time in short walking bouts compared to long walking bouts, as depicted by a higher alpha score compared to controls and AD participants. Importantly, there were no significant differences between DLB and AD groups.

Only the number of bouts taken per day and alpha scores were examined in adjusted models as the other variables were not normally distributed and therefore, parametric analysis was inappropriate. Significant differences between PDD and all other groups remained when controlling for age and sex, and age, sex and cognitive impairment. However, these differences disappeared when controlling for age, sex and motor disease severity, and age, sex, motor disease severity and cognitive impairment.

Table 6-1 Comparison of macro gait characteristics across controls and disease subtypes

					Unadjusted model		Controlling for age and sex		Controlling for age, sex and UPDRS		Controlling for age, sex and ACE-III		Controlling for age, sex, UPDRS-III and ACE-III	
	Controls	**AD**	**DLB**	**PDD**	F	(p)	F	(p)	F	(p)	F	(p)	F	(p)
Walking time per day (mins)	204 (76-336)^{D,P}	172 (22-265)^{P}	137 (21-373)^{C}	108 (20-193)$^{C.A}$	22.1	**≤ .001**								
Steps per day	14724 (5079-22599)^{D,P}	11435 (1608-20246)^{P}	9664 (1375-27242)^{C}	7361 (1141-14312)^{C,A}	23.6	**≤ .001**								
Bouts per day	630 ± 166	615 ± 211	565 ± 213	459 ± 159	3.1	.031	1.7	.168	.5	.666	1.6	.184	.7	.560
% time walking per day	14 (5-23)^{D,P}	12 (2-18)^{P}	10 (2-26)^{C}	8 (1-13)^{C,A}	22.1	**≤ .001**								
Mean bout length (secs)	19 (13-27)^{D,P}	17 (10 – 32)^{P}	16 (10 – 22)^{C}	14 (6 – 17)^{C,A}	21.8	**≤ .001**								
Variability	.904 (.72 – 1.03)^{D,P}	.835 (.67 – 1.08)	.816 (.68 - .96)^{C}	.792 (.50 - .90)^{C}	14.2	**.003**								
Alpha	1.811 ± .038^{P}	1.622 ± .046^{P}	1.640 ± .054	1.678 ± .108^{C,A}	4.8	**.004**	10.8	**≤ .001**	.5	.701	9.4	**≤ .001**	.3	.801

Significant values refer to differences between controls, Alzheimer's disease and Lewy body disease groups in unadjusted model. Normally distributed data and data analysed using one-way ANOVAs displayed as (mean ± standard deviation). Non-normally distributed data analysed using Kruskal Wallis tests displayed as (median (minimum-maximum)). C = different to controls, A = different to AD, D = different to DLB, P = different to PDD. Only data appropriate for parametric analysis was used for ANCOVAs and reported as adjusted model

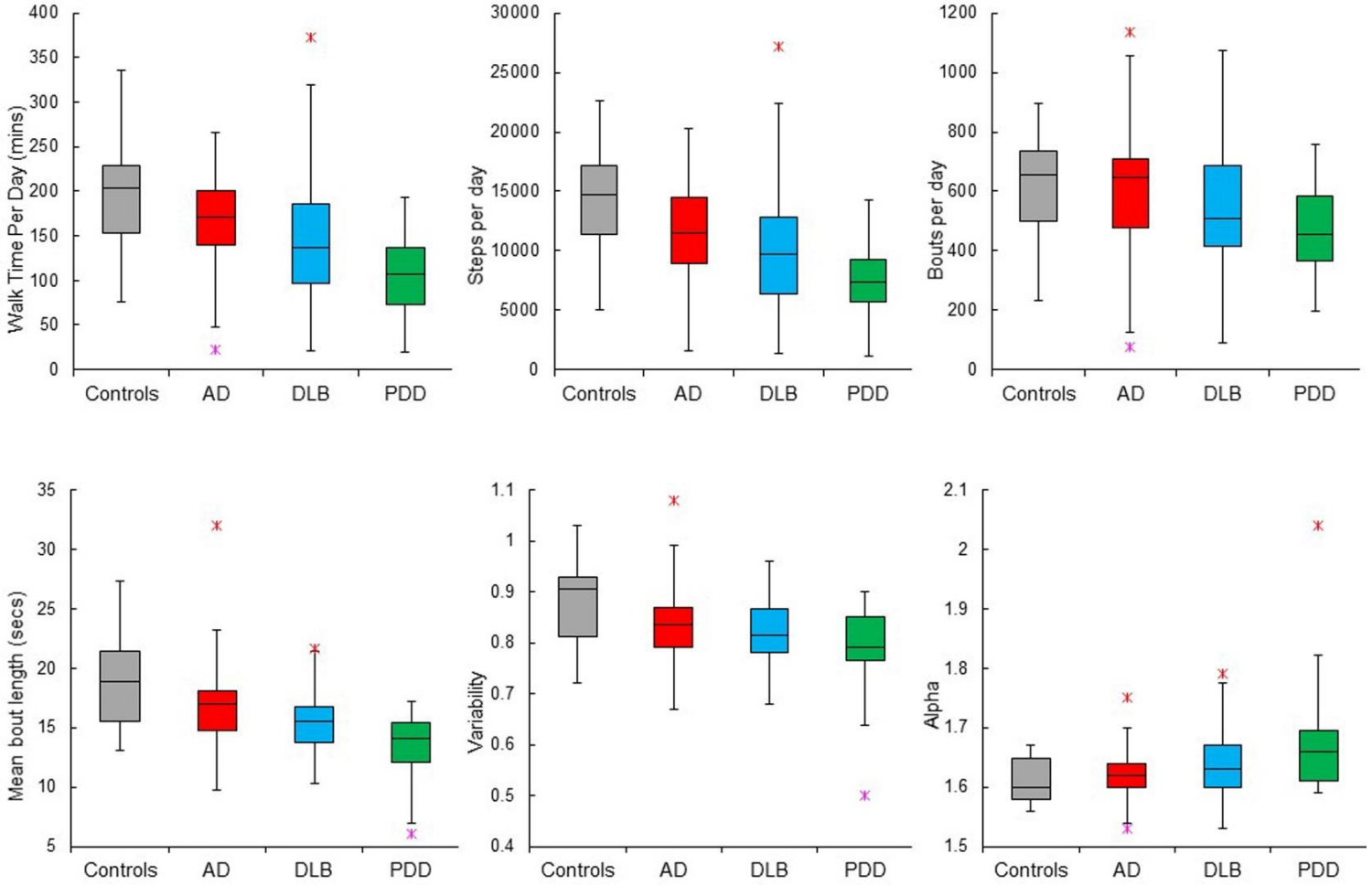

Figure 6-3 Boxplots illustrating the range of data for macro gait characteristics in controls, Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia

** depicts outliers in each group*

To further understand habitual walking behaviours in people with dementia and its subtypes, the amount of time spent walking per day in very short (<10 second) ambulatory bouts; short (10-30 second) bouts, medium (30-60 second) bouts and sustained (> 60 second) bouts were considered.

Habitual walking behaviour in controls and disease subtypes

All disease groups spent the majority of their walking bouts in very short bouts (AD 59%, DLB 59% and PDD 61% of total walking bouts; see Figure 6-4). All groups spent 32% of their total walking bouts in short bouts and 6% in medium bouts. Sustained bouts accounted for 3% of both AD and DLB's and 2% of PDD's total walking bouts. One participant with PDD had no over 60 second bouts.

Group differences were primarily found in sustained bouts (see Table 6-2 for details). The PDD group demonstrated shorter bout lengths in very short ($p \leq .001$) and medium bouts ($p \leq .001$) compared to controls. During sustained bouts, all disease groups took fewer steps and bouts per day compared to controls ($p \leq .01$ for all; see Figure 6-5). Participants with DLB and PDD also spent less time walking ($p \leq .001$ for both) and took shorter bouts ($p \leq .001$ for both) during sustained walking compared to controls. These findings were considered statistically significant under the more conservative threshold $p \leq .01$.

The DLB group took shorter bouts ($p \leq .05$) compared to controls in very short bouts. Similarly, participants with PDD spent less time walking and took fewer bouts per day compared to controls in short and medium bouts ($p \leq .05$ for all), and took less steps ($p = .005$) in medium bouts. In sustained walking, people with AD spend less time walking ($p = .020$) compared to controls. However, these results were not significant when the threshold $p \leq .01$ was applied.

Habitual walking behaviour between disease subtypes

The PDD group spent demonstrated shorter bout lengths in very short bouts ($p \leq .001$) compared to the AD group (see Table 6-2). In sustained walking bouts, the PDD group also took less steps ($p = .002$) and bouts per day ($p = .007$) compared to participants with AD (see Figure 6-5).

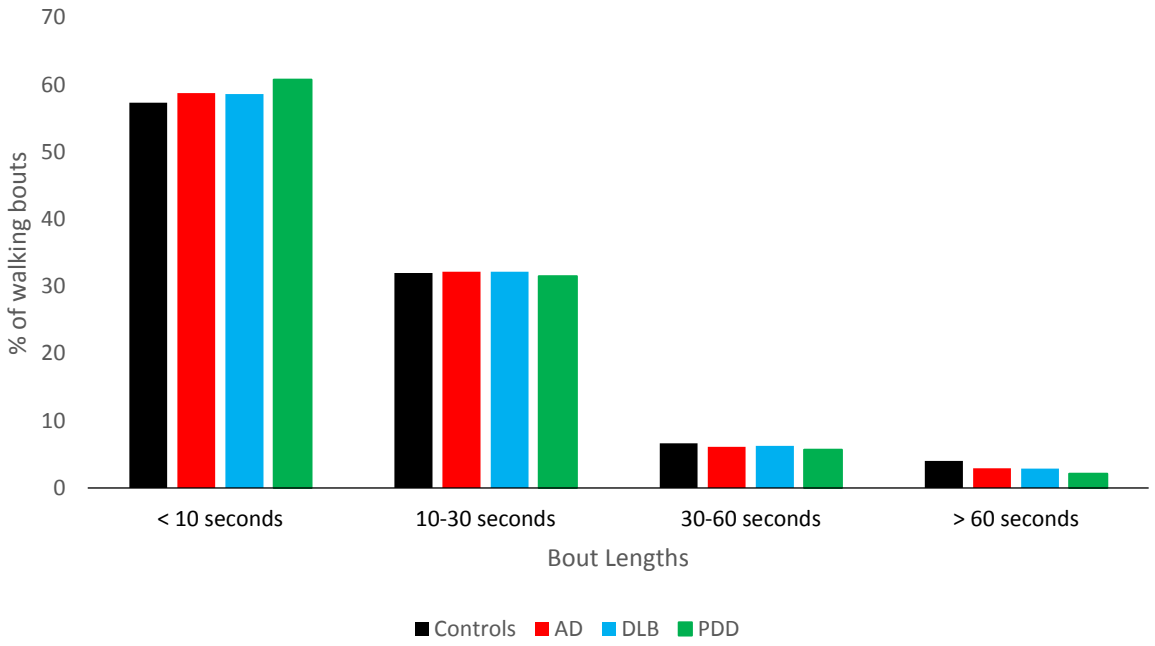

Figure 6-4 Distribution of walking bout lengths

Percentage of walking bouts calculated as ((number of bouts in X bout length/total number of bouts) x 100). Bar chart demonstrates distribution of bout lengths in controls, Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia groups.

Although not significant under the threshold of $p \leq .01$, the DLB group took shorter bouts ($p \leq .05$) compared to AD groups in very short bouts. Similarly, participants with PDD spent less time walking and took fewer bouts per day compared to AD participants in short and medium bouts ($p \leq .05$ for all). They also demonstrated shorter bouts in medium bout lengths compared to both DLB ($p = .050$) and AD groups ($p = .041$). In sustained walking, people with PDD demonstrate shorter bouts ($p = .021$) compared to AD, and take less bouts per day ($p = .034$) compared to the DLB group.

Summary of group differences across different bout lengths

All disease groups took less steps and bouts per day in sustained bouts compared to controls. The DLB and PDD group also spent less time walking and took shorter bouts in sustained bouts compared to controls, and the PDD participants took less steps and bouts per day in sustained bouts compared to the AD group. The PDD group also took shorter bouts in very short bouts compared to controls and AD participants, and in medium bouts compared to controls

Table 6-2 Amount of walking time in each bout length threshold between controls and disease subtypes

	Controls	AD	DLB	PDD	t/χ2	p
< 10 second bouts						
Walk Time Per Day (mins)	37 ± 10	36 ± 14	33 ± 13	27 ± 9	2.4	.071
Steps Per Day	1788 ± 538	1774 ± 697	1747 ± 692	1505 ± 469	.8	.489
Bouts Per Day	361 ± 101	360 ± 144	331 ± 125	279 ± 87	2.0	.125
Mean Bout Length (secs)	6.1 ± .1[P]	6.1 ± .2[P]	6.0 ± .2	5.9 ± .3[C,A]	5.2	**.002**
10-30 second bouts						
Walk Time Per Day (mins)	58 ± 17	56 ± 19	52 ± 22	41 ± 19	2.8	.044
Steps Per Day	3733 ± 1090	3667 ± 1248	3519 ± 1398	2954 ± 1366	1.5	.233
Bouts Per Day	201 ± 60	197 ± 67	182 ± 73	145 ± 66	2.8	.042
Mean Bout Length (secs)	17.3 (16.3- 17.9)	17.3 (16.4 - 18.2)	17.1 (15.8 - 18.3)	17.2 (15.0 - 18.3)	1.5	.694
30-60 second bouts						
Walk Time Per Day (mins)	28.7 ± 10[L]	25 ± 10	24 ± 13	18 ± 9	3.4	**.020**
Steps Per Day	2099 ± 701	1835 ± 754	1791 ± 979	1369 ± 703	2.8	.043
Bouts Per Day	42 ± 14	38 ± 15	36 ± 18	26 ± 14	3.3	.025
Mean Bout Length (secs)	41.1 ± .7[P]	40.7 ± .9	40.6 ± 1.1	40.0 ± 1.5[C]	4.0	**.010**
> 60 second bouts						
Walk Time Per Day (mins)	68 (11 - 161)[D,P]	45 (3-155)[P]	28 (4 - 154)[C]	20 (3 - 41)[C,A]	26.5	**≤ .001**
Steps Per Day	6443 (1051 - 14088)[A,D,P]	3790 (221-13575)[C,,P]	2453 (297 - 13859)[C]	1648 (200 - 3130)[C,A]	29.2	**≤ .001**
Bouts Per Day	26 ± 12[A,D,P]	18 ± 9[C,P]	16 ± 11[C]	10 ± 5[C,A]	9.3	**≤ .001**
Mean Bout Length (secs)	159.1 (96.7 - 271.0)[D,P]	145.6 (91.2 - 258.5)	121.6 (92.8 - 237.1)[C]	121.4 (88.2 - 246.4)[C]	17.4	**≤ .001**

Normally distributed data and data analysed using one-way ANOVAs and Student's t-tests displayed as (mean ± standard deviation). Non-normally distributed data analysed using Kruskal Wallis tests and Mann Whitney U tests displayed as (median (minimum-maximum)). C = different to controls, A = different to AD, D = different to DLB, P = different to PDD

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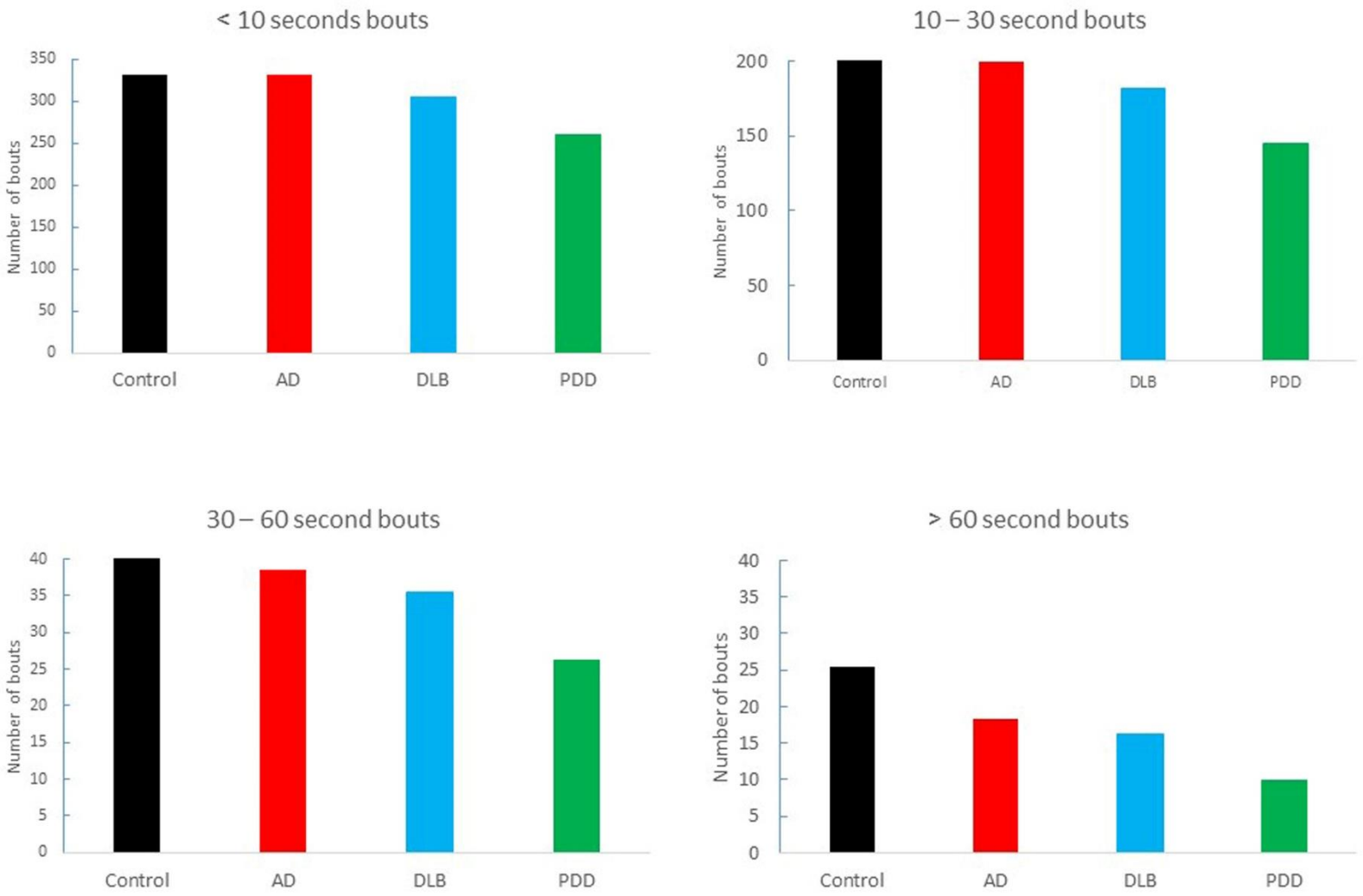


Figure 6-5 Number of bouts taken in each bout length threshold

Bar charts demonstrate number of bouts taken per bout length threshold in controls, Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia groups.

6.4.3 Explanatory factors of habitual walking activity

Factors associated with habitual walking behaviours in controls

In order to understand factors that contribute to reduced walking quantity and variability, and differences in walking patterns in a cognitively impaired population, it is important to first understand factors associated with habitual walking behaviours in normal ageing. As such, associations between habitual walking behaviour and variables related to age, health, motor disease, cognition, sleepiness, depression, and balance confidence were explored.

There were moderate positive associations between higher alpha scores and older age (see Table 6-3 for rho and p values). Slower information processing speed (TMT-A) demonstrated moderate negative associations with shorter walking bouts and less variability of bout lengths. Similarly, greater attentional impairment (Simple RT) showed moderate negative associations with less variability of bout lengths.

Table 6-3 Spearman's correlations between habitual walking behaviour in normal ageing and associated variables

	Walk Time Per Day	Steps Per Day	Bouts Per Day	Mean Bout Length	Variability	Alpha
Age	-.139 (.500)	-.143 (.487)	.139 (.499)	-.433 (.027)	-.308 (.126)	.396 (.045)
CIRS-G	.061 (.768)	.149 (.468)	.085 (.681)	-.151 (.461)	-.107 (.603)	.203 (.319)
UPDRS-III	.040 (.851)	.044 (.837)	.033 (.879)	-.178 (.406)	-.109 (.612)	.081 (.705)
ACE-III Memory	-.258 (.204)	-.152 (.457)	-.020 (.922)	-.213 (.296)	-.262 (.195)	.268 (.186)
ACE-III Visuospatial	-.112 (.586)	-.094 (.649)	.085 (.679)	-.133 (.518)	-.109 (.595)	.137 (.504)
ACE-III Total Score	-.154 (.454)	-.036 (.860)	.050 (.807)	-.086 (.675)	-.103 (.618)	.245 (.228)
TMT A	-.221 (.278)	-.250 (.218)	.043 (.836)	-.402 (.042)	-.465 (.017)	.238 (.242)
FAS	.037 (.856)	.118 (.567)	.000 (1.000)	.107 (.604)	.139 (.497)	-.005 (.981)
RT Simple	-.205 (.315)	-.252 (.214)	-.035 (.867)	-.347 (.082)	-.447 (.022)	.156 (.448)
ESS	.378 (.057)	.358 (.073)	.187 (.359)	.292 (.148)	.305 (.130)	-.122 (.552)
GDS	.191 (.350)	.177 (.388)	.333 (.097)	-.083 (.686)	-.221 (.278)	-.098 (.634)
ABC	.002 (.991)	-.054 (.793)	-.223 (.273)	.196 (.336)	.234 (.250)	-.241 (.235)

Data displayed as (rho (p value)). Data highlighted in dark blue refers to significant correlations, light blue refers to rho values > .200. Details re missing data can be found in Appendix G CIRS-G = Cumulative Illness Rating Scale –Geriatric, UPDRS-III = Unified Parkinson's Disease Rating Scale III, ACE-III = Addenbrookes Cognitive Examination III, TMT A = Trail Making Task A, FAS = FAS Test, RT Simple = Simple Reaction Time Task, GDS = Geriatric Depression Scale, ESS = Epworth Sleepiness Scale, ABC = Activities Balance Confidence Scale, BADLS = Bristol's Activities of Daily Living.

Explanatory factors of habitual walking behaviours in controls

In order to examine explanatory variables of habitual walking behaviour in ageing, univariate regressions were employed (see Appendix I). Multivariate regressions were not feasible due to small sample size. None of the possible contributing variables explained quantity of walking (walk time per day, steps per day and bouts per day) in controls.

Shorter bout length was explained by greater attentional impairment (13.9 % of variance) and being female (26.5% of variance; see Table 6-4). Less variability of bout length was explained by being female (22.5% of variance), greater attentional impairment (17.3% of variance) and slower information processing (11.6% of variance). Higher alpha scores were explained by being female (19.1% of variance), older age (16.2% of variance) and lower balance confidence (13.4% of variance; see Table 6-4). However, balance confidence did not remain a significant explanatory variable once removing the outlier depicted in Figure 6-6.

Table 6-4 Significant explanatory variables for habitual walking behaviour in normal ageing

Mean Bout Length	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (male)	4.1	1.3	3.2	**.004**	10.0	.543	.295	.265	1.5	6.8
RT Simple (secs)	-.03	.01	-2.3	**.034**	4.1	.417	.174	.139	-.1	-.002
Variability	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (male)	.08	.03	2.9	**.008**	8.3	.506	.256	.225	.02	.14
TMT A (secs)	-.003	.002	2.1	**.049**	4.3	.389	.151	.116	-.01	.000
RT Simple (secs)	-.001	.000	2.5	**.020**	6.2	.454	.206	.173	-.001	.000
Alpha	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (male)	-.04	.01	2.6	**.015**	6.9	.472	.223	.191	-.06	-.01
Age	.002	.001	2.4	**.024**	5.8	.442	.196	.162	.000	.004

Table only reports significant explanatory factors of habitual walking behaviour; Appendix I includes all variables considered TMT A = Trail Making Task A, RT Simple = Simple Reaction Time Task, ABC = Activities Balance Confidence Scale

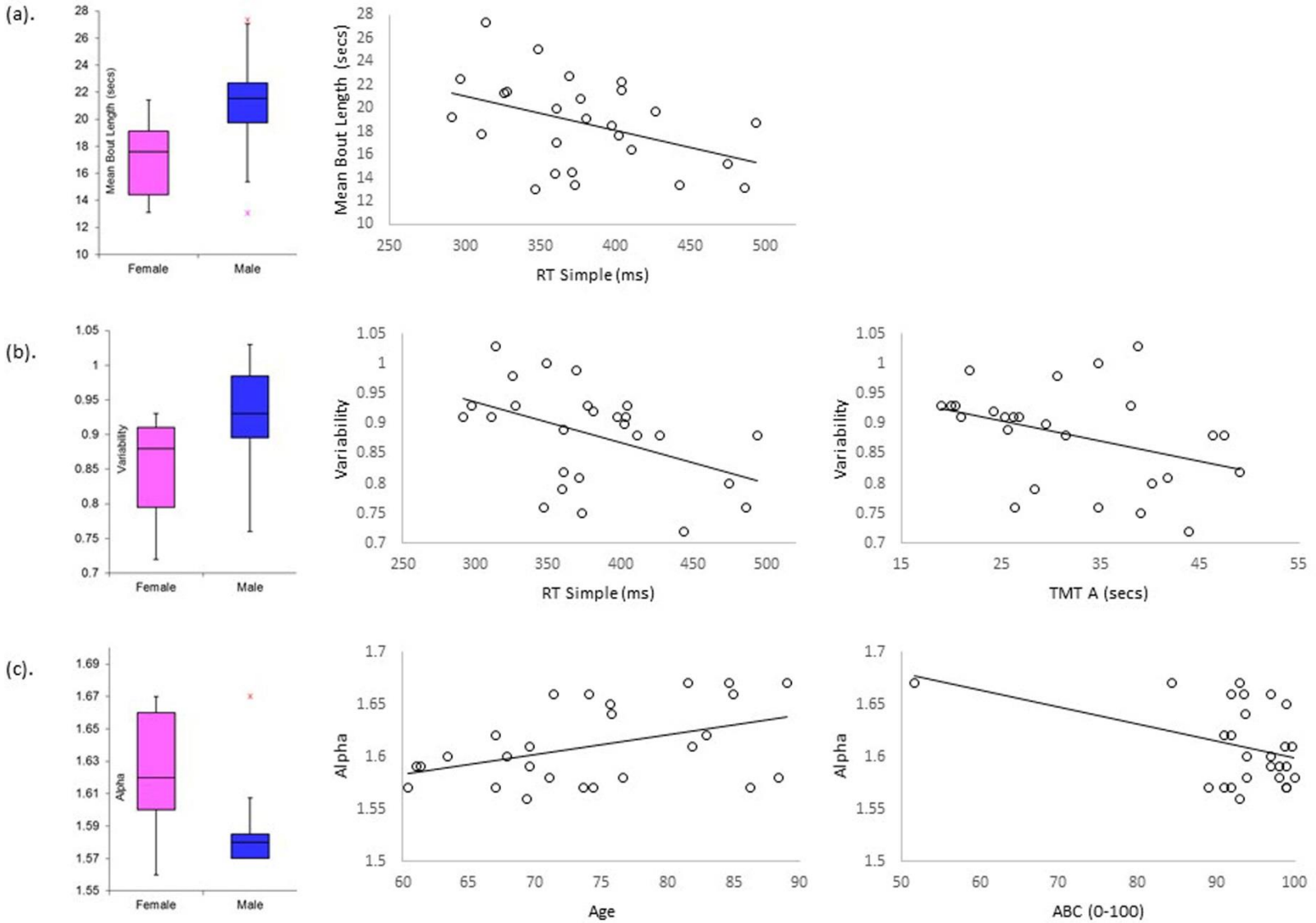


Figure 6-6Variables explaining habitual walking behaviours in controls

a). depicts significant variables explaining mean bout length, (b). variability of bout lengths, and (c). alpha scores.

Factors associated with habitual walking behaviours in the cognitively impaired population

Some strong to weak correlations were found between habitual walking behaviours impaired in people with cognitive impairment and variables related to health, motor disease severity, cognition, mood, balance confidence and sleepiness (see Table 6-5 for details).

Table 6-5 Spearman's correlations between habitual walking behaviour and associated factors

	Walk Time Per Day	Steps Per Day	Bouts Per Day	Mean Bout Length	Variability	Alpha
Age	-.156 (.162)	-.136 (.222)	-.161 (.147)	-.060 (.591)	-.014 (.900)	.017 (.878)
CIRS-G	-.205 (.068)	-.171 (.129)	-.176 (.118)	-.145 (.199)	.030 (.789)	.090 (.428)
UPDRS-III	**-.534 (<.001)**	**-.510 (<.001)**	**-.440 (<.001)**	**-.351 (.002)**	-.137 (.230)	**.264 (.019)**
ACE-III Mem	-.147 (.195)	-.133 (.241)	-.200 (.075)	.077 (.499)	.148 (.189)	-.134 (.237)
ACE-III VS	.167 (.139)	.122 (.281)	.090 (.426)	.210 (.061)	.153 (.177)	-.198 (.078)
ACE-III Total	-.025 (.826)	-.035 (.758)	-.122 (.281)	.197 (.080)	.190 (.091)	**-.240 (.032)**
TMT A	**-.245 (.040)**	**-.248 (.037)**	-.093 (.440)	**-.299 (.011)**	-.210 (.079)	**.307 (.009)**
FAS	**.358 (.001)**	**.337 (.003)**	**.281 (.013)**	**.336 (.003)**	.192 (.093)	**-.279 (.014)**
RT Simple	**-.299 (.009)**	**-.291 (.011)**	**-.234 (.043)**	-.219 (.059)	-.096 (.411)	.167 (.152)
ESS	**-.237 (.034)**	**-.222 (.048)**	-.195 (.083)	-.119 (.293)	-.015 (.895)	.020 (.860)
GDS	-.141 (.213)	-.136 (.230)	**-.236 (.035)**	.017 (.880)	.053 (.639)	-.084 (.458)
ABC	**.357 (.001)**	**.360 (.001)**	**.305 (.006)**	**.248 (.026)**	.124 (.271)	-.188 (.093)
BADL	**-.315 (.007)**	**-.312 (.007)**	**-.238 (.043)**	-.203 (.085)	-.061 (.609)	.126 (.287)

Data displayed as (rho (p value)). Data highlighted in dark blue refers to significant correlations, light blue refers to rho values > .200. Details re missing data can be found in Appendix G. CIRS-G = Cumulative Illness Rating Scale –Geriatric, UPDRS-III = Unified Parkinson's Disease Rating Scale III, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = visuospatial subscale, TMT A = Trail Making Task A, FAS = FAS Test, RT Simple = Simple Reaction Time Task, GDS = Geriatric Depression Scale, ESS = Epworth Sleepiness Scale, ABC = Activities Balance Confidence Scale, BADLS = Bristol's Activities of Daily Living.

Associations with motor disease

Greater motor disease severity (UPDRS-III) was strong-moderately negatively associated with less walk time per day, steps per day, bouts per day and mean bout length (see Table 6-5 for rho and p values) and weak positive associations with higher alpha scores.

Associations with cognition

Slower information processing ability demonstrated weak negative associations with less time spent walking (walk time and steps per day) and shorter walking bouts (see Table 6-5 for rho and p values), and positive associations with higher alpha scores.

Greater verbal fluency impairment (FAS) demonstrated moderate-weak positive associations with less time spent walking per day, steps per day, number of bouts per day and shorter walking bouts, and also had weak negative associations with higher alpha scores.

There were weak negative associations between greater attentional impairment and less time walking per day, number of steps and walking bouts taken per day, and shorter bout length.

Associations with balance confidence, mood and activities of daily living

Positive moderate associations were found between less balance confidence (ABC scale) and less time spent walking per day, steps per day and bouts per day and weak positive associations shorter walking bouts (see Table 6-5 for rho and p values).

Higher scores for depression (GDS) also demonstrated weak negative associations with less walking bouts taken per day. Similarly, greater sleepiness (ESS) demonstrated weak negative associations with less time walking per day and steps taken per day.

Weak-moderate negative associations were found with greater impairments in ADLs scores with less time spent walking, steps and bouts per day.

Explantory factors of habitual walking behaviour in people with cognitive impairment

To further understand the associations between habitual walking behaviours and motor disease severity, cognition, mood and balance confidence along with known covariates age and sex, the relationships between potential explanatory variables were further examined using univariate regression (see Appendix J).

Variables that significantly explained aspects of habitual walking behaviour in people with cognitive impairment in a univariate analysis were placed into backwards stepwise regression models (removal: $p \leq .10$) in order to identify significant explanatory variables for habitual walking behaviours (see Table 6-6).

Total walk time, steps and bouts per day were explained by greater motor disease severity and greater impairments in ADLs (see Table 6-6); explaining 26.1% of the variance in time spent walking; 20.8% of the variance for steps taken per and 17.1% of the variance for bouts taken per day.

Longer bout lengths were explained by a diagnosis of cognitive impairment due to AD, accounting for 7.5% of the variance (see Figure 6-3). Greater variability of bout length was explained by incidence of a fall within the previous year and greater balance confidence (see Figure 6-7); less variability demonstrated trends of diagnosis of PDD – this model explained

15.2% of the variance. Higher alpha scores were explained by greater motor disease severity, and greater verbal fluency impairment demonstrated similar trends – this model explained 8.9% of the variance.

Table 6-6 Significant univariate regressions and backwards stepwise regression models for habitual walking behaviour in cognitively impaired participants

Total Walk Time Per Day (mins)	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
UPDRS-III	-1.6	0.3	-4.8	**≤.001**	23.2	0.481	0.231	.221	-2.3	-0.9
AD Subtype	35	13.8	2.6	**.013**	6.5	.274	.075	.063	7.7	62.4
PDD Subtype	-52.1	16.9	3.1	**.003**	9.5	.325	.106	.095	-85.8	-18.4
FAS	1.6	0.5	3.4	**≤.001**	11.9	0.367	0.135	0.124	0.7	2.5
ABC (0-100)	1.2	0.3	3.6	**≤.001**	12.9	0.374	0.14	0.129	0.5	1.8
BADLS (0-60)	-3.1	1	3.3	**≤.001**	11	.366	.134	.121	-5	-1.3
Final Model				**≤.001**	12.8	.532	.283	.261		
UPDRS-III	-1.1	.3	3.4	**.001**					-1.7	-0.4
BADLS	-2.0	.8	2.3	**.022**					-3.6	-.3
Steps Per Day	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
UPDRS-III	-104	25	-4.2	**≤.001**	17.6	.431	.186	.175	-154	-55
AD Subtype	2233	1003	2.2	**.029**	5.0	.242	.058	.047	237	4230
PDD Subtype	-3562	1232	2.9	**.005**	8.4	.208	.095	.083	-6013	-1110
FAS	102	34	3.0	**.003**	9.2	.329	.108	.096	35	168
ABC (0-100)	83	24	3.5	**≤.001**	11.9	.362	.131	.120	35	130
BADLS (0-60)	-211	69	3	**.003**	9.3	.340	.115	.103	-349	-73
Final Model				**≤.001**	9.8	.482	.232	.208		
UPDRS-III	-70	24	2.9	**.004**					-118	-23
BADL	-132	63	2.1	**.041**					-258	-5
Bouts Per Day	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Faller Status (Faller)	-99	45	2.2	**.032**	4.8	.237	.056	.044	-189	-9
UPDRS-III	-4	1	3.7	**≤.001**	13.9	.390	.152	.141	-7	-2
PDD Subtype	-133	57	2.4	**.021**	5.5	.254	.065	.053	-246	-20
FAS	4	2	2.6	**.011**	6.8	.286	.082	.070	.9	7
ABC (0-100)	3	1	2.8	**.007**	7.6	.296	.088	.076	1	5
BADLS (0-60)	-10	3	3.1	**.003**	9.8	.348	.121	.108	-16	-4
Final Model				**≤.001**	7.9	.442	.195	.171		
UPDRS-III	-2	1	2.0	**.049**					-5	-.01
BADL	-8	3	2.5	**.014**					-13	-2
Mean Bout Length (secs)	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
UPDRS-III	-.1	.02	-2.9	**.005**	8.6	.316	.100	.088	-.1	-.02
AD Subtype	2.1	.7	2.9	**.005**	8.3	.206	.094	.082	.7	3.6
PDD Subtype	-2.5	.9	2.8	**.007**	7.6	.294	.086	.075	-4.4	-.7
FAS	.1	.03	2.0	**.045**	4.2	.228	.052	.039	.001	.1

ABC (0-100)	.1	.02	2.6	**.011**	6.8	.282	.080	.068	.01	.1
Final Model				**.009**	7.1	.296	.088	.075		
AD Subtype	2.0	.8	2.7	**.009**					.5	3.5
Variability	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Faller Status (Faller)	.04	.02	2.2	**.030**	4.9	.239	.057	.045	.004	.074
PDD Subtype	-.048	.022	2.2	**.031**	4.8	.239	.057	.045	-.092	-.005
ABC (0-100)	.001	.000	2.1	**.039**	4.4	.230	.053	.041	.000	.002
Final Model				**.001**	5.7	.429	.184	.152		
ABC	.001	.000	2.3	**.039**					.000	.002
Faller Status	.052	.017	3.0	**.003**					.018	.087
PDD Subtype	-.043	.023	1.9	.066					-.089	.003
Alpha	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
UPDRS-III	.001	.000	2.7	**.008**	7.4	.296	.088	.076	.000	.002
AD Subtype	-.031	.015	2.1	**.035**	4.6	.233	.054	.042	-.060	-.002
PDD Subtype	.048	.018	2.7	**.010**	7.1	.285	.081	.070	.012	.084
FAS	-.001	.000	-2.6	**.012**	6.6	.283	.080	.068	-.002	.000
GDS (0-15)	-.002	.002	-.8	.423	.7	.091	.008	-.004	-.007	.003
ABC (0-100)	-.001	.000	3.4	**.001**	11.2	.353	.125	.114	-.002	.000
Final Model				**.013**	4.6	.336	.113	.089		
UPDRS-III	.001	.000	2.0	**.045**					.000	.001
FAS	-.001	.000	1.7	.098					-.001	.000

Significant values in bold. Table only reports significant explanatory factors of habitual walking behaviour; Appendix J includes all variables considered. UPDRS-III = Unified Parkinson's Disease Rating Scale III, FAS = FAS Test, RT Simple = Simple Reaction Time Task, ABC = Activities Balance Confidence Scale, BADLS = Bristol's Activities of Daily Living.

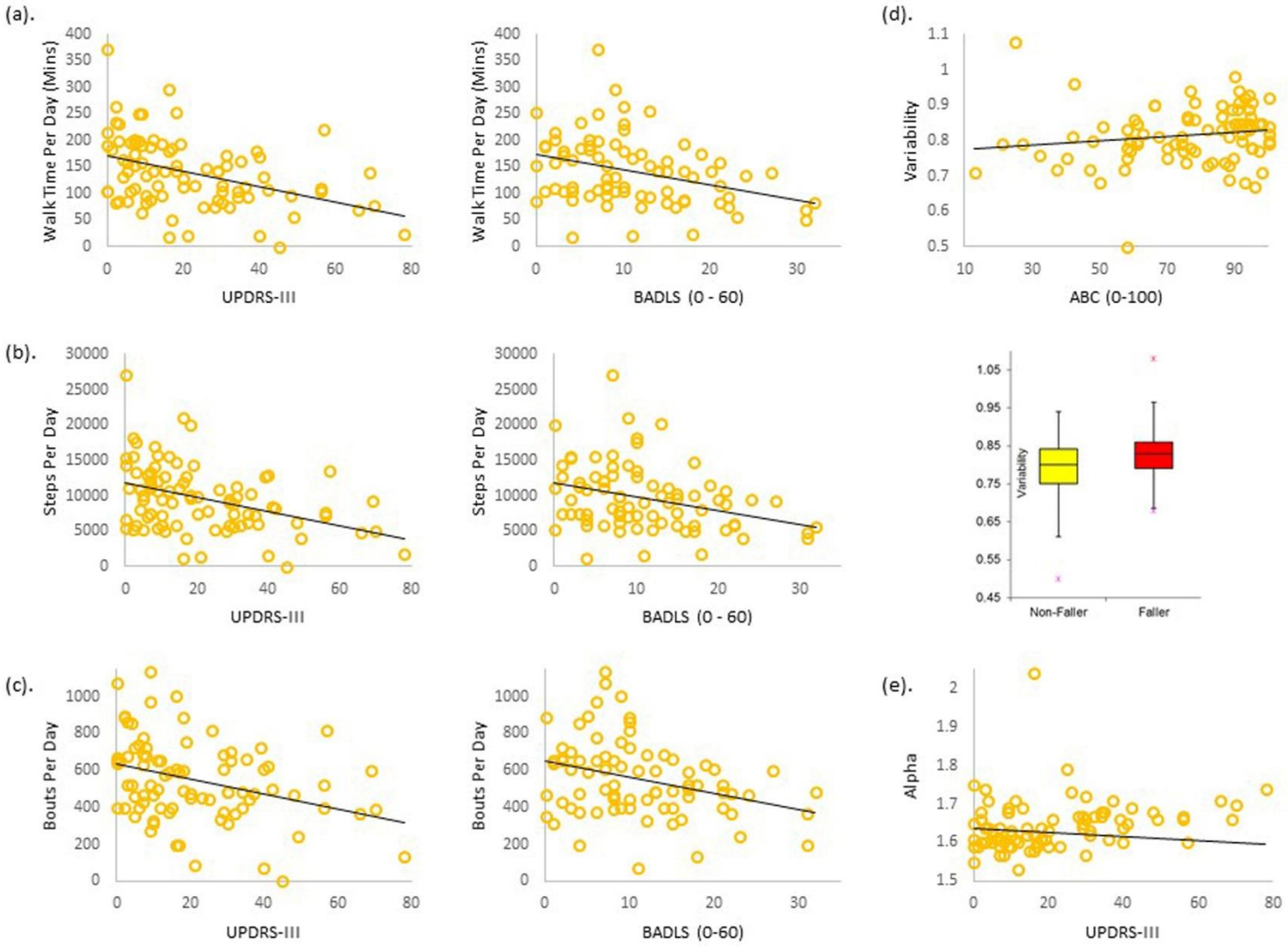


Figure 6-7 Variables explaining habitual walking behaviours in cognitive impairment

Figure depicts variables explaining (a). walk time per day, (b). steps per day, (c). bouts per day, (d). variability of bout lengths and (e). alpha scores

Factors associated with habitual walking behaviour in people with Alzheimer's disease

Motor disease severity (UPDRS-III) had moderate negative associations with time spent walking, steps and bouts per day (see Table 6-7 for rho and p values). There were also moderate positive associations between balance confidence (ABC) and time spent walking and steps per day. There were moderate positive associations between global cognition (ACE-III) and variability of bout lengths. There were significant differences for variability of bout length between male and females (p = .049); men were more variable in their bout lengths. There were no other significant differences between males and females.

In summary, greater motor disease severity and lower balance confidence was associated with less time spent walking and fewer steps per day. Greater motor disease severity was also associated with taking fewer walking bouts per day. Greater cognitive impairment was associated with less variability in bout lengths and women in the AD group were less variable in bout length.

Table 6-7 Spearman's correlations between habitual walking behaviour and associated factors in Alzheimer's disease

	Walk Time Per Day	Steps Per Day	Bouts Per Day	Mean Bout Length	Variability	Alpha
Age	-.084 (.625)	-.068 (.692)	-.159 (.353)	.041 (.814)	.125 (.466)	-.117 (.497)
UPDRS-III	-.417 (.013)	-.425 (.011)	-.346 (.042)	-.016 (.928)	.007 (.968)	.030 (.863)
ACE-III	-.052 (.764)	<.001 (1.000)	-.146 (.394)	.288 (.088)	.338 (.044)	-.321 (.056)
TMT A	.054 (.757)	.005 (.978)	.112 (.522)	-.236 (.173)	-.130 (.456)	.302 (.078)
FAS	.191 (.271)	.241 (.164)	.195 (.261)	.106 (.545)	.084 (.633)	-.074 (.672)
RT Simple	-.183 (.293)	-.189 (.278)	-.152 (.383)	-.127 (.467)	-.096 (.584)	.162 (.353)
ABC	.363 (.029)	.372 (.025)	.232 (.173)	.209 (.222)	.055 (.749)	-.155 (.366)
BADLS	-.255 (.151)	-.272 (.126)	-.171 (.340)	-.155 (.390)	-.070 (.697)	.103 (.569)

Data displayed as (rho (p value)). Data highlighted in dark blue refers to significant correlations, light blue refers to rho values > .200. *UPDRS-III = Unified Parkinson's Disease Rating Scale III, ACE-III = Addenbrookes Cognitive Examination III, TMT A = Trail Making Task A, FAS = FAS Test, RT Simple = Simple Reaction Time Task, ABC = Activities Balance Confidence Scale, BADLS = Bristol's Activities of Daily Living.*

Factors associated with habitual walking behaviour in people with dementia with Lewy bodies

Motor disease severity (UPDRS-III) had moderate negative associations with walk time and bouts taken per day (see Table 6-8 for rho and p values). There were moderate-strong positive associations between balance confidence (ABC) and walk time, steps and bouts taken per day. There were no significant differences between males and females for any variable.

In summary greater motor disease severity and lower balance confidence is associated with less time spent walking and fewer bouts per day. Lower balance confidence is also associated with fewer steps taken per day.

Table 6-8 Spearman correlations between habitual walking behaviour and associated factors in dementia with Lewy bodies

	Walk Time Per Day	Steps Per Day	Bouts Per Day	Mean Bout Length	Variability	Alpha
Age	-.176 (.353)	-.204 (.279)	-.036 (.850)	-.213 (.259)	-.287 (.125)	.201 (.287)
UPDRS-III	-.382 (.041)	-.324 (.086)	-.385 (.039)	-.221 (.250)	-.023 (.906)	.178 (.356)
ACE-III	-.030 (.877)	-.080 (.679)	-.147 (.448)	.205 (.286)	.242 (.205)	-.275 (.149)
TMT A	-.145 (.529)	-.127 (.582)	-.114 (.624)	-.190 (.410)	-.284 (.211)	.247 (.281)
FAS	.273 (.160)	.233 (.232)	.163 (.407)	.365 (.056)	.308 (.111)	-.361 (.059)
RT Simple	-.246 (.236)	-.202 (.334)	-.304 (.139)	-.105 (.619)	-.017 (.936)	.078 (.712)
ABC	.412 (.024)	.373 (.042)	.509 (.004)	.154 (.417)	.052 (.785)	-.097 (.609)
BADLS	.206 (.323)	.164 (.434)	.152 (.468)	.173 (.407)	-.005 (.982)	-.243 (.241)

Data displayed as (rho (p value)). Data highlighted in dark blue refers to significant correlations, light blue refers to rho values > .200. UPDRS-III = Unified Parkinson's Disease Rating Scale III, ACE-III = Addenbrookes Cognitive Examination III, TMT A = Trail Making Task A, FAS = FAS Test, RT Simple = Simple Reaction Time Task, ABC = Activities Balance Confidence Scale, BADLS = Bristol's Activities of Daily Living.

Factors associated with habitual walking behaviour in people with Parkinson's disease dementia

Motor disease severity had strong negative correlations with walk time and steps per day and strong positive associations with alpha (see Table 6-9 for rho and p values). Greater motor disease severity is associated with less time spent walking, fewer steps taken per day and taking a greater proportion of short walking bouts compared to long walking bouts. There were no significant differences between males and females for any variable.

Table 6-9 Spearman's correlations between habitual walking behaviour and associated factors in Parkinson's disease dementia

	Walk Time Per Day	Steps Per Day	Bouts Per Day	Mean Bout Length	Variability	Alpha
Age	-.349 (.185)	-.265 (.321)	-.303 (.254)	-.052 (.850)	.057 (.833)	.031 (.910)
UPDRS-III	-.618 (.014)	-.525 (.044)	-.386 (.156)	-.429 (.111)	-.182 (.516)	.575 (.025)
ACE-III	.363 (.184)	.224 (.421)	.255 (.359)	.323 (.240)	-.059 (.834)	-.368 (.177)
TMT A	-.025 (.930)	-.089 (.752)	<.001 (<.001)	.168 (.550)	.250 (.369)	-.064 (.820)
FAS	.507 (.054)	.415 (.124)	.489 (.064)	.349 (.202)	.036 (.899)	-.306 (.267)
RT Simple	.061 (.830)	.114 (.685)	.068 (.810)	.121 (.666)	.254 (.362)	.004 (.990)
ABC	-.143 (.611)	-.127 (.652)	-.243 (.383)	.209 (.454)	.166 (.554)	-.304 (.271)
BADLS	-.411 (.128)	-.379 (.164)	-.386 (.155)	-.030 (.914)	.297 (.283)	.197 (.482)

Data displayed as (rho (p value)). Data highlighted in dark blue refers to significant correlations, light blue refers to rho values > .200. UPDRS-III = Unified Parkinson's Disease Rating Scale III, ACE-III = Addenbrookes Cognitive Examination III, TMT A = Trail Making Task A, FAS = FAS Test, RT Simple = Simple Reaction Time Task, ABC = Activities Balance Confidence Scale, BADLS = Bristol's Activities of Daily Living.

6.5 Discussion

The aim of this chapter was to describe habitual walking behaviours in dementia disease subtypes, and to identify some of the factors contributing to the amount, variability and patterns of walking behaviours in normal ageing and cognitive impairment. Key findings demonstrate that individuals with cognitive impairment spend less time walking and take shorter walking bouts which vary less in duration compared to controls. These findings are pronounced in walking bouts over 60 seconds, and particularly prominent in people with cognitive impairment due to PD. The amount of walking activity (time, bouts and bout length) in people with cognitive impairment is explained by greater motor disease severity and impairments in ADLs.

6.5.1 What does habitual walking activity look like in cognitive impairment?

This study is the first to compare habitual walking behaviour in cognitive impairment due to AD, DLB and PD. The finding of lower quantities of walking in LBD subtypes, along with trends to a lower quantity of walking in AD, supports Hypothesis 6.1 and is consistent with existing literature (Hausdorff *et al.*, 2017); a systematic review in 2016 reported lower step counts and overall physical activity in people with cognitive impairment when assessed in free-living conditions over at least 24 hours (Block *et al.*, 2016). Reduced habitual walking activity was most prominent in participants with cognitive impairment due to PD, who also took proportionally more short bouts which varied less in duration compared to controls – this is consistent with previous findings in PD without cognitive impairment (Lord *et al.*, 2013c; Block *et al.*, 2016).

There were no significant differences between AD and normal ageing, in contrast to previous work (Erickson *et al.*, 2013). A potential explanation could be the relatively mild population of AD participants. In support of this, previous work using the same methodology in a mild AD cohort describes similar values for habitual walking behaviours (Mc Ardle *et al.*, 2018). An alternative explanation may be the use of different thresholds for bout length employed by different studies (Del Din *et al.*, 2016b). Higher cut-off thresholds of activity may underestimate step counts as demonstrated by Figure 6-4, which shows approximately 60% of total walking bouts are spent in very short bouts. When considering high cut-off thresholds (e.g. bouts > 60 seconds) compared to all bout lengths, differences of approximately 7,500 steps have been found (Del Din *et al.*, 2016b). In this study, participants with AD took fewer steps and bouts per day only in sustained bouts compared to controls, supporting Hypothesis 6.2. This implies that habitual walking behaviour is similar between groups but people with

AD may find periods of sustained walking more functionally challenging. What seems clear is that only taking quantity of habitual walking into account is most likely insufficient to understand habitual walking behaviours in people with cognitive impairment.

Other features of habitual walking behaviours such as the pattern and variability of walking bouts allow a more nuanced approach to understand the data (Lord *et al.*, 2013c). Trends indicate all disease subtypes have shorter and less variable bouts of walking. Within this study's population, differences in variability and pattern of walking may indicate less engagement with different types of activity and shorter bouts may reflect a more constrained environment and less time spent outside the home (Del Din *et al.*, 2017). For example, proportionally shorter bouts may be taken when moving around the home such as room to room, while sustained bouts may be taken when going for a walk or taking part in social activities. Greater variability of bouts may demonstrate a person engaging with a variety of tasks such as housework, shopping and social calls representing a greater repertoire of activities. Future research is required to provide context to these metrics and by doing so will allow wearable technology to provide detailed pictures of an individual's day-to-day function. This may improve our understanding of the impact of cognitive impairment on daily living and support the development of improved methods for disease management.

6.5.2 What factors influence habitual walking behaviours in normal ageing and cognitive impairment?

Many external and internal factors influence habitual walking activity. This study aimed to examine the contribution of disease-related impairments such as disease subtype, cognitive dysfunction, motor disease severity and impairments in ADLs, along with behavioural and perceptual variables e.g. mood, balance confidence. The explanatory variables of habitual walking behaviour differed between controls and people with cognitive impairment. For example, age and gender explained variability and patterns of walking in normal ageing (see Table 6-4). Taking longer variable walking bouts was explained by being a man, while spending a greater proportion of time in short walking bouts was explained by being older and a woman. Previous literature has reported older women walking less and in shorter durations than older men, possibly as a result of greater engagement with household tasks which may make up shorter walking bouts (Lee, 2005). Such findings may reflect gender differences in the older generation. Interestingly, this was not apparent in all disease subtypes. Only the AD group showed significant differences between males and females for variability of bout length – similar to controls, men were more variable. There may be a breakdown of gender roles within dementia disease groups resulting from reduced ability to perform a variety of tasks

such as partaking in sports and community activities or carrying out daily household tasks and shopping, and increased dependency and need for care. The disease groups included in this study did not have equal numbers or a similar ratio of males to females and as such, interpretation of such findings is limited. Future work should strive to look at this interaction in larger samples and consider the interaction between activity of the individual with cognitive impairment and their caregiver. By doing so, we may gain a unique insight into the loss of independence and evolution of caregiving in these populations.

Less variable and shorter walking bouts could also be explained by slower information processing and attentional reaction times in normal ageing, perhaps reflecting lower abilities to engage cognitively with different kinds of activities in the home and community. Interestingly, information processing and attention were not explanatory of habitual walking behaviour in people with cognitive impairment. This contradicts Hypothesis 6.4 and the literature associating lower daily activity with greater progression of cognitive decline (Buchman *et al.*, 2008; Buchman *et al.*, 2012). This may be due to differences in type of activity considered; however Hausdorff *et al.* (2017) found statistically significant differences for walking outcomes in sustained bouts disappeared between people with MCI and controls when controlling for cognition. Sustained walking activities may require more cognitive contribution than shorter bouts but make up the smallest percentage of walking bouts. Alternatively, walking is a complex multi-dimensional activity and several barriers to engagement may be relevant to cognitive impairment, such as motor problems, lack of independence and low balance confidence. Poorer cognitive function may be a primary barrier to habitual walking activity in normal ageing, but may be secondary in established cognitive impairment.

This suggestion is supported by the finding of lower amounts of habitual walking can be explained by greater motor disease severity and impairments in ADLS in cognitive impairment, partially confirming Hypothesis 6.3. Motor disease severity has previously been shown to predict lower walking activity in PD (Lord *et al.*, 2013c) and this finding (as assessed by a rating scale specific to PD motor disease symptoms) in discrete disease subtypes highlights the importance of considering motor problems in treatment protocols. Cognitive impairment and motor problems tend to be considered separately in clinical practice and may therefore be neglected in individuals without visually observable motor symptoms – such as people with AD. Advice and interventions for prodromal and mild cognitive impairment should be provided to best maintain activity levels and personal independence, as well as maintaining or improving quality of life, mood and cognitive

function (Bize *et al.*, 2007; Orgeta *et al.*, 2010; Bherer *et al.*, 2013). Greater proportion of time spent in short walking bouts was also explained by greater motor disease severity, suggesting that it may be a significant barrier to engaging in sustained walking bout.

People with cognitive impairment who presented with poorer balance confidence but no history of falls had less variable bout lengths. This may be due to adapting behaviours due to greater fear of falling, and may also represent conflicts between perception of balance and objective fall risk (i.e. participants with a fall history may have better balance confidence). Delbaere *et al.* (2010) has indicated the interplay of physiological and perceived fall risk influences physical activity (self-reported) in older adults; older adults with a high physiological risk but low perceived fall risk maintained a more active life style compared to those with high physiological and perceived fall risks. This supports this study's finding and may reflect lack of insight in this population – it would be interesting to further explore how disparity between objective and subjective measures of fall risk influences habitual walking behaviours and gait performance in cognitively impaired populations.

6.5.3 Limitations in our understanding and interpretation of free-living data

The explanatory variables described in this study only explain a small amount of the variance in habitual walking activity and it's important to realise that a broad range of explanatory variables are associated with these outcomes. Specific health conditions, apathy and depression, fatigue, loss of dependence, caregiver burden and health, lack of access to transportation, bad weather and environmental constraints may all act as barriers to engaging in habitual walking activities (van Alphen *et al.*, 2016). For example, an 83 year old woman with PDD had the lowest amount of walking (average of 20 minutes per day) and highest alpha score (2.04). She had low balance confidence (ABC: 25/100) and reported that she only felt safe walking when her husband was walking alongside her. She showed impairments in ADLs (BADLS: 13/60) and reported that her husband was now in charge of all household jobs that had traditionally been delegated to her. The presence of motor disease, loss of independence, high levels of caregiving and lack of confidence in walking independently may all have influenced the low amount of walking and preference for short bouts.

While low quantities of walking activity and presence of barriers to walking were expected, the large range of activity within this sample is notable (see Table 6-1 and Figure 6-3 for more details). van Alphen *et al.* (2016) suggested that there are a range of motivators and facilitators for people with cognitive impairment to engage in activity, including dog ownership, social activities and routine. When considering motivators and facilitators on a

case study basis, the person who spent the most time walking (373 minutes per day) was a 78-year-old man diagnosed with MCI due to LB. He reported being an active member of a walking club that meets regularly; this may partially account for the 155 minutes per day he spent in sustained bouts. An 80-year-old man diagnosed with DLB spent 288 minutes per day walking – 145 of these were in sustained bouts. He reported owning a dog which he took for long walks every day and this may somewhat account for the long periods of walking recorded. Similarly, an 82-year-old woman with a diagnosis of AD spent 267 minutes walking, 155 in sustained bouts. She reported enjoyment associated with walking and tried to take two walks every day.

These case studies are simply highlighting that one size does not fit all. Individuals have a range of personal, interpersonal, environmental, cultural and social factors that influence their engagement in behavioural activities such as walking and that should be recognised when interpreting snapshots of ambulatory activity. Free-living data is complex, personal and highly variable. Therefore, monitoring individual trajectories of change within free-living behaviours may be more clinically useful than applying thresholds of "at-risk" behaviour (Kaye *et al.*, 2012).

6.5.4 Conclusion

In conclusion, this is the first study to compare the amount, variability and pattern of habitual walking activity across dementia disease subtypes. It had demonstrated differences in habitual walking behaviours in cognitive impairment compared to normal ageing and suggested motor disease and impairments in ADLs partially explain these findings. By garnering a detailed picture of habitual walking behaviour in conjunction with patterns of gait impairment, we are beginning to gain a more complete understanding of how neurodegeneration and cognitive impairment affects daily life. Future research should consider spatiotemporal gait impairment within the context provided by macro gait characteristics.

Chapter 7 Within the context: Patterns of gait impairment depend on length of walking bout in free-living environments

This chapter considers spatiotemporal gait characteristics in the context supplied by Chapter 5, examining how the length of a walking bout influences patterns of gait impairment across disease subtypes. It also explores the associations between cognitive impairment, motor disease severity and gait impairments across very short, short, medium and sustained walking bouts.

7.1 Introduction

Free-living gait analysis is a relatively novel area of research, and as such, there are still a number of methodological considerations to be addressed (Del Din *et al.*, 2016b). As discussed in Chapter 5 and Chapter 6, unlike laboratory conditions, gait assessment in free-living conditions provides a picture of an individual's habitual behaviour, rather than their capacity to engage in a task. However, given the large amount of data captured continuously and unobtrusively, it is important to consider spatiotemporal gait characteristics within the limited context provided, i.e. macro gait characteristics.

The influence of context may be considered by describing patterns of gait impairment within different walking bout lengths. Different lengths of walking bouts are likely to reflect differing contexts. For example, if a person is walking from one room to the next, we may expect a short walking bout (<30 second; Orendurff *et al.*, 2008), while a period of sustained walking (>60 seconds) is more likely to involve walking outside in a community environment (Del Din *et al.*, 2016b). In line with previous research (Orendurff *et al.*, 2008), individuals spend perform mostly very short walking bouts (<10 seconds) and very few sustained walking bouts (2-3% of all walking bouts), as described in Chapter 6. The number of walking bouts taken in each bout length described (very short, short, medium and sustained) also varied according to dementia disease subtype. This may have affected the findings of Chapter 5, as data from all walking bouts were grouped together.

There is still no consensus surrounding the optimal bout length in which to consider patterns of gait impairment. A walking bout can be considered as anything over three consecutive steps to a period of walking longer than 60 seconds (Weiss *et al.*, 2013; van Schooten *et al.*, 2015; Brodie *et al.*, 2016; Del Din *et al.*, 2016a; Del Din *et al.*, 2016b; Del Din *et al.*, 2017). Del Din *et al.* (2016b) reported differences in gait impairment between people with Parkinson's disease (PD) and controls are dependent on length of walking bout, and cannot be

detected in very short walking bouts. Therefore, considering patterns of gait impairment in different bout lengths, such as very short, short, medium and sustained bouts, may be useful for differentiating disease subtypes.

Additionally, given the suggestion that different bout lengths may represent different activities, the role of cognition in gait may depend on bout length. By exploring the gait-cognition associations in different bout length, a greater insight into the dynamic nature of cognition in the maintenance and modulation of gait may be gained. As Chapter 4 and Chapter 5 have demonstrated greater motor disease is associated with greater gait impairment in AD, it is important to consider if such associations are also impacted by bout length.

7.2 Aims and hypotheses

Based on the current literature and the results described in Chapter 5 and Chapter 6, this chapter addresses two key aims and their respective hypotheses with regard to gait in free-living environments.

- Investigate the impact of bout length on spatiotemporal gait characteristics and patterns of gait impairment.
- Explore associations between cognitive impairment, motor disease and gait impairments across bout length.

Hypotheses

7.1. Gait is faster with larger steps, less variability and asymmetry and quicker timing of the gait cycle as walking bout length increases. As such, patterns of gait impairment will differ dependent on bout length.

7.2. Medium bouts (30-60 seconds) and sustained bouts of walking (>60 seconds) will be the most useful for distinguishing patterns of gait impairment between disease subtypes.

7.3. The role of cognition in gait will vary depending on length of walking bout. Gait impairment in longer walking bouts will require greater cognitive contributions from attentional, executive and visuospatial functions, while gait impairment in shorter walking bouts will be associated with greater motor disease severity.

7.4. The role of cognition in gait will be different between disease subtypes. Gait impairments in Alzheimer's Disease (AD) will be predominately associated with motor disease severity, while in Parkinson's disease dementia (PDD) and dementia

with Lewy bodies (DLB) they will be more greatly associated with impairments in attention, executive and visuospatial function and information processing.

7.3 Methods

The descriptions of study participants and protocol for collecting free-living gait data is described in Chapter 5. Figure 7-1 outlines number of participants approached, recruited and included in this study. This doctoral candidate conducted 105 clinical and cognitive assessments; 10 assessments were carried out as part of the SUPERB study – an ongoing longitudinal study investigating the use of biomarkers for an accurate diagnosis of dementia with Lewy bodies (see Chapter 3). Information pertaining to clinical and cognitive assessment can be found in Chapter 6.

7.3.1 Data processing and analysis

The procedure for processing and analysing free-living data is largely described in Chapter 5 and Chapter 6. Figure 5-2 also demonstrates this process. This chapter will focus on the fourteen micro gait characteristics described in Chapter 5: step velocity, step length, step, stance and swing time, variability of step, stance and swing time, step length and step velocity, asymmetry of step, stance and swing time and step length.

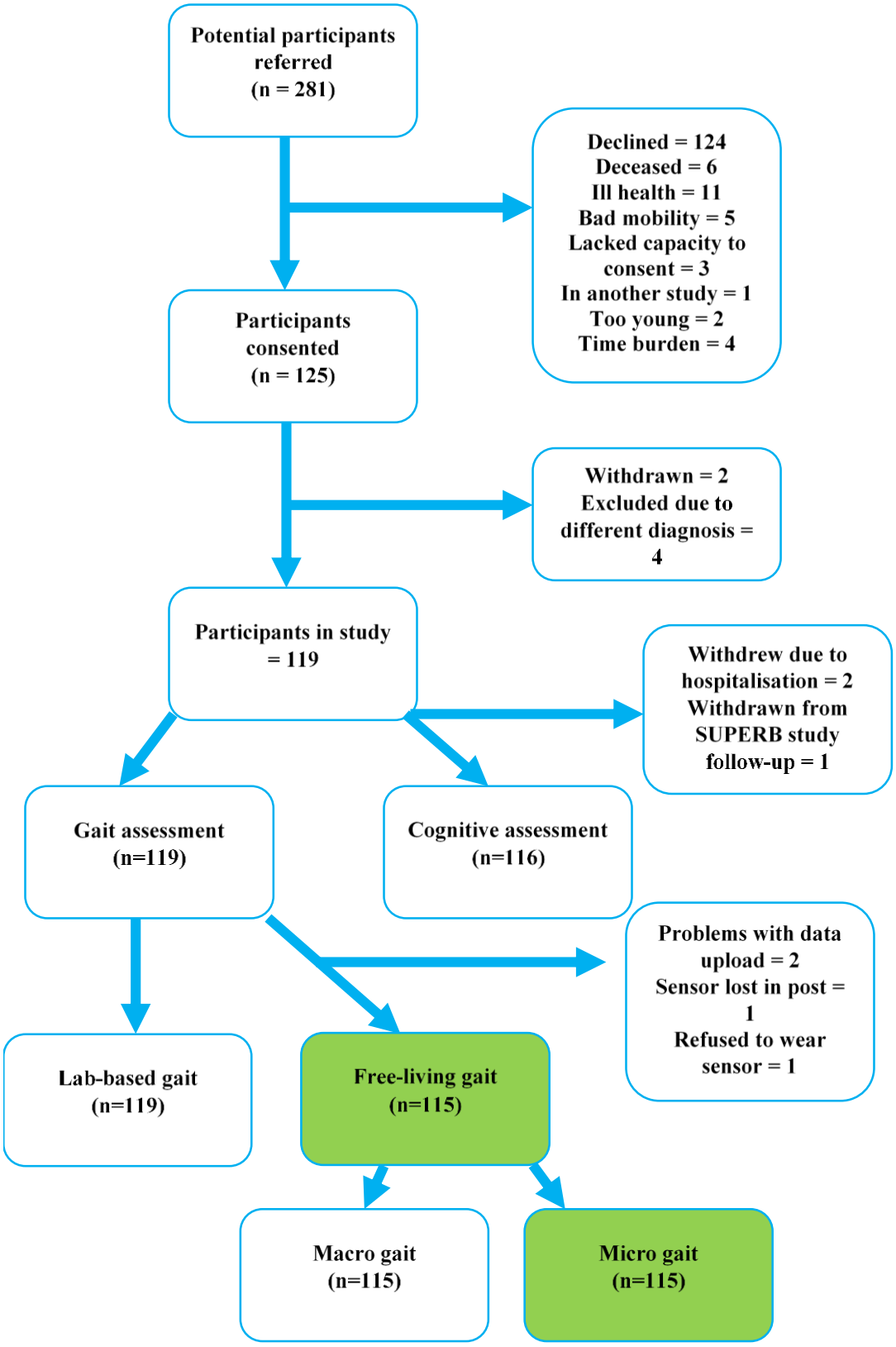


Figure 7-1 Participant approach, recruitment and assessment.

Figure 7-2 Illustration of gait protocol from initial body-worn monitor placement to data output.

7.3.2 Data analysis

Statistical analysis for demographic and clinical information is described in Chapter 3.

The first part of this analysis investigated the impact of bout length on spatiotemporal gait characteristics in controls and disease subtypes. Bouts were grouped depending on their length (<10 seconds, 10-30 seconds, 30-60 seconds, > 60 seconds). Friedman's test and Wilcoxon Signed Rank Tests were used to assess the effect of bout length on spatiotemporal gait characteristics in each group. Independent t-tests and Mann Whitney U tests assessed between-group differences in each bout length.

The second part of the analysis investigated differences in micro gait characteristics between controls and disease subtypes: AD, DLB and Parkinson's disease dementia (PDD). Between-group differences in gait were considered in each bout length using one-way ANOVAs and Kruskal Wallis tests. Fischer's LSD post hocs and Mann Whitney U tests established where group differences lay. The value of statistical significance was set at ($p \leq .01$) in order to account for multiple comparisons.

As a key aim of this thesis was to establish if gait analysis can differentiate AD and DLB, independent t-tests investigated differences between these groups in order to verify findings from LSD post hocs, and one-way ANCOVAs were conducted to control for age, sex and height. Effect sizes (partial eta squared; η^2) were calculated for key significant differences between these disease groups. Effect sizes were interpreted in accordance to guidelines (Richardson, 2011); as small (.01-.06), medium (.06-.14) and large (> .14).

Spearman's Rho correlations were used to identify associations between cognitive measures and motor disease with gait variables in each disease subtype across all bout lengths. Due to small sample sizes, multivariate regression models were inappropriate for this analysis.

7.4 **Results**

Information about recruitment, demographics, clinical and cognitive information of participants in the controls and disease subtypes can be found in Chapter 5. The proportion of total bouts that controls, AD, DLB and PDD groups spend in very short (>10 seconds), short (10-30), medium (30-60) and sustained (>60) bouts is detailed in Chapter 6.

7.4.1 Impact of bout length on gait impairments in dementia disease subtypes

Effect of bout length on gait characteristics in controls and dementia disease subtypes

In summary, all groups walked faster with longer steps and less asymmetry in longer walking bouts compared to short walking bouts. All groups also became less variable – however this was less obvious in PDD. Steo, stance and swing time and step length variability were not significantly affected by bout length in the PDD group (see Figure 7-3). Repeated-measures analysis of bout lengths can be found in Appendix K. Patterns of gait impairment will be examined further in very short, short, medium and sustained bout lengths.

Gait impairments in < 10 second walking bouts in dementia disease subtypes

Differences between disease subtypes and controls

In under 10 second bouts, both the DLB and PDD groups had shorter steps ($p \leq .001$) with greater variability ($p \leq .05$) and greater asymmetry for step length ($p \leq .01$) compared to controls (see Figure 7-4 and Table 7-1). Participants in the PDD group also had shorter step ($p \leq .001$), stance ($p \leq .001$) and swing time ($p \leq .001$) compared to controls, and the DLB group had shorter step, stance and swing times compared to controls ($p \leq .05$ for all).

When considering the more conservative threshold $p \leq .01$, people with DLB and PDD had shorter step lengths with greater asymmetry, and people with PDD had shorter step, stance and swing times compared to controls.

Differences between Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia

Both the DLB and PDD groups demonstrated shorter steps ($p \leq .001$) and less step length asymmetry ($p \leq .01$) compared to the AD groups (see Figure 7-4 and Table 7-1). Participants with PDD also had quicker step ($p \leq .001$), stance ($p \leq .001$) and swing time ($p \leq .001$) compared to AD. These differences remained significant at $p \leq .01$.

The DLB group also had quicker step, stance and swing times compared to AD ($p \leq .05$ for all). They also had longer step ($p = .025$), stance ($p = .025$) and swing time ($p = .016$) compared to PDD. However, these differences did not remain significant under the more conservative threshold.

Differences between Alzheimer's disease and dementia with Lewy bodies

When considered independently, the DLB group demonstrated shorter steps ($p = .001$; $\eta^2 = .152$), quicker step ($p = .029$; $\eta^2 = .074$) and stance times ($p = .034$; $\eta^2 = .070$) and less

asymmetry for step (p = .039; η^2 = .066) and stance times (p = .041; η^2 = .065).and step length (p = .001; η^2 = .163; see Figure 7-4 and Table 7-1). Only step length and step length asymmetry were significantly different when the more conservative statistical threshold was applied.

When controlling for age, sex and height, participants with DLB still demonstrated shorter steps (p = .010; η^2 = .108), quicker step (p = .025; η^2 = .082) and swing times (p = .043; η^2 = .068),.and less step length asymmetry (p = .002; η^2 = .109). Only step length and step length asymmetry remained significant at p ≤ .01.

Gait impairments in 10-30 second walking bouts in dementia disease subtypes

Differences between disease subtypes and controls

In 10-30 second bouts, both the DLB and PDD groups took shorter steps (p ≤ .001) with greater step length asymmetry (p ≤ .01) compared to controls (see Figure 7-4 and Table 7-1). Participants with PDD had quicker step (p ≤ .001), stance (p ≤ .001) and swing times (p = .002) compared to controls.

Although not significant at p ≤ .01, people with AD took shorter steps (p = .039) and the PDD group demonstrated greater stance variability (p = .007) compared to controls.

Differences between Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia

Both DLB (p = .003) and PDD (p = .002) had less asymmetric step lengths compared to AD and the PDD group took shorter steps (p ≤ .001) with shorter step (p ≤ .001), stance (p ≤ .001) and swing times (p ≤ .001) compared to AD (see Figure 7-4 and Table 7-1).

Although not significant under the conservative threshold, the DLB group took shorter steps (p = .019), and the PDD group were more variable for stance time (p = .017) compared to AD participants. Participants with PDD also took shorter steps (p = .039) with longer step (p = .014), stance (p = .014) and swing time (p = .022) compared to DLB.

Differences between Alzheimer's disease and dementia with Lewy bodies

When considered independently, the DLB group had shorter steps (p = .026; η^2 = .077) and less asymmetry for step length (p = .007; η^2 = .112) compared to AD (see Figure 7-4 and Table 7-1). Only step length asymmetry remained significant at p ≤ .01.

When controlling for age, sex and height, the DLB group demonstrated less step length asymmetry (p = .023; η^2 = .085) compared to AD. This was not considered significant when the more stringent statistical threshold was applied.

Gait impairments in 30-60 second walking bouts in dementia disease subtypes

Differences between disease subtypes and controls

When considering 30-60 second bouts, both the DLB and PDD groups took shorter steps ($p \leq .01$) compared to controls (see Figure 7-5 and Table 7-2). Participants with PDD were more variable for step, swing and stance time ($p \leq .01$ for all), had shorter step ($p \leq .01$), swing ($p = .025$) and stance times ($p \leq .01$) and greater asymmetry for step ($p \leq .05$), stance ($p \leq .05$) and swing time ($p \leq .01$) compared to controls.

When considering the threshold $p \leq .01$, people with DLB and PDD took shorter steps, and people with PDD had greater step, swing and stance time variability, longer stance time and greater swing time asymmetry compared to controls.

Differences between Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia

Participants with PDD were more variable for step, swing and stance time ($p \leq .01$ for all), had shorter stance times ($p \leq .01$) and greater asymmetry for swing time ($p \leq .01$) compared to the AD group (see Figure 7-5 and Table 7-2). They also took shorter steps ($p \leq .01$) compared to both AD and DLB groups, and had shorter swing times ($p = .005$) compared to AD participants. They were also more asymmetrical for swing time ($p = .005$) compared to participants with DLB. These results remained significant when applying a more conservative threshold.

Although not significant at $p \leq .01$, the PDD group had shorter step times ($p \leq .01$) and less asymmetry for step ($p \leq .05$) and stance time ($p \leq .05$) compared to AD and DLB groups. They were more variable for step ($p = .034$), stance ($p = .021$) and swing ($p = .033$) time, and had shorter stance ($p = .014$) and swing times ($p= .022$) compared to DLB participants.

Differences between Alzheimer's disease and dementia with Lewy bodies

When considered independently, participants with DLB were less asymmetric for step length ($p = .040$; $\eta^2 = .065$) compared to people with AD (see Figure 7-5 and Table 7-2). These results did not remain significant when a more stringent statistical threshold was applied, and no differences remained when controlling for age, sex and height.

Gait impairments in > 60 second walking bouts in dementia disease subtypes

Differences between disease subtypes and controls

In ≥ 60 second bouts, all disease subtypes demonstrated greater asymmetry for swing time compared to controls (see Figure 7-5 and Table 7-2). Both DLB and PDD groups had shorter steps ($p \leq .01$) compared to controls. Participants with PDD were more variable for step ($p \leq .001$), stance ($p \leq .001$) and swing time ($p \leq .001$) compared to controls.

Although not significant at $p \leq .01$, all disease subtypes were slower ($p \leq .05$) with greater step and stance asymmetry ($p \leq .05$) compared to controls. Participants with AD and DLB were more variable for step, stance and swing time and asymmetric for step length compared to controls ($p \leq .05$ for all). The AD group also took smaller steps ($p = .028$) compared to controls. The PDD group were more variable for step velocity ($p \leq .05$) compared to controls.

Differences between Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia

The PDD group were more variable for step velocity ($p \leq .05$) compared to DLB and AD groups. They also took shorter steps ($p = .045$) and were more variable for stance ($p = .027$) and swing time ($p = .020$) compared to AD participants. These differences were not significant at $p \leq .01$.

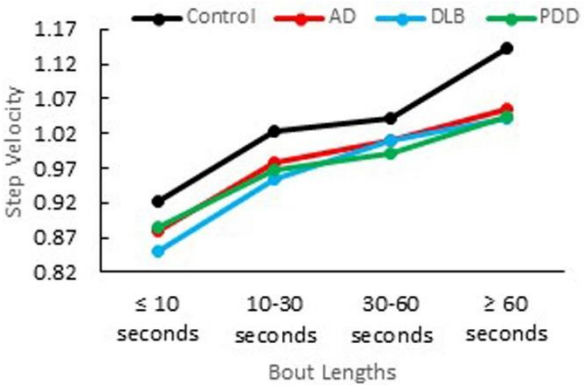
Differences between Alzheimer's disease and dementia with Lewy bodies

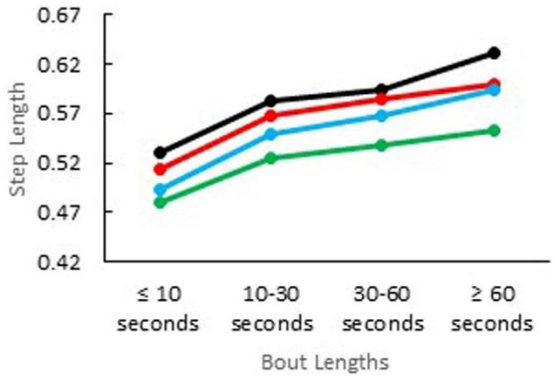
There were no differences between AD and LBD in walking bouts over 60 seconds.

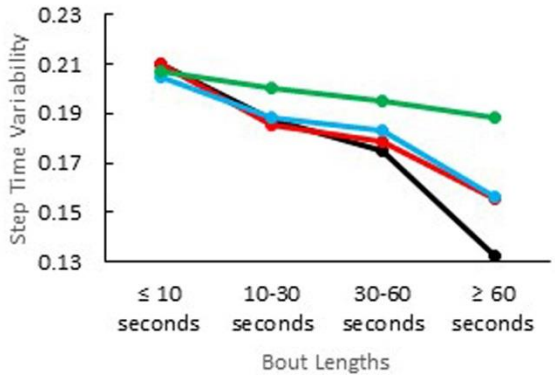
Summary of key findings

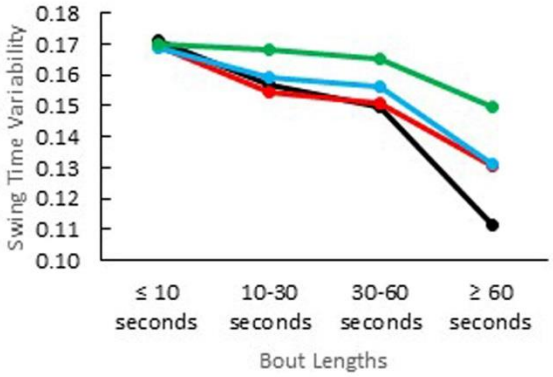
Across all bout lengths, gait impairments distinguished DLB and PDD from controls; however, only in >60 second bouts could AD be distinguished from controls. In all bouts lengths except >60 seconds, PDD could be distinguished from AD but could only be differentiated from DLB in 30-60 second bouts.

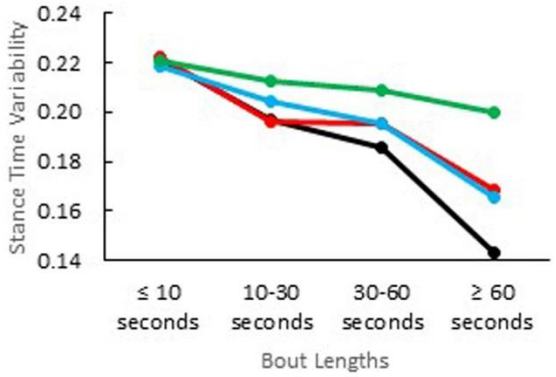
Importantly, AD and DLB could only be differentiated in under 10 second bouts as people with DLB took shorter steps and demonstrated less step length asymmetry (which remained when controlling for age, sex and height), and in 10-30 second bouts as the DLB group had less asymmetric step lengths (which did not remain when controlling for age sex and height).

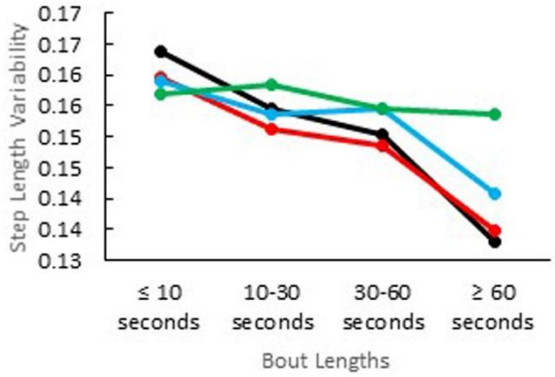

Control
AD
DLB
PDD
Step Velocity
1.17
1.12
1.07
1.02
0.97
0.92
0.87
0.82
≤ 10 seconds
10-30 seconds
30-60 seconds
≥ 60 seconds
Bout Lengths

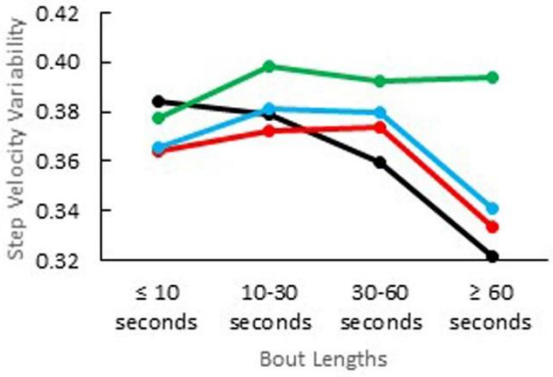

Step Length
0.67
0.62
0.57
0.52
0.47
0.42
≤ 10 seconds
10-30 seconds
30-60 seconds
≥ 60 seconds
Bout Lengths

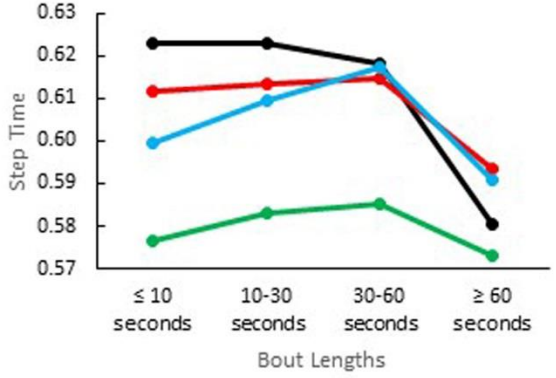

Step Time Variability
0.23
0.21
0.19
0.17
0.15
0.13
≤ 10 seconds
10-30 seconds
30-60 seconds
≥ 60 seconds
Bout Lengths

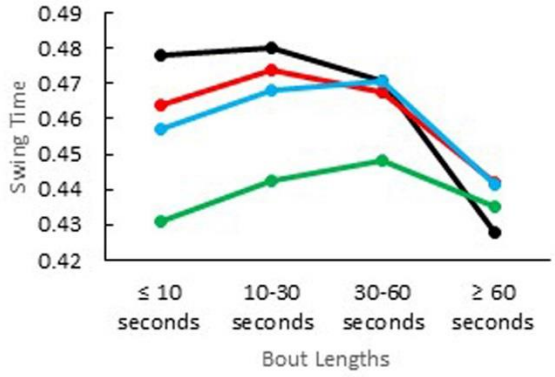

Swing Time Variability
0.18
0.17
0.16
0.15
0.14
0.13
0.12
0.11
0.10
≤ 10 seconds
10-30 seconds
30-60 seconds
≥ 60 seconds
Bout Lengths


Stance Time Variability
0.24
0.22
0.20
0.18
0.16
0.14
≤ 10 seconds
10-30 seconds
30-60 seconds
≥ 60 seconds
Bout Lengths


Step Length Variability
0.17
0.17
0.16
0.16
0.15
0.15
0.14
0.14
0.13
≤ 10 seconds
10-30 seconds
30-60 seconds
≥ 60 seconds
Bout Lengths


Step Velocity Variability
0.42
0.40
0.38
0.36
0.34
0.32
≤ 10 seconds
10-30 seconds
30-60 seconds
≥ 60 seconds
Bout Lengths


Step Time
0.63
0.62
0.61
0.60
0.59
0.58
0.57
≤ 10 seconds
10-30 seconds
30-60 seconds
≥ 60 seconds
Bout Lengths


Swing Time
0.49
0.48
0.47
0.46
0.45
0.44
0.43
0.42
≤ 10 seconds
10-30 seconds
30-60 seconds
≥ 60 seconds
Bout Lengths

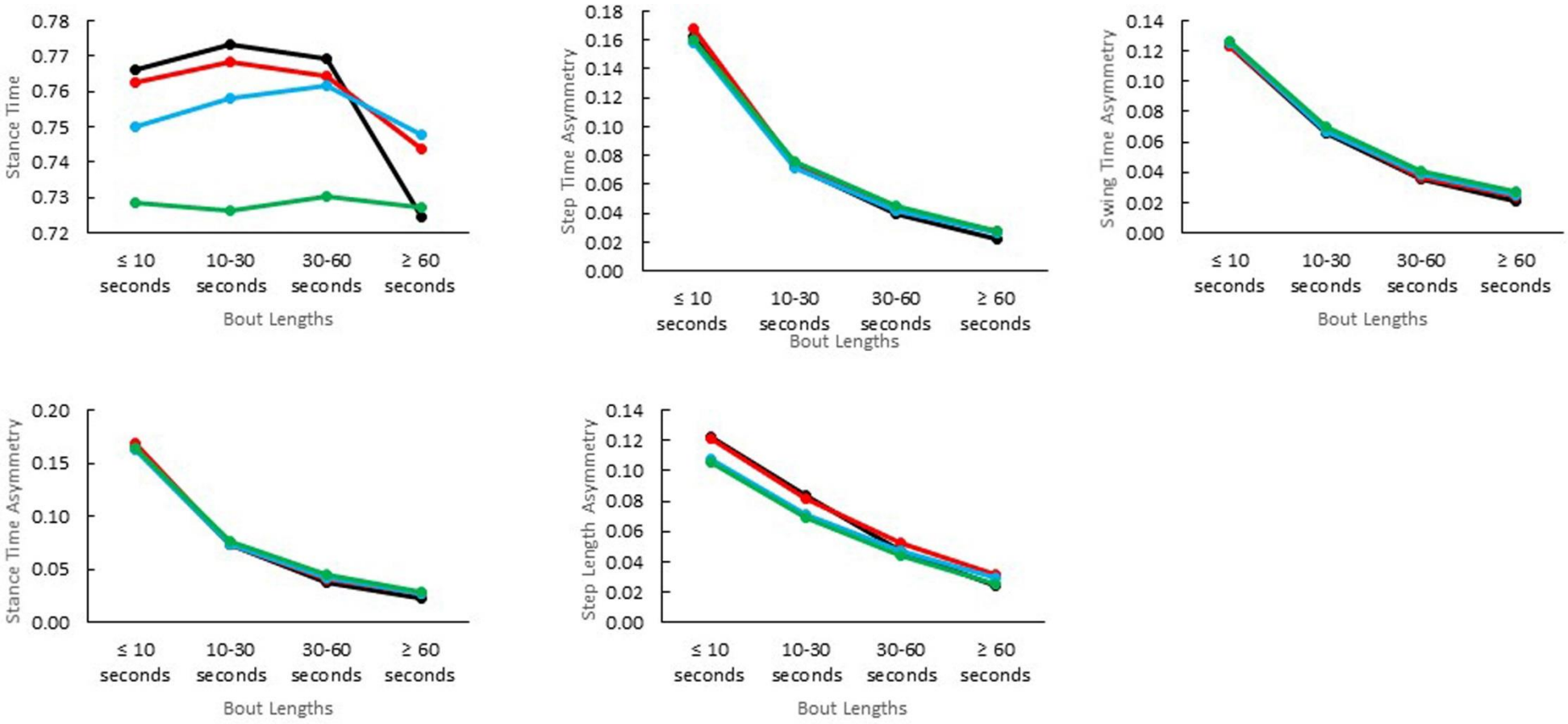


Figure 7-3 Comparison of micro gait characteristics across different bout lengths in controls, Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia groups

Each data point reflects a median value. Black lines = controls, red = Alzheimer's disease, blue = dementia with Lewy bodies, green = Parkinson's disease dementia

Table 7-1 Comparison of micro gait characteristics between controls, Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia under very short and short bout lengths

	< 10 Second bouts						10-30 Second bouts					
	Controls	**AD**	**DLB**	**PDD**	**F**	**(p)**	**Controls**	**AD**	**DLB**	**PDD**	**F**	**(p)**
Pace												
Step Velocity (m/s)	.91 ± .05	.89 ± .09	.86 ± .08	.87 ± .07	2.2	.096	1.01 ± .06	.98 ± .09	.96 ± .09	.96 ± .08	2.5	.060
Step Length (m)	.53 ± .02^{D,P}	.52 ± .03^{D,P}	.49 ± .03^{C,A}	.48 ± .04^{C,A}	11.8	**≤.001**	.58 ± .03^{D,P}	.56 ± .04^{P}	.54 ± .04^{C}	.52 ± .04^{C,A}	12.5	**≤.001**
Swing SD (s)	.169 ± .012	.169 ± .013	.170 ± .012	.168 ± .011	0.03	.991	.155 ± .014	.156 ± .015	.160 ± .015	.166 ± .016	2.4	.074
Step Time SD (s)	.205 ± .014	.207 ± .015	.205 ± .013	.207 ± .015	0.2	.918	.182 ± .016	.185 ± .016	.189 ± .017	.199 ± .022	3.4	.022
Stance SD (s)	.218 ± .014	.221 ± .015	.220 ± .014	.224 ± .017	0.5	.712	.197 (.15-.22)	.196 (.16 - .23)	.204 (.16 - .25)	.213 (.17 - .26)	8.3	.040
Variability (SD)												
Step Velocity SD (m/s)	.383 ± .027	.377 ± .043	.371 ± .044	.369 ± .034	0.6	.601	.377 ± .032	.372 ± .039	.379 ± .044	.385 ± .036	0.5	.691
Step Length SD (m)	.163 ± .007	.158 ± .009	.156 ± .009	.156 ± .008	3.6	.017	.152 ± .009	.151 ± .009	.154 ± .008	.157 ± .006	1.9	.131
Rhythm												
Step Time (ms)	.617 ± .022^{P}	.615 ± .029^{P}	.600 ± .026	.582 ± .030^{C,A}	7.9	**≤.001**	.619 ± .027^{P}	.619 ± .029^{P}	.608 ± .032	.584 ± .036^{C,A}	5.7	**≤.001**
Swing (ms)	.473 ± .023^{P}	.472 ± .028^{P}	.459 ± .024	.440 ± .020^{C,A}	7.6	**≤.001**	.474 ± .028^{P}	.477 ± .31^{P}	.466 ± .030	.445 ± .025^{C,A}	4.9	**.003**
Stance (ms)	.765 ± .024^{P}	.764 ± .029^{P}	.748 ± .031	.727 ± 038^{C,A}	7.2	**≤.001**	.767 ± .028^{P}	.767 ± .029^{P}	.755 ± .037	.729 ± .046^{C,A}	5.3	**.002**
Asymmetry												
Step Time Asy (ms)	.161 ± .013	.169 ± .021	.160 ± .013	.164 ± .019	1.9	.140	.071 ± .008	.075 ± .012	.072 ± .009	.080 ± .011	6.4	.096
Swing Asy (ms)	.122 ± .011	.127 ± .018	.122 ± .011	.126 ± .013	1	.417	.066 ± .008	.070 ± .011	.067 ± .009	.072 ± .009	2.1	.107
Stance Asy (ms)	.164 ± .012	.171 ± .019	.162 ± .014	.165 ± .017	1.8	.148	.073 ± .008	.076 ± .012	.073 ± .009	.079 ± .010	1.9	.134
Postural Control												
Step Length Asy (m)	.121 ± .010^{D,P}	.122 ± .015^{D,P}	.109 ± .014^{C,A}	.108 ± .017^{C,A}	7.1	**≤.001**	.081 ± .008^{D,P}	.081 ± .013^{D,P}	.073 ± .012^{C,A}	.072 ± .013^{C,A}	5.8	**≤.001**

Significant values refer to differences between groups. Data displayed as (mean ± standard deviation) was analysed using independent t-tests. Data displayed as (median (minimum-maximum)) was analysed using Mann Whitney U tests. SD = variability, asy = asymmetry

Table 7-2 Comparison of micro gait characteristics between controls, Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia under medium and sustained bout lengths

	30-60 Second bouts						> 60 Second bouts					
	Controls	**AD**	**DLB**	**PDD**	**F**	**(p)**	**Controls**	**AD**	**DLB**	**PDD**	**F**	**(p)**
Pace												
Step Velocity (m/s)	1.05 ± .06	1.02 ± .08	1.00 ± .10	.98 ± .08	2.4	.070	1.16 ± .11	1.07 ± .13	1.05 ± .13	1.07 ± 1.4	3.8	.013
Step Length (m)	.60 ± .06^{D,P}	.58 ± .04^{P}	.56 ± .04$^{C.P}$	.53 ± .05^{C,A,D}	10.1	**≤.001**	.63 ± .06$^{D.P}$	.60 ± .06	.60 ± .06^{C}	.56 ± .06^{C}	5	**.003**
Swing SD (s)	.148 ± .011^{P}	.152 ± .015^{P}	.156 ± .018	.166 ± .021 ^{C,A}	4.8	**.004**	.114 ± .018^{P}	126 ± .024	.130 ± .025	.142 ± .028^{C}	15.4	**≤.001**
Step Time SD (s)	.174 ± .013^{P}	.179 ± .019^{P}	.184 ± .021	.197 ± .026^{C,A}	4.7	**.004**	.132 (.10 - .19)^{P}	.156 (.09 - .20)	.156 (.08 - .21)	.189 (.09 - .21)^{C}	13.2	**.004**
Stance SD (s)	.185 ± .013^{P}	.190 ± .021^{P}	.195 ± .022	.197 ± .026^{C,A}	5.4	**.002**	.143 (.10 - .19)^{P}	.168 (.09 - .21)	.166 (.08 - .22)	.200 (.10 - .22)^{C}	14.2	**.003**
Variability (SD)												
Step Velocity SD (m/s)	.365 ± .031	.365 ± .036	.373 ± .043	.388 ± .036	1.7	.169	.318 ± .054	.322 ± .060	.334 ± .059	.374 ± .055	3.5	.018
Step Length SD (m)	.150 ± .011	.147 ± .012	.151 ± .010	.155 ± .006	2.1	.108	.133 ± .028	.133 ± .024	.139 ± .020	.147 ± .019	1.7	.177
Rhythm												
Step Time (ms)	.615 ± .026	.616 ± .024	.611 ± .038	.585 ± .039	3.9	.011	.581 (.45 - .62)	.594 (.52 - .65)	.591 (.50 - .68)	.573 (.46 - .63)	6	.110
Swing (ms)	.467 ± .0253	.470 ± .024^{P}	.466 ± .035	.446 ± .026^{A}	2.9	.040	.428 (.32 - .47)	.442 (.38 - .49)	.442 (.36 - .53)	.435 (.33 - .46)	6.2	.105
Stance (ms)	.764 ± .029^{P}	.764 ± .026	.759 ± .043	.731 ± .051^{C}	3.5	.018	.724 (.58 - .78)	.744 (.66 - .81)	.748 (.64 - .85)	.727 (59 - .79)	5.1	.166
Asymmetry												
Step Time Asy (ms)	.039 (.03-.05)	.042 (.03 - .06)	.042 (.03 - .05)	.045 (.04 - .07)	10.7	.013	.023 ±.6	.027 ± .006	.027 ± .007	.029 ± .006	3.9	.012
Swing Asy (ms)	.036 ± .005^{P}	.038 ± .006^{P}	.038 ± .006^{P}	.044 ± .008^{C,A,D}	6.2	**≤.001**	.021 ± .005^{A,D,P}	.025 ± .006^{C}	.025 ± .006^{C}	.027 ± .006^{C}	4.4	**.006**
Stance Asy (ms)	.035 ± .005	.041 (.03 - .06)	.043 (.03 - .06)	.045 (.04 - .07)	11	.012	.023 ± .005	.027 ± .006	.027 ± .007	.029 ± .007	3.9	.011
Postural Control												
Step Length Asy (m)	.048 ± .006	.51 ± .010	.046 ± .009	.048 ± .016	1.4	.260	.025 (.02-.05)	.031 (.02 - .09)	.030 (.02 - .-06)	.025 (.02 - .07)	8.2	.042

Significant values refer to differences between groups. Data displayed as (mean ± standard deviation) was analysed using independent t-tests. Data displayed as (median (minimum-maximum)) was analysed using Mann Whitney U tests. SD = variability, asy = asymmetry

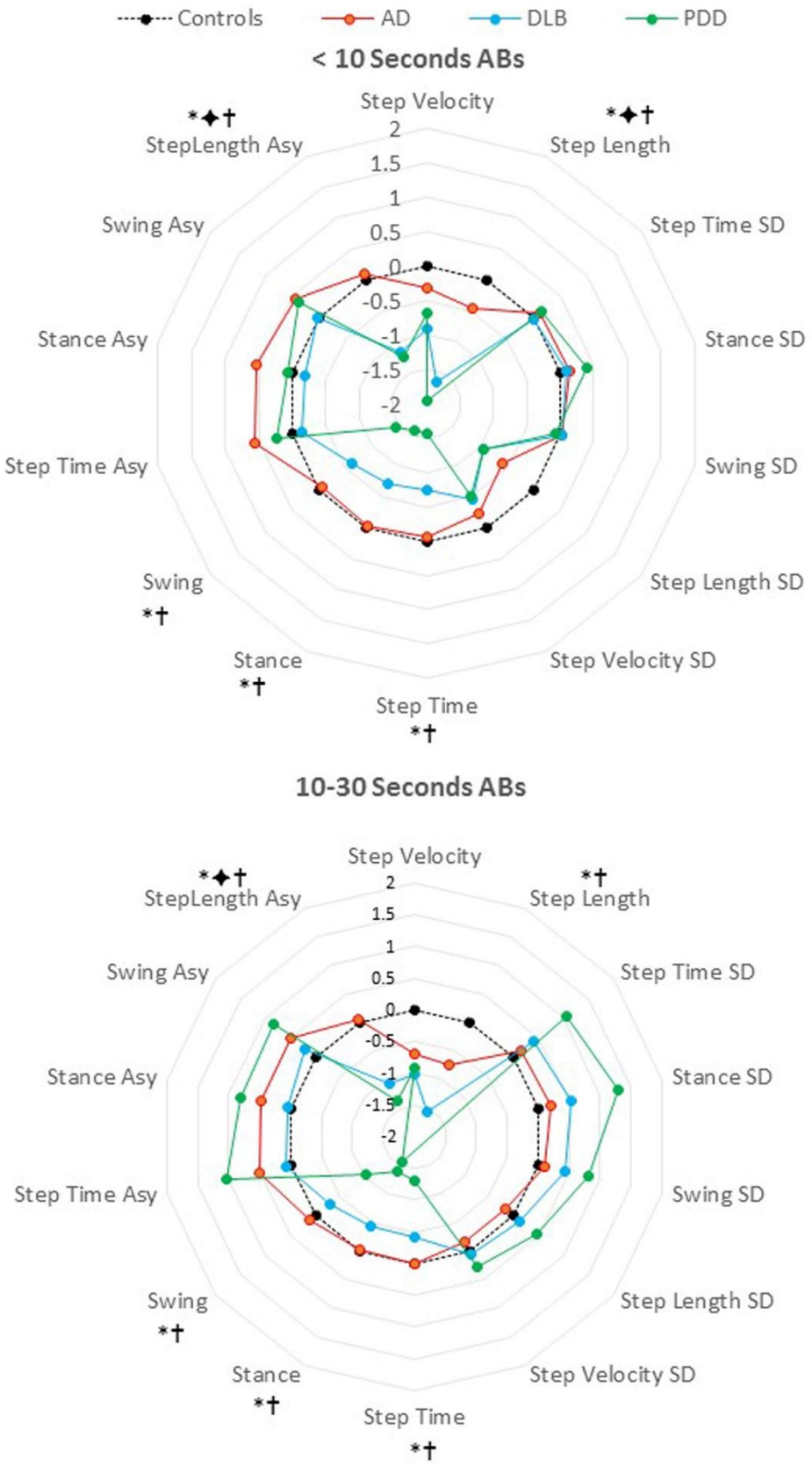


Figure 7-4 Radar plots illustrating patterns of impairment across 14 gait characteristics in controls and disease dementia groups during very short and short walking bouts.

*The central black line represents control data, and the lines representing AD, DLB and PDD demonstrate how many standard deviations from zero (z scores based on control means and standard deviations). Transformed data used from non-normally distributed variables previously described. * = differences between controls and disease subtypes, † = differences between AD and PDD, ✦ = differences between AD and DLB*

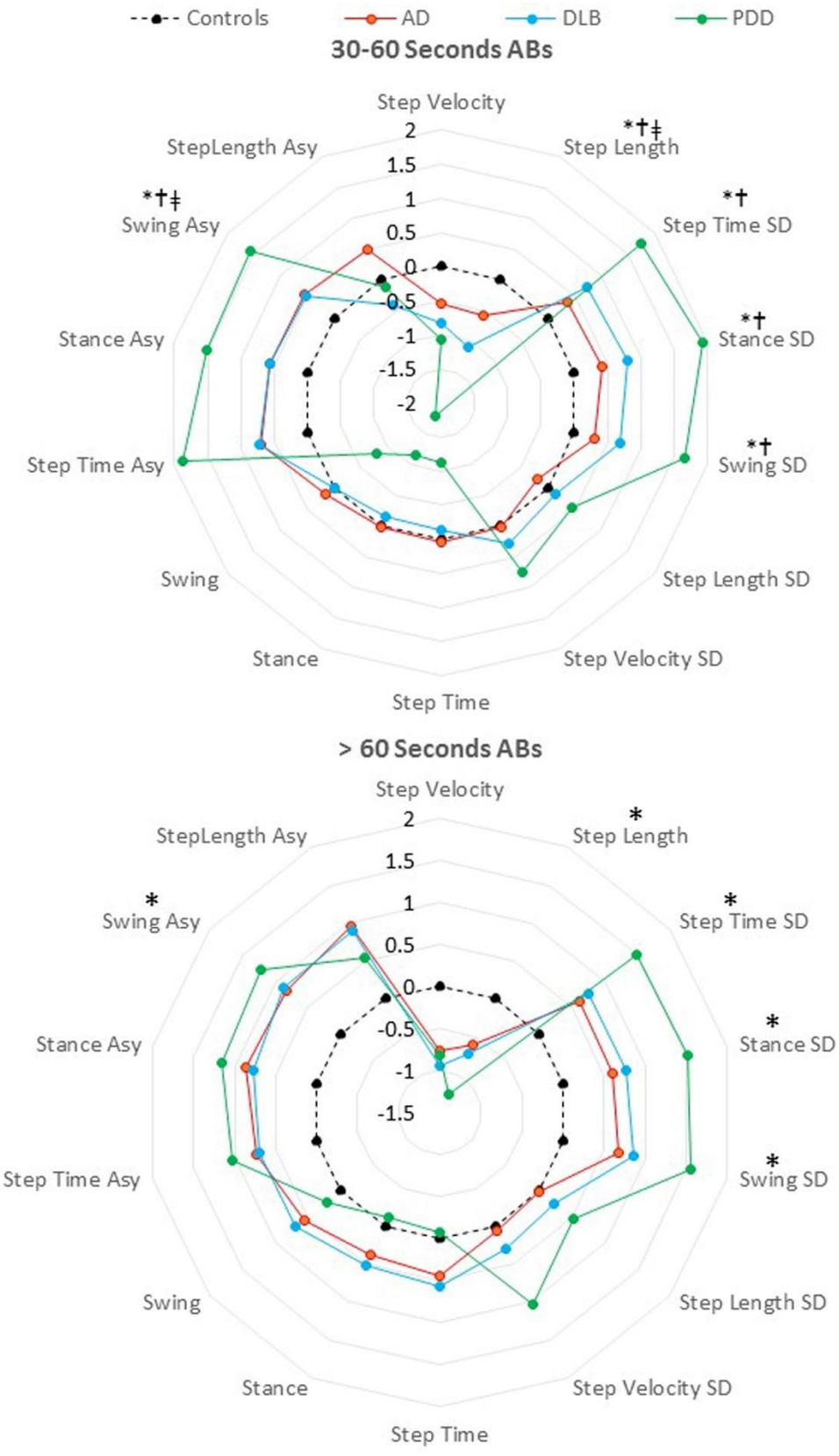


Figure 7-5 Radar plots illustrating patterns of impairment across 14 gait characteristics in controls and disease dementia groups during medium and sustained walking bouts

*The central black line represents control data, and the lines representing AD, DLB and PDD demonstrate how many standard deviations from zero (z scores based on control means and standard deviations). Transformed data used from non-normally distributed variables previously described. * = differences between controls and disease subtypes, † = differences between AD and PDD, ǂ = differences between DLB and PDD*

7.4.2 Associations between cognitive impairment, motor disease severity and gait impairment across different bout lengths

In line with Chapter 5, associations between motor disease severity, cognitive function and all fourteen gait characteristics were considered as this is a novel exploratory analysis. Motor disease severity was measured using the UPDRS-III. The following cognitive measures were considered: sMMSE and ACE-III for global cognition, ACE-III memory subscale, ACE-III visuospatial subscale, TMT A measuring information processing, FAS test as a measure of verbal fluency, considered an executive function, and the Simple RT test as a measure of attention.

Associations in <10 second bouts in disease subtypes

Alzheimer's disease

In < 10 second bouts, greater step time variability (rho = .348, p = .044) was moderately associated with greater motor disease (see Appendix L).

Dementia with Lewy bodies

In under 10 second bouts, greater step (rho = .404, p = .030), stance (rho = .375, p = .045) and swing time variability (rho = .482, p = .008), shorter step (rho = .423, p = .022), stance (rho = .463, p = .022) and swing times (.437, p = .018), and less swing time (rho = .372, p = .047) and step length asymmetry (rho = .406, p = .029) are moderately associated with greater motor disease severity (see Appendix M).

Shorter steps (rho = .400, p = .029) and shorter step (rho = .382, p = .037) and stance times (rho = .395, p = .031) are moderately associated with poorer global cognition. Shorter stance times (rho = .470, p = .032) are also moderately associated with slower information processing. Less swing time asymmetry is moderately associated with greater visuospatial impairment (rho = .400, p = .032) and slower information processing (rho = .487, p = .025).

Parkinson's disease dementia

In under 10 second bouts, shorter steps (rho = .761, p ≤ .001), shorter step (rho = .629, p = .012) and stance times (rho = .604, p = .017) and less stance (rho = .518, p = .048) and step length asymmetry (rho = .736, p = .002) were moderate-strongly associated with greater motor disease severity (see Appendix N).

Shorter steps were strongly associated with impaired visuospatial abilities (rho = .688, p = .005), global cognition (rho = .612, p = .015) and attention (rho = .532, p = .041). Less swing

time variability (rho = 573, p = .026) was strongly associated with greater visuospatial impairment.

Quicker step times were associated with greater impairments in visuospatial abilities (rho = .560, = .030), global cognition (rho = .609, p = .016), verbal fluency (rho = .553, p = .032) and attention (rho = .536, p = .040). Shorter stance times were also associated with greater impairments in visuospatial abilities (rho = .647, p = .009), global cognition (rho = .589, p = .021), verbal fluency (rho = .593, p = .020) and slower information processing (rho = .514, p = .050). Shorter swing times were associated with greater impairments in global cognition (sMMSE: rho = 526, p = .036; ACE-III: rho = .610, p = .016). and verbal fluency (rho = .571, p = .026).

Less step length asymmetry was also associated greater impairments in global cognition (rho = .519, p = .047) and attention (rho = .571, p = .026).

Associations in 10-30 second bouts in disease subtypes

Alzheimer's disease

In 10-30 second bouts, greater swing time variability (rho = .346, p = .045), step (rho = .355, p = 036) and stance time (rho = .384, p = .023) were moderately associated with greater motor disease severity (see Appendix L). Greater stance time variability (rho = .346, p = .045) was associated with less impairment of global cognition.

Dementia with Lewy bodies

In 10-30 second bouts, less step length asymmetry (rho = .407, p = .028) was moderately associated with greater motor disease severity (see Appendix M). Shorter step length (rho = .499, p = .005) was moderately associated with greater impairments in global cognition.

Parkinson's disease dementia

In 10-30 second bouts, shorter steps were strongly associated with greater motor disease severity (rho = .636, p = .011) and greater impairments in visuospatial abilities (rho = .710, p = .003) and global cognition (rho = .594, p = .019; see Appendix N).

Quicker step time was strongly associated with greater impairments in global cognition (rho = .548, p = .035). and attention (rho = .614, = .015). Shorter stance times were strongly associated with greater impairment in visuospatial skills (rho = .595, p = .019), information processing (rho = .514, p = .050), and verbal fluency (rho = .525, p = .045). Shorter swing times (rho = .529, p = .043) were strongly associated with greater attention impairment.

Associations in 30-60 second bouts in disease subtypes

Alzheimer's disease

In 30-60 second bouts, shorter steps (rho = .347, p = .044), greater variability for step (rho = .397, p = .020), stance (rho = .391, p = .022) and swing time (rho = .420, p = .013), and step length (rho = .361, p = .036), and greater asymmetry for stance (rho = .382, p = .026) and swing time (rho = .487, p = .003) were moderately associated with greater motor disease severity (see Appendix L).

Dementia with Lewy bodies

In 30-60 seconds, less step length asymmetry (rho = .610, $p \leq .001$) was strongly associated with greater motor disease severity (see Appendix M). Shorter steps were moderately associated with greater global cognition (rho = .487, p = .006) and slower information processing (rho = .574, p = .007).

Parkinson's disease dementia

In 30-60 second bouts, shorter steps were strongly associated with greater motor disease severity (rho = .693, p = .004) and impairments in visuospatial functions (rho = .658, p = .008) and global cognition (sMMSE: rho = .509, p = .044; ACE-III: rho = .713, p = .005; see Appendix N).

Shorter step (rho = .636, p = .011), stance (rho = .582, p = .023) and swing time (rho = .668, p = .007) were strongly associated with greater attentional impairment. Shorter stance time was also strongly associated with greater visuospatial impairments (rho = .580, p = .023) and slower information processing (rho = .550, p = .034).

Less swing (rho = .525, p = .044) and stance asymmetry (rho = .595, p = .019) were strongly associated with greater attentional impairment.

Associations in >60 second bouts in disease subtypes

Alzheimer's disease

In > 60 second bouts, slower step velocity (rho = .494, p = .003), shorter steps (rho = .409, p = .016), longer step (rho = .369, p = .032), stance (rho = .357, p = .038) and swing times (rho = .387, p = .024), and greater step (rho = .367, p = .033), stance (rho = .495, p = .003) and swing time asymmetry (rho = .361, p = .036) were moderately associated with greater motor disease severity (see Appendix L).

Dementia with Lewy bodies

In > 60 second bouts, there were no significant associations between gait and motor disease severity or cognition (see Appendix M).

Parkinson's disease dementia

In > 60 seconds, shorter steps (rho = .604, p = .017), shorter step (rho = .632, p = .011) and stance time (rho = .614, p = .015) and less swing (rho = .525, p = .044) and step length asymmetry (rho = .518, p = .048) were strongly associated with greater motor disease severity (see Appendix N).

Slower step velocity was strongly associated with greater visuospatial impairment (rho = .561, p = .037) and slower information processing (.565, p = .035). Shorter steps were strongly associated with greater impairments in global cognition (rho = .666, p = .009), visuospatial function (rho = .648, p = .012) and verbal fluency (rho = .718, p = .004) and slower information processing (rho = .670, p = .009).

Greater step time variability (rho = .552, p = .041) was strongly associated with slower information processing. Greater step velocity variability (rho = .607, p = .016) was strongly associated with greater global cognitive impairment.

Quicker step and stance times were strongly associated with greater impairments in global cognition (step: rho = .655, p = .011; stance: rho = .677, p = .008) and attention (step: rho = .644, p = .013; stance: rho = .609, p = .021). Shorter stance time was also strongly associated with verbal fluency impairment (rho = .584, p = .028) and shorter swing time (rho = .591, p = .026) with impaired attention.

Less stance asymmetry (rho = .552, p = .041) was strongly associated with greater attentional impairment.

Summary of key findings

Across all walking bouts, the AD group predominately demonstrated associations between gait impairments and greater motor disease severity.

In very short walking bouts, the DLB group demonstrated many moderate associations between gait impairments and greater motor disease severity, while also showing some associations between gait and global cognition, information processing and visuospatial function. In short and medium bout lengths, only less step length asymmetry was associated with greater motor disease severity, while shorter step length was associated with greater global cognitive impairment and slower information processing. Interestingly, there were no

associations between gait impairments, motor disease severity and cognitive impairments in sustained walking bouts.

Across all walking bouts, the PDD group demonstrated strong associations with shorter steps and quicker timing characteristics of gait and greater motor disease severity, visuospatial, attentional, information processing and global cognitive impairment. In very short and medium bouts, less asymmetry was associated with greater attentional impairment, while in very short and sustained walking bouts, less asymmetry was associated with greater motor disease severity.

7.5 Discussion

The aim of this chapter was to consider free-living micro gait characteristics within the context in which they were performed, using bout length as a proxy measure. Key findings demonstrate that AD and DLB can only be differentiated in very short walking bouts, while gait impairments in people with PDD are most prominent in medium bout lengths. This suggests that patterns of gait impairment change depending on context and should be considered when interpreting free-living gait data. Findings also suggest that gait impairments may be more prominent in PDD compared to other disease subtypes due to their significant motor disease severity coupled with cognitive impairment; these associations are demonstrated across all bout lengths and may reflect a loss in the ability to adapt gait performance to the context in which walking occurs.

7.5.1 Considering patterns of gait impairment across disease subtypes within context

Although no significant differences in free-living gait were found between AD and DLB in Chapter 5, this in-depth exploration revealed that people with DLB take significantly shorter steps and have less asymmetric step lengths in very short walking bouts (<10 seconds), with medium effect sizes. This is an important finding, as AD and DLB subtypes are often misdiagnosed (Toledo *et al.*, 2013; Kane *et al.*, 2018), and this leads to incorrect care, treatment and disease management. Interestingly, significant differences were not apparent across longer walking bouts, as illustrated in Figure 7-3, demonstrating that patterns of gait impairment depend on bout length as suggested by Hypothesis 7.1. This may be due to the context in which very short bouts take place. These are likely to involve negotiation of constrained environments (e.g. house settings with furniture to move around) and turning behaviours (Orendurff *et al.*, 2008; Zampieri *et al.*, 2011). Walking past objects and turning behaviours are associated with slower gait speeds, which may require shortening step length. As people with PD are reported to take more steps per turn compared to healthy older adults

(El-Gohary *et al.*, 2013; Mancini *et al.*, 2018), it is plausible that this is similar in DLB – although this has yet to be investigated. Therefore, it could be speculated that shorter and less asymmetric step lengths in very short walking bouts may be reflecting impaired turning behaviour in people with DLB. As of yet, there are no studies comparing turning behaviours in people with DLB and AD; this was not feasible within the current study as the accelerometers used were not equipped with gyroscopes. Future research should consider this a possible avenue for discriminating these two disease subtypes.

Similar to the results of Chapter 5, people with PDD demonstrated prominent gait impairments in free-living conditions across all bout lengths. Interestingly, they were most distinguishable in medium bout lengths, the only bout length in which they could be discriminated from DLB, somewhat agreeing with Hypothesis 7.2. Results have demonstrated that gait characteristics pertaining to step length, variability and timing are not significantly different in medium bout lengths (30-60 seconds) compared to other bout lengths in people with PDD, unlike all other groups (see Figure 7-3). This may suggest that they are unable to adapt their gait to the context in which they are walking (Maidan *et al.*, 2017). Del Din *et al.* (2016b) suggested that medium bouts may represent walking in constrained community environments such as shopping centres, while sustained bouts (>60 seconds) may involve walking outdoors. Both environments require modulation and maintenance of gait characteristics and gradual turning on curved paths (Orendurff *et al.*, 2008); therefore requiring the ability to adapt one's gait.

Although demonstrated people with PDD could not be distinguished from other disease subtypes in sustained walking bouts, trends indicate their gait is more impaired, and this lack of findings may be due to people with PDD taking significantly less walking bouts over 60 seconds, as demonstrated in Chapter 6. Additionally, sustained walking bouts were the most useful for distinguishing cognitive impairment from normal ageing, as they differentiated all disease subtypes from controls, but were the least useful for distinguishing disease subtypes. This suggests examining gait in sustained walking bouts may be useful as a marker for neurodegeneration but may lack specificity when considering discrete pathologies.

7.5.2 What can the role of cognition tell us about gait impairments within context?

The results of this chapter have suggested that different disease subtypes may employ different motor-cognition strategies in the facilitation of gait, reflecting the findings of Chapter 4 and Chapter 5. In line with Hypothesis 7.4, gait impairments in AD are predominately associated with motor disease severity, while both DLB and PDD demonstrate

associations with motor disease and cognitive functions mediated by the prefrontal cortex. The associations between motor disease severity, cognitive impairment and gait impairment appear to depend on bout length, agreeing Hypothesis 7.3. Key points to note here are that in the AD group, the only cognitive-gait association was found in short walking bouts (10-30 seconds), while longer bouts (>30 seconds) demonstrated a great number of moderate associations between motor disease severity and gait impairments. Inversely, in the DLB group, a range of cognition-gait and motor disease-gait associations were found in very short walking bouts, while gait was predominately associated with cognition for short and medium bout lengths. This suggests that cognition and motor function play differing roles in the facilitation of gait between AD and DLB, and as such, it would have been expected that these groups would demonstrate more significant differences in gait impairment. It is possible that small sample sizes and participants with mixed pathology makes these differences undetectable. Future research should strive to recruit large samples, use validated biomarkers to increase confidence in differential diagnosis and follow participants up to post-mortem when possible. Given that this was not within the scope of this thesis, we cannot be wholly certain of our diagnostic groups and thus any distinguishing gait characteristics found should be considered as promising.

Across all bout lengths, the PDD group demonstrate associations with motor disease and gait characteristics; however, it must be noted that they have numerous strong associations between step length and timing characteristics of gait and cognitive measures related to the prefrontal cortex. Weiss *et al.* (2015a) previously reported associations between frequency-based gait metrics and attention and executive functions; the current study has expanded on these findings by demonstrating that cognitive function is strongly associated with gait impairments across very short to sustained bouts of walking. As the PDD group do not adapt their timing and variability of gait according to bout length, perhaps impaired modulation of gait is due to the breakdown in communication between the basal ganglia and cognitive networks, such as the prefrontal cortex and the pre-supplementary motor area, which mediates internally-generated movements (MacDonald and Halliday, 2002; Leek and Johnston, 2009). This may cause increased reliance on the prefrontal cognitive networks to carry out a previously automatic task (Shine *et al.*, 2013); however, these networks are impaired in PDD and may contribute to inability modulate gait according to context. In order to explore this hypothesis further, future research should establish the types of contexts (e.g. inside the home or in the outside community) in which different bout lengths are predominately undertaken, and also examine how disease progression in PD affects ability to modulate characteristics of

gait across bout lengths, with respect to cognitive decline and degeneration of the basal ganglia.

7.5.3 Conclusions

The data presented in this chapter is the first to compare micro gait characteristics across different free-living bout lengths in AD, DLB and PDD disease subtypes. Key findings demonstrate that AD and DLB can only be differentiated in very short walking bouts, while gait impairment is prominent in PDD across all bout lengths. Additionally, people with PDD may be unable to adapt their gait performance to the context in which they are walking. This may be due to their increased reliance on cognitive resources to mediate gait in complex environments. Further research is required to truly underpin the clinical utility of free-living gait assessment to differentiate AD and DLB groups, such as following participants up post-mortem to enhance diagnostic certainty.

Chapter 8 Thesis overview and conclusions

The key aim of this thesis was to explore the potential for gait analysis to discriminate cognitive impairment from normal ageing, and differentiate dementia disease subtypes, with a focus on distinguishing AD and DLB. These subtypes can be difficult to diagnose due to similar clinical presentations, and this has implications for care, disease management and treatment. Therefore, it is important to develop clinical tools to aid differential diagnosis. Biomarkers such as DAT scans have demonstrated abilities to discriminate these subtypes. However, such methods are costly and may not be feasible to employ on a wide scale. As such, an inexpensive diagnostic tool to aid clinicians' decisions during the diagnostic process may prove useful. This study therefore considered the potential of gait analysis to support differential diagnosis by first establishing discriminatory patterns of gait impairment between mild dementia disease subtypes in traditional laboratory settings, and expanding on this with inexpensive wearable technology in free-living conditions.

A structured review reported in Chapter 2 aimed to synthesize information surrounding quantitatively assessed gait differences between dementia disease subtypes (AD, LBD and VaD) and normal ageing, and identify gait characteristics that differentiate disease subtypes. All disease subtypes demonstrated gait impairments compared to controls, particularly in pace, variability and rhythm gait characteristics. People with LBD walked slower with impaired timing and greater variability compared to AD; however, only two studies compared these two common subtypes, demonstrating a significant gap in the literature. Furthermore, a lack of standardisation in methods of measuring and reporting gait characteristics was notable. Therefore, although the findings were limited, the potential to employ gait analysis in the discrimination of disease subtypes was evident and worthy of further pursuit.

Chapter 4 explored the use of gait assessment in traditional laboratory conditions to distinguish dementia disease from normal ageing, and differentiate disease subtypes. Without exception, all disease subtypes were slower, with shorter steps and greater variability compared to controls. Importantly, people with LBD were demonstrably different to AD as they walked with significantly greater step time and length variability and more asymmetric step, stance and swing time. Interestingly, gait impairments in LBD were explained by both motor disease and executive dysfunction, while only motor disease severity appeared to be a significant explanatory variable for AD. This suggests different disease pathologies lead to different cognitive-motor strategies to control gait, based on the stage of disease that affects the prefrontal networks in each subtype. From this work, gait analysis does appear a useful

method to discriminate disease subtypes, and different signatures of gait impairment may reflect different underlying pathological processes in AD and LBD.

Chapter 5 extended the examination of gait in dementia disease subtypes to free-living conditions. Whilst gait assessment in laboratory conditions assesses an individual's functional capacity, free-living gait assessment measures their habitual function – providing a more ecologically valid picture of their gait. All disease subtypes walked with slower, shorter steps compared to controls. However, gait impairments were most prominent in LBD subtypes as they were more variable in their gait, and people with PDD were more asymmetric. Importantly, free-living gait assessment could only differentiate PDD from other disease subtypes; they were more variable than AD, and more asymmetric than both AD and DLB. Gait impairments in AD were predominately associated with greater motor disease severity, while in PDD, cognitive functions mediated by the prefrontal cortex were strongly associated with impaired gait characteristics. Although free-living gait analysis did not appear useful for discriminating AD and DLB, which was the key aim of this thesis, previous research in PD has demonstrated that the context of gait performance, represented by bout length, influence patterns of gait impairment.

Chapter 6 considered gait in terms of the bigger pictures and explored habitual walking behaviours, providing a broader perspective of function. People with LBD walk less, take less steps per day and shorter less variable walking bouts compared to controls. These findings were most pronounced in PDD as they also demonstrated significant differences with the AD group. Importantly, results demonstrated that people with PDD were unable to sustain longer walking bouts. As such, the exaggeration of gait impairment in PDD in free-living conditions may be due to their greater inactivity, and less time spent in longer walking bouts – in which people generally walk faster, with less variability and asymmetry. Therefore, it is important to consider patterns of gait impairment by bout length as an uneven distribution of bout lengths within the overall data may disguise group differences. Additional findings from this chapter demonstrate that habitual walking inactivity in controls and people with cognitive impairment are explained by different variables, and motor disease severity and impairments in activities of daily living appear to most strongly affect all disease subtypes' quantity of walking.

Chapter 7 described patterns of gait impairment within different walking bout lengths. Importantly, in < 10 second bout lengths people with DLB have significantly shorter steps and less step length asymmetry compared to AD; as such this may be a useful bout length in which to discriminate these subtypes. In line with results from Chapter 5, gait was prominently impaired in PDD across all bout lengths, but appeared most discriminatory in

medium bouts. Once again, the associations between motor disease severity, cognitive impairment and gait suggest that different disease subtypes are using different cognitive-motor strategies to mediate and modulate gait, and shows that people with PDD may be most reliant on cognitive input during gait, which may be compensatory for their dysfunctional motor networks. As cognitive decline is progressing with the disease, the coupling of motor and cognitive impairments may be enhancing their gait impairments when they are required to navigate complex environments involving spatial navigation, object recognition and information processing.

Overall, this study has demonstrated the ability for gait analysis to discriminate mild AD and LBD groups in laboratory conditions and shows promise for free-living gait assessment to aid discrimination of AD and DLB in an inexpensive and unobtrusive manner. It has also provided further evidence for the relationship between gait and cognition, showing agreement with the suggestion that gait is mediated through higher-order cognitive functions associated with the prefrontal networks. Therefore, this study has provided an exploratory look at signatures of gait impairment in different dementia disease subtypes, evidence for the use of body-worn monitors to assess micro and macro gait characteristics in free-living environments, and differential gait-cognition associations dependent on disease subtype. Further research in larger disease cohorts with validated biomarkers and follow-up to post mortem are required to test the sensitivity and specificity of these findings.

8.1 Clinical implications

Early stages of cognitive impairment can be difficult to distinguish from normal ageing, affecting abilities to make an early diagnosis (Kenigsberg *et al.*, 2016). As reported in this thesis, participants with MCI had recognisable gait impairments that mirrored those with established dementia. This supports the use of gait analysis as an early clinical biomarker. Establishing clinical biomarkers for identification of cognitive disorders is not only clinically useful, it allows researchers to gain better insight into the disease process in its early stages, by increasing our knowledge of prodromal dementia and potentially providing novel targets for drug therapy. Timely diagnosis also allows people with dementia and their families to understand the diagnosis, plan ahead, and facilitate appropriate care and management (Kenigsberg *et al.*, 2016). Clinical biomarkers are most beneficial in prodromal or early dementia cases as there are likely to be fewer co-morbidities, leading to higher correlations between clinical disease features and neuropathological changes (Bayer, 2018).

Differential diagnosis is also important for ensuring provision of correct treatments. As previously discussed, accurate diagnosis is vital to identify and manage concurrent symptoms such as cognitive fluctuations and falls in DLB, for consideration of expectations of prognosis and for prescribing appropriate medication as certain subtypes such as DLB have high sensitivity to anti-psychotic medications leading to adverse outcomes (Pink *et al.*, 2018). Clinical biomarkers are needed to enhance recruitment into disease-specific clinical trials (Bayer, 2018). They can also act as surrogate markers for intervention efficacy; for example, anti-dementia drug studies in AD have demonstrated decreases in stride time variability in the intervention groups compared to control groups (Beauchet *et al.*, 2015b). Although biomarkers such as imaging, blood and cerebrospinal fluid markers have been highlighted as useful and incorporated into diagnostic criteria (McKhann *et al.*, 2011; McKeith, 2017), gait analysis may prove useful in the first step of the screening process as it is easily implemented and interpretable and with advancing technology, becoming increasingly cost-effective.

There is also growing interest in the use of wearable technology for improving personalised care, and monitoring disease progression and intervention efficacy (Weiss *et al.*, 2011; Pavel *et al.*, 2013; Del Din *et al.*, 2016b; Espay *et al.*, 2016; Arneric *et al.*, 2017; Samus *et al.*, 2018; Teipel *et al.*, 2018). This thesis has demonstrated the feasibility of continuously monitoring micro and macro gait characteristics in different disease subtypes, and using them to provide a comprehensive picture of an individual's habitual gait function. Wearable technology provides an inexpensive method to monitor individual behaviours and clinically relevant characteristics. It could therefore be a complementary clinical tool for diagnosis, disease predication and care management. Provision of body-worn monitors in annual clinical assessments could track changes in habitual walking behaviours and gait over time that may warrant further investigation. The ability of body-worn monitors to continuously monitor data over prolonged periods of time allows us to examine under-served areas and move beyond the need for well-controlled environments to assess models of "best-practice" (Samus *et al.*, 2018). This reduces observer bias and the inclusion of highly selective and homogenous groups in research – for example, it allows inclusion of populations that may be too functionally impaired to participate in a study requiring many strenuous motor assessments or are at higher risk of recall bias when using subjective outcomes.

8.2 Strengths, limitations and recommendations for future research

This was the largest study to investigate gait impairments in AD and LBD, almost doubling the sample size reported in Fritz et al., (2016). It used both an instrumented walkway (GaitRite) and body-worn monitors (Axivity) to measure gait, both of which have shown high

test-retest reliability in people with dementia (Wittwer *et al.*, 2008; Mc Ardle *et al.*, 2018). Additionally, it investigated sixteen quantitative gait characteristics using a model of gait as a framework, allowing results to be compared to previous research in PD (Galna *et al.*, 2015; Del Din *et al.*, 2016a; Del Din *et al.*, 2017; Morris *et al.*, 2017). This study did not consider composite measures of gait domains as considering discrete gait characteristics allows easier interpretation of results for clinical purposes, allows a comprehensive examination of gait patterns across disease subtypes and identifies key gait characteristics to investigate in future diagnosis. Disease diagnosis used relevant diagnostic criteria, and required consensus of three clinicians, making this a well-characterised cohort.

However, lack of diagnostic certainty is still considered a limitation for this study. Dementia disease subtypes can only be diagnosed as probable or possible in living people; final diagnosis is made at post-mortem. Clinical raters were not blind to the clinical diagnosis each participant had – this may have biased the subsequent consensus diagnosis. As this study is cross-sectional only, it is beyond our scope and time limitations to follow-up our participants post mortem. Additionally, no imaging or recognised biomarkers were taken as part of this study; individuals' diagnosis was based on clinical information and consensus between three clinicians. Biomarkers and imagining where therefore only considered if taken clinically or in other research studies – collecting this information was beyond the scope of the GaitDem study. Therefore, certainty in clinical diagnosis is limited – particularly due to cross-pathology between AD and DLB. This study also failed to recruit a useful number of participants with VaD. This is due to the rarity of true VaD cases without mobility issues, and should be noted when considering future research into VaD and gait impairment. The current study was a pilot and underpowered based on a power calculation prior to the study. Larger disease cohorts, characterised through recognised biomarkers and followed up at autopsy may provide clearer results and consider explanatory variables of gait impairment. However, it should still be noted that despite small sample sizes, group differences were found and gait characteristics demonstrated the potential for discriminating between different disease groups. Further analysis of the sensitivity and specificity of gait characteristics would further emphasis the diagnostic potential for discrete gait characteristics to differentiate between dementia disease subtypes; this is a key aim of future work in this area.

In this study, we also looked at groups with a spectrum of cognitive impairment. This was to allow for greater recruitment of participants within a small catchment area, and often the MCI and mild dementia cases were barely distinguishable for cognitive scores or impairments in ADLs. However, this approach still has limitations as MCI has high reversion rates and not all

participants may progress to dementia(Ferman *et al.*, 2013b; Kaduszkiewicz *et al.*, 2014). Additionally, the concept of disease-specific MCI criteria and diagnosis is only emerging. Previously, MCI was considered either amnestic or non-amnestic. There is now a movement to define people with MCI by their Lewy body disease symptoms, based on the diagnostic criteria for dementia with Lewy bodies (McKeith *et al.*, 2017), along with biomarkers such as positive DAT scans (Thomas *et al.*, 2019). The criteria has shown good face validity for the diagnosis of MCI due to LBD (Donaghy and McKeith, 2014b); however, it has not yet been validated using pathological findings post-mortem – this is an area of ongoing investigation. Future studies can address this issue through longitudinal follow-up assessments – this may give insight to gait's utility at predicting progression from MCI to dementia.

Throughout this thesis, a battery of clinical cognitive assessments were used to explore the relationship between discrete gait characteristics and specific cognitive functions. However, cognitive tests inherently utilise multiple cognitive functions, limiting our interpretation of which cognitive functions are associated with gait. This multi-domain approach may be heightened in clinical assessments, as they are designed to gain an insight of cognitive impairment in a timely manner. The cognitive functions considered clinically relevant may not fully encompass the cognitive functions that may mediate gait. For example, this assessment battery did not include any way-finding or spatial navigation measures (e.g. Sea Hero Quest (Coutrot *et al.*, 2018); functions that may arguably play an important role in free-living gait. Future research should consider broadening the scope of cognitive assessments when exploring the gait-cognition relationship in order to provide a more detailed understanding of these two interacting processes. Furthermore, as demonstrated in Appendix G, not all participants were able or willing to complete the cognitive battery. Task difficulty and disease stage should be considered when choosing which cognitive assessments to use in future research.

The use of wearable technology clinically is limited by the lack of gold standard for data collection, processing, extraction and interpretation (Teipel *et al.*, 2018). Datasets are large, complex and heterogeneous making interpretation of findings difficult without contextual information. Current techniques allow broad measures of activity but emerging research had demonstrated novel metrics of habitual activities, such as variability and alpha described here (Lord *et al.*, 2013c; Schwenk *et al.*, 2014; Del Din *et al.*, 2016a; Del Din *et al.*, 2016b; Mc Ardle *et al.*, 2018), smart-home based metrics such as time out of home, sleep restlessness, and total night-time activity (Skubic *et al.*, 2009; Kaye *et al.*, 2011) and fine-grained assessment of clinically useful measurements such as spatiotemporal gait characteristics

(Weiss *et al.*, 2013; Weiss *et al.*, 2014; van Schooten *et al.*, 2015; Weiss *et al.*, 2015a; Weiss *et al.*, 2015b; Brodie *et al.*, 2016; Del Din *et al.*, 2016a; Del Din *et al.*, 2016b; Del Din *et al.*, 2016c; Del Din *et al.*, 2017; Mancini *et al.*, 2018; Mc Ardle *et al.*, 2018). Future research should consider establishing a useful combination of such metrics for differentiation of disease subtypes, while maintaining the view to keep assessment inexpensive and unobtrusive.

8.3 Conclusions

This thesis provides an initial exploration to determine the ability of gait analysis to differentiate cognitive impairment from normal ageing, and differentiate disease subtypes. It used a comprehensive approach for measuring both gait and cognitive variables, and diagnostic consensus when signposting participants to disease groups. It is evident that gait can discriminate dementia disease subtypes in traditional gait laboratory settings, and provides promising results for the use of free-living gait assessment to aid the diagnostic process. The key conclusions of this thesis are:

1. A structured review demonstrated limited evidence of the ability to discriminate disease subtypes using gait analysis and highlighted a gap in the research.
2. Even in very mild stages of disease, dementia affects gait and walking behaviours compared to normal ageing, and this is evident in both laboratory and free-living settings.
3. In laboratory conditions, DLB and PDD demonstrate similar patterns of gait impairment, but can be distinguished in free-living environments.
4. In laboratory conditions, LBD can be discriminated from AD by a unique signature of gait impairments, with greater step time and length variability, and greater step, swing and stance time asymmetry.
5. It is feasible to use wearable technology to collect free-living gait data in different disease subtypes, including people with DLB, which has not previously been shown.
6. In free-living conditions, gait is prominently impaired in PDD, and only very short bout lengths are useful for distinguishing DLB and AD.
7. The relationship between gait and cognition appears strongest in PDD, while gait impairments are explained by greater motor disease severity in AD. These findings appear relevant in both laboratory and free-living conditions and suggesting different disease subtypes use unique motor-cognitive strategies to control gait due to differences in progression of disease pathology, which affects motor and cognitive function.

Chapter 9 Appendices

Appendix A: Quality assessment of all studies included in the review in Chapter 2, as conducted by reviewers R.M.A and J.W.

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 outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?**	**Were clinical diagnostic criteria and severity ratings for dementia reported and adhered to?**	**Were key potential confounding variables measured and adjusted statistically for their impact on the outcome(s)?**	**Quality Assessment: Reviewer 1 (R.M.A.)**	**Quality Assessment: Reviewer 2 (J.W.)**
Visser [1]	Yes	No	Yes	No	No	No	No	No	Poor (2/8)	Poor (2/8)
Tanaka, et al. [2]	Yes	Yes	n/a	No	No	No	R.M.A Yes J.W. No	No	Poor (3/8)	Poor (2/8)
Nakamura, et al. [3]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Mediocre (6/8)	Mediocre (6/8)
Nakamura, et al. [4]	Yes	Yes	n/a	Yes	No	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)
Goldman, et al. [5]	Yes	Yes	No	Yes	No	Yes	R.M.A No J.W. Yes	Yes	Mediocre (5/8)	Mediocre (6/8)
Goldman, et al. [6]	No	Yes	R.M.A Yes J.W. No	Yes	No	Yes	No	Yes	Mediocre (5/8)	Mediocre (4/8)
Webster, et al. [7]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Mediocre (6/8)	Mediocre (6/8)
Merory, et al. [8]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Mediocre (6/8)	Mediocre (6/8)
Gillain, et al. [9]	Yes	Yes	n/a	Yes	Yes	Yes	Yes	No	Mediocre (6/8)	Mediocre (6/8)
Nadkarni, et al. [10]	Yes	Yes	n/a	Yes	No	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)
Nadkarni, et al. [11]	Yes	Yes	n/a	Yes	No	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)

Ries, et al. [12]	Yes	Yes	Yes	Yes	No	Yes	R.M.A. No J.W. Yes	No	Mediocre (5/8)	Mediocre (6/8)
Maquet, et al. [13]	Yes	Yes	n/a	Yes	No	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)
Choi, et al. [14]	Yes	No	n/a	No	No	Yes	No	No	Poor (2/8)	Poor (2/8)
Lamoth, et al. [15]	Yes	Yes	n/a	Yes	No	Yes	Yes	No	Mediocre (5/8)	Mediocre (5/8)
Coelho, et al. [16]	Yes	No	R.M.A. Yes J.W. No	R.M.A. No J.W. Yes	No	Yes	Yes	No	Mediocre (4/8)	Mediocre (4/8)
Muir, et al. [17]	Yes	Yes	n/a	Yes	No	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)
Nadkarni, et al. [18]	Yes	Yes	n/a	Yes	No	No	Yes	Yes	Mediocre (5/8)	Mediocre (5/8)
Suttanon, et al. [19]	Yes	Yes	n/a	Yes	R.M.A. No J.W. Yes	Yes	No	Yes	Mediocre (5/8)	Mediocre (6/8)
Hsu, et al. [20]	No	Yes	n/a	Yes	No	Yes	No	No	Poor (3/8)	Poor (3/8)
Barbieri, et al. [21]	Yes	No	R.M.A. Yes J.W. n/a	No	No	Yes	No	Yes	Mediocre (4/8)	Poor (3/8)
Gras, et al. [22]	Yes	No	n/a	No	No	Yes	No	Yes	Poor (3/8)	Poor (3/8)
Simieli, et al. [23]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)
Allali, et al. [24]	Yes	Yes	Yes	Yes	No	No	No	Yes	Mediocre (4/8)	Mediocre (5/8)
Fritz, et al. [25]	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)
Lin, et al. [26]	Yes	Yes	n/a	No	No	Yes	No	Yes	Mediocre (4/8)	Mediocre (4/8)
									Total: 0 Good 21 Mediocre 5 Poor	Total: 0 Good 20 Mediocre 6 Poor

Appendix B Differences between controls and cognitively impaired groups for laboratory-based gait characteristics

As shown in Appendix Table 1, ten of the sixteen gait characteristics measured were significantly different between controls and cognitively impaired groups. In order to use parametric tests, transformations were applied to non-normally distributed variables – swing, step time, stance, step velocity, step length and step width variability and stance were logarithmic transformed, while square root transformation was used on step, swing and stance time and step length asymmetry.

Both MCI and dementia groups walked more slowly with a shorter step length, greater stance and step time, more variable gait and a wider step width ($p \leq .01$ for all; see Figure 4-2). There were no statistically significant differences between MCI and dementia groups. To further investigate differences in gait impairment across the spectrum of cognitive impairment, the overall cognitively impaired group were split based on their MMSE scores into a mild cognitively impaired (n=39), mild dementia (n=40) and moderate dementia groups (n=9). There were no statistically significant differences between groups for any of the gait outcomes investigated ($p \geq .05$ for all). As this study recruited a very mild dementia group and there were also few demographic and clinical differences between groups, MCI and dementia groups were combined into one group (see Appendix Table 1). Appendix Table 2 also demonstrates the differences between MCI and dementia groups in each subtype.

Appendix Table 1 Comparison of gait characteristics across controls and cognitively impaired groups

					Statistically significant differences between controls and cognitively impaired groups									
					Unadjusted Model		Controlling for age, sex and height		Controlling for age, sex, height and ACE-III		Controlling for age, sex, height and UPDRS-III		Controlling for age, sex, height, ACE-III and UPDRS-III	
	Control	MCI	Dementia	Cognitive impairment	F	(p)	F	(p)	F	(p)	F	(p)	F	(p)
Pace														
Step Velocity (m/s)	1.26 ± .19	1.01±.25	.96±.23	.99±.24	31.3	**≤.001**	25.3	**≤.001**	16.5	**≤.001**	9.3	**.003**	6.2	.014
Step Length (m)	.70 ±.09	.57±.12	.55±.11	.56±.12	23.2	**≤.001**	23.9	**≤.001**	15.3	**≤.001**	7.4	**.008**	4.7	.033
Swing SD (ms)^{ln}	14 ± 4	24±10	27±14	25±12	43.2	**≤.001**	30.6	**≤.001**	9.3	**.003**	7.6	**.007**	8.7	**.004**
Step Time SD (ms)^{ln}	15 ± 4	26±11	30±15	28±13	41.9	**≤.001**	31.4	**≤.001**	5.6	.017	6.2	.014	5.1	.026
Stance SD (ms)^{ln}	19 ± 6	33±15	38±21	35±17	41.1	**≤.001**	33.1	**≤.001**	4	.047	5.9	.017	3.8	.053
Variability (SD)														
Step Velocity SD (m/s)^{ln}	.06 ± .02	.07±.02	.08±.03	.07±.02	19.9	**≤.001**	16.1	**≤.001**	2.2	.145	5.4	.022	.4	.509
Step Length SD (m)^{ln}	.022 ± .006	.033±.010	.035±.011	.034±.010	47	**≤.001**	34.9	**≤.001**	13.4	**≤.001**	11.7	**≤.001**	9.1	**.003**
Step Width SD (m)^{ln}	.021±.005	.024±.007	.023±.007	.023±.007	1.5	.219	.7	.422	2.8	.100	2.5	.118	5.9	.017
Rhythm														
Step Time (ms)	536 ±48	567±66	580±61	575±65	8.9	**.003**	7.8	**.006**	5.6	.020	4.2	.042	3.1	.080
Swing (ms)	391±32	386±49	394±41	392±46	0	.945	0	.855	0	.937	.4	.541	.5	.478
Stance (ms)^{ln}	682 ± 67	748±101	766±94	759±99	16.2	**≤.001**	13.3	**≤.001**	8.5	**.004**	5.7	.018	4.2	.042
Asymmetry														
Step Time Asy (ms)^{sqrt}	12±11	17±14	16±11	16±13	4.3	.040	2.6	.112	1.8	.179	0	.841	.5	.479
Swing Asy (ms)^{sqrt}	9±7	14±11	12±9	12±10	3	.088	.7	.401	1.9	.168	1	.330	.9	.337
Stance Asy (ms)^{sqrt}	8 ±7	14±12	12±10	13±11	3.1	.080	.8	.385	1.8	.181	1.5	.222	1.2	.274
Postural Control														
Step Length Asy (m)^{sqrt}	.020±.014	.025±.025	.024±.020	.024±.022	.6	.461	0.7	.789	.1	.816	2	.163	.6	.444
Step Width (m)	.081± .023	.108±.025	.101±.031	.103±.026	14.8	**≤.001**	10.6	**≤.001**	11.4	**≤.001**	9	**.003**	10.0	**.002**

Data displayed as (mean ± standard deviation). Significant values refer to differences between controls and cognitively impaired group. SD= variability, asy = asymmetry, ln = logarithmic transformed, sqrt = square root transformed. Values described for transformed variables refer to original untransformed values.

Appendix Table 2: Comparison of lab-based gait characteristics across mild cognitive impairment and dementia in each subgroup, and between DLB and PDD groups

	AD-MCI	AD	p	DLB-MCI	DLB	p
	15	21		12	18	
Pace						
Step Velocity (m/s)	1.12±.24	.98±.23	.074	.98±.24	.98±24	.645
Step Length (m)	.61±.13	.55±.10	.135	.58±.10	.56±.12	.645
Swing SD (ms)^{ln}	18(9-33)	21(10-45)	.101	25(11-49)	23(13-42)	.841
Step Time SD (ms)^{ln}	19(9-38)	24 (14-48)	.111	30(13-55)	24(15-80)	.604
Stance SD (ms)^{ln}	26(12-49)	31(15-69)	.104	34(16-76)	32(18-118)	.492
Variability (SD)						
Step Velocity SD (m/s)^{ln}	.061(.03-.11)	.066(.05-.10)	.391	.076(.05-.15)	.074(.05-.14)	.253
Step Length SD (m)^{ln}	.029(.01-.04)	.030(.02-.04)	.252	.034(.02-.08)	.034(.02-.06)	.535
Step Width SD (m)^{ln}	.021(.01-.04)	.022(.02-.03)	.774	.022(.01-.04)	.021(.01-.04)	.071
Rhythm						
Step Time (ms)	549±57	577±55	.145	597±59	580±77	.814
Swing (ms)	387±45	393±52	.665	412±42	391±56	.962
Stance (ms)^{ln}	682(615-883)	763(632-905)	.095	787(599-923)	725(626-981)	.768
Asymmetry						
Step Time Asy (ms)^{sqrt}	9(.66-34)	13(.44-30)	.710	13(2-46)	18(6-49)	.963
Swing Asy (ms)^{sqrt}	6(.50-28)	7(.34-31)	.597	14(7-38)	11(3-29)	.057
Stance Asy (ms)^{sqrt}	9(.20-28)	8(.33-33)	.474	15(.43-36)	11(.13-32)	.209
Postural Control						
Step Length Asy (m)^{sqrt}	.02(0-.13)	.01(0-.10)	.192	.015(0-.07)	.020(0-.06)	.919
Step Width (m)	.108±.024	.093±.031	.127	.105±.030	.107±.021	.831
	PD-MCI	PDD	p	Combined DLB	Combined PDD	p
n	8	7		30	45	
Pace						
Step Velocity (m/s)	.83±.21	.98±.27	.270	.98 ± .23	.90 ± .24	.312
Step Length (m)	.48±.11	.54±.13	.336	.57 ± .11	.51 ± .12	.147
Swing SD (ms)^{ln}	27(12-52)	29(11-87)	.922	23 (11-49)	29 (11-87)	.263
Step Time SD (ms)^{ln}	33(15-60)	31(13-60)	.926	26 (13-80)	32 (13-60)	.324
Stance SD (ms)^{ln}	41(20-76)	35(14-59)	.661	34 (16-118)	37 (14-76)	.761
Variability (SD)						
Step Velocity SD (m/s)^{ln}	.066(.06-.10)	.070(.05-.14)	.855	.074 (.05-.15)	.068 (.05-.14)	.625
Step Length SD (m)^{ln}	.035(.02-.06)	.035(.02-.05)	.985	.034 (.02-.08)	.035 (.02-.06)	.856
Step Width SD (m)^{ln}	.023(.01-.04)	.022(.02-.05)	.137	.022 (.01-.04)	.022 (.01-.05)	.403
Rhythm						
Step Time (ms)	589±93	564±43	.525	587 ± 70	577 ± 73	.677
Swing (ms)	370±67	391±34	.461	400 ± 51	380 ± 53	.231
Stance (ms)^{ln}	813(627-1029)	733(638-850)	.276	779 (599-981)	777 (627-1029)	.962
Asymmetry						
Step Time Asy (ms)^{sqrt}	15(6-65)	7(2-52)	.484	17 (2-49)	15 (2-65)	.867
Swing Asy (ms)^{sqrt}	16(2-44)	11(.57-28)	.334	14 (3-38)	12 (.57-44)	.999

Stance Asy (ms)^{sqrt}	16(6-47)	9(1-28)	.182	14 (.13-36)	12 (1-47)	.531
Postural Control						
Step Length Asy (m)^{sqrt}	.007(0-.06)	.024(.01-.05)	.137	.02 (0-.07)	.021 (0-.06)	.865
Step Width (m)	.112±.02	.094±.020	.147	.106 ± .025	.103 ± .024	.710

Appendix C Missing clinical and cognitive data relevant to Chapter 4

Clinical/Cognitive tests	% complete	Missing data per group	Reasons for incompletion
sMMSE	100%		
ACE-III (including subscales)	98%	LBD (n = 2)	Wasn't included in protocol (n = 1) Hospitalised before study completion (n = 1)
TMT A	90%	AD (n = 1) LBD (n = 10)	Wasn't included in protocol (n = 9) Hospitalised before study completion (n=1) Refused to do (n=1)
FAS	96%	AD (n = 1) LBD (n = 3)	Wasn't included in protocol (n = 1) Hospitalised before study completion (n=1) Refused to do (n=2)
Simple RT	93%	AD (n = 1) LBD (n = 6)	Wasn't included in protocol (n = 4) Hospitalised before study completion (n=1) Refused to do (n=2)
Angles Test	93%	AD (n = 1) LBD (n=6)	Wasn't included in protocol (n = 4) Hospitalised before study completion (n=1) Refused to do (n=2)
Stroop Test	87%	AD (n =2) LBD (n = 12)	Wasn't included in protocol (n = 9) Hospitalised before study completion (n=1) Refused to do (n=1) Could not do (n = 3)
CDR	100%		
Faller status	96%	Controls (n = 3) AD (n = 1)	Wasn't included in protocol (n = 3) Refused to do (n = 1)
CIRS-G	98%	LBD (n = 2)	Wasn't included in protocol (n = 2)
UPDRS-III	96%	Controls (n = 3) AD (n = 1) LBD (n =1)	Wasn't included in protocol (n = 4) Refused to do (n = 1)
BMI	99%	Control (n=1)	Assessment not complete (n=1)
ABC	99%	LBD (n=1)	Time constraint (n =1)
GDS	98%	LBD (n=2)	Wasn't included in protocol (n = 1) Hospitalised before study completion (n = 1)
BADLS	86%	Controls (n = 6) AD (n=3) LBD (n = 6)	Wasn't included in protocol (n = 6) No informant (n = 9)
NART	98%	AD (n = 1) LBD (n =1)	Refused to do (n = 1) Hospitalised before study completion (n = 1)

**MMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time, CDR – Clinical dementia rating scale, CIRS-G = Cumulative Illness Rating Scale – Geriatric, UPDRS-III = Unified Parkinson's disease rating scale –III, BMI = Body mass index, ABC = Activities Balance Confidence Scale, GDS = Geriatric Depression Scale, ESS = Epworth Sleepiness Scale, BADLS = Bristol Activities of daily living scale, NART = national adult reading test, AD = Alzheimer's disease, LBD = Lewy body disease*

Appendix D Univariate regressions investigating explanatory variables for laboratory-based gait impairment in Alzheimer's disease

Step Velocity	β	SE	t	p	F	R	R^2	Adjusted R^2	95% CI Lower Bound	95% CI Upper Bound
Age	-.008	.006	-1.2	.229	1.5	.205	.042	.014	-.020	.005
Sex (male)	-.004	.082	-0.1	.958	.003	.009	.000	-.029	-.170	.162
Height (m)	-.234	.386	-0.6	.550	.4	.103	.011	-.018	-1.019	.552
UPDRS-III	.019	.000	-2.8	**.009**	7.8	.436	.190	.166	-.031	-.005
MMSE	-.001	.010	-0.1	.910	.01	.019	.000	-.029	-.022	.020
ACE-III VS	.007	.014	0.5	.640	.2	.081	.006	-.023	-.022	.036
TMT A (secs)	-.001	.001	-0.8	.417	.7	.142	.020	-.010	-.002	.001
FAS	.003	.003	1.0	.317	1.0	.174	.030	.001	-.003	.008
RT Simple (ms)	-9E-05	.000	-0.3	.787	.07	.047	.002	-.028	-.001	.001

Step Length (m)	β	SE	t	p	F	R	R^2	Adjusted R^2	95% CI Lower Bound	95% CI Upper Bound
Age	-.006	.003	-2.0	**.051**	4.1	.327	.107	.081	-.012	.000
Sex (male)	.036	.038	0.9	.352	.9	0.16	0.026	-0.003	-.041	.113
Height (m)	.136	.182	0.7	**.461**	.6	.127	.016	-.013	-.234	.506
UPDRS-III	-.007	.003	-2.3	**.029**	5.2	.369	.136	.110	-.013	-.001
MMSE	.002	.005	0.5	.644	.2	.080	.006	-.023	-.008	.012
ACE-III VS	.007	.007	1.0	.337	1.0	.165	.027	-.001	-.007	.020
TMT A (secs)	.000	.000	-0.5	**.587**	.3	.095	.009	-.021	-.001	.000
FAS	.000	.001	0.4	**.724**	.1	.062	.004	-.026	-.002	.003
RT Simple (ms)	3E-05	.000	0.2	**.818**		.040	.002	-.029	.000	.000

Step Time SD	β	SE	t	p	F	R	R^2	Adjusted R^2	95% CI Lower Bound	95% CI Upper Bound
Age	.077	.230	0.3	.740	.1	.057	.003	-.026	-.390	.543
Sex (male)	.103	2.944	0.0	.972	.001	.006	.000	-.029	-5.881	6.087
Height (m)	11.486	13.872	0.8	.413	.7	.141	.020	-.009	-16.706	39.678
UPDRS-III	.630	.230	2.7	**.010**	7.5	.430	.185	.160	.162	1.098
MMSE	-.240	.372	-0.6	.523	.4	.110	.012	-.017	-.996	.516
ACE-III VS	-.583	.508	-1.1	**.259**	1.3	.193	.037	.009	-1.615	.449
TMT A (secs)	.019	.025	0.7	**.465**	.6	.128	.016	-.014	-.033	.070
FAS	-.025	.100	-0.3	**.803**	.06	.044	.002	-.028	-.228	.178
RT Simple (ms)	.003	.011	0.3	**.788**	.07	-.020	.026	-.028	-.020	.026

Stance Time SD	β	SE	t	p	F	R	R^2	Adjusted R^2	95% CI Lower Bound	95% CI Upper Bound
Age	.232	.322	0.7	.476	.5	.123	.015	-.014	-.422	.886
Sex (male)	.051	4.153	0.0	.990	.000	.002	.000	-.029	-8.390	8.492
Height (m)	12.837	19.641	0.7	.518	.4	.111	.012	-.017	-27.078	52.752
UPDRS-III	.987	.317	3.1	**.004**	9.7	.477	.228	.204	.343	1.631
MMSE	-.702	.514	-1.4	**.181**	1.9	.228	.052	.024	-1.746	.342
ACE-III VS	-.939	.712	-1.3	**.196**	1.7	.220	.049	.021	-2.386	.509
TMT A (secs)	.047	.035	1.3	**.190**	1.8	.227	.052	.023	-.024	.118
FAS	-.123	.139	-0.9	**.382**	.8	.152	.023	-.006	-.406	.160

RT Simple (ms)	.009	.016	0.5	.591	.3	.094	.009	-.021	-.024	.041
Step Velocity SD	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Age	.000	.001	-0.4	.717	.1	.063	.004	-.025	-.001	.001
Sex (male)	-.009	.006	-1.4	.160	2.1	.239	.057	.029	-.022	.004
Height (m)	-.035	.030	-1.2	.250	1.4	.197	.039	.010	-.097	.026
UPDRS-III	.000	.001	0.7	.484	.5	0.122	0.015	-0.015	-.001	.002
MMSE	-.002	.001	-2.5	**.016**	6.5	.400	.160	.135	-.003	.000
ACE-III VS	-.002	.001	-1.7	**.100**	2.9	.278	.077	.050	-.004	.000
TMT A (secs)	4E-05	.000	0.8	.455	.6	.130	.017	-.013	.000	.000
FAS	0E+00	.000	1.3	.197	1.7	.223	.050	.021	.000	.001
RT Simple (ms)	1E-05	.000	0.5	.619	.3	.087	.008	-.022	.000	.000
Stance Time Asymmetry	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Age	.598	.233	2.6	.015	6.6	.403	.163	.138	.125	1.071
Sex (male)	2.986	3.217	0.9	.360	.9	.157	.025	-.004	-3.550	9.523
Height (m)	5.466	15.470	0.4	.726	.1	.060	.004	-.026	-25.973	36.906
UPDRS-III	0.437	0.268	1.6	0.112	2.7	0.273	0.075	0.047	-0.108	0.983
MMSE	-.046	.414	-0.1	.911	.01	.019	.000	-.029	-.887	.795
ACE-III VS	-0.936	0.55	-1.7	0.098	2.9	0.28	0.078	0.051	-2.053	0.182
TMT A (secs)	.046	.027	1.7	.100	2.9	.283	.080	.052	-.009	.101
FAS	-.075	.110	-0.7	.499	.5	.118	.014	-.016	-.299	.148
RT Simple (ms)	4E-03	.013	0.3	**.779**	.08	.049	.002	-.028	-.022	.029

. MMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

Appendix E Univariate regressions investigating explanatory variables for laboratory-based gait impairment in Lewy body disease

Step Velocity	β	SE	t	p	F	R	R^2	Adjusted R^2	95% CI Lower Bound	95% CI Upper Bound
Age	-.006	.006	-1.1	.295	1.1	.160	.025	.003	-.018	.006
Sex (male)	.129	.096	1.3	.188	1.8	.200	.040	.018	-.065	.322
Height (m)	.584	.384	1.5	.136	2.3	.226	.051	.029	-.191	1.359
UPDRS-III	-.005	.002	-2.9	**.005**	8.7	.410	.168	.149	-.008	-.002
MMSE	.009	.010	0.9	.384	.8	.133	.018	-.005	-.011	.028
ACE-III VS	.010	.011	0.9	.365	.8	.142	.020	-.004	-.013	.034
TMT A (secs)	.000	.000	-1.7	.094	3.0	.288	.083	.055	-.001	.000
FAS	.005	.003	2.1	**.040**	4.5	.318	.101	.078	.000	.011
RT Simple (ms)	.000	.000	-1.7	**.103**	2.8	.265	.070	.045	.000	.000
Total Model				.009	5.4	.464	.215	.175		
FAS	.004	.003	1.7	.097					-.001	.009
UPDRS-III	-.004	.002	-2.4	**.022**					-.008	-.001

Step Length (m)	β	SE	t	p	F	R	R^2	Adjusted R^2	95% CI Lower Bound	95% CI Upper Bound
Age	-.003	.003	-1.1	**.291**	1.1	.161	.026	.003	-.009	.003
Sex (male)	.120	.045	2.6	.012	7.0	.373	.139	.119	.028	.211
Height (m)	.667	.169	4.0	**.000**	15.6	.516	.267	.250	.327	1.007
UPDRS-III	-.003	.001	-4.2	**.000**	17.4	.537	.288	.272	-.005	-.002
MMSE	.005	.005	1.0	.314	1.0	.154	.024	.001	-.005	.015
ACE-III VS	.005	.006	1.0	.338	.9	.150	.022	-.001	-.006	.017
TMT A (secs)	.000	.000	-2.0	**.057**	3.9	.325	.106	.079	.000	.000
FAS	.003	.001	2.4	**.020**	5.8	.357	.127	.105	.000	.006
RT Simple (ms)	-6E-05	.000	-1.7	**.102**	2.8	.266	.071	.046	.000	.000
Total Model*				**.001**	13.3	.637	.406	.376		
UPDRS-III	-.003	.001	-3.5	**.001**					-.004	-.001
Height (m)	.543	.167	3.3	**.002**					.206	.880

Step Time SD	β	SE	t	p	F	R	R^2	Adjusted R^2	95% CI Lower Bound	95% CI Upper Bound
Age	.308	.362	0.9	.399	.4	.129	.017	-.006	-.422	1.038
Sex (male)	-7.607	5.842	-1.3	.200	1.7	.195	.038	.016	-19.388	4.174
Height (m)	-37.433	23.256	-1.6	.115	2.6	.238	.057	.035	-84.333	9.467
UPDRS-III	.183	.106	1.7	**.092**	3.0	.254	.065	.043	-.031	.397
MMSE	-.943	.580	-1.6	.111	2.7	.241	.058	.036	-2.112	.226
ACE-III VS	-.949	.676	-1.4	**.168**	2.0	.214	.046	.023	-2.314	.416
TMT A (secs)	.014	.011	1.3	**.220**	1.6	.213	.045	.016	-.008	.035
FAS	-.375	.154	-2.4	**.019**	5.9	.360	.129	.108	-.686	-.064
RT Simple (ms)	.005	.004	1.2	**.234**	1.5	.195	.038	.012	-.003	.014

Stance Time SD	β	SE	t	p	F	R	R^2	Adjusted R^2	95% CI Lower Bound	95% CI Upper Bound

Age	.390	.504	0.8	.443	.6	.117	.014	-.009	-.626	1.405
Sex (male)	-11.858	8.072	-1.5	.149	2.2	.219	.048	.026	-28.137	4.421
Height (m)	-36.276	32.796	-1.1	.275	1.2	.166	.028	.005	-102.415	29.864
UPDRS-III	.234	.148	1.6	**.122**	2.5	.234	.055	.033	-.065	.533
MMSE	-1.588	.793	-2.0	**.052**	4.0	.292	.085	.064	-3.188	.012
ACE-III VS	-1.667	.928	-1.8	**.080**	3.2	.270	.073	.050	-3.542	.208
TMT A (secs)	.017	.015	1.1	**.261**	.8	.195	.038	.009	-.014	.048
FAS	-.533	.214	-2.5	**.017**	6.2	.366	.134	.113	-.966	-.100
RT Simple (ms)	.006	.006	1.1	.296	1.1	.172	.029	.003	-.006	.019

Step Velocity SD	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Age	-5E-07	.001	0.0	.999	0.0	.000	.000	-.023	-.001	.001
Sex (male)	-.008	.011	-0.7	.461	.6	.113	.013	-.010	-.029	.014
Height (m)	-.036	.043	-0.8	.401	.7	.128	.016	-.006	-.122	.050
UPDRS-III	.000	.000	0.7	.509	.4	0.101	0.01	-0.013	.000	.001
MMSE	-.002	.001	-1.8	**.081**	3.2	.263	.069	.048	-.004	.000
ACE-III VS	-.002	.001	-1.2	**.225**	1.5	.189	.036	.012	-.004	.001
TMT A (secs)	2E-05	.000	0.8	.423	.7	.140	.020	-.010	.000	.000
FAS	.000	.000	-1.3	.196	1.7	.204	.041	.017	-.001	.000
RT Simple (ms)	-4E-06	.000	-0.5	.612	.3	.084	.007	-.020	.000	.000

Stance Time Asymmetry	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Age	.157	.292	0.5	.595	.3	.081	.007	-.016	-.433	.746
Sex (male)	-6.86	4.67	-1.5	0.149	2.2	0.219	0.048	0.026	-16.277	2.558
Height (m)	-24.007	18.89	-1.3	0.211	1.6	0.19	0.036	0.014	-62.103	14.088
UPDRS-III	-0.106	0.087	-1.2	0.229	1.5	0.183	0.033	0.011	-0.281	0.069
MMSE	0.349	0.477	0.731	0.468	0.5	0.111	0.012	-0.011	-0.613	1.311
ACE-III VS	0.492	0.559	0.9	0.384	0.8	0.136	0.019	-0.005	-0.637	1.622
TMT A (secs)	-0.008	0.009	-0.9	0.377	0.8	0.154	0.024	-0.006	-0.026	0.01
FAS	0.006	0.134	0.0	0.966	0.002	0.007	0	-0.025	-0.264	0.276
RT Simple (ms)	0.001	0.003	0.2	0.849	0.04	0.031	0.001	-0.026	-0.006	0.008

. MMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

Appendix F Differences between controls and cognitively impaired groups for free-living gait characteristics

As shown in Appendix Table , six of the fourteen micro gait characteristics measured demonstrated significant differences between groups ($p \leq .01$). Both MCI and dementia groups walked more slowly ($p \leq .01$) with shorter steps ($p \leq .001$) and greater variability for step ($p \leq .01$), swing ($p \leq .01$) and stance time ($p \leq .01$). The dementia group were also more asymmetrical for swing time ($p = .002$) compared to controls. As there were no significant differences between MCI and dementia, the groups were combined to create a cognitively impaired group (see Appendix Table 3 and 4).

Appendix Table 3 Comparison of micro gait characteristics between controls and cognitively impaired groups

					Unadjusted Model		Controlling for age, sex and height		Controlling for age, sex, height and UPDRS-III		Controlling for age, sex, height and ACE-III		Controlling for age, sex, height, ACE-III and UPDRS-III	
	Control	**MCI**	**Dementia**	**Cognitive Impairment**	**F**	**(p)**	**F**	**(p)**	**F**	**(p)**	**F**	**(p)**	**F**	**(p)**
Pace														
Step Velocity (m/s)	1.09 ±.08	1.01±.08	.99±.10	1.00±.10	18	**≤.001**	14.4	**≤.001**	5.3	.023	9.4	**.003**	3.7	.058
Step Length (m)	.61±.04	.57±.05	.55±.05	56±05	21.3	**≤.001**	17.2	**≤.001**	4.3	.040	7.5	**.007**	1.2	.278
Swing SD (s)	.139 ±.012	.150±.015	.154±.0160	.152±.016	15.5	**≤.001**	12	**≤.001**	4.3	.041	5.3	.024	2	.161
Step Time SD (s)	.166±.015	.179±.018	.183±.020	.182±.191	16.2	**≤.001**	11.5	**≤.001**	4.5	.035	6.2	.015	2.6	.110
Stance SD (s)	.176±.016	.192±.021	.196±.022	.195±.021	15.7	**≤.001**	11.6	**≤.001**	4.2	.043	5.5	.021	2.0	.160
Variability (SD)														
Step Velocity SD (m/s)	.359±.032	.336±029	.373±.043	.370±.036	1.9	.175	.7	.401	.128	.721	.02	.866	0.2	.688
Step Length SD (m)	.149±.016	.151±.010	.152±.011	.152±.010	1.3	.266	.3	.584	.228	.634	.001	.975	0.5	.463
Rhythm														
Step Time (ms)	595±30	599±29	598±31	598±30	.4	.534	1.1	.305	4.3	.041	3.2	.077	7.2	**.008**
Swing (ms)	445±28	453±27	455±28	454±27	2.2	.141	3.3	.071	5.3	.024	3.3	.071	5.1	.026
Stance (ms)	743±34	747±34	746±36	746±35	0.2	.658	.7	.406	4.1	.047	3.5	.065	8.4	**.005**
Asymmetry														
Step Time Asy (ms)	.092±.009	.098±.011	.100±.014	.099±.013	6	.016	3.8	.054	2.4	.123	2.1	.146	1.6	.207
Swing Asy (ms)	.085±.008	.090±.010	.092±.013	.091±.012	5.5	.021	4.3	.039	2.6	.111	3.2	.075	2.4	.122
Stance Asy (ms)	.094±.008	.099±.011	.100±.014	.100±.012	7.5	**.009**	3.7	.056	2.2	.139	2.6	.109	1.9	.170
Postural Control														
Step Length Asy (m)	.086±.007	.086±.010	.084±.014	.085±.012	.2	.690	.1	.772	2.2	.143	.7	.423	3.4	.067

Significant values refer to differences between controls and cognitively impaired group. Data displayed as (mean ± standard deviation). SD = variability, Asy = asymmetry.

Appendix Table 4: Comparison of gait characteristics across mild cognitive impairment and dementia groups in each subtype

	AD-MCI		AD		p
	Mean	SD	Mean	SD	
Pace					
Step Velocity (m/s)	1.04	0.10	1.00	0.11	0.446
Step Length (m)	0.58	0.04	0.57	0.05	0.485
Swing SD (ms)^{ln}	0.15	0.01	0.15	0.02	0.59
Step Time SD (ms)^{ln}	0.17	0.02	0.18	0.02	0.505
Stance SD (ms)^{ln}	0.19	0.02	0.19	0.02	0.526
Variability (SD)					
Step Velocity SD (m/s)^{ln}	0.36	0.02	0.36	0.04	0.612
Step Length SD (m)^{ln}	0.15	0.01	0.15	0.01	0.8
Rhythm					
Step Time (ms)	0.60	0.03	0.61	0.02	0.294
Swing (ms)	0.45	0.03	0.47	0.02	0.975
Stance (ms)^{ln}	0.75	0.03	0.76	0.02	0.727
Asymmetry					
Step Time Asy (ms)	0.10	0.01	0.10	0.01	0.751
Stance Asy (ms)	0.10	0.01	0.10	0.01	0.526
Swing Asy (ms)	0.09	0.01	0.09	0.01	0.68
Postural Control					
Step Length Asy (m)	0.09	0.01	0.09	0.01	0.776
	DLB-MCI		DLB		p
	Mean	SD	Mean	SD	
Pace					
Step Velocity (m/s)	0.98	0.10	0.98	0.10	0.287
Step Length (m)	0.56	0.05	0.55	0.04	0.158
Swing SD (ms)	0.15	0.01	0.15	0.02	0.287
Step Time SD (ms)	0.18	0.01	0.18	0.02	0.232
Stance SD (ms)	0.19	0.01	0.20	0.02	0.171
Variability (SD)					
Step Velocity SD (m/s)	0.37	0.04	0.37	0.04	0.899
Step Length SD (m)	0.15	0.01	0.15	0.01	0.832
Rhythm					
Step Time (ms)	0.61	0.02	0.60	0.03	0.672
Swing (ms)	0.46	0.02	0.45	0.03	0.933
Stance (ms)	0.75	0.02	0.75	0.04	0.8
Asymmetry					
Step Time Asy (ms)	0.09	0.01	0.10	0.01	0.395
Stance Asy (ms)	0.09	0.01	0.10	0.01	0.553
Swing Asy (ms)	0.09	0.01	0.09	0.01	0.672
Postural Control					
Step Length Asy (m)	0.08	0.01	0.08	0.01	0.307
	PD-MCI		PDD		p
	Mean	SD	Mean	SD	
Pace					
Step Velocity (m/s)	0.98	0.08	0.98	0.08	0.878
Step Length (m)	0.53	0.05	0.52	0.04	0.442
Swing SD (ms)	0.16	0.02	0.16	0.02	1
Step Time SD (ms)	0.19	0.03	0.20	0.02	0.878
Stance SD (ms)	0.21	0.03	0.21	0.02	0.575

Variability (SD)					
Step Velocity SD (m/s)	0.37	0.04	0.40	0.03	0.065
Step Length SD (m)	0.16	0.00	0.16	0.01	0.161
Rhythm					
Step Time (ms)	0.59	0.04	0.57	0.02	0.505
Swing (ms)	0.44	0.03	0.43	0.02	0.382
Stance (ms)	0.73	0.05	0.71	0.03	0.721
Asymmetry					
Step Time Asy (ms)	0.11	0.01	0.10	0.02	0.442
Stance Asy (ms)	0.11	0.01	0.10	0.02	0.721
Swing Asy (ms)	0.10	0.01	0.10	0.02	0.574
Postural Control					
Step Length Asy (m)	0.08	0.01	0.08	0.02	0.878

Appendix G Missing clinical and cognitive data relevant to all free-living analysis

Clinical/Cognitive tests	% complete	Missing data per group	Reasons for incompletion
sMMSE	100%		
ACE-III (including subscales)	98%	DLB (n =1) PDD (n = 1)	Wasn't included in protocol (n = 1) Hospitalised before study completion (n = 1)
TMT A	90%	AD (n = 1) DLB (n = 9) PDD (n = 1)	Wasn't included in protocol (n = 9) Hospitalised before study completion (n=1) Refused to do (n=1)
FAS	96%	AD (n = 1) DLB (n = 2) PDD (n =1)	Wasn't included in protocol (n = 1) Hospitalised before study completion (n=1) Refused to do (n=2)
Simple RT	93%	AD (n = 1) LBD (n = 6)	Wasn't included in protocol (n = 4) Hospitalised before study completion (n=1) Refused to do (n=2)
Angles Test	93%	AD (n = 1) DLB (n=3) PDD (n = 3)	Wasn't included in protocol (n = 4) Hospitalised before study completion (n=1) Refused to do (n=2)
Stroop Test	87%	AD (n =2) DLB (n = 8) PDD (n = 4)	Wasn't included in protocol (n = 9) Hospitalised before study completion (n=1) Refused to do (n=1) Could not do (n = 3)
CDR	100%		
Faller status	96%	Controls (n = 3) AD (n = 1)	Wasn't included in protocol (n = 3) Refused to do (n = 1)
CIRS-G	98%	DLB (n = 2)	Wasn't included in protocol (n = 2)
UPDRS-III	96%	Controls (n = 3) AD (n = 1) PDD (n =1)	Wasn't included in protocol (n = 4) Refused to do (n = 1)
BMI	99%	Control (n=1)	Assessment not complete (n=1)
ABC	99%	PDD (n=1)	Time constraint (n =1)
GDS	98%	DLB (n=1) PDD (n =1)	Wasn't included in protocol (n = 1) Hospitalised before study completion (n = 1)
BADLS	86%	Controls (n = 5) AD (n=3) DLB (n = 5) PDD (n = 1)	Wasn't included in protocol (n = 6) No informant (n = 8)
NART	98%	AD (n = 1) PDD (n =1)	Refused to do (n = 1) Hospitalised before study completion (n = 1)

**MMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time, CDR – Clinical dementia rating scale, CIRS-G = Cumulative Illness Rating Scale – Geriatric, UPDRS-III = Unified Parkinson's disease rating scale –III, BMI = Body mass index, BADLS = Bristol Activities of daily living scale, NART = national adult reading test, AD = Alzheimer's disease, LBD = Lewy body disease*

Appendix H Differences between controls and cognitively impaired groups for macro gait characteristics

Four of the seven macro gait characteristics showed significant between-group differences ($p \leq .01$). Both MCI and dementia spent less time walking (MCI: $p = .011$; dementia: $p \leq .001$) and took less steps per day (MCI: $p = .003$; dementia: $p \leq .001$) compared to controls. They also took shorter walking bouts (MCI: $p = .002$; dementia: $p \leq .001$), with less variability in bout length (MCI: $p = .004$; dementia: $p \leq .001$). Table 6-1 provides a detailed overview of habitual walking behaviours in controls, MCI and dementia groups.

When considering significant between-group differences ($p \leq .05$), the dementia group also took a proportionately higher number of short walking bouts compared to long walking bouts (alpha; $p = .015$) compared to controls.

As there were no differences between MCI and dementia groups and the dementia group recruited were very mild, data were combined to form a cognitively impaired group (see Table 6-1).

Appendix Table 5 Comparison of macro gait characteristics across controls, combined cognitive impairment groups and disease subtypes

					Unadjusted model		Controlling for age and sex		Controlling for age, sex and UPDRS		Controlling for age, sex and ACE-III		Controlling for age, sex, UPDRS-III and ACE-III	
	Controls	MCI	Dementia	Cognitive Impairment	F	(p)	F	(p)	F	(p)	F	(p)	F	(p)
Walking time per day (mins)	196 ± 63	153 ± 65	139 ± 65	145 ± 65	12.4	≤ **.001**	10	**.002**	1.5	.224	8.2	**.005**	1.9	.167
Steps per day	14204 ± 4817	10476 ± 4831	9526 ± 4618	9910 ± 4701	16.6	≤ **.001**	13.7	≤ **.001**	3.6	.060	11.3	≤ **.001**	4	.048
Bouts per day	630 ± 166	573 ± 194	545 ± 222	557 ± 210	2.7	.106	1.2	.274	.1	.741	2	.164	.1	.757
% time walking per day	14 ± 4	11 ± 5	10 ± 5	10 ± 5	12.4	≤ **.001**	10	**.002**	1.5	.224	8.2	**.005**	1.9	.167
Mean bout length (secs)	19 ± 4	16 ± 3	15 ± 4	15 ± 4	16.8	≤ **.001**	17.7	≤ **.001**	6.4	.013	10	**.002**	3.5	.063
Variability	.882 ± .083	.821 ± .070	.811 ± .088	.815 ± .081	13.8	≤ **.001**	15.9	≤ **.001**	7.6	**.007**	8	**.006**	3.6	.060
Alpha	1.611 ± .038	1.634 ± .050	1.647 ± .075	1.642 ± .066	5.1	.026	4.7	.032	.7	.420	1.6	.206	.1	.826

Significant values refer to differences between controls and combined cognitive impairment group. Normally distributed data and data analysed using one-way ANOVAs displayed as (mean ± standard deviation.

Appendix Table 6: Comparison of gait characteristics across mild cognitive impairment and dementia groups

	AD-MCI	**AD**	**t**	**p**
n	**15**	**21**		
Walking time per day (mins)	174±45	163±62	.6	.494
Steps per day	11974±3547	11033±4612	.7	.494
Bouts per day	629±178	606±236	.3	.742
% time walking per day	12±3	11±4	.6	.494
Mean bout length (secs)	17±3	17±4	.2	.826
Variability	.840±.076	.831±.087	.3	.733
Alpha	1.616±.033	1.627±.051	.8	.436
	DLB-MCI	**DLB**	**t**	**p**
n	**11**	**19**		
Walking time per day (mins)	165±87	136±62	.9	.403
Steps per day	11535±6394	9423±4428	.8	.453
Bouts per day	598±229	546±208	.5	.607
% time walking per day	12±6	10±4	.9	.403
Mean bout length (secs)	16±3	15±3	1.0	.343
Variability	.842±.065	.807±.069	1.1	.306
Alpha	1.634±.062	1.645±.050	.3	.748
	PD-MCI	**PDD**	**t**	**p**
n	**8**	**8**		
Walking time per day (mins)	113±48	99±44	.6	.554
Steps per day	7758±3141	6851±3031	.6	.565
Bouts per day	476±152	442±175	.4	.685
% time walking per day	8±3	7±3	.6	.554
Mean bout length (secs)	14±3	13±3	.6	.554
Variability	.780±.057	.779±.123	.03	.975
Alpha	1.655±.057	1.701±.143	.8	.416

Appendix I Univariate regressions investigating explanatory variables for habitual walking behaviour in controls

Walk Time Per Day (mins)	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (male)	32.3	24.8	1.3	.206	1.7	.256	.066	.027	-18.9	83.5
Age	-.7	1.5	.5	.634	.2	.098	.010	-.032	-3.8	2.4
Faller Status (Faller)	14.6	32.4	.5	.657	.2	.095	.009	-.036	-52.7	81.9
UPDRS-III	3.8	5.1	.7	.456	0.6	.156	.024	-.020	-6.8	14.4
ACE-III (0-100)	-4	4.4	-.9	.375	.8	.181	.033	-.007	-13.1	5.1
TMT A (secs)	-1.1	1.4	-.8	.427	0.7	.163	.026	-.014	-4	1.7
FAS	.03	1.0	.04	.973	.001	.007	.000	-.042	-2.1	2.1
GDS (0-15)	8.8	10.1	.9	.391	.8	.176	.031	-.010	-12	29.6
ABC (0-100)	-.5	1.4	-.4	.700	.2	.079	.006	-.035	-3.4	2.3
RT Simple (secs)	-.3	.2	-1.2	.262	1.3	.228	.052	.013	-.7	.2
Total Steps Per Day	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (male)	2008	1908	1.1	.303	1.1	.210	.044	.004	-1931	5946
Age	-73	113	-.6	.526	.4	.130	.017	-.024	306	160
Faller Status (Faller)	2601	2413	1.1	.293	1.2	.224	.050	.007	-2402	7605
UPDRS-III	254	389	.7	.520	.4	.138	.019	-.026	-553	1061
ACE-III (0-100)	-229	337	-.7	.504	.5	.137	.019	-.022	-925	467
TMT A (secs)	-110	105	1.1	.305	1.1	.209	.044	.004	-325	106
FAS	33	77	.4	.675	.2	.086	.007	-.034	127	193
GDS (0-15)	697	764	.9	.371	.8	.183	.033	-.007	-881	2274
ABC (0-100)	-53	105	-.5	.615	.3	.103	.011	-.031	-269	162
RT Simple (secs)	-23	17	1.3	.204	1.7	.257	.066	.027	-58	13
Bouts per day	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (male)	-33	67	.5	.629	.2	.099	.010	-.031	-171	106
Age	4	4	1	.344	1	.193	.037	-.003	-4	12
Faller Status (Faller)	24	85	.3	.780	.1	.060	.004	-.042	-153	201
UPDRS-III	8	13	.6	.564	.3	.124	.015	-.029	-20	36
ACE-III (0-100)	.4	12	.03	.976	.001	.006	.000	-.042	-24	25
TMT A (secs)	1	4	.3	.741	.1	.068	.005	-.037	-6	9
FAS	-1	3	.4	.698	.2	.080	.006	-.035	-7	5
GDS (0-15)	48	25	1.9	.065	3.7	.367	.135	.099	-3	100
ABC (0-100)	-6	3	1.8	.089	3.1	.340	.116	.079	-13	1
RT Simple (secs)	.2	1	.3	.796	.1	.053	.003	-.039	-1	1
Mean Bout Length	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI**	**95% CI**

									Lower Bound	Upper Bound
Sex (male)	4.1	1.3	3.2	**.004**	10.0	.543	.295	.265	1.5	6.8
Age	-.2	.1	-1.7	.096	3.0	.333	.111	.074	-.3	.03
Faller Status (Faller)	.7	2	.4	.718	.1	.078	.006	-.039	-3.4	4.8
UPDRS-III	.1	.3	.3	.769	.1	.063	.004	-.041	-.6	.7
ACE-III (0-100)	-.3	.3	-1.3	.224	1.6	.247	.061	.022	-.9	.2
TMT A (secs)	-.1	.1	-1.6	.118	2.6	.314	.099	.061	-.3	.04
FAS	.03	.1	.4	.674	.2	.087	.007	-.034	-.1	.2
GDS (0-15)	-.5	.6	-.8	.436	.6	.160	.025	-.015	-1.7	.8
ABC (0-100)	.1	.1	1.1	.273	1.3	.223	.050	.010	-.1	.3
RT Simple (secs)	-.03	.01	-2.3	**.034**	4.1	.417	.174	.139	-.1	-.002

Variability	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (male)	.08	.03	2.9	**.008**	8.3	.506	.256	.225	.02	.14
Age	-.003	.002	1.5	.148	2.2	.292	.085	.047	-.007	.001
Faller Status (Faller)	.05	.04	1.1	.285	1.2	.227	.052	.009	-.04	.1
UPDRS-III	.002	.01	.2	.811	.1	.052	.003	-.043	-.01	.02
ACE-III (0-100)	-.005	.006	-.8	.415	.7	.167	.028	-.013	-.02	.01
TMT A (secs)	-.003	.002	2.1	**.049**	4.3	.389	.151	.116	-.01	.000
FAS	.001	.001	1.2	.262	1.3	.228	.052	.013	-.001	.004
GDS (0-15)	-.02	.1	-1.2	.247	1.4	.235	.055	.016	-.04	.01
ABC (0-100)	.002	.002	1.3	.192	1.8	.264	.070	.031	-.001	.01
RT Simple (secs)	-.001	.000	2.5	**.020**	6.2	.454	.206	.173	-.001	.000

Alpha	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (male)	-.04	.01	2.6	**.015**	6.9	.472	.223	.191	-.06	-.01
Age	.002	.001	2.4	**.024**	5.8	.442	.196	.162	.000	.004
Faller Status (Faller)	-.001	.02	.1	.962	.002	.010	.000	-.045	-.04	.04
UPDRS-III	.000	.003	-.1	.929	.01	.019	.000	-.045	-.001	.01
ACE-III (0-100)	.003	.003	1.2	.246	1.4	.236	.056	.016	-.002	.01
TMT A (secs)	.001	.001	1.2	.250	1.4	.234	.055	.015	-.001	.003
FAS	.000	.001	.2	.849	.04	.039	.002	-.040	-.001	.001
GDS (0-15)	.002	.01	.3	.771	.1	.060	.004	-.038	-.01	.01
ABC (0-100)	-.002	.001	2.2	**.037**	4.9	.411	.169	.134	-.003	.000
RT Simple (secs)	.000	.000	1.3	.203	1.7	.258	.067	.028	.000	.000

Significant values are highlighted in bold. UPDRS-III = Unified Parkinson's Disease Rating Scale III, ACE-III = Addenbrookes Cognitive Examination III, TMT A = Trail Making Task A, FAS = FAS Test, RT Simple = Simple Reaction Time Task, GDS = Geriatric Depression Scale, ESS = Epworth Sleepiness Scale, ABC = Activities Balance Confidence Scale, BADLS = Bristol's Activities of Daily Living.

Appendix J Univariate regressions and backwards stepwise regression models investigating explanatory variables for habitual walking behaviour in cognitively impaired group

Total Walk Time Per Day (mins)	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (Male)	-16.4	14.7	1.1	.268	1.2	.124	.015	.003	-45.7	12.9
Age	-1.4	1.2	-0.12	.232	1.5	0.134	.018	.006	-3.7	0.9
Faller Status (Faller)	-20.3	14.1	-1.4	.153	2.1	.159	.025	.013	-48.3	7.7
UPDRS-III	-1.6	0.3	-4.8	**≤.001**	23.2	0.481	0.231	.221	-2.3	-0.9
ACE-III (0-100)	-0.1	0.5	-0.1	.912	0.01	0.013	0	-.013	-1.1	0.9
AD Subtype	35	13.8	2.6	**.013**	6.5	.274	.075	.063	7.7	62.4
DLB Subtype	-1.9	14.7	.1	.897	.02	.014	.000	.012	-31.2	27.4
PDD Subtype	-52.1	16.9	3.1	**.003**	9.5	.325	.106	.095	-85.8	-18.4
TMT A (secs)	-0.1	0.04	-1.9	.064	3.5	0.221	0.049	0.035	-0.2	0.01
FAS	1.6	0.5	3.4	**≤.001**	11.9	0.367	0.135	0.124	0.7	2.5
GDS (0-15)	-3.2	2.3	-1.4	.165	2	0.157	0.025	0.012	-7.7	1.3
ABC (0-100)	1.2	0.3	3.6	**≤.001**	12.9	0.374	0.14	0.129	0.5	1.8
RT Simple (secs)	-0.02	0.02	-1.4	.174	1.9	0.159	0.025	0.012	-0.06	.011
BADLS (0-60)	-3.1	1	3.3	**≤.001**	11	.366	.134	.121	-5	-1.3
Full Model										
Full Model				**≤.001**	12.8	.532	.283	.261		
UPDRS-III	-1.1	.3	3.4	**.001**					-1.7	-0.4
BADLS	-2.0	.8	2.3	**.022**					-3.6	-.3
Steps Per Day	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (Male)	-829	1069	-.8	.440	0.6	.086	.007	-.005	-2956	1299
Age	-84	85	-1	.325		.11	.012	.000	-253	85
Faller Status (Faller)	-940	1026	0.9	.362	.8	.102	.010	-.002	-2981	1101
UPDRS-III	-104	25	-4.2	**≤.001**	17.6	.431	.186	.175	-154	-55
ACE-III (0-100)	-8	36	-.2	.831	.1	.024	.001	-.012	-80	64
AD Subtype	2233	1003	2.2	**.029**	5.0	.242	.058	.047	237	4230
DLB Subtype	40	1065	.03	.970	.001	.004	.000	-.012	-2080	2160
PDD Subtype	-3562	1232	2.9	**.005**	8.4	.208	.095	.083	-6013	-1110
TMT A (secs)	-5	3	-1.7	.102	2.8	.196	.038	.024	-11	1
FAS	102	34	3.0	**.003**	9.2	.329	.108	.096	35	168
GDS (0-15)	-232	163	-1.4	.159	2.0	.159	.025	.013	-556	93
ABC (0-100)	83	24	3.5	**≤.001**	11.9	.362	.131	.120	35	130
RT Simple (secs)	-1.5	1.3	-1.2	.243	1.4	.136	.019	.005	-4	1
BADLS (0-60)	-211	69	3	**.003**	9.3	.340	.115	.103	-349	-73
Full Model										
Full Model				**≤.001**	9.8	.482	.232	.208		
UPDRS-III	-70	24	2.9	**.004**					-118	-23
BADL	-132	63	2.1	**.041**					-258	-5

Bouts Per Day	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (Male)	-68	48	1.4	.162	2	.156	.024	.012	-163	28
Age	-6	4	1.6	0.124	2.4	0.171	0.029	0.017	-13.5	1.7
Faller Status (Faller)	-99	45	2.2	**.032**	4.8	.237	.056	.044	-189	-9
UPDRS-III	-4	1	3.7	**≤.001**	13.9	.390	.152	.141	-7	-2
ACE-III (0-100)	-1	2	.8	.428	.6	.090	.008	-.005	-5	2
AD Subtype	87	46	1.9	.060	3.7	.209	.044	.032	-4	178
DLB Subtype	-3	48	.1	.956	.003	.006	.000	-.012	-99	93
PDD Subtype	-133	57	2.4	**.021**	5.5	.254	.065	.053	-246	-20
TMT A (secs)	-.2	.1	1.6	.118	2.5	.187	.035	.021	-.5	.1
FAS	4	2	2.6	**.011**	6.8	.286	.082	.070	.9	7
GDS (0-15)	-13	7	1.8	.070	3.4	.204	.042	.029	-28	1
ABC (0-100)	3	1	2.8	**.007**	7.6	.296	.088	.076	1	5
RT Simple (secs)	-.1	.1	1.3	.206	1.6	.148	.022	.008	-.2	.04
BADLS (0-60)	-10	3	3.1	**.003**	9.8	.348	.121	.108	-16	-4
Full Model										
Full Model				**≤.001**	7.9	.442	.195	.171		
UPDRS-III	-2	1	2.0	**.049**					-5	-.01
BADL	-8	3	2.5	**.014**					-13	-2
Mean Bout Length (secs)	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (Male)	-.2	.8	-.3	.796	.1	.029	.001	-.012	-1.8	1.4
Age	-.001	.1	-.01	.992	.000	.001	.000	-.012	-.1	.1
Faller Status (Faller)	.9	.8	1.2	.230	1.5	.134	.018	.006	-.6	2.4
UPDRS-III	-.1	.02	-2.9	**.005**	8.6	.316	.100	.088	-.1	-.02
ACE-III (0-100)	.02	.03	.9	.373	.8	.101	.010	-.003	-.03	.1
AD Subtype	2.1	.7	2.9	**.005**	8.3	.206	.094	.082	.7	3.6
DLB Subtype	.5	.8	.7	.510	.4	.074	.005	-.007	-2.1	1.1
PDD Subtype	-2.5	.9	2.8	**.007**	7.6	.294	.086	.075	-4.4	-.7
TMT A (secs)	-.002	.002	-1.0	.343	.9	.114	.013	-.001	-.01	.002
FAS	.1	.03	2.0	**.045**	4.2	.228	.052	.039	.001	.1
GDS (0-15)	.1	.1	.8	.416	.7	.092	.008	-.004	-.1	.3
ABC (0-100)	.1	.02	2.6	**.011**	6.8	.282	.080	.068	.01	.1
RT Simple (secs)	.000	.001	-.5	.653	.2	.053	.003	-.011	-.002	.002
BADLS (0-60)	-.05	.06	.8	.406	.7	.099	.010	-.004	-.2	.1
Full Model										
Full Model				**.009**	7.1	.296	.088	.075		
AD Subtype	2.0	.8	2.7	**.009**					.5	3.5
Variability	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (Male)	.02	.02	1.0	.305	1.1	.115	.013	.001	-.02	.06
Age	.000	.001	.2	.822	.1	.025	.001	-.012	-.003	.003
Faller Status (Faller)	.04	.02	2.2	**.030**	4.9	.239	.057	.045	.004	.074

UPDRS-III	-.001	.000	-1.2	.249	1.4	.131	.017	.004	-.002	.000
ACE-III (0-100)	.001	.001	1.2	.232	1.5	.135	.018	.006	.000	.002
AD Subtype	.029	.018	1.6	.111	2.6	.177	.031	.019	-.007	.064
DLB Subtype	.002	.019	.1	.904	.02	.014	.000	-.012	-.035	.039
PDD Subtype	-.048	.022	2.2	**.031**	4.8	.239	.057	.045	-.092	-.005
TMT A (secs)	-1.1	.000	-.2	.847	.04	.023	.001	-.014	.000	.000
FAS	.001	.001	1.5	.128	2.4	.174	.030	.017	.000	.002
GDS (0-15)	.003	.003	1.1	.273	1.2	.124	.015	.003	-.003	.01
ABC (0-100)	.001	.000	2.1	**.039**	4.4	.230	.053	.041	.000	.002
RT Simple (secs)	1.8	.000	.7	.440	.6	.091	.008	-.005	.000	.000
BADLS (0-60)	.000	.001	.1	.921	.01	.012	.000	-.014	-.002	.003
Full Model										
Full Model				**.001**	5.7	.429	.184	.152		
ABC	.001	.000	2.3	**.039**					.000	.002
Faller Status	.052	.017	3.0	**.003**					.018	.087
PDD Subtype	-.043	.023	1.9	.066					-.089	.003

Alpha	**β**	**SE**	**t**	**p**	**F**	**R**	**R^2**	**Adjusted R^2**	**95% CI Lower Bound**	**95% CI Upper Bound**
Sex (Male)	-.01	.02	-.6	.584	.3	.061	.004	-.009	-.04	.02
Age	.001	.001	.7	.502	.5	.075	.006	-.007	-.002	.003
Faller Status (Faller)	-.02	.02	1.1	.262	1.3	.125	.016	.003	-.05	.013
UPDRS-III	.001	.000	2.7	**.008**	7.4	.296	.088	.076	.000	.002
ACE-III (0-100)	-.001	.001	1.2	.241	1.4	.133	.018	.005	-.002	.000
AD Subtype	-.031	.015	2.1	**.035**	4.6	.233	.054	.042	-.060	-.002
DLB Subtype	.001	.015	.1	.961	.002	.005	.000	-.012	-.030	.031
PDD Subtype	.048	.018	2.7	**.010**	7.1	.285	.081	.070	.012	.084
TMT A (secs)	2.2	.000	.5	.623	.2	.059	.004	-.011	.000	.000
FAS	-.001	.000	-2.6	**.012**	6.6	.283	.080	.068	-.002	.000
GDS (0-15)	-.002	.002	-.8	.423	.7	.091	.008	-.004	-.007	.003
ABC (0-100)	-.001	.000	3.4	**.001**	11.2	.353	.125	.114	-.002	.000
RT Simple (secs)	.001	.001	.7	.507	.5	.079	.006	-.008	-.001	.003
BADLS (0-60)	7.4	.000	.4	.695	.2	.046	.002	-.012	.000	.000
Full Model										
Full Model				**.013**	4.6	.336	.113	.089		
UPDRS-III	.001	.000	2.0	**.045**					.000	.001
FAS	-.001	.000	1.7	.098					-.001	.000

Significant values in bold. Data displayed as (rho (p value)). UPDRS-III = Unified Parkinson's Disease Rating Scale III, ACE-III = Addenbrookes Cognitive Examination III, TMT A = Trail Making Task A, FAS = FAS Test, RT Simple = Simple Reaction Time Task, GDS = Geriatric Depression Scale, ESS = Epworth Sleepiness Scale, ABC = Activities Balance Confidence Scale, BADLS = Bristol's Activities of Daily Living

Appendix K Repeated measures analysis investigating change in gait characteristics across different lengths in all disease subtypes and controls

In summary, all groups walked faster with shorter steps and less asymmetry in longer walking bouts compared to short walking bouts. All groups also became less variable – however this was less obvious in PDD. The PDD group's step, stance and swing time and step length variability was not significantly affected by bout length.

All groups

All groups walked faster ($p \leq .01$) in over 60 second bouts compared to 10-30 second bouts and under 10 second bouts and slower ($p \leq .001$) in under 10 second bouts compared to 30-60 second bouts.

All groups had shorter steps ($p \leq .01$) in under 10 second bouts compared to all longer bouts and in 10-30 second bouts compared to over 60 second bouts. All groups demonstrated less variability for step ($p \leq .01$), and swing time ($p \leq .01$) in over 60 second bouts compared to 10-30 second bouts and under 10 second bouts, and less variability for step ($p \leq .01$) and stance time ($p \leq .01$) in 30-60 second bouts compared to under 10 second bouts.

All groups demonstrated less asymmetry for step ($p \leq .01$), stance ($p \leq .01$) and swing time ($p \leq .01$) and step length ($p \leq .01$) in over 60 second bouts compared to 10-30 and under 10 second bouts, and in 30-60 second bouts compared to under 10 second bouts.

When considering statistically significant differences between bout lengths at ($p \leq .05$), all disease subtypes walked faster ($p \leq .01$) in 30-60 second bouts compared to 10-30 second bouts.

Alzheimer's disease and dementia with Lewy bodies

Both AD and DLB groups walked slower ($p \leq .001$) in under 10 second bouts compared to 10-30 second bouts.

They also demonstrated greater variability for step ($p \leq .001$), stance ($p \leq .001$) and swing time ($p \leq .001$) in under 10 second bouts compared to 10-30 second bouts, and greater stance time ($p \leq .01$) variability in under 10 second bouts compared to 30-60 second bouts. They also demonstrated greater variability for step length ($p \leq .01$) in under 10 second bouts compared to 30-60 and over 60 second bouts and less variability for step velocity ($p \leq .01$) in over 60 second bouts compared to 10-30 and 30-60 second bouts.

The AD and DLB groups showed quicker step ($p \leq .001$), and swing time ($p \leq .001$) in over 60 second bouts compared to 30-60 second bouts. They also demonstrated quicker swing time in over 60 second bouts compared to 10-30 second bouts.

The DLB and AD groups also demonstrated greater step ($p \leq .01$), stance ($p \leq .01$) and swing time asymmetry ($p \leq .01$) in under 10 second bouts compared to 10-30 second bouts, in 10-30 second bouts compared to 30-60 second bouts and in 30-60 second bouts compared to over 60 second bouts.

The AD and DLB groups demonstrated greater variability for step ($p \leq .05$) and stance time ($p \leq .05$) in 30-60 second bouts compared to over 60 second bouts. They had quicker stance time ($p \leq .05$) in over 60 second bouts compared to 30-60 second bouts.

Alzheimer's disease

The AD group demonstrated greater step length variability ($p \leq .001$) in under 10 second bouts compared to 10-30 second bouts and greater step velocity variability ($p \leq .001$) in under 10 second bouts compared to over 60 second bouts.

They also had a quicker step time ($p \leq .001$) in over 60 second bouts compared to 10-30 and a quicker swing time compared to under 10 second bouts.

The AD group also demonstrated less step length asymmetry ($p \leq .001$) in over 60 second bouts compared to 30-60 second bouts.

The AD group demonstrated shorter steps ($p = .016$) in 10-30 second bouts compared to 30-60 second bouts, and less swing time variability ($p = .012$) in over 60 second bouts compared to 30-60 second bouts. They also showed less step length variability ($p = .021$) in over 60 second bouts compared to 10-30 second bouts. They had a quicker stance time ($p \leq .01$) in over 60 second bouts compared to 10-30 and under 10 second bouts.

Dementia with Lewy bodies

The DLB group demonstrated shorter steps ($p = .009$) in 10-30 second bouts compared to 30-60 second bouts and less swing time variability ($p = .004$) in over 60 second bouts compared to 30-60 second bouts. They also showed less variability in step length ($p = .002$) over 60 second bouts compared to 10-30 second bouts.

The DLB group demonstrated greater step velocity variability ($p = .028$) in under 10 second bouts compared to over 60 second bouts.

They had quicker stance (p = .009) and step time (p= .036) in under 10 second bouts compared to 30-60 second bouts. They also had a slower step time (p = .036) in 10-30 second bouts compared to over 60 second bouts and a slower stance time (p = .036) in 30-60 second bouts compared to over 60 second bouts. They had a quicker swing time (p = .046) in under 10 second bouts compared to 10-30 and a slower swing time (p = .046) compared to over 60 second bouts.

They also demonstrated less step length asymmetry (p = .016) in over 60 second bouts compared to 30-60 second bouts.

Parkinson's disease dementia

PDD walked slower in under 10 second bouts compared to 10-30 second bouts (p = .016),with less stance variability in over 60 second bouts compared to 30-60 second bouts (p = .034) and less stance time variability in over 60 second bouts compared to 10-30 second bouts. They also had greater step velocity variability (p = .011) in under 10 second bouts compared to 10-30 and 30-60 second bouts.

They also demonstrated greater step (p = .034), stance (p = .034) and swing time asymmetry (p =.034) and step length asymmetry (p = .034) in under 10 second bouts compared to 10-30 second bouts, in 10-30 second bouts compared to 30-60 second bouts and in 30-60 second bouts compared to over 60 second bouts.

The PDD group demonstrated no differences across bout lengths for step, stance and swing time and for step length variability.

Appendix L Spearman's Correlations between motor disease severity, cognitive function and free-living gait characteristics across different walking bout lengths in the Alzheimer's disease group

< 10 seconds

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
Age	.022 (.898)	-.212 (.220)	*.414 (.013)*	*.350 (.039)*	*.435 (.009)*	.271 (.116)	*.438 (.008)*	*-.405 (.016)*	*-.372 (.028)*	-.300 (.080)	*.353 (.037)*	*.348 (.041)*	.316 (.064)	.106 (.544)
Height (m)	-.119 (.495)	-.010 (.955)	.250 (.147)	*.348 (.041)*	.157 (.367)	-.045 (.797)	-.056 (.750)	.153 (.379)	.105 (.549)	.133 (.448)	-.042 (.810)	-.054 (.758)	.231 (.182)	-.030 (.865)
UPDRS	-.038 (.830)	-.088 (.622)	*.348 (.044)*	.270 (.123)	.319 (.065)	-.027 (.878)	.050 (.777)	-.063 (.725)	-.090 (.613)	.006 (.973)	.113 (.525)	.062 (.727)	.121 (.495)	.042 (.812)
sMMSE	.174 (.316)	.192 (.269)	-.207 (.233)	-.126 (.470)	-.169 (.333)	-.170 (.330)	-.069 (.693)	.082 (.640)	.165 (.345)	-.068 (.700)	-.185 (.287)	-.185 (.288)	-.025 (.888)	.039 (.823)
ACE-III Mem	.297 (.084)	.198 (.255)	-.203 (.242)	-.184 (.290)	-.193 (.267)	.044 (.801)	.065 (.711)	-.158 (.363)	-.094 (.592)	-.180 (.300)	-.008 (.964)	-.010 (.956)	-.095 (.585)	.132 (.449)
ACE-III VS	.247 (.152)	.207 (.233)	-.046 (.792)	-.027 (.877)	.017 (.923)	.116 (.507)	.086 (.621)	-.077 (.660)	.062 (.724)	-.230 (.184)	.017 (.921)	.077 (.661)	.177 (.308)	.235 (.173)
ACE-III Total	.311 (.069)	.299 (.081)	-.151 (.385)	-.145 (.406)	-.146 (.404)	.025 (.888)	.046 (.794)	-.068 (.698)	.034 (.844)	-.186 (.283)	-.051 (.773)	-.039 (.823)	-.018 (.918)	.191 (.271)
TMT A	-.070 (.695)	-.110 (.535)	.048 (.787)	.014 (.938)	.014 (.938)	.155 (.381)	.008 (.962)	-.052 (.770)	-.080 (.655)	.020 (.912)	.052 (.770)	.009 (.961)	.114 (.522)	.018 (.921)
FAS	.098 (.580)	.149 (.399)	.034 (.850)	-.053 (.768)	.025 (.889)	.124 (.486)	.054 (.762)	-.014 (.937)	.056 (.752)	-.142 (.422)	.155 (.381)	.130 (.464)	.132 (.457)	.234 (.183)
Simple RT	-.123 (.489)	-.052 (.771)	-.072 (.687)	-.065 (.715)	-.186 (.293)	-.101 (.569)	-.049 (.782)	.017 (.924)	-.110 (.537)	.176 (.318)	-.180 (.309)	-.267 (.127)	-.191 (.280)	-.206 (.242)

Data displayed as (rho (p)). Numbers of missing data for each variable can be found in Appendix G. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

10-30 seconds

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
Age	.005 (.976)	-.290 (.092)	.339 (.046)	.337 (.047)	.331 (.052)	.346 (.042)	.399 (.018)	-.295 (.086)	-.319 (.061)	-.206 (.234)	.201 (.248)	.259 (.133)	.309 (.071)	.133 (.446)
Height (m)	-.170 (.330)	.046 (.793)	.284 (.098)	.425 (.011)	.271 (.115)	-.014 (.938)	-.098 (.575)	.355 (.036)	.384 (.023)	.327 (.055)	-.077 (.661)	-.021 (.905)	.109 (.534)	-.031 (.859)
UPDRS	-.187 (.290)	-.297 (.088)	.290 (.096)	.276 (.114)	.346 (.045)	.240 (.171)	.076 (.671)	-.033 (.855)	-.018 (.921)	.003 (.986)	.105 (.555)	.049 (.781)	.219 (.214)	-.001 (.996)
sMMSE	.119 (.496)	.193 (.266)	-.203 (.241)	-.159 (.361)	-.173 (.321)	-.047 (.789)	-.103 (.556)	-.019 (.915)	.069 (.693)	-.137 (.431)	-.102 (.561)	-.056 (.751)	.031 (.858)	-.059 (.735)
ACE-III Mem	.290 (.091)	.215 (.215)	-.288 (.093)	-.260 (.131)	-.266 (.122)	-.057 (.745)	-.065 (.711)	-.192 (.269)	-.152 (.382)	-.177 (.309)	-.126 (.471)	-.157 (.369)	-.161 (.357)	-.080 (.650)
ACE-III VS	.257 (.136)	.244 (.158)	-.024 (.891)	-.071 (.684)	.021 (.907)	.121 (.490)	.050 (.773)	-.061 (.727)	.031 (.862)	-.180 (.302)	.167 (.337)	.189 (.278)	.239 (.167)	.215 (.214)
ACE-III Total	.268 (.120)	.253 (.143)	-.223 (.197)	-.187 (.282)	-.183 (.292)	-.018 (.919)	-.044 (.802)	-.120 (.492)	.003 (.985)	-.199 (.252)	-.052 (.767)	-.083 (.635)	-.041 (.815)	.010 (.953)
TMT A	.043 (.809)	-.052 (.768)	.226 (.199)	.202 (.252)	.172 (.329)	.052 (.768)	.027 (.881)	.046 (.798)	.004 (.983)	.096 (.588)	.012 (.945)	.063 (.723)	.073 (.682)	.009 (.961)
FAS	.062 (.727)	-.030 (.865)	-.060 (.738)	-.056 (.752)	-.034 (.848)	.230 (.191)	.079 (.657)	-.130 (.465)	-.013 (.940)	-.227 (.196)	.127 (.476)	.077 (.663)	.139 (.433)	.039 (.827)
Simple RT	-.063 (.723)	.092 (.603)	.060 (.736)	.051 (.775)	.011 (.949)	-.102 (.566)	-.003 (.987)	.092 (.603)	-.004 (.983)	.251 (.153)	-.160 (.367)	-.170 (.337)	-.140 (.428)	-.019 (.915)

Data displayed as (rho (p)). Numbers of missing data for each variable can be found in Appendix G.. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

30-60 seconds

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
Age	-.078 (.657)	-.355 (.036)	.317 (.064)	.237 (.171)	.316 (.064)	.232 (.181)	.379 (.025)	-.183 (.294)	-.190 (.275)	-.180 (.302)	.257 (.136)	.259 (.133)	.199 (.251)	.067 (.702)
Height (m)	-.059 (.736)	.187 (.283)	.146 (.402)	.191 (.270)	.101 (.563)	-.107 (.542)	-.046 (.793)	.416 (.013)	.456 (.006)	.317 (.063)	.034 (.846)	.099 (.573)	.136 (.437)	-.024 (.893)
UPDRS	-.297 (.088)	-.347 (.044)	.397 (.020)	.391 (.022)	.420 (.013)	.361 (.036)	.278 (.111)	.016 (.927)	.063 (.722)	-.044 (.803)	.295 (.090)	.382 (.026)	.487 (.003)	-.087 (.623)
sMMSE	-.050 (.777)	.104 (.552)	-.141 (.419)	-.048 (.784)	-.098 (.577)	.040 (.818)	-.131 (.452)	<.001 (<.001)	.109 (.535)	-.134 (.443)	-.150 (.390)	-.109 (.533)	.060 (.734)	.014 (.938)
ACE-III Mem	.190 (.274)	.194 (.265)	-.169 (.333)	-.157 (.369)	-.120 (.491)	.021 (.903)	-.076 (.662)	-.236 (.172)	-.168 (.336)	-.232 (.181)	-.041 (.815)	-.050 (.777)	-.012 (.946)	-.101 (.564)
ACE-III VS	.170 (.329)	.195 (.261)	<.001 (.999)	-.028 (.873)	.077 (.660)	.194 (.263)	.165 (.343)	-.046 (.795)	.091 (.605)	-.158 (.365)	.121 (.488)	.101 (.564)	.082 (.641)	.307 (.073)
ACE-III Total	.108 (.536)	.156 (.371)	-.145 (.406)	-.136 (.437)	-.067 (.701)	.091 (.604)	-.003 (.985)	-.143 (.414)	-.003 (.986)	-.251 (.145)	-.002 (.992)	-.013 (.942)	.094 (.590)	-.024 (.891)
TMT A	.262 (.135)	.070 (.695)	.254 (.147)	.255 (.146)	.239 (.173)	.191 (.280)	.201 (.254)	.034 (.847)	-.050 (.779)	.126 (.477)	.052 (.768)	.028 (.874)	-.068 (.701)	.012 (.945)
FAS	-.049 (.784)	-.094 (.595)	-.092 (.604)	-.082 (.646)	.003 (.988)	.244 (.164)	.150 (.396)	-.101 (.570)	.030 (.868)	-.260 (.137)	.204 (.248)	.211 (.231)	.235 (.180)	-.012 (.948)
Simple RT	.127 (.475)	.235 (.181)	.086 (.627)	.096 (.590)	-.018 (.917)	-.176 (.318)	-.056 (.751)	.173 (.327)	.062 (.728)	.268 (.126)	-.125 (.481)	-.190 (.283)	-.129 (.466)	.065 (.717)

Data displayed as (rho (p)). Numbers of missing data for each variable can be found in Appendix G.. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

> 60 seconds

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
	-.179	-.171	-.032	-.033	-.061	-.042	-.058	.078	.027	.140	.151	.225	.160	.267
Age	(.303)	(.325)	(.854)	(.849)	(.727)	(.809)	(.740)	(.655)	(.879)	(.424)	(.387)	(.195)	(.358)	(.120)
	.089	.251	-.054	.022	-.042	-.024	-.029	.287	.323	.230	.137	.043	-.005	.103
Height (m)	(.610)	(.145)	(.756)	(.900)	(.811)	(.893)	(.871)	(.094)	(.059)	(.185)	(.432)	(.807)	(.978)	(.556)
	-.494	-.409	.203	.266	.199	.134	.112	.369	.357	.387	.367	.495	.361	-.006
UPDRS	(.003)	(.016)	(.249)	(.128)	(.258)	(.451)	(.528)	(.032)	(.038)	(.024)	(.033)	(.003)	(.036)	(.973)
	-.082	-.028	-.023	.037	-.028	-.040	-.088	.180	.260	.001	.054	.137	.183	-.096
sMMSE	(.638)	(.874)	(.896)	(.831)	(.874)	(.820)	(.617)	(.300)	(.132)	(.995)	(.759)	(.433)	(.292)	(.585)
	.285	.218	-.156	-.136	-.141	-.138	-.148	-.159	-.114	-.250	-.101	-.136	-.055	-.151
ACE-III Mem	(.097)	(.208)	(.372)	(.436)	(.420)	(.428)	(.395)	(.362)	(.516)	(.147)	(.563)	(.436)	(.753)	(.387)
	.141	.156	.066	.029	.095	.008	.021	.091	.183	-.082	.030	-.080	-.020	.114
ACE-III VS	(.418)	(.371)	(.705)	(.868)	(.587)	(.963)	(.905)	(.605)	(.291)	(.640)	(.866)	(.647)	(.908)	(.513)
	.194	.145	-.041	-.030	-.016	-.006	-.053	-.018	.058	-.184	.086	.049	.032	-.132
ACE-III Total	(.264)	(.407)	(.817)	(.862)	(.928)	(.973)	(.763)	(.920)	(.740)	(.289)	(.625)	(.782)	(.857)	(.450)
	.077	.045	-.015	-.017	-.022	.129	.099	-.231	-.241	-.138	.165	.030	-.049	-.018
TMT A	(.664)	(.800)	(.934)	(.923)	(.904)	(.468)	(.578)	(.188)	(.169)	(.438)	(.350)	(.866)	(.782)	(.920)
	.159	.109	-.172	-.191	-.170	.016	-.085	-.134	-.088	-.197	.268	.170	.194	.064
FAS	(.369)	(.540)	(.330)	(.280)	(.337)	(.930)	(.634)	(.450)	(.619)	(.263)	(.125)	(.337)	(.271)	(.721)
	-.086	-.067	.137	.187	.096	-.004	.040	.013	-.022	.143	-.040	-.040	-.136	.003
Simple RT	(.629)	(.705)	(.439)	(.291)	(.589)	(.980)	(.821)	(.943)	(.900)	(.419)	(.823)	(.823)	(.445)	(.987)

Data displayed as (rho (p)). Numbers of missing data for each variable can be found in. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

Appendix M Spearman's Correlations between motor disease severity, cognitive function and free-living gait characteristics across different walking bout lengths in the dementia with Lewy bodies group

< 10 seconds

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
	-.243	-.124	.130	.233	.166	-.080	-.228	.131	.079	.191	.009	-.007	-.020	-.108
Age	(.197)	(.514)	(.492)	(.215)	(.382)	(.675)	(.226)	(.491)	(.678)	(.312)	(.964)	(.971)	(.918)	(.571)
	-.056	.233	.415	.473	.329	.117	-.106	.307	.179	.428	.159	.114	.207	.094
Height (m)	(.769)	(.216)	(.023)	(.008)	(.075)	(.538)	(.577)	(.099)	(.344)	(.018)	(.401)	(.550)	(.273)	(.621)
	-.054	-.325	-.404	-.482	-.375	-.100	-.130	-.423	-.463	-.437	-.272	-.324	-.372	-.406
UPDRS	(.779)	(.086)	(.030)	(.008)	(.045)	(.606)	(.502)	(.022)	(.011)	(.018)	(.154)	(.086)	(.047)	(.029)
	.169	.400	.201	.220	.165	.289	.041	.382	.395	.270	.132	.172	.239	.324
sMMSE	(.371)	(.029)	(.286)	(.242)	(.384)	(.121)	(.828)	(.037)	(.031)	(.149)	(.488)	(.362)	(.203)	(.081)
	.046	.066	.033	.058	.040	.085	.028	.035	.137	-.116	.074	.082	.212	.069
ACE-III Mem	(.813)	(.735)	(.865)	(.766)	(.838)	(.662)	(.884)	(.858)	(.477)	(.550)	(.703)	(.671)	(.270)	(.721)
	.182	.220	.294	.342	.280	.304	.225	.210	.255	.087	.200	.262	.400	.295
ACE-III VS	(.345)	(.251)	(.122)	(.069)	(.141)	(.109)	(.240)	(.275)	(.182)	(.652)	(.299)	(.170)	(.032)	(.120)
	.104	.243	.157	.159	.139	.169	.062	.250	.333	.065	.134	.174	.289	.269
ACE-III Total	(.591)	(.204)	(.416)	(.410)	(.473)	(.382)	(.751)	(.191)	(.077)	(.739)	(.488)	(.368)	(.128)	(.158)
	-.073	-.299	-.164	-.332	-.117	-.245	-.058	-.406	-.470	-.245	-.208	-.294	-.487	-.249
TMT A	(.754)	(.188)	(.478)	(.141)	(.614)	(.284)	(.801)	(.067)	(.032)	(.284)	(.366)	(.197)	(.025)	(.276)
	.035	.261	.252	.100	.233	.104	.040	.157	.195	.001	.170	.167	.180	.268
FAS	(.862)	(.180)	(.196)	(.614)	(.232)	(.597)	(.840)	(.426)	(.320)	(.997)	(.388)	(.397)	(.361)	(.168)
	.137	-.107	-.038	-.099	-.020	-.038	.097	-.175	-.178	-.116	-.045	-.132	-.247	-.077
Simple RT	(.514)	(.611)	(.858)	(.637)	(.924)	(.855)	(.645)	(.404)	(.393)	(.580)	(.832)	(.528)	(.234)	(.715)

Data displayed as (rho (p)). Numbers of missing data for each variable can be found in. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

10-30 seconds

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
	-.346	-.202	.207	.186	.205	-.139	-.140	.176	.130	.229	-.002	.051	.072	-.284
Age	(.061)	(.285)	(.273)	(.324)	(.278)	(.464)	(.462)	(.352)	(.493)	(.224)	(.990)	(.787)	(.704)	(.128)
	-.187	.201	.329	.333	.255	-.105	-.063	.376	.343	.479	.075	.076	.083	.068
Height (m)	(.323)	(.288)	(.076)	(.072)	(.173)	(.580)	(.740)	(.041)	(.064)	(.007)	(.693)	(.690)	(.662)	(.721)
	-.058	-.305	-.269	-.295	-.246	-.057	-.144	-.305	-.311	-.288	-.250	-.242	-.213	-.407
UPDRS	(.765)	(.107)	(.159)	(.121)	(.199)	(.767)	(.457)	(.108)	(.100)	(.130)	(.190)	(.205)	(.267)	(.028)
	.183	.499	-.102	-.063	-.158	-.136	-.116	.220	.241	.201	.067	.127	-.010	.232
sMMSE	(.334)	(.005)	(.591)	(.742)	(.406)	(.474)	(.540)	(.242)	(.200)	(.286)	(.725)	(.504)	(.958)	(.217)
	.019	.169	-.121	-.104	-.143	-.172	-.175	.065	.181	.029	-.077	-.023	-.047	.062
ACE-III Mem	(.923)	(.382)	(.531)	(.591)	(.460)	(.373)	(.363)	(.736)	(.348)	(.880)	(.691)	(.906)	(.809)	(.750)
	.209	.315	.113	.123	.134	.163	.167	.052	.124	.061	.158	.193	.203	.308
ACE-III VS	(.276)	(.096)	(.559)	(.525)	(.489)	(.399)	(.385)	(.787)	(.521)	(.753)	(.413)	(.315)	(.290)	(.105)
	.103	.345	-.090	-.073	-.117	-.108	-.136	.156	.252	.119	.015	.074	.035	.254
ACE-III Total	(.595)	(.067)	(.644)	(.706)	(.547)	(.576)	(.481)	(.419)	(.188)	(.537)	(.938)	(.702)	(.857)	(.184)
	-.145	-.417	.081	-.110	.064	-.006	.051	-.288	-.395	-.136	-.278	-.358	-.282	-.251
TMT A	(.529)	(.060)	(.729)	(.634)	(.784)	(.978)	(.827)	(.205)	(.077)	(.556)	(.223)	(.111)	(.216)	(.273)
	.134	.302	.074	-.019	.052	-.105	-.060	.157	.260	.061	.136	.079	.096	.286
FAS	(.496)	(.119)	(.708)	(.922)	(.791)	(.595)	(.761)	(.425)	(.181)	(.758)	(.489)	(.689)	(.628)	(.140)
	.046	-.156	.205	.115	.152	.111	.113	-.138	-.205	-.055	-.148	-.214	-.191	-.094
Simple RT	(.827)	(.456)	(.325)	(.583)	(.470)	(.598)	(.590)	(.509)	(.327)	(.793)	(.479)	(.305)	(.361)	(.655)

Data displayed as (rho (p)). Numbers of missing data for each variable can be found in. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

30-60 seconds

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
Age	-.460 (.010)	-.351 (.057)	.273 (.144)	.220 (.243)	.300 (.107)	-.041 (.829)	-.200 (.290)	.306 (.100)	.279 (.136)	.293 (.116)	.190 (.316)	.235 (.212)	.257 (.170)	-.115 (.547)
Height (m)	-.143 (.451)	.206 (.275)	.249 (.185)	.317 (.088)	.177 (.349)	.095 (.616)	-.008 (.965)	.369 (.045)	.339 (.067)	.468 (.009)	.146 (.442)	.099 (.604)	.125 (.510)	.228 (.225)
UPDRS	-.137 (.479)	-.297 (.117)	-.222 (.247)	-.248 (.195)	-.152 (.432)	-.054 (.782)	-.129 (.505)	-.184 (.339)	-.192 (.318)	-.203 (.290)	-.300 (.114)	-.195 (.311)	-.299 (.116)	-.610 (<.001)
sMMSE	.197 (.296)	.487 (.006)	-.186 (.324)	-.193 (.306)	-.233 (.216)	-.150 (.428)	-.096 (.612)	.074 (.699)	.069 (.716)	.091 (.631)	-.065 (.733)	-.103 (.588)	-.148 (.435)	.109 (.566)
ACE-III Mem	.029 (.881)	.204 (.289)	-.180 (.349)	-.189 (.327)	-.170 (.379)	-.253 (.186)	-.097 (.616)	-.014 (.941)	.043 (.826)	-.025 (.899)	-.118 (.543)	-.119 (.540)	-.243 (.204)	-.007 (.973)
ACE-III VS	.216 (.260)	.335 (.075)	.058 (.766)	.032 (.868)	.058 (.764)	.003 (.988)	.173 (.369)	-.021 (.915)	-.019 (.921)	-.058 (.767)	.106 (.585)	.016 (.936)	-.128 (.507)	.074 (.701)
ACE-III Total	.145 (.453)	.358 (.057)	-.153 (.427)	-.138 (.474)	-.148 (.443)	-.172 (.373)	-.078 (.686)	.025 (.896)	.083 (.669)	-.007 (.971)	-.018 (.926)	-.071 (.715)	-.198 (.302)	.174 (.368)
TMT A	-.217 (.345)	-.574 (.007)	-.043 (.854)	-.014 (.951)	.029 (.902)	.025 (.915)	-.075 (.746)	-.127 (.582)	-.151 (.515)	-.009 (.969)	-.229 (.319)	-.165 (.475)	-.030 (.898)	-.147 (.526)
FAS	.132 (.504)	.288 (.138)	.019 (.925)	.008 (.966)	.041 (.838)	-.034 (.864)	-.004 (.986)	.076 (.702)	.168 (.393)	.013 (.949)	.043 (.829)	-.155 (.431)	-.329 (.087)	.338 (.078)
Simple RT	-.017 (.936)	-.165 (.429)	-.035 (.867)	-.078 (.709)	-.028 (.893)	-.115 (.585)	-.051 (.810)	-.088 (.677)	-.116 (.580)	-.012 (.956)	-.181 (.387)	-.059 (.779)	-.028 (.893)	-.244 (.240)

Data displayed as (rho (p)). Numbers of missing data for each variable can be found in Appendix G. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

> 60 seconds

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
	-.321	-.256	-.033	-.008	-.029	-.102	-.207	.258	.188	.222	-.047	<.001	.056	-.058
Age	(.084)	(.172)	(.864)	(.966)	(.878)	(.590)	(.272)	(.169)	(.320)	(.238)	(.804)	(.998)	(.768)	(.761)
	-.032	.280	.104	.087	.060	.172	.076	.536	.450	.592	.046	.131	.206	-.018
Height (m)	(.867)	(.134)	(.585)	(.646)	(.752)	(.364)	(.691)	(.002)	(.013)	(.001)	(.808)	(.490)	(.275)	(.926)
	-.168	-.354	.049	.045	.089	.101	.107	-.143	-.150	-.153	-.197	-.129	-.180	-.314
UPDRS	(.383)	(.060)	(.800)	(.818)	(.645)	(.603)	(.579)	(.458)	(.438)	(.427)	(.306)	(.505)	(.350)	(.098)
	.150	.205	.132	.132	.155	.311	.267	.057	.039	.079	.046	.180	.117	.089
sMMSE	(.428)	(.277)	(.486)	(.488)	(.413)	(.095)	(.154)	(.765)	(.838)	(.677)	(.808)	(.342)	(.538)	(.639)
	-.159	-.041	.250	.245	.248	.266	.145	.289	.337	.261	-.170	-.079	-.094	.091
ACE-III Mem	(.409)	(.832)	(.191)	(.201)	(.195)	(.163)	(.454)	(.128)	(.074)	(.172)	(.379)	(.682)	(.629)	(.638)
	.055	.128	.289	.291	.288	.316	.340	.100	.194	.085	-.057	.027	.026	.249
ACE-III VS	(.778)	(.509)	(.128)	(.125)	(.130)	(.095)	(.071)	(.605)	(.313)	(.663)	(.769)	(.891)	(.895)	(.193)
	.015	.100	.202	.201	.214	.279	.184	.207	.265	.182	-.097	-.004	-.035	.181
ACE-III Total	(.940)	(.607)	(.294)	(.296)	(.266)	(.142)	(.339)	(.282)	(.164)	(.345)	(.616)	(.984)	(.858)	(.346)
	-.119	-.271	-.196	-.155	-.208	-.186	-.230	-.209	-.262	-.152	-.083	-.166	-.174	-.081
TMT A	(.606)	(.234)	(.394)	(.504)	(.366)	(.420)	(.316)	(.363)	(.251)	(.511)	(.720)	(.471)	(.451)	(.729)
	.041	.159	.165	.097	.151	.224	.172	.288	.297	.280	.075	-.042	-.148	-.028
FAS	(.835)	(.418)	(.401)	(.622)	(.442)	(.252)	(.381)	(.137)	(.124)	(.149)	(.706)	(.830)	(.452)	(.888)
	-.173	-.302	.317	.372	.304	.212	.140	-.111	-.132	-.065	.374	.324	.260	-.022
Simple RT	(.408)	(.143)	(.123)	(.067)	(.140)	(.308)	(.504)	(.598)	(.531)	(.756)	(.066)	(.114)	(.209)	(.919)

Data displayed as (rho (p)). Numbers of missing data for each variable can be found in Appendix G. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

Appendix N Spearman's Correlations between motor disease severity, cognitive function and free-living gait characteristics across different walking bout lengths in the Parkinson's disease dementia group

< 10 seconds

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
	-.462	-.618	-.184	-.269	-.037	-.187	-.362	-.431	-.468	-.231	-.202	-.238	-.188	-.492
Age	(.072)	(.011)	(.495)	(.313)	(.892)	(.488)	(.168)	(.095)	(.068)	(.389)	(.454)	(.374)	(.485)	(.053)
	.156	.150	.076	.397	.209	.262	.059	.021	.100	.397	.032	.071	.079	-.118
Height (m)	(.564)	(.579)	(.778)	(.128)	(.438)	(.327)	(.829)	(.940)	(.713)	(.128)	(.905)	(.795)	(.770)	(.664)
	-.393	-.761	-.350	-.446	-.132	-.343	-.121	-.629	-.604	-.421	-.475	-.518	-.493	-.736
UPDRS	(.147)	(.001)	(.201)	(.095)	(.639)	(.211)	(.666)	(.012)	(.017)	(.118)	(.074)	(.048)	(.062)	(.002)
	.056	.366	.012	.128	-.086	-.090	-.101	.474	.433	.526	.353	.445	.314	.420
sMMSE	(.836)	(.163)	(.965)	(.638)	(.752)	(.739)	(.710)	(.063)	(.094)	(.036)	(.180)	(.084)	(.236)	(.106)
	.164	.364	.255	.382	.160	.131	.087	.315	.302	.415	.306	.397	.422	.342
ACE-III Mem	(.560)	(.182)	(.359)	(.160)	(.569)	(.642)	(.757)	(.253)	(.274)	(.124)	(.268)	(.143)	(.117)	(.212)
	.473	.688	.302	.573	.228	.513	.256	.560	.647	.200	.124	.193	.330	.473
ACE-III VS	(.075)	(.005)	(.274)	(.026)	(.414)	(.050)	(.358)	(.030)	(.009)	(.475)	(.659)	(.491)	(.230)	(.075)
	.226	.612	.336	.413	.260	.205	-.039	.609	.589	.610	.368	.465	.424	.519
ACE-III Total	(.418)	(.015)	(.221)	(.126)	(.349)	(.464)	(.889)	(.016)	(.021)	(.016)	(.177)	(.081)	(.116)	(.047)
	-.107	-.418	-.046	-.114	.082	-.243	-.021	-.461	-.514	-.286	-.064	-.107	-.100	-.364
TMT A	(.704)	(.121)	(.869)	(.685)	(.771)	(.383)	(.940)	(.084)	(.050)	(.302)	(.820)	(.704)	(.723)	(.182)
	-.168	.297	.115	.081	.149	.106	-.227	.553	.593	.571	-.050	.018	-.050	.188
FAS	(.549)	(.282)	(.684)	(.775)	(.597)	(.708)	(.415)	(.032)	(.020)	(.026)	(.859)	(.950)	(.859)	(.502)
	-.189	-.532	-.443	-.318	-.307	-.332	.075	-.536	-.507	-.339	-.407	-.400	-.411	-.571
Simple RT	(.499)	(.041)	(.098)	(.248)	(.265)	(.226)	(.791)	(.040)	(.054)	(.216)	(.132)	(.140)	(.128)	(.026)

Data displayed as (rho (p)). Numbers of missing data for each variable can be found in Appendix G. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

10-30 seconds

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
Age	-.453 (.078)	-.678 (.004)	-.155 (.568)	-.234 (.383)	-.231 (.389)	-.066 (.807)	-.166 (.538)	-.496 (.051)	-.430 (.097)	-.380 (.147)	-.132 (.625)	-.188 (.485)	.041 (.880)	-.472 (.065)
Height (m)	.141 (.602)	.209 (.438)	.409 (.116)	.444 (.085)	.315 (.235)	.347 (.188)	.032 (.905)	.197 (.464)	.235 (.380)	.309 (.244)	<.001 (1<.001)	.071 (.795)	.312 (.240)	.012 (.966)
UPDRS	-.264 (.341)	-.636 (.011)	.207 (.459)	.189 (.499)	.168 (.550)	.250 (.369)	<.001 (<.001)	-.368 (.177)	-.364 (.182)	-.175 (.533)	.157 (.576)	-.114 (.685)	.029 (.919)	-.511 (.052)
sMMSE	-.067 (.806)	.338 (.200)	-.151 (.576)	-.053 (.844)	-.187 (.488)	-.169 (.531)	-.313 (.238)	.415 (.110)	.307 (.248)	.394 (.131)	.073 (.789)	.169 (.531)	.133 (.622)	.316 (.233)
ACE-III Mem	.058 (.837)	.349 (.202)	.095 (.737)	.147 (.600)	.005 (.985)	-.005 (.985)	-.189 (.499)	.280 (.312)	.158 (.573)	.379 (.164)	.024 (.933)	-.069 (.807)	.078 (.782)	.149 (.595)
ACE-III VS	.411 (.128)	.710 (.003)	.248 (.372)	.274 (.323)	.304 (.271)	.163 (.561)	.350 (.201)	.467 (.079)	.595 (.019)	.222 (.426)	.007 (.979)	.271 (.329)	.174 (.535)	.380 (.163)
ACE-III Total	.065 (.819)	.594 (.019)	.083 (.770)	.090 (.750)	.065 (.819)	-.110 (.698)	-.248 (.373)	.548 (.035)	.456 (.088)	.494 (.061)	.093 (.741)	.253 (.363)	.259 (.352)	.438 (.102)
TMT A	-.168 (.550)	-.468 (.079)	.029 (.919)	-.036 (.899)	.071 (.800)	-.021 (.940)	.104 (.713)	-.454 (.089)	-.514 (.050)	-.296 (.283)	.057 (.840)	-.271 (.328)	-.121 (.666)	-.386 (.156)
FAS	-.272 (.326)	.308 (.264)	-.014 (.960)	-.079 (.780)	.047 (.869)	-.118 (.675)	-.303 (.273)	.428 (.112)	.525 (.045)	.260 (.350)	.021 (.939)	.494 (.061)	.278 (.317)	.455 (.089)
Simple RT	-.125 (.657)	-.457 (.087)	-.182 (.516)	-.186 (.508)	-.143 (.612)	.036 (.899)	.193 (.491)	-.614 (.015)	-.504 (.056)	-.529 (.043)	-.293 (.289)	-.368 (.177)	-.382 (.160)	-.439 (.101)

Data displayed as (rho (p)). Numbers of missing data for each variable can be found in Appendix G.. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

30-60 seconds

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
Age	-.761 (.001)	-.764 (.001)	-.172 (.524)	-.193 (.474)	-.172 (.524)	-.104 (.700)	-.311 (.242)	-.411 (.114)	-.362 (.168)	-.318 (.230)	-.203 (.451)	-.185 (.492)	.006 (.983)	-.241 (.368)
Height (m)	.303 (.254)	.115 (.672)	.279 (.295)	.265 (.322)	.294 (.269)	.459 (.074)	.191 (.478)	.112 (.680)	.132 (.625)	.032 (.905)	-.153 (.572)	-.056 (.837)	.065 (.812)	-.088 (.745)
UPDRS	-.332 (.226)	-.693 (.004)	.211 (.451)	.193 (.491)	.189 (.499)	.400 (.140)	.179 (.524)	-.400 (.140)	-.436 (.104)	-.414 (.125)	-.054 (.850)	-.229 (.413)	-.254 (.362)	-.357 (.191)
sMMSE	.216 (.421)	.509 (.044)	-.190 (.481)	-.185 (.492)	-.199 (.461)	-.169 (.531)	-.230 (.392)	.356 (.176)	.365 (.165)	.316 (.233)	-.022 (.935)	.191 (.478)	.077 (.777)	.120 (.658)
ACE-III Mem	.255 (.359)	.451 (.091)	.075 (.792)	.095 (.737)	.071 (.802)	.140 (.618)	-.027 (.923)	.231 (.407)	.215 (.442)	.220 (.430)	-.069 (.807)	.118 (.675)	.071 (.802)	-.078 (.782)
ACE-III VS	.428 (.111)	.658 (.008)	.259 (.350)	.245 (.380)	.287 (.299)	.098 (.728)	.404 (.135)	.495 (.061)	.580 (.023)	.432 (.108)	.063 (.823)	.072 (.798)	.085 (.763)	.265 (.340)
ACE-III Total	.379 (.164)	.713 (.003)	.077 (.784)	.056 (.844)	.084 (.765)	.095 (.736)	-.038 (.894)	.469 (.078)	.478 (.072)	.431 (.109)	.088 (.755)	.285 (.302)	.233 (.402)	.122 (.665)
TMT A	.014 (.960)	-.443 (.098)	.011 (.970)	.007 (.980)	-.004 (.990)	.379 (.164)	.264 (.341)	-.486 (.066)	-.550 (.034)	-.432 (.108)	-.061 (.830)	-.189 (.499)	-.239 (.390)	-.446 (.095)
FAS	.177 (.527)	.464 (.082)	-.002 (.995)	-.061 (.829)	.011 (.970)	.104 (.713)	-.086 (.761)	.381 (.161)	.485 (.067)	.292 (.291)	.179 (.523)	.321 (.244)	.224 (.423)	.238 (.393)
Simple RT	.143 (.612)	-.425 (.114)	-.196 (.483)	-.186 (.508)	-.218 (.435)	.264 (.341)	.304 (.271)	-.636 (.011)	-.582 (.023)	-.668 (.007)	-.382 (.160)	-.525 (.044)	-.596 (.019)	-.468 (.079)

Data displayed as (rho (p)). Numbers of missing data for each variable can be found in Appendix G. sMMSE= Mini Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

> 60 seconds

rho(p)	Step Velocity	Step Length	Step Time SD	Stance Time SD	Swing Time SD	Step Length SD	Step Velocity SD	Step Time	Stance Time	Swing Time	Step Time Asy	Stance Time Asy	Swing Time Asy	Step Length Asy
Age	-.559 (.030)	-.561 (.029)	.079 (.781)	.127 (.652)	.064 (.820)	-.091 (.747)	.016 (.955)	-.273 (.324)	-.381 (.162)	-.136 (.629)	-.229 (.412)	-.075 (.790)	-.123 (.661)	-.474 (.075)
Height (m)	.100 (.723)	.021 (.940)	.168 (.550)	.271 (.328)	.150 (.594)	.189 (.499)	.132 (.639)	.075 (.791)	.136 (.630)	-.054 (.850)	-.139 (.621)	-.111 (.694)	-.082 (.771)	-.489 (.064)
UPDRS	-.221 (.428)	-.604 (.017)	.111 (.694)	-.025 (.930)	.114 (.685)	.211 (.451)	.318 (.248)	-.632 (.011)	-.614 (.015)	-.475 (.074)	-.261 (.348)	-.296 (.283)	-.525 (.044)	-.518 (.048)
sMMSE	.150 (.595)	.503 (.056)	-.231 (.408)	-.155 (.581)	-.263 (.343)	-.425 (.114)	-.607 (.016)	.490 (.064)	.508 (.053)	.391 (.150)	.202 (.471)	.124 (.659)	.306 (.267)	.416 (.123)
ACE-III Mem	.142 (.629)	.312 (.277)	-.092 (.754)	.128 (.662)	-.097 (.742)	-.043 (.885)	-.200 (.493)	.317 (.270)	.339 (.235)	.236 (.417)	.232 (.426)	.178 (.544)	.362 (.204)	.164 (.575)
ACE-III VS	.561 (.037)	.648 (.012)	.161 (.583)	.053 (.858)	.145 (.621)	-.048 (.870)	-.048 (.870)	.446 (.110)	.508 (.064)	.163 (.577)	.094 (.749)	-.133 (.650)	.085 (.773)	.356 (.211)
ACE-III Total	.345 (.227)	.666 (.009)	-.053 (.857)	.029 (.922)	-.062 (.833)	-.184 (.530)	-.319 (.267)	.655 (.011)	.677 (.008)	.396 (.161)	.252 (.384)	.228 (.433)	.372 (.191)	.363 (.202)
TMT A	-.565 (.035)	-.670 (.009)	.552 (.041)	.415 (.140)	.530 (.051)	.341 (.233)	.292 (.311)	-.284 (.326)	-.407 (.149)	-.116 (.692)	.178 (.543)	-.051 (.864)	-.051 (.864)	-.240 (.409)
FAS	.496 (.072)	.718 (.004)	.055 (.852)	-.134 (.647)	.068 (.817)	-.209 (.473)	-.053 (.858)	.471 (.089)	.584 (.028)	.176 (.547)	.020 (.946)	.093 (.753)	-.002 (.994)	.335 (.242)
Simple RT	-.108 (.714)	-.499 (.069)	.327 (.253)	.134 (.648)	.284 (.326)	.174 (.553)	.363 (.203)	-.644 (.013)	-.609 (.021)	-.591 (.026)	-.292 (.311)	-.552 (.041)	-.530 (.051)	-.345 (.227)

Data displayed as (rho (p)). Numbers of missing data for each variable can be found in Appendix G. sMMSE = Standardised Mental State Exam, ACE-III = Addenbrookes Cognitive Examination III, Mem = Memory subscale, VS = Visuospatial subscale, TMT A = Trail Making Test Part A, FAS = FAS test, Simple RT = Simple Reaction Time Test Mean Time

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