Gait as a predictor for cognitive decline in Parkinson's disease

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PhD

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"Walking becomes a task which cannot be performed without considerable attention. The legs are not raised to that height, or with that promptitude which the will directs, so that the utmost care is necessary to prevent frequent falls'

James Parkinson, 1817

Abstract

Cognitive decline and dementia are core features of Parkinson's disease (PD) with major personal and socioeconomic impact. Identifying individuals at risk of cognitive decline and dementia is vital in order to optimise clinical management and develop novel therapeutics. However, biomarkers for cognitive decline remain a major unmet need. A large structured review undertaken as part of this thesis revealed discrete gait characteristics predicted cognitive decline and dementia in older adults but to date no such study has been conducted in PD. Thus, the primary aim of this thesis was to investigate gait as a clinical biomarker for cognitive decline in PD.

Newly diagnosed PD participants (n=118) and controls (n=184) completed a detailed quantitative gait assessment under single and dual task conditions at baseline. Additionally, a comprehensive battery of neuropsychological assessments were completed at baseline, 18 and 36 months later. Mixed-effects models identified significant gait predictors of cognitive decline over three years. Baseline cognition was also explored as a predictor for cognitive decline. Finally, gait was collected in the free-living environment using a body-worn monitor (BWM) and cross-sectional analysis explored free-living gait-cognition associations.

Original contributions to knowledge were that gait characteristics under single and dual task in an incident cohort of PD predicted decline in discrete cognitive domains over three years. Critically, in comparison to gait, baseline neuropsychological assessment performance did not predict cognitive decline. Additionally, cross-sectional analysis in early PD revealed discrete gait-cognition associations in free-living signifying future clinical utility for gait as a clinical biomarker.

This thesis provides the first evidence for gait as a clinical biomarker for cognitive decline in PD. Discrete gait characteristics may provide a low cost clinical biomarker and make an important contribution to prognostic models of dementia risk in PD.

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I would like to acknowledge those who have supported me throughout my project over the last three years at Newcastle University. Firstly, I would like to thank my supervisors Professor Lynn Rochester, Dr Sue Lord and Professor David Burn who have provided me with support over the past three years. Their expertise and guidance throughout has been invaluable.

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Statement of work undertaken

Professor Lynn Rochester is the Chief Investigator for the Incidence of Cognitive Impairments in Cohorts with Longitudinal Evaluation in Parkinson's disease- Gait (ICICLE-Gait) study and was responsible for the study design and grant application. The ICICLE-Gait study is a nested study within ICICLE-PD of which Professor David Burn is the Chief Investigator. Baseline and/or 18 month data collection commenced prior to my PhD and was collected by the following; Dr Sue Lord, Dr Brook Galna, Dadirayi Mhiripiri, Dr Tien Khoo, Dr Alison Yarnall and Dr Gordon Duncan. Dr Brook Galna, Dr Rachael Lawson, Leanne Thompson, Victoria Foster and I contributed to both 18 and 36 month data collection. Additionally, Philip Brown contributed to 36 month ICICLE-Gait data collection. Data checking and cleaning was completed by myself, Dr Lawson, Dr Yarnall, Dr Duncan, Dr Fionnuala Johnston, Dr Khoo, Philip Brown and Heather Hunter. Body worn monitor data collection was managed and completed by myself, data was processed by Aodhán Hickey and the Matlab® code was developed by Dr Alan Godfrey and Dr Silvia Del Din.

As part of the ICICLE-PD study, I have completed over 200 participant assessments for ICICLE-Gait as well as contributing to ICICLE-PD testing. I have also continued to complete participant visits at 54 and 72 assessments which are not a part of this thesis. Since commencing this PhD I have helped manage the ICICLE-Gait project, overseen data collection and data checks as well as submitting ethical amendments when needed.

Statistical analysis was run independently by me with and with statistical support and advice from Dr Shirley Coleman and Dr Rachael Lawson. I was responsible for the writing of this thesis.

Awards and publications arising from this Thesis

Awards

- Best poster- National BRU Postgraduate Event

- Best oral presentation- NIHR Trainee Camp

- Guarantors of Brain Travel Grant (£800 in 2016)

- World Parkinson's Congress Travel Grant ($900 in 2016)

- British Geriatric Society; Therapist Travel Grant (£300 in 2016)

- Private Physiotherapy Educational Foundation; Individual Scholarship Scheme A (£2000 in 2015)

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Publications

Morris R, Lord S, Bunce J, Burn D, Rochester L. Gait and cognition: mapping the global and discrete relationships in ageing and neurodegenerative disease. 2016. Neuroscience and Biobehavioural Reviews.

Morris R, Hickey A, Del Din S, Godfrey A, Lord S, Rochester L. A model of free-living gait; a factor analysis in Parkinson's disease. 2016. Gait and Posture.

Morris R, Lord S, Lawson RA, Coleman S, Galna B, Duncan GW, Khoo TK, Yarnall AJ, Burn DJ, Rochester L. Gait rather than cognition predicts cognitive decline in early Parkinson's disease. *Under review.* Journal of Gerontology Series A

Other publications:

Rochester L, Galna B, Lord S, Yarnall AJ, **Morris R**, Duncan G, Khoo T, Mollenhauer B, Burn DJ. Decrease in Alpha Beta 1-42 predicts dopa-resistant gait progression in early Parkinson's disease. 2016. Neurology, *under review*.

Godfrey A, Bourke A, Del Din S, **Morris R**, Hickey A, Helbostad J, Rochester L. Towards holistic free-living assessment in Parkinson's disease: unification of gait and fall algorithms with a single accelerometer. 2016. Engineering in Medicine and Biology Society (EMBC), 2016 38th Annual International Conference of the IEEE

Ladha C, Del Din S, Nazarpour K, Hickey A, **Morris R**, Catt M, Rochester L, Godfrey A. Toward a low-cost gait analysis system for clinical and free-living assessment. 2016. Engineering in Medicine and Biology Society (EMBC), 2016 38th Annual International Conference of the IEEE

Del Din S, Hickey A, Woodman S, Hiden H, **Morris R**, Watson P, Nazarpour K, Catt M, Rochester L, Godfrey A. Accelerometer-based gait assessment: pragmatic deployment on an international scale. 2016. IEEE Workshop on Statistical Signal Processing

Godfrey A, **Morris R**, Hickey A, Del Din S. Beyond the front end: investigating a thigh worn accelerometer device for step count and bout detection in Parkinson's disease. 2016. Medical Engineering & Physics.

Oral presentations

North East Parkinson's Research Interest Group (4th July 2016, Hancock Museum)
Feedback from the ICICLE-Gait study

Parkinson's Interest Group Local, Education and Training (PIGLET, 10th June 2016, Bowburn Hall, Durham)
Update on falls; cause, prevention and management
Pint of Science (25th May 2016, The Core, Newcastle upon Tyne, UK)
Mind your step! The impact of cognition on walking

Parkinson's Matters- PPI event (9th November 2015, The Beacon, Newcastle upon Tyne)

Feedback from the ICICLE-Gait study

Physiotherapy UK Conference (16th-17th October 2015, Liverpool, UK)

Gait predicts decline in attention over 18 months in early Parkinson's disease

NIHR Trainee Camp (July, 2015. Ashbridge Business School, Berkhamstead) - **Prize winner**

Gait as a predictor for cognitive decline in early Parkinson's disease

BRC Postgraduate Student Translational Research Day- Invited Presentation (1st June 2015, Newcastle, United Kingdom)

What can gait tell us about cognition and Parkinson's disease? Two different perspectives

Newcastle Hospitals Therapy Services Conference (5th February, 2015)

Gait as a predictor for cognitive decline in early Parkinson's disease

Demands Journal Club (February, 2015)

Gait as a predictor for cognitive decline in Parkinson's disease

Parkinson's disease UK (November 3rd- 4th 2014, York, United Kingdom)

Gait as a predictor for decline cognition in early Parkinson's disease

Poster presentations

World Parkinson's Congress (20th-23rd September 2016, Portland, Oregon) - **selected for guided poster tour**

Gait rather than cognition predicts cognitive decline in early Parkinson's disease

International Congress of Parkinson's disease and Movement Disorders (18/06/2016-23/06/2016 Berlin, Germany)

Gait and cognition: mapping the global and discrete relationships in ageing and neurodegenerative disease

International Congress of Parkinson's disease and Movement Disorders (18/06/2016-23/06/2016 Berlin, Germany)
Gait rather than cognition predicts cognitive decline in early Parkinson's disease

National biomedical research unit (BRU) postgraduate event (September, 2015. London)-**Prize winner**
Gait predicts decline in attention over three years in Parkinson's disease

International society for posture and gait research (28/06/2015- 02/07/2015, Seville, Spain)
Comparing single and dual-task gait as predictors of decline in attention in people with Parkinson's disease.

International Congress of Parkinson's disease and Movement Disorders (14/06/2015-18/06/2015 San Diego, USA)
Gait predicts decline in attention over three years in an incident cohort of Parkinson's disease

BRC Allied Health Professionals Event (13th April, 2015)
Gait as a predictor for cognitive decline in Parkinson's disease

Newcastle Hospitals Therapy Services Conference (27th February, 2014)
Predicting cognitive decline in Parkinson's disease using gait analysis

CONTENTS

List of Tables

List of Figures

Abbreviations

5HT= Serotonin

AB= Ambulatory Bout

ABC= Activities Balance Confidence questionnaire

Ach= Acetylcholine

AchE= Acetylcholinesterase

AD= Alzheimer's disease

ADL= Activities of Daily Living

BG= Basal Ganglia

BMI= Body Mass Index

BWM= Body Worn Monitors

CANTAB= Cambridge Neuropsychological Test Automated Battery

CDR= Cognitive Drug Research

CI= Cognitive Impairment

CRT= Choice Reaction Time

CSF= Cerebrospinal Fluid

CV= Coefficient of Variation

DLB= Dementia with Lewy Bodies

DSM= Diagnostic and Statistical Manual

DV= Digit Vigilance

EEG= Electroencephalogram

EGF= Epidermal Growth Factor

f-MRI= Functional Magnetic Resonance Imaging

FOG= Freezing of Gait

FTD= Frontotemporal Dementia

H & Y= Hoehn and Yahr

iTug= Instrumented Timed up and Go

GDS= Geriatric Depression Scale

ICICLE= Incidence of Cognitive Impairment in Cohorts of Longitudinal Evaluation

L5= Fifth Lumbar Vertebrae

LB= Lewy Bodies

LBD= Lewy Body Dementia

LEDD= Levadopa Equivalent Daily Dose

LMEM= Linear Mixed Effect Model

LRRK2= Leucine Rich Repeat Kinase 2

MCI= Mild Cognitive Impairment

MCR= Motor Cognitive Risk

MDS-UPDRS= Movement Disorders Society Unified Parkinson's disease Rating Scale

MeSH= Medical Subject Headings

MMSE= Mini Mental Status Examination

MoCA= Montreal Cognitive Assessment

MRI= Magnetic Resonance Imaging

MSA= Multiple System Atrophy

NART= National Adult Reading Test

nbM= nucleus basalis of Meynert

NICE= National Institute for Clinical Excellence

NMS= Non-Motor Symptoms

OA= Older Adults

OTS= One Touch Stockings

PAL= Paired Associate Learning

PCA= Principle Components Analysis

PD= Parkinson's disease

PDD= Parkinson's disease Dementia

PFc= Prefrontal Cortex

PIGD= Postural Instability and Gait Difficulty

PPN= Pendunculopontine Nucleus

PRM= Pattern Recognition Memory

PSP- Progressive Supranuclear Palsy

RAVLT= Rey Auditory Verbal Learning Test

REM= Rapid Eye Movement

SAI= Short Latency Afferent Inhibition

SNpc= Substantia Nigra pars compacta

SPECT= Single Photon Emission Computed Tomography

SRM= Spatial Recognition Memory

SRT= Simple Reaction Time

TOL= Tower of London

X^2= Chi-squared

Chapter 1 : Parkinson's disease and setting the context

1.1 Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder which was first described by the General Practitioner James Parkinson in 1817 in his essay on the 'shaking palsy' (Parkinson, 2002). Two hundred years since James Parkinson first described the disorder, the National Institute for Clinical Excellence (NICE) has outlined PD as a progressive neurodegenerative condition which still remains a huge challenge to both patients with PD and those involved in their care (NICE, 2006).

PD is the second most common neurodegenerative disorder, behind that of Alzheimer's disease (AD). Standardised incidence rates are reported as between 8-18 per 100 000 (de Lau and Breteler, 2006) and in the Newcastle-Gateshead area incidence has been reported at 15.9 per 100 000 (Khoo *et al.*, 2013). An increase in PD incidence is seen in those who are older (Schrag *et al.*, 2000; Van Den Eeden *et al.*, 2003; de Lau and Breteler, 2006; Wickremaratchi *et al.*, 2009) thus, with an ageing population incidence is only expected to increase (Dorsey *et al.*, 2007).

PD is most commonly described as a movement disorder with motor symptoms which include bradykinesia (slowness of movement), rigidity and a tremor at rest with two out of three of these cardinal symptoms required for diagnosis (Archibald and Burn, 2008). Non-motor symptoms (NMS) are common in PD and include cognitive impairment, mental health problems, depression and sleep disturbance (NICE, 2006). NMS are a significant factor in PD, affecting the majority of patients. Previous incidence studies have identified that only 1.6-3% of patients reported an absence of NMS (Martinez-Martin *et al.*, 2007; Bostantjopoulou *et al.*, 2013) and often these symptoms have the worst impact on quality of life (Rahman *et al.*, 2008).

Pathologically, PD stems from the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) (Fearnley and Lees, 1991) as well as abnormal aggregation of α-synuclien that collate to form Lewy bodies (LB) (Braak *et al.*, 2004). The above features are both prerequisites of post-mortem diagnosis of

1

PD (Gelb *et al.*, 1999). Though dopaminergic deficiency is most associated with PD, some symptoms appear to be 'dopa-resistant' (Gotham *et al.*, 1988; Devos *et al.*, 2010). This suggests involvement of other neurotransmitter systems such as acetylcholine (Ach) and serotonin (5HT). Two sources of cholinergic output are shown to decline in PD; the nucleus basalis of Meynert (nbM) and the pedunculopontine nucleus (PPN) with the nbM projecting to the frontal lobe and the PPN to the thalamus, cerebellum and nbM (Yarnall *et al.*, 2011). In addition to the cholinergic system, there is dysfunction to the serotonergic system with loss of serotonin markers in PD patients (Tohgi *et al.*, 1993). Degeneration and disruption to the serotonergic system is associated with tremor (Doder *et al.*, 2003), depression, fatigue and visual hallucinations (Politis and Niccolini, 2015).

1.2 Cognition in Parkinson's disease

One of the most debilitating NMS is that of cognitive impairment and Parkinson's disease dementia (PDD). In his original essay, James Parkinson did not highlight cognitive impairment and stated 'the senses and intellects being uninjured' (Parkinson, 2002). However, he did describe that towards the end of the disease patients may experience a slight delirium (Parkinson, 2002). More definitive recognition was proposed by Charcot who some years later in 1875 recognised 'the mind becomes clouded and memory is lost' (Lees and Smith, 1983). Following this, studies in the mid 1900's began to explore the nature of cognitive decline in PD and recognised cognitive functions other than memory are affected (Warburton, 1967; Reitan and Boll, 1971).

It is now well understood that cognitive deficits in PD occur across a number of different cognitive domains. The profile of cognitive deficit in PD appears complex however with different cognitive profiles amongst patients (Aarsland *et al.*, 2010; Yarnall *et al.*, 2014). The domains of cognitive deficit in PD include; global cognition, working memory, attention, fluctuating attention, executive function, memory and visuospatial function. These domains will now be discussed in turn.

1.2.1 Global cognition

Cognitive impairment in PD is evident in early disease (Cooper *et al.*, 1991; Foltynie *et al.*, 2004) and identified by global cognitive assessments such as the Montreal Cognitive Assessment (MoCA) or Mini Mental Status Examination (MMSE). Although the MoCA and MMSE are both used to assess global cognition, the MoCA is a better tool for diagnosing dementia in PD (Hoops *et al.*, 2009; Dalrymple-Alford *et al.*, 2010) due to its increased sensitivity (Nazem *et al.*, 2009). Although assessments of global cognition show sensitivity to cognitive decline in PD, they lack specificity and often require additional assessments (Hoops *et al.*, 2009).

1.2.2 Working memory

Working memory is described as a system which 'provides temporary storage and manipulation of the information necessary for such complex cognitive tasks as language comprehension, learning and reasoning' (Baddeley, 1992). Working memory is impaired in PD compared to healthy older adults (Beato *et al.*, 2008) and deficits tend to increase with progression of PD (Owen *et al.*, 1997). This has been associated with further dopamine depletion as dopaminergic medication has a positive effect on working memory task performance (Lewis *et al.*, 2005). However, working memory is also thought to draw on executive function and attention (McCabe *et al.*, 2010), which are also known to be affected in PD.

1.2.3 Attention

Attention is an overarching system which interacts with many areas of the brain (Posner and Petersen, 1990). Attention is thought to be built on three individual networks; alerting, orientating and executive (Posner and Petersen, 1990; Peterson and Posner, 2012). One of the main cognitive deficits recognised in PD is attention with impairment evident at diagnosis (Aarsland *et al.*, 2010; Lord *et al.*, 2014; Yarnall *et al.*, 2014) and progression of symptoms apparent in the early years following diagnosis (Muslimović *et al.*, 2005; Aarsland *et al.*, 2010). Compared to AD, PDD and Dementia with Lewy bodies (DLB) patients perform worse on tests of attention (Noe *et al.*, 2004) with some assessments identifying patients at risk of future PDD (Taylor *et al.*, 2008; Pedersen *et al.*, 2013).

Importantly, attentional measures also determine poorer performance on activities of daily living (ADL) (Bronnick *et al.*, 2006), which demonstrates direct impact on function. Recent evidence suggests attentional deficits are due to dysregulation of the cholinergic system attributed to changes of the nbM and PPN (Yarnall *et al.*, 2011). Further evidence is provided by intervention studies by which Rivastigmine improves attention levels in PDD (Emre *et al.*, 2004; Wesnes *et al.*, 2005).

1.2.4 Fluctuating attention

Compared to attention, fluctuating attention has been poorly explored in PD. A study by Ballard and colleagues measured fluctuating attention in DLB, AD, PDD, PD and healthy older adults. Ballard *et al.* (2002) found fluctuating attention to be worse in PDD compared to PD when using the Cognitive Drug Research (CDR) randomised battery. Previous work by Lord *et al.* (2014) found fluctuating attention as measured by the coefficient of variation (CV) for choice reaction time (CRT) to be significantly worse in PD compared to controls within 6 months of diagnosis. Compared to PD, fluctuating attention has better been explored in DLB. Critically, PDD and DLB are often classified under the same umbrella term of Lewy Body Dementia (LBD), thought to be disorders on the same continuum. In LBD, fluctuating cognition, as recognised by fluctuating attention, is one of three core features for disease diagnosis (McKeith *et al.*, 1996).

1.2.5 Executive function

Executive function is defined as "a set of cognitive skills that are responsible for the planning, initiation, sequencing and monitoring of complex goal-directed behaviour" (Royall *et al.*, 2002). Due to executive function deficits, people with PD present with difficulties with planning and problem solving (Bronnick *et al.*, 2006). Impaired executive function in PD has been shown in previous research (Morris *et al.*, 1988; Cooper *et al.*, 1991; Dujardin *et al.*, 2001; Williams-Gray *et al.*, 2009a; Bronnick *et al.*, 2011) and is evident in those with newly diagnosed PD (Muslimović *et al.*, 2005) by use of assessments such as the Tower of London (TOL) task (Morris *et al.*, 1988; Kehagia *et al.*, 2010). Janvin *et al.* (2005) performed a longitudinal study in PD and identified Stroop Third Card assessment was independently associated with onset of dementia. Compared to

attention, executive function is dependent on the fronto-striatal dopamine network with dopaminergic function of the caudate nucleus related to impaired assessment performance (Brück *et al.*, 2001). Although a number of studies have recognised impairment in executive function and attention, it has to be noted that the terms 'executive function' and 'attention' are often used interchangeably or combined (e.g. executive-attention) (Emre *et al.*, 2007).

1.2.6 Memory

Memory impairment is present in newly diagnosed PD (Aarsland *et al.*, 2010; Yarnall *et al.*, 2014) who demonstrate deficits compared to healthy control subjects (Bronnick *et al.*, 2011). Memory is mediated by the basal ganglia and frontal cortex (Cabeza *et al.*, 1997; McNab and Klingberg, 2008), two areas of dysregulation in PD. Longitudinal cohorts have identified memory deficits over three to five years (Williams-Gray *et al.*, 2007; Muslimović *et al.*, 2009) in PD with prominent memory deficits in those with mild cognitive impairment (MCI) found to be a predictive marker of future transition to PDD (Aarsland *et al.*, 2010). However, it has been argued that deficits identified in memory are due to executive-attention processes needed for successful assessment completion (Ivory et al., 1999).

1.2.7 Visuospatial function

Visuospatial function is defined as a skill which includes observation of a visual stimuli and judging its location in space (Quental et al., 2013), such as the distance and orientation of the stimulus. Visuospatial function is known to deteriorate as disease progresses and is impaired in PD patients with and without dementia (Williams-Gray et al., 2009). A previous study identified one visuospatial assessment, pentagons, was found to be predictive of future PDD (Levin *et al.*, 1991; Williams-Gray *et al.*, 2007). Visuospatial deficits in PD have been compared to other dementias, with worse deficits in PDD compared to AD (Starkstein et al., 1996; Mosimann et al., 2004) but similar deficits seen in DLB (Mosimann et al., 2004). One explanation is a blood perfusion deficit observed in visual processing areas seen in those with DLB and PDD but not AD (Firbank et al., 2003). As with other domains of cognition, visuospatial function requires

executive-attention control (Crucian et al., 2000); however this notion is still under dispute.

1.3 The spectrum of cognitive decline in Parkinson's disease

A spectrum of cognitive impairment is evident in PD, as shown in **Figure 1-1**. Patients often present with cognitive deficits compared to age-matched controls (Leung *et al.*, 2015) and may or may not transition to MCI and advance to PDD.
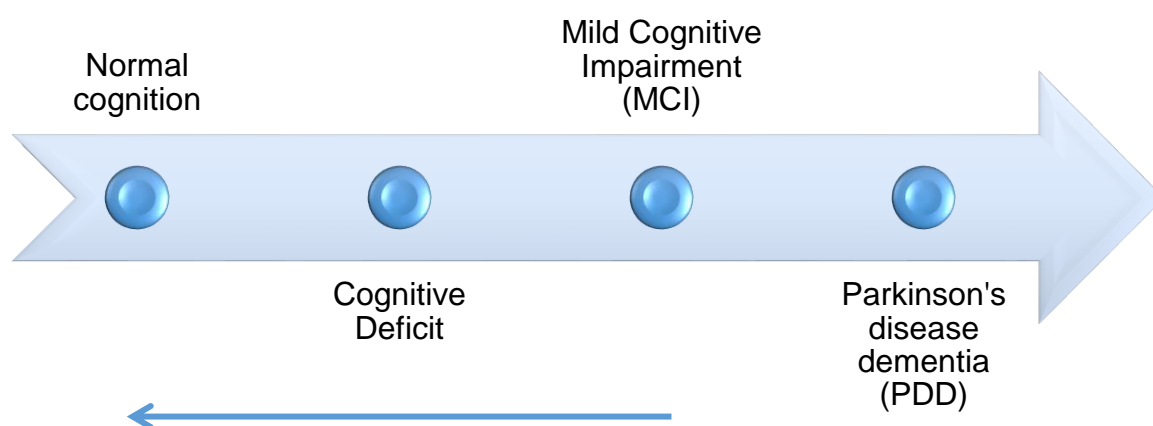
Figure 1-1 The spectrum of cognitive decline in Parkinson's disease.
[Cognitive deficits are often seen in patients compared to age matched controls. As disease progresses patients may transition to mild cognitive impairment (MCI) and lastly Parkinson's disease dementia (PDD). A number of patients may revert from MCI to normal cognition, as depicted by the solid blue line].

1.3.1 Mild cognitive impairment

MCI is thought to be a transitioning stage of cognitive deficit towards PDD. Incidence of MCI is high in those with newly diagnosed PD; one cross-sectional study focusing on patients at diagnosis identified an incidence of 42.5% in a cohort of 219 subjects (Yarnall *et al.*, 2014). In contrast, the Norwegian Park West study identified 18.9% of their cohort met the criteria for MCI at diagnosis

which was a twofold increase on incidence compared to age matched controls (Aarsland *et al.*, 2010). A longitudinal study from 2006 found 52.8% (38 participants) met criteria for MCI with a number of MCI subtypes identified (Janvin *et al.*, 2006). More recently, incident cohort studies have explored cognitive impairment over time. The CamPaIGN cohort highlighted that incidence of MCI increases as disease progresses, they demonstrated that 3-5 years post diagnosis 57% of a cohort of 239 patients had developed MCI (Williams-Gray *et al.*, 2007). Due to heterogeneity of PD-MCI definition, a recent task force was used to outline PD-MCI in order to produce a diagnostic criterion (Litvan *et al.*, 2012). Importantly the criteria stipulate that PD-MCI is not just a 'memory-complaint' but must occur across different cognitive domains. Although a number of patients prove to have stable MCI, those with MCI are most at risk of transitioning to PDD. For example, Pedersen *et al.* (2013) identified significantly more patients with MCI at diagnosis converted to PDD compared to non-MCI participants. It must be noted however that 21.6% of patients with MCI at baseline reverted back to normal cognition (as characterised in **Figure 1-1**). Critically, those with persistent MCI at both baseline and one year follow-up were much more likely to develop dementia (45.5%) with only 9.1% of this group reverting back to normal cognition (Pedersen *et al.*, 2013).

1.3.2 Parkinson's disease dementia

The final stage of the spectrum of cognitive decline is PDD (**Figure 1-1**). Contrary to previous understanding, the prevalence of PDD in Parkinson's disease patients is high with one systematic review identifying a PDD point prevalence of 24-31% (Aarsland *et al.*, 2005). Cumulative prevalence also shows that the incidence of PDD could be as high as 17% in one cohort of patients within 5 years of diagnosis (Williams-Gray *et al.*, 2009a) and 75% in those who survive longer than 10 years with the disease (Aarsland and Kurz, 2010). Diagnostic criteria for PDD specify impairment must be present in more than one cognitive domain, represent decline from a premorbid level and importantly have deficits that are severe enough to impact on ADL's (Emre *et al.*, 2007).

A number of risk factors have been linked to the development of PDD. One of the most noted risk factors is both age and age at disease onset (Aarsland *et al.*,

2001; Levy *et al.*, 2002; Hobson and Meara, 2004; Buter *et al.*, 2008) this is not surprising as age is the most prominent risk factor throughout all dementias (Ott *et al.*, 1998; Aarsland and Kurz, 2010). Additionally, worse Parkinsonism symptoms, represented by higher Hoehn & Yahr (H & Y) and Movement Disorder Society- Unified Parkinson's disease Rating Scale (MDS-UPDRS) scores have also been shown to be a risk factor for PDD (Aarsland *et al.*, 2001; Levy *et al.*, 2002; Hobson and Meara, 2004). Furthermore, patients who present with MCI (Aarsland *et al.*, 2001) and other specific cognitive dysfunctions (Williams-Gray *et al.*, 2009a) are at higher risk of developing PDD. The nature of cognitive impairment for future PDD is still under debate, for example a dual syndrome hypothesis has been proposed for cognitive impairment in PD and PDD. The dual syndrome hypothesis proposes that those with posterior cortical and temporal lobe dysfunction (i.e. visuospatial and semantic fluency) are at higher risk of conversion to PDD compared to those with frontal executive function difficulties (Kehagia *et al.*, 2013). Other risk factors include visual hallucinations, depression, apathy and Rapid Eye Movement (REM) sleep disorder amongst others (Emre *et al.*, 2007; Aarsland and Kurz, 2010; Postuma *et al.*, 2012).

1.3.3 Treatment for cognitive decline and dementia in PD

Currently there is no cure for cognitive decline and dementia in PD. A number of transmitter based treatments have shown to improve symptoms in patients due to the involvement of dopaminergic, cholinergic, noradrenergic and glutamatergic neurotransmitters.

Cholinesterase inhibitors i.e. Rivastigmine and Donepezil have shown the most promise amongst transmitter based treatments. A large study observing the use of Rivastigmine in 541 patients with PDD found Rivastigmine to improve performance on measures of global cognition, attention and visuospatial tests (Emre *et al.*, 2004). Other than PDD, Rivastigmine has also shown to benefit patients with PD-MCI (Mamikonyan *et al.*, 2015). Studies focusing on specific cognitive domains found Rivastigmine to improve performance on attention (Wesnes *et al.*, 2005) and executive function (Schmitt *et al.*, 2010) assessments. More recently, the long-term safety of Rivastigmine has been assessed and the drug has been deemed safe for long term use although several adverse events

were reported including nausea, vomiting, tremor and falls (Emre *et al.*, 2014). A small study (n=22) observing the use of Donepezil reported modest benefits from the drug (Ravina *et al.*, 2005), however a larger and more recent trial (n=550) identified an improvement in global cognition and executive function (Dubois *et al.*, 2012). A number of studies have explored Memantine as a treatment, the drug appears to be well tolerated among patients but only modest benefits have been seen (Ravina *et al.*, 2005; Aarsland *et al.*, 2009). A Movement Disorder evidence based medicine update review concluded that Rivastigmine was an effective treatment for cognitive decline but that there was insufficient evidence for Donepezil and Memantine. However it was decided these medications could be used as investigational treatments (Seppi *et al.*, 2011).

Due to the limitations of pharmacological treatments, nonpharmacological treatments which include cognitive training and exercise have been sought. A number of studies have assessed the effect of cognitive training including computer and paper based tests. One study identified improvement in several cognitive domains including attention, executive function and memory when training for 45 minutes, three times per week for four weeks (París *et al.*, 2011). Although benefits have been seen, studies are of poor quality and contain only small numbers of participants (Hindle *et al.*, 2013).

Physical exercise has recently come into the literature as a treatment to improve cognition. One study observed a control group (normal daily routine) and a training group with a varied training programme for six months (the exercise programme included aerobics, balance, motor-coordination and stretching). The training group demonstrated a significant improvement in executive function compared to the control group (Tanaka *et al.*, 2009). Other exercises such as passive cycling have also shown to improve executive functioning (Ridgel *et al.*, 2011). A more recent study spanning a two year intervention observed two exercise groups, firstly a combination of balance, stretching and breathing exercises and secondly a weight lifting programme. The study found both groups to improve on tests of working memory and attention (David *et al.*, 2015). Finally, one study observing both fitness and cognition identified that after an intervention of aerobic exercise, PD participants improved both in terms of aerobic capacity

and executive function (Duchesne *et al.*, 2015) demonstrating multiple benefits from exercise programmes in PD.

1.3.4 The Importance of cognitive decline

Previously the high incidence of cognitive impairment in PD was described. The effect on each individual can have devastating impact on personal, social and economic levels. Dementia in PD has been identified as an independent predictor of reduced quality of life in a study of 70 Italian patients (Winter *et al.*, 2011). Additionally, cross sectional work reveals that deficits in cognitive domains can reduce quality of life (Barone *et al.*, 2009) even in early PD (Duncan *et al.*, 2014). Longitudinally, in a large cohort of PD recruited at diagnosis, attentional deficits were found to be the strongest predictor of quality of life as well as MCI status (Lawson *et al.*, 2016). In addition, presence of dementia in PD increases burden on carers and reduces their quality of life (Leroi *et al.*, 2012) as well as increased healthcare costs. One study identified that the costs of patients with dementia were three times that of normal cognition with the majority of increased costs stemming from institutionalised care (Vossius *et al.*, 2011). Notably, those with cognitive impairment preceding dementia were also associated with higher costs in the same study. As expected, cognitive decline in PD also leads to increased risk of nursing home admittance (Aarsland *et al.*, 2000), with cost increase per patient resulting in a 500% rise (Findley *et al.*, 2003). Importantly, dementia can reduce life expectancy and this has been seen specifically in PDD (Levy *et al.*, 2002).

The above gives just a few examples of the devastating effects of cognitive decline in this patient group. Thus, detecting those at risk of cognitive decline and dementia early in disease is of upmost importance. There is evidence in AD that early detection increases the effectiveness of treatment with cholinesterase inhibitors (Chang and Silverman, 2004) and in PD early treatment with Memantine predicts longer survival in patients with PDD (Stubendorff *et al.*, 2014). Such treatments allow patients to benefit from improved cognition, but early effective treatment would also allow for improved psychological wellbeing and increased time to plan future treatment, care and finances for both patients

and their carers (Chang and Silverman, 2004). In order to identify those at risk, early biomarkers need to be sought.

1.4 Biomarkers for cognitive decline in PD

Currently, prognostic indicators of cognitive decline in PD continue to be sought. Additionally, only 25% of patients are recognised as having dementia in the clinical setting (Hu *et al.*, 2011) proving current diagnostic tools are inadequate. Cognitive testing such as the MoCA and Scopa-Cog are often used to assess cognitive decline and monitor progression to PDD. However, such assessments provide a 'blunt tool' and identify cognitive decline and dementia long after the pathological changes have occurred, as seen in AD (Chang and Silverman, 2004). Therefore, there is a need to identify biomarkers for cognitive decline that are sensitive and specific to a prodromal state of PDD. A biomarker is defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention' (Biomarkers Definitions Working, 2001). Thus, effective biomarkers in PD would improve patient management and stimulate the development of novel therapeutics.

There has been a recent surge to identify biomarkers for PDD (Aarsland and Kurz, 2010). Due to the complexity of cognitive decline in PD however, one biomarker alone will not be adequate and in fact a combinational approach is required. Already, a number of biomarkers have been associated with cognitive impairment in PD. Biomarkers are often classified as 'wet' biomarkers i.e. the source is a bodily fluid and 'dry' biomarkers i.e. imaging and other neurophysiological assessments (Alves *et al.*, 2015). A number of biomarkers in the literature will be discussed here and are displayed in **Table 1-1**.

A number of 'wet' biomarkers are contained in cerebrospinal fluid (CSF). CSF is usually the focus of biomarkers in neurodegenerative disease due to its anatomical location (Alves *et al.*, 2015). Reduced levels of Aβ (1-42) have been identified in an incident cohort of PD (Yarnall *et al.*, 2014) and found to be an independent predictor of cognitive decline in a separate study (Siderowf *et al.*, 2010). A large study of 414 early and untreated PD participants identified that lower CSF levels of a-synuclein contributes to early dysfunction of executive-

attention and that Aβ 1-42 was decreased in MCI but not in non-MCI PD patients (Skogseth *et al.*, 2015). In addition, reduced levels of Aβ 1-40 have been identified in PD-MCI but not those with normal cognitive function (Yarnall *et al.*, 2014). Another component of CSF, tau protein, has shown marginally elevated levels in those with PDD, but does not appear to be as sensitive as amyloid-beta markers (Mollenhauer *et al.*, 2006). However, a recent study found tau levels to predict decline on assessments of executive function and memory (Liu *et al.*, 2015). Overall, components of CSF are showing promise as biomarkers but obtaining CSF is an invasive procedure making screening of patients problematic.

Other 'wet' biomarkers include those found in blood. One study identified low blood plasma levels of epidermal growth factor (EGF) was associated with poor cognitive test scores and predicted an eight fold increased risk of development of dementia (Chen-Plotkin *et al.*, 2011). Additionally, a study in drug naïve patients found EGF levels to be related to frontal and posterior cognitive function over two years (Pellecchia *et al.*, 2012). More recently, low baseline EGF levels have been associated with poor visuospatial performance (Lim *et al.*, 2016).

In comparison, 'dry' biomarkers such as imaging and other neuropsychological tests (e.g. electroencephalogram (EEG)) have received little attention. Structural magnetic resonance imaging (MRI) has identified posterior cortical atrophy in patients with MCI, over time this atrophy extends anteriorly in PDD patients (Song *et al.*, 2011; Melzer *et al.*, 2012). In a cohort of recently diagnosed PD patients, those with PD-MCI showed significantly more severe thinning of temporo-parietal regions and frontal regions relative to those with normal cognition (Mak *et al.*, 2015). In comparison, functional-MRI (fMRI) studies have shown less promise (Duncan *et al.*, 2013). Functional imaging of dopaminergic and cholinergic systems however have shown interesting results (Klein *et al.*, 2010), in particular cortical acetylcholinesterase was reduced in those with poor performance on attention and executive function assessments (Bohnen *et al.*, 2005). However, imaging is an expensive resource and thus would be an expensive screening tool.

Alternative 'dry' biomarkers include short latency afferent inhibition (SAI). In a study of 22 patients with early PD, those with MCI (n=11) showed significantly less inhibition than both control and PD patients of normal cognition (Yarnall *et al.*, 2013). One study identified a 'dry' biomarker in EEG which identified a hazard of dementia development in those with low background rhythm frequency (Klassen *et al.*, 2011). Although evidence is building, there is still some way to go before an established prognostic battery is available. Additionally, given the pragmatic issues surrounding biomarkers such as high cost and invasive nature, there is a need to identify clinical biomarkers (biomarkers which can be obtained quickly and easily in the clinic environment) for PDD.

A recent study combined neuropsychological measures and cognitive assessments and found the combination of simple and obtainable measures provided a strong battery of clinical biomarkers that can be utilised in the clinical setting (Olde Dubbelink *et al.*, 2014). However, other cost-effective and clinic friendly assessments are still being sought. A recent concept in older adults is motoric cognitive risk syndrome (MCR). MCR provides a clinically accessible risk tool that does not contain complex neuropsychological or imaging assessments (Verghese *et al.*, 2015). The MCR tool is dependent on four criteria; cognitive complaints using a simple questionnaire, slow gait speed, preserved activities of daily living scale and an absence of dementia (Verghese *et al.*, 2012). Thus, MCR provides a battery of simple assessments, including measurement of gait that can be used clinically in numerous populations as further described below.

Table 1-1 Current biomarkers associated with cognitive decline and Parkinson's disease dementia.

Category	Biomarker	Author	Outcome	Issues
Wet	CSF- Aβ 1-42	Yarnall *et al.* (2014)	Newly diagnosed cohort, significantly lower levels of CSF Aβ 1-42 in those with PD-MCI.	Invasive Expensive
		Mollenhauer *et al.* (2006)	Levels of CSF Aβ 1-42 significantly lower in PDD compared to PD and healthy controls.	
		Siderowf *et al.* (2010)	Reduced levels of CSF Aβ 1-42 at baseline assessment associated with more rapid cognitive decline over one year.	
		Skogseth *et al.* (2015)	Levels of CSF Aβ 1-42 significantly decreased in PD-MCI compared to healthy controls and PD without MCI.	
	CSF Aβ 1-40	Yarnall *et al.* (2014)	Newly diagnosed cohort, significantly lower levels of CSF Aβ 1-40 in those with PD-MCI.	Invasive Expensive
	CSF Tau	Mollenhauer *et al.* (2006)	Levels of CSF Tau protein significantly higher in PDD compared to PD and healthy controls.	Invasive Expensive
		Liu *et al.* (2015)	After levodopa treatment initiated higher Tau protein predicted cognitive decline on assessments of memory and executive function.	
	Blood Serum EGF	Chen-Plotkin *et al.* (2011)	Low levels of plasma EGF correlated with poor cognitive test scores at baseline and predicted an 8-fold greater risk of cognitive decline. Results significantly replicated in a separate cohort.	Invasive
		Pellecchia *et al.* (2012)	Levels of plasma EGF associated with semantic fluency performance at baseline. At 2 year follow up, levels of EGF associated with semantic fluency and Stroop-colour-word test performance.	
		Lim *et al.* (2016)	Low levels of plasma EGF predicted poorer cognitive outcomes. In PD, low levels of EGF associated with poorer performance on visuospatial tasks.	
Dry	Structural	Song *et al.* (2011)	PD-MCI had significantly decreased grey matter in right frontal middle area	Expensive

	MRI		compared to PD non-MCI. PDD patients had decreased GM in right parietal, middle frontal, insular and lentiform areas. Grey matter atrophy in the posterior cingulate greater in those with shorter disease duration before dementia.	
		Melzer *et al.* (2012)	PD MCI and PDD showed grey matter atrophy compared to PD non-MCI. PDD showed extensive atrophy in the temporal lobe, intracalcarine and lingual gyri, posterior cingulate gyrus, frontal regions and bilateral caudate. Grey matter loss associated with global cognitive score.	
		Mak *et al.* (2015)	Widespread cortical thinning evident in PD-MCI. At baseline regional cortical thickness associated with global cognitive score. Over 18 months, those with PD-MCI had severe cortical thinning in frontal and temporo-parietal cortices including hippocampal atrophy.	
	fMRI	Klein *et al.* (2010)	Dopaminergic and cholinergic deficits present in patients with PDD and DLB. Cholinergic deficits critical for development of dementia.	Expensive
		Bohnen *et al.* (2005)	Cortical AChE activity reduced in PDD and PD compared to controls. Cholinergic denervation in both PD and PDD associated with worse performance on assessments of attention and executive function.	
	SAI	Yarnall *et al.* (2013)	Significantly less short latency afferent inhibition in group with mild PD-MCI compared to healthy controls.	Minimal evidence
	EEG	Klassen *et al.* (2011)	PD patients with low background rhythm frequency were 13 times more likely to develop dementia than those with high background rhythm frequency.	Minimal evidence

[MCI= mild cognitive impairment, PDD= Parkinson's disease dementia, EGF= epidermal growth factor, AChE= acetylcholinesterase.]

1.5 Gait

Gait is defined as the walking pattern of an individual. Gait provides a marker of global health and is an important tool as a predictor for health status and survival in older adults (Hausdorff *et al.*, 2001; Studenski *et al.*, 2011). Previously gait was regarded as purely an automatic task reliant on subcortical structures such as the brainstem and spinal cord (Takakusaki, 2013). However, gait is no longer regarded as purely a motor task. An extensive body of research has established that safe and effective gait requires input from higher cognitive areas (Hausdorff, 2005). Research over the past decade has refined our understanding of the relationship between gait and cognition to reveal compensatory cognitive strategies which vary as a function of age and pathology (Hausdorff, 2005). Cross sectional studies identify associations between gait and cognition in normal ageing and neurodegenerative disease (Yogev *et al.*, 2005; Ijmker and Lamoth, 2012; Verlinden *et al.*, 2013; Lord *et al.*, 2014) as supported by neuroimaging studies (Holtzer *et al.*, 2014). Longitudinally, gait emerges as a strong and significant predictor of future cognitive impairment and dementia in older adults (Marquis *et al.*, 2002; Verghese *et al.*, 2007; Buracchio *et al.*, 2010; Mielke *et al.*, 2013). However, it is not clear as to whether gait would provide a clinical biomarker in PD as to date no longitudinal studies have been conducted in this patient group.

Gait speed is universally used to reflect gait because of its utility and robust clinometric properties (Wade, 1992). Gait, however is a complex task and due to its inherent complexity and because it is a multidimensional construct comprised of a number of discrete spatiotemporal characteristics, gait cannot be represented by a single outcome.

1.5.1 Spatiotemporal gait characteristics

Gait characteristics are often measured as spatiotemporal variables; these are different aspects of gait measured in distance and time, which can be seen in **Figure 1-2**. Previously Lord et al. (2013b) identified 16 spatio-temporal characteristics to describe gait performance. Spatial characteristics of gait measured by Lord *et al.* (2013b) included step length and step width with temporal characteristics including step time, swing time and stance time. In

addition the variability and asymmetry of these characteristics have been calculated to identify the differences from one step to the next and the differences between the right and left foot respectively. For example, other gait characteristics include step length asymmetry, step width variability and step time variability. Discrete gait characteristics, such as those described above, are known to change both in normal ageing and onset of neurodegenerative disease amongst other conditions. It is critical to measure discrete gait characteristics as although gait speed is sensitive to pathology, it is neither discriminative nor reflective of subtle and selective alterations of gait expressed in response to change in neuropathology in ageing and disease (Stolze *et al.*, 2001; Verghese *et al.*, 2007; Lord *et al.*, 2014). For example, stride time variability over and above gait speed is able to discriminate between carriers and non-carriers of the LRRK2-G2019S mutation, a pre-cursor for PD (Mirelman *et al.*, 2011). Selective identification of gait characteristics is therefore critical for discrimination of pathology, identifying specific features of disease progression and discerning the effect of age.
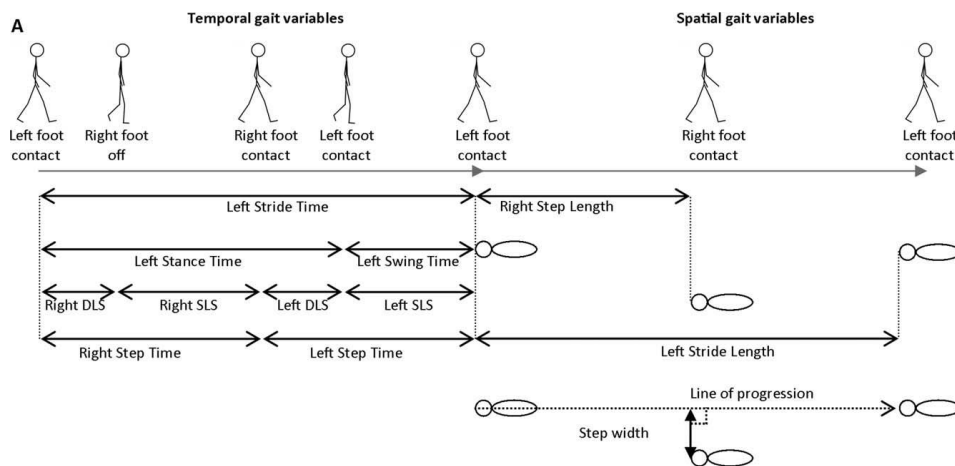
Figure 1-2 Spatiotemporal features of gait. Taken from Lord et al., 2013

1.5.2 Gait Factor Domains

Due to high specificity and sensitivity, a large number of gait variables are useful; however this can also be problematic. A high co-variance exists between certain

gait characteristics (e.g. step velocity and step length) which therefore leads to redundancy and a complex method by which to explain findings.

In response, several groups have proposed gait models that group gait characteristics into gait domains using data reduction techniques such as principle component analysis (PCA) (Verghese *et al.*, 2007; Hollman *et al.*, 2011; Lord *et al.*, 2013b; Verlinden *et al.*, 2013). Whilst the models are comparable, there are subtle differences. For example Verghese *et al.* (2007) and colleagues collated eight gait characteristics to form three domains; pace, variability and rhythm. Other models have produced more novel domains such as tandem and turning (Verlinden *et al.*, 2013) allowing for inclusion of more complex motor tasks. A model developed by Lord *et al.* (2013b) in older adults assessed 16 gait characteristics forming five domains of gait (pace, rhythm, variability, asymmetry and postural control) which was later validated in PD (Lord *et al.*, 2013a) (**see chapter 3, figure 3-4**). Although such models address the concern of redundancy they also come at a cost in that the strength of an independent gait variable is diluted among its factor. In order to address this, analysis should be completed on both independent gait variables and their factors in order to distinguish differences in the results and strongest variables among factors.

1.5.3 Measuring Gait

It has now been established that measurement of a comprehensive battery of gait characteristics is of upmost importance. Traditionally, comprehensive gait assessments were carried out in controlled gait laboratories using specialised validated equipment such as instrumented walkways (e.g. GaitRite) (Nelson *et al.*, 2002; Menz *et al.*, 2004) and infra-red camera systems (e.g. Vicon) (Barker *et al.*, 2006). Recent advances in technology has allowed for the development of a more novel method of gait data collection by using accelerometer based body worn monitors (BWM). The use of BWM allows for the measurement of quantitative gait characteristics in the clinic and in the 'free-living'; the patient's habitual environment i.e. home and local community. Algorithms have been developed to calculate comprehensive gait characteristics from older adults and patients with PD which have been validated against the 'gold-standard' instrumented walkway (Del Din *et al.*, 2016b; Del Din *et al.*, 2016c). The field of

gait measurement using BWM is expanding and this will be discussed further in Chapter 6.

1.5.4 Gait in Parkinson's disease

Gait impairment in PD is one of the main motor symptoms of the disorder which is recognised as a slow, shuffling walk often with a flexed posture. Gait impairments are critical in PD as they lead to increased risk of falls and poorer quality of life (Muslimovic *et al.*, 2008).

Problems with mobility that are recognised in PD such as bradykinesia and hypokinesia are ultimately down to changes in quantitative gait variables (Peterson and Horak, 2016). For example, one study found the ability to regulate stride length to be the underlying deficit fundamental for gait hypokinesia (Morris *et al.*, 1994). Although older adults show an alteration of gait characteristics with ageing, differences in the spatiotemporal parameters of gait can be seen in those with PD compared to healthy control participants even when optimally medicated (Morris *et al.*, 1996; Wild *et al.*, 2013).

One of the most recognised gait deficits in PD is decreased pace e.g. gait velocity as shown in work by the Morris group (Morris *et al.*, 1994; Morris *et al.*, 1996). Since this work, a number of studies have replicated this finding (Baltadjieva *et al.*, 2006; Hass *et al.*, 2012; Rochester *et al.*, 2012; Lord *et al.*, 2013a; Wild *et al.*, 2013) as well as more discrete impairments such as decreased step and stride length (Morris *et al.*, 1998; Baltadjieva *et al.*, 2006; Hass *et al.*, 2012; Rochester *et al.*, 2012). Importantly, deficits in pace of gait (i.e. velocity and step length) have been recognised in very early PD (Galna *et al.*, 2015). Deficits in rhythm, the ability to maintain a steady and stable walking pattern, have also been noted in early PD (Galna *et al.*, 2015). Deficits in rhythm have been demonstrated in a number of characteristics including stride time and swing time (Hausdorff *et al.*, 1998; Hausdorff *et al.*, 2003; Frenkel-Toledo *et al.*, 2005) as well as gait domains in PD (Amboni *et al.*, 2012).

Other than pace and rhythm, impairment also affects other discrete gait characteristics of variability and asymmetry. At diagnosis, a number of characteristics of variability and asymmetry are significantly higher in PD subjects

compared to age matched older adults (Lord *et al.*, 2014). Characteristics of asymmetry are associated with an increase in Levodopa, suggesting significant implication of the dopaminergic system in these characteristics. Stride length variability in particular has been associated with increased falls risk (Hausdorff *et al.*, 2001), marking the importance of measuring characteristics other than gait velocity.

Another gait domain critical to PD is postural control. Postural control is affected in people with PD both statically and during movement (Peterson and Horak, 2016). In particular, one feature of gait related postural control, step width variability, demonstrates impairment in early PD (Galna *et al.*, 2015). Importantly, step width variability is another important measure for predicting falls (Brach *et al.*, 2005), this once again signifies the importance of measuring additional gait characteristics over and above gait velocity.

1.5.5 Pathology of gait in PD

Primarily, gait impairment has been related to the dopaminergic system. It has been hypothesised that gait impairment originates from hyperactivity of inhibitory projections of the basal ganglia (BG) this in turn alters projections to the supplementary motor area (SMA) and the primary motor cortex. It is thought that the 'cue' from the BG is affected and leads to poor preparation of movement and thus a slowing or absence of an internal cue from the BG leads to slower and reduced performance of sequencing tasks, such as gait (Morris *et al.*, 1994; Phillips *et al.*, 1994). A number of studies have observed the response of gait to dopaminergic therapy. Firstly, Galna *et al.* (2015) found that in the first 18 months of PD step length, a measurement of pace, improved with medication although it did not fully compensate for the impairment. In addition, measures of rhythm declined even though levels of dopaminergic medication significantly increased. In the same cohort, characteristics of step length and step time variability were shown to be dopa-resistant over the first three years of disease (Rochester, 2016). A separate study by Curtze *et al.* (2015) observed 104 patients in PD identified dopaminergic medication to improve some, but not all aspects of gait. Such studies therefore indicate the involvement of other neurotransmitters in the control of gait. For example, in newly diagnosed PD, slower gait speed has been

associated with an impaired cholinergic system (Rochester *et al.*, 2012). The above evidence highlights that gait impairment in PD is complex and involves multiple neural regions and transmitters.

1.6 Gait and cognition

In 'An Essay of the Shaking Palsy' James Parkinson wrote 'Walking becomes a task which cannot be performed without considerable attention. The legs are not raised to that height, or with that promptitude which the will directs, so that the utmost care is necessary to prevent frequent falls' (Parkinson, 2002). This was the first indication of the importance of cognition on gait in PD.

The ability to complete two tasks at once is critical for everyday functional tasks such as walking while carrying objects, walking and focusing on another task or walking and talking. This concept was tested in the work of Lundin-Olsson *et al.* (1997) who produced a short report in elderly nursing home residents identifying older adults who stopped walking when they started to talk. Lundin-Olsson *et al.* (1997) described that those who stopped walking when talking had less safe gait, decreased gait velocity and were more dependent on activities of daily living. Furthermore, these participants were significantly more likely to fall in the following 6 months compared to those who were able to complete the two tasks simultaneously. This simple study suggests cognition is required to refine gait patterns on the premise that if gait and cognition were dependent on separate resources, gait would not alter when cognitive load increased.

1.6.1 Dual task methodology

Lundin-Olsson *et al.* (1997) was one of the original studies to utilise what is now referred to as a dual task paradigm. Since the study by Lundin-Olsson *et al.* (1997) dual task paradigms have become one of the most popular methods of assessing the gait-cognition relationship. Under more recent dual task protocols, subjects complete a walking task as well as concurrently completing a cognitively demanding task. Such concurrent tasks vary between protocols but examples include serial number subtraction, verbal recall, semantic fluency and Stroop tasks.

Alongside the increased use of dual task paradigms there has been heightened interest in the theoretical models underpinning dual task (Yogev-Seligmann *et al.*, 2008; Strouwen *et al.*, 2015). Three of the most researched models include the bottleneck theory, the central capacity-sharing model and the multiple resource model. The bottle-neck theory suggests that cognitive resources of the same neural network cannot be divided between different tasks i.e. there is a bottle-neck when competing for the resource (Pashler, 1994). This theory depicts that neural network resource allocation for a secondary task is delayed until the first task is no longer utilising the resource. The bottle-neck theory therefore suggests that if gait and cognitive processes are reliant on the same neural networks then there will be poorer performance to one of the tasks i.e. gait or the concurrent cognitive task. Second, the central capacity-sharing model extends on the bottle-neck theory which suggests that at particular stages during dual tasking the neural network resources can be allocated to the two tasks, however, there is a limited capacity of resource and thus there will be poorer performance on both tasks i.e. gait and concurrent cognitive task (Tombu and Jolicœur, 2003). Third, the multiple resource model depicts that there can be competition for neural network resources but that this can be multi-dimensional as opposed to one-dimensional (Wickens, 2008). This model identifies that there is a finite capacity of resources and therefore performance on dual tasking is dependent on the capacity to utilise different resources concurrently.

Dual tasking is dependent on attentional resources and therefore in PD dual task deficits are thought to be exacerbated due to frontal executive-attention dysfunction commonly seen in this patient population (Yogev-Seligmann *et al.*, 2008). A number of studies have explored dual task gait in PD. Dual task deficits emerge in PD as reduced pace (i.e. slower speed and reduced step length) (Al-Yahya *et al.*, 2011), increased variability (Plotnik *et al.*, 2011), reduction in cadence (Al-Yahya *et al.*, 2011) and increased asymmetry (Yogev *et al.*, 2006). The largest study assessing dual task performance in PD was explored early in disease and identified characteristics of gait related postural control to be most susceptible to dual task conditions in comparison to age matched controls (Rochester *et al.*, 2014).

Dual task paradigms provide a useful tool to assess the gait-cognition relationship but due to methodological inconsistencies it is essential to measure gait under single task conditions (Kelly *et al.*, 2012). When measured under single task conditions, gait can be associated with cognitive assessments and thus allow for the ability to tease out the cognitive elements needed for refinement of gait.

1.6.2 Gait and cognition selective associations

Current understanding of disease pathology provides insight into potential associations of gait and cognition. For example, people with AD present foremost with deficits in amnestic ability predominantly due to amyloid deposition in the entorhinal cortex and hippocampus (Braak and Braak, 1995), with concordant findings of an association between atrophy of the hippocampus and decreased gait velocity and step length (Callisaya *et al.*, 2013). Similarly, for people with PD who present with executive-attention deficits due to compromised fronto-striatal circuitry (Stern *et al.*, 1993; Burton *et al.*, 2004) attention has been significantly associated with reduced gait velocity and step length (Lord *et al.*, 2014). The question remains however if discrete gait domains share a different association dependent upon cognitive function? Furthermore, if the relationship between gait and cognitive variables is selective one may expect a different signature of impairments to emerge underpinned by the selective influence of pathology. A better understanding of this relationship would strengthen an understanding of the mechanisms of gait impairment, the shared neural and pathological correlates of gait and cognitive function and validate the role of gait as a clinical biomarker of cognitive decline, dementia and pathology (Lord *et al.*, 2014; Mollenhauer *et al.*, 2014). The relationship between gait and cognition however is still an emerging area of work, largely due to recent advances in the understanding of gait and improvement in the ability to measure its discrete characteristics. This thesis firstly aims to provide a better understanding of this topic as detailed below.

1.7 Thesis outline, aims and hypothesis

This thesis was designed to explore the role of gait as a predictor for cognitive decline in PD, the significance of which has been highlighted in this chapter. This thesis is split into a further five chapters which are outlined below.

1.7.1 Chapter 2: Gait and cognition: mapping the global and discrete relationships in ageing and neurodegenerative disease

This chapter forms a published structured review exploring associations of gait and cognition in three cohorts; older adults, cognitive impairment and Parkinson's disease. The review also explores longitudinal studies of gait and cognition. This structured review was undertaken to provide a clear understanding of current associations in the literature to further inform this thesis.

Aims:

- Explore evidence for the associations between independent features of gait and cognitive function in older adults, cognitive impairment and PD
- Identify the longitudinal nature of relationships in the same cohorts

Hypothesis:

- Independent gait characteristics will be related to discrete cognitive functions in a specific rather than global manner and the pattern of association will be different with respect to pathology and ageing

1.7.2 Chapter 3: General methods- the ICICLE-Gait study

Chapter 3 provides an overview of the ICICLE-Gait study, the longitudinal study that formed the basis of this thesis. Chapter 3 provides details on the ICICLE-gait study aims, participant recruitment, participant retention, gait and cognitive testing and statistical analysis applicable to all chapters. Further specific methodology is described in subsequent chapters where needed.

1.7.3 Chapter 4: Single task gait as a predictor for cognitive decline in PD

Chapter 4 presents an investigation of single task gait as a predictor for cognitive decline in PD. Linear mixed effects analysis explores the predictive ability of both gait domains and gait characteristics at diagnosis of PD as predictors of decline in several cognitive domains over three years. The chapter also observes the predictive ability of cognition to determine if gait provides a more sensitive predictor over neuropsychological cognitive assessments. The chapter concludes by exploring potential underpinning mechanisms behind findings.

Aims:

- Examine whether gait under single task conditions can predict cognitive decline in PD
- Determine whether the pattern of association is global or specific
- Determine whether gait predictors are specific to PD pathology
- Determine whether gait is superior to a clinically used cognitive measure

Hypothesis:

- It is hypothesised that discrete gait characteristics will be sensitive to early cognitive decline in PD.

1.7.4 Chapter 5: Dual task gait as a predictor for cognitive decline in PD

Chapter 5 follows on from chapter 4, exploring whether gait under dual task conditions is able to predict cognitive decline in PD. In addition, the chapter will compare findings with chapter 4 to decipher whether dual task gait provides a more sensitive predictor. Once again, this chapter will conclude by exploring potential underpinning mechanisms as well as discussing clinical significance of findings.

Aims:

- Examine dual task gait characteristics and domains as predictors for cognitive decline in PD

- Determine whether dual task gait is superior to a baseline cognitive measure
- Determine whether predictors are specific to PD pathology
- Compare predictive value to single task gait characteristics

Hypothesis:

- It is hypothesised that dual task gait will be able to predict cognitive decline in PD and that gait characteristics will be more sensitive to this decline compared to single task gait.

1.7.5 Chapter 6: Gait and cognition in free-living; an exploratory look

This chapter provides exploratory analysis of the relationship between gait and cognition in 'free-living' measuring gait with accelerometer BWM. This chapter focuses on a cross-sectional approach at three years post PD diagnosis. The chapter will be split into two sections which are described below.

Section 1: A model of free-living gait; a factor analysis in PD

This first section of chapter 6 will explore a factor-analysis approach to free-living gait characteristics in order to develop a conceptual gait model for free-living data similar to the model used as a framework in the previous chapters. The chapter explores conceptual gait models using BWM both in controlled (laboratory) and free-living environments in PD and healthy older adults. The results from section one will be used to further inform analysis in section two.

Aims:

- Explore a gait model using body-worn monitors in controlled and free-living environments in older adults and PD
- Compare the models to a previous GaitRite™ derived model

Hypothesis:

- Due to differences in measurement tools, free-living derived gait characteristics will load differently onto a conceptual gait model

Section 2: The gait-cognition relationship in free-living

This section provides exploratory analysis of the gait-cognition relationship in free-living compared to laboratory. This chapter is of cross-sectional design focusing on associations between gait and cognition at three years post diagnosis in PD.

Aims:

- Explore gait-cognition associations using a BWM in relation to protocol i.e. laboratory v's free-living conditions in PD
- Explore the effect of ambulatory bout length on gait and cognition associations in PD

Hypotheses:

- Gait-cognition associations will be more evident in the laboratory setting due to primed attention
- Gait and cognition associations will be more evident during shorter ambulatory bouts due to the likelihood of increased environment complexity

1.7.6 Chapter 7: Thesis summary

Chapter 7 provides the final section of this thesis and provides an overall summary of all chapters. The chapter outlines the clinical implications of this thesis and provides an overview limitations and direction for future research.

Chapter 2 : Gait and cognition: mapping the global and discrete relationships in ageing and neurodegenerative disease*

As discussed in chapter one, both gait and cognition are affected in PD. However, recent literature has recognised associations between gait and cognition and have explored this concept through cross-sectional and longitudinal studies. In order to further understand this concept, a structured literature review was performed which forms the basis of this chapter.

2.1 Introduction

To date a comprehensive investigation of the selective associations between independent gait and cognition characteristics in ageing and neurodegenerative disease has not been undertaken. The purpose of this review was therefore to undertake a detailed comparison of studies exploring discrete relationships of gait and cognitive domains. For this review, studies were limited to measuring gait under single task conditions. Gait under single task conditions reflects the ability of the cognitive system to control locomotion and to compensate for motor and cognitive deficit as a consequence of ageing and pathology. Therefore it is expected that changes in cognitive function would be reflected in changes in gait performance. Although dual task paradigm studies are extensively used to examine associations of gait and cognition, inconsistent findings are reported due to methodological issues such as diverse concurrent tasks, controlling for baseline task demand and different analysis of calculating dual task interference (Rochester *et al.*, 2014). In addition to these inconsistencies, the underlying cognitive nature of dual task methodology remains unclear and does not reflect baseline cognitive influence on gait; therefore making it difficult to tease out direct underlying neural correlates.

In light of this, the aims of this review are to i) explore evidence for the associations between independent features of gait and cognitive function and ii) identify the longitudinal nature of relationships. It is hypothesised that independent gait characteristics would be related to discrete cognitive functions in a specific rather than global manner and the pattern of association would be different with respect to pathology and ageing. In order to address this

*This chapter has been published in Neuroscience and Biobehavioural Reviews

hypothesis a model of gait previously used in older adults was adopted (Lord *et al.*, 2013b)(**Figure 2-1**) and a comprehensive range of cognitive domains previously described (Emre *et al.*, 2007) were chosen. This was done in order to improve consistency, reduce redundancy and retain independence between gait and cognitive features respectively to ease interpretation of results. Individual gait domains (or respective characteristics) were mapped to individual cognitive functions to develop a matrix from which to identify discrete relationships. Three different cohorts were included: older adults (OA); those with cognitive impairment (CI); and people with PD, in order to explore gait-cognition associations in pathology and normal ageing. Cross-sectional and longitudinal study designs were examined to identify causality. It is hoped this review will not only to provide a clear understanding of current associations but in addition identify gaps in the literature to inform recommendations for future work.

2.2 Methods

2.2.1 Search Strategy

Three databases were used for the search: Medline, Psychinfo and Scopus. For each of the databases used, three separate searches were performed for the three cohorts included in the review; OA, CI and PD. In total, nine separate searches were completed. Each search used the key terms 'Gait', 'Cognition' and either 'Parkinson's disease', 'dementia' or 'older adults'. For each of the key terms, a list of synonyms were correlated and entered into the search (**Table 2-1**). Where possible, MESH headings were used for Medline and Psychinfo. The search was limited for papers published since 1990 to February 2014, written in English language and restricted to full journal articles only.

The initial nine searches were combined into three master databases; 'Parkinson's disease', 'Cognitive Impairment' and 'Older Adults'. Duplicates were then deleted and an initial title screen was performed by the reviewer (RM). After the initial title screen, the titles and abstracts were reviewed by independent reviewers (authors Rosie Morris and Jennifer Bunce). A review of the full text was

needed in incidences where it was unclear from the abstract whether the paper was suitable for inclusion.

Pace	•Step velocity (m/s) •Step length (m) •Step time variabiltiy (ms) •Step swing time variability (ms) •Step stance time variability (ms)
Rhythm	•Step time (ms) •Step swing time (ms) •Step stance time (ms)
Variability	•Step velocity variability (m/s) •Step length variability (m) •Step width variabiltiy (m)
Asymmetry	•Step time asymmetry (ms) •Step swing asymmetry (ms) •Step stance asymmetry (ms)
Postural Control	•Step width (m) •Step length asymmetry (m)

Figure 2-1: Model of gait proposed by Lord et al, 2013 in older adults.

Table 2-1: Key terms search table for structured literature review.

	Medline	**Psychinfo**	**Scopus**
Gait	MESH Headings: Gait, locomotion, walking, Keywords: symmetry, asymmetry, frequency, variability, pace, rhythm, speed, velocity, step	MESH Headings: Gait, locomotion, walking Keywords; symmetry, asymmetry, base of support, frequency, variability, speed/velocity, stance	Keyword Search: Gait OR locomotion OR walking OR symmetry OR asymmetry OR frequency OR variability OR speed OR velocity OR stance OR step OR swing OR stride OR "double limb"
Cognition	MESH Headings: Cognition, cognition disorders, memory, neuropsychological tests, attention, executive function, reaction time, psychomotor performance Keywords; Processing speed, visuospatial, verbal fluency	MESH Headings; cognition, cognitive ability (tick spatial ability, verbal ability, cognitive assessment, cognitive impairment, cognitive processing speed, executive function, metacognition) Memory, Attention, visuospatial ability, verbal fluency, reaction time Keywords; psychomotor performance	Keyword Search: Cognition* OR "global intelligence" OR cognitive* OR memory OR attention OR "executive function" OR "processing speed" OR psychomotor OR visuospatial OR "verbal fluency" OR "reaction time"
Cohort	**PD:** MESH: Parkinson's disease	**PD:** MESH: Parkinson's disease	**PD:** Parkinson*
	Dementia: MESH: Dementia (explode), Alzheimer's disease,	**Dementia:** MESH: Dementia (explode dementia- cognitive impairment, Alzheimer's disease, dementia with lewy bodies, vascular dementia)	**Dementia:** Alzheimer*, "lewy body", dementia, "frontal lobe dementia", "intellectual impairment"
	Older Adults: Seniors, older*, aging, elderly*	**Older Adults:** Seniors, older*, aging, elderly*	**Older Adults:** Older* OR elderly* OR Seniors OR aging

Table includes the three databases used, the individual terms for each cohort and MESH headings where applicable.

2.2.2 Inclusion and Exclusion Criteria

Articles were included if they assessed OA and patients with either a degree of cognitive impairment or PD completing a gait assessment under single task conditions and independently completing a minimum of one cognitive assessment. Cognitive assessments included global cognitive tests (e.g. MMSE/MOCA) as well as tests of attention, executive function, memory, language, processing speed and visuospatial skills. Articles must have completed analysis for gait assessment under single task conditions. Articles were excluded if they only completed cognitive tasks under dual task conditions or if analysis was only reported for dual task conditions. Intervention studies were excluded as well as studies focusing on falls, freezing of gait (FOG) and overall physical activity.

2.2.3. Data Extraction

A title and abstract screen was undertaken by two independent reviewers; RM and JB. Three separate data extraction forms were created for the three cohorts. Data from the extraction forms was then transferred into a table. Information included; participant groups, participant characteristics, study type, gait variables measured, gait analysis tool, cognitive domains tested, cognitive assessments used and main study findings. The cognitive impairment cohort included the type of cognitive impairment and for the PD cohort whether participants were ON or OFF medication.
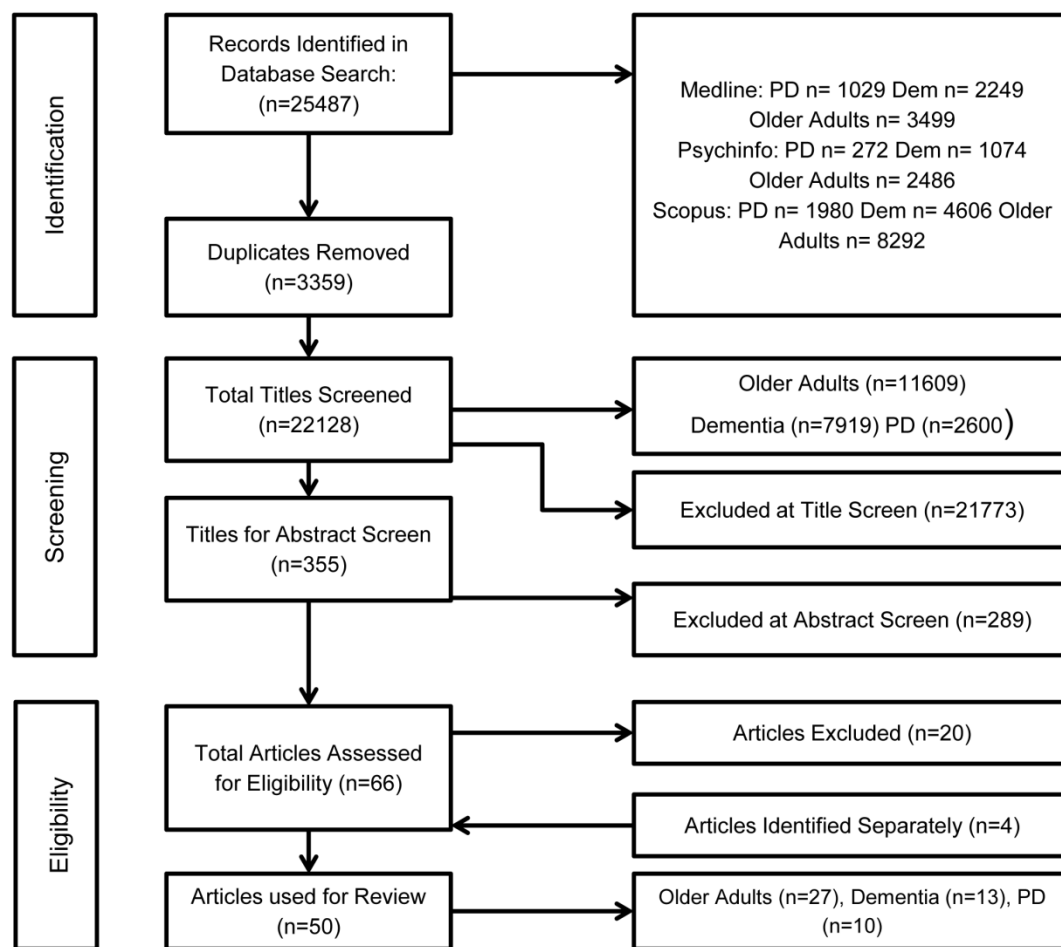
Figure 2-2: Prisma diagram presenting the search yield for the structured review.

2.3 Results

2.3.1 Search Yield

The search strategy generated a total of 43,828 papers; after exclusion criteria were applied the search strategy generated a total of 25,487 papers. After duplicates were removed, a total number of 22,128 papers were yielded from the search. The total number of papers were compiled into three databases; OA (*n*=11609), CI (*n*=7919 and PD (*n*=2600). After the initial title screen, the total number of papers of interest for each group were OA (*n*=168), CI (*n*=119) and PD (*n*=62).

After an abstract screen, 66 papers were eligible for data extraction (*n*=34 OA, *n*=22 CI, *n*=10 PD). 11 papers were excluded due to inability to access paper

(*n*=7), duplicate findings (*n*=1) and studies which were not full journal articles (*n*=3). Data extraction was completed for a total of 55 papers; 30 for the OA cohort, 15 for the CI cohort and 10 for the PD cohort. After data extraction, 9 papers were excluded due to completing only dual task conditions (*n*=4), not associating gait and cognition (*n*=1), associating fast speed only (*n*=1), participants being too young (*n*=1, all <60 years), not completing both independent cognitive domains and gait variables (*n*=1) and focusing on cognitive reserve (*n*=1). Four papers (Dodge *et al.*, 2012; Lord *et al.*, 2014) (Kaye *et al.*, 2012; Xu *et al.*, 2014) have been identified since the search closed and were added to the data extraction process. The total number of papers used was 50. The search yield is demonstrated in **Figure 2-2**. All articles were originally published in the English language. Publication dates ranged from 2002 (Lord and Menz, 2002; Marquis *et al.*, 2002) to 2014 (Lord *et al.*, 2014; Xu *et al.*, 2014).

2.3.2 Measurement of gait and cognition – methodological comparisons

Gait measurement techniques included the use of activity monitors (Rochester *et al.*, 2004; Rochester *et al.*, 2005; Rochester *et al.*, 2008; Gillain *et al.*, 2009; Lord *et al.*, 2010; Maquet *et al.*, 2010; Ijmker and Lamoth, 2012), gait walkway systems (Holtzer *et al.*, 2006; Hollman *et al.*, 2007; van Iersel *et al.*, 2008; Beauchet *et al.*, 2012; Coelho *et al.*, 2012; Holtzer *et al.*, 2012; Muir *et al.*, 2012; Beauchet *et al.*, 2013; Lord *et al.*, 2013b; Martin *et al.*, 2013; Verlinden *et al.*, 2013; Lord *et al.*, 2014), optokinetic systems (Ble *et al.*, 2005; Amboni *et al.*, 2012), foot pressure sensors (Sheridan *et al.*, 2003; Allali *et al.*, 2010b), infra-red cameras (Kaye *et al.*, 2012; Wild *et al.*, 2013), timed up and go test (Donoghue *et al.*, 2012; Smulders *et al.*, 2013; Xu *et al.*, 2014), timed to walk (Fitzpatrick *et al.*, 2007; Auyeung *et al.*, 2008; Duff *et al.*, 2008; Persad *et al.*, 2008; McGough *et al.*, 2011) and 6 minute walk distance test (Lord and Menz, 2002). A number of studies used a combination of techniques listed above (Hausdorff *et al.*, 2005; Yogev *et al.*, 2005; Lamoth *et al.*, 2011; Bramell-Risberg *et al.*, 2012). The majority of studies assessed single gait characteristics but five studies utilised gait domains (Verghese *et al.*, 2007; Amboni *et al.*, 2012; Lord *et al.*, 2013b; Verlinden *et al.*, 2013; Lord *et al.*, 2014).

A variety of cognitive assessments were utilised as shown in **Tables 2-6, 2-7, 2-8 and 2-9** however, several of the same assessments were used in different studies and reported as testing different cognitive domains. Therefore for clarity we've noted studies that either assessed single cognitive assessments in association with gait; (Lord and Menz, 2002; Marquis *et al.*, 2002; Sheridan *et al.*, 2003; Rochester *et al.*, 2004; Ble *et al.*, 2005; Hausdorff *et al.*, 2005; Rochester *et al.*, 2005; Yogev *et al.*, 2005; Alfaro-Acha *et al.*, 2007; Atkinson *et al.*, 2007; Fitzpatrick *et al.*, 2007; Hollman *et al.*, 2007; Inzitari *et al.*, 2007; Auyeung *et al.*, 2008; Duff *et al.*, 2008; Persad *et al.*, 2008; Rochester *et al.*, 2008; van Iersel *et al.*, 2008; Deshpande *et al.*, 2009; Gillain *et al.*, 2009; Allali *et al.*, 2010a; Atkinson *et al.*, 2010; Buracchio *et al.*, 2010; Lord *et al.*, 2010; Maquet *et al.*, 2010; Auyeung *et al.*, 2011; Lamoth *et al.*, 2011; McGough *et al.*, 2011; Beauchet *et al.*, 2012; Bramell-Risberg *et al.*, 2012; Coelho *et al.*, 2012; Donoghue *et al.*, 2012; Ijmker and Lamoth, 2012; Muir *et al.*, 2012; Taniguchi *et al.*, 2012; Beauchet *et al.*, 2013; Lord *et al.*, 2013b; Smulders *et al.*, 2013; Wild *et al.*, 2013; Xu *et al.*, 2014) or grouped assessments to form domains (Holtzer *et al.*, 2006; Verghese *et al.*, 2007; Watson *et al.*, 2010; Amboni *et al.*, 2012; Dodge *et al.*, 2012; Holtzer *et al.*, 2012; Kaye *et al.*, 2012; Martin *et al.*, 2013; Verlinden *et al.*, 2013; Lord *et al.*, 2014).

Table 2-2: Colour correlation table to display gait and cognitive correlations in older adults.

Domain/Factor	Global cognition	Executive function	Attention	Visuospatial	Memory	Language	Processing Speed
Pace *Step Velocity (m/s)* *Step Length (m)* *Step Time Variability (ms)* *Step Swing Time Variability (ms)* *Step Stance Time Variability (ms)*	(G)4 (G)5 (G)17 (G)19; (G)20; (R)3 (R)6 (R)7 (R)8 (R)11; (R)12 (R)13 (R)18	(G)1 (G)4 (G)7 (G)9* (G)10*; (G)14* (G)16 (G)20; (R)2 (R)11 (R)13 (R)15	(G)5 (G)9* (G)11 (G)13; (G)10* (G)14* (G)20	(G)5 (G)11; (R)14	(G)4 (G)5 (G)9 (G)10; (G)20; (R)7 (R)11 (R)13; (R)14 (R)15 (R)16	(G)5 (G)9 (G)10	(G)4 (G)9† (G)11; (G)14 (G)20; (R)16
Variability *Step Velocity Variability (m/s)* *Step Length Variability (m)* *Step Width Variability (m)*	(R)11 (R)13	(G)10*; (R)11 (R)13 (R)14* (R)15; (R)16	(G)10*; (R)11 (R)13 (R)14*	(R)14	(R)10 (R)11 (R)13; (R)14 (R)15 (R)16	(R)10	(R)11 (R)14; (R)16
Rhythm *Step Time (ms)* *Step Swing Time (ms)* *Step Stance Time (ms)*	(R)7 (R)13	(G)10*; (R)7 (R)13 (R)14* (R)16	(G)10*; (R)13 (R)14*	(R)14	(G)10; (R)7 (R)13 (R)14; (R)16	(R)10	(G)14 (G)16
Asymmetry *Step Time Asymmetry (ms)* *Step Swing Asymmetry (ms)* *Step Stance Asymmetry (ms)*	(R)13	(R)13	(R)13		(R)13		
Postural Control *Step Width (m)* *Step Length Asymmetry (m)*	(R)13	(G)13 (G)14*; (R)15 (R)16	(G)14*; (R)13	(G)14	(R)13 (R)14 (R)15; (R)16		(G)14; (R)16

[1]Beauchet et al. (2012); [2]Ble et al. (2005); [3]Bramell-Risberg et al. (2012); [4]Donoghue et al. (2012); [5]Duff et al. (2008); [6]Fitzpatrick et al. (2007); [7]Hausdorff et al. (2005); [8]Hollman et al. (2007); [9]Holtzer et al. (2006); [10]Holtzer et al. (2012); [11] Kaye et al. (2012); [12]Lord and Menz (2002); [13]Lord et al. (2013b); [14]Martin et al. (2013); [15] van Iersel et al. (2008); [16]Verlinden et al. (2013). From longitudinal studies: [17]Alfaro-Acha et al. (2007); [18]Atkinson et al. (2010); [19]Deshpande et al. (2009); [20]Watson et al. (2010). * Referred executive function and attention as 'Executive Attention'. † speed of executive attention. **Green indicates an association was found, red indicates no association found.**

Table 2-3: Colour correlation table to display cognitive and gait correlations in the cognitive impairment cohort.

Domain/Factor	AD[i]	FTD[i]	CI	Global Cognition	Executive Function	Attention	Visuospatial	Memory	Language	Processing speed
Pace *Step Velocity (m/s)* *Step Length (m)* *Step Time Variability (ms)* *Step Swing Time Variability (ms)* *Step Stance Time Variability (ms)*	🟢4 🟢5 🟢6 🟢8 🟢11 🟢12 🔴1 🔴3 🔴7 🔴10	🟢1 🟢6	🟢2 🔴3 🔴5 🔴10	🟢8**	🟢9 🟢11*** 🔴12	🟢8**				
Variability *Step Velocity Variability (m/s)* *Step Length Variability (m)* *Step Width Variability (m)*										
Rhythm *Step Time (ms)* *Step Swing Time (ms)* *Step Stance Time (ms)*	🟢6 🔴4 🔴5 🔴7 🔴8 🔴10	🟢6	🟢5 🟢8 🔴10	🟢8**		🔴8**				
Asymmetry *Step Time Asymmetry (ms)* *Step Swing Asymmetry (ms)* *Step Stance Asymmetry (ms)*										
Postural Control *Step Width (m)* *Step Length Asymmetry (m)*	🔴5 🔴8		🔴5 🔴8	🔴8**		🔴8**				

[1]Allali et al. (2010a); [2]Auyeung et al. (2008); [3]Beauchet et al. (2013); [4]Coelho et al. (2012); [5]Gillain et al. (2009); [6]Ijmker and Lamoth (2012); [7]Lamoth et al. (2011); [8]Maquet et al. (2010); [9]McGough et al. (2011), [10]Muir et al. (2012); [11]Persad et al. (2008); [12]Sheridan et al. (2003).*results found for those with dementia as well as healthy controls; analysed as whole cohort.** MCI group only. *** Had AD or MCI with executive function impairment. **Green indicates an association was found, red indicates no association found.**

Table 2-4: Colour correlation table to display cognitive and gait correlations in Parkinson's disease.

Domain/Factor	Global Cognition	Executive Function	Attention	Visuospatial	Memory	Language	Processing speed
Pace *Step velocity (m/s)* *Step Length (m)* *Step Time Variability (ms)* *Step Swing Time Variability (ms)* *Step Stance Time Variability (ms)*	(red) 3 (red) 4 (red) 9	(green) 4 (green) 5 (green) 7 (green) 9 (green) 10 / (red) 1 (red) 2 (red) 3 (red) 6 (red) 8**	(green) 2 (green) 3 / (red) 8**	(green) 1 / (red) 3	(green) 3 / (red) 1		
Variability *Step Velocity Variability (m/s)* *Step Length Variability (m)* *Step Width Variability (m)*	(green) 3	(red) 1 (red) 3	(red) 3	(green) 1 / (red) 3	(red) 1 (red) 3		
Rhythm *Step Time (ms)* *Step Swing Time (ms)* *Step Stance Time (ms)*	(red) 3 (red) 4	(green) 3* / (red) 1 (red) 4 (red) 8**	(red) 3 (red) 8**	(red) 1 (red) 3	(red) 1 (red) 3		
Asymmetry *Step Time Asymmetry (ms)* *Step Swing Asymmetry (ms)* *Step Stance Asymmetry (ms)*	(red) 3	(red) 3	(red) 3	(red) 3	(red) 3		
Postural Control *Step Width (m)* *Step Length Asymmetry (m)*	(red) 3	(red) 1 (red) 3	(red) 3	(green) 1 / (red) 3	(green) 3 / (red) 1		

[1]Amboni et al. (2012); [2]Lord et al. (2010); [3]Lord et al. (2014); [4]Rochester et al. (2004); [5]Rochester et al. (2005); [6]Rochester et al. (2008); [7]Smulders et al. (2013); [8]Wild et al. (2013); [9]Xu et al. (2014); [10]Yogev et al. (2005). *PIGD phenotype only. ** Executive Function and attention classified as one domain.
Green indicates an association was found, red indicates no association found.

Table 2-5: Colour correlation table to display cognitive and gait correlations from longitudinal studies (older adults only).

Domain/Factor	Global cognition	Executive Function	Attention	Visuospatial	Memory	Language	Processing Speed
Pace *Step Velocity (m/s)* *Step Length (m)* *Step Time Variability (ms)* *Step Swing Time Variability (ms)* *Step Stance Time Variability (ms)*	🟢1 🟢2† 🟢3 ⚫4 🟢6 🟢9Ɨ 🟢10 🟢11 ⚫12 🔴5 🔴5 🔴7*	🟢4 🟢11 ⚫12	🟢8 🔴11 🔴12*		🟢12 🔴11		🟢8 🔴12*
Variability *Step Velocity Variability (m/s)* *Step Length Variability (m)* *Step Width Variability (m)*	🟢11**	🔴11	🔴11		🔴11		
Rhythm *Step Time (ms)* *Step Swing Time (ms)* *Step Stance Time (ms)*	🟢11** 🔴10	🔴11	🔴11		🟢11		
Asymmetry *Step Time Asymmetry (ms)* *Step Swing Asymmetry (ms)* *Step Stance Asymmetry (ms)*							
Postural Control *Step Width (m)* *Step Length Asymmetry (m)*							

[1]Buracchio et al. (2010); [2]Dodge et al. (2012); [3]Alfaro-Acha et al. (2007); [4]Atkinson et al. (2007); [5]Atkinson et al. (2010); [6]Auyeung et al. (2011); [7]Deshpande et al. (2009); [8]Inzitari et al. (2007); [9]Marquis et al. (2002); [10]Taniguchi et al. (2012); [11]Verghese et al. (2007); [12]Watson et al. (2010). No circle outline= gait as predictor, black circle outline= cognition as a predictor. *= seen at baseline but not longitudinal. **= associated with the onset of dementia. †= classified as na-MCI where there was an impairment in any domain other than memory but particular domain not specified. Ɨ gait speed enhanced prediction model. **Green indicates an association was found, red indicates no association found.**

2.3.3 Associations between gait domains and cognition

Associations between independent cognitive functions were explored with respect to independent gait domains (**Figure 2-1**). Individual gait characteristics were mapped onto their respective domains such that relationships are explored with respect to broad gait domains. Where possible, studies which outlined their own domains were appropriately matched to the most relevant domain in the model used in this review as individual gait characteristic associations were mainly not reported. In addition, the strongest statistical analysis has been reported for each study (e.g. if the analysis included consideration of covariates). **Tables 2-2**, **2-3**, **2-4** and **2-5** summarises the findings into associations for each cohort which are colour coded to show whether an association was found (green) or not (red). Tables 2-6, 2-7, 2-8 and 2-9 provide further details on each individual study. **Figures 2-3** and **2-4** complete the schema map of associations for cross-sectional (**Figure 2-3**) and longitudinal studies (**Figure 2-4**).

2.3.3.1 Pace

Pace was the most frequently assessed gait variable in all three cohorts (Lord and Menz, 2002; Sheridan *et al.*, 2003; Rochester *et al.*, 2004; Ble *et al.*, 2005; Hausdorff *et al.*, 2005; Rochester *et al.*, 2005; Yogev *et al.*, 2005; Holtzer *et al.*, 2006; Fitzpatrick *et al.*, 2007; Hollman *et al.*, 2007; Auyeung *et al.*, 2008; Duff *et al.*, 2008; Persad *et al.*, 2008; Rochester *et al.*, 2008; van Iersel *et al.*, 2008; Deshpande *et al.*, 2009; Gillain *et al.*, 2009; Allali *et al.*, 2010b; Atkinson *et al.*, 2010; Lord *et al.*, 2010; Maquet *et al.*, 2010; Watson *et al.*, 2010; Lamoth *et al.*, 2011; McGough *et al.*, 2011; Amboni *et al.*, 2012; Beauchet *et al.*, 2012; Bramell-Risberg *et al.*, 2012; Donoghue *et al.*, 2012; Holtzer *et al.*, 2012; Kaye *et al.*, 2012; Muir *et al.*, 2012; Beauchet *et al.*, 2013; Lord *et al.*, 2013b; Martin *et al.*, 2013; Smulders *et al.*, 2013; Verlinden *et al.*, 2013; Wild *et al.*, 2013; Lord *et al.*, 2014; Xu *et al.*, 2014). In addition, a number of studies assessed specific gait characteristics that loaded onto the pace domain (Sheridan *et al.*, 2003; Rochester *et al.*, 2004; Hausdorff *et al.*, 2005; Yogev *et al.*, 2005; Holtzer *et al.*, 2006; Hollman *et al.*, 2007; van Iersel *et al.*, 2008; Gillain *et al.*, 2009; Allali *et al.*, 2010b; Maquet *et al.*, 2010; Lamoth *et al.*, 2011; Amboni *et al.*, 2012; Beauchet *et al.*, 2012; Coelho *et al.*, 2012; Holtzer *et al.*, 2012; Ijmker and Lamoth, 2012; Muir

et al., 2012; Beauchet *et al.*, 2013; Lord *et al.*, 2013b; Martin *et al.*, 2013; Verlinden *et al.*, 2013; Lord *et al.*, 2014) (**Figure 2-1**). In OA, associations were evident between pace and attention as shown by 7 of 7 studies (Holtzer *et al.*, 2006; Duff *et al.*, 2008; Watson *et al.*, 2010; Holtzer *et al.*, 2012; Kaye *et al.*, 2012; Lord *et al.*, 2013b; Martin *et al.*, 2013), executive function as shown by 8 of 12 studies (Hausdorff *et al.*, 2005; Holtzer *et al.*, 2006; Watson *et al.*, 2010; Beauchet *et al.*, 2012; Donoghue *et al.*, 2012; Holtzer *et al.*, 2012; Martin *et al.*, 2013; Verlinden *et al.*, 2013), processing speed as shown by 5 of 6 studies (Holtzer *et al.*, 2006; Watson *et al.*, 2010; Donoghue *et al.*, 2012; Kaye *et al.*, 2012; Martin *et al.*, 2013), language as shown by 3 of 3 studies (Holtzer *et al.*, 2006; Duff *et al.*, 2008; Holtzer *et al.*, 2012) and visuospatial skills as shown by 2 of 3 studies (Duff *et al.*, 2008; Kaye *et al.*, 2012). In OA no association was evident between pace and global cognition (Hausdorff *et al.*, 2005; Fitzpatrick *et al.*, 2007; Hollman *et al.*, 2007; Irani *et al.*, 2007; Atkinson *et al.*, 2010; Bramell-Risberg *et al.*, 2012; Lord *et al.*, 2013b) and pace and memory (Hausdorff *et al.*, 2005; van Iersel *et al.*, 2008; Kaye *et al.*, 2012; Lord *et al.*, 2013b; Martin *et al.*, 2013; Verlinden *et al.*, 2013). In the CI cohort pace was assessed in nine studies with AD participants (Sheridan *et al.*, 2003; Persad *et al.*, 2008; Gillain *et al.*, 2009; Allali *et al.*, 2010a; Maquet *et al.*, 2010; Lamoth *et al.*, 2011; Coelho *et al.*, 2012; Ijmker and Lamoth, 2012; Muir *et al.*, 2012; Beauchet *et al.*, 2013), two with FTD (Allali *et al.*, 2010a; Ijmker and Lamoth, 2012), one with CI (Auyeung *et al.*, 2008) and three with MCI (Gillain *et al.*, 2009; Muir *et al.*, 2012; Beauchet *et al.*, 2013). Slower gait speed was associated with AD (Sheridan *et al.*, 2003; Persad *et al.*, 2008; Gillain *et al.*, 2009; Maquet *et al.*, 2010; Coelho *et al.*, 2012; Ijmker and Lamoth, 2012), FTD (Allali *et al.*, 2010a) and CI (Auyeung *et al.*, 2008; Ijmker and Lamoth, 2012) but not MCI (Gillain *et al.*, 2009; Muir *et al.*, 2012; Beauchet *et al.*, 2013). In the CI cohort, an association between pace and executive function was supported by 2 of 3 studies (Persad *et al.*, 2008; McGough *et al.*, 2011). Only one study associated pace with global cognition and attention (Maquet *et al.*, 2010). In PD, an association was evident between pace and attention with 2 of 3 studies obtaining this result (Lord *et al.*, 2010; Lord *et al.*, 2014). Evidence was inconclusive for pace and executive function with 5 studies finding an association (Rochester *et al.*, 2004; Rochester *et al.*, 2005; Yogev *et al.*, 2005;

Smulders *et al.*, 2013; Xu *et al.*, 2014) and 5 not (Rochester *et al.*, 2008; Lord *et al.*, 2010; Amboni *et al.*, 2012; Wild *et al.*, 2013; Lord *et al.*, 2014), pace and visuospatial with one study finding an association (Amboni *et al.*, 2012) and one study not (Lord *et al.*, 2014) and pace and memory with one study finding an association (Lord *et al.*, 2014) and one study not (Amboni *et al.*, 2012). There was no association between pace and global cognition for PD.

2.3.3.2 Variability

Characteristics of gait variability including step velocity variability, step length variability and step width variability (**Figure 2-1**) were comprehensively assessed in OA (van Iersel *et al.*, 2008; Holtzer *et al.*, 2012; Kaye *et al.*, 2012; Lord *et al.*, 2013b; Martin *et al.*, 2013; Verlinden *et al.*, 2013) but were limited in PD (Amboni *et al.*, 2012; Lord *et al.*, 2014) and were not studied in CI. In OA no consistent associations were evident with any of the cognitive domains (van Iersel *et al.*, 2008; Holtzer *et al.*, 2012; Kaye *et al.*, 2012; Lord *et al.*, 2013b; Martin *et al.*, 2013). In PD only two studies explored variability and cognition (Amboni *et al.*, 2012; Lord *et al.*, 2014). One study assessed global cognition for which an association was found (Lord *et al.*, 2014). Evidence was inconclusive for visuospatial ability with one study finding an association (Amboni *et al.*, 2012) and the other study refuting these findings (Lord *et al.*, 2014). No associations were found with executive function, attention or memory in PD.

2.3.3.3 Rhythm

Characteristics of rhythm including step time, step swing time and step stance time (**Figure 2-1**) were assessed throughout the three cohorts (Rochester *et al.*, 2004; Hausdorff *et al.*, 2005; Gillain *et al.*, 2009; Allali *et al.*, 2010a; Maquet *et al.*, 2010; Lamoth *et al.*, 2011; Coelho *et al.*, 2012; Holtzer *et al.*, 2012; Ijmker and Lamoth, 2012; Muir *et al.*, 2012; Lord *et al.*, 2013b; Martin *et al.*, 2013; Verlinden *et al.*, 2013; Wild *et al.*, 2013; Lord *et al.*, 2014). Five studies in OA assessed rhythm (Hausdorff *et al.*, 2005; Holtzer *et al.*, 2012; Lord *et al.*, 2013b; Martin *et al.*, 2013; Verlinden *et al.*, 2013) providing evidence for an association with processing speed (Martin *et al.*, 2013; Verlinden *et al.*, 2013) but no other domains. Rhythm was assessed in AD (Gillain *et al.*, 2009; Maquet *et al.*, 2010; Lamoth *et al.*, 2011; Coelho *et al.*, 2012; Ijmker and Lamoth, 2012; Muir *et al.*,

2012), FTD (Ijmker and Lamoth, 2012) and MCI (Gillain *et al.*, 2009; Maquet *et al.*, 2010; Muir *et al.*, 2012) with only inconclusive evidence associating rhythm deficit in FTD (Ijmker and Lamoth, 2012) and MCI (Gillain *et al.*, 2009; Maquet *et al.*, 2010). In the CI group, only one study assessed global cognition for which an association was found (Maquet *et al.*, 2010). There was no evidence for an association between rhythm and attention (Maquet *et al.*, 2010). In PD, rhythm was measured by four studies (Rochester *et al.*, 2004; Amboni *et al.*, 2012; Wild *et al.*, 2013; Lord *et al.*, 2014) with no evidence for associations with cognition. One study which sub-grouped motor phenotype (Lord *et al.*, 2014) associated rhythm and executive function in the postural instability/gait difficulty (PIGD) phenotype only.

2.3.3.4 Asymmetry

Asymmetry was the least frequently tested gait variable with characteristics of step time asymmetry, step swing asymmetry and step stance asymmetry (Lord *et al.*, 2013b; Lord *et al.*, 2014) assessed in OA and PD only (**Figure 2-1**). There were no associations with cognition.

2.3.3.5 Postural Control

Postural control characteristics of step width and step length asymmetry (**Figure 2-1**) were assessed by a total of seven studies (van Iersel *et al.*, 2008; Amboni *et al.*, 2012; Lord *et al.*, 2013b; Martin *et al.*, 2013; Verlinden *et al.*, 2013; Lord *et al.*, 2014) throughout the cohorts. In OA one study assessed postural control and visuospatial function, and reported a significant association (Martin *et al.*, 2013). Evidence was inconclusive in OA for an association with executive function, attention and processing speed with 2 of 4 studies (Lord *et al.*, 2013b; Martin *et al.*, 2013), 1 of 2 studies (Martin *et al.*, 2013) and 1 of 2 (Martin *et al.*, 2013) studies observing associations respectively. No association was evident in OA for postural control for global cognition (Lord *et al.*, 2013b) and memory (van Iersel *et al.*, 2008; Lord *et al.*, 2013b; Martin *et al.*, 2013; Verlinden *et al.*, 2013). There was no evidence for associations in the CI cohort. Two studies observed postural control in PD (Amboni *et al.*, 2012; Lord *et al.*, 2014) with inconclusive evidence for associations with memory (Lord *et al.*, 2014) and visuospatial (Amboni *et al.*, 2012). In PD there were no associations with global cognition (Amboni *et al.*,

2012; Lord *et al.*, 2014), executive function (Amboni *et al.*, 2012; Lord *et al.*, 2014) or attention (Lord *et al.*, 2014).

Table 2-6: Main characteristics of the studies assessing cross-sectional gait and cognitive domains in older adults.

Study	Participant Characteristics	Gait Variables Measured	Gait Analysis Tool	Cognitive Domains Associated	Main Findings
1. Beauchet *et al.* (2012)	**Older Adults** (n=78) Age; 69.9±0.9	Stride Time Variability (*%CV*)	SMTEC Gait Walkway (10m + 2m pre and post)	Executive Function (*Digit Span Test, TMT A & B, Stroop Colour Word Test*)	↑Stride time variability correlated with ↓ executive function.
2. Ble *et al.* (2005)	**Older Adults** (n=926) Age; 74.6±6.7, 44% M, MMSE 25.5±2.8, Education 5.6±3.3	Gait Velocity (m/sec)	Photocells (4m)	Executive Function (*TMT A & B*)	No correlation found after adjusting for variables.
3.Bramell-Risberg *et al.* (2012)	**Older Adults** (n=2115) split into 3 groups depending on word recall score: **Cases** (0/3) ; Age 75.8±10.2, **Intermediate** (1/3) Age 71.8±9.5, **Controls** (2-3/3) Age 69.0±9.1	Gait Velocity (*m/sec*)	TUG (3m, turn, 3m), Time to Walk Test (15m, turn, 15m)	Global Cognition (*MMSE- 3 word delayed recall subsection*)	No correlation found at usual pace walking.
4.Donoghue *et al.* (2012)	**Older Adults** (n=4998) Age: 62, 54%F, MMSE 29	Gait Velocity (*s*)	TUG (3m, turn, 3m)	Global Cognition (*MMSE, MOCA*), Executive Function (*CTT, Clock drawing, Cube drawing, SART, Word fluency, Letter fluency*), Processing Speed (*CTT, CRT, SART*)	↓TUG correlated with ↓ global cognition, EF, memory and processing speed.
5.Duff *et al.* (2008)	Older Adults (n=675) Age; 73.2±5.8, 288M & 387F	Gait Velocity (*s, split into 3 groups: <14 secs, 14-17s, >17s*)	Time to Walk Test (25ft, turn, 25ft)	Attention, Language, Visuospatial and Memory (*Repeatable Battery for the Assessment of Neuropsychological Status Domains*)	↓Velocity was associated with ↓ global RBANS score as well as each RBANS domain.
6.Fitzpatrick *et al.* (2007)	Older Adults (n=3070) Age; 78.6±3.3, 53.9% M,	Gait Velocity (*m/s*)	Time to Walk Test (15ft)	Global Cognition (*3MSE*)	No correlation was found between gait velocity and global cognition.
7.Hausdorff *et al.* (2005)	Older Adults (n=43) Age; 71.9±6.4, 22W & 21M, MMSE 29.0±1.1, Education 13.7±2.1	Gait Velocity (*m/s*), Stride Time (*s*), Stride time Variability (*%CV*)	Force-sensitive Sensors, Time to Walk (10m + 7.5m pre/post)	Global Cognition (MMSE), Executive Function (Stroop Test), Verbal Memory (*Verbal Memory Test*)	↑ Stride time variability but not stride time correlated with ↓ executive function after adjusting for covariates.
8.Hollman *et al.* (2007)	**Older Adults** (n=20), Age 81±5, 7M & 13W **Middle Aged adults** (n=20) age 48±5, 9M & 11W **Younger Adults** (n=20) age 25±3, 9M & 11W	Gait Velocity (*cm/s*), Stride Time Variability (*%CV*)	GaitRite 80Hz (8.3m + 1m pre/post walkway)	Global cognition (*Short Test of Mental Status*)	No correlation found under ST conditions
9.Holtzer *et al.* (2006)	**Older Adults** (n=186) Age; 78.00±4.50, 43.4%M, Education 14.30±3.30	Gait Velocity (*cm/s*), Step Length (*cm*), Stride Length (*cm*), Stride Length Variability (*%CV*), Double Support time (*s*)	GaitRite (12ft), including 3ft pre/post walkway)	Factor analysis domains: Verbal IQ (*Information, vocabulary, digit span, Boston naming test, FAS*). Attention/Executive speed (*Block design, Digit Symbol, TMT A & B*). Memory (*Category Fluency, FCSRT*)	Only correlated gait velocity. All cognitive domains were associated.
10.Holtzer *et al.* (2012)	**Older Adults** (N=671) Age; 79±5.2, 60%F, Education 13.8±3.5	Gait Velocity (*cm/s*), Stride Length (*cm*), Stride length	GaitRite (12ft including 3ft pre/post	Executive Attention, Memory, Verbal IQ (*Battery Included: Vocabulary,*	All domains associated with pace. Memory and executive

		Variability (*%CV*), Cadence (*Steps/min*)	walkway)	*Information, Digit Span, Digit Symbol, Block Design, WAIS, FCSRT, total free recall, Boston Naming Test, letter fluency, category fluency, TMT A and B*)	attention correlated with cadence. Executive attention was correlated with stride length variability.
11.Kaye *et al.* (2012)	**Older Adults** (n=76) Age; 85.9±4.9, 86%F, MMSE 28.3±1.7, Education 15.5±2.5	Gait Velocity (*cm/s*), Gait Velocity (*%CV*), Mean Number walks/day, Number walks/ day (*%CV*)	Passive Infra-red motion sensor fixed in-home (Avg 500 walks per month)	Global Cognition (*MMSE*), Executive Function (*TMT-B, Category Fluency*), Working Memory (*Letter-number sequencing*), Attention/Processing Speed (*Digit Span Forward, Digit Symbol, TMT-A*), Memory (*Logical Memory II, Visual Reproduction II, Word-List Recall*), Visuospatial (*Picture Completion, Block Design*)	↑Attention, processing speed and visuospatial scores associated with mean ↑ walking velocity.
12.Lord and Menz (2002)	**Older Adults** (n=515) Age; 79.5±6.4, 76M & 439F	Gait Distance (*m*)	6 Minute Walk Test	Global Cognition (*MMSE*)	No correlation was found between gait velocity and global cognition.
13.Lord *et al.* (2013b)	**Older Adults** (n=189) Age; 69.5±7.6, 79M & 110F, MMSE 29.3±1.0	16 Gait Variables into 5 domains: *Pace* (step velocity m/s), mean step length m, swing time variability ms), *Rhythm* (step time ms, swing time ms, stance time ms), *Variability* (step velocity variability m.s-1, step length variability m, step time variability ms, stance time variability ms), *Asymmetry* (swing time asymmetry ms, step time asymmetry ms, stance time asymmetry ms), *Postural Control* (step length asymmetry m, step width m, step width variability m)	GaitRite (7m), 2min walk around 25m circuit	Global Cognition (*MMSE*), Power of Attention (*CDR; SRT, CRT, DV*), Memory (*PRM, SRM*), Executive Function (*One Touch Stocking of Cambridge*)	↑Executive function correlated ↑postural control. ↑Attention correlated with ↑pace.
14.Martin *et al.* (2013)	**Older Adults** (n=422) Age; 72.0±7.0, 238M & 184F, GDS 2.05±2.3	Gait Velocity (*cm/s*), Step Time (*ms CV%*), Step Length (*cm, CV%*), Support Base (*cm, CV%*), Double Support Phase (*ms, CV%*)	GaitRite (4.6m, + 2m pre/post walkway)	Executive/Attention (*Controlled word association test, category fluency, stoop test, digit span*), Processing Speed (*Symbol Search, Digit Symbol Coding*), Visuospatial Ability (*Rey Complex Figure Copy Task*), Memory (*Hopkins Verbal Learning Test*)	Executive /Attention correlated with velocity, step length, step time variability, double support time, double support time variability. Processing speed correlated with velocity, step time, step length, DSP and DSP variability. Visuospatial correlated with DSP variability.
15.van Iersel *et al.* (2008)	**Older Adults** (n=100) Age; 80.6±4.0, 64M & 36F	Gait Velocity (*m/s*) Stride Length Variability (*%CV*), Stride Time Variability (*%CV*), Mediolateral body	GaitRite (5.6m + 2m pre/post walkway)	Executive Function (*TMT A & B, Stroop Colour-Word Test*), Memory (*CANTAB; PAL, PRM*)	No correlation found under single task conditions

		sway (*degrees*)			
16.Verlinden *et al.* (2013)	**Older Adults** (n=1232) Age; 66.3 ±11.8, 558M & 674F, MMSE 28.0 ± 1.8	Factors; Rhythm (single support time [s], swing time [s], step time [s], stride time [s], cadence [steps/min], stance time [s]) Variability (stride length SD [cm], step length SD [cm], stride velocity SD [cm/s], stride time SD [s], step time SD [s], stance time SD [s], swing time SD [s], single support time SD [s], double support time SD [s], Phases (single support [%GC], swing [%GC], stance [%GC], double support [%GC], double support time [%GC], Pace (stride length [cm], step length [cm], velocity [cm/s]), Tandem (Sum of feet surface [fraction], sum of step distance [cm], double step [n]), Turning (turning step count [n], turning time [s]), Base of support (stride width SD [cm], stride width [cm]).	GaitRite (5.79m)	Memory (*immediate and delayed recall of 15 word verbal learning test*), Executive Function (*stroop interference, word fluency, LDST*), Information Processing Speed (*stroop reading, stroop colour naming & LDST*), Fine Motor Speed (*Purdue Pegboard Test*), Global Cognition (*average of all above test scores*)	After adjusting for covariates (including independence of cognitive domains); information processing speed correlated with rhythm, executive function associated with pace.

Abbreviations as follows; 3MSE, modified mini mental state examination; CDR, cognitive drug research battery; CRT, choice reaction time; CTT, colour trails test; DV, digit vigilance; FCSRT, free and cued selective reminding test; LDST, letter digit substitution test; MMSE, mini mental examination; MoCA, Montreal cognitive assessment; PAL, paired associate learning; PRM, pattern recognition memory; SART, sustained attention response task; SRM, spatial recognition memory; SRT, simple reaction time; TMT, trail making test; TUG, timed up and go; WAIS, Wechsler adult intelligence scale.

Table 2-7: Main characteristics of the studies assessing cross-sectional gait and cognitive domains in cognitive impairment and dementia.

	Study	Participant Characteristics	Gait Variables Measured (*Units*)	Gait Analysis Tool (Distance)	Cognitive Domains Tested (*Test Used*)	Main Study Findings
1.	**Allali *et al.* (2010a)**	**HC** (*n*=22) Age 71.0±0.5, 8M & 14F **AD** (*n*=19) Age 79.3±8.4 6 6M & 13F, MMSE 19± 7 **FTD** (*n*=19) Age 66.8±9.7 10M & 9F, MMSE 26 ± 6	Stride Time (Mean & CV)	SMTEC Footswitch System (10m)	Global cognition (*MMSE, Mattis Dementia Rating Scale*), Frontal Cognition (*FCRT*)	Stride time variability was ↑ in FTD after adjusting for variables.
2.	**Auyeung *et al.* (2008)**	**Cognitively Intact** (n=NR) M=72.18±0.11 W=71.87±0.13 **Cognitively Impaired** (n=NR) M= 76.43±0.59, W=74.64±0.26	Gait Velocity (*m/s*)	Timed to Walk Test (6m)	Global cognition (*MMSE*), Dementia Severity (*Community Screening Instrument for Dementia*)	Gait velocity correlated with CI in men and women.
3.	**Beauchet *et al.* (2013)**	**HC** (n=44) Age 74.5±6.5 14M & 28F, MMSE 29.0±1.1 **MCI** (n=39) Age 73.6±6.1 24M & 15F, MMSE 27.8±1.4 **AD** with mild dementia (n=21) Age 79.2±5.6 12M & 21F, MMSE 25.0±2.3	Gait Velocity (*cm/s*), Stride time Variability (CV%)	GaitRite 60Hz (9.72m, + 2m pre/post walkway)	Global cognition (*MMSE*), Frontal lobe assessment (*FAB*), AD Severity (*ADAS-Cog*)	Under usual pace walking there were no differences between MCI or AD after adjusting for variables.
4.	**Coelho *et al.* (2012)**	**Mild AD** (n=12) Age 75.7±6.8, MMSE 22.0±2.2, Education 5.5±3.0 **Moderate AD** (n=11) Age 80.1±7.5, MMSE 16.2±2.2, Education 3.5±1.1	Stride Length (*m*), Stride Speed (*m/sec*), Cadence (*Strides/sec*)	GaitRite 60Hz (8m)	Executive Function (*FAB & Clock Drawing Test*), Attention (*Symbol Search*)	Moderate AD had ↓ stride length and ↓ stride speed compared to mild AD. Did not assess EF and attention in association with ST conditions.
5.	**Gillain *et al.* (2009)**	**HC** (n=14) Age 73.53, MMSE 28.21± 1.58, Education 13.71±3.73 **MCI** (n=14) Age 72.85, MMSE 26.71±1.68, Education 13.64±3.30 **AD** (n=6) Age 73.66, MMSE 22.83±2.14, Education 9.33±3.78	Gait Velocity (*m/s*), Stride Frequency (*Hz*), Stride Length (*m*), Stride regularity, Stride symmetry	Locometrix 3 Axis Accelerometer (30m)	Global cognition (*MMSE & Mattis*), Episodic Memory (*Graber & Buschke-version of*), Visuoconstructive/Visuospatial ability (*Rey's Complex Figure Test*), Attention (*TAP*)	Velocity and stride length were↓ in AD compared to HC. Those with MCI had ↓ stride frequency compared to HC. Associations between domains under ST conditions were unclear.
6.	**Ijmker and Lamoth (2012)**	**HC Elderly** (n=14) Age 76.9±4.1, 12M & 2F, MMSE 28.5±1.16 **HC Younger** (n=12) Age 64.3±2.8, 9M & 3F, MMSE 29.1±0.93 **Dem** (AD and FTD, n=15) Age 81.7±6.3, 13M and 2F, MMSE 19.6±3.58	Gait velocity (*m/s*), mean stride time (*m*), stride time variability (*%CV*)	Dynaport®Ambulant Accelerometer (3 mins on 10m course)	Global cognition (*MMSE*), Processing speed (*Category Fluency*), Psychomotor Speed (*Stroop*), Executive Function (*Stroop*), Attention (*Digit Span Forward/Backward & TMT*), Working Memory (*Digit Span*)	Those with Dem had ↓ gait velocity; ↑ stride time and ↑ stride time variability compared to both HC groups. Cognitive domains associated with gait as whole cohort only so therefore not reported.
7.	**Lamoth *et al.* (2011)**	**HC** (n=13) Age 79.38±5.55, 10M&16F, MMSE 28.23±1.09 **AD** (n=13) Age 82.62±4.29, 6M&7F, MMSE 18.00±3.54	Gait Velocity (m/sec), Stride Frequency (strides/sec), Stride Time (s), Stride Time Variability (%CV), Phase Variability Index (%)	Timed to walk test, Dynaport® Tri-Axial Ambulant Accelerometer (160m)	Global cognition (*MMSE, 7min Screening*)	No correlations found under ST conditions.
8.	**Maquet *et al.* (2010)**	**HC** (n=14) Age 74±5, 7M&7F **MCI** (n=14) Age 73±4, 7M&7F **Mild AD** (n=6) Age 74±4, 3M&3F	Gait Velocity(ms-1), Stride Frequency (*Hz*), Stride length (*m*), Step	Locometrix ™ Acceleration Sensor (90m)	Global Cognition (*MMSE & Mattis*), Episodic Memory (*Grober & Buschke*),	↓gait velocity and ↓stride length in AD compared to HC and MCI. MCI s.d to controls for stride

#	Study	Participants	Gait Variables	Gait Measurement	Cognitive Domains	Findings
			Asymmetry (*Sym*)		Visuoconstruction/Visuospatial Ability (*Rey's Complex Figure Test*), Attention (*TAP*)	In MCI group, correlation between ↓velocity and ↓stride length and ↓cognition and ↓attention and stride frequency and global cognition.
9.	McGough *et al.* (2011)	**CI** (n=201) Age; 84.6±5.7, 80.1% female, high school educated 97.5%	Gait Velocity (*m/s*)	Timed to Walk Test (2.4m)	Executive Function (*TMT-B & Stroop Word-Colour*)	↓ gait velocity associated with lower executive function score
10.	Muir *et al.* (2012)	**HC** (n=22) Age 71.0±5.0, 3M &19F, MMSE 29.5±0.6, MOCA 28.2±1.5 **MCI** (n=29) Age 73.6±6.2, 12M&17F, MMSE 27.5±1.9, MOCA 23.4±2.8 **AD** (n=23) Age 77.5±5.0, 9M&14F, MMSE 24.2±2.3, MOCA 17.2±3.4	Gait Velocity (*cm/s*), Stride Time (*ms*) Stride Time Variability (*CV%*)	GaitRite (6m + 1m pre/post walkway)	Global Cognition (*MMSE, MOCA, CDR*)	No difference in gait variables under ST conditions
11.	Persad *et al.* (2008)	**HC** (N=12) Age 70.0±5.8, 7M&5W, MMSE 27.8±2.2, Education 17.0±2.6 **MCI-EF** (n=14) Age 72.5±4.6, 10M&4W, MMSE 26.6±2.1, Education 16.57±3.2 **MCI+EF** (n=10) Age 75.1±6.9, 6M&4W, MMSE 25.8±2.0, Education 15.8±3.2 **AD** (n=12) Age 77.5±5.3, 9M&3W, MMSE 22.6±2.3, Education 14.8±2.9	Gait Velocity (*s*)	Timed to Walk Test (10m)	Executive Function (*Map Planning & Paper Folding*), Visual Short Term Attention (*Corsi Block Task & Benton Form Visual Discrimination*), Visuo-Motor (*Block-Design*), Memory (*Delayed Recall*)	Those with AD and MCI+EF had a ↓gait velocity compared to HC and MCI-EF. Walking speed correlated with EF.
12.	Sheridan *et al.* (2003)	**Patients diagnosed with probable AD** (n=28) Age; 77.9±6.9, MMSE 13.8±7.9	Velocity (msec), Stride Time Variability (*%CV*)	Footswitch System (100Hz) (~500ft)	Global Cognition (*MMSE*), Executive Function (*Clox I & II, Verbal Fluency*) Dementia Severity (*CDR*)	Those with AD had ↓ gait velocity and ↑ increased stride time variability. No correlation with executive function under ST conditions

Abbreviations as follows; AD, Alzheimer's disease; ADAS-cog, Alzheimer's disease assessment scale-cognition; CDR, cognitive drug research battery; FAB, frontal assessment battery; FCRT, free and cued recall test; FTD, fronto-temporal dementia; HC, healthy control; MCI, mild cognitive impairment; Dem, dementia; MCI-/+ EF, MCI with or without impairment in executive function; MMSE, mini mental examination; MoCA, Montreal cognitive assessment; TAP, test of attentional performance; TMT, trail making test.

Table 2-8; Main characteristics of the studies assessing cross-sectional gait and cognitive domains in Parkinson's disease.

Study	Participant Characteristics	Gait Variables Measured (*Units*)	Gait Analysis Tool/ Distance Walked	Cognitive Domains Tested (*test used*)	Main Findings from Study
1. **Amboni *et al.* (2012)**	HC: (n=20) Age; 63.5±3.14, 10M & 10F PD-MCI: (n=24) Age; 64.08±6.44, 20M & 4F, Disease duration; 5.42±2.80 FOG-Q; 5.83±5.71 PD+MCI: (n=19) Age; 65.1±6.85, 13M & 6F, Disease duration; 5.47±2.71 FOG-Q; 7.26±6.17 *Med: On and Off*	*Factors:* *Pace* (stance phase (*s*), swing phase (*s*), cadence (*steps/min*), velocity (m/s) *Stability* (step length (*m*), single/double support time ratio, step length variability (*COV*), swing time variability (*COV*).	Optokinetic system (6 camera, 240Hz) 8M	Episodic memory (*Rey 15 words*), executive function (*Phonemic Fluency, FAB, Stroop II & III*), visuospatial (*spatial span, constructive apraxia, Raven's PM 47, Ten point clock test*)	The Pace 'domain' was not correlated with a cognitive domain. ↓Stability of gait strongly correlated with ↓visuospatial ability.
2. **Lord et al. (2010)**	PD: n= 29 Age; 71.3±7.4, 19M & 10F, MMSE 26.9±2.8, Disease duration; 5.8±5.5 *Med: Off*	Gait Velocity (*m/s*)	Vitaport Activity Monitor (6.5m ±1.5m)	Executive Function (*Brixton*), Attention (*Telephone Search & Lottery Task*)	Those with impaired sustained attention had ↓ gait velocity.
3. **Lord *et al.* (2014)**	HC: n=184, Age; 69.4±7.7, 78M & 106F, NART 116.9±7.6 PD: n=121, Age; 67.0±10.4, NART 114.9±11.0, UPDRS III 25.5±10.4, H & Y; I (28), II (72), III (21) *Med: on*	16 Gait Variables into 5 domains: *Pace* (step velocity m/s), mean step length m, swing time variability ms), *Rhythm* (step time ms, swing time ms, stance time ms), *Variability* (step velocity variability m.s-1, step length variability m, step time variability ms, stance time variability ms), *Asymmetry* (swing time asymmetry ms, step time asymmetry ms, stance time asymmetry ms), *Postural Control* (step length asymmetry m, step width m, step width variability m)	GaitRite Platinum Model (7m)	Global cognition (MoCA), Working Memory (Forward Digit Span), Power of Attention (Mean single reaction time, mean choice reaction time, mean digit vigilance), Fluctuating Attention (*Single reaction time CV, Choice reaction time CV, Digit Vigilance CV*), Executive Function (*one touch stocking, Semantic Fluency, Hayling & Brixton*), Memory (*Pattern recognition memory, spatial recognition memory, paired associate learning*), Visuospatial (*Pentagons, MoCA Item 1*)	PD & HC: those with ↑pace had ↑attention test scores. PD: ↑ postural control and better working memory, ↑gait variability associated with ↓global cognition. HC: those with ↑postural control had ↑ attention scores.
4. **Rochester *et al.* (2004)**	HC: (n=10) Age; 63.5±7.03, 6M & 4F, MMSE 28.90 PD: (n=20) Age; 64.6±7.96, 12M & 8F, MMSE 27.15±1.98 H&Y 2.7±0.69. Disease duration; 10.0±1.6 *Med: On*	Gait velocity (*m/s*), step frequency (*steps/s*), step length (*m*)	Vitaport Activity Monitor (6.60±1.51m)	Global cognition (*MMSE*), Executive Function (*Hayling & Brixton*)	↓gait velocity was correlated with ↓ executive function scores.
5. **Rochester *et al.* (2005)**	HC: (n=10) Age; 63.5±7.03, 6M & 4F, MMSE 28.90 PD: PD: (n=20) Age; 64.6±7.96, 12M & 8F, MMSE 27.15±1.98	Gait Velocity (*m/s*)	Vitaport Activity Monitor (6.60±1.51m)	Executive Function (*Hayling & Brixton*)	↓gait velocity was correlated with ↓ executive function scores.

	H&Y 2.7±0.69. Disease duration; 10.0±1.6 *Med: On*				
6. **Rochester et al. (2008)**	PD: (n=153). Age; 66.61±7.57, 78M & 52F, MMSE 28.30±1.77, UPDRS III; 33.05±11.28, Disease duration 8.26±4.90 *Med: On*	Gait Velocity (*m/s*)	Vitaport Activity Monitor (6m, turn, 6m)	Executive Function (*Brixton*)	No correlation was found under single task conditions.
7. **Smulders *et al.* (2013)**	PD: (n=232). Age; 64.4±7.9, 153M & 79F, MMSE 28.1±1.6, UPDRS III 33.4±9.1 *Med: NR*	Gait Velocity (*s*)	TUG (3m, turn, 3m)	Executive Function (*Spatial working memory, Set Shift Test, Auditory Stroop Paradigm, Phonological and Semantic Cue*)	↓Executive function correlated with ↓TUG time.
8. **Wild et al. (2013)**	HC: (n=18)Age; 69.44±1.41, 8M & 10F PD: (n=18) Age; 69.33±2.65, 8M & 10F *Med: On*	Gait velocity (*Km/h*), Mean swing time (*s*), Relative stance time (*s*)	Fixed Infra-Red Camera (8m)	Executive function/attention (*Winconsin Card Sorting Test, Stroop Colour and Word*)	No correlation was found under single task conditions.
9. **Xu *et al.* (2014)**	HC: (n=20) Age; 68.9 ± 4.8, 65% M, MMSE 28.7 ± 1.1, Education 12.7 ± 3.4 PD: (n=20) Age 65.9 ± 9.4, 65% M, MMSE 27.6 ± 1.6, Education 12.4 ± 2.5, Disease duration 6.0 ± 3.8, UPDRS III 26.6 ± 10.8, H & Y 1.4 ± 0.9 *Med: On*	Gait Velocity (*s*)	TUG (3m, turn, 3m)	Global cognition (*MMSE, Addenbrooke's*), Executive function (*TMT-A, TMT-B*)	↓ Executive function associated with ↓ pace in PD but not control.
10. **Yogev *et al.* (2005)**	HC: (n=28) Age; 69.8±6.3, MMSE 29.1±1.1, Education 13.7±2.1 PD: (n=30) Age; 70.9±.9, MMSE 28.1±1.6, Education 13.9±3.8, UPDRS III 17.5±8.3, H &Y 2.3±0.4 *Med: NR*	Gait velocity (*m/s*), stride time (*s*), swing time (*s*), stride time variability (*%*), swing time variability (*%*)	Timed to walk test (2 min), In-Shoe Pressure sensor (100Hz)	Executive function (*Stroop & Go-Nogo*), Memory (*Trail Recall*)	Only associated stride and swing variability with EF. Correlation was found between ↓executive function and ↑stride and swing time variability.

Abbreviations as follows; FAB, frontal assessment battery; FOG-Q, freezing of gait questionnaire; H & Y, Hoehn & Yahr disease severity classification; HC, healthy controls; MCI; mild cognitive impairment; MCI+/MCI-, with/without mild cognitive impairment; MMSE, mini mental examination; MoCA, Montreal cognitive assessment; PD, Parkinson's disease; UPDRS, unified Parkinson's disease rating scale.

Table 2-9: Main characteristics of the studies assessing longitudinal gait and cognitive domains in older adults.

Study	Participant Characteristics	Gait Variables Measured (*Units*)	Gait Analysis Tool (Distance)	Cognitive Domains Tested (*Test used*)	Main Study Findings
1. **Buracchio *et al.* (2010)**	**HC** (n=109) Age 79.0±8.8, 60M & 49F, MMSE 28.3±1.5, Years Education 14.5±2.7 **Converters to MCI** (n=95) Age 83.5±7.0, 37M & 58F, MMSE 28.1±1.6, Education 14.7±2.6	Gait Velocity (*m/s*)	Timed to Walk Test (30ft)	Global Cognition (*MMSE*), Dementia Rating Scale (*CDR*)	Those who converted to MCI had ↓ gait velocity up to 12.1 years prior to MCI.
2. **Dodge *et al.* (2012)**	**HC** (n=54) Age 84.9±4.0, 91% female, MMSE 29.0±1.3 **aMCI** (n=8) Age 84.5±2.6, 88% female, MMSE 28.3±1.2 **naMCI** (n=31) Age 83.8±6.0, 84% female, MMSE 28.1±1.6	Gait velocity (cm/s), Gait velocity variability (*%CV*)	Passive Infra-red motion sensor fixed in-home	Global Cognition (*MMSE*), Memory (*Logical Memory Delayed*), Executive Function (*Category Fluency, TMT Part B*), Attention (*WAIS Digit Symbol*), Language (*Boston Naming Test*), Visuospatial (*WAIS Revised Block Design*)	naMCI had ↓ gait velocity compared to HC and showed decline in gait velocity over time, those with naMCI had ↑ gait speed variability in the home.
3. **Alfaro-Acha *et al.* (2007)**	**Older Adults** (n=1218) Age; 71.7±5.7, 57.5% F, MMSE 26.5±2.9, Education 5.4±3.9	Gait Velocity (*Split into quartiles: 1; ≥9s, 2;6-8s, 3; 4-5s, 4; <4s*)	Time to Walk Test (8ft)	Global Cognition (*MMSE*)	No correlation at baseline. At 7 year follow up association between slow gait velocity and ↓cognition.
4. **Atkinson *et al.* (2007)**	**Older Adults** (n=2349) Age; 75.6±2.9, 52.3% F	Gait Velocity (*m/s*)	Time to Walk Test (20m)	Global Cognition (*MMSE, 3MS*), Executive Function (*Clox 1, EXIT 15*)	Greater gait velocity decline over 3 years was seen in those with lowest cognition and EF scores.
5. **Atkinson *et al.* (2010)**	**Older Adults** (n=1793) Age; 70.3±3.7, 3MS Score 95.1±4.4	Gait Velocity (*m/s*)	Time to Walk Test (6m)	Global Cognition (*3MS*)	Gait speed was not associated with 3MS score at baseline when adjusting for covariates. Baseline 3MS did not predict decline in gait speed (or vice versa) after adjusting for covariates.
6. **Auyeung *et al.* (2011)**	**Older Adults** (n=2737) M=1514 Age 71.6±4.58, MMSE 27.4±2.25 F=1223 Age 71.5±4.85 MMSE 25.8±2.80	Gait Velocity (*m/s*), Step Length (*m*), Step Number	Time to Walk Test (6m)	Global Cognition (*MMSE*)	In male subjects, stride length correlated with decline MMSE score but not gait velocity after adjusting for covariates.
7. **Deshpande *et al.* (2009)**	**Older Adults** (n=660) Age; 74.6±5.3, 54.2% F, Education 5.8±3.4	Gait Velocity (*m/s*)	Timed to Walk Test (7m)	Global Cognition (*MMSE*)	Baseline; those with ↓MMSE had ↓gait speed. Longitudinal; Gait velocity at fast pace only predicted decline in cognition.
8. **Inzitari *et al.* (2007)**	**Older Adults** (n=3075) Age; 73.6±2.9, 1491M & 1584F	Gait Velocity (m/s)	Timed to Walk Test (6m)	Global Cognition (*3MS*), Attention and Psychomotor Speed (*Digit Symbol Substitution Test*)	↑global cognition scores related to ↑ gait speed. Gait speed predicted ↓attention and ↓ psychomotor speed at 5 years. Difference in gait speed at baseline related to ↑ risk of decline in attention and psychomotor speed.
9. **Marquis *et al.* (2002)**	**Older Adults** (n=108) Age; 83.2±7.9, 40M & 68W	Gait Velocity (*s*), Step Number (excluding turn)	Timed to Walk Test (4.5m, turn, 4.5m)	Global Cognition (*MMSE*), Dementia Severity (*CDR*), Memory (*Wechsler Memory*	Time to walk aided the prediction model of onset of persistent cognitive impairment.

					Scale)	
10. **Taniguchi *et al.* (2012)**	**Older Adults** (n=853) Age; 77.5±5.4, 47.3% M, MMSE 28.1±1.7, Education 8.3±2.2, GDS 4.0±2.4	Gait Velocity (*m/s*), Mean Step Length (*cm*), Step Frequency (*times/min*)	Timed to Walk Test (5m)		Global Cognition (*MMSE*)	↓Gait velocity and ↓step length associated with decline in general cognition. Step length found to be a better predictor of cognitive decline than gait speed.
11. **Verghese *et al.* (2007)**	**Older Adults** (n=399) Non-dementia; Age 78.9±4.7, 56.3%M, Education 13.4±3.5. **Developed Dem**; (n=33) Age 82.6±5.7, 57.6%M, Education 14.0±3.6	Pace (Gait Velocity (*cm/s*), Stride Length (*cm*)) Rhythm (Cadence (*steps/min*), Double Support (*s*), Swing Time (*s*), Stance Time (*s*)) Variability (stride length variability, swing time variability)	GaitRite(180 inches +3ft Pre/Post Walkway)		Global Cognition (*Blessed Information Memory-Concentration Test*), Memory (*Free & Cued Selective Reminding Test*), Executive Function (*Digit Symbol Substitution & Letter Fluency Test*), Attention (*Digit Span*)	Rhythm was associated ↓memory; pace was associated with ↓ executive function. Rhythm and variability associated with dementia onset. Pace of gait predicted vascular dementia.
12. **Watson *et al.* (2010)**	**Older Adults** (n=909) Age; 75.2±2.8, 49.4%M, Education below 12y 78.4%	Gait Velocity (m/s)	Time to Walk Test (20m)		Global Cognition (*3MS*), Memory (*Buschke Selective Reminding Test*), Executive Function (*EXIT 15*), Psychomotor Speed (*Box and Digit Copying*), Attention (*Pattern and Letter Comparison Test*)	Cross sectional; All cognitive domains correlated with gait velocity. Longitudinal; ↓ global cognition, memory and executive function associated with greater speed decline per year.

Abbreviations as follows; 3MS, modified mini mental state examination; a/na MCI, amnestic/ non-amnestic mild cognitive impairment; CDR, cognitive drug research battery; EXIT 15, the executive interview; MCI, mild cognitive impairment; MMSE, mini mental examination; TMT, trail making test; WAIS, Wechsler adult intelligence scale.

2.3.4 Longitudinal studies of the gait-cognition relationship

Twelve studies investigated longitudinal relationships between gait and cognition (Marquis *et al.*, 2002; Alfaro-Acha *et al.*, 2007; Atkinson *et al.*, 2007; Inzitari *et al.*, 2007; Verghese *et al.*, 2007; Deshpande *et al.*, 2009; Atkinson *et al.*, 2010; Buracchio *et al.*, 2010; Watson *et al.*, 2010; Auyeung *et al.*, 2011; Dodge *et al.*, 2012; Taniguchi *et al.*, 2012). Eleven studies assessed healthy OA at baseline (Marquis *et al.*, 2002; Alfaro-Acha *et al.*, 2007; Atkinson *et al.*, 2007; Inzitari *et al.*, 2007; Verghese *et al.*, 2007; Deshpande *et al.*, 2009; Atkinson *et al.*, 2010; Buracchio *et al.*, 2010; Watson *et al.*, 2010; Auyeung *et al.*, 2011; Taniguchi *et al.*, 2012). One study observed three cohorts at different stages of MCI (Dodge *et al.*, 2012). 9 of the 12 studies assessed gait as a predictor for cognitive decline (Marquis *et al.*, 2002; Alfaro-Acha *et al.*, 2007; Inzitari *et al.*, 2007; Verghese *et al.*, 2007; Auyeung *et al.*, 2008; Deshpande *et al.*, 2009; Buracchio *et al.*, 2010; Dodge *et al.*, 2012; Taniguchi *et al.*, 2012), 2 of 12 assessed cognition as a predictor for gait decline (Atkinson *et al.*, 2007; Watson *et al.*, 2010) and 1 of 12 studied the decline of gait and cognition simultaneously (Atkinson *et al.*, 2010).

2.3.4.1 Gait as a predictor for cognitive decline

All nine studies assessing gait as a predictor measured pace. Evidence was strong for pace as a predictor for global cognition as shown by 7 of 9 studies (Marquis *et al.*, 2002; Alfaro-Acha *et al.*, 2007; Verghese *et al.*, 2007; Buracchio *et al.*, 2010; Auyeung *et al.*, 2011; Dodge *et al.*, 2012; Taniguchi *et al.*, 2012) with two studies refuting these findings (Deshpande *et al.*, 2009; Atkinson *et al.*, 2010).Two studies observed cognitive domains (Inzitari *et al.*, 2007; Verghese *et al.*, 2007). Pace predicted a decline in executive function (Verghese *et al.*, 2007) and processing speed (Inzitari *et al.*, 2007). Evidence was inconclusive for decline in attention with one study finding this (Inzitari *et al.*, 2007) and one not (Verghese *et al.*, 2007). Pace was not found to be a predictor of memory decline (Verghese *et al.*, 2007). One study assessed variability of gait (Verghese *et al.*, 2007) which predicted dementia onset but not domains of global cognition, attention, executive function or memory. Two studies assessed rhythm of gait (Verghese *et al.*, 2007; Taniguchi *et al.*, 2012). An association between rhythm and decline in memory was identified by one study (Verghese *et al.*, 2007).

Evidence was inconclusive for rhythm as a predictor of global cognitive decline (Verghese *et al.*, 2007; Taniguchi *et al.*, 2012) with one study identifying rhythm as a risk factor for dementia onset (Verghese *et al.*, 2007) . No links were found between rhythm and decline in executive function or attention (Verghese *et al.*, 2007).

2.3.4.2 Cognition as a predictor for gait decline

All three studies assessed pace only. Evidence suggested that global cognition (Atkinson *et al.*, 2007; Watson *et al.*, 2010), executive function (Atkinson *et al.*, 2007; Watson *et al.*, 2010) and memory (Watson *et al.*, 2010) predicted a decline in pace. There were no evidence for processing speed (Watson *et al.*, 2010) or attention (Watson *et al.*, 2010) as predictors of decline in pace.

2.4 Discussion

To the knowledge of the author this is the first structured review to summarise the relationship between single task gait and cognition in older adults with and without cognitive impairment, and in PD. Key findings from this structured review are that for all groups the pace domain of gait (driven predominantly by gait speed) is associated with a broad range of cognitive functions but also selectively associated with executive attention. Gait speed is also a strong predictor of cognitive decline in OA, however there is also some evidence of reverse causality. Other relationships are emerging but restricted by a limited scope of gait and cognitive outcomes as well as methodological inconsistencies. Results from this study partly confirm our hypotheses. Independent gait characteristics relate to discrete cognitive functions and the pattern of association varies as a function of pathology and age. This specificity will help inform our understanding of co-incident pathology and shared neural networks, and help identify the pattern of change for each over time. In all three groups the pace domain of gait was also associated almost universally with cognitive measures. Although less discrete, this sensitivity provides a basis for understanding the broader relationship between gait and cognition, and provides a platform for more specific inquiry.

2.4.1 Gait and cognition a global relationship

This review identified a broad range of cognitive correlates for gait. Of all gait characteristics measured, those from the pace domain (particularly gait speed) yielded the strongest relationships. Reasons for this are twofold. With one exception, gait speed was universally measured in all studies which increased the likelihood of chance findings and dominated the results. Secondly, of the 16 gait characteristics reflected in the gait model, gait speed is the most sensitive and least specific metric. It reflects global gait impairment but does not inform about the underlying cause of that impairment. Gait speed may be considered 'the final common expression' of gait, and associations with cognition are therefore likely to be more evident for this global measure.

2.4.2 Gait and cognition; a selective relationship

A number of studies adopted a broader approach to measurement where selective associations became evident (Verghese *et al.*, 2007; Verlinden *et al.*, 2013; Lord *et al.*, 2014). Assessments were particularly limited in pathological cohorts and in addition, sample sizes tended to be small, albeit with some exceptions (Rochester *et al.*, 2008; McGough *et al.*, 2011; Amboni *et al.*, 2012; Smulders *et al.*, 2013; Lord *et al.*, 2014). Despite limitations, subtle emergent associations have been mapped that appear specific to pathology which are discussed below. These findings contribute to our understanding of underlying pathology and the mechanisms that underpin cognitive and gait functions with respect to that pathology. What is evident is that common neural substrates for gait and cognition emerge which may differ according to age and pathology. This knowledge will ultimately lead to refinement of diagnostics and development of novel therapeutics.

Evidence associating pace with attention and executive function (considered here as the executive attention domain (Perry and Hodges, 1999; Woodruff-Pak and Papka, 1999; Emre *et al.*, 2007; Wild *et al.*, 2013) was demonstrated in all three groups. This was most evident in OA as demonstrated by large number of high quality studies. In disease cohorts this association was not as strong, due to a smaller number of studies which were more varied in quality and therefore must

be interpreted with more caution. Lesion (Wilkins *et al.*, 1987) and imaging studies (Collette *et al.*, 2006) implicate the prefrontal cortex (PFc) as the site for executive attention which initiates purposeful, goal directed behaviours essential to daily living (Criado *et al.*, 1997; Perry and Hodges, 1999) . In addition, the PFc drives executive attention processes during locomotion to modulate gait (Malouin *et al.*, 2003; Koenraadt *et al.*, 2014). In normal ageing, executive attention declines (Gunning-Dixon and Raz, 2000; Grieve *et al.*, 2007) with more pronounced deficits occurring in neurological disorders including PD (Emre, 2003) and AD (Perry and Hodges, 1999). Decline in PFc function is associated with increased white matter lesions in older adults and pathology (Bartzokis *et al.*, 2003; Resnick *et al.*, 2003) resulting in deficits in velocity and step length of gait (Nadkarni *et al.*, 2009; de Laat *et al.*, 2012). An important caveat to interpretation of imaging data is that not all brain structures potentially implicated in gait and cognitive processing are imaged, and this may lead to an incomplete view. The notion of shared cognitive and gait neural substrates is supported elsewhere. For example, in PD, dopaminergic neuronal loss of the SNpc impacts on the PFc via a complex network of neuronal pathways and connections (Gotham *et al.*, 1988). This loss attenuates cognitive resource in people with PD, which in turn compromises the ability to cognitively compensate for gait deficit (Yogev-Seligmann *et al.*, 2008). Other neurotransmitters are implicated in this relationship. For example, acetyl-choline (Ach) mediates attentional processes of the PFc (Yarnall *et al.*, 2011) which is associated with a slower gait speed (Rochester *et al.*, 2012). Preliminary results report beneficial effects of Rivastigmine, an acetylcholinesterase inhibitor, on reducing step time variability in people with PD (Henderson *et al.*, 2016), considered a proxy of falls. Thus, age-related degeneration in white matter may elicit an associated decline in pace and executive attention, predominantly due to cholinergic burden. This burden may be exacerbated in disease such as dementia and PD. Development of cognitive enhancement therapies is likely to expand as our understanding of the effect of cognitive processes on gait becomes more refined.

Specific to PD pathology but not dementia, postural control and variability were both associated with cognition. Postural control is an essential component of gait, and similarly to pace, cortical networks are used to modulate postural control

(Kelly *et al.*, 2015) via activation of executive-attention networks (Lord *et al.*, 2013b; Martin *et al.*, 2013). The ability to regulate postural control is compromised by white matter pathology in these and other cortical networks (de Laat *et al.*, 2011; Rosano *et al.*, 2012). Executive-attention also mediates visuo-spatial function which is critical to postural control (Suarez *et al.*, 2011). This association of visuospatial function was noted in older adults (Martin *et al.*, 2013), although this was reported only in one study. However previous literature has identified an association of visual performance and measures of balance in older people (Brach *et al.*, 2008). This relationship may be exacerbated, in people with PD with freezing of gait (FOG), who perform worse on tests of visuospatial ability compared to non-FOG (Cowie *et al.*, 2010) possibly due to decreased grey matter in posterior cortical areas (Tessitore *et al.*, 2012). Evidence of association for postural control and memory was contradictory for the two studies that examined these features (Amboni *et al.*, 2012; Lord *et al.*, 2014). Both studies used valid tests as recognised by the PDD movement disorder task force (Dubois *et al.*, 2007), Lords' study showed an association used working memory (forward digit span) (Lord *et al.*, 2014) in contrast to Amboni's study which did not show an association used the Rey Auditory Verbal Learning Test (RAVLT) (Amboni *et al.*, 2012). Important to note is the association in Lord's study was driven by the PIGD phenotype (Lord *et al.*, 2014), which further sensitised results. Associations for global cognition and visuospatial ability with variability were also evident for people with PD but once again were contradictory. A positive association was found with global cognition using the MoCA (Lord *et al.*, 2014) but not the MMSE (Amboni *et al.*, 2012) essentially because the MoCA is a more sensitive test of cognition in those with PD (Zadikoff *et al.*, 2008). Similarly for visuospatial outcomes, an association was found when a rigorous visuospatial assessment battery was used, thus optimising neural correlates (Lord *et al.*, 2014). However, once again these results were in the FOG cohort. The same results were not replicated in OA suggesting the relationship is mediated by visuospatial difficulties in PD and not normal ageing. However, the data emerges from a small number of studies and, although promising, will need to be explored in future research.

For participants with cognitive impairment and dementia an association emerged between cognitive function and the rhythm domain of gait, possibly mediated by the hippocampus which is affected by cognitive decline and FTD (Fellgiebel *et al.*, 2004; Franceschi *et al.*, 2005). The hippocampus plays an important role in motor and gait tasks (Bland and Oddie, 2001; Paylor *et al.*, 2001; Malouin *et al.*, 2003), and is key to effective spatial navigation (Epstein, 2008). However, this data should be interpreted cautiously because AD and FTD groups were combined, and this may have confounded results. More surprisingly, rhythm was also associated with executive function in PIGD phenotype of PD (Lord *et al.*, 2014). People with PD who present with the PIGD phenotype deteriorate at a faster rate in both gait and cognitive function and are at a higher risk of developing dementia than those with the tremor-dominant phenotype (Burn *et al.*, 2006) making the association more sensitive. Unexpectedly, rhythm was also associated with processing speed in older adults (Martin *et al.*, 2013; Verlinden *et al.*, 2013). The authors suggested this may be linked to the velocity aspect of rhythm and to the timing nature of cognitive assessments (Martin *et al.*, 2013; Verlinden *et al.*, 2013). In addition, cognitive tests of processing speed may overlap with executive-attentional elements (Donoghue *et al.*, 2012) which may well have contributed to this association. Although rhythm is considered a 'rudimentary' characteristic of gait (Lord *et al.*, 2013b) controlled by subcortical brain regions including the brain stem and spinal cord (Taniguchi *et al.*, 2012), in response to pathology and ageing it may become more cortically mediated.

There were no reported associations between the asymmetry domain of gait and cognition, although only four studies assessed asymmetry across all cohorts (Gillain *et al.*, 2009; Maquet *et al.*, 2010; Lord *et al.*, 2013b; Lord *et al.*, 2014). Asymmetry comprises both spatial and temporal features of gait. Spatial asymmetry is more likely to be associated with cognitive function given its relationship with step length which, as evidenced by this review, is frontally mediated (Martin *et al.*, 2013). In contrast, temporal features of asymmetry are driven subcortically (Barrière *et al.*, 2008) and cognitive correlates are therefore less likely. However, the single study in early PD that examined these features separately did not find a relationship between spatial asymmetry and cognition. Although spatial asymmetry was significantly worse in PD compared to controls,

the threshold for cognitive deficit to provide a signal with asymmetry was not reached.

2.4.3 Gait as a predictor of cognitive decline

This review provides robust evidence of the capacity of gait to predict cognitive decline, with a number of large, community based studies in older adults supporting this view (**Table 2-5**). Risk of developing vascular dementia or decline in executive attention is predicted by impairment in the pace domain of gait (Gootjes *et al.*, 2004; Verghese *et al.*, 2007) signalling that gait is sensitive to early changes in WMH. This finding is also evident in older adults (Nadkarni *et al.*, 2009) suggesting sensitivity of gait to more subtle cognitive burden. Studies that take a nuanced approach have found specific associations (Verghese *et al.*, 2007). For example, Verghese and colleagues reported that change over time in gait rhythm was a predictor of memory decline and risk of future dementia in healthy older adults (Verghese *et al.*, 2007) which may reflect early pathology in the hippocampus (Braak and Braak, 1997).

The question of reverse causality however cannot be ignored. Several studies (although smaller in number) report that cognition was predictive of decline in the pace domain of gait (Atkinson *et al.*, 2007; Watson *et al.*, 2010). These findings further indicate the intricate relationship between gait and cognition and argue for a comprehensive and sensitive battery of testing for both in order to tease out their relative burden and temporal course. **Figure 2-5** explores this complexity in more detail. It is plausible, for example, for cognitive and gait deficit to coincide in response to ageing and the time course of decline to occur in parallel or for one to precede the other (Tabbarah *et al.*, 2002; Gale *et al.*, 2014)(**Figure 2-5**, concept 1 & 2). By contrast, this is less likely to be the case for pathology where different pathophysiological substrates define the initial magnitude and direction of change, and their putative course (**Figure 2-5**, concept 4). In the absence of data we are left to speculate and future research will examine these questions in greater depth and discern these complex processes. No longitudinal studies on the relationship between gait and cognition have been conducted in PD, and the field is open at this stage to interpretation. Based on current evidence (Lord *et al.*, 2014), we speculate that for people with PD, decline in cognition and

development of dementia will be predicted by frontal and pre-frontal mechanisms that manifest as deficits in the pace domain of gait (**Figure 2-5**, concept 3 & 4).

The time course of the relationships between gait and cognition is likely to be variable and disease-specific, although there is limited evidence to support this. Most cross sectional studies in established AD report an association with pace but not rhythm (Sheridan *et al.*, 2003; Gillain *et al.*, 2009; Allali *et al.*, 2010a; Maquet *et al.*, 2010; Coelho *et al.*, 2012; Ijmker and Lamoth, 2012; Muir *et al.*, 2012) suggesting as disease progresses cortical influences on gait may become more dominant (Braak and Braak, 1995). One longitudinal study supported an association between early change in gait variability and global cognitive decline, similar to cross sectional findings (Verlinden *et al.*, 2013; Lord *et al.*, 2014). However, further work is required to examine these features.
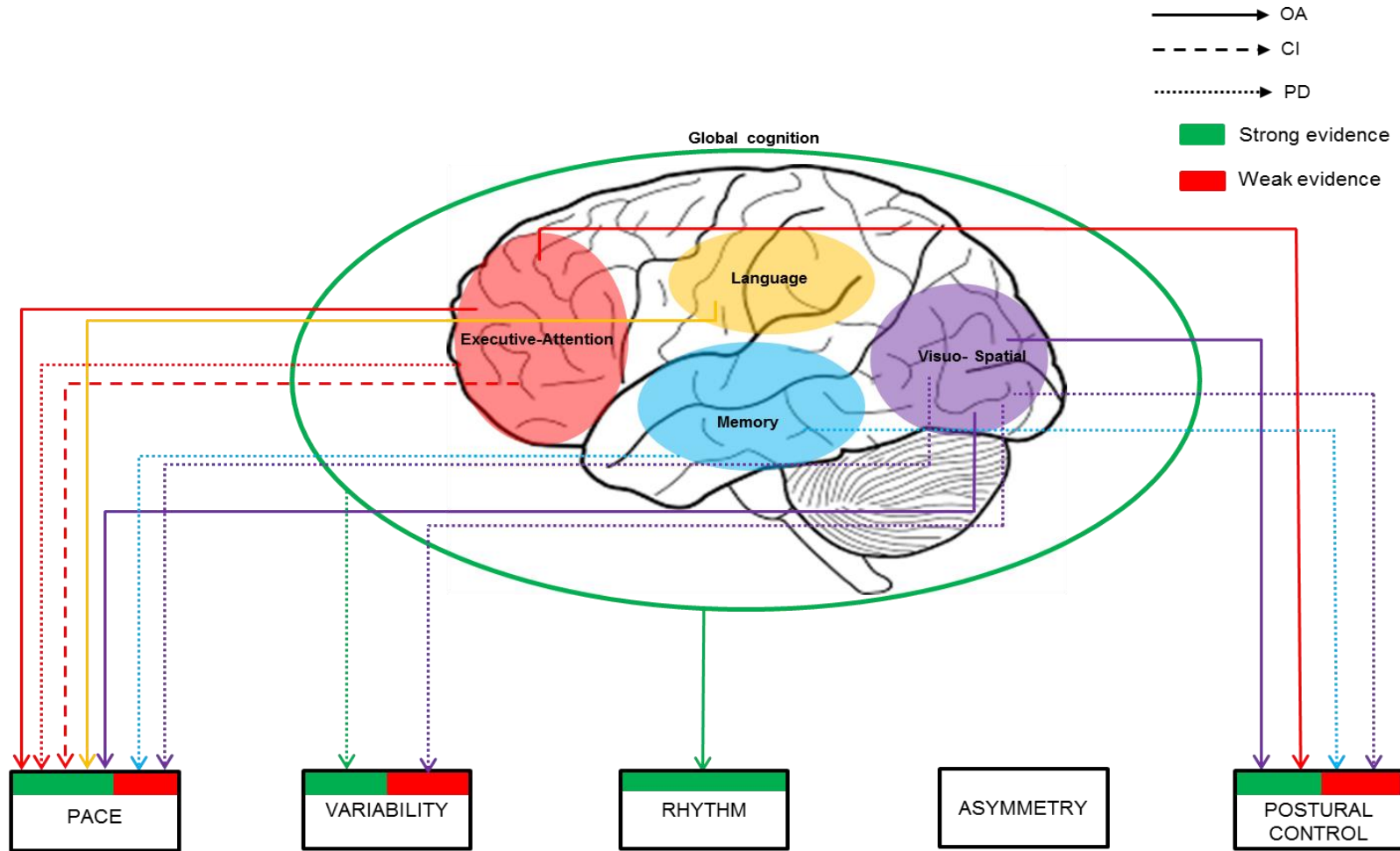
Figure 2-3 Map of cross sectional associations between gait and cognitive domains.
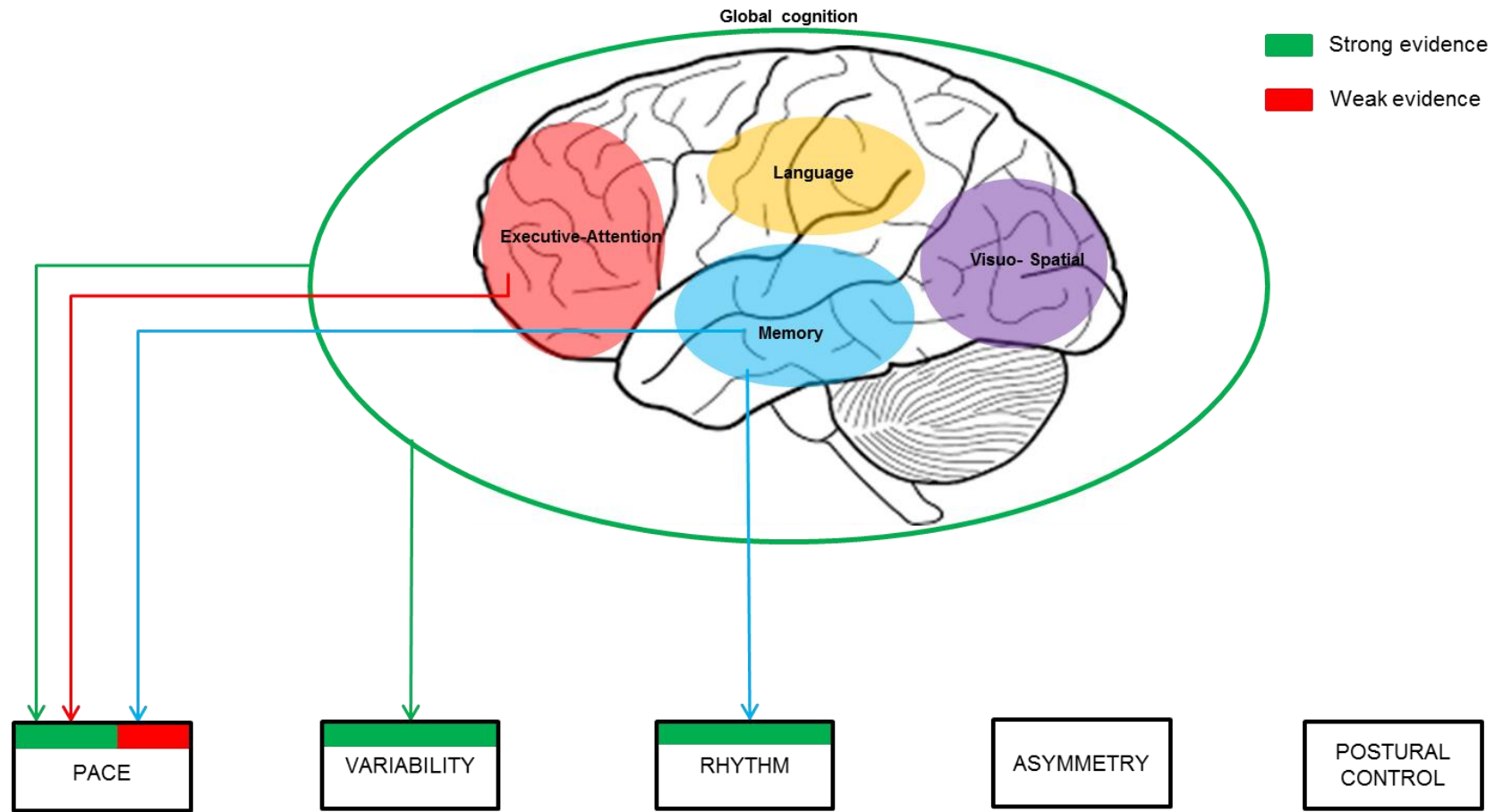
Figure 2-4 Map of longitudinal associations between gait and cognitive domains.

2.4.4 Recommendations and future work

The key recommendation from this review is that future studies need to incorporate comprehensive batteries of gait and cognition in order to robustly identify associations. In addition, this review has demonstrated the wide range of gait acquisition systems utilised in the literature (**Tables 2-6**, **2-7**, **2-8** and **2-9**) which makes findings subject to protocol. For example, measurement of reliable gait variability requires testing protocols to acquire over 30 steps (Galna *et al.*, 2013). Furthermore, some protocols utilise continuous walks (Lord *et al.*, 2014) as opposed to intermittent walks; continuous walks derive measurement of steady state walking which may impact on cognitive associations over and above short intermittent walks. In the future, use of standardised protocols and gait acquisition systems will therefore ensure consistency and aid interpretation. Advances in technology via use of validated body worn senses mean that gait can now be measured in home and community environments rather than the laboratory (Godfrey *et al.*, 2014a). Not only do sensors provide a simple and cost-effective method of data collection, their use also facilitates measurement in naturalistic environments which reflect habitual gait patterns. The cognitive correlates of naturalistic gait may be different to what we have reported here (Hagler *et al.*, 2010) and this is an exciting field of future research.

Limitations to this review include the use of a model of gait that was familiar to structure the analysis. We may have found more associations if we had included more gait characteristics or used a different model. However, we were confident in selecting the model because it has been validated in PD and older adults, and it allowed for a more structured and robust interpretation. Nevertheless, it is important to recognise the interdependence of both gait characteristics (and therefore gait domains), and cognitive functions which also overlap. This has the potential to obfuscate findings and challenge interpretation. Secondly, a quality assessment tool was not used within this structured review which may have limited interpretation. Early on our review process clearly indicated predominance of measurement for the pace domain of gait to the exclusion of other domains. We felt this would bias results if a full systematic review with grading for study quality had been undertaken. Our findings highlight the need for a more robust methodological approach in this field, which warrants further investigation.

Finally, dual task conditions were not reviewed here because we were interested in habitual gait performance. Also, dual task protocols vary widely and findings are inconsistent (Kelly *et al.*, 2015). Methodological issues include diversity of concurrent tasks, inadequate control of baseline task demand, and a varied approach to calculating and interpreting dual task interference (Rochester *et al.*, 2014). However, not including dual task studies may have attenuated findings. Studies report an increase in gait variability (Hollman *et al.*, 2007), rhythm (Yogev *et al.*, 2005) and asymmetry (Yogev *et al.*, 2006) in OA and PD under dual task conditions, reflecting an inability to compensate cognitively for gait deficit. Selective associations with cognitive outcomes have been reported, but it is beyond the scope of this review to comment on these.

In conclusion, this review has systematically examined and reported on a large number of studies concerning the relationship between gait and cognition which is firmly established. Future research will consolidate findings and procure a more nuanced understanding.
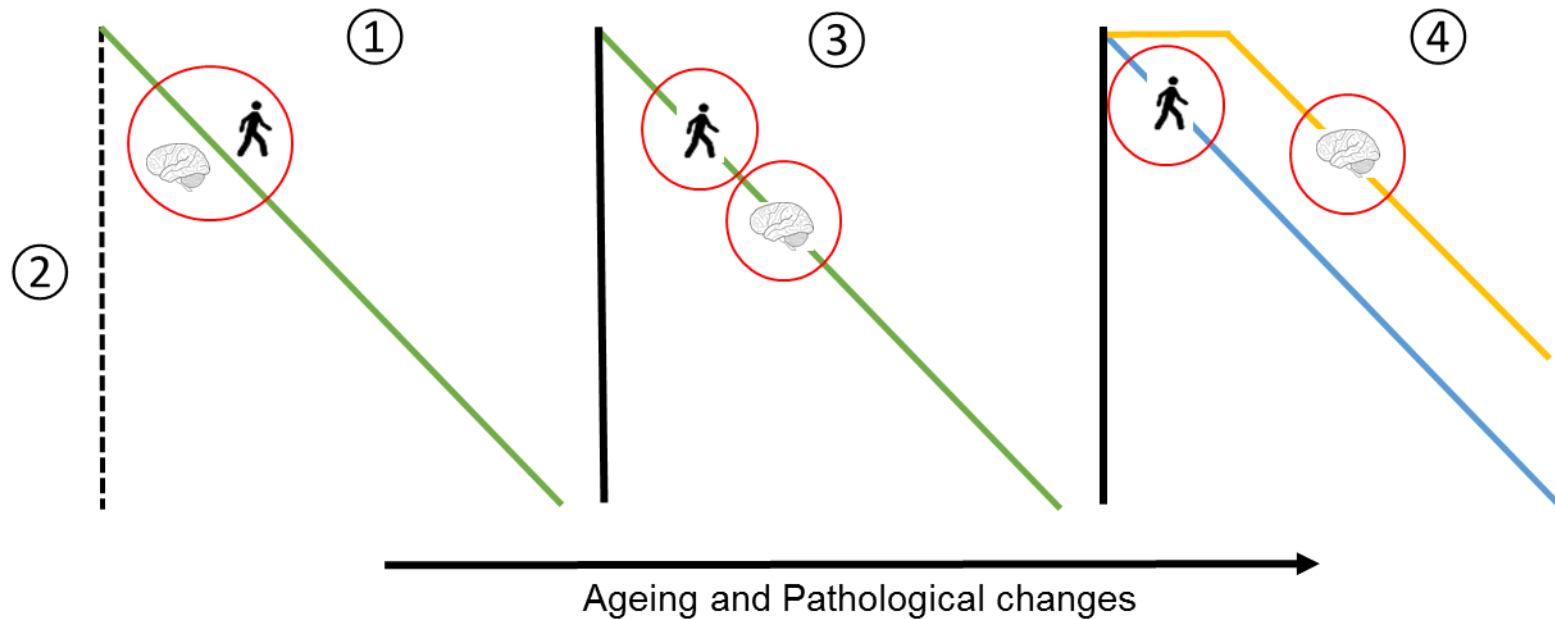
Figure 2-5 Hypothesised relationship of cognitive decline with respect to the temporal course of decline in gait and cognition in ageing and neurodegenerative disease.

① Gait and cognition decline concurrently, this may occur in normal ageing – and explains evidence for reverse causality (Tabbarah et al., 2002)

② The temporal nature of decline with age is unknown, it is unclear therefore if gait and cognition decline together or if one precedes the other in normal ageing (Gale et al., 2014)

③ Neural substrate (pathological change) underpins decline in cognition, but gait proves a more sensitive metric of cognitive change (due to role of cognition in gait) than global cognitive measures which are in common use.

④ Common neural substrate with a different temporal course (pathology affects motor function prior to cognitive   function), gait therefore declines prior to cognition

Chapter 3 : Methods- the ICICLE-Gait Study

This study was approved by the NHS Local Research Ethics Committee, Newcastle and North Tyneside 1. All participants gave written consent and had cognitive capacity to give informed consent.

3.1 Study overview

The Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation-PD (ICICLE-PD) study recruited potential participants between June 2009 and December 2011 (Khoo *et al.*, 2013). The ICICLE-PD study is a longitudinal observational study of which the ultimate aim is to further understand anatomical, biochemical and genotypic mechanisms associated with the transition from PD to PDD. The study aims to determine which clinical features may provide clinical biomarkers for the prediction of PDD. The ICICLE-Gait study is a nested sub-study of ICICLE assessing gait, balance and falls to provide a better understanding of the predictive value of gait for cognitive decline and transition to PDD.

ICICLE participants underwent a comprehensive battery of assessments, first at baseline (newly diagnosed PD) and every 18 months with current assessments at 54 and 72 months. Participants were asked to complete a number of clinical and neuropsychological assessments at each follow-up assessment. A number of participants also consented to a number of the following assessments; blood tests, cerebrospinal fluid (CSF), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), short latency afferent inhibition (SAI) and sleep analysis. This PhD thesis focuses on clinical, neuropsychological and gait assessments at baseline, 18 month and 36 month assessments of which further details are given below.

3.2 Participants and Recruitment

3.2.1 Parkinson's disease participants

People with newly diagnosed PD were asked to participate in the ICICLE Study. Participants were recruited through outpatient clinics in Newcastle-upon-Tyne, Cambridge and Gateshead. All patients had newly diagnosed idiopathic PD which was confirmed by a movement disorder specialist and met the Queen's Square Brain Bank Criteria (Hughes *et al.*, 1992). ICICLE-GAIT recruited a subset of the cohort alongside ICICLE. A number of exclusion criteria were specified as following; memory impairment (classed as ≤ 24 on the mini mental state exam [MMSE]), met the DSM-IV criteria for dementia or the Movement Disorder Society criteria (Emre *et al.*, 2007), diagnosis of PD onset before start of study, insufficient English language so as poor understanding of neuropsychological assessments, inability to consent and diagnosis of parkinsonism disorders other than PD including; Dementia with Lewy bodies (DLB), drug induced parkinsonism, vascular parkinsonism, progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and cortico-basal degeneration.

3.2.2 Control participants

To provide a comparison of cognitive decline with normal ageing, controls of a similar age and sex were recruited from community sources. Control participants were recruited in two separate cohorts, the first cohort (*N*=94) completed assessments at baseline and 36 months, the second cohort (*N*=100) completed assessments at all three time points.

Control participants from the first cohort were recruited through word of mouth and local advertising to allow for normative data. Control participants were over the age of 45 years of age. Inclusion criteria of this cohort included sufficient knowledge of English language so that neuropsychological assessments could be understood, able to walk independently without a mobility aid, no previous history of cognitive impairment or dementia. Control participants were excluded if they scored ≤ 24 on the MMSE, met DSM-IV criteria for dementia, had history of

a psychiatric or movement disorders and if they were unable to give informed consent.

For an overview of participants recruited and assessed throughout the ICICLE-Gait study up to 36 months, see **Figure 3-1**.

3.3 Clinical Assessment

Clinical assessments were undertaken in collaboration with the ICICLE-PD study. At each time point age, height and weight were recorded for all participants. In addition, all participants underwent a medical history examination at every session. Specific to this thesis, premorbid intelligence was assessed at baseline only using the National Adult Reading Test (NART, **Appendix 1.0**) (Nelson and O'Connell, 1978). and depression, using the geriatric depression scale (GDS-15, **Appendix 2.0**) (Yesavage *et al.*, 1982) was assessed at each time point.

3.3.1 Parkinson's disease specific outcomes

A number of PD specific clinical assessments were completed. Motor disease severity was assessed using the Movement Disorders Society Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III, **Appendix 3.0**) (Goetz *et al.*, 2008). The MDS-UPDRS-III gives a maximum score of 136 of which a higher score represents worse disability. Overall disease severity was rated with the widely used Hoehn & Yahr (H & Y, **Appendix 4.0**) clinical scale. The H & Y derived a score ranging from 0-5 with a higher score representing worsening disability. To assess dopamine dose for each patient at each assessment, Levodopa equivalent daily dose was calculated (LEDD) as per (Tomlinson *et al.*, 2010) providing a useful tool to asses dose intensity. All clinical testing was completed one hour after medication to ensure optimal performance.

PD

Referred from
ICICLE-PD
N=150

Excluded N=23:
Declined/ time constraints N=12
Comorbidities affecting gait
N=11

ICICLE-Gait
N=127

Excluded N=8:
Gait outliers N=3
Negative DatScan N=2
Differential diagnosis N = 3

Baseline
N=119

Deceased N=2
Ill health N=4
Withdrawn N=3
Time commitments N= 1
Lost to follow up N= 2
Outside window N= 1

18 Months
N=106

Deceased N= 2
Ill health N=4
Withdrawn N=15
Lost to follow up N=5
Outside window N=1

36 Months
N=81

Readmitted to study N= 2

Control

Referred from
ICICLE-PD
N=100

Additional Recruitment N=94

Excluded n=10
Comorbidities affecting gait
N=10

ICICLE-Gait
N=184

Deceased *N*=1
Ill health *N*=6
Withdrawn *N*=4
Time commitments *N*= 3
Lost to follow up *N*= 3
Gait outlier N=1
No reassessment N=94

Baseline
N=184

18 Months
N= 72

Deceased *N*=4
Ill health *N*=13
Withdrawn *N*=9
Time commitments *N*= 2
Lost to follow up *N*= 21
No data *N*= 1

36 Months
N=118

Invited back to study N=94
Readmitted N=2

Figure 3-1 - Flowchart of participants recruited and assessed throughout the ICICLE-Gait study.

70

3.4 Neuropsychological Assessment

A comprehensive battery of cognitive assessments was completed by all participants at each time point in collaboration with ICICLE-PD. The battery involved a number of cognitive assessments in order to measure previously defined domains of cognition (Lord *et al.*, 2014); global cognition, working memory, attention, fluctuating attention, executive function, visual memory and visuospatial function. Participants were asked not to consume caffeine or smoke up to one hour before appointments and during sessions in order to prevent increased stimulant effects during neuropsychological assessment.

3.4.1 Global cognition

To assess global cognition, participants completed the Montreal Cognitive Assessment (MoCA, **Appendix 5.0**). The MoCA was developed as a brief cognitive screening tool for clinicians to identify mild cognitive impairment (MCI) (Nasreddine *et al.*, 2005). For PD, the MoCA has been shown to be a more sensitive measure to identify early cognitive impairment in comparison to other global assessments such as the Mini Mental State Examination (MMSE).

3.4.2 Working memory

Working memory was assessed using the maximum forward digit span from the Wechsler adult intelligence scale (Wechsler, 1958). The forward digit span assessment starts initially with two numbers being played over a loud speaker which participants are then asked to recall. This continues until a maximum of nine digits is reached. The assessment consists of three trials per span length of digits, participants must get two out of three recalls correct, once the participants fails to get two out of three trials correct, the maximum digit span is determined. Digits are spoken over the loud speaker at a rate of one digit per second. The forward digit span in particular is a simple assessment that can be used clinically to assess working memory (Wilde *et al.*, 2004).

3.4.3 Attention

Attention was assessed using the cognitive drug research battery (CDR) (Nicholl *et al.*, 1995) computerised system to objectively assess attention. Three separate assessments were completed by participants; simple reaction time (SRT), choice reaction time (CRT) and digit vigilance (DV). In brief, participants were given a number of computerised tests and responded by pressing one of two buttons 'Yes' or 'No'. Full details of each assessment are given in **Table 3-1**.

The CDR system was initially designed to provide both a reliable and sensitive assessment for repeated measures of cognitive function (Wesnes, 2003). The system has been validated in older adults as well as patient populations including PD (Wesnes *et al.*, 2005) and dementia (Simpson *et al.*, 1991). A higher score determines worse impairment of attention on all three tests.

3.4.4 Fluctuating attention

Fluctuating attention was also assessed with the CDR battery as in section 3.4.3. Fluctuating attention was measured using the coefficient of variance (CV%) scores of the SRT, CRT and DV assessments. Coefficient of variance scores look at the consistency of response from a participant and have been used previously to measure fluctuations in attention (Allcock *et al.*, 2009). Further details can be found in **Table 3-1**.

3.4.5 Executive function

A number of assessments were used to assess executive function; one touch stockings (OTS), Hayling and Brixton and semantic fluency. The OTS assessment is one of the tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB). The CANTAB battery is used to assess neural substrates of learning and memory and is used in dementia as well as patients with frontal and temporal lobe lesions (Robbins *et al.*, 1994). The OTS assessment is a modified form of the Tower of London (TOL) task assessing planning with the use of working memory (Foltynie *et al.*, 2004). Participants are given twenty trials and one point is given for each successful trial giving a maximum score of twenty. A description of the OTS assessment can be seen in **Table 3-2**.

The Hayling test is a paper based assessment which measures both initiation and inhibition components of executive functioning (Burgess and Shallice, 1997) (**Appendix 6.0**). In the first part of the test the participant is presented with a sentence of which the last word is omitted, the participant is then asked to complete the sentence with one word which fits the context. In the second part of the test participants are given additional sentences with the last word omitted of which they must respond with one word which makes no sense in terms of context. The second part of the test causes the natural response to be inhibited. Reduced performance of the Hayling task has been identified in patients with frontal lobe lesions (Burgess and Shallice, 1996) as well as frontotemporal dementia (Hornberger *et al.*, 2008) and PD (Bouquet *et al.*, 2003). The Brixton test is another paper based test examining executive function (Burgess and Shallice, 1997) and is shown in **Figure 3-2** (**Appendix 6.0**). For the Brixton test, participants are presented with a page of ten circles with one of the circles filled on each trial as in **Figure 3-2**. For each trial the coloured circle moves position in line with a sequence e.g. circle 1, 2, 3, 4. The participant is asked to say which circle would be filled on the following page according to the sequence. The Brixton assessment has been validated in a number of patient groups with impairment noted in Korsakoff's syndrome, stroke and anterior lobe lesions (Burgess and Shallice, 1997; Van Den Berg *et al.*, 2009).

The semantic fluency test was the final assessment to measure executive function. In this assessment, participants were asked to name as many animals as possible in 90 seconds. Semantic fluency, which utilises executive searching and retrieval, is notably impaired in PD (Williams-Gray *et al.*, 2007).
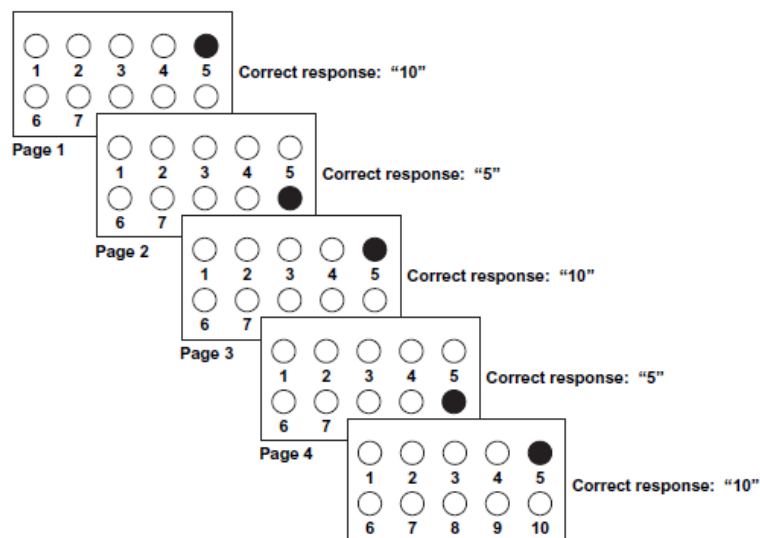
Figure 3-2 - An example of a sequence from the Brixton test to examine Executive Function ability.

Test derived by Burgess and Shallice (1997) and image taken from Van Den Berg et al. (2009).

3.4.6 Visual memory

Visual memory assessments were completed using the CANTAB battery (described in section 3.4.5). Three assessments were undertaken; pattern recognition memory (PRM), spatial recognition memory (SRM) and paired associate learning (PAL). Descriptions of all three tests are placed in **Table 3-2**. The PRM assessment has been shown to be sensitive to temporal lobe function (Owen *et al.*, 1995), participants are given a total of two trials totalling 12 patterns giving a maximum score of 24. The SRM is more sensitive to frontal lobe function (Owen *et al.*, 1995); participants are given four trials of five prompts totalling a maximum score of twenty points. The PAL assesses visual memory and new learning and requires visual pattern and visuospatial memory, previously deficits have been demonstrated in severely impaired PD patients (Owen *et al.*, 1993).

3.4.7 Visuospatial

Visuospatial skills were evaluated using the pentagon's copying task, a sub-section of the MMSE (**Appendix 7.0**). Scores were graded between 0 and 2 according to modified scoring scale in which two points indicates that all 10 angles are evident and the two pentagons are intersecting, one point indicating

74

intersecting pentagons with one shape having less than 5 angles and 0 not meeting the above criteria (Ala *et al.*, 2001; Williams-Gray *et al.*, 2007).
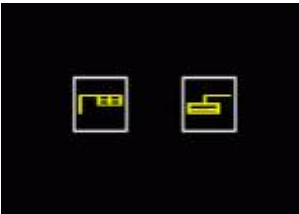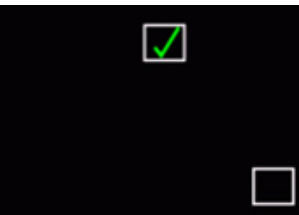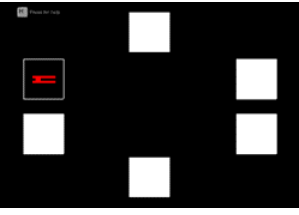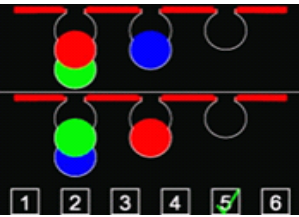
Table 3-1 - An outline of assessments used from the Cognitive Drug Research battery.

Test	Description	Measure
Simple reaction time (SRT)	*The word 'yes' will appear on the computer screen. The participant has to press the YES button as fast as possible every time the YES word appears on the computer screen.*	Mean reaction time (*ms*), coefficient of variance (*CV%*)
Choice reaction time (CRT)	*Either the word 'yes' or 'no' will appear on the computer screen. The participant must press the 'yes' button as fast as possible when the word yes appears on the computer screen. The participant must also press the NO button as soon as possible when the word 'no' appears on the computer screen*	Mean reaction time (*ms*), coefficient of variance (*CV%*)
Digit Vigilance (DV)	*A random whole number is chosen by the computer programme and is displayed continuously on the screen throughout the assessment To the left of this digit, on the centre of the screen a series of digits will appear one at a time at a rate of 150 per minute. The participant must press the YES button when the two numbers on the computer screen are matched.*	Mean reaction time (*ms*), coefficient of variance (*CV%*)

Three assessments were used; Simple Reaction Time (SRT), Choice Reaction Time (CRT) and Digit Vigilance (DV). Mean and coefficient of variance was calculated for each test. Further details of assessments and participant instructions can be found in the above table.

Table 3-2 - An outline of assessments used from the CANTAB

Test	Image	Instruction	Outcome
PRM		'12 patterns will flash up on the screen one by one. After all 12 patterns have been displayed you will be presented with a choice of two patterns. Please press the pattern you have seen before'	Number Correct
SRM		'Five squares will appear one by one at a different location on the screen. You will then be presented with a choice of two squares. Please select the square you have seen in that location before'	Number Correct
PAL		'Boxes are displayed on the screen and opened in a random order; one or more box will contain a pattern. The patterns shown previously in the boxes will now be shown one at a time in the centre of the screen, touch the box the pattern was in'	Mean trials to success (total number of trials completed)
OTS		'You will see two separate displays of three coloured balls (green, red and blue) in 'stockings'. Work out how many moves of the balls it would take to make the bottom display match the top display'	Number of problems solved

Neuropsychological Test Automated Battery (CANTAB). Four assessments were used;

Pattern Recognition Memory (PRM), Spatial Recognition Memory (SRM), Paired

Associate Learning (PAL) and One Touch Stockings (OTS, a modified version of the

Tower of London). Further details of assessments and instructions given to participants

can be found in the table above.

3.5 Gait Assessment

Gait assessments were completed at each session; testing was completed one hour after medication in PD participants to ensure optimal performance. Participants were assessed on a separate day or in the afternoon from the neuropsychological assessment to allow for medication intake.

3.5.1 Assessment

All gait assessments were completed in the gait laboratory at the Clinical Ageing Research Unit (CARU), Newcastle University. Gait was assessed using a 7m long x 0.6m wide instrumented walkway (Platinum model GaitRite™, software version 4.5, CIR systems Inc, United States of America), a valid and reliable method for gait capture both in ageing and pathology (Bilney *et al.*, 2003). Participants were asked to walk at their 'comfortable walking pace' for two minutes around a 25m continuous circuit which was inclusive of the GaitRite™ mat (**Figure 3-3**). To avoid acceleration phases, participants began walking 2.5m in front of the walkway. In addition, cones guided participants around the circuit to ensure participants were walking in a straight line before stepping onto the walkway. Gait was repeatedly sampled as they walked over the mat and continued the circuit with a minimum of five passes over the mat (allowing for over collection of over 40 steps per participant). The continuous condition under which gait data was collected allowed for an increased number of steps to be derived which provides a more reliable estimate of gait variability (Galna *et al.*, 2013).
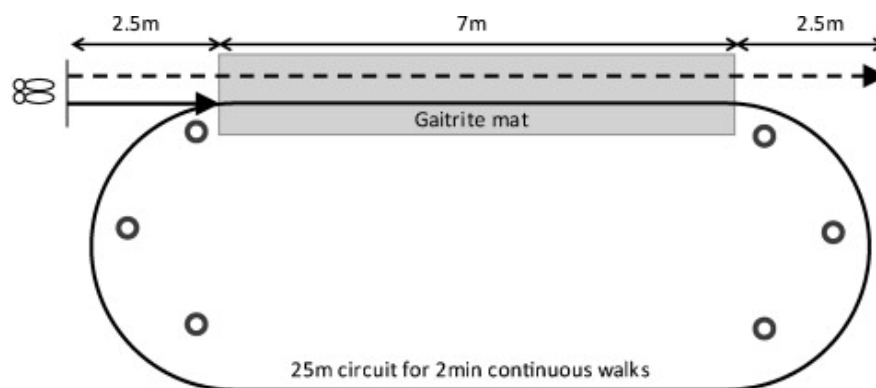
Figure 3-3 - Laboratory set up for gait assessment.

3.5.2 Task conditions

Participants completed gait assessment under single and dual task conditions. The order of single and dual-task conditions was randomised across participants. For single task conditions participants were asked to 'concentrate on their walking'. For dual task conditions participants were asked to 'concentrate equally on their walking and the concurrent task'. The Wechsler Forward Digit Span (Wechsler, 1958) provided the concurrent cognitive task; a validated task of working memory tailored to individual performance. Maximum digit span was assessed in sitting; this was determined as the longest digit span a participant could recall in two out of three attempts. Participants were asked to recall continuous strings of their maximum digit span whilst completing the two minute walk.

3.5.3 Gait outcomes

Sixteen gait characteristics were derived from the GaitRite™ mat which load onto five gait domains developed in older adults and which has been validated in PD (Lord *et al.*, 2013a; Lord *et al.*, 2013b), **Figure 3-4**. This thesis is going to use the model portrayed in **Figure 3-4** as a framework throughout, speaking both to domains of gait (i.e. pace) and characteristics representative of domains (i.e. step velocity, a representative of pace). Gait characteristics were derived from left and right steps which were calculated separately and reported as mean values of left and right steps. Variability characteristics were calculated using the standard

deviation (SD of left and right steps calculated separately and then combined). Asymmetry characteristics were calculated as the absolute difference between the mean of the right and left steps (Galna *et al.*, 2015). **Figure 1-2** illustrates the spatial and temporal gait characteristics measured for this study. Gait domains (as shown in **Figure 1-2**) were also calculated using the Z score (for PD participants this was relative to control) and then multiplying the Z score by the corresponding loading factor from the PCA (Lord *et al.*, 2013b).
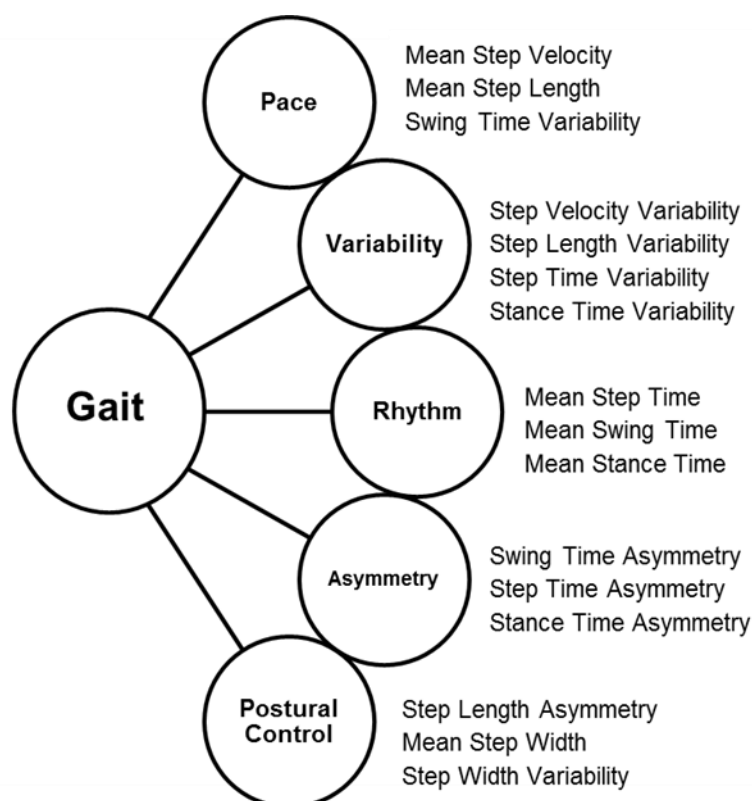
Figure 3-4 - A gait model validated in Parkinson's disease. Lord et al. (2013a).

3.5.4 Gait assessment in free-living

For both control and PD participants at each assessment a seven day gait assessment was conducted in the free-living environment using BWM. Following laboratory assessment, participants were asked to wear a single BWM (AX3; Axivity, York, UK; 100Hz, ±8g) located at the fifth lumbar vertebra (L5). The BWM was attached with a hydrogel adhesive (PALStickies, PAL Technologies, Glasgow, UK) and Hypafix (BSN Medical Limited, Hull, UK). Participants were

asked to wear the BWM continuously for seven days and only to remove when bathing. Once data collection had been completed, participants sent the monitors back via recorded delivery and the data was downloaded. The BWM allows for measurement of 14 of the 16 characteristics displayed in **Figure 3-4**. Further specific methodology for BWM data collection can be found in **Chapter 6,** an instruction sheet can be found in **Appendix 8.0**.

3.6 Data Analysis

Statistical analyses were performed using SPSS software (version 19.0; SPSS, Inc., Chicago, IL) and R Software (R Core Team, 2013). Data were initially examined for normality and distribution using the Skewness-Kurtosis test and by inspection of boxplots and histograms. Student's t-tests and Chi Squared tests were used as appropriate. Pearson chi-squared (X^2) tests were used to compare frequency differences between groups. Further specific statistical analyses are detailed in each chapter where needed.

Chapter 4 : Single task gait as a predictor of cognitive decline

This chapter explores gait under single task conditions as a predictor for cognitive decline in PD. In addition, gait is compared to a global cognitive test as a predictor of cognitive decline to see if gait proves to be a more sensitive measure.

4.1 Introduction

Cognitive decline and PD dementia (PDD) significantly impact on day to day functioning and quality of life (Lawson *et al.*, 2016), and ultimately reduce life expectancy (Levy *et al.*, 2002). Detecting 'at risk' individuals in early disease is of upmost importance to optimise clinical management and progress novel therapeutics. However, as reviewed in chapter 1, clinical biomarkers remain a major unmet need. Due to complexity underlying pathology, a single biomarker to predict cognitive decline and dementia is unlikely to be sufficient with a combinatorial approach now considered optimal (Mollenhauer *et al.*, 2014). Clinical biomarkers make an important contribution to a combinatorial battery given the complexity, cost and invasive nature of some laboratory and imaging biomarkers (Williams-Gray *et al.*, 2009b; Mollenhauer *et al.*, 2014; Olivier *et al.*, 2016).

The previous chapters of this thesis outlined that gait has potential to provide a simplistic and non-invasive clinical biomarker for cognitive decline in PD. This is based on findings identified in chapter two which show gait changes precede and predict cognitive decline and dementia in older adults (Verghese *et al.*, 2007; Mielke *et al.*, 2013). Additionally, findings from chapter two demonstrated that there is a robust relationship between gait and cognition in early PD but that the longitudinal nature of the relationship has yet to be established (Lord *et al.*, 2014; Morris *et al.*, 2016). Moreover, previous work in this field lacks a consistent and detailed approach to evaluating gait characteristics, limiting interpretation (Morris *et al.*, 2016).

Although gait analysis may provide a simplistic and cost-effective clinical biomarker, it may be questioned as to whether gait is superior to cognitive assessments which also provide non-invasive and pragmatic clinical biomarkers. Therefore, it is of interest to see if discrete gait characteristics are more sensitive than global cognitive measures to early cognitive decline. Previous interim analysis by Lord *et al.* (2013c) demonstrated that baseline gait was able to predict a decline in attention yet baseline attention itself was unable to predict a decline in attention over 18 months. Thus far evidence suggests that gait may be a more superior clinical biomarker compared to baseline cognitive assessment.

This chapter explores a comprehensive battery of gait characteristics to determine i) if gait can predict cognitive decline in early PD, ii) if gait characteristics are global or specific predictors, iii) if predictors are specific to PD pathology and iv) if gait is more sensitive than cognition in predicting cognitive decline. Based on current associative literature (Morris *et al.*, 2016) and our previous cross-sectional work (Lord *et al.*, 2014), it is hypothesised that discrete gait characteristics will be sensitive to cognitive decline in early PD.

4.2 Methods

4.2.1 Participants

Subjects with newly diagnosed idiopathic PD were recruited to the ICICLE-Gait study. ICICLE-Gait is a nested study within ICICLE-PD (Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation in Parkinson's disease); potential participants were recruited between June 2009 and December 2011 (Khoo *et al.*, 2013). Idiopathic PD was diagnosed according to the UK Parkinson's disease Brain Bank Criteria (Hughes *et al.*, 1992). PD participants were assessed over three sessions (1) baseline, (2) 18 months and (3) 36 months. PD participants were excluded according to criteria outlined in chapter 3 section 3.2.1. Participants were assessed 'on' medication, defined as one hour after PD medication.

To provide a comparison of cognitive decline with normal ageing, controls of a similar age and sex were recruited from community sources. Control participants

were recruited in two cohorts; the first cohort completed assessments at sessions 1 and 3, the second cohort completed assessments at all three time points. Inclusion criteria for control participants is outlined in chapter 3, section 3.2.2.

4.2.2 Clinical assessment

Age, sex, height and weight were recorded at each session. The National Adult Reading Test (NART) score was collected at baseline to assess premorbid intelligence (Nelson and O'Connell, 1978). Depression using the Geriatric Depression Scale (GDS-15) (Yesavage *et al.*, 1982) was assessed at each session. PD specific assessments included: disease motor severity using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (Goetz *et al.*, 2008), Hoehn and Yahr (H & Y) (Hoehn and Yahr, 2001) and Levodopa equivalent daily dose (LEDD) (Tomlinson *et al.*, 2010).

4.2.3 Gait assessment

Participants walked for two minutes at a comfortable pace around a 25m circuit inclusive of a 7m x 0.6m instrumented walkway (Platinum model GaitRite™, CIR systems Inc, USA) (**Figure 3-3**). Gait assessment was completed under single task conditions for which participants were asked to 'concentrate on their walking'. Gait outcomes were derived from a model of gait developed in older adults (Lord *et al.*, 2013b) and validated in PD (Lord *et al.*, 2013a). The model describes 16 discrete gait characteristics representing domains of pace, rhythm, variability, asymmetry and postural control (**Figure 3-4**).

4.2.4 Cognitive assessment

A comprehensive battery of cognitive assessments was completed at all sessions. Individual tests were represented by seven domains of cognition. *Global cognition* was measured using the MoCA (Nasreddine *et al.*, 2005). *Attention* was measured using the Cognitive Drug Research battery (CDR); simple reaction time (SRT), choice reaction time (CRT) and digit vigilance (DV) (Nicholl *et al.*, 1995). *Fluctuating attention* was measured using the coefficient of variance (CV) of the SRT, CRT and DV from the CDR. *Visual memory* was measured with the Cambridge Neuropsychological Test Automated Battery

(CANTAB) (Robbins *et al.*, 1994); spatial recognition memory (SRM), pattern recognition memory (PRM) and paired associate learning (PAL). *Executive function* was measured using a modified one touch stockings (OTS) version of the Tower of London (TOL) task from CANTAB, semantic fluency; number of animals in 90 seconds (Goodglass *et al.*, 2001) and the Hayling and Brixton (Burgess and Shallice, 1997). *Visuospatial function* was measured using the interlocking pentagon's copying composite score from the MMSE (Ala *et al.*, 2001). *Working memory* was assessed using Wechsler forward digit span (Wechsler, 1958).

4.2.5 Data analysis

The first stage was univariate to describe gait and cognitive data using SPSS V.21. Distribution of continuous variables was tested for normality using the Skewness-Kurtosis test and by inspection of boxplots and histograms. Paired Samples *t*-test was used to examine differences in baseline and final assessment for clinical characteristics. Student's *t*-test and Chi-square test were used to examine differences between those who did and did not complete assessments at 36 months (*p*=.05).

The second stage of analysis utilised linear mixed effects (LMEM)(R (R Core Team, 2013),'*lme4*' (Bates D, 2014)) to model cognitive decline and its predictors. LMEM were chosen as they do not assume independence between the data and account for random effects. LMEM provides a robust statistical analysis technique in cases of missing data and prevents omission of participants with missing data at one time point (Field A, 2012). Random intercept models were used to give each participant a unique intercept and regression coefficient. Firstly, LMEM were used to identify cognitive change in PD and controls over the three sessions. Initially, univariate analysis was conducted to determine cognitive assessments that significantly changed over time. Cognitive assessments which changed significantly were then entered into an adjusted model. Covariates included age, NART and gender as fixed effects, as well as interactions of session with GDS-15 (GDS-15 x Session) and LEDD (LEDD x Session). For each cognitive test a backward stepwise method was employed to remove non-significant covariates.

Secondly, LMEM were used to identify baseline gait characteristics as predictors of cognitive decline. Cognitive decline was determined for each domain using the strongest representative of each domain i.e. greatest decline over time. Base models were constructed for each cognitive assessment using baseline predictor variables only (age, gender, NART, GDS-15 and LEDD) which were entered into the models as fixed effects. A backward stepwise method was employed to remove non-significant predictors. Gait characteristics at baseline were then entered into the model as a fixed effect to determine whether gait characteristics in addition to covariates were a significant predictor of cognitive decline.

The final step was to identify whether baseline global cognition could predict change in cognition over time in PD participants. MoCA and each gait characteristic at baseline were added to base models to assess which was a stronger predictor of cognitive decline. In order to further validate findings, additional linear regression analysis was performed to identify whether baseline cognitive measures could predict change in the same measure over time. For this analysis cognitive change was entered as the dependent variable with age, sex and NART entered in the first block and baseline cognition entered in the second block.

Log-likelihood ratio tests were used to compare fit between all models. Due to the exploratory nature of this study, multiple comparisons were not adjusted for in order to reduce the risk of type II error (Rothman, 1990). In order to reduce inflation of type I error a stringent *p* value of ≤.01 was used to determine significance.

4.3 Results

4.3.1 Study participants & demographics

Figure 3-1 summarises participant recruitment and attrition in the ICICE-Gait study. Initially 150 participants with PD were referred, of whom 127 consented with 194 controls consented. After exclusions, 119 PD and 184 control subjects completed baseline assessment. At 18 months, 106 (89%) PD and 72 (39%)

control participants completed assessments, at 36 months 81 (68%) PD and 118 (64%) control participants returned. **Table 4-1** displays demographic and clinical characteristics of participants at baseline and 36 months. The PD group contained proportionally more males throughout the study whereas the control group contained proportionally more females. The average duration of PD at baseline was 6.29 ± 4.67 months. Over three years, PD motor disease severity significantly increased ($p<.001$) as did LEDD ($p<.001$). Depression did not significantly change in either group. There were no significant differences in clinical demographics for PD or control participants who withdrew from the study compared to those who completed assessments at 36 months (**Appendix 9.0**).

4.3.2 Baseline gait

Table 4-2 presents baseline gait characteristics for all participants. Comparing gait characteristics for PD subjects at baseline between those that did and did not complete assessments at 36 months; step length variability was significantly higher ($p=.02$) in those who did not complete final assessment (**Appendix 10.0**). In control subjects; step velocity ($p <.01$) and step length ($p <.01$) were significantly reduced and swing time SD ($p <.01$), step time SD ($p <.01$) and stance time SD ($p <.01$) were significantly increased in those who did not complete assessments at 36 months (**Appendix 10.0**).

4.3.3 Change in cognition

Table 4-3 presents descriptive data on cognitive test performance at each session for both PD and control participants. **Table 4-4** presents univariate and modelled change in cognition for both groups. Over three years, PD participants significantly declined on eight of 16 cognitive assessments. Attention declined on SRT (19.41ms per session, $p=.01$), CRT (36.65ms per session, $p<.01$) and DV (8.89ms session, $p <.01$). Fluctuating attention increased on CRT CV (1.29% per session, $p <.01$). PD participants declined on executive function; OTS (0.75 points per session, $p. <01$) and Brixton (0.31 points per session, $p <.01$). Finally, PD participants declined on visual memory; SRM (0.71 points per session, $p <.01$) and PAL (0.13 points per session, $p. <.01$). Control participants declined on two of 16 assessments; CRT (10.23ms per session, $p <.01$) and SRM (0.37

points per session, p <.01). PD participants who withdrew before 36 months had significantly worse baseline working memory, attention, visual memory and increased fluctuating attention (**Appendix 11.0**).

Table 4-1 - Demographic and clinical characteristics of participants at baseline and 36 month assessment.

Demographic	PD				Control			
	Baseline	36 Month	Paired Samples T-test		Baseline	36 Month	Paired Samples T-test	
			T	P			T	P
Sex (M & F)	79 & 40	55 & 26	-	-	78 & 106	53 & 64	-	-
Age (years)	66.11 (9.90)	69.13 (9.90)	-89.96	**<.01**	68.87 (7.10)	72.64 (7.06)	102.89	**<.01**
Height (m)	1.70 (.08)	1.69 (.09)	3.41	**<.01**	1.68 (0.10)	1.68 (0.09)	-2.39	**.02**
NART	115.02 (11.13)	-	-	-	117 (7.72)	-	-	-
Disease Duration (months)	6.29 (4.67)	-	-	-	-	-	-	-
LEDD (mg/day)	172.26 (129.53)	515.05 (256.08)	-12.94	**<.01**	-	-	-	**-**
UPDRS III	24.97 (10.44)	38.04 (12.50)	-11.33	**<.01**	-	-	-	-
GDS	2.59 (2.23)	2.80 (2.41)	-0.89	.38	1.28 (2.03)	1.41 (2.34)	-0.71	.48
Hoehn and Yahr stage n (%)	I (28) II (70) III (21) IV (0)	I (1) II (82) III (9) IV (2)	-	-	-	-	-	-

Table 4-2 – Single task gait characteristics at baseline.

Gait Domain	Gait Variable	PD *n*=119		Control *n*=184	
		Mean	*SD*	*Mean*	*SD*
Pace					
	Step velocity (*m/s*)	1.12	0.21	1.26	0.19
	Step length (*m*)	0.62	0.10	0.67	0.08
	Swing time SD (*ms*)‡	2.81	0.32	2.67	0.30
Variability					
	Step time SD (*ms*)‡	2.88	0.33	2.74	0.30
	Stance time SD (*ms*)‡	3.06	0.38	2.92	0.34
	Step velocity SD (*m/s*)	0.054	0.017	0.053	0.013
	Step length SD (*m*)	0.023	0.009	0.020	0.006
Rhythm					
	Step time (*ms*)	559.89	48.74	536.96	46.90
	Swing time (*ms*)	391.83	33.20	386.75	30.14
	Stance time (*ms*)	728.40	76.80	687.66	71.68
Asymmetry					
	Step time asymmetry (*ms*)‡	4.15	2.34	3.03	1.44
	Swing time asymmetry (*ms*)‡	3.69	1.97	2.67	1.34
	Stance time asymmetry (*ms*)‡	3.67	1.93	2.66	1.34
Postural Control					
	Step length asymmetry (*m*)	0.146	0.067	0.129	0.061
	Step width (*m*)	0.093	0.031	0.089	0.025
	Step width SD (*m*)	0.019	0.006	0.022	0.005

‡ *variability characteristics log transformed and asymmetry characteristics square root transformed.*

4.3.4 Single task gait as a predictor for cognitive decline

Table 4-5 and **Figure 4-1** summarise significant baseline gait predictors of cognitive decline over 36 months in PD participants. In PD, increase in fluctuating attention was predicted by pace (slower velocity (β 4.05 p <.01); reduced step length (β 8.64 p < .01)), variability (increased swing time SD (β 2.56 p < .01); step stance variability (β 1.98 p=.01) and step length variability (β 115.68 p <.01)) and gait-related postural control (increased step width (β 26.69 p <.01). Decline in visual memory was also predicted by pace (reduced step length (β 2.93 p= .01). Prediction of decline in attention by variability was near significance (increased step length variability (β 1639.29 p=.04)) but decline in executive function was not predicted by any gait characteristic. All gait characteristics improved the fit of the model except for step width as a predictor of increased fluctuating attention (χ^2 =5.91, p= .05). For domains of gait, increase in fluctuating attention was predicted by postural control (β -0.59±0.23, p=.01) with the pace domain near significance (β -0.61±0.26, p= .02). Decline in visual memory predicted by pace was also close to significance (β 0.26±0.11, p=.02). Results from all gait characteristics and domains as predictors for cognitive decline in PD can be found in the appendices; **Appendix 12.0** and **13.0**.

Table 4-6 and **Figure 4-1** summarise significant baseline gait predictors of cognitive decline in control participants. For control participants decline in attention was predicted by rhythm (reduced step time (β -0.21± 0.08, p=<.01) and reduced stance time (β -0.14±0.05, p=<.01)). In addition, decline in executive function was predicted by variability (increased step length variability, β -57.78±20.08, p=<.01). No gait characteristics were able to predict increase in fluctuating attention or visual memory. For controls stance time as a predictor of decline in attention significantly improved the fit of the model (χ^2 8.79, p=.01) as did step length variability as a predictor for decline in executive function (χ^2 9.93, p <.01). Of the gait domains, decline in attention was significantly predicted by rhythm of gait (β 8.90±3.23, p=<.01). Results from all gait characteristics and domains as predictors for cognitive decline in controls can be found in the appendices; **Appendix 14.0** and **15.0**.

Table 4-3 - Descriptive data of cognitive assessments at baseline, 18 and 36 months for PD and control.

	PD						Control					
	BL		18 Months		36 Months		BL		18 Months		36 Months	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Global Cognition												
MoCA	25.22	3.57	26.05	3.62	25.74	4.03	-	-	-	-	-	-
Working memory												
Forward digit span	5.82	1.11	5.97	1.38	5.94	1.17	6.18	1.22	6.19	1.25	6.30	1.13
Attention												
Reaction time (mean)	347.48	101.16	361.5	90.95	387.10	141.28	325.03	63.46	316.59	61.07	331.34	74.69
Choice reaction time (mean)	528.95	85.64	569.92	117.06	598.01	162.79	521.75	74.13	525.47	77.93	540.08	82.95
Digit Vigilance (mean)	479.53	56.27	483.23	63.8	496.19	65.30	455.33	49.94	458.15	47.92	461.44	45.75
Fluctuating Attention												
Reaction time (CV) (%)	17.00	5.55	17.88	6.41	18.21	6.13	17.19	5.64	17.86	5.01	17.69	5.73
Choice reaction time (CV) (%)	18.93	3.85	20.62	6.00	21.18	6.21	17.88	3.90	18.38	4.50	18.86	4.43
Digit Vigilance (CV) (%)	16.08	3.74	16.35	4.36	17.17	4.95	14.65	3.91	14.94	4.22	15.83	5.51
Executive Function												
One touch stocking (problems solved)	14.06	4.30	14.49	5.00	12.70	5.91	15.92	3.15	16.89	2.11	15.82	3.26
Semantic Fluency (animals in 90 secs)	21.77	6.38	22.14	7.12	21.34	8.12	24.24	6.06	24.18	6.39	23.12	5.18
Hayling Score	5.28	1.68	5.43	1.62	5.43	1.64	-	-	-	-	-	-
Brixton Score	4.54	2.36	3.99	2.48	4.04	2.47	-	-	-	-	-	-
Visual Memory												
Pattern Recognition memory (number correct)	19.91	2.78	19.96	2.97	19.66	3.52	20.81	2.30	20.75	2.69	20.71	2.65
Spatial Recognition memory (number correct)	15.46	2.18	14.58	2.75	14.11	2.35	16.20	1.86	15.71	2.06	15.58	2.17
Paired associate learning (mean trials to success)	2.10	0.85	2.26	0.93	2.27	1.11	-	-	-	-	-	-
Visuospatial												
Pentagon copying	1.91	0.29	1.74	0.57	1.81	0.52	1.91	0.31	1.95	0.22	1.94	0.27

Table 4-4 - Modelled change in cognitive assessments over three years.

	PD								Control							
	Univariate change				Modelled Change Adjusted				Univariate change				Modelled Change Adjusted			
	Change per session	*SE*	*T*	*p*	*Change per session*	*SE*	*T*	*p*	*Change per session*	*SE*	*T*	*p*	*Change per session*	*SE*	*T*	*p*
Global Cognition																
MoCA	0.23	0.14	1.62	.12					-	-	-	-				
Working memory																
Forward digit span	0.03	0.06	0.50	.62					0.05	0.05	1.10	.27				
Attention																
Reaction time (mean)[2]	19.20	7.23	2.67	**.01**	19.41	7.31	2.66	**.01**	5.50	3.26	1.69	.09				
Choice reaction time (mean)[1,2]	37.02	5.77	6.42	**<.01**	36.65	5.76	6.36	**<.01**	9.97	3.46	2.88	**<.01**	10.23	3.46	2.96	**<.01**
Digit Vigilance (mean)[1]	9.08	2.35	3.86	**<.01**	8.89	0.44	3.75	**<.01**	4.00	1.87	2.14	.03				
Fluctuating Attention																
Reaction time (CV) (%)[3]	0.63	0.32	1.92	.06					0.28	0.30	0.95	.35				
Choice reaction time (CV) (%)[1]	1.31	0.29	4.47	**<.01**	1.29	0.29	4.45	**<.01**	0.50	0.21	2.43	.02				
Digit Vigilance (CV) (%)[1]	0.57	0.26	2.17	.03					0.61	0.25	2.47	.02				
Executive Function																
One touch stocking (prob. solved)[4]	-0.76	0.23	-3.35	**<.01**	-0.75	0.23	-3.34	**<.01**	-0.09	0.11	-0.83	.41				
Semantic Fluency (Animals in 90s)	-0.33	0.32	-1.03	.30					-0.66	0.31	-2.13	.04				
Hayling Score[2]	0.04	0.09	0.43	.67					-	-	-	-				
Brixton Score[2]	-0.33	0.12	-2.90	**<.01**	-0.31	0.11	-2.72	**<.01**	-	-	-	-				
Visual Memory																
Pattern Recognition memory (number correct)[2]	-0.20	0.13	-1.50	.14					-0.17	0.11	-1.50	.14				
Spatial Recognition memory (number correct)[2]	-0.72	0.12	-5.89	**<.01**	-0.71	0.12	-5.83	**<.01**	-0.36	0.10	-3.62	**<.01**	-0.37	0.10	-3.76	**<.01**
Paired associate learning (mean trials to success)[2]	0.14	0.04	3.45	**<.01**	0.13	0.04	3.20	**<.01**	-	-	-	-				
Visuospatial																
Pentagon copying[2]	-0.06	0.03	-2.40	.02					0.02	0.02	1.21	.23				

[Covariates as follows; [1] Age, [2] Age, NART, [3] Age, GDS, [4] Age, NART, LEDD, [5] Age, NART, GDS, Gender.]

Table 4-5 - Linear mixed effects models identifying single task gait characteristic predictors of cognitive decline in PD.

Cognitive Domain	Cognitive Assessment	Predictor Domain	Predictor Characteristic	Regression Coefficients			
				β	SE	T	P
Attention	CRT	Variability	Step length SD x Session	1639.29	807.78	2.10	.04
Fluctuating Attention	CRTCV	*Pace*	Step Velocity x Session	-4.05	1.34	-3.02	**<.01**
			Step Length x Session	-8.64	2.86	-3.02	**<.01**
			Swing Time SD x Session	2.56	0.93	2.75	**<.01**
		Variability	Step Time SD x Session	2.14	0.90	2.38	.02
			Stance Time SD x Session	1.98	0.77	2.58	**.01**
			Step Length SD x Session	115.68	40.41	2.86	**<.01**
		Rhythm	Stance time x Session	0.01	0.03	2.26	.03
		Postural control	Step Width x Session	26.69	9.02	2.96	**<.01**
Visual Memory	SRM	*Pace*	Step Velocity x Session	1.32	0.56	2.33	.02
			Step Length x Session	2.93	1.19	2.47	**.01**

[P value significant at <0.01]

Table 4-6 - Linear mixed effects models identifying single task gait characteristic predictors of cognitive decline in controls.

				Control			
Cognitive Domain	**Cognitive Assessment**	**Predictor Domain**	**Predictor Characteristic**	**Regression Coefficients**			
				β	*SE*	*T*	*P*
Attention	CRT	*Pace*	Step Velocity x Session	46.91	20.39	2.30	0.02
		Rhythm	Step Time x Session	-0.21	0.08	-2.73	**<.01**
			Stance Time x Session	-0.14	0.05	-2.81	**<.01**
Visual Memory	SRM	*Rhythm*	Stance Time x Session	<.01	<.01	-2.05	.04
Executive Function	OTS	*Variability*	Step Length SD x Session	-57.78	20.08	-2.88	**<.01**

[P value significant at <0.01]
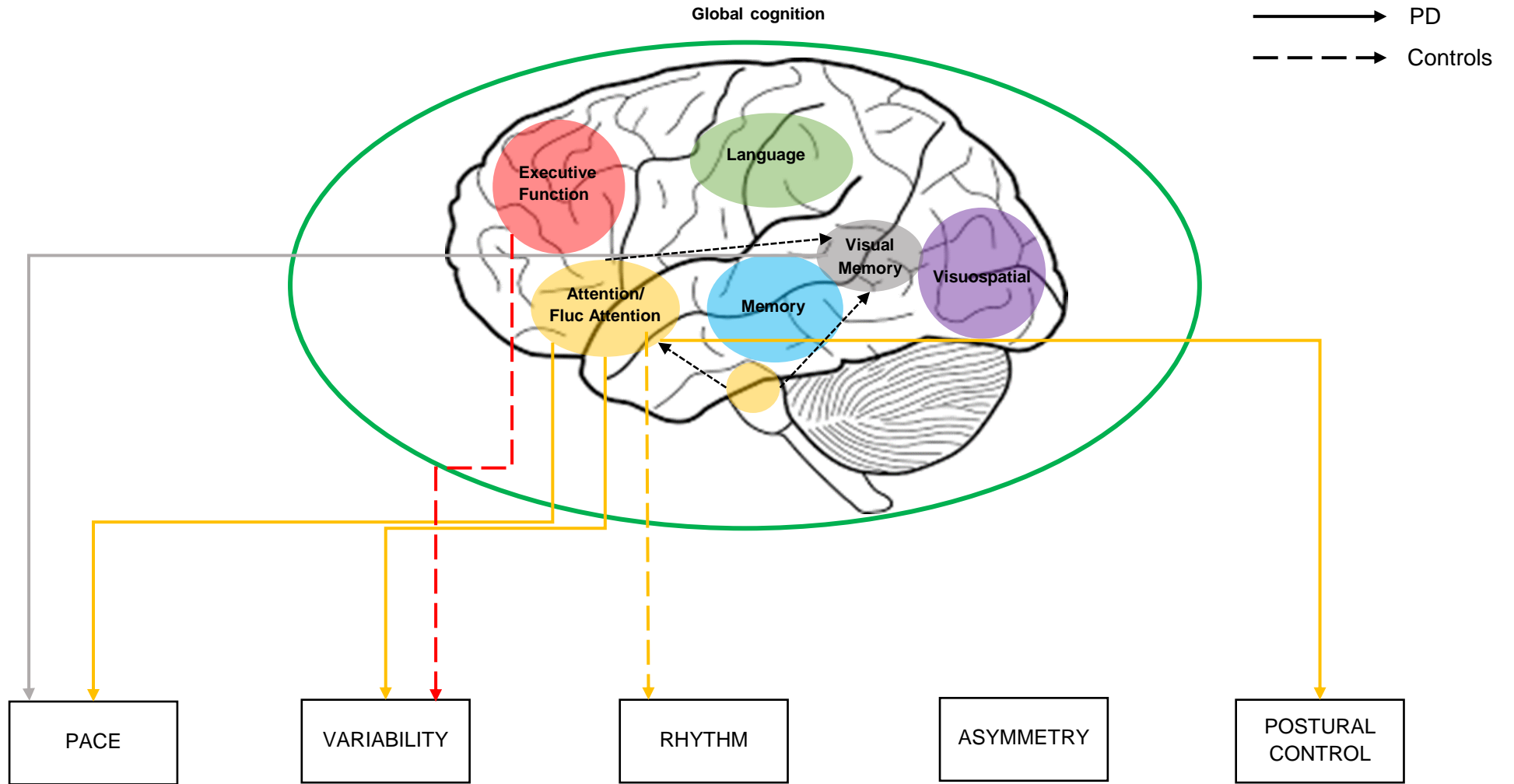
Figure 4-1 - Map of associations adapted from Morris et al, 2016 for longitudinal gait and cognition associations in PD and controls under single task conditions. Black dotted lines signify attentional influence on visual memory.

4.3.5 Gait vs. global cognition as a predictor for cognitive decline

Compared to gait characteristics shown in **Table 4-7**, MoCA was a significant predictor of a decline in attention ($p<.01$) but could not predict an increase in fluctuating attention ($p=.04$) or visual memory ($p= .15$) during single task gait in PD participants.

A number of characteristics of pace and variability proved better predictors of increased fluctuating attention compared to MoCA; step velocity ($\chi^2=10.93$, $p<.01$), step length ($\chi^2=11.22$, $p<.01$) and step length variability ($\chi^2=8.75$, $p=.01$). In addition, characteristics of pace (step velocity and step length) were significantly better at predicting visual memory decline than MoCA ($\chi^2=8.70$ $p=.01$ and $\chi^2=10.90$, $p<.01$ respectively). However, swing time SD ($\chi^2=6.73$, $p=.03$) and stance time variability ($\chi^2=7.11$, $p=.03$) did not improve the fit of the model for increase in fluctuating attention, although these gait measures remained significant in the model whilst MoCA did not. Additional linear regression analysis revealed baseline CRTCV was unable to predict an increase in CRTCV over three years ($p=.75$) (**Appendix 16.0**).

Table 4-7 - Linear mixed effects models identifying baseline MoCA as predictors of cognitive decline in PD.

Cognitive Assessment	Predictor	Regression Coefficients			
		β	SE	T	P
Attention (CRT)	MoCA	-5.68	1.54	-3.70	**<.01**
Fluctuating Attention (CRTCV)	*MoCA*	-1.68	0.80	-2.10	**.04**
Visual Memory (SRM)	*MoCA*	0.05	0.03	1.45	.15

4.4 Discussion

This chapter forms the first study to determine the role of quantitative gait characteristics as independent predictors of cognitive decline in early PD. Moreover this was a large study in an incident cohort followed from diagnosis allowing for prognostic significance of gait in early disease to be determined. Gait predicted cognitive decline over three years and this was selective to discrete gait characteristics, discrete cognitive domains and was specific to PD pathology. Importantly, gait was a stronger predictor than baseline cognition. This therefore provides the first evidence for the utility of gait as a clinical biomarker for early cognitive changes in PD.

4.4.1 Gait predicts decline in specific cognitive domains

As hypothesised, an increase in fluctuating attention and visual memory was independently predicted by single task gait characteristics represented by domains of gait describing pace, variability and gait related postural control (Lord *et al.*, 2013a). Slower pace (represented by slower step velocity and shorter step length), higher gait variability (represented by step length variability and step stance variability) and more unstable postural control (represented by increased step width variability) at diagnosis independently predicted an increase in fluctuating attention. In addition, slower pace (represented by shorter step length) independently predicted decline in visual memory. By comparison, characteristics representing rhythm and asymmetry were unable to predict cognitive decline. This is the first longitudinal study to explore the gait-cognition relationship in PD and therefore direct comparisons from other studies cannot be drawn. The study findings however can be related to evidence from robust gait-cognition associations reported in cross-sectional studies in PD (Morris *et al.*, 2016) and parallels can be drawn from work in older adults.

Firstly, cross-sectional studies have found associations between pace and attention in PD (Morris *et al.*, 2016). Only two studies to date (Lord *et al.*, 2010; Lord *et al.*, 2014) have directly measured attention with both finding an association with pace. An additional study did not find an association between pace and attention but this study combined broad measures of executive-function and attention which may have impacted on findings (Wild *et al.*, 2013). However,

the association between pace and attention does not appear to be specific to PD as it is also evident in cohorts of ageing and cognitive impairment (Morris *et al.*, 2016). This suggests ageing may drive this association which is further emphasised by pathology. The majority of gait-cognition association studies measure only gait speed, increasing the evidence for gait-cognition associations for the pace domain with minimal evidence for other gait domains. In addition to pace, this study identified measures of variability and gait related postural control to be predictors of fluctuating attention. Findings from chapter two revealed that associations of variability and postural control were specific to PD but not dementia pathology (Amboni *et al.*, 2012; Lord *et al.*, 2014; Morris *et al.*, 2016), further supporting the findings from this study. Previous cross-sectional findings highlighted a relationship between variability with global cognition and visuospatial function (Amboni *et al.*, 2012; Lord *et al.*, 2014) and postural control with visuospatial function and working memory (Amboni *et al.*, 2012; Lord *et al.*, 2014). These findings support the cognitive control theories of both variability and postural control, however cognitive associations differ from the findings here. Work in older adults which has explored both cross-sectional and longitudinal gait-cognition associations identified findings to differ with study design i.e. cross-sectional and longitudinal (Mielke *et al.*, 2013). Thus, gait and cognition associations compared to predictors do differ. As this is the only longitudinal study in PD we can only speculate that baseline gait deficits in variability and postural control are specific to cognitive decline in PD. In comparison, rhythm and asymmetry characteristics were not found to be associated with cognitive decline in this cohort of PD. This is in agreement with previous cross-sectional findings although studies are limited in number (Morris *et al.*, 2016). Previously, rhythm has been associated with attention in the Postural Instability and Gait Disorder (PIGD) phenotype of PD only. This phenotype of PD is linked to worse gait, cognition and more rapid cognitive decline (Burn *et al.*, 2006) which may have driven this relationship. Notably one characteristic of rhythm was close to significance as a predictor of fluctuating attention (step stance time, *p*=.03). It could be speculated this result would have reached significance if analysed in the PIGD phenotype only. However, for this study model prediction was not split into PD phenotypes largely because phenotype classification is unstable over disease course and additionally numbers for analysis would have been small.

Parallels can be drawn from an extensive body of longitudinal research in older adults that show prognostic associations between slow gait speed and increased gait variability with cognitive decline (including executive-attention) (Verghese *et al.*, 2007; Mielke *et al.*, 2013). Compared to cross-sectional work, longitudinal studies assessing both quantitative gait characteristics and comprehensive batteries of cognitive assessments are few and far between in older adults (Kikkert *et al.*, 2016). Previously, rhythm has been assessed by two studies (Verghese *et al.*, 2007; Taniguchi *et al.*, 2012) with links associating decline in global cognition but not attention (Verghese *et al.*, 2007). Similarly, variability in older adults has been associated with onset of dementia in one study (Verghese *et al.*, 2007) however; it was not associated with attention. Results from older adults in this study revealed rhythm predicted decline in attention and variability predicted decline in executive function. Reasons for differences compared to previous literature may be twofold. Firstly, the study by Verghese *et al.* (2007) used the digit span to assess attention. Here, digit span was used to asses working memory which did not significantly decline in this cohort of older adults. Thus, differences in protocol may underpin this with the computerised batteries in this study providing more sensitive measures of attention and executive function. Secondly, a decline in global cognition and memory related to variability and rhythm were not identified here. This may be due to the younger age of our cohort and the shorter duration of the study. Importantly, characteristics of postural control did not predict change in cognition in older adults. To date, no other longitudinal studies have assessed postural control characteristics making it difficult to draw comparisons but it can be speculated that characteristics of postural control are specific to decline in cognition in PD.

4.4.2 Cognitive profiles in early Parkinson's disease

Progression of cognitive impairment over 36 months in our early PD cohort was characterised by attention, fluctuating attention, executive function and visual memory. The greatest decline was seen in assessments of choice reaction time (CRT, both mean and coefficient of variation) and spatial recognition memory (SRM). A number of studies have tracked cognitive decline in incident cohorts to which the findings can be compared. Firstly, the results show consistency with Muslimović *et al.* (2009) who conducted a study in 115 patients with PD. At three

years Muslimović *et al.* (2009) found the greatest decline in psychomotor speed and attention with modest decline in executive function, memory and visuospatial measures. The Campaign study, assessing 239 patients with PD, found visual memory and executive function were early cognitive features to decline at three years with common deficits seen in assessments of Tower of London (TOL) and SRM (Williams-Gray *et al.*, 2007). Consistent with findings here, the Campaign study saw minimal deficits on assessments of pattern recognition memory (PRM) at three years. This further validates our findings and suggest this assessment is not sensitive to cognitive decline in PD. Notably, the Campaign group did not assess attention and therefore we cannot draw parallels with the domain demonstrating most prominent decline in our study (Williams-Gray *et al.*, 2007). Finally, a study by Pedersen *et al.* (2013) focused on MCI status in 238 participants with PD. Pedersen *et al.* (2013) importantly identified that those who transitioned from MCI to PDD showed greatest deficits on assessments of attention and verbal memory; however this group did not assess fluctuating attention. It is important to note that discrepancies in findings may be due to different methods of assessment with different test batteries used in cohorts. Guidelines have been outlined in PD identifying appropriate assessments for cognition and cognitive domains (Litvan *et al.*, 2012) which may help with consistency in future studies. For this study, the test battery was limited for measures of language and visuospatial function domains which is addressed further in the limitations below. Even though decline in attention is in agreement with the literature, sensitivity to attention in this study may have been induced by the precision of computerised batteries (Wesnes *et al.*, 1999).

4.4.3 Is fluctuating attention a marker of dementia?

Gait characteristics were able to predict an increase in fluctuating attention and visual memory and importantly this was specific to PD. This finding is highly relevant given the contribution both assessments make to the evolution of cognitive decline and dementia in PD. Fluctuating attention was particularly sensitive to baseline gait in this study. Previous work has shown that these cognitive features may be important precursors for dementia in PD. Woods and Trőster (2003) identified that those with 'prodromal' PDD i.e. those who converted to PDD within one year, performed worse on frontal cognitive assessments and

poorer performance was predictive of future dementia. In addition a more recent study identified attentional deficits to be the most prominent deficit in those with PD MCI who went on to convert to PDD (Pedersen *et al.*, 2013). Fluctuating attention (measured by choice reaction time standard deviation) is significantly worse in Lewy Body Dementias (LBD (an overarching term comprising both PDD and DLB) compared to AD (Walker *et al.*, 2000) and is able to discriminate between the dementias (McKeith *et al.*, 1996). Fluctuating attention is one of three core symptoms in LBD and has an impact on patients day-to-day functioning and activities of daily living (Ballard *et al.*, 2001) which was more recently found in PDD (Bronnick *et al.*, 2006). Fluctuation of attention, for the purpose of this study, was measured using choice reaction time (CRT) coefficient of variation (CV). CRT variability is the strongest measure of fluctuating cognition (Taylor *et al.*, 2013) with CRT shown to be sensitive to discriminating between different dementias (Ballard *et al.*, 2002). Previously the majority of studies have assessed this using CRT SD (Ballard *et al.*, 2002; Taylor *et al.*, 2013) however the CV provides an advantage over the SD. The CV provides a measure of dispersion and describes the extent of variability of a variable relative to the mean; it is an easily understood measure as it is expressed as a percentage of variation. This is particularly useful when comparing measures that have different scoring mechanisms, as unlike SD's the CV has no units of measurement.

 Visual and memory components play a vital role in spatial recognition memory (SRM) which is temporally-mediated, however, lesion (Owen *et al.*, 1995) and cognitive cohort studies (Foltynie *et al.*, 2004) also suggest a role for frontal involvement, indicating overlap of underlying mechanisms. Thus, it is plausible this association was driven by attentional mechanisms; this is depicted with the black dashed lines in **Figure 4-1**. However, these findings do have an interesting implication in regards to the dual syndrome hypothesis (Kehagia *et al.*, 2013). Kehagia *et al.* (2013) proposed that those who exhibit a more rapid decline to PDD demonstrate primarily posterior cortical and temporal lobe dysfunction such as visuospatial function deficits. This study identified step length at baseline was a significant predictor of decline on a SRM task. Although it remains unclear at present, in accordance with the dual syndrome hypothesis the findings for prediction of SRM decline may be of significant importance for identifying future

dementia. Due to the overlapping attentional and visual mechanisms needed for this battery this may be sensitive to cognitive decline in PDD.

4.4.4 Potential underlying mechanisms

Underlying pathology of gait and cognition is poorly understood but evidence suggests they share at least some substrates. Gait is not purely dopaminergic (Galna *et al.*, 2015) but interacts with other systems. Previous work implicates the cholinergic system in gait dysfunction, demonstrated by short-latency afferent inhibition (Rochester *et al.*, 2012) and intervention (Henderson *et al.*, 2016) studies.

Two sources of cholinergic output are shown to decline in PD; the nucleus basalis of Meynert (nbM) and the pedunculopontine nucleus (PPN) (Yarnall *et al.*, 2011) with the nbM projecting to the frontal lobe and thalmic nuclei and the PPN to the thalamus, cerebellum, brainstem and nbM. The nbM has a recognised role in gait, for example, in rodents' dual dopaminergic and cholinergic lesions led to more frequent falls (Kucinski *et al.*, 2013). In humans, imaging work has identified increased activation of the prefrontal cortex both during goal directed gait (Hamacher *et al.*, 2015) and maintaining balance whilst standing (Mahoney *et al.*, 2016). Slower walking in particular has been associated with basal forebrain cholinergic degeneration (Bohnen *et al.*, 2013). The PPN also plays an intrinsic role in mobility. Cholinergic loss from the PPN is related in particular to postural instability and falls (Bohnen *et al.*, 2009; Bohnen and Albin, 2011; Yarnall *et al.*, 2011; Müller and Bohnen, 2013). Previous work has identified cholinergic cell loss of the PPN in PD fallers compared to non-fallers (Karachi *et al.*, 2010) and in addition, cholinergic dysregulation of the thalamus is heightened in fallers compared to non-fallers (Bohnen *et al.*, 2009).

Importantly, the cholinergic system also has an essential role in cognition. Deficits in attention and increased fluctuating attention may arise from dysfunction of both the nbM and PPN. Previously, lesions to the nbM and its projections have revealed deficits in attention and fluctuating attention (Baxter and Chiba, 1999; Gratwicke *et al.*, 2015; Colloby *et al.*, 2016a; Colloby *et al.*, 2016b). The PPN has a primary role in executive function and attention (Winn, 2006; Gut and Winn, 2016) demonstrated in animal studies in which selective

lesions to cholinergic cells of the PPN has demonstrated in deficits in sustained attention (Cyr *et al.*, 2015). In human studies, stimulation of the PPN has been achieved using deep brain stimulation (DBS) and has shown to improve sustained alertness (Fischer *et al.*, 2015). Work in patients with DLB has identified that the thalamus plays a critical role in fluctuating cognition (Delli Pizzi *et al.*, 2015). Delli Pizzi *et al.* (2015) identified structural changes as well as impaired cholinergic function to thalamic regions associated both with alertness and attention in patients with DLB compared to controls. Due to intrinsic cholinergic projections from both the NbM and PPN the thalamus may also play a critical role in fluctuating attention in PD. Imaging evidence suggests changes to perfusion network alterations as opposed to specific neural structures may underpin dysfunctions in fluctuating attention (Taylor *et al.*, 2013; Colloby *et al.*, 2016b). Taylor *et al.* (2013) conducted single photon emission computed tomography (SPECT) in patients with AD and DLB and demonstrated specific perfusion patterns, thought to be mediated by cholinergic activity, in patients with DLB. Importantly, these perfusion networks were associated with poorer attention and increased fluctuating cognition that was not seen in patients with AD. More recently, Colloby *et al.* (2016b) conducted SPECT imaging in patients with PDD and healthy older adults and identified dysfunctional cholinergic perfusion networks in those with PDD compared to controls, of interest these networks mapped onto resting state networks critical for attention and working memory.

It has to be noted that the precise neurobiological underpinnings of fluctuating attention are not completely understood but it is proposed here that there is a common cholinergic underpinning to neural correlates of gait (namely pace, variability and postural control) and cognition (namely fluctuating attention). Furthermore the role of attention may also mediate visual deficits (Gratwicke *et al.*, 2015; Colloby *et al.*, 2016b) contributing to decline in SRM. Interestingly, gait was unable to predict decline in executive function which has been shown to be an early feature of cognitive decline (Williams-Gray *et al.*, 2007). This may reflect the overarching role of attention in mediating cognitive function (Lückmann *et al.*, 2014), or sensitivity of attentional measures over measures of executive function in this early stage of the disease.

4.4.5 Comparison of gait and cognitive outcomes; clinical implications

One aim of this study was to identify whether discrete gait characteristics were more sensitive than cognitive measures to early cognitive decline. Our findings suggest that this is the case. Global cognition (described by MoCA) did not predict an increase in fluctuating attention or visual memory. Furthermore, the additional analysis carried out to substantiate gait findings showed that fluctuating attention did not predict future cognition decline. These findings strengthen the case for the role of discrete gait characteristics as predictors of cognitive decline in early PD. It is proposed that gait is a sensitive predictor of increased fluctuating attention and visual memory, prior to cognitive assessments and that future work will identify gait and fluctuating attention to be critical in the advancing pathology to PDD. This hypothesis is explored in **Figure 4-2**.

The use of cognitive batteries proves problematic due to lack of equipment, validation, staff competence and resources (Lee *et al.*, 2012) with computerised assessments difficult for some patients resulting in data loss (Williams-Gray *et al.*, 2007). Comprehensive gait assessments, however, are evolving from laboratory to clinical settings via BWM providing a simple and cost effective method of collecting discrete gait characteristics. This further demonstrates the potential for gait as a clinical biomarker for specific cognitive decline in PD. As suggested in chapter one, one biomarker is insufficient and combinatorial markers are essential to create 'biomarker batteries' to determine 'at risk' individuals. Recently a combinatorial biomarker inclusive of gait has been identified in older adults. Verghese *et al.* (2012) proposed a four point risk battery; motoric cognitive risk syndrome (MCR), including gait speed, to identify those at risk of dementia. The study identified that those who met criteria for MCR had greater predictive ability for future dementia, in particular vascular dementia. This study only measured gait speed, whereas the use of quantitative gait characteristics may improve sensitivity and specificity of the battery.

4.4.6 Study strengths and limitations

This study has a number of strengths. The ICICLE study forms a large incident cohort study following patients at diagnosis of PD with assessments every 18 months. The nature of the study has allowed for the predictive ability of gait to be

determined from very early disease which is key for a clinical biomarker. Furthermore, to predict cognitive decline, quantitative gait analysis has been utilised measuring sixteen gait characteristics that form a gait model validated in PD. To date, the majority of longitudinal studies only measure gait speed- the final common expression of gait leading to loss of sensitivity and specificity. The importance of utilising quantitative gait analysis has been stressed when associating gait and cognition (Kikkert *et al.*, 2016) and here this has been done thoroughly, allowing for a strong foundation for future work.

It also has to be addressed that this study has several limitations. Firstly, the cognitive battery was comprehensive for attention, executive function and memory but less comprehensive for visuospatial. Significant visuospatial decline was not apparent in this cohort but other work identified pentagons to decline in early PD (Williams-Gray *et al.*, 2007) suggesting this assessment was adequate. Secondly, the main outcome from this study was gait as a predictor of increasing fluctuating attention. Fluctuating attention was defined here as the coefficient of variance (CoV) which is calculated by mean reaction time/ standard deviation for each individual person. This is a central tendency measure which can inflate sensitivity when the mean is a negative value or zero. However, for this outcome all measures were positive values and greater than zero which limits potential sources of error. Thirdly, the longitudinal nature of the study inevitably leads to attrition. Attrition rates in this study totaled 32%, comparable to similarly designed studies (Williams-Gray *et al.*, 2007; Muslimović *et al.*, 2009). Baseline scores revealed that those who withdrew were representative of the whole sample for clinical demographics and gait. However, those who withdrew were worse on a number of cognitive assessments. This may indicate that those with more rapid decline were more likely to withdraw and would have been of interest to this study. In an attempt to alleviate bias, LMEM were chosen as this modeling technique is able to handle missing data yet it is possible that rate of cognitive decline was underestimated. Additionally, the population was drawn from an incident PD cohort followed from diagnosis with repeat assessments every 18 months. While misdiagnosis may have contributed this is unlikely to have made a major impact. Diagnosis followed a stringent process and revised diagnosis over

the course of the study revealed that the numbers were low. Finally, the findings need to be replicated in an independent cohort.

4.4.7 Conclusions

In conclusion, this is the first study to identify gait as a predictor of cognitive decline, specific to fluctuating attention and visual memory in a large incident PD cohort. The novel findings provide evidence for gait as a non-invasive clinical biomarker for cognitive decline in PD. Work focused on specific assessments of cognitive decline, a critical approach providing further understanding of the underlying pathology of gait and cognition. Future work will focus on gait as a predictor of PDD as the cohort continues to evolve.
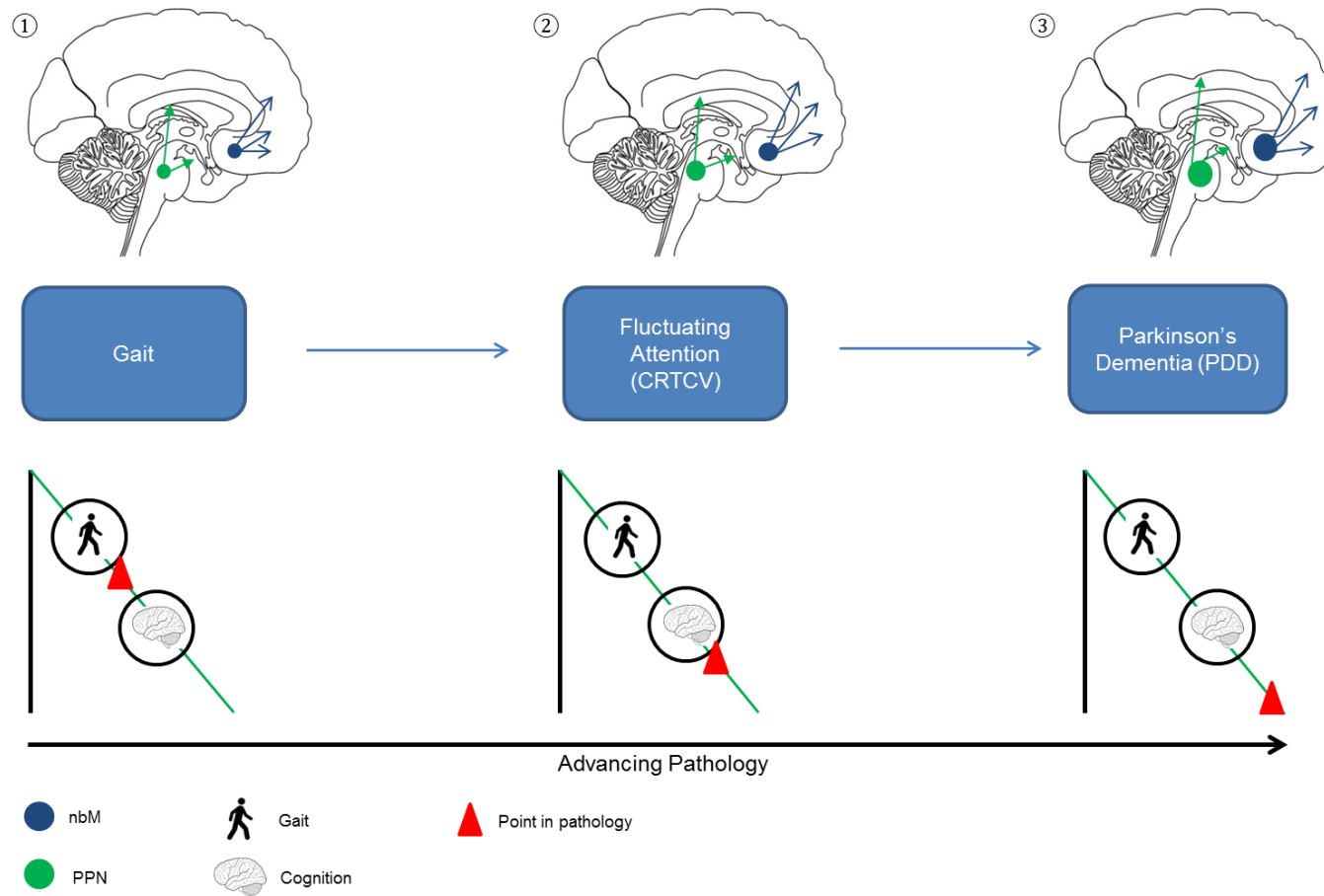
Figure 4-2 - Hypothesised relationship of cognitive decline in PD and the temporal course of gait and cognition deficits in response to advancing pathology.

① In early pathology discrete changes to networks including the cholinergic system stemming from the nbM and PPN become apparent in deficits of gait characteristics. ② as pathology progresses, deficits in cognition, namely fluctuating attention become affected. ③ Pathology advances to a diagnosis of PDD.

Chapter 5 : Dual task gait as a predictor of cognitive decline

The notion of dual task gait was introduced in chapter 1. This chapter will explore the role of gait under dual task as a predictor for cognitive decline in PD. This chapter will decipher whether gait under dual task provides a more sensitive clinical predictor than single task conditions, and will discuss the clinical implications of findings.

5.1 Introduction

This thesis has so far outlined the importance of detecting cognitive decline in those with early PD. Current biomarkers were outlined in chapter 1 with chapter 4 demonstrating the first evidence for gait under single task conditions as a predictor for cognitive decline over the first three years of PD. It became evident in chapter 4 that a number of features of gait under single task conditions were able to predict an increase in fluctuating attention and decline in visual memory, mediated through frontal attentional mechanisms. Due to the sensitivity to decline in these resources, it is critical that we explore the predictive capability of dual task gait characteristics for cognitive decline, as these may be more sensitive than single task.

The notion of dual task paradigms were introduced in chapter 1, a popular method in which to assess the gait-cognition relationship. A number of theoretical models underpin dual task gait performance which depict that resource allocation (of attentional and executive functional processes) is challenged under dual task conditions (Pashler, 1994; Tombu and Jolicœur, 2003; Wickens, 2008). The effect of dual task gait paradigms is further illustrated in **Figure 5-1.** Due to the underlying pathology, dual task deficit is exacerbated in PD compared to healthy adults as demonstrated in **Figure 5-1C**.

Previously in the ICICLE study, cross-sectional analysis was completed at baseline (diagnosis) to identify associations between dual task gait and cognition (Rochester *et al.*, 2014). Surprisingly, dual task gait was not found to associate

with cognitive assessments of global cognition, attention or executive function. The authors speculated this was due to the mild stage of PD as in contrast; work in later stage disease found executive function and attention deficits to correlate with dual task performance (Rochester *et al.*, 2008; Lord *et al.*, 2010). In addition, a number of studies in older adults, dementia and PD have identified gait-cognition associations only to be evident under dual task but not single task gait (Sheridan *et al.*, 2003; Yogev *et al.*, 2005; Wild *et al.*, 2013). It also has to be acknowledged that gait-cognition associations and predictors do differ (Mielke *et al.*, 2013). One study to date explored the role of dual task gait as a marker of cognitive decline but did not find the measure to be superior to single task (Deshpande *et al.*, 2009). However, interpretation of findings is limited as the authors only assessed global measures of gait and cognition. In addition, Deshpande *et al.* (2009) studied older adults only and due to the underlying pathology it would be expected that a longitudinal relationship would be more evident in PD over and above other cohorts. Evidence to date is not robust but it could be hypothesised that gait under more challenging conditions may provide a better predictor of cognitive decline compared to single task conditions in PD.

Clinically, identifying whether dual task provides a stronger predictor than single task gait is of importance as there is much less burden on patients to complete a single task gait assessment. In addition, dual task paradigms would require additional training for clinicians. Therefore, this chapter aims to i) explore dual task gait characteristics as predictors for cognitive decline in PD, ii) identify if dual task gait characteristics are global or specific predictors iii) compare dual task gait predictors to single task iii) identify whether dual task predictors are specific to pathology and finally iv) assess if dual task gait is more sensitive than cognition in predicting cognitive decline. It is hypothesised that dual task gait will be able to predict cognitive decline in PD and that gait characteristics will be more sensitive to this decline compared to single task gait.
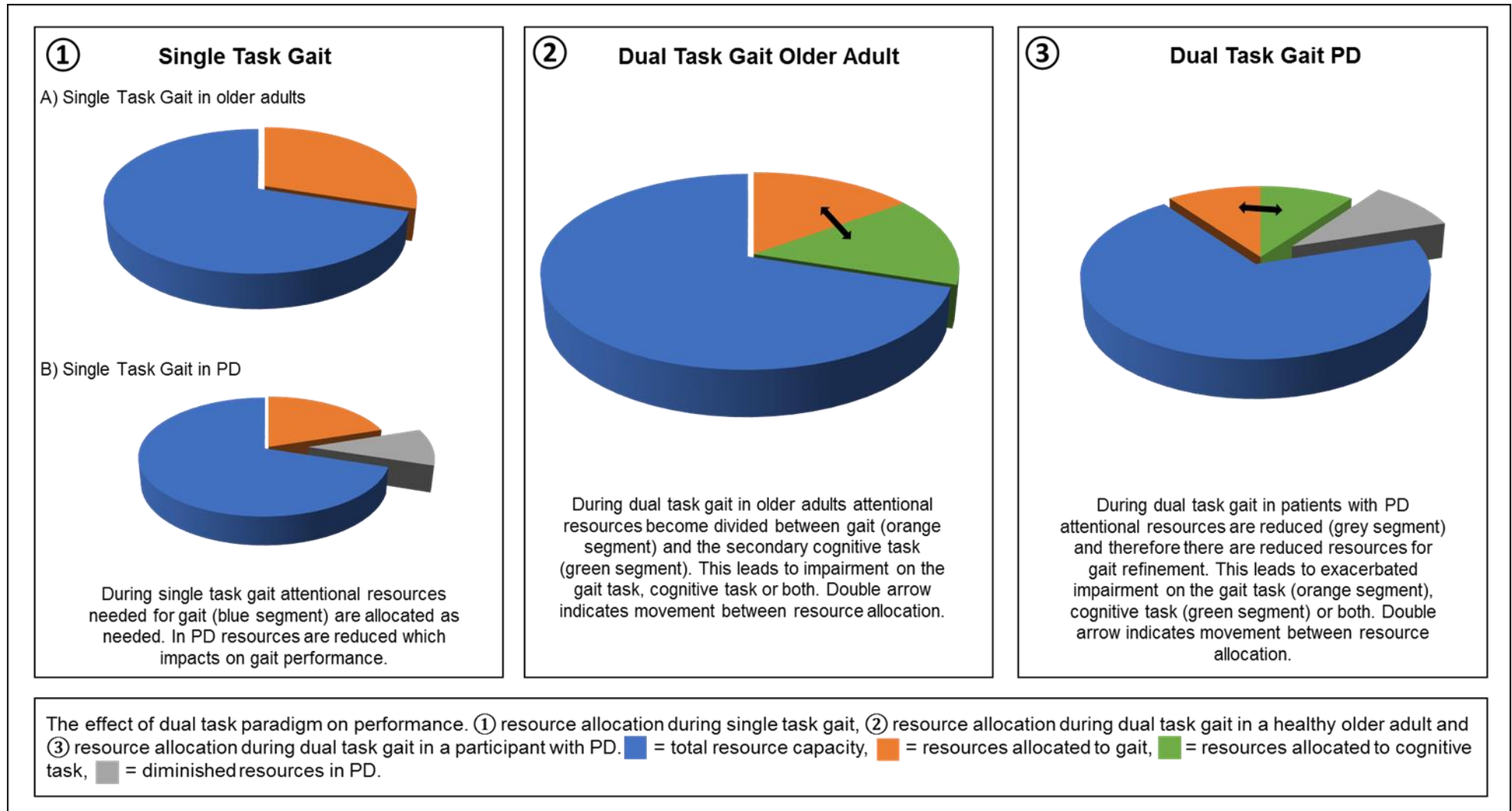
Figure 5-1. Dual task gait paradigms in older adults and people with Parkinson's disease.

5.2 Methods

For the dual task study, participants were once again recruited from ICICLE-Gait as outlined in chapter 3. The same cognitive assessments were analysed as in chapter 4 and all participants (*n*=119) completed dual task gait assessment at baseline. Participant recruitment and attrition can be found in **Figure 3-1**. Participants completed assessments 'on' medication, defined as within one hour of PD medication.

5.2.1 Dual task paradigm

Participants completed the gait assessment as outlined in chapter 4 (section 4.2.3), but for dual task conditions participants were asked to 'concentrate equally on their walking and the concurrent task'. To recap, the Wechsler Forward Digit Span (Wechsler, 1958) was adopted for the concurrent cognitive task; a validated task of working memory tailored to individual performance. Maximum digit span was assessed in sitting; this was determined as the longest digit span a participant could recall in two out of three attempts. Participants were asked to recall continuous strings of their maximum digit span whilst completing the two minute walk.

5.2.2 Data analysis

Univariate analysis was used initially to describe the data, these were inspected for normality and met criteria for parametric analysis. Paired samples t-tests were used to decipher significant differences between single and dual task gait (significance *p* ≤.05). Student's t-tests were used to determine differences in those who did and did not complete assessments at 36 months (significance *p* ≤.05). Linear mixed effects models (LMEM) were used for analysis as in chapter 4 to derive dual task gait predictors of cognitive decline. Briefly, random intercept models were used to give each participant a unique intercept and regression coefficient. Cognitive change over the three sessions was modelled as in chapter 4 using LMEM with an adjusted model with appropriate covariates determined by the backward stepwise method. LMEM were used to identify baseline gait characteristics under dual task conditions as predictors of cognitive decline. Base models were once again constructed for each cognitive assessment using

baseline predictor variables only and were entered as fixed effects. Dual task gait characteristics at baseline were then entered into the model as a fixed effect to determine whether gait characteristics under dual task conditions in addition to covariates were a significant predictor of cognitive decline. Once again, the predictive value of dual task gait characteristics versus a global cognitive test (MoCA) was assessed. MoCA and each gait characteristic under dual task condition were added to base models to assess which was a stronger predictor of cognitive decline. Similarly to the analysis for chapter 4, for LMEM a stringent p value of ≤.01 was required for significance to guide interpretation in an attempt to correct for multiple comparisons.

5.3 Results

5.3.1 Baseline dual task gait

Table 5-1 and **Table 5-2** summarise descriptive gait characteristics under dual task for PD and control subjects respectively. Comparing dual task gait characteristics for PD subjects at baseline between those who did and did not complete assessments at 36 months; step velocity variability ($p <.01$) and step length variability ($p <.01$) were significantly higher in those who did not complete assessments at 36 months, see **Appendix 17.0**. Comparing dual task gait characteristics for control subjects at baseline between those who did and did not complete assessments at 36 months; step velocity ($p <.01$), step length ($p <.01$) and step width variability ($p <.01$) were significantly reduced in those who withdrew and step time variability and step time asymmetry were significantly increased (p .02 and $p <.01$ respectively), see **Appendix 17.0**.

5.3.2 Dual task v's single task gait characteristics

Table 5-1 and **Table 5-2** compare single and dual task gait at baseline in PD and control subjects respectively. In PD gait under dual task was poorer; gait was slower with shorter steps, it was more variable, more asymmetrical and with poorer postural control. All characteristics of pace were significantly worse under dual task; step velocity was slower ($p=<.01$), step length was shorter ($p=<.01$) and swing time SD increased ($p=<.01$) compared to single task. All

characteristics of variability were significantly worse under dual task compared to single task with step time SD (p=<.01), stance time SD (p=<.01), step velocity SD (p=<.01) and step length SD (p=.01) all significantly increased. For characteristics of rhythm, step time (p=<.01) and stance time (p=<.01) significantly increased under dual task compared to single task but swing time did not significantly change (p=.84). All characteristics of asymmetry significantly increased under dual task; step time asymmetry (p=.01), swing time asymmetry (p=.01) and stance time asymmetry (p=.02). Only one characteristic of postural control changed under dual task with step width significantly increasing (p=<.01). In contrast, neither step length asymmetry (p=.37) nor step width variability (p=.16) changed under dual task.

For control subjects (**Table 5-2**), overall gait was poorer with reduced pace, increased variability and poorer gait related postural control under dual task as opposed to single task. All characteristics of pace were significantly poorer under dual task; step velocity was slower (p <.01), step length was shorter and swing time SD was increased (p <.01). All characteristics of variability were significantly higher under DT; step time variability (p <.01), stance time variability (p <.01), step velocity variability (p <.01) and step length variability (p <.01). All characteristics of rhythm were significantly higher; step time (p <.01), swing time (p <.01) and stance time (p <.01). Two measures of gait related postural control were less stable demonstrated by increased step width (p <.01) and step width variability (p <.01). Asymmetry characteristics were not significantly different in controls under dual task conditions .

Table 5-1 - Dual task gait characteristics in PD subjects at baseline.

Gait Domain	Gait Variable	ST (n=119)		DT (n=119)		Paired Samples Test	
		Mean	SD	Mean	SD	t	P
Pace							
	Step velocity (*m/s*)	1.12	0.21	1.06	0.22	9.55	**<.01**
	Step Length (*m*)	0.62	0.10	0.59	0.10	10.81	**<.01**
	Swing time SD (*ms*)‡	2.81	0.32	2.92	0.32	-5.25	**<.01**
Variability							
	Step time SD (*ms*)‡	2.88	0.33	3.04	0.36	-6.71	**<.01**
	Stance time SD (*ms*)‡	3.06	0.38	3.27	0.41	-7.24	**<.01**
	Step velocity SD (*m/s*)	0.054	0.017	0.060	0.018	-3.66	**<.01**
	Step length SD (*m*)	0.023	0.009	0.025	0.009	-3.38	**<.01**
Rhythm							
	Step time (*ms*)	559.89	48.74	571.05	53.41	-5.31	**<.01**
	Swing time (*ms*)	391.83	33.20	391.58	34.84	0.21	.84
	Stance time (*ms*)	728.40	76.80	751.03	85.45	-7.13	**<.01**
Asymmetry							
	Step time asymmetry (*ms*)‡	4.15	2.34	4.51	2.52	-2.52	**<.01**
	Swing time asymmetry (*ms*)‡	3.69	1.97	3.98	1.97	-2.66	**<.01**
	Stance time asymmetry (*ms*)‡	3.67	1.93	3.95	2.01	-2.35	**.02**
Postural Control							
	Step length asymmetry (*m*)‡	0.146	0.067	0.149	0.076	-0.90	.37
	Step width (*m*)	0.093	0.031	0.095	0.032	-3.80	**<.01**
	Step width SD (*m*)	0.019	0.006	0.018	0.005	1.43	.16

[‡ *variability characteristics log transformed and asymmetry characteristics square root transformed*]

Table 5-2 - Dual task gait characteristics in control subjects at baseline.

Gait Domain	Gait Variable	Control				Paired Samples Test	
		ST (n=184)		DT (n=184)			
		Mean	*SD*	*Mean*	*SD*	*t*	*P*
Pace							
	Step velocity (*m/s*)	1.26	0.19	1.19	0.20	11.06	**<.01**
	Step Length (*m*)	0.67	0.08	0.65	0.08	13.01	**<.01**
	Swing time SD (*ms*)‡	2.67	0.30	2.77	0.33	-5.98	**<.01**
Variability							
	Step time SD (*ms*)‡	2.74	0.30	2.91	0.35	-7.83	**<.01**
	Stance time SD (*ms*)‡	2.92	0.34	3.11	0.39	-7.90	**<.01**
	Step velocity SD (*m/s*)	0.053	0.013	0.060	0.016	-5.30	**<.01**
	Step length SD (*m*)	0.020	0.006	0.022	0.006	-5.19	**<.01**
Rhythm							
	Step time (*ms*)	536.96	46.90	549.57	54.22	-7.16	**<.01**
	Swing time (*ms*)	386.75	30.14	390.02	33.36	-3.15	**<.01**
	Stance time (*ms*)	687.66	71.68	709.77	82.71	-8.60	**<.01**
Asymmetry							
	Step time asymmetry (*ms*)‡	3.03	1.44	3.16	1.67	-1.38	.17
	Swing time asymmetry (*ms*)‡	2.67	1.34	2.80	1.54	-1.41	.16
	Stance time asymmetry (*ms*)‡	2.66	1.34	2.82	1.52	-1.75	.08
Postural Control							
	Step length asymmetry (*m*)‡	0.129	0.061	0.132	0.060	-1.04	.30
	Step width (*m*)	0.089	0.025	0.094	0.027	-8.43	**<.01**
	Step width SD (*m*)	0.022	0.005	0.023	0.006	-3.32	**<.01**

[‡ variability characteristics log transformed and asymmetry characteristics square root transformed]

5.3.3 Dual task gait as a predictor for cognitive decline

Table 5-3 and **Figure 5-2** summarise the baseline dual task gait characteristics that predicted cognitive decline over 36 months in PD. Decline in attention was predicted by one measure of variability (increased step time variability (β 42.54± 16.30, p=.01)). An increase in fluctuating attention was predicted by characteristics from all gait domains; pace (slower velocity (β -3.86±1.24, p <.01), reduced step length (β -8.37 ± 2.69, p <.01) and increased swing time SD (β 2.83± 0.89, p <.01)), variability (increased step time SD (β 2.35±0.82, p=.01)), rhythm (increased stance time (β 0.01 ± <0.01, p= .01)), asymmetry (increased stance time asymmetry (β 0.36± 0.14, p=.01)) and postural control (increased step width (β 27.70± 8.86, p <.01)). Decline in visual memory was predicted by pace (slower velocity (β 1.36 ± 0.52, p=.01) and reduced step length (β 3.00±1.13, p <.01)) and variability (increased step stance variability (β -0.76±0.30, p=.01)). Decline in executive function was not predicted by any gait characteristic. All gait characteristics improved the fit of the model except for step time variability as a predictor of decline in attention (χ^2=7.50, p= .02) and stance time asymmetry as a predictor of increased fluctuating attention (χ^2=6.55, p= .04). Calculated gait domains were less sensitive at predicting cognitive decline, decline in visual memory was predicted by the pace domain only (β 0.30 ± 0.10, p <.01). Full results of dual task gait characteristics and domain predictors in PD can be found in the appendices **18.0** and **19.0**.

Table 5-4 and **Figure 5-2** summarise the baseline dual task gait predictors of cognitive decline in control subjects. Decline in attention was predicted by rhythm (reduced step time (β -0.17 ± 0.07, p .01) and reduced stance time (β -0.12 ± 0.04, p <.01)) and decline in executive function was predicted by pace (higher swing time SD (β -1.01 ± 0.40, p .01). No gait characteristics predicted either increased fluctuating attention or a decline in visual memory. For controls, only stance time as a predictor of attention improved the fit of the model (χ^2=9.40, p <.01) compared to the base model. For calculated gait domains, decline in attention was predicted by rhythm (β 7.94 ± 3.01, p <.01). Full results of dual task gait characteristics and domain predictors in controls can be found in the appendices; **20.0** and **21.0.**

5.3.4 Dual task gait vs. global cognition as a predictor for cognitive decline

As described in chapter 4, MoCA was a significant predictor of decline in attention ($p<.01$) but was unable to predict increased fluctuating attention ($p=.04$) or visual memory ($p=.15$) in PD during single task gait. For further details see **Table 4-7**.

A number of dual task gait characteristics provided a stronger predictor of fluctuating attention and visual memory decline compared to baseline MoCA. Step velocity (X^2 12.10, $p=<.01$), step length (X^2 11.76, $p=<.01$) and swing time SD (X^2 8.52, $p=.01$) from the pace domain improved the fit of the model when combined with MoCA and remained significant whereas MoCA did not. In comparison, step time variability did not improve the fit of the model for fluctuating attention (X^2 7.70, $p=.02$). For stance time as a predictor of fluctuating attention gait improved the model fit and remained significant (X^2 9.80, $p=<.01$). However, both stance time asymmetry and step width did not improve the fit of the model for fluctuating attention (X^2 7.34, $p=.03$ and X^2 6.90, $p=.03$ respectively). For decline in visual memory, both step velocity and step length improved the fit of the model (X^2 9.65, $p=<.01$ and X^2 11.25, $p=<.01$ respectively). In addition step stance variability also improved the fit of the model for decline in visual memory (X^2 9.71, $p=<.01$).

Table 5-3 - Linear mixed effects models for DT gait predictors of cognitive decline in PD.

Cognitive Domain	Cognitive Assessment	Predictor Domain	Predictor Characteristic	Regression Coefficients			
				β	*SE*	*T*	*P*
Attention	CRT	*Variability*	Step Time SD x Session	42.54	16.30	2.61	**0.01**
Fluctuating Attention	CRTCV	*Pace*	Step Velocity x Session	-3.86	1.24	-3.11	**<0.01**
			Step Length x Session	-8.37	2.69	-3.12	**<0.01**
			Swing Time SD x Session	2.83	0.89	3.17	**<0.01**
		Variability	Step Time SD x Session	2.35	0.82	2.87	**0.01**
		Rhythm	Stance time x Session	0.01	<0.01	2.93	**<0.01**
		Asymmetry	Stance Time Asy x Session	0.36	0.14	2.55	**0.01**
		Postural control	Step Width x Session	27.70	8.86	3.13	**<0.01**
Visual Memory	SRM	*Pace*	Step Velocity x Session	1.36	0.52	2.60	**0.01**
			Step Length x Session	3.00	1.13	2.65	**<0.01**
		Variability	Stance Time SD x Session	-0.76	0.30	-2.51	**0.01**

[CRT= choice reaction time, CRTCV= choice reaction time coefficient of variation, SRM= spatial recognition memory]

Table 5-4 - Linear mixed effects methods for DT gait predictors of cognitive decline in control.

				Control			
				Regression Coefficients			
Cognitive Domain	**Cognitive Assessment**	**DT Predictor Domain**	**DT Predictor Characteristic**	*β*	*SE*	*T*	*P*
Attention	CRT	*Rhythm*	Step Time x Session	-0.17	0.07	-2.57	**0.01**
		Rhythm	Stance Time x Session	-0.12	0.04	-2.72	**<0.01**
Executive Function	OTS	*Pace*	Swing Time SD x Session	-1.01	0.40	-2.54	**0.01**

[CRT= choice reaction time, OTS= one touch stockings]

Global cognition

PD

Controls

Executive Function

Language

Visual Memory

Visuospatial

Attention/ Fluc Attention

Memory

PACE

VARIABILITY

RHYTHM

ASYMMETRY

POSTURAL CONTROL
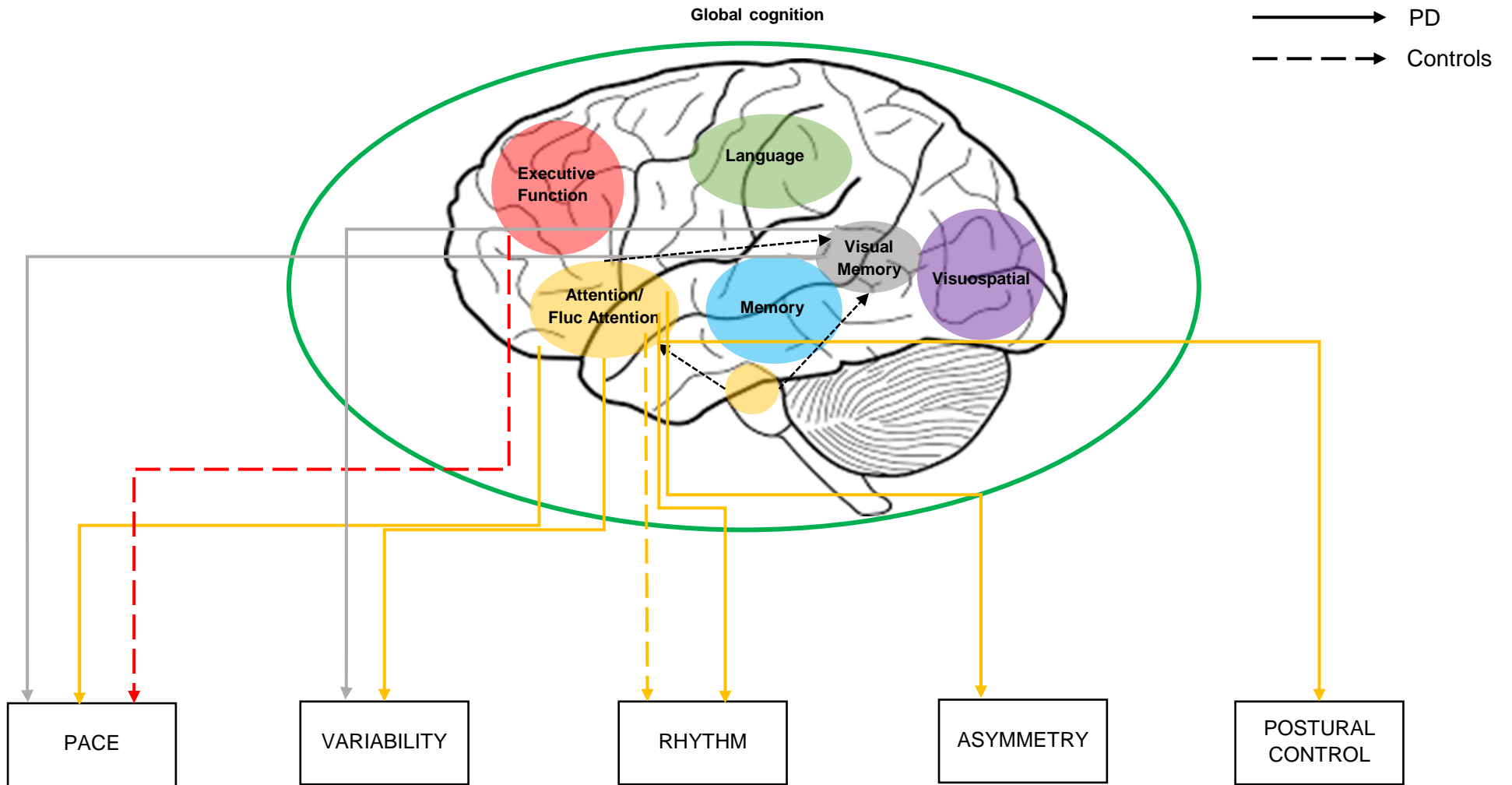
Figure 5-2. Map of dual task associations adapted from Morris et al, 2016 for longitudinal gait and cognition associations in PD and controls. Black dotted lines signify attentional influence on visual memory.

5.4 Discussion

This chapter extended results from chapter 4 by exploring gait characteristics under dual task as predictors for specific domains of cognitive decline. Prior to this study, there was insufficient evidence to decipher whether gait under more challenging conditions improved the accuracy of prediction of cognitive decline in PD. Importantly, knowledge of dual task gait as a prognostic marker has been extended by taking a comprehensive measurement approach which has highlighted the specificity of gait to cognitive decline. The results demonstrate that discrete gait characteristics under dual task predict decline in a number of cognitive domains. However, contrary to the hypothesis, dual task gait showed similar predictive ability to single task. Reasons and implications for these findings will be discussed below.

5.4.1 Dual task gait predicts decline in specific cognitive domains

As hypothesised, selective gait characteristics under dual task were able to predict cognitive decline in specific cognitive domains. Compared to single task, gait predictors stemmed from a wider range of gait domains. Slower pace (represented by slower step velocity, shorter step length and higher swing time SD), increased gait variability (represented by step time variability) faster rhythm (represented by step stance time), increased asymmetry (represented by stance asymmetry) and more unstable postural control (represented by increased step width) predicted an increase in fluctuating attention. In addition, increased gait variability (represented by step time variability) predicted decline in attention. Furthermore, slower pace (represented by slower velocity and shorted step length) and more unstable postural control (represented by increased step width variability) predicted decline in visual memory. Similar to chapter 4 there have been no previous studies exploring dual task gait as a predictor for cognitive decline in PD which makes comparison and interpretation of findings challenging.

A number of cross-sectional studies have explored associations between gait and cognition under dual task, from this, parallels can be drawn with the findings here. A number of cross-sectional studies have identified pace (Rochester *et al.*, 2004; Lord *et al.*, 2010; Plotnik *et al.*, 2011; Kelly *et al.*, 2012) and variability (Yogev *et al.*, 2005; Lord *et al.*, 2011; Plotnik *et al.*, 2011; Kelly *et al.*, 2012) under dual task

to be associated with frontal cognitive assessments, mainly attention and executive function- complementing the findings here. However, similar to single task findings, this is not specific to PD pathology (Ble *et al.*, 2005; Holtzer *et al.*, 2006; Springer *et al.*, 2006). In disagreement with this literature, baseline cross-sectional results from the dual-task protocol of ICICLE-gait did not find the same associations with attention and executive function (Rochester *et al.*, 2014). Reasons for this could be twofold. First, perhaps the cohort was too early in pathology to detect dual task deficit to the same degree as previous studies with later-stage PD participants. Second, results may have been desensitised by the use of a dual task paradigm tailored to each individual's cognitive capacity, which is not done in other studies. However, within the current study use of the same tailored dual task paradigm demonstrated dual task gait was sensitive to decline in cognition. This suggests that, similar to single task (Mielke *et al.*, 2013), specificity between gait-cognition associations and predictors are distinct.

Dual task studies exploring rhythm and asymmetry, much like single task, are less abundant than those assessing pace. Deficits in rhythm of gait have been reported in both older adults and people with PD under dual task in the majority of studies (Al-Yahya *et al.*, 2011), with greater deficit identified in PD (O'Shea *et al.*, 2002). In comparison, deficits in asymmetry have been noted in PD but not older adults under dual task (Yogev *et al.*, 2006). However, Yogev *et al.* (2006) did not find an association between dual task asymmetry with either attention or executive function. The authors concluded this may be due to individual response of resource allocation during dual tasking (Yogev *et al.*, 2006). Our findings may demonstrate differences in associations and predictors once again, or possibly due to the sensitive computer battery assessments used here to measure attention and executive function (Wesnes *et al.*, 1999).

Postural control as a predictor of cognitive decline complements previous findings from the ICICLE-Gait study. Previously using this dual task paradigm significant dual task gait deficit was seen for characteristics of postural control in PD compared to control subjects (Rochester *et al.*, 2014). Other than the study by Rochester *et al.* (2014) associations of cognition and gait related postural control are limited. However, parallels can be drawn from static postural control tasks which demonstrate deficits under dual task conditions (Morris *et al.*, 2000;

Marchese *et al.*, 2003), most likely related to prefrontal cortex control (Mahoney *et al.*, 2016). Previous associative work in older adults has recognised a relationship between postural control and attention (Lord *et al.*, 2013b; Martin *et al.*, 2013; Lord *et al.*, 2014), however postural control was not sensitive to attentional decline in older adults in this study suggesting this is driven by PD pathology.

Parallels once again can be drawn from longitudinal cohorts of older adults and cognitive impairment but studies remain small in number. A study by Chong *et al.* (2013) assessed single task and dual task gait under a number of dual task paradigms in subjects who did and did not convert to MCI. Chong *et al.* (2013) identified dual task performance was significantly worse in MCI converters under one dual task paradigm. In agreement with findings from this study, this suggests that dual task gait may be sensitive to future cognitive decline, however it must be noted the study contained small numbers and therefore results should be interpreted with caution. The study by Deshpande *et al.* (2009) assessed single task, dual task and fast walking in a cohort of 660 older adults but only found fast gait speed to predict cognitive decline. It is important to note that the single task findings by Deshpande *et al.* (2009) contradict the majority of the literature including those that only assessed global cognition (Morris *et al.* (2016), see chapter 2). This may indicate a difference in their cohort, e.g. they only followed the cohort for three years, a shorter duration than most studies in older adults. The authors hypothesised that dual task gait would be the most sensitive condition to cognitive decline and were surprised by their findings. It was reasoned that dual tasking may actually represent cognitive flexibility as opposed to assessing cognitive capacity. Over and above these findings, the results of fast walking as a predictor are interesting. Fast walking conditions increase cortical demand to the task, similar to cueing for gait in PD. Deshpande *et al.* (2009) identified that those who were in the slowest quartile under fast walking conditions were more likely to decline cognitively. This was identified after controlling for factors of age, BMI and depression suggesting that those who were unable to achieve fast speed had reduced cognitive capacity. It would be interesting to explore the predictive ability of fast gait in the ICICLE-Gait cohort,

considering the reduced attentional resources in PD it would be hypothesised that fast gait would be a sensitive predictor of cognitive decline.

5.4.2 Dual task compared to single task as a predictor

It was hypothesised that dual task would provide a better predictor than single task conditions and this hypothesis can be accepted in part. Characteristics of pace, variability and postural control were independent predictors but in addition under dual task characteristics of rhythm and asymmetry proved significant independent predictors.

A number of gait characteristics under both conditions predicted an increase in fluctuating attention and visual memory but there was minimal difference in strength of predictors. For example step velocity (single task; β -4.05±1.34, p=<.01 and dual task; β -3.86 ± 1.24, p=<.01) and step length (single task; β -8.64±2.86, p=<.01 and dual task; β -8.37 ± 2.69, p=<.01) were both significant independent predictors. Furthermore, both characteristics improved the accuracy of prediction compared to the base model under both conditions (e.g. step length: single task; X^2 11.22, p=<.01 and dual task; $X^2$11.76, p=<.01). On the other hand, characteristics of rhythm and asymmetry became independent predictors under dual task. In particular, the predictive ability of asymmetry may be of importance. Asymmetry, unlike other gait measures, is not affected under dual task in older adults (Yogev *et al.*, 2006) suggesting asymmetry is no longer generated subcortically in PD and it is presumed cortical refinement becomes necessary in PD pathology (Yogev *et al.*, 2006). It is plausible that under dual task discrete latent deficits in these domains emerge providing an early marker of cognitive deficit which are specific to PD. This theory supports findings from older adults in this study for whom asymmetry did not prove to be a significant predictor, however it remains speculative due to limited work measuring asymmetry in older adults and other dementia subtypes (Morris *et al.*, 2016). Thus, further work in PD and other cohorts is needed to validate this notion.

The marginal differences between task conditions, although only speculative, may be down to the dual task paradigm used in this study. The paradigm used in the ICICLE-Gait appears to be less sensitive to dual task deficit compared to other paradigms (Yogev *et al.*, 2005; Hollman *et al.*, 2007; Kelly *et al.*, 2012).

However, by tailoring task difficulty to each individual rather than conducting a standardised task allows for avoidance of over-estimation of dual task interference and allows for true dual-task interference to be determined. Protocols in other pathologies have tailored levels of task demand and identified gait deficits compared to single task conditions (Hamilton *et al.*, 2009). It would be interesting to see if dual task gait using a standardised protocol proved more sensitive to cognitive decline over time in PD.

5.4.3 Gait under both single and dual task predicted decline in the same cognitive domains

Increased fluctuating attention and a decline in visual memory was predicted by gait characteristics from the same domains. Additionally, decline in attention was predicted by one characteristic of pace (step time variability) under dual task.

The predictive ability of gait under dual task for an increase in fluctuating attention and decline in visual memory further emphasises the hypothesis of underpinning pathology discussed in chapter 4, section 4.4.3 and further demonstrated in **Figure 4-2**. This finding suggests a common neural correlate of gait and fluctuating attention of which gait under natural and stressed conditions is sensitive to fluctuating attention decline. Importantly, under dual task, step time variability was able to predict decline in attention. It must be stressed that this characteristic was weaker than predictors of fluctuating attention as it did not significantly improve the fit of the model ($p=.02$). However, step time variability in particular is a gait characteristic that has previously been indicated as sensitive to pathology, including frontal cognitive measures under single (Hausdorff *et al.*, 2001; Sheridan *et al.*, 2003; Beauchet *et al.*, 2012; Henderson *et al.*, 2016) and dual task gait (Mirelman *et al.*, 2011). The fact that those with poorer dual but not single task gait at baseline had significant attentional decline may point to subtle differences in underlying neural correlates of gait and cognition. Depending on the sub-domain of attention, the underpinning mechanisms differ. For example, the cholinergic system is associated with 'lower level' attentional systems (e.g. sustained or orientating attention), whereas the dopaminergic system is thought to underpin more complex 'executive' aspects of attention (Berger *et al.*, 1989; Coull, 1998). This is demonstrated by unaffected sustained attention with intake

of Haloperidol (Berger *et al.*, 1989) indicating the role of other systems. It is plausible that additional neural correlates corresponding to higher attention mechanisms are needed to refine gait in more challenging conditions. This interpretation is only speculative however as no other work has been done and further work in independent cohorts is needed.

In addition to fluctuating attention, decline in visual memory (measured by SRM) was sensitive to both single and dual task gait. As noted previously in chapter 4 it is hypothesised that SRM performance is frontally mediated and therefore reliant on attentional mechanisms. This is depicted by the dashed lines in **Figure 5-2**. Under dual task, one representative of variability (stance time variability) was also sensitive to visual memory decline suggesting that variability in particular relies on cognitive mechanisms under challenging walking conditions. This finding further emphasises the importance of evaluating comprehensive batteries of gait characteristics as well as under different conditions.

5.4.4 Clinical implications

The clinical implications of these findings need to be discussed. If dual task gait does not provide much more sensitivity over single task then only a simple walking assessment is required as a clinical biomarker. This is beneficial for patients as they would not be required to complete a complex assessment during a screening process. In addition, dual task paradigms in the literature are highly variable and as it remains unknown whether different dual task paradigms would provide more sensitive predictors of cognitive decline. Before dual task gait can be utilised as a clinical biomarker, a standardised task would need to be used throughout the patient population.

Neither a titrated or standardised dual task represents real life dual tasking with dual task protocols providing an unnatural stress condition. Possibly observing real life complexity will provide a natural dual task paradigm. Free-living gait (gait in the home and community environment) gives us insight into naturalistic gait patterns that are not impacted by false environmental or attentional manipulation. Free-living gait can now be assessed in habitual environments using BWM. Associations between free-living gait and cognition are starting to emerge in the literature and this will be discussed further in the following chapter (Chapter 6).

5.4.5 Limitations

There are a number of limitations to this study, a number of which were outlined in Chapter 4, section 4.6.6. In addition, this study only assessed one dual task paradigm for which findings have previously differed from the literature. It is possible that the nature of the dual task paradigm used in this study reduced predicative ability. Future work should compare the effect of standardised and titrated tasks on gait and whether one provides a more sensitive predictor of future cognitive decline. Regardless, it can be argued that a dual task paradigm tailored to individual performance provides a better representative of individual ability under stressed conditions.

5.4.6 Conclusions

This chapter has identified dual task gait as a predictor of early cognitive decline in PD, specific to fluctuating attention and visual memory. Assessment of dual task revealed characteristics of additional domains were able to predict decline in attention, increased fluctuating attention and a decline in visual memory. The significance of this will become apparent with the evolution of the cohort to PDD.

Chapter 6 : Gait and cognition in free-living; an exploratory look*

The previous chapters of this thesis have identified that a comprehensive gait assessment is able to predict decline in cognition in PD specific to fluctuating attention and visual memory. However, in order for this biomarker to be transferable into the clinic, measurement needs to become portable and cost-effective. Recently the use of body worn monitors (BWM), such as tri-axial accelerometers, has enabled gait measurement in the free-living environment. This chapter will firstly explore a model of gait in the free-living environment and secondly examine the gait-cognition relationship using BWM both in the laboratory and free-living.

*Section 1 is published in Gait and Posture; Morris et al (2016)

Section 1: A model of free-living gait; a factor analysis in PD

6.1. Overview

As discussed in chapter one, when measuring a large number of gait characteristics covariance is high and in a bid to eliminate redundancy and ease interpretation, conceptual gait models have been developed both in older adults and PD (Verghese *et al.*, 2007; Hollman *et al.*, 2011; Lord *et al.*, 2013a; Lord *et al.*, 2013b). The model framework which has been used throughout this thesis identified five domains of gait comprising 16 gait characteristics derived from the GaitRite™ system (Lord *et al.*, 2013a) (**Figure 6-1A**). Subsequently, the model has been used to demonstrate associations of gait with age, gender and cognition (Lord *et al.*, 2013a; Lord *et al.*, 2014). In addition, this thesis has used the structure of the conceptual gait model to predict changes in cognition.

To date neither laboratory nor free-living gait characteristics derived from BWM have been applied to a conceptual framework, limiting their utility. Differences occur in gait metrics when comparing GaitRite™ with BWM as the latter measures continuous motion and the former measures discrete events (separate foot-falls). As a result, BWM demonstrate increased sensitivity to asymmetry and variability characteristics (Del Din *et al.*, 2016c). In addition, BWM derive 14 of the previous 16 characteristics due to limitations measuring step width and step width variability with single tri-axial accelerometers (Del Din *et al.*, 2016c). Therefore in the first section of this chapter, a conceptual gait model using a BWM both in a controlled laboratory environment and in free-living is explored. It is hypothesised, due to differences in measurement tools, free-living characteristics will load differently onto a conceptual gait model. The aims of this short study were to i) explore a gait model using a BWM in controlled and free-living environments in older adults and PD, and ii) compare to our previous GaitRite™ derived model.

6.2 Specific methods

6.2.1 Participants

Subjects with idiopathic PD were recruited from the ICICLE-Gait study. PD was diagnosed according to UK PD brain bank criteria. Participants were excluded if they presented with memory impairment (MMSE ≤24), dementia with Lewy bodies, Parkinson's plus syndrome and poor English. PD participants were tested three years post diagnosis. Age matched controls were recruited that were >60 years, able to walk independently and had no significant cognitive impairment, mood or movement disorder. The study was approved by the Newcastle and North Tyneside research and ethics committee.

6.2.2 Clinical Assessment

Age, sex and body mass index (BMI) were recorded for all participants. Disease severity was measured using the Movement Disorders Society Unified Parkinson's disease rating scale part III (MDS-UPDRS III).

6.2.3 Gait Assessment

Participants were asked to wear a single tri-axial accelerometer BWM (AX3; Axivity, York, UK; 100Hz, ±8g) located at the fifth lumbar vertebra (L5). During controlled assessment, participants walked for two minutes around a 25m circuit at preferred pace in a laboratory. The BWM was attached with a hydrogel adhesive (PALStickies, PAL Technologies, Glasgow, UK) and Hypafix (BSN Medical Limited, Hull, UK). For free-living assessment, participants wore the BWM continuously for 7 days (Godfrey *et al.*, 2014b). See **Appendix 8.0** for instructions.

6.2.4 Data Processing

Recorded signals were stored locally on the sensor's internal memory and downloaded on completion of assessment. Raw acceleration data for controlled and free-living assessments were analysed using a bespoke MATLAB® (Version 2015a) program, further details of controlled and free living data processing are detailed in (Del Din *et al.*, 2016c) and (Del Din *et al.*, 2016a) respectively. 14

previously validated spatiotemporal gait characteristics were quantified (Del Din *et al.*, 2016c) (**Figure 6-1**).

6.2.5 Statistical analysis

Free-living data were screened so that full 7 day data were included in the analysis only. Data were inspected for outliers with histograms and boxplots. Student t-tests and Chi-squared (X^2) tests were used to compare demographic data. Principle component analysis (PCA) was conducted to identify independent gait domains in controlled and free-living environments. A varimax rotation was applied to derive orthogonal factor scores with the minimum eigenvalue for extraction set at 1. Items which met a minimum loading of 0.6 were considered significant. Loading value was increased from previous work due to fewer participants (Field, 2013; Lord *et al.*, 2013b).

6.3 Results

6.3.1 Participants

PD and control participants were matched for age (69.8±9.74, and 72.34 years respectively, p=.068) and BMI (27.23±5.10 and 27.23±5.61, p=.998 respectively). The PD group had significantly fewer females than controls (46M & 21F, versus 49M & 54F, p<.01). PD participants presented with a mean (SD) MDS-UPDRS score of 37.18±11.98. PD participants scored significantly lower on the MoCA (p<.01), were significantly lower in mood (p<.01) and had significantly reduced balance confidence (p<.01).

Table 6-1 - Demographic data of PD and control participants

Demographic	PD (*n*=67)	Control (*n*=107)	*p*
Age (years)	69.83 ± 9.74	72.34 ± 6.74	.068
Sex (M & F)	46M & 21F	49M & 54F	**.007[ł]**
BMI	27.23 ± 5.10	27.23 ± 5.61	.998
MoCA	26.24 ± 3.49	27.53 ± 2.31	**.009**
NART	114.91 ± 11.58	117.54 ± 7.83	.107
GDS	2.57 ± 2.22	1.34 ± 2.24	**.001**
ABC (%)	80.28 ± 20.89	91.18 ± 13.82	**<.001**
UPDRS III	37.18 ± 11.98	-	-

[ł = X^2]

6.3.2 Controlled conditions

A total of 103 control and 67 PD participants completed laboratory based assessment. The mean total number of steps performed by PD and control participants was 226 ± 22 and 237 ± 23 respectively.

Fourteen gait characteristics were entered into the PCA yielding four factors (pace, variability, rhythm and asymmetry) and accounted for 84.84% and 88.43% of variance for control and PD participants respectively(pace; 17.18%, 13.29%, variability; 26.58%, 32.15%, rhythm; 22.27%, 21.38%, asymmetry; 18.82%, 21.67% for controls and PD respectively). All item loadings were >0.6 except for step length asymmetry in both groups with cross-loading evident for variability in controls (**Table 6-2** and **Table 6-3, Figure 6-1B**).

6.3.3 Free-living conditions

Ninety-nine controls and 64 PD participants completed free-living assessment. Ten controls and 6 PD participants did not wear the BWM for the amount of time specified and were removed from the analysis. Thus, a total of 89 controls and 58 PD participants were included.

The mean total number of steps per day completed by PD and control participants were 11899 ± 5183 and 13434 ± 4393 respectively. Fourteen gait characteristics were entered into the PCA yielding four factors in both groups (pace, variability, rhythm and asymmetry) and accounted for 90.00% and 93.03% of total variance for control and PD respectively (pace; 13.60%, 13.49%, variability; 22.08%, 21.10%, rhythm; 25.53%, 27.92%, asymmetry; 28.79%, 30.52% for control and PD respectively). All item loadings were >0.6 with cross-loading evident for variability in both groups (**Table 6-4** and **Table 6-5, Figure 6-1C**).

Table 6-2 - Item loadings of the principle component analysis for controlled (laboratory) BWM gait in controls.

Item	Pace	Rhythm	Asymmetry	Variability
Pace				
Step Velocity	**0.936**	0.201	-0.100	-0.024
Step Length	**0.845**	-0.422	-0.143	-0.082
Step Length Asymmetry	**0.578**	-0.203	0.231	0.171
Rhythm				
Step Time	-0.100	**0.970**	0.115	0.152
Stance Time	-0.039	**0.938**	0.133	0.052
Swing Time	-0.161	**0.856**	0.074	0.245
Asymmetry				
Step Time Asymmetry	0.126	0.118	**0.808**	-0.039
Stance Time Asymmetry	-0.076	0.089	**0.956**	0.071
Swing Time Asymmetry	-0.056	0.085	**0.965**	0.070
Variability (SD)				
Step Time	-0.038	0.228	-0.024	**0.922**
Stance Time	-0.074	0.244	0.025	**0.919**
Swing Time	-0.163	0.281	0.039	**0.905**
Step Length	0.400	-0.079	0.079	**0.782**
Step Velocity	0.473	-0.280	0.080	**0.679**
% Variance (84.84%)	*17.18%*	*22.27%*	*18.82%*	*26.58%*

Table 6-3 - Item loadings of the principle component analysis for controlled (laboratory) BWM gait in PD.

Item	Pace	Rhythm	Asymmetry	Variability
Pace				
Step Velocity	**0.974**	0.108	-0.132	0.131
Step Length	**0.888**	-0.415	-0.143	0.010
Rhythm				
Step Time	-0.065	**0.951**	0.052	0.285
Stance Time	-0.067	**0.880**	0.152	0.192
Swing Time	-0.050	**0.855**	-0.055	0.332
Asymmetry				
Step Time Asymmetry	-0.035	-0.048	**0.927**	0.104
Stance Time Asymmetry	-0.112	0.074	**0.968**	0.089
Swing Time Asymmetry	-0.093	0.098	**0.961**	0.099
Step Length Asymmetry	-0.184	0.352	**0.405**	0.251
Variability (SD)				
Step Time	-0.027	0.222	0.196	**0.922**
Stance Time	-0.048	0.269	0.129	**0.922**
Swing Time	-0.065	0.275	0.126	**0.920**
Step Length	0.133	0.227	0.058	**0.889**
Step Velocity	0.177	0.098	0.042	**0.909**
% Variance (88.43%)	*13.29%*	*21.38%*	*21.67%*	*32.15%*

Table 6-4 - Item loadings of the principle component analysis for free-living BWM gait for controls.

Item	Pace	Rhythm	Asymmetry	Variability
Pace				
Step Velocity	**0.797**	-0.054	-0.109	-0.156
Step Length	**0.970**	-0.558	0.119	-0.027
Rhythm				
Step Time	-0.110	**0.982**	0.072	0.120
Stance Time	-0.065	**0.950**	0.166	0.132
Swing Time	-0.191	**0.936**	-0.033	0.136
Asymmetry				
Step Time Asymmetry	-0.104	0.085	**0.968**	0.099
Stance Time Asymmetry	-0.082	0.043	**0.968**	0.115
Swing Time Asymmetry	-0.082	0.096	**0.915**	0.117
Step Length Asymmetry	0.227	-0.053	**0.728**	0.047
Variability (SD)				
Step Time	-0.251	0.358	0.493	**0.704**
Stance Time	-0.241	0.280	0.525	**0.711**
Swing Time	-0.229	0.448	0.451	**0.682**
Step Length	-0.100	0.228	-0.070	**0.784**
Step Velocity	0.123	-0.193	0.033	**0.946**
% Variance (90.00%)	*13.60%*	*25.53%*	*28.79%*	*22.08%*

Table 6-5 - Item loadings of the principle component analysis for free-living BWM gait in PD.

Item	Pace	Rhythm	Asymmetry	Variability
Pace				
Step Velocity	**0.991**	-0.024	-0.016	0.014
Step Length	**0.789**	-0.562	0.122	0.140
Rhythm				
Step Time	-0.088	**0.974**	0.160	0.114
Stance Time	-0.067	**0.927**	0.248	0.166
Swing Time	-0.131	**0.945**	0.014	0.079
Asymmetry				
Step Time Asymmetry	-0.002	0.130	**0.959**	0.209
Stance Time Asymmetry	-0.029	0.130	**0.967**	0.140
Swing Time Asymmetry	-0.060	0.101	**0.950**	0.119
Step Length Asymmetry	0.274	0.058	**0.780**	0.240
Variability (SD)				
Step Time	-0.165	0.463	0.522	**0.664**
Stance Time	-0.182	0.465	0.533	**0.624**
Swing Time	-0.215	0.542	0.435	**0.660**
Step Length	0.088	0.226	0.073	**0.856**
Step Velocity	0.242	-0.261	0.231	**0.869**
% Variance (93.03%)	*13.49%*	*27.92%*	*30.52%*	*21.10%*
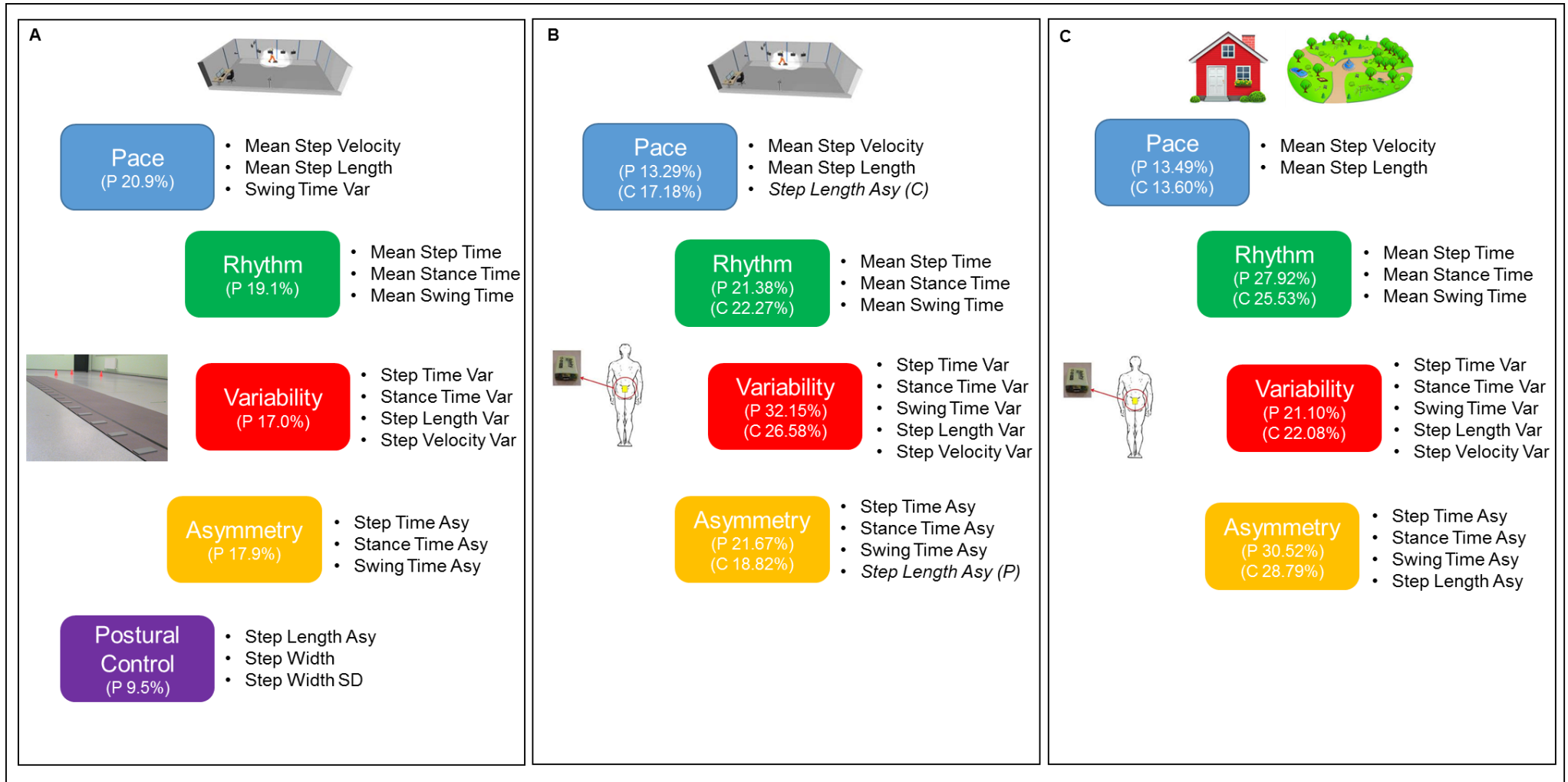
Figure 6-1 - Conceptual gait models derived A) previously using a pressure-sensor walkway in the laboratory B) with BWM in controlled conditions and C) with BWM in the free-living environment.(C) = control only, (P) = PD only

6.4 Discussion

This is the first study to explore conceptual gait models with BWM from controlled and free-living gait characteristics. Furthermore, the models remained stable compared to our previously published model derived from laboratory based GaitRite™ data (Lord *et al.*, 2013a).

When creating the model, four discrete gait domains were identified under both conditions (pace, rhythm, variability and asymmetry), which showed that the domains are not protocol dependent. Unexpectedly, step length asymmetry loaded onto pace for controls. Previously, gait domains appear more discrete in pathological cohorts than healthy older adults (Lord *et al.*, 2013a); this complements our findings and demonstrates the impact of PD on gait. Interestingly, step length asymmetry loaded onto the asymmetry domain in free-living for both groups. BWM are more sensitive at detecting characteristics of asymmetry (Del Din *et al.*, 2016c), but in addition, perhaps due to environment complexity, asymmetry increased in free-living (Del Din *et al.*, 2016a) thereby emphasising it.

The postural control domain was unable to be replicated, which in the earlier model had been expressed by three gait characteristics (step width, step width variability and step length asymmetry). Step width and step width variability cannot be measured using our BWM, and their omission from the PCA altered the factor loading for step length asymmetry. This is a limitation as postural control is a critical aspect of gait. Future algorithm development is underway for measurement of these characteristics with BWM. However, BWM do provide a nuanced approach to postural control measurement (Lowry *et al.*, 2009) which could be used in addition to our gait model for simplistic clinical interpretation.

Although loading of variability characteristics demonstrated instability compared to other domains, in contrast to our previous model, characteristics loaded onto one domain. Reasons may be twofold: similarly to asymmetry, BWM analysis appears to be more sensitive to variability characteristics compared to GaitRite™(Del Din *et al.*, 2016c) and; measures of variability become more accurate with increased step count (Galna *et al.*, 2013).

This work shows stability of the gait model when using BWM derived characteristics. This is an important finding to inform future clinical research with the progression of gait assessment into free-living.

Section 2: The gait-cognition relationship in free-living

Following on from section one, the conceptual framework of gait in free-living will now be applied to data from the ICICLE-Gait study to explore gait-cognition associations in controlled and free-living environments.

6.5 Overview

Although gait measurement in the laboratory provides a controlled and detailed assessment it also poses a number of limitations. The process is expensive, requiring complex equipment and highly trained staff, and in addition equipment can be cumbersome. Thus, laboratory gait assessment provides a challenge for widespread clinical use. Furthermore, laboratory gait measurement is usually a one-off assessment, leading to only a snapshot of a participant's ability. This is particularly problematic in disorders such as PD for which there are often fluctuations in symptoms according to medication status.

Gait assessment environment can also play a factor in participant performance. In particular, the relationship between attention and gait is strong in data derived from laboratory settings (Morris *et al.*, 2016). This association may be derived from primed attention during laboratory or clinical setting assessments leading to an improved performance compared to the participant's norm. This is often termed the 'Hawthorne effect' in which performance alters under overt evaluation compared to covert evaluation (Robles-García *et al.*, 2015). This has been demonstrated in PD in which differences in gait using the instrumented timed up and go (iTug) in controlled and habitual environments were identified (Zampieri *et al.*, 2011). Currently, there is limited research on the effect of environment on a comprehensive battery of gait characteristics and the effect this has on the gait-cognition relationship.

A number of studies have explored gait and cognition associations in the free-living. In older adults, Kaye *et al.* (2012) used an infra-red motion system for four weeks in the home allowing for continuous testing conditions. Kaye *et al.*

measured the mean and variability of number of walks per day and walking speed and found associations between number of daily walks and mean speed with global cognition as well as mean speed with attention and visuospatial function. Using the same device, gait in the home was measured as a predictor for cognitive decline in participants with MCI (Dodge *et al.*, 2012). Dodge *et al.* (2012) found that those with a slower gait speed and increased variability in walking speed (average, calculated weekly) were more likely to develop non-amnestic MCI. Both these studies demonstrate the gait-cognition relationship remains evident in habitual environments. However, the studies pose limitations in that only global gait measurements were assessed and walking bouts were only measured at one indoor location.

Gait and cognition associations in free-living are likely to reflect environment context. For example, free-living data contains both short bouts of dual tasking (e.g. carrying objects whilst walking in the home) and long periods of steady state walking (e.g. walking through the park). To reflect this, ambulatory activity can be analysed using ambulatory bouts (AB) which provide gait characteristics for different bout lengths e.g. short bouts (10-20 seconds) and longer bouts (≥120 seconds). One recent publication assessed gait during AB ≥60 seconds using a BWM for a three day period and explored associations with cognition (Weiss *et al.*, 2015). The study found associations with gait and postural control with global cognition, attention and executive function. Specifying AB over 60 seconds poses limitations as gait characteristics differ according to bout length (Del Din *et al.*, 2016a) and very few AB over 60 seconds are completed in people with PD, thus leading to significant data loss (Del Din *et al.*, 2016a). This limits interpretation of the gait-cognition relationship in free-living and to date associations have not been explored in shorter AB.

This exploratory study aimed to i) explore gait-cognition associations using a BWM in relation to protocol i.e. laboratory v's free-living conditions and ii) explore the effect of short versus long AB length on gait-cognition associations in PD. Although this study is exploratory, it is hypothesised that i) gait-cognition associations will be more evident in the laboratory setting due to primed attention and ii) gait and cognition associations will be more evident in shorter AB due to the likelihood of increased environment complexity.

6.6 Specific methods

6.6.1 Participants

PD participants were recruited from the ICICLE-Gait study as previously described in chapter 3. This exploratory study was of cross-sectional design at the 36 month assessment (three years post diagnosis). Age, sex and height were recorded for all participants. Premorbid intelligence was assessed using the National Adult Reading Test (NART) (Nelson and O'Connell, 1978). PD specific assessments included; disease severity using the Movement Disorders Society Unified Parkinson's disease rating scale (MDS-UPDRS) (Goetz *et al.*, 2008) (**Appendix 3.0**) and Hoehn and Yahr scale (Hoehn and Yahr, 2001) (**Appendix 4.0**).

6.6.2 Neuropsychological assessment

A comprehensive battery of neuropsychological assessments examined seven domains of cognition; *global cognition* using the MoCA, *working memory* using the Wechsler forward digit span (Wechsler, 1958), *attention* using the mean score of simple reaction time (SRT), digit vigilance (DV) and choice reaction time (CRT) from the cognitive drug research battery (CDR), *fluctuating attention* using the coefficient of variance (CV) of the SRT, DV and CRT from the CDR, *executive function* using the one touch stockings (OTS) from the Cambridge Neuropsychological Test Automated Battery (CANTAB*), visual memory* using pattern recognition memory (PRM) and spatial recognition memory (SRM) from the CANTAB and *visuospatial* using the intersected pentagons test. For further details see chapter 3, section 3.4.

6.6.3 Gait assessment and outcomes

Fourteen gait characteristics were assessed representing four domains of gait derived from the conceptual framework in section 1 (**Figure 6-1**) using the BWM in controlled and free-living environments. Gait characteristics represented domains of pace (step velocity, step length), rhythm (step time, stance time, swing time), variability (step time SD, stance time SD, swing time SD, step length SD, step velocity SD) and asymmetry (step time asymmetry, stance time

asymmetry, swing time asymmetry, step length asymmetry). Firstly, gait laboratory data was collected under continuous walking conditions (as described in section 6.2.3) using a BWM positioned at the fifth lumbar vertebrae (L5). Secondly, to examine gait in the free-living participants wore the BWM positioned at L5 as described in section 6.2.3. Free-living data was collected over 7 days with data extracted as above in section 6.6.4. Free-living gait characteristics for a short and longer AB were also determined.

6.6.4 Data processing

BWM data was processed using the same stages as described in section 6.1.2. Additional AB data was also derived. Individual AB were extracted using MATLAB® with AB detected by applying selective thresholds on the standard deviation and magnitude vector of triaxial accelerations, as in previous work (Lyons *et al.*, 2005; Del Din *et al.*, 2016a). The fourteen gait characteristics as depicted in **Figure 6-1** were evaluated for a short and long AB selected according to previous work (Del Din *et al.*, 2016a); 10s-≤20 secs and ≥ 120 secs.

6.6.5 Data Analysis

All statistical analysis was carried out using SPSS v.21. Normality of data was first inspected with histograms and boxplots and tested using Shapiro-Wilk, all data met normality assumptions. Univariate and bivariate analysis was initially used to describe data.

First, in order to explore associations between gait and cognition for participants in both the laboratory and free-living were partial correlations were conducted controlling for age, gender and NART. To further identify independent gait-cognition associations multivariate linear regression analysis was then performed. Fourteen independent models (for each gait characteristic) were examined for two minute continuous walks in the laboratory and for free-living data for the following conditions; AB of 10s-≤20 secs and AB ≥ 120 secs. For each model, gait characteristics were added as the dependent variable with independent variables added in two stages. Demographics of age, gender and NART scores were entered in the first block for all models using the enter procedure. Cognitive assessments (MoCA, Digit Span, SRT, DV, CRT, SRT CV,

DV CV, CRT CV, PRM, SRM, OTS, Pentagons) that reached significance (p ≤.01) in partial correlations for controlled laboratory conditions and each AB condition (10s-≤s20s and AB≥120s) were entered into the second block using the stepwise procedure. Due to the exploratory nature of this study multiple comparisons were not controlled for, however, in order to reduce the risk of Type II statistical error a stringent threshold of p ≤.01 was used for interpreting results.

6.7 Results

6.7.1 Participant demographics

Tables 6-6 and Table 6-7 display descriptive data for demographic, clinical and cognitive characteristics for all participants. The group contained proportionally more males than females, the majority were classed as 'mild Parkinsonism' (H & Y II) and had an average MoCA score of 26.33 ± 3.34.

Table 6-6 - Demographic and clinical data for participants.

	PD (*N*=55)	
	Mean	*SD*
Age	69.60	9.48
Male/Female (*n*)	35/20	
NART	114.93	10.94
MDS-UPDRS III	36.93	11.50
LEDD	528.02	268.18
H & Y Stage (I-IV)	(I) 1; (II) 49; (III) 5	

[NART= National Adult Reading Test, MDS-UPDRS= Movement Disorders Society Unified Parkinson's disease Rating Scale, LEDD=levodopa equivalent dose, H&Y= Hoehn & Yahr]

Table 6-7 - Descriptive data of cognitive characteristics.

Cognitive domain/test	PD (*N*=55)	
	Mean	SD
Global Cognition		
MoCA	26.33	3.34
Working Memory		
Digit span	5.80	1.21
Attention		
Simple Reaction Time (*ms*)	360.89	88.77
Digit Vigilance (*ms*)	489.15	59.80
Choice Reaction Time (*ms*)	578.56	111.93
Fluctuating Attention		
Simple Reaction Time CV (*%*)	17.72	0.05
Digit Vigilance CV (*%*)	17.05	0.05
Choice Reaction Time CV (*%*)	21.10	0.07
Visual Memory		
Pattern Recognition Memory	20.05	2.90
Spatial Recognition Memory	14.49	1.91
Executive Function		
One Touch Stocking	13.76	5.04
Visuospatial		
Pentagons	1.91	0.40

6.7.2 The effect of protocol

Figure 6-2 shows a radar plot of the fourteen gait characteristics for PD subjects both in the laboratory using the BWM (central dotted line) and in relation to gait characteristics measured in free-living. AB over 120 seconds are represented by the green line. Steady state walking in free-living had significantly higher pace, rhythm and variability compared to the laboratory. Asymmetry was similar to laboratory performance except for step length asymmetry which was significantly reduced in free-living ($p<.01$) (**Appendix 22.0**). One PD participant did not complete any AB ≥120 seconds and therefore was not included in further analysis. Significant associations (partial correlations controlling for age, gender and NART) between gait and cognition are shown in **Table 6-8**. Partial correlations identified that in controlled conditions reduced pace (step velocity) was associated with increased fluctuating attention ($p<.01$), increased asymmetry (step length asymmetry) was associated with poorer attention ($p<.01$) and increased variability was associated with poorer attention (swing time SD, $p<.01$), increased fluctuating attention (swing time SD, $p<.01$) and poorer visual memory

(step time SD, *p*<.01). In free-living partial correlations identified increased stance time asymmetry was associated with increased fluctuating attention (p<.01) and increased step time asymmetry was associated with poorer visual memory (p<.01). All partial correlations can be found in **Appendix 24.0** and **25.0**. Multivariate linear regression results from the laboratory revealed that representatives of pace, asymmetry and variability were associated with cognition (**Table 6-9**). A colour correlation table (**Table 6-12**), adapted from Morris et al, 2016, depicts associations between gait and cognition during laboratory conditions. Slower pace (step velocity) was associated with poorer fluctuating attention (β -.359, *p*=.009) explaining 25.3% of total variance. Increased asymmetry (step length asymmetry) was associated with poorer attention (β .467, *p*=.003) explaining 11.8% of total variance. Finally, increased variability (step time SD (β -.620, *p*=.000), stance time SD (β -.617, *p*=.000 and swing time SD β -.610, *p*=.001)) was associated with poorer visual memory explaining 21.2%, 20.0% and 19.1% of variance respectively. In free-living, only gait characteristics representative of asymmetry were associated with cognition during steady state walking (see **Table 6-9** and for colour correlation see **Table 6-13**). Increased step time asymmetry (β -.414, *p*=.008) was associated with worse visual memory and increased stance time (β .379, *p*=.005) and swing time (β .341, *p*=.010) asymmetry were associated with worse fluctuating attention explaining 9.0%, 17.3% and 19.8% of variance respectively.

Table 6-8 - Partial correlations between gait and cognition in steady state walking in the laboratory and free-living.

Gait Domain	Ax L5 Lab	AB ≥120 sec
Pace	-.393 (.009) FA (SRT CV)	
Rhythm		
Asymmetry	.441 (.003) ATT (DV)	.391 (.005) FA; -.371 (.008) VM
Variability	.400 (.008) ATT (SRT) .434 (.004) FA (SRT CV) -.513 (<.001) VM (SRM)	

[ATT= attention, FA= fluctuating attention, VM=visual memory]. Controlling for age and NART]

Table 6-9 - Multivariate linear regression analysis for independent gait-cognition associations in the laboratory (BWM lab) and free-living AB over 120 seconds (AB ≥120).

	Gait Domain	Gait Characteristic	Cognitive Domain	Cognitive Assessment	β	p	Adjusted R²	ΔR	ANOVA F	ANOVA p
BWM Lab[A]	Pace	Step Velocity	FA	SRT CV	-.359	.009	.253	.124	4.8	.003
	Asymmetry	Step Length Asy	ATT	DV	.467	.003	.118	.194	2.5	.056
	Variability	Step Time SD	VM	SRM	-.620	<.001	.212	.257	4.0	.008
		Stance Time SD	VM	SRM	-.617	<.001	.200	.255	3.8	.010
		Swing Time SD	VM	SRM	-.610	.001	.191	.249	3.7	0.12
AB ≥120[B]	Asymmetry	Step Time Asy	VM	SRM	-.414	.008	.090	.134	2.3	.074
		Stance Time Asy	FA	SRT CV	.379	.005	.173	.137	3.7	.010
		Swing Time Asy			.341	.010	.198	.111	4.2	.005

[For both models age, gender and NART entered in the first step. For model a; SRT, DV, SRT CV and SRM and for model b; SRT CV and SRM were entered on stepwise mode. ATT= attention, FA= fluctuating attention, VM= visual memory].
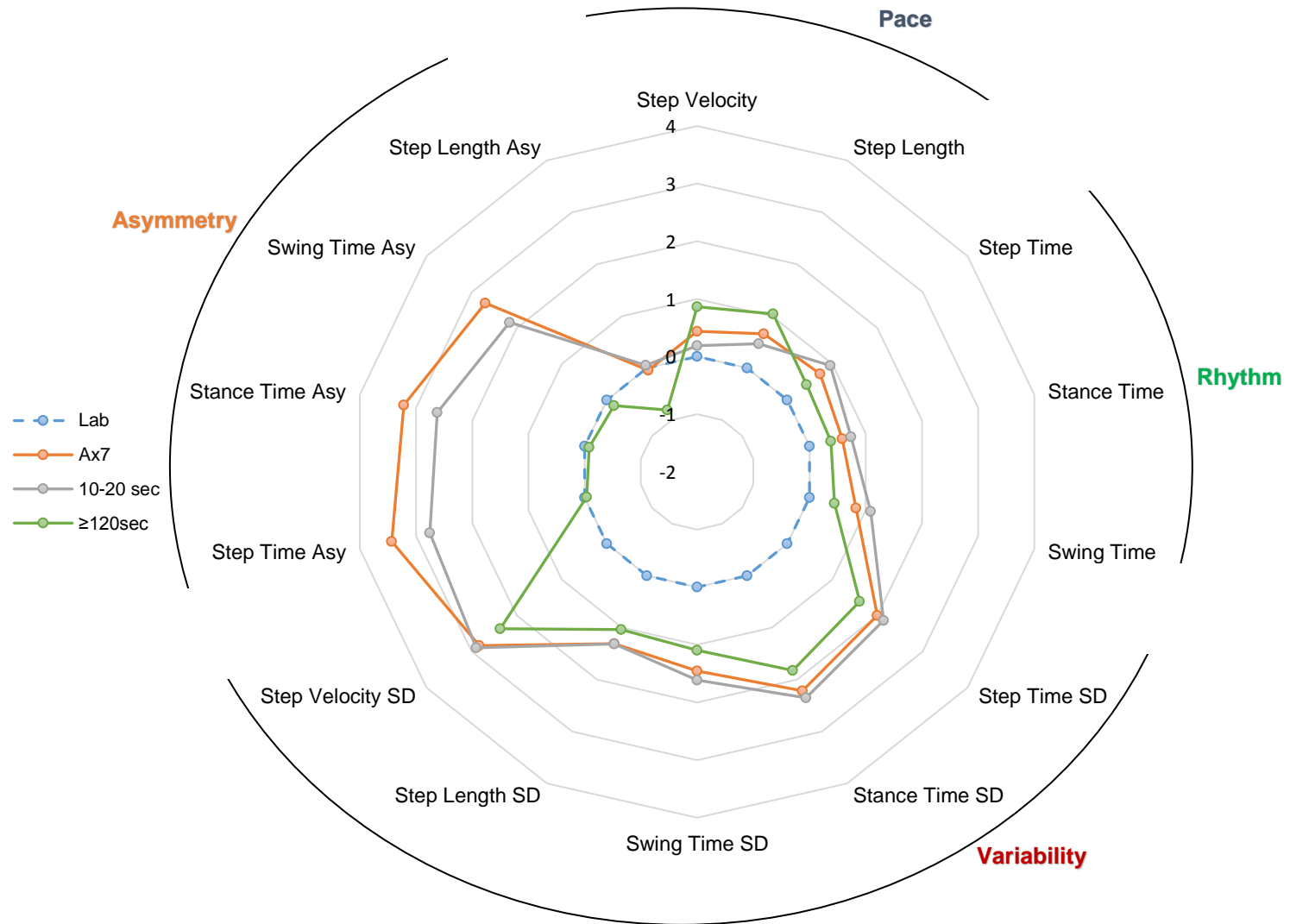
Figure 6-2 - Radar plot illustrating the 14 gait characteristics for AB lengths for people with PD.
[The central dotted line represents data collected from the BWM in the laboratory. Data deviating away from this line represents standard deviations. Free-living data differs from laboratory data for all bouts (Ax7, orange line) and each bout category (grey; AB 10-20 secs and green; AB ≥120 secs)].

6.7.3 The effect of shorter bout length

Compared to longer AB, for shorter AB pace decreased, rhythm increased and both variability and asymmetry increased (**Figure 6-2**). Descriptive data of gait characteristics of the AB lengths can be found in **Appendix 23.0**. Associations (partial correlations) between gait and cognition for shorter AB are shown in **Table 6-10**. All partial correlations can be found in the appendices (**Appendix 26.0**). **Table 6-11** reports the multivariate linear regression analysis of gait and cognition associations for shorter AB, see **Table 6-14** for colour correlation. **Figure 6-3** provides a schematic representation of gait-cognition associations according to AB lengths.

For AB of 10-20 seconds, increased rhythm (stance time) was associated with worse visual memory (β -.454, *p*=.002) explaining 18.0% of total variance. Increased asymmetry (step time asymmetry [β .428, *p*=.002] and stance time asymmetry [β .405, *p*=.004]) was associated with worse attention, explaining 13.9% and 13.4% of total variance respectively. Increased asymmetry (swing time asymmetry [β .427, *p*=.002]) was associated with increased fluctuating attention explaining 17.0% of total variance. Increased variability (step time variability [β -.532, *p*=.000], stance time variability [β -.503, *p*=.000] and swing time variability [β -.503, *p*=.000]) was associated with worse visual memory explaining 31.7%, 34.5% and 28.3% of total variance respectively. Additionally, increased variability was associated with increased fluctuating attention (step time variability [β .331, *p*=.007] and stance time variability [β .412, *p*=.001]).

Table 6-10 - Partial correlations for cognitive assessment and gait characteristics for shorter AB 10-20secs.

	Gait Domain	PD
AB 10-20	**Pace**	
	Rhythm	-.420 (.002) VM
	Asymmetry	.418 (.002) ATT; .431 (.002) FA
	Variability	.414 (.003) FA; -.491 (<.001) VM

[GC= global cognition, ATT= attention, FA= fluctuating attention, VM= visual memory. Table shows most significant associations from the gait characteristics and tests depicted here as domains]

Table 6-11 - Multivariate linear regression analysis for significant independent associations between gait and cognition in free-living for shorter AB 10-20 secs.

	Gait Domain	Gait Characteristic	Cognitive Domain	Cognitive Assessment	β	p	Adjusted R^2	ΔR	ANOVA F	ANOVA p
	Rhythm	Stance Time	VM	SRM	-.454	.002	.180	.162	3.9	.008
	Asymmetry	Step Time Asy	ATT	SRT	.428	.002	.139	.169	3.1	.022
		Stance Time Asy			.405	.004	.134	.151	3.0	.025
AB 10-20		Swing Time Asy	FA	SRT CV	.427	.002	.170	.175	3.7	.010
	Variability	Step Time SD	VM	SRM	-.532	<.001	.317	.229	5.9	<.001
			FA	CRT CV	.331	.007		.101		
		Stance Time SD	VM	SRM	-.503	<.001	.345	.206	6.6	<.001
			FA	CRT CV	.412	.001		.157		
		Swing Time SD	VM	SRM	-.503	<.001	.283	.200	6.2	<.001

[Age, gender and NART entered on first step. SRT, SRT CV, CRT CV and SRM entered on stepwise for second step.]

Table 6-12 Colour correlation table to display cognitive and gait associations in controlled conditions.

Domain/Factor	Global cognition	Working Memory	Attention	Fluctuating Attention	Visual Memory	Executive Function	Visuospatial Function
Pace *Step Velocity* *Step Length*	🔴	🔴	🔴	🟢 [1]	🔴	🔴	🔴
Rhythm *Step Time* *Stance Time* *Swing Time*	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Asymmetry *Step Time Asymmetry* *Stance Time Asymmetry* *Swing Time Asymmetry* *Step Length Asymmetry*	🔴	🔴	🟢 [2]	🔴	🔴	🔴	🔴
Variability (SD) *Step Time SD* *Stance Time SD* *Swing Time SD* *Step Length SD* *Step Velocity SD*	🔴	🔴	🔴	🔴	🟢 [3]	🔴	🔴

[1] *Simple Reaction Time CV,* [2] *Digit Vigilance,* [3] *Spatial Recognition Memory.* **Green indicates an association was found, red indicates no association found.**

Table 6-13 Colour correlation table to display cognitive and gait associations in free-living AB ≥120 seconds.

Domain/Factor	Global cognition	Working Memory	Attention	Fluctuating Attention	Visual Memory	Executive Function	Visuospatial Function
Pace *Step Velocity* *Step Length*	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Rhythm *Step Time* *Stance Time* *Swing Time*	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Asymmetry *Step Time Asymmetry* *Stance Time Asymmetry* *Swing Time Asymmetry* *Step Length Asymmetry*	🔴	🔴	🔴	🟢[1]	🟢[2]	🔴	🔴
Variability (SD) *Step Time SD* *Stance Time SD* *Swing Time SD* *Step Length SD* *Step Velocity SD*	🔴	🔴	🔴	🔴	🔴	🔴	🔴

[1] *Simple Reaction Time CV;* [2] *Spatial Recognition Memory.* **Green indicates an association was found, red indicates no association found.**

Table 6-14 Colour correlation table to display cognitive and gait associations in free-living AB 10-20 seconds.

Domain/Factor	Global cognition	Working Memory	Attention	Fluctuating Attention	Visual Memory	Executive Function	Visuospatial Function
Pace *Step Velocity* *Step Length*	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Rhythm *Step Time* *Stance Time* *Swing Time*	🔴	🔴	🔴	🔴	🟢[1]	🔴	🔴
Asymmetry *Step Time Asymmetry* *Stance Time Asymmetry* *Swing Time Asymmetry* *Step Length Asymmetry*	🔴	🔴	🟢[2]	🟢[3]	🔴	🔴	🔴
Variability (SD) *Step Time SD* *Stance Time SD* *Swing Time SD* *Step Length SD* *Step Velocity SD*	🔴	🔴	🔴	🟢[4]	🟢[1]	🔴	🔴

[1] *Spatial Recognition Memory;* [2] *Simple Reaction Time;* [3] *Simple Reaction Time CV;* [4] *Choice Reaction Time CV.* **Green indicates an association was found, red indicates no association found.**
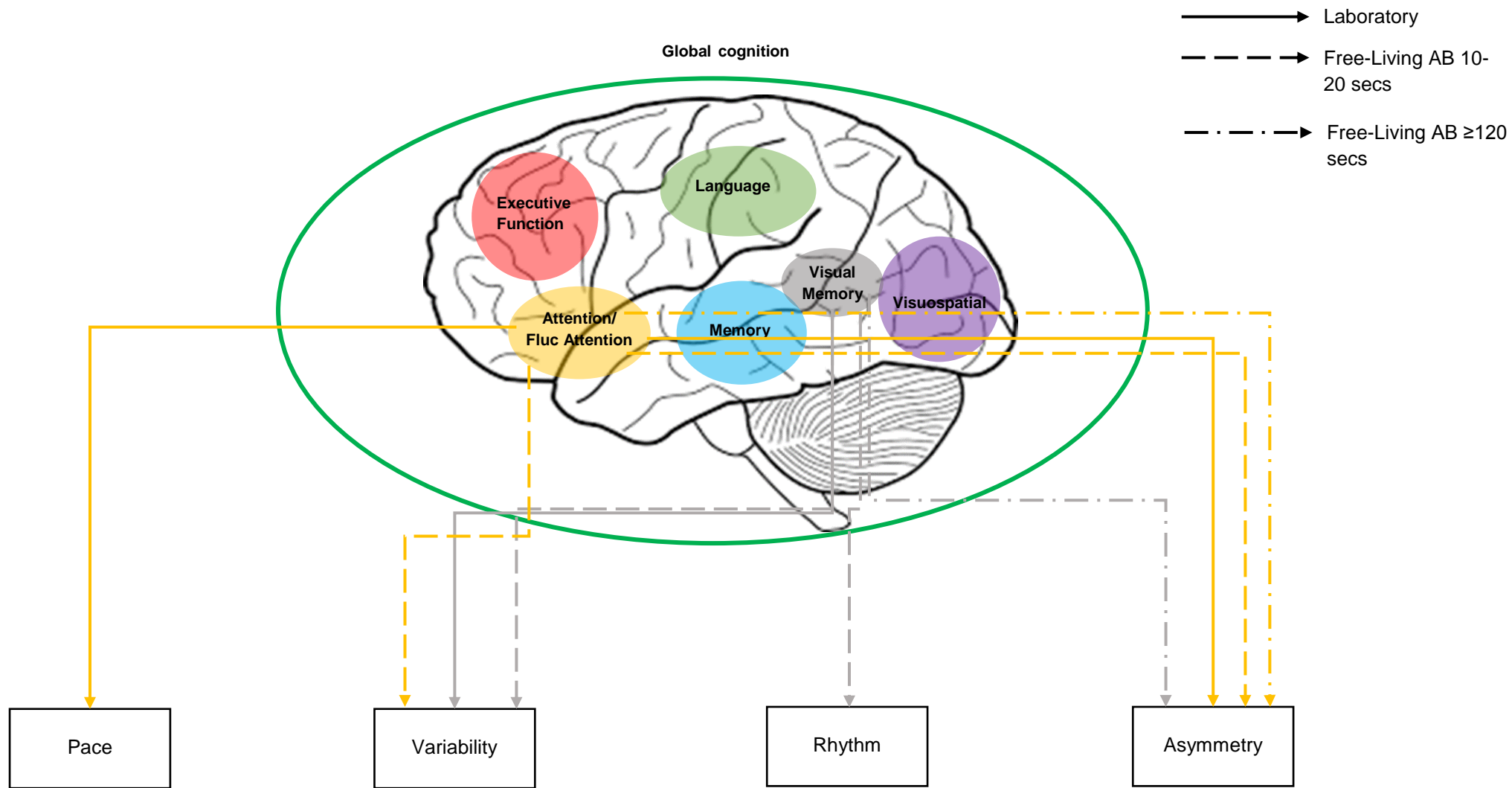
Figure 6-3 - Gait and cognition associtions in free-living for different AB. Figure adapted from Morris et al, 2016.

6.8 Discussion

This exploratory chapter deciphered differences in gait and cognition associations between controlled laboratory and habitual free-living environments. Additionally, gait and cognition associations of short and long ambulatory bout lengths (AB) in the free-living were explored. During steady state walking, cognition was more evidently associated with gait in controlled conditions compared to free-living. Furthermore, shorter AB in free-living showed greater association with cognition compared to longer AB. Importantly, this study used a comprehensive battery of gait characteristics to explore gait and cognition during free-living.

6.8.1 The effect of environment

It was hypothesised that gait and cognition associations would be more evident in controlled rather than habitual environments. In the laboratory, pace was associated with fluctuating attention, asymmetry was associated with attention and variability was associated with visual memory. In comparison, during steady state walking in free-living only asymmetry of gait was associated with visual memory. These findings are in agreement with the hypothesis that gait-cognition associations are more evident when measuring gait in controlled environments compared to long bouts of steady state walking in free-living.

The majority of associations in the laboratory were with characteristics of asymmetry and variability. As discussed in **chapter 2**, there are few previous studies that associate gait and cognition for domains other than pace in the laboratory (Morris *et al.*, 2016). Additionally, to date there are no studies which have assessed a comprehensive battery of gait characteristics in relation to cognition in controlled conditions using a BWM. Nevertheless, one previous study measured both variability and asymmetry using the GaitRite™ system (Lord *et al.*, 2014). This study found global cognition to associate with variability however there were no associations for asymmetry. Contrasting findings are likely due to differences in measurement tool. BWM have shown heightened sensitivity to characteristics of variability and asymmetry, with laboratory equipment such as the GaitRite™ unable to detect subtle deficits in characteristics from these domains (Del Din *et al.*, 2016c). Additionally, the laboratory protocol used here contains regular gentle turns which may have impacted on gait asymmetry. It is

also plausible that with progression of disease in this cohort (+3 years) characteristics of variability and asymmetry have become more dependent on cognition.

Characteristics of pace and variability were associated with fluctuating attention and visual memory respectively in the controlled environment, but these results were not replicated in free-living. These findings may signify heightened attentional control of gait in the controlled environment. Gait in a laboratory setting forms a formal environment which increases alertness, anxiety and attention and reflects an individual's 'best' performance (Brodie *et al.*, 2016). This exploratory study demonstrates that cognitive domains associated with gait (i.e. attention) remain when using a BWM in a controlled environment and further emphasise the importance of the role of frontal cognition on gait. In comparison to the laboratory, steady state walking in free-living identified associations between gait asymmetry and attention as well as visual memory. Importantly, the same cognitive domains remain associated with gait signifying gait is reliant on the same cognitive resources despite differences in environment. One previous study has associated gait and cognition in free-living to which comparisons can be drawn (Weiss *et al.*, 2015). Similar to this study, gait was associated with frontal cognitive measures but in contrast only characteristics of asymmetry were associated with cognition. In additional analysis of isolated ABs of 60-120 seconds it was found that variability was associated with spatial recognition memory (SRM) which is frontally mediated. One possible explanation is that associations found by Weiss *et al.* (2015) were driven by AB of a slightly shorter duration than 120 seconds. AB over 120 seconds are likely to reflect steady state walking in an outdoor environment where gait becomes more rhythmical and automatic. However, associations with asymmetry and attention during steady-state walking in free-living suggests attention plays an important role in refining asymmetry even during rhythmical gait, which is possibly due to a more complex environment. It is important to note that differences seen between gait and free-living may also be dependent on other aspects of protocol. For example, medication status is a confounding factor in this study as in controlled conditions participants were 'on' medication whereas medication status is likely be variable over the free-living assessment period (continuous 7 days). Overall, gait and

cognition associations during steady state walking in different environments appears to reflect the same common neural correlate as discussed in **chapter 4**. It would be interesting to measure gait in the free-living in response to cholinergic treatment, in particular response of variability and asymmetry would be of interest due to the increased sensitivity driven both by measurement tool and environment complexity.

6.8.2 The effect of bout length

The second aim of this chapter was to observe associations between gait and cognition for short and longer AB lengths during free-living gait. It was hypothesised that shorter AB would be correlated with cognition more so than longer AB. It was found that for AB of 10-20 seconds there were associations for rhythm, variability and asymmetry with attention, fluctuating attention and visual memory but for AB ≥120 seconds only asymmetry was associated with fluctuating attention and visual memory. This confirms the hypothesis that gait during shorter AB is associated more with cognition compared to gait during longer AB. To date the only work associating gait and cognition in the free-living using BWM only analysed longer bouts and therefore it is difficult to compare findings (Weiss *et al.*, 2015). It will be interesting to compare findings from shorter AB in an independent cohort in the future. In the shorter AB, variability and asymmetry were seen to increase which is most likely due to the complexity of the environment and reflecting gait adjustment in order to navigate and respond to obstacles. Additionally, shorter AB reflect natural dual tasking such as walking while carrying objects or walking while having a conversation which may also reflect an increase in asymmetry and variability.

6.8.3 Clinical Implications

This exploratory study demonstrated that gait and cognition are associated in free-living when using a single portable, easily implemented and cost-effective BWM. This has important implications for clinical practice and provides a basis for future studies to explore gait in the free-living as clinical biomarkers of cognitive decline. The use of BWM allows gait to be measured in the home and clinic environment and enable data to be quickly processed. This exploratory work has demonstrated that AB length is important when identifying gait and

cognition associations and that AB length needs to be taken into account for future longitudinal or cross-sectional studies.

6.8.4 Limitations

This chapter aimed to explore gait and cognition associations in free-living conditions, however further work is needed to determine the importance of environment and AB length in gait assessment. For this exploratory study, continuous two minute walks in the gait lab were compared to steady state walking in the free-living. This was chosen in order to evaluate similar walking periods, however continuous walks under this protocol contain gentle turns as participants walk in a circuit. This may have led to changes in gait (i.e. reduced velocity and step length and changes to variability and asymmetry) which may not be encountered so frequently in free-living during steady state walking (>120secs). In addition, the design of this circuit may have heightened attention further in the laboratory. These factors therefore may have confounded results. In the laboratory all participants were assessed 'on' medication but in free-living medication status will fluctuate. This will have a direct effect on both gait and cognition. To further understand this, work is currently underway at Newcastle University to determine the effect of medication intake on free-living gait and may lead to further refinement of free-living gait data. Finally, despite choosing a stringent p value of ≤.01 it has to be acknowledged that this cannot completely account for multiple comparisons. However due to the exploratory nature of this study it was necessary to explore a wide range of gait characteristics and cognitive domains. It is hoped this study will provide a foundation for future refined analysis.

6.8.5 Conclusions

This chapter presented the first exploratory study to measure a comprehensive battery of gait characteristics both in controlled laboratory and free-living environments, and their association with cognition. Furthermore, this is the first study to identify gait-cognition associations in accordance to different AB. This study identified gait and cognition associations are evident in free-living in PD and differ depending on AB length, which provides a basis for future studies to explore gait and cognition in free-living in PD.

Chapter 7 : Thesis overview and conclusions

The original aim of this thesis was to explore gait as a predictor for cognitive decline in PD. PD is the second most common neurodegenerative disorder presenting with both motor and NMS. Of the range of NMS, cognitive impairment and PDD have a high incidence both in early and late disease and have major personal, social and economic impact. In order to optimise clinical management and develop novel therapeutics, it is vital that individuals 'at risk' of cognitive decline and dementia are identified early in disease. Current biomarkers are complex, costly and invasive highlighting a need for future clinical biomarkers. Previous work indicates that gait may provide a low-cost and non-invasive clinical biomarker.

In order to explore this concept further, a structured review was conducted in **chapter 2** exploring i) cross-sectional associations between gait and cognition and ii) the longitudinal nature of these relationships in three groups; older adults, cognitive impairment and PD. This structured review found gait and cognition associations were evident in older adults, cognitive impairment and PD. In addition, gait provided a strong predictor of cognitive decline in older adults. Importantly, the review identified that to date no longitudinal research had been undertaken in PD. Furthermore, it was recognised that throughout all studies there was a lack of a comprehensive approach to measurements of independent gait characteristics and cognitive domains as well as use of consistency of gait acquisition systems. This has led to a lack of sensitivity and specificity for gait predictors of cognitive decline and therefore to date has limited findings.

The two main chapters from this thesis (**chapters 4** and **5**) provided a comprehensive and robust approach to exploring independent gait characteristics as predictors of cognitive decline over three years in an early, incident cohort of PD. Both chapters demonstrated that gait, at diagnosis of PD, predicted cognitive decline over the first three years of disease and that this was selective to discrete gait characteristics and discrete cognitive domains. Importantly, gait provided a stronger predictor than baseline cognition. This work provided the first evidence for gait as clinical biomarker for early cognitive decline in PD.

Chapter 4 explored the role of single task gait as a predictor for cognitive decline. This chapter demonstrated that characteristics of pace, variability and postural control were able to predict a decline in fluctuating attention. In addition, characteristics of pace were able to predict a decline in visual memory. Importantly, these findings were isolated to PD pathology when compared to older adults. Critically, neuropsychological assessments were unable to predict decline in either fluctuating attention or visual memory. It was hypothesised that both gait and cognition rely on a common neural correlate, likely to stem from the cholinergic system. From this work, it would appear that gait is sensitive to early changes in a common pathology but neuropsychological assessments are not. It was hypothesised that fluctuating attention is an early indicator of future PDD pathology due to its vital role in Lewy body dementia (LBD) and therefore these findings may prove critical once an evolved cohort has been assessed.

Chapter 5 explored the role of gait under a dual task paradigm as a predictor of cognitive decline. Dual task paradigms are often used in gait protocols and are a popular method in which to assess gait and cognition relationships. **Chapter 5** demonstrated that characteristics of pace, variability, rhythm, asymmetry and postural control were able to predict decline in fluctuating attention. In addition, characteristics of pace were able to predict a decline in visual memory. Furthermore, one characteristic of pace was able to predict decline in attention. These results further validated the findings from **chapter 4** identifying the sensitivity of gait to decline in frontal cognitive assessments, mainly fluctuating attention. Dual task gait showed similar predictive ability to single task gait and although this may be due to the dual task paradigm used throughout this study, it may also indicate that single task gait may be sufficient for a clinical biomarker.

Chapters 4 and **5** provided the first evidence for gait as a predictor of early cognitive decline in PD, indicating future utility as a clinical biomarker for cognitive decline and PDD. However, in order for gait to be a pragmatic and cost-effective clinical biomarker measurement has to be transferred from the laboratory to the free-living (i.e. clinic, home and community environments). Thus, the final results chapter, **chapter 6**, provided an exploratory look at gait and cognition in free-living. First, in order to provide a conceptual gait framework, a factor analysis was conducted on free-living gait characteristics. The factor

analysis derived four independent gait domains in PD and older adults; pace, rhythm, variability and asymmetry. The second part of **chapter 6** used this conceptual framework to explore associations between gait and cognition in free-living. Gait and cognition associations were primed in the laboratory compared to steady state gait in free-living, possible due to heightened attention mechanisms thought to occur in overt testing conditions. Free-living gait and cognition associations were then explored in finer detail by analysing gait and cognition associations at different free-living ambulatory bout lengths. Gait and cognition associations were more evident in shorter compared to longer bouts, likely reflecting bout specific activities. This chapter demonstrated that gait and cognition associations remain in the free-living when assessed with a body worn monitor (BWM) as opposed to laboratory equipment. Furthermore, associations were most evident for domains of attention, fluctuating attention and visual memory- further validating the importance of these cognitive domains in PD pathology. This study provided an exploratory approach of comprehensive measurement of gait and cognition, how they are associated in different environments and how different AB activity may relate. This provides a foundation for further work in free-living gait.

7.1 Clinical implications

This thesis has identified the first evidence for gait as a predictor for decline in specific cognitive domains in PD. These findings have implications for future clinical practice by identifying a possible novel clinical biomarker for prediction of PD cognitive decline and PDD. It is important to identify patients at risk of cognitive decline and PDD as this helps reduce both direct and indirect effects of dementia pathology on patients (Woods and Trőster, 2003). Early detection of cognitive decline and dementia may help to modify medical as well as psychological treatment for both patients and their carers. Furthermore, it may help with future financial, personal and social planning which in turn would improve quality of life. Finally, it is hoped that early detection of 'at risk' patients will delay PDD onset and improve current impact of PDD on patients. As identified in **chapter 1**, current biomarkers are costly and invasive. Gait however

provides a simple and non-invasive assessment and with the use of BWM gait can provide a comprehensive evaluation in clinical and free-living environments. Ultimately, a battery of biomarkers is optimal in order to detect those at risk due to the complexity of pathology. This thesis identifies the first evidence for gait as a valuable addition to a comprehensive battery of biomarkers that can be obtained in the clinic. Currently, gait as a biomarker is limited by the wide range of gait protocols and gait acquisition systems. A standardised gait protocol needs to be employed across the literature in order to aid consistency of future findings.

7.2 Limitations and Future work

Whilst this thesis has identified novel and new evidence, further studies are needed to validate the role of gait as a clinical biomarker for cognitive decline in PD and more specifically PDD. This study provided a comprehensive and robust approach to identifying independent gait predictors of cognitive decline, however, it was limited by follow-up period. Critically, gait and cognition were assessed at point of diagnosis in PD which allowed for the prognostic significance of gait in very early disease to be determined. However, cognitive decline was only measured over three years. This has provided critical knowledge regarding underlying pathology but it remains unknown which gait characteristics will predict an end point diagnosis of PDD. Therefore, further work needs to be completed once the cohort has evolved to determine which gait characteristics are independent predictors of PDD. This thesis also provided an exploratory look at gait and cognition associations in free-living. From this analysis it was determined that gait and cognition associations were still evident in free-living data when using a different measuring tool. However, it is understood from the literature that gait and cognition associations differ from predictors. This work was limited to a cross-sectional analysis and therefore future work needs to determine which gait characteristics are independent predictors of cognitive decline when assessing a comprehensive battery of gait characteristics using a BWM.

Throughout this thesis a comprehensive battery of cognitive assessments was utilised in accordance to previously defined domains (Lord *et al.*, 2014). However, it has to be acknowledged that this cannot omit the multi-determinate nature of neuropsychological assessments. For example, executive function and attention

often underpin assessment of other cognitive domains. Throughout the literature one neuropsychological assessment may be classified into several domains which was demonstrated in chapter 2. The Movement Disorder task force recognises that allocation of individual neuropsychological assessments is subjective (Litvan *et al.*, 2012). In light of this, task force criteria have now been put in place to define neuropsychological assessment domains (Litvan *et al.*, 2012), a step which is critical in order for consistency in future work.

Finally, analyses throughout this thesis were conducted without an adjustment for multiple comparisons. In order to account for this a stringent p value of ≤.01 was used throughout. It is important to note however, this is the first study to assess gait as a predictor for cognitive decline in PD and therefore it was critical that a comprehensive approach was used and from here future work can be refined by using this project as a foundation.

7.3 Conclusions

This thesis provided a comprehensive and robust approach to exploring gait in early PD as a predictor for cognitive decline over three years. Ultimately, this thesis has provided the first evidence for the utility as gait for a clinical biomarker for cognitive decline in early PD which proved to be specific to particular cognitive domains. The final conclusions from this thesis are as follows;

1) A large structured review concluded gait and cognition associations were evident in PD, gait had the ability to predict cognitive decline and dementia in older adults but there was a lack of comprehensive measurement approach to gait and cognition throughout the literature
2) Cognitive decline is evident in early PD compared to age matched controls
3) Specific gait characteristics under single task conditions were significant predictors of increased fluctuating attention and poorer visuospatial memory over three years
4) Specific gait characteristics under dual task conditions were also significant predictors of poorer attention, increased fluctuating attention

and poorer visual memory and provided similar predictive scope to single task gait

5) A common neural correlate is thought to underpin both gait and cognition with gait demonstrating heightened sensitivity to pathological changes over cognitive assessments

6) Gait and cognition associations remain evident in free-living demonstrating future ability for gait as a low-cost and non-invasive clinical biomarker for cognitive decline in PD

Chapter 8 : **Appendices**

1. Appendix 1.0: National Adult Reading Test (NART)

National Adult Reading Test (NART)

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

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

2. Appendix 2.0: Geriatric Depression Scale (GDS-15)

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

Please circle:

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

Total score:

Answers in **bold** indicate depression. Although differing sensitivities and specificities have been obtained across studies, for clinical purposes a score > 5 points is suggestive of depression and should warrant a follow-up interview. Scores > 10 are almost always depression.

3. Appendix 3.0: Movement Disorders Society-Unified Disease Rating Scale Part III (MDS-UPDRS III)

2156   C.G. GOETZ ET AL.

Part III: Motor Examination

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

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

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:
   ON is the typical functional state when patients are receiving medication and have a good response.
   OFF is the typical functional state when patients have a poor response in spite of taking medications.

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

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

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

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

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

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

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

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

3c Is the patient on Levodopa ?   ☐ No   ☐ Yes
     3.C1 If yes, minutes since last levodopa dose: _____

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

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

	SCORE

3.5 HAND MOVEMENTS

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problem.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task.

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

R ☐

L ☐

3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence.

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing c) the amplitude decrements starting after the 1st supination-pronation sequence.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

R ☐

L ☐

	SCORE
3.7 TOE TAPPING	

Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problem.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps.

2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task.

3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

☐ R

☐ L

3.8 LEG AGILITY

Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task.

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

☐ R

☐ L

Chapter 8: Appendices

	SCORE

3.9 ARISING FROM CHAIR

Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum up to two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13

0: Normal: No problems. Able to arise quickly without hesitation.

1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair.

2: Mild: Pushes self up from arms of chair without difficulty.

3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help.

4: Severe: Unable to arise without help.

3.10 GAIT

Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13

0: Normal: No problems.

1: Slight: Independent walking with minor gait impairment.

2: Mild: Independent walking but with substantial gait impairment.

3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person.

4: Severe: Cannot walk at all or only with another person's assistance.

C.G. GOETZ ET AL.

	SCORE

3.11 FREEZING OF GAIT

Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment.

0: Normal: No freezing.

1: Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking.

2: Mild: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking.

3: Moderate: Freezes once during straight walking.

4: Severe: Freezes multiple times during straight walking.

3.12 POSTURAL STABILITY

Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13

0: Normal: No problems: Recovers with one or two steps.

1: Slight: 3-5 steps, but subject recovers unaided.

2: Mild: More than 5 steps, but subject recovers unaided.

3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner.

4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.

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

Chapter 8: Appendices

	SCORE

3.16 KINETIC TREMOR OF THE HANDS

Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen.

0: Normal: No tremor.

1: Slight: Tremor is present but less than 1 cm in amplitude.

2: Mild: Tremor is at least 1 but less than 3 cm in amplitude.

3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude.

4: Severe: Tremor is at least 10 cm in amplitude.

R

L

3.17 REST TREMOR AMPLITUDE

Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor.
As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating.

Extremity ratings

0: Normal: No tremor.

1: Slight.:   < 1 cm in maximal amplitude.

2: Mild: > 1 cm but < 3 cm in maximal amplitude.

3: Moderate: 3 - 10 cm in maximal amplitude.

4: Severe: > 10 cm in maximal amplitude.

Lip/Jaw ratings

0: Normal: No tremor.

1: Slight: < 1 cm in maximal amplitude.

2: Mild: > 1 cm but < 2 cm in maximal amplitude.

3: Moderate: > 2 cm but < 3 cm in maximal amplitude.

4: Severe: > 3 cm in maximal amplitude.

RUE

LUE

RLE

LLE

Lip/Jaw

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

4. Appendix 4.0: Hoehn and Yahr (H & Y)

Hoehn and Yahr Scale
1: Only unilateral involvement, usually with minimal or no functional disability
2: Bilateral or midline involvement without impairment of balance
3: Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
4: Severely disabling disease; still able to walk or stand unassisted
5: Confinement to bed or wheelchair unless aided

5. Appendix 5.0: Montreal Cognitive Assessment (MoCA)

6. Appendix 6.0: The Hayling and Brixton Tests

the **Hayling** and **Brixton** tests

TVTC
Thames Valley
Test Company
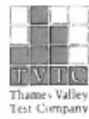
Scoring sheet

Subject and test details

Name

Age

Date of test

Further details

The Hayling Sentence Completion Test

Score summary

Box A   Box B   Box C   Total scaled scores

   +   +   =

(Section 1 Scaled score)   (Section 2 Scaled score)   (Section 2 Errors scaled score)

Hayling overall scaled score

Table E		
Total scaled scores	Overall scaled score	Classification
23	10	Very superior
22	9	Superior
21	8	Good
20	7	High average
17–19	6	Average
15–16	5	Moderate ave.
13–14	4	Low average
11–12	3	Poor
10	2	Abnormal
< 10	1	Impaired

Hayling Section 1: sensible completion

- *In a moment I am going to read you a series of sentences, each of which has the last word missing from it. I want you to listen carefully to each sentence, and when I have finished each one, your job is to give me a word which completes the sentence. Do you understand?*

Practice

- *Before we start, I'll give you a couple of practice sentences so that you can get the hang of it. Are you ready?*

                Response   Time

P1 The rich child attended a private

P2 The crime rate has gone up this

Test

- *OK, that's the end of the practice items. The next few sentences I'll read aren't really any more difficult than the two you've just done. But the important thing is that I want you to give me your answer as quickly as you can – the faster the better. Is that clear?*

1 He posted a letter without a
    or: He mailed a letter without a

2 In the first space enter your
    or: In the first blank enter your

3 The old house will be torn

4 It's hard to admit when one is

5 The job was easy most of the

6 When you go to bed turn off the

7 The game was stopped when it started to

8 He scraped the cold food from his

9 The dispute was settled by a third

10 Three people were killed in a major motorway
    or: Three people were killed in an interstate

11 The baby cried and upset her

12 George could not believe that his son had stolen a

13 He crept into the room without a

14 Billy hit his sister on the

15 Too many men are out of

              Total time (raw score)   →

       Scaled score (transfer this to box A in score summary above)

Table A		
Raw score	Scaled score	Comment
0	7	High ave.
1–9	6	Average
10–18	5	Moderate ave.
19–22	4	Low ave.
23–50	3	Poor
51–60	2	Abnormal
>60	1	Impaired

1

180

Hayling Section 2: unconnected completion

- *Now we are going to move on to the second section of the test. In this section I will read you a set of sentences with the last word missing just like the ones you have already done, but this time I want you to give me a word which does not fit at the end of the sentence – I want the word you give me to be completely unconnected to the sentence in every way. Do you understand?'*

Practice

- *Before we start, I'll give you a couple of practice sentences so that you can get the hang of what is required'.*

Response   Time

P1   London is a very busy

P2   Her new shoes were the wrong

- If the subject makes an error refer to instructions in Manual (page 8).

Test

- *'OK, that's the end of the practice items. Remember that the words you give me must be unconnected to the sentence, and that it is important for you to give me your answer as quickly as you can. Are you ready?'*

1   The captain wanted to stay with the sinking

2   They went as far as they

3   Most cats see very well at

4   Jean was glad the affair was

5   The whole town came to hear the mayor

6   Most sharks attack very close to

7   None of the books made any

8   The dough was put in the hot

9   She called the husband at his

10 All the guests had a very good

11 He bought them in the sweet
    or: He bought them in the candy

12 His leaving home amazed all his

13 At last the time for action had

14 The dog chased our cat up the

15 At night they often took a short

Columns: Correct (unconnected) | Category A error (connected) | Category B error (somewhat connected)

A score

Total Category A errors	A score
1	3
2	6
3	10
4	14
5	18
6	24
7	30
8	36
9	42
10	48
11	54
12	60
13	66
14	72
15	78

B score

Total Category B errors	B score
1	1
2	2
3	3
4	4
5	9
6	14
7	19
8	24
9	29
10	34
>10	50

Total time (raw score)

Scaled score (transfer this to box B in score summary on page 1)

Total Cat. A errors   A score   Total Cat. B errors   B score   Converted score (A score + B score)

Table B

Raw score	Scaled score	Comment
0	8	Good
1–2	7	High average
3–50	6	Average
51–60	5	Moderate ave.
61–100	4	Low average
101–120	3	Poor
121–130	2	Abnormal
>130	1	Impaired

Table C

Converted score	Scaled score	Comment
0	8	Good
1–3	7	High average
4–9	6	Average
10–12	5	Moderate ave.
13–14	4	Low average
15–17	3	Poor
18–29	2	Abnormal
≥30	1	Impaired

Hayling 2 errors scaled score (transfer this to box C in score summary on page 1)

The Brixton Spatial Anticipation Test

- 'There are many pages here which all have the same basic design on them. There are always ten positions, and one of them is always coloured blue' [point to filled circle on page one]. 'However the coloured one moves around according to various patterns that come and go without warning. These numbers [point to numbers underneath the circles] are just here to refer to the position – there is nothing complicated or mathematical about this test'.
- 'Now, as I turn the pages over, your job is to pick up on the pattern as best you can, and point to where you think the blue one is going to be on the next page. It's not guess-work – you can work it out. For instance, imagine the blue one was here [point to position 6], and then when I turn the page it goes to 7, and then to 8, then to 9 – you might reasonably expect it next to go to 10'.
- 'From time to time the pattern changes without warning, and then it is your job to pick up on the new pattern as best you can. Do you understand?'
- Give further assistance if necessary
- 'Obviously the first time you have nothing to go on, so your first answer will have to be a guess – have a guess as to where the blue one will be next'

Item/ page	Correct answer	Subject's response	Correct/ incorrect
1	any		
2	3		☐
3	4		☐
4	5		☐
5	6		☐
6 *	7		☐
7	4		☐
8	3		☐
9	2		☐
10	1		☐
11	10		☐
12 *	9		☐
13	10		☐
14	5		☐
15	10		☐
16	5		☐
17	10		☐
18	5		☐
19 *	10		☐
20	7		☐
21	8		☐
22	9		☐
23	10		☐
24	1		☐
25	2		☐
26 *	3		☐
27	10		☐
28	9		☐

Item/ page	Correct answer	Subject's response	Correct/ incorrect
29 *	8		☐
30	1		☐
31	2		☐
32	3		☐
33	4		☐
34 *	5		☐
35	4		☐
36	10		☐
37	4		☐
38	10		☐
39	4		☐
40	10		☐
41 *	4		☐
42	9		☐
43	9		☐
44	9		☐
45	9		☐
46	9		☐
47	9		☐
48 *	9		☐
49	9		☐
50	8		☐
51	9		☐
52	8		☐
53	9		☐
54	8		☐
55	9		☐

Total number of errors (raw score) ↓ ←

* Scaled score

Table D		
Raw score	Scaled score	Classification
0–7	10	Very superior
8	9	Superior
9–10	8	Good
11–13	7	High average
14–17	6	Average
18–20	5	Moderate ave.
21–23	4	Low average
24–25	3	Poor
26–31	2	Abnormal
>31	1	Impaired

3

7. Appendix 7.0: Pentagons

Ask patient to copy a pair of intersecting pentagons
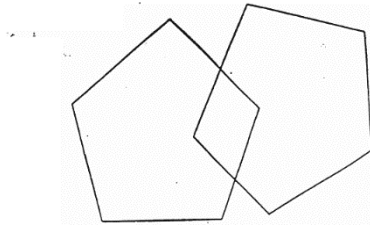
8. Appendix 8.0: Body Worn Monitor (BWM) patient information sheet

Newcastle Biomedicine   Clinical Research Platforms

Clinical Ageing Research Unit
Telephone: 0191 248 1250
Fax: 0191 248 1251
www.ncl.ac.uk/crp

Continuous Wave Accelerometer Instructions

1. Attach the device using the tapes provided as illustrated below:

(a) This side out

(b)

Attach the device at the level of the 'small of your back' using the tape provided (see diagram) opposite
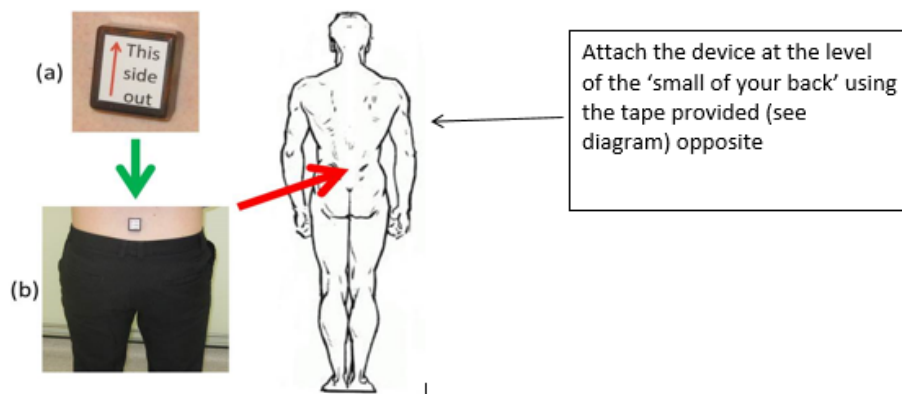
2. There are no switches/buttons on the device; it will remain 'on' for the full duration.
3. The device is NOT waterproof and CANNOT be worn whilst bathing/showering so, please remove to have a shower/bath and replace once skin is completely dry using new tape provided.
4. Please try to wear the device at all other times, including at night, for the full 7 days.
5. Take the device to the post office, after 7 days, and send it back in the pre-paid self-addressed envelope provided.
6. Any problems please contact **Rosie Morris on 0191 248 1284 or Dr Sue Lord on 0191 248 1247**

Version 2: 23rd October 2013

Newcastle University   The Newcastle upon Tyne Hospitals **NHS** NHS Foundation Trust

9. Appendix 9.0: Demographic characteristics of completers and non-completers

Demographic	PD Completers (n=81)		Non-completers (n=38)		T	p	Control Completers (n=118)		Non-Completers (n=66)		T	p
	Mean	SD	Mean	SD			Mean	SD	Mean	SD		
Sex (M & F)	55M & 26F		24M & 14F		.26*	0.68*	54M & 64 F		24M & 42F		1.11*	0.29*
Age (years)	66.11	9.91	68.72	11.60	-1.27	0.21	68.91	7.15	70.36	8.57	-1.23	0.22
Height (m)	1.70	0.08	1.69	0.08	0.93	0.35	1.69	0.10	1.66	0.10	1.89	0.06
NART	115.26	11.08	114.49	11.37	0.35	0.73	117.48	7.69	116.16	7.74	1.11	0.27
LEDD (mg/day)	158.86	114.67	212.20	188.31	-1.61	0.11	-	-	-	-		
UPDRS III	24.35	10.32	27.55	10.37	-1.58	0.12	-	-	-	-		
GDS	2.65	2.30	2.50	1.89	0.36	0.72	1.28	2.03	0.99	1.44	1.15	0.25
Hoehn & Yahr stage n (%)	I (21) II (47) III (13) IV (0)		I (7) II (23) III (8) IV (0)		-		-	-	-	-		

185

10. Appendix 10.0: Single task gait characteristics; completers and non-completers

Gait Domain	Gait Variable	PD Completers (n=81)		PD Non-Completers (n=38)		PD T-Test		Control Completers (n=118)		Control Non-Completers (n=66)		Control T-Test	
		Mean	SD	Mean	SD	T	p	Mean	SD	Mean	SD	T	p
Pace													
	Step velocity (*m/s*)	1.14	0.21	1.08	0.22	1.41	0.16	1.30	0.17	1.20	0.21	3.69	**<0.01**
	Step Length (*m*)	0.63	0.10	0.60	0.11	1.55	0.12	0.69	0.07	0.64	0.09	3.95	**<0.01**
	Swing time SD (*ms*)	2.79	.28	2.88	0.39	-1.44	0.15	2.62	0.27	2.75	0.33	-2.98	**<0.01**
Variability													
	Step time SD (*ms*)	2.85	0.30	2.95	0.38	-1.56	0.12	2.68	0.27	2.85	0.32	-3.84	**<0.01**
	Stance time SD (*ms*)	3.02	0.36	3.16	0.43	-1.97	0.05	2.85	0.30	3.03	0.37	-3.45	**<0.01**
	Step velocity SD (*ms*)	0.052	0.014	0.057	0.213	-1.42	0.16	0.052	0.013	0.055	0.012	-1.38	0.17
	Step length SD (*m*)	0.022	0.006	0.025	0.010	-2.29	**0.02**	0.019	0.001	0.020	0.001	-1.20	0.23
Rhythm													
	Step time (*ms*)	558.84	45.47	562.15	55.66	-.034	0.73	533.78	46.30	542.51	47.78	-1.22	0.23
	Swing time (*ms*)	392.25	33.19	390.94	33.63	0.20	0.84	385.80	30.58	388.41	29.52	-0.56	0.57
	Stance time (*ms*)	725.76	72.43	734.01	86.10	-0.54	0.59	682.31	68.69	697.00	76.26	-1.34	0.18
Asymmetry													
	Step time asymmetry (*ms*)	4.13	2.34	4.21	2.36	-0.18	0.86	2.88	1.21	3.27	1.60	-1.61	0.11
	Swing time asymmetry (*ms*)	3.73	2.01	3.61	1.89	0.32	0.75	2.63	1.16	2.74	1.60	-0.49	0.62
	Stance time asymmetry (*ms*)	3.70	1.99	3.61	1.82	0.24	0.81	2.60	1.21	2.75	1.55	-0.70	0.49
Postural Control													
	Step length asymmetry (*m*)	0.141	0.071	0.154	0.057	-0.97	0.33	0.122	0.062	0.140	0.057	-1.95	0.05
	Step width (*m*)	0.091	0.032	0.095	0.027	-0.60	0.55	0.089	0.025	0.090	0.026	-0.14	0.89
	Step width SD (*m*)	0.019	0.006	0.019	0.005	-0.24	0.81	0.023	0.006	0.021	0.005	1.54	0.13

11. Appendix 11.0: Cognitive data; completers and non-completers

	Completers (n=81)		Non-Completers (n=38)		T-test (BL-36)	
	Mean	*SD*	*Mean*	*SD*	*T*	*P*
Global Cognition						
MMSE	28.83	1.09	28.32	1.63	1.76	.08
MoCA	25.64	3.38	24.35	3.83	1.83	.07
Working memory						
Forward digit span	5.98	1.14	5.47	0.98	2.34	**.02**
Attention						
Reaction time (mean)	343.71	114.25	355.31	66.86	-0.58	.56
Choice reaction time (mean)	520.02	79.37	547.51	95.84	-1.64	.10
Digit Vigilance (mean)	471.11	52.19	497.04	61.00	-2.38	**.02**
Fluctuating Attention						
Reaction time (CV) (%)	16.51	5.69	18.01	5.16	-1.38	.17
Choice reaction time (CV) (%)	18.39	3.34	20.05	4.58	-1.99	**.05**
Digit Vigilance (CV) (%)	15.84	3.52	16.57	4.16	-0.93	.33
Executive Function						
One touch stocking (problems solved)	14.35	3.65	13.44	5.44	1.05	.39
Semantic Fluency (animals in 90 secs)	22.56	6.05	20.08	6.82	1.97	.05
Hayling Score	5.44	1.61	4.92	1.81	1.58	.12
Brixton Score	4.53	2.36	4.56	2.41	-0.05	.96
Visual Memory						
Pattern Recognition memory (number correct)	20.14	2.86	19.19	2.87	1.64	.10
Spatial Recognition memory (number correct)	15.73	2.16	14.75	2.32	2.19	**.03**
Paired associate learning (mean trials to success)	1.95	0.67	2.54	1.32	-3.13	**.02**
Visuospatial						
Pentagon copying	1.94	0.24	1.84	0.37	1.50	.14

12. Appendix 12.0: Single task gait characteristic predictors of cognitive decline in PD

		CRT				CRTCV				SRM				OTS			
		β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p
Pace	Step Velocity	-48.30	27.59	-1.75	0.08	-4.05	1.34	-3.02	<.01 X^2 13.74*	1.32	0.56	2.33	0.02 X^2 7.50	1.07	1.08	0.10	0.32
	Step Length	-114.78	58.46	-1.96	0.05	-8.64	2.86	-3.02	<.01 X^2 15.26*	2.93	1.19	2.47	0.01 X^2 10.48*	3.43	2.27	1.51	0.13
Variability	Swing Time SD	35.04	18.75	1.87	0.06	2.56	0.93	2.75	<.01 X^2 11.00*	-0.66	0.39	-1.69	0.09	-0.45	0.76	-0.60	0.55
	Step Time SD	31.23	18.13	1.72	0.09	2.14	0.90	2.38	0.02 $X2$ 8.57*	-0.75	0.38	-1.96	0.05	0.03	0.74	0.04	0.97
	Step Stance SD	30.12	15.49	1.95	0.06	1.98	0.77	2.58	0.01 X^2 9.46*	-0.54	0.33	-1.61	0.11	0.13	0.64	0.21	0.83
	Vel SD	311.01	364.88	0.85	0.40	-2.82	18.66	-0.15	0.88	-5.91	8.22	-0.72	0.47	19.55	15.65	1.25	0.21
	Len SD	1639.29	807.78	2.10	0.04 X^2 4.61	115.68	40.41	2.86	<.01 X^2 11.58*	-27.21	16.05	-1.70	0.09	-8.19	32.71	-0.25	0.80
Rhythm	Step time	0.03	0.13	0.21	0.83	0.01	0.01	1.45	0.15	-<.01	<.01	-0.66	0.51	<.01	<.01	0.81	0.42
	Swing time	-0.11	0.18	-0.60	0.55	-0.01	0.01	-0.84	0.41	<.01	<.01	1.10	0.27	0.01	<.01	1.59	0.11
	Stance time	0.04	0.08	0.52	0.60	0.01	0.03	2.26	0.03 X^2 5.91	-<.01	<.01	-1.34	0.18	<.001	<.01	0.30	0.77
Asymmetry	Step Asy	0.16	2.55	0.06	0.95	0.08	0.13	0.60	0.55	-0.06	0.05	1.14	0.25	0.11	0.10	1.10	0.28
	Swing Asy	-0.91	2.95	-0.31	0.76	0.18	0.15	1.23	0.22	-0.08	0.06	-1.42	0.16	0.12	0.11	1.10	0.28
	Stance Asy	-0.23	2.99	-0.08	0.94	0.27	0.15	1.81	0.07	-0.07	0.06	-1.14	0.25	0.15	0.11	1.29	0.20
Postural Control	Length Asy	60.17	83.14	0.72	0.47	6.54	4.12	1.59	0.12	-2.00	1.73	-1.56	0.25	2.42	3.22	0.75	0.45
	Width	-74.97	187.31	95.65	0.69	26.69	9.02	2.96	<.01 X^2 8.32	-3.49	3.96	-0.88	0.38	-1.48	7.38	-0.20	0.84
	Step Width SD	216.68	953.93	0.23	0.82	58.53	47.49	1.23	0.22	23.94	19.72	1.21	0.23	51.24	36.57	1.40	0.16

Bright green= significant predictors, medium green= near significant predictors. [CRT= choice reaction time, CRTCV= choice reaction time coefficient of variance, SRM= spatial recognition memory, OTS= one touch stockings.]

13. Appendix 13.0: Single task gait domain predictors of cognitive decline in PD.

	CRT				CRTCV				SRM				OTS			
	β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p
Pace	-11.02	5.26	-2.09	0.04	-0.61	0.26	-2.31	0.02	0.26	0.11	2.34	0.02	0.36	0.21	1.76	0.08
Rhythm	1.92	5.67	0.34	0.73	0.0068	0.028	0.58	0.98	-0.13	0.12	-1.09	0.28	-0.23	0.23	-1.0	0.32
Asymmetry	1.17	3.54	0.33	0.74	-0.17	0.17	-0.97	0.34	0.08	0.07	1.13	0.26	-0.17	0.13	-1.25	0.21
Variability	-5.83	4.98	-1.17	0.24	-0.33	0.25	-1.28	0.20	0.03	0.11	0.37	0.71	-0.21	0.20	-1.00	0.32
Postural Control	-1.01	4.81	-0.21	0.83	-0.59	0.23	-2.52	0.01	0.13	0.10	1.33	0.19	-0.01	0.19	-0.05	0.96

Bright green= significant predictors, medium green= near significant predictors. [CRT= choice reaction time, CRTCV= choice reaction time coefficient of variance, SRM= spatial recognition memory, OTS= one touch stockings.]

14. Appendix 14.0 Single task gait characteristic predictors of cognitive decline in controls.

		CRT				CRTCV				SRM				OTS			
		β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p
Pace	Step Velocity	46.91	20.39	2.30	0.02 X^2 12.04*	0.58	1.21	0.48	0.63	0.73	0.55	1.34	0.18	0.13	0.63	0.20	0.84
	Step Length	25.70	45.80	0.56	0.58	2.07	2.71	0.76	0.46	0.04	1.27	0.03	0.98	1.24	1.44	0.86	0.39
Variability	Swing Time SD	-10.74	12.04	-0.89	0.37	-0.61	0.71	-0.86	0.39	-0.46	0.34	-1.35	0.18	-0.50	0.40	-1.26	0.21
	Step Time SD	-13.38	12.13	-1.10	0.27	-0.93	0.72	-1.30	0.20	-0.60	0.34	-1.76	0.08	-0.24	0.40	-0.60	0.55
	Step Stance SD	-12.29	10.85	-1.13	0.26	-0.54	0.64	-0.84	0.40	-0.49	0.31	-1.62	0.11	<0.01	0.36	0.02	0.99
	Vel SD	479.85	274.32	1.75	0.08	-11.51	16.44	-0.70	0.49	-2.15	7.65	-0.28	0.78	-13.81	8.55	-1.62	0.11
	Len SD	191.68	649.31	0.30	0.77	-24.33	38.48	-0.63	0.53	-11.38	17.95	-0.63	0.53	-57.78	20.08	-2.88	<0.01 X^2 9.93
Rhythm	Step time	-0.21	0.08	-2.73	<0.01 X^2 8.00	-<0.01	<0.01	-0.04	0.97	-<0.01	<0.01	-2.00	0.05	<0.01	<0.01	0.91	0.37
	Swing time	-0.21	0.11	-1.84	0.07	<0.01	<0.01	0.06	0.95	-<0.01	<0.01	1.58	0.12	<0.01	<0.01	0.26	0.79
	Stance time	-0.14	0.05	-2.81	<0.01 X^2 8.79*	<0.01	<0.01	-0.08	0.93	-<0.01	<0.01	-2.05	0.04 X^2 11.42*	<0.01	<0.01	1.15	0.25
Asymmetry	Step Asy	-0.34	2.67	-0.13	0.90	0.18	0.16	1.16	0.25	-0.05	0.08	-0.73	0.47	-0.10	0.09	1.22	0.22
	Swing Asy	3.10	2.72	1.14	0.26	0.19	0.16	1.21	0.23	-0.07	0.08	-0.96	0.34	-0.08	0.09	-1.0	0.33
	Stance Asy	0.87	2.69	0.32	0.75	0.30	0.16	1.92	0.06	-0.09	0.08	-1.19	0.24	-0.10	0.09	-1.22	0.22
Postural Control	Length Asy	-94.05	55.01	-1.71	0.09	-0.52	3.28	-0.16	0.88	-1.71	1.59	-1.08	0.28	-3.56	1.81	-1.98	0.05
	Width	-7.69	140.06	-0.06	0.96	2.35	8.29	0.28	0.78	2.15	3.99	0.54	0.59	0.78	4.55	0.17	0.86
	Step Width SD	-555.11	616.26	-0.90	0.37	-14.73	36.54	-0.40	0.69	9.66	17.50	0.55	0.58	-25.04	19.63	-1.28	0.20

Bright green= significant predictors, medium green= near significant predictors. [CRT= choice reaction time, CRTCV=choice reaction time coefficient of variance, SRM= spatial recognition memory, OTS= one touch stockings]. *= Log-likelihood ratio test significance.

15. Appendix 15.0: Single task gait domain predictors of cognitive decline in controls.

	CRT				CRTCV				SRM				OTS			
	β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p
Pace	4.60	3.83	1.20	0.23	0.24	0.23	1.05	0.29	0.11	0.11	1.04	0.30	-0.03	0.12	-0.21	0.83
Rhythm	8.90	3.23	2.68	<0.01	0.05	0.20	0.23	0.82	0.13	0.09	1.43	0.15	-0.12	0.11	-1.09	0.28
Asymmetry	-4.29	3.59	-1.20	0.23	-0.39	0.21	-1.86	0.06	0.08	0.10	0.75	0.45	0.17	0.11	1.50	0.13
Variability	-4.16	3.47	-1.20	0.23	0.16	0.21	0.79	0.43	<0.01	<0.01	<0.01	0.1	0.21	0.11	1.91	0.06
Postural Control	3.85	3.42	1.13	0.26	-0.02	0.20	-0.1	0.92	0.01	0.01	0.15	0.88	0.16	0.12	1.35	0.18

Bright green= significant predictors, medium green= near significant predictors. [CRT= choice reaction time, CRTCV= choice reaction time coefficient of variation, SRM= spatial recognition memory, OTS= one touch stockings].

16. Appendix 16.0: Multivariate linear regression model.

Dependent Variable		Predictors	β	P	R	Adjusted R²	F Change	ANOVA Sig
Fluctuating Attention (CRTCV)	Model 1	Age	.151	.162	.236	.022	1.648	.185
		NART	-.065	.541				
		Gender	-.152	.160				
	Model 2	Age	.156	.155	.238	.011	.102	.297
		NART	-.068	.526				
		Gender	-.156	.154				
		CRT CV BL	-.035	.750				

NART= national adult reading test, CRT CV= choice reaction time coefficient of variance, BL= baseline. CRTCV change score was entered as the dependent variable with age, sex and NART entered in the first block and baseline CRTCV entered in the second block as independent variables.

17. Appendix 17.0: Dual task gait characteristics; completers and non-completers

Gait Domain	Gait Variable	PD						Control					
		Completers (*n*=80)		Non-Completers (n=39)		T-Test		Completers (*n*=118)		Non-Completers (n=66)		T-Test	
		Mean	*SD*	*Mean*	*SD*	*T*	*P*	*Mean*	*SD*	*Mean*	*SD*	*T*	*P*
Pace													
	Step velocity (*m/s*)	1.08	0.23	1.02	0.20	1.44	0.15	1.23	0.18	1.14	0.21	2.89	**<.01**
	Step Length (*m*)	0.61	0.10	0.57	0.10	1.73	0.09	0.66	0.08	0.62	0.09	3.46	**<.01**
	Swing time SD (*ms*)	2.89	0.31	2.96	0.35	-1.12	0.27	2.72	0.27	2.86	0.39	-2.55	**.01**
Variability													
	Step time SD (*ms*)	3.00	0.34	3.13	0.37	-1.94	0.06	2.86	0.30	2.99	0.42	-2.32	**.02**
	Stance time SD (*ms*)	3.22	0.40	3.38	0.43	-2.00	0.05	3.07	0.36	3.19	0.44	-1.98	.05
	Step velocity SD (*ms*)	0.057	0.016	0.066	0.018	-2.95	**<.01**	0.060	0.017	0.059	0.015	0.47	.64
	Step length SD (*m*)	0.023	0.008	0.029	0.009	-3.15	**<.01**	0.022	0.006	0.022	0.007	0.35	.73
Rhythm													
	Step time (*ms*)	571.20	52.07	570.74	56.74	.044	0.97	547.00	51.63	554.07	58.60	-0.85	.40
	Swing time (*ms*)	393.48	35.01	387.67	34.60	0.85	0.40	389.34	31.53	391.21	36.54	-0.36	.72
	Stance time (*ms*)	749.36	84.82	754.43	87.73	-0.30	0.76	705.40	78.27	717.41	90.05	-0.95	.35
Asymmetry													
	Step time asymmetry (*ms*)	4.58	2.48	4.36	2.62	0.44	0.66	2.89	1.43	3.63	1.95	-2.95	**<.01**
	Swing time asymmetry (*ms*)	4.10	1.98	3.75	1.95	0.89	0.38	2.66	1.42	3.05	1.72	-1.65	.10
	Stance time asymmetry (*ms*)	4.01	2.07	3.84	1.89	0.44	0.66	2.65	1.29	3.11	1.82	-1.80	.08
Postural Control													
	Step length asymmetry (*m*)	0.148	0.075	0.150	0.079	-0.14	0.89	0.126	0.058	0.141	0.063	-1.64	.10
	Step width (*m*)	0.094	0.033	0.097	0.030	-0.55	0.58	0.095	0.027	0.094	0.028	0.03	.98
	Step width SD (*m*)	0.018	0.005	0.019	0.005	-0.83	0.41	0.024	0.005	0.022	0.005	3.17	**<.01**

18. Appendix 18.0: Dual task gait characteristic predictors of cognitive decline in PD.

		CRT β	CRT St. Err	CRT T	CRT p	CRTCV β	CRTCV St. Err	CRTCV T	CRTCV p	SRM β	SRM St. Err	SRM T	SRM p	OTS β	OTS St. Err	OTS T	OTS p
Pace	Step Velocity	-41.44	25.63	-1.62	0.11	-3.86	1.24	-3.11	<0.01 X^2 15.02*	1.36	0.52	2.60	0.01 X^2 8.56*	1.37	0.99	1.38	0.17
Pace	Step Length	-81.13	55.66	-1.46	0.15	-8.37	2.69	-3.12	<0.01 X^2 15.06*	3.00	1.13	2.65	<0.01 X^2 10.53*	3.18	2.15	1.48	0.14
Variability	Swing Time SD	43.15	17.99	2.40	0.02 X^2 6.68	2.83	0.89	3.17	<0.01 X^2 13.16*	-0.88	0.39	-2.29	0.02 X^2 7.40	-0.38	0.73	-0.52	0.61
Variability	Step Time SD	42.54	16.30	2.61	0.01 X^2 7.50	2.35	0.82	2.87	0.01 X^2 10.57*	-0.85	0.35	-2.43	0.02 X^2 9.96*	-0.50	0.66	-0.76	0.45
Variability	Step Stance SD	28.32	14.39	1.97	0.05	1.50	0.72	2.08	0.04 X^2 6.85	-0.76	0.30	-2.51	0.01 X^2 9.09*	-0.60	0.58	-1.03	0.30
Variability	Vel SD	426.95	330.19	1.29	0.20	-4.10	16.75	-0.25	0.81	-9.52	7.06	-1.35	0.18	-4.99	13.25	-0.38	0.71
Variability	Len SD	1050.06	678.34	1.55	0.12	82.47	33.50	2.46	0.02 X^2 7.02	-28.06	14.46	-1.94	0.05	-24.58	27.42	-0.90	0.37
Rhythm	Step time	0.11	0.11	1.00	0.32	0.01	0.01	2.16	0.03 X^2 5.74	-<.01	<.01	-1.11	0.27	-<.01	<.01	-0.29	0.77
Rhythm	Swing time	0.04	0.17	0.23	0.82	-<.01	0.01	-0.52	0.60	<.01	<.01	0.69	0.49	<.01	<.01	0.57	0.57
Rhythm	Stance time	0.08	0.07	1.11	0.27	0.01	0.003	2.93	<0.01 X^2 10.97*	-<.01	<.01	-1.64	0.10	-<.01	<.01	-0.58	0.56
Asymmetry	Step Asy	0.98	2.45	0.40	0.69	0.27	0.12	2.29	0.02 X^2 5.03	-0.04	0.05	-0.80	0.43	-<.01	0.09	-0.05	0.96
Asymmetry	Swing Asy	-0.53	3.01	-0.18	0.86	0.31	0.15	2.10	0.04 X^2 4.34	-0.07	0.06	-1.21	0.23	0.15	0.11	1.34	0.18
Asymmetry	Stance Asy	0.05	2.95	0.02	0.99	0.36	0.14	2.55	0.01 X^2 6.55	-0.03	0.06	-0.46	0.64	0.13	0.11	1.24	0.22
Postural Control	Length Asy	-18.86	75.40	-0.25	0.80	4.68	3.74	1.25	0.21	-2.98	1.55	-1.92	0.06	1.85	2.91	0.64	0.53
Postural Control	Width	-45.74	184.63	-0.25	0.80	27.70	8.86	3.13	<0.01 X^2 9.46*	-3.04	3.89	-0.78	0.44	-2.01	7.26	-0.28	0.78
Postural Control	Step Wid SD	1659.43	1095.11	1.52	0.13	20.24	55.82	0.36	0.72	36.15	22.54	1.60	0.11	30.34	46.07	0.72	0.47

*Bright green= significant predictors, medium green= near significant predictors. [CRT= choice reaction time, CRTCV=choice reaction time coefficient of variance, SRM= spatial recognition memory, OTS= one touch stockings]. *= Log-likelihood ratio test significance.*

19. Appendix 19.0: Dual task gait domains as predictors of cognitive decline in PD.

	CRT				CRTCV				SRM				OTS			
	β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p
Pace	-8.48	4.97	-1.71	0.09	-0.59	0.25	-2.41	0.02	0.30	0.10	2.91	<.01	0.35	0.19	1.80	0.07
Rhythm	-4.30	5.60	-0.80	0.44	-0.07	0.28	-0.25	0.80	-0.08	0.12	-0.69	0.49	-0.02	0.23	-0.09	0.93
Asymmetry	0.80	3.58	0.22	0.82	-0.36	0.18	-2.07	0.04	0.04	0.07	0.58	0.56	-0.16	0.14	-1.17	0.25
Variability	-8.86	4.69	-1.89	0.06	-0.19	0.24	-0.78	0.44	0.079	0.01	0.78	0.43	0.05	0.19	0.25	0.81
Postural Control	2.42	4.36	0.55	0.58	-0.52	0.21	-2.46	0.02	0.15	0.09	1.70	0.1	-0.01	0.17	-0.05	0.96

Bright green= significant predictors, medium green= near significant predictors. [CRT= choice reaction time, CRTCV= choice reaction time coefficient of variance, SRM= spatial recognition memory, OTS= one touch stockings.]

20. Appendix 20.0: Dual task gait characteristic predictors of cognitive decline in controls.

		CRT				CRTCV				SRM				OTS			
		β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p
Pace	Step Velocity	39.80	18.73	2.12	0.03 X^2 11.69*	0.69	1.11	0.62	0.54	0.42	0.52	0.80	0.43	0.48	0.60	0.81	0.42
	Step Length	35.21	44.85	0.79	0.43	2.06	2.66	0.78	0.44	-0.27	1.26	-0.22	0.83	2.07	1.42	1.46	0.15
Variability	Swing Time SD	-2.22	12.13	-0.18	0.86	0.19	0.72	0.26	0.79	-0.64	0.34	-1.86	0.06	-1.01	0.40	-2.54	0.01 X^2 7.62
	Step Time SD	-5.81	10.98	-0.53	0.60	-0.29	0.65	-0.45	0.65	-0.42	0.31	-1.34	0.18	-0.72	0.36	-2.00	0.05
	Step Stance SD	-9.03	9.36	-0.97	0.34	-0.29	0.55	0.52	0.61	-0.31	0.27	-1.16	0.25	-0.64	0.30	-2.12	0.04 X^2 5.24
	Vel SD	423.20	211.51	2.00	0.05	-5.87	12.71	-0.46	0.65	2.65	5.79	0.46	0.65	-12.08	6.45	-1.87	0.06
	Len SD	767.71	592.33	1.30	0.20	19.98	35.25	0.57	0.57	2.64	15.60	0.17	0.87	-34.75	17.42	-1.99	0.05
Rhythm	Step time	-0.17	0.07	-2.57	0.01 X^2 8.05	-<0.01	<.001	-0.30	0.76	-<0.01	<0.01	-1.65	0.10	<0.01	<0.01	0.52	0.61
	Swing time	-0.18	0.11	-1.66	0.1	-<0.01	<0.01	-0.16	0.87	-<0.01	<0.01	-1.26	0.21	<0.01	<0.01	0.33	0.74
	Stance time	-0.12	0.04	-2.72	<0.01 X^2 9.40*	-<0.01	<0.01	-0.30	0.77	-<0.01	<0.01	-1.67	0.10	<0.01	<0.01	0.56	0.58
Asymmetry	Step Asy	-2.52	2.33	-1.08	0.28	0.16	0.14	1.16	0.25	-0.04	0.07	-0.64	0.52	-0.01	0.08	-0.16	0.87
	Swing Asy	2.37	2.33	1.02	0.31	0.10	0.14	0.75	0.45	-0.03	0.07	-0.52	0.60	-0.04	0.08	-0.55	0.58
	Stance Asy	3.08	2.47	1.25	0.21	0.09	0.15	0.59	0.56	-0.10	0.07	-1.41	0.16	-0.01	0.08	-0.16	0.87
Postural Control	Length Asy	-69.46	58.78	-1.18	0.24	0.61	3.49	0.17	0.86	-3.18	1.67	-1.91	0.06	-2.72	1.91	-1.42	0.16
	Width	-21.99	127.24	-0.17	0.86	2.47	7.53	0.33	0.74	1.67	3.65	0.46	0.65	1.55	4.16	-0.37	0.71
	Step Wid SD	315.87	649.35	0.49	0.63	-16.89	38.34	-0.44	0.66	-7.75	18.23	-0.43	0.67	-40.96	20.27	-2.02	0.04 X^2 4.15

*Bright green= significant predictors, medium green= near significant predictors. [CRT= choice reaction time, CRTCV=choice reaction time coefficient of variance, SRM= spatial recognition memory, OTS= one touch stockings.] *=Log-likelihood ratio test significance.*

21. Appendix 21.0: Dual task gait domains as predictors of cognitive decline in controls.

Domain DT Control	CRT				CRTCV				SRM				OTS			
	β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p	β	St. Err	T	p
Pace	5.47	3.62	1.51	0.13	0.15	0.21	0.72	0.47	0.05	0.10	0.53	0.60	0.12	0.12	1.01	0.31
Rhythm	7.94	3.014	2.53	0.01	0.06	0.19	0.34	0.73	0.13	0.09	1.48	0.14	-0.06	0.10	-0.61	0.54
Asymmetry	-3.61	3.05	-1.18	0.24	-0.19	0.18	-1.04	0.30	0.06	0.09	0.65	0.51	0.03	0.10	0.31	0.76
Variability	-6.61	3.01	-2.20	0.03	0.02	0.18	0.12	0.90	-0.02	0.08	-0.28	0.78	0.22	0.10	2.44	0.02
Postural Control	3.73	3.44	1.08	0.28	-0.12	0.20	-0.61	0.54	0.06	0.10	0.64	0.52	0.08	0.11	0.69	0.49

Bright green= significant predictors, medium green= near significant predictors. [CRT= choice reaction time, CRTCV= choice reaction time coefficient of variation, SRM= spatial recognition memory, OTS= one touch stockings]

22. Appendix 22.0. Steady state walking; environment differences using a BWM

Gait Domain/Characteristic	Lab		Free-living		Paired Samples
	Mean	SD	Mean	SD	P
Pace					
Step Velocity	1.01	0.05	1.07	0.13	<.01
Step Length	0.53	0.07	0.59	0.05	<.01
Rhythm					
Step Time	0.57	0.06	0.59	0.04	<.01
Stance Time	0.72	0.06	0.74	0.05	<.01
Swing Time	0.41	0.06	0.44	0.04	<.01
Asymmetry					
Step Time Asy	0.022	0.006	0.024	0.023	.60
Stance Time Asy	0.025	0.025	0.022	0.006	.36
Swing Time Asy	0.026	0.026	0.020	0.006	.13
Step Length Asy	0.084	0.071	0.025	0.100	<.01
Variability					
Step Time SD	0.06	0.06	0.16	0.04	<.01
Stance Time SD	0.06	0.06	0.17	0.05	<.01
Swing Time SD	0.06	0.06	0.13	0.03	<.01
Step Length SD	0.084	0.053	0.137	0.028	<.01
Step Velocity SD	0.153	0.077	0.332	0.065	<.01

23. Appendix 23.0. Descriptive data for gait characteristics in free-living for all AB.

Gait Domain/ Characteristic	All Bouts		AB 10-20		AB ≥120	
	Mean	SD	Mean	SD	Mean	SD
Pace						
Step Velocity	1.009	0.090	0.973	0.082	1.066	0.132
Step Length	0.570	0.035	0.558	0.031	0.595	0.050
Rhythm						
Step Time	0.607	0.032	0.620	0.034	0.593	0.042
Stance Time	0.757	0.039	0.768	0.040	0.748	0.051
Swing Time	0.459	0.028	0.475	0.033	0.439	0.036
Asymmetry						
Step Time Asy	0.101	0.022	0.086	0.024	0.022	0.006
Stance Time Asy	0.103	0.023	0.088	0.026	0.022	0.006
Swing Time Asy	0.093	0.020	0.079	0.021	0.020	0.006
Step Length Asy	0.078	0.012	0.084	0.014	0.025	0.009
Variability						
Step Time SD	0.182	0.024	0.189	0.024	0.161	0.042
Stance Time SD	0.196	0.029	0.203	0.030	0.175	0.048
Swing Time SD	0.152	0.018	0.159	0.016	0.132	0.031
Step Length SD	0.153	0.011	0.152	0.008	0.139	0.027
Step Velocity SD	0.368	0.034	0.370	0.033	0.334	0.061

24. Appendix 24.0: Partial correlations for controlled laboratory assessment.

Gait Domain/ Gait Characteristic Lab Ax	MoCA	Digit Span	SRT	DV	CRT	SRT CV	DV CV	CRT CV	PRM	SRM	OTS	Pent
Pace												
Step Velocity	.235	.171	-.164	-.225	-.270	**-.393**	-.104	-.144	.061	.066	-.002	-.131
	(.129)	(.274)	(.293)	(.146)	(.080)	**(.009)**	(.508)	(.357)	(.698)	(.674)	(.990)	(.401)
Step Length	.014	.091	-.158	-.117	-.192	-.262	-.047	.007	-.085	-.112	-.046	-.228
	(.928)	(.563)	(.313)	(.456)	(.219)	(.090)	(.763)	(.964)	(.589)	(.476)	(.772)	(.141)
Rhythm												
Step Time	**-.365**	-.194	.063	.216	.143	.234	.084	.234	-.196	-.287	-.050	-.143
	(.016)	(.212)	(.688)	(.164)	(.359)	(.130)	(.593)	(.130)	(.208)	(.062)	(.751)	(.362)
Stance Time	**-.374**	-.080	.055	.224	.120	.297	.017	.120	-.192	**-.308**	.013	-.089
	(.013)	(.612)	(.725)	(.149)	(.443)	(.053)	(.914)	(.444)	(.218)	**(.044)**	(.933)	(.571)
Swing Time	**-.309**	-.280	.061	.181	.148	.141	.142	**.317**	-.176	-.228	-.107	-.180
	(.044)	(.069)	(.697)	(.245)	(.343)	(.368)	(.364)	**(.038)**	(.258)	(.142)	(.496)	(.249)
Asymmetry												
Step Time Asy	-.208	-.094	.087	.056	**.307**	.203	-.103	.178	-.193	-.173	-.181	.043
	(.181)	(.550)	(.581)	(.722)	**(.045)**	(.191)	(.511)	(.254)	(.215)	(.267)	(.247)	(.785)
Stance Time Asy	-.120	-.053	.076	-.036	.213	.154	-.091	**.357**	-.019	-.020	-.116	.105
	(.444)	(.736)	(.630)	(.816)	(.170)	(.324)	(.560)	**(.019)**	(.901)	(.896)	(.457)	(.504)
Swing Time Asy	-.103	-.040	.051	-.078	.173	.161	-.082	**.338**	.004	-.020	-.064	.141
	(.510)	(.801)	(.744)	(.621)	(.267)	(.302)	(.601)	**(.027)**	(.979)	(.896)	(.686)	(.367)
Step Length Asy	**-.337**	-.062	.220	**.441**	.251	.150	-.039	.241	.101	.097	-.015	.088
	(.027)	(.693)	(.157)	**(.003)**	(.105)	(.336)	(.806)	(.120)	(.521)	(.538)	(.923)	(.573)
Variability												
Step Time SD	**-.364**	**-.308**	**.382**	.261	.230	**.428**	.124	.248	-.163	**-.513**	-.164	**-.385**
	(.016)	**(.045)**	**(.012)**	(.091)	(.138)	**(.004)**	(.429)	(.108)	(.297)	**(<.001)**	(.294)	**(.011)**
Stance Time SD	**-.362**	-.297	**.386**	.251	.234	**.431**	.121	.271	-.151	**-.509**	-.166	**-.365**
	(.017)	(.053)	**(.011)**	(.105)	(.131)	**(.004)**	(.439)	(.078)	(.333)	**(<.001)**	(.287)	**(.016)**
Swing Time SD	**-.378**	-.275	**.400**	.261	.259	**.434**	.138	.284	-.154	**-.502**	-.177	**-.373**
	(.012)	(.074)	**(.008)**	(.091)	(.094)	**(.004)**	(.379)	(.065)	(.325)	**(.001)**	(.257)	**(.014)**
Step Length SD	-.239	-.159	.267	**.322**	.278	.182	.220	**.312**	-.054	**-.329**	-.258	**-.341**
	(.123)	(.309)	(.084)	**(.035)**	(.071)	(.242)	(.156)	**(.042)**	(.732)	**(.031)**	(.094)	**(.025)**
Step Velocity SD	-.092	-.148	.112	-.027	.066	.190	.024	.143	-.184	-.019	-.140	.188
	(.540)	(.320)	(.453)	(.858)	(.659)	(.201)	(.872)	(.337)	(.215)	(.899)	(.349)	(.206)

Bright green= significant predictors, medium green= near significant predictors. MoCA= Montreal Cognitive Assessment, SRT= simple reaction time, DV= digit vigilance, CRT= choice reaction time, CV= coefficient of variation, PRM= pattern recognition memory, SRM= spatial recognition memory, OTS= one touch stockings, Pent= pentagons.

25. Appendix 25.0: Partial correlations for gait and cognition for ≥120 second AB in PD.

Gait Domain/ Gait Characteristic ≥120	MoCA	Digit Span	SRT	DV	CRT	SRT CV	DV CV	CRT CV	PRM	SRM	OTS	Pent
Pace												
Step Velocity	-.080 (.580)	.137 (.342)	**-.289 (.042)**	-.107 (.459)	.004 (.978)	.142 (.327)	.080 (.582)	.018 (.900)	-.153 (.288)	.102 (.483)	-.078 (.592)	-.025 (.862)
Step Length	-.182 (.205)	.143 (.322)	-.251 (.078)	-.076 (.598)	.069 (.636)	.176 (.221)	.036 (.806)	.073 (.615)	-.148 (.306)	.027 (.854)	-.129 (.372)	-.039 (.789)
Rhythm												
Step Time	-.092 (.524)	-.101 (.483)	.268 (.060)	.166 (.250)	.193 (.180)	.023 (.874)	-.006 (.967)	.250 (.080)	.096 (.505)	-.230 (.107)	-.059 (.683)	.002 (.991)
Stance Time	-.088 (.545)	-.085 (.559)	.260 (.068)	.170 (.237)	.190 (.187)	.040 (.780)	.001 (.994)	.231 (.106)	.105 (.469)	-.243 (.090)	-.053 (.717)	-.001 (.997)
Swing Time	-.106 (.465)	-.124 (.389)	.237 (.098)	.186 (.196)	.202 (.160)	-.016 (.911)	-.048 (.742)	**.289 (.042)**	.070 (.628)	-.201 (.161)	-.074 (.609)	-.027 (.855)
Asymmetry												
Step Time Asy	**-.299 (.035)**	-.074 (.608)	.203 (.157)	.071 (.626)	.207 (.149)	**.331 (.019)**	-.082 (.569)	.109 (.453)	**-.288 (.042)**	**-.371 (.008)**	-.158 (.273)	-.145 (.315)
Stance Time Asy	-.215 (.134)	-.073 (.615)	.173 (.231)	.087 (.547)	.191 (.183)	**.391 (.005)**	.036 (.804)	.226 (.114)	-.199 (.166)	**-.313 (.027)**	-.067 (.642)	-.091 (.531)
Swing Time Asy	-.265 (.063)	-.125 (.388)	.252 (.078)	.049 (.734)	.270 (.058)	**.362 (.010)**	.094 (.514)	**.336 (.017)**	-.236 (.099)	**-.316 (.025)**	-.148 (.306)	-.133 (.358)
Step Length Asy	.032 (.825)	-.012 (.932)	-.138 (.341)	-.240 (.093)	-.015 (.918)	.067 (.646)	.235 (.100)	.242 (.091)	-.058 (.691)	.056 (.697)	-.042 (.773)	.072 (.617)
Variability												
Step Time SD	-.031 (.830)	-.125 (.388)	.255 (.074)	.196 (.172)	.185 (.199)	.109 (.452)	.049 (.737)	.197 (.170)	-.014 (.922)	-.276 (.053)	-.004 (.979)	-.016 (.911)
Stance Time SD	-.028 (.846)	-.152 (.291)	.252 (.078)	.201 (.161)	.202 (.159)	.097 (.504)	.035 (.809)	.240 (.094)	-.005 (.973)	-.267 (.061)	-.012 (.933)	-.014 (.926)
Swing Time SD	.003 (.983)	-.085 (.557)	.230 (.108)	.184 (.201)	.145 (.313)	.094 (.518)	.043 (.768)	.153 (.290)	.005 (.971)	-.276 (.053)	.038 (.794)	-.021 (.884)
Step Length SD	-.082 (.572)	-.082 (.571)	.082 (.571)	.151 (.296)	.010 (.943)	.172 (.231)	-.074 (.609)	-.148 (.307)	-.113 (.433)	**-.294 (.038)**	.041 (.780)	-.046 (.751)
Step Velocity SD	.001 (.997)	-.055 (.703)	.029 (.841)	.131 (.365)	.002 (.990)	.152 (.292)	-.016 (.915)	-.076 (.599)	-.130 (.370)	-.247 (.083)	.079 (.584)	-.050 (.728)

Bright green= significant predictors, medium green= near significant predictors. MoCA= Montreal Cognitive Assessment, SRT= simple reaction time, DV= digit vigilance, CRT= choice reaction time, CV= coefficient of variation, PRM= pattern recognition memory, SRM= spatial recognition memory, OTS= one touch stockings, Pent= pentagons.

26. Appendix 26.0: Partial correlations for gait and cognition for 10-20 second AB in PD.

Gait Domain/ Gait Characteristic AB 10-20	MoCA	Digit Span	SRT	DV	CRT	SRT CV	DV CV	CRT CV	PRM	SRM	OTS	Pent
Pace												
Step Velocity	.157	-.015	-.030	.017	-.034	.169	.083	-.066	-.101	-.015	.081	-.080
	(.271)	(.915)	(.837)	(.903)	(.815)	(.235)	(.564)	(.643)	(.482)	(.916)	(.574)	(.577)
Step Length	.252	.160	.015	.087	-.013	.154	-.033	-.040	-.020	-.063	.216	-.104
	(.075)	(.261)	(.917)	(.542)	(.925)	(.280)	(.817)	(.780)	(.889)	(.659)	(.129)	(.468)
Rhythm												
Step Time	-.048	.010	.234	.197	.183	.117	-.130	**.287**	.026	**-.340**	.044	-.026
	(.741)	(.945)	(.098)	(.165)	(.198)	(.414)	(.363)	**(.041)**	(.856)	**(.015)**	(.760)	(.858)
Stance Time	-.130	-.071	.275	.195	.192	.191	-.117	**.324**	-.038	**-.420**	-.003	-.059
	(.364)	(.621)	(.051)	(.169)	(.177)	(.179)	(.413)	**(.020)**	(.794)	**(.002)**	(.984)	(.680)
Swing Time	.040	.072	.129	.167	.186	-.006	-.077	.262	.075	-.157	.080	.017
	(.778)	(.617)	(.366)	(.241)	(.191)	(.968)	(.591)	(.063)	(.601)	(.270)	(.575)	(.907)
Asymmetry												
Step Time Asy	-.194	-.192	**.418**	.129	.263	**.382**	.104	**.324**	-.092	**-.351**	-.177	-.107
	(.172)	(.176)	**(.002)**	(.366)	(.062)	**(.006)**	(.467)	**(.020)**	(.523)	**(.012)**	(.214)	(.456)
Stance Time Asy	-.196	-.193	**.399**	.106	.249	**.394**	.083	**.344**	-.090	-.276	-.177	-.049
	(.169)	(.176)	**(.004)**	(.459)	(.078)	**(.004)**	(.564)	**(.014)**	(.531)	(.050)	(.213)	(.733)
Swing Time Asy	-.191	-.131	**.392**	.077	.188	**.431**	.095	.232	-.114	-.275	-.166	-.031
	(.179)	(.360)	**(.004)**	(.589)	(.187)	**(.002)**	(.509)	(.101)	(.428)	(.051)	(.244)	(.830)
Step Length Asy	.111	-.044	.148	.066	.076	.269	.153	.174	-.010	-.241	.076	-.075
	(.440)	(.761)	(.301)	(.646)	(.595)	(.056)	(.283)	(.222)	(.942)	(.088)	(.597)	(.599)
Variability												
Step Time SD	**-.319**	-.162	**.310**	**.330**	.269	**.338**	.054	**.336**	-.132	**-.491**	-.159	-.141
	(.022)	(.256)	**(.027)**	**(.018)**	(.056)	**(.015)**	(.705)	**(.016)**	(.355)	**(<.001)**	(.265)	(.324)
Stance Time SD	**-.311**	-.218	**.328**	**.294**	**.296**	**.353**	.073	**.414**	-.133	**-.465**	-.172	-.121
	(.026)	(.124)	**(.019)**	**(.037)**	**(.035)**	**(.011)**	(.611)	**(.003)**	(.353)	**(.001)**	(.228)	(.396)
Swing Time SD	**-.354**	-.131	**.279**	**.326**	.210	.263	.008	**.278**	-.138	**-.481**	-.159	-.090
	(.011)	(.359)	**(.048)**	**(.019)**	(.139)	(.063)	(.957)	**(.048)**	(.335)	**(<.001)**	(.266)	(.528)
Step Length SD	-.232	-.104	.088	.170	.071	.211	.180	.113	-.066	**-.345**	-.146	-.129
	(.102)	(.468)	(.537)	(.234)	(.621)	(.137)	(.205)	(.428)	(.647)	**(.013)**	(.307)	(.366)
Step Velocity SD	-.144	-.169	.022	.124	.014	.184	.100	.038	-.158	-.157	-.012	-.136
	(.312)	(.235)	(.878)	(.387)	(.922)	(.196)	(.483)	(.793)	(.269)	(.271)	(.935)	(.340)

Bright green= significant predictors, medium green= near significant predictors. MoCA= Montreal Cognitive Assessment, SRT= simple reaction time, DV= digit vigilance, CRT= choice reaction time, CV= coefficient of variation, PRM= pattern recognition memory, SRM= spatial recognition memory, OTS= one touch stockings, Pent= pentagons.

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