Vision and gait in Parkinson's disease: impact of cognition and response to visual cues

Samuel George Stuart BSc (Hons), MSc

PhD

A thesis submitted for the degree of Doctor of Philosophy

Research undertaken at the Clinical Ageing Research Unit

Institute of Neuroscience

Newcastle University Institute for Ageing

January 2016

Abstract

Gait impairment is a core feature of Parkinson's disease (PD) which is difficult to treat due to its multi-factorial nature. Gait dysfunction in PD has been linked to cognitive and visual deficits through separate strands of research. However cognitive and visual functions likely interact (termed visuo-cognition) and have a combined impact on gait. Attempting to further understand the roles of cognition and vision in gait in PD was the motivation behind this thesis. The *primary aim* was therefore to investigate visuo-cognition and its role in gait in PD.

Saccade frequency during gait represents the amount of visual sampling employed when walking and is a useful online behavioural measure of visuo-cognition. However, previous investigations have been limited by lack of robust methodologies, technology and outcome measures. A *key objective* was therefore to establish robust saccadic measurement with mobile eye-tracking technology in PD and older adult controls.

My *original contributions to knowledge* were that a mobile eye-tracker can measure saccadic activity during gait in PD and controls, but with variable accuracy and reliability for certain characteristics. Cognitive and visual functions were significantly related in both PD and controls, with stronger association in PD. Saccade frequency during gait was significantly reduced in people with PD compared to controls, particularly under dual task. Impaired saccade frequency can be ameliorated with a visual cue; as such intervention significantly increased saccade frequency in PD and controls which was maintained under dual task. Saccade frequency during gait was independently associated with cognitive and visual functions in PD. A structured model demonstrated that visuo-cognitive dysfunction had an indirect effect on gait in PD, with a central role for attention in all relationships involved.

The *major conclusion* from this thesis was that gait impairment in PD is influenced by visuo-cognitive dysfunction, with implication for poor mobility and falls risk.

Acknowledgements

I would like to acknowledge everyone who has supported me and the project during my three year period at Newcastle University. Special thanks to my supervisors Professor Lynn Rochester, Dr Sue Lord and Dr Brook Galna for their continued input through my PhD. In addition, thanks to Dr Alan Godfrey and Aodhàn Hickey for their engineering and technical assistance with the complex data processing tools created and used within this project. I am indebted to Dr Elizabeth Hill who provided a second 100% data check for this project to ensure robustness of reported results.

The Clinical Ageing Research Unit, part of the Institute of Neuroscience and Newcastle University Institute of Ageing, provided me with an excellent working environment for undertaking this research. Thanks to Barbara Tait (Head of Physiotherapy, Newcastle upon Tyne Hospitals NHS Trust) for allowing me to continue my clinical practice one day per week on an honorary basis. Similarly, thanks go to Professor David Burn and Professor Lynn Rochester for allowing me to work as a physiotherapist half a day per week within the Movement Disorders clinic at the CRESTA clinic, Newcastle. I would like to thank all of the patients recruited through the Movement Disorders clinic who participated in this study, as well as the control participants who took time out of their schedules to assist me with this project. This study and my salary were funded by the National Institute for Health Research (NIHR) Biomedical Research Unit (BRU) in Newcastle upon Tyne, based within the Newcastle upon Tyne Hospitals NHS Trust and Newcastle University.

Last but definitely not least, I would like to thank my partner Rosie Morris for all of her support throughout the course of my PhD. I would like to dedicate this thesis to her, as over the past three years she has had to listen to me moan and complain about the endless workload, presentations, manuscripts, and various other activities I have endured. It is thanks to her (and her baking) that I have made it through this process, as behind every great man is a great woman.

Statement of work undertaken

This study was conceived prior to my starting as a PhD student by Professor Lynn Rochester, Dr Sue Lord and Dr Brook Galna. All of the Parkinson's disease and control assessments contained within this thesis were carried out by me at the Clinical Ageing Research Unit in Newcastle upon Tyne. Data processing and analysis was also carried out by me, with some assistance processing the data from Aòdhan Hickey (Human Movement science Research Technician) and a few of the initial Vicon trials processed by an MRes Biomedical Science student (Henry King), who was undertaking a project with me. I ran all of the testing sessions independently to collect the raw data, with only technical assistance provided from Dr Brook Galna and Aòdhan Hickey, when required.

The data cleaning and checking (100% of data collected) was completed by me and Dr Elizabeth Hill (Clinical Fellow) at the Clinical Ageing Research Unit in Newcastle. I analysed all the data independently and performed statistical analysis, with advice taken from Professor Lynn Rochester, Dr Sue Lord, Dr Brook Galna and Dr Shirley Coleman (Industrial Statistics Research Unit, Newcastle University). Data management was carried out by me as part of the Human Movement Science Team (now the Brain and Movement Research Group) at Newcastle University. I was responsible for the writing of this thesis.

Chapters 2, 3, 4, 5 and 6 of this thesis have been published as 5 original peer-reviewed papers, which are listed in the following section along with other papers arising from this body of work that I have been involved in. I have also presented results from this thesis as preliminary and complete data sets, at national and international conferences which are also listed in the following section.

Awards, publications and presentations arising from this thesis

Awards

- World Parkinson's Congress Travel Grant ($900 in 2016)
- Guarantors of Brain Travel Grant (£600 in 2016)
- British Geriatric Society; Therapist Travel Grant (£300 in 2016)
- Best Allied Health Professional Poster Award at NIHR BRC/BRU post-graduate research showcase (£500 award in 2015)
- Private Physiotherapy Educational Foundation; Travel grant (£1870 in 2014, £1500 in 2015)
- Newcastle University, Institute of Neuroscience PhD Travel Grant (£500 in 2015)
- British Geriatric Society; Therapist Travel Grant (£300 in 2015)
- Movement Disorders Society; Student Bursary ($1000 in 2015)

Publications

Hill, E., **Stuart, S.**, Lord, S., Del Din, S. and Rochester, L. (2016) 'Vision, visuo-cognition and postural control in Parkinson's disease: a closer look', *Gait and Posture.*

Stuart, S., Lord, S., Hill, E., and Rochester, L. (2016) 'Gait in Parkinson's disease: a visuo-cognitive challenge', *Neuroscience and Biobehavioural Reviews.*

Stuart, S., Alcock, L., Godfrey, A., Lord, S., Rochester, L., and Galna, B. (2016) 'Accuracy and re-test relaibaility of mobile eye-tracking in Parkinson's disease and older adults', *Medical Engineering and Physics.*

Stuart, S., Galna, B., Lord, S. and Rochester, L. (2016) 'A protocol to examine vision and gait in Parkinson's disease: impact of cognition and response to visual cues', *F1000 Research,* 4:1379.

Stuart, S., Galna, B., Lord, S., Rochester, L. and Godfrey, A. (2014) 'Quantifying Saccades While Walking: Validity of a Novel Velocity-Based Algorithm for Mobile Eye Tracking', *Engineering in Medicine and Biology Society, 2014. 36th Annual International Conference of the IEEE*. Chicago, Illinois, USA, 26-30 Aug. 2014.

Stuart, S., Alcock, L., Galna, B., Lord, S. and Rochester, L. (2014) 'The measurement of visual sampling during real-world activity in Parkinson's disease and healthy controls: A structured literature review', *Journal of Neuroscience Methods*, 222, pp. 175-88.

National and International Presentations

Stuart, S., Galna, B., Lord, S. and Rochester, L. (2016) 'Visuo-cognition in gait in Parkinson's disease: response to visual cues', Poster presentation at the 4th World Parkinson's Congress, Portland, Oregon, USA.

Stuart, S., Galna, B., Lord, S. and Rochester, L. (2016) 'Cognition, vision and visuo-cognition in gait in Parkinson's disease', Poster presentation at the Movement Disorders Society 20th International Congress, Berlin, Germany.

Stuart, S., Galna, B., Godfrey, A., Lord, S. and Rochester, L. (2015) 'Look where you're going! Do visual cues enhance visual exploration while walking in people with Parkinson's disease?', Poster presentation at the Physiotherapy UK conference, Liverpool, UK.

Stuart, S., Galna, B., Lord, S. and Rochester, L. (2015) 'Visual exploration during gait in Parkinson's disease and its cognitive correlates, Poster presentation at the National Institute for Health Research (NIHR) Dementia Biomedical Research Unit post-graduate trainee event, University College London, London, UK.

Stuart, S. (2015) 'Real-world eye tracking: what are the methodological considerations?', Oral symposium presentation at the 3rd World Congress of the International Society of Posture and Gait Research, Seville, Spain. Presented within a symposium create and organised by Sam Stuart in conjunction with Professor Lynn Rochester entitled: *'Gazing from bench to beyond: visual control of gait in the real-world and methodological challenges.'*

Stuart, S., King, H., Galna, B., Godfrey, A., Lord, S. and Rochester, L. (2015) 'Visual exploration during gait in Parkinson's disease and association with cognitive characteristics', Poster presentation at the Movement Disorders Society 19th International Congress, San Diego, California, USA.

Stuart, S., Galna, B., Lord, S. and Rochester, L. (2015) ‘Visual exploration during gait in Parkinson's disease and association with cognitive characteristics’, Poster presentation at the National Institute for Health Research (NIHR) Newcastle BRC/BRU Postgraduate Research Showcase, Newcastle upon Tyne, UK.

Stuart, S. and Morris, R. (2015) ‘Cognition and Gait in Parkinson’s disease: two different perspectives’, Oral presentation at the National Institute for Health Research (NIHR) Newcastle BRC/BRU Postgraduate Research Showcase, Newcastle upon Tyne, UK.

Yarnell, A., Morris, R., Stuart, S., Rochester, L. and Burn, D. (2014) ‘Research at Newcastle: moving forward in cognition and gait in Parkinson's’, Oral presentation (3rd speaker) at the Parkinson’s UK research conference, York, UK.

Stuart, S., Galna, B., Lord, S., Rochester, L. and Godfrey, A. (2014) ‘Quantifying Saccades While Walking: Validity of a Novel Velocity-Based Algorithm for Mobile Eye Tracking’, Poster presentation at the 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Chicago, Illinois, USA.

Stuart, S., Alcock, L., Galna, B., Lord, S. and Rochester, L. (2014) ‘Re-test reliability and accuracy of the Dikablis eye-tracker when sitting, standing and walking’, Poster presentation at the 2nd World Congress of the International Society of Posture and Gait Research, Vancouver, Canada.

Stuart, S., Alcock, L., Galna, B., Lord, S. and Rochester, L. (2014) ‘Visual sampling in Parkinson's disease: current methodological issues’, Poster presentation at the 2nd World Congress of the International Society of Posture and Gait Research, Vancouver, Canada.

Stuart, S., Alcock, L., Galna, B., Lord, S. and Rochester, L. (2013) ‘Re-test reliability and accuracy of the Dikablis eye-tracker when sitting, standing and walking’, Poster presentation at the British Oculomotor Group Meeting, Manchester, UK.

Table of Contents

List of Tables

List of Figures

Abbreviations

ACC = anterior cingulate cortex

ACE-R = Addenbrookes cognitive examination (revised version)

ANCOVA = analysis of co-variance

ANOVA = analysis of variance

BG = basal ganglia

CN = caudate nucleus

CS = contrast sensitivity

EEG = electroencephalogram

EOG = electro-oculography

FEF = frontal eye-field

FES-I = falls efficacy scale (international version)

fNIRs = functional near-infrared spectroscopy

FoA = fluctuation of attention

FOG = Freezing of gait

FOGQ = freezing of gait questionnaire

GDS-15 = geriatric depress scale (short form)

GPe = globus pallidus external

GPi = globus pallidus internal

H&Y = Hoehn and Yahr scale

ICC = intra-class correlation coefficient

IT = infero-temporal cortex

JLO = judgement of line orientation

LED = levodopa equivalent dose

LGN = lateral geniculate nucleus

LIP = lateral intraparietal area

LTIT = landmark and traffic sign identification task

M1 = primary motor cortex

MCI = mild cognitive impairment

MD = medio-dorsal thalamus

MeSH = medical subject headings

MMSE = mini mental state examination

MoCA = Montreal cognitive assessment

MT = middle temporal area (also known as V5)

NR = not reported

PD = Parkinson's disease

PDD = Parkinson's disease dementia

PEF = parietal eye-field

PFC = pre-frontal cortex

PIGD = postural instability and gait disorder

PoA = power of attention

PPC = posterior parietal cortex

PPN = pedunculopontine nucleus

SC = superior colliculus

SEF = supplementary eye field

SEM = structural equation modelling

SMA = supplementary motor area

SNc = substantia nigra pars compacta

SNr = substantia nigra pars reticulate

STN = subthalamic nucleus

TD = tremor dominant

UPDRS = unified Parkinson's disease rating scale

VA = visual acuity

VAN = ventral anterior nucleus

VL = ventral lateral nucleus

VM = ventral medial nucleus

VOR = vestibular ocular-reflex

VOSP = visual object and space perception battery

X^2 = chi-squared

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder characterised by cardinal motor symptoms such as rigidity, bradykinesia, tremor, postural instability and gait deficit (Jankovic, 2008). Gait impairments in PD include both continuous (constantly present) and episodic (freezing of gait; FOG) (Nutt *et al.*, 2011). Continuous gait impairment typically manifests as reduced velocity, step length, arm swing, increased gait variability and reduced automaticity. While episodic impairments emerge with increasing disease severity and are seen as hesitations when turning, a 'freezing' block in small spaces such as doorways and difficulty with gait initiation (Giladi *et al.*, 2013a). Gait impairments underpin difficulty walking in real-world environments such as maintaining a straight trajectory during gait (veering) (Davidsdottir *et al.*, 2008), negotiating obstacles (Vitorio *et al.*, 2013), and navigation (e.g. difficulties with narrow spaces such as doorways (Cowie *et al.*, 2010) and misjudgement of object distance (Davidsdottir *et al.*, 2005)). Moreover these problems are common and linked to falls (Paul *et al.*, 2014). Although these problems emphasise the motor complications of PD, it is however widely recognised that gait impairment is complex and reflects input from multiple systems that include both motor and non-motor systems (Grabli *et al.*, 2012). For example, there is abundant evidence of the role of cognition in gait and increasing evidence of the role of vision. Understanding their respective contributions is critical in order to inform the mechanisms that drive gait impairment and to contribute to targeted therapeutic development to improve gait, independent mobility and falls risk.

A large body of evidence supports a robust relationship between cognition and gait, highlighting that gait is underpinned by cognitive functions (Lord *et al.*, 2014). Cognitive impairments are common in PD with an estimated 40% of patients presenting with mild cognitive impairment (MCI) at diagnosis (Yarnall *et al.*, 2014) and up to ~75% with dementia at ten years (Aarsland and Kurz, 2010). Previous studies have extensively investigated the relationship between gait and cognition (Amboni *et al.*, 2013) using two methodological approaches. Associative protocols measure gait and cognition as separate behaviours and explore their relationship (correlation) to identify links between them (Lord *et al.*,

2014). Online protocols on the other hand, manipulate cognition particularly attention during walking through the use of dual-task protocols which show in real-time the contribution of cognition to gait (Kelly *et al.*, 2012b). Such protocols demonstrate gait deficit such as reduced velocity and step length are associated with impaired cognition (Lord *et al.*, 2014), and exacerbated using dual-tasks in PD (Kelly *et al.*, 2012b).

Visual impairments are also common with up to 75% of people with PD experiencing at least one symptom such as blurred vision (Davidsdottir *et al.*, 2005; Urwyler *et al.*, 2013). The relationship between vision and gait in PD has also been investigated by either exploring relationships between separate visual functions and gait or use of on-line protocols where vision is manipulated during gait (i.e. light or dark rooms) (Azulay *et al.*, 1999; Almeida *et al.*, 2005). Selective gait impairments are associated with deficits in visual functions (Moes and Lombardi, 2009), and exacerbated by visual manipulation in PD (Cowie *et al.*, 2012). Studies have shown that visual functions contribute to gait control in PD (Azulay *et al.*, 1999; Azulay *et al.*, 2002; Khattab *et al.*, 2012).

To date the relationship between gait, cognition and vision has received scant attention and is poorly understood. Cognition, vision and gait potentially interact in a selective but overlapping manner in order to plan routes and make ongoing modifications appropriate to changing environments. Static and more recently dynamic test protocols have been used to examine the interplay between cognition and vision. Static protocols range from simple associations between separate cognitive and visual outcomes, to more complex neuro-imaging or computerised saccadic (fast, jump-like) eye-movement assessment. Evidence from static tests supports an interaction between cognition and vision (Lee *et al.*, 2015), and vice versa (Bertone *et al.*, 2007; Toner *et al.*, 2012). This interaction is encompassed by the term *visuo-cognition*, which is a global descriptor of interaction between cognitive and visual functions across multiple levels of information processing (Antal *et al.*, 1998; Bandini *et al.*, 2002). Visuo-cognition is therefore distinct from limited terms such as *visuo-spatial* function, which refers to the cognitive ability of the posterior parietal cortex to perceive the spatial relationship of objects (Benton and Tranel, 1993; Possin, 2010). Deficits in visual functions impact visuo-spatial ability due to their interaction (Stoerig and Cowey,

1997), but this exhibits only one aspect of visuo-cognition. Recent technological advances in mobile eye-tracking devices have facilitated measurement of saccadic eye movements during dynamic protocols (Land, 2006), which serve as a proxy measure of visuo-cognition during gait in PD (Stuart *et al.*, 2014a) (i.e. between group differences in saccadic activity during various tasks reflect altered visuo-cognitive processing). Such studies have shown differences in saccadic activity between people with PD and older adults, but findings have been limited due to methodological issues. To provide a detailed account of the role of vision and cognition during gait in PD there is a need to understand the independent relationships, their interaction and combined impact on gait. A more refined understanding will provide insight into the underlying mechanism of gait impairment in PD and will also inform targeted therapeutic development.

1.1. Scope of Thesis

Overall this thesis was designed to further understand the roles of cognition and vision in gait in PD specifically this thesis focuses on investigation of the interaction between visual function and cognition (defined as visuo-cognition) and the role of visuo-cognition (measured via saccade frequency) in gait in PD. However before these investigations took place a secondary aim was addressed, which was to establish robust methods for saccadic data collection and analysis. An outline of the thesis structure, along with key research objectives and hypotheses to be addressed are provided in the following section.

1.2. Thesis Outline

1.2.1. Chapter 2 – Cognition, vision and visuo-cognition in gait in Parkinson's disease

Key Objective:

- To review current knowledge about the relationship between gait, cognition and vision in PD and older adults

Chapter 2 provides a narrative review, which forms the background to this thesis. The narrative review covered a substantial amount of literature regarding gait, cognition, vision and visuo-cognition in PD and older adults. A model of visuo-

cognition in gait in PD (Figure 2-1) was used to highlight the currently recognised and the unclear relationships between these features.

1.2.2. Chapter 3 – Measurement of visual sampling during real-world activities in Parkinson's disease and older adults

Key Objective:

- To review current visual sampling measurement and interpretation of outcomes in PD and older adults

Chapter 3 provides a structured review that aimed to highlight the current visual sampling (combination of saccades and fixations) measurement instruments used within PD and older adult research. This included visual sampling outcome measures and previously reported PD impairments. A series of recommendations for the methodology used in this thesis were also developed.

1.2.3. Chapter 4 - General Methodology

Chapter 4 provides an overview of the methods which were common to all of the studies contained in this thesis. Detailing participant recruitment, cognitive and visual function testing, mobile eye-tracking and gait equipment. Specific methods are also contained in relevant chapters detailing individual study methodology.

1.2.4. Chapter 5 – Quantification of saccades during gait in mobile eye-tracking data

Key Objective:

- To establish accurate measurement of saccades using mobile eye-tracking data during gait in people with PD and controls

Chapter 5 provides a preliminary study which involved the development and validation of a novel algorithm for the quantification of saccades within mobile eye-tracking data collected during gait in people with PD and older adult controls. This study provided the primary outcome (saccade frequency) of the main experimental studies contained within this thesis.

1.2.5. Chapter 6 - Accuracy and re-test reliability of mobile eye-tracking

Key Objective:

- To establish accuracy and reliability of mobile eye-tracking data collection and analysis during gait in people with PD and controls

Chapter 6 provides a preliminary study conducted to evaluate the accuracy and reliability of the mobile eye-tracking device used in this thesis in people with PD and older adult controls. This study was vital to establish robust data collection and analysis.

1.2.6. Chapter 7 - Visual sampling during gait in Parkinson's disease: attentional manipulation

Key Objective:

- To investigate saccade frequency during gait in PD under different attentional manipulation

Chapter 7 presents the primary investigation of saccade frequency during gait in PD with attentional manipulation via environmental challenge and dual task. Further analysis pertains to investigation of demographic, cognitive and visual functions underlying saccade frequency during gait. This chapter concludes by detailing saccade frequency during gait impairment in PD, and discusses potential mechanisms involved.

Hypotheses:

1. Saccade frequency will be reduced during gait in people with PD compared to age-matched controls
2. For both people with PD and controls, saccade frequency during gait will change with attentional manipulation; increasing with environmental challenge and decreasing with dual task
3. Selective cognitive and visual functions will be associated in PD and controls
4. Demographic features along with cognitive and visual functions will be associated with saccade frequency during gait, but attention will have stronger relationship than visual function

5. Saccade frequency will be associated with selective gait characteristics in PD and controls

1.2.7. Chapter 8 - Visual sampling during gait in Parkinson's disease: response to visual cues

Key Objective:

- To investigate saccade frequency response to visual cues during gait in PD

Chapter 8 presents an investigation regarding saccade frequency during gait in PD when attention was manipulated using a commonly used gait intervention; a visual cue with and without a dual task. This chapter concludes by detailing saccade frequency response and provides further analysis regarding underlying demographic, cognitive and visual functions involved in saccade frequency during gait when using a visual cue.

Hypotheses:

1. Saccade frequency during gait in PD will increase with attentional manipulation via a visual cue and will be maintained (similar to single task) under dual task
2. Saccade frequency during gait with a visual cue will relate to demographic features as well as cognitive and visual functions, particularly attention in PD

1.2.8. Chapter 9 - Modelling direct and indirect relationships

Key Objective:

- To explore direct and indirect relationships between cognitive and visual functions, saccade frequency during gait and gait in PD

Chapter 9 further investigates the a *priori* model of visuo-cognition in gait in PD, depicted in Figure 2-1. Structural equation modelling was used to examine direct and indirect relationships between cognitive and visual functions, saccade frequency during gait and gait in people with PD. The first model relates to visuo-cognition in gait in PD, the model was then manipulated by entering data from the

visual cue investigation into a second model. This chapter discusses the relationships between all of the visuo-cognitive features and gait in PD.

Hypotheses:

1. Gait impairment in PD will be related to visuo-cognitive dysfunction
2. Cognition, particularly attention will have direct effect on all visuo-cognitive processes in gait in PD
3. Association between visuo-cognitive features (attention and visual function) and saccade frequency will be selectively altered in PD with a visual cue

1.2.9. Chapter 10 – Thesis summary

Chapter 10 is the final instalment of this thesis, and provides an overall summary pertaining to all of the included studies. This chapter outlines the clinical implications and limitations of this thesis, and also discusses directions for future research with final conclusions based on all of the presented work.

2. Cognition, vision and visuo-cognition in gait in Parkinson's disease

2.1. Summary[1]

This chapter reviews literature involving cognition, vision and visuo-cognition in gait in PD. For clarity, evidence described in this chapter was synthesised into a model to provide an overview of the independent and interactive roles of vision and cognition in gait in PD (Figure 2-1). This model will be used within this thesis to help guide investigation and analysis. The model shows that previous studies have demonstrated that cognition and vision (Figure 2-1(A&B)) are related to selective gait characteristics in PD, which was discovered through separate research strands. The gap in knowledge relates to interaction between these features during gait (Figure 2-1(C)) and the impact of visuo-cognition (measured via saccade frequency) on gait in PD (Figure 2-1(D)).

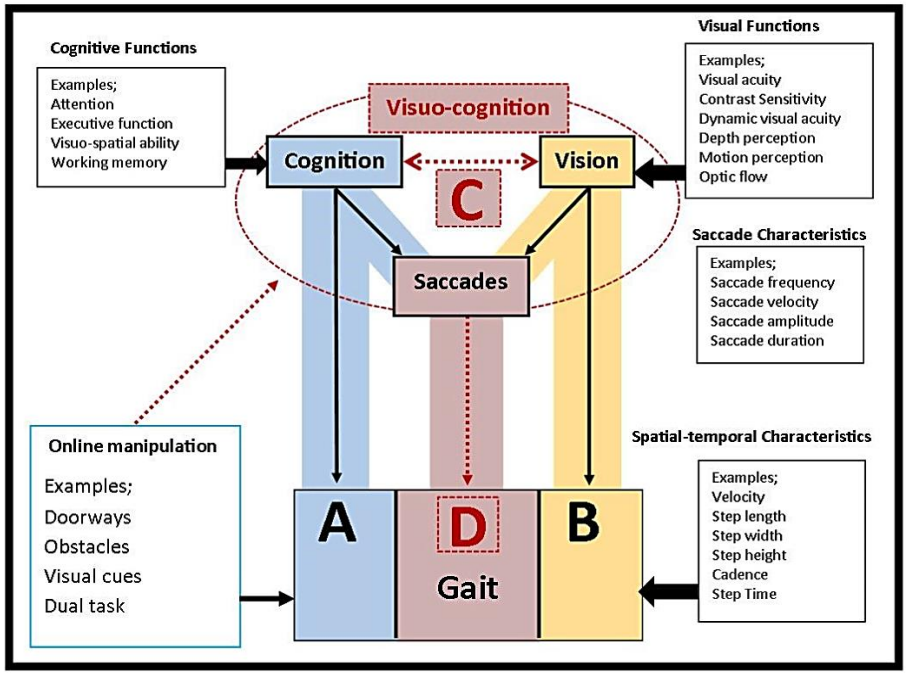


Figure 2-1 - A model detailing online relationships between vision, cognition and gait in Parkinson's disease

[Four main pathways are involved in gait; A) Cognition and gait, B) Vision and gait, C) Interaction between vision and cognition (visuo-cognition), and finally D) Visuo-cognition (measured through saccades) and gait. Recognised pathways that have been assessed using both associative and online protocols are represented by black lines. Unclear pathways that have not been assessed using both associative and online protocols are represented by dashed red lines]

[1] Sections from this chapter have been published in the journal of Neuroscience & Biobehavioural Reviews

2.2. Parkinson's disease

PD is the second most common neuro-degenerative condition in the United Kingdom after Alzheimer's disease (de Lau and Breteler, 2006), for which there is no cure. The incidence of PD has been estimated at 16 per 100,000 in the Newcastle-Gateshead area of the United Kingdom (Duncan *et al.*, 2014), which was reported as comparable to other European and American studies. The exact cause of PD remains unknown, but it is recognised that there are various stages of pathological progression (Braak *et al.*, 2003). However the disease is typified by the degeneration of dopaminergic neurones in the substantia nigra pars compacta (SNc) within the basal ganglia (BG) (Jellinger, 2014), when the disease becomes symptomatic, which is accompanied by accumulation of alpha-synuclein 'Lewy' bodies throughout the brain (Lotharius and Brundin, 2002; Fahn, 2003).

Interestingly PD has been known for possibly thousands of years, with one of the earliest records of parkinsonian symptoms being found in the ancient text '*Charaka Samhitha'* (c. 2500 BC) (Goldman and Goetz, 2007). Within this text PD was known as *Kampa vata* and involved symptoms which denote PD in modern medicine, such as no inclination to move (akinesia or bradykinesia), drooling of saliva, love of solitude (probably due to depression), constant somnolence, tremor (*or Kampa*), rigidity, dementia and, relevant to the current thesis fixation of the eyes (Goldman and Goetz, 2007). Further this ancient disease was treated with herbal seeds, which contained dopaminergic and anticholinergic agents (Manyam, 1990), some of the current treatments for PD. The most pivotal account of PD and from where it gets its current name, is that of James Parkinson's *'An Essay on the Shaking Palsy'* (Parkinson, 2002; Goetz, 2011). The '*Shaking Palsy'* (*or paralysis agitans*) was first described in western medicine by Galen (175 AD), but it was James Parkinson's essay that established PD as a recognised medical (neurological) condition (Kempster *et al.*, 2007). Due to the accurate description of motor problems in the original essay traditionally PD has been characterised as a movement (motor) disorder (Goetz, 2011). However non-motor symptoms (such as sleep disturbance, constipation and autonomic dysfunction) were recognised by James Parkinson (1755-1824) and further explored in the early work of Jean-Martin Charcot (1825-1893), the French

physician who coined the name 'Parkinson's disease' (Goldman and Goetz, 2007). Extensive research has been conducted on the motor disorder aspect of PD resulting in accurate diagnosis, robust rating scales and treatments (Chaudhuri *et al.*, 2006). Despite these advances, recent evidence shows that non-motor symptoms occur in up to 88% of PD patients and can have greater impact on health related quality of life than motor symptoms (Simuni and Sethi, 2008). This has led to more resources being allocated (Olesen and Leonardi, 2003; Chaudhuri *et al.*, 2006; Chaudhuri *et al.*, 2010) to study the impact of non-motor symptoms such as; psychiatric disorders (e.g. depression, anxiety) (Gallagher and Schrag, 2012), cognitive impairment stages (e.g. mild cognitive impairment and dementia) (Aarsland and Kurz, 2010), specific cognitive domain impairment (e.g. executive dysfunction, visuospatial and attention abnormalities) (Svenningsson *et al.*, 2012), and sensory abnormalities (e.g. visual impairments) (Armstrong, 2011; Uc *et al.*, 2011; Sauerbier and Ray Chaudhuri, 2013). Therefore the current understanding of the disease is one including both motor (such as gait disturbance) and non-motor (such as cognitive and visual impairment) symptoms, and suggests that PD is a complex multi-system neurodegenerative disorder.

2.3. Gait in Parkinson's disease

The ability to safely, effectively and efficiently walk is essential for a high quality, independent life (Giladi *et al.*, 2013b). As noted, gait disturbance presents early and is the defining feature of PD, developing into a significant cause of disability. Indeed, gait disturbance in PD has been related to secondary consequences such as impaired quality of life (Muslimović *et al.*, 2008), deconditioning, mood disorder (Lord *et al.*, 2013a), morbidity and mortality (de Lau *et al.*, 2014).

Traditionally PD gait impairment was thought of as disruption of automatic motor control through the role that the BG play in integrating planning, sequencing (involving internal motor cues) and execution of movements (Grasso *et al.*, 1999; Desmurget *et al.*, 2004b). Indeed, previous studies have demonstrated that PD impacts the BG-thalamo-cortical loops (DeLong and Wichmann, 2007; Obeso *et al.*, 2008a; Obeso *et al.*, 2008b), particularly output to the supplementary motor area (SMA) (Rascol *et al.*, 1992; Boecker *et al.*, 1998; Akkal *et al.*, 2007; DeLong and Georgopoulos, 2011). Such impairment leads to abnormal spatial temporal

gait characteristics (Figure 2-1) (Bovonsunthonchai *et al.*, 2014), as well as reduced ability to initiate, correctly sequence or switch movements compared to age-matched older adults (Morris *et al.*, 2001; Mohammadi *et al.*, 2015). Communication between the BG, SMA and motor cortex can be normalised with dopaminergic medication (Buhmann *et al.*, 2003; Buhmann *et al.*, 2004). However, in later stages of the disease treatment options are limited given the refractory nature of gait response to dopaminergic therapy and surgery (e.g. deep brain stimulation) (Rochester *et al.*, 2011; Rochester *et al.*, 2012a; Galna *et al.*, 2015). Improvements, particularly in step length and gait velocity are marked early in response to dopaminergic therapies, but this attenuates over time and severe gait disturbances such as festination (Giladi *et al.*, 2001a), freezing of gait (FOG) (Giladi *et al.*, 2001b) and falls (Mactier *et al.*, 2015) become established. Indeed, increased disease severity has been related to increased continuous gait disturbance (Morris *et al.*, 2005), episodic FOG (Mohammadi *et al.*, 2015), hesitation (Burleigh-Jacobs *et al.*, 1997) and festination (Giladi *et al.*, 2001a). The traditional dysfunctional BG-cortical loop theory has therefore been superseded as recent work has demonstrated that large networks within the central and peripheral nervous systems are involved in gait (Dietz, 2003; Tessitore *et al.*, 2012; Bohnen and Jahn, 2013; Giladi *et al.*, 2013b; Takakusaki, 2013), including external sensory input (Ferrucci *et al.*, 2000; Lord *et al.*, 2013b).

Several recent reviews have highlighted that dysfunction and lesions within extra-dopaminergic regions may relate to PD gait disorder (Grabli *et al.*, 2012; Herman *et al.*, 2013). Several recent studies have alluded to the role of brainstem regions within the reticular formation such as the mesencephalic locomotor region in gait in PD (Snijders *et al.*, 2011; Weiss *et al.*, 2015), with atrophy of grey matter in this region implicated in FOG (Snijders *et al.*, 2011). Specifically, dysfunctional cholinergic neurons of the pedunculopontine nucleus (PPN) within this structure (Zweig *et al.*, 1989) in PD may relate to gait deficit (Pahapill and Lozano, 2000) and falls (Karachi *et al.*, 2010). Other cortical, sub-cortical, brainstem and spinal cord structures such as the cerebellum, locus coeruleus (norepinephrine system), raphe nucleus and cerebral cortices have also been implicated (Hanakawa *et al.*, 1999; Del Tredici and Braak, 2012; Grabli *et al.*, 2012; Shine *et al.*, 2013c; Wu

and Hallett, 2013). However the application of non-dopaminergic therapies such as cholinesterase inhibitors remains limited (Yarnall *et al.*, 2011).

Structural changes, reduced functional connectivity and non-dopaminergic neurotransmitter involvement in gait deficit in PD have been related to impaired cognitive and sensory (visual) functions due to dysfunctional frontal and parietal processing (Hanakawa *et al.*, 1999; Tessitore *et al.*, 2012; Herman *et al.*, 2013; Shine *et al.*, 2013a). Gait disturbance is more marked in the Postural Instability and Gait Disturbance (PIGD) phenotype (Vervoort *et al.*, 2015), which may relate to more rapid cognitive decline than the tremor-dominant (TD) phenotype (Kelly *et al.*, 2015). Another explanation relates to greater grey matter atrophy in cognitive, motor, associative and sub-cortical regions with PIGD (Rosenberg-Katz *et al.*, 2013). Similarly those with more severe gait disturbance in PD have been shown to have increased activation of vision related areas such as the right parietal cortex during gait initiation and termination within motor imagery tasks (Crémers *et al.*, 2012; Wai *et al.*, 2012). This evidence highlights the complex nature of gait impairment in PD, which cannot solely be attributed to BG dysfunction with dopaminergic depletion.

The mentioned motor and non-motor deficits impact straight walking (Morris *et al.*, 2001) and more complex activities such as turning, which is a particularly problematic task for people with PD (Carpenter and Bloem, 2011). Turns are a primary trigger for FOG (Moore *et al.*, 2008; Nieuwboer *et al.*, 2009) and are associated with increased falls risk (Canning *et al.*, 2014; Mactier *et al.*, 2015), which is of importance to this thesis. Notably falls which occur during a turn have been reported as more likely to lead to hip fracture in people with PD compared to older adults (Cumming and Klineberg, 1994; Melton *et al.*, 2006). Further understanding gait in PD may therefore inform appropriate therapeutic intervention to lower falls risk and improve mobility, leading to healthy ageing and more effective disease management.

2.3.1. Summary of gait in Parkinson's disease

The pathophysiology of gait disturbance in PD remains poorly understood, with evidence demonstrating that both dopaminergic and non-dopaminergic contributors such as cholinergic degeneration play a role. The automatic and

rhythmic nature of gait implies that it is a simple task; however gait requires integration of numerous levels of information processing, including integration of internal cortical, sub-cortical, brainstem and spinal cord neural networks with external sensory input (Figure 2-1 and 2-2). Ageing and pathology can affect any number of these levels to cause gait disturbance in PD, hence gait is no longer thought of as purely a motor task or reflexive activity, but as mentioned is viewed as a complex multisystem disorder which involves non-motor mechanisms such as cognitive and sensory (visual) processes.

2.4. Cognition

Cognition is a multi-dimensional construct represented by interdependent functions, such as attention, executive function, visuo-spatial ability and working memory, each of which are considered in this thesis (see Table 2-1 for definitions). Complex relationships exist between these interdependent cognitive functions, which indicate both separate and overlapping features. Indeed, attentional and executive functions (which may or may not include working memory (Kane and Engle, 2002; Kane *et al.*, 2007)) overlap to the extent that they are often considered as one cognitive process (Engle, 2002; Engle and Kane, 2004; Kane *et al.*, 2006), representing a unitary domain (Posner and Raichle, 1996; Berger and Posner, 2000).

Attention is itself a complex, multi-dimensional process which is often considered to have overarching capacity (Lückmann *et al.*, 2014), as a '*supervisory system*' or '*gatekeeper*' that allocates resources to competing processes (cognitive, visual or motor) (Posner and Boies, 1971; Baddeley, 1992; Posner and Rothbart, 2007). Therefore if attentional deficit is present, other cognitive functions are also compromised (Posner and Petersen, 1990), which impacts data interpretation. For example, as noted in Table 2-1 working memory is dependent on attentional processes to determine capacity and allocation (Kane *et al.*, 2006). Working memory involves temporary storage of information (Hikosaka *et al.*, 2000), which has severely limited capacity with only 3 to 4 objects able to be maintained at once (Sperling, 1960; Irwin and Andrews, 1996; Luck and Vogel, 1997; Vogel *et al.*, 2001). Attention ensures only goal-directed items enter the limited working memory space (Awh *et al.*, 2006), including visuo-spatial information used for navigation (Huestegge and Koch, 2012). Attention and visuo-spatial ability also

share a complex relationship in PD (Crucian *et al.*, 2010), with the lateral geniculate nucleus (LGN) acting as an attentional 'gatekeeper' to visuo-spatial processing (O'Connor *et al.*, 2002). Standard visuo-spatial assessments require attentional input from an early stage of visual processing to select focal areas of interest (Finton *et al.*, 1998; Baluch and Itti, 2011; White *et al.*, 2013). One study demonstrated that visuo-spatial deficits in PD disappeared when controlling for attention (Bondi *et al.*, 1993), indicating need for a cautious approach to interpretation.

Interpretation is complicated by the lack of a single and clear-cut definition of attention (Yogev-Seligmann *et al.*, 2008). As a result attention is often classified into separate activities to help guide interpretation, such as set shifting, inhibitory control or selection (focusing on and ignoring information), alternating, divided and vigilance/sustained attention (Yogev-Seligmann *et al.*, 2008; Iansek *et al.*, 2013). Different theoretical and neuroanatomical models of attention also exist to guide interpretation which vary in application to vision and gait research (Posner and Petersen, 1990; Baddeley, 1992; Itti and Koch, 2001; Knudsen, 2007; Baluch and Itti, 2011; Petersen and Posner, 2012). The type of attention and the model used to describe attention play an important role in the dissemination of findings. This thesis concentrates primarily on attentional inhibition (also known as selective attention) and uses a neuroanatomical model in an attempt to highlight specific PD impairments (Figure 2-2).

Most neuroanatomical models describe that attentional projections originate from executive activity in the pre-frontal cortex (PFC) (Aleman and van't Wout, 2008), which extend to broader cortical networks including those with BG input (McNab and Klingberg, 2008). However attentional arousal also originates from sub-cortical noradrenaline and cholinergic projections, involving structures such as the locus coeruleus, thalamus, PPN and nucleus basalis of Meynert (Gratwicke *et al.*, 2015). Therefore large scale neural networks are involved in attention with various distributions of processing (Mesulam, 1990), and cortical epicentres located in the pre-frontal, frontal (dorso-lateral PFC, FEF, SEF ACC) and posterior-parietal cortices (LIP, PEF) (Mesulam, 1999), as depicted in Figure 2-2. Dysfunction in any of these cortical or sub-cortical attentional networks with age or pathology may impact cognitive, visual or gait processes.

Baluch and Itti (2011) provided a neuroanatomical model of attention, based upon structural micro-stimulation and lesion studies. This model was adapted in Figure 2-2 and depicts a complex network of top-down (voluntary or cognitive) and bottom-up (reflexive or automatic) attentional projections from cortical and sub-cortical structures. The model primarily relates to visual processing but can be extended to gait, as it contains the fronto-striatal and fronto-parietal pathways alluded to within cognition and gait research (Hausdorff *et al.*, 2010). Dysfunction in the fronto-striatal pathway (involving the PFC and caudate nucleus) is common in PD (Owen, 2004; Robbins and Cools, 2014) and impacts attention, executive function and working memory (Stamenović *et al.*, 2004), which have been related to continuous gait deficit. Similarly, fronto-parietal pathway dysfunction (involving the PFC and parietal-cortex) has been associated with episodic gait impairments such as FOG (Hashimoto, 2006; Jha *et al.*, 2015).

In keeping with the visual neuroscience nature of the topic discussed, throughout this thesis unless otherwise stated the term '***attention'*** will refer to top-down attention which involves executive function. Reflexive (stimuli driven) attention will be referred to as '*bottom-up attention*', which is involved in initial saliency filtering (Itti, 2005; Bruce and Tsotsos, 2009). Therefore within this thesis attention refers to goal-directed signals that originate from executive processes at the PFC (Aleman and van't Wout, 2008), which are used for information selection via inhibitory control (suppression) of bottom-up attention, and subsequent processing of selected information (Berger and Posner, 2000).

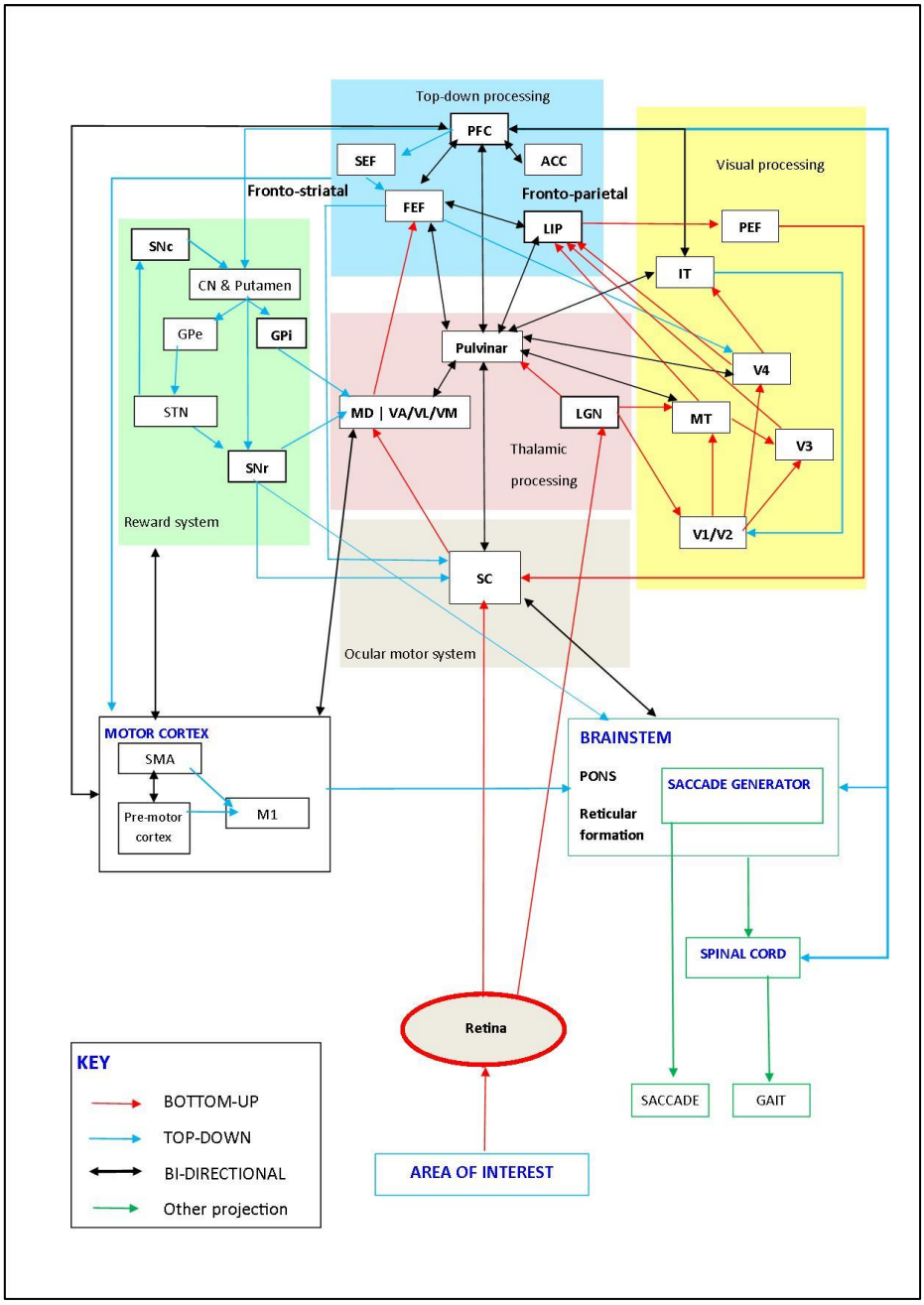


Figure 2-2 - Model of attention adapted from Baluch and Itti (2011)

[The complex array of connections are not all-encompassing but indicate the most likely attentional projection between two areas; either top-down attentional projection (blue arrow), bottom-up attentional projection (red arrow), or bi-directional attentional projection (black double headed arrow). Top-down processing: PFC = pre-frontal cortex, SEF = supplementary eye field, FEF = frontal eye-field, LIP = lateral intraparietal area, ACC = anterior cingulate cortex. Thalamic processing: VA = ventral anterior nucleus, VL = ventral lateral nucleus, VM = ventral medial nucleus, MD = medio-dorsal thalamus, LGN = lateral geniculate nucleus. Visual processing: PEF = parietal eye-field, IT = infero-temporal cortex, MT = middle temporal area (also known as V5). Reward system: SNr = substantia nigra pars reticulate, CN = caudate nucleus, GPe = globus pallidus external, GPi = globus pallidus internal, SNc = substantia nigra pars compacta, STN = subthalamic nucleus. Ocular motor system: SC = superior colliculus. Motor Cortex: SMA = supplementary motor area, M1 = primary motor cortex]

2.4.1. Cognition in Parkinson's disease

Cognitive impairments in PD are diverse (and summarised in Table 2-1), with severity and progression to dementia varying between different sub-groups (Pagonabarraga and Kulisevsky, 2012), and classification of dysfunction based on criteria from the Movement Disorders Society taskforce (Litvan *et al.*, 2012). Most commonly there are deficits in attention, executive function, visuo-spatial ability, working memory and memory (Caccappolo and Marder, 2010), whereas other processes such as language are usually less affected (Barone *et al.*, 2011 3103). Such deficits occur early and insidiously (Pfeiffer *et al.*, 2014; Yarnall *et al.*, 2014), and are dominated by attentional deficit (Taylor *et al.*, 2008; Svenningsson *et al.*, 2012). Most people with PD will eventually develop cognitive deficits, but progression (decline) is dependent upon genetic factors and pathological changes in different substrates (Svenningsson *et al.*, 2012), such as fronto-striatal dysfunction (slow decline) (Jokinen *et al.*, 2013) and posterior-cortical deficits (rapid decline) (Pagonabarraga and Kulisevsky, 2012). Fronto-striatal defects are related to dopaminergic dysfunction and can react to dopaminergic medication (Emre *et al.*, 2014), whereas posterior-cortical deficits perhaps result from degeneration of cholinergic innervation from the basal forebrain (Pagonabarraga and Kulisevsky, 2012). Age-related cognitive deficits which are typically more amnestic and represent increased cholinergic burden (Petersen *et al.*, 1999; Bohnen *et al.*, 2006) also contribute to PD cognitive impairment, especially in more advanced disease (Bohnen and Albin, 2011).

Of particular importance to this thesis is the role of attention within inhibitory control (Crawford *et al.*, 2002), which also involves executive function and working memory (Gurvich *et al.*, 2007; Baglio *et al.*, 2011; Munakata *et al.*, 2011; Parker *et al.*, 2013). Although people with PD largely have difficulties with initiating movements (Favre *et al.*, 2013), they also have deficits in action selection (Benis *et al.*, 2014) and inhibitory control (Gauggel *et al.*, 2004; Gurvich *et al.*, 2007; Jahanshahi *et al.*, 2015). For example, people with PD have increased anti-saccade errors due to impaired inhibitory control of reflexive saccades (Crawford *et al.*, 2002; de Boer *et al.*, 2014). Inhibitory impairment in PD relates to reduced attentional resources (Conway and Engle, 1994) and dysfunctional attentional activation within motor areas (SMA and other pre-motor

areas; Figure 2-2) (Gauggel *et al.*, 2004; Seiss and Praamstra, 2004; van den Wildenberg *et al.*, 2006; Yugeta *et al.*, 2010; Alegre *et al.*, 2013; Jahanshahi, 2013; Benis *et al.*, 2014; Jahanshahi *et al.*, 2015; Rae *et al.*, 2015), which Levodopa medication does not impact (Obeso *et al.*, 2011b). Notably, fronto-striatal atrophy and frontal dysfunction with PD have been linked to impaired inhibitory control, and increased distractibility (Fonoff *et al.*, 2015).

Impaired inhibition of automatic responses can lead to dysfunctions in a range of actions in PD, including gait (Baglio *et al.*, 2011; Obeso *et al.*, 2011a) and eye-movements (Crawford *et al.*, 2002; Grande *et al.*, 2006; Joti *et al.*, 2007; van Stockum *et al.*, 2008; Terao *et al.*, 2011; de Boer *et al.*, 2014). Disease severity further impacts inhibitory control mechanisms (Ye *et al.*, 2015). Indeed, accelerated attentional decline has been shown in people with PD within the PIGD phenotype compared to the TD phenotype (Burn *et al.*, 2006; Domellof *et al.*, 2011). Similarly recent evidence has demonstrated greater disruption of inhibitory control in those with FOG (Cohen *et al.*, 2014; Bissett *et al.*, 2015; Walton *et al.*, 2015), with reduced recruitment of cortical and sub-cortical regions implicated (Shine *et al.*, 2013a).

The neural mechanisms underlying attentional control are transient in nature and tend to fluctuate in efficiency over time (West and Alain, 2000b), which can impact decision making capabilities in PD (Damier, 2015; Trachsel *et al.*, 2015). Therefore another vital cognitive feature to this thesis is that of fluctuation of cognition, specifically attention, which occurs in all of the major dementias (Ballard *et al.*, 2001). Fluctuation of attention is sensitive to age-related cognitive decline (Salthouse, 1996) and is characteristic of PD dementia (PDD) (Emre, 2003). It is also characteristic of dementia with Lewy bodies (DLB) (Walker *et al.*, 2000) and is useful in the differential diagnosis of Alzheimer's disease (AD) (Bradshaw *et al.*, 2004; Mosimann *et al.*, 2004; Taylor *et al.*, 2013), particularly variability (i.e. coefficient of variability) in measures of simple and choice reaction time (CRT) (Ballard *et al.*, 2001). Cognitively intact people with PD have not been shown to experience fluctuation of attention, but individuals with PDD do experience impaired attentional reaction time, vigilance and fluctuation of attention (particularly CRT) that is comparable to that found in DLB (Ballard *et al.*, 2002; Burn and McKeith, 2003). Indeed, fluctuation of attention is a dominant

factor in determining diagnosis and disability in PDD (Burn and Yarnall, 2014). PDD and DLB are very similar conditions that are extremely difficult to differentiate between (Ballard *et al.*, 2002) and are often conjointly referred to as 'Lewy body dementias' (Burn and Yarnall, 2014; Cromarty *et al.*, 2016). PDD and DLB share many clinical and pathological features and are often considered part of the same disease spectrum (McKeith, 2000; Burn and McKeith, 2003; Donaghy and McKeith, 2014), therefore similar pathological mechanisms may underpin clinical features (i.e. fluctuation of attention) (Bosboom *et al.*, 2004).

Fluctuation of attention and its relationship to eye movements (visual stimuli) have been studied for over 100 years (Hylan, 1898; Ferree, 1906; Liddell, 1919; Guilford, 1927). Despite this the underlying mechanisms involved in fluctuation of attention are not fully understood which likely reflect the lack of a 'gold-standard' clinical measure for cognitive fluctuations (Lee *et al.*, 2012a), although CRT variation may provide the strongest objective attentional measure that associates with fluctuation (Taylor *et al.*, 2013). Recent work has reported that fluctuations may relate to distributed functional network perturbations rather than specific structural abnormalities (Taylor *et al.*, 2013). Further, evidence from DLB research has shown reduced functional connectivity or desynchronization in cortical and sub-cortical networks related to the fronto-parietal attentional network are related to severity and frequency of fluctuations (Franciotti *et al.*, 2013; Peraza *et al.*, 2014). Impaired thalamo-cortical connectivity and thalamic cholinergic imbalance have also been related to cognitive fluctuation in DLB, with reduced thalamic projections to the PFC and parieto-occipital cortices (Delli Pizzi *et al.*, 2014). Cholinergic dysfunction may also have a role in PDD as the application of levodopa medication relates to increased attentional fluctuations in this group (Molloy *et al.*, 2006), whereas cholinesterase inhibitors reduce fluctuations (Emre *et al.*, 2004). Increased cholinergic burden with PD has been related to gait (Rochester *et al.*, 2012b) and cognitive dysfunction (Burn *et al.*, 2006), and within PDD the PIGD phenotype is over-represented (Burn *et al.*, 2003). Similarly, greater fluctuation of attention (i.e. reaction time variability) has been associated with increased fall frequency in PD and was a stronger falls predictor than absolute attention (i.e. mean reaction time or power of attention)

(Allcock *et al.*, 2009). Fluctuation of attention may therefore be a sensitive measure of attentional decline in PD, with links to gait dysfunction and fall risk.

Table 2-1 - Overview of Cognitive Deficits in Parkinson's disease and Older Adults

Cognitive Function	Definition/Background	Older adults	Parkinson's disease
Attention	An overarching cognitive function (Lückmann *et al.*, 2014). Ability to focus, select information and mediate parallel processes, allocating limited central processing capacity where relevant (Noudoost *et al.*, 2010).	Declines with age • Declines more rapidly than other cognitive functions (Sweeney *et al.*, 2001) • Deficits impact various aspects of attentional control such as inhibition seen in a number of tests such as the Stroop test (West and Alain, 2000a)	Impaired • Commonly impaired even in those without dementia (Palavra *et al.*, 2013) • Relates to dysfunctional fronto-striatal and fronto-parietal networks (Gerrits *et al.*, 2015) • Cholinergic dysfunction is also involved via nucleus basalis of Meynert and pedunculo-pontine nucleus input to the thalamus and cerebral cortex (Yarnall *et al.*, 2011) • Shown via neuropsychological tests and prolonged P3 latencies (Suna *et al.*, 2014) which increase with disease severity (Lopes *et al.*, 2014; Tang *et al.*, 2015)
Executive Function	Ability to plan and execute goal-directed behaviours (Ding *et al.*, 2015).	Declines with age • Linked to age-related frontal-striatal deterioration (Buckner, 2004) • Impairments impact on intention, initiation, inhibition and switching performance (Hull *et al.*, 2008)	Impaired • Sensitive to neuropsychological tests such as the Trail Making Test (Lewis *et al.*, 2003) • Early impairment which primarily involves the pre-frontal cortex (Zgaljardic *et al.*, 2006) • Reflected by impairment in a range of cognitive skills such as poor inhibitory response (Ding *et al.*, 2015) • Linked to increased motor slowing and difficulties in planning (Weintraub *et al.*, 2005)
Working Memory	Ability to maintain and manipulate information over short time periods, which is linked to attentional control (Baddeley, 1992; Awh *et al.*, 2006).	Declines with age • Decline related to deterioration of attention (Gazzaley *et al.*, 2005) • Involved in attentional inhibition and decreased functional connectivity within large-scale brain networks (Fabiani *et al.*, 2015)	Impaired • Impairment is related to fronto-striatal (Robbins and Cools, 2014) and right hemisphere dysfunction (Foster *et al.*, 2013) • Not always apparent without the use of sensitive neuropsychological tests (Possin *et al.*, 2008)
Visuo-spatial ability	Ability to visually perceive the spatial relationships of objects. It is linked to attention and memory (Richards *et al.*, 1993).	Declines with age • Declines more than verbal cognitive tasks (Jenkins *et al.*, 2000) • Declines related to changes in underlying neural mechanisms (Klencklen *et al.*, 2012), which involve altered fronto-parietal signals (Drag *et al.*, 2015)	Impaired • Can be less impaired than other cognitive domains (Possin, 2010; Caproni *et al.*, 2014) • Associated with increased motor severity and freezing of gait (Nantel *et al.*, 2012) • Related to frontal and parietal lobe deterioration (Biundo *et al.*, 2013), with right hemisphere dysfunction implicated (Karádi *et al.*, 2015; Seichepine *et al.*, 2015) • Underlying structural changes of grey matter in frontal and temporal-parietal cortices impact this function (Pereira *et al.*, 2009; Rektorova *et al.*, 2014)

(Older adult impairments are from articles comparing older adults (>50 years old) to either younger adults or pathological groups, Parkinson's disease impairments relate to comparisons to healthy older adults)

2.4.2. Cognition and gait

The relationship between gait and cognition in PD (Figure 2-1(A)) is particularly strong and supported by mechanistic and imaging work (Grabli *et al.*, 2012; Maillet *et al.*, 2012). Various relationships between selective gait characteristics and cognitive functions have been found, however attention has a central role in gait in PD (Yogev-Seligmann *et al.*, 2008).

Recent work from our group examined the association between gait and cognition in older adults and PD (Lord *et al.*, 2014), using a comprehensive battery of cognitive and gait measures. We found a strong relationship between attention and the 'pace' domain of gait (comprising gait velocity, step length and step time). Similarly, online studies utilising dual task protocols which manipulate attention in real-time demonstrate an increase in gait variability, reduced velocity, swing time and step length in older adults (Hollman *et al.*, 2007; Verghese *et al.*, 2007a; Hausdorff *et al.*, 2008) and PD (Yogev *et al.*, 2005; Rochester *et al.*, 2008; Kelly *et al.*, 2012a). However dual task interpretation is challenging because of the complex intertwined nature of attention, executive function and working memory (Yogev-Seligmann *et al.*, 2008; Rochester *et al.*, 2014), which have overlapping influences on dual task performance (Kelly *et al.*, 2012b).

Executive dysfunction is related to gait deficit in PD, particularly in those who report FOG (Amboni *et al.*, 2008; Heremans *et al.*, 2013) and people with the PIGD phenotype (Lord *et al.*, 2014), who present with greater frontal impairment (Burn *et al.*, 2006; Maidan *et al.*, 2015). Associations between gait and cognition have reported that executive dysfunction related to reduced gait velocity, increased variability, step time and swing time in older adults (Ble *et al.*, 2005; Springer *et al.*, 2006; van Iersel *et al.*, 2008; Liu-Ambrose *et al.*, 2010; Holtzer *et al.*, 2012) and PD (Plotnik *et al.*, 2009; Lord *et al.*, 2010; Lord *et al.*, 2014). Interpretation is complicated by the intimate relationship between executive function and attention (Kudlicka *et al.*, 2011), which has prompted these functions to be discussed both separately as well as a unitary domain (i.e. executive-attention) (Holtzer *et al.*, 2006; Verghese *et al.*, 2008; MacAulay *et al.*, 2014). Discerning their individual role in gait is therefore challenging, and highlights a need for precise cognitive assessment and outcome reporting.

As another closely related cognitive function, working memory is also associated with gait deficit in older adults, for example with gait velocity (Holtzer *et al.*, 2006; Soumare *et al.*, 2009), step time (Holtzer *et al.*, 2012), step time variability, double support time and step length (Holtzer *et al.*, 2006; Martin *et al.*, 2013). The relationship in PD is less clear with research showing contradictory results (Amboni *et al.*, 2012; Lord *et al.*, 2014; Stegemoller *et al.*, 2014). Inconsistencies in PD associations are possibly due to the use of subtly different working memory assessments (i.e. digit span forward or backward, or Rey Auditory Verbal Learning Test) and limited consideration for features that potentially sensitise the relationship such as disease phenotype, as reported by Lord *et al.* (2014).

Visuo-spatial ability has been related to Parkinsonian gait, possibly due to impairment of attentional networks common to visuo-spatial function and gait control (Menant *et al.*, 2014). Amboni et al. (2012) reported an association in PD between impaired visuo-spatial ability and deficits in their 'stability' gait domain. Correspondingly, deficits are implicated in falls in older adults (Reed-Jones *et al.*, 2013) and PD (Davidsdottir *et al.*, 2005; Allen *et al.*, 2013). Visuo-spatial impairment with age and PD also relates to reduced step length (Nadkarni *et al.*, 2010), gait velocity (Beurskens and Bock, 2011), and increased double support time, stride time variability (Menant *et al.*, 2014), step length variability (Martin *et al.*, 2013) and reduced timed up and go speed (Donoghue *et al.*, 2012). Findings are however contradictory (Soumare *et al.*, 2009; Plotnik *et al.*, 2011), at least partly due to lack of comprehensive and rigorous visuo-spatial assessment (Lord *et al.*, 2014). Again, the relationship may also depend on disease severity, as reported previously for the PIGD phenotype (Domellof *et al.*, 2011) and in those who experience FOG (Nantel *et al.*, 2012; Heremans *et al.*, 2013) (Table 2-1). A recent study involving a large number of people with PD (n=783) found that visuo-spatial ability was significantly related only with FOG severity (Kelly *et al.*, 2015), possibly due to greater frontal and right posterior-parietal cortex deficits in those with FOG (Velu *et al.*, 2013; Handojoseno *et al.*, 2015). Understanding of visuo-spatial contribution to gait is further limited by lack of online studies (Kelly *et al.*, 2012b). For example, a recent study by Ricciardi *et al.* (2014) manipulated visuo-spatial ability during gait in a small cohort of PD using a dual task (i.e. completion of a visuo-spatial assessment shown on a projector screen while

walking), but did not report gait characteristics during the task which limited findings. Test paradigms are not always considered with respect to other cognitive (i.e. attention) and visual functions which are not routinely assessed. A further issue is that laboratory manipulations may also be unrepresentative of real-world environments (Dowiasch *et al.*, 2015; Ottosson *et al.*, 2015).

2.4.3. Evidence from imaging

Imaging the brain while walking is impossible as the head has to remain still. To overcome this, protocols have used motor imagery or assays of gait in an attempt to understand the neural correlates of gait. Imaging studies generally demonstrate that gait involves a widely distributed neural network (Maillet *et al.*, 2012; Bohnen and Jahn, 2013; Herman *et al.*, 2013; Holtzer *et al.*, 2014). Although most studies have focussed on motor control, more recent work demonstrates overlap with neural networks associated with cognitive function such as the pre-frontal and frontal cortex (Seidler *et al.*, 2010; Shine *et al.*, 2013a). More recent work has used techniques such as functional near infra-red spectroscopy (fNIRs) that allow activity in the frontal cortex to be measured while a person is walking (Ferrari and Quaresima, 2012). These studies have shown that episodic gait impairment and postural control in PD are associated with online changes in frontal cortex activation (cerebral oxygenation: HbO_2) levels (Mahoney *et al.*; Maidan *et al.*, 2015). Similarly, fNIRs studies have shown increased PFC activation during dual task gait in older adults (Holtzer *et al.*, 2011; Doi *et al.*, 2013; Beurskens *et al.*, 2014). Also, studies exploring network functions and connectivity have shown a breakdown in connectivity between regions related to gait, attention, executive function (Fasano *et al.*, 2015; Sarasso *et al.*, 2015) and visuo-spatial ability (Nantel *et al.*, 2012), accompanied by greater right hemisphere dysfunction (Tessitore *et al.*, 2012; Fling *et al.*, 2013; Shine *et al.*, 2013b; Peterson *et al.*, 2014). To date, limitations to this emerging area of research include recruitment of mostly advanced cohorts and test protocols using techniques such as motor imagery or virtual reality, which may only partially represent online execution and therefore require cautious application (Cohen *et al.*, 2011).

2.4.4. Summary of cognition and gait in Parkinson's disease

In summary, the role of cognition in gait in PD is complex and multi-factorial, but associations and online gait deficits have been extensively researched. Robust evidence within this section demonstrates a potentially central or overarching role of attention in gait in PD. This is impacted by PD impairment of the fronto-striatal and fronto-parietal pathways, as stated in Table 2-1. Overarching attention also complicates cognitive assessment and data interpretation due to its links with visual, cognitive and gait processes. To date no studies pertaining to the association or online manipulation (dual task) of cognition in gait have addressed the confounding role that vision may have in gait in PD (Figure 2-1(C)), this is further discussed in section 2.6.

2.5. Vision

Vision is a complex sensory system, involving integration of multiple structures and levels of information processing (Kaas, 2008). Critically vision relies on creation of various components (i.e. form, colour and movement) to allow interpretation of complex visual scenes (Cavanagh, 2011). Visual processes begin at the retina where photoreceptors absorb light and visual functions begin to break down the retinal image into its components (Itti and Koch, 2001) before sending the information to high-level areas for further processing (Wolfe, 1994) (Table 2-2). Integrity of these low-level visual functions is therefore vital for adequate vision.

2.5.1. Visual function in Parkinson's disease

Visual impairment is common in PD and is associated with gait dysfunction, although methodological issues (summarised in Table 2-2) necessitate cautious interpretation. The impact of visual impairment on gait has primarily been investigated in healthy young and older adults, with limited evidence in PD. Such studies demonstrate that age-related deficit in visual function is associated with reduction in activities of daily living, quality of life, mobility and is an independent risk factor for falls (Reed-Jones *et al.*, 2013; Uiga *et al.*, 2015). Visual pathology, such as glaucoma, cataracts and macular de-generation are a common and often under-reported problem in older adults. However these visual problems are seen in PD along with a wide range of other visual impairments, from impairment of

basic functions such as visual acuity (VA) and contrast sensitivity (CS) to more complex processes such as depth perception, motion perception and optic flow (Armstrong, 2011), as shown in Table 2-2. Associations between visual impairments and gait in older adults may be stronger in PD especially as visual deficits increase with disease progression.

2.5.2. Vision and gait

Methodological paradigms that explore the association between visual function and gait characteristics or manipulate vision in real-time while the participant is walking (e.g. navigating narrow doorway, lines on the floor, light and dark rooms) provide some understanding of the contribution of vision to gait in PD, as depicted in Figure 2-1(B).

Impaired visual functions such as VA have been associated in PD and older adults with reduced step length (Spaulding *et al.*, 1994; Hallemans *et al.*, 2010) and gait velocity (Shin *et al.*, 2015), although this finding is not consistent (Klein *et al.*, 2003). In PD, VA is the most commonly and often only assessed visual function. Changes in vision may not be adequately represented by VA alone (Geldmacher, 2003). CS is considered more applicable to real-world vision during gait, where the contrast of light and shade is critical. Indeed, impaired CS has been associated with reduced step width (Wood *et al.*, 2009), step length (Wood *et al.*, 2009; Swigler *et al.*, 2012), gait velocity (Moes and Lombardi, 2009; Wood *et al.*, 2009), physical activity levels (Black *et al.*, 2011), and fear of falling (Wang *et al.*, 2012). Other functions related to real-world vision such as dynamic VA have also been associated with falls (Honaker and Shepard, 2011). This indicates a need for comprehensive visual function assessment and more stringent methodological consideration. More complex assessments involving depth perception have been associated with increased obstacle contacts during gait (Menant *et al.*, 2010), likely due to impairment of obstacle height perception (Yamaji *et al.*, 2011). Motion perception (described in Table 2-2) has been associated with reduced functional task (e.g. driving) performance (Owsley, 2011), however despite obvious ties to gait it has largely been overlooked (Armstrong and Kergoat, 2015).

Optic flow is a similar concept to motion perception as described in Table 2-2, and has predominantly been studied using online manipulation. Manipulation of optic flow while walking is carried out using video or projection based visual input (i.e. projected dots on a screen) shown at varying velocities to provide a sense of depth. In PD, significant gait impairments are found in velocity and step length (Lebold and Almeida, 2010) as well as increased veering (Davidsdottir *et al.*, 2008), with dysfunctional right parietal cortex implicated (Davidsdottir *et al.*, 2008; Putcha *et al.*, 2014). Optic flow protocols however require intact depth perception (Simpson, 1993) and a limitation of these studies is that they do not control for visual deficits, as noted in Table 2-2. As a consequence it is unclear if gait impairment is a result of impaired depth perception (Lord *et al.*, 2002; Menant *et al.*, 2010) or indeed optic flow as suggested. Lack of an appropriate control group (older adults) in optic flow studies in PD (Lebold and Almeida, 2010; Almeida and Bhatt, 2012) and use of attentional tasks (such as lines on the floor to step on) which alter optic flow without consideration of cognitive processes further confound interpretation of findings.

Other studies with simple visual manipulations such as doorways (Cowie *et al.*, 2010; Cowie *et al.*, 2012) have shown reduction in gait velocity and step length, and increased step time in PD (Lebold and Almeida, 2010; Pieruccini-Faria *et al.*, 2014). These studies suggest that people with PD become reliant on vision for gait (Azulay *et al.*, 1999; Azulay *et al.*, 2002; Khattab *et al.*, 2012). However many previous studies have involved visual occlusion (i.e. walk in a dark room) which merely provides a comparison of the contribution of proprioception compared to vision during gait (Stuart *et al.*, 2014a). When vision is occluded (Azulay *et al.*, 1999; Adamovich *et al.*, 2001; Almeida *et al.*, 2005), visual processing still occurs with visuo-spatial information obtained from working memory (Jackson *et al.*, 1995) which adds unnatural cognitive load during gait. Mimicking real-world environments with more subtle visual manipulations (such as adding a doorway) may provide insight into real-world impairments (Jackson *et al.*, 1994).

2.5.3. Summary of vision and gait in Parkinson's disease

In summary, the role of vision in gait in PD has not been as rigorously investigated as the role of cognition in gait. Despite this, evidence within this section demonstrates that deficits in selective gait characteristics have been

linked to visual dysfunctions in PD and older adults. To date however no studies have addressed the role of cognition during association or online manipulation of vision in gait in PD (Figure 2-1(C)). Online manipulation studies merely compare gait performance with and without vision or visual manipulation, and attribute gait deficits solely to visual processes. This evidence highlights the limitations of protocols exploring the role of vision in gait in PD as they do not consider the confounding influence of cognition (this is further discussed in section 2.6).

Table 2-2 - Overview of Visual Deficits in Parkinson's disease and Older Adults

Visual Function	Definition	Older adults	Parkinson's disease	Key Methodological Issues
Visual acuity (VA)	The ability to distinguish small details and shapes of objects (Kaiser, 2009).	Declines with age • Susceptible to decline from changes in ocular media (Sjostrand *et al.*, 2011), and changes in neural processing (Hennelly *et al.*, 1998)	Impaired • Associated with subjective reports of blurred vision (Jones *et al.*, 1992; Archibald *et al.*, 2011; Armstrong, 2011) • Linked to dopamine depletion in the retina (Archibald *et al.*, 2009)	Often non-significant impairment in PD compared to controls reported due to small sample sizes e.g. Galna *et al.* (2012). Often only visual function assessed.
Contrast sensitivity (CS)	The ability to differentiate between objects and their background (Evans and Ginsburg, 1985).	Declines with age • Susceptible to decline from changes in ocular media (Ross *et al.*, 1984), and changes in neural processing (Sloane *et al.*, 1988)	Impaired • Seen via standard visual chart assessment (Galna *et al.*, 2012) • Specific losses for spatial frequencies (Bodis-Wollner *et al.*, 1987; Price *et al.*, 1992; Swigler *et al.*, 2012) • Significant deficit in orientation discrimination for horizontal but not for vertical gratings (Mestre *et al.*, 1990)	Often non-significant impairment in PD compared to controls reported due to small sample sizes e.g. Galna *et al.* (2012).
Dynamic visual acuity	The ability to perceive an object when there is motion between the observer and the target (Ishigaki and Miyao, 1994).	Declines with age • Under all luminance, velocity, and duration conditions (Long and Crambert, 1990)	Impaired • Under all luminance, velocity, and duration conditions (Uc *et al.*, 2005b; Taweekarn *et al.*, 2009)	Not often assessed.
Depth perception	The ability to perceive the world in three dimensions (3D) and the distance of an object (Omoto *et al.*, 2010).	Declines with age • Common in the absence of ocular morbidity (Wright and Wormald, 1992) • Decline is marked in those >60 years old (Garnham and Sloper, 2006)	Impaired • Common in drug naïve patients (Kim *et al.*, 2011) • Linked to reduction in gray matter volume in the right extra-striate visual cortex (Koh *et al.*, 2013)	Some studies limited by not assessing for nor excluding patients with vision affecting eye conditions e.g. Goodale and Haffenden (1998).
Motion perception	The process of inferring the speed and direction of elements in a scene (Ehrenstein, 2003).	Declines with age • Motion perception thresholds shown to be approximately two times higher in those 70-80 years old than individuals under thirty (Trick and Silverman, 1991)	Impaired • Motion perception thresholds significantly elevated (Trick *et al.*, 1994) • Linked to VA and CS impairment (Uc *et al.*, 2005b)	Not often assessed.

Optic flow	Refers to the motion of the environment projected on the retina during movement in the world (Kelly *et al.*, 2005).	Declines with age • Decline in ability to localise and detect optic flow patterns (Berard *et al.*, 2009) • Affects navigation and steering control (Berard *et al.*, 2011)	Impaired • Linked to gait impairments such as veering and navigation issues (Davidsdottir *et al.*, 2008; Lin *et al.*, 2014) • Relates to impaired neural processing in visuo-vestibular (Putcha *et al.*, 2014) and feed-forward visuo-motor regions (van der Hoorn *et al.*, 2014)	Many studies use artificial assessment devices which require depth perception, but do not control for or exclude based on depth perception deficits.

(Older adult impairments are from articles comparing older adults (>50 years old) to either younger adults or pathological groups, Parkinson's disease impairments relate to comparisons to healthy older adults)

2.6. The interaction between visual and cognitive function: Visuo-cognition

To date no studies have considered how visual and cognitive functions (Tables 2-1 and 2-2) may interact during gait in PD (Figure 2-1(C)). Instead gait deficits are attributed solely to individual cognitive or visual functions, despite such functions being related with common gait characteristics (Callisaya *et al.*, 2009). However evidence from static studies indicates that cognitive and visual functions are associated in older adults (Lin *et al.*, 2004) and PD (Harris, 1998).

A recent review by Archibald *et al.* (2009) supported the notion that cognitive and visual functions interact in PD. Indeed, foveal retinal dopaminergic depletion (Bodis-Wollner, 2009) and structural changes (Bodis-Wollner, 2013) such as retinal thinning (Adam *et al.*, 2013; Bodis-Wollner *et al.*, 2013) can distort signals from visual functions and impact cognitive processes in PD. Abnormal visual processing within BG loops is also suggested to cause people with PD to become reliant on attentional compensation (Redgrave *et al.*, 2010). Imaging data demonstrates that attention can compensate for visual function deficits in healthy adults (Meppelink *et al.*, 2009), a mechanism which may be intact in early PD. Attention has been shown to improve visual functions such as spatial resolution (Yeshurun and Carrasco, 1998; Carrasco *et al.*, 2002) and CS (Carrasco *et al.*, 2000; Pestilli and Carrasco, 2005; Carrasco, 2006) by affecting change in stimulus appearance (Carrasco *et al.*, 2004), and enhancing contrast and salience via V4 neurons by up to 51% (Reynolds *et al.*, 2000). Attention is also involved in increasing visual processing speed in neurons as early as V1 (Carrasco and McElree, 2001; Pestilli and Carrasco, 2005). However, despite attentional compensation and the ability for levodopa to sustain dopamine within the retina (Archibald *et al.*, 2009) visual deficits such as slow visual processing persist in PD (Woollacott and Shumway-Cook, 2002). Importantly, compensation via attention is constrained because it is also impaired due to pathology, as noted above. Of further interest is the attenuation of visual control during gait when attentional demands increase, for example when walking under dual task conditions.

Cognitive and visual functions share the same neural resources and BG-cortical loops, with PD cognitive and visual loops overlapping in striatal regions which have greater dopaminergic activity (e.g. ventral striatum) (Helmich *et al.*, 2010), which further implicates a role for PD pathology in visuo-cognitive interactions during gait. However, these interactions in PD are complex and remain unclear (Figure 2-1(C)). Cognitive functions, particularly attention activate and inhibit many structures during visual processing (Buhmann *et al.*, 2015), giving rise to an internal priority (saliency) map (Baluch and Itti, 2011). Executive processes at the PFC signal an initial 'guess' at the main visual priority (based on task goals) and project back via attentional circuits to the temporal cortex where selection is integrated into further automatic visual processing (Bar *et al.*, 2006). Therefore early cognitive biasing of visual input selection occurs before the automatic (bottom-up) visual processing cascade (Baluch and Itti, 2011), and would indicate that even though the two systems (vision and cognition) work in unison, cognitive functions may underpin visual functions (Borji *et al.*, 2011), especially during goal-orientated tasks such as gait.

2.6.1. Visual sampling within static environments

Investigation of visual sampling (combination of saccades and fixations) during static tasks is one methodology that has allowed study of visuo-cognition in older adults and PD (van Stockum *et al.*, 2012). Saccades in particular are the mechanisms through which individuals sample their environment (Land, 2006) and provide an online behavioural measure of visuo-cognition due to their links to both visual (Bridgeman *et al.*, 1981; Hernandez *et al.*, 2008) and cognitive functions, particularly attention (van Stockum *et al.*, 2011b) (Figure 2-1). Saccades are integral to accurate task completion, as they align areas of interest in the environment with our fovea to produce high quality visual information (Bodis-Wollner, 2013; Bodis-Wollner *et al.*, 2013) for further cognitive processing.

Visuo-cognitive deficits in older adults are evidenced by ineffective visual search strategies (Becic *et al.*, 2008) and impaired saccades (Ridderinkhof and Wijnen, 2011) during static testing. Similarly people with PD demonstrate saccadic impairment when compared to older adults (Chan *et al.*, 2005; Mosimann *et al.*, 2005), with impaired voluntary (cognitively activated) and to a lesser extent

reflexive (visual stimuli activated) saccades (Terao *et al.*, 2013). Voluntary saccades have been shown to be impaired more in advanced PD than early or moderate PD (Blekher *et al.*, 2000). Similarly Briand *et al.* (2001) and Terao *et al.* (2013) demonstrated that reflexive saccades are relatively preserved in early PD but worse in advanced PD. Other specific PD saccadic impairments have been highlighted in several recent reviews (Anderson and MacAskill, 2013; Srivastava *et al.*, 2014; Antoniades and Kennard, 2015), such as; hypometric saccades, initiation deficits including increased errors during anti-saccade tasks, reduced gain, increased latency of voluntary saccades, reduced latency of reflexive saccades and abnormal facilitation during inhibition of return tasks.

Static studies have provided insight into underlying mechanisms involved in saccadic impairment in PD. Voluntary saccades are controlled by interaction between the frontal cortex, BG and brain stem (Javaid *et al.*, 2012; Matsumoto *et al.*, 2012). Recent investigations have shown that frontal pathology rather than motor severity is linked to saccadic deficits in PD (Perneczky *et al.*, 2011; Macaskill *et al.*, 2012; Tommasi *et al.*, 2015). However, dysfunctional BG in PD also cause deficits in voluntary (top-down) saccades due to impairment of cortico-BG loops (Tommasi *et al.*, 2015). The BG inhibit and disinhibit information based on attentional signal from the PFC. Excessive inhibition on the superior colliculus (SC) by the BG in PD can cause problems with voluntary and reflexive (bottom-up) saccades, seen via increased pro and anti-saccade task errors (Armstrong, 2011). Reflexive saccades are primarily controlled by the parietal cortex (posterior-parietal cortex and posterior eye-field) and the brain stem cholinergic system rather than the dopaminergic reward system (Terao *et al.*, 2013), which indicates why they are relatively spared in early PD. However the ability to inhibit reflexive saccades degrades with PD progression. In early disease, BG impairment can be circumvented with inhibition elicited via direct top-down influence from the PFC to the SC (Pierrot-Deseilligny *et al.*, 2004). Progressive dopamine depletion in the striatum with PD reduces the PFC inhibitory effect (Tommasi *et al.*, 2015). Therefore reduced PFC activity and disruption of the BG-thalmo-cortical loops results in an inability to suppress reflexive saccades (Deijen *et al.*, 2006). Combined voluntary saccade impairment and increased

distractibility in PD during static tasks has implication for gait in PD, as such visuo-cognitive impairment likely impacts gait control.

2.7. The role of visuo-cognitive processes in gait

As noted above, investigation of the role of vision and cognition as separate entities with respect to gait has led to some understanding of the mechanisms involved (see Figure 2-1 (A&B)). However because vision and cognition interact (Figure 2-1(C)) this is likely to have important implications for gait in PD (Figure 2-1(D)). Knowledge of visuo-cognitive processes during gait is therefore important and critical to fully understand mechanisms underlying gait impairment and help target effective interventions.

Visuo-cognitive processes during gait in PD have largely been investigated through monitoring visual sampling during real-world activities such as gait. To date however no one has examined the relationship between saccadic and gait outcomes in PD (Figure 2-1(D)), but online studies have revealed important findings. The structured review within chapter 3 was carried out in order to highlight current online visual sampling findings and provide some methodological guidance for the studies contained within this thesis (Stuart *et al.*, 2014a).

2.8. Interventions to improve gait that utilise vision and cognition: visual cues

This is an emergent area of research, therefore any commentary on interventions that exploit visuo-cognitive processes to improve gait in PD is tentative. However, one therapy that aligns itself to these processes and is widely accepted as an effective strategy to improve gait in PD is use of visual cues (Rochester *et al.*, 2011), which consist of transverse taped lines on the floor to step over (Nieuwboer, 2008). Visual cue response however is variable, selective to certain gait characteristics (e.g. step length) and often only has short term effect (Munoz-Hellin *et al.*, 2013). Two alternate theories dominate understanding of response to cues in PD (Vitorio *et al.*, 2014), which separate the contribution of cognition and vision to gait. The first implicates a role for attentional control (Morris *et al.*, 1996), which is suggested to by-pass BG impairment through attentional

projection from the frontal cortex (i.e. PFC, ACC etc.) to the caudate nucleus (Rubinstein *et al.*, 2002; Leisman *et al.*, 2014). This theory involves the shift of gait control from automatic to more voluntary control (i.e. attention drawn to each step) (Morris *et al.*, 1994b; Morris *et al.*, 1994a; Morris *et al.*, 1996). The second involves optic flow (Azulay *et al.*, 1999), which is thought to heighten feed-back from self-motion and compensate for visual deficits that impact gait (Almeida and Bhatt, 2012). Other studies dissent from this, and suggest it is unlikely that attention or optic flow solely influence cue response (Azulay *et al.*, 2006; Lebold and Almeida, 2011). However, previous research has overlooked interaction between cognitive and visual functions (Figure 2-1(C)) during visually cued gait, which makes it difficult to draw conclusions as visuo-cognition may influence gait response (Figure 2-1(D)). One example of a visuo-cognitive response to visual cues involves an initial attentional signal to the cue, followed by saliency filtering and selection of appropriate areas of interest (Velik *et al.*), and subsequent interaction with visual functions such as optic flow. However, this is speculative and greater understanding of visuo-cognition during gait in PD is first required. Ultimately, this understanding will inform mechanisms involved in gait impairment and visual cue response, and allow for targeted development of interventions.

2.9. Summary and Conclusions

Understanding the role of vision, cognition and visuo-cognition in gait in PD is critical to inform mechanisms of gait impairment and targeted therapeutic development to improve gait, independent mobility and falls risk. This review has covered a substantial body of literature and used a theoretical model to explore the contribution of vision, cognition and visuo-cognition to gait in PD. The use of associative and online protocols revealed a complex interdependence of these functions with evidence suggesting that attention may play a pivotal role. Exacting research is required to illuminate the field of inquiry and enhance our understanding of this relationship. This consolidated knowledge will inform optimised management of gait dysfunction in PD through application of appropriate therapeutic interventions, and thereby enhance overall function and quality of life for people with PD.

3. Measurement of visual sampling during real-world activities in Parkinson's disease and older adults

3.1. Summary[2]

This chapter presents a structured review and critical evaluation of the literature regarding visual sampling (a combination of saccades and fixations) during real-world activities (i.e. gait, obstacle crossing, reaching etc.) in people with PD and older adult controls. This review highlighted the current interpretation of knowledge pertaining to visual sampling impairment in PD compared to older adults. The review also informed the research design and methodology used within this thesis to investigate saccade frequency during gait in PD and controls.

3.2. Introduction

Advancements in eye-tracking technology have enabled visual sampling to be monitored during real-world activity (e.g. gait, obstacle crossing, reaching and driving). This progress is vital as visual sampling is a critical feature of motor control, which may depend on task specific goals (Marigold and Patla, 2007). For example: during locomotion over even ground in healthy control subjects long fixation durations are not necessarily required, yet saccadic frequency, amplitude and duration of fixations increase in healthy subjects when walking over uneven terrain (Land, 2006; Patla and Greig, 2006). Eye-tracking technology has been used to further understand the visual strategies of PD subjects since the 1960's (Terao *et al.*, 2011; van Stockum *et al.*, 2012). However until recently most research using eye-trackers involved small sample sizes (Anderson and MacAskill, 2013). Similarly most PD studies of visual sampling are limited to static examination of eye movements alone or involve simple single-segment motor tasks (e.g. mouse clicks). Of the PD studies investigating visual sampling during real-world activity, a wide range of protocols have been used indicating a lack of standardisation, which limits interpretation. Investigators who want to conduct similar research are left with the choice between numerous protocols, which differ in many respects. In the process of developing robust protocols it is often helpful to have evidence-based recommendations. This review therefore examined

[2] This study has been published in the Journal of Neuroscience methods; Stuart et al. (2014a)

previous work that assessed visual sampling during real-world activities in PD and control participants, in order to provide some guidance regarding the selection of appropriate methodology.

This review focused on the following: 1) visual sampling instrumentation used during real-world activities involving both PD and controls; 2) commonly reported visual sampling outcomes; 3) PD specific influences on these visual outcomes; and, 4) recommendations concerning protocol. For the purpose of this review a real-world activity was considered to be a goal-orientated motor task, which involved more than one body segment (such as walking, reaching, turning etc.).

3.3. Methods

3.3.1. Search Strategy

The key terms were “Parkinson’s disease”, “visual sampling” and “motor task”. A list of synonyms was created for each key term (Figure 3-1). Key terms were matched and exploded with medical subject headings (MeSH) in each separate database where appropriate. Databases searched included Medline (from 1950), Embase (from 1974), PsychInfo (from 1806), Scopus, Web of Knowledge (from 1900), PubMed (from 1950) and the Cochrane library (from 1800) to February 2013[3]. Studies were relevant if they incorporated terminology which focused on visual sampling during a real-world activity in both PD and healthy control subjects in the title, abstract or keywords. Articles with titles related to ‘sleep’, ‘monkeys’, ‘rats’ and ‘hallucinations’ were excluded using separate key terms.

An initial title screen for relevant articles was performed by the reviewer (Sam Stuart; SS) once the searched database results had been combined. After the initial title screen, both the titles and abstracts of the selected articles were reviewed by two independent reviewers (SS and Dr Lisa Alcock). A review of the full text was required if it was not clear from the title or abstract whether the study met the review criteria.

[3] Since this period another relevant study has been published; Vitorio et al. 2014, which has been added to the tables and review body

KEY TERMS

Parkinson's disease: "parkinson*" TITLE-ABS-KEY

Visual sampling: ("vision" OR "visuomotor" OR "gaze" OR "visuospatial" OR "eye movement" OR "ocular motor" OR "ocular movement" OR "oculomotor" OR "sensorimotor" OR "visual movement" OR "visual behaviour" OR "visual behavior" OR "orientat*" OR "attention" OR "saccad*" OR "eye track*" OR "visual sampling" OR "visual search" OR "visual field" OR "visual exploration" OR "oculo motor" OR "ocularmotor") TITLE-ABS-KEY

Motor task: ("gait" OR "locomot*" OR "abulat*" OR "walk*" OR "move*" OR "motor*" OR "hand" OR "reach*" OR "grasp" OR "turn*" OR "leg" OR "arm" OR "motor control" OR "motor co-ordination" OR "driv*" OR "prehension" OR "motor activity" OR "motor performance" OR "mobilization") TITLE-ABS-KEY

NOT ("sleep*" OR "monkey*" OR "rat*" OR "hallucination") TITLE

('*' indicates a wildcard and 'TITLE-ABS-KEY' indicates a title, abstract and keyword search).

Figure 3-1 - Search strategy used to screen for relevant articles included in this review. This illustrates the three key terms used for this review and the synonyms used for each

3.3.2. Inclusion and Exclusion Criteria

Articles were included if they reported use of a measurement instrument to quantify visual sampling (saccades and fixations) during performance of a real-world activity. Studies were included only if they tested a control cohort for comparison with PD cohorts so that PD-specific differences could be identified. Whereby articles included another clinical cohort (i.e. progressive supranuclear palsy), or an additional static visual task, only the data relating to PD and control cohorts whilst sampling the visual environment during a real-world activity was reviewed.

Articles were excluded if they involved simple motor tasks relying on single-segment movement (such as; button pressing with a finger or wrist flexion/extension only) as they were not considered real-world activities. Visual tracking studies were excluded as they primarily involve smooth pursuit eye movements, and only saccades and fixations were reviewed. Only articles written in English were considered for review and any abstracts, case studies, reviews,

commentaries, discussion papers, editorials or conference proceedings were excluded.

3.3.3. Data Extraction

Data was extracted by the reviewer (SS) using a custom form to support standardised extraction. Data was synthesised into table format by the reviewer (SS) and a second reviewer (Dr Lisa Alcock) confirmed the entered data (Tables 3-1, 3-2 and 3-3). Data included demographic, visual sampling and motor task measurement instruments, visual sampling outcomes, study protocol and key findings.

3.4. Results

3.4.1. The Evidence Base

The search strategy yielded 2814 articles, excluding duplicates (Figure 3-2; Adapted from (Moher *et al.*, 2009)). An initial screening resulted in 287 articles of interest of which 14 were identified for inclusion by the first reviewer (SS) and 20 by the second reviewer (Dr Lisa Alcock), with 6 disagreements. A consensus was made for inclusion of 16 articles for review after consultation with the third reviewer (Dr Sue Lord).

Reasons for exclusion were: performance of a simple motor task (n=3) (Shimizu *et al.*, 1981; Weinrich and Bhatia, 1986; Yoshida *et al.*, 2005); not including a healthy control group (n=1) (Inzelberg *et al.*, 2008); and, eye movement data removed as artefact of electroencephalogram (EEG) data (n=1) (Tropini *et al.*, 2011). The majority of screened studies (n=220) were excluded because they were either not relevant or did not provide a quantitative measurement of visual sampling (e.g. restricted vision). Of the title screened studies that used a quantitative visual sampling measure, 47 were excluded for not meeting inclusion criteria (Appendix 1.0; Supplementary data 1).

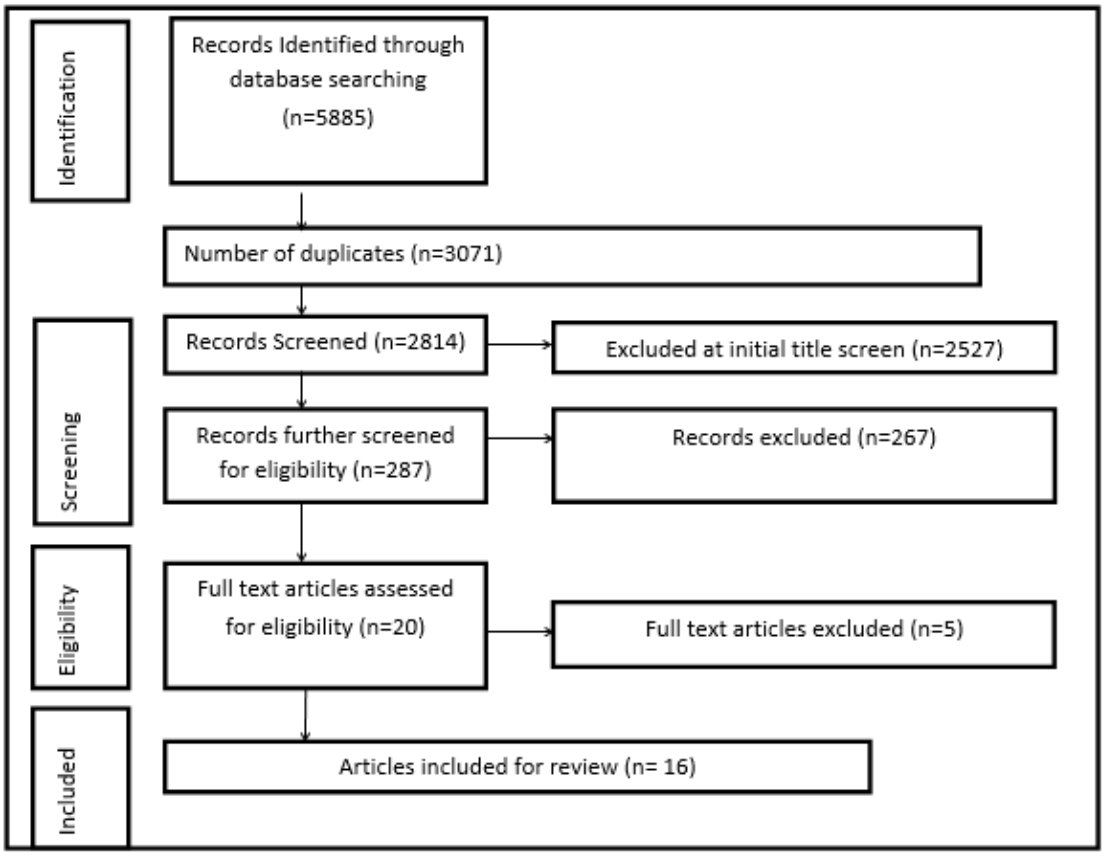


Figure 3-2 - PRISMA flow chart of study design. This illustrates the yield of the search strategy at each stage of the study selection process

3.4.2. Participants

The reviewed articles (n=16) investigated controls with a mean age of 63.9 (±7.5) years. One article (Uc *et al.*, 2006) did not report control demographics. The mean age of the PD subjects was 63.8 (±8.2) years. Both male and female participants were recruited to the majority of the studies, although one study (Lee *et al.*, 2012b) did not report gender characteristics. Generally, PD participants were assessed when they were 'ON' medication, and one study (Sacrey *et al.*, 2011) assessed PD subjects both 'ON' and 'OFF' medication.

3.4.3. Reliability and Validity

Of the articles reviewed, none commented upon the validity and reliability of the instrumentation used. One study assessed inter-rater reliability (Uc *et al.*, 2006), reporting a 95% agreement between examiners using the 'Landmark and Traffic Sign Identification Task'. Similarly, there was a lack of detail reported about the

manufacturers specification of the equipment used. Two studies (Lee *et al.*, 2012b; Marx *et al.*, 2012) provided the manufacturer specifications regarding the precision and degree of accuracy of their eye-tracking devices, but provided no evidence to substantiate this information.

3.4.4. Instruments

Visual sampling was measured using a variety of instruments in the reviewed articles, which depended upon the movement evaluated. For example; activities which involved head movement or the need for wireless equipment (e.g. walking, driving, turns-in-place) used mobile devices such as head-mounted eye-trackers, camcorders or electrooculography (EOG). Whereas other studies which restricted head movement (via a chin rest) used EOG or a desk-mounted infra-red eye tracker. Fifteen articles described various biomechanical instruments: head-mounted eye-trackers (e.g. infra-red and video-oculography) (n=6); EOG (n=7); 2D video camcorders (n=2); and a static infra-red eye-tracker (n=1). The temporal resolution used to sample eye tracking data was found to vary considerably, even when using similar devices (frequency range = 30-1000 Hz, see Table 3-1).

Only one study did not measure visual sampling directly (Uc *et al.*, 2006), and instead used a quantitative performance-based test called the ‘Landmark and Traffic Sign Identification Task’ (LTIT), which had been used with stroke patients and Alzheimer’s subjects previously (Uc *et al.*, 2005a). The LTIT requires subjects to visually sample (via saccades (McPeek *et al.*, 2000)) the environment and locate (and fixate on) specific landmarks/traffic signs during driving resulting in an visual sampling score (PD = 47.8% and control = 58.7%).

Table 3-1 - Participant characteristics, PD diagnosis, motor task, visual sampling instrument and motor task instrument of the reviewed studies

Author	Participants	PD Diagnosis	Motor Task	Visual Sampling Instrument	Motor task Instrument
(Anastasopoulos *et al.*, 2011)	10 idiopathic PD (aged 58.3 ± 11 years) 6 males, 4 females 10 Control (aged 52 ± 2.6 years) (from a previous study)	H & Y I n = 4, H & Y II n = 6 Disease duration: range 1-9 years	Turning in place	EOG sampling at 240 Hz	3D motion analysis
(Desmurget *et al.*, 2004a)	*Study 1* - 7 PD (aged 56 ± 11 years) 3 males, 4 females 7 Control (aged 53 ± 7 years) 4 males, 3 females *Study 2* - 5 PD (aged 46 ± 8 years) 2 males, 3 females 5 Control (aged 55 ± 10 years) 2 males, 3 females	*Study 1 and 2 combined* H & Y II n=5*, H & Y III n=4, H & Y IV n=3 * One patient was classified as H & Y 2.5 Disease duration: range 6-17 years	Seated reaching task	EOG sampling at 1000 Hz	Finger movements were recorded using a magnetic tracking system
(Galna *et al.*, 2012)	21 idiopathic PD (aged 67.6 ± 9.9 years) 14 males, 7 females 12 Control (aged 67.4 ± 8.7 years) 5 males, 7 females	H & Y I n = 1, H & Y II n = 13, H & Y III n = 7 Disease duration: 46.3 ± 50.9 months	Walking and turning (through a doorway)	EOG sampling at 1000 Hz	3D motion analysis
(Heremans *et al.*, 2012)	14 PD (aged 59.1 ± 9.6 years) 9 males, 5 females. 14 Control (aged 61.1 ± 6.6 years) 8 males, 6 females.	H & Y I n = 5*, H & Y II n = 5, H & Y III n= 4 * One patient was classified as H & Y 1.5 Disease duration: range 0.5-17 years	Upper limb tasks	EOG sampling at 1024 Hz A chin rest restricted head movements	EMG of the forearm sampling at 1024Hz
(Lee *et al.*, 2012b)	2 PD (aged 56 and 59 years, driving history of 37 and 40 years, respectively) and 6 Control (aged 49.8 ± years)	56 year old PD: H & Y: 1.7, Disease duration: 4 years 59 year old PD: H & Y: 1.9, Disease duration: 6 years	Driving task (simulator)	Mobile infra-red eye tracker sampling at 60 Hz	NR
(Lohnes and Earhart, 2011)	23 idiopathic PD; 90 degree turn: n = 22 (aged 68.7 ± 10.2 years), 14 males, 8 females * 180 degree turn: n = 20 (aged 68.6 ± 10.8 years), 13 males, 7 females * Freezers (n=8), Non-freezers (n=12) 19 Control (68.8 ± 11.4) 11 males, 8 females * Data for the 90 degree turn (n = 1) and 180 degree turn (n = 2) was omitted due to poor oculomotor data quality	Numbers represent those for 90(180) degree turns H & Y I n = 1(1), H & Y II n = 19(17)*, H & Y III n = 2(2) * 10 of the participants in H & Y II were classified as H & Y 2.5 Disease duration: 90 degree turn: 7.4 ± 5.8 years 180 degree turn: 6.8 ± 5.6 years	Turning in place	Mobile eye tracker sampling at 360 Hz EOG sampling at 1000 Hz used as a secondary measure if unable to get data from eye tracker	3D motion analysis

(Marx *et al.*, 2012)	11 PD (aged 65.5 ± 12.7 years) 8 males, 3 females (2 PD were wheelchair-bound) 10 Control (aged 68.3 ± 9.1 years) 4 males, 6 females	H & Y I n = 2, H & Y II n = 3, H & Y III n = 6 Disease duration: 6.2 ± 4.7 years	Walking	Mobile video oculography, gaze and head videos were sampled at 25 Hz and eye movements at 300 Hz	Head movements extracted via a fixed head camera and two high-speed cameras
(Muilwijk *et al.*, 2013)	15 early stage PD (aged 61.1 ± 8.4 years) 10 males, 5 females 15 age-matched Control (aged 56.0 ± 6.4 years) 6 males, 9 females	H&Y ranged between I and II Disease duration: 3.7 ± 2.4 years	Eye-hand co-ordination during a computer based task	Static infra-red eye tracker sampling at 200 Hz	3D motion analysis of upper limbs sampling at 200 Hz Touch screen sampling at 60 Hz
(Sacrey *et al.*, 2009)	8 mild PD (≤ 2.5 H&Y) (aged 63.9 ± 8.3 years) 2 males, 6 females 7 advanced PD (≥ 2.5 H&Y) (aged 75.0 ± 6.7 years) 4 males, 3 females 15 older adults Control (aged 62.8 ± 7.52 to 81.7 ± 5.0) 7 males, 8 females 11 young adult Control (aged 22.3 ± 3.9) 7 males, 4 females	H & Y I n = 2*, H & Y II n = 9**, H & Y III n = 1, H & Y IV n = 2 * One patient was classified as H & Y 1.5 ** Three patients were classified as H & Y 2.5 Disease duration: NS	Seated reaching task	Mobile infra-red eye tracker sampling at 60 Hz	Digital video camera recorded sagittal plane motion at 500 Hz. Data were digitised using Peak Motus
(Sacrey *et al.*, 2011)	8 PD (aged 70.3 ± 6.8 years) 6 males, 2 females 8 Control (aged 69.0 ± 5.78 years) 3 males, 5 females	H & Y I n = 4*, H & Y II n = 2**, H & Y III, n = 2 * Three patients were classified as H & Y 1.5 ** One patient was classified as H & Y 2.5 Disease duration: NS	Seated reaching task	Mobile infra-red eye tracker sampling at 30 Hz	Digital video camera recorded sagittal plane motion at 30 Hz. Data were digitised using Peak Motus
(Uc *et al.*, 2006)	79 PD (aged 66.0 ± 8.6) 64 males, 15 females 151 Control (aged 65.3 ± 11.5 years), 75 males, 76 females	Mean H & Y: 2.1 ± 0.7 Disease duration: 5.6 ± 5.0 years	Driving task	Landmark and traffic sign identification test (LTIT)	ARGOS (Automobile for Research in Ergonomics and Safety) instrumented vehicle composed of hidden instrumentation and motion sensors. Miniature cameras mounted inside the vehicle sampling at 30 Hz
(Ventre-Dominey *et al.*, 2001)	6 PD (aged 55.0 ± 10 years) 3 males, 3 females 9 Control (aged 53.5 ± 8.4 years) 5 males, 4 females	H & Y I n = 4*, H & Y II n = 2 * All four patients were classified as H & Y 1.5 Disease duration: 4.8 ± 2.1 years	Repetitive pointing task	EOG: Signals were filtered at 40 Hz and then digitised using a sampling frequency of 250 Hz	Touch-sensitive screen sampling at 1 kHz

(Ventre-Dominey *et al.*, 2002)	9 PD (aged 54.9 ± 10.5 years) 6 males, 3 females A subgroup of 6 PD participants were assessed for both separate and coupled eye and hand movement: 6 PD (aged 55.0 ± 10 years) 3 males, 3 females 9 Control (aged 53.5 ± 8.4 years) 5 males, 4 females	PD cohort (n = 9) H & Y I n = 7*, H & Y II n = 2 * Six patients were classified as H & Y 1.5 Disease duration: PD cohort (n = 9) – 4.1 ± 2.1 years Sub-group (n = 6) – 4.8 ± 2.1 years	Repetitive pointing task	EOG: Signals were filtered at 40 Hz and then digitised using a sampling frequency of 250 Hz	Touch-sensitive screen sampling at 1 kHz
(Vitorio *et al.*, 2012)	12 idiopathic PD (aged 69.8 ± 5.72 years), 8 males, 4 females12 Control (aged 69.6 ± 6.04 years), gender not stated for control cohort	H & Y I n = 10*, H & Y II, n = 2** *5 were classed as H & Y 1.5, **1 was classed as H & Y 2.5 Disease duration: NS	Self-paced walking under 3 visual conditions: (i) dynamic (normal lighting), (ii) static (static visual samples), (iii) voluntary visual sampling	Liquid crystal glasses for manipulation of vision Camcorder sampling at 60 Hz	3D referencing system and a force plate sampling at 200 Hz
(Vitorio *et al.*, 2013)	12 idiopathic PD (aged 69.8 ± 5.72 years), 8 males, 4 females 12 Control (aged 69.6 ± 6.04 years) , gender not stated for control cohort	H & Y I n = 10*, H & Y II n = 2** *5 were classed as H & Y 1.5, **1 was classed as H & Y 2.5, Disease duration: NS	Walking and obstacle crossing	Liquid crystal glasses for manipulation of vision Camcorder sampling at 60 Hz	Two digital camcorders with 3D referencing system.
(Vitorio *et al.*, 2014)	19 idiopathic PD (aged 64.79 ± 9.27 years) 15 Control (aged 66.8 ± 7.71 years) (*Only 14 PD and 12 Control included in visual sampling analysis due to data drop out)	UPDRS-III score = 24.33 ± 8.5	Walking with and without visual cues (transverse lines to step on)	Mobile infra-red eye-tracker sampling at 30 Hz	Optotrak wireless system 120Hz

[NR: Not Reported, EOG: Electro-oculography, H&Y: Hoehn and Yahr, PD: Parkinson's disease, control: Healthy older adult, Data are presented as means ± standard deviation unless otherwise stated]

Table 3-2 - Inclusion and exclusion criteria, study aims, research design and outcome measures

Author	Inclusion Criteria	Exclusion Criteria	Design and Aims	Test Protocol	Visual outcome definition
(Anastasopoulos *et al.*, 2011)	- 'ON' medication (2hrs prior) - All were right side dominant - Cohort were physically fit	- None of the cohort wore spectacles	**Experimental -** To assess whether hypometric saccades are secondary to low head movement velocity in PD	Turns-in-place from standing to visual (LED) cues placed at 45, 90, 135 and 180 degrees.	NR
(Desmurget *et al.*, 2004a)	All participants were: - Right handed - Absence of dementia and any other neurological disorders (other than PD for the PD cohort) - No signs of tremor - PD's were tested 'OFF' medication (12hr withdrawal)	NR	**Experimental -** To investigate the process of on-line motor correction in PD patients.	2 conditions: Relevant to this review was a seated upper-limb task	A single saccade was defined as an eye movement occurring >50°/sec
(Galna *et al.*, 2012)	- Able to walk independently without an aid - Adequate vision, hearing and language skills to comply with testing and provide a fully informed consent	- Dementia (MOCA <17) - Dyskinesia, vision or hearing impairment - Moderate or severe tremor - No confounding co-morbidity (cardiovascular disease)	**Exploratory -** To compare saccade frequency and timing in PD and control while walking through environments of differing complexity under single and dual task.	4 walking conditions - Straight walk single task - Straight walk dual task - Turn single task - Turn dual task	NR
(Heremans *et al.*, 2012)	- PD diagnosed by a neurologist using the Brain Bank Criteria - PD participants were assessed 'ON' medication	- MMSE <24 - Severe tremor - Any neurological comorbidity - Unpredictable motor fluctuations - Eye movement abnormalities - Severe orthopedic problems of the upper limb - Receiving treatment with deep brain stimulation (PD only)	**Experimental -** To investigate whether cues (visual, auditory) positively affect mental imagery performance in PD patients.	Relevant to this review was a seated upper limb task PD subjects performed the tasks with their most affected side. Control did it side-matched. Head movement restricted with a chin rest.	Fixations were defined as stable gaze maintained for >100ms. Eye movements included 1 single primary saccade and 1 or more corrective saccades.
(Lee *et al.*, 2012b)	All participants wore corrective spectacles	NR	**Experimental -** To assess the reliability of driving assessments made from the back seat by two occupational therapists	Subjects drove a fixed route in a computer-based driving simulator.	
(Lohnes and Earhart, 2011)	*Common criteria* - Aged 30 years or older - Normal central and peripheral neurological function (excluding PD participants) - Able to stand independently for at least 30mins Walk independently without assistive device - No history of vestibular disease	- Any serious medical condition other than PD - Use of neuroleptic or other dopamine-blocking drugs - Use of medication known to affect balance (eg. benzodiazepines) - Evidence of abnormality on brain imaging - Other neurological deficits	**Experimental -** To determine whether saccadic activity is impaired whilst turning in PD.	Turns-in-place from standing to 90 and 180 degrees, right and left. No visual or auditory cues were provided.	A single saccade was defined as an eye movement occurring >30°/sec

	- No evidence of dementia *PD only* - 'OFF' dopaminergic medication - Diagnosis of definite PD by neurologist	(stroke or muscle disease) - Surgical management of PD (DBS or pallidotomy)			
(Marx *et al.*, 2012)	- Clinically probable PD - No history of alcohol or substance abuse - Free from neurologic, systemic, or psychiatric disorder (other than PD for those participants) - PD participants were tested 'ON' medication	- Neurological disorders - Dementia (MMSE <24) - Any presently active psychiatric disorder - Any structural brain lesion, cataracts or other neuro-ophthalmological disorder - Visual correction by glasses as glasses cannot be worn with the eye tracker	**Experimental -** To establish mobile eye tracker usage in PD, control and Progressive supra-nuclear palsy cases and validate its power to discriminate eye movements between these groups	2 tasks: Relevant to this study was a walking condition.	A single saccade was defined as an eye movement occurring >60°/sec
(Muilwijk *et al.*, 2013)	- >45 years old - had normal cognitive function - were classified as having mild PD (PD cohort only; < 2.5 H&Y) - PD patients were tested 'ON' medication	- Dyskinesia - Coexistence of other neurological or psychiatric disorder - History of ocular pathology	**Experimental -** To quantify visuomotor coordination in early-stage PD patients	4 seated upper-limb tasks. Head movement restricted via chin rest.	A single saccade was defined as an eye movement occurring >50°/sec
(Sacrey *et al.*, 2009)	All were required to have normal or corrected to normal (contact lens) vision Control's self-reported good health and had no history of neurological disorder PD's were required to be 'ON' medications	NR	**Experimental –** To investigate the effect of music (auditory cue) on sensory and motor impairments (during reaching task)	3 seated upper-limb conditions	NR
(Sacrey *et al.*, 2011)	*Common criteria:* Normal or corrected to normal (contact lens) vision Control's *only:* No history of neurological disorder *PD only:* Diagnosis of PD by experienced neurologist	NR	**Experimental -** To investigate the effects of music and medication on sensory control in PD (sensory monitoring and shifts during reach to eat task)	A seated upper-limb task PD participants were tested both 'ON' (1.5hr prior) and 'OFF' (12hr withdrawal) medication	NR
(Uc *et al.*, 2006)	- Independently living and held a full and valid driver's license *PD only:* - Driving experience of at least 10years	- Cessation of driving before assessment - Acute illness or confounding medical conditions (vestibular disease) - Alcoholism or other substance abuse - Other neurological disease leading to dementia - Concomitant treatments - Treatment with investigational medication - Major psychiatric disorder	**Experimental -** 1. To assess visual search using the landmark and traffic sign identification task (LTIT) while driving 2. To assess whether PD drivers make more safety errors as a result of the increased cognitive load imposed by the LTIT 3. To determine whether performance on the LTIT and safety errors could be accurately estimated by the measures (visual,	A driving assessment in a car on the road PD participants were tested whilst 'ON' medication. All participants underwent a visual and cognitive testing battery that incorporated tests of visual functions (contrast sensitivity and both near and far visual acuity) and visual perception.	No specific saccadic or fixation outcomes were assessed

		- Ocular disease with normal or corrected visual acuity less than 20/50	cognitive and motor) known to decline in PD		
(Ventre-Dominey *et al.*, 2001)	- All participants were right handed PD's were tested 'ON' medication and displayed asymmetric akinetic-rigid syndrome Controls had no history of neurological or ophthalmological disorders	NR	**Experimental -** To investigate the role of the basal ganglia in eye-hand co-ordination (repetitive pointing)	A seated upper-limb task. Head movements were restricted via chin rest.	NR
(Ventre-Dominey *et al.*, 2002)	*PD only:* - Tested 'ON' levodopa medication - Asymmetric akinetic-rigid syndrome - Diagnosis of PD (UK Brain Bank Criteria) Controls had no history of neurological or ophthalmological disorder	NR	**Experimental -** To investigate predictive saccades without hand pointing. Then investigate predictive saccade and pointing performance in an eye–hand coordination condition	A seated upper-limb task (same as that described in (Ventre-Dominey *et al.*, 2001)) under two conditions: with and without visual stimulus. Head movements were restricted via chin rest	NR
(Vitorio *et al.*, 2012)	- Walk independently - Cognitively intact - No history of neurological, musculoskeletal or cardiorespiratory disease (other than PD for the PD cohort) PD's were tested 'ON' medication.	No PD participants experienced freezing of gait	**Experimental -** To investigate the role of visual information and locomotor control in people with PD.	2 walking conditions Participants wore liquid crystal glasses that manipulated visual input. Glasses were either opaque or transparent.	No specific saccadic or fixation outcomes were assessed.
(Vitorio *et al.*, 2013)	PD and control cohorts were matched for age, body height, body mass and gender - Walk independently - No cognitive, neurological, musculoskeletal or cardiorespiratory impairments PD participants were assessed 'ON' medication (1hr prior)	NR	**Experimental -** To investigate the role of visual information on locomotor control in PD as they negotiated obstacles	3 walking conditions (under static and voluntary visual sampling) Participants wore liquid crystal glasses that manipulated visual input. Glasses were either opaque or transparent.	No specific saccadic or fixation outcomes were assessed.
(Vitorio *et al.*, 2014)	PD diagnosis from at least one neurologist, and have gait impairment (slowness, hypo-metric step or shuffling). At least one of the gait portion of the UPDRS-III PD participants were assessed 'ON' medication (1hr prior) No cognitive (at least 27 on MMSE), neurological, musculoskeletal or cardiorespiratory impairments.	Freezers were excluded	**Experimental -** To investigate the role of visual information on gait and gait improvements in PD as they used a visual cue, looking at step accuracy and precision	3 walking conditions Participants wore a wireless mobile eye-tracker (30Hz) to record eye movement.	NR

[NR denotes not reported]

Table 3-3 - Summary of the previously reported visual sampling outcomes and PD impairments during real-world activities

	Saccade						Fixation		Visual sampling	
Visual Outcome / Motor Task	**Velocity**	**Direction**	**Duration**	**Frequency**	**Latency**	**Amplitude**	**Duration**	**Frequency**	**Saccades and Fixations Frequency**	**Saccades and Fixations Duration**
Gait	✓ (↑)	✓ (-)	✓ (↑)	✓ (↓)	NR	✓ (↑)	NR	NR	✓ (↓)	✓ (↓)
Obstacle crossing	NR	NR	NR	NR	NR	NR	NR	NR	✓ (↓)	✓ (↓)
Visual cue	NR	NR	NR	NR	NR	NR	✓ (↑)	✓ (↑)	NR	NR
Turning in place	✓ (↓)	NR	NR	✓ (↑)	✓ (↓)	✓ (↓)	NR	NR	NR	NR
Upper-limb tasks	✓ (↓)	NR	✓ (↑)	NR	✓ (↑)	✓ (↓)	NR	NR	NR	NR
Driving	NR	NR	NR	NR	NR	NR	NR	✓ (↓)	✓ (↓)	NR

[✓= Reported outcome for both PD and Control, NR denotes not reported, '↓' indicates PD subjects less than Control, '↑' indicates PD subjects more than Control, '-' indicates no difference between PD and Control]

3.4.5. Outcome measures

The majority of the studies provided no visual outcome (saccade and fixation) definitions. Five studies (Desmurget *et al.*, 2004a; Lohnes and Earhart, 2011; Heremans *et al.*, 2012; Marx *et al.*, 2012; Muilwijk *et al.*, 2013) did provide outcome definitions, but definitions varied between studies. Thirteen studies specified the visual sampling outcome variables obtained, which often involved saccade or fixation measurements (such as saccade frequency, duration, velocity, amplitude, latency, fixation frequency and duration, Table 3-2). Three studies (Uc *et al.*, 2006; Vitorio *et al.*, 2012; Vitorio *et al.*, 2013) reported overall visual sampling (i.e. combined saccade and fixation measurement). However, Table 3-3 demonstrates that many saccadic and fixation outcomes were not reported in the reviewed studies, likely because they were not deemed relevant to the study.

3.4.6. Interpretation of outcomes

The influence of PD on visual sampling outcomes was inconsistent likely due to the small sample sizes, with several studies reporting non-significant differences between PD and control subjects (Ventre-Dominey *et al.*, 2002; Anastasopoulos *et al.*, 2011; Marx *et al.*, 2012; Vitorio *et al.*, 2012; Vitorio *et al.*, 2013). PD-specific visual sampling outcomes were impaired during all of the real-world activities compared to control participants (summarised in Table 3-3). These differences appeared to be task-dependant with several visual sampling outcome measures (i.e. saccade frequency, amplitude and velocity) changing according to task demand. For example, during level gait, PD subjects made larger, faster but less frequent saccades in comparison to control (Galna *et al.*, 2012; Marx *et al.*, 2012). However, during other tasks (e.g. upper-limb tasks and turns-in-place) these related outcomes were oppositely impaired (i.e. reduced saccade velocity and amplitude and increased frequency) (Ventre-Dominey *et al.*, 2001; Ventre-Dominey *et al.*, 2002; Desmurget *et al.*, 2004a; Sacrey *et al.*, 2009; Anastasopoulos *et al.*, 2011; Lohnes and Earhart, 2011; Sacrey *et al.*, 2011), illustrating a selective effect of impairment.

Notable methodological limitations were found. Relationship between visual sampling and PD motor (i.e. FOG), cognitive and visual deficits was assessed in

four of the reviewed studies (Uc *et al.*, 2006; Lohnes and Earhart, 2011; Galna *et al.*, 2012; Lee *et al.*, 2012b), however the majority did not report or control for cognition or visual function (VA and CS). Many studies either excluded or did not assess for cognition (Desmurget *et al.*, 2004a; Sacrey *et al.*, 2009; Lohnes and Earhart, 2011; Marx *et al.*, 2012; Vitorio *et al.*, 2012; Vitorio *et al.*, 2013; Vitorio *et al.*, 2014). Two studies (Uc *et al.*, 2006; Galna *et al.*, 2012) assessed visual function and several studies did not include participants who wore glasses (Sacrey *et al.*, 2009; Anastasopoulos *et al.*, 2011; Sacrey *et al.*, 2011). Two studies (Sacrey *et al.*, 2009; Sacrey *et al.*, 2011) reported including contact lens wearers, most likely because contact lenses do not affect measurement tools, such as optical eye-trackers, to the same extent as glasses.

3.5. Discussion

This structured review examined 16 studies reporting visual sampling in PD and older adult subjects during real-world activities. Explicitly reviewing; (i) how visual sampling was measured; (ii) the specific outcomes assessed and how they were defined; and (iii) the differences reported between PD and control subjects in these outcomes during real-world activities. This review has demonstrated that the measurement of visual sampling during real-world activities in PD is emerging, but further work is warranted to establish the validity and reliability of visual sampling instrumentation, and the nature of task-dependent visual sampling impairments in PD.

3.5.1. Instruments

Several studies have shown progression from constrained seated activities (e.g. chin rest in place and pointing on a computer screen) to unconstrained real-world activities (e.g. walking or driving), which was achievable only by using mobile visual sampling instrumentation (Land, 2006; Lohnes and Earhart, 2011; Marx *et al.*, 2012; Vitorio *et al.*, 2014). However, the progression from constrained to unconstrained mobile instrumentation came at the cost of reduced temporal resolution, illustrating the trade-off between mobility and accuracy. Mobile eye-trackers generally have temporal resolutions of 30-60Hz, whereas static devices have higher resolutions of 200-1000Hz. This impacts on instrument validity, as saccade velocity based algorithms require at least a 50Hz system to accurately

detect a saccade and 200Hz to accurately measure saccade durations (Holmqvist and Nystrom, 2011). Importantly, clear evidence of validity and reliability of instrumentation is essential for confidence in these measures we found this was not adequately addressed with only one study (Uc *et al.*, 2006) examining this and two studies (Lee *et al.*, 2012b; Marx *et al.*, 2012) providing inadequate information. Many studies used EOG, which permits data collection during unconstrained tasks at a high temporal resolution (200-1000Hz). However, inaccuracy with EOG measurements/data have been reported, especially for the detection of small corrective saccades (<2°) (Desmurget *et al.*, 2004a), which may be important as healthy adults have been shown to undershoot targets by <2° at visual angles of >10° (Robinson *et al.*, 1993). Similarly, EOG limits visual sampling characteristic selection (Galna *et al.*, 2012), as no spatial data is collected and only horizontal saccades can be accurately obtained (with eye-lid movement significantly affecting vertical saccades) (Wilson *et al.*, 1992). Therefore, both these issues must be considered when using mobile eye-tracking equipment or reporting EOG measurements alone.

In the absence of a 'gold standard' instrument it may be prudent to use a combination of devices, such as EOG and infra-red eye-tracking, to obtain the high temporal resolution and spatial outcomes required. EOG and mobile infra-red eye-tracking are reported to have 'exceptional' comparison during horizontal saccades, although this was not quantified (Lohnes and Earhart, 2011). Reporting the reliability and validity of eye-tracking methodologies is advocated due to the internal (e.g. parallax (Pelz and Canosa, 2001) and calibration error (Pelz and Canosa, 2001; Nystrom *et al.*, 2013)) and external (e.g. head movement (Marx *et al.*, 2012)) influences upon eye-tracking. Overall the review findings indicate the need for reporting the reliability and validity of the instruments used to measure visual sampling during real-world tasks.

3.5.2. Outcomes

Visual outcome results from small cohorts may not be an accurate representation of the general population and furthermore create a lack of statistical power and inconsistency in findings. This was evident in this review with many non-significant outcomes reported by studies with small participant numbers (Table 3-

1 and Appendix 2.0; Supplementary data 2). For example; Galna *et al.* (2012) stated that visual sampling frequency was decreased in PD (n=21) compared to control when walking, while Vitorio *et al.* (2012) stated that it was similar (n=12) even though they found a non-significant decrease in visual sampling frequency. Since 2011, sample sizes have increased coinciding with the use of mobile eye-tracking devices (Table 3-1), which offer relatively quick data acquisition and analysis.

Currently, there are no gold-standard algorithms/definitions for the detection of visual outcomes (Nystrom and Holmqvist, 2010) or for reporting visual outcome measures. This may explain why many of the reviewed studies (Ventre-Dominey *et al.*, 2001; Ventre-Dominey *et al.*, 2002; Sacrey *et al.*, 2009; Anastasopoulos *et al.*, 2011; Sacrey *et al.*, 2011; Galna *et al.*, 2012) did not provide definitions for visual outcomes reported. As a result, velocity thresholds for saccades vary hugely in eye movement literature from 30°/sec (Chan *et al.*, 2005; Chen *et al.*, 2010) to 350°/sec (Beenen *et al.*, 1986), but usually range from 30-100°/sec (Holmqvist and Nystrom, 2011, pp. 152). Depending upon the thresholds set for outcome detection, valuable information may be discarded or irrelevant data included. For example, a velocity-based algorithm with a 130°/sec threshold will detect saccades over 3° (Duchowski, 2007), and below this threshold, data would be classed as a fixation. However, depending on the specific aims and methodology, this algorithm may not be relevant or accurate.

Despite the lack of consistency, many studies used visual outcome definitions and reported visual outcomes in a task-dependent manner (Hayhoe and Ballard, 2005; Land, 2006; Marigold and Patla, 2007; Owsley, 2011; Peltsch *et al.*, 2011). In the reviewed studies, upper limb tasks reported latencies or durations, whereas during whole body tasks (e.g. walking, driving etc.) frequencies or overall scores were provided. Similarly, low velocity thresholds (e.g. 30°/sec (Chan *et al.*, 2005; Versino *et al.*, 2005; Peltsch *et al.*, 2011)) tend to be used for constrained studies, whereas during unconstrained studies higher thresholds (e.g. 50-60°/sec (Desmurget *et al.*, 2004a; Marx *et al.*, 2012; Muilwijk *et al.*, 2013)) are used to exclude interference from other visual events (e.g. vestibular ocular reflex). Substantial variation makes direct comparisons between studies and real-world activities difficult. Comparison of several reviewed studies that did

report the same visual outcome measures (Desmurget *et al.*, 2004a; Anastasopoulos *et al.*, 2011; Galna *et al.*, 2012; Marx *et al.*, 2012) indicated possible task-dependent impairments in PD subjects, but due to a lack of available studies and methodological variations, definitive conclusions cannot be drawn. This confirms the need for quantification of visual sampling during real-world activities to determine the effect of a real-world activity and the consequences of PD on 'real-life' situations (Marx *et al.*, 2012). Creating a gold-standard for visual event detection and outcome measure reporting is challenging due to variations in instrumentation and differing methodologies. Therefore, current research should report visual event definitions and either use a task-dependent or an adaptable algorithm (Nystrom and Holmqvist, 2010).

PD influenced real-world activity performance and visual sampling outcomes in all of the reviewed studies. A common phenomenon of PD is freezing of gait (FOG), which has been linked to reduced function and increased falls incidence (Okuma, 2006; Vercruysse *et al.*, 2012). Only two of the reviewed studies (Anastasopoulos *et al.*, 2011; Lohnes and Earhart, 2011) reported visual sampling in relation to FOG. They demonstrated reduced velocity and latency of saccades in PD subjects who experience FOG, while other aspects such as saccade amplitude and frequency remained similar to non-FOG subjects. Reduced saccade latency during turns-in place was attributed to a compensatory strategy adopted to prevent falling, and to compensate for reduced movement times (of the head, trunk etc.), as the eyes contributed more than other segments in PD subjects during turning (Anastasopoulos *et al.*, 2011). However, similar outcomes have been found in older adults who fixate on stepping targets significantly earlier than younger subjects (Di Fabio *et al.*, 2003; Chapman and Hollands, 2006), with increased cognitive (visuomotor) processing time required (Chapman and Hollands, 2006; Chapman and Hollands, 2010; Uiga *et al.*, 2015). Another study stated that PD subjects reduced saccadic impairment during real-world activities or used saccadic activity to compensate for motor deficiencies (Marx *et al.*, 2012). Similar differences in saccadic activity during gait in older adults are suggested to reflect compensatory adaptations in an attempt to maintain online control of real-world tasks (Uiga *et al.*, 2015) despite visual and cognitive impairment, and the same could be true for those with PD. However it

is unclear if compensatory strategies exist due to incomprehensive reporting of visual sampling outcomes, small sample sizes and methodological variations (*such as not controlling for cognitive or visual dysfunctions).*

3.5.3. Interpretation of outcomes

Six studies (Uc *et al.*, 2006; Sacrey *et al.*, 2009; Sacrey *et al.*, 2011; Galna *et al.*, 2012; Heremans *et al.*, 2012; Vitorio *et al.*, 2014) assessed for visual or cognitive function. Visual and cognitive processes underpin visual sampling during real-world activities (Chapter 2), with top-down cognitive control most prevalent during such situations (Anderson and MacAskill, 2013). Cognitive and visual deficits influence visual sampling in PD and older adults (van Stockum *et al.*, 2008; van Stockum *et al.*, 2011a; van Stockum *et al.*, 2012; van Stockum *et al.*, 2013), and real-world activity performance resulting in visuo-cognitive deficits, such as increased visual processing time (Chapman and Hollands, 2006; Antal *et al.*, 2008; Chapman and Hollands, 2010), perceptual deficits (Bodis-Wollner, 2003; Young *et al.*, 2010) and abnormal environment scanning (Matsumoto *et al.*, 2011; Matsumoto *et al.*, 2012). Similarly, visual function impairments, such as VA and CS are common in ageing, but are further implicated in PD due to dopamine depletion within retinal and primary visual structures (Archibald *et al.*, 2009; Bodis-Wollner, 2013; Bodis-Wollner *et al.*, 2013). Such visual deficits have been linked to functional impairments during real-world activities and falls in older adults (Archibald *et al.*, 2009; Moes and Lombardi, 2009; Owsley, 2011). Although, visual acuity impairment is variable in PD (Geldmacher, 2003), as it can be corrected with prescription glasses (Antal *et al.*, 2008). Conversely, contrast sensitivity has been related to everyday task impairment in PD and older adults (Geldmacher, 2003; Moes and Lombardi, 2009; Owsley, 2011). Therefore, it was surprising that most of the reviewed studies either excluded subjects with cognitive or visual deficits, or did not test for them. The exclusion of these subjects limits the generalisability of the findings and may obscure the underlying mechanisms of visual sampling impairment in PD.

Visual and cognitive impairments in PD were associated with reduced visual sampling (Uc *et al.*, 2006; Galna *et al.*, 2012; Heremans *et al.*, 2012) and increased fixation durations (Sacrey *et al.*, 2009; Sacrey *et al.*, 2011) during real-

world activities. Although similar impairment is seen during static tests of visual sampling (Clark *et al.*, 2010; Matsumoto *et al.*, 2011; Matsumoto *et al.*, 2012; Archibald *et al.*, 2013), it is likely that visual sampling was influenced by the increased cognitive demand of a real-world activity (Ho *et al.*, 2001). Age, disease progression, and disease-specific motor characteristics (e.g. FOG) have also been implicated in cognitive and visual processing time (Di Fabio *et al.*, 2003; Chapman and Hollands, 2006; Sacrey *et al.*, 2009; Chapman and Hollands, 2010; Lord *et al.*, 2012). Therefore, measurement of not only motor but also cognitive and visual impairment is required when investigating visual sampling in PD and older adult subjects, due to the aforementioned internal and external influences (Maltz and Shinar, 1999; Ho *et al.*, 2001; Archibald *et al.*, 2013).

3.5.4. Test Protocols

Pelz and Canosa (2001) acknowledged that many previous studies investigating visual sampling have incorporated simple tasks involving stationary observers, with subjects interacting with their environment via button presses or mouse clicks. These experiments provide valuable information concerning specific mechanisms behind visual sampling and allow for experimental manipulation. However, they lack ecological validity because movements during real-world activities commonly involve multiple motor, cognitive and visual processes. In contrast, sixteen studies included in this review examine real-world activities under dynamic conditions providing insight into visual behaviour and the interplay between motor function, cognition and vision. Previous investigations of vision during real-world activities, neglect the quantitative objective measurement of visual sampling (i.e. measurement of eye-movements). For example, previous studies manipulated visual input during real-world activities by testing under conditions where vision was present (light or no occlusion) or restricted (dark or occluded) (Klockgether and Dichgans, 1994; Azulay *et al.*, 1999; Adamovich *et al.*, 2001; Vaillancourt *et al.*, 2001a; Vaillancourt *et al.*, 2001b; Almeida *et al.*, 2005; Schettino *et al.*, 2006; Rand *et al.*, 2010). These studies provide global information on the contribution of vision compared to proprioception (Ghez *et al.*, 1994), but unlike studies involving eye-tracking technology they do not assess

specific visual sampling outcomes during real-world activities. Recommendations for future protocols are made in Table 3-4.

Table 3-4 - Recommendations for future research

Recommendations for future visual sampling during real-world activities research
• Use task-appropriate instrumentation to measure visual sampling with temporal resolution ≥50Hz for saccade detection • If measuring saccade durations use a temporal resolution of ≥200Hz, which may involve combining devices • Report the reliability and validity of any instrument used to monitor visual sampling • Use an adequately powered sample size • Define all visual outcomes and measure using a task-dependent or adaptable algorithm • Routinely assess and control for visual function and cognition

3.6. Conclusions

Previous studies have been limited by methodological issues and a lack of robust techniques involving novel technology (i.e. mobile eye-tracking), which will be addressed in the first two experimental chapters of this thesis (Chapter 5 and 6). Precise quantitative measures of visual sampling during real-world activities are essential for characterising the impairments involved in PD. However, no single device or combination of devices has been established as the most informative indicator of these processes. Although mobile infra-red eye–trackers are the most comprehensive method available to date, the validity and reliability of such devices during real-world activities in people with PD or older adults are yet to be determined.

The implications of visual sampling during real-world activities remain unclear, but research in this area is emerging. Variations in visual sampling during different real-world activities infer not only an impairment of eye-movements in PD, but may relate to a task-specific alteration influenced by a combination of motor (i.e. gait), cognitive and visual deficits. Further quantification of visual sampling is needed to understand PD-specific impairments and explore the underlying visual and cognitive relationships, which will enhance understanding of visuo-cognition in gait.

4. General Methodology

4.1. Summary[4]

Each of the following experimental chapters (Chapters 5, 6, 7, 8 and 9) contain a methods section specific to the experimental design used. However certain procedures remained constant across all the studies presented in this thesis, which are described in the following chapter. Definitions and calculations are provided for all outcome measures obtained, with details of all assessments conducted.

4.2. Methodological design

4.2.1. Research design and sample recruitment

The study used a repeat measures observational design with PD participants (across a range of cognitive ability but non-demented) recruited from the Newcastle upon Tyne NHS Movement Disorder service over a two year period (July 2013 - February 2015). In addition, healthy aged-matched control older adults (controls) were recruited via advertisement using posters (Appendix 3.0) and email (Appendix 4.0), specifically posters were displayed within neurology and geriatric departments in Newcastle and an email was sent via the Newcastle University e-mail system to staff and students. A total of 100 participants (60 PD and 40 controls) were recruited and included in the study. Figure 4-1 provides a detailed account of study recruitment, illustrating that 95 PD participants were referred to the study, with 22 declining to participate and 13 being un-contactable. Of the 64 PD participants that consented to be screened for the study, one was considered to have an unstable medical condition; specifically prostate cancer. Similarly three other PD participants were excluded due to vision specific pathology which would affect the ability to monitor eye-movements (nystagmus n=2 and acute blepharitis n=1).

The control cohort comprised of people who expressed an interest in the study advertisements (Appendix 3.0 and 4.0), with a total of 54 people getting in contact. Four of the controls that contacted declined after receiving further

[4] This study protocol has been published in F1000 Research; Stuart et al. (2015)

information about the study, and ten potential controls were uncontactable once they had made their initial contact via phone or e-mail. One control was excluded after screening as they did not meet the group criteria of ≥26 of the Montreal cognitive assessment (MoCA) (see section 4.4), which may indicate MCI. As a result they were excluded and their general practitioner was informed.

4.3. Ethical Approval

The study was approved by an NHS Local Research Ethics Committee (REC) and all participants gave written informed consent prior to inclusion in the study (Newcastle and North Tyneside 1 REC; Reference: 13/NE/0128). The trial was also registered with ClinicalTrials.gov (ID: NCT02610634).

4.4. Inclusion/Exclusion Criteria

Participants who expressed an interest in the study were included if they met specific inclusion criteria, as well as meeting none of the exclusion criteria.

Common Inclusion Criteria:

- Aged ≥50 years
- Able to walk unaided
- Adequate hearing (as evaluated by the whisper test; stand 2m behind subject and whisper a 2 syllable word, subject repeats word) and vision capabilities (as measured using a Snellen VA chart – 6/18-6/12).
- Stable medication for the past 1 month and anticipated over a period of 6 months

Common Exclusion Criteria:

- Psychiatric co-morbidity (e.g., major depressive disorder as determined by geriatric depression scale - GDS-15; ≤10 (Aikman and Oehlert, 2001))
- Clinical diagnosis of dementia or other severe cognitive impairment (MoCA ≥21 but <26 (Dalrymple-Alford *et al.*, 2010))
- History of stroke, traumatic brain injury or other neurological disorders (other than PD, for that group)
- Acute lower back or lower extremity pain, peripheral neuropathy, rheumatic and orthopaedic diseases

- Unstable medical condition including cardio-vascular instability in the past 6 months
- Unable to comply with the testing protocol or currently participating in another interfering research project
- Interfering therapy

Vision specific (identified via medical notes):

- Any pupillary diameter disorder; such as significantly non-round pupils, Adies pupil (tonic or dilated pupil), Argyll-Robertson pupil (absence of light reaction), unilateral small pupil
- Neuro-motility disorders, such as Nystagmus or other ocular oscillations
- Significant left eye disorders (i.e. squint, twitching, Ptosis [drooping eyelids])
- Known significant visual field deficits; such as hemianopia
- Optic nerve disease
- Optic disc elevation
- Optic disc swelling; such as Papilledema or Papillitis

Participants with PD specific criteria:

- Diagnosis of idiopathic PD, as defined by the UK Brain Bank criteria (Hughes *et al.*, 1992)
- Hoehn and Yahr stage I-III (Hoehn and Yahr, 1967)
- Stable medication for past 1 month and anticipated over next 6 months or stable Deep Brain Stimulation for at least one month and expected following 6 months
- Score ≥21/30 on MoCA which is used to classify non-demented PD (PD dementia is <21/30) (Nasreddine *et al.*, 2005; Smith *et al.*, 2007)
- Free from any neurological disorders that may have caused cognitive impairment

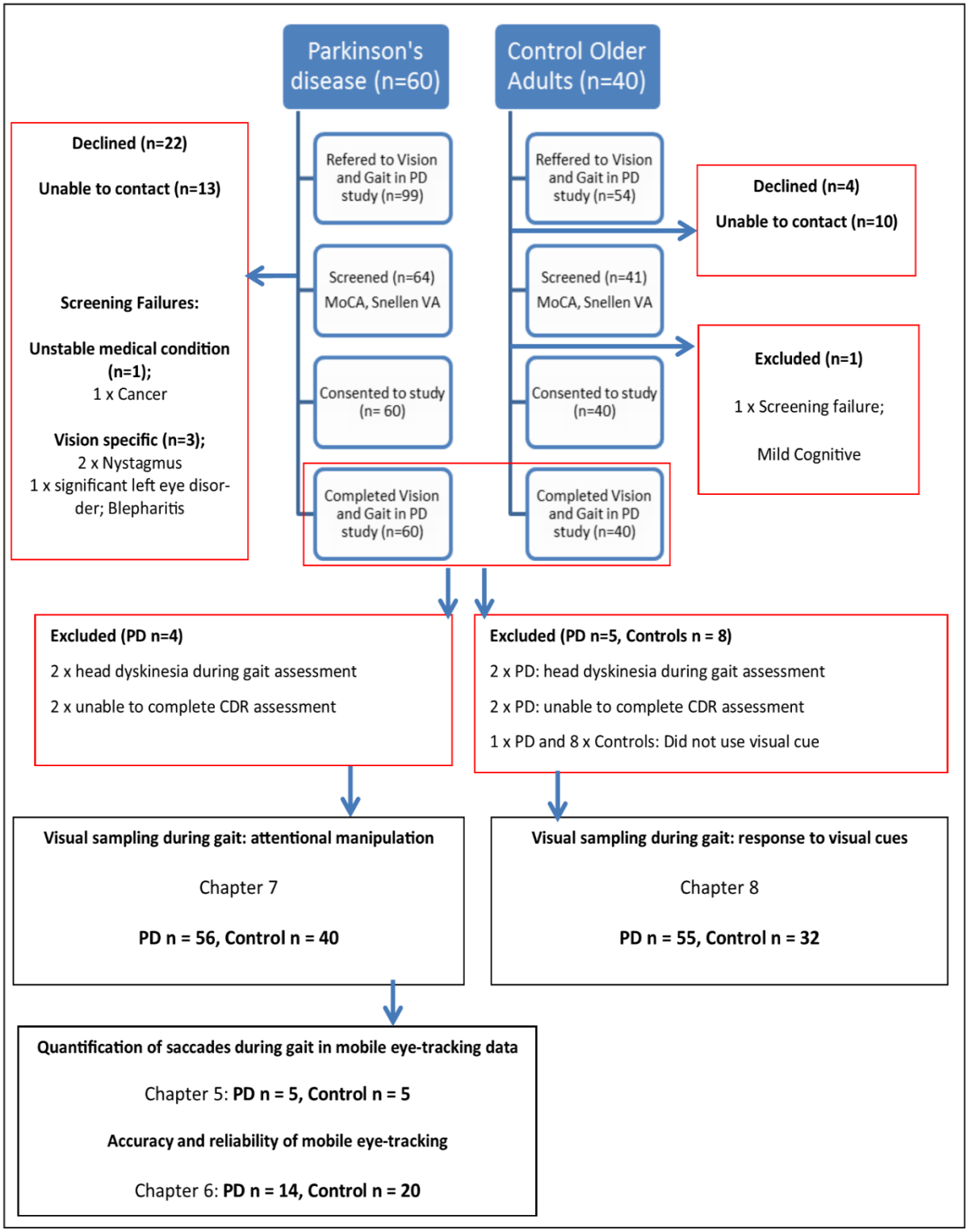


Figure 4-1 – Study recruitment flow chart

All data collection was completed in one session (lasting ~3 hours), apart from participant screening which was conducted separately within the movement disorder clinics by the principle investigator (SS). Individual demographic data was collected at the start of the session, including; retrospective falls history and medications. No restriction was made for medication usage provided participants were on stable doses of medication or treatment. PD medications were converted to levodopa equivalent doses (LED) using published criteria (Tomlinson *et al.*, 2010).

4.5. Global Neuropsychological Assessment

Global cognition was assessed via the MoCA (Appendix 5.0) and the Addenbrookes cognitive examination (revised version) (ACE-R; Appendix 6.0), which were used as descriptive measures (Dalrymple-Alford *et al.*, 2010). The MoCA was performed during screening and used to exclude control participants with cognitive impairment (MoCA < 26) and PD participants with dementia (MoCA < 21) (Aarsland *et al.*, 2010). The MoCA is a valid and standardized neuropsychological test for rapid screening of global cognitive dysfunction (Dalrymple-Alford *et al.*, 2010), and assesses several different cognitive domains (attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation). ACE-R has also been shown to be valuable in differential diagnosis of PD when compared to the Mini mental state examination (MMSE) (Rittman *et al.*, 2013). Similar to the MoCA, the ACE-R involves testing multiple cognitive domains, such as; attention, orientation, memory, fluency, language and visuospatial abilities.

Data on depressive symptoms was collected using the geriatric depression scale (GDS-15; Appendix 7.0) short form. The GDS-15 was created in 1986 by Sheikh and Yesavage and involves 15 questions about the mood of participants (Yesavage and Sheikh, 1986). Scores of 0 to 4 to be in the normal range, 5 to 9 to indicate mild depression, and 10 to 15 to indicate moderate to severe depression (Aikman and Oehlert, 2001). The GDS-15 is a relatively quick and valid assessment of depression (Meara *et al.*, 1999; de Craen *et al.*, 2003).

4.6. Specific Cognitive Domain Assessment

4.6.1. Attention

Attention (specifically top-down attention) was measured via the Cognitive Drug Research (CDR) battery (United Biosource Corporation, UK). The CDR battery involved three sub-sections of simple reaction time, digit vigilance and choice reaction time, as shown in Table 4-1. These sub-sections consist of computerised tests, which the participants respond to by pressing one of two buttons (YES or NO buttons). The measurements acquired during these tasks provide specific measures of attention, including; composite measures of power of attention and fluctuation of attention (Allcock *et al.*, 2009). Power of attention is the sum of the reaction time (ms) scores from the three tasks and fluctuation of attention is sum of the coefficient of variance (CV%) of reaction time scores from the three tasks (Allcock *et al.*, 2009). Use of composite measures, particularly CV% (Mean/SD x 100) allowed for normalisation of the attentional measures used for each individual. The attention CDR is a valid means of testing attention and has been used in a number of studies involving people with PD, cognitive impairment and control individuals (Wesnes *et al.*, 2005).

4.6.2. Executive function

Clock drawing, specifically Royall's CLOX 1 (Appendix 8.0) (Royall *et al.*, 1998) was used as a measure of executive function (i.e. planning) (Salthouse, 2005). Clock drawing assessment is a measure of cognitive impairment, which is internally consistent with good reliability between raters, and is easy to administer (Royall *et al.*, 2003; Zuverza-Chavarria and Tsanadis, 2011). Participants were required to plan and draw a clock with the numbers and arrows pointed at a particular time, which is then marked out of 15 for certain criteria (e.g. hour hand shorter than the minute hand = one point).

Table 4-1 - Cognitive Drug Research (CDR) battery

CDR Assessment	Description	Measure
Simple reaction time	Participant has to press the YES button as fast as possible every time the word YES appears on the computer screen.	Reaction time (ms) and coefficient of variance (CV%)
Digit vigilance	A random whole number (digit) is chosen by the programme and is displayed on the screen. To the left of this, in the centre of the screen, a series of digits (one at a time) was then presented at the rate of 150 per minute. The participant was required to press the YES button when the two numbers on the screen matched. There were 45 numbers in the series.	Reaction time (ms) and coefficient of variance (CV%), % of accurate responses, number of errors
Choice reaction time	Participant had to press either the YES or NO button as fast as possible every time the corresponding word appeared on the computer screen. 30 stimuli were randomly delivered.	Reaction time (ms) and coefficient of variance (CV%), % of accurate responses

4.6.3. Visuo-spatial assessment

Visuo-spatial ability (i.e. the ability to identify the spatial relationship of objects) was assessed using a variety of standardised tests, including; Benton's Judgement of Line Orientation (JLO; Appendix 9.0), Royall's CLOX 2 and sub-sections of the visual object and space perception battery (VOSP).

The JLO was used as it has high test-retest reliability and has been shown to have good neuropsychological construct validity via neuroanatomical localization studies (Calamia *et al.*, 2011). The JLO assessment involves a participant viewing a set of numbered lines (placed in a semi-circle) and then simultaneously being shown two lines which have the same orientation as two of the numbered lines. They then have to name the numbers that the two lines correspond to.

Clock copying, specifically Royall's CLOX 2 (Appendix 8.0) (Royall *et al.*, 1998) was used as it is a visuo-spatial task linked with right parietal pathology (Matsuoka *et al.*, 2011). To complete the CLOX 2 assessment the researcher draws a clock and the participant must then copy the drawn clock, similar to the cube copying task in the MoCA and ACE-R.
Sub-sections of the visual object and space perception battery (VOSP) were used for more specific visuo-spatial assessment (Rapport *et al.*, 1998), such as; incomplete letters (visual object perception), dot counting and position discrimination (both spatial perception). The VOSP has been shown to be a valid measure of visuo-spatial ability (Binetti *et al.*, 1998) and has been used in previous studies involving older adults and people with neurological disorders (Bonello *et al.*, 1997; Lawrence *et al.*, 2000; Herrera-Guzman *et al.*, 2004).

4.6.4. Working Memory

Working memory was assessed using the maximal Wechsler forward digit span (Wechsler, 1945), which was performed while seated. The forward digit span is reported as a simple span test, which measures storage and manipulation of information by working memory (Wilde *et al.*, 2004).

The forward digit span consists initially of two numbers being played over loud speaker for the participants to recall, and continues to a maximum of nine numbers (Wilde *et al.*, 2004). There were three trials per span length and the test continues until a participant fails two out of three trials. The maximal length of the digit span was determined, defined as the most numbers a participant could remember two out of three times without error.

4.7. Visual function assessment

Binocular basic visual functions of visual acuity (VA) and contrast sensitivity (CS) were assessed using standardised charts which are commonly used in clinical practice. Participants wore any visual correction (e.g. contact lenses or glasses) that they usually wore during walking when performing these assessments of visual functions.

A high contrast LogMAR chart (Figure 4-2, chart on left) was used to measure VA in both PD and control groups. Participants were seated at a distance of 4m from

the chart and instructed to read aloud each line of letters on the chart starting from the top left. All correct answers were recorded on a pre-set score sheet and the test was terminated when a participant either made 2 consecutive errors or reached the last letter of the chart.

A mars letter CS chart (Mars Percetrix™, New York, USA; Figure 4-2, chart on right) was placed on an adjustable holder 50cm in front of the participants and used to measure CS. The CS chart consisted of 48 Latin letters of uniform height which are read aloud line by line from the top left and reduced in contrast with letter progression. Room illumination was adjusted so that the average CS chart luminance was between 80 and 120cd/m², which was measured via a luminance meter. Errors were recorded on a pre-set score sheet and testing was terminated if participants either made 2 consecutive errors or read the final letter. The final scores for both LogMar VA (1) and LogCS (2) were calculated via specific formulas, representing the number of letters read correctly during the tests.

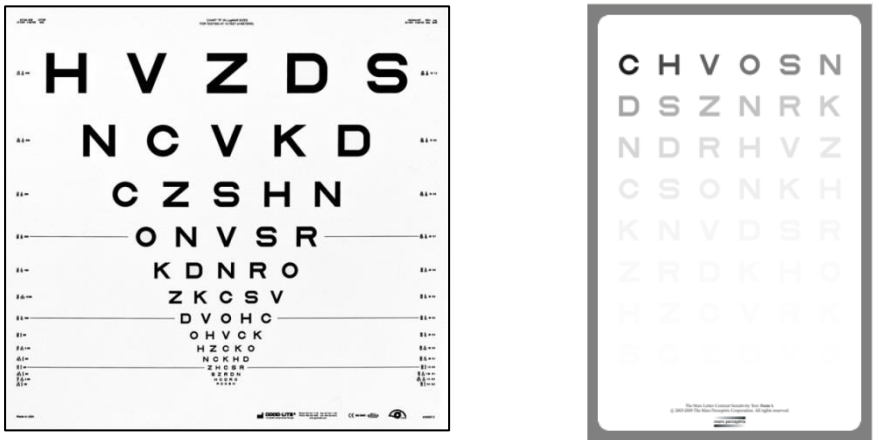


Figure 4-2 – Visual function charts; LogMar visual acuity (Left), LogCS contrast sensitivity (right)

$$(1) \quad \text{LogMar VA} = \left(score\ of\ the\ line\ before\ termination\right) - \left(0.02\ x\ number\ of\ errors\right) + \left(0.02\ x\ correct\ answers\ in\ the\ terminal\ line\right)$$

$$(2) \quad \text{LogCS} = \left(score\ of\ final\ correct\ letter\ before\ termination\right) - \left(0.04\ x\ number\ of\ errors\ prior\ to\ stopping\right)$$

4.8. Parkinson's disease specific assessment

4.8.1. The Unified Parkinson's Disease Rating Scale UPDRS (Appendix 10.0)

The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was used to assess motor (MDS-UPDRS part III) and non-motor features of PD and overall disease severity. The MDS-UPDRS is scored from a total of 195 points; higher scores reflect worsening disability.

4.8.2. Hoehn & Yahr (H & Y) (Appendix 11.0)

The Hoehn and Yahr rating scale is a widely used clinical rating scale, which defines broad categories of motor function in Parkinson's disease (PD). All participants were included provided they had a mild-moderate H &Y score (stages I-III).

The PD cohort were restricted to mild to moderate (H&Y I-III) disease severity because the focus of this thesis involved gait which required individuals to still be able to safely walk, who were potentially at less risk of trips and falls during the testing procedures than those in later stages of the disease.

4.8.3. The FOG questionnaire (FOGQ) (Appendix 12.0)

Freezing of gait (FOG) was evaluated using the new FOG questionnaire. This is a 10 item questionnaire intended to classify gait disturbance. The questionnaire has 3 parts; distinction of freezers from non-freezers, freezing severity, frequency and duration and impact of freezing on daily life.

4.9. Older adult and Parkinson's disease specific assessment

4.9.1. Falls efficacy scale – International (FES-I) (Appendix 13.0)

Fear of falling was measured using the falls efficacy scale – international (FES-I) version. This is a short and valid measure of fear of falling in older adults, which assesses basic and demanding activities (both physical and social) (Yardley *et al.*, 2005). It consists of 16 scenarios (e.g. cleaning the house) and subjects must rate their fear of falling on a scale from 1 (Not at all concerned) to 4 (Very concerned).

4.10. Equipment

The equipment used within the following chapters remained consistent. The following devices were all synchronised so that simultaneous eye and body movement recording could be performed.

4.10.1. Mobile eye-tracker

A Dikablis mobile eye-tracker (Ergoneers, Germany) with a sampling rate of 50Hz was used to track participant visual sampling, definitions for visual sampling outcome measures are shown in Table 4-2. Details regarding data processing, as well as accuracy and reliability of this device are contained within Chapters 5 and 6. The Dikablis was head-mounted on each participant along with a wireless electro-oculography (EOG) device (Zerowire, Aurion, Italy) (Figure 4-3), which monitored horizontal eye movement. The Dikablis and EOG were synchronized using a 3D motion capture system (Vicon, Oxford, UK). The Dikablis consisted of a light-weight head-unit and backpack containing the transmitter (weight: 69g) (Figure 4-3). The head-unit was taped to the participants' forehead to prevent error due to slippage using double-sided tape.

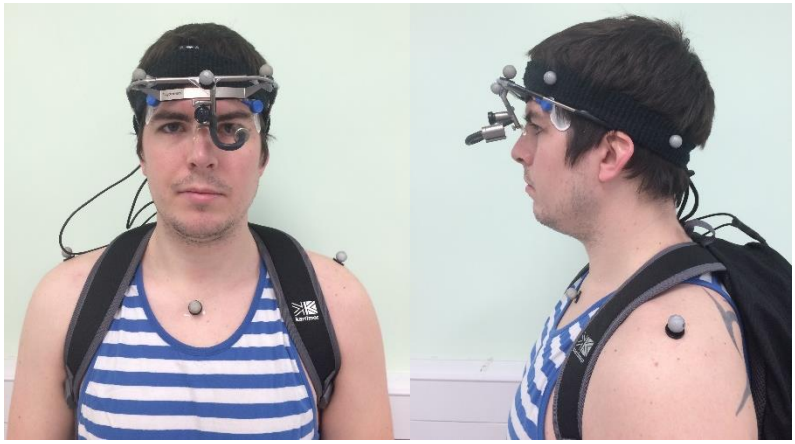


Figure 4-3- Mobile eye-tracker and EOG placement

Participants wore any visual correction (e.g. contact lenses or glasses) that they usually wore during walking throughout use of the eye-tracking devices. Calibration was performed with individual participants at the start of each session, which was kept as consistent as possible with a standardised procedure (Figure 4-4). Manufacturer four-point calibration procedure was performed. However, in

order to calibrate the eye-tracker to the environment and minimise parallax error, targets were replaced with four orange cones with illuminous markers which were placed on the floor within the four-point locations (Figure 4-4; two ~2.5m from the participant and 2 at the end of the gait laboratory; ~5m from the participant).

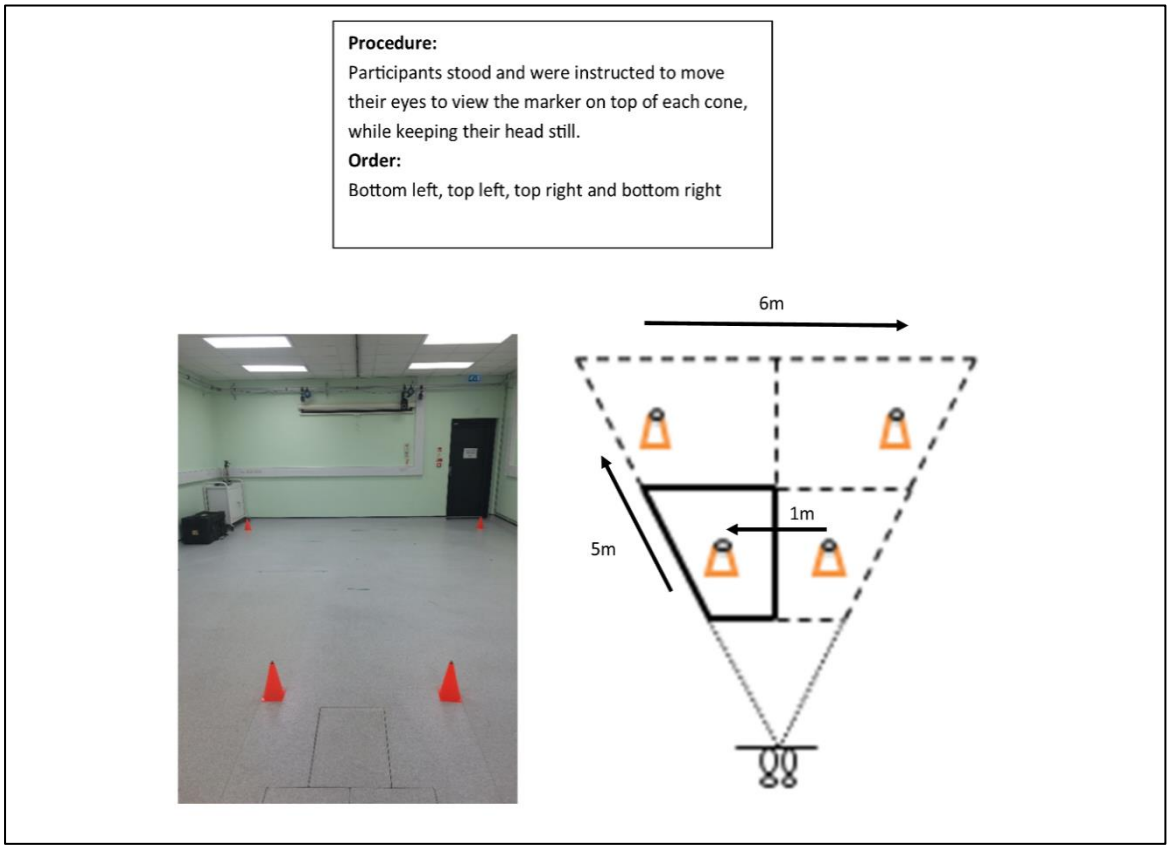


Figure 4-4- Mobile eye-tracker calibration procedure

4.10.2. Electro-oculography (EOG)

Wireless EOG was also used to record visual sampling, specifically horizontal saccades at a sampling rate of 1000Hz. The visual sampling outcome measures obtained via EOG are defined in Table 4-2. Electrodes (~4mm) were placed bi-temporally as close to the (left and right) lateral canthus as possible without blocking participant vision. EOG has been shown to be a valid and reliable method for assessing visual sampling in younger adults (Duchowski, 2007), and has previously been used during gait with older adults and in people with PD (Galna *et al.*, 2012).

The EOG system was calibrated for each participant while seated 6m from a wall. Initially a target was placed on the wall straight in front of the participants and they were asked to blink for a period of 20 seconds in time with a 60bpm metronome. The rest of the calibration procedure required participants to move their eyes between two targets placed at set distances (5°, 10° and 15°; Figure 4-5) relative to participant field of view, again in time with the metronome for 30 seconds. A maximum distance of 15° was used as most naturally occurring saccades occur within this threshold (Bahill *et al.*, 1975). Horizontal eye movements (5°, 10° and 15°) for were recorded via EOG (1000Hz) and Dikablis mobile eye tracker (50Hz) simultaneously.

The specific commands for the calibration were as follows: *"Looking straight ahead, blink every time you hear the metronome beat."* Then for eye-movements: *"Move your eyes between each marker to fixate the other marker every time you hear the metronome beat."*

The average (mean) for each visual sampling variable (Table 4-2) was calculated over three trails.

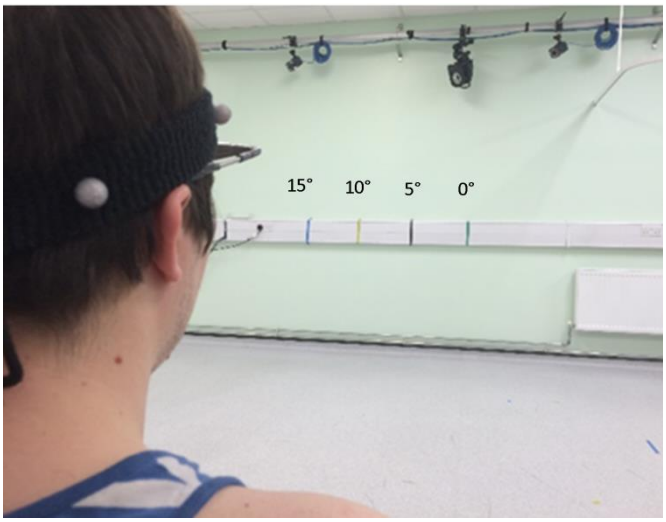


Figure 4-5 – Photograph of electro-oculography (EOG) calibration procedure; lines on the wall represent the targets set at 5^0, 10^0 and 15^0

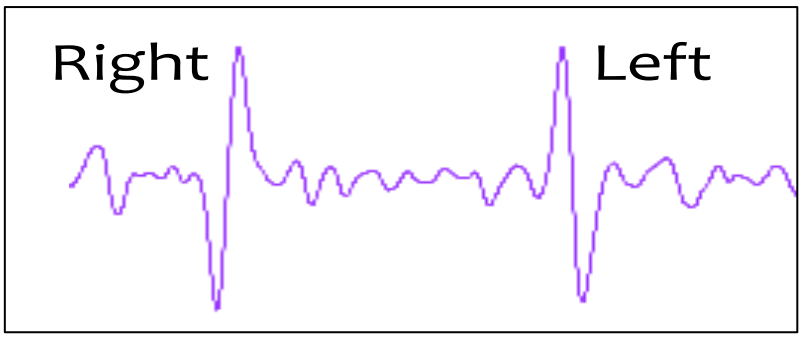


Figure 4-6 - A standard electro-oculography (EOG) trace during one of the calibration tasks; horizontal saccadic eye movements to right and left

[Left: the cornea approaches the electrode near the outer canthus of the left eye, resulting in a positive to negative change in the recorded potential. Right: the cornea approaches the electrode near the inner canthus of the left eye, resulting in a negative to positive change in the recorded potential]

Table 4-2 – Visual sampling outcome measures

Device	Variable	Unit	Definition
Dikablis	Saccade frequency*	Saccades/second	Number of fast eye movements made each second of a trial
	Saccade number	Number	Total number of fast eye movements made during a trial
	Fixation number	Number	Total number of fixations made in a trial
	Blink number	Number	Total number of blinks made during a trial
EOG	Saccade duration	Milli-seconds (ms)	Time taken to move between fixations
	Saccade amplitude	Degrees (^{0})	Distance of fast eye movement between two fixations
	Saccade peak velocity	Degrees/second	The highest velocity reached during a saccade
	Saccade peak acceleration	Degrees/second^2	The highest acceleration reached during a saccade
	Fixation duration	Seconds	Length of time the eye is paused on an area of interest between saccades

*Primary outcome for main experimental studies

4.10.3. 3D motion capture system

Kinematic data were recorded using a 3D motion capture system (VICON, Oxford, UK), which recorded each participant whilst walking through the gait lab. There were 12 cameras in the system, each with a resolution of 1266 x 1024 and a temporal resolution of 100Hz. 3D motion analysis is a valid and reliable method of assessing the spatiotemporal parameters of gait in people with PD and controls (Huang *et al.*, 2008), and is considered the 'gold-standard' for gait analysis.

A total of 20 reflective spherical markers were placed on participants at various body locations (Figure 4-7; 2x shoulders, 1x sternum, 2x anterior superior iliac spine, 2x posterior superior iliac spine, 2x big toe, 2x instep, 2x heel, 4x head and 3x Dikablis). Each marker position was labelled and a full body model was created for each participant. This simple body mark-up was created to allow quick participant set-up, with an adequate number of markers to create segments for major body locations (i.e. head, shoulders, pelvis and feet). The feet markers (big toe and heel) were the only markers used to derive gait characteristics. Calibration was performed before any data collection occurred using a static frame capture (in order to set the capture volume origin), which was then followed by the dynamic capture trials.

Participant gait and head movement data was derived from the Vicon Nexus software, which involved manual processing of all 3600 trials collected within the Nexus software. Manual processing involved the creation of a participant model and filling any capture gaps that may have occurred. Capture gaps were only occasional and occurred as a result of cameras being unable to record marker placement, which occurred when the participant was at the start or the end of the capture volume or when occluded by a body segment (e.g. arm). Gaps (no more than 5 frames) were filled frame-by-frame using an interpolation (gap-filling) algorithm within the Vicon Nexus software. Once manual processing of the raw 3D motion capture data had been completed, gait data (Table 4-3) and head movement data could be processed and exported via Nexus to a .CSV file to be read into MATLAB® 2012a (Mathworks, Natick, MA, USA) for amalgamation, and further analysis. The mean for each variable (Table 4-3) was calculated over

three trials and data for each limb was calculated separately before calculating the overall mean.

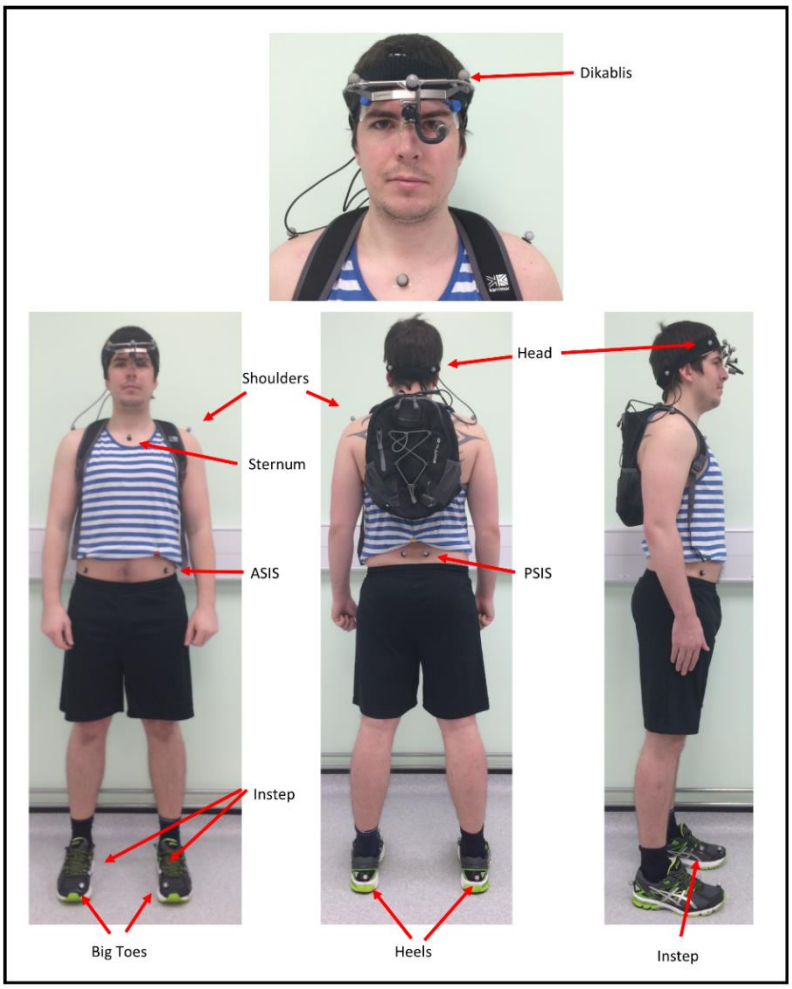


Figure 4-7 – Reflective marker placement on body segment

Table 4-3 – Gait Characteristics

Variable	Units	Definition
Time to Door	Seconds	Time for each participant to walk from the start point to the door position
Step Length	Metres	Distance between the point of initial heel contact with the floor on one foot to the point of initial heel contact with the floor on the other foot
Gait Velocity	Metres/second	The distance covered by the individual in unit time
Step Time	Seconds	Time taken for each step
Single Support Time	Seconds	Time where only one limb is supporting the body
Double Support Time	Seconds	Time where both limbs are supporting the body

4.11. Dual Task

In order to manipulate cognitive (primarily attentional) load during gait within the main experimental studies presented within this thesis (Chapters 7 and 8), participants completed walks under single and dual task. The dual task involved maximal Wechsler digit span (Wechsler, 1945). As mentioned in section 4.6.4, the maximal length of forward digit span was determined in sitting. The participants were played a string of digits (set to their individual maximal string) over loud speaker during the walking tasks and participants repeated the strings back to the researcher, the number of errors were recorded during each dual task walk.

The command prior to dual task walking were as follows; *"A string of numbers will be played as you begin your walk, when you have completed the walk repeat the numbers back in the order you heard them".*

4.12. Statistical procedures

Statistical techniques specific to individual chapters are included in relevant specific methods sections, but this section contains procedures common to all analyses. Data were analysed using the SPSS version 21 statistical package (SPPS, Inc. an IBM company). Data were assessed for normality with visual histograms and Kolmogorov-Smirnov tests, meeting criteria for parametric analysis (Expósito-Ruiz *et al.*, 2010; Ghasemi and Zahediasl, 2012; Field, 2013).

Descriptive statistics such as means and standard deviations (SD) were calculated for continuous dependent and independent variables. Descriptive statistics were tabulated and presented graphically for clarity. Independent t-tests were used to compare descriptive data between groups. Pearson chi-square (X^2) test was used for comparison of frequency data between groups.

This thesis contains the first exploration of cognition, vision, visual sampling and gait in PD and older adults. Due to the exploratory nature of the studies contained in this thesis control for multiple comparisons and for various independent variables was not performed for much of the analysis, in order to avoid Type II error (i.e. failing to observe a difference between PD and controls when there is a difference). To this end, all statistical tests were carried out with a significance

level $p < .05$, and all reported p-values are two-tailed. Significant values less than $p = .001$ were abbreviated to $p < .001$ in text.

4.12.1. Sample size justification

The studies contained within this thesis were exploratory and therefore few specific previous examples were available to guide the sample size required. The sample size estimate was based on results from previous work in this research area (PD; n=21) (Galna *et al.*, 2012) and preliminary pilot work with the Dikabilis mobile eye-tracker, which is a new tool for this type of research. Similar studies in this research area (Anastasopoulos *et al.*, 2011; Lee *et al.*, 2012b; Lohnes and Earhart, 2012b; Lohnes and Earhart, 2012a; Vitorio *et al.*, 2012; Vitorio *et al.*, 2013) have used smaller sample sizes (n=2-26), demonstrating both significant and non-significant differences between PD and control groups. A larger sample size than previous research was chosen to ensure differences between groups would be evident (≥40 participants in each group). It is a general recommendation to have around 30 cases per group to be able to carry out basic statistical tests (Expósito-Ruiz *et al.*, 2010). However this is a guideline and many analyses can be carried out with fewer cases, depending upon the nature of the variability shown in the participants and the type of statistical tests applied. An interim analysis was undertaken after testing half of the full cohort (20 PD and 20 controls) to ensure that adequate precision of key visual sampling outcomes (i.e. saccade frequency) would be achieved within the full cohort.

5. Quantification of saccades during gait in mobile eye-tracking data

5.1. Summary[5]

There is currently no 'gold standard' algorithm with which to measure visual sampling outcomes (saccades and fixations), as highlighted in chapter 3. This chapter details a preliminary study that was carried out in order to establish robust measurement of saccadic activity within mobile eye-tracker data. A novel custom made MATLAB® 2012a (Mathworks, Natick, MA, USA) computer programme (algorithm) was developed and evaluated in order to provide saccadic measurement from mobile eye-tracking data used for this thesis.

5.2. Introduction

Eye-tracking has been used since the 1700's, with early static investigations during reading (Porterfield, 1752). Since then progression has been made to mobile eye-tracking investigation, which is becoming a very useful tool in the development of protocols that investigate cognitive and visual processes during real-world tasks (Salvucci and Anderson, 2001). The eye has a distinct black circle in its centre called the pupil, which is used as a frame of reference by infra-red and video-based eye-tracking technology to denote movement of the eye (Duchowski, 2007; Holmqvist and Nystrom, 2011). Some but not all eye-trackers also track the reflection of the cornea (Duchowski, 2007), which can be used to monitor camera position in relation to head movement. Eye-tracking devices generally track these features using a camera and provide co-ordinates.

In order to provide saccade and fixation data from raw co-ordinate data acquired by mobile eye-tracking devices an algorithm is required. There are several different methods to extract this data (for an overview see; Salvucci and Goldberg (2000)). Velocity based saccade and fixation identification is the simplest method to understand and implement in eye-tracking data analysis. This method consists of separating fixations and saccades based on their point to point (co-ordinate)

[5] This study has been published in IEEE EMBC (available on IEEE Xplore); Stuart et al (2014b)

velocities. Typically, fixations are classified as low velocities (i.e. <100°/sec) and saccades as high velocities (i.e. >300°/sec) (Salvucci and Goldberg, 2000). Due to the velocity differences the discrimination of saccadic eye-movements and fixations is relatively simple and robust. In view of this researchers have called for a readily adaptable algorithm for velocity based eye-movement detection (Nystrom and Holmqvist, 2010), which is particularly relevant when eye-tracking in mobile environments where other eye-movements (i.e. vestibular-ocular reflex (VOR)), could infiltrate the thresholds (Holmqvist and Nystrom, 2011).

Most medically orientated studies involving the analysis of visual sampling characteristics/outcomes aim to uncover the impairments of certain disease groups, such as people with PD during certain tasks. However, until recently almost all previous research was conducted in restricted static conditions and involved simple tasks such as button pressing (Stuart *et al.*, 2014a), as mentioned in chapter 3. These studies provide information about the mechanisms behind visual sampling characteristics and allow for experimental manipulation, but results may not be relevant to real-world activities that involve multiple motor, cognitive and visual processes (Pelz and Canosa, 2001). Static conditions also limit the amount of error seen within eye-tracking data, as other artefacts associated with movement are not present (i.e. VOR). These artefacts must either be ruled out or controlled for when analysing for specific visual sampling characteristics during real-world (highly mobile) activities, such as gait.

The aim of this preliminary study was to provide a simple, yet robust algorithm for the detection of saccades from mobile eye-tracker data. The work involved the development and validation of an algorithm to detect visual sampling outcomes (saccades and fixations) from mobile eye-tracker co-ordinate data.

5.3. Specific Methods

5.3.1. Participants

This study involved the recording of eye-movements made while walking under different conditions (such as walking in a straight line, through a door frame, while turning, and under single and dual task) in people with PD and older adult controls. In total, data from ten participants were used to evaluate the algorithm.

Five people with PD and five older adults (controls) (≥50 years old) were chosen at random from the larger 'Vision and Gait in PD' study cohort.

5.3.2. Equipment

A Dikablis mobile eye-tracker was used to track gaze co-ordinates (*x*, *y*) by means of infra-red illumination, which allows for detection of the blackness of the pupil. Importantly for this thesis the 50Hz sampling rate of the Dikablis is adequate for the detection of saccades, although it may not be able to provide precise information on saccade durations or peak velocity as these features require higher sampling frequencies (>200Hz) (Duchowski, 2007; Holmqvist and Nystrom, 2011; Stuart *et al.*, 2014a).

The Dikablis uses a dual-camera system, with one monocular infra-red eye camera and one fish-eye field camera. With the use of a four point calibration, the video output from these cameras are overlaid with a cross-hair provided on the video as a spatial view of pupil location. The raw co-ordinate data is derived from this cross-hair (Figure 5-1). Overall the Dikablis provided videos of the eye itself, the scene and a combination of the two with a cross-hair of pupil location. This enabled analysis of the video data using the accompanying D-Lab software, which allowed selection of individual frames of the video (gold standard reference), so frame by frame analysis was possible.

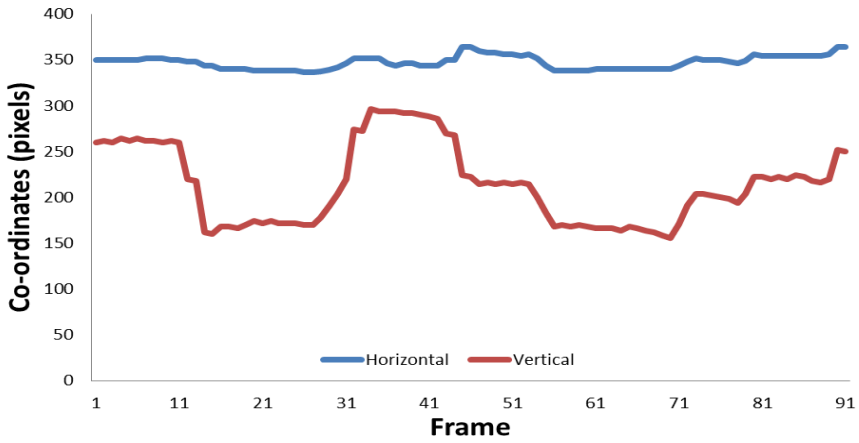


Figure 5-1 - Example raw data from Dikablis mobile eye-tracker during walking

5.3.3. Procedure

Participants walked 5m in a straight line in the gait laboratory. They did this with and without a doorframe to walk through and repeated the same task several

times for each condition. Eye-movements were tracked during these walks in order to provide data on the visual sampling strategies employed by older adults and people with PD during a natural everyday task.

5.3.4. Feature Selection and Evaluation

Ten videos from each of the subjects (*n*=10) were visually inspected by a single examiner (SS) frame by frame, in order to compare to the algorithm results (100 videos in total). The number of visually detected saccades during the walking trials was recorded and then compared to the number measured by the algorithm. To calibrate visual inspection the participants began by making saccades between two markers set at 5° distance while sitting static. This was viewed and measured by the examiner prior to viewing the walking videos in order to provide a reference for the eye-movement distance.

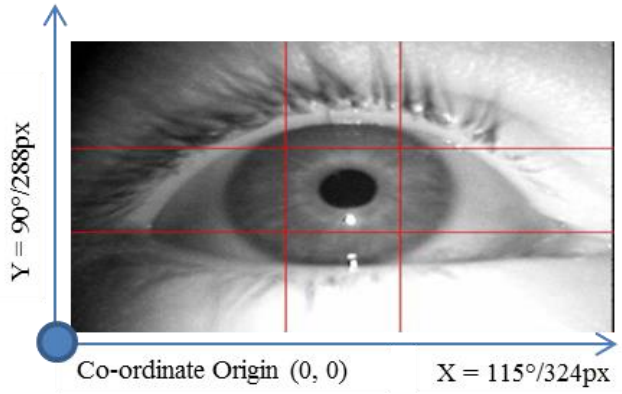


Figure 5-2 – Eye-view camera alignment and co-ordinates (px = pixels)

5.3.5. Detection of visual sampling characteristics via algorithm

While a full representation the algorithm is presented in Figure 5-3, the following details the algorithm used for the mobile eye-tracking data:

Stage 1*: Distance, velocity and acceleration*

Each parameter of interest was calculated for saccades and fixations, via a velocity based algorithm developed using MATLAB® 2012a (Mathworks, Natick, MA, USA) software. Firstly the algorithm begins by calculating the point to point position change of the *x* and *y* co-ordinates for each frame in the raw data (Figure

5-2), which provides a distance in pixels (1; where t1 and t2 refer to time point 1 and 2 respectively).

(1) $$\text{Distance} = \sqrt{(x_{t1} - x_{t2})^2 + (y_{t1} - y_{t2})^2}$$

The velocities (2) and accelerations (3) are then calculated as the change in distance and change in velocity from one frame to the next (or previous) (Time was measured in milliseconds).

(2) $$\text{Velocity} = \left(\frac{\text{Distance}}{\text{Time}}\right)$$

(3) $$\text{Acceleration} = \left(\frac{\text{Velocity}_{t1} - \text{Velocity}_{t2}}{\text{Time}}\right)$$

Stage 2(a): *Conversion of pixels to degrees*

The raw eye camera *x* and *y* co-ordinate data in pixels (Figure 5-2 and 5-3) was then converted to degrees, calculated using the pixel to degree conversion ratio of 1:0.31 (Table 5-1).

Table 5-1 Eye-View Camera Co-ordinate Conversion

	Eye view max pixels (px)	Eye view max degrees (°)	Eye view conversion (°/px)
X (horizontal)	384	115	0.30
Y (vertical)	288	90	0.31
X + Y	672	205	0.31

Stage 2(b): *Removal of data caused by blinking and flicker*

The raw data was filtered using set criteria for blinks and flickers, which were based upon the raw co-ordinate data and the velocities of the individual points. Blinks (closing of the eye) were classified as any frames that had co-ordinates equal to that of the origin (0, 0; Figure 5-2) and flickers (i.e. eye-tracker confusing eye-lashes or other black areas for the pupil) were classified as any point to point movement with a velocity of over 1000°/sec or acceleration of over 100,000°/sec². These artefacts were removed from the data before any further analysis was performed and linear interpolation was used to fill in gaps after the removal of missing data.

***Stage 3**: Saccade and fixation detection*

Following calculation of velocities and accelerations for each frame in the raw data the algorithm then classified each point above a certain velocity threshold (i.e. >240°/sec (5°)) as a saccade. A threshold of above 5° distance was chosen due to previous work using the same threshold for eye-tracking with EOG during walking (Galna *et al.*, 2012). This threshold was used to rule out most of the intrusions from other eye-movements (e.g. VOR) and provide purposeful eye-movement data which was adaptable depending upon the task (i.e. lower threshold for static tasks). If the frame velocity did not reach the velocity threshold it was classified as a fixation. An acceleration threshold (i.e. >3,000°/sec^2) was then employed within the algorithm above which data was classified as a *saccade* and below a *fixation*. Any saccadic durations longer than 5 frames (100ms) were discarded as saccades are not known to occur over this time threshold (Holmqvist and Nystrom, 2011), and for similar reasons fixations less than 100ms were also discarded. Once the saccade and fixation frames were located, the algorithm grouped together fixation and saccade points that were next to one another. Saccade distances were then calculated by summing the angular displacements of adjacent frames classified as saccades.

***Stage 4**: Quantifying saccades and fixations*

Once the visual sampling characteristics had been detected the following features were extracted: Saccade number, frequency, velocity, amplitude, direction, duration and fixation number, duration and timing (Figure 5-3). Then the level of agreement for saccade number between visual inspection and the algorithm output was examined.

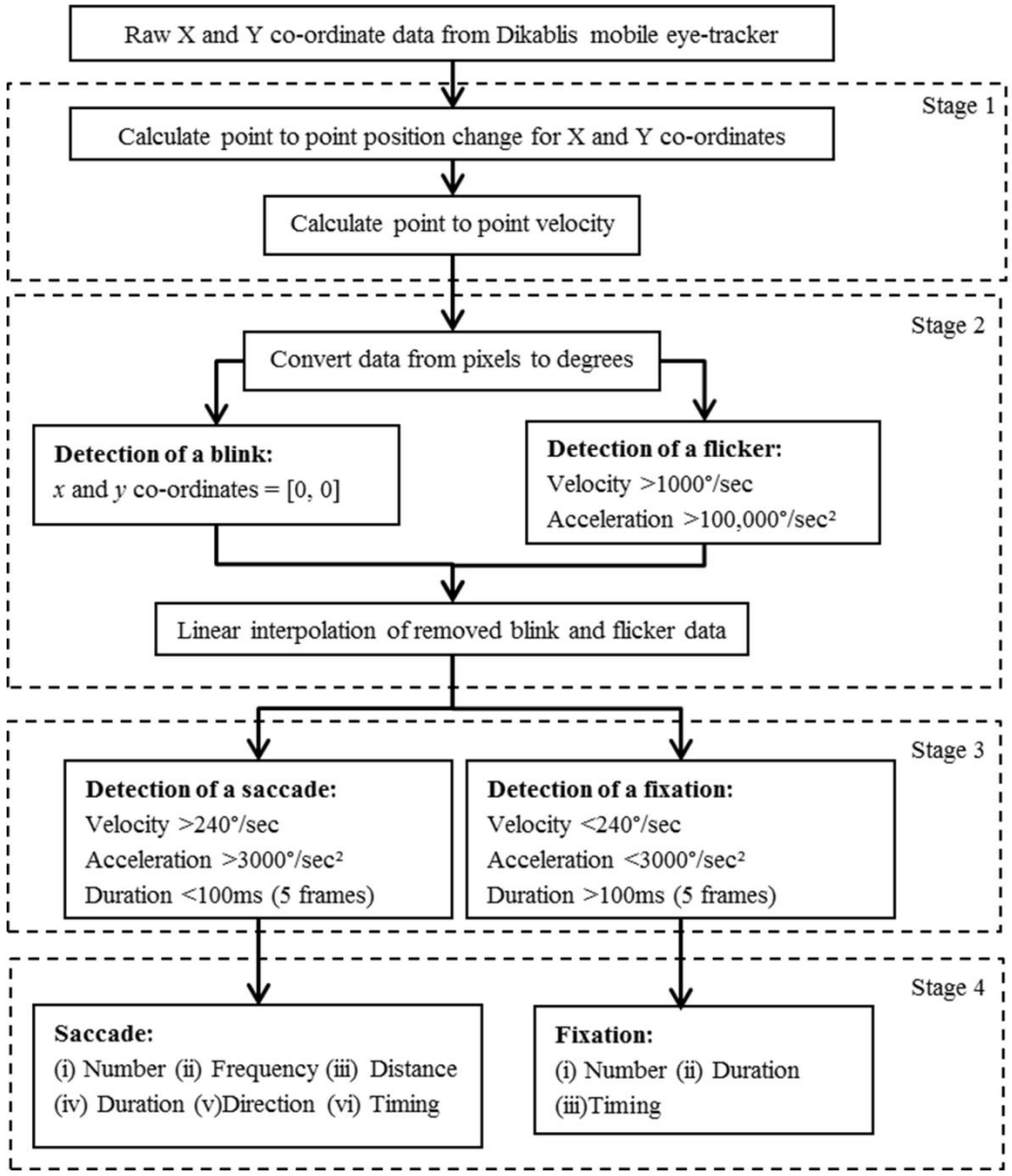


Figure 5-3 - Algorithm Flow Chart

5.3.6. Data Analysis

Detection of a saccade via frame by frame video analysis was compared to output from the MATLAB® algorithm, with respect to the following criteria:

- Correct detection: Algorithm saccade detection was marked as correct if it was found in the corresponding video (measured via sum of saccades).
- Undetected: Algorithm saccade detection was marked as undetected if the saccade was found in the corresponding video, but not in the algorithm output.

- Spurious: Algorithm saccade detection was marked as spurious if it was in the algorithm output but not in the corresponding video.

Intra-class Correlations ($ICC_{2,1}$) were quantified using SPSS (v21) to assess the absolute agreement of overall number of saccades detected by visual inspection and the algorithm. $ICC_{2,1}$ were interpreted as follows: excellent >0.90, good ≥0.75-0.89, fair ≥0.50-0.74, and poor <0.49 (Rosner, 2006).

5.4. Results

The results demonstrate that agreement between the algorithm and visual inspection was similar in PD subjects (*n*=5) ($ICC_{2,1}$; .940) compared to controls (*n*=5) ($ICC_{2,1}$; .941). The algorithm correctly detected an average of 81% of the saccades made while walking for controls and 85% for PD. Higher average undetected saccades were found for controls (17%) compared to PD (11%), but lower average spurious saccades were found for controls (2%) compared to PD (4%).

Table 5-2 - Algorithm Performance: Controls

Participant	Control1	Control2	Control3	Control4	Control5
Saccades – visual inspection*	34	35	23	5	29
Saccades – algorithm*	31	27	24	3	27
Correct detections: n (%)	31 (91)	26 (72)	22 (88)	3 (60)	27 (93)
Undetected: n (%)	3 (9)	9 (25)	1 (4)	2 (40)	2 (7)
Spurious: n (%)	0 (0)	1 (3)	2 (8)	0 (0)	0(0)

* Sum of saccades made over 10 trials.

Table 5-3 - Algorithm Performance: PD

Participant	PD1	PD2	PD3	PD4	PD5
Saccades – visual inspection*	23	2	15	36	25
Saccades – algorithm*	21	2	16	28	22
Correct detections: n (%)	20 (83)	2 (100)	14 (82)	28 (78)	21 (81)
Undetected: n (%)	3 (13)	0 (0)	1 (6)	8 (22)	4 (15)
Spurious: n (%)	1 (4)	0 (0)	2 (12)	0 (0)	1 (4)

* Sum of saccades made over 10 trials.

5.5. Discussion

The present study was developed with the aim of providing and validating a simple algorithm for the detection of visual sampling characteristics such as saccades within mobile eye-tracking raw data (Figure 5-3). This is fundamental for accurate automated evaluation of eye-tracking data obtained within this thesis. The major advantage of the mobile eye-tracking data analysis performed with the developed algorithm over other algorithms is that it is simple and easily implemented (Salvucci and Goldberg, 2000; Salvucci and Anderson, 2001). The accuracy of velocity based algorithms has been shown to be lower than other algorithms such as dispersion thresholds (Salvucci and Goldberg, 2000; Nystrom and Holmqvist, 2010). However, the balance of speed and precision with a velocity based algorithm makes it ideal for many applications such as eye-tracking during dynamic tasks (i.e. analysing eye-tracking data during gait). For this study frame by frame visual inspection of the eye movement videos from the experimental trials with ten different individuals served as the ground truth for evaluating the detection performance of the algorithm (Table 5-2 and 5-3). This was similar to previous work which assessed blink number during eye-tracking (Pedrotti *et al.*, 2011).

5.5.1. Robustness across participants

For the experimental evaluation, participants performed the same walking tasks and data were analysed using the same fixed algorithm settings, and compared to visual inspection. Under these conditions, the algorithm developed for detecting visual sampling characteristics (i.e. saccades) in mobile eye-tracking data proved relatively robust, overall correctly detecting 194 out of 227 (85%) saccades made by the participants (n=10) during the walks (100 in total), with 33 undetected and 7 spurious detections (Tables 5-2 and 5-3). The intra-class correlation coefficients ($ICC_{2,1}$) also demonstrated that the algorithm had excellent agreement (overall $ICC_{2,1}$; .937) when compared to the ground truth used in this study (visual inspection). For several participants, however lower correct detection scores (72-80%) were seen because of more undetected and spurious detection in their trials (Tables 5-2 and 5-3). Upon further inspection of the raw frame by frame eye movement video data from these participants, it was

clear that saccades were undetected due to several issues. One issue is flickering of the fixation cross-hair with particular eye-movements (i.e. vertical – looking down) and during blinks, a limitation of all infra-red eye-tracking devices (Kevin O'Regan *et al.*, 2000; Duchowski, 2007; Holmqvist and Nystrom, 2011). These flickers and other data infiltrations would have been picked up in the visual inspection but would have been discounted in the algorithm. Another possible issue is that Control2, Control4, and PD4 had corrected vision via glasses or contact lenses, which are known to impact eye-tracking data quality as they cause infra-red light refraction making pupil detection difficult (Holmqvist and Nystrom, 2011). The few spurious saccade detections likely occurred due to other eye-movements such as VOR infiltrating the data, a problem not encountered while recording static eye-tracking. These could further be controlled for by recording head movement during walking (Shaikh *et al.*, 2013). However, the achieved detection performance seen in this study demonstrates that the algorithm is adequate for saccadic eye-movement analysis carried out during the walking protocols performed by older adults and people with PD.

5.5.2. Study Limitations

One limitation of the current work is that during visual inspection it was difficult to accurately measure saccade amplitude. The algorithm detects movement of the pupil cross-hair over 5° amplitude (i.e. >240°/sec velocity threshold) and is capable of ruling out other movement of the cross-hair via set criteria. During calibration the examiner was able to view and measure 5° movement of the cross hair made by each participant prior to analysing the walks. However, it remained difficult for the examiner to differentiate between movements of slightly lower distance using the video/still images alone. This may be why many of the visual inspection saccade numbers are higher (Table 5-2). Future work could improve this by using a lower velocity threshold (i.e. 2-3° amplitude) (Wass *et al.*, 2013), although this may allow further data intrusions from other eye-movements (i.e. VOR) in the algorithm output.

Few studies are available that provide and validate mobile eye-tracker algorithms, as testing algorithms against a ground truth (such as visual inspection) is time consuming. As a result we had little basis to develop a

methodology to evaluate the algorithm within this study. Although visual inspection has been used in this study other possibly more appropriate ground truth comparisons are possible. For example; comparison to simultaneously recorded EOG or recording of eye-movements between targets at set distances while walking, which have been carried out in previous static studies (Salvucci and Anderson, 2001; Hess *et al.*, 2009). This will build on this initial work allowing further validation of visual sampling characteristic detection algorithms in mobile eye-tracking data, which is necessary due to the impact algorithms have on further analysis (Salvucci and Goldberg, 2000).

5.6. Conclusion

This study successfully developed a simple and robust algorithm for detecting visual sampling characteristics. This algorithm can detect saccadic eye-movements from raw mobile eye-tracker data obtained during gait in people with PD and older adults.

6. Accuracy and re-test reliability of mobile eye-tracking in Parkinson's disease and older adults

6.1. Summary[6]

There is currently no 'gold standard' visual sampling measurement instrument, which is accompanied by a general lack visual sampling device validity or reliability reporting, as highlighted in chapter 3. This chapter details a preliminary study that was carried out to establish the psychometric properties of the mobile eye-tracking protocols used for this thesis. Mobile eye-tracker accuracy and reliability was assessed during static (sitting, standing) and gait (on a treadmill) protocols in PD and older adults.

6.2. Introduction

Eye-tracking provides data regarding the acquisition of visual information through visual sampling, which is crucial for the safe and effective performance of many real-world activities, such as gait. Both mechanistic and clinical research requires accurate and reliable devices. However, the review in chapter 3 highlighted that previous studies do not report the accuracy or reliability of their eye-tracking devices (Stuart *et al.*, 2014a). This is likely due to a lack of 'gold-standard' eye-tracking device or standardised protocol for comparison. As such, there is sparse information regarding the psychometric properties of mobile eye-tracking devices in people with PD and controls.

Previous studies have evaluated the reliability of static eye-tracking devices in various clinical populations, measuring saccades for specific phenomena using highly specialised study protocols (Klein and Fischer, 2005; Blekher *et al.*, 2009; Farzin *et al.*, 2011; Farris-Trimble and McMurray, 2013). For example, Farzin et al. (2011) reported that their static eye-tracker (Tobii, T120, 300Hz) was reliable in reporting the number and duration of fixations, and pupillary response during a seated picture-viewing protocol in Fragile X syndrome patients and controls. Similarly, other studies have assessed the reliability of eye-movement characteristics measured with static devices but focus on specific assessments

[6] This study has been published in the Journal of Medical Engineering and Physics

such as anti- or pro-saccade tests (Ettinger *et al.*, 2003; Klein and Fischer, 2005; Blekher *et al.*, 2009), and attribute reliability differences to disease-related influences rather than the device (Blekher *et al.*, 2009). The results of these highly specialised protocols are not easily generalised, highlighting the need for an easily implemented standardised protocol.

A previous study reported the accuracy of a desk-mounted Tobii eye-tracker (TX300, 300 Hz) was 0.5° when participants were required to walk on a treadmill and look at targets at various locations on a screen (Serchi *et al.*, 2014a). The static device accounted for head movement as long as participants stayed within 200cm of the screen and had a high sampling frequency (300Hz). As such, the results may not apply to head-mounted mobile eye-tracking devices which capture at lower frequencies (i.e. 50-60Hz) but do not require movement of the head or person to be restricted (Andersson *et al.*, 2010).

The previous algorithm study in chapter 5 has shown that by using a velocity-based algorithm mobile eye-trackers can accurately detect saccades during gait (Stuart *et al.*, 2014b), however little is known about the accuracy or reliability of specific saccade characteristics (e.g. amplitude) recorded via mobile eye-trackers during static or dynamic tasks (Stuart *et al.*, 2014a). This is important as such characteristics can inform disease-related impairment. This preliminary study aimed to evaluate the accuracy and re-test reliability of a Dikablis mobile eye-tracker in the measurement of saccade amplitude in people with PD and controls when sitting, standing and walking. There is a lack of information regarding the accuracy or reliability of mobile eye-tracking devices, therefore this study developed a simple protocol using visual targets placed at set distances which could be used to evaluate other devices and across different populations.

6.3. Specific Methods

6.3.1. Participants

Fourteen people with PD along with twenty age-matched controls from the primary study took part in this investigation. For inclusion and exclusion criteria see chapter 4. PD participants were tested on the peak dose of their anti-Parkinson’s medication.

6.3.2. Equipment

Dikablis Mobile Eye-tracker

A Dikablis mobile eye-tracker (50Hz) measured saccade amplitude (the distance between two fixations), which has an adequate sampling frequency to detect saccades (Holmqvist and Nystrom, 2011; Stuart *et al.*, 2014b). The system was used in the same manner within the previous sub-study and calibrated using the manufacturer's four-point procedure (Figure 6-1) for each participant before data acquisition (Stuart *et al.*, 2014b). Calibration was performed on the same testing board that the study protocol was to be conducted on in order to avoid parallax error.

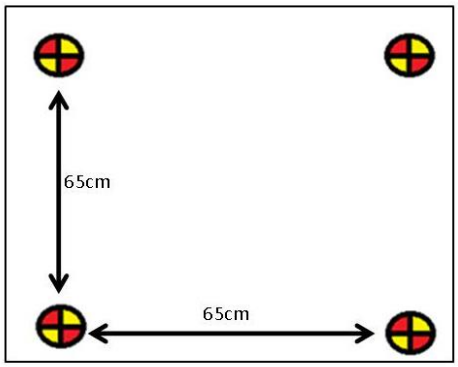


Figure 6-1 - Calibration board and procedure

[Participants were seated and had a chin rest in place, and were then asked to move only their eyes to look at the targets on the board (65cm square) starting at the bottom left target and continuing in a clockwise direction]

Monitoring Head Movement

Head and eye-movements are interdependent (Freedman, 2001), as such head movement can impact saccade amplitude measurement when the head is unconstrained (Proudlock *et al.*, 2004). Therefore, head movement was recorded using a tri-axial accelerometer (Axivity AX3, York, 100Hz) fixed to the Dikablis head-unit to examine whether head movement affected the findings.

6.3.3. Protocol

The study consisted of two sessions, carried out approximately one week apart. Accuracy was assessed using data from session 1 and re-test reliability was

assessed using data from both sessions. Prior to testing, participants underwent demographic, clinical and cognitive assessments (MoCA and MMSE).

6.3.4. Accuracy (session 1)

Accuracy of saccade amplitude was examined by tracking eye-movements as participants looked between two targets placed at set distances (5°, 10° and 15°, Figure 6-2) in time with a metronome (1 Hz) for 20 seconds.

Highly salient targets (coloured red and yellow to attract visual attention) were placed on a white board 200cm from the participant, with the fixed central target at eye-level (Figure 6-2). There were only two targets visible to the participants during each trial. A maximal target distance of 15° was chosen because most naturally occurring saccades occur within this range (Bahill *et al.*, 1975). Beyond 15°, co-ordinated eye-head movement is required (Maurer *et al.*, 2001). A brief (30 second) rest was permitted at the end of each trial to avoid the effect of fatigue, as previous studies have reported that fatigue occurs after a sequence of 36 seconds of eye-movements (Wilson *et al.*, 1992).

Eye-Movement Procedure:

A peripheral target was placed on the board and participants were instructed to move their fixation from the central target to the peripheral target (Figure 6-2). Order of conditions was as follows:

1) Horizontally: 5°, 10°, 15°
2) Vertically: 5°, 10°, 15°

Tasks:

The eye-movement procedure was repeated during:

1) Static sitting (with a chin rest; restricted head movement)
2) Static standing (asked to not move their head; self-restricted head movement)
3) Walking on a treadmill (Force Link, Netherlands) (head movement permitted). Treadmill speed was set to 80% of that achieved during a 10m walk test carried out at the start of the session. One of the assessors provided verbal feedback to ensure participants stayed 2m from the test board, this ensured that the angles of eye movements were not influenced.

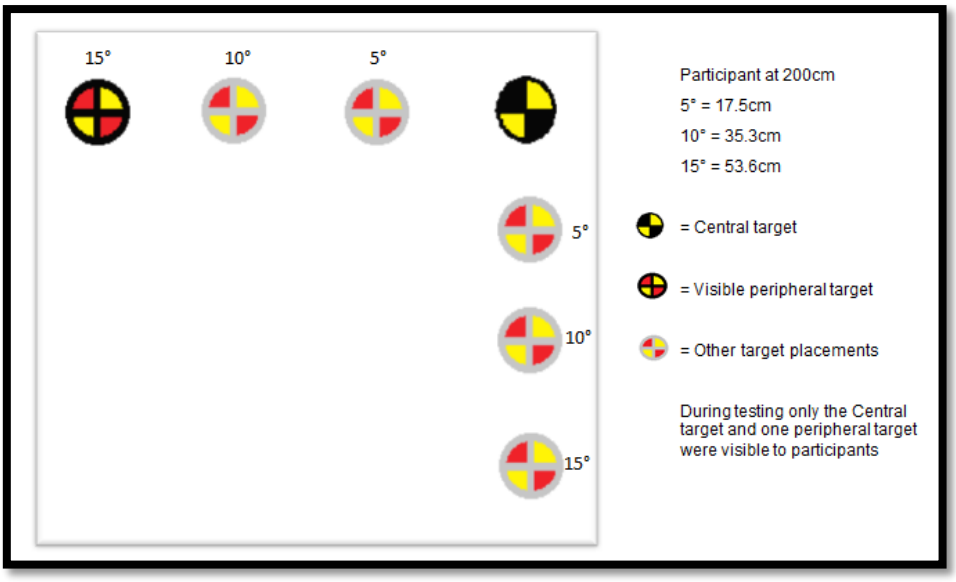


Figure 6-2 - Diagram illustrating the testing board used during sitting, standing and walking

6.3.5. Reliability

To assess re-test reliability, the same protocol described in section 6.3.4 was repeated approximately one week later (Mean: 7, SD: 2 days). All testing conditions were kept as consistent as possible, with trials conducted by the same researcher (SS) using the same procedure, instructions and testing sequences.

6.3.6. Older Adult without Visual Correction

To assess potential influence of visual correction (i.e. glasses or contact lenses) on accuracy and reliability, a subset of 10 control participants with no visual correction was re-analysed (Table 6-6).

6.4. Data Processing and Analysis

6.4.1. Eye and Head Movement

Saccade amplitude and head movement were derived using a validated velocity-based algorithm (MATLAB® 2012a, Mathworks, Natick, MA, USA) (Stuart *et al.*, 2014b). To quantify the effect of head movement on saccade amplitude, raw vertical and horizontal eye position data was compared to medio-lateral and superior-inferior head accelerations using cross-correlations (peak-correlation) as a measure of combined eye-head movement (Lee, 1999; Pelz *et al.*, 2001;

Kavanagh *et al.*, 2004; Kavanagh and Menz, 2008). Head accelerations were low-pass filtered using a 4th order 30Hz Butterworth filter (Kavanagh *et al.*, 2004; Kavanagh *et al.*, 2005).

6.4.2. Statistical Analysis

Statistical analysis was performed using SPSS (v21). Data were assessed for normality using Kolmogorov–Smirnov tests. Between groups (PD and control) comparison of saccade amplitude was not performed as this was not the focus of this study.

As a majority of variables were non-normally distributed, intra-class correlation or Bland-Altman plots were not calculated. Instead, accuracy is described in terms of the bias and consistency of saccades. Bias was determined by subtracting known target distance from median saccade amplitude measured using the eye-tracker (median saccade amplitude – target distance). Consistency was calculated as the range (Maximum - Minimum) of error between the measured and target saccade amplitude across participants.

Re-test reliability was described using the median and range of between-session difference (median session 2 – median session 1), and formally tested using a series of Wilcoxon signed-rank tests for each target amplitude. Relative agreement between the two sessions was assessed using Spearman's *rho* correlations. Correlation coefficients were interpreted as follows: excellent >0.90, good ≥0.75-0.89, fair ≥0.50-0.74, and poor <0.49 (Rosner, 2006). A threshold of $p<0.05$ was used to guide interpretation.

6.5. Results

6.5.1. Demographics

Participant characteristics are described in Table 6-1. Several participants (control n=2, PD n=1) were unable to complete session 2 but their data was retained for the accuracy analysis. There were no significant differences in age, sex or education level of the groups. Participants wore any visual correction that they usually wore to walk during testing, with significantly more PD participants wearing visual correction ($p = 0.03$). The PD group had moderate motor symptoms as assessed using the UPDRS-III and H&Y scale.

6.5.2. Eye and Head Movement

Low cross-correlation coefficients indicated that head movement did not influence saccade amplitude (*r* ranged from 0.01 to 0.12 for walking; see Appendix 14.0). As such, standing and walking head movement data was not included in further analyses. The poor correlations were likely due to the maximum target distance of 15°, as saccades greater than 20° are needed to elicit combined eye-head movement (Gandhi and Sparks, 2001; Crawford *et al.*, 2003).

Table 6-1 - Demographics

Characteristic	Controls (n=20) median (range)	Parkinson's disease (n=14) median (range)	*p*
Age (yrs)	68.5 (51, 86)	68.0 (61, 81)	.88
Sex, n (%)			
Men	12 (60%)	9 (64%)	.85†
Women	8 (40%)	5 (36%)	
Height (cm)	170.5 (143, 184)	168.5 (150, 183)	.85
Weight (kg)	72.9 (58, 101)	78.3 (51, 107)	.36
Glasses, n (%)			
None	10 (50%)	2 (14.2%)	-
Bifocals	2 (10%)	4 (28.6%)	-
Varifocals	4 (20%)	4 (28.6%)	-
Contact lenses	3 (15%)	0 (0%)	-
Distance	1 (5%)	4 (28.6%)	-
Glasses Worn During Testing	10 (50%)	12 (86%)	.03*
MMSE	30 (26, 30)	29 (24, 30)	.26
MoCA	28 (21, 30)	27 (23, 30)	.42
Years of Education	13 (7, 20)	12 (10, 19)	.31
H & Y stage (n)	-	I (4), II (8), III (2)	-
UPDRS-III	-	34.5 (8, 63)	-
10m Walk (sec)	7.73 (5.97, 13.84)	8.14 (6.01, 13.73)	.55
Walk speed (km/hr)	4.67 (2.61, 6.05)	4.43 (2.63, 6.01)	.58

[MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; UPDRS-III: Unified Parkinson's disease Rating Scale – motor symptoms, H & Y stage: Hoehn and Yahr stage *: $p<.05$, † X^2]

6.5.3. Accuracy

Overall, saccade amplitude consistently increased with increasing target distance (Tables 6-2 and 6-3). In relation to overall accuracy, a bias of -1.23° and -1.17°

was observed for PD and control participants respectively. However, a poor consistency (large range of error between participants) was observed within each group (PD: -7.48° to 5.18°; control: -7.73° to 5.81°), which was dependent upon target distance (5°, 10° and 15°) and direction (horizontal or vertical). Task (sitting, standing and walking) did not significantly affect accuracy.

The magnitude of bias was related to the magnitude of eye-movement, whereby participants tended to 'undershoot' when looking between targets set 10° and 15° apart. This was consistent for all tasks and for both groups. In addition, the range of error was greatest for the larger saccades (10° and 15°).

Bias was also related to saccade direction (horizontal, vertical), such that participants undershot the target distance considerably more when performing vertical compared to horizontal saccades.

6.5.4. Reliability

Overall, the median difference (session 2 – session 1) in saccade amplitude was low in both groups (PD; -0.14°, Controls; 0.02°, Tables 6-2 and 6-3). Similarly, the median difference for the individual tasks and amplitudes (Tables 6-2 and 6-3) was low (<1°). Only one variable (Controls; walking, horizontal, 15°) showed a significant difference between the sessions (p=0.02) but the median difference was still low (-0.95°). However, there was a wide range of difference between sessions across the participants (-12.60° to 16.75°). Relative agreement varied greatly from poor to good (*rho* range: 0.14, 0.85). The test condition did not have a consistent influence on bias or relative agreement. In contrast, larger saccades were associated with a greater range of change between sessions.

6.5.5. Influence of Visual Correction

Greater accuracy and re-test reliability results were found in the sub-set of controls with no vision correction (Tables 6-2 and 6-4). With regards to accuracy, median bias from target reduced from -1.17° to -1.15° and error was more consistent across the participants. Median difference in saccadic amplitude between sessions (reliability) was similar but the between-person range was much smaller. Modest improvements were also seen in the relative agreement between sessions when considering people who did not use visual correction.

Table 6-2 – Accuracy (session 1) and re-test reliability (comparison between session 1 and session 2): Controls

			Accuracy (Session 1) – Saccade Amplitude (°)			Re-test Reliability (Session 2 – Session 1) – Saccade Amplitude (°)				
Task	**Direction**	**°**	**Median (Min, Max) #1**	**Bias**	**Range of Error**	**Median (Min, Max) #2**	**Median Difference**	**Range of Difference**	***p***	**Spearman's rho (p)**
Sitting	**Horizontal**	**5**	5.69 (4.84, 9.56)	0.69	-0.16, 4.56	5.96 (4.41, 8.08)	-0.03	-5.51, 2.20	0.98	.42 (.07)
		10	10.23 (7.66, 13.18)	0.23	-2.34, 3.18	9.87 (8.59, 13.50)	-0.09	-8.28, 3.35	0.60	.35 (.14)
		15	12.71 (9.87, 14.52)	-2.29	-0.13, 4.52	13.28 (10.93, 14.71)	0.45	-11.76, 2.03	0.27	.20 (.42)
	Vertical	**5**	4.88 (4.05, 7.00)	-0.12	-0.95, 2.00	5.13 (4.05, 21.09)	0.21	-7.00, 16.75	0.14	.34 (.16)
		10	7.42 (6.20, 11.77)	-2.58	-3.80, 1.77	7.74 (6.34, 20.90)	0.07	-6.52, 12.53	0.32	.27 (.27)
		15	9.55 (7.27, 13.70)	-5.45	-7.73, -1.30	9.84 (7.85, 20.70)	0.26	-8.37, 12.15	0.29	.27 (.38)
Median			-	-1.21	-7.73, 4.56	-	-	-	-	-
Standing	**Horizontal**	**5**	6.16 (4.77, 10.81)	1.16	-0.23, 5.81	6.38 (4.98, 9.76)	-0.22	-6.23, 4.64	0.90	.48 (.30)
		10	10.01 (4.77, 10.81)	0.01	-5.23, 4.77	10.57 (8.48, 14.46)	0.39	-7.92, 2.62	0.55	.36 (.13)
		15	12.68 (10.51, 14.77)	-2.32	-4.49, -0.23	13.22 (10.91, 13.99)	0.06	-11.69, 2.83	0.81	.21 (.39)
	Vertical	**5**	5.15 (3.98, 10.38)	0.15	-1.02, 5.38	4.98 (4.05, 15.96)	-0.27	-4.65, 11.13	0.35	.30 (.21)
		10	7.55 (5.81, 11.97)	-2.45	-4.19, 1.97	7.58 (5.95, 19.03)	0.32	-6.22, 11.32	0.11	.61 (.005)
		15	10.17 (7.96, 12.00)	-4.83	-7.04, -3.00	9.79 (7.11, 21.15)	-0.36	-8.68, 9.16	0.89	.66 (.002)
Median			-	-1.16	-7.04, 5.81	-	-	-	-	-
Walking	**Horizontal**	**5**	5.41 (4.68, 8.16)	0.41	-0.32, 3.16	5.81 (4.30, 9.60)	0.21	-5.59, 4.92	0.07	.30 (.28)
		10	9.59 (7.02, 14.48)	-0.41	-2.98, 4.48	9.44 (7.33, 13.79)	-0.55	-8.71, 3.05	0.88	.26 (.29)
		15	13.07 (9.55, 14.37)	-1.93	-5.45, -0.63	11.96 (10.25, 13.41)	-0.95	-12.60, 3.51	**0.02***	.14 (.57)
	Vertical	**5**	4.93 (4.46, 7.24)	-0.07	-0.54, 2.24	5.22 (4.17, 7.53)	-0.04	4.90, 2.97	0.34	.53 (.24)
		10	7.22 (5.52, 9.35)	-2.78	-4.28, -0.65	7.43 (5.86, 9.12)	-0.09	-6.67, 2.10	1.00	.45 (.06)
		15	10.21 (7.87, 12.01)	-4.79	-7.13, -2.99	10.63 (7.93, 12.06)	0.10	-8.22, 2.86	0.32	.75 (.001)
Median			-	-1.17	-7.13, 4.48	-	-	-	-	-
Group Median			-	-1.17	-7.73, 5.81	-	0.02	-12.60, 12.53	-	-

[*Significance level p<0.05, Degrees (º), Horizontal or vertical and 5, 10 or 15 = Target location, #1 = session 1 and #2 = session 2, Median difference = Median #2 – Median #1]

Table 6-3 – Accuracy (session 1) and re-test reliability (comparison between session 1 and session 2): Parkinson's disease

			Accuracy (Session 1) – Saccade Amplitude (°)			Re-test Reliability (Session 2 – Session 1) – Saccade Amplitude (°)				
Task	Direction	°	Median (Min, Max) #1	Bias	Range of Error	Median (Min, Max) #2	Median Difference	Range of Difference	*p*	Spearman's rho (*p*)
Sitting	**Horizontal**	**5**	5.81 (4.45, 6.74)	0.81	-0.55, 1.74	6.10 (4.99, 7.74)	0.05	-5.18, 3.19	0.27	.17 (.59)
		10	9.52 (7.02, 13.40)	-0.48	-2.98, 3.40	9.80 (7.59, 12.69)	-0.25	-9.08, 2.88	0.89	.51 (.07)
		15	12.31 (8.80, 14.98)	-2.69	-6.20, -0.02	12.56 (10.24, 14.01)	-0.02	-11.40, 2.42	0.91	.37 (.29)
	Vertical	**5**	4.81 (4.03, 6.26)	-0.19	-0.97, 1.26	4.76 (4.05, 6.87)	-0.29	-4.51, 2.12	0.36	.14 (.65)
		10	7.31 (6.01, 9.00)	-2.69	-3.99, -1.00	7.00 (6.04, 10.84)	-0.55	-6.97, 2.62	0.69	.64 (.18)
		15	9.34 (7.80, 11.70)	-5.66	-7.20, -3.30	9.25 (7.89, 11.19)	-0.31	-8.65, 1.23	0.46	.67 (.01)
Median			-	-1.59	-7.20, 3.40	-	-	-	-	-
Standing	**Horizontal**	**5**	5.94 (4.81, 10.18)	0.94	-0.19, 5.18	6.05 (4.32, 7.59)	-0.13	-5.32, 1.37	0.73	.76 (.002)
		10	10.13 (8.20, 12.08)	0.13	-1.80, 2.08	10.28 (6.91, 13.50)	-0.21	-9.53, 2.23	0.24	.85 (.000)
		15	12.20 (9.90, 13.62)	-2.80	-5.10, -1.38	12.50 (10.13, 17.47)	0.45	-10.63, 5.03	0.15	.64 (.02)
	Vertical	**5**	4.79 (4.25, 5.53)	-0.21	-0.75, 0.53	4.56 (3.91, 11.08)	-0.08	-4.58, 6.63	0.37	.38 (.20)
		10	8.02 (6.10, 12.25)	-1.98	-3.90, 2.25	7.52 (6.08, 10.14)	-0.41	-6.63, 1.42	0.51	.38 (.20)
		15	9.82 (7.54, 11.91)	-5.18	-7.46, -3.09	9.11 (7.19, 12.54)	-0.75	-8.65, 1.10	0.10	.50 (.08)
Median			-	-1.10	-7.46, 5.18	-	-	-	-	-
Walking	**Horizontal**	**5**	5.62 (4.65, 9.90)	0.62	-0.35, 4.90	5.58 (4.95, 6.24)	-0.01	-5.15, 0.91	0.62	.20 (.51)
		10	9.70 (6.29, 12.94)	-0.30	-3.71, 2.94	9.93 (7.99, 13.00)	0.15	-8.82, 2.11	0.20	.63 (.02)
		15	12.38 (8.53, 13.82)	-2.62	-6.47, -1.18	12.92 (11.09, 15.67)	0.23	-11.40, 5.24	0.16	.14 (.65)
	Vertical	**5**	4.80 (4.35, 6.98)	-0.20	-0.65, 1.98	4.68 (4.32, 5.77)	-0.15	-4.45, 0.72	0.10	.44 (.13)
		10	7.37 (5.92, 10.28)	-2.63	-4.08, 0.28	6.95 (5.83, 16.30)	-0.11	-6.63, 6.55	0.67	.45 (.13)
		15	10.06 (7.52, 12.31)	-4.94	-7.48, 2.31	9.52 (7.28, 11.67)	-0.27	-8.68, 1.45	0.21	.80 (.001)
Median			-	-1.46	-7.48, 4.90	-	-	-	-	-
Group Median			-	-1.23	-7.48, 5.18	-	-0.14	-11.40, 5.24	-	-
Overall Median (PD and Controls)			-	-1.21	-7.73, 5.81	-	-0.09	-12.60, 16.75	-	-

[*Significance level p<0.05, Degrees (º), Horizontal or vertical and 5, 10 or 15 = Target location, #1 = session 1 and #2 = session 2, Median difference = Median #2 – Median #1]

Table 6-4 – Accuracy (Session 1) and re-test reliability (comparison of Session 1 and Session 2) of controls with no vision correction (n=10)

			Accuracy – Saccade amplitude (°)			Re-test Reliability (Session 2 – Session 1) – Saccade Amplitude (°)				
Task	Direction	°	Session 1 Median (Min, Max)	Bias	Range of Error	Session 2 Median (Min, Max)	Median Difference	Range of Difference	*p*	Spearman's rho (*p*)
Sitting	**Horizontal**	**5**	5.58 (4.84, 7.48)	0.58	-0.16, 2.48	5.91 (5.21, 6.98)	0.24	-0.52, 1.34	0.14	.29 (.42)
		10	9.86 (7.66, 12.35)	-0.14	-2.34, 2.35	9.48 (8.59, 13.50)	-0.09	-2.87, 3.35	1.00	.89 (.05)
		15	13.13 (9.87, 14.52)	-1.87	-5.13, -0.48	12.78 (10.93, 14.54)	0.27	-2.10, 1.63	0.95	.33 (.35)
	Vertical	**5**	4.75 (4.05, 5.35)	-0.25	-0.95, 0.35	4.88 (4.05, 5.42)	0.04	-0.83, 0.94	0.36	.13 (.73)
		10	6.76 (6.20, 9.03)	-3.24	-3.80, -0.97	7.42 (6.40, 9.00)	0.43	-2.30, 1.78	0.26	.83 (.08)
		15	9.14 (7.27, 10.88)	-5.86	-7.73, -4.12	9.70 (7.85, 11.44)	0.64	-1.04, 1.43	0.07	.76 (.01)
	Median		-	-1.06	-7.73, 2.48	-	-	-	-	-
Standing	**Horizontal**	**5**	5.97 (4.77, 7.17)	0.97	-0.23, 2.17	5.89 (4.98, 7.47)	0.23	-0.56, 1.44	0.38	.77 (.009)
		10	10.01 (7.98, 14.42)	0.01	-2.02, 4.42	10.41 (8.48, 12.61)	0.20	-2.59, 2.62	0.84	.32 (.36)
		15	12.80 (10.85, 14.77)	-2.20	-4.15, 4.77	13.20 (10.91, 13.84)	-0.06	-1.42, 1.96	0.92	.20 (.59)
	Vertical	**5**	4.76 (3.98, 6.10)	-0.24	-1.02, 1.10	4.92 (4.05, 5.57)	0.12	-1.06, 1.18	0.88	.17 (.65)
		10	6.57 (5.81, 8.16)	-3.43	-4.19, -1.84	7.04 (5.95, 8.32)	0.32	-1.27, 1.61	0.26	.53 (.12)
		15	9.55 (7.96, 11.12)	-5.45	-7.04, -3.88	8.82 (7.11, 10.43)	-0.48	-2.89, 0.70	0.15	.43 (.21)
	Median		-	-1.22	-7.04, 4.77	-	-	-	-	-
Walking	**Horizontal**	**5**	5.40 (4.80, 5.77)	0.40	-0.20, 0.77	5.76 (4.30, 6.13)	0.09	-4.80, 0.82	0.37	.40 (.28)
		10	9.93 (7.02, 14.30)	-0.07	-2.98, 4.30	8.86 (7.33, 13.23)	-0.63	-8.37, 2.30	0.40	.23 (.56)
		15	13.85 (10.46, 14.37)	-1.15	-4.56, 4.37	12.47 (10.82, 13.41)	-1.19	-10.49, 0.12	0.01*	.43 (.25)
	Vertical	**5**	4.81 (4.58, 7.24)	-0.19	-0.42, 2.24	5.24 (4.17, 6.11)	0.19	-4.90, 0.72	0.40	.44 (.24)
		10	7.14 (4.58, 7.24)	-2.86	-5.42, -2.76	6.83 (5.86, 8.05)	-0.09	-6.29, 0.95	0.35	.42 (.27)
		15	9.97 (7.87, 10.89)	-5.03	-7.13, -4.11	9.21 (7.93, 11.08)	0.04	-8.01, 0.84	1.00	.74 (.02)
Median			-	-0.67	-7.13, 4.37	-	-	-	-	-
Group Median			-	-1.15	-7.73, 4.77	-	0.11	-10.49, 3.35	-	-

[*Significance level p<0.05, Degrees (º), Horizontal or vertical and 5, 10 or 15 = Target location, #1 = session 1 and #2 = session 2, Median difference = Median #2 – Median #1]

6.6. Discussion

To date, this is the first study to examine accuracy and reliability of a mobile eye-tracker in people with PD and controls. The results provide evidence that mobile eye-trackers can measure saccade amplitude in people with PD and controls although the accuracy and reliability depend on several factors. These findings contribute to the development of novel protocols for establishing the psychometric properties of mobile eye-tracking devices.

6.6.1. Accuracy

Median saccade amplitude, as measured by the mobile eye-tracker, increased with increasing target distance (Tables 6-2 and 6-3). This indicates that the mobile eye-tracker can discern change in saccade amplitude. However, the measured saccade amplitudes were smaller than target distance (5°, 10° or 15°), especially for larger and vertical saccades. In addition, bias was inconsistent across the participants, especially for larger saccades.

Although the previous chapter (Chapter 5) has shown that the Dikablis mobile eye-tracker can accurately detect saccade occurrence (Stuart *et al.*, 2014b), this study indicates saccade amplitude may not be measured with the same degree of certainty. This suggests that saccade detection outcomes (number or frequency) may be more robust than saccade amplitude. Regardless, the overall bias (median -1.21°) and range of error (-7.73° to 5.81°) is acceptable for certain protocols, such as dynamic protocols involving saccade detection which often use a minimum threshold of ≥5° saccade amplitude (Galna *et al.*, 2012) to account for artefact error (e.g. vestibular ocular-reflex) (Stuart *et al.*, 2014b). However, this degree of accuracy may not be acceptable for protocols where precision of large saccade amplitude is important.

6.6.2. Reliability

Re-test reliability varied across conditions and participants. Although the median difference between sessions was low (<1°), the difference ranged from -12.60° to 16.75° across participants. Similarly, relative agreement ranged from poor to good between conditions (*rho*; 0.14 to 0.85). Variable reliability indicates that saccade amplitude measurement may not be stable over time and is likely due to

several sources of error, which are discussed in the next section. Until robust protocols are developed which are stable over time, this study cannot recommend saccade amplitude as a reliable outcome when using a mobile eye-tracker across multiple assessments.

6.7. Potential Challenges and Recommendations

Error affecting the accuracy and reliability of the mobile eye-tracker stems from technological, human and study protocol factors. A better understanding of these sources of error is important for design of future protocols and devices.

6.7.1. Technology Factors

Manufacturer reported accuracy (0.5°) was not observed in this study. In contrast, a previous preliminary study (involving four young adults) using a static eye-tracker (Tobii, TX300; 300Hz) during treadmill walking reported eye-tracker accuracy was consistent with manufacturer specifications (0.5°) regardless of target locations or saccade amplitude (Serchi *et al.*, 2014a; Serchi *et al.*, 2014b). Overlooking the preliminary nature of the referenced study (Serchi *et al.*, 2014a), inconsistency between the current study and this previous report may be due to the lower sampling frequency of the mobile eye-tracker used in this study (50Hz) compared to the static device (300Hz) (Andersson *et al.*, 2010). A sampling frequency of 50 Hz enables saccade detection (Holmqvist and Nystrom, 2011), but higher frequency (>200Hz) devices may be more accurate at reporting specific saccade characteristics (Stuart *et al.*, 2014a). For example; a sampling frequency of 50 Hz assumes that the eye is in a fixed location for 20ms (50Hz) whereas a higher frequency system (1000Hz) assumes this for only 1ms, providing better temporal accuracy and more eye position data (Andersson *et al.*, 2010; Holmqvist and Nystrom, 2011). Therefore, a mobility-resolution trade-off exists. Higher sampling frequency of static devices may offer improved accuracy and reliability but in order to use them, studies must limit participant mobility during dynamic tasks. That is, participants must walk on a treadmill and be at a set distance from visual targets (Serchi *et al.*, 2014a), limiting the tasks and context within which vision can be measured. However, protocols which limit mobility can limit validity of the characteristics measured (Nevalainen and Sajaniemi, 2004). For example, restricted head movements during static

protocols may facilitate abnormal visual processing, seen through alterations in saccade responses (van Stockum *et al.*, 2013).

Some bias may be due to eye curvature induced error (Zhiwei and Qiang, 2007). The eye, in particular the cornea, is a convex curved lens with a horizontal movement range of ~100° and vertical range of ~90° (Botha *et al.*, 2008). As previously mentioned, many eye-trackers locate the pupil via the black pixels recorded by an infra-red eye-camera and uses specific circular pupil shape parameters to derive the pupil centre. Depending upon the location of the eye-camera in relation to the eye, the pupil shape will appear as an ellipse and therefore the circular pupil shape parameters would lead to inaccurate tracking. This is most relevant for large saccades, where the person is looking furthest from the camera. The Dikablis eye-tracker used in this study demonstrated such an error by recording an 'undershoot' for all targets at 15° and may have contributed to the poorer accuracy seen for 15° saccades. This error could be controlled for in future technology with the use of convex cost function algorithms (De Santis and Iacoviello, 2009) or corneal reflection tracking (Mele and Federici, 2012), which would provide further means of tracking eye-in-head movements (Hennessey and Lawrence, 2009) and control for pupil tracking errors (Li *et al.*, 2008).

6.7.2. Human Factors

6.7.3. Visual Correction and Obstruction of the Eye

Pupil tracking may have been compromised by a number of general eye-tracker issues, such as inaccuracies due to poor calibration (Nystrom *et al.*, 2013) by the researcher, long or drooping eye lashes/lids (i.e. ptosis), infra-red refraction due to visual correction (e.g. glasses), obstruction by hair and any slippage of the 'one-size-fits-all' eye-tracker from original placement when recording (Holmqvist and Nystrom, 2011). During the data collection eye lids/lashes and visual correction (particularly bi-focal glasses) were observed as the main cause of error, particularly for vertical saccades and large saccades of any direction. These challenges are inherent to any infra-red eye-tracking device and although some can be controlled within an experiment, many are dependent upon the researcher's ability to identify and address these issues on an individual basis.

For example, using double sided tape to minimise slippage of the device and requesting participants not wear make-up around the eye where to ways which anecdotally improved accuracy.

The impact of visual correction on the accuracy and re-test reliability was also assessed by looking at a subset of 10 controls who wore no visual correction (Table 6-4). The results showed that the accuracy and reliability were better in individuals who did not use visual correction, likely due to visual correction affecting pupil detection via infra-red refraction (Holmqvist and Nystrom, 2011). Unfortunately, exclusion of participants with visual correction may not be appropriate when selecting participants for research studies, particularly with groups likely to have increased use of visual correction such as older adults. Therefore, the negative effect of visual correction on eye-tracker accuracy and reliability must be considered when designing robust protocols and is a challenge which still needs to be addressed by manufacturers of the next generation of eye-trackers.

6.7.4. Attention

Participant saccades were voluntary and therefore involved attention (top-down) which is influenced by internal factors (Baluch and Itti, 2011) and may have affected amplitude results. Factors such as level of fatigue between sessions (Faber *et al.*, 2012), ethnicity of participants (Blignaut and Wium, 2014), prior knowledge of testing protocols (learning effect) (Kim and Rehder, 2011), individual emotional state (Oatley *et al.*, 2011) and motivation (Kaplan *et al.*, 2012) could all have influenced saccade measures. Future studies could control for such factors by investigating saccade latencies compared to auditory signal, or quantifying total saccade number to compare to a set amount (i.e. 20 saccades within 20 seconds).

In addition, this study did not consider the inhibition of return mechanism whereby a person orientates their attention to novel locations and stimuli, as the target appearance, location and saliency (t Hart *et al.*, 2013) remained the same. Once a peripheral location is foveated (fixated on) there is a delayed response in returning attention to subsequent stimuli in the same location (Klein, 2000). Programming of the next saccade occurs even before the previous saccade is

completed (McPeek *et al.*, 2000), therefore introducing a time constraint (1 second) and using the same targets/locations may have led to inaccuracies in saccade programming and execution. Therefore, some of the error observed in this study may have been due to inaccurate saccades rather than error introduced by the mobile eye-tracker.

6.8. Study Protocol Limitations

Future work should address the limitations of this study to establish a 'gold standard' accuracy and reliability method that can be applied to differing devices and various populations. Novel peripheral targets in varying locations which require reflexive (involuntary) saccades should be used, with variations on saccadic timings. For example; a light board or computer-based programme where objects or targets randomly appear (similar to that used by Serchi *et al.* (2014a) for their static eye-tracker) could be used with mobile devices. Future studies could also examine the impact of combined eye-head movement on saccade amplitude accuracy, particularly for larger saccades (>20°) where coordinated eye-head movement is required.

6.9. Conclusion

This study found that the Dikablis mobile eye-tracker had variable accuracy and reliability when recording saccade amplitude in people with PD and older adult controls during sitting, standing and walking. Importantly for this thesis, accuracy was acceptable for certain protocols such as saccade detection during gait, but more precision may be necessary when investigating specific saccade characteristics.

Accuracy and reliability of saccade amplitude was affected by use of visual correction (e.g. glasses and contact lenses) and should therefore be considered when reporting differences measured via infra-red mobile eye-trackers, particularly with groups of older adults given the increased prevalence of visual correction. In addition, several technological, human and study-specific factors need to be addressed to achieve more robust testing protocols. Devices with high sampling frequencies (>200Hz) that do not rely on infra-red pupil detection (such as EOG) may provide a more accurate means to gather specific visual sampling characteristics such as saccade amplitude.

7. Visual sampling during gait in Parkinson's disease: attentional manipulation

7.1. Summary

The purpose of this chapter was to investigate visuo-cognition in gait in a large group of people with PD and older adult controls. Saccade frequency and gait were assessed during attentional manipulation. Bivariate correlational analyses were used to examine the interactions between cognition and vision (termed visuo-cognition) (Figure 2-1(C)), and underlying mechanisms involved in the impairment of saccade frequency during gait. Finally, further bivariate analysis was used to explore visuo-cognitive influence (represented by saccade frequency) on gait in PD (Figure 2-1(D)).

7.2. Introduction

Saccades provide a non-invasive online behavioural measure of visuo-cognition (Leigh and Kennard, 2004). Saccade frequency (the number of fast eye movements per second) during gait in particular is a clinically relevant measure that describes the amount of visual sampling employed when walking, and impairment may lead to trips or falls. Between group differences in saccade frequency during gait reflect altered visuo-cognitive processing, and may be a particularly sensitive measure in PD due to the known visual, cognitive and saccadic impairments. However saccade frequency during gait is likely impacted by a number of age-related or pathological impairments, which may elicit non-linear response within specific populations under different conditions. Saccades have been related to a variety of demographic (as well as cognitive and visual) features during static and dynamic conditions, such as age (Munoz *et al.*, 1998; Butler *et al.*, 1999; Peltsch *et al.*, 2011; Bowling *et al.*, 2015), ocular-motor control (Crowdy *et al.*, 2000), depression (Sweeney *et al.*, 1998; Shafiq-Antonacci *et al.*, 1999; Jazbec *et al.*, 2005), fear of falling (Turano *et al.*, 2002; West *et al.*, 2011; Young and Hollands, 2012), visual functions (Kulikowski, 1971; Ko *et al.*, 2010) and cognition (Liversedge and Findlay, 2000). Saccadic impairments are well recognised in PD (Anderson and MacAskill, 2013) and during dynamic tasks such as gait, various visual sampling impairments have been found in small cohorts of

PD and older adults (described in chapter 3), however underlying mechanisms remain unclear. Altered visual sampling during gait has been hypothesised to be an attempt to compensate for underlying visual, cognitive and motor deficits associated with PD. For example; reduced saccade latencies and longer fixation durations during gait in PD (Anastasopoulos *et al.*, 2011; Lohnes and Earhart, 2011) may be needed due to increased visual processing times required for motor programming, which attention is unable to expedite due to resources being preferentially allocated to maintaining gait (Lee *et al.*, 2003). However saccadic differences are likely due to a number of underlying visuo-cognitive interactions yet to be fully investigated even during static testing, such as; imbalance between the dopaminergic (mainly voluntary saccades) and cholinergic (mainly reflexive saccades) systems (Noudoost and Moore, 2011), abnormal frontal processes involved in saccade facilitation influencing the SC, fluctuations of inhibitory mechanisms or facilitation from other regions such as the frontal and supplementary eye-fields (Terao *et al.*, 2011; van Stockum *et al.*, 2011b; van Stockum *et al.*, 2012; Terao *et al.*, 2013; van Stockum *et al.*, 2013). The fronto-striatal attentional pathway (involving the PFC and BG) is particularly involved in voluntary saccade generation and inhibitory influence on the SC (O'Callaghan *et al.*, 2013), with implications for PD impairment. Similarly given that visual and cognitive loops overlap in striatal regions, and that saccade programming and integration of visuo-cognitive input with motor output are performed in connected cortical regions (Kravitz *et al.*, 2011), it is likely that impaired saccadic activity contributes to gait impairment in PD.

The primary aim of this chapter was therefore to examine visual sampling during gait in PD and age-matched controls, under two different attentional manipulations which are common to real-world gait; environmental challenge and dual task. Specific hypotheses have been highlighted in section 1.2. Primarily they were that saccade frequency would be reduced in PD compared to controls, and this reduction would be associated with gait impairment. It was also hypothesised *a priori* that demographic features (such as age, depression, global cognition and disease severity) along with cognitive and visual functions would relate to saccade frequency during gait in PD.

To answer the specific hypotheses set out within the introduction of this thesis, a series of questions were raised. For clarity, these questions form the structure of the data analysis, results and discussion of this study.

Questions that this study will answer;

- What are the descriptive differences between PD and controls?
- What is the effect of attentional manipulation on saccade frequency during gait?
- What is the effect of attentional manipulation on gait?
- What are the relationships between saccade frequency, cognition, vision and gait?
    - What is the relationship between cognition and vision?
    - What is the relationship between demographics, vision, cognition and gait?
    - What is the relationship between demographics, vision, cognition and saccade frequency?
    - What is the relationship between saccade frequency and gait?

7.3. Specific Methods[7]

7.3.1. Participants

Within this study results from 56 people with PD and 40 age-matched control older adults are discussed. Inclusion and exclusion criteria, along with study recruitment are provided within Chapter 4. Clinical and further testing (detailed in Chapter 4) took place 1 hour after medication intake to ensure optimal function ('On' state of medication was verified at the beginning of the assessments through observation of hand clasping, finger and foot tapping parts of the UPDRS III).

7.3.2. Specific experimental design and procedure

Saccade frequency during gait and change scores were measured while attention was manipulated using two different strategies, increasing the *environmental*

[7] The methods contained within this chapter have been published; Stuart et al. (2015)

challenge and performing a *dual task*. These attentional manipulations were chosen to mimic real-world conditions that people with PD have difficulties with.

7.3.3. Environmental Challenge

Participants were asked to walk at their usual pace during several different environmental conditions (Figure 7-1 and Appendix 15.0); straight walking, straight walking through a door and turning 40° left and right. Photographs of the walking conditions can be seen in Appendix 15.0.

The commands used for each condition were as follows:

"Begin looking straight ahead at the camera, I will count down from 3 during which remain looking at the camera. When I say 'Go' you are free to look wherever you want. Also, on go begin walking straight ahead to the white line at the end of the room (or turn to the left or right once through the door and walk over the white line on the floor)."

For all walking conditions the participants completed a 5m walk, however only the first 2.5m of the walks prior to the doorway (Figure 7-1) were analysed. This ensured that participants were consistently within the capture volume of the 3D motion capture system, to allow for simultaneous body and eye movement tracking. Three trials of each walking condition were performed and further analysed.

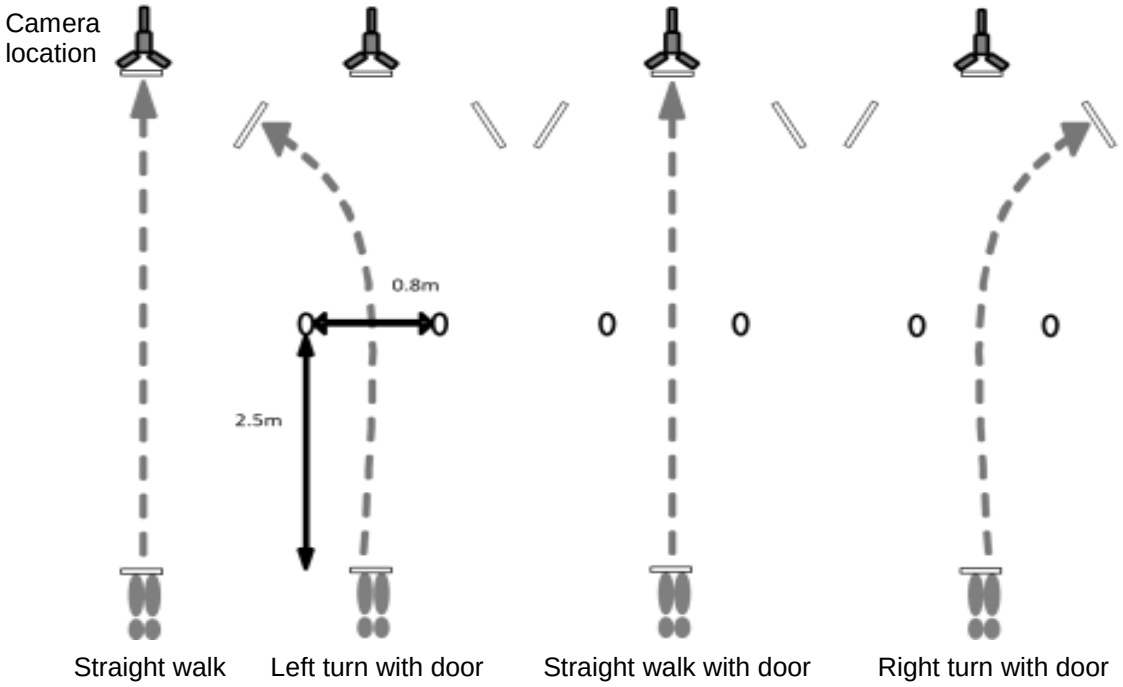


Figure 7-1 - Walking conditions

7.3.4. Dual Task

Single and dual task walks were completed by the participants. The dual task involved repetition of individuals maximal digit span during gait as described in Chapter 4 (section 4.11). Participants were played a string of digits over loud speaker and had to repeat the number strings back once they had passed the doorway (2.5m point; Figure 7-1). The order of walking conditions were randomised, with the straight walking condition always first to ensure participants could complete the conditions safely and the three subsequent conditions randomly undertaken, as were the blocks of single and dual tasks (Figure 7-2).

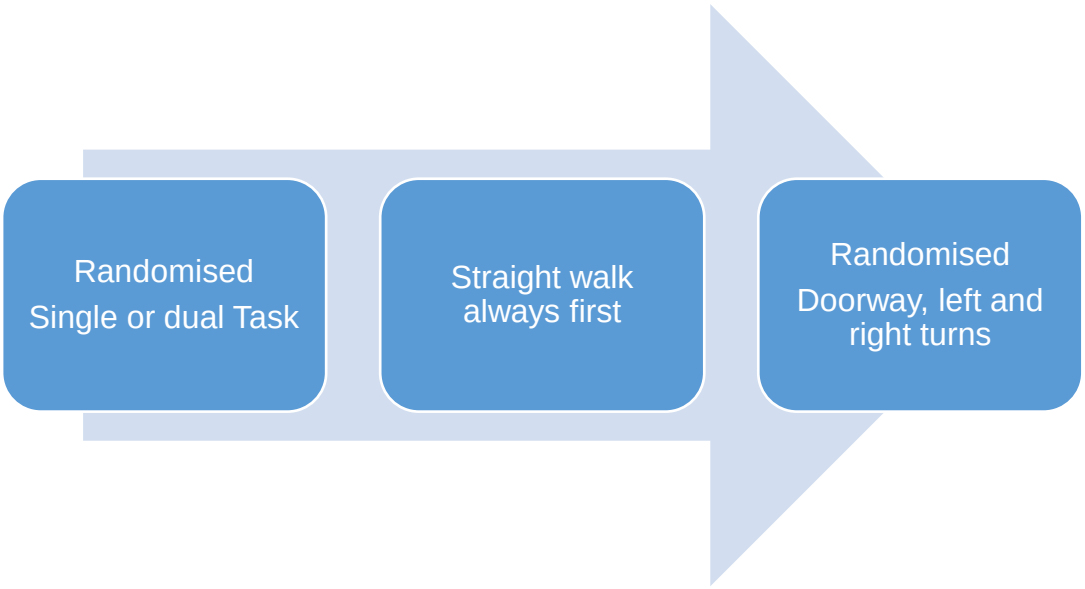


Figure 7-2 – Randomisation procedure of walking conditions

7.3.5. Equipment

As described in Section 4.10, saccades were measured using mobile eye-tracker and EOG systems, which were calibrated at the start of each session. Participants were asked to keep their face as relaxed as possible and to not repeat any numbers during dual task before the doorway position in order to avoid data infiltration from muscle contraction artefact in the EOG data. Gait and head movement were measured using a 3D motion capture system.

7.3.6. Outcome measures

The primary outcome for this study was saccade frequency (number of saccades per second) during gait which was reported as descriptive data and change (Δ) scores. Saccade frequency change scores (change in saccade frequency with environment; ΔDoor or ΔTurn) were calculated via set formula (1 and 2) for all participants within the single and dual task conditions, in order to assess effect of environment under single and dual task.

(1) Straight walk with door - Straight walk = ΔDoor

(2) Turn with door - Straight walk = ΔTurn

This study reports saccade frequency in terms of absolute values measured during gait and change scores in order to overcome some of the measurement limitations observed within the accuracy and reliability testing (Chapter 6). Errors

introduced into measurement will vary dependent on the individual, therefore calculating change score allows for mitigation of the intrinsic errors associated with mobile eye-tracking (i.e. each individual acts as their own control for the session).

Secondary visual sampling characteristics were also included for comprehensive data reporting, such as; saccade number, duration, peak velocity and peak acceleration; and fixation number and duration, and blink number. Other secondary outcomes included gait characteristics, such as; time taken to walk to the door location (Time to Door), step length, walk velocity, step time, single support and double support. Head movement (raw signal and velocity) was also recorded in a sub-group of participants (control n=15 and PD n=15) for comparison to the eye movement signal via peak cross-correlation to assess the effect of head movement on saccade characteristics (presented in Appendix 17.0).

7.3.7. Data and statistical analysis

Data were assessed for normality with visual histograms and Kolmogorov-Smirnov tests, meeting criteria for parametric analysis (Expósito-Ruiz *et al.*, 2010; Ghasemi and Zahediasl, 2012; Field, 2013). All statistical tests were two-tailed and due to the exploratory nature of the study a significance value of $p<0.05$ was set. Therefore control for multiple comparisons via Bonferroni or other methods was not performed for ANOVA, correlation or regression analysis. The primary reason for this lack of control was to avoid "over-pruning" the data (i.e. removal of real significant differences between the groups) (Hilderman and Peckham, 2007), thus preventing Type II error.

Preliminary pairwise analysis via t-tests showed that there was no significant difference in the primary outcome of saccade frequency between the two straight walking conditions or the two turning conditions within either group; therefore for further analysis (i.e. analysis of variance (ANOVA)) data were collapsed into straight walking (Mean(Straight, Door)) and a single turning (Mean(Left, Right)) variable in order to avoid Type I error. The same was done for the gait characteristics to allow for comparison.

Figure 7-3 shows the four step analysis performed in order to answer the specific questions set out at the start of this chapter, and further details follow.

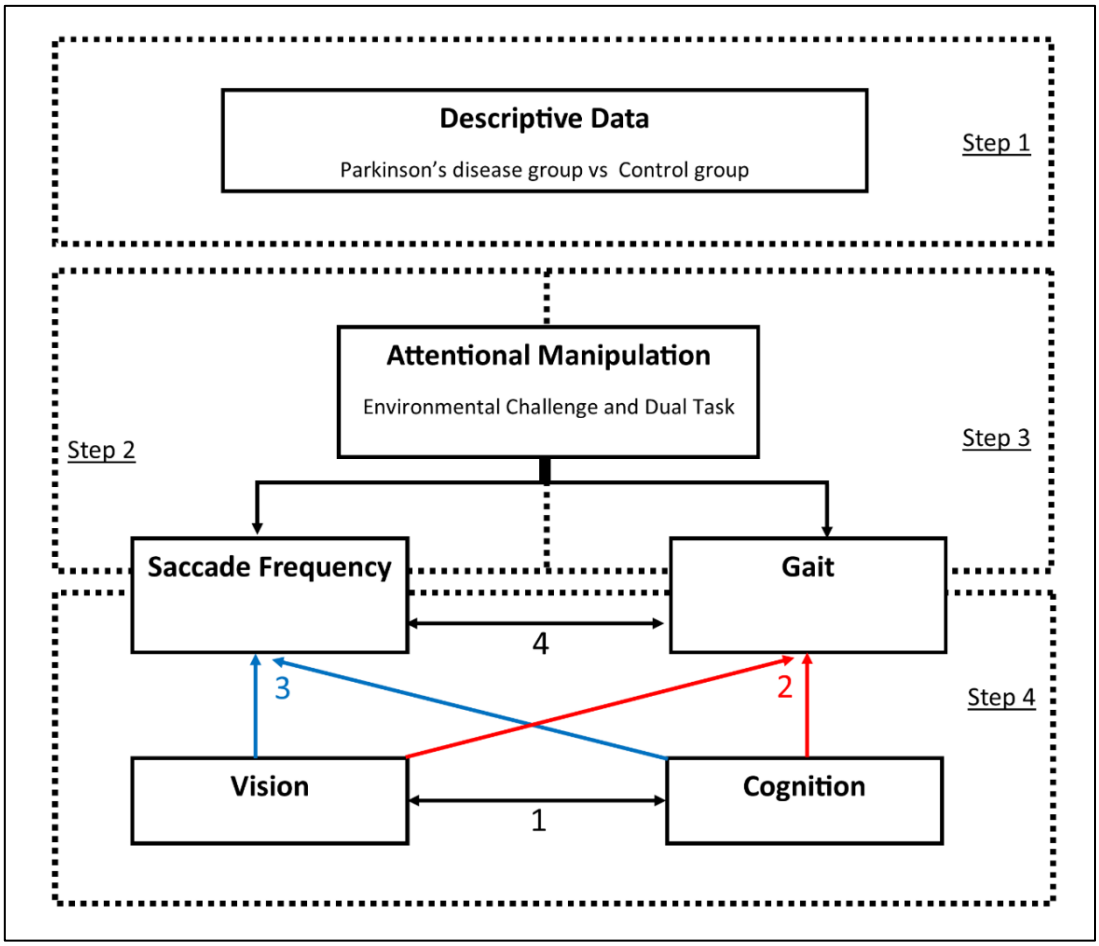


Figure 7-3 – Data analysis flow chart

<u>Step 1:</u> What are the descriptive differences between PD and controls?

To address this question, analysis for descriptive data described in chapter 4 section 4.12 was performed.

<u>Step 2:</u> What is the effect of attentional manipulation on saccade frequency during gait?

To answer this question a repeat measures ANOVA was used to compare the effect of attentional manipulation via environmental challenge (straight and turn) and dual task (single or dual) on saccade frequency, with group (PD or control) as a between subject factor. A second repeat measures ANOVA was conducted to compare the effect of environmental challenge and dual task on saccade

frequency change scores (ΔDoor and ΔTurn), with group as a between subject factor.

Step 3: What is the effect of attentional manipulation on gait?

To answer this question several repeat measures ANOVAs were used to compare the effect of environmental challenge (straight and turn) and dual task (single and dual) on gait (trial duration, step length, gait velocity etc.), with group (PD or control) as a between subject factor.

There is no proper facility in SPSS for producing *post hoc* tests for repeat measures ANOVAs (Field, 2013). Therefore in order to interpret two and three-way interactive relationships data were plotted and presented graphically. Three-way interaction (environment x dual task x group) was further examined using two separate repeat measures ANOVAs which were conducted as *post hoc* tests, in line with other similar gait analysis performed in previous research (Errington *et al.*, 2013; Menant *et al.*, 2014). These assessed gait differences between the groups due to environmental challenge separately under single and dual task (i.e. environmental challenge under single task, then environmental challenge under dual task with group as a between subject factor in each repeat measures ANOVA).

Step 4: What are the relationships between saccade frequency, cognition, vision and gait?

In order to answer this complex question the relationships were broken down into the following four smaller questions;

1. *What is the relationship between vision and cognition?*

To answer this question, a matrix of Pearson correlation coefficients was used to explore the relationships between cognitive and visual functions in PD and controls.

2. *What is the relationship between demographics, cognition, vision and gait?*

To answer this question, relationships between demographic, clinical, cognitive and visual functions and gait were also explored using Pearson correlation

coefficients. Correlation matrices are presented in Appendix 19.0 and 20.0 as these relationships have been shown before in previous studies, and gait was a secondary outcome for this study.

3. *What is the relationship between demographics, cognition, vision and saccade frequency?*

To answer this question, data analysis was conducted in two stages (3a and 3b), see below;

3(a): Correlation

Initially Pearson correlation coefficients were calculated to explore associations between saccade frequency during gait (absolute and change scores) and independent demographic, cognitive, visual functions and clinical variables.

3(b): Multiple Regression

As this question pertains to the independent cognitive and visual mechanisms underlying the primary outcome of this study, further exploratory regression analysis was performed. Saccade frequency change scores (∆Door, ∆Turn) were used to represent saccade frequency not only to remove some individual measurement error, but also due to their consistent significant correlation with independent variables (Allison, 1990). Four models (steps) were created for each saccade frequency outcome. Demographic features were entered into the first step (Model 1), cognitive (Model 2) and visual functions (Model 3) in separate steps, and a final combined model is presented (Model 4) (model variables follow).

Demographics of age, disease severity (represented by UPDRS III), global cognition (represented by MoCA) and depression (represented by GDS-15) were entered into the models. Fear of falling (represented by FES-I) was not entered due to the known interaction with depression/anxiety (van Haastregt *et al.*, 2008; Iaboni and Flint, 2013) and a lack of pathological cause limiting interpretation (Legters, 2002). Variables that were significantly different between people with PD and controls, shown via univariate analysis were used to represent cognitive and visual functions. Cognitive functions consisted of attention (represented by

FoA), executive function (represented by CLOX 1), visuo-spatial ability (represented by JLO) and working memory (represented by Digit span), only one variable was chosen to represent each cognitive function to avoid overfitting. As power of attention (PoA) and fluctuation of attention (FoA) were highly correlated ($r = .70$, $p < .001$), FoA was chosen to represent attention within the regression models due to its higher correlation with both saccade frequency and gait outcomes (Chapters 7 and 8, Appendix 20.0). Visual function consisted of VA and CS.

Co-linearity statistics (Tolerance and VIF) were inspected and indicated that multi co-linearity was not a concern (all Tolerance >.30 and VIF <10), and the Durbin-Watson statistic was used to identify autocorrelation (values less than 1 and greater than 3 were identified as problematic) and indicated that data met the assumption of independent errors (Field, 2013). Standardised residuals were inspected for normality via histograms which indicated all data contained approximately normally distributed errors, as did the P-P plot of standardised residuals, which showed that points were not completely on the line but were close to it (Field, 2013).

4. *What is the relationship between saccade frequency and gait?*

Finally, to answer this question a matrix of Pearson correlation coefficients explored the relationship between saccade frequency (absolute and change scores) and gait characteristics. Trial duration was not included in this matrix to avoid Type I error, as this variable was used to derive saccade frequency (number of saccades/trial duration=saccade frequency).

7.4. Results

7.4.1. Step 1: What are the descriptive differences between PD and controls?

Participant demographic, clinical, cognitive and visual descriptors are shown in Table 7-1. PD and controls were well matched for age ($p = .605$) but were significantly different in terms of education ($p = .023$) and gender, with males being over represented in the PD group compared to controls ($p = .036$).

Surprisingly people with PD were significantly taller (p = .017) and heavier (p = .005) than controls, possibly due to increased number of males within this group. People with PD also had significantly higher rates of depression (GDS-15; p < .001) and fear of falling (FES-I; p < .001) than controls. Similarly a non-significant greater number of retrospective falls were reported by people with PD. The PD group consisted of a heterogeneous participant group (Mean disease duration, ~68 ± 72 months) who had moderate disease severity (UPDRS-III; ~37 ± 14). When comparing the global cognitive ability of the groups differences were seen in both the MoCA (p < .001) and ACE-R (p < .001), demonstrating cognitive impairment in PD compared to controls. Attention (PoA and FoA, p < .001), executive function (CLOX 1, p = .002), visuo-spatial ability (JLO, p = .029) and working memory (Digit span, p < .001) were also seen to be significantly impaired in people with PD compared to controls. Visual functions of VA (p = .005) and CS (p < .001) were significantly impaired in people with PD compared to controls.
A comprehensive account of the visual sampling characteristics employed by the PD and control participants during the various gait tasks can be seen in Table 7-2 for saccade frequency and Appendix 16.0 for other variables. There were few significantly different visual sampling characteristics between the two groups, with reduced saccade frequency and number (measured initially via independent t-tests) under dual task being the only consistent difference in PD compared to controls. However, there were non-significant differences between the groups (PD, control) for all of the visual sampling characteristics, as shown in Appendix 16.0. During the gait tasks the people with PD had non-significantly higher saccade peak velocities, peak accelerations and their fixations had longer durations than the control group. People with PD also had reduced saccade amplitude, fixation and blink number than the controls within the majority of the walking conditions.

Descriptive data for gait characteristics are shown in Table 7-3, along with results from the mixed-model ANOVAs. Figure 7-3 presents graphically the gait characteristic data used within the ANOVA analysis. Main effects for group showed that gait was impaired in PD compared to controls, regardless of task. Gait velocity was significantly impaired (p < .001), which signified that people with PD walked significantly slower than controls within all of the walking conditions.

People with PD also took significantly longer to complete the tasks (time to door; p = .009), had significantly shorter step length (p = .002) and longer double support time (p = .003) on all tasks compared to controls.

Table 7-1- Demographic, cognitive, visual and clinical characteristics

		Control (n=40) Mean (SD)	PD (n=56) Mean (SD)	*p*
Demographic	Age (years)	66.93 (10.86)	67.91 (7.78)	.605
	Sex	17M/ 23F	37M/19F	**.036†**
	Height (cm)	166.42 (10.65)	171.32 (9.03)	**.017***
	Weight (kg)	72.26 (12.62)	82.62 (19.77)	**.005***
	Education (years)	14.80 (3.03)	13.20 (3.55)	**.023***
	Depression scale (GDS-15)	0.70 (0.88)	2.66 (2.67)	**.000***
	Falls efficacy scale (FES-I)	18.98 (4.15)	24.55 (8.14)	**.000***
	Retrospective Falls (no. in 12 months)	0 (1)	1 (3)	.089
Cognition	Montreal Cognitive Assessment (MoCA)	28.45 (1.28)	26.73 (2.17)	**.000***
	Addenbrookes (ACE-R)	95.03 (4.00)	89.84 (7.16)	**.000***
Attention	Power of attention (PoA)	1266.08 (144.76)	1452.56 (269.37)	**.000***
	Fluctuation of attention (FoA)	48.22 (8.85)	59.37 (14.35)	**.000***
Executive function	Royals CLOX 1	13.60 (1.17)	12.71 (1.45)	**.002***
Visuo-spatial ability	Royals CLOX 2	13.90 (1.03)	13.46 (1.57)	.129
	Judgement of line orientation (JLO)	25.15 (4.02)	23.07 (4.85)	**.029***
	VOSP - Total	48.83 (1.28)	47.71 (3.56)	.062
	VOSP - Incomplete letters	19.43 (0.63)	19.11 (1.11)	.106
	VOSP - Dot counting	9.88 (0.34)	9.82 (0.51)	.562
	VOSP - Position Discrimination	19.53 (0.93)	18.79 (2.98)	.133
Working memory	Max Digit Span Length (sitting)	6.50 (1.01)	5.66 (1.13)	**.000***
Visual function	Visual acuity (LogMar)	-0.06 (0.13)	0.03 (0.16)	**.005***
	Contrast sensitivity (LogCS)	1.62 (0.09)	1.55 (0.14)	**.000***
Clinical	Hoehn and Yahr stage (H&Y)	-	I (21)/II (30)/III (5)	-
	Disease duration (months)	-	67.65 (72.04)	-
	UPDRS part I	-	10.77 (5.24)	-
	UPDRS part II	-	10.82 (7.26)	-
	UPDRS part III	-	36.75 (14.10)	-
	UPDRS part IV	-	2.45 (3.07)	-
	FOGQ	-	3.52 (6.24)	-
	LED	-	599.87 (402.56)	-

[*significance level p<0.05, LED= levodopa equivalent daily dosage, FOGQ = Freezing of gait questionnaire, VOSP= visual object and spatial perception battery, † = X^2]

7.4.2. <u>Step 2:</u> What is the effect of attentional manipulation on saccade frequency during gait?

The primary outcome of saccade frequency illustrates the amount of visual sampling employed by the participants during the various conditions, and descriptive data are shown in Table 7-2. Repeat measure ANOVA results (Table 7-2) showed that there were main effects for group ($p = .002$), environment ($p < .001$) and dual task ($p < .001$) on saccade frequency during gait, which are depicted in Figure 7-2. This demonstrated that controls made significantly more frequent saccades during gait than the people with PD, and saccade frequency significantly increased for both groups with greater environmental challenge (a turn) and significantly reduced with a dual task (Figure 7-2).

There was a main effect for environment on saccade frequency change score (ΔDoor and ΔTurn; $p < .001$), indicating that both groups changed their saccade frequency significantly more with a turn than with a door. There was also a trend toward significance for group by environment interaction ($p = .077$), as people with PD tended to change their saccade frequency more than controls during a single task, but less than controls during dual task (Table 7-2).

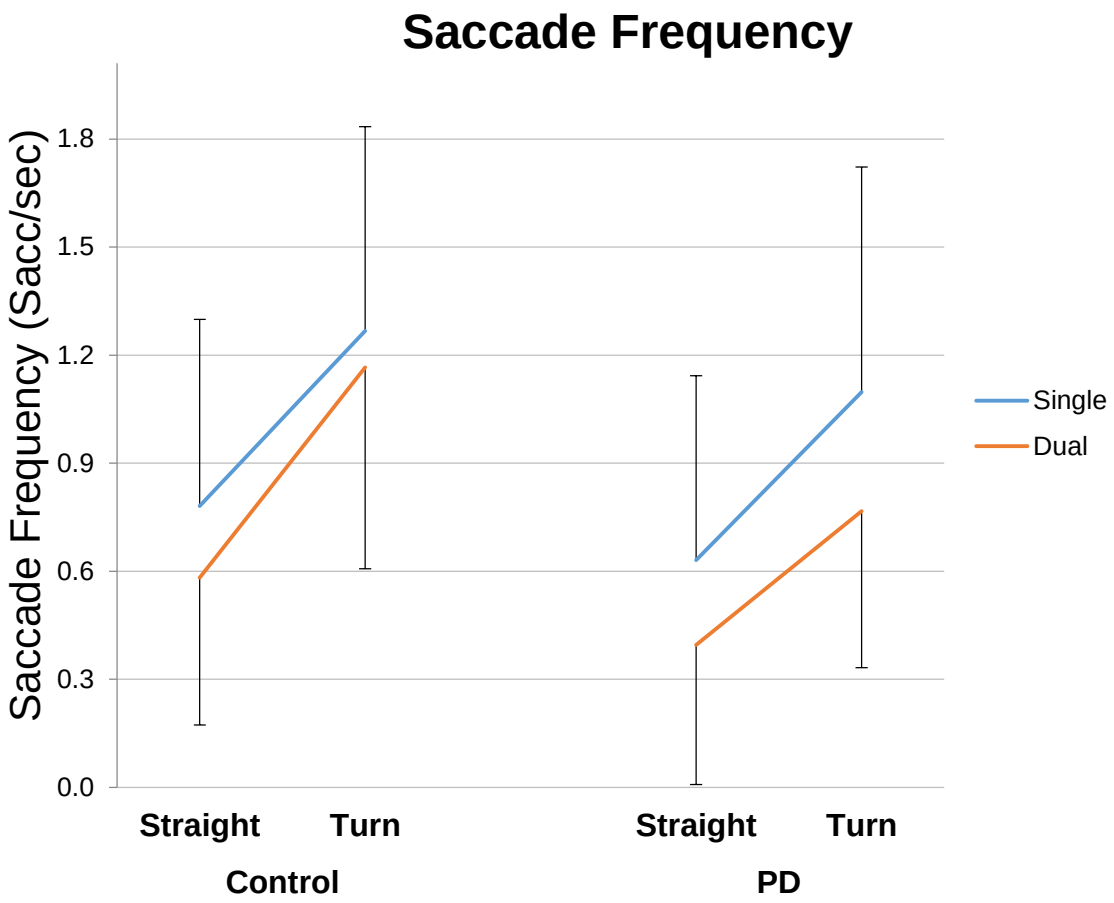


Figure 7-4 - Saccade Frequency during gait

[Straight and Turn, Single and Dual; same data as used in ANOVA, Means and SDs displayed]

Table 7-2 – Saccade frequency during gait with summary of repeat measures ANOVAs for saccade frequency and change score

Group	Attentional manipulation: Task	Attentional manipulation: Environment	Saccade Frequency (Sacc/sec) Mean (SD)
Control	Single	Straight	0.76 (0.62)
		Door	0.77 (0.57)
		Turn	1.24 (0.58)
		ΔDoor	0.14 (0.59)
		ΔTurn	0.48 (0.61)
	Dual	Straight	0.53 (0.49)
		Door	0.60 (0.42)
		Turn	1.15 (0.56)
		ΔDoor	0.07 (0.39)
		ΔTurn	0.61 (0.52)
PD	Single	Straight	**0.48 (0.54)†**
		Door	0.67 (0.61)
		Turn	1.03 (0.52)
		ΔDoor	0.19 (0.64)
		ΔTurn	0.55 (0.63)
	Dual	Straight	**0.31 (0.37)†**
		Door	**0.39 (0.39)†**
		Turn	**0.75 (0.44)†**
		ΔDoor	0.08 (0.31)
		ΔTurn	0.44 (0.37)

Effect	Saccade Frequency (Sacc/sec)		Change Score (Δsacc/sec)	
	F	***p***	**F**	***p***
Group	**9.89**	**.002***	.073	.788
Environment	**159.51**	**.000***	**113.50**	**.000***
Dual	**28.70**	**.000***	.009	.926
Group x Environment	1.72	.193	3.20	.077
Group x Dual	2.17	.144	2.62	.109
Environment x Dual	.213	.646	.392	.533
Group x Environment x Dual	2.25	.137	.035	.507

[† independent t-test PD vs controls significance level p <0.05, *significance level p<0.05, saccade, frequency was calculated from a Dikablis mobile eye-tracker (50Hz)]

7.4.3. <u>Step 3:</u> What is the effect of attentional manipulation on gait?

Table 7-3 demonstrates that there were main effects for environmental challenge on time to door (p < .001), step length (p < .001), gait velocity (p < .001), step time (p =.001) and double support time (p = .003). These results highlighted that both groups took longer (walked slower), had shorter steps, and increased step and double support time with environment challenge (i.e. more conservative gait with a turn compared to straight walking). Surprisingly both groups (PD and control) also had greater velocity and step length when walking through a door

compared to straight walking, which was the opposite effect of turning, although this was non-significant.

Main effects were also seen for dual task on time to door ($p < .001$), step length ($p < .001$), gait velocity ($p < .001$), step time ($p < .001$), single support time ($p < .001$) and double support time ($p < .001$). This indicated that both groups walked slower, had shorter steps, with increased step time, single support time and double support time under a dual task.

Of greater interest were the interactions between group, environmental challenge and dual task, which are depicted in Figure 7-5.

Group by environment interactions for step length ($p < .001$) and velocity ($p = .041$) unexpectedly demonstrated that controls had greater reduction in step length and velocity than people with PD during straight walking compared to turning. Similarly, group by dual task interactions for step length ($p = .004$), velocity ($p = .001$) and step time ($p = .045$) showed that controls had longer steps, greater velocity and shorter step time than people with PD under both single and dual task. However reduction in step length, velocity and increase in step time between the groups was larger during single task. Environment by dual task interaction for double support time ($p = .047$) and velocity ($p < .001$) indicated that for both groups a dual task made double support time longer and velocity slower when walking straight than when turning.

A three-way interaction between group, environment and dual task ($p = .030$) demonstrated that velocity was different between the groups across attentional manipulations. Figure 7-5 demonstrates that both groups significantly reduced their velocity with environmental challenge and further with a dual task, this was greater in PD on all walking conditions. Post hoc analysis (two separate repeat measures ANOVAs) revealed that although people with PD walked significantly slower which worsened under dual task, both groups reduced their velocity the same in response to environmental challenge under a dual task ($p = .317$). Whereas under single task, controls reduced their velocity significantly more than people with PD when making a turn compared to straight walking ($p = .008$), shown within Figure 7-5.

Table 7-3 - Gait characteristics with summary of mixed model ANOVAs

	Attentional manipulation		Time to Door (s)	Step Length (m)	Velocity (m/s)	Step Time (s)	Single Support Time (s)	Double Support Time (s)
Group	**Task**	**Environment**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Control	Single	Straight	2.65 (0.43)	0.69 (0.09)	1.24 (0.18)	0.55 (0.05)	0.43 (0.04)	0.26 (0.07)
		Door	2.68 (0.50)	0.70 (0.09)	1.29 (0.19)	0.54 (0.04)	0.42 (0.03)	0.27 (0.06)
		Turn	2.81 (0.48)	0.60 (0.05)	1.09 (0.15)	0.56 (0.05)	0.43 (0.04)	0.28 (0.06)
	Dual	Straight	3.04 (0.53)	0.64 (0.08)	1.07 (0.20)	0.59 (0.06)	0.45 (0.04)	0.30 (0.07)
		Door	2.87 (0.44)	0.64 (0.08)	1.12 (0.20)	0.57 (0.06)	0.43 (0.04)	0.29 (0.07)
		Turn	3.06 (0.51)	0.57 (0.07)	0.98 (0.16)	0.59 (0.06)	0.45 (0.05)	0.31 (0.06)
PD	Single	Straight	3.05 (0.60)	0.62 (0.10)	1.06 (0.19)	0.58 (0.07)	0.44 (0.05)	0.32 (0.10)
		Door	2.95 (0.59)	0.62 (0.10)	1.09 (0.20)	0.57 (0.05)	0.43 (0.05)	0.31 (0.09)
		Turn	3.15 (0.61)	0.54 (0.09)	0.95 (0.17)	0.59 (0.07)	0.43 (0.05)	0.34 (0.12)
	Dual	Straight	3.18 (0.64)	0.59 (0.09)	0.98 (0.20)	0.60 (0.09)	0.45 (0.06)	0.34 (0.10)
		Door	3.11 (0.59)	0.60 (0.09)	1.00 (0.19)	0.59 (0.07)	0.43 (0.05)	0.33 (0.08)
		Turn	3.32 (0.62)	0.53 (0.09)	0.90 (0.16)	0.61 (0.08)	0.44 (0.06)	0.34 (0.08)

Effect	**F**	***p***	**F**	***p***	**F**	***p***	**F**	***p***	**F**	***p***	**F**	***p***
Group	7.20	**.009***	9.74	**.002***	14.93	**.000***	2.87	.094	.019	.890	.197	**.003***
Environment	53.66	**.000***	240.91	**.000***	217.57	**.000***	12.02	**.001***	.040	.841	15.06	**.000***
Dual	51.09	**.000***	76.39	**.000***	98.93	**.000***	48.03	**.000***	19.23	**.000***	8.74	**.000***
Group x Environment	1.13	.290	2.38	.126	4.31	**.041***	.712	.401	3.73	.057	.748	.389
Group x Dual	3.427	.067	8.54	**.004***	12.49	**.001***	4.13	**.045***	3.54	.063	3.15	.079
Environment x Dual	.000	.985	25.83	**.000***	28.85	**.000***	2.54	.114	.887	.349	4.06	**.047***
Group x Environment x Dual	.640	.426	2.41	.124	4.85	**.030***	.027	.871	1.37	.245	1.41	.238

[*significance level p<0.05]

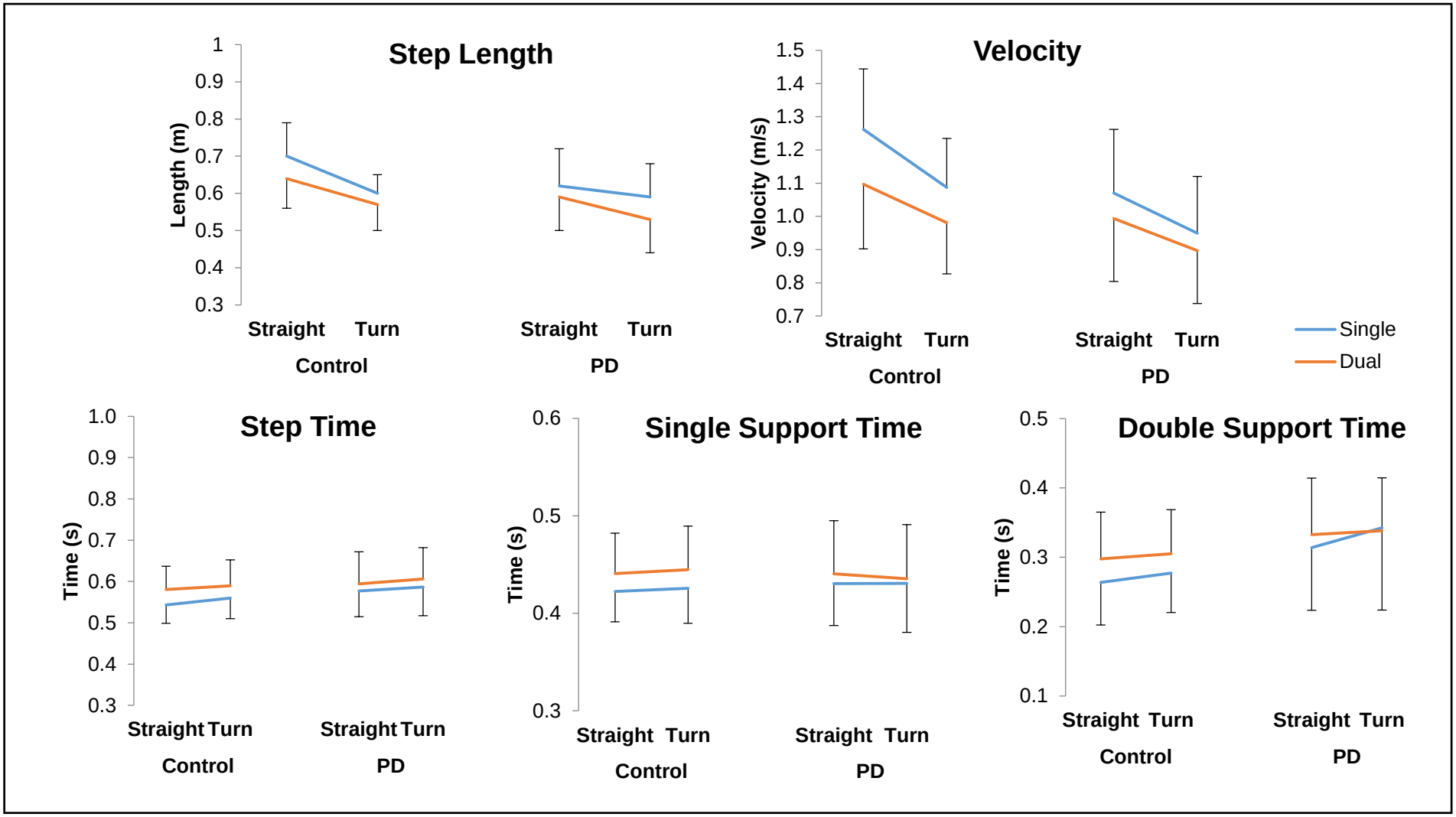


Figure 7-5 – Gait characteristics used in ANOVA analysis

[Straight = Mean(Straight, Door), Turn = Mean(Left, Right), Means and SDs are shown]

7.4.4. Step 4: What are the relationships between saccade frequency, cognition, vision and gait?

1.1 1. Relationship between cognition and vision

Correlations between cognitive and visual functions which were significantly different between PD and controls are shown in Table 7-4. Importantly for regression analysis to avoid co-linearity, none of the cognitive or visual functions entered into the models had high correlation (>0.70) (Chiulli, 1999; Field, 2013). However there were several weaker but significant correlations between these features.

In both groups (PD and control) poorer cognition was related to poorer visual function. For people with PD, poorer global cognition (ACE-R; r = .31, *p* = .022), as well as poorer specific cognitive functions of attention (PoA; r = -.44, *p* = .001 and FoA; r = -.48, *p* <.001) and visuo-spatial ability (JLO; r = .28, *p* = .035) were significantly related to worse visual functions (VA, CS). Similarly for controls, poorer working memory (Digit span; r = .32, *p* = .044) was related to poorer visual function (CS).

1.2 2: Relationship between demographics, cognition, vision and gait

Correlation between demographics, cognition, visual functions and gait characteristics (step length, velocity and double support time) for PD and controls are shown in Appendix 19.0 and 20.0. Unsurprisingly, demographic features of age, height, weight and fear of falling (FES-I) were selectively related to gait characteristics in controls. Similarly, height, disease severity (UPDRS-III), fear of falling, depression (GDS-15) and FOG severity (FOGQ) were related to gait in PD. These findings showed that poorer gait related to older age, shorter height and increased fear of falling in both groups, and that in PD greater disease severity, FOG and depression were also related. As expected, there were a number of significant associations between cognition, vision and gait in PD, but significant relationships were only evident in controls when turning or under dual task. Under single task, greater step length and velocity during all of the walking conditions in PD were significantly related to better global cognition (MoCA, ACE-R), attention (FoA) and visuo-spatial ability (JLO).

Table 7-4 - Association between cognitive and visual functions

r (*p*)	MoCA	ACE-R	PoA	FoA	CLOX 1	JLO	Digit Span	VA	CS
Controls (n = 40)									
MoCA	-								
ACE-R	**.488 (.001)***	-							
PoA	.077 (.637)	.070 (.666)	-						
FoA	-.262 (.103)	**-.323 (.042)***	**.436 (.005)***	-					
CLOX 1	.226 (.162)	**.335 (.034)***	-.242 (.133)	-.254 (.114)	-				
JLO	.016 (.920)	.253 (.115)	-.183 (.257)	.014 (.934)	**.551 (<.001)***	-			
Digit span	.257 (.109)	.269 (.094)	-.012 (.943)	-.207 (.201)	.302 (.058)	.170 (.294)	-		
VA	.039 (.812)	.006 (.970)	-.075 (.645)	-.032 (.843)	-.308 (.053)	-.105 (.518)	.020 (.901)	-	
CS	-.179 (.270)	.069 (.672)	.144 (.375)	.130 (.423)	.002 (.990)	.078 (.633)	**.321 (.044)***	**-.340 (.032)***	-
PD (n = 56)									
MoCA	-								
ACE-R	**.736 (<.001)***	-							
PoA	**-.368 (.005)***	**-.404 (.002)***	-						
FoA	**-.363 (.006)***	**-.355 (.007)***	**.696 (.000)***	-					
CLOX 1	**.398 (.002)***	**.387 (.003)***	-.249 (.065)	-.213 (.116)	-				
JLO	**.438 (.001)***	**.385 (.003)***	**-.278 (.038)***	**-.393 (.003)***	**.353 (.008)***	-			
Digit span	.184 (.174)	.121 (.374)	-.167 (.219)	-.052 (.706)	.106 (.437)	.130 (.338)	-		
VA	-.115 (.398)	-.193 (.155)	**.373 (.005)***	**.353 (.008)***	-.174 (.201)	-.246 (.068)	-.226 (.094)	-	
CS	.075 (.583)	**.305 (.022)***	**-.444 (.001)***	**-.480 (.000)***	.193 (.155)	**.282 (.035)***	.213 (.115)	**-.664 (<.001)***	-

[*significance level $p<0.05$]

1.3 3(a): Relationship between demographics, cognition, vision and saccade frequency; Correlation

A matrix of correlations between saccade frequency during gait (absolute and change scores), clinical and demographic variables for controls and PD is presented in Table 7-5. Further correlations between saccade frequency during gait (absolute and change scores), cognitive and visual variables are presented in two matrices; Table 7-6 for controls and Table 7-7 for PD. There were few significant associations for both PD and controls.

The only consistent significant association was seen in PD between attention (PoA and FoA) and single task saccade frequency change scores (ΔDoor and ΔTurn) (Table 7-7). This relationship showed that people with PD with poorer attention changed their saccade frequency less with environmental challenge than those with better attention (Table 7-7). Similar non-significant associations were found under dual task (PoA and ΔTurn; r = -.20, p = .135, FoA and ΔDoor; r = .21, p = .119). Change score results may relate to the surprising finding that poorer attention in PD was associated with more frequent saccades when walking straight under single task (PoA; r = .27, p = .049 and FoA; r = .24, p = .072). More frequent saccades in PD when walking straight were also associated with advanced age (Age; r = .28, p = .040, Table 7-5). In contrast, when walking straight through a door under single task more frequent saccades related to better executive function (CLOX 1; r = .27, p = .043).

Other associations for people with PD were found using saccade frequency change scores. Greater disease severity was associated with less change with a turn under single task (ΔTurn) (UPDRS-III; r = -.30, p = .023, Table 7-5). Under dual task relationships appeared contradictory, as greater change with a door (ΔDoor) was associated with better visuo-spatial ability (JLO and CLOX 2) whereas greater change with a turn (ΔTurn) was associated with poorer working memory (Digit span; r = -.33, p = .013).

For controls, Tables 7-5 and 7-6 show that more frequent saccades during single task turns were significantly associated with younger age (Age; r = -.38, p = .017) and better attention (PoA; r = -.34, p = .032). During dual task more frequent

saccades were related to better cognition (ACE-R; r = -.32, *p* = .045) during turns and lower depression rate (GDS-15; r = -.32, *p* = .045) during straight walking.

Table 7-5 – Demographic and clinical correlations with saccade frequency in controls and Parkinson's disease

r (*p*)	Attentional manipulation		Demographic			Clinical			
Group	Task	Environment	Age	GDS-15	FES-I	UPDRS III	FOGQ	LED	PD duration
Control	Single	Straight	-.063 (.699)	.070 (.667)	-.161 (.321)	-	-	-	-
		Door	-.189 (.243)	.065 (.690)	-.125 (.443)	-	-	-	-
		Turn	**-.375 (.017)***	-.166 (.307)	-.210 (.193)	-	-	-	-
		ΔDoor	-.118 (.468)	-.011 (.946)	.049 (.765)	-	-	-	-
		ΔTurn	-.294 (.066)	-.230 (.153)	-.036 (.823)	-	-	-	-
	Dual	Straight	-.086 (.596)	**-.319 (.045)***	-.066 (.684)	-	-	-	-
		Door	-.099 (.542)	-.100 (.539)	-.048 (.767)	-	-	-	-
		Turn	-.131 (.420)	-.123 (.450)	-.068 (.678)	-	-	-	-
		ΔDoor	.001 (.995)	.292 (.067)	.031 (.849)	-	-	-	-
		ΔTurn	-.061 (.709)	.164 (.310)	-.011 (.946)	-	-	-	-
PD	Single	Straight	**.275 (.040)***	-.044 (.747)	-.182 (.180)	.226 (.093)	-.118 (.388)	-.161 (.250)	-.049 (.721)
		Door	-.012 (.928)	-.033 (.808)	.036 (.791)	.052 (.704)	-.071 (.604)	-.121 (.388)	-.019 (.890)
		Turn	.079 (.564)	-.178 (.189)	-.146 (.283)	-.130 (.341)	-.071 (.605)	-.136 (.332)	-.028 (.837)
		ΔDoor	-.245 (.068)	.006 (.965)	.188 (.164)	-.143 (.293)	.033 (.810)	.030 (.834)	.024 (.863)
		ΔTurn	-.173 (.202)	-.109 (.423)	.036 (.791)	**-.303 (.023)***	.043 (.751)	.026 (.853)	.019 (.890)
	Dual	Straight	.140 (.303)	-.119 (.381)	.044 (.748)	.240 (.075)	.030 (.825)	.109 (.436)	.000 (1.00)
		Door	.034 (.801)	-.038 (.781)	-.049 (.720)	.261 (.052)	.038 (.783)	-.022 (.878)	.043 (.753)
		Turn	.118 (.388)	-.003 (.980)	-.060 (.662)	.098 (.473)	.030 (.825)	-.087 (.535)	-.111 (.415)
		ΔDoor	-.124 (.362)	.095 (.487)	-.114 (.404)	.041 (.764)	.011 (.936)	-.157 (.260)	.054 (.694)
		ΔTurn	-.003 (.982)	.116 (.393)	-.114 (.401)	-.127 (.351)	.005 (.971)	-.214 (.124)	-.131 (.337)

[*significance level p < 0.05]

Table 7-6 – Cognitive and visual function correlations with saccade frequency in controls

r (*p*)	Attentional manipulation		Cognition									Visual function	
Group	**Task**	**Environment**	**MoCA**	**ACE-R**	**PoA**	**FoA**	**JLO**	**CLOX 1**	**CLOX 2**	**VOSP-Total**	**Digit span**	**VA**	**CS**
Control	Single	Straight	.182 (.261)	.137 (.399)	-.085 (.603)	.039 (.810)	-.051 (.753)	.095 (.560)	-.081 (.619)	-.162 (.319)	-.062 (.705)	-.096 (.555)	.001 (.995)
		Door	.049 (.764)	.055 (.736)	.015 (.927)	.004 (.980)	-.210 (.193)	-.056 (.731)	-.029 (.861)	-.036 (.826)	-.023 (.889)	.016 (.920)	-.075 (.644)
		Turn	-.023 (.889)	.113 (.488)	**-.340 (.032)***	-.065 (.691)	.151 (.351)	.273 (.089)	.151 (.352)	.132 (.417)	.031 (.847)	-.288 (.071)	.111 (.495)
		ΔDoor	-.145 (.371)	-.092 (.574)	.105 (.521)	-.038 (.818)	-.151 (.351)	-.156 (.337)	.058 (.723)	.136 (.402)	.043 (.792)	.118 (.468)	-.075 (.647)
		ΔTurn	-.208 (.199)	-.032 (.845)	-.239 (.138)	-.102 (.531)	.197 (.223)	.164 (.313)	.227 (.159)	.291 (.068)	.093 (.568)	-.177 (.273)	.105 (.518)
	Dual	Straight	.134 (.411)	.239 (.137)	.029 (.861)	-.035 (.832)	-.044 (.788)	.092 (.573)	.045 (.785)	-.051 (.754)	-.112 (.492)	.211 (.191)	-.244 (.129)
		Door	-.014 (.930)	.082 (.614)	.067 (.680)	.126 (.438)	-.023 (.889)	.005 (.976)	.138 (.396)	.223 (.166)	-.269 (.094)	.124 (.447)	-.168 (.301)
		Turn	.016 (.923)	**.319 (.045)***	-.253 (.115)	-.187 (.247)	.121 (.457)	.216 (.181)	.124 (.447)	.124 (.444)	-.151 (.352)	.081 (.619)	-.146 (.369)
		ΔDoor	-.183 (.258)	-.212 (.190)	.037 (.821)	.180 (.267)	.031 (.852)	-.110 (.499)	.093 (.567)	.305 (.055)	-.150 (.355)	-.131 (.420)	.125 (.443)
		ΔTurn	-.107 (.510)	.121 (.457)	-.299 (.061)	-.169 (.296)	.171 (.291)	.147 (.365)	.092 (.573)	.182 (.262)	-.059 (.717)	-.109 (.504)	.070 (.669)

[*significance level p < 0.05]

Table 7-7 – Cognitive and visual function correlations with saccade frequency in Parkinson's disease

r (*p*)	Attentional manipulation		Cognition									Visual function	
Group	**Task**	**Environment**	**MoCA**	**ACE-R**	**PoA**	**FoA**	**JLO**	**CLOX 1**	**CLOX 2**	**VOSP-Total**	**Digit span**	**VA**	**CS**
PD	Single	Straight	-.093 (.493)	-.077 (.571)	**.265 (.049)***	.259 (.054)	-.030 (.825)	.046 (.735)	-.032 (.816)	-.059 (.668)	-.039 (.775)	.042 (.757)	-.016 (.907)
		Door	.052 (.703)	.104 (.447)	-.057 (.675)	-.149 (.273)	.029 (.831)	**.271 (.043)***	.116 (.395)	.124 (.364)	-.007 (.959)	-.136 (.319)	.086 (.528)
		Turn	-.068 (.620)	-.130 (.339)	-.052 (.706)	-.113 (.406)	.026 (.850)	.023 (.864)	.053 (.697)	.002 (.990)	-.241 (.073)	.020 (.881)	.015 (.915)
		ΔDoor	.128 (.345)	.164 (.228)	**-.278 (.038)***	**-.361 (.006)***	.053 (.697)	.217 (.108)	.136 (.316)	.166 (.220)	.026 (.847)	-.164 (.227)	.095 (.486)
		ΔTurn	.025 (.857)	-.041 (.765)	**-.271 (.043)***	**-.318 (.017)***	.047 (.729)	-.021 (.880)	.072 (.600)	.052 (.703)	-.166 (.221)	-.020 (.886)	.026 (.849)
	Dual	Straight	-.188 (.166)	-.203 (.133)	.151 (.266)	.090 (.511)	-.197 (.146)	-.119 (.381)	-.161 (.237)	-.061 (.658)	.113 (.406)	.017 (.903)	-.039 (.776)
		Door	-.005 (.974)	-.001 (.994)	.051 (.711)	-.094 (.489)	.035 (.799)	.023 (.868)	.064 (.639)	-.091 (.504)	-.045 (.739)	-.086 (.529)	.088 (.520)
		Turn	.007 (.958)	-.110 (.420)	.067 (.625)	-.091 (.506)	-.061 (.656)	-.093 (.494)	-.017 (.902)	-.062 (.648)	-.185 (.173)	.152 (.263)	-.066 (.630)
		ΔDoor	.218 (.106)	.241 (.074)	-.117 (.392)	-.225 (.095)	**.278 (.038)***	.171 (.208)	**.272 (.043)***	-.042 (.758)	-.192 (.156)	-.127 (.349)	.156 (.250)
		ΔTurn	.198 (.144)	.076 (.578)	-.074 (.587)	-.194 (.145)	.127 (.350)	.011 (.937)	.142 (.295)	-.012 (.929)	**-.332 (.013)***	.162 (.233)	-.038 (.781)

[*significance level p < 0.05]

1.4 3(b): Relationship between demographics, cognition, vision and saccade frequency; Regression

A series of multivariate regression models were used to further investigate saccade frequency during gait in PD and controls. Model characteristics (Beta coefficients and *p*-values) under single and dual task are shown in Table 7-8 for controls and Table 7-9 for PD. The focus of this analysis was the exploration of independent associations between demographic, cognitive and visual variables and saccade frequency during gait. Overall model characteristics (r^2, ANOVA *F and p*) were not the focus of this analysis and were not significant for any of the models; hence they are presented in the Appendix 21.0.

Table 7-8 demonstrates that there were no significant associations within the final regression models (Model 4) for controls. Although under dual task greater depression (GDS-15; Model 4; ΔDoor, ß = .31, *p* = .075) trended towards significant association with increased saccade frequency change score within all of the models (Models 1 to 4). Similarly, older age was related to lower saccade frequency change score (ΔTurn; ß = -.31, *p* = .050) within the single task demographic model (Model 1) for controls, but association reduced once cognitive or visual functions were added into the model. This indicated that cognitive and visual functions may mediate age association with saccade frequency in controls.

By contrast, people with PD had several significant independent explanatory variables under single task. For example; poorer attention (FoA) was related to lower saccade frequency change scores (ΔDoor; ß = -.45, *p* = .009 and ΔTurn; ß = -.36, *p* = .041). There was also a trend for visual function association with saccade frequency (ΔDoor; ß = -.37, *p* = .089). Under dual task however there were very few significant relationships in PD, as only one condition (∆Turn) had a significant association within the final model (Model 4, Table 7-9). Better working memory (Digit span) was related to lower saccade frequency change scores (ΔDoor; ß = -.28, *p* = .055, ∆Turn ß = -.34, *p* = .018), which was present within the separate cognition model (Model 2) and weakened once visual functions were entered into the model (Model 4). Increased disease severity (UPDRS-III) trended towards association with greater saccade frequency change score under

dual task (ΔDoor; Model 4; ß = .33, p = .074), but association was reduced when visual and cognitive functions were entered into the model together (Model 4).

Overall, attention (FoA) was the only explanatory variable consistently associated with saccade frequency change scores in PD under single task (ΔDoor, ΔTurn, Table 7-9), independent of demographic characteristics. Attention however was not significantly associated with saccade frequency change scores (ΔDoor, ΔTurn) within the separate cognition model (Models 2). Only once cognitive and visual functions were both added to the model (Model 4) were significant relationships seen.

Table 7-8 - Demographic, cognitive and visual function association with saccade frequency for controls

			Pearsons	Model 1		Model 2		Model 3		Model 4	
Task	**Visual sampling**		**r (*p*)**	**ß**	***p***	**ß**	***p***	**ß**	***p***	**ß**	***p***
Single	ΔDoor	Age	-.118 (.468)	-.139	.405	-.197	.335	-.193	.281	-.259	.248
		MoCA	-.145 (.371)	-.163	.329	-.169	.356	-.186	.279	-.210	.275
		GDS-15	-.011 (.946)	.005	.974	-.020	.907	.008	.960	-.021	.904
		FoA	-.038 (.818)			.014	.945			.077	.731
		JLO	-.151 (.351)			-.154	.479			-.179	.429
		CLOX 1	-.156 (.337)			-.120	.589			-.074	.765
		Digit span	.043 (.792)			.129	.483			.174	.410
		VA	.118 (.468)					.164	.382	.118	.591
		CS	-.075 (.647)					-.057	.753	-.129	.544
	ΔTurn	Age	-.294 (.066)	-.308	.050	-.279	.146	-.286	.090	-.253	.234
		MoCA	-.208 (.199)	-.240	.122	-.281	.105	-.228	.159	-.277	.132
		GDS-15	-.230 (.153)	-.198	.299	-.295	.231	-.200	.206	-.193	.249
		FoA	-.102 (.531)			.025	.900			.006	.978
		JLO	.197 (.223)			.037	.854			.052	.807
		CLOX 1	.164 (.313)			.100	.627			.071	.764
		Digit span	.093 (.568)			.106	.536			.115	.566
		VA	-.177 (.273)					-.064	.713	-.064	.757
		CS	.105 (.518)					.042	.805	-.009	.966
Dual	ΔDoor	Age	-.118 (.468)	-.049	.760	-.113	.563	-.012	.945	-.057	.790
		MoCA	-.145 (.371)	-.199	.214	-.127	.469	-.182	.273	-.099	.593
		GDS-15	-.011 (.946)	.303	.061	.308	.070	.300	.069	.310	.075
		FoA	-.038 (.818)			.128	.528			.076	.723
		JLO	-.151 (.351)			-.116	.577			-.141	.518
		CLOX 1	-.156 (.337)			-.097	.649			-.144	.550
		Digit span	.043 (.792)			-.104	.555			-.129	.527
		VA	.118 (.468)					-.111	.537	-.114	.591
		CS	-.075 (.647)					.047	.788	.080	.697
	ΔTurn	Age	-.294 (.066)	-.091	.585	.095	.627	-.064	.721	.145	.504
		MoCA	-.208 (.199)	-.124	.454	-.163	.358	-.115	.506	-.135	.471
		GDS-15	-.230 (.153)	.176	.289	.222	.190	.175	.304	.223	.198
		FoA	-.102 (.531)			-.291	.159			-.339	.126
		JLO	.197 (.223)			.216	.306			.237	.285
		CLOX 1	.164 (.313)			.064	.765			.025	.919
		Digit span	.093 (.568)			-.128	.472			-.157	.447
		VA	-.177 (.273)					-.084	.656	-.098	.646
		CS	.105 (.518)					.015	.935	.086	.679

[*significance level *p*<.05, Model 1 = demographic, Model 2 = cognition, Model 3 = visual function, Model 4 = cognition and visual function, Model performance can be found in the Appendix]

Table 7-9 - Demographic, cognitive and visual function association with saccade frequency for Parkinson's disease

			Pearsons	Model 1		Model 2		Model 3		Model 4	
Task	**Visual sampling**		**r (*p*)**	**ß**	***p***	**ß**	***p***	**ß**	***p***	**ß**	***p***
Single	ΔDoor	Age	-.245 (.068)	-.233	.114	-.122	.420	-.271	.109	-.244	.156
		UPDRS III	-.143 (.293)	-.094	.581	-.045	.806	-.119	.492	-.061	.737
		MoCA	.128 (.345)	.039	.806	-.083	.634	.008	.959	-.166	.358
		GDS-15	.006 (.965)	-.017	.915	.044	.785	-.032	.841	.019	.906
		FoA	**-.361 (.006)***			-.367	**.022***			-.449	**.009***
		JLO	.053 (.697)			-.140	.376			-.096	.550
		CLOX 1	.217 (.108)			.213	.194			.220	.177
		Digit span	.026 (.847)			.015	.914			.049	.725
		VA	-.164 (.227)					-.203	.276	-.182	.310
		CS	.095 (.486)					-.191	.352	-.365	.089
	ΔTurn	Age	-.173 (.202)	-.053	.717	-.021	.893	-.262	.108	-.154	.382
		UPDRS III	**-.303 (.023)***	-.317	.064	-.216	.255	-.393	**.022***	-.210	.268
		MoCA	.025 (.857)	-.167	.289	-.202	.265	-.216	.168	-.280	.137
		GDS-15	-.109 (.423)	-.020	.896	-.049	.769	-.056	.711	-.059	.724
		FoA	**-.318 (.017)***			-.249	.124			-.359	**.041***
		JLO	.047 (.729)			.028	.863			.092	.580
		CLOX 1	-.021 (.880)			.015	.931			.028	.868
		Digit span	-.166 (.221)			-.111	.432			-.043	.767
		VA	-.020 (.886)					-.079	.657	.071	.699
		CS	.026 (.849)					-.206	.298	-.255	.246
Dual	ΔDoor	Age	-.124 (.362)	-.078	.592	-.080	.587	.009	.956	-.029	.865
		UPDRS III	.041 (.764)	.179	.289	.333	.067	.317	.052	.333	.074
		MoCA	.218 (.106)	.298	.061	.244	.157	.209	.229	.275	.134
		GDS-15	.095 (.487)	.041	.790	-.058	.713	.052	.740	-.053	.744
		FoA	-.225 (.095)			-.200	.192			-.160	.341
		JLO	**.278 (.038)***			.257	.100			.234	.151
		CLOX 1	.171 (.208)			-.027	.866			-.031	.846
		Digit span	-.192 (.156)			-.254	.062			-.277	.055
		VA	-.127 (.349)					.019	.918	-.002	.990
		CS	.156 (.250)					.186	.362	.112	.600
	ΔTurn	Age	-.003 (.982)	.101	.488	.100	.503	.098	.551	.106	.533
		UPDRS III	-.127 (.351)	-.133	.432	-.037	.837	-.116	.499	-.015	.936
		MoCA	.198 (.144)	.177	.263	.233	.179	.208	.193	.249	.169
		GDS-15	.116 (.393)	.217	.168	.125	.433	.231	.141	.142	.377
		FoA	-.194 (.145)			-.150	.328			-.164	.325
		JLO	.127 (.350)			.041	.792			.052	.745
		CLOX 1	.011 (.937)			-.054	.737			-.049	.759
		Digit span	**-.332 (.013)***			-.368	**.008***			-.343	**.018***
		VA	.162 (.233)					.287	.120	.247	.169
		CS	-.038 (.781)					.156	.441	.146	.488

[*significance level *p*<.05, Model 1 = demographic, Model 2 = cognition, Model 3 = visual function, Model 4 = cognition and visual function, Model performance can be found in the Appendix]

1.5 4: Relationship between saccade frequency and gait

The matrix of correlations between saccade frequency (absolute and change scores) and gait characteristics are presented in Table 7-10, showing that there were no significant relationships between saccade frequency and any of the gait characteristics in PD. In contrast, more frequent saccades during turns were weakly but significantly associated with greater step length (r = .33, p = .038) and velocity (r = .35, p = .026) in controls, which indicated relationship between saccade frequency and gait in older adults. However there was a similar trend in PD for saccade frequency change score (ΔDoor) towards association with dual task step length (r = .26, *p* = .055) and velocity (r = .25, *p* = .069) when walking through a door. This trend demonstrated that similar to controls, people with PD who made more frequent saccades when walking through a doorway in comparison to straight walking, had better gait under this condition.

Table 7-10 - Correlations between saccade frequency during gait and gait characteristics in Parkinson's disease and controls

Group	Attentional manipulation		Step Length (m)	Velocity (m/s)	Step Time (s)	Single support (s)	Double support (s)
	Task	Environment	r (*p*)	r (*p*)	r (*p*)	r (*p*)	r (*p*)
Control	Single	Straight	-.074 (.648)	.046 (.777)	-.188 (.245)	-.209 (.196)	-.076 (.642)
		Door	.107 (.510)	.116 (.477)	-.043 (.791)	-.102 (.532)	-.014 (.931)
		Turn	.308 (.053)	**.351 (.026)***	-.184 (.256)	-.070 (.666)	-.133 (.412)
		ΔDoor	.200 (.215)	.109 (.502)	.154 (.342)	.056 (.731)	.045 (.783)
		ΔTurn	.312 (.050)	.228 (.157)	.055 (.737)	.149 (.358)	-.061 (.709)
	Dual	Straight	-.209 (.197)	-.176 (.276)	.107 (.511)	.066 (.688)	.103 (.527)
		Door	-.064 (.697)	-.042 (.798)	-.007 (.967)	.024 (.881)	.033 (.840)
		Turn	**.329 (.038)***	.295 (.064)	-.201 (.213)	-.182 (.260)	-.091 (.578)
		ΔDoor	.115 (.479)	.168 (.300)	-.141 (.384)	-.112 (.490)	-.140 (.390)
		ΔTurn	.299 (.061)	.296 (.063)	-.174 (.282)	-.153 (.347)	-.124 (.445)
PD	Single	Straight	-.049 (.718)	-.041 (.763)	-.036 (.790)	.015 (.913)	.000 (.999)
		Door	-.039 (.775)	-.007 (.962)	-.066 (.628)	-.080 (.560)	.021 (.879)
		Turn	.042 (.761)	.140 (.304)	-.179 (.192)	-0.50 (.717)	-.068 (.621)
		ΔDoor	-.020 (.885)	-.018 (.893)	-.014 (.918)	-.043 (.754)	.054 (.693)
		ΔTurn	.112 (.412)	.091 (.504)	-.002 (.986)	-.015 (.913)	.064 (.643)
	Dual	Straight	-.118 (.385)	-.044 (.746)	-.090 (.508)	-.151 (.267)	-.020 (.884)
		Door	.051 (.708)	.093 (.496)	-.126 (.355)	-.164 (.266)	.017 (.899)
		Turn	.029 (.830)	.143 (.292)	-.206 (.132)	-.160 (.245)	-.105 (.447)
		ΔDoor	.258 (.055)	.245 (.069)	-.040 (.770)	.002 (.990)	-.055 (.688)
		ΔTurn	.128 (.348)	.208 (.125)	-.109 (.429)	.002 (.988)	-.145 (.290)

[Gait characteristics from each individual task were correlated with saccade frequency from the same task, change scores were correlated with gait characteristics during the attentional task (door or turn)]

7.5. Discussion

The primary aim of this study was to investigate saccade frequency during gait in PD under different attentional manipulations common to real-world gait (environmental challenge and dual task). The results support the hypothesis that saccade frequency during gait is impaired (reduced) in PD compared to age-matched controls and is influenced by attention.

Descriptive data showed that regardless of attentional manipulation people with PD made less frequent saccades during gait compared to controls. This may be due to impairment of voluntary saccade initiation related to limited dopaminergic resource (van Stockum *et al.*, 2011b) and greater cognitive burden of gait in PD (Seidler *et al.*, 2010; Shine *et al.*, 2013a). People with PD also walked significantly slower, with shorter steps and increased double support time than controls within all walking conditions. This was expected as it is widely acknowledged that people with PD present with gait impairment compared to controls, including reduced step length and gait velocity which worsen with attentional manipulation (Lord *et al.*, 2010; Lord *et al.*, 2014). Less frequent saccades during gait likely contributed to gait deficit as saccades are critical to safe and effective walking, aligning areas of interest in the environment (e.g. hazards) with the fovea to produce high quality visual information for further cognitive processing (Beserra Gomes *et al.*, 2013; Bodis-Wollner, 2013; Bodis-Wollner *et al.*, 2013).

Descriptive results also showed that there was a significant reduction in saccade frequency during walking without attentional manipulation in people with PD compared to controls, which has not been seen in previous research (Galna *et al.*, 2012; Vitorio *et al.*, 2012). Previous studies have reported that visual sampling (saccade frequency (Galna *et al.*, 2012) or frequency of voluntary visual samples made via manipulation of liquid crystal glasses rather than saccades (Vitorio *et al.*, 2012)) during straight walking was not different between people with PD and controls, despite non-significant reductions within their studies which were likely due to the small cohorts involved. However Galna *et al.* (2012) alluded to the fact that online saccade deficits in PD may be highlighted with attentional manipulation, which was further investigated within the current study.

7.5.1. What is the effect of environmental challenge on saccade frequency during gait?

Despite people with PD making less frequent saccades than controls during all walking conditions, both groups increased their saccade frequency in response to increased environmental challenge (Door, Turn), which was consistent with previous literature (Galna *et al.*, 2012). Galna *et al.* (2012) previously demonstrated a non-significant increase in horizontal saccade frequency when turning in a small group of people with PD. However unlike the current study, Galna *et al.* (2012) were limited to reporting only horizontal saccades due to the EOG technology used to monitor eye-movements when walking, which limits generalisability of results. Methodological differences also limit comparison to other studies, although as mentioned in chapter 3 several turning in place studies have demonstrated that saccade frequency was increased in PD compared to controls (Anastasopoulos *et al.*, 2011; Lohnes and Earhart, 2011). Increase in saccade frequency with external environmental stimuli (Door, Turn) may relate to more reflexive (bottom-up attention) saccades being made. Indeed, previous research has alluded to people with PD making saccades later than controls when walking through doorways (i.e. last 30% of the trial when walking through a doorway) (Galna *et al.*, 2012), which is likely due to greater amount of reflexive saccades occurring when stimulus (a doorway) were in peripheral view. Reflexive saccades are known to occur with greater peak velocity than voluntary saccades, as shown via pro- and anti-saccade tasks (Reingold and Stampe, 2002). Within this study there was a non-significant increase in saccade peak velocities with the addition of environmental stimuli (Door) for both people with PD and controls, likely due to an increased number of reflexive saccades which are relatively spared in PD (primarily early PD) (Terao *et al.*, 2013). This is further supported by increased saccade velocities and accelerations for people with PD compared to controls when performing a dual task, as with distraction of attention people with PD likely cannot inhibit reflexive saccades as well as controls (Terao *et al.*, 2011).

7.5.2. What is the effect of a dual task on saccade frequency during gait?

Saccade frequency reduced for both people with PD and controls under a dual task during all of the walking trials. However saccade frequency was significantly reduced in people with PD compared to controls under dual task, which was similar to previous research (Galna *et al.*, 2012). In contrast, control participants were able to maintain their saccade frequency under a dual task better than people with PD, particularly within the most complex walking condition (turning under dual task; Figure 7-4). Reduction under dual task suggests that cognitive, particularly attentional processes underpin saccade frequency during gait which is comparable to previous saccadic control research (Hoffman and Subramaniam, 1995). For example; saccadic impairment under dual task has been found before in static testing involving simple motor tasks such as reaching (Pashler *et al.*, 1993) or button pressing (Huestegge and Koch, 2009), with interference in saccade planning by competing task (i.e. gait) goals implicated (Moehler and Fiehler, 2014).

Dual task gait performance has been linked to attentional processes involving the PFC (Rochester *et al.*, 2014) and is limited by neural resource availability. Attentional saccadic control also involves the PFC and its complex interaction with the BG and brain stem (Chan *et al.*, 2005; Le Heron *et al.*, 2005; Hood *et al.*, 2007; Matsumoto *et al.*, 2011; Javaid *et al.*, 2012; Matsumoto *et al.*, 2012), with brain stem saccade mechanisms reportedly unaffected in PD (Gorges *et al.*, 2014). As mentioned in Chapter 2 (section 2.4), attentional projections from the PFC control the BGs inhibition or disinhibition of the SC (Terao *et al.*, 2011), however BG impairment with PD impacts cortico-BG loops (Tommasi *et al.*, 2015) which control voluntary saccade initiation. Voluntary saccade initiation is further impaired by dopamine depletion within the striatum with PD which reduces PFC signal to the BG (Tommasi *et al.*, 2015).

Overall, performance of a dual task likely saturates attentional capacity in PD (Galna *et al.*, 2012) due to the limited neural resources available and preferential allocation of resource to gait control (Lee *et al.*, 2003) or the secondary cognitive task rather than saccadic control. In the absence of attentional inhibitory control

(from PFC) under dual task, parietal cortical loops involved in bottom-up attention would dominate saccade generation (N'Guyen *et al.*, 2014) and lead to increased reflexive saccades. However not all saccades under dual task would be reflexive, as fluctuation between top-down and bottom-up attentional control is most plausible during gait in PD due to 'leaky' BG inhibitory control of saccades (Terao *et al.*, 2011). For example; fluctuation in the level of BG inhibition on the SC would mean that suppression of reflexive saccades would work occasionally, but not consistently.

7.5.3. What is the effect of attentional manipulation on gait?

Attentional manipulation via increased environmental challenge also influenced gait. Gait impairments with environmental challenge in both PD and controls were similar to previous research, with reduced step length and velocity (Cowie *et al.*, 2010; Cowie *et al.*, 2012), and increased step time and double support time (Lebold and Almeida, 2010; Pieruccini-Faria *et al.*, 2014). A surprising result was that under single task controls slowed their gait and reduced their step length more than people with PD during a turn compared to straight walking, which may signify that people with PD are unable to modify their gait appropriately compared to controls with increased environmental challenge.

Another unexpected result was the non-significant increase in step length and velocity that was seen within both groups while walking through a doorway, which differed from previous research (Cowie *et al.*, 2010; Cowie *et al.*, 2012; Ehgoetz Martens *et al.*, 2013). Disparity between the current study and previous literature may relate to a learning effect, as to ensure participants could complete the walks safely straight walks were always conducted first followed by randomised walking with a turn or door. An alternative explanation could be that previous studies have focused on small cohorts of freezers (Almeida and Lebold, 2010; Cowie *et al.*, 2010; Cowie *et al.*, 2012; Ehgoetz Martens *et al.*, 2013) rather than the large heterogeneous PD group involved in this study. People with PD and FOG often report that freezing episodes (shortened steps etc.) occur in narrow spaces such as doorways (Ehgoetz Martens *et al.*, 2013), likely due to further impairment of cortico-BG loops (Muralidharan *et al.*, 2013), fronto-parietal pathway (visual attention) disruption (van der Hoorn *et al.*, 2014; Walton *et al.*, 2015) and

impaired visuo-spatial processing (Lord *et al.*, 2012) within this group. Although this study involved several people with PD who reported FOG, none experienced any freezing episodes during testing and this disease phenomenon was not the focus of the current study, but it may warrant future investigation.

Attentional manipulation via a dual task impacted gait in PD and older adults similar to previous studies, with reduced step length and velocity, and increased step time, single and double support time seen in both groups (Canning, 2005; Hausdorff *et al.*, 2008; Beurskens and Bock, 2012; Kelly *et al.*, 2012b). The dual task modulation of gait characteristics was expected due to the extensive evidence linking high level cognitive functions (executive, attentional, working memory function) and gait, particularly in PD (Chapter 2, section 2.4.2). Of greater interest were the interactions between group, environment, and dual task, which showed selective impairments in both groups dependent upon the walking condition. Both groups reduced their velocity under dual task with greater reduction in controls, whereas environmental challenge selectively altered velocity within the groups. For example; controls reduced their velocity more under dual task when walking straight than with a turn, whereas people with PD reduced their velocity under dual task similarly within both environments (Door, Turn). This response was probably due to people with PD already walking slower than controls during single task, which limited the reduction seen under dual task. However, it could relate to an inability to adjust gait appropriately in PD in response to a dual task, as the degree to which people with PD can modify their gait with a dual task remains unclear (Kelly *et al.*, 2012b). Overall, different patterns of gait alteration were seen with different attentional manipulation within the groups, with people with PD perhaps not modifying gait appropriately for the task undertaken. This suggests that underlying processes may vary dependent on the visuo-cognitive demands of the task.

7.5.4. What are the relationships between demographics, cognition, vision and gait?

Gait impairments in PD compared to controls (reduced step length, velocity and increased double support time) were associated with selective demographic features, and visual and cognitive functions, which are shown in Appendix 19.0

and 20.0. Associations with demographic variables such as age and disease severity were expected, but previous research has shown that cognition influences gait in PD independent of these features (Lord *et al.*, 2014). Within PD, impaired global cognition, attention (particularly FoA) and visuo-spatial ability were significantly related to reduced step length and velocity within all walking conditions. Increased double support time was also associated with deficits in visual functions (VA and CS) in PD. These associations were expected due to the robust relationship between gait and cognition (Rochester *et al.*, 2004; Ble *et al.*, 2005; Rochester *et al.*, 2005; Yogev *et al.*, 2005; Holtzer *et al.*, 2006; Verghese *et al.*, 2007a; Verghese *et al.*, 2007b; Iersel *et al.*, 2008; Rochester *et al.*, 2008; Soumare *et al.*, 2009; Lord *et al.*, 2010) and the increasing evidence for the role of vision in gait in PD and older adults (Wood *et al.*, 2009). However previous studies have not considered that vision and cognition may interact during gait or that they may have visuo-cognitive impact on gait control.

As hypothesised within the introduction, cognitive and visual functions were significantly related in both groups (PD and control), similar to previous static research (Bodis-Wollner and Jo, 2006; Antal *et al.*, 2008; Cavanagh, 2011). In fact, stronger relationships between cognitive and visual functions were found in PD, particularly between attention (PoA and FoA) and visual functions (VA and CS). This may reflect attentional compensation for static visual deficits such as impaired VA and CS, and could help to explain the increased attentional and visual connectivity found in PD (Onu *et al.*, 2015). Attentional compensation may also be required for visual function impairment during gait, as association between visual functions (VA and CS) and double support time disappeared under attentional dual task in PD (Appendix 20.0). This associative evidence highlights the known separate relationships between vision, cognition and gait in PD, but also provides some limited insight into visuo-cognitive interactions that may occur during gait.

7.5.5. What are the relationships between demographics, cognition, vision and saccade frequency?

As mentioned, saccades have known links to cognitive and visual processes. Surprisingly associations between saccade frequency (absolute and change

scores) and demographic, clinical, cognitive and visual functions demonstrated few significant findings within PD and controls. Further regression analysis also showed that within controls there were no significant associations between these features and saccade frequency (change scores). Lack of association may relate to the cognitive profile of each cohort, as this study involved a cognitively 'normal' (MoCA ≥ 26) control group and a large heterogeneous group of non-demented people with PD (MoCA ≥ 21, Table 7-1). Despite the PD group having saccade frequency impairment during gait, over the disease course PD likely impacts processes underlying saccades differently. This may have limited association interpretation due to the inclusion of people with PD at different stages of the disease, future studies may control for this with specific disease duration inclusion criteria such as use of an incident cohort. Another explanation would be that saccade frequency during gait may be driven by processes (attention or visual processing) too subtle to be noted within traditional standardised cognitive or visual function assessments.

Irrespective of the limited number of significant associations, cognitive functions (primarily attention) were significantly related to saccade frequency in PD independent of demographic features, particularly under single task. Whereas counter to the study hypotheses no relationship was found between visual functions and saccade frequency in PD or controls, which differs from previous research (Clark *et al.*, 2010; Galna *et al.*, 2012). However under single task, attentions relationship with saccade frequency in PD was strengthened once it was combined within a regression model with visual functions (Model 4), which indicated potential visuo-cognitive interaction. This was further substantiated by significant relationship between attention and visual functions in PD.

In general people with PD made less frequent saccades than controls during gait, but within PD there may be a non-linear saccadic impairment related to disease severity (depicted in Figure 7-6). An interesting finding was that greater disease severity (UPDRS-III) related to less change in saccade frequency in PD (ΔTurn), which differed from previous saccadic literature that reported no relationship between these features (Perneczky *et al.*, 2011; Macaskill *et al.*, 2012). Disease severity was not significantly related to absolute saccade frequency during the walking conditions (Straight, Door, Turn), but influenced the ability to change the

frequency of saccades with increased environmental complexity. This may be due to fewer saccades being made by those with milder PD during straight walking (Hypo-reflexive) than those with more advanced PD (Hyper-reflexive), which could be due to their ability to control reflexive saccadic activity (distraction) (Figure 7-6). For example; with a change in environment (a Door or Turn) people with milder PD could increase their saccade frequency from the frequency made during straight walking, whereas those with more advanced PD likely made a similar frequency of saccades during all conditions (i.e. inability to control saccades). However the correlation between disease severity and change in saccade frequency was likely mediated by cognition, particularly under single task. For example; when cognitive functions were entered into the regression model the relationship significantly weakened. These findings suggest that cognition, particularly attention plays a key role in saccade frequency (absolute and change scores) during gait in PD.

7.5.6. Saccade frequency during gait is underpinned by attention in Parkinson's disease

Consistent with previous reports of saccadic activity (Seidlits *et al.*, 2003; Mazer, 2011), attention was associated with saccade frequency during gait under single task in PD. Poorer attention in PD was consistently related to less change in saccade frequency with environmental challenge (a door and turn). Those with better attention were able to increase their saccade frequency with environmental challenge (a door or turn), whereas those with poor attention had similar saccade frequency in all environments. This most likely relates to the finding that those with PD who had poorer attention made more frequent saccades during straight walking (PoA; r = 27, p = .049, Table 7-7, Figure 7-6), which was consistent with previous research (Galna *et al.*, 2012). Poorer attention in PD relates to numerous dysfunctions, including reduced PFC activity and disruption of cortico-BG loops (Gorges *et al.*, 2015) and impacts inhibition (Deijen *et al.*, 2006), which during straight walking likely led to increased reflexive saccades (hyper-reflexive) to irrelevant stimuli (Figure 7-6). For example, those with better attention were unable to initiate top-down saccades during straight walking but suppressed reflexive saccades to areas not relevant to the task, whereas those with poor attention were more distractible. This is consistent with previous reports of

difficulties distinguishing between relevant and irrelevant areas to a given task in PD (Verleger *et al.*, 2014), which impacts saccade target selection within cortico-BG loops (N'Guyen *et al.*, 2014). Impaired attention in PD therefore led to a lack of control over saccade initiation and suppression, which presented as altered saccade frequency response during the walking conditions.

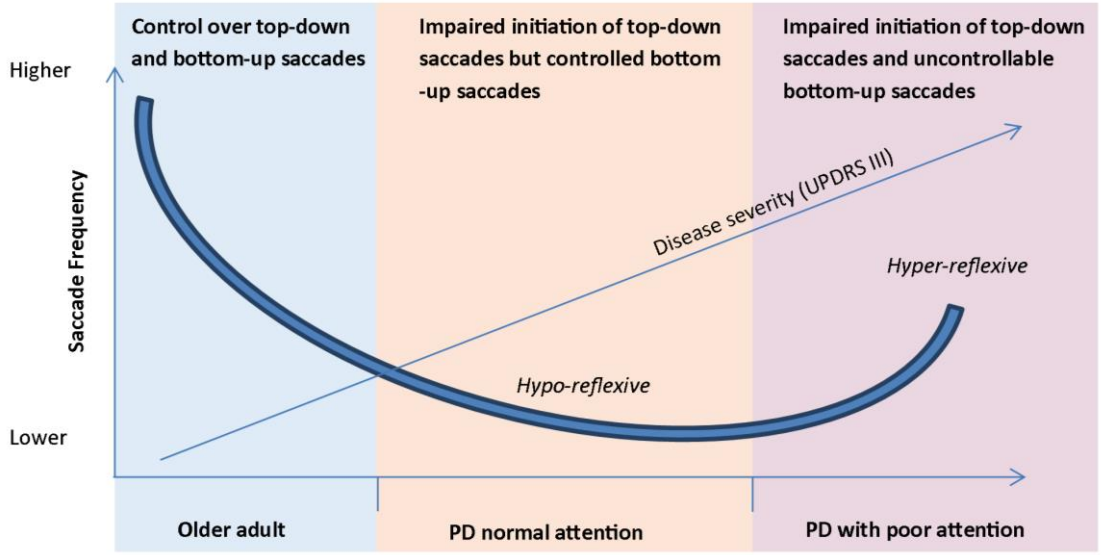


Figure 7-6 –Non-linearity of saccade frequency during straight walking in Parkinson's disease

Surprisingly, association between attention and saccade frequency was not evident under dual task, likely due to greater cognitive burden triggering abnormal saccade facilitation (van Stockum *et al.*, 2012) and inhibitory fluctuation (Anderson and MacAskill, 2013). However, working memory (Digit span) was found to be significantly associated with saccade frequency in PD under dual task. In contrast to attention under single task, poorer working memory related to higher saccade frequency change scores under dual task in PD. Therefore when attentional resources were saturated, those with poorer working memory may have been unable to inhibit reflexive saccades (Terao *et al.*, 2013) (Figure 7-6). Working memory has previously been implicated in saccade inhibitory control (Kane *et al.*, 2006) (mentioned in section 2.4.1), therefore despite lack of association it is likely that attention (with executive function) (Rochester *et al.*, 2014) influenced this relationship. The nature of dual task methodologies when investigating saccade frequency during gait has not been investigated, with only one previous PD study of saccade frequency during gait using a dual task

(Galna *et al.*, 2012). Although dual tasks are used to represent real-world distraction during gait and likely interfere with frontal voluntary saccadic and gait control in PD, the exact mechanisms that impact saccades during gait remain unclear.

7.5.7. Saccade frequency and gait: a complex relationship

Cognition and vision are known to influence both saccades and gait, however there was no significant association between saccade frequency (absolute or change scores) and gait in PD (Table 7-10). In contrast, more frequent saccades during gait were significantly associated with walking faster, with longer steps during a turn for controls. This evidence is important as no previous study has examined the association between saccade frequency during gait and gait characteristics in people with PD or older adults.

Lack of association was unexpected, but highlights the complexity of the underlying visuo-cognitive mechanisms that influence PD gait impairment, as the underlying contributions undoubtedly vary depending upon the individual participant and task being undertaken. Indeed, saccade frequency and gait were both selectively impaired in PD compared to controls when walking regardless of attentional manipulation. However impaired saccade frequency and gait characteristics were both significantly associated with common cognitive dysfunctions in PD, such as impaired attention. Further, saccade frequency was independently associated with attention rather than demographic features, similar to previous findings in Parkinsonian gait (Lord *et al.*, 2014). The complex relationships between cognition, vision, saccade frequency and gait in PD require further investigation to assess the specific visuo-cognitive interactions that relate to gait impairment (Chapter 9 extends this investigation). Ultimately however if attention influences saccade frequency and visual functions, then visual information would be reduced with PD impairment, with implications for safe and effective navigation.

7.6. Conclusions

In summary, the study described in this chapter demonstrated that both gait and visual sampling during gait are impaired in people with PD compared to age-matched controls, particularly when distracted by a dual task. Attentional

manipulation via environmental challenge led to more conservative gait patterns and increased saccade frequency in both groups even under a dual task, however saccade frequency was still reduced in PD compared to controls. Surprisingly, gait characteristics and saccade frequency during gait were not related in PD but were in controls. However both gait and saccade frequency were selectively influenced by online attentional manipulation in both groups, and were associated with similar visuo-cognitive features in PD. Cognitive and visual functions were significantly related in both groups, but more so in PD. Cognitive functions, particularly attention were independently associated with saccade frequency in PD.

Within the PD group only, those who had poorer attention made more frequent saccades during gait and changed saccadic frequency less in response to environmental challenge. It is therefore likely that impaired attentional processes in PD led to dysfunctional saccade generation during gait. For example; greater burden on the PFC for gait control and impaired inhibitory influence of the BG (controlled by projections from the PFC) likely contributed to less frequent voluntary saccade generation particularly when distracted (PFC further burdened) and fluctuations in inhibitory control of reflexive saccades.

8. Visual sampling during gait in Parkinson's disease: response to visual cues

8.1. Summary

The purpose of this chapter was to investigate whether visual cues influence saccade frequency during gait in PD and older adult controls. Descriptive, correlational and regression analysis were used to examine the response of saccade frequency during gait when using a visual cue and the underlying mechanisms involved. Although not the primary focus of this study, gait characteristics were included as a secondary outcome. Correlational analysis between saccade frequency and gait characteristics when using a visual cue was also performed (Figure 2-1(D)).

8.2. Introduction

Dopaminergic medication has limited effect on gait characteristics in PD (Munoz-Hellin *et al.*, 2013). To ameliorate gait deficits in PD, attentional interventions such as visual cues (transverse lines to step over) are often taught (Brown and Marsden, 1988; Peterson and Smulders, 2015), which are shown to improve gait characteristics such as step length (Bagley *et al.*, 1991; Baker *et al.*, 2007). Indeed a recent systematic review on visual cueing in PD reported that gait characteristics, turning execution, dual task performance, freezing incidence and falls were all improved with the use of visual cues (Munoz-Hellin *et al.*, 2013). Intervention response however is variable with some studies reporting no improvement with cueing (Almeida *et al.*, 2002), and response is selective to certain gait characteristics (i.e. step length) and often only has short term effect (Morris *et al.*, 2010). Regardless of limitations, visual cues are a recommended physiotherapy intervention for PD gait impairment (Keus *et al.*, 2007), but the mechanisms underlying response are poorly understood. As mentioned in Chapter 2 (section 2.8), Vitorio *et al.* (2014) stated that there are currently two primary theories of visual cue response. The first suggests that visual cue response is due to *attention* and the second suggests that *optic flow* is responsible. These theories separate the roles of cognitive and visual functions

during gait when using visual cues; however it is likely that these functions interact during gait and have visuo-cognitive influence on cue response.

Visuo-cognitive processes, measured via saccadic eye movements, involve a range of structures and functions that have previously not been robustly investigated when examining visual cue response. For example; attentional networks and structures (e.g. PFC, PPC, parietal eye-field etc.) involved in both circumventing dysfunctional BG to maintain gait and also visual processing and saccade generation, such as; top-down and bottom-up attention (Baluch and Itti, 2011). Visuo-cognitive processes are likely an important contributor to the mechanisms underlying beneficial response seen with visual cues. Indeed, recent evidence from Vitorio *et al.* (2014) alluded to a non-significant increase in fixation number and duration being linked with stepping behaviour when using a visual cue in people with PD and older adults. However this study only measured fixations in a small cohort of PD and did not investigate saccades which limited conclusions. Alterations in saccades with visual cues may be an important factor involved in cue response, as the integration of visuo-cognitive information, cortical saccade programming and planning/executing motor output is performed in the same cortical regions (Kravitz *et al.*, 2011). For example, visual and cognitive loops interact and use the same resources in striatal regions, and the PFC and motor cortex are involved in saccadic and gait control.

The purpose of this chapter was therefore to investigate response in saccade frequency during gait in PD and controls with attentional manipulation using a visual cue under both single and dual task. Specific hypotheses were that saccade frequency would increase in PD and controls with a visual cue which would be maintained under dual task. As in chapter 7, due to the multi-factorial nature of saccades it was hypothesised *a priori* that demographic features along with cognitive and visual functions would be associated with saccade frequency in PD.

To assess these specific hypotheses a series of questions were raised, which form the structure of the analysis, results and discussion of this study.

Questions that this study will answer;

- What are the descriptive differences between PD and controls?
- What is the effect of a visual cue on saccade frequency during gait?
- What is the effect of a visual cue on gait?
- What are the relationships between saccade frequency, cognition, vision and gait with a visual cue?
    - What is the relationship between demographics, vision, cognition and gait when using a visual cue?
    - What is the relationship between demographics, vision, cognition and saccade frequency when using a visual cue?
    - What is the relationship between saccade frequency and gait when using a visual cue?

8.3. Specific methods[8]

8.3.1. Participants

As described in section 4.2.1, this study involved 55 people with PD and 32 age-matched older adult controls. Inclusion and exclusion criteria, along with study recruitment are provided within chapter 4. Clinical and further testing (detailed in Chapter 4) took place 1 hour after medication intake to ensure optimal function ('On' state of medication was verified at the beginning of the gait assessments through observation of hand clasping, finger and foot tapping aspects of the UPDRS III).

8.3.2. Specific experimental design and procedure

Saccade frequency during gait was measured while attention was manipulated using two different strategies; 1) a commonly used gait intervention namely a *visual cue (with and without a door),* and 2) performance of a *dual task*.

1) Visual cue

Participants were asked to walk at their usual pace during several straight walking conditions (Figure 8-1 and Appendix 15.0); straight with no visual cue, straight through a door with no visual cue, straight with a visual cue and straight

[8] The methods contained within this chapter have been published; Stuart et al. (2015)

with a visual cue through a door. Photographs of the walking conditions can be seen in Appendix 15.0.

The commands used for each condition were as follows;

"Begin looking at the camera, I will count down from 3 during which remain looking at the camera. When I say 'Go' you are free to look wherever you want. Also, on 'Go' begin walking straight ahead to the white line at end of the room (and step over the lines on the floor (visual cue conditions only))."

For all walking conditions the participants completed a 5m walk however only the first 2.5m (Figure 8-1) of the walk was analysed (to the location of the door), in keeping with chapter 7 (section 7.3.3). Three trials of each walking condition were performed and analysed. The visual cue consisted of highly salient black taped transverse lines placed on a white floor 50cm apart (approximately a normal step length) (Lewis *et al.*, 2000; de Melo Roiz *et al.*, 2011). Unlike some previous studies (Jiang and Norman, 2006; Espay *et al.*, 2010) the cue was not tailored to individuals gait pattern as change in gait characteristics were not the primary focus of this study.

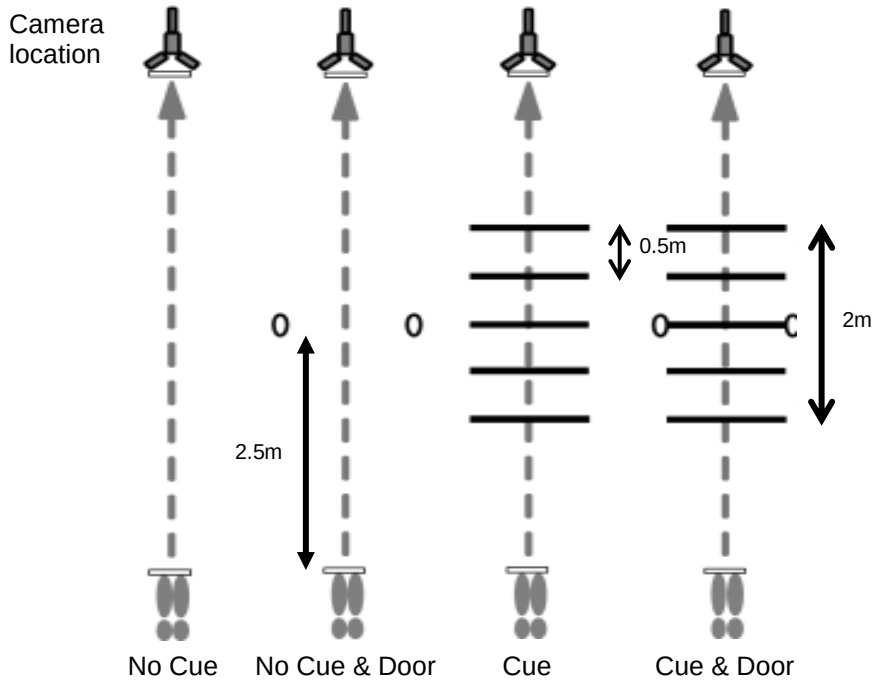


Figure 8-1- Walking Conditions

2) Dual Task

Single and dual task walks were completed by the participants. The dual task was the same as used in chapter 7, and involved repetition of individuals maximal Wechsler Digit Span (Wechsler, 1945) during gait. The order of walking conditions were randomised (Figure 8-2), with non-cued straight walking always first to ensure participants could complete the task. Subsequent conditions were then randomly undertaken, as were the blocks of single and dual tasks.

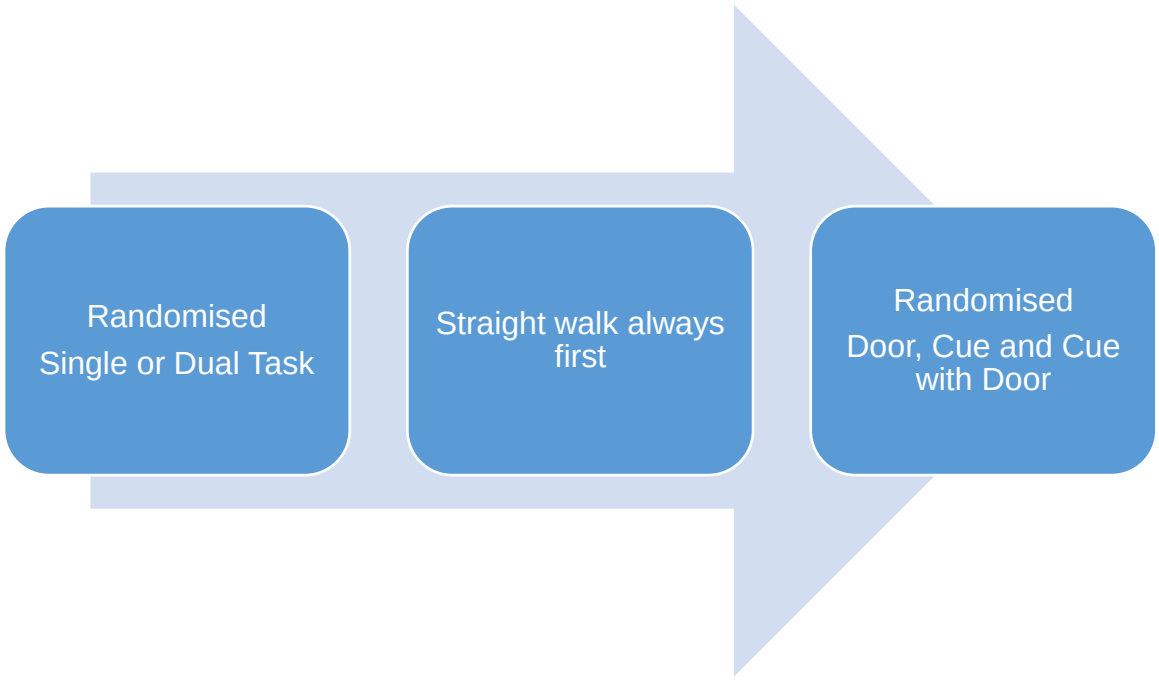


Figure 8-2 – Randomisation procedure of walking conditions

8.3.3. Equipment

Saccade frequency was measured using mobile eye-tracker and EOG systems in the same manner as described in section 4.10. Participants were asked to keep their face as relaxed as possible and to not to repeat any numbers during dual task before the doorway position, to avoid EOG data infiltration from muscle contraction artefact. Gait was measured using a 3D motion capture system.

8.3.4. Outcome measures

The primary outcome for this study was saccade frequency during gait. Saccade frequency change (Δ) scores (change in saccade frequency with a visual cue) were also created via set formula (1 and 2) to inform visual cue response under single and dual task.

$$(1)\ \text{Cue} - \text{No Cue} = \Delta\text{Cue}$$

$$(2)\ \text{Cue \& Door} - \text{No Cue \& Door} = \Delta\text{Cue\&Door}$$

This study reports saccade frequency in terms of absolute values measured during gait and change scores in order to overcome some of the measurement limitations observed within the accuracy and reliability testing (Chapter 5 and 6). Errors introduced into measurement will vary dependent on the individual, therefore calculating change score allows for mitigation of the intrinsic errors associated with mobile eye-tracking (i.e. each individual acts as their own control for the session).

Secondary visual sampling characteristics were comprehensively reported but not formerly assessed, these included saccade number, duration, peak velocity, peak acceleration; fixation number and duration, and blink number. Other secondary outcomes included gait characteristics, such as; time taken to walk to the door location, step length, walk velocity, step time, double support, single support and cadence.

8.3.5. Data and statistical analysis

Data were assessed for normality with visual histograms and Kolmogorov-Smirnov tests, meeting criteria for parametric analysis (Expósito-Ruiz *et al.*, 2010; Ghasemi and Zahediasl, 2012; Field, 2013). Statistical tests were two-tailed and due to the exploratory nature of the study a significance value of $p<0.05$ was set. Preliminary pair-wise analysis via t-tests showed that there was no significant difference between the two straight walking conditions (No Cue or No Cue & Door) or the two cueing tasks (Cue or Cue & Door), therefore for further analysis data were collapsed into a none cued straight walking and a single cueing variable in order to avoid Type I error. The same was done for the gait characteristics to allow for comparison.

Figure 8-3 shows the four step analysis that was performed in order to answer the specific questions set out at the start of this chapter, and further details follow.

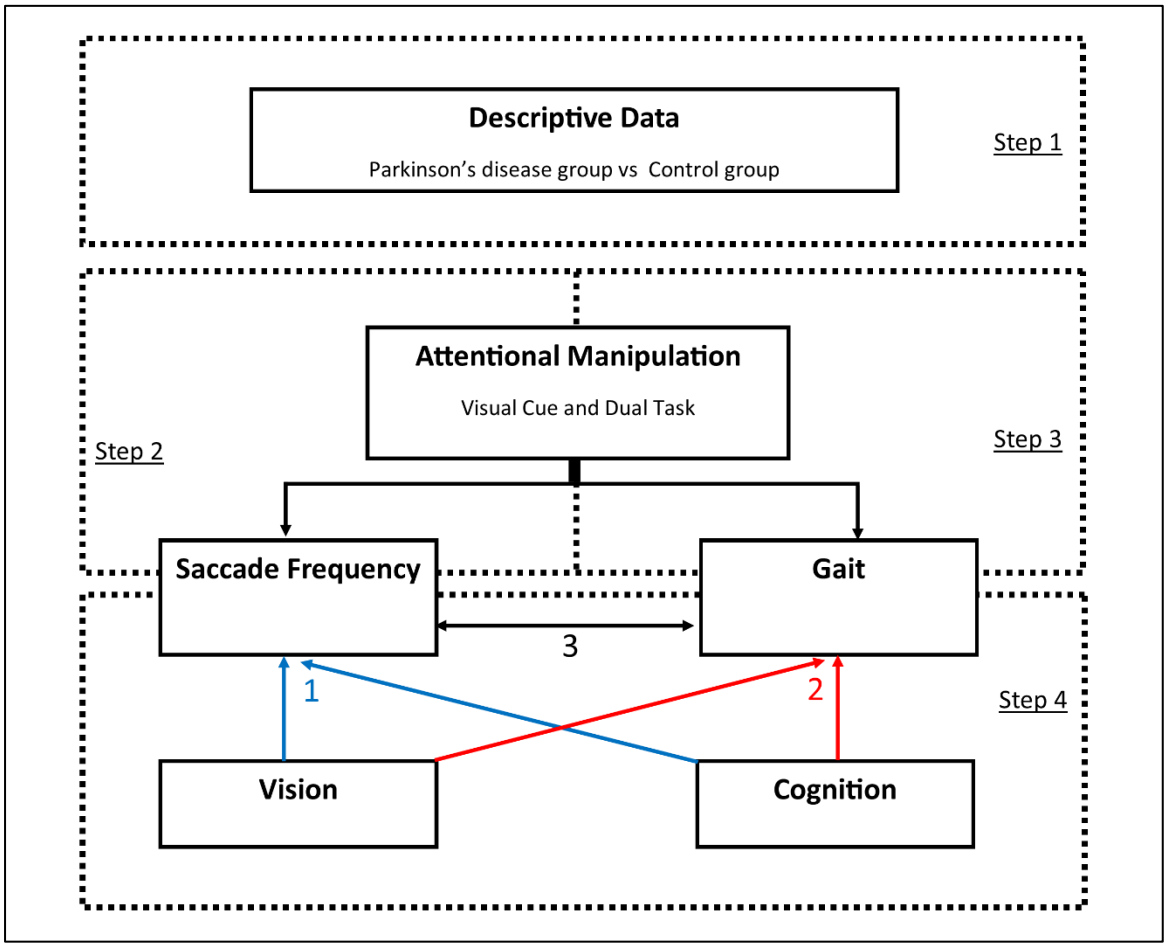


Figure 8-3 – Data analysis flow chart

<u>Step 1:</u> What are the descriptive differences between PD and controls?

To address this question, analysis for descriptive data described in chapter 4 section 4.12 was performed. Univariate analysis was also performed to assess performance on the dual task (digit span) during the gait trials.

<u>Step 2:</u> What is the effect of a visual cue on saccade frequency during gait?

To answer this question a repeat measures ANOVA was used to compare the effect of attentional manipulation via visual cue (No Cue or Cue) and dual task (single or dual) on saccade frequency, with group (PD or control) as a between subject factor. A second repeat measures ANOVA was conducted to compare the effect of a visual cue (none cued and cued) and dual task on change scores (ΔCue and ΔCue&Door), with group (PD or control) as a between subject factor.

In order to interpret two way interactive relationships data were plotted and presented graphically (Field, 2013).

Step 3: What is the effect of a visual cue on gait?

Gait was not the primary focus of this study. However several repeat measures analysis of co-variance (ANCOVA) were used to compare the effect of cueing and dual task on gait outcomes, with group as a between subject factor and height entered as a covariate. To interpret two and three-way interactive relationships data were plotted and presented graphically. To further examine three-way interaction (environment x cue x group) several separate *post hoc* repeat measures ANCOVAs were conducted, similar to gait analysis performed in previous research (Errington *et al.*, 2013; Menant *et al.*, 2014). This was carried out as there is no proper facility in SPSS for producing *post hoc* tests for repeat measures ANCOVAs (Field, 2013).

Step 4: what are the relationships between saccade frequency, cognition, vision and gait with a visual cue?

1. *What is the relationship between demographics, cognition, vision and gait when using a visual cue?*

To answer this question, relationships between demographic, clinical, cognitive and visual functions and gait were also explored using Pearson correlation coefficients, these are presented in Appendix 19.0 and 20.0 as gait was a secondary outcome for this study.

2. *What is the relationship between demographics, cognition, vision and saccade frequency when using a visual cue?*

To answer this question, the analysis was conducted in two stages (2a and 2b);

2(a): Correlation

Initially Pearson correlation coefficients were calculated to explore associations between saccade frequency (absolute and change scores) during gait and independent demographic, cognitive, visual functions and clinical variables.

2(b): Multiple Regression

The same exploratory regression analysis used in chapter 7 was used to further investigate the underlying mechanisms involved in saccade frequency during gait with a visual cue. Saccade frequency change scores (e.g. ΔCue, ΔCue&Door) were used to represent visual sampling (Allison, 1990). The same regression models detailed in chapter 7 were developed within this study. Demographic features (Age, MoCA, UPDRSIII, GDS-15) were entered into the first step (Model 1), cognitive (Model 2) and visual functions (Model 3) in separate steps, and a final model is presented (Model 4).

Co-linearity statistics (Tolerance and VIF) were inspected and indicated that multi co-linearity was not a concern (all Tolerance >.30 and VIF <10), and the Durbin-Watson statistic was used to identify autocorrelation (values less than 1 and greater than 3 were identified as problematic) and indicated that data met the assumption of independent errors (Field, 2013). Standardised residuals were inspected for normality via histograms which indicated all data contained approximately normally distributed errors, as did the P-P plot of standardised residuals, which showed that points were not completely on the line but were close to it (Field, 2013).

3. *What is the relationship between saccade frequency and gait when using a visual cue?*

Finally, to answer this question a matrix of Pearson correlation coefficients explored the relationship between saccade frequency (absolute and change scores) and gait characteristics when using a visual cue. Trial duration was not included in this second matrix to avoid type I error, as it was used to derive saccade frequency (number of saccades/trial duration = saccade frequency).

8.4. Results

8.4.1. Step 1: What are the descriptive differences between PD and controls?

Table 8-1 demonstrates that both groups were well matched for age (p = .657), sex (p = .115) and education (p = .063). Surprisingly people with PD weighed

significantly more (p = .026) than the controls, possibly due to the increased number of males within the PD group despite lack of significant difference. PD group depression rates (GDS-15) and fear of falling (FES-I) (p < .001) were significantly higher. The PD group consisted of a heterogeneous participant group (Mean disease duration, ~69 ± 72 months) who had moderate disease severity (UPDRS III, ~37 ± 14). In line with chapter 7, Table 8-1 shows that people with PD had impaired global cognitive ability compared to controls, with significantly lower MoCA (p < .001) and ACE-R (p < .001) scores. Similar to the previous study, differences were expected as the PD group involved non-demented participants (MoCA ≥ 21) whereas the control group were required to be cognitively 'normal' (MoCA ≥ 26). Other specific cognitive functions were significantly different between the groups. Attention (PoA and FoA, p < .001), executive function (CLOX, p = .013), visuo-spatial ability (JLO, p = .019) and working memory (Digit span, p < .001) were all significantly impaired in PD compared to controls. Basic visual functions of VA (p = .007) and CS (p = .004) were also significantly impaired in PD compared to controls.

Table 8-2 shows the percentage of incorrect responses on the dual task during gait by the two groups (PD and controls), with and without a visual cue. Results indicate that dual task error significantly reduced with a visual cue in both groups. Dual task error reduction was also evident within both walking conditions (Straight, Door) within the PD group.

A comprehensive account of the visual sampling characteristics employed by people with PD and controls during the various gait tasks can be seen in Table 8-3 and Appendix 18.0. The groups were different on all visual sampling characteristics, but few significant differences were seen. People with PD had reduced fixation number without a visual cue compared to controls. However fixation number increased in response to a visual cue for both groups, more so in people with PD. People with PD also generally had longer saccade durations, smaller amplitudes, higher peak velocities and accelerations, longer fixation duration and reduced number of blinks than controls.

Table 8-1- Demographic, cognitive, visual and clinical characteristics

		Control (n=32) Mean (SD)	PD (n=55) Mean (SD)	*p*
Demographic	Age (years)	67.03 (10.80)	67.93 (7.86)	0.657
	Sex	15M/17F	36M/19F	0.115†
	Height (cm)	168.36 (10.12)	171.40 (9.10)	0.153
	Weight (kg)	73.98 (12.70)	82.98 (19.78)	**0.026***
	Education (years)	14.63 (2.83)	13.24 (3.57)	0.063
	Depression scale (GDS-15)	0.78 (0.94)	2.56 (2.60)	**0.000***
	Falls efficacy scale (FES-I)	18.88 (2.34)	24.62 (8.21)	**0.000***
	Retrospective Falls (no. in 12 months)	0 (1)	1 (3)	0.259
Cognition	Montreal Cognitive Assessment (MoCA)	28.41 (1.24)	26.71 (2.18)	**0.000***
	Addenbrookes (ACE-R)	95.13 (3.46)	89.87 (7.22)	**0.000***
Attention	Power of attention	1274.22 (151.83)	1441.5 (258.84)	**0.001***
	Fluctuation of attention	49.02 (9.65)	59.55 (14.42)	**0.000***
Executive function	Royals CLOX 1	13.50 (1.14)	12.75 (1.44)	**0.013***
Visuo-spatial ability	Royals CLOX 2	13.72 (1.02)	13.44 (1.57)	0.366
	Judgement of line orientation	25.56 (3.98)	23.12 (4.87)	**0.019***
	VOSP - Total	48.81 (1.06)	47.71 (3.59)	0.095
	VOSP - Incomplete letters	19.38 (0.66)	19.09 (1.11)	0.191
	VOSP - Dot counting	9.88 (0.34)	9.82 (0.51)	0.577
	VOSP - Position Discrimination	19.56 (0.80)	18.80 (3.00)	0.164
Working memory	Max Digit Span Length (sitting)	6.56 (1.01)	5.69 (1.12)	**0.000***
Visual function	Visual acuity (LogMar)	-0.07 (0.13)	0.03 (0.16)	**0.007***
	Contrast sensitivity (LogCS)	1.64 (0.09)	1.55 (0.14)	**0.004***
Clinical	Hoehn and Yahr stage	-	I (20)/II (30)/III (5)	-
	Disease duration (months)	-	68.67 (72.30)	-
	UPDRS part I	-	10.64 (5.19)	-
	UPDRS part II	-	10.95 (7.27)	-
	UPDRS part III	-	36.80 (14.22)	-
	UPDRS part IV	-	2.47 (3.09)	-
	FOGQ	-	3.58 (6.27)	-
	LED	-	599.87 (402.56)	-

[*significance level p<0.05, LED= levodopa equivalent daily dosage, FOGQ = Freezing of gait questionnaire, VOSP= visual object and spatial perception battery, † = X^2]

Table 8-2 - Dual task errors

Group	Environment	Digit Span Errors (%) Mean (SD)		*p*
		No Cue	Cue	
Control	Straight	27.08 (31.04)	12.50 (27.76)	**.004***
	Door	18.75 (25.31)	18.97 (26.56)	.214
PD	Straight	28.48 (32.34)	20.61 (26.05)	.279
	Door	26.67 (32.33)	12.82 (21.43)	**.007***

[*significance level p<0.05]

8.4.2. ***Step 2:* What is the effect of a visual cue on saccade frequency during gait?**

Descriptive data and repeat measure ANOVA results for the primary outcome of saccade frequency during gait are shown in Table 8-3 and depicted in Figure 8-4. Results demonstrated that there was no main effect for group (p = .467), which showed that there was no significant difference in saccade frequency during gait between people with PD and controls, regardless of condition. However in general people with PD made less frequent saccades during all of the non-cued walking conditions (No Cue, No Cue & Door). There were main effects for visual cue (p < .001) and dual task (p = .001) on saccade frequency during gait. This showed that both groups made significantly more frequent saccades when using a visual cue (with slightly greater effect in PD), and significantly less frequent saccades under a dual task, which is shown in Figure 8-4. There was also a main effect for dual task on saccade frequency change scores (p = .008), demonstrating that when using a visual cue both people with PD and controls increased their saccade frequency more under dual task than single task.

The most interesting finding was that under dual task saccade frequency (change scores) during gait was maintained (comparable to single task) with a visual cue for both groups (Figure 8-4), which was shown by a visual cue by dual task interaction (Table 8-3). There was also a trend towards significance for a three-way interaction (group x visual cue x dual task; p = .055) for saccade frequency (change scores), which showed that this study may have been under-powered to detect the subtle differences seen when using a visual cue or visual cue with a doorway (i.e. cue response differs depending on attentional manipulation and pathology).

Table 8-3 - Visual sampling characteristics with summary of the repeated measures ANOVAs for saccade frequency and change score

Group	Cognitive Task	Environment	Saccade Frequency (Sacc/sec) Mean (SD)
Control (n=32)	Single	No Cue	0.70 (0.48)
		Cue	1.08 (0.46)
		No Cue & Door	0.69 (0.53)
		Cue & Door	1.19 (0.56)
		ΔCue	0.38 (0.62)
		ΔCue&Door	0.50 (0.75)
	Dual	No Cue	0.41 (0.36)
		Cue	1.05 (0.60)
		No Cue & Door	0.55 (0.37)
		Cue & Door	1.21 (0.66)
		ΔCue	0.65 (0.73)
		ΔCue&Door	0.57 (0.61)
PD (n=55)	Single	No Cue	0.48 (0.55)
		Cue	1.15 (0.61)
		No Cue & Door	0.69 (0.53)
		Cue & Door	1.15 (0.60)
		ΔCue	0.67 (0.85)
		ΔCue&Door	0.47 (0.68)
	Dual	No Cue	0.30 (0.38)
		Cue	1.07 (0.59)
		No Cue & Door	0.39 (0.39)
		Cue & Door	1.20 (0.66)
		ΔCue	0.77 (0.71)
		ΔCue&Door	0.82 (0.66)

Effect	Saccade frequency (sacc/sec)		Change score (Δsacc/sec)	
	F	*p*	F	*p*
Group	.533	.467	2.08	.153
Cue	117.42	**.000***	.173	.678
Dual	11.97	**.001***	7.45	**.008***
Group x Cue	2.08	.153	.119	.731
Group x Dual	.018	.893	.592	.444
Cue x Dual	7.45	**.008***	.071	.790
Group x Cue x Dual	.119	.731	3.79	.055

[*significance level p<0.05 Controls vs PD, Saccade frequency was calculated from a Dikablis mobile eye-tracker (50Hz), repeat measures ANOVA for straight walking with and without a cue presented]

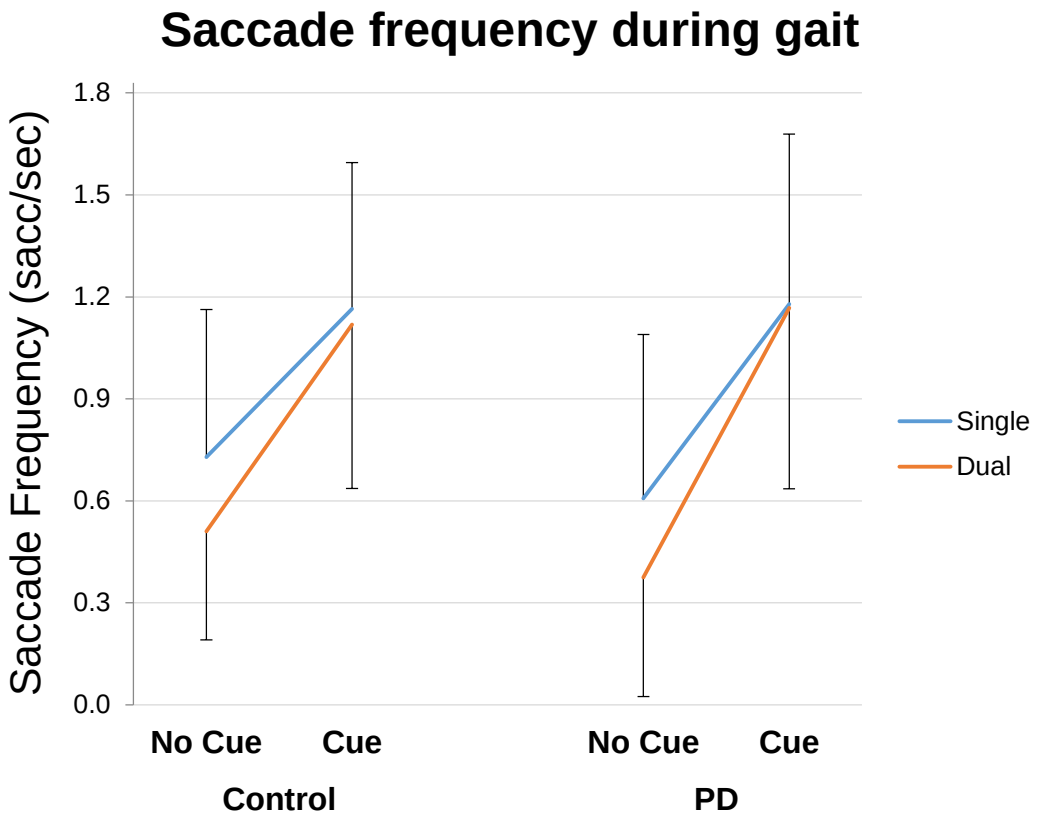


Figure 8-4 – Saccade frequency during gait with and without a visual cue

[No Cue = Mean(No Cue, No Cue & Door), and Cue = Mean(Cue, Door & Cue), Single and Dual; same data as used in repeat measures ANOVA, Means and SDs displayed]

8.4.3. Step 3: What is the effect of a visual cue on gait?

Response of specific gait characteristics to visual cues was not the focus of this study, but for comprehensive data reporting all recorded gait characteristics are described in Table 8-4 and depicted in Figure 8-5. Descriptive data for the participants gait characteristics indicated that regardless of the walking condition people with PD overall had worse gait than controls (i.e. short step lengths, slower velocity etc.).

Unexpectedly the visual cue condition reduced step length and velocity for both groups, however the range of step length indicated that individual gait characteristics and response varied. Several participants in the PD group had large step lengths comparable to controls (0.85-0.87m, Table 8-4). Change in step length ranged from 0.40-0.85m (No Cue) to 0.46-0.68m (Visual cue), which meant that when using a visual cue participant step length was closer to the cued distance (50cm). Some people increased their step length with a visual cue (from 0.40m to 0.46m), whereas others adapted their gait by reducing step length to complete the visual cue condition. People with PD who increased their step length with a visual cue (n = 15) had shorter baseline (No Cue) step length (mean 0.51m, SD 0.04m, range 0.40-0.55m) than those whose step length reduced (n = 40) with a visual cue (mean 0.66m, SD 0.08m, range 0.54-0.85m).

Two-way interactions for group with cue and dual task (step time and single support time; Table 8-4) indicated that step time and single support time were increased in PD (i.e. longer steps) but reduced in controls (i.e. quicker steps) with a cue, under single and dual task. Three-way interaction (Group x Cue x Dual) was seen for step length and velocity. Post hoc analysis showed that people with PD did not reduce their step length and velocity as much as controls with a visual cue (step length; $p = .001$, velocity; $p = .031$) or dual task (step length; $p = .001$, velocity; $p = .002$). However step length ($p = .472$) and velocity ($p = .271$) were similar for both groups with a cue under single and dual task. Overall, with a visual cue both groups reduced velocity and step length (closer to 50cm), which was maintained (similar to single task) under dual task (Figure 8-5).

Table 8-4 - Gait characteristics with summary of the repeat measures ANCOVAs

Group	Attentional manipulation		Time to Door (s)	Step Length (m)		Velocity (m/s)	Step Time (s)	Single Support Time (s)	Double Support Time (s)
	Cognitive Task	Environment	Mean (SD)	Mean (SD)	Range (Min - Max)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Control (n=32)	Single	No Cue	2.70 (0.44)	0.70 (0.08)	0.56 – 0.85	1.26 (0.18)	0.55 (0.05)	0.43 (0.04)	0.26 (0.06)
		Cue	2.83 (0.55)	0.59 (0.08)	0.52 –0.90	1.13 (0.17)	0.53 (0.04)	0.41 (0.04)	0.27 (0.05)
		No Cue & Door	2.75 (0.52)	0.71 (0.08)	0.56 – 0.89	1.31 (0.18)	0.54 (0.05)	0.42 (0.03)	0.26 (0.06)
		Cue & Door	2.77 (0.41)	0.60 (0.09)	0.53 – 0.98	1.13 (0.18)	0.53 (0.04)	0.42 (0.03)	0.26 (0.06)
	Dual	No Cue	3.08 (0.56)	0.65 (0.07)	0.53 – 0.83	1.11 (0.19)	0.58 (0.06)	0.45 (0.04)	0.29 (0.07)
		Cue	2.85 (0.40)	0.59 (0.07)	0.53 – 0.81	1.08 (0.16)	0.55 (0.05)	0.43 (0.03)	0.28 (0.06)
		No Cue & Door	2.87 (0.46)	0.65 (0.07)	0.51 – 0.85	1.15 (0.19)	0.57 (0.06)	0.43 (0.04)	0.28 (0.06)
		Cue & Door	2.87 (0.43)	0.59 (0.06)	0.52 – 0.79	1.08 (0.15)	0.55 (0.05)	0.42 (0.03)	0.28 (0.06)
PD (n=55)	Single	No Cue	3.05 (0.60)	0.62 (0.10)	0.40 – 0.85	1.06 (0.19)	0.58 (0.06)	0.44 (0.05)	0.32 (0.10)
		Cue	3.19 (0.58)	0.57 (0.03)	0.46 – 0.68	0.96 (0.17)	0.60 (0.09)	0.45 (0.06)	0.33 (0.14)
		No Cue & Door	2.94 (0.60)	0.63 (0.10)	0.38 – 0.87	1.09 (0.19)	0.57 (0.05)	0.42 (0.04)	0.31 (0.09)
		Cue & Door	3.16 (0.59)	0.57 (0.03)	0.48 – 0.69	0.97 (0.14)	0.59 (0.08)	0.45 (0.05)	0.33 (0.14)
	Dual	No Cue	3.19 (0.64)	0.59 (0.09)	0.39 – 0.84	0.98 (0.20)	0.60 (0.09)	0.45 (0.06)	0.34 (0.10)
		Cue	3.27 (0.60)	0.56 (0.03)	0.40 – 0.65	0.94 (0.14)	0.62 (0.11)	0.46 (0.06)	0.35 (0.14)
		No Cue & Door	3.13 (0.59)	0.59 (0.09)	0.39 – 0.83	1.00 (0.19)	0.59 (0.07)	0.43 (0.05)	0.33 (0.08)
		Cue & Door	3.26 (0.54)	0.56 (0.05)	0.39 – 0.63	0.94 (0.14)	0.61 (0.09)	0.45 (0.06)	0.35 (0.14)

Effect	**F**	***p***	**F**	***p***	**F**	***p***	**F**	***p***	**F**	***p***	**F**	***p***
Group	8.409	**.005***	21.085	**.000***	23.065	**.000***	8.951	**.004***	3.050	.084	7.632	**.007***
Cue	.267	.607	8.318	**.005***	3.812	.054	3.207	.077	1.225	.272	.003	.955
Dual	1.197	.277	.017	.896	2.074	.154	2.437	.122	1.506	.223	2.467	.120
Group x Cue	7.504	**.008***	8.603	**.004***	1.345	.249	13.289	**.000***	16.430	**.000***	.684	.410
Group x Dual	.193	.662	7.387	**.008***	7.492	**.008***	.345	.559	.154	.696	.033	.857
Cue x Dual	1.604	.209	.258	.613	.456	.501	.054	.816	.112	.739	1.067	.305
Group x Cue x Dual	2.951	.089	7.597	**.007***	7.838	**.006***	1.224	.272	1.434	.234	.020	.888

[*significance level p<0.05, Straight walking with and without a cue, Height was entered as a covariate]

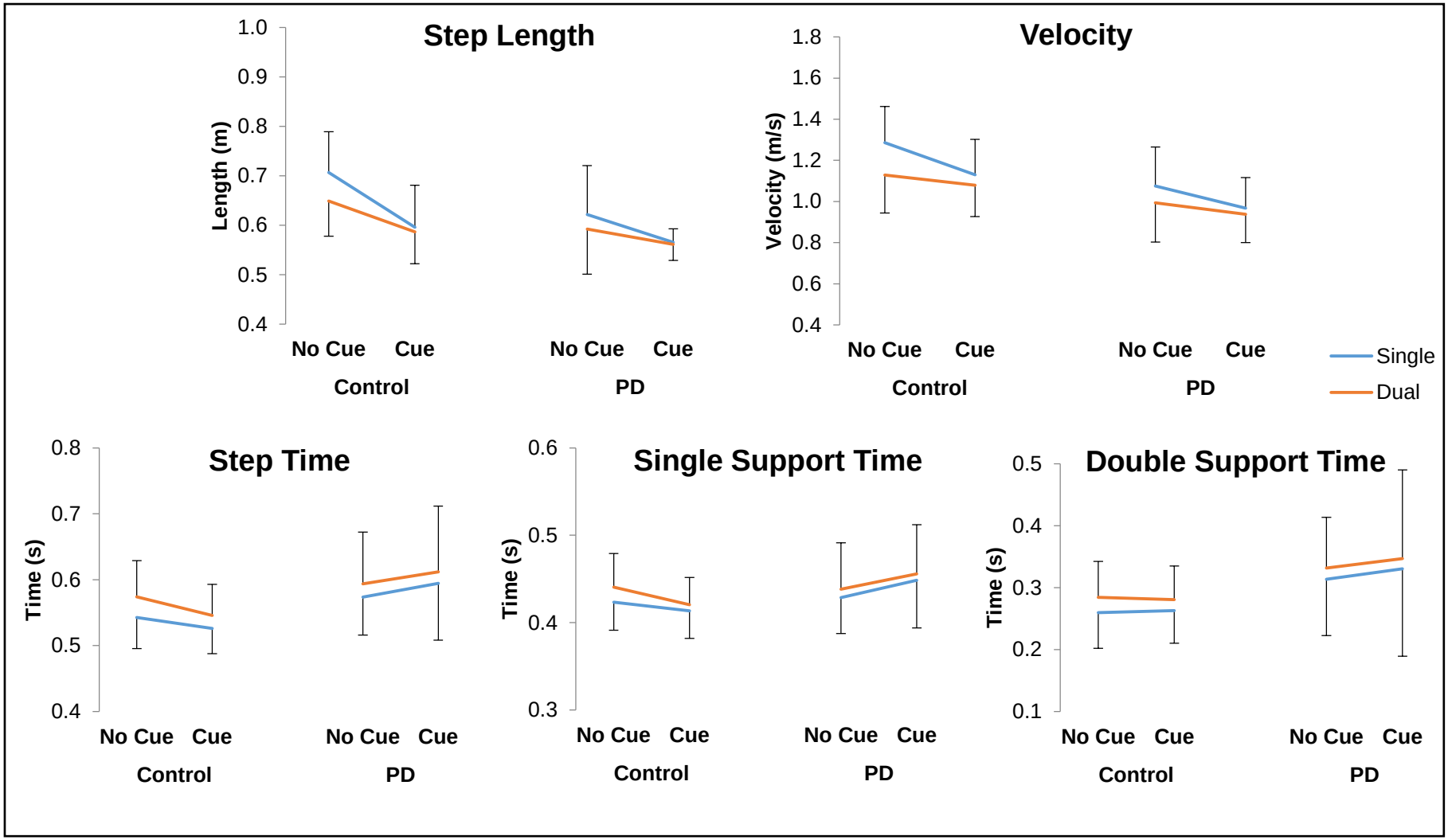


Figure 8-5 - Gait characteristics during walking with cue and no cue [used in repeat measures ANCOVAs]

8.4.4. Step 4: What are the relationships between saccade frequency, cognition, vision and gait with a visual cue?

1: Relationship between demographics, cognition, vision and gait when using a visual cue

Gait characteristics were secondary outcomes for this study and therefore correlations between demographic features, cognition, vision and gait are shown in Appendix 19.0 and 20.0 for controls and PD respectively. As expected, selective significant associations between these features were evident when using a visual cue in PD. For people with PD, worse depression, fear of falling and disease severity related to poorer gait with a visual cue under single and dual task. Increased velocity when using a visual cue was related to better global cognition (e.g. MoCA; r = .29, *p* = .032), attention (e.g. FoA; r = -.34, *p* = .011) and visuo-spatial ability (e.g. JLO; r = .36, *p* = .008). Increased double support time was also related to poorer visual function (e.g. VA; r = .35, *p* = .010).

Surprisingly there were no significant cognitive or visual function relationships with gait for controls. However, there were several demographic features that were significantly related with gait for controls. Advanced age (e.g. r = -.42, *p* = .007), greater weight (e.g. r = .39, *p* = .014), worse depression (e.g. r = .34, *p* = .030) and fear of falling (e.g. r = .35, *p* = .026) in controls were significantly association with selective gait impairments when using a visual cue under single and dual task.

2(a): Relationship between demographics, cognition, vision and saccade frequency when using a visual cue; Correlation

A matrix of correlations between saccade frequency (absolute and change scores) and clinical and demographic variables is presented in Table 8-5 for people with PD and controls. Correlations between saccade frequency (absolute and change scores) and cognitive and visual functions are presented in Table 8-6 for controls and Table 8-7 for PD.

Surprisingly, there were few significant relationships between saccade frequency during gait and the other independent variables, and correlations that were significant tended to be weak to moderate (r <.30 to .50). Despite this there were

several significant correlations for saccade frequency during gait variables. During straight walking (No Cue and No Cue & Door), increased saccade frequency in PD was associated with poorer attention (PoA; r = .27, p = .047 and FoA; r = .25, p = .070), greater disease severity (UPDRS III; r = .27, p = .050) and advanced age (Age; r = .28, p = .041), particularly under single task. Whereas with a visual cue, better global cognition (MoCA; r = -.37, p = .038), attention (FoA; r = .35, p = .047) and visual function (CS; r =.37, p = .039) related to higher saccade frequency in controls, but not PD. Similarly, better visuo-spatial ability, executive function and working memory related to increased saccade frequency with a cue under dual task for controls (Table 8-5).

Greater change in saccade frequency with a cue (∆Cue) under single task was significantly associated with better attention (FoA; r = -.27, p = .049) in PD. However the only consistent relationship was found in PD between lower saccade frequency change scores (∆Cue and ∆Cue&Door) and greater disease severity, under single (r = -.27, p = .048) and dual task (r = -.30 p = .028, r = -.31 p = .021). Interestingly, for both PD and controls fear of falling (FES-I) was related to saccade frequency (absolute and change score) with a visual cue under dual task. However, the relationship between fear of falling and saccade frequency was opposite within the groups. Specifically people with PD who had greater fear of falling made less frequent saccades during gait with a visual cue (r = -.31, p = .022), and changed their saccade frequency less with a visual cue (r = -.28, p =.037), whereas the opposite was true for controls (Table 8-5).

Table 8-5 – Demographic and clinical relationships with saccade frequency during gait in Parkinson's disease and controls

r (*p*)			Demographics			Clinical			
		Saccade frequency	Age	GDS-15	FES-I	UPDRS III	FOGQ	LED	PD duration
Control	ST	No Cue	-.093 (.612)	.109 (.551)	-.017 (.925)	-	-	-	-
		No Cue & Door	-.115 (.532)	.095 (.606)	-.053 (.774)	-	-	-	-
		Cue	.270 (.135)	-.068 (.711)	.196 (.282)	-	-	-	-
		Cue & Door	.014 (.941)	-.104 (.572)	-.212 (.244)	-	-	-	-
		ΔCue	.272 (.132)	-.135 (.461)	.159 (.385)	-	-	-	-
		ΔCue&Door	.091 (.622)	-.143 (.433)	-.120 (.512)	-	-	-	-
	DT	No Cue	-.101 (.581)	-.342 (.055)	-.274 (.129)	-	-	-	-
		No Cue & Door	-.018 (.924)	-.112 (.543)	-.118 (.521)	-	-	-	-
		Cue	-.059 (.747)	-.084 (.647)	**.504 (.003)***	-	-	-	-
		Cue & Door	-.106 (.565)	-.192 (.291)	-.067 (.714)	-	-	-	-
		ΔCue	.001 (.994)	.101 (.583)	**.552 (.001)***	-	-	-	-
		ΔCue&Door	-.087 (.636)	-.110 (.551)	.010 (.957)	-	-	-	-
PD	ST	No Cue	**.276 (.041)***	-.054 (.697)	-.180 (.187)	.227 (.095)	-.116 (.399)	-.161 (.250)	-.046 (.738)
		No Cue & Door	-.014 (.919)	-.007 (.962)	.031 (.824)	.050 (.720)	-.079 (.566)	-.121 (.388)	-.030 (.830)
		Cue	.065 (.638)	.071 (.604)	.024 (.859)	-.170 (.214)	.007 (.959)	.012 (.931)	.038 (.785)
		Cue & Door	.092 (.505)	-.026 (.848)	-.145 (.293)	-.118 (.391)	-.218 (.109)	-.041 (.771)	-.026 (.849)
		ΔCue	-.132 (.338)	.086 (.534)	.134 (.330)	**-.268 (.048)***	.080 (.562)	.111 (.429)	.057 (.682)
		ΔCue&Door	.094 (.496)	-.017 (.900)	-.155 (.258)	-.149 (.270)	.204 (.135)	.073 (.605)	.003 (.980)
	DT	No Cue	.143 (.299)	-.155 (.258)	.051 (.714)	.244 (.073)	.039 (.778)	.109 (.436)	.012 (.933)
		No Cue & Door	.037 (.791)	.046 (.740)	-.074 (.590)	.266 (.050)	.047 (.731)	-.022 (.878)	.056 (.683)
		Cue	.168 (.220)	-.175 (.202)	**-.309 (.022)***	-.203 (.138)	.150 (.273)	-.043 (.761)	-.041 (.765)
		Cue & Door	.207 (.130)	-.114 (.408)	-.187 (.171)	-.151 (.270)	-.200 (.143)	.037 (.790)	-.061 (.659)
		ΔCue	.064 (.644)	-.062 (.650)	**-.282 (.037)***	**-.296 (.028)***	-.201 (.142)	-.093 (.508)	-.040 (.771)
		ΔCue&Door	.186 (.174)	-.070 (.611)	-.163 (.234)	**-.310 (.021)***	-.229 (.093)	.051 (.719)	-.095 (.492)

[*significance level p<0.05, ST = single task, DT = Dual task]

Table 8-6 - Cognitive and visual function relationships with saccade frequency during gait in controls

r (*p*)		Cognition									Visual functions	
	Saccade frequency	**MoCA**	**ACE-R**	**PoA**	**FoA**	**JLO**	**CLOX 1**	**CLOX 2**	**VOSP-Total**	**Digit span**	**VA**	**CS**
ST	No Cue	-.080 (.665)	.016 (.931)	.017 (.927)	.099 (.588)	.117 (.525)	.146 (.424)	-.099 (.591)	.243 (.181)	-.076 (.681)	-.245 (.176)	.013 (.942)
	No Cue & Door	-.112 (.542)	.132 (.472)	.011 (.950)	.034 (.855)	-.175 (.337)	-.133 (.467)	-.153 (.403)	.022 (.905)	-.102 (.579)	-.018 (.921)	-.049 (.790)
	Cue	-.285 (.114)	-.118 (.520)	.103 (.576)	**.354 (.047)***	.139 (.448)	.052 (.778)	.022 (.903)	.107 (.558)	.085 (.642)	-.210 (.250)	**.366 (.039)***
	Cue & Door	**-.369 (.038)***	-.016 (.930)	-.171 (.350)	.075 (.682)	.059 (.748)	-.057 (.756)	-.046 (.802)	-.036 (.843)	-.031 (.866)	-.032 (.860)	.040 (.826)
	ΔCue	-.150 (.412)	-.100 (.586)	.063 (.731)	.185 (.309)	.013 (.944)	-.075 (.685)	.093 (.613)	-.108 (.557)	.122 (.507)	.034 (.853)	.261 (.148)
	ΔCue&Door	-.195 (.284)	-.104 (.570)	-.135 (.462)	.032 (.860)	.167 (.361)	.051 (.781)	.073 (.691)	-.042 (.818)	.048 (.792)	-.011 (.951)	.064 (.727)
DT	No Cue	-.122 (.506)	.158 (.387)	.025 (.893)	.076 (.679)	.139 (.450)	.078 (.670)	-.181 (.320)	.007 (.969)	-.219 (.228)	.126 (.492)	-.199 (.274)
	No Cue & Door	-.177 (.333)	-.112 (.543)	.059 (.749)	.223 (.221)	-.017 (.925)	-.103 (.573)	.005 (.977)	.152 (.406)	**-.469 (.007)***	.147 (.423)	-.165 (.366)
	Cue	-.255 (.159)	-.002 (.990)	-.043 (.815)	-.149 (.414)	**.371 (.036)***	.127 (.489)	.125 (.495)	.158 (.387)	-.201 (.270)	-.038 (.836)	.001 (.996)
	Cue & Door	-.047 (.799)	.031 (.866)	-.235 (.196)	-.092 (.616)	.249 (.169)	.322 (.073)	**.376 (.034)***	.138 (.451)	-.091 (.620)	-.273 (.130)	-.052 (.776)
	ΔCue	-.150 (.413)	-.081 (.661)	-.048 (.795)	-.161 (.379)	.237 (.191)	.066 (.721)	.193 (.289)	.127 (.488)	-.057 (.757)	-.094 (.609)	.100 (.587)
	ΔCue&Door	.065 (.724)	.097 (.597)	-.253 (.162)	-.222 (.223)	.241 (.184)	**.361 (.042)***	.345 (.053)	.034 (.852)	.204 (.264)	-.343 (.055)	.053 (.773)

[*significance level p<0.05, ST = single task, DT = Dual task]

Table 8-7 - Cognitive and visual function relationships with saccade frequency during gait in Parkinson's disease

r (*p*)		Cognition									Visual functions	
	Saccade frequency	**MoCA**	**ACE-R**	**PoA**	**FoA**	**JLO**	**CLOX 1**	**CLOX 2**	**VOSP-Total**	**Digit span**	**VA**	**CS**
ST	No Cue	.032	-.076	**.269**	.264	-.028	.051	-.036	-.059	-.034	.042	-.016
		(.815)	(.579)	**(.047)***	(.052)	(.840)	(.709)	(.796)	(.669)	(.805)	(.758)	(.907)
	No Cue & Door	.060	.101	-.029	-.161	.021	.260	.131	.125	-.027	-.137	.087
		(.662)	(.464)	(.836)	(.240)	(.880)	(.055)	(.341)	(.362)	(.842)	(.319)	(.527)
	Cue	-.111	-.258	.088	-.138	.241	-.090	.178	.009	.066	.047	-.047
		(.422)	(.057)	(.522)	(.314)	(.076)	(.514)	(.195)	(.948)	(.633)	(.736)	(.731)
	Cue & Door	.063	.093	-.075	-.168	.247	.011	.242	.147	.003	-.062	-.031
		(.646)	(.499)	(.588)	(.220)	(.070)	(.937)	(.076)	(.285)	(.985)	(.655)	(.825)
	ΔCue	-.017	-.135	.111	**-.267**	.190	-.097	.150	.044	.069	.006	-.023
		(.900)	(.325)	(.429)	**(.049)***	(.165)	(.480)	(.275)	(.747)	(.617)	(.966)	(.865)
	ΔCue&Door	.002	-.008	.073	-.004	.199	-.224	.096	.017	.027	.069	-.105
		(.991)	(.952)	(.605)	(.978)	(.145)	(.100)	(.486)	(.902)	(.845)	(.618)	(.444)
DT	No Cue	-.198	-.201	.125	.102	-.189	-.104	-.177	-.062	.138	.017	-.040
		(.147)	(.142)	(.364)	(.460)	(.166)	(.451)	(.195)	(.653)	(.314)	(.899)	(.774)
	No Cue & Door	-.014	.003	.014	-.083	.046	.043	.049	-.093	-.022	-.086	.088
		(.917)	(.982)	(.916)	(.547)	(.740)	(.754)	(.724)	(.499)	(.874)	(.534)	(.524)
	Cue	.017	.028	.026	-.158	.108	-.093	.047	.046	-.038	.098	-.010
		(.905)	(.840)	(.852)	(.250)	(.432)	(.498)	(.733)	(.738)	(.781)	(.478)	(.942)
	Cue & Door	.159	.064	-.104	-.187	.075	.085	**.286**	-.082	.002	.096	-.130
		(.245)	(.643)	(.449)	(.171)	(.585)	(.540)	**(.034)***	(.549)	(.991)	(.484)	(.343)
	ΔCue	.118	.129	-.093	-.184	.189	-.022	.132	.071	-.105	.071	.013
		(.391)	(.349)	(.508)	(.179)	(.167)	(.872)	(.335)	(.608)	(.447)	(.605)	(.927)
	ΔCue&Door	.169	.062	.051	-.139	.048	.059	.259	-.027	.015	.148	-.183
		(.219)	(.652)	(.719)	(.313)	(.725)	(.668)	(.056)	(.842)	(.916)	(.282)	(.181)

[*significance level p<0.05, ST = single task, DT = Dual task]

2(b): Relationship between demographics, cognition, vision and saccade frequency when using a visual cue; Regression

A series of multivariate regression models were used to further investigate saccade frequency during gait with a visual cue in PD and controls. Model characteristics (Beta coefficients and *p*-values) under single and dual task are shown in Tables 8-8 (controls) and 8-9 (PD). Associations between variables was the focus of this analysis, therefore overall model characteristics (r^2, ANOVA *F, p*) are presented within the Appendix 21.0.

Table 8-8 demonstrates that there were no explanatory variables within the final regression models (Model 4) for controls, although under dual task several independent variables trended towards significant association. When using a visual cue poorer attention (FoA; ∆Cue, ß = -.47, *p* = .090), visuo-spatial ability (JLO; ∆Cue, ß = .46, *p* = .078) and visual function (VA; ∆Cue&Door, ß = -.47, *p* = .050) trended towards association with lower saccade frequency change scores. These associations increased within the final visuo-cognitive model compared to separate models.

In contrast, Table 8-9 shows that there were several significantly associated variables with saccade frequency change scores in PD. Attention (FoA; ß = -.35, *p* = .035) and visual function (CS; ß = -.45, *p* = .033) were significantly related to change in saccade frequency with a visual cue (ΔCue). Poorer CS and better attention (FoA) related to greater change in saccade frequency with a visual cue in PD. There was also a trend for visuo-spatial ability (JLO; ß = .34, *p* = .051) and executive function (CLOX1; ß = -.31, *p* = .075) towards association with saccade frequency change with a cue and door (ΔCue&Door). This indicated that visuo-cognitive association with change in saccade frequency may be task-dependent. However trend associations were weak and may have occurred by chance.

Under dual task there were very few significant associations in PD, as only one condition had a significant variable within the final model (Model 4, Table 8-9). Greater disease severity (UPDRS III; ß = -.43, *p* = .024) was related to lower saccade frequency change score with a cue and door (ΔCue&Door). Disease severity was significantly associated with change scores within several single task demographic and visual function models (Model 1 and Model 3, Table 8-9).

However with the addition of cognitive functions the association between disease severity and saccade frequency change score became non-significant, seen via separate models (Model 2 and Model 4). Similarly, advanced age was found to relate to greater change in saccade frequency with a cue and door (ΔCue&Door, Model 1 and 2) under dual task in PD. However association with age was not present with the inclusion of visual functions in the model (Model 3 and Model 4). This evidence indicated that association between demographics and saccade frequency change score may have been mediated by cognitive and visual functions in PD.

Overall, cognitive (attention; FoA) and visual functions (CS) were significantly associated with saccade frequency (change score) independent of demographic characteristics, particularly under single task conditions. Significant cognitive and visual function relationships with saccade frequency (change score) were primarily seen within the final combined model (Model 4), which may indicate interaction between cognitive and visual functions.

Table 8-8 - Demographic, cognitive and visual function association with saccade frequency in controls

Task	Visual sampling		Pearsons r (*p*)	Model 1 ß	Model 1 *p*	Model 2 ß	Model 2 *p*	Model 3 ß	Model 3 *p*	Model 4 ß	Model 4 *p*
Single	ΔCue	Age	.272 (.132)	.280	.146	.240	.354	.249	.212	.232	.410
		MoCA	-.150 (.412)	-.061	.746	-.112	.609	-.025	.895	-.055	.813
		GDS-15	-.135 (.461)	-.168	.365	-.141	.480	-.161	.391	-.139	.500
		FoA	.185 (.309)			.060	.822			.050	.859
		JLO	.013 (.944)			.045	.852			.061	.814
		CLOX 1	-.075 (.685)			-.072	.774			-.067	.812
		Digit span	.122 (.507)			.207	.350			.125	.621
		VA	.034 (.853)					.071	.721	.026	.917
		CS	.261 (.148)					.248	.215	.199	.407
	ΔCue&Door	Age	.091 (.622)	.068	.727	.134	.612	.070	.736	.165	.574
		MoCA	-.195 (.284)	-.164	.401	-.198	.382	-.161	.431	-.205	.404
		GDS-15	-.143 (.433)	-.136	.475	-.104	.611	-.134	.499	-.096	.655
		FoA	.032 (.860)			-.070	.797			-.092	.753
		JLO	.167 (.361)			.167	.505			.189	.487
		CLOX 1	.051 (.781)			-.010	.969			-.048	.870
		Digit span	.048 (.792)			.078	.730			.102	.700
		VA	-.011 (.951)					-.015	.943	-.082	.754
		CS	.064 (.727)					.019	.929	-.032	.898
Dual	ΔCue	Age	.001 (.994)	-.062	.752	.216	.390	-.046	.825	.300	.270
		MoCA	-.150 (.413)	-.179	.363	-.156	.463	-.171	.404	-.136	.544
		GDS-15	.101 (.583)	.128	.503	.158	.416	.138	.487	.183	.358
		FoA	-.161 (.379)			-.400	.130			-.472	.090
		JLO	.237 (.191)			.377	.119			.455	.078
		CLOX 1	.066 (.721)			-.132	.590			-.241	.380
		Digit span	-.057 (.757)			-.114	.593			-.104	.667
		VA	-.094 (.609)					-.088	.677	-.221	.359
		CS	.100 (.587)					.056	.790	.051	.822
	ΔCue&Door	Age	-.087 (.636)	-.056	.778	.104	.681	.025	.900	.280	.281
		MoCA	.065 (.724)	.062	.752	-.052	.810	.054	.783	-.089	.677
		GDS-15	-.110 (.551)	-.108	.575	-.079	.687	-.085	.653	-.033	.862
		FoA	-.222 (.223)			-.189	.472			-.317	.226
		JLO	.241 (.184)			.076	.750			.207	.388
		CLOX 1	**.361 (.042)***			.273	.277			.054	.836
		Digit span	.204 (.264)			.071	.743			.202	.386
		VA	-.343 (.055)					-.356	.089	-.468	.050
		CS	.053 (.773)					-.058	.771	-.171	.438

[*significance level *p*<.05, ß = standardised regression coefficient, Model 1 = demographic, Model 2 = cognition, Model 3 = visual function, Model 4 = cognition and visual function, Model performance can be found in the Appendix]

Table 8-9 - Demographic, cognitive and visual function association with saccade frequency in Parkinson's disease

Task	Visual sampling		Pearsons r (*p*)	Model 1 ß	Model 1 *p*	Model 2 ß	Model 2 *p*	Model 3 ß	Model 3 *p*	Model 4 ß	Model 4 *p*
Single	ΔCue	Age	-.132 (.338)	-.051	.720	-.074	.627	-.151	.357	-.281	.097
		UPDRS III	**-.268 (.048)***	-.431	**.012***	-.297	.113	-.466	**.008***	-.294	.101
		MoCA	-.017 (.900)	-.205	.185	-.215	.231	-.231	.144	-.346	.057
		GDS-15	.086 (.534)	.220	.158	.187	.256	.205	.192	.154	.326
		FoA	**-.267 (.049)***			-.196	.216			-.348	**.035***
		JLO	.190 (.165)			.113	.483			.209	.189
		CLOX 1	-.097 (.480)			-.151	.359			-.129	.411
		Digit span	.069 (.617)			.096	.482			.190	.167
		VA	.006 (.966)					-.052	.772	-.008	.961
		CS	-.023 (.865)					-.230	.252	-.451	**.033***
	ΔCue&Door	Age	.094 (.496)	.138	.359	.017	.912	.084	.631	-.067	.715
		UPDRS III	-.149 (.278)	-.240	.173	-.124	.516	-.259	.156	-.123	.526
		MoCA	.002 (.991)	-.079	.623	-.002	.993	-.092	.580	-.055	.778
		GDS-15	-.017 (.900)	.100	.540	-.013	.940	.092	.579	-.026	.881
		FoA	-.010 (.945)			.106	.513			.044	.804
		JLO	.199 (.145)			.305	.071			.344	.051
		CLOX 1	-.224 (.100)			-.319	.063			-.310	.075
		Digit span	.027 (.845)			.005	.974			.043	.773
		VA	.069 (.618)					-.016	.933	-.003	.989
		CS	-.105 (.444)					-.119	.574	-.183	.418
Dual	ΔCue	Age	.064 (.644)	.131	.371	.121	.449	.144	.393	.121	.513
		UPDRS III	**-.296 (.028)***	-.369	**.033***	-.301	.121	-.357	.045	-.290	.143
		MoCA	.118 (.391)	-.022	.890	-.016	.931	-.004	.979	-.010	.960
		GDS-15	-.062 (.650)	.121	.772	.073	.667	.130	.420	.080	.644
		FoA	-.184 (.179)			-.069	.673			-.077	.666
		JLO	.189 (.167)			.109	.513			.116	.509
		CLOX 1	-.022 (.872)			-.045	.789			-.043	.804
		Digit span	-.105 (.447)			-.146	.306			-.133	.379
		VA	.071 (.605)					.131	.481	.120	.531
		CS	.013 (.927)					.100	.627	.066	.772
	ΔCue&Door	Age	.186 (.174)	.283	**.048***	.348	**.027***	.201	.215	.251	.158
		UPDRS III	**-.310 (.021)***	-.380	**.023***	-.440	**.021***	-.404	**.019***	-.434	**.024***
		MoCA	.169 (.219)	.058	.700	.024	.892	.046	.764	-.034	.855
		GDS-15	-.070 (.611)	.172	.260	.231	.161	.164	.286	.219	.189
		FoA	-.139 (.313)			-.066	.677			-.141	.410
		JLO	.048 (.725)			-.172	.289			-.124	.460
		CLOX 1	.059 (.668)			.163	.321			.175	.292
		Digit span	.015 (.916)			-.015	.911			.035	.811
		VA	.148 (.282)					.043	.809	.050	.783
		CS	-.183 (.181)					-.141	.475	-.182	.405

[*significance level *p*<.05, ß = standardised regression coefficient, Model 1 = demographic, Model 2 = cognition, Model 3 = visual function, Model 4 = cognition and visual function, Model performance can be found in the Appendix]

3: Relationship between saccade frequency and gait when using a visual cue

Table 8-10 demonstrates associations between gait characteristics and saccade frequency (absolute and change scores) when using a visual cue. Results indicate that there were no significant relationships between these features for controls, but there were for people with PD. More frequent saccades during gait in PD were related to better gait performance shown by reduced step time (r = -.28, *p* = .037) under single task, and increased velocity (r = .34, *p* = .012), reduced step time (r = -.32, *p* = .017) and single support time (r = -.30, *p* = .027) under dual task. Similarly greater change in saccade frequency with a visual cue (ΔCue and ΔCue&Door) in PD related to reduced step time under single (r = -.32, *p* = .016) and dual task (r = -.30, *p* = .028), and increased velocity (r = .30, *p* = .028) under dual task.

Table 8-10 - Correlations between saccade frequency during gait and gait characteristics with a visual cue

	Attentional manipulation		Step Length (m)	Velocity (m/s)	Step Time (s)	Single Support Time (s)	Double Support Time (s)
Group	**Cognitive Task**	**Environment**	**r (*p*)**	**r (*p*)**	**r (*p*)**	**r (*p*)**	**r (*p*)**
Control	Single	Cue	-.077 (.674)	-.083 (.651)	.069 (.706)	.045 (.807)	-.031 (.867)
		Cue & Door	.082 (.656)	-.043 (.813)	.184 (.313)	.154 (.402)	.071 (.699)
		ΔCue	-.066 (.720)	-.046 (.802)	.019 (.920)	.085 (.642)	-.113 (.537)
		ΔCue&Door	-.233 (.199)	-.251 (.166)	.029 (.875)	-.086 (.641)	.059 (.746)
	Dual	Cue	-.181 (.322)	-.044 (.812)	-.073 (.693)	.017 (.928)	.018 (.922)
		Cue & Door	-.015 (.937)	.024 (.897)	-.121 (.509)	-.088 (.633)	-.050 (.785)
		ΔCue	-.314 (.080)	-.214 (.238)	.043 (.814)	.044 (.812)	.137 (.453)
		ΔCue&Door	-.056 (.761)	-.119 (.516)	.075 (.682)	.017 (.928)	.074 (.687)
PD	Single	Cue	.032 (.814)	.185 (.176)	-.169 (.217)	-.247 (.069)	.034 (.806)
		Cue & Door	-.116 (.399)	.127 (.356)	**-.283 (.037)***	-.195 (.154)	-.251 (.065)
		ΔCue	.047 (.732)	.140 (.309)	-.142 (.303)	-.191 (.163)	.016 (.906)
		ΔCue&Door	.028 (.837)	.203 (.137)	**-.323 (.016)***	-.219 (.108)	-.208 (.127)
	Dual	Cue	.062 (.652)	**.336 (.012)***	**-.320 (.017)***	**-.298 (.027)***	-.152 (.267)
		Cue & Door	.159 (.247)	.149 (.279)	-.161 (.241)	-.069 (.616)	.056 (.682)
		ΔCue	.033 (.812)	**.296 (.028)***	**-.296 (.028)***	-.218 (.110)	-.158 (.250)
		ΔCue&Door	.258 (.058)	.109 (.427)	-.037 (.791)	.039 (.780)	.094 (.494)

[Gait characteristics from each individual task were correlated with saccade frequency from the same task, change scores were correlated with gait characteristics during the attentional task (e.g. cue or cue & door)]

8.5. Discussion

This is the first study to examine response in saccade frequency during gait to a visual cue in PD and aged-matched controls, under both single and dual task. The findings of this investigation support the hypothesis that visual cues increase saccade frequency during gait in people with PD and controls, and that response is maintained under dual task.

Descriptive data showed that saccade frequency was less frequent in PD compared to controls during gait and reduced for both groups under a dual task, which was in line with chapter 7 and previous research (Galna *et al.*, 2012; Vitorio *et al.*, 2012). Similarly both people with PD and controls increased saccade frequency during gait when they walked through a door. However, within the current study, the main focus was investigation of saccade frequency during gait when attention was manipulated by using a visual cue (under single and dual task) and results demonstrated a significant response.

8.5.1. What is the effect of a visual cue on saccade frequency during gait?

The novel finding from this study was that visual cues ameliorated reduction in saccade frequency during gait in PD, a finding that was maintained under dual task. Saccade frequency significantly increased in both groups (PD, control) when using a visual cue, and saccade frequency under a dual task was similar to single task performance. To date no previous studies have assessed saccade frequency response to visual cues, which limits methodological comparison. Vitorio *et al.* (2013) investigated visual sampling (frequency of voluntary visual samples made using liquid crystal glasses rather than saccades; described in chapter 3) during a similar task of stepping over an obstacle and reported that people with PD sampled their environment significantly less than controls. The same authors also investigated the number of fixations made during gait when using a visual cue (transverse lines 60cm apart to step on) (Vitorio *et al.*, 2014), and demonstrated a non-significant increase in fixation number within a small group of people with PD and controls, similar to the current study. Due to saccades and fixations being coupled (i.e. saccades are the movements between fixations), it is likely that within the previous study saccade frequency and number

were also increased in both groups with a visual cue. As discussed in chapter 7, an increase in saccade frequency during gait with environmental stimuli may relate to attentional mechanisms (i.e. an increase in bottom-up reflexive saccades), which most likely influenced visual cue response.

Similar to previous research (Galna *et al.*, 2012), saccade frequency during gait was seen to significantly decrease under dual task when walking without a visual cue in both groups. Saccade frequency reduction under dual task was previously discussed in chapter 7, with attention implicated. When attention was manipulated with a visual cue under dual task saccade frequency significantly increased in both groups to a level comparable to response under single task. Maintenance of saccade response under dual task possibly relates to a combination of resource allocation away from inhibitory control and the influence of the external stimuli (taped lines) on saccade initiation. For example, visual cues may trigger more reflexive saccades (bottom-up) and free attentional resources (top-down) to be applied to other concurrent tasks (i.e. cognitive or gait task). Indeed, both groups improved on the secondary cognitive task when using a cue with greater response in PD (Table 8-2), which is comparable to previous cue research (van Wegen *et al.*, 2006; Baker *et al.*, 2007; Rochester *et al.*, 2007; Mak *et al.*, 2013). Therefore saccade frequency response to a visual cue may be driven primarily by bottom-up attention, particularly in PD. This is further supported by evidence from PD dementia (PDD) research which demonstrated that despite frontal deterioration people with PDD respond to external cues (Gräber *et al.*, 2014), showing improved gait (Azulay *et al.*, 2002; Azulay *et al.*, 2006). However unlike PD patients with normal cognition once the cue was removed PDD patients had worse gait (Rochester *et al.*, 2010), likely due to being unable to activate bottom-up attention without external stimuli. Attentional mechanisms (top-down and bottom-up) likely drive saccade frequency during gait in PD (this is further discussed in section 8.5.5).

8.5.2. What is the effect of a visual cue on gait?

Gait outcomes were not the primary focus of this study. However people with PD were seen to have significantly impaired gait (step length, velocity, step time and double support time) compared to controls during all of the walking conditions (no

cue or cue). An unexpected finding was that the visual cue significantly reduced step length in both people with PD and controls, whereas previous studies that have investigated visual cues have demonstrated increased step length (Morris *et al.*, 1996; Lewis *et al.*, 2000). Disparity between the current study and previous research most probably relates to limitations of the visual cue protocol, such as the set distance of the transverse lines. With a visual cue both groups adapted their gait strategy to complete the task (i.e. step over the lines placed 50cm apart). However the majority of the participants (PD n = 40, control n = 29) had a large mean baseline step length (un-cued; >50cm) and adapted their gait by reducing step length. Whereas only a minority of participants (PD n = 15, control n = 3) had a small baseline step length (un-cued; <50cm) and increased step length with a cue. Reduction in step length with a cue was therefore a result of the use of a set distance, rather than tailoring the distance to individual baseline step length (e.g. 20% greater than baseline step length). These findings support the theory that cue response is individual in terms of gait adaptation (Holmes *et al.*, 2015).

Regardless of the protocol limitation, people with PD did not adapt their gait (i.e. reduce step length and velocity) as much as controls with a visual cue or dual task. Diminished response may have been related to the reduced step length in PD compared to controls during gait (un-cued) under single and dual task, which would have limited reduction seen with a cue or dual task. It could also relate to an inability to appropriately alter gait in response to increased attentional demand. Lack of gait adaptation in PD may also be impacted by a variety of mechanical and sensory impairments, such as; disease severity (Schwed *et al.*, 2013; Catalá *et al.*, In Press; 2016), response to levodopa medication (Roemmich *et al.*, 2014), rigidity and bradykinesia (Winogrodzka *et al.*, 2005), and impaired integration of sensory (visual, proprioceptive, vestibular) and motor information (Wright *et al.*, 2010; Pieruccini-Faria *et al.*, 2014; Ashoori *et al.*, 2015). Gait adaptation with a cue however led to comparable step lengths between the groups (PD and controls) under both single and dual task (i.e. closer to the 50cm visual cue distance). Step lengths were also more consistent within the groups (i.e. a lower SD with a cue, Figure 8-5), which is possibly because participants altered gait to step closer to the 50cm distance.

8.5.3. What are the relationships between demographics, cognition, vision and gait when using a visual cue?

Gait was selectively associated with demographic features, cognitive and visual functions when using a visual cue. Surprisingly, cued gait (step length, velocity and double support time) was not associated with cognitive and visual functions for controls, unlike un-cued gait (Appendix 19.0). However several demographic features (age, weight, depression and fear of falling) in controls were related to gait outcomes. In contrast, poorer gait when using a visual cue was significantly associated with selective impairment of demographic features (depression, fear of falling, disease severity), as well as cognitive (attention and visuo-spatial ability) and visual functions (VA) in people with PD (Appendix 20.0). This was expected as people with PD may require greater cognitive and visual input for gait when using a visual cue compared to controls (Azulay *et al.*, 2006).

8.5.4. What are the relationships between demographics, cognition, vision and saccade frequency when using a visual cue?

Saccade frequency (absolute and change scores) during gait was not related to many demographic, clinical, cognitive and visual function variables within both groups. This may have been due to fluctuations in the type of saccades being generated during gait (voluntary or reflexive) (Anderson and MacAskill, 2013), which involve neural networks that may be too subtle to be evaluated with standard cognitive or visual assessments. Lack of association may also relate to the fact that the cues were high contrast compared to the floor and specific instructions were provided to step over the lines, and therefore the visual cues may not have challenged visual or cognitive mechanisms. Despite limitations there were several significant but weak associations, which were important to highlight.

In line with results of chapter 7, associations between attention and saccade frequency in PD indicated that without a visual cue people with PD who have better attention may have intact or better inhibitory control of saccades during gait (i.e. saccades are voluntary movements controlled by top-down attention). Whereas people with PD who have poorer attention have less capability to inhibit

reflexive (bottom-up) saccades (Terao *et al.*, 2011) and become easily distracted, and hence make saccades to irrelevant areas without a visual cue to focus visual sampling. Indeed, people with PD who had poorer attention made significantly more frequent saccades during single task straight un-cued walking and did not change their saccade frequency with a visual cue as much as those with better attention. In contrast, better attention was seen to relate to more frequent saccades with a visual cue for controls, indicating that older adults may primarily use top-down attention to respond to visual cues during gait.

As mentioned, the two main theories on visual cue response involve *attention* (cognitive function) and *optic flow* (visual function), however previous studies have alluded to the fact that individual cognitive or visual functions cannot solely influence cue response in PD (Azulay *et al.*, 2006; Lebold and Almeida, 2011). Response may be underpinned by interaction between such functions (i.e. visuo-cognition); however this has not previously been investigated. Unexpectedly visual function was not correlated with saccade frequency during gait in PD, but was in controls. However attention (FoA) and visual functions (CS) may interact in PD, and interaction may influence association with saccade frequency (change score) with a visual cue. Indeed, when cognitive and visual functions were combined within the same regression model both features (FoA and CS) had significant association with saccade frequency (ΔCue, Model 4) in PD, unlike relationship within the separate cognitive and visual function models.

Other relationships with saccade frequency in PD and controls were similar to previous saccadic activity research, such as association with age (Munoz *et al.*, 1998), global cognition (Liversedge and Findlay, 2000), visuo-spatial ability (Pearson and Sahraie, 2003), working memory (Mitchell *et al.*, 2002; Chun, 2011) and fear of falling (Turano *et al.*, 2002; West *et al.*, 2011; Young and Hollands, 2012). These associations suggested that there was some truth to the *a priori* hypothesis that demographic features would relate to saccade frequency with a cue, along with cognitive and visual variables. Indeed, disease severity (UPDRS III) appeared to be consistently associated with change in saccade frequency during gait with a cue in PD, particularly under dual task. For example; more advanced PD related to less change in saccade frequency with a visual cue, which was similar to results of environmental challenge found in Chapter 7.

Generally people with PD made less frequent saccades than controls during gait and a similar frequency when using a visual cue (Figure 8-4), however within PD there may be a non-linear impairment of saccade frequency during straight walking which impacts change score results (Figure 7-6). There was no significant relationship between disease severity and absolute saccade frequency scores in PD (Straight, Cue, Cue&Door). However, Figure 7-6 depicts that people with milder PD may not make as many saccades during straight walking (Hypo-reflexive) as those with more advanced PD (Hyper-reflexive), likely due to an inability to initiate top-down saccades but intact ability to control reflexive (bottom-up) saccades. People with PD were able to increase their saccade frequency with a visual cue (ΔCue, ΔCue&Door), however those with more advanced PD increased their frequency less than those with milder PD. There was no strict bi-modal response seen, but the results may relate to greater control/inhibition of reflexive saccades in mild PD (i.e. they made few reflexive saccades during straight walking but with the addition of visual stimuli more reflexive saccades were permitted). Alternatively those with more severe PD made more reflexive saccades during straight walking (i.e. unable to control reflexive activity), which only mildly increased with the addition of visual stimulus.

Cognition, particularly attention may have influenced disease severity association, as the same relationships with saccade frequency were found for attention. Attentional impairment is common with more severe disease such as those who report FOG (Sarasso *et al.*, 2015) or people who are within the PIGD phenotype (Taylor *et al.*, 2008), who present with greater motor impairment (i.e. higher UPDRS III score) (Amboni *et al.*, 2015). Indeed, saccades have been found to be further impaired in FOG compared to no-FOG (Lohnes and Earhart, 2011). Similarly splitting the PD group into motor phenotypes demonstrated that PIGD phenotype had greater UPDRS III scores (n = 23; 42.87 ± 14.99) compared to those in the TD phenotype (n = 28; 32.04 ± 12.59), which suggests that disease severity associations may relate to motor phenotype with links to attentional impairment despite lack of significant association. Overall, regression analysis disproved the *a priori* hypothesis that demographic features would relate to saccade frequency along with cognitive and visual functions. Results demonstrated that cognitive and visual functions were significantly associated

with saccade frequency independent of demographic and clinical features in PD. However, when cognition was saturated via a dual task such features (UPDRS III) significantly related to saccade frequency in the final model (Model 4), which highlighted that cognition may mediate demographic and clinical relationships.

8.5.5. Attentional response to visual cues: Top-down and Bottom-up

Attentional contribution was required when using a visual cue due to the use of goal-orientated instructions to step over the transverse lines (Macdonald and Tatler, 2013). Traditionally, the theory of attentional response to visual cues considers attentional signal to come from the frontal cortex (i.e. PFC, ACC etc.) to the caudate nucleus (Leisman *et al.*, 2014), which allows people with PD to circumvent BG impairment (Rubinstein *et al.*, 2002). However people with PD rely on attention for both gait (Redgrave *et al.*, 2010; Seidler *et al.*, 2010; Shine *et al.*, 2013a) and saccadic control (Baluch and Itti, 2011; Borji *et al.*, 2011), which increases PFC burden and may lead to voluntary saccade impairment or fluctuation during gait (Lemos *et al.*, 2015). Therefore other attentional mechanisms and structures (e.g. PPC, parietal eye-field) that have not been considered in previous gait research may also be involved in saccade frequency cue response, such as bottom-up attention which is relatively spared in PD (Terao *et al.*, 2013). Indeed, a recent imaging study demonstrated that people with PD who were ‘ON’ medication had greater activation of both PFC and posterior (occipital and parietal lobes) regions than controls when performing pro- and anti-saccades than PD ‘OFF’ medication or controls (Lemos *et al.*, 2015), implicating both frontal and parietal attentional networks in PD saccade facilitation. Visual cues which are especially prominent or salient may circumvent top-down (frontal) attentional influence during gait and facilitate saccade generation in a reflexive bottom-up (parietal controlled) attentional manner (Connor *et al.*, 2004; Bressler *et al.*, 2008; Mannan *et al.*, 2008; Noudoost *et al.*, 2010; Theeuwes, 2010; Botha and Carr, 2012), which may indicate artificial drive of eye movements while walking with a cue.

The theory of increased reflexive saccade generation during gait is further supported by higher saccade peak velocities and accelerations seen for people with PD compared to controls during all of the walking conditions (Reingold and

Stampe, 2002) (Appendix 18.0). However within both groups, there was also a non-significant reduction in peak velocities and accelerations when using a visual cue. Similar reduction in peak velocities have occurred in PD when making saccades to remembered target locations (Lueck *et al.*, 1990), with working memory implicated (Sawaguchi and Goldman-Rakic, 1991). Saccade frequency response to visual cues may therefore be due to an increase in memory guided saccades (a type of voluntary saccade), which could indicate that participants pre-planned locations to visually sample prior to walking, and then carried out this plan during gait. However an increase in memory guided saccades would increase burden on the PFC and impact concurrent tasks (cognition or gait) (Sawaguchi and Goldman-Rakic, 1991), which was not seen in this study. Therefore it is more likely that an increase in reflexive saccades driven by bottom-up attention was responsible for the increase in saccade frequency during gait with a visual cue. Bottom-up attentional processing of stimuli does not place a large demand on the PFC and would allow neural resource to be allocated to other processes (Beck and Kastner, 2009). However the type of saccades (voluntary or reflexive) being initiated during gait in PD remains unclear as these are complex processes yet to be fully understood or investigated.

8.5.6. What is the relationship between saccade frequency and gait when using a visual cue?

Saccade frequency during gait when using a visual cue may contribute to gait control, as processes involved in saccade generation interact with motor output in conjoined cortical regions (Kravitz *et al.*, 2011). For example, visuo-motor processing from sensory input to final motor output involves some of the same anatomical structures and regions such as the pre-frontal, frontal and motor cortex (Wurtz *et al.*, 2001). Further, saccade frequency and gait may be coupled when using a visual cue, particularly in people with PD. Within this study all participants (PD and controls) increased their saccade frequency during gait and adapted their gait strategy with a visual cue. However, better gait characteristics (increased velocity, reduced step time and single support time) when using a visual cue were significantly associated with increased saccade frequency for people with PD, particularly under dual task. This evidence further supports an increase in reflexive saccades in PD, as a visual cue probably triggered bottom-

up attention and freed attentional (top-down) resources which were subsequently applied to gait. Gait response to visual cues therefore related to saccade frequency response, undoubtedly due to common visuo-cognitive mechanisms.

Saccade frequency was independently associated with cognitive (attention) and visual functions (CS) rather than demographic features, similar to previous findings in Parkinsonian cognition and gait research (Lord *et al.*, 2014). The complex relationships between cognition, vision, saccade frequency and gait in PD when using a visual cue require further exploration (Chapter 9 extends this investigation). Ultimately, an increase in saccade frequency with a visual cue would increase visual information during gait to be used for gait control, with implication for safe and effective navigation.

8.6. Conclusions

In summary, the study described in this chapter showed that saccade frequency during gait occurred less frequently in people with PD compared to controls, which was in line with chapter 7. However the novel finding of this study was that saccade frequency during gait significantly increased with a visual cue in both people with PD and controls, which was maintained (similar to single task) under a dual task. Cognitive and visual functions were independently associated with saccade frequency response to a visual cue in PD. Attention and visual function may interact in people with PD to influence relationship with saccade frequency. Saccade frequency response in PD was associated with selective gait characteristics when using a visual cue. Greater understanding of these features (cognition, visual function, saccade frequency and gait) is required which will allow for the development of more effective intervention.

9. Modelling direct and indirect relationships

9.1. Summary

The purpose of this chapter was to present data relating to gait impairment in PD and its relationship to visuo-cognition (interaction between cognitive and visual functions, measured through saccade frequency). The visuo-cognitive and gait data discussed within previous chapters (Chapters 7 and 8) were analysed. Data were given a structure based on an *a priori* hypothesised model in order to determine whether gait impairment in PD results from dysfunctional visuo-cognition or is facilitated by indirect relationship through cognition or visual function. The structured model was also manipulated via entering data obtained when using a visual cue to further understand the effect of cues on visuo-cognition and gait in PD.

9.2. Introduction

Within this chapter an *a priori* hypothesised model of visuo-cognition in gait in PD (Figure 9-1) was investigated, which was based upon the background to this thesis (Chapters 2 and 3; Figure 2-1). Previous studies including analysis performed in chapters 7 and 8 have investigated multivariate relationships between visuo-cognitive and gait features in PD. Such investigation has shown that relationships between cognition, visual function, saccade frequency and gait exist. Subsequent multiple regression analysis (Chapters 7 and 8) has shown that cognitive (primarily attention) and visual functions dominate association with saccade frequency in PD independent of demographic characteristics (age, disease severity, global cognition, depression). Despite cognitive and visual functions being related to saccade frequency and gait characteristics in PD, there was no association between saccade frequency and gait. This chapter explores this further to understand the nature of the relationship between cognitive and visual function, and their interactive visuo-cognitive impact on gait in PD.

Bivariate and multivariate analyses have allowed for a broad amalgamation of visuo-cognitive features and their relationship to gait in PD, but provide sparse information regarding interactions or indirect effects between these features. The important and novel aspect of this chapter is that these relationships are now

given a structure through an *a priori* model, which involves multiple analyses and will provide a basis for future hypothesis generation. Once a robust model is developed it can then be manipulated for various predictions related to the effect of visual cues and development of effective gait rehabilitation in PD. This is a vital step for the field as such a model would bring together visuo-cognitive features in gait with interactions and allow testing of the underlying mechanisms involved in PD saccade frequency and gait impairment or response.

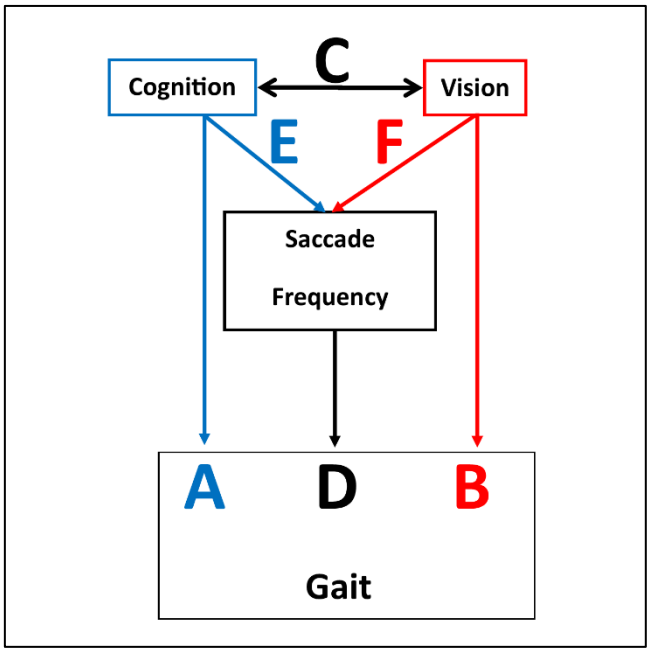


Figure 9-1– Full model of visuo-cognition in gait in Parkinson's disease

[Six pathways are involved within the full model; A) Cognition and gait, B) Vision and gait, C) Interaction between cognitive and visual functions (termed visuo-cognition), D) Saccade frequency and gait, E) Cognition and saccade frequency, and F) Visual functions and saccade frequency]

Structural equation modelling (SEM) provides a useful method to examine relationships between visuo-cognitive features and gait in people with PD (Figure 9-1). SEM allows investigation of direct and indirect relationships between cognitive and visual functions, saccade frequency during gait and gait. SEM represents multivariate analysis and involves the combination of correlation, regression, ANOVA, path analysis and factor analysis (Musil *et al.*, 1998), which enables examination of relationships between both observed and latent (un-observed) variables. Therefore SEM is an ideal statistical technique for testing *a priori* models as it can identify various direct and indirect relationships between different variables, with use of hypothesised pathways.

Within this study an SEM was created based on the *a priori* hypothesis that interactions between cognitive and visual functions (visuo-cognition, Figure 9-1(C)) underpin saccade frequency (Figure 9-1(E and F)) and gait (Figure 9-1(D)) in PD. Based on correlations and regression results within previous chapters (Chapters 7 and 8), it was hypothesised that cognition, particularly attention would play a central role in all visuo-cognitive and gait relationships. However when using a visual cue, it was hypothesised that association between visuo-cognitive features (attention and visual function) and saccade frequency would be selectively altered.

To assess these specific hypotheses several questions were raised, which form the structure of the analysis, results and discussion of this study.

Questions that this study will answer;

- How does visuo-cognition relate to gait impairment in Parkinson's disease?
- How does a visual cue influence the relationship between visuo-cognition and gait in Parkinson's disease?

9.3. Specific methods

Data from the previous two chapters (Chapters 7 and 8) was used to explore direct and indirect relationships between cognitive and visual functions, saccade frequency and gait in PD. For descriptive data regarding these features see the results sections within chapters 7 and 8.

9.3.1. Statistics for Structural Equation Modelling

Data were assessed for normality with visual histograms and Kolmogorov-Smirnov tests, meeting criteria for parametric analysis (Expósito-Ruiz *et al.*, 2010; Ghasemi and Zahediasl, 2012; Field, 2013). In order to assess the presented theoretical visuo-cognition in gait in PD model (Figure 9-1), two SEMs were created in SPSS AMOS (version 22.0) (Byrne, 2013). A model to assess relationships with gait was first conducted and then the same model was applied to gait when using a visual cue in order to assess the effect of a visual cue on the model. SEM showed the direct and indirect relationships between cognitive and visual functions, saccade frequency (change score) and gait in PD.

SEM analysis for gait and gait with a visual cue was conducted using current industry recommendations (Xiong *et al.*, 2015). This was achieved through the following four steps;

Step 1: Creation of latent variables

The same cognitive, visual function, saccade frequency and gait variables used within the regression analysis performed in previous chapters (Chapters 7 and 8) were used in SEM analysis. First, four latent variables were created from the independent (observed) variables; saccade frequency (ΔDoor and ΔTurn), cognition (FoA, JLO, CLOX 1 and Digit span), visual functions (VA and CS) and gait (step length, velocity and double support time during straight walking). Independent variables for each latent variable were inter-correlated (Table 7-4) and latent variable variance was fixed to 1.0 to represent a causal factor. Straight walking step length, velocity and double support time were initially chosen to represent gait in PD, as they were significantly impaired in PD compared to controls (Chapter 7) indicating effect of underlying pathology. The full models from SPSS AMOS are shown in Appendix 22.0 and 23.0.

Step 2: Exclusion of poor latent variable representations

Second, variables that did not meet a standardised factor loading of ≥0.70 were systematically removed from each latent variable (Hancock and Mueller, 2011; Xiong *et al.*, 2015), to ensure that high quality observed variables were chosen to serve as indicator variables of latent constructs (Mueller and Hancock, 2008). Consequently the use of low quality (<0.70 loading factor) indicators can lead to an inference of acceptable data-model fit regarding the structural portion (Hancock and Mueller, 2011) and poor latent variable representation, which may lead to inappropriate model acceptance.

Step 3: Find 'perfect' variable representations

Third, any observed variable that had a standardised factor loading of ≥1.00 (representing perfect representation (Xiong *et al.*, 2015)) was used in place of the latent variable to avoid overfitting and to account for SEM sample size parameters (i.e. at least a 5:1 ratio (Bentler and Chou, 1987; Xiong *et al.*, 2015)).

Overfitting is the tendency for a model to show good fit by capturing noise (error), and can lead to inaccurate model acceptance (Preacher, 2006).

Step 4: Model trimming and calculation of effect

Finally, model trimming was performed to systematically remove associations (connection arrows) which were not significant in the hypothesised model (Kline, 2011). The total effect of each predictor variable (cognition, visual function and saccade frequency) on saccade frequency and gait was determined by summing the direct and indirect effects of the variable (Menz *et al.*, 2007). Direct effects are those where a single path connects one variable to another. Indirect effects are those where the effect of one variable on another goes through a third variable (i.e. more than one path connects two variables) (Hayes, 2009). To determine specific indirect effects, the full SEM were subsequently broken into various sub-models (i.e. three variable relationships, such as; visual function, cognition and gait), the coefficients for each path were multiplied (Menz *et al.*, 2007). Significance levels were obtained from AMOS (bias-corrected bootstrapped 95% confidence intervals based on 200 samples), and output tabulated. It is important to note that SEM cannot test directionality of relationships and that the direction arrows within SEM represent only hypothesised causality (Menz *et al.*, 2007).

Goodness of fit of the model was examined via chi-squared (X^2), goodness-of-fit-index (GFI) and root mean square error approximation (RMSEA). Representative of good model fit, chi-square should not be significant, GFI should be high (>0.90) and RMSEA should be small (<0.08) (Byrne, 2004; Hooper *et al.*, 2008).

9.4. Results

9.4.1. How does visuo-cognition relate to gait impairment in Parkinson's disease?

To explore relationships between cognition, visual functions, saccade frequency and gait in PD (n = 56), the first SEM was created (Figure 9-2). Various models were formulated (Appendix 22.0), but due to the lack of significant relationships for controls and limited quality of indicators (factor loadings <0.70) within dual task or gait with a door or turn models, SEM analysis was confined to single task gait (straight walk) in people with PD. Limited dual task findings are probably due

to the impact of the dual task on cognitive influence over gait (e.g. under a dual task gait may predominantly be a motor task and consequently cannot be measured within the SEM structure). Standardised regression coefficients (ß) are shown for associations between each variable in the model (next to each arrow in Figure 9-2) and the amount of variance explained (r^2) by the model are provided in bold above appropriate variables. For example; r^2 above saccade frequency represents the variance in saccadic activity explained by cognition and visual function, and r^2 above gait represents variance in walking explained by all other variables (cognition, visual function and saccade frequency). After the SEM was appropriately trimmed, hypothesised relationships were examined between two latent (visual function and saccade frequency) and two observed variables (FoA and straight gait velocity) (Figure 9-2). Three non-significant paths (represented by dashed lines within Figure 9-2) were trimmed and the overall fit of the model was confirmed with $X^2 = 4.0$ (d.f. = 8, $p = .853$), GFI (0.977) and RMSEA (0.000) (Figure 9-2), which indicated acceptable goodness-of-fit. The final model explained 18% of the variance in saccade frequency (change score) and 10% of the variance in gait velocity in PD.

Several direct, indirect and total effects existed between cognitive (represented by FoA) and visual functions (VA, CS), saccade frequency (change score; ΔDoor, ΔTurn) and gait (straight walk velocity) in PD within the SEM (Figure 9-2). There was a significant direct effect of cognition on both saccade frequency (ß = -.42, $p = .011$) and gait velocity (ß = -.32, $p = .012$) in PD, but no direct effect was seen for visual function on these variables. This demonstrated that poorer cognition directly related to smaller change scores for saccade frequency and slower gait (e.g. poorer performance). Cognition also shared a significant relationship with visual function (ß = .46, $p = .014$). This showed that better visual function (as VA was entered into the model first and a lower score is better) related to better cognition in PD, which was consistent with correlation analysis in chapter 7. In line with previous analysis (Chapter 7 and Appendix 22.0), there was no significant direct relationship between visual functions and saccade frequency (ß = .13, $p = .482$) or gait velocity (ß = -.10, $p = .531$). Similarly there was also no significant direct relationship between saccade frequency and gait (ß = .04, $p = .756$).

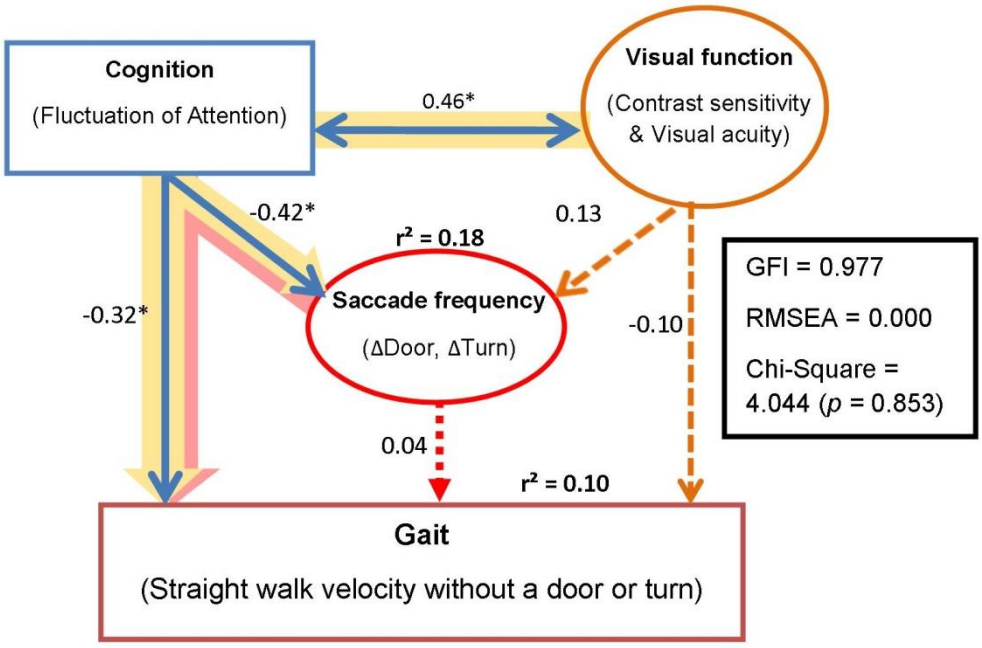


Figure 9-2 - Parkinson's disease structural equation model for visuo-cognition in gait

[*significance level p<.05, dashed lines are indirect non-significant pathways, indirect pathways are also represented by faded block arrows underlying direct pathways, solid arrows are direct pathways, GFI = goodness-of-fit-index, RMSEA = root mean square error approximation, Latent variables are represented via circles and Observed variables via rectangles]

Direct, indirect and total effects are summarised in Table 9-1, which demonstrated that cognition rather than visual function was involved in significant indirect relationships within all of the features explored. Table 9-1 shows that both visual function (ß = -.15, *p* =.008) and saccade frequency (ß = .13, *p* =.011) had a significant indirect effect on gait through cognition, specifically attention (FoA). Better visual function and greater change in saccade frequency indirectly related to faster gait velocity in PD through better attention. However comparable to the direct effects, the total effects of visual function (ß = -.25, *p* =.054) and saccade frequency (ß = .16, *p* =.756) on gait were still non-significant, which indicated that these features only related to gait through attention. Alternatively attention did not have any significant indirect effect on gait through either visual function or saccade frequency.

Consistent with previous correlations and regression analysis (Chapter 7), saccade frequency (change scores; ΔDoor, ΔTurn) was directly related to attention within the SEM. Specifically better attention was significantly associated with greater change in saccade frequency (ß = -.42, *p* = .011). Similarly visual function was not directly related to saccade frequency (ß = .13, *p* = .482), but there was a significant indirect effect of visual function on saccade frequency through attention (ß = -.19, *p* = .006). This indicated that poorer visual function related to greater change in saccade frequency, but these features only relate through attention shown by the lack of significant direct and total effect (ß = -.06, *p* = .482). Attention did not have any significant indirect effect on saccade frequency or gait through visual function. Overall, cognition represented by attention (FoA) had a central role in all of the hypothesised relationships in PD (Figure 9-1), with indirect effects of visual function and saccade frequency on gait through attention.

Table 9-1 – Visuo-cognition in gait direct, indirect and total effects in Parkinson's disease

Outcome	Predictor	Direct effect pathway	Indirect effect pathways			Total effect
			Cognition	Visual Function	Saccade Frequency	
		ß (*p*)	ß (*p*)	ß (*p*)	ß (*p*)	ß (*p*)
Gait						
	Cognition	**-.323 (.012)***	-	-.046 (.376)	-.017 (.823)	**-.386 (.012)***
	Visual Function	-.103 (.531)	**-.151 (.008)***	-	.005 (.509)	-.249 (.054)
	Saccade Frequency	.035 (.756)	**.135 (.011)***	-.013 (.502)	-	.157 (.756)
Saccade Frequency						
	Cognition	**-.420 (.011)***	-	.059 (.361)	-	**-.361 (.011)***
	Visual Function	.134 (.482)	**-.192 (.006)***	-	-	-.058 (.482)

[*significance level p<0.05, Direct effect pathway = path between Outcome and Predictor, Indirect effect pathways = path between Outcome and Predictor through *x* (where *x* represents either cognition, visual function or saccade frequency), Total effect = sum of all direct and indirect effects, ß = standardised coefficient]

9.4.2. How does a visual cue influence the relationship between visuo-cognition and gait in Parkinson's disease?

The gait model was further manipulated to explore visuo-cognitive and gait relationships in PD (n = 55) when using a visual cue (Figure 9-3). After the SEM was trimmed, hypothesised relationships were examined between one latent (visual function) and three observed (FoA, ΔCue and straight gait velocity) variables (Figure 9-3). The model showed that the same relationships found within the gait model (Figure 9-2) were present when using a visual cue (Figure 9-3), although variable associations were slightly altered. After trimming three non-significant paths (represented by dashed lines within Figure 9-3), the overall fit of the model was confirmed with X^2 = 2.3 (d.f. = 5, p = .806), GFI (0.984) and RMSEA (0.000) (Figure 9-3), which indicated acceptable goodness-of-fit. The final model explained 7% of the variance in saccade frequency (ΔCue) and 13% of the variance in gait velocity when using a visual cue in PD, which was slightly reduced from the gait model (Figure 9-2).

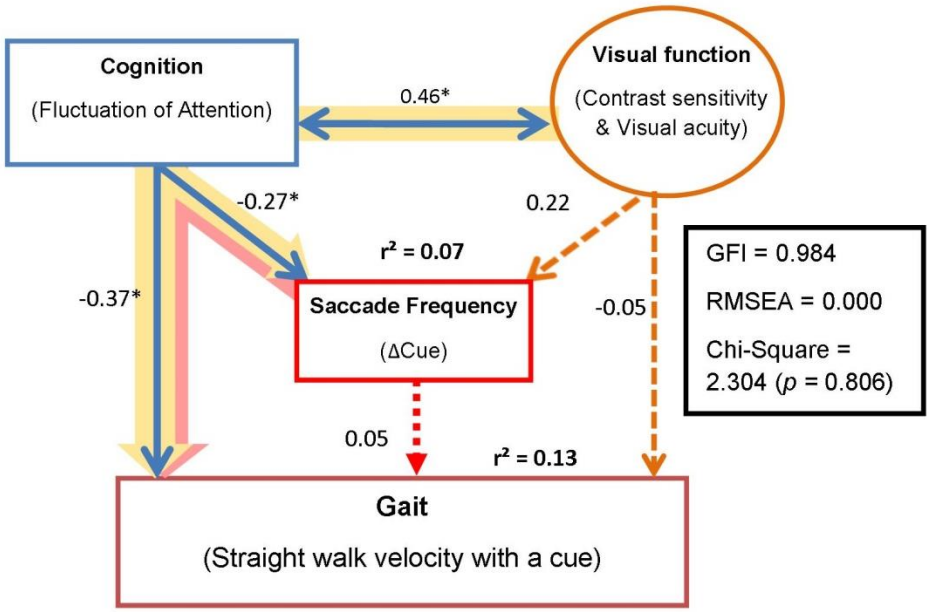


Figure 9-3 - Parkinson's disease structural equation model for visuo-cognition in gait with a visual cue

[*significance level p<.05, dashed lines are indirect non-significant pathways, indirect pathways are also represented by faded block arrows underlying direct pathways, solid arrows are direct pathways, GFI = goodness-of-fit-index, RMSEA = root mean square error approximation, Latent variables are represented via circles and Observed variables via rectangles]

Within the visual cue model (Figure 9-3), the same relationships found within the gait model (Figure 9-2) between cognition, visual function, saccade frequency and gait were evident. For example; significant shared relationship was seen between visual function (VA, CS) and cognition (ß = .46, *p* = .028). Similarly, cognition (represented by FoA) also had significant direct relationship with saccade frequency (change score; ΔCue; ß = -.27, *p* = .037) and gait (straight velocity with a visual cue; ß = -.37, p = .036). This demonstrated that better attention related to greater change in saccade frequency and faster gait with a visual cue. Visual function and gait however did not have a significant direct relationship (ß = .03, *p* = .837), nor did visual function and saccade frequency (ß = .22, *p* = .113) or saccade frequency and gait (ß = .05, *p* = .602).

Table 9-2 – Visuo-cognition in gait direct, indirect and total effects in Parkinson's disease with a visual cue

ß(*p*)		Direct effect pathway	Indirect effect pathways			Total effect
Outcome	Predictor		Cognition	Visual Function	Saccade Frequency	
		ß (*p*)	ß (*p*)	ß (*p*)	ß (*p*)	ß (*p*)
Gait						
	Cognition	**-.367 (.036)***	-	-.023 (.774)	-.013 (.657)	**-.403 (.034)***
	Visual Function	-.047 (.940)	**-.168 (.005)***	-	.010 (.774)	-.205 (.073)
	Saccade Frequency	.054 (.602)	**.098 (.031)***	.010 (.546)	-	.162 (.602)
Saccade Frequency						
	Cognition	**-.267 (.037)***	-	.099 (.054)	-	**-.168 (.045)***
	Visual Function	.217 (.113)	**-.122 (.008)***	-	-	.095 (.782)

[*significance level p<0.05, Direct effect pathway = path between Outcome and Predictor, Indirect effect pathways = path between Outcome and Predictor through *x* (where *x* represents either cognition, visual function or saccade frequency), Total effect = sum of all direct and indirect effects]

Interestingly, there was weaker relationship between cognition (attention) and saccade frequency (change score; ΔCue) with a visual cue (ß = -.27, *p* = .037, Figure 9-3) than without a visual cue (ß = -.42, *p* = .011, Figure 9-2). Visual function (VA, CS) was also shown to have a slightly stronger direct relationship (ß = .22, *p* = .113) with saccade frequency than within the gait model (ß = .13, *p* =

.482; Figure 9-2), although it was still non-significant (Table 9-2). Table 9-2 demonstrates that the same indirect relationships between visual function, saccade frequency and gait (velocity with a cue) through cognition (attention) found in the gait model (Figure 9-2) were present in the visual cue model (Figure 9-3). However the indirect effect of saccade frequency on gait through attention was slightly reduced with a visual cue (ß = .10, *p* = .031) compared to gait (ß = .14, *p* = .011). Interestingly, the indirect effect of visual function on saccade frequency through attention was also slightly reduced with a visual cue (ß = .12, *p* = .008) compared to gait (ß = 0.19, *p* = .006). In contrast, the indirect effect of visual function on gait was increased with a visual cue (ß = .16, *p* = .005) compared to gait (ß = .15, *p* = .008).

9.5. Discussion

This is the first study to explore direct and indirect relationships (effects) between cognitive and visual function, saccade frequency during gait and gait in people with PD. Comparison between the current study and previous research is therefore limited, as earlier studies have separately assessed relationships between cognition or vision and gait in people with PD and older adults. The findings of this investigation suggest that gait impairment in PD is influenced by visuo-cognitive dysfunction, with direct and indirect effects through attention. A final model of visual-attention and gait in PD is presented in Figure 9-4, in order to help explain the complex processes discussed.

SEM of the associations among the variables in the present study was devised to test direct and indirect relationships between visuo-cognition and gait in PD. The inclusion or exclusion of variables and their connections within the SEM were largely driven by the presented theoretical model (Figure 9-1). Although a range of models were tested (Appendix 22.0) and the final model (Figure 9-2) explained a reasonable level of variance in both saccade frequency and gait, it is acknowledged that other models could be constructed from the data obtained in this thesis. Regardless, this study demonstrates the benefits of such multivariate analysis techniques when attempting to explain complex relationships between visuo-cognitive and gait variables in PD, and provided useful insights and future hypotheses about how these features interact.

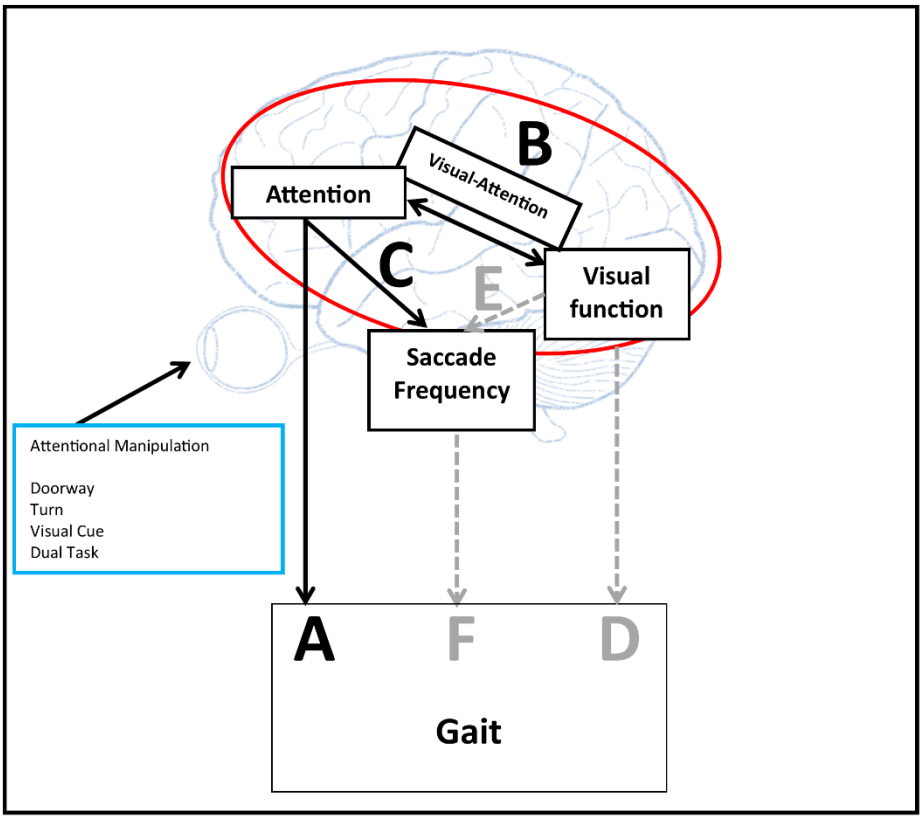


Figure 9-4 - Final model detailing visual-attention and gait in Parkinson's disease

[There are three direct pathways primarily involved; A) Attention and gait, B) Interactions between visual function and attention (termed visual-attention), and C) Attention and saccade frequency. There are also three indirect pathways through attention involved; D) Visual function and gait, E) Visual function and saccade frequency, and F) Saccade frequency and gait. Full black lines represent direct pathways and dashed grey lines represent indirect pathways]

9.5.1. How does visuo-cognition relate to gait impairment in Parkinson's disease?

Visuo-cognition (interaction between cognitive and visual functions, with impairments measured by alterations in saccade frequency) explained a small amount of gait variance in PD, which was expected due to the complex and multifactorial nature of gait. SEM demonstrated that visuo-cognition explained 10% of the variance in gait (straight walk velocity) in PD and attention was the only variable significantly associated with gait. The amount of explained variance and relationship with attention were similar to previous gait research in PD (Lord *et al.*, 2010) and older adults (Liu-Ambrose *et al.*, 2010; MacAulay *et al.*, 2014). Unsurprisingly, visuo-cognition explained greater variance in saccade frequency (change score) (18%), which also only had significant relationship with attention. Level of explained variance and relationship with attention were similar to

previous saccadic research (Hoffman and Subramaniam, 1995; Wang *et al.*, 2013; Buhmann *et al.*, 2015). The other remaining variance in both gait (90%) and saccade frequency (82%) may be explained via numerous influences on these behavioural outcomes that were either not assessed or controlled for within the current exploratory study. These include level of fatigue (Faber *et al.*, 2012), motivation (Kaplan *et al.*, 2012), physical condition, motor severity (primarily influencing gait), medication, prior knowledge of testing procedures (learning effect between walks) (Kim and Rehder, 2011) and emotional state (Oatley *et al.*, 2011). Variance in saccade frequency could also be due to specific visual influences such as colour properties of the visual scene (Amano *et al.*, 2012) and saliency of objects (i.e. doorway) (t Hart *et al.*, 2013). Irrespective of other influences, a number of important associations were identified among the visuo-cognitive and gait variables. However cognition, specifically attention (represented by FoA) was found to be the only variable directly associated with all of the other features, which was consistent both during non-cued gait (Figure 9-2) and visually cued gait (Figure 9-3).

9.5.2. Visual-attention and gait in Parkinson's disease

The final SEM presented in Figure 9-2 provides a coherent and logical structure linking cognition (attention), vision (visual functions), saccade frequency (change scores) and gait (straight walk velocity), which demonstrated relationships that were not evident within previous analysis (Chapter 7 and 8). Results demonstrated that people with PD who had poorer attention, also had worse visual function, changed their saccade frequency less in response to environmental challenge, and had slower gait. However in line with specific hypotheses, attention had a central role within the theoretical visuo-cognition in gait in PD model. As mentioned in the thesis introduction, visuo-cognition is a global descriptor of cognitive and visual function interactions. However due to the central role of attention, the more specific term of visual-attention could be applied within this study (Figure 9-4).

Visuo-cognition was shown to influence gait in PD primarily through attention, with direct effect of attention and indirect effect of visual-attention on gait (Figure 9-4(B)). Attention was directly related to all of the visuo-cognitive features (visual

function and saccade frequency) and gait in PD, which suggests an over-arching or dominant role of attention in gait impairment (Lord *et al.*, 2014; Lückmann *et al.*, 2014), depicted in Figure 9-4. As hypothesised, attention and visual functions shared a significant direct relationship in PD, which demonstrated that these features interact with each other, and subsequently form visual-attention which impacted gait. In line with previous results (Chapter 7), visual function had no direct relationship (effect) with saccade frequency or gait in PD (Figure 9-4(D)). Instead a significant indirect relationship was facilitated through attention (i.e. slower gait velocity and less change in saccade frequency were impacted by poorer visual function, through impaired attention), which has not been seen in previous vision and gait research (Swigler *et al.*, 2012). Results were similar to previous SEM analysis in older adult drivers (Ball *et al.*, 1993), which showed that better visual functions directly related to better attention (measured using the useful field of view test) but not task outcomes (i.e. driving ability). Similarly, saccade frequency (change score) had no direct relationship with gait (Figure 9-4(F)), but there was a significant indirect relationship through attention (i.e. slower gait velocity was impacted by less change in saccade frequency, through poorer attention).

These findings highlight the pivotal role that cognitive, particularly attentional dysfunction plays in visuo-cognition and gait and are comparable to the extensive literature regarding relationship between attention and gait in PD (Lord *et al.*, 2014). Attention also facilitated the role of vision in gait in PD, with visual function not directly related to gait in PD (Figure 9-2 and Table 9-1) or controls (Appendix 19.0), which has not been considered in previous research (Chapter 2).

9.5.3. Task-dependent visual-attention in Parkinson's disease: visual cues

When the SEM was manipulated by entering data obtained when walking with a visual cue in place (Figure 9-3), the same direct and indirect relationships (effects) seen within the gait model occurred however selective interactions were slightly altered. Similar to non-cued gait, direct and indirect effects on gait with a visual cue were seen through attention, which signified that the visual cue influenced visual-attention in PD (Figure 9-4). Further, visuo-cognition explained

slightly greater gait variance with a visual cue (13%) compared to without (10%), likely due to subtle variation in underlying visual-attention relationships which may underpin response to cues seen in PD (discussed in Chapter 8).

Association between attention, visual function and saccade frequency was task-dependent. For example, Figure 9-2 demonstrated that during gait only better attention related to greater change in saccade frequency, whereas Figure 9-3 showed that when using a visual cue better attention and poorer visual function had similar relationship with greater change in saccade frequency. As hypothesised, saccade frequency during gait was primarily driven by attention, but when using a visual cue association with attention reduced and relationship with visual function increased. These subtle changes in underlying visual-attention features when using a visual cue may be due to unburdening of attention ('top-down') with external stimulus, which was discussed in Chapter 8 (section 8.5.5).

Previous research has demonstrated that visual search deficits in PD were ameliorated when bottom-up attention was influenced by highly salient targets and top-down attention was provided with specific goals prior to the task (e.g. step over these lines) (Horowitz *et al.*, 2006). Therefore the use of a visual cue probably influenced decision making regarding relevance of information. For example, when using the cue less demand may have been placed on attention, with saccade guidance provided by the visual cue rather than online decision making, and the saliency of the transverse lines likely triggered bottom-up attentional processing (reflexive saccades). Similarly, due to problems with cognitive flexibility people with PD may be less distractible when using a cue (i.e. make fewer saccades to irrelevant areas) due to the specific instructions provided (Hanes *et al.*, 1995; Cools *et al.*, 2001). This was further demonstrated by the reduction in explained saccade frequency variance by visual-attention within the visual cue model compared to the gait model (e.g. change in saccade frequency without a cue r^2 = 18% and with a cue; r^2 = 7%). Similarly, relationship (direct and total effect) between saccade frequency and gait in PD with a visual cue was slightly stronger (Tables 9-1 and 9-2), and indirect effect through attention when using a visual cue was slightly weaker (e.g. gait β = .14, p = .011, visual cue β = .10, p = .031). This evidence further highlights the role that visual cues may have

in guidance of visual sampling during gait in PD, which may free attentional resources to be used for gait or other tasks.

9.5.4. Attentional compensation in Parkinson's disease

The pivotal role of attention within visuo-cognition and gait in PD (Figure 9-4) may indicate attentional compensation for underlying visual or motor (gait) deficits. These relationships are possibly due to those with better attention having more neural resources available to circumvent impairment (Rubinstein *et al.*, 2002; Tombu and Jolicoeur, 2003; Heuninckx *et al.*, 2008; Yogev-Seligmann *et al.*, 2008). For example, an increase in association between poorer visual function and greater change in saccade frequency when using a visual cue may reflect a compensatory attentional mechanism. Increased saccade frequency has been found in several static visual search studies which involved individuals with visual impairment (Barraga, 1964; Bowers and Reid, 1997; Hawelka and Wimmer, 2005). Target (visual cue) saliency would become reduced with impairment of visual function. Therefore attentional compensation (both top-down and bottom-up, but primarily the latter) may be required to influence more frequent sampling in order to filter the visual scene and distinguish the transverse lines from the floor (Horowitz *et al.*, 2006). This is complicated by attentional impairment with PD progression (Taylor *et al.*, 2008), which would lead to impairment of visual function, saccade frequency and gait, with implication for poor mobility, with increased trips and falls risk (Allcock *et al.*, 2009).

9.5.5. Study Strengths

A major strength of this chapter was the use of SEM analysis (Figures 9-2 and 9-3) and a clear *a priori* hypothesis to guide analysis, which uncovered important relationships between attention and visual function, and indirect effects of visuo-cognitive features on gait through attention. These relationships would not have been evident with the use of factor analysis followed by regression techniques, as these treat the independent variables the same without ordering potential influential relationships. To date SEM has been an uncommon technique for gait analysis (Chau, 2001), likely due to some reports that state a minimum sample size of 200 cases is required (Mueller and Hancock, 2008). However, it has been recognised that such a high sample size is unrealistic for certain studies and

other researchers have suggested that a modest sample of 5-20 cases per independent variable is more realistic while remaining statistically valid (Bentler and Chou, 1987; Tanguma, 2001; Menz *et al.*, 2007; Byrne, 2013; Hoyle and Gottfredson, 2014; Xiong *et al.*, 2015). Therefore the sample size used in this study (PD, n = 56 for the gait model and n = 55 for the visual cue model) allowed for the development of SEMs regarding visuo-cognition and gait in PD.

9.6. Conclusions

In summary, this study explored an *a priori* model of the direct and indirect relationships between cognitive and visual functions, saccade frequency during gait and gait in PD. The findings suggest that visuo-cognitive dysfunction or more specifically visual-attention influences gait impairment in PD. Attention has a central role within visuo-cognition and gait, with indirect relationships with gait through attention for visual functions and saccade frequency. Manipulation via a visual cue demonstrated that task-dependent relationships between attention, visual function, saccade frequency and gait occur in PD, which may relate to cue response.

10. Thesis Summary

The aims of this thesis were to further understand the roles of cognition and vision in gait in PD, which involved examination of the relationship between cognitive and visual functions (termed visuo-cognition) and the role of visuo-cognition in gait in PD. Gait in PD is multi-factorial with contributions from a variety of motor and non-motor features, which is widely recognised. However previous accounts of non-motor features such as cognitive and visual functions and their role in gait in PD have segregated investigation into separate strands (i.e. cognition and gait, or vision and gait). The natural environment is complex and involves a variety of terrains, obstacles, hazards, different luminance, depth and lighting. Therefore in order to safely navigate through such complex spaces cognitive and visual functions are required. The burden placed onto cognitive and visual functions may be further heightened in PD due to everyday walking becoming a more attentional demanding task.

This thesis reported novel research and investigation into mobile eye-tracking technology (Chapter 5 and 6), and robust evaluation of the primary outcome (saccade frequency) used within the main experimental studies (Chapters 7, 8 and 9) in people with PD and controls. Chapter 5 successfully developed and evaluated methods for extracting visual sampling outcomes during gait from mobile eye-tracking data in people with PD and controls. Next, chapter 6 provided the first study to evaluate the accuracy and reliability of a mobile eye-tracking device, showing that for the purposes of this thesis these factors were adequate. These preliminary studies were vital to the primary investigation, providing evidence of robust data collection and analysis which has scarcely been contemplated within previous research.

As stated earlier, PD is a complex multisystem disorder which commonly involves cognitive, visual and gait impairments, which were all demonstrated in this thesis. The remaining chapters (Chapters 7, 8 and 9) demonstrated that there is a complex functional relationship between cognition, visual function, saccade frequency and gait in PD, which is underpinned by attentional mechanisms.

The main experimental study (Chapter 7) clearly showed that selective gait characteristics and saccade frequency during gait were significantly impaired in people with PD compared to age-matched controls, with implication for poor mobility, trips and falls. A surprising finding was that gait characteristics and saccade frequency were not associated in people with PD but were in controls. Despite this, online results demonstrated that gait and saccade frequency were influenced by greater environmental challenge and dual task in both groups, indicative of common underlying visuo-cognitive mechanisms.

Saccade frequency was reduced in PD compared to controls within all conditions. Interestingly, saccade frequency increased with greater environmental challenge and decreased under dual task in both groups. General reduction in saccade frequency during gait seen with PD furthers previous static and dynamic work, but builds on previous results to provide a comprehensive account of visual sampling during gait. Within this thesis saccade frequency impairment in PD was suggested to be due to difficulties with initiation of voluntary saccades during gait, which implicates dysfunctional attentional networks/signals. This is possibly due to dopaminergic depletion and added attentional burden of gait in PD. Both top-down and bottom-up attention had influence on saccade frequency during gait in both groups. However, impairments with PD pathology primarily impact top-down attention, which has inhibitory control over saccade generation and suppression. This was evidenced by further reduction in saccade frequency under dual task. Similarly, increased saccade frequency with greater environmental challenge under single and dual task likely relates to increased initiation of reflexive saccades via bottom-up (stimuli driven) attention in PD. However not all of the saccades made with increased environmental challenge will be reflexive. Rather fluctuations between top-down and bottom-up saccade generation during gait in PD is quite plausible.

The second experimental study (Chapter 8) demonstrated that saccade frequency during gait significantly increased in both groups with a visual cue, which was maintained under dual task with greater response seen in people with PD. Use of a visual cue with specific instructions may have reduced difficulties distinguishing between relevant and irrelevant information during gait for people with PD, further freeing attentional resources to be used on the secondary

cognitive task, saccade generation and gait. As discussed, the saliency of the visual cue and goal-directed nature of the task would trigger more efficient visual sampling, underpinned by visuo-cognitive features. Indeed, a particularly novel finding within chapters 7 and 8 pertained to saccade frequency having significant relationship with cognitive (attention) and visual functions (CS) independent of demographic features in PD under single task conditions. This supported the hypothesis that visuo-cognitive features underpin saccade frequency in PD. As hypothesised, attention determined saccade frequency during gait whereas when using a visual cue attention and visual function were independently associated. This demonstrated that mechanisms underlying saccade frequency may be task-dependent, with greater input from visual functions with a more complex visual task (a visual cue). However the analysis within chapters 7 and 8 was limited, as results provided only direct relationships with little evidence for interaction between variables or indirect effects.

The final hypothesis-driven study (Chapter 9) provided a structured multivariate model of the relationships involved in visuo-cognition in gait in PD (Figure 9-4), demonstrating that attention had a central role in all relationships. Attention shared a direct relationship with visual function in PD, forming visual-attention. Evidence demonstrated that attention had separate direct effect on gait and saccade frequency in PD, but that visual function and saccade frequency only affected gait indirectly through their combination with attention. Visuo-cognitive dysfunction consequently influenced gait deficit in PD, predominantly through attention (direct pathway) forming visual-attention (indirect pathway). Therefore within PD attention was shown to be an overarching system, which may be required to compensate for deficits within visual and motor domains. Attentional decline with PD progression likely elicit visual-attention impairments and impact gait, with implication for poor mobility and increased falls risk.

Manipulation of the structured model via entering saccade frequency and gait data obtained while using a visual cue demonstrated that the same visuo-cognitive (or more specifically visual-attention) relationships existed. Gait in PD was still influenced by visuo-cognition (indirectly) and attention maintained its central role in all of the relationships involved. However contribution of attention and visual function to saccade frequency during gait altered in a task-dependent

manner in line with specific hypotheses, which also validates the experimental protocol used within this thesis. With use of a visual cue the role of attention in saccade frequency was reduced compared to gait without a visual cue and visual function had a slightly greater role. Weaker attentional association indicated that the external stimulus (visual cue) may have unburdened attention by guiding visual sampling through stimuli driven behaviour rather than ad-hoc (fluctuating) voluntary response suppression and selection. Reduction in attentional demand for saccade frequency during gait was also likely the reason why saccade frequency response was maintained (similar to single task) under a dual task and participants performed better on the secondary cognitive task. Future studies may be able to manipulate the model to assess underlying mechanisms involved in various gait interventions in PD, as different visual cueing paradigms may selectively impact model relationships.

10.1. Clinical Implications

This thesis has identified impairment of visuo-cognition during gait in PD and has shown that this was related to gait impairment through attentional dysfunction. These findings have implication for the clinical assessment and management of gait in people with PD. As discussed, saccade frequency was reduced and selective gait characteristics were impaired in people with PD compared to controls during all of the walking conditions, and this worsened with distraction (dual task). The main implication of these findings is that reduction in saccade frequency during gait may lead to reduced mobility, and also has connotations for trips and falls. Therefore, when assessing gait in people with PD, it may be useful to examine how often an individual observes their environment. This may be particularly relevant when the environment becomes more challenging or when distracted by a secondary task, as these are common real-world situations.

Saccade frequency during gait was also found to increase with greater environmental challenge (a door or turn) and further increased when attention was manipulated with a visual cue, which provides a potential method for intervention. Targeting dysfunctional visual sampling during gait with specific attentional therapeutic interventions (visual cues), rehabilitation (e.g. eye movement training (Zampieri and Di Fabio, 2008)) or pharmacological

manipulation may improve visual sampling and gait for people with PD, which could reduce falls risk. Further research is required to understand the specific mechanisms driving saccades when using visual cues in order to inform the most appropriate method of intervention. However, this thesis has provided some initial evidence on which to base future clinical practice and research**.**

10.2. Limitations and Future Research

Whilst this thesis generated new knowledge, further studies are warranted to tease out the specific nature of saccadic activity during gait in PD. It was evident within the analysis presented in this thesis that attention influenced saccade frequency during gait in PD (Figure 9-4), but identifying specific attentional networks involved was beyond the scope of this work. This is the main difficultly with investigation of saccades during dynamic tasks, as unlike static tasks unrestricted movement may be driven by multiple underlying processes and networks. Without extensive static saccadic assessment the exact underlying attentional processes (top-down or bottom-up) remain unclear. As a result definitive conclusions on whether changes in saccade frequency during gait were primarily due to voluntary attentional control or automatic bottom-up attention triggered via external stimuli can only be alluded to. Future studies should consider a much more detailed 'visual neuroscience' approach to better define underlying mechanisms involved in saccade frequency during gait in PD, perhaps involving static pro- and anti-saccade testing, imaging or electrophysiological work (e.g. mobile fNIRS or electroencephalogram (EEG)). Such an approach would allow saccade frequency to be exactly mapped to underlying brain networks or structures. It may also help to define how saccade frequency differences contribute to gait deficit in PD, as there was only an indirect relationship between saccade frequency and gait.

Further, investigation of saccade frequency in PD longitudinally may provide useful information about deficits across the disease course and how they impact activities of daily living. Greater insight into the precise attentional processes involved will aid in the development of interventions to improve saccade frequency and gait in PD. Similarly in line with conclusions from a recent study in older adults (Dowiasch *et al.*, 2015), another limitation was the use of laboratory

based manipulations rather than a real-world environment. Laboratory based saccade frequency during gait or gait outcomes may only partly resemble those of the real-world and future research should attempt to assess saccade frequency during gait in more natural environments (i.e. home-based assessment).

Another limitation within the work reported in chapter 8 was that due to gait characteristics not being the primary focus of the study a set distance (50cm) visual cue was used, which led to gait characteristics not being improved in every participant. Future studies should consider tailoring the visual cue to each individual (e.g. distance 20% larger than participant baseline step length). Due to technological limitations this thesis did not assess where participants looked (i.e. what they fixated on in the environment), although during assessment it was obvious that participants were looking at the visual cue (transverse lines). Not being able to assess where people where fixating during gait meant that the use of saccades was difficult to establish. Results were also unable to indicate whether participants were viewing their current or future foot placements. This is important in future studies as it may indicate compensation for other underlying impairments such as proprioceptive deficits. Future studies could also attempt to improve interventions via tailoring them to individuals' saccade frequency response, and perhaps develop improved cueing techniques that harness involved visual-attentional processes in PD. For example; motion activated laser beam visual cues which provide the same transverse lines but may target reflexive bottom-up attention.

Increased saccade frequency with visual cues in both groups was attributed to increased attention to gait and the relevant area of the floor where participants were walking over. Increased downward attention to the ground with the use of horizontal lines is the standard visual cue protocol used in research and clinical practice (Holmes *et al.*, 2015), however this protocol has limitations related to gaze location. The visual cues direct individuals attention to the ground directly in front of them (approximately one to two steps ahead), which has previously been found to increase obstacle collisions in healthy individuals (Patla, 1998; Matthis and Fajen, 2014). Interestingly a recent study by Vitorio *et al.* (2014) demonstrated that visual cues can improve gait in PD regardless of the ability to

see the first one to two steps ahead or not, which indicates that immediate downward attention may not be required. Increased downward attention likely relates to the horizontal placement of the cues which focus attention on the stepping process (i.e. more attention to each step taken). The increased saccade frequency seen with visual cues may therefore have been artificially driven by the protocol provided (i.e. stepping over horizontal lines) and may have meant that visual information was actually more restricted (i.e. looking at floor immediately in front rather than ahead). The nature of the visual cue (i.e. horizontal step position) and the instructions provided may therefore have influenced the increase in saccades, as participants looked at each line to step over but individuals may not have been exploring the walking environment with the cue. Alternative visual cues such as a vertical cue (e.g. one line along the walkway through the centre of the doorway) may provide focus on veering of gait (i.e. participant attempts to keep the line in the middle of their centre of mass) (Bestaven *et al.*, 2012), rather than the stepping process. As a result vertical cues may drive different visual sampling or gait outcomes, such as increased fixation duration with focus ahead in the walking direction. Future studies could investigate this further with investigation of the different visual sampling and gait strategies used with horizontal or vertical visual cues with varied instructions (i.e. please step over these lines or no instructions about the lines etc.). Further investigation of the specific visual sampling and gait characteristics employed when using various visual cueing techniques could tease out the complex underlying mechanisms involved in cue response.

Another methodological limitation of the current thesis was the limited range of vision testing, as VA and CS are only basic visual functions. Other perhaps more relevant vision measures or full ophthalmic assessment should be included in future studies, as other visual mechanisms may have a greater role within the hypothesised visuo-cognition in gait in PD model. Future studies should consider assessment of visual functions including depth perception, motion perception, dynamic visual acuity and optic flow to provide a comprehensive battery of vision.

Other directions for future work include development of further understanding of visuo-cognition in gait which may involve participants with various other

neurological disorders which impact cognition, vision and gait. It is likely that visuo-cognitive relationships would differ depending on disease pathology.

Finally, this was the largest study (n = 100 in total) to explore saccade frequency during gait in PD and the underlying mechanisms involved, and it was the first to examine how saccade frequency relates to gait impairment. However a very important limitation of this thesis was that although significant associations were found between these features the majority were quite low (mostly weak (r = .10 to .30) or moderate (r = .30 to .50)), and many comparisons were made without control. This was appropriate due to the exploratory nature of the main experimental chapters (Chapter 7, 8 and 9) and meant that potentially meaningful findings were not discarded (i.e. avoid Type II error). The limited strength of associations was not surprising given the complex nature of both saccadic activity and gait (Antonisamy *et al.*, 2010). For example, gait and saccades are multifactorial and various features not included within this thesis may have impacted associations, such as fatigue, motivation, musculoskeletal conditioning, ethnicity etc. Eye-tracker measurement error discussed in chapters 5 and 6 may also have contributed to the weak to moderate associations. However, now that relationships between cognition, visual function, saccade frequency and gait have been uncovered, future studies could use a more stringent approach to interpretation. This could be achieved with classification of correlations by importance (i.e. looking at r^2 values) or use of Bonferroni or other techniques to control for multiple comparisons.

10.3. Conclusions

This thesis provides support for a different approach to studying the role that cognition and vision play in gait in PD, in which such functions are not entirely separate processes as previously supposed. The key new finding that has emerged from this thesis is that visuo-cognition during gait is impaired in PD and indirectly related to gait impairment through attention. The final conclusions from this thesis are as follows;

1) Cognitive and visual functions are significantly related in PD and controls, with stronger association in PD

2) Saccade frequency during gait is reduced in PD compared to age-matched controls, and attentional distraction reduces sampling frequency irrespective of pathology
3) Impaired saccade frequency during gait in PD can be ameliorated with the use of a visual cue which increases attention, and this is maintained under attentional distraction (dual task)
4) Gait impairment in PD is influenced by visuo-cognitive dysfunction, but attention facilitates all relationships involved
5) Interventions targeting attention (visual cues) may be used to improve saccade frequency and gait, with implications for falls risk reduction

11. Appendices

1. Appendix 1.0 – Structured review supplementary data 1; Reason for exclusion of studies (n = 47)

NON MOTOR TASK			MOTOR TASK				No age-matched controls
Computer based task	Visual function	Visual task	Simple motor Task	Bulletin/ review/ conference	Unrelated visual sampling & motor task	No measure of visual sampling	
(Archibald *et al.*, 2013)	(Corin *et al.*, 1972)	(de Hemptinne *et al.*, 2013)	(Shimizu *et al.*, 1981)	(Baziyan *et al.*, 2007)	(Bekkering *et al.*, 2001)	(Tropini *et al.*, 2011)	(Lohnes and Earhart, 2012a)
(Cameron, 2011)	(Harris *et al.*, 2003)	(Economou and Stefanis, 1978)	(Weinrich and Bhatia, 1986)	(Naushahi *et al.*, 2012)	(Crawford *et al.*, 1989)		(Temel *et al.*, 2008)
(Cools *et al.*, 2010)	(Duval and Beuter, 1998)	(Flowers and Downing, 1978)	(Yoshida *et al.*, 2005)		(Lohnes and Earhart, 2012b)		(Temel *et al.*, 2009)
(Fielding *et al.*, 2006b) (Fielding *et al.*, 2006a)		(Gibson *et al.*, 1987) (Hansen *et al.*, 1990)			(Lord *et al.*, 2012)		(Velasques *et al.*, 2007)
(Gurvich *et al.*, 2007)		(Highstein *et al.*, 1969)					
(Hodgson *et al.*, 2002)		(Hochstadt, 2009)					
(Inzelberg *et al.*, 2008)		(Horowitz *et al.*, 2006)					
(Joti *et al.*, 2007)		(MacHner *et al.*, 2010)					
(Kimmig *et al.*, 2002)		(Marino *et al.*, 2007)					
(Kuechenmeister *et al.*, 1977)		(Pinnock *et al.*, 2010)					
(Mannan *et al.*, 2008)		(Poujois *et al.*, 2007)					
(van Stockum *et al.*, 2008)		(Praamstra *et al.*, 1998)					
(van Stockum *et al.*, 2011b)		(Sampaio *et al.*, 2011)					
(van Stockum *et al.*, 2012)		(Shibasaki *et al.*, 1979)					
(van Stockum *et al.*, 2013)		(Terao *et al.*, 2011)					
		(van Koningsbruggen *et al.*, 2009)					
		(von Noorden and Preziosi, 1966)					

2. Appendix 2.0 – Structured review supplementary data 2: Detailed visual outcome measures and key findings

Author	Visual Outcome Measures	Key Findings
(Anastasopoulos *et al.*, 2011)	Initial saccade: Velocity Amplitude Frequency Latency	1. PD participants made more eye movements than control (P < .0001) with reduced contribution from the trunk and head during turning (Eye movements were observed first followed by head/trunk movement). 2. Reduced initial saccade velocity was recorded in PD participants compared to control (non-significant) 3. PD participants demonstrated smaller initial saccade amplitudes than control (non-significant) 4. Significantly decreased single-step saccade frequency (P = .0006) was observed in PD patients. As well as no significant group difference in latencies.
(Desmurget *et al.*, 2004a)	Eye position (mm) Initial saccade: Latency Peak velocity Duration Amplitude	1. PD participants demonstrated longer saccadic reaction times compared to control (Statistical trends were observed) 2. On-line (in vision) movement corrections are impaired in PD subjects compared to control due to an inability to adjust force control with changing requirements. 3. Initial saccade peak velocity and amplitude are all reduced in PD compared to control 4. Initial saccade duration and latency were increased in PD compared to control None of the vision contrasts between PD and control were statistically significant
(Galna *et al.*, 2012)	Frequency of early and late saccades (under single and dual task conditions)	1. People with PD explored their environment less than control , particularly when approaching a turn or when distracted (dual tasking) 2. Under single task conditions, PD participants made 30% less saccades than control (non-significant) 3. PD participants made less saccades than control under dual task conditions (p < .04)
(Heremans *et al.*, 2012)	Eye movement: Time between fixations Frequency Amplitude	Goal-directed aiming task (GDAT) and Box and block task (BBT) 1. No differences were found between the number of eye movements or amplitudes observed during the physical execution and mental imagery tasks, but no significant differences were noted between cohorts.
(Lee *et al.*, 2012b)	Visual fixations were monitored with respect to seven AOI's. Analyses of fixations were relative to seven predefined AOI in the car (i.e. mirrors, speedometer etc.)	1. PD subjects kept their head still and made reduced eye movements in comparison to the control group 2. PD subjects reportedly made fewer fixations on AOI's compared with that observed in control subjects for all testing parameters
(Lohnes and Earhart, 2011)	Number of saccades Initial saccade: Velocity Amplitude Total frequency	1. Saccades were impaired during turning in people with PD 2. PD participants made the initial saccade earlier compared to control. The earlier saccade was accompanied by reduced initial saccade velocity (p < .01) and amplitude (p < .01, only for 180 degree turn) compared to that of control 3. PD participants demonstrated increased saccade frequency than control (p < .01)
(Marx *et al.*, 2012)	Saccades: Peak velocity Amplitude Duration Direction	1. PD subjects demonstrated reduced saccade duration compared to control (p < .05) 2. PD subjects 'compensate' for saccade activity impairments when walking 3. Saccade peak velocity, amplitude and duration are all increased in PD compared to control when walking (non-significant) 4. There was no difference between the groups for saccade direction
(Muilwijk *et al.*, 2013)	Saccade latency	1. Initiation of saccades in goal directed tasks was not affected. 2. Eye movements (during tasks ii and iii) were initiated faster by PD participants. The authors attributed this to a difficulty suppressing reflexive saccades in early stage PD 3. Hand movements were delayed in PD participants (tasks i and ii) 4. Saccade latency of PD participants was equal to or less than control in 3 of the 4 tasks (pro, anti-tapping and dual planning). PD subject saccade latency was

		increased compared to control in the spatial memory task.
(Sacrey *et al.*, 2009)	Saccadic activity: Latency Fixation duration	1. Visual activity during reaching in mild PD is similar to control subjects (both young and old), but was impaired in advanced PD compared to control. 2. The time from visual engagement to the grasping of the food item and the time from grasping the food item to visual disengagement was significantly longer in the advanced PD cohort compared to the three other groups (mild PD, young adults and older adults; $p < .0001$)
(Sacrey *et al.*, 2011)	Saccadic activity: Latency Fixation duration	1. When listening to music, PD participants (both medicated and un-medicated) took longer to initiate a reaching movement after a visual fixation compared with control ($p > .05$). They exhibited an impaired switching of visual attention and somatosensory guidance 2. Medicated PD subjects have to fixate for a similar duration as control participants, whereas un-medicated PD fixated significantly longer ($p < .05$) 3. Saccade latencies were significantly increased in both medicated and non-medicated PD compared to control participants ($p < .05$)
(Uc *et al.*, 2006)	LTIT: Visual search score which included the per cent of landmarks and traffic signs identified and the number of at fault safety errors	Visual search was quantified by the score derived from the LTIT. The findings indicated that: 1. Visual search was impaired in PD compared to control participants (total identification of landmarks and traffic signals was significantly less and the number of at-fault errors was significantly greater; $p < .001$. These differences persisted even when accounting for familiarity of the location/ region, far and near visual acuity, gender, driving exposure and level of education) 2. Cognitive (visuospatial and attention), visual (visual acuity and contrast sensitivity), and balance deficits were observed in PD participants
(Ventre-Dominey *et al.*, 2001)	Saccades: Latency	1. Eye-hand coupling is preserved in PD participants 2. PD subjects demonstrated longer saccade latencies for both hands compared to control ($p < .0001$) 3. Differences in saccade latencies were even more pronounced when PD participants pointed with the 'affected hand'.
(Ventre-Dominey *et al.*, 2002)	Initial saccade: Amplitude Latency Frequency	1. Pointing reduced saccade frequencies in PD subjects compared to control's but increased frequencies when using PD affected limb. 2. Saccade latencies were longer in PD subjects than control (non-significant)
(Vitorio *et al.*, 2012)	Voluntary visual samples: Frequency Duration	1. No significant differences were found between PD and control participants in terms of their visual activity during walking. 2. Under single task PD made 25% less visual samples than control (non-significant) 3. Duration of VS was less in PD subjects than control (non-significant)
(Vitorio *et al.*, 2013)	Voluntary visual samples: Frequency Duration	1. People with PD are more dependent on dynamic visual information than control 2. PD subjects made significantly less visual samples than control subjects 3. Reduced duration of VS in PD compared with control (non-significant)
(Vitorio *et al.*, 2014)	Fixations: number and duration (ms and % of time) Location of fixation by frame-by-frame analysis of eye-tracker videos	1. People with PD fixate on visual cue prior to placing foot on floor 2. People with PD made less fixations than controls, with longer durations with a visual cue 3. Percentage of time spent fixating during a walk with a visual cue was loner in people with PD

3. Appendix 3.0 - Recruitment Poster

Newcastle University

NHS National Institute for Health Research

Version 1.0, April 2013

Clinical Ageing Research Unit
Newcastle University
Campus for Ageing & Vitality
Newcastle upon Tyne
NE4 5PL

Director: Professor David J Burn

Telephone: 0191 248 1250
Fax: 0191 248 1251
www.ncl.ac.uk/crp

Healthy volunteers needed for Research

Are you aged between 50 & 85?

Would you like to help us learn more about vision during walking?

Who are we?

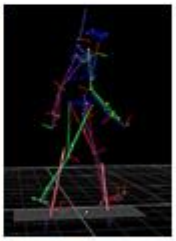
We are based in the state-of-the-art Clinical Ageing Research Unit (CARU) located at the Campus for Ageing & Vitality. We are interested in the study of human movement.

We are looking for volunteers, to attend a session to perform some assessments that examine vision during walking. The assessments are simple and do not require significant preparation. The assessments would be carried out at CARU.

If you are interested in finding out more and think you might like to take part, then please contact:

Sam Stuart
Clinical Ageing Research Unit
Campus for Ageing and Vitality
Newcastle University
Newcastle upon Tyne
NE4 5PL

Telephone: 0191 248 1242
Fax: 0191 248 1251
Email: sam.stuart@ncl.ac.uk



4. Appendix 4.0 - Recruitment Email

Newcastle University

Version 1.0, March 2013

NHS National Institute for Health Research

Dear Sir/Madam,

RE: An invitation to participate in a human movement research study.

The study is investigating vision during walking, which will be carried out at the Clinical Ageing Research Unit, at the Campus of Ageing and Vitality, Newcastle University. The overall aim of this study is to observe the differences in visual function during walking between healthy control subjects, Parkinson's disease subjects and Parkinson's disease subjects with mild cognitive impairment.

If you are aged 50-85 years I would like to invite you to participate in the study, as I require healthy individuals to do several assessments.

I have attached a recruitment poster to this email, which contains further information and contact details if you are interested in the study. Please pass on the recruitment poster to any eligible individuals you may know, such as parents, other family members or friends.

I hope that you will assist me in this exciting project.

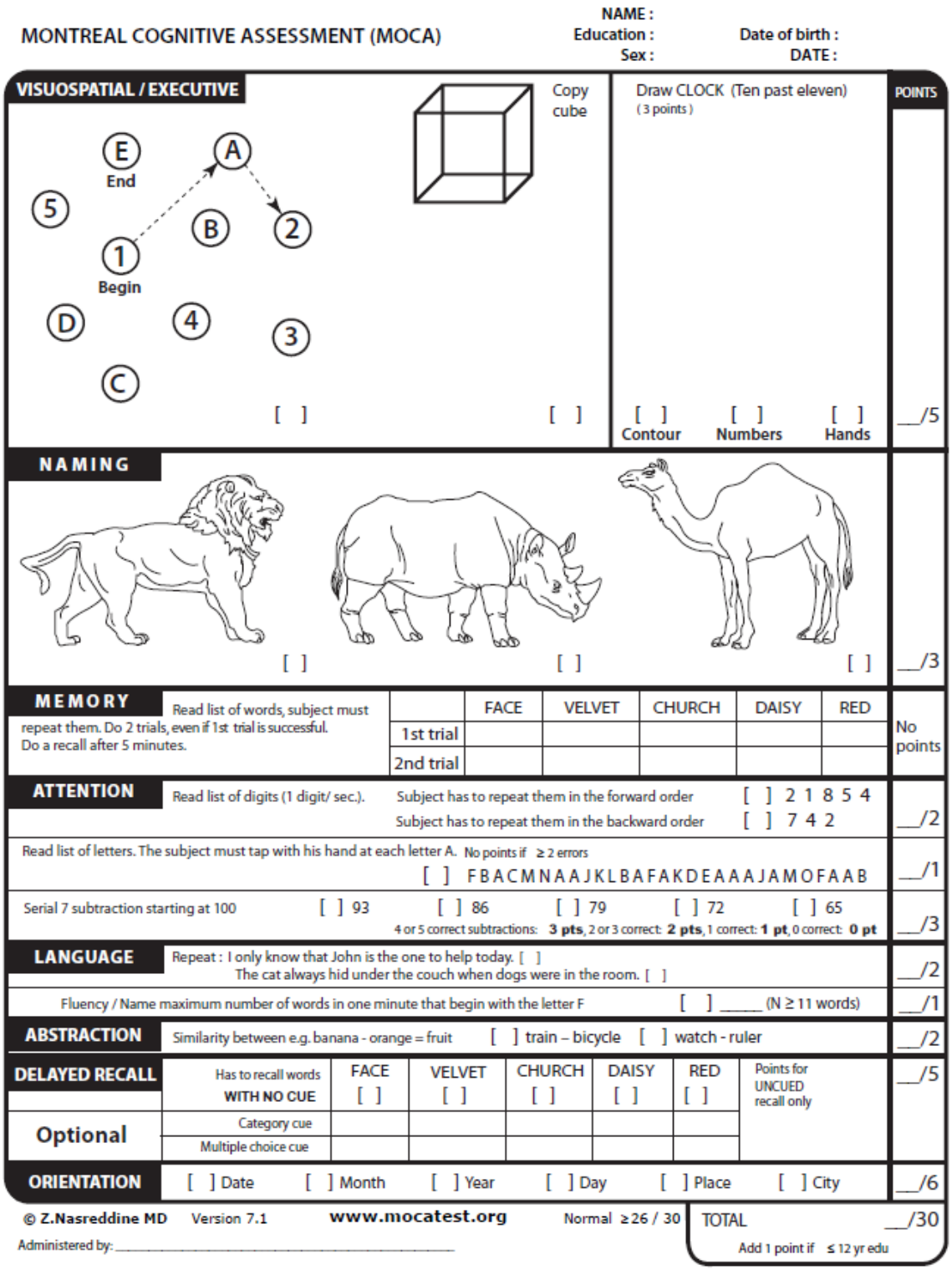
Kind Regards,

Sam Stuart BSc (Hons), M.Sc.

Research Assistant and PhD student
Clinical Ageing Research Unit
Institute for Ageing and Health
Newcastle University
Campus for Ageing and Vitality
Newcastle upon Tyne
NE4 5PL

Tel: +44 (0) 191 248 1242
E-mail: sam.stuart@newcastle.ac.uk
http://www.ncl.ac.uk/iah

5. Appendix 5.0 - Montreal Cognitive Assessment (MOCA)



MONTREAL COGNITIVE ASSESSMENT (MOCA)

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

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube

[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands — __/5

NAMING

[ ] [ ] [ ] — __/3

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

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

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

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

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

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

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — __/1

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

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

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

The cat always hid under the couch when dogs were in the room. [ ] — __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) — __/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler — __/2

DELAYED RECALL

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

__/5

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City — __/6

© Z.Nasreddine MD Version 7.1 www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

6. Appendix 6.0 – Addenbrooke's Cognitive Examination (ACE-R)

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R

Final Revised Version A (2005)

Name :
Date of birth :
Hospital no. :

Addressograph

Date of testing: ..... /...../.....
Tester's name: .....
Age at leaving full-time education: .....
Occupation: .....
Handedness: .....

ORIENTATION

➢ Ask: What is the	Day	Date	Month	Year	Season	[Score 0-5]
➢ Ask: Which	Building	Floor	Town	County	Country	[Score 0-5]

REGISTRATION

➢ Tell: 'I'm going to give you three words and i'd like you to repeat after me: lemon, key and ball'. After subject repeats, say 'Try to remember them because i'm going to ask you later'. Score only the first trial (repeat 3 times if necessary).

Register number of trials .....

[Score 0-3]

ATTENTION & CONCENTRATION

➢ Ask the subject: ' could you take 7 away from a 100? After the subject responds, ask him or her to take away another 7 to a total of 5 subtractions. If subject make a mistake, carry on and check the subsequent answer (i.e. 93, 84, 77, 70, 63 -score 4)

Stop after five subtractions (93, 86, 79, 72, 65). ....

➢ Ask: 'could you please spell **WORLD** for me? Then ask him/her to spell it backwards:

....

[Score 0-5]
(for the best performed task)

MEMORY - Recall

➢ Ask: 'Which 3 words did I ask you to repeat and remember?'

....

[Score 0-3]

MEMORY - Anterograde Memory

➢ Tell: ' I'm going to give you a name and address and I'd like you to repeat after me. We'll be doing that 3 times, so you have a chance to learn it. I'll be asking you later'

Score only the third trial

[Score 0-7]

	1st Trial	2nd Trial	3rd Trial
Harry Barnes	....	....	....
73 Orchard Close	....	....	....
Kingsbridge	.....	.....	.....
Devon	.....	.....	.....

MEMORY - Retrograde Memory

➢ Name of current Prime Minister .....
➢ Name of the woman who was Prime Minister .....
➢ Name of the USA president .....
➢ Name of the USA president who was assassinated in the 1960's .....

[Score 0 -4]

ATTENTION&ORIENTATION MEMORY

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R *Final Revised Version (2006)*

VERBAL FLUENCY - Letter 'P' and animals

➢ **Letters**

Say: 'I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. Are you ready? You've got a minute and the letter is P'

[Score 0 - 7] ☐

>17	7
14-17	6
11-13	5
8-10	4
6-7	3
4-5	2
2-3	1
<2	0
total	correct

➢ **Animals**

Say: 'Now can you name as many animals as possible, beginning with any letter?

[Score 0 - 7] ☐

>21	7
17-21	6
14-16	5
11-13	4
9-10	3
7-8	2
5-6	1
<5	0
total	correct

FLUENCY

LANGUAGE - Comprehension

➢ Show written instruction:

[Score 0-1] ☐ ☐

Close your eyes

➢ 3 stage command:
'Take the paper in your right hand. Fold the paper in half. Put the paper on the floor'

[Score 0-3] ☐ ☐

LANGUAGE - Writing

➢ Ask the subject to make up a sentence and write it in the space below:
Score 1 if sentence contains a subject and a verb (see guide for examples)

[Score 0-1] ☐ ☐

LANGUAGE

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R *Final Revised Version (2006)*

LANGUAGE - Repetition

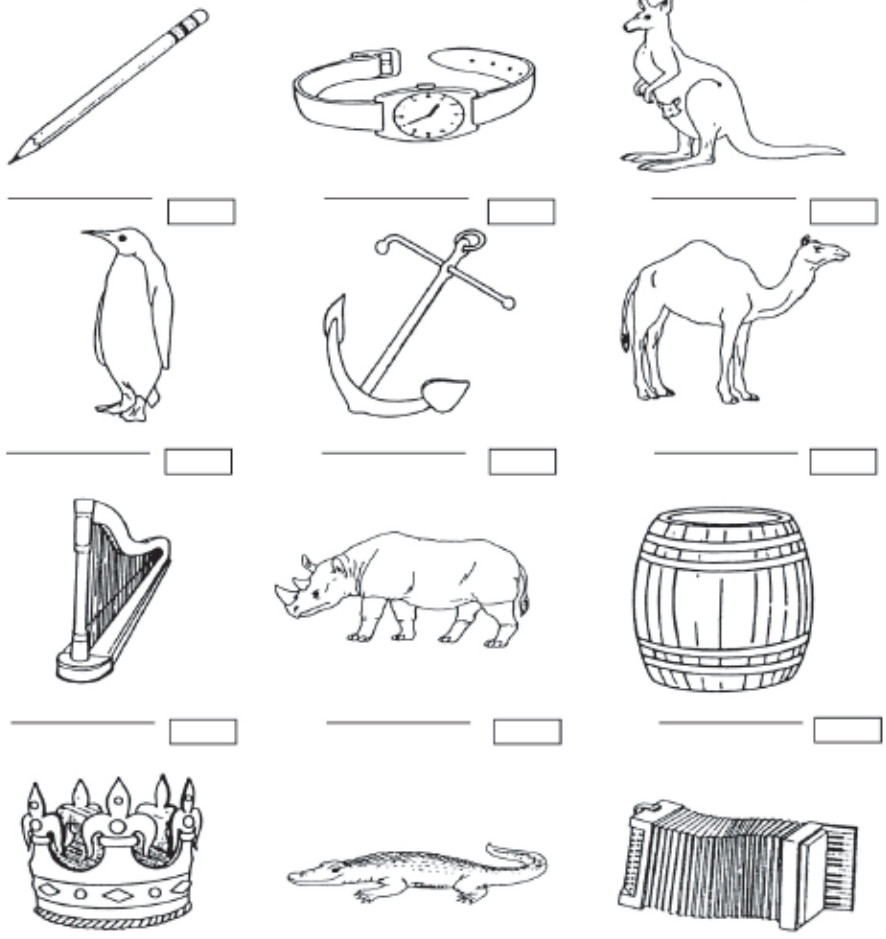
➢ Ask the subject to repeat: **' hippopotamus'; 'eccentricity; 'unintelligible'; 'statistician'**
Score 2 if all correct; 1 if 3 correct; 0 if 2 or less. [Score 0-2] ☐

➢ Ask the subject to repeat: **'Above, beyond and below'** [Score 0-1] ☐

➢ Ask the subject to repeat: **'No ifs, ands or buts'** [Score 0-1] ☐ ☐

LANGUAGE - Naming

➢ Ask the subject to name the following pictures: [Score 0-2] pencil + watch ☐ ☐ [Score 0-10] ☐



LANGUAGE - Comprehension

➢ Using the pictures above, ask the subject to: [Score 0-4] ☐

- Point to the one which is associated with the monarchy _____
- Point to the one which is a marsupial _____
- Point to the one which is found in the Antarctic _____
- Point to the one which has a nautical connection _____

LANGUAGE

ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R *Final Revised Version (2006)*

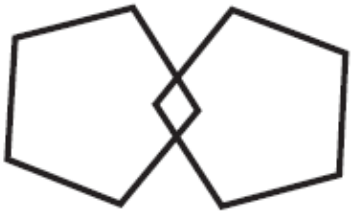
LANGUAGE - Reading

➢ Ask the subject to read the following words: [Score 1 only if all correct] [Score 0-1] ☐

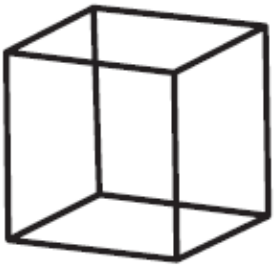
sew
pint
soot
dough
height

VISUOSPATIAL ABILITIES

➢ Overlapping pentagons: Ask the subject to copy this diagram: [Score 0-1] ☐



➢ Wire cube : Ask the subject to copy this drawing (for scoring, see instructions guide) [Score 0-2] ☐



➢ Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (for scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct) [Score 0-5] ☐

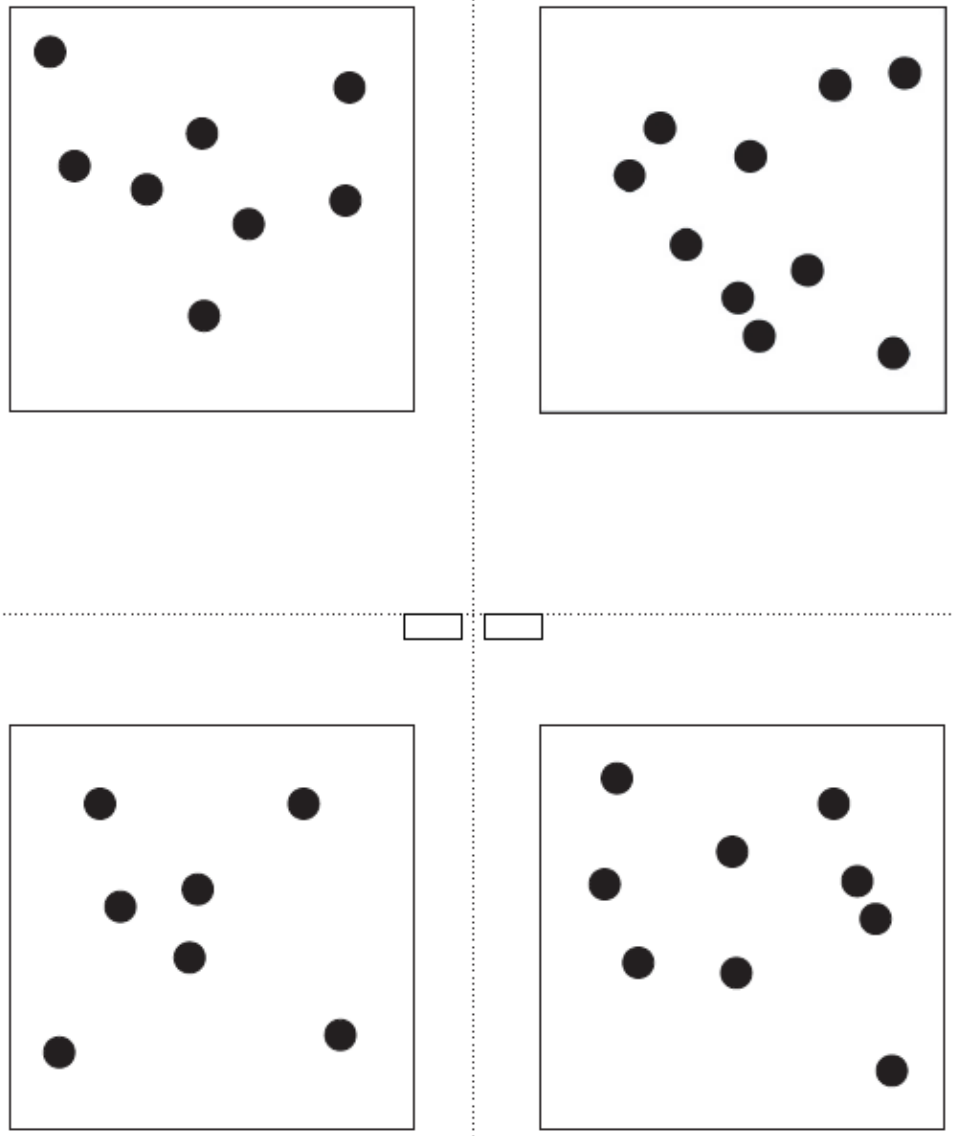
ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R *Final Revised Version (2006)*

PERCEPTUAL ABILITIES

VISUOSPATIAL

➢ Ask the subject to count the dots without pointing them

[Score 0-4]



ADDENBROOKE'S COGNITIVE EXAMINATION - ACE-R

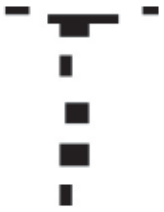
Final Revised Version A (2006)

PERCEPTUAL ABILITIES

➢ Ask the subject to identify the letters

[Score 0-4] ☐

VISUOSPATIAL



RECALL

➢ Ask "Now tell me what you remember of that name and address we were repeating at the beginning"

Harry	Barnes	....
73	Orchard	Close ....
	Kingsbridge	.....
	Devon	.....

[Score 0-7] ☐

MEMORY

RECOGNITION

➢ This test should be done if subject failed to recall one or more items. If all items were recalled, skip the test and score 5. If only part is recalled start by ticking items recalled in the shadowed column on the right hand side. Then test not recalled items by telling "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point which is added to the point gained by recalling.

[Score 0-5] ☐

Jerry Barnes		Harry Barnes		Harry Bradford		recalled	
37		73		76		recalled	
Orchard Place		Oak Close		Orchard Close		recalled	
Oakhampton		Kingsbridge		Dartington		recalled	
Devon		Dorset		Somerset		recalled	

General Scores

SCORE

MMSE	/30
ACE-R	/100

Subscores

Attention and Orientation	/18
Memory	/26
Fluency	/14
Language	/26
Visuospatial	/16

Normative values based on 63 controls aged 52-75 and 142 dementia patients aged 46-86

Cut-off <88 gives 94% senstivity and 89% specificity for dementia
Cut-off <82 gives 84% sensitivity and 100% specificity for dementia

7. Appendix 7.0 - Geriatric depression scale (GDS-15)

Geriatric Depression Scale (short form)

Instructions: Circle the answer that best describes how you felt over the past week.

1.	Are you basically satisfied with your life?	yes	no
2.	Have you dropped many of your activities and interests?	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 things?	yes	no
10.	Do you feel that you have more problems with memory than most?	yes	no
11.	Do you think it is wonderful to be alive now?	yes	no
12.	Do you feel 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 think that most people are better off than you are?	yes	no

Total Score _____

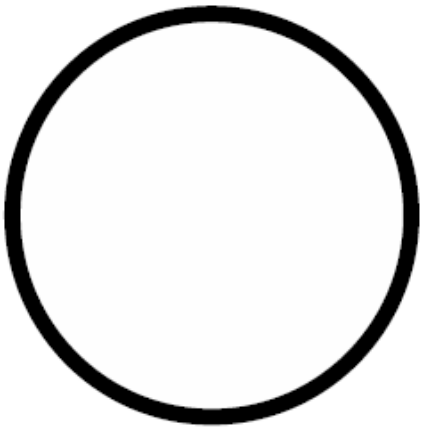
8. Appendix 8.0 – Royals CLOX 1 and 2

CLOX: An Executive Clock Drawing Task

STEP 1: Turn this form over on a light colored surface so that the circle below is visible. Have the subject draw a clock on the back. Instruct him or her to **" Draw me a clock that says 1:45. Set the hands and numbers on the face so that a child could read them."** Repeat the instructions until they are clearly understood. Once the subject begins to draw, no further assistance is allowed. Rate this clock in the CLOX 1 column.

STEP 2: Return to this side and let the subject observe you draw a clock in the circle below. Place 12, 6, 3, and 9 first, then fill in the rest of the numbers. Set the hands again to "1:45". Make the hands into arrows. Make the hour hand shortest. Invite the subject to copy your clock in the lower right corner. Rate this clock in the CLOX 2 column.

ORGANIZATIONAL ELEMENTS	Point Value	CLOX 1	CLOX 2
Does the figure resemble a clock?	1		
Circular face present?	1		
Dimensions > 1 inch?	1		
All numbers inside the perimeter?	1		
No sectoring or tic marks?	1		
12, 6, 3, & 9 placed first?	1		
Spacing intact? (Symmetry on either side of 12 and 6 o'clock?)	1		
Only Arabic numerals?	1		
Only numbers 1 — 12 among the numerals present?	1		
Sequence 1 — 12 intact? (No omissions or intrusions)	1		
Only two hands present? (Ignore sectoring/tic marks)	1		
All hands represented as arrows?	1		
Hour hand between 1 and 2 o'clock?	1		
Minute hand obviously longer than the hour hand?	1		
None of the Following 1) hand point to 4 or 5 o'clock 2) "1:45" present? 3) Any other notations (e.g. "9:00")? 4) Any arrows point inward? 5) Intrusions from "hand" or "face" present? 6) Any letters, words, or pictures? 7) Any intrusions from circles below?	1		
	TOTAL:		



9. Appendix 9.0 – Bentons Judgement of Line Orientation (JLO)

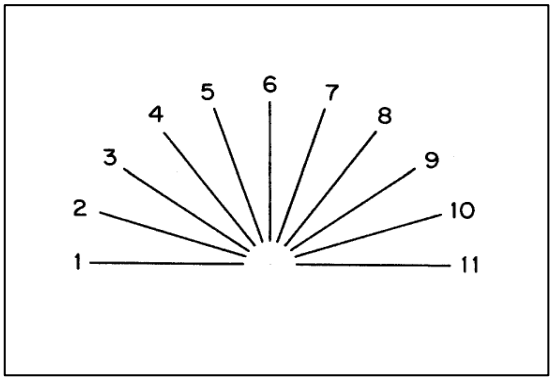
Record each response. Circle all errors.

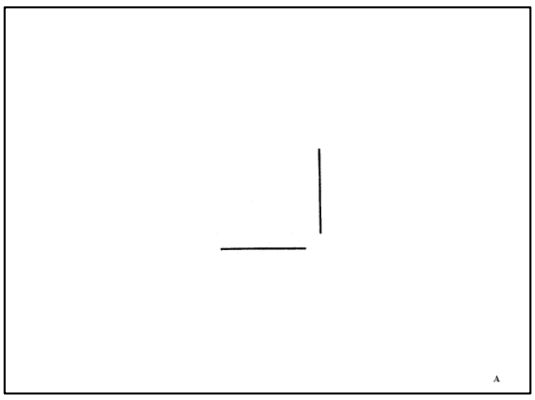
JLO Answer Sheet - Form V

Name: _____ Clinic Number: _____ Date: _____

- Practice Items
  - A ___ 1-6
  - B ___ 4-8
  - C ___ 4-10
  - D ___ 7-8
  - E ___ 2-4
  - A'__ 1 __ 6
  - B'__ 4 __ 8
  - C'__ 4 __ 10
  - D'__ 7 __ 8
  - E'__ 2 __ 4
- Test Items
  - 1 ____ 5-10 HH
  - 2 ____ 2-11 MM
  - 3 ____ 1-2 LL
  - 4 ____ 1-7 HH
  - 5 ____ 6-7 HH
  - 6 ____ 5-6 LL
  - 7 ____ 4-5 HH
  - 8 ____ 1-3 MM
  - 9 ____ 5-11 MM
  - 10 ____ 1-10 HH
  - 11 ____ 1-7 MM
  - 12 ____ 2-6 HH
  - 13 ____ 7-9 MM
  - 14 ____ 2-5 HL
  - 15 ____ 1-9 LL
- Test Items *(cont.)*
  - 16 ____ 7-8 MM
  - 17 ____ 3-5 HH
  - 18 ____ 10-11 MH
  - 19 ____ 1-4 MM
  - 20 ____ 3-11 LL
  - 21 ____ 6-10 LL
  - 22 ____ 2-9 LL
  - 23 ____ 3-8 HH
  - 24 ____ 9-11 HH
  - 25 ____ 3-4 LM
  - 26 ____ 8-9 LL
  - 27 ____ 8-11 HH
  - 28 ____ 7-10 HL
  - 29 ____ 3-10 HL
  - 30 ____ 5-8 HM

Correct ____





10. Appendix 10.0 – Movement Disorders Society – Unified Parkinson's disease Rating Scale

MDS-UPDRS

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

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

The authors of this new version are:

Chairperson: Christopher G. Goetz
Part I: Werner Poewe (chair), Bruno Dubois, Anette Schrag
Part II: Matthew B. Stern (chair), Anthony E. Lang, Peter A. LeWitt
Part III: Stanley Fahn (chair), Joseph Jankovic, C. Warren Olanow
Part IV: Pablo Martinez-Martin (chair), Andrew Lees, Olivier Rascol, Bob van Hilten
Development Standards: Glenn T. Stebbins (chair), Robert Holloway, David Nyenhuis
Appendices: Cristina Sampaio (chair), Richard Dodel, Jaime Kulisevsky
Statistical Testing: Barbara Tilley (chair), Sue Leurgans, Jean Teresi,
Consultant: Stephanie Shaftman, Nancy LaPelle

Contact person: Christopher G. Goetz, MD
Rush University Medical Center
1725 W. Harrison Street, Suite 755
Chicago, IL USA 60612

Telephone 312-942-8016
Email: cgoetz@rush.edu

July 1, 2008

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Overview: This portion of the scale assesses the non-motor impact of Parkinson's disease (PD) on patients' experiences of daily living. There are 13 questions. Part 1A is administered by the rater (six questions) and focuses on complex behaviors. Part 1B is a component of the self-administered Patient Questionnaire that covers seven questions on non-motor experiences of daily living.

Part 1A:
In administering Part IA, the examiner should use the following guidelines:

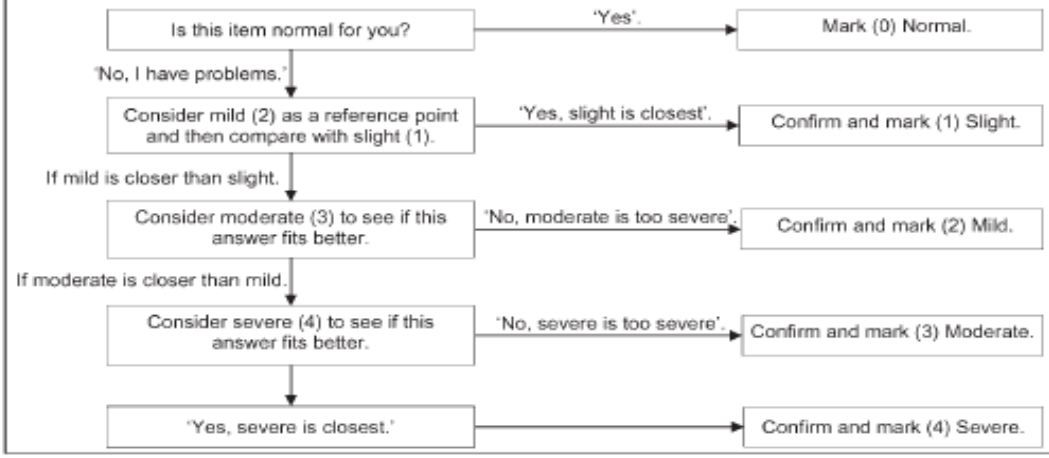
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (no half points, no missing scores). In the event that an item does not apply or cannot be rated (e.g., amputee who cannot walk), the item is marked UR for Unable to Rate.
4. The answers should reflect the usual level of function and words such as "usually", "generally", "most of the time" can be used with patients.
5. Each question has a text for you to read (Instructions to patients/caregiver). After that statement, you can elaborate and probe based on the target symptoms outlined in the Instructions to examiner. You should NOT READ the RATING OPTIONS to the patient/caregiver, because these are written in medical terminology. From the interview and probing, you will use your medical judgment to arrive at the best response.
6. Patients may have co-morbidities and other medical conditions that can affect their function. You and the patient must rate the problem as it exists and do not attempt to separate elements due to Parkinson's disease from other conditions.

EXAMPLE OF NAVIGATING THROUGH THE RESPONSE OPTIONS FOR PART 1A

Suggested strategies for obtaining the most accurate answer:
After reading the instructions to the patient, you will need to probe the entire domain under discussion to determine Normal vs. problematic: If your questions do not identify any problem in this domain, record 0 and move on to the next question.

If your questions identify a problem in this domain, you should work next with a reference anchor at the mid-range (option 2 or Mild) to find out if the patient functions at this level, better or worse. You will not be reading the choices of responses to the patient as the responses use clinical terminology. You will be asking enough probing questions to determine the response that should be coded.

Work up and down the options with the patient to identify the most accurate response, giving a final check by excluding the options above and below the selected response.



Patient Name or Subject ID	Site ID	(mm-dd-yyyy) Assessment Date	Investigator's Initials
_____	_____	_____	_____

MDS UPDRS
Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Part 1A: Complex behaviors: [completed by rater]

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

To be read to the patient: I am going to ask you six questions about behaviors that you may or may not experience. Some questions concern common problems and some concern uncommon ones. If you have a problem in one of the areas, please choose the best response that describes how you have felt MOST OF THE TIME during the PAST WEEK. If you are not bothered by a problem, you can simply respond NO. I am trying to be thorough, so I may ask questions that have nothing to do with you.

1.1 COGNITIVE IMPAIRMENT — **SCORE**

Instructions to examiner: Consider all types of altered level of cognitive function including cognitive slowing, impaired reasoning, memory loss, deficits in attention and orientation. Rate their impact on activities of daily living as perceived by the patient and/or caregiver.

Instructions to patients [and caregiver]: Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town? [If yes, examiner asks patient or caregiver to elaborate and probes for information]

0: Normal:	No cognitive impairment.	
1: Slight:	Impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions.	☐
2: Mild:	Clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions.	
3: Moderate:	Cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions.	
4: Severe:	Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions.	

	SCORE
1.2 HALLUCINATIONS AND PSYCHOSIS Instructions to examiner: Consider both illusions (misinterpretations of real stimuli) and hallucinations (spontaneous false sensations). Consider all major sensory domains (visual, auditory, tactile, olfactory and gustatory). Determine presence of unformed (for example sense of presence or fleeting false impressions) as well as formed (fully developed and detailed) sensations. Rate the patients insight into hallucinations and identify delusions and psychotic thinking. *Instructions to patients (and caregiver): Over the past week have you seen, heard, smelled or felt things that were not really there?* [If yes, examiner asks patient or caregiver to elaborate and probes for information] 0: Normal: No hallucinations or psychotic behaviour. 1: Slight: Illusions or non-formed hallucinations, but patient recognizes them without loss of insight. 2: Mild: Formed hallucinations independent of environmental stimuli. No loss of insight. 3: Moderate: Formed hallucinations with loss of insight. 4: Severe: Patient has delusions or paranoia.	☐
1.3 DEPRESSED MOOD Instructions to examiner: Consider low mood, sadness, hopelessness, feelings of emptiness or loss of enjoyment. Determine their presence and duration over the past week and rate their interference with the patient's ability to carry out daily routines and engage in social interactions. *Instruction to the patient (and caregiver): Over the past week have you felt low, sad, hopeless or unable to enjoy things? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you carry out your usual activities or to be with people?* If yes, examiner asks patient or caregiver to elaborate and probes for information] 0: Normal: No depressed mood. 1: Slight: Episodes of depressed mood that are not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2: Mild: Depressed mood that is sustained over days, but without interference with normal activities and social interactions. 3: Moderate: Depressed mood that interferes with, but does not preclude, the patient's ability to carry out normal activities and social interactions. 4: Severe: Depressed mood precludes patient's ability to carry out normal activities and social interactions.	☐

	SCORE
1.4 ANXIOUS MOOD Instructions to examiner: Determine nervous, tense, worried or anxious feelings (including panic attacks) over the past week and rate their duration and interference with the patient's ability to carry out daily routines and engage in social interactions. *Instructions to patients [and caregiver]: Over the past week have you felt nervous, worried or tense? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you to follow your usual activities or to be with other people?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No anxious feelings. 1: Slight: Anxious feelings present but not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2: Mild: Anxious feelings are sustained over more than one day at a time, but without interference with patient's ability to carry out normal activities and social interactions. 3: Moderate: Anxious feelings interfere with, but do not preclude, the patient's ability to carry out normal activities and social interactions. 4: Severe: Anxious feelings preclude patient's ability to carry out normal activities and social interactions.	☐
1.5 APATHY Instructions to examiner: Consider level of spontaneous activity, assertiveness, motivation and initiative and rate the impact of reduced levels on performance of daily routines and social interactions. Here the examiner should attempt to distinguish between apathy and similar symptoms that are best explained by depression. *Instructions to patients (and caregiver): Over the past week, have you felt indifferent to doing activities or being with people?* If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No apathy. 1: Slight: Apathy appreciated by patient and/or caregiver, but no interference with daily activities and social interactions. 2: Mild: Apathy interferes with isolated activities and social interactions. 3: Moderate: Apathy interferes with most activities and social interactions. 4: Severe: Passive and withdrawn, complete loss of initiative.	☐

1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME	SCORE
Instructions to examiner: Consider involvement in a variety of activities including atypical or excessive gambling (e.g. casinos or lottery tickets), atypical or excessive sexual drive or interests (e.g., unusual interest in pornography, masturbation, sexual demands on partner), other repetitive activities (e.g. hobbies, dismantling objects, sorting or organizing), or taking extra non-prescribed medication for non-physical reasons (i.e., addictive behavior). Rate the impact of such abnormal activities/behaviors on the patient's personal life and on his family and social relations (including need to borrow money or other financial difficulties like withdrawal of credit cards, major family conflicts, lost time from work, or missed meals or sleep because of the activity). *Instructions to patients [and caregiver]: Over the past week, have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop?* [Give patient examples such as gambling, cleaning, using the computer, taking extra medicine, obsessing about food or sex, all depending on the patients. 0: Normal: No problems present. 1: Slight: Problems are present but usually do not cause any difficulties for the patient or family/caregiver. 2: Mild: Problems are present and usually cause a few difficulties in the patient's personal and family life. 3: Moderate: Problems are present and usually cause a lot of difficulties in the patient's personal and family life. 4: Severe: Problems are present and preclude the patient's ability to carry out normal activities or social interactions or to maintain previous standards in personal and family life.	☐

The remaining questions in Part I (Non-motor Experiences of Daily Living) [Sleep, Daytime Sleepiness, Pain and Other Sensation, Urinary Problems, Constipation Problems, Lightheadedness on Standing, and Fatigue] are in the **Patient Questionnaire** along with all questions in Part II [Motor Experiences of Daily Living].

Part III: Motor Examination

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.18 CONSTANCY OF REST TREMOR	SCORE
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.	☐

Part IV: Motor Complications

Overview and Instructions: In this section, the rater uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. As in the other sections, rate using only integers (no half points allowed) and leave no missing ratings. If the item cannot be rated, place UR for Unable to Rate. You will need to choose some answers based on percentages, and therefore you will need to establish how many hours generally are awake hours and use this figure as the denominator for "OFF" time and Dyskinesias. For "OFF dystonia", the total "Off" time will be the denominator. Operational definitions for examiner's use.

Dyskinesias: Involuntary random movements
Words that patients often recognize for dyskinesias include "irregular jerking", "wiggling", "twitching". It is essential to stress to the patient the difference between dyskinesias and tremor, a common error when patients are assessing dyskinesias.

Dystonia: contorted posture, often with a twisting component:
Words that patients often recognize for dystonia include "spasms", "cramps", "posture".

Motor fluctuation: Variable response to medication:
Words that patients often recognize for motor fluctuation include "wearing out", "wearing off", "roller-coaster effect", "on-off", "uneven medication effects".

OFF: Typical functional state when patients have a poor response in spite of taking mediation or the typical functional response when patients are on NO treatment for parkinsonism. Words that patients often recognize include "low time", "bad time", "shaking time", "slow time", "time when my medications don't work."

ON: Typical functional state when patients are receiving medication and have a good response:
Words that patients often recognize include "good time", "walking time", "time when my medications work."

A . DYSKINESIAS [exclusive of OFF-state dystonia]

4.1 TIME SPENT WITH DYSKINESIAS

SCORE

Instructions to examiner: Determine the hours in the usual waking day and then the hours of dyskinesias. Calculate the percentage. If the patient has dyskinesias in the office, you can point them out as a reference to ensure that patients and caregivers understand what they are rating. You may also use your own acting skills to enact the dyskinetic movements you have seen in the patient before or show them dyskinetic movements typical of other patients. Exclude from this question early morning and nighttime painful dystonia.

Instructions to patient [and caregiver]. Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping? Alright, if you sleep ___ hrs, you are awake ____ hrs. Out of those awake hours, how many hours in total do you have wiggling, twitching or jerking movements? Do not count the times when you have tremor, which is a regular back and forth shaking or times when you have painful foot cramps or spasms in the early morning or at nighttime. I will ask about those later. Concentrate only on these types of wiggling, jerking and irregular movements. Add up all the time during the waking day when these usually occur. How many hours ____ (use this number for your calculation).

0: Normal:	No dyskinesias.	
1: Slight:	≤ 25% of waking day.	
2: Mild:	26 - 50% of waking day.	1. Total Hours Awake: _____
3: Moderate:	51 - 75% of waking day.	2. Total Hours with Dyskinesia: _____
4: Severe:	> 75% of waking day.	3. % Dyskinesia = ((2/1)*100): _____

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS	SCORE
Instructions to examiner: Determine the degree to which dyskinesias impact on the patient's daily function in terms of activities and social interactions. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer. *Instructions to patient [and caregiver]: Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?* 0: Normal: No dyskinesias or no impact by dyskinesias on activities or social interactions. 1: Slight: Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods. 2: Mild: Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods. 3: Moderate: Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes. 4: Severe: Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.	☐

B . MOTOR FLUCTUATIONS	
4.3 TIME SPENT IN THE OFF STATE Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the "OFF" state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the typical number of OFF hours, because you will need this number for completing 4.6 *Instructions to patient [and caregiver]: Some patients with Parkinson's disease have a good effect from their medications throughout their awake hours and we call that "ON" time. Other patients take their medications but still have some hours of low time, bad time, slow time or shaking time. Doctors call these low periods "OFF" time. Over the past week, you told me before that you are generally awake ____ hrs each day. Out of these awake hours, how many hours in total do you usually have this type of low level or OFF function ____ (Use this number for your calculations).* 0: Normal: No OFF time. 1: Slight: ≤ 25% of waking day. 2: Mild: 26 - 50% of waking day. 3: Moderate: 51 - 75% of waking day. 4: Severe: > 75% of waking day. 1. Total Hours Awake: _____ 2. Total Hours OFF: _____ 3. % OFF = ((2/1)*100): _____	☐

	SCORE
4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS Instructions to examiner: Determine the degree to which motor fluctuations impact on the patient's daily function in terms of activities and social interactions. This question concentrates on the difference between the ON state and the OFF state. If the patient has no OFF time, the rating must be 0, but if patients have very mild fluctuations, it is still possible to be rated 0 on this item if no impact on activities occurs. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer. *Instructions to patient [and caregiver]: Think about when those low or "OFF" periods have occurred over the past week. Do you usually have more problems doing things or being with people than compared to the rest of the day when you feel your medications working? Are there some things you usually do during a good period that you have trouble with or stop doing during a low period?* 0: Normal: No fluctuations or No impact by fluctuations on performance of activities or social interactions. 1: Slight: Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state. 2: Mild: Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state. 3: Moderate: Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods. 4: Severe: Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.	☐
4.5 COMPLEXITY OF MOTOR FLUCTUATIONS Instructions to examiner: Determine the usual predictability of OFF function whether due to dose, time of day, food intake or other factors. Use the information provided by the patients and caregiver and supplement with your own observations. You will ask if the patient can count on them always coming at a special time, mostly coming at a special time (in which case you will probe further to separate slight from mild), only sometimes coming at a special time or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer. *Instructions to patient [and caregiver]: For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods always come at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?"* 0: Normal: No motor fluctuations. 1: Slight: OFF times are predictable all or almost all of the time (> 75%). 2: Mild: OFF times are predictable most of the time (51-75%). 3: Moderate: OFF times are predictable some of the time (26-50%). 4: Severe: OFF episodes are rarely predictable. (≤ 25%).	☐

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient [and caregiver]: In one of the questions I asked earlier, you said you generally have ___ hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total ____ hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

0: Normal:	No dystonia OR NO OFF TIME.
1: Slight:	< 25% of time in OFF state.
2: Mild:	26-50% of time in OFF state.
3: Moderate:	51-75% of time in OFF state.
4: Severe:	> 75% of time in OFF state.

☐

1. Total Hours Off: _____
2. Total Off Hours w/Dystonia: _____
3. % Off Dystonia = ((2/1)*100): _____

Summary statement to patient: READ TO PATIENT

This completes my rating of your Parkinson's disease. I know the questions and tasks have taken several minutes, but I wanted to be complete and cover all possibilities. In doing so, I may have asked about problems you do not even have, and I may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this scale with me.

Patient Questionnaire:

Instructions:

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today. Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	
1.7 SLEEP PROBLEMS Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning. 0: Normal: No problems. 1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep. 2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep. 3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night. 4: Severe: I usually do not sleep for most of the night.	**SCORE** ☐
1.8 DAYTIME SLEEPINESS Over the past week, have you had trouble staying awake during the daytime? 0: Normal: No daytime sleepiness. 1: Slight: Daytime sleepiness occurs but I can resist and I stay awake. 2: Mild: Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV. 3: Moderate: I sometimes fall asleep when I should not. For example, while eating or talking with other people. 4: Severe: I often fall asleep when I should not. For example, while eating or talking with other people.	☐

	SCORE
1.9 PAIN AND OTHER SENSATIONS Over the past week, have you had uncomfortable feelings in your body like pain, aches tingling or cramps? 0: Normal: No uncomfortable feelings. 1: Slight: I have these feelings. However, I can do things and be with other people without difficulty. 2: Mild: These feelings cause some problems when I do things or am with other people. 3: Moderate: These feelings cause a lot of problems, but they do not stop me from doing things or being with other people. 4: Severe: These feelings stop me from doing things or being with other people.	☐
1.10 URINARY PROBLEMS Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents? 0: Normal: No urine control problems. 1: Slight: I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities. 2: Mild: Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents. 3: Moderate: Urine problems cause a lot of difficulties with my daily activities, including urine accidents. 4: Severe: I cannot control my urine and use a protective garment or have a bladder tube.	☐

	SCORE
1.11 CONSTIPATION PROBLEMS Over the past week have you had constipation troubles that cause you difficulty moving your bowels? 0: Normal: No constipation. 1: Slight: I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable. 2: Mild: Constipation causes me to have some troubles doing things or being comfortable. 3: Moderate: Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything. 4: Severe: I usually need physical help from someone else to empty my bowels.	☐
1.12 LIGHT HEADEDNESS ON STANDING Over the past week, have you felt faint, dizzy or foggy when you stand up after sitting or lying down? 0: Normal: No dizzy or foggy feelings. 1: Slight: Dizzy or foggy feelings occur. However, they do not cause me troubles doing things. 2: Mild: Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down. 3: Moderate: Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling. 4: Severe: Dizzy or foggy feelings cause me to fall or faint.	☐

	SCORE
1.13 FATIGUE Over the past week, have you usually felt fatigued? This feeling is not part of being sleepy or sad 0: Normal: No fatigue. 1: Slight: Fatigue occurs. However it does not cause me troubles doing things or being with people. 2: Mild: Fatigue causes me some troubles doing things or being with people. 3: Moderate: Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything. 4: Severe: Fatigue stops me from doing things or being with people.	☐
Part II: Motor Aspects of Experiences of Daily Living (M-EDL)	
2.1 SPEECH Over the past week, have you had problems with your speech? 0: Normal: Not at all (no problems). 1: Slight: My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself. 2: Mild: My speech causes people to ask me to occasionally repeat myself, but not everyday. 3: Moderate: My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood. 4: Severe: Most or all of my speech cannot be understood.	☐

	SCORE
2.2 SALIVA & DROOLING Over the past week, have you usually had too much saliva during when you are awake or when you sleep? 0: Normal: Not at all (no problems). 1: Slight: I have too much saliva, but do not drool. 2: Mild: I have some drooling during sleep, but none when I am awake. 3: Moderate: I have some drooling when I am awake, but I usually do not need tissues or a handkerchief. 4: Severe: I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.	☐
2.3 CHEWING AND SWALLOWING Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped or blended to avoid choking? 0: Normal: No problems. 1: Slight: I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared. 2: Mild: I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week. 3: Moderate. I choked at least once in the past week. 4: Severe: Because of chewing and swallowing problems, I need a feeding tube.	☐

	SCORE
2.4 EATING TASKS Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knifes, spoons, chopsticks? 0: Normal: Not at all (No problems). 1: Slight: I am slow, but I do not need any help handling my food and have not had food spills while eating. 2: Mild: I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat. 3: Moderate: I need help with many eating tasks but can manage some alone. 4: Severe: I need help for most or all eating tasks.	☐
2.5 DRESSING Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? 0: Normal: Not at all (no problems). 1: Slight: I am slow but I do not need help. 2: Mild: I am slow and need help for a few dressing tasks (buttons, bracelets). 3: Moderate: I need help for many dressing tasks. 4: Severe: I need help for most or all dressing tasks.	☐

	SCORE
2.6 HYGIENE Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair or with other personal hygiene? 0: Normal: Not at all (no problems). 1: Slight: I am slow but I do not need any help. 2: Mild: I need someone else to help me with some hygiene tasks. 3: Moderate: I need help for many hygiene tasks. 4: Severe: I need help for most or all of my hygiene tasks.	☐
2.7 HANDWRITING Over the past week, have people usually had trouble reading your handwriting? 0: Normal: Not at all (no problems). 1: Slight: My writing is slow, clumsy or uneven, but all words are clear. 2: Mild: Some words are unclear and difficult to read. 3: Moderate: Many words are unclear and difficult to read. 4: Severe: Most or all words cannot be read.	☐
2.8 DOING HOBBIES AND OTHER ACTIVITIES Over the past week, have you usually had trouble doing your hobbies or other things that you like to do? 0: Normal: Not at all (no problems). 1: Slight: I am a bit slow but do these activities easily. 2: Mild: I have some difficulty doing these activities. 3: Moderate: I have major problems doing these activities, but still do most. 4: Severe: I am unable to do most or all of these activities.	☐

	SCORE
2.9 TURNING IN BED Over the past week, do you usually have trouble turning over in bed? 0: Normal: Not at all (no problems). 1: Slight: I have a bit of trouble turning, but I do not need any help. 2: Mild I have a lot of trouble turning and need occasional help from someone else. 3: Moderate: To turn over I often need help from someone else. 4: Severe: I am unable to turn over without help from someone else.	☐
2.10 TREMOR Over the past week, have you usually had shaking or tremor? 0: Normal: Not at all. I have no shaking or tremor. 1: Slight: Shaking or tremor occurs but does not cause problems with any activities. 2: Mild: Shaking or tremor causes problems with only a few activities. 3: Moderate: Shaking or tremor causes problems with many of my daily activities. 4: Severe: Shaking or tremor causes problems with most or all activities.	☐
2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair? 0: Normal: Not at all (no problems). 1: Slight: I am slow or awkward, but I usually can do it on my first try. 2: Mild: I need more than one try to get up or need occasional help. 3: Moderate: I sometimes need help to get up, but most times I can still do it on my own. 4: Severe: I need help most or all of the time.	☐

	SCORE
2.12 WALKING AND BALANCE Over the past week, have you usually had problems with balance and walking? 0: Normal: Not at all (no problems). 1: Slight: I am slightly slow or may drag a leg. I never use a walking aid. 2: Mild: I occasionally use a walking aid, but I do not need any help from another person. 3: Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person. 4: Severe: I usually use the support of another persons to walk safely without falling.	☐
2.13 FREEZING Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor. 0: Normal: Not at all (no problems). 1: Slight: I briefly freeze but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing. 2: Mild: I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing. 3: Moderate: When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help. 4: Severe: Because of freezing, most or all of the time, I need to use a walking aid or someone's help.	☐
This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.	

11. Appendix 11.0 - Hoehn and Yahr (H&Y) Scale

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

12. Appendix 12.0 – The Freezing of gait questionnaire (FOGQ)

Freezing of Gait Questionnaire:

Part I - Distinction freezer – non-freezer	**Score**
1. Do you experience "freezing episodes"? Freezing is the feeling that your feet are transiently glued to the floor while trying to initiate walking, making a turn or when walking through narrow spaces or in crowded places? Sometimes it can be accompanied with trembling of the legs and small shuffling steps. 0. I never had such a feeling or episode 1. I have experienced such a feeling or episode over the past month	
Part II – Freezing severity; frequency and duration of the freezing episodes	
2.How frequently do you experience freezing episodes? 0. Less than once a week 1. Rarely, about once a week 2. Often, about once a day 3. Very often, more than once a day	
3. How frequently do you experience freezing episodes during turning? 0. Never 1. Very rarely, about once a month 2. Rarely, about once a week 3. Often, about once a day 4. Very often, more than once a day ***If you answer 1 or more go to question #4. If the answer is 0, go directly to question #5.***	
4.How long is your longest freezing episode during turning? 1. Very short, 1 sec 2. Short 2 - 5 s. 3. Long, between 5 and 30 s. 4. Very long, unable to walk for more than 30 s.	
5. How frequently do you experience typical start hesitation episodes (freezing when initiating the first step)? 0. Never 1. Very rarely, about once a month 2. Rarely, about once a week 3. Often, about once a day 4. Very often, more than once a day ***If you answer 1 or more go to question #6. If the answer is 0, go directly to question 7.***	
6. How long is your longest typical start hesitation episode (freezing when initiating the first step)?	

1. Very short 1 s. 2. Short 2-5 Sec 3. Long, between 5 and 30 s. 4. Very long, unable to walk for more than 30 s.	
Part III - Impact of freezing on daily life	
7. How disturbing are the freezing episodes for your daily walking? 0. Not at all 1. Very little 2. Moderately 3. Significantly	
8. Do you think the freezing episodes are causing insecurity and fear of falling? 0. Not at all 1. Minimally 2. Have a moderate effect 3. Have a very significant contribution	

9. As a result of your freezing episodes can you walk: 0. Independently 1. With mild dependence on others (requiring supervision only) 2. With moderate dependence on others (occasional physical help or walking) 3. With severe dependence on others (requiring regular physical help for walking) 4. Can not walk at all	
10. Are your freezing episodes affecting your daily activities? 0. Not at all, I continue doing things as normal 1. Mildly, I avoid some but not many daily activities 2. Moderately, I avoid a significant amount of daily activities 3. Severely, I am very restricted in carrying out most daily activities	

Total Score:
Part 1:
Part II:
Part III:

13. Appendix 13.0 – Falls and Efficacy scale (FES-1)

Now we would like to ask some questions about how concerned you are about the possibility of falling. For each of the following activities, please circle the opinion closest to your own to show how concerned you are that you might fall if you did this activity. Please reply thinking about how you usually do the activity. If you currently don't do the activity (e.g. if someone does your shopping for you), please answer to show whether you think you would be concerned about falling IF you did the activity.

		Not at all concerned 1	*Somewhat concerned* 2	*Fairly concerned* 3	*Very concerned* 4
1	Cleaning the house (e.g. sweep, vacuum or dust)	*1*	*2*	*3*	*4*
2	Getting dressed or undressed	*1*	*2*	*3*	*4*
3	Preparing simple meals	*1*	*2*	*3*	*4*
4	Taking a bath or shower	*1*	*2*	*3*	*4*
5	Going to the shop	*1*	*2*	*3*	*4*
6	Getting in or out of a chair	*1*	*2*	*3*	*4*
7	Going up or down stairs	*1*	*2*	*3*	*4*
8	Walking around in the neighbourhood	*1*	*2*	*3*	*4*
9	Reaching for something above your head or on the ground	*1*	*2*	*3*	*4*
10	Going to answer the telephone before it stops ringing	*1*	*2*	*3*	*4*
11	Walking on a slippery surface (e.g. wet or icy)	*1*	*2*	*3*	*4*
12	Visiting a friend or relative	*1*	*2*	*3*	*4*
13	Walking in a place with crowds	*1*	*2*	*3*	*4*
14	Walking on an uneven surface (e.g. rocky ground, poorly maintained pavement)	*1*	*2*	*3*	*4*
15	Walking up or down a slope	*1*	*2*	*3*	*4*
16	Going out to a social event (e.g. religious service, family gathering or club meeting)	*1*	*2*	*3*	*4*

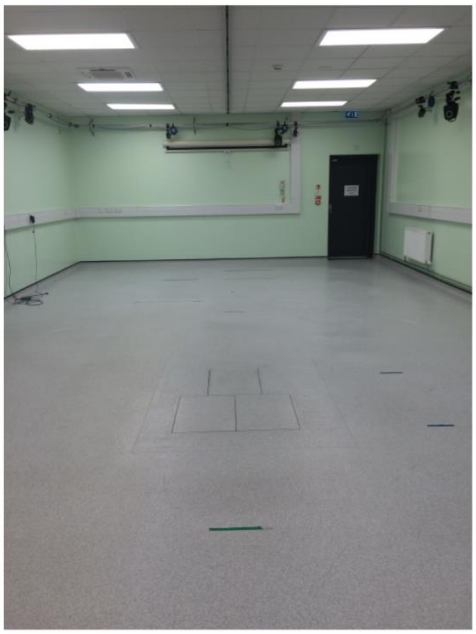
14. Appendix 14.0 - Eye and Head Movement Peak Cross Correlations During Walking

		Session 1						Session 2					
		HORIZONTAL			VERTICAL			HORIZONTAL			VERTICAL		
Group	Participan	5	10	15	5	10	15	5	10	15	5	10	15
Older Adults	**1**	0.0	0.0	0.1	0.1	0.6	0.1	0.1	0.0	0.1	0.0	0.1	0.1
	2	0.0	0.1	0.0	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.1	0.0
	3	0.0	0.0	0.2	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1
	4	0.1	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.1	0.0	0.1	0.1
	5	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.0	0.0	0.1
	6	0.0	0.1	0.1	0.1	0.0	0.0	0.1	0.1	0.2	0.1	0.1	0.1
	7	0.0	0.1	0.0	0.0	0.0	0.0	0.4	0.1	0.1	0.0	0.0	0.1
	8	0.0	0.1	0.1	0.0	0.0	0.1	0.1	0.1	0.1	0.0	0.0	0.0
	9	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0
	10	0.0	0.0	0.0	0.1	0.0	0.1	0.1	0.0	0.1	0.0	0.0	0.0
	11	0.0	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.1	0.1
	12	0.0	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0
	13	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.0	0.1
	14	0.1	0.1	0.1	0.0	0.1	0.0	No follow up data available					
	15	0.1	0.0	0.1	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.0	0.1
	16	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.1	0.1
	17	0.0	0.0	0.0	0.0	0.1	0.0	No follow up data available					
	18	0.2	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0
	19	0.1	0.1	0.0	0.0	0.1	0.0	0.1	0.1	0.1	0.0	0.0	0.1
	20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0
	Average	0.1	0.1	0.1	0.0	0.1	0.0	0.1	0.1	0.1	0.0	0.0	0.0
Parkinson's	**1**	0.1	0.1	0.1	0.0	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0
	2	0.1	0.0	0.0	0.0	0.1	0.0	0.1	0.1	0.1	0.4	0.3	0.1
	3	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	0.0	0.0	0.0
	4	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
	5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	6	0.0	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.1	0.0
	7	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0
	8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	10	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0
	11	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	12	0.1	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0
	13	0.0	0.0	0.1	0.0	0.0	0.1	No follow up data available					
	14	0.0	0.1	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.0	0.0	0.1
	Average	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0

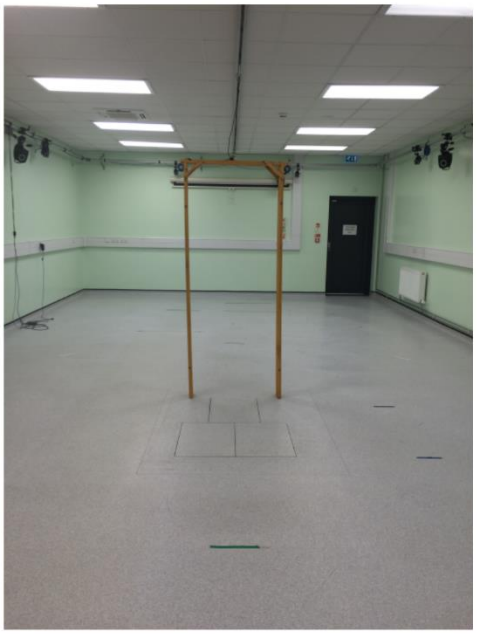
[Horizontal comparison = eye x trace compared to medio-lateral g trace, Vertical comparison = eye y trace compared to superior-inferior g trace]

15. Appendix 15.0 – Photos of walking conditions

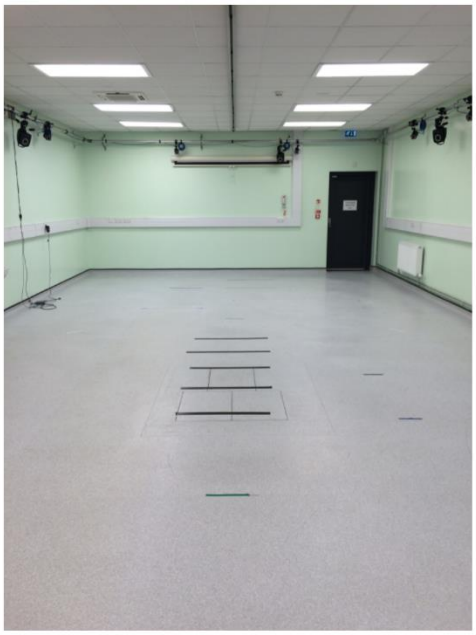
Straight



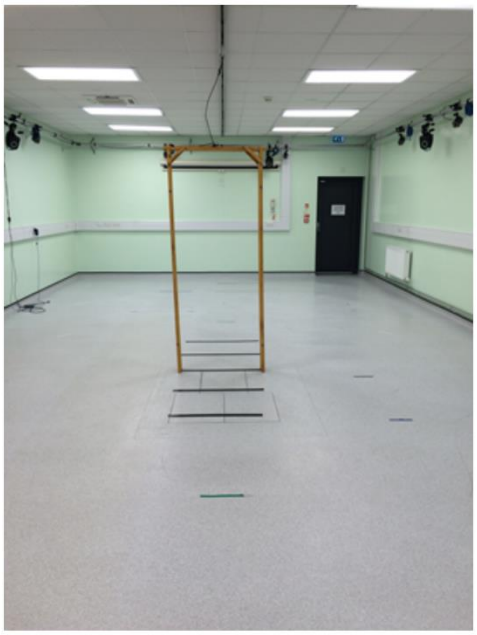
Door and Turn



Cue



Cue and Door



16. Appendix 16.0 - Visual sampling characteristics during gait

			Saccades					Fixations		Blinks
	Attentional manipulation		Number (no.)	Duration (ms)	Amplitude (°)	Peak Velocity (°/sec)	Peak Acceleration (°/sec²)	Number (no.)	Duration (sec)	Number (no.)
Group	Cognitive Task	Environment	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Control	Single	Straight	1.97 (1.59)	77.49 (21.68)	8.39 (4.13)	410.69 (117.43)	5010.15 (2486.94)	2.45 (1.21)	1.21 (0.78)	4.83 (3.40)
		Door	2.03 (1.54)	64.25 (23.55)	9.12 (4.27)	438.08 (112.61)	5712.74 (3480.96)	2.48 (1.18)	1.08 (0.73)	4.38 (3.04)
		Turn	3.36 (1.46)	78.40 (16.61)	9.51 (4.08)	511.42 (104.54)	5866.16 (3095.26)	3.56 (1.16)	0.76 (0.59)	4.03 (2.66)
	Dual	Straight	1.56 (1.45)	71.79 (26.92)	9.30 (4.63)	436.92 (157.58)	5927.32 (4216.98)	2.16 (1.15)	1.38 (0.89)	6.08 (3.74)
		Door	1.73 (1.21)	67.16 (34.09)	9.09 (7.87)	426.26 (120.56)	7016.05 (6607.70)	2.40 (1.11)	1.28 (0.74)	6.70 (3.73)
		Turn	3.38 (1.52)	70.53 (13.07)	9.93 (4.85)	502.70 (100.26)	6459.38 (4131.21)	3.62 (1.26)	0.80 (0.58)	6.45 (3.33)
PD	Single	Straight	1.47 (1.70)	74.70 (21.68)	8.04 (3.45)	461.24 (128.48)	7956.80 (9059.84)	2.19 (1.46)	1.28 (0.96)	4.04 (4.25)
		Door	1.92 (1.76)	71.90 (26.73)	8.99 (5.37)	477.47 (110.80)	8204.80 (8894.48)	2.59 (1.48)	1.25 (1.01)	4.34 (4.71)
		Turn	3.13 (1.46)	71.02 (21.81)	8.89 (4.96)	508.51 (116.62)	7903.71 (9514.41)	3.55 (1.30)	1.10 (0.92)	3.64 (3.19)
	Dual	Straight	**0.97 (1.22)†**	70.93 (29.53)	**6.83 (2.14)†**	438.00 (114.42)	7862.66 (10489.95)	1.80 (1.11)	1.50 (1.00)	5.64 (4.04)
		Door	**1.21 (1.20)†**	68.26 (27.61)	8.55 (3.98)	457.96 (116.24)	8123.58 (9766.17)	**1.95 (1.01)†**	1.50 (1.04)	5.50 (4.56)
		Turn	**2.43 (1.42)†**	70.57 (16.69)	8.61 (3.26)	493.59 (103.75)	8226.40 (9044.50)	**2.88 (1.18)†**	1.05 (0.87)	4.96 (3.84)

[† independent t-test PD vs controls significance level p <0.05, saccade, fixation and blink number were calculated from a Dikablis mobile eye-tracker (50Hz), all other characteristics were calculated using EOG (1000Hz) for horizontal saccades only]

17. Appendix 17.0 – Relationship between eye and head movement during gait

Eye-head co-ordination analysed via peak cross correlation between the raw eye and head movement signals was similar between both groups, and within each of the walking conditions, as shown in Table 11-1. This evidence demonstrated that head movement was only moderately correlated (r = .38 to .45) with eye movement across the trials within both groups (PD and controls). A large range (Min: r = .15 to Max: r = .77) of eye-head co-ordination was also seen within both groups indicating that eye-head co-ordination was variable throughout the walking conditions for both groups. Head movement was therefore not used in further analysis.

Table 11-1 - Head movement characteristics

			Eye-Head movement		Head Movement Data	
	Attentional manipulation		Peak Cross Correlation X	Peak Cross Correlation Y	Mean Velocity X (°/sec)	Mean Velocity Y (°/sec)
Group	Task	Env	Mean r (Min-Max)	Mean r (Min-Max)	Mean (SD)	Mean (SD)
Control (n=15)	Single	Straight	0.41 (0.25-0.58)	0.42 (0.28-0.61)	12.76 (19.29)	18.89 (31.67)
		Door	0.39 (0.24-0.59)	0.39 (0.23-0.59)	18.59 (17.99)	23.52 (27.36)
		Turn	0.46 (0.29-0.59)	0.44 (0.14-0.59)	26.05 (12.53)	31.24 (18.39)
	Dual	Straight	0.38 (0.15-0.56)	0.35 (0.21-0.48)	6.12 (13.36)	10.21 (22.81)
		Door	0.41 (0.19-0.55)	0.40 (0.18-0.52)	14.52 (15.57)	19.43 (15.57)
		Turn	0.42 (0.25-0.69)	0.41 (0.25-0.63)	30.89 (17.05)	23.02 (11.69)
PD (n=15)	Single	Straight	0.42 (0.20-0.65)	0.39 (0.25-0.63)	14.78 (17.00)	18.48 (23.26)
		Door	0.39 (0.21-0.70)	0.41 (0.22-0.71)	16.33 (29.85)	20.75 (42.61)
		Turn	0.43 (0.21-0.77)	0.40 (0.20-0.58)	21.01 (12.51)	25.15 (16.05)
	Dual	Straight	0.42 (0.18-0.66)	0.40 (0.23-0.60)	9.50 (15.28)	11.62 (20.39)
		Door	0.45 (0.22-0.72)	0.42 (0.19-0.71)	9.13 (10.63)	10.93 (15.75)
		Turn	0.38 (0.25-0.52)	0.42 (0.29-0.65)	23.11 (14.97)	17.25 (10.13)

[X represents horizontal eye movement and Medio-lateral head movement, Y represents vertical eye movement and sagittal head movement, Env = environment]

18. Appendix 18.0 - Visual sampling characteristics during gait with a visual cue

			Saccade					Fixation		Blink
			Number (no.)	Duration (ms)	Amplitude (°)	Peak Velocity (°/sec)	Peak Acceleration (°/sec²)	Number (no.)	Duration (sec)	Number (no.)
Group	Cognitive Task	Environment	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Control	Single	No Cue	1.87 (1.31)	76.35 (16.72)	7.84 (3.04)	411.16 (118.45)	5084.88 (2082.86)	2.38 (1.02)	1.21 (0.83)	5.25 (3.64)
(n=32)		Cue	3.01 (1.25)	79.79 (40.11)	6.87 (4.15)	437.07 (152.39)	6960.88 (7419.09)	3.38 (1.07)	1.33 (0.85)	5.59 (3.40)
		No Cue & Door	1.91 (1.55)	65.96 (24.74)	7.54 (2.16)	418.41 (103.77)	5272.87 (2848.30)	2.38 (1.22)	1.19 (0.77)	4.66 (3.25)
		Cue & Door	3.26 (1.64)	49.15 (14.29)	7.24 (5.31)	415.19 (121.36)	5682.60 (5048.08)	3.39 (1.40)	1.31 (0.77)	5.59 (3.15)
	Dual	No Cue	1.19 (1.01)	70.85 (28.20)	9.75 (5.16)	438.35 (171.02)	6304.57 (4587.38)	1.88 (0.88)	1.25 (0.98)	6.00 (3.89)
		Cue	2.97 (1.65)	55.29 (24.32)	6.76 (3.19)	430.14 (135.98)	5679.70 (5864.42)	3.15 (1.29)	1.59 (0.78)	6.94 (3.59)
		No Cue & Door	1.55 (1.05)	72.34 (36.13)	7.54 (2.16)	408.35 (103.58)	6483.74 (4511.19)	2.21 (0.95)	1.32 (0.72)	6.75 (3.93)
		Cue & Door	3.20 (1.64)	59.20 (27.88)	6.25 (4.53)	391.17 (120.48)	5347.33 (4874.93)	3.41 (1.33)	1.46 (0.71)	6.50 (3.22)
PD	Single	No Cue	1.46 (1.71)	75.05 (35.66)	8.14 (3.48)	462.51 (129.86)	7954.45 (9188.34)	2.18 (1.47)	1.28 (0.97)	4.09 (4.27)
(n=55)		Cue	3.59 (1.89)	65.77 (24.60)	6.81 (3.01)	449.91 (123.31)	7110.78 (8761.12)	3.85 (1.64)	1.32 (1.02)	4.42 (4.03)
		No Cue & Door	1.95 (1.77)	71.37 (26.92)	8.99 (5.37)	479.03 (111.71)	8279.71 (8991.55)	2.61 (1.49)	1.23 (1.02)	4.40 (4.73)
		Cue & Door	3.56 (1.74)	**66.67 (18.63)†**	6.44 (3.49)	445.61 (156.53)	6815.15 (9203.18)	3.91 (1.56)	1.24 (1.05)	**4.00 (3.40)†**
	Dual	No Cue	0.96 (1.23)	70.93 (29.53)	**6.83 (2.14)†**	438.00 (114.42)	7862.66 (10489.95)	1.79 (1.12)	1.47 (1.00)	5.67 (4.27)
		Cue	3.37 (1.77)	65.87 (33.25)	6.68 (2.79)	450.40 (142.82)	6511.72 (7621.52)	3.62 (1.57)	1.35 (0.96)	5.29 (4.54)
		No Cue & Door	1.20 (1.21)	69.16 (27.36)	8.64 (4.02)	457.50 (117.72)	8161.92 (9890.78)	1.95 (1.02)	1.50 (1.05)	5.55 (4.59)
		Cue & Door	3.80 (1.98)	65.16 (27.68)	6.09 (3.02)	442.61 (156.53)	6931.52 (8264.81)	4.00 (1.56)	1.47 (1.10)	**4.89 (3.74)†**

[† independent t-test PD vs controls significance level p <0.05, saccade, fixation and blink number were calculated from a Dikablis mobile eye-tracker (50Hz), all other characteristics were calculated using EOG (1000Hz) for horizontal saccades only]

19. Appendix 19.0 - Associations between cognitive and visual functions, and gait characteristics in older adult controls

Attentional Task		Gait Characteristic	MoCA	ACE-R	PoA	FoA	CLOX 1	JLO	Digit Span	VA	CS
Single	Straight	Step length	-.001 (.997)	.149 (.357)	-.100 (.538)	-.081 (.620)	.293 (.067)	.289 (.071)	.199 (.218)	-.065 (.690)	.062 (.706)
		Velocity	.158 (.331)	.224 (.165)	.038 (.815)	-.044 (.786)	.212 (.189)	.173 (.285)	.297 (.063)	-.063 (.700)	.077 (.635)
		Double support time	-.162 (.319)	-.148 (.363)	-.014 (.934)	.081 (.617)	.050 (.761)	.066 (.687)	-.150 (.357)	.121 (.459)	-.073 (.656)
	Door	Step length	-.029 (.858)	.106 (.513)	-.079 (.628)	.013 (.937)	.187 (.247)	.307 (.054)	.198 (.220)	-.022 (.891)	.123 (.448)
		Velocity	.133 (.413)	.139 (.393)	.029 (.860)	.012 (.942)	.116 (.478)	.166 (.307)	.232 (.149)	-.048 (.768)	.087 (.595)
		Double support time	-.236 (.142)	-.205 (.204)	.006 (.969)	.218 (.177)	-.046 (.776)	.043 (.793)	-.223 (.167)	.012 (.939)	.069 (.673)
	Turn	Step length	.050 (.759)	.111 (.495)	-.156 (.337)	-.090 (.583)	**.329 (.038)***	**.396 (.011)***	.008 (.959)	-.075 (.645)	-.063 (.701)
		Velocity	.181 (.263)	.150 (.356)	-.058 (.722)	-.137 (.399)	.250 (.120)	.203 (.209)	.132 (.417)	-.058 (.723)	-.084 (.606)
		Double support time	-.130 (.425)	-.090 (.579)	-.052 (.750)	.096 (.555)	.013 (.937)	.025 (.878)	-.130 (.423)	.106 (.514)	-.106 (.516)
	Cue	Step length	.055 (.766)	.194 (.287)	-.185 (.310)	-.086 (.640)	.111 (.546)	.121 (.511)	.213 (.241)	.042 (.821)	.005 (.979)
		Velocity	.219 (.228)	.282 (.117)	-.066 (.720)	-.130 (.479)	.178 (.330)	.138 (.451)	.271 (.133)	-.001 (.995)	-.124 (.499)
		Double support time	-.257 (.156)	-.256 (.157)	-.182 (.318)	-.021 (.909)	-.101 (.582)	-.052 (.776)	-.253 (.162)	.098 (.595)	.165 (.368)
	Cue & Door	Step length	.035 (.849)	.154 (.400)	-.182 (.318)	-.051 (.783)	.079 (.669)	.091 (.622)	.194 (.288)	.019 (.918)	-.005 (.976)
		Velocity	.142 (.437)	.211 (.247)	-.031 (.866)	-.063 (.732)	.107 (.562)	.058 (.753)	.201 (.271)	-.029 (.877)	-.098 (.594)
		Double support time	-.220 (.226)	-.172 (.347)	-.276 (.126)	-.111 (.545)	-.045 (.805)	.019 (.919)	-.092 (.616)	.156 (.394)	.116 (.528)
Dual	Straight	Step length	-.104 (.522)	.004 (.981)	.009 (.957)	.085 (.601)	.198 (.221)	**.343 (.030)***	.129 (.429)	-.055 (.737)	.106 (.517)
		Velocity	.047 (.775)	.004 (.981)	.203 (.210)	.112 (.490)	.055 (.734)	.150 (.355)	.107 (.510)	-.066 (.687)	.059 (.718)
		Double support time	-.018 (.914)	-.081 (.620)	-.215 (.183)	-.123 (.448)	.061 (.708)	-.039 (.812)	-.157 (.335)	.169 (.298)	-.272 (.089)
	Door	Step length	-.072 (.659)	.050 (.758)	-.082 (.617)	-.028 (.863)	***.325 (.040)****	**.398 (.011)***	.114 (.485)	-.055 (.735)	.038 (.815)
		Velocity	.081 (.619)	.086 (.596)	.096 (.556)	-.016 (.924)	.231 (.152)	.244 (.130)	.119 (.465)	-.084 (.606)	.000 (.999)
		Double support time	-.041 (.801)	-.075 (.645)	-.081 (.621)	-.112 (.493)	-.008 (.962)	-.223 (.168)	-.102 (.531)	.127 (.433)	-.167 (.303)
	Turn	Step length	.060 (.712)	.123 (.451)	-.209 (.196)	-.153 (.344)	**.421 (.007)***	**.383 (.015)***	-.025 (.878)	-.076 (.643)	-.088 (.590)
		Velocity	.195 (.228)	.082 (.614)	.014 (.934)	-.067 (.680)	.287 (.072)	.205 (.203)	.074 (.648)	-.024 (.882)	-.120 (.462)
		Double support time	-.121 (.456)	-.052 (.751)	-.079 (.627)	-.083 (.610)	-.001 (.993)	-.114 (.485)	-.135 (.406)	.016 (.921)	-.070 (.667)
	Cue	Step length	.016 (.932)	.092 (.617)	-.237 (.191)	-.080 (.662)	.126 (.491)	.085 (.645)	.098 (.594)	.070 (.702)	-.081 (.660)
		Velocity	.160 (.381)	.233 (.199)	.000 (.999)	-.111 (.547)	.203 (.266)	.065 (.722)	.154 (.399)	-.030 (.871)	-.164 (.369)
		Double support time	-.307 (.088)	-.219 (.229)	-.181 (.321)	.034 (.852)	-.187 (.305)	-.085 (.642)	-.163 (.373)	.064 (.726)	.241 (.183)
	Cue & Door	Step length	-.002 (.993)	.055 (.766)	-.257 (.156)	-.110 (.550)	.103 (.575)	.104 (.571)	.074 (.687)	.088 (.633)	-.142 (.439)
		Velocity	.138 (.453)	.097 (.596)	-.033 (.856)	-.072 (.697)	.123 (.503)	.064 (.728)	.047 (.797)	.105 (.566)	-.301 (.094)
		Double support time	-.251 (.165)	-.150 (.411)	-.233 (.199)	-.055 (.766)	-.043 (.813)	-.109 (.554)	-.068 (.712)	.005 (.979)	.201 (.269)

[*significance level p < .05, r (*p*) presented in table]

Appendix 19.1 - Associations between demographic and gait characteristics in older adult controls

Attentional Task		Gait Characteristic	Age	Height	Weight	GDS-15	FES-I
Single	Straight	Step length	-.247 (.125)	**.559 (<.001)***	**.322 (.043)***	-.117 (.474)	-.150 (.354)
		Velocity	-.219 (.174)	.286 (.073)	-.010 (.952)	-.171 (.292)	-.278 (.082)
		Double support time	.273 (.088)	.001 (.993)	**.372 (.018)***	.199 (.219)	**.401 (.010)***
	Door	Step length	-.283 (.076)	**.565 (<.001)***	**.365 (.021)***	-.117 (.474)	-.150 (.356)
		Velocity	-.294 (.065)	.250 (.119)	.030 (.853)	-.219 (.175)	-.305 (.055)
		Double support time	**.340 (.032)***	.133 (.414)	**.338 (.033)***	.194 (.231)	**.449 (.004)***
	Turn	Step length	**-.395 (.012)***	.258 (.107)	.097 (.552)	-.045 (.783)	-.092 (.573)
		Velocity	**-.403 (.010)***	-.013 (.938)	-.194 (.231)	-.201 (.214)	-.311 (.051)
		Double support time	.286 (.073)	.102 (.531)	**.339 (.033)***	.238 (.140)	**.365 (.021)**
	Cue	Step length	**-.422 (.007)***	.102 (.531)	.023 (.886)	-.228 (.157)	-.182 (.262)
		Velocity	**-.447 (.004)***	.049 (.762)	-.169 (.297)	-.284 (.076)	-.292 (.068)
		Double support time	.189 (.243)	-.012 (.942)	**.386 (.014)***	**.344 (.030)***	**.353 (.026)***
	Cue & Door	Step length	**-.435 (.005)***	.098 (.549)	.025 (.880)	-.229 (.156)	-.110 (.500)
		Velocity	**-.430 (.006)***	.050 (.761)	-.153 (.344)	-.278 (.082)	-.251 (.118)
		Double support time	.161 (.322)	-.021 (.898)	**.376 (.017)**	.278 (.083)	**.351 (.027)***
Dual	Straight	Step length	-.146 (.370)	**.587 (<.001)***	**.371 (.018)***	-.145 (.371)	.004 (.979)
		Velocity	-.045 (.783)	**.327 (.039)***	.100 (.539)	-.201 (.213)	-.098 (.548)
		Double support time	.021 (.898)	-.179 (.269)	.172 (.289)	.242 (.132)	.227 (.159)
	Door	Step length	-.229 (.155)	**.558 (<.001)***	**.319 (.045)***	-.116 (.478)	-.047 (.774)
		Velocity	-.141 (.387)	**.313 (.049)***	.057 (.728)	-.156 (.336)	-.167 (.304)
		Double support time	.145 (.371)	-.274 (.088)	.080 (.624)	.169 (.296)	**.323 (.042)***
	Turn	Step length	**-.359 (.023)***	**.359 (.023)***	.130 (.424)	-.104 (.524)	-.050 (.760)
		Velocity	-.188 (.245)	.247 (.124)	-.036 (.827)	-.156 (.336)	-.218 (.176)
		Double support time	.102 (.531)	-.233 (.148)	.087 (.592)	.186 (.251)	**.414 (.008)***
	Cue	Step length	**-.361 (.022)***	.180 (.266)	.134 (.410)	-.188 (.246)	-.051 (.754)
		Velocity	**-.354 (.025)***	.193 (.234)	-.023 (.890)	-.273 (.088)	-.183 (.259)
		Double support time	.212 (.188)	-.132 (.416)	.281 (.079)	.287 (.073)	**.340 (.032)**
	Cue & Door	Step length	**-.428 (.006)***	.093 (.568)	.034 (.837)	-.229 (.155)	-.063 (.698)
		Velocity	**-.380 (.016)***	.142 (.383)	-.007 (.964)	-.274 (.087)	-.233 (.147)
		Double support time	.185 (.253)	-.076 (.640)	.292 (.068)	.290 (.070)	**.387 (.014)***

[*significance level p < .05, r (*p*) presented in table]

20. Appendix 20.0 - Associations between cognitive and visual functions, and gait characteristics in Parkinson's disease

Gait Characteristic			MoCA	ACE-R	PoA	FoA	CLOX 1	JLO	Digit Span	VA	CS
Single	Straight	Step length	**.333 (.012)***	**.282 (.035)***	-.162 (.232)	**-.327 (.014)***	.263 (.050)	**.299 (.025)***	-.127 (.351)	-.076 (.576)	.091 (.505)
		Velocity	.258 (.055)	**.301 (.024)***	**-.284 (.034)***	**-.377 (.004)***	**.297 (.026)***	**.288 (.031)***	.026 (.847)	-.119 (.384)	.205 (.131)
		Double support time	-.128 (.348)	-.161 (.235)	.145 (.285)	.226 (.094)	-.052 (.706)	-.148 (.277)	-.178 (.190)	**.325 (.015)***	**-.366 (.006)***
	Door	Step length	**.286 (.033)***	**.286 (.033)***	-.180 (.184)	**-.264 (.049)***	.189 (.163)	**.285 (.033)***	-.092 (.502)	.002 (.986)	.040 (.768)
		Velocity	.245 (.068)	**.274 (.041)***	-.238 (.077)	**-.359 (.007)***	.209 (.122)	**.299 (.025)***	.062 (.647)	-.023 (.864)	.145 (.286)
		Double support time	-.049 (.721)	-.035 (.798)	-.077 (.575)	.033 (.810)	.048 (.727)	-.062 (.648)	-.196 (.148)	.214 (.114)	-.246 (.067)
	Turn	Step length	**.267 (.047)***	.238 (.077)	-.208 (.124)	**-.337 (.011)***	.049 (.722)	.183 (.176)	-.030 (.824)	.071 (.602)	.053 (.698)
		Velocity	**.318 (.017)***	**.288 (.031)***	**-.267 (.046)***	**-.453 (<.001)***	.193 (.153)	.255 (.058)	.037 (.788)	.004 (.979)	.125 (.358)
		Double support time	-.065 (.638)	-.044 (.752)	.007 (.961)	.169 (.218)	.100 (.468)	-.031 (.823)	-.099 (.472)	**.288 (.033)***	-.244 (.073)
	Cue	Step length	.009 (.948)	.006 (.967)	-.139 (.313)	-.067 (.626)	-.014 (.921)	**.296 (.028)***	.166 (.226)	.015 (.912)	.043 (.754)
		Velocity	.229 (.092)	.142 (.300)	-.156 (.255)	**-.362 (.007)***	.076 (.580)	**.356 (.008)***	.181 (.187)	-.120 (.381)	.191 (.162)
		Double support time	-.015 (.913)	-.068 (.622)	.027 (.845)	.113 (.412)	.126 (.358)	-.074 (.590)	-.224 (.101)	**.357 (.007)***	**-.312 (.021)***
	Cue & Door	Step length	.038 (.785)	-.014 (.917)	-.072 (.602)	-.048 (.728)	.003 (.984)	.096 (.487)	.228 (.094)	.063 (.646)	-.040 (.773)
		Velocity	.243 (.074)	.171 (.212)	-.225 (.099)	**-.420 (.001)***	.063 (.648)	**.312 (.020)***	.200 (.143)	-.116 (.397)	.202 (.140)
		Double support time	-.044 (.751)	-.104 (.452)	.070 (.610)	.132 (.337)	.101 (.463)	-.045 (.742)	-.239 (.079)	**.379 (.004)***	**-.323 (.016)***
Dual	Straight	Step length	**.313 (.019)***	.178 (.189)	-.104 (.447)	**-.292 (.029)***	.150 (.270)	**.320 (.016)***	-.151 (.267)	.001 (.996)	-.071 (.604)
		Velocity	**.309 (.020)***	.163 (.230)	-.087 (.523)	**-.307 (.021)***	.166 (.221)	**.328 (.014)***	.007 (.960)	.027 (.845)	-.052 (.701)
		Double support time	-.117 (.392)	.039 (.776)	.014 (.916)	.145 (.286)	-.042 (.757)	-.152 (.264)	.123 (.366)	-.056 (.679)	.051 (.711)
	Door	Step length	**.329 (.013)***	.215 (.111)	-.174 (.200)	**-.364 (.006)***	.225 (.096)	**.354 (.007)***	-.098 (.472)	-.003 (.984)	.000 (.999)
		Velocity	**.321 (.016)***	.226 (.094)	-.121 (.374)	**-.357 (.007)***	.213 (.115)	**.377 (.004)***	.079 (.561)	-.046 (.738)	.055 (.685)
		Double support time	-.183 (.176)	-.093 (.494)	.058 (.673)	.205 (.129)	-.147 (.279)	-.216 (.110)	-.032 (.817)	.051 (.711)	-.123 (.366)
	Turn	Step length	**.334 (.012)***	.215 (.112)	-.242 (.072)	**-.426 (.001)***	.169 (.212)	**.325 (.015)***	-.148 (.275)	.024 (.863)	.037 (.787)
		Velocity	**.348 (.009)***	.210 (.119)	-.169 (.214)	**-.421 (.001)***	.190 (.160)	**.324 (.015)***	.044 (.748)	-.018 (.892)	.052 (.701)
		Double support time	-.234 (.086)	-.107 (.438)	-.011 (.938)	.149 (.277)	-.160 (.243)	-.212 (.120)	-.078 (.569)	.088 (.522)	-.113 (.413)
	Cue	Step length	.022 (.872)	-.100 (.468)	-.014 (.919)	-.056 (.684)	-.040 (.770)	.092 (.504)	.139 (.312)	.023 (.868)	-.071 (.606)
		Velocity	**.290 (.032)***	.194 (.157)	-.125 (.365)	**-.340 (.011)***	.084 (.544)	**.355 (.008)***	.156 (.255)	-.049 (.721)	.050 (.716)
		Double support time	-.085 (.536)	-.119 (.386)	.024 (.865)	.108 (.431)	.126 (.361)	-.095 (.490)	-.224 (.100)	**.346 (.010)***	-.210 (.125)
	Cue & Door	Step length	.229 (.093)	.093 (.499)	-.059 (.668)	-.157 (.254)	-.025 (.857)	.029 (.836)	.166 (.226)	.051 (.711)	.008 (.956)
		Velocity	**.311 (.021)***	.180 (.189)	-.137 (.317)	**-.352 (.008)***	.115 (.404)	**.318 (.018)***	.143 (.299)	-.065 (.638)	.083 (.545)
		Double support time	-.083 (.545)	-.114 (.409)	.064 (.645)	.152 (.269)	.114 (.409)	-.117 (.393)	-.216 (.114)	**.366 (.006)***	-.260 (.055)

[*significance level p < .05, r (*p*) presented in table]

Appendix 20.1 - Associations between demographic, clinical and gait characteristics in Parkinson's disease

Attentional Task		Gait Characteristic	Age	Height	Weight	GDS-15	FES-I	UPDRS-III	FOGQ	LED	PD duration
Single	Straight	Step length	-.172 (.206)	**.334 (.012)***	.071 (.605)	-.183 (.178)	**-.374 (.005)***	**-.488 (<.001)***	**-.319 (.016)***	-.028 (.845)	-.083 (.545)
		Velocity	-.195 (.149)	.144 (.288)	.008 (.952)	**-.383 (.004)***	**-.370 (.005)***	**-.411 (.002)***	-.204 (.132)	.028 (.840)	-.001 (.995)
		Double support time	**.267 (.047)***	.123 (.366)	-.016 (.907)	.166 (.222)	**.334 (.012)***	.194 (.152)	-.010 (.942)	.173 (.216)	-.046 (.736)
	Door	Step length	-.102 (.456)	**.304 (.023)***	.099 (.470)	**-.318 (.017)***	**-.396 (.003)***	**-.507 (<.001)***	**-.273 (.042)***	-.081 (.566)	-.020 (.886)
		Velocity	-.110 (.421)	.136 (.316)	.033 (.807)	**-.429 (.001)***	**-.428 (.001)***	**-.452 (<.001)***	-.185 (.172)	-.022 (.873)	.018 (.895)
		Double support time	.112 (.413)	**.286 (.033)***	.229 (.089)	.262 (.051)	**.459 (<.001)***	.194 (.152)	.042 (.756)	.234 (.092)	-.065 (.635)
	Turn	Step length	-.090 (.511)	.189 (.162)	-.024 (.859)	**-.354 (.007)***	**-.324 (.015)***	**-.540 (<.001)***	-.249 (.065)	.034 (.807)	.024 (.861)
		Velocity	-.109 (.422)	.065 (.636)	-.029 (.831)	**-.446 (.001)***	**-.401 (.002)***	**-.461 (<.001)***	-.192 (.156)	.067 (.631)	.055 (.689)
		Double support time	.138 (.310)	.204 (.132)	.139 (.309)	.181 (.183)	**.429 (.001)***	.079 (.564)	.035 (.798)	.256 (.064)	.036 (.795)
	Cue	Step length	.190 (.161)	.067 (.625)	.078 (.568)	**-.510 (<.001)***	-.238 (.077)	**-.368 (.005)***	-.079 (.561)	.018 (.901)	.066 (.628)
		Velocity	.093 (.496)	-.087 (.522)	-.151 (.267)	**-.609 (<.001)***	**-.567 (<.001)***	**-.428 (.001)***	-.188 (.164)	-.034 (.807)	.100 (.463)
		Double support time	.183 (.176)	.139 (.306)	.021 (.880)	.192 (.155)	**.437 (.001)***	.136 (.318)	-.022 (.875)	.181 (.194)	-.063 (.645)
	Cue & Door	Step length	.144 (.289)	.209 (.123)	.170 (.209)	**-.424 (.001)***	-.156 (.250)	**-.298 (.026)***	-.023 (.869)	.084 (.551)	.048 (.725)
		Velocity	.040 (.768)	.017 (.902)	-.064 (.638)	**-.524 (<.001)***	**-.568 (<.001)***	**-.522 (<.001)***	-.224 (.097)	.007 (.958)	.095 (.486)
		Double support time	.230 (.088)	.127 (.352)	.039 (.775)	.152 (.262)	**.459 (<.001)***	.160 (.240)	-.044 (.747)	.167 (.232)	-.070 (.607)
Dual	Straight	Step length	-.109 (.425)	**.331 (.013)**	.068 (.620)	-.084 (.539)	**-.282 (.035)***	**-.344 (.009)***	-.254 (.059)	.014 (.921)	-.114 (.402)
		Velocity	-.105 (.442)	.107 (.432)	-.015 (.912)	-.145 (.285)	**-.349 (.008)***	-.231 (.086)	-.095 (.486)	.107 (.446)	-.015 (.913)
		Double support time	.037 (.784)	.112 (.411)	**.327 (.014)**	.133 (.328)	.186 (.171)	-.012 (.932)	.103 (.448)	.013 (.929)	.010 (.942)
	Door	Step length	-.141 (.299)	**.336 (.011)**	.121 (.376)	-.116 (.395)	**-.303 (.023)***	**-.421 (.001)***	**-.291 (.030)**	.021 (.881)	-.103 (.449)
		Velocity	-.182 (.179)	.120 (.379)	.020 (.883)	-.153 (.260)	**-.388 (.003)***	**-.287 (.032)***	-.097 (.478)	.083 (.555)	-.015 (.913)
		Double support time	.240 (.075)	.217 (.109)	.212 (.117)	.124 (.363)	.225 (.096)	.213 (.114)	-.033 (.807)	.026 (.856)	.009 (.949)
	Turn	Step length	-.108 (.429)	.223 (.098)	.025 (.852)	-.157 (.249)	-.212 (.116)	**-.485 (<.001)***	**-.303 (.023)***	.038 (.788)	-.074 (.588)
		Velocity	-.154 (.258)	.053 (.697)	-.003 (.983)	-.209 (.122)	**-.337 (.011)***	**-.328 (.014)***	-.110 (.422)	.108 (.443)	.036 (.794)
		Double support time	.161 (.239)	.241 (.077)	.184 (.179)	.158 (.249)	**.318 (.018)***	.153 (.264)	-.009 (.948)	.076 (.593)	-.042 (.763)
	Cue	Step length	**.287 (.032)**	.133 (.327)	.024 (.860)	-.215 (.112)	-.212 (.117)	-.231 (.087)	-.154 (.259)	.017 (.905)	-.206 (.129)
		Velocity	.047 (.730)	.054 (.693)	.023 (.866)	**-.375 (.004)***	**-.477 (<.001)***	**-.337 (.011)**	-.083 (.543)	.126 (.368)	.142 (.295)
		Double support time	.191 (.159)	.093 (.496)	-.040 (.770)	.111 (.415)	**.450 (.001)***	.118 (.386)	-.076 (.577)	.118 (.400)	-.069 (.613)
	Cue & Door	Step length	.152 (.262)	.110 (.419)	.045 (.743)	-.119 (.382)	-.147 (.280)	**-.311 (.020)***	-.103 (.451)	.057 (.683)	-.131 (.336)
		Velocity	.025 (.855)	.019 (.887)	-.067 (.623)	**-.433 (.001)***	**-.475 (<.001)***	**-.402 (.002)***	-.132 (.332)	.074 (.598)	.144 (.289)
		Double support time	.206 (.129)	.141 (.300)	.023 (.866)	.129 (.345)	**.443 (.001)***	.150 (.270)	-.015 (.910)	.174 (.214)	-.042 (.760)

[*significance level p < .05, r (*p*) presented in table]

21. Appendix 21.0 – Regression model performance

Visual sampling regression model performance: Parkinson's disease group

Attentional Task		Model 1			Model 2			Model 3			Model 4		
		r^2	*F*	*p*	r^2	*F*	*p*	r^2	*F*	*p*	r^2	*F*	*p*
Single	ΔDoor	.075	1.04	.395	.197	1.45	.203	.100	.903	.500	.248	1.49	.177
	ΔTurn	.084	1.16	.338	.144	.989	.457	.161	1.57	.175	.196	1.10	.386
	ΔCue	.136	1.96	.115	.201	1.45	.204	.165	1.58	1.74	.307	1.95	.053
	ΔCue&Door	.047	.617	.652	.154	1.04	.418	.057	.480	.820	.173	.918	.526
Dual	ΔDoor	.086	1.20	.323	.232	1.78	.106	.108	.993	.441	.239	1.41	.205
	ΔTurn	.077	1.06	.385	.221	1.67	.131	.123	1.15	.350	.254	1.53	.160
	ΔCue	.107	1.50	.216	.140	.936	.497	.117	1.06	.402	.148	.763	.663
	ΔCue&Door	.168	.253	.052	.199	1.43	.210	.191	1.89	.102	.225	1.28	.272

[*F and p from ANOVA*]

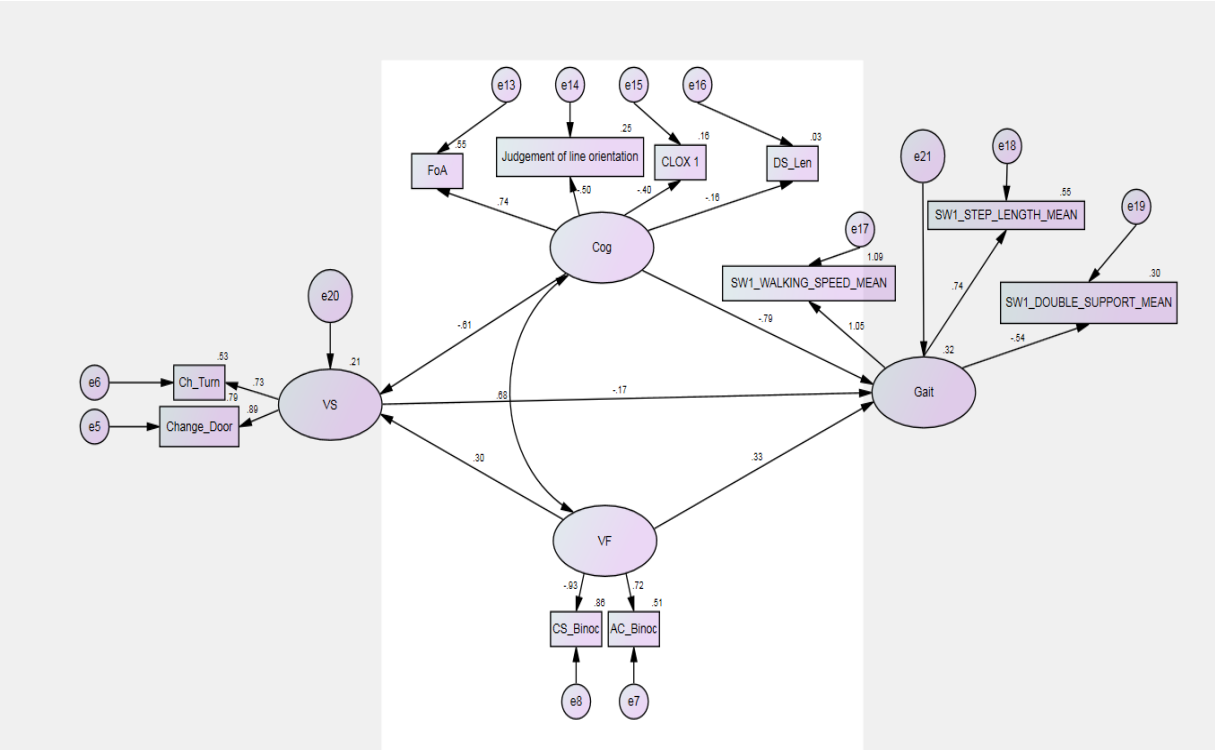
Visual sampling regression model performance: Control group

Attentional Task		Model 1			Model 2			Model 3			Model 4		
		r^2	*F*	*p*	r^2	*F*	*p*	r^2	*F*	*p*	r^2	*F*	*p*
Single	ΔDoor	.040	.500	.684	.095	.480	.842	.073	.538	.746	.128	.490	.869
	ΔTurn	.186	2.74	.057	.216	1.26	.301	.193	1.63	.179	.219	.933	.511
	ΔCue	.095	1.26	.303	.214	1.24	.309	.161	.995	.440	.242	1.06	.417
	ΔCue&Door	.125	1.71	.182	.166	.911	.511	.058	.322	.895	.187	.765	.649
Dual	ΔDoor	.125	1.71	.182	.166	.911	.511	.141	1.12	.368	.187	.765	.649
	ΔTurn	.048	.802	.618	.152	.816	.581	.128	.159	.179	.170	.682	.719
	ΔCue	.040	.386	.764	.191	.811	.587	.053	.293	.913	.239	.769	.645
	ΔCue&Door	.021	.198	.897	.169	.700	.672	.129	.773	.578	.306	1.08	.417

[*F and p from ANOVA*]

22. Appendix 22.0 – Full Structural Equation Models for Parkinson's disease Group

Straight Walk Gait



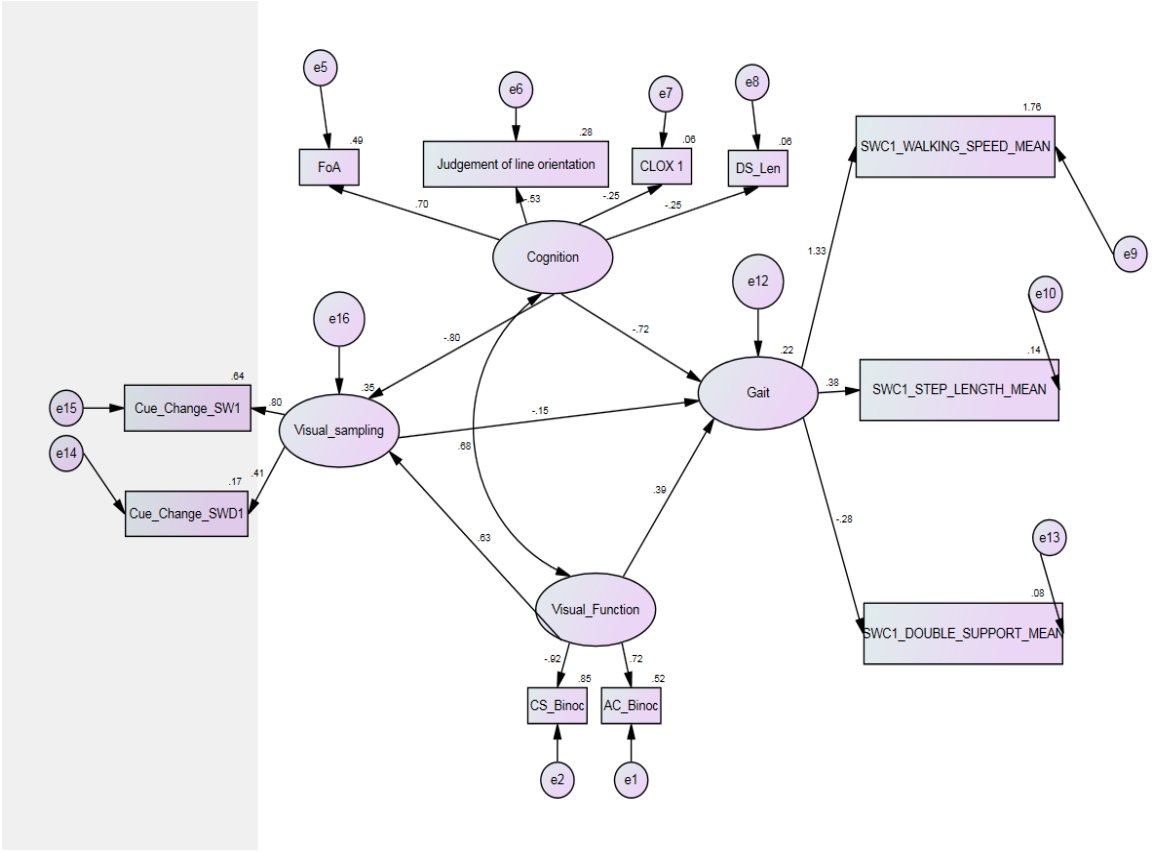
Regression Weights: (Group number 1 - Default model)

			Estimate	S.E.	C.R.	P
VS	<---	VF	1.813	1.789	1.014	.311
VS	<---	Cog	-.046	.028	-1.612	.107
Gait	<---	VS	-.071	.079	-.901	.367
Gait	<---	Cog	-.019	.012	-1.543	.123
Gait	<---	VF	.682	.692	.985	.325
Change_Door	<---	VS	1.000			
Ch_Turn	<---	VS	.510	.301	1.698	.089
AC_Binoc	<---	VF	1.000			
CS_Binoc	<---	VF	-1.147	.316	-3.635	***
FoA	<---	Cog	1.000			
JLO	<---	Cog	-.236	.084	-2.800	.005
CLOX_1	<---	Cog	-.066	.025	-2.650	.008
DS_Len	<---	Cog	-.026	.019	-1.361	.174
SW1_WALKING_SPEED_MEAN	<---	Gait	1.000			
SW1_STEP_LENGTH_MEAN	<---	Gait	.346	.065	5.339	***
SW1_DOUBLE_SUPPORT_MEAN	<---	Gait	-.246	.063	-3.898	***

Standardized Regression Weights: (Group number 1 - Default model)

			Estimate
VS	<---	VF	.292
VS	<---	Cog	-.590
Gait	<---	VS	-.248
Gait	<---	Cog	-.850
Gait	<---	VF	.383
Change_Door	<---	VS	1.116
Ch_Turn	<---	VS	.581
AC_Binoc	<---	VF	.715
CS_Binoc	<---	VF	-.929
FoA	<---	Cog	.655
JLO	<---	Cog	-.450
CLOX_1	<---	Cog	-.423
DS_Len	<---	Cog	-.209
SW1_WALKING_SPEED_MEAN	<---	Gait	1.069
SW1_STEP_LENGTH_MEAN	<---	Gait	.728
SW1_DOUBLE_SUPPORT_MEAN	<---	Gait	-.532

Visual Cue



Regression Weights: (Group number 1 - Default model)

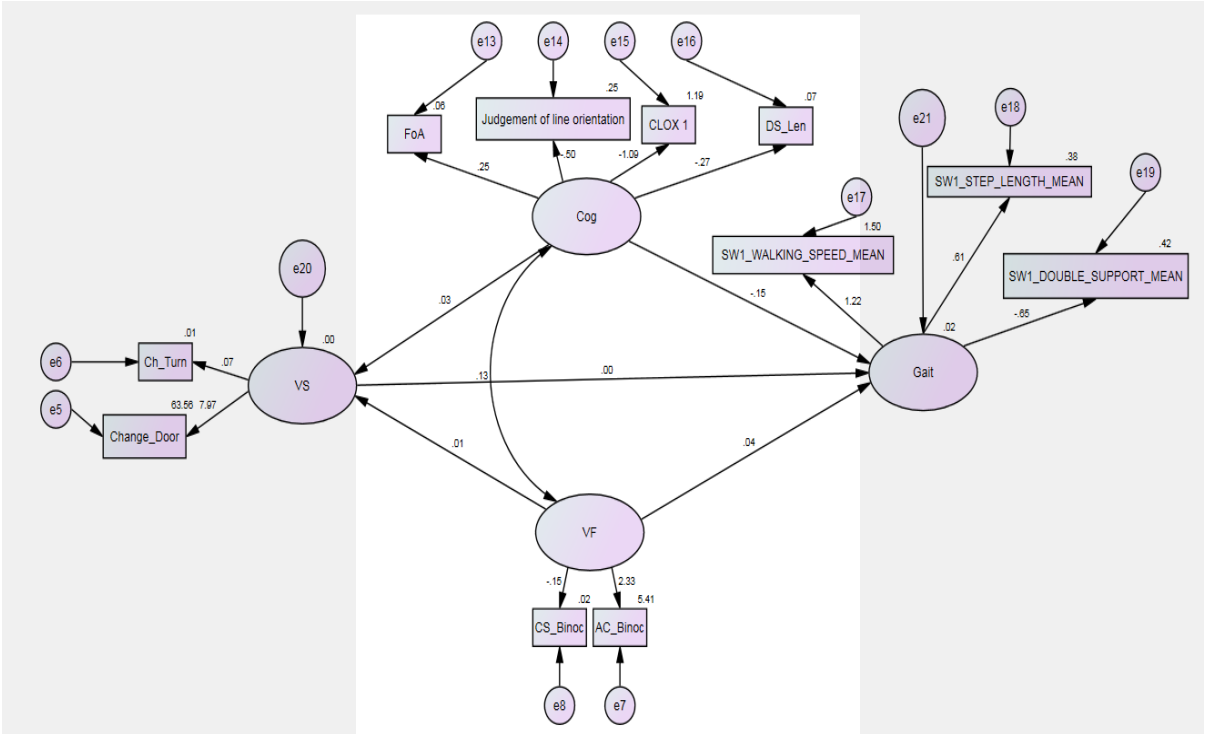
		Estimate	S.E.	C.R.	P
Visual_sampling	<--- Cognition	-.022	.021	-1.065	.287
Visual_sampling	<--- Visual_Function	1.477	1.404	1.052	.293
Gait	<--- Cognition	-.016	.012	-1.331	.183
Gait	<--- Visual_Function	.729	.764	.954	.340
Gait	<--- Visual_sampling	-.118	.229	-.516	.606
AC_Binoc	<--- Visual_Function	1.000			
CS_Binoc	<--- Visual_Function	-1.128	.286	-3.941	***
FoA	<--- Cognition	1.000			
JLO	<--- Cognition	-.263	.080	-3.273	.001
CLOX_1	<--- Cognition	-.037	.023	-1.620	.105
DS_Len	<--- Cognition	-.029	.018	-1.621	.105
SWC1_WALKING_SPEED_MEAN	<--- Gait	1.000			
SWC1_STEP_LENGTH_MEAN	<--- Gait	.052	.036	1.451	.147
SWC1_DOUBLE_SUPPORT_MEAN	<--- Gait	-.179	.135	-1.325	.185
Cue_Change_SWD1	<--- Visual_sampling	1.000			
Cue_Change_SW1	<--- Visual_sampling	2.470	2.000	1.235	.217

Standardized Regression Weights: (Group number 1 - Default model)

		Estimate
Visual_sampling	<--- Cognition	-.798
Visual_sampling	<--- Visual_Function	.626
Gait	<--- Cognition	-.723
Gait	<--- Visual_Function	.393
Gait	<--- Visual_sampling	-.150
AC_Binoc	<--- Visual_Function	.721
CS_Binoc	<--- Visual_Function	-.921
FoA	<--- Cognition	.697
JLO	<--- Cognition	-.534
CLOX_1	<--- Cognition	-.252
DS_Len	<--- Cognition	-.252
SWC1_WALKING_SPEED_MEAN	<--- Gait	1.326
SWC1_STEP_LENGTH_MEAN	<--- Gait	.381
SWC1_DOUBLE_SUPPORT_MEAN	<--- Gait	-.276
Cue_Change_SWD1	<--- Visual_sampling	.413
Cue_Change_SW1	<--- Visual_sampling	.799

23. Appendix 23.0 – Other Structural Equation Models

Control Group – Straight Walking Gait



Regression Weights: (Group number 1 - Default model)

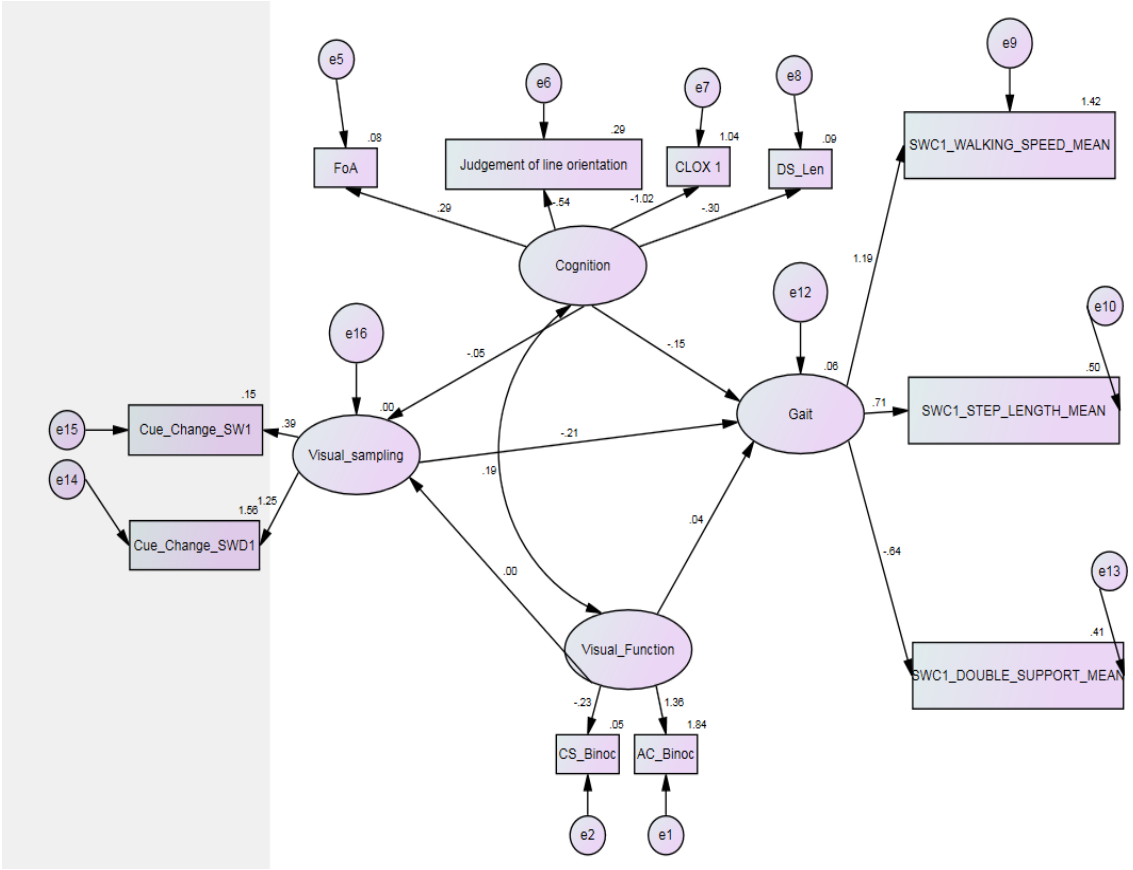
		Estimate	S.E.	C.R.	P
VS	<--- VF	.107	.699	.153	.878
VS	<--- Cog	.056	.049	1.129	.259
Gait	<--- VS	.000	.000	.000	1.000
Gait	<--- Cog	-.015	.013	-1.171	.242
Gait	<--- VF	.027	.180	.153	.879
Change_Door	<--- VS	1.000			
Ch_Turn	<--- VS	.009	.613	.015	.988
AC_Binoc	<--- VF	1.000			
CS_Binoc	<--- VF	-.044	.279	-.157	.876
FoA	<--- Cog	1.000			
JLO	<--- Cog	-.905	.553	-1.638	.102
CLOX_1	<--- Cog	-.571	.388	-1.471	.141
DS_Len	<--- Cog	-.121	.093	-1.310	.190
SW1_WALKING_SPEED_MEAN	<--- Gait	1.000			
SW1_STEP_LENGTH_MEAN	<--- Gait	.235	.063	3.727	***
SW1_DOUBLE_SUPPORT_MEAN	<--- Gait	-.190	.048	-3.993	***

Standardized Regression Weights: (Group number 1 - Default model)

		Estimate
VS	<--- VF	.006
VS	<--- Cog	.026
Gait	<--- VS	.000
Gait	<--- Cog	-.153
Gait	<--- VF	.035
Change_Door	<--- VS	7.972
Ch_Turn	<--- VS	.073
AC_Binoc	<--- VF	2.325
CS_Binoc	<--- VF	-.146
FoA	<--- Cog	.253
JLO	<--- Cog	-.504
CLOX_1	<--- Cog	-1.090
DS_Len	<--- Cog	-.268
SW1_WALKING_SPEED_MEAN	<--- Gait	1.223
SW1_STEP_LENGTH_MEAN	<--- Gait	.613
SW1_DOUBLE_SUPPORT_MEAN	<--- Gait	-.650

Control Group – Visual Cue

Appendices



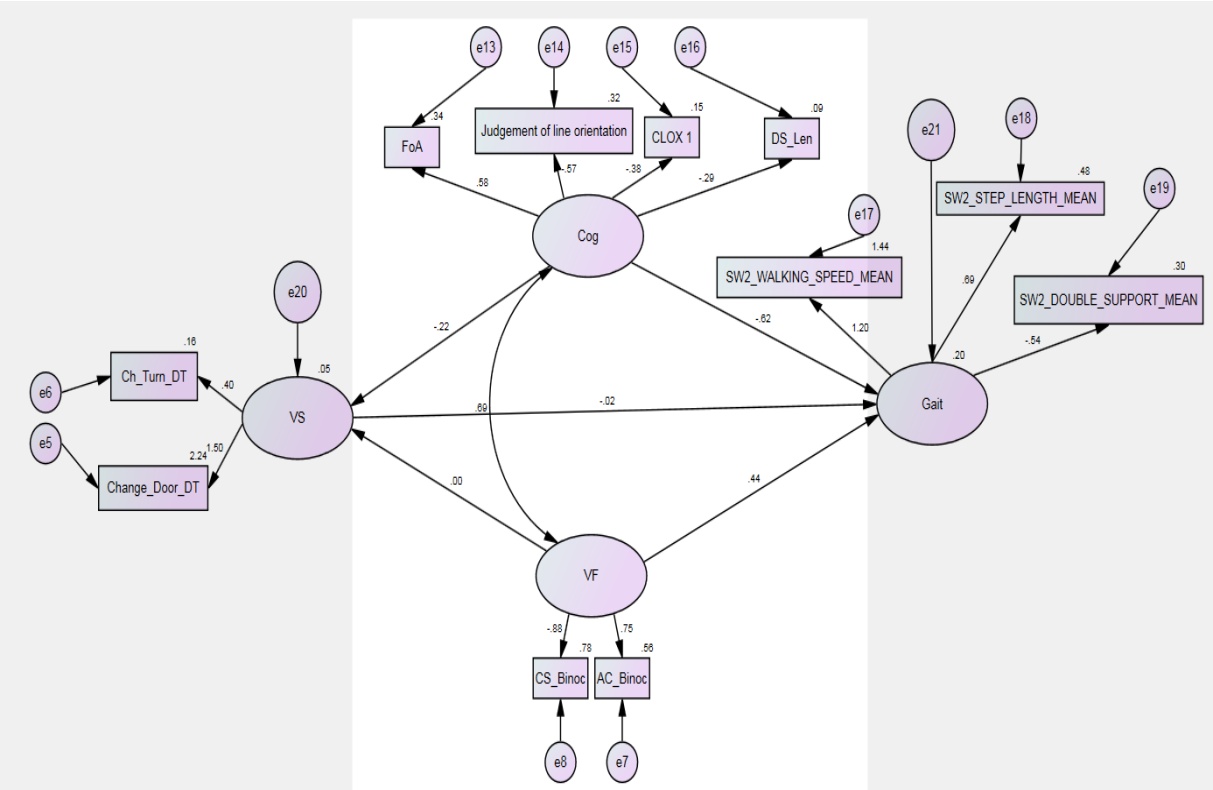
Regression Weights: (Group number 1 - Default model)

		Estimate	S.E.	C.R.	P
Visual_sampling	<--- Cognition	-.018	.048	-.368	.713
Visual_sampling	<--- Visual_Function	-.004	.546	-.007	.994
Gait	<--- Cognition	-.011	.010	-1.090	.276
Gait	<--- Visual_Function	.040	.173	.232	.816
Gait	<--- Visual_sampling	-.044	.057	-.780	.435
AC_Binoc	<--- Visual_Function	1.000			
CS_Binoc	<--- Visual_Function	-.114	.412	-.278	.781
FoA	<--- Cognition	1.000			
JLO	<--- Cognition	-.767	.492	-1.559	.119
CLOX_1	<--- Cognition	-.413	.294	-1.404	.160
DS_Len	<--- Cognition	-.109	.088	-1.242	.214
SWC1_WALKING_SPEED_MEAN	<--- Gait	1.000			
SWC1_STEP_LENGTH_MEAN	<--- Gait	.284	.059	4.800	***
SWC1_DOUBLE_SUPPORT_MEAN	<--- Gait	-.165	.040	-4.126	***
Cue_Change_SWD1	<--- Visual_sampling	1.000			
Cue_Change_SW1	<--- Visual_sampling	.256	.314	.817	.414

Standardized Regression Weights: (Group number 1 - Default model)

		Estimate
Visual_sampling	<--- Cognition	-.052
Visual_sampling	<--- Visual_Function	-.001
Gait	<--- Cognition	-.154
Gait	<--- Visual_Function	.035
Gait	<--- Visual_sampling	-.206
AC_Binoc	<--- Visual_Function	1.356
CS_Binoc	<--- Visual_Function	-.234
FoA	<--- Cognition	.290
JLO	<--- Cognition	-.541
CLOX_1	<--- Cognition	-1.019
DS_Len	<--- Cognition	-.301
SWC1_WALKING_SPEED_MEAN	<--- Gait	1.191
SWC1_STEP_LENGTH_MEAN	<--- Gait	.709
SWC1_DOUBLE_SUPPORT_MEAN	<--- Gait	-.644
Cue_Change_SWD1	<--- Visual_sampling	1.250
Cue_Change_SW1	<--- Visual_sampling	.388

PD Group - Dual Task



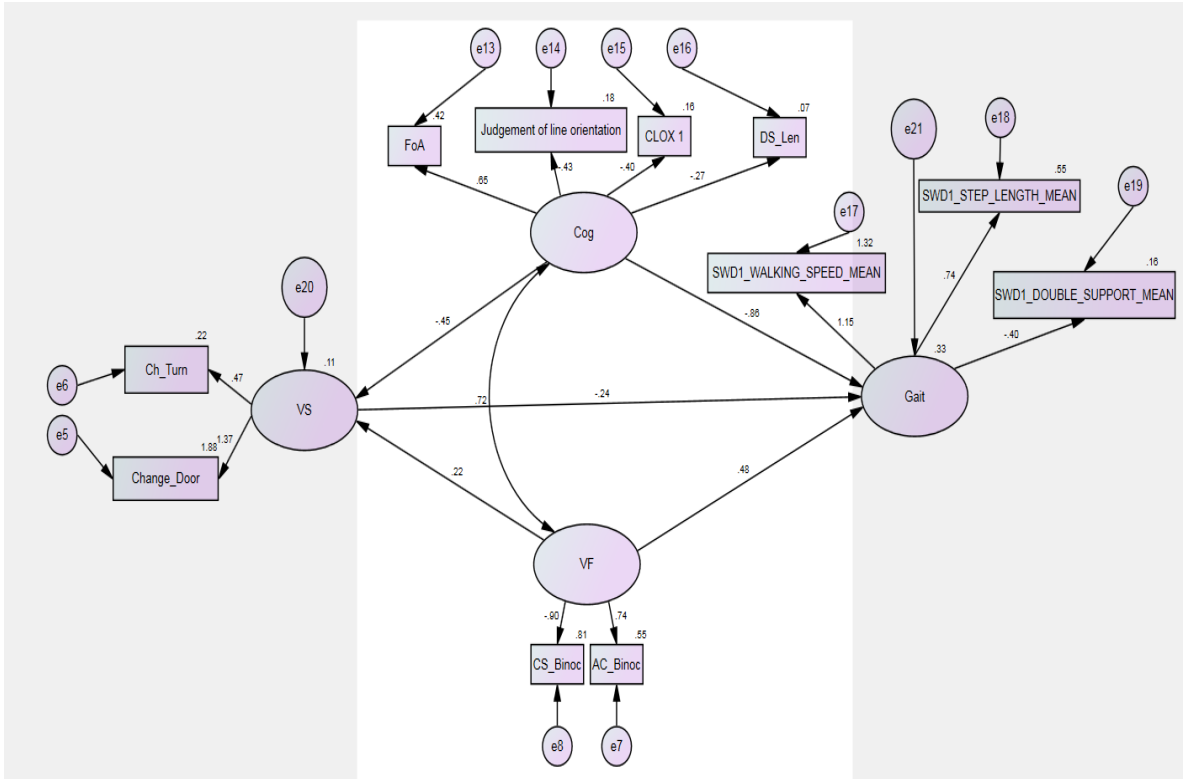
Regression Weights: (Group number 1 - Default model)

			Estimate	S.E.	C.R.	P
VS	<---	VF	-.008	.671	-.012	.990
VS	<---	Cog	-.013	.012	-1.066	.287
Gait	<---	VS	-.008	.039	-.215	.830
Gait	<---	Cog	-.018	.010	-1.732	.083
Gait	<---	VF	.850	.536	1.587	.113
Change_Door_DT	<---	VS	1.000			
Ch_Turn_DT	<---	VS	.315	.497	.633	.527
AC_Binoc	<---	VF	1.000			
CS_Binoc	<---	VF	-1.039	.253	-4.112	***
FoA	<---	Cog	1.000			
JLO	<---	Cog	-.335	.111	-3.010	.003
CLOX_1	<---	Cog	-.068	.030	-2.245	.025
DS_Len	<---	Cog	-.040	.023	-1.780	.075
SW2_WALKING_SPEED_MEAN	<---	Gait	1.000			
SW2_STEP_LENGTH_MEAN	<---	Gait	.266	.051	5.180	***
SW2_DOUBLE_SUPPORT_MEAN	<---	Gait	-.239	.060	-3.962	***

Standardized Regression Weights: (Group number 1 - Default model)

			Estimate
VS	<---	VF	-.002
VS	<---	Cog	-.222
Gait	<---	VS	-.017
Gait	<---	Cog	-.623
Gait	<---	VF	.440
Change_Door_DT	<---	VS	1.497
Ch_Turn_DT	<---	VS	.398
AC_Binoc	<---	VF	.751
CS_Binoc	<---	VF	-.884
FoA	<---	Cog	.582
JLO	<---	Cog	-.567
CLOX_1	<---	Cog	-.384
DS_Len	<---	Cog	-.293
SW2_WALKING_SPEED_MEAN	<---	Gait	1.198
SW2_STEP_LENGTH_MEAN	<---	Gait	.693
SW2_DOUBLE_SUPPORT_MEAN	<---	Gait	-.545

PD Group - Door Gait



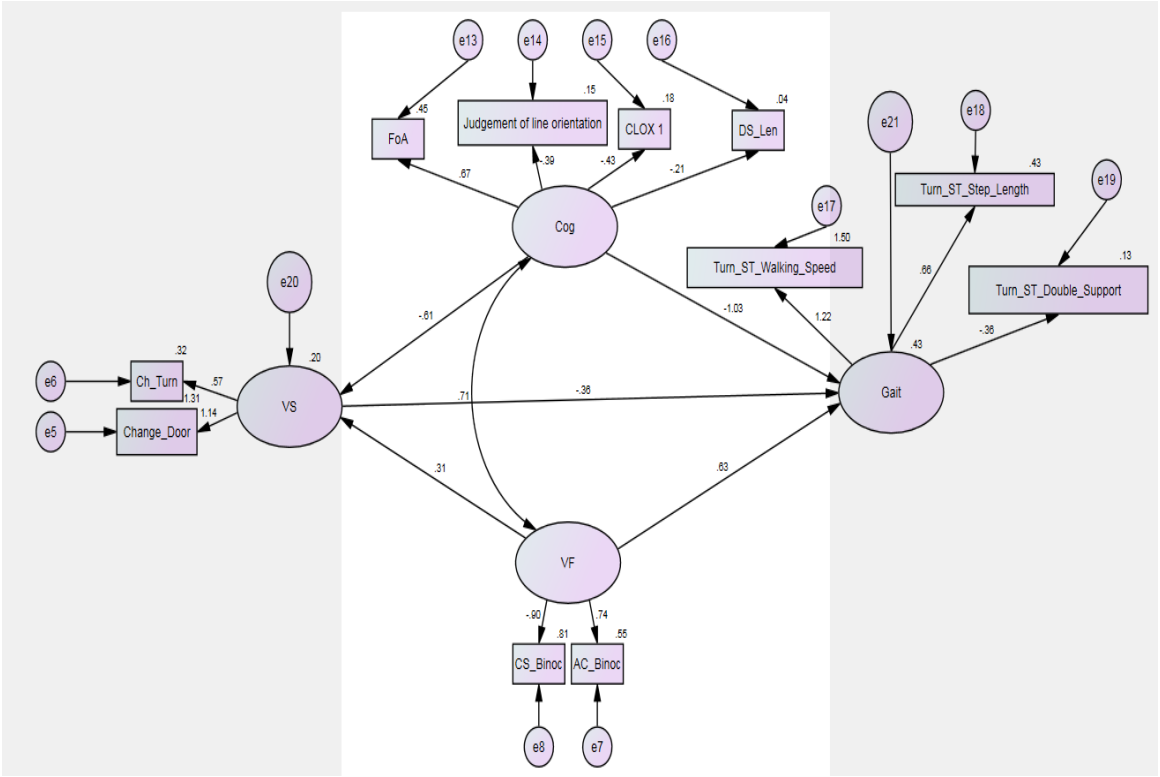
Regression Weights: (Group number 1 - Default model)

		Estimate	S.E.	C.R.	P
VS	<--- VF	1.607	1.840	.873	.382
VS	<--- Cog	-.043	.030	-1.442	.149
Gait	<--- VS	-.061	.075	-.820	.412
Gait	<--- Cog	-.021	.013	-1.585	.113
Gait	<--- VF	.914	.761	1.201	.230
Change_Door	<--- VS	1.000			
Ch_Turn	<--- VS	.339	.300	1.131	.258
AC_Binoc	<--- VF	1.000			
CS_Binoc	<--- VF	-1.073	.276	-3.888	***
FoA	<--- Cog	1.000			
JLO	<--- Cog	-.227	.081	-2.782	.005
CLOX_1	<--- Cog	-.063	.024	-2.619	.009
DS_Len	<--- Cog	-.033	.019	-1.796	.073
SWD1_WALKING_SPEED_MEAN	<--- Gait	1.000			
SWD1_STEP_LENGTH_MEAN	<--- Gait	.336	.063	5.297	***
SWD1_DOUBLE_SUPPORT_MEAN	<--- Gait	-.161	.054	-2.977	.003

Standardized Regression Weights: (Group number 1 - Default model)

		Estimate
VS	<--- VF	.218
VS	<--- Cog	-.445
Gait	<--- VS	-.238
Gait	<--- Cog	-.855
Gait	<--- VF	.484
Change_Door	<--- VS	1.370
Ch_Turn	<--- VS	.473
AC_Binoc	<--- VF	.739
CS_Binoc	<--- VF	-.898
FoA	<--- Cog	.649
JLO	<--- Cog	-.428
CLOX_1	<--- Cog	-.401
DS_Len	<--- Cog	-.269
SWD1_WALKING_SPEED_MEAN	<--- Gait	1.148
SWD1_STEP_LENGTH_MEAN	<--- Gait	.741
SWD1_DOUBLE_SUPPORT_MEAN	<--- Gait	-.398

PD Group - Turning Gait



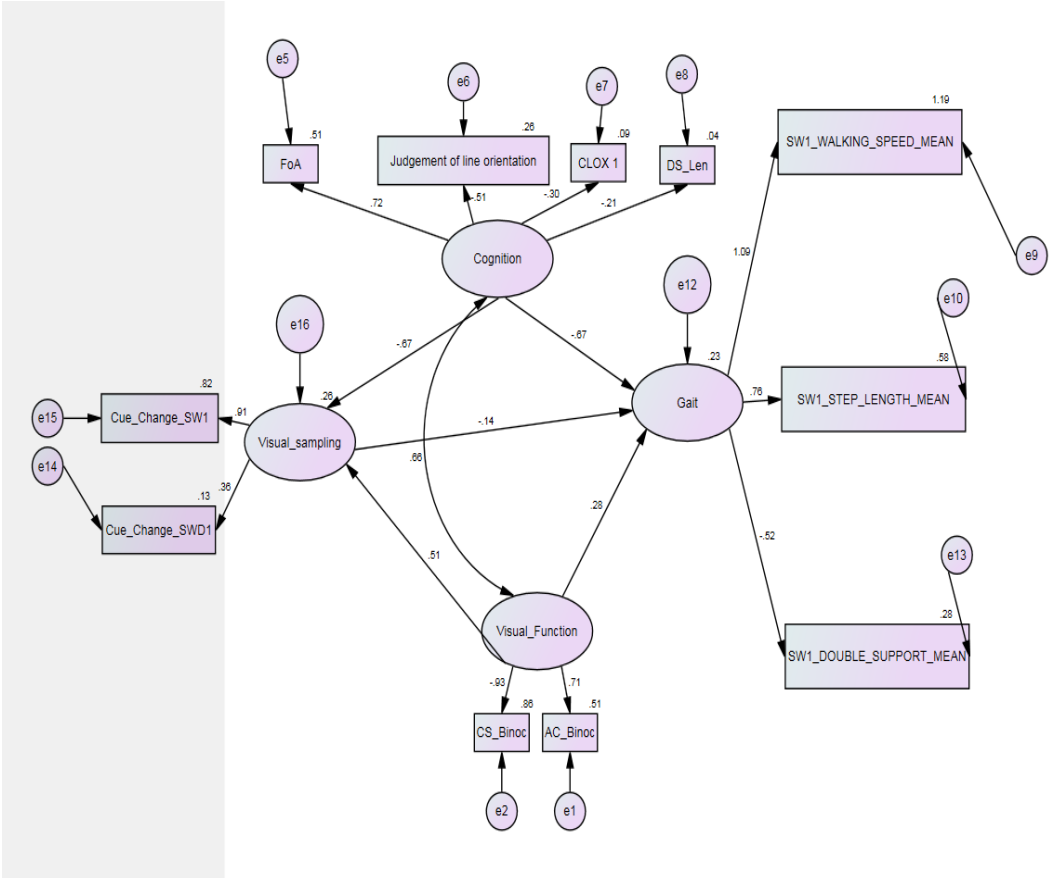
Regression Weights: (Group number 1 - Default model)

		Estimate	S.E.	C.R.	P
VS	<--- VF	1.884	1.918	.982	.326
VS	<--- Cog	-.047	.030	-1.587	.112
Gait	<--- VS	-.101	.091	-1.117	.264
Gait	<--- Cog	-.023	.014	-1.582	.114
Gait	<--- VF	1.101	.819	1.345	.179
Change_Door	<--- VS	1.000			
Ch_Turn	<--- VS	.486	.249	1.951	.051
AC_Binoc	<--- VF	1.000			
CS_Binoc	<--- VF	-1.071	.263	-4.070	***
FoA	<--- Cog	1.000			
JLO	<--- Cog	-.201	.074	-2.733	.006
CLOX_1	<--- Cog	-.065	.022	-2.965	.003
DS_Len	<--- Cog	-.025	.017	-1.463	.144
Turn_ST_Walking_Speed	<--- Gait	1.000			
Turn_ST_Step_Length	<--- Gait	.287	.071	4.036	***
Turn_ST_Double_Support	<--- Gait	-.200	.077	-2.589	.010

Standardized Regression Weights: (Group number 1 - Default model)

		Estimate
VS	<--- VF	.307
VS	<--- Cog	-.607
Gait	<--- VS	-.355
Gait	<--- Cog	-1.028
Gait	<--- VF	.629
Change_Door	<--- VS	1.144
Ch_Turn	<--- VS	.567
AC_Binoc	<--- VF	.740
CS_Binoc	<--- VF	-.897
FoA	<--- Cog	.670
JLO	<--- Cog	-.392
CLOX_1	<--- Cog	-.427
DS_Len	<--- Cog	-.207
Turn_ST_Walking_Speed	<--- Gait	1.223
Turn_ST_Step_Length	<--- Gait	.657
Turn_ST_Double_Support	<--- Gait	-.356

PD Group - Visual Cue with Straight Walk Gait



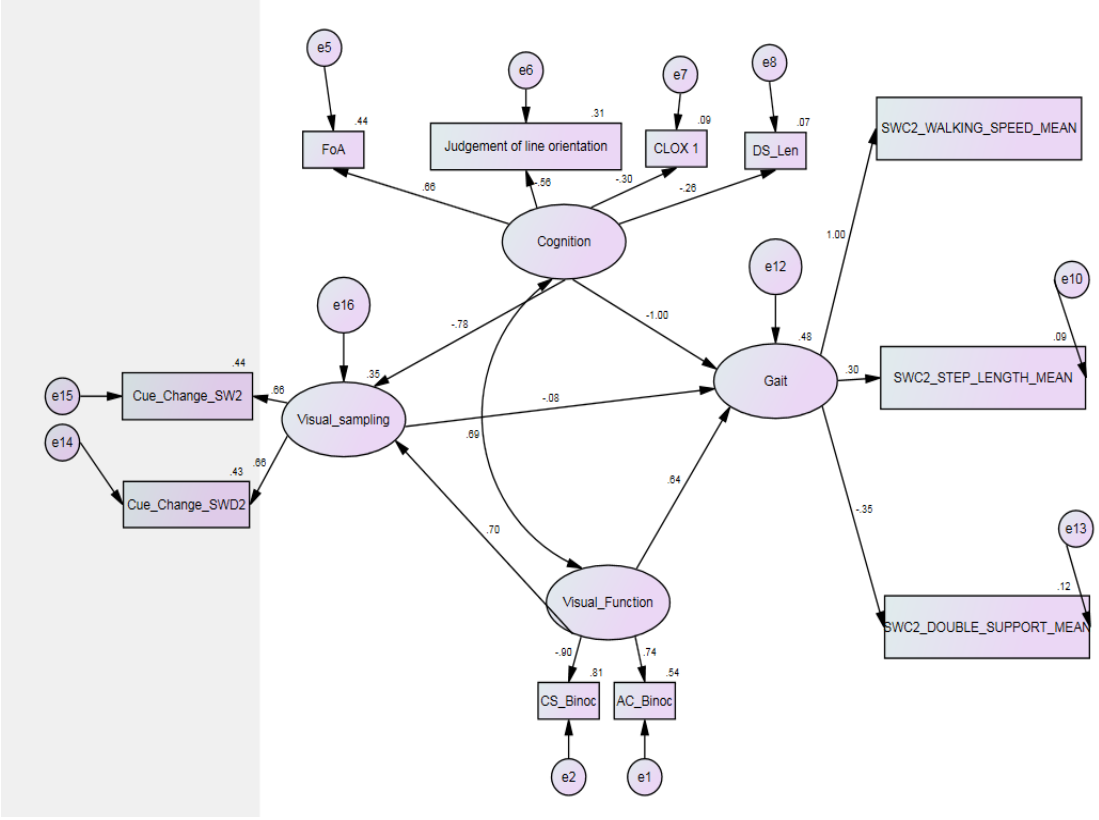
Regression Weights: (Group number 1 - Default model)

		Estimate	S.E.	C.R.	P
Visual_sampling	<--- Cognition	-.016	.019	-.847	.397
Visual_sampling	<--- Visual_Function	1.068	1.279	.835	.404
Gait	<--- Cognition	-.014	.010	-1.440	.150
Gait	<--- Visual_Function	.509	.630	.808	.419
Gait	<--- Visual_sampling	-.118	.199	-.593	.553
AC_Binoc	<--- Visual_Function	1.000			
CS_Binoc	<--- Visual_Function	-1.150	.300	-3.829	***
FoA	<--- Cognition	1.000			
JLO	<--- Cognition	-.247	.080	-3.081	.002
CLOX_1	<--- Cognition	-.043	.023	-1.907	.057
DS_Len	<--- Cognition	-.023	.017	-1.339	.181
SW1_WALKING_SPEED_MEAN	<--- Gait	1.000			
SW1_STEP_LENGTH_MEAN	<--- Gait	.357	.060	5.975	***
SW1_DOUBLE_SUPPORT_MEAN	<--- Gait	-.241	.062	-3.926	***
Cue_Change_SWD1	<--- Visual_sampling	1.000			
Cue_Change_SW1	<--- Visual_sampling	3.192	3.356	.951	.342

Standardized Regression Weights: (Group number 1 - Default model)

		Estimate
Visual_sampling	<--- Cognition	-.671
Visual_sampling	<--- Visual_Function	.510
Gait	<--- Cognition	-.675
Gait	<--- Visual_Function	.284
Gait	<--- Visual_sampling	-.138
AC_Binoc	<--- Visual_Function	.714
CS_Binoc	<--- Visual_Function	-.930
FoA	<--- Cognition	.717
JLO	<--- Cognition	-.514
CLOX_1	<--- Cognition	-.304
DS_Len	<--- Cognition	-.211
SW1_WALKING_SPEED_MEAN	<--- Gait	1.090
SW1_STEP_LENGTH_MEAN	<--- Gait	.762
SW1_DOUBLE_SUPPORT_MEAN	<--- Gait	-.525
Cue_Change_SWD1	<--- Visual_sampling	.364
Cue_Change_SW1	<--- Visual_sampling	.908

PD Group - Visual Cue Dual Task



Regression Weights: (Group number 1 - Default model)

		Estimate	S.E.	C.R.	P
Visual_sampling	<--- Cognition	-.036	.025	-1.449	.147
Visual_sampling	<--- Visual_Function	2.519	1.639	1.537	.124
Gait	<--- Cognition	-.015	.011	-1.372	.170
Gait	<--- Visual_Function	.745	.684	1.089	.276
Gait	<--- Visual_sampling	-.025	.126	-.198	.843
AC_Binoc	<--- Visual_Function	1.000			
CS_Binoc	<--- Visual_Function	-1.080	.260	-4.148	***
FoA	<--- Cognition	1.000			
JLO	<--- Cognition	-.292	.088	-3.313	***
CLOX_1	<--- Cognition	-.046	.024	-1.896	.058
DS_Len	<--- Cognition	-.031	.019	-1.638	.102
SWC2_WALKING_SPEED_MEAN	<--- Gait	1.000			
SWC2_STEP_LENGTH_MEAN	<--- Gait	.071	.030	2.339	.019
SWC2_DOUBLE_SUPPORT_MEAN	<--- Gait	-.365	.132	-2.768	.006
Cue_Change_SWD2	<--- Visual_sampling	1.000			
Cue_Change_SW2	<--- Visual_sampling	1.090	.558	1.953	.051

Standardized Regression Weights: (Group number 1 - Default model)

		Estimate
Visual_sampling	<--- Cognition	-.782
Visual_sampling	<--- Visual_Function	.697
Gait	<--- Cognition	-1.003
Gait	<--- Visual_Function	.645
Gait	<--- Visual_sampling	-.078
AC_Binoc	<--- Visual_Function	.736
CS_Binoc	<--- Visual_Function	-.901
FoA	<--- Cognition	.661
JLO	<--- Cognition	-.561
CLOX_1	<--- Cognition	-.300
DS_Len	<--- Cognition	-.257
SWC2_WALKING_SPEED_MEAN	<--- Gait	1.000
SWC2_STEP_LENGTH_MEAN	<--- Gait	.303
SWC2_DOUBLE_SUPPORT_MEAN	<--- Gait	-.352
Cue_Change_SWD2	<--- Visual_sampling	.656
Cue_Change_SW2	<--- Visual_sampling	.664

References

Aarsland, D., Bronnick, K., Williams-Gray, C., Weintraub, D., Marder, K., Kulisevsky, J., Burn, D., Barone, P., Pagonabarraga, J., Allcock, L.M., Santangelo, G., Foltynie, T., Janvin, C., Larsen, J.P., Barker, R.A. and Emre, M. (2010) 'Mild cognitive impairment in Parkinson disease: A multicenter pooled analysis', *Neurology* 75, p. 1038.

Aarsland, D. and Kurz, M.W. (2010) 'The epidemiology of dementia associated with Parkinson's disease', *Brain Pathol*, 20(3), pp. 633-9.

Adam, C.R., Shrier, E., Ding, Y., Glazman, S. and Bodis-Wollner, I. (2013) 'Correlation of inner retinal thickness evaluated by spectral-domain optical coherence tomography and contrast sensitivity in Parkinson disease', *J Neuroophthalmol*, 33(2), pp. 137-42.

Adamovich, S.V., Berkinblit, M.B., Hening, W., Sage, J. and Poizner, H. (2001) 'The interaction of visual and proprioceptive inputs in pointing to actual and remembered targets in Parkinson's disease', *Neuroscience*, 104(4), pp. 1027-1041.

Aikman, G.G. and Oehlert, M.E. (2001) 'Geriatric Depression Scale', *Clinical Gerontologist*, 22(3-4), pp. 63-70.

Akkal, D., Dum, R.P. and Strick, P.L. (2007) 'Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output', *The Journal of Neuroscience*, 27(40), pp. 10659-10673.

Alegre, M., Lopez-Azcarate, J., Obeso, I., Wilkinson, L., Rodriguez-Oroz, M.C., Valencia, M., Garcia-Garcia, D., Guridi, J., Artieda, J., Jahanshahi, M. and Obeso, J.A. (2013) 'The subthalamic nucleus is involved in successful inhibition in the stop-signal task: A local field potential study in Parkinson's disease', *Experimental Neurology*, 239(1), pp. 1-12.

Aleman, A. and van't Wout, M. (2008) 'Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex disrupts digit span task performance', *Neuropsychobiology*, 57(1-2), pp. 44-8.

Allcock, L.M., Rowan, E.N., Steen, I.N., Wesnes, K., Kenny, R.A. and Burn, D.J. (2009) 'Impaired attention predicts falling in Parkinson's disease', *Parkinsonism Relat Disord*, 15(2), pp. 110-5.

Allen, N.E., Schwarzel, A.K. and Canning, C.G. (2013) 'Recurrent Falls in Parkinsons Disease: A Systematic Review', *Parkinsons Disease*, 1(1), pp. 1-16.

Allison, P.D. (1990) 'Change scores as dependent variables in regression analysis', *Sociological methodology*, 20(1), pp. 93-114.

Almeida, Q.J. and Bhatt, H. (2012) 'A Manipulation of Visual Feedback during Gait Training in Parkinson's Disease', *Parkinsons Dis*, 1(1), pp. 1-7.

Almeida, Q.J., Frank, J.S., Roy, E.A., Jenkins, M.E., Spaulding, S., Patla, A.E. and Jog, M.S. (2005) 'An evaluation of sensorimotor integration during locomotion toward a target in Parkinson's disease', *Neuroscience*, 134(1), pp. 283-93.

Almeida, Q.J. and Lebold, C.A. (2010) 'Freezing of gait in Parkinson's disease: a perceptual cause for a motor impairment?', *J Neurol Neurosurg Psychiatry*, 81(5), pp. 513-8.

Almeida, Q.J., Wishart, L.R. and Lee, T.D. (2002) 'Bimanual coordination deficits with Parkinson's disease: the influence of movement speed and external cueing', *Mov Disord*, 17(1), pp. 30-7.

Amano, K., Foster, D.H., Mould, M.S. and Oakley, J.P. (2012) 'Visual search in natural scenes explained by local color properties', *J Opt Soc Am A Opt Image Sci Vis*, 29(2), pp. A194-9.

Amboni, M., Barone, P. and Hausdorff, J.M. (2013) 'Cognitive contributions to gait and falls: evidence and implications', *Movement Disorders*, 28(11), pp. 1520-1533.

Amboni, M., Barone, P., Iuppariello, L., Lista, I., Tranfaglia, R., Fasano, A., Picillo, M., Vitale, C., Santangelo, G., Agosti, V., Iavarone, A. and Sorrentino, G. (2012) 'Gait patterns in Parkinsonian patients with or without mild cognitive impairment', *Movement Disorders*, 27(12), pp. 1536-1543.

Amboni, M., Cozzolino, A., Longo, K., Picillo, M. and Barone, P. (2008) 'Freezing of gait and executive functions in patients with Parkinson's disease', *Mov Disord*, 23(3), pp. 395-400.

Amboni, M., Stocchi, F., Abbruzzese, G., Morgante, L., Onofrj, M., Ruggieri, S., Tinazzi, M., Zappia, M., Attar, M., Colombo, D., Simoni, L., Ori, A., Barone, P. and Antonini, A. (2015) 'Prevalence and associated features of self-reported freezing of gait in Parkinson disease: The DEEP FOG study', *Parkinsonism & Related Disorders*, 21(6), pp. 644-649.

Anastasopoulos, D., Ziavra, N., Savvidou, E., Bain, P. and Bronstein, A.M. (2011) 'Altered eye-to-foot coordination in standing parkinsonian patients during large gaze and whole-body reorientations', *Mov Disord*, 26(12), pp. 2201-11.

Anderson, T.J. and MacAskill, M.R. (2013) 'Eye movements in patients with neurodegenerative disorders', *Nat Rev Neurol*, 9(2), pp. 74-85.

Andersson, R., Nyström, M. and Holmqvist, K. (2010) 'Sampling frequency and eye-tracking measures: how speed affects durations, latencies, and more', *Journal of Eye Movement Research*, 3(3), pp. 1-12.

Antal, A., Bandini, F., Keri, S. and Bodis-Wollner, I. (1998) 'Visuo-cognitive dysfunctions in Parkinson's disease', *Clin Neurosci*, 5(2), pp. 147-52.

Antal, A., Terney, D. and Bodis-Wollner, I. (2008) 'Parkinson's Disease, Aging, and Visual Cognition', *Topics in Geriatric Rehabilitation*, 24(2), pp. 166-181

Antoniades, C.A. and Kennard, C. (2015) 'Ocular motor abnormalities in neurodegenerative disorders', *Eye*, 29(2), pp. 200-207.

Antonisamy, B., Christopher, S. and Samuel, P.P. (2010) *Biostatistics: principles and practice*. New Delhi, India: Tata McGraw Hill Education.

Archibald, N.K., Clarke, M.P., Mosimann, U.P. and Burn, D.J. (2009) 'The retina in Parkinson's disease', *Brain*, 132(Pt 5), pp. 1128-45.

Archibald, N.K., Clarke, M.P., Mosimann, U.P. and Burn, D.J. (2011) 'Visual symptoms in Parkinson's disease and Parkinson's disease dementia', *Mov Disord*, 26(13), pp. 2387-95.

Archibald, N.K., Hutton, S.B., Clarke, M.P., Mosimann, U.P. and Burn, D.J. (2013) 'Visual exploration in Parkinson's disease and Parkinson's disease dementia', *Brain*, 136(Pt 3), pp. 739-50.

Armstrong, R. and Kergoat, H. (2015) 'Oculo-visual changes and clinical considerations affecting older patients with dementia', *Ophthalmic and Physiological Optics*, 35(4), pp. 352-376.

Armstrong, R.A. (2011) 'Visual symptoms in Parkinson's disease', *Parkinsons Dis*, 1(2011), pp. 1-9.

Ashoori, A., Eagleman, D.M. and Jankovic, J. (2015) 'Effects of Auditory Rhythm and Music on Gait Disturbances in Parkinson's Disease', *Frontiers in Neurology*, 6, p. 234.

Awh, E., Vogel, E.K. and Oh, S.H. (2006) 'Interactions between attention and working memory', *Neuroscience*, 139(1), pp. 201-208.

Azulay, J.P., Mesure, S., Amblard, B., Blin, O., Sangla, I. and Pouget, J. (1999) 'Visual control of locomotion in Parkinson's disease', *Brain*, 122(1), pp. 111-120.

Azulay, J.P., Mesure, S., Amblard, B. and Pouget, J. (2002) 'Increased Visual Dependence in Parkinson's Disease', *Perceptual and Motor Skills*, 95(3f), pp. 1106-1114.

Azulay, J.P., Mesure, S. and Blin, O. (2006) 'Influence of visual cues on gait in Parkinson's disease: contribution to attention or sensory dependence?', *J Neurol Sci*, 248(1-2), pp. 192-5.

Baddeley, A. (1992) 'Working memory', *Science*, 255(5044), pp. 556-9.

Bagley, S., Kelly, B., Tunnicliffe, N., Turnbull, G.I. and Walker, J.M. (1991) 'The Effect of Visual Cues on the Gait of Independently Mobile Parkinson's Disease Patients', *Physiotherapy*, 77(6), pp. 415-420.

Baglio, F., Blasi, V., Falini, A., Farina, E., Mantovani, F., Olivotto, F., Scotti, G., Nemni, R. and Bozzali, M. (2011) 'Functional brain changes in early Parkinson's disease during motor response and motor inhibition', *Neurobiology of Aging*, 32(1), pp. 115-124.

Bahill, A.T., Adler, D. and Stark, L. (1975) 'Most naturally occurring human saccades have magnitudes of 15 degrees or less', *Invest Ophthalmol*, 14(6), pp. 468-9.

Baker, K., Rochester, L. and Nieuwboer, A. (2007) 'The immediate effect of attentional, auditory, and a combined cue strategy on gait during single and dual tasks in Parkinson's disease', *Arch Phys Med Rehabil*, 88(12), pp. 1593-600.

Ball, K., Owsley, C., Sloane, M.E., Roenker, D.L. and Bruni, J.R. (1993) 'Visual attention problems as a predictor of vehicle crashes in older drivers', *Invest Ophthalmol Vis Sci*, 34(11), pp. 3110-23.

Ballard, C., O'Brien, J., Gray, A., Cormack, F., Ayre, G., Rowan, E., Thompson, P., Bucks, R., McKeith, I., Walker, M. and Tovee, M. (2001) 'Attention and fluctuating attention in patients with dementia with Lewy bodies and Alzheimer disease', *Arch Neurol*, 58(6), pp. 977-82.

Ballard, C.G., Aarsland, D., McKeith, I., O'Brien, J., Gray, A., Cormack, F., Burn, D., Cassidy, T., Starfeldt, R., Larsen, J.P., Brown, R. and Tovee, M. (2002) 'Fluctuations in attention: PD dementia vs DLB with parkinsonism', *Neurology*, 59(11), pp. 1714-20.

Baluch, F. and Itti, L. (2011) 'Mechanisms of top-down attention', *Trends Neurosci*, 34(4), pp. 210-24.

Bandini, F., Pierantozzi, M. and Bodis-Wollner, I. (2002) 'The visuo-cognitive and motor effect of amantadine in non-Caucasian patients with Parkinson's disease. A clinical and electrophysiological study', *J Neural Transm*, 109(1), pp. 41-51.

Bar, M., Kassam, K.S., Ghuman, A.S., Boshyan, J., Schmid, A.M., Dale, A.M., Hamalainen, M.S., Marinkovic, K., Schacter, D.L., Rosen, B.R. and Halgren, E. (2006) 'Top-down facilitation of visual recognition', *Proc Natl Acad Sci U S A*, 103(2), pp. 449-54.

Barone, P., Aarsland, D., Burn, D., Emre, M., Kulisevsky, J. and Weintraub, D. (2011) 'Cognitive impairment in nondemented Parkinson's disease', *Movement Disorders*, 26(14), pp. 2483-2495.

Barraga, N. (1964) *Increased visual behavior in low vision children*. New York: American Foundation for the Blind.

Baziyan, B.K., Chigaleichik, L.A., Teslenko, E.L. and Lachinova, D.R. (2007) 'Analysis of trajectories of eye, head, and hand movements for early diagnosis of Parkinson's disease', *Bulletin of Experimental Biology and Medicine*, 143(5), pp. 553-555.

Becic, E., Boot, W.R. and Kramer, A.F. (2008) 'Training older adults to search more effectively: scanning strategy and visual search in dynamic displays', *Psychol Aging*, 23(2), pp. 461-6.

Beck, D.M. and Kastner, S. (2009) 'Top-down and bottom-up mechanisms in biasing competition in the human brain', *Vision Research*, 49(10), pp. 1154-1165.

Beenen, N., Büttner, U. and Lange, H.W. (1986) 'The diagnostic value of eye movement recording in patients with Huntington's disease and their offspring', *Electroencephalography and Clinical Neurophysiology*, 63(2), pp. 119-127.

Bekkering, H., Neggers, S.F.W., Walker, R., Gleibner, B., Dittrich, W.H. and Kennard, C. (2001) 'The preparation and execution of saccadic eye and goal-directed hand movements in patients with Parkinson's disease', *Neuropsychologia*, 39(2), pp. 173-183.

Benis, D., David, O., Lachaux, J.-P., Seigneuret, E., Krack, P., Fraix, V., Chabardès, S. and Bastin, J. (2014) 'Subthalamic nucleus activity dissociates proactive and reactive inhibition in patients with Parkinson's disease', *NeuroImage*, 91(1), pp. 273-281.

Bentler, P.M. and Chou, C.-P. (1987) 'Practical Issues in Structural Modeling', *Sociological Methods & Research*, 16(1), pp. 78-117.

Benton, A. and Tranel, D. (1993) 'Visuoperceptual, visuospatial, and visuoconstructive disorders', in Heilman, K.M. and Valenstein, E. (eds.) *Clinical neuropsychology (3rd ed.)*. New York, NY, US: Oxford University Press, pp. 165-213.

Berard, J., Fung, J., McFadyen, B. and Lamontagne, A. (2009) 'Aging affects the ability to use optic flow in the control of heading during locomotion', *Experimental Brain Research*, 194(2), pp. 183-190.

Berard, J.R., Fung, J. and Lamontagne, A. (2011) 'Evidence for the use of rotational optic flow cues for locomotor steering in healthy older adults', *Journal of neurophysiology*, 106(3), pp. 1089-1096.

Berger, A. and Posner, M.I. (2000) 'Pathologies of brain attentional networks', *Neuroscience & Biobehavioral Reviews*, 24(1), pp. 3-5.

Bertone, A., Bettinelli, L. and Faubert, J. (2007) 'The impact of blurred vision on cognitive assessment', *Journal of Clinical and Experimental Neuropsychology*, 29(5), pp. 467-476.

Beserra Gomes, R., Motta de Carvalho, B. and Marcos Garcia Gonçalves, L. (2013) 'Visual attention guided features selection with foveated images', in Pang, Y., Cao, X., Zhang, L. and Hussein, A. (eds.) *Neurocomputing: Image Feature Detection and Description*. pp. 34-44.

Bestaven, E., Guillaud, E. and Cazalets, J.-R. (2012) 'Is "Circling" Behavior in Humans Related to Postural Asymmetry?', *PLoS ONE*, 7(9), p. e43861.

Beurskens, R. and Bock, O. (2011) 'Role of motor skills and visual demand for age-related deficits in dual-task walking', *Ageing Research*, 2(1), pp. 1-26.

Beurskens, R. and Bock, O. (2012) 'Age-Related Deficits of Dual-Task Walking: A Review', *Neural Plasticity*, 1(2012), pp. 1-9.

Beurskens, R., Helmich, I., Rein, R. and Bock, O. (2014) 'Age-related changes in prefrontal activity during walking in dual-task situations: a fNIRS study', *International Journal of Psychophysiology*, 92(3), pp. 122-128.

Binetti, G., Cappa, S.F., Magni, E., Padovani, A., Bianchetti, A. and Trabucchi, M. (1998) 'Visual and spatial perception in the early phase of Alzheimer's disease', *Neuropsychology*, 12(1), p. 29.

Bissett, P., Logan, G., van Wouwe, N., Tolleson, C., Phibbs, F., Claassen, D. and Wylie, S. (2015) 'Generalized motor inhibitory deficit in Parkinson’s disease patients who freeze', *Journal of Neural Transmission*, 122(12), pp. 1-9.

Biundo, R., Calabrese, M., Weis, L., Facchini, S., Ricchieri, G., Gallo, P. and Antonini, A. (2013) 'Anatomical Correlates of Cognitive Functions in Early Parkinson's Disease Patients', *PLoS ONE*, 8(5), p. e64222.

Black, A.A., Wood, J.M. and Lovie-Kitchin, J.E. (2011) 'Inferior visual field reductions are associated with poorer functional status among older adults with glaucoma', *Ophthalmic and Physiological Optics*, 31(3), pp. 283-291.

Ble, A., Volpato, S., Zuliani, G., Guralnik, J.M., Bandinelli, S., Lauretani, F., Bartali, B., Maraldi, C., Fellin, R. and Ferrucci, L. (2005) 'Executive Function Correlates with Walking Speed in Older Persons: The InCHIANTI Study', *Journal of the American Geriatrics Society*, 53(3), pp. 410-415.

Blekher, T., Siemers, E., Abel, L.A. and Yee, R.D. (2000) 'Eye movements in Parkinson's disease: before and after pallidotomy', *Invest Ophthalmol Vis Sci*, 41(8), pp. 2177-83.

Blekher, T., Weaver, M.R., Cai, X., Hui, S., Marshall, J., Jackson, J.G., Wojcieszek, J., Yee, R.D. and Foroud, T.M. (2009) 'Test-retest reliability of saccadic measures in subjects at risk for Huntington disease', *Invest Ophthalmol Vis Sci*, 50(12), pp. 5707-11.

Blignaut, P. and Wium, D. (2014) 'Eye-tracking data quality as affected by ethnicity and experimental design', *Behav Res Methods*, 46(1), pp. 67-80.

Bodis-Wollner, I. (2003) 'Neuropsychological and perceptual defects in Parkinson's disease', *Parkinsonism & Related Disorders*, 9(Suppl 2), pp. 83-89.

Bodis-Wollner, I. (2009) 'Retinopathy in Parkinson Disease', *J Neural Transm*, 116(11), pp. 1493-501.

Bodis-Wollner, I. (2013) 'Foveal vision is impaired in Parkinson's disease', *Parkinsonism Relat Disord*, 19(1), pp. 1-14.

Bodis-Wollner, I., Glazman, S. and Yerram, S. (2013) 'Fovea and foveation in Parkinson's disease', *Behav Neurosci*, 127(2), pp. 139-50.

Bodis-Wollner, I. and Jo, M.-Y. (2006) 'Getting around and communicating with the environment: visual cognition and language in Parkinson's disease', *Parkinson's Disease and Related Disorders (16th ICPD)*. Berlin. Journal of Neural Transmission: Springer-Verlag, pp. 333–338.

Bodis-Wollner, I., Marx, M.S., Mitra, S., Bobak, P., Mylin, L. and Yahr, M. (1987) 'VISUAL DYSFUNCTION IN PARKINSON'S DISEASE: LOSS IN SPATIOTEMPORAL CONTRAST SENSITIVITY', *Brain*, 110(6), pp. 1675-1698.

Boecker, H., Dagher, A., Ceballos-Baumann, A.O., Passingham, R.E., Samuel, M., Friston, K.J., Poline, J.B., Dettmers, C., Conrad, B. and Brooks, D.J. (1998) 'Role of the human rostral supplementary motor area and the basal ganglia in motor sequence control: investigations with H2 15O PET', *Journal of Neurophysiology*, 79(2), pp. 1070-1080.

Bohnen, N.I. and Albin, R.L. (2011) 'The cholinergic system and Parkinson disease', *Behav Brain Res*, 221(2), pp. 564-73.

Bohnen, N.I. and Jahn, K. (2013) 'Imaging: What can it tell us about parkinsonian gait?', *Mov Disord*, 28(11), pp. 1492-500.

Bohnen, N.I., Kaufer, D.I., Hendrickson, R., Ivanco, L.S., Lopresti, B.J., Constantine, G.M., Mathis, C.A., Davis, J.G., Moore, R.Y. and DeKosky, S.T. (2006) 'Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia', *Journal of Neurology*, 253(2), pp. 242-247.

Bondi, M.W., Kaszniak, A.W., Bayles, K.A. and Vance, K.T. (1993) 'Contributions of frontal system dysfunction to memory and perceptual abilities in Parkinson's disease', *Neuropsychology*, 7(1), pp. 89-102.

Bonello, P.J., Rapport, L.J. and Millis, S.R. (1997) 'Psychometric properties of the visual object and space perception battery in normal older adults', *The Clinical Neuropsychologist*, 11(4), pp. 436-442.

Borji, A., Sihite, D. and Itti, L. (2011) 'Computational Modeling of Top-down Visual Attention in Interactive Environments', in Hoey, J., McKenna, S. and Trucco, E. (eds.) *Proceedings of the British Machine Vision Conference*. BMVA Press, pp. 85.1-85.12.

Bosboom, W.J.L., Stoffers, D. and Wolters, C.E. (2004) 'Cognitive dysfunction and dementia in Parkinson's disease', *Journal of Neural Transmission*, 111(10), pp. 1303-1315.

Botha, C.P., de Graaf, T., Schutte, S., Root, R., Wielopolski, P., van der Helm, F., Simonsz, H.J. and Post, F.H. (2008) 'MRI-based Visualisations of Orbital Fat Deformation DUring Eye Motion', in Linsen, L., Hagen, H. and Hamann, B. (eds.) *Visualization in Medicine and Life Sciences*. Berlin Heidelberg: Springer-Verlag.

Botha, H. and Carr, J. (2012) 'Attention and visual dysfunction in Parkinson's disease', *Parkinsonism Relat Disord*, 18(6), pp. 742-7.

Bovonsunthonchai, S., Vachalathiti, R., Pisarnpong, A., Khobhun, F. and Hiengkaew, V. (2014) 'Spatiotemporal Gait Parameters for Patients with Parkinson's Disease Compared with Normal Individuals', *Physiotherapy Research International*, 19(3), pp. 158-165.

Bowers, A.R. and Reid, V.M. (1997) 'Eye movements and reading with simulated visual impairment', *Ophthalmic and Physiological Optics*, 17(5), pp. 392-402.

Bowling, A.C., Lindsay, P., Smith, B.G. and Storok, K. (2015) 'Saccadic eye movements as indicators of cognitive function in older adults', *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*, 22(2), pp. 201-19.

Braak, H., Tredici, K.D., Rüb, U., de Vos, R.A.I., Jansen Steur, E.N.H. and Braak, E. (2003) 'Staging of brain pathology related to sporadic Parkinson's disease', *Neurobiology of Aging*, 24(2), pp. 197-211.

Bradshaw, J., Saling, M., Hopwood, M., Anderson, V. and Brodtmann, A. (2004) 'Fluctuating cognition in dementia with Lewy bodies and Alzheimer's disease is qualitatively distinct', *Journal of Neurology, Neurosurgery & Psychiatry*, 75(3), pp. 382-387.

Bressler, S.L., Tang, W., Sylvester, C.M., Shulman, G.L. and Corbetta, M. (2008) 'Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention', *J Neurosci*, 28(40), pp. 10056-61.

Briand, K.A., Hening, W., Poizner, H. and Sereno, A.B. (2001) 'Automatic orienting of visuospatial attention in Parkinson's disease', *Neuropsychologia*, 39(11), pp. 1240–1249.

Bridgeman, B., Kirch, M. and Sperling, A. (1981) 'Segregation of cognitive and motor aspects of visual function using induced motion', *Perception & Psychophysics*, 29(4), pp. 336-342.

Brown, R.G. and Marsden, C.D. (1988) 'INTERNAL VERSUS EXTERNAL CUES AND THE CONTROL OF ATTENTION IN PARKINSON'S DISEASE', *Brain*, 111(2), pp. 323-345.

Bruce, N.D. and Tsotsos, J.K. (2009) 'Saliency, attention, and visual search: an information theoretic approach', *J Vis*, 9(3), pp. 5 1-24.

Buckner, R.L. (2004) 'Memory and Executive Function in Aging and AD: Multiple Factors that Cause Decline and Reserve Factors that Compensate', *Neuron*, 44(1), pp. 195-208.

Buhmann, C., Bussopulos, A. and Oechsner, M. (2003) 'Dopaminergic response in Parkinsonian phenotype of Machado-Joseph disease', *Movement disorders*, 18(2), pp. 219-221.

Buhmann, C., Gorsler, A., Bäumer, T., Hidding, U., Demiralay, C., Hinkelmann, K., Weiller, C., Siebner, H.R. and Münchau, A. (2004) 'Abnormal excitability of premotor–motor connections in de novo Parkinson's disease', *Brain*, 127(12), pp. 2732-2746.

Buhmann, C., Kraft, S., Hinkelmann, K., Krause, S., Gerloff, C. and Zangemeister, W.H. (2015) 'Visual Attention and Saccadic Oculomotor Control in Parkinson's Disease', *European Neurology*, 73(5-6), pp. 283-293.

Burleigh-Jacobs, A., Horak, F.B., Nutt, J.G. and Obeso, J.A. (1997) 'Step initiation in Parkinson's disease: influence of levodopa and external sensory triggers', *Movement Disorders*, 12(2), pp. 206-215.

Burn, D.J. and McKeith, I.G. (2003) 'Current treatment of dementia with Lewy bodies and dementia associated with Parkinson's disease', *Movement Disorders*, 18(S6), pp. 72-79.

Burn, D.J., Rowan, E.N., Allan, L.M., Molloy, S., O'Brien, J.T. and McKeith, I.G. (2006) 'Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies', *J Neurol Neurosurg Psychiatry*, 77(5), pp. 585-9.

Burn, D.J., Rowan, E.N., Minett, T., Sanders, J., Myint, P., Richardson, J., Thomas, A., Newby, J., Reid, J., O'Brien, J.T. and McKeith, I.G. (2003) 'Extrapyramidal features in Parkinson's disease with and without dementia and dementia with Lewy bodies: A cross-sectional comparative study', *Mov Disord*, 18(8), pp. 884-9.

Burn, D.J. and Yarnall, A.J. (2014) 'Dementia in Parkinson's disease', in Chaudhuri, K.R., Tolosa, E., Schapira, A.H.V. and Poewe, W. (eds.) *Non-motor Symptoms of Parkinsons Disease*. 2 edn. Oxford, UK.: Oxford University Press, pp. 158-171.

Butler, K.M., Zacks, R.T. and Henderson, J.M. (1999) 'Suppression of reflexive saccades in younger and older adults: age comparisons on an antisaccade task', *Mem Cognit*, 27(4), pp. 584-91.

Byrne, B.M. (2004) 'Testing for Multigroup Invariance Using AMOS Graphics: A Road Less Traveled', *Structural Equation Modeling: A Multidisciplinary Journal*, 11(2), pp. 272-300.

Byrne, B.M. (2013) *Structural equation modeling with AMOS: Basic concepts, applications, and programming*. 2nd edn. Routledge: Taylor and Francis Group.

Caccappolo, E. and Marder, K. (2010) 'Cognitive impairment in non-demented patients with Parkinson's disease', in Emre, M. (ed.) *Cognitive Impairment and Dementia in Parkinson's Disease*. 2nd edn. Oxford, UK: Oxford University Press, pp. 203-223.

Calamia, M., Markon, K., Denburg, N.L. and Tranel, D. (2011) 'Developing a short form of Benton's Judgment of Line Orientation Test: an item response theory approach', *Clin Neuropsychol*, 25(4), pp. 670-84.

Callisaya, M.L., Blizzard, L., McGinley, J.L., Schmidt, M.D. and Srikanth, V.K. (2009) 'Sensorimotor Factors Affecting Gait Variability in Older People—A Population-Based Study', *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 65(4), pp. 386-392.

Cameron, I.G.M. (2011) 'Executive function and fronto-striatal circuitry: Insights from antisaccades, task switching, and Parkinson's disease', *Dissertation Abstracts International: Section B: The Sciences and Engineering*, 72(4-B), p. 1940.

Canning, C.G. (2005) 'The effect of directing attention during walking under dual-task conditions in Parkinson's disease', *Parkinsonism Relat Disord*, 11(2), pp. 95-9.

Canning, C.G., Paul, S.S. and Nieuwboer, A. (2014) 'Prevention of falls in Parkinson's disease: a review of fall risk factors and the role of physical interventions', *Neurodegenerative disease management*, 4(3), pp. 203-221.

Caproni, S., Muti, M., Di Renzo, A., Principi, M., Caputo, N., Calabresi, P. and Tambasco, N. (2014) 'Subclinical Visuospatial Impairment in Parkinson's Disease: The Role of Basal Ganglia and Limbic System', *Frontiers in Neurology*, 5(152), pp. 1-7.

Carpenter, M.G. and Bloem, B.R. (2011) 'A new twist on turning movements in Parkinson's disease patients', *Mov Disord*, 26(12), pp. 2151-3.

Carrasco, M. (2006) 'Covert attention increases contrast sensitivity: psychophysical, neurophysiological and neuroimaging studies', in Martinez-Conde, S., Macknik, S.L., Martinez, L.M., Alonso, J.M. and Tse, P.U. (eds.) *Progress in Brain Research*. New York: Elsevier, pp. 33-70.

Carrasco, M., Ling, S. and Read, S. (2004) 'Attention alters appearance', *Nature Neuroscience*, 7(3), pp. 308-313.

Carrasco, M. and McElree, B. (2001) 'Covert attention accelerates the rate of visual information processing', *Proceedings of the National Academy of Sciences*, 98(9), pp. 5363-5367.

Carrasco, M., Penpeci-Talgar, C. and Eckstein, M. (2000) 'Spatial covert attention increases contrast sensitivity across the CSF: support for signal enhancement', *Vision Research*, 40(10–12), pp. 1203-1215.

Carrasco, M., Williams, P.E. and Yeshurun, Y. (2002) 'Covert attention increases spatial resolution with or without masks: Support for signal enhancement', *Journal of Vision*, 2(6), pp. 467-479.

Catalá, M.M., Woitalla, D. and Arampatzis, A. (In Press; 2016) 'Reactive but not predictive locomotor adaptability is impaired in young parkinson's disease patients', *Gait & Posture*.

Cavanagh, P. (2011) 'Visual cognition', *Vision Res*, 51(13), pp. 1538-51.

Chan, F., Armstrong, I.T., Pari, G., Riopelle, R.J. and Munoz, D.P. (2005) 'Deficits in saccadic eye-movement control in Parkinson's disease', *Neuropsychologia*, 43(5), pp. 784-96.

Chapman, G.J. and Hollands, M.A. (2006) 'Evidence for a link between changes to gaze behaviour and risk of falling in older adults during adaptive locomotion', *Gait Posture*, 24(3), pp. 288-94.

Chapman, G.J. and Hollands, M.A. (2010) 'Age-related differences in visual sampling requirements during adaptive locomotion', *Exp Brain Res*, 201(3), pp. 467-78.

Chau, T. (2001) 'A review of analytical techniques for gait data. Part 2: neural network and wavelet methods', *Gait Posture*, 13(2), pp. 102-20.

Chaudhuri, K.R., Healy, D.G. and Schapira, A.H.V. (2006) 'Non-motor symptoms of Parkinson's disease: diagnosis and management', *The Lancet Neurology*, 5(3), pp. 235-245.

Chaudhuri, K.R., Prieto-Jurcynska, C., Naidu, Y., Mitra, T., Frades-Payo, B., Tluk, S., Ruessmann, A., Odin, P., Macphee, G., Stocchi, F., Ondo, W., Sethi, K., Schapira, A.H., Martinez Castrillo, J.C. and Martinez-Martin, P. (2010) 'The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire', *Mov Disord*, 25(6), pp. 704-9.

Chen, A.L., Riley, D.E., King, S.A., Joshi, A.C., Serra, A., Liao, K., Cohen, M.L., Otero-Millan, J., Martinez-Conde, S., Strupp, M. and Leigh, R.J. (2010) 'The disturbance of gaze in progressive supranuclear palsy: implications for pathogenesis', *Front Neurol*, 1(147), pp. 1-19.

Chiulli, R.M. (1999) *Quantitative analysis: An introduction*. Amsterdam, Netherlands: Gordon and Breach Science Publishers.

Chun, M.M. (2011) 'Visual working memory as visual attention sustained internally over time', *Neuropsychologia*, 49(6), pp. 1407-9.

Clark, U.S., Neargarder, S. and Cronin-Golomb, A. (2010) 'Visual exploration of emotional facial expressions in Parkinson's disease', *Neuropsychologia*, 48(7), pp. 1901-13.

Cohen, R.G., Chao, A., Nutt, J.G. and Horak, F.B. (2011) 'Freezing of gait is associated with a mismatch between motor imagery and motor execution in narrow doorways, not with failure to judge doorway passability', *Neuropsychologia*, 49(14), pp. 3981-8.

Cohen, R.G., Klein, K.A., Nomura, M., Fleming, M., Mancini, M., Giladi, N., Nutt, J.G. and Horak, F.B. (2014) 'Inhibition, executive function, and freezing of gait', *Journal of Parkinson's disease*, 4(1), p. 111.

Connor, C.E., Egeth, H.E. and Yantis, S. (2004) 'Visual attention: bottom-up versus top-down', *Curr Biol*, 14(19), pp. R850-2.

Conway, A.R. and Engle, R.W. (1994) 'Working memory and retrieval: a resource-dependent inhibition model', *J Exp Psychol Gen*, 123(4), pp. 354-73.

Cools, R., Barker, R.A., Sahakian, B.J. and Robbins, T.W. (2001) 'Mechanisms of cognitive set flexibility in Parkinson's disease', *Brain*, 124(12), pp. 2503-2512.

Cools, R., Rogers, R., Barker, R.A. and Robbins, T.W. (2010) 'Top-down attentional control in Parkinson's disease: Salient considerations', *Journal of Cognitive Neuroscience*, 22(5), pp. 848-859.

Corin, M.S., Elizan, T.S. and Bender, M.B. (1972) 'Oculomotor function in patients with Parkinson's disease', *Journal of the Neurological Sciences*, 15(3), pp. 251-265.

Cowie, D., Limousin, P., Peters, A. and Day, B.L. (2010) 'Insights into the neural control of locomotion from walking through doorways in Parkinson's disease', *Neuropsychologia*, 48(9), pp. 2750-7.

Cowie, D., Limousin, P., Peters, A., Hariz, M. and Day, B.L. (2012) 'Doorway-provoked freezing of gait in Parkinson's disease', *Mov Disord*, 27(4), pp. 492-9.

Crawford, J.D., Martinez-Trujillo, J.C. and Klier, E.M. (2003) 'Neural control of three-dimensional eye and head movements', *Current Opinion in Neurobiology*, 13(6), pp. 655-662.

Crawford, T., Goodrich, S., Henderson, L. and Kennard, C. (1989) 'Predictive responses in Parkinson's disease: manual keypresses and saccadic eye movements to regular stimulus events', *Journal of Neurology, Neurosurgery & Psychiatry*, 52(9), pp. 1033-42.

Crawford, T.J., Bennett, D., Lekwuwa, G., Shaunak, S. and Deakin, J.F.W. (2002) 'Cognition and the inhibitory control of saccades in schizophrenia and Parkinson's disease', in Hyona, J., Munoz, D.P., Heide, W. and Radach, R. (eds.) *Progress in Brain Research: The Brain's eye: Neurobiological and clinical aspects of oculomotor research*. Elsevier, pp. 449-466.

Crémers, J., D'Ostilio, K., Stamatakis, J., Delvaux, V. and Garraux, G. (2012) 'Brain activation pattern related to gait disturbances in Parkinson's disease', *Movement Disorders*, 27(12), pp. 1498-1505.

Cromarty, R.A., Elder, G.J., Graziadio, S., Baker, M., Bonanni, L., Onofrj, M., O'Brien, J.T. and Taylor, J.-P. (2016) 'Neurophysiological biomarkers for Lewy body dementias', *Clinical Neurophysiology*, 127(1), pp. 349-359.

Crowdy, K.A., Hollands, M.A., Ferguson, I.T. and Marple-Horvat, D.E. (2000) 'Evidence for interactive locomotor and oculomotor deficits in cerebellar patients during visually guided stepping', *Experimental Brain Research*, 135(4), pp. 437-454.

Crucian, G.P., Armaghani, S., Armaghani, A., Foster, P.S., Burks, D.W., Skoblar, B., Drago, V. and Heilman, K.M. (2010) 'Visual-spatial disembedding in Parkinson's disease', *J Clin Exp Neuropsychol*, 32(2), pp. 190-200.

Cumming, R.G. and Klineberg, R.J. (1994) 'Fall frequency and characteristics and the risk of hip fractures', *Journal of the American Geriatrics Society*, 42(7), pp. 774-778.

Dalrymple-Alford, J.C., MacAskill, M.R., Nakas, C.T., Livingston, L., Graham, C., Crucian, G.P., Melzer, T.R., Kirwan, J., Keenan, R., Wells, S., Porter, R.J., Watts, R. and Anderson, T.J. (2010) 'The MoCA: well-suited screen for cognitive impairment in Parkinson disease', *Neurology*, 75(19), pp. 1717-25.

Damier, P. (2015) 'Why do Parkinson's Disease Patients Sometimes Make Wrong Decisions?', *Journal of Parkinson's Disease*, (Preprint), pp. 1-6.

Davidsdottir, S., Cronin-Golomb, A. and Lee, A. (2005) 'Visual and spatial symptoms in Parkinson's disease', *Vision Res*, 45(10), pp. 1285-96.

Davidsdottir, S., Wagenaar, R., Young, D. and Cronin-Golomb, A. (2008) 'Impact of optic flow perception and egocentric coordinates on veering in Parkinson's disease', *Brain*, 131(Pt 11), pp. 2882-93.

de Boer, C., Pel, J.J.M., van den Dorpel, J.J.A., Boon, A.J.W. and van der Steen, J. (2014) 'Behavioral inhibition errors in Parkinson's disease tested using an antisaccade and antitapping task', *Journal of Parkinson's disease*, 4(4), pp. 599-608.

de Craen, A.J.M., Heeren, T.J. and Gussekloo, J. (2003) 'Accuracy of the 15-item geriatric depression scale (GDS-15) in a community sample of the oldest old', *International Journal of Geriatric Psychiatry*, 18(1), pp. 63-66.

de Hemptinne, C., Ivanoiu, A., Lefevre, P. and Missal, M. (2013) 'How does Parkinson's disease and aging affect temporal expectation and the implicit timing of eye movements?', *Neuropsychologia*, 51(2), pp. 340-8.

de Lau, L.M.L. and Breteler, M.M.B. (2006) 'Epidemiology of Parkinson's disease', *The Lancet Neurology*, 5(6), pp. 525-535.

de Lau, L.M.L., Verbaan, D., Marinus, J. and van Hilten, J.J. (2014) 'Survival in Parkinson's disease. Relation with motor and non-motor features', *Parkinsonism & Related Disorders*, 20(6), pp. 613-616.

de Melo Roiz, R., Azevedo Cacho, E.W., Cliquet, A., Jr. and Barasnevicius Quagliato, E.M. (2011) 'Analysis of parallel and transverse visual cues on the gait of individuals with idiopathic Parkinson's disease', *Int J Rehabil Res*, 34(4), pp. 343-8.

De Santis, A. and Iacoviello, D. (2009) 'Robust real time eye tracking for computer interface for disabled people', *Computer Methods and Programs in Biomedicine*, 96(1), pp. 1-11.

Deijen, J.B., Stoffers, D., Berendse, H.W., Wolters, E. and Theeuwes, J. (2006) 'Abnormal susceptibility to distracters hinders perception in early stage Parkinson's disease: a controlled study', *BMC Neurol*, 6(43), pp. 1-9.

Del Tredici, K. and Braak, H. (2012) 'Dysfunction of the locus coeruleus–norepinephrine system and related circuitry in Parkinson's disease-related dementia', *Journal of Neurology, Neurosurgery & Psychiatry*, 84(7), pp. 774-783.

Delli Pizzi, S., Franciotti, R., Taylor, J.-P., Thomas, A., Tartaro, A., Onofrj, M. and Bonanni, L. (2014) 'Thalamic Involvement in Fluctuating Cognition in Dementia with Lewy Bodies: Magnetic Resonance Evidences', *Cerebral Cortex*.

DeLong, M.R. and Georgopoulos, A.P. (2011) 'Motor functions of the basal ganglia', in *Comprehensive Physiology*. John Wiley & Sons, pp. 1017-1061.

DeLong, M.R. and Wichmann, T. (2007) 'Circuits and circuit disorders of the basal ganglia', *Archives of neurology*, 64(1), pp. 20-24.

Desmurget, M., Gaveau, V., Vindras, P., Turner, R.S., Broussolle, E. and Thobois, S. (2004a) 'On-line motor control in patients with Parkinson's disease', *Brain*, 127(Pt 8), pp. 1755-73.

Desmurget, M., Grafton, S.T., Vindras, P., Grea, H. and Turner, R.S. (2004b) 'The basal ganglia network mediates the planning of movement amplitude', *European Journal of Neuroscience*, 19(10), pp. 2871-2880.

Di Fabio, R.P., Zampieri, C. and Greany, J.F. (2003) 'Aging and saccade-stepping interactions in humans', *Neuroscience Letters*, 339(3), pp. 179-182.

Dietz, V. (2003) 'Spinal cord pattern generators for locomotion', *Clin Neurophysiol*, 114(8), pp. 1379-89.

Ding, W., Ding, L.J., Li, F.F., Han, Y. and Mu, L. (2015) 'Neurodegeneration and cognition in Parkinson's disease: a review', *Eur Rev Med Pharmacol Sci*, 19(12), pp. 2275-81.

Doi, T., Makizako, H., Shimada, H., Park, H., Tsutsumimoto, K., Uemura, K. and Suzuki, T. (2013) 'Brain activation during dual-task walking and executive function among older adults with mild cognitive impairment: a fNIRS study', *Aging Clinical and Experimental Research*, 25(5), pp. 539-544.

Domellof, M.E., Elgh, E. and Forsgren, L. (2011) 'The relation between cognition and motor dysfunction in drug-naive newly diagnosed patients with Parkinson's disease', *Mov Disord*, 26(12), pp. 2183-9.

Donaghy, P.C. and McKeith, I.G. (2014) 'The clinical characteristics of dementia with Lewy bodies and a consideration of prodromal diagnosis', *Alzheimer's Research & Therapy*, 6(4), pp. 1-12.

Donoghue, O.A., Horgan, N., Savva, G.M., Cronin, H., O'Regan, C. and Kenny, R.A. (2012) 'Association between timed up-and-go and memory, executive function, and processing speed', *Journal of the American Geriatrics Society*, 60(9), pp. 1681-1686.

Dowiasch, S., Marx, S., Einhäuser, W. and Bremmer, F. (2015) 'Effects of aging on eye movements in the real world', *Frontiers in human neuroscience*, 9(46), pp. 1-12.

Drag, L., Light, S., Langenecker, S., Hazlett, K., Wilde, E., Welsh, R., Steinberg, B. and Bieliauskas, L. (2015) 'Patterns of frontoparietal activation as a marker for unsuccessful visuospatial processing in healthy aging', *Brain Imaging and Behavior*, 1(1), pp. 1-11.

Duchowski, A. (2007) *Eye tracking methodology theory and practice*. 2nd edn. London, UK: Springer.

Duncan, G.W., Khoo, T.K., Coleman, S.Y., Brayne, C., Yarnall, A.J., O'Brien, J.T., Barker, R.A. and Burn, D.J. (2014) 'The incidence of Parkinson's disease in the North-East of England', *Age Ageing*, 43(2), pp. 257-63.

Duval, C. and Beuter, A. (1998) 'Fluctuations in tremor at rest and eye movements during ocular fixation in subjects with Parkinson's disease', *Parkinsonism and Related Disorders*, 4(2), pp. 91-97.

Economou, S.G. and Stefanis, C.N. (1978) 'Changes of electrooculogram (EOG) in Parkinson's disease', *Acta Neurologica Scandinavica*, 58(1), pp. 44-52.

Ehgoetz Martens, K.A., Pieruccini-Faria, F. and Almeida, Q.J. (2013) 'Could sensory mechanisms be a core factor that underlies freezing of gait in Parkinson's disease?', *PLoS One*, 8(5), p. e62602.

Ehrenstein, W.H. (2003) 'Basics of seeing motion', *Arquivos brasileiros de oftalmologia*, 66(5), pp. 44-52.

Emre, M. (2003) 'Dementia associated with Parkinson's disease', *Lancet Neurol*, 2(4), pp. 229-37.

Emre, M., Aarsland, D., Albanese, A., Byrne, E.J., Deuschl, G., De Deyn, P.P., Durif, F., Kulisevsky, J., van Laar, T., Lees, A., Poewe, W., Robillard, A., Rosa, M.M., Wolters, E., Quarg, P., Tekin, S. and Lane, R. (2004) 'Rivastigmine for dementia associated with Parkinson's disease', *N Engl J Med*, 351(24), pp. 2509-18.

Emre, M., Ford, P.J., Bilgiç, B. and Uç, E.Y. (2014) 'Cognitive impairment and dementia in Parkinson's disease: Practical issues and management', *Movement Disorders*, 29(5), pp. 663-672.

Engle, R.W. (2002) 'Working memory capacity as executive attention', *Current directions in psychological science*, 11(1), pp. 19-23.

Engle, R.W. and Kane, M.J. (2004) 'Executive attention, working memory capacity, and a two-factor theory of cognitive control', *Psychology of learning and motivation*, 44, pp. 145-200.

Errington, J.A., Menant, J.C., Suttle, C.M., Bruce, J. and Asper, L.J. (2013) 'The effects of vertical yoked prisms on gait', *Invest Ophthalmol Vis Sci*, 54(6), pp. 3949-56.

Espay, A.J., Baram, Y., Dwivedi, A.K., Shukla, R., Gartner, M., Gaines, L., Duker, A.P. and Revilla, F.J. (2010) 'At-home training with closed-loop augmented-reality cueing device for improving gait in patients with Parkinson disease', *J Rehabil Res Dev*, 47(6), pp. 573-81.

Ettinger, U., Kumari, V., Crawford, T.J., Davis, R.E., Sharma, T. and Corr, P.J. (2003) 'Reliability of smooth pursuit, fixation, and saccadic eye movements', *Psychophysiology*, 40(4), pp. 620-628.

Evans, D.W. and Ginsburg, A.P. (1985) 'Contrast sensitivity predicts age-related differences in highway-sign discriminability', *Human Factors: The Journal of the Human Factors and Ergonomics Society*, 27(6), pp. 637-642.

Expósito-Ruiz, M., Pérez-Vicente, S. and Rivas-Ruiz, F. (2010) 'Statistical inference: Hypothesis testing', *Allergologia et immunopathologia*, 38(5), pp. 266-277.

Faber, L.G., Maurits, N.M. and Lorist, M.M. (2012) 'Mental Fatigue Affects Visual Selective Attention', *PLoS ONE*, 7(10), p. e48073.

Fabiani, M., Zimmerman, B. and Gratton, G. (2015) 'Working Memory and Aging: A Review', in Jolicoeur, P., Lefebvre, C. and Martinez-Trujillo, J. (eds.) *Mechanisms of Sensory Working Memory: Attention and Perfomance XXV*. London, UK: Elsevier, pp. 131-148.

Fahn, S. (2003) 'Description of Parkinson's disease as a clinical syndrome', *Annals of the New York Academy of Sciences*, 991(1), pp. 1-14.

Farris-Trimble, A. and McMurray, B. (2013) 'Test-retest reliability of eye tracking in the visual world paradigm for the study of real-time spoken word recognition', *J Speech Lang Hear Res*, 56(4), pp. 1328-45.

Farzin, F., Scaggs, F., Hervey, C., Berry-Kravis, E. and Hessl, D. (2011) 'Reliability of eye tracking and pupillometry measures in individuals with fragile X syndrome', *J Autism Dev Disord*, 41(11), pp. 1515-22.

Fasano, A., Herman, T., Tessitore, A., Strafella, A.P. and Bohnen, N.I. (2015) 'Neuroimaging of Freezing of Gait', *Journal of Parkinson's disease*, 5(2), pp. 241-254.

Favre, E., Ballanger, B., Thobois, S., Broussolle, E. and Boulinguez, P. (2013) 'Deep Brain Stimulation of the Subthalamic Nucleus, but not Dopaminergic Medication, Improves Proactive Inhibitory Control of Movement Initiation in Parkinson's Disease', *Neurotherapeutics*, 10(1), pp. 154-167.

Ferrari, M. and Quaresima, V. (2012) 'A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application', *Neuroimage*, 63(2), pp. 921-935.

Ferree, C.E. (1906) 'An Experimental Examination of the Phenomena Usually Attributed to Fluctuation of Attention', *The American Journal of Psychology*, 17(1), pp. 81-120.

Ferrucci, L., Bandinelli, S., Benvenuti, E., Iorio, A., Macchi, C., Harris, T.B. and Guralnik, J.M. (2000) 'Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study', *Journal of the American Geriatrics Society*, 48(12), pp. 1618-1625.

Field, A. (2013) *Discovering statistics using IBM SPSS statistics*. 4th edn. London, UK: Sage.

Fielding, J., Georgiou-Karistianis, N., Millist, L. and White, O. (2006a) 'Temporal variation in the control of goal-directed visuospatial attention in basal ganglia disorders', *Neuroscience research*, 54(1), pp. 57-65.

Fielding, J., Georgiou-Karistianis, N. and White, O. (2006b) 'The role of the basal ganglia in the control of automatic visuospatial attention', *Journal of the International Neuropsychological Society*, 12(05), pp. 657-667.

Finton, M.J., Lucas, J.A., Graff-Radford, N.R. and Uitti, R.J. (1998) 'Analysis of visuospatial errors in patients with Alzheimer's disease or Parkinson's disease', *J Clin Exp Neuropsychol*, 20(2), pp. 186-93.

Fling, B.W., Cohen, R.G., Mancini, M., Nutt, J.G., Fair, D.A. and Horak, F.B. (2013) 'Asymmetric pedunculopontine network connectivity in parkinsonian patients with freezing of gait', *Brain*, 136(8), pp. 2405-2418.

Flowers, K.A. and Downing, A.C. (1978) 'Predictive control of eye movements in Parkinson disease', *Annals of Neurology*, 4(1), pp. 63-66.

Fonoff, F.C., Fonoff, E.T., Barbosa, E.R., Quaranta, T., Machado, R.B., de Andrade, D.C., Teixeira, M.J. and Fuentes, D. (2015) 'Correlation Between Impulsivity and Executive Function in Patients With Parkinson Disease Experiencing Depression and Anxiety Symptoms', *Journal of Geriatric Psychiatry and Neurology*, 28(1), pp. 49-56.

Foster, P.S., Yung, R.C., Drago, V., Crucian, G.P. and Heilman, K.M. (2013) 'Working memory in Parkinson's disease: The effects of depression and side of onset of motor symptoms', *Neuropsychology*, 27(3), pp. 303-313.

Franciotti, R., Falasca, N.W., Bonanni, L., Anzellotti, F., Maruotti, V., Comani, S., Thomas, A., Tartaro, A., Taylor, J.-P. and Onofrj, M. (2013) 'Default network is not hypoactive in dementia with fluctuating cognition: an Alzheimer disease/dementia with Lewy bodies comparison', *Neurobiology of Aging*, 34(4), pp. 1148-1158.

Freedman, E.G. (2001) 'Interactions between eye and head control signals can account for movement kinematics', *Biological Cybernetics*, 84(6), pp. 453-462.

Gallagher, D.A. and Schrag, A. (2012) 'Psychosis, apathy, depression and anxiety in Parkinson's disease', *Neurobiology of Disease*, 46(3), pp. 581-589.

Galna, B., Lord, S., Burn, D.J. and Rochester, L. (2015) 'Progression of gait dysfunction in incident Parkinson's disease: Impact of medication and phenotype', *Movement Disorders*, 30(3), pp. 359-367.

Galna, B., Lord, S., Daud, D., Archibald, N., Burn, D. and Rochester, L. (2012) 'Visual sampling during walking in people with Parkinson's disease and the influence of environment and dual-task', *Brain Res*, 1473, pp. 35-43.

Gandhi, N.J. and Sparks, D.L. (2001) 'Experimental control of eye and head positions prior to head-unrestrained gaze shifts in monkey', *Vision Research*, 41(25–26), pp. 3243-3254.

Garnham, L. and Sloper, J.J. (2006) 'Effect of age on adult stereoacuity as measured by different types of stereotest', *Br J Ophthalmol*, 90(1), pp. 91-5.

Gauggel, S., Rieger, M. and Feghoff, T.A. (2004) 'Inhibition of ongoing responses in patients with Parkinson's disease', *Journal of Neurology, Neurosurgery & Psychiatry*, 75(4), pp. 539-544.

Gazzaley, A., Cooney, J.W., Rissman, J. and D'Esposito, M. (2005) 'Top-down suppression deficit underlies working memory impairment in normal aging', *Nat Neurosci*, 8(10), pp. 1298-300.

Geldmacher, D.S. (2003) 'Visuospatial dysfunction in the neurodegenerative diseases', *Frontiers in Bioscience*, 8(1), pp. e428-436.

Gerrits, N.J.H.M., van der Werf, Y.D., Verhoef, K.M.W., Veltman, D.J., Groenewegen, H.J., Berendse, H.W. and van den Heuvel, O.A. (2015) 'Compensatory fronto-parietal hyperactivation during set-shifting in unmedicated patients with Parkinson's disease', *Neuropsychologia*, 68(1), pp. 107-116.

Ghasemi, A. and Zahediasl, S. (2012) 'Normality Tests for Statistical Analysis: A Guide for Non-Statisticians', *International Journal of Endocrinology and Metabolism*, 10(2), pp. 486-489.

Ghez, C., Gordon, J., Ghilardi, M.F. and SAINBURG, R. (1994) 'Contributions of vision and proprioception to accuracy of limb movements', in Gazzaniga, M.S. (ed.) *The Cognitive Neurosciences*. Cambridge, MA.: MIT Press, pp. 549-564.

Gibson, J.M., Pimlott, R. and Kennard, C. (1987) 'Ocular motor and manual tracking in Parkinson's disease and the effect of treatment', *Journal of Neurology Neurosurgery and Psychiatry*, 50(7), pp. 853-860.

Giladi, N., Hausdorff, J.M. and Balash, Y. (2013a) 'Episodic and continuous gait disturbances in Parkinson's disease ', in Galvez-Jimenez, N. (ed.) *Scientific Basis for the Treatment of Parkinson's Disease*. 2nd edn. Florida, USA: Taylor and Francis, pp. 417-430.

Giladi, N., Horak, F.B. and Hausdorff, J.M. (2013b) 'Classification of gait disturbances: distinguishing between continuous and episodic changes', *Movement Disorders*, 28(11), pp. 1469-1473.

Giladi, N., Shabtai, H., Rozenberg, E. and Shabtai, E. (2001a) 'Gait festination in Parkinson's disease', *Parkinsonism & related disorders*, 7(2), pp. 135-138.

Giladi, N., Treves, T.A., Simon, E.S., Shabtai, H., Orlov, Y., Kandinov, B., Paleacu, D. and Korczyn, A.D. (2001b) 'Freezing of gait in patients with advanced Parkinson's disease', *Journal of neural transmission*, 108(1), pp. 53-61.

Goetz, C.G. (2011) 'The history of Parkinson's disease: early clinical descriptions and neurological therapies', *Cold Spring Harb Perspect Med*, 1(1), p. a008862.

Goldman, J.G. and Goetz, C.G. (2007) 'History of Parkinson's disease', *Handbook of Clinical Neurology*, 83(1), pp. 107-128.

Goodale, M.A. and Haffenden, A. (1998) 'Frames of Reference for Perception and Action in the Human Visual System', *Neuroscience & Biobehavioral Reviews*, 22(2), pp. 161-172.

Gorges, M., Müller, H.-P., Lulé, D., Pinkhardt, E., Ludolph, A. and Kassubek, J. (2015) 'The association between alterations of eye movement control and cerebral intrinsic functional connectivity in Parkinson's disease', *Brain Imaging and Behavior*, 1(1), pp. 1-13.

Gorges, M., Pinkhardt, E.H. and Kassubek, J. (2014) 'Alterations of Eye Movement Control in Neurodegenerative Movement Disorders', *Journal of Ophthalmology*, 1(2014), pp. 1-11.

Gräber, S., Liepelt-Scarfone, I., Csoti, I., Maetzler, W., Sultan, F. and Berg, D. (2014) 'Post-Cueing Deficits with Maintained Cueing Benefits in Patients with Parkinson's Disease Dementia', *Frontiers in Neurology*, 5(236), pp. 1-6.

Grabli, D., Karachi, C., Welter, M.L., Lau, B., Hirsch, E.C., Vidailhet, M. and Francois, C. (2012) 'Normal and pathological gait: what we learn from Parkinson's disease', *J Neurol Neurosurg Psychiatry*, 83(10), pp. 979-85.

Grande, L.J., Crosson, B., Heilman, K.M., Bauer, R.M., Kilduff, P. and McGlinchey, R.E. (2006) 'Visual selective attention in Parkinson's disease: dissociation of exogenous and endogenous inhibition', *Neuropsychology*, 20(3), pp. 370-82.

Grasso, R., Peppe, A., Stratta, F., Angelini, D., Zago, M., Stanzione, P. and Lacquaniti, F. (1999) 'Basal ganglia and gait control: apomorphine administration and internal pallidum stimulation in Parkinson's disease', *Experimental brain research*, 126(2), pp. 139-148.

Gratwicke, J., Jahanshahi, M. and Foltynie, T. (2015) 'Parkinson's disease dementia: a neural networks perspective', *Brain*, 138(Pt 6), pp. 1454-76.

Guilford, J.P. (1927) ''Fluctuations of Attention' with Weak Visual Stimuli', *The American Journal of Psychology*, 38(4), pp. 534-583.

Gurvich, C., Georgiou-Karistianis, N., Fitzgerald, P.B., Millist, L. and White, O.B. (2007) 'Inhibitory control and spatial working memory in Parkinson's disease', *Movement Disorders*, 22(10), pp. 1444-1450.

Hallemans, A., Ortibus, E., Meire, F. and Aerts, P. (2010) 'Low vision affects dynamic stability of gait', *Gait & Posture*, 32(4), pp. 547-551.

Hanakawa, T., Katsumi, Y., Fukuyama, H., Honda, M., Hayashi, T., Kimura, J. and Shibasaki, H. (1999) 'Mechanisms underlying gait disturbance in Parkinson's disease', *Brain*, 122(7), pp. 1271-1282.

Hancock, G.R. and Mueller, R.O. (2011) 'The Reliability Paradox in Assessing Structural Relations Within Covariance Structure Models', *Educational and Psychological Measurement*, 71(2), pp. 306-324.

Handojoseno, A.M.A., Gilat, M., Ly, Q.T., Chamtie, H., Shine, J.M., Nguyen, T.N., Tran, Y., Lewis, S.J.G. and Nguyen, H.T. (2015) 'An EEG study of turning freeze in Parkinson's disease patients: The alteration of brain dynamic on the motor and visual cortex', *Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE*. Milan, Italy, 25-29 Aug. 2015. IEEE, pp. 6618-6621.

Hanes, K.R., Andrewes, D.G. and Pantelis, C. (1995) 'Cognitive flexibility and complex integration in Parkinson's disease, Huntington's disease, and schizophrenia', *Journal of the International Neuropsychological Society*, 1(06), pp. 545-553.

Hansen, H.C., Gibson, J.M., Zangemeister, W.H. and Kennard, C. (1990) 'The effect of treatment on eye-head coordination in Parkinson's disease', *Journal of Vestibular Research*, 1(2), pp. 181-186.

Harris, J. (1998) 'Vision in Parkinson’s disease: what are the deficits and what are their origins?', *Neuro-Ophthalmology*, 19(3), pp. 113-135.

Harris, J.P., Atkinson, E.A., Lee, A.C., Nithi, K. and Fowler, M.S. (2003) 'Hemispace differences in the visual perception of size in left hemiParkinson's disease', *Neuropsychologia*, 41(7), pp. 795-807.

Hashimoto, T. (2006) 'Speculation on the responsible sites and pathophysiology of freezing of gait', *Parkinsonism & Related Disorders*, 12(1), pp. S55-S62.

Hausdorff, J.M., Schweiger, A., Herman, T., Yogev-Seligmann, G. and Giladi, N. (2008) 'Dual-task decrements in gait: contributing factors among healthy older adults', *Journals of Gerontology Series A-Biological Sciences & Medical Sciences*, 63(12), pp. 1335-43.

Hausdorff, J.M., Zitser, J., Mirelman, A. and Giladi, N. (2010) 'Interaction between cognition and gait in patients with Parkinson’s disease', in Emre, M. (ed.) *Cognitive Impairment and Dementia in Parkinson's Disease*. 2nd edn. Oxford, UK: Oxford University Press, pp. 91-107.

Hawelka, S. and Wimmer, H. (2005) 'Impaired visual processing of multi-element arrays is associated with increased number of eye movements in dyslexic reading', *Vision Research*, 45(7), pp. 855-863.

Hayes, A.F. (2009) 'Beyond Baron and Kenny: Statistical mediation analysis in the new millennium', *Communication monographs*, 76(4), pp. 408-420.

Hayhoe, M. and Ballard, D. (2005) 'Eye movements in natural behavior', *Trends Cogn Sci*, 9(4), pp. 188-94.

Helmich, R.C., Derikx, L.C., Bakker, M., Scheeringa, R., Bloem, B.R. and Toni, I. (2010) 'Spatial Remapping of Cortico-striatal Connectivity in Parkinson's Disease', *Cerebral Cortex*, 20(5), pp. 1175-1186.

Hennelly, M.L., Barbur, J.L., Edgar, D.F. and Woodward, E.G. (1998) 'The effect of age on the light scattering characteristics of the eye', *Ophthalmic and Physiological Optics*, 18(2), pp. 197-203.

Hennessey, C.A. and Lawrence, P.D. (2009) 'Improving the accuracy and reliability of remote system-calibration-free eye-gaze tracking', *IEEE Trans Biomed Eng*, 56(7), pp. 1891-900.

Heremans, E., Nieuwboer, A., Feys, P., Vercruysse, S., Vandenberghe, W., Sharma, N. and Helsen, W.F. (2012) 'External cueing improves motor imagery quality in patients with Parkinson disease', *Neurorehabil Neural Repair*, 26(1), pp. 27-35.

Heremans, E., Nieuwboer, A., Spildooren, J., Vandenbossche, J., Deroost, N., Soetens, E., Kerckhofs, E. and Vercruysse, S. (2013) 'Cognitive aspects of freezing of gait in Parkinson's disease: a challenge for rehabilitation', *J Neural Transm*, 120(4), pp. 543-57.

Herman, T., Giladi, N. and Hausdorff, J.M. (2013) 'Neuroimaging as a window into gait disturbances and freezing of gait in patients with Parkinson's disease', *Curr Neurol Neurosci Rep*, 13(12), p. 411.

Hernandez, T.D., Levitan, C.A., Banks, M.S. and Schor, C.M. (2008) 'How does saccade adaptation affect visual perception?', *Journal of Vision*, 8(8), pp. 3-3.

Herrera-Guzman, I., Pena-Casanova, J., Lara, J.P., Gudayol-Ferre, E. and Bohm, P. (2004) 'Influence of age, sex, and education on the Visual Object and Space Perception Battery (VOSP) in a healthy normal elderly population', *Clin Neuropsychol*, 18(3), pp. 385-94.

Hess, C.W., Muri, R. and Meienberg, O. (2009) 'Recording of Horizontal Saccadic Eye Movements: Methodological Comparison Between Electro-Oculography and Infrared Reflection Oculography', *Neuro-opthalmology*, 6(3), pp. 189-197.

Heuninckx, S., Wenderoth, N. and Swinnen, S.P. (2008) 'Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons', *J Neurosci*, 28(1), pp. 91-9.

Highstein, S., Cohen, B. and Mones, R. (1969) 'Changes in saccadic eye movements of patients with Parkinson's disease before and after L-dopa', *Transactions of the American Neurological Association*, 94(1), pp. 277-279.

Hikosaka, O., Takikawa, Y. and Kawagoe, R. (2000) 'Role of the Basal Ganglia in the Control of Purposive Saccadic Eye Movements', *Physiological Reviews*, 80(3), pp. 953-978.

Hilderman, R.J. and Peckham, T. (2007) 'Statistical methodologies for mining potentially interesting contrast sets', in Guiller, F. and Hamilton, H.J. (eds.) *Quality Measures in Data Mining*. New York: Springer, pp. 153-177.

Ho, G., Scialfa, C.T., Caird, J.K. and Graw, T. (2001) 'Visual Search for Traffic Signs: The Effects of Clutter, Luminance, and Aging', *Human Factors: The Journal of the Human Factors and Ergonomics Society*, 43(2), pp. 194-207.

Hochstadt, J. (2009) 'Set-shifting and the on-line processing of relative clauses in Parkinson's disease: results from a novel eye-tracking method', *Cortex*, 45(8), pp. 991-1011.

Hodgson, T.L., Tiesman, B., Owen, A.M. and Kennard, C. (2002) 'Abnormal gaze strategies during problem solving in Parkinson's disease', *Neuropsychologia*, 40(4), pp. 411-422.

Hoehn, M.M. and Yahr, M.D. (1967) 'Parkinsonism: onset, progression and mortality', *Neurology*, 17(5), pp. 427-442.

Hoffman, J.E. and Subramaniam, B. (1995) 'The role of visual attention in saccadic eye movements', *Perception & psychophysics*, 57(6), pp. 787-795.

Hollman, J.H., Kovash, F.M., Kubik, J.J. and Linbo, R.A. (2007) 'Age-related differences in spatiotemporal markers of gait stability during dual task walking', *Gait & Posture*, 26(1), pp. 113-119.

Holmes, J.D., Brigham, L.K., Jenkins, M.E., Ready, E.A., Lutz, S.G., Johnson, A.M. and Grahn, J.A. (2015) 'The Effects of Manipulating Spatial Location of Visual Cue Placement on Gait among Individuals with Parkinson's Disease: A Pilot Study', *Physical and Occupational Therapy in Geriatrics*, 33(3), pp. 263-278.

Holmqvist, K. and Nystrom, M. (2011) *Eye tracking: A comprehensive guide to methods and measures*. Oxford, UK: Oxford University Press.

Holtzer, R., Epstein, N., Mahoney, J.R., Izzetoglu, M. and Blumen, H.M. (2014) 'Neuroimaging of mobility in aging: a targeted review', *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 69(11), pp. 1375-1388.

Holtzer, R., Mahoney, J.R., Izzetoglu, M., Izzetoglu, K., Onaral, B. and Verghese, J. (2011) 'fNIRS Study of Walking and Walking While Talking in Young and Old Individuals', *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 66(8), pp. 879-87.

Holtzer, R., Verghese, J., Xue, X. and Lipton, R.B. (2006) 'Cognitive processes related to gait velocity: Results from the Einstein aging study', *Neuropsychology*, 20(2), pp. 215-223.

Holtzer, R., Wang, C., Lipton, R. and Verghes, e.J. (2012) 'The Relationship of Executive Functions and Episodic Memory with Gait Speed Decline in Aging Defined in the Context of Cognitive Reserve', *Journal of the American Geriatrics Society*, 60(11), pp. 2093-2098.

Honaker, J.A. and Shepard, N.T. (2011) 'Use of the Dynamic Visual Acuity Test as a screener for community-dwelling older adults who fall', *J Vestib Res*, 21(5), pp. 267-76.

Hood, A.J., Amador, S.C., Cain, A.E., Briand, K.A., Al-Refai, A.H., Schiess, M.C. and Sereno, A.B. (2007) 'Levodopa slows prosaccades and improves antisaccades: an eye movement study in Parkinson's disease', *J Neurol Neurosurg Psychiatry*, 78(6), pp. 565-70.

Hooper, D., Coughlan, J. and Mullen, M. (2008) 'Structural equation modelling: Guidelines for determining model fit', *Electronic Journal of Business Research Methods*, 6(1), pp. 53-60.

Horowitz, T.S., Choi, W.Y., Horvitz, J.C., Cote, L.J. and Mangels, J.A. (2006) 'Visual search deficits in Parkinson's disease are attenuated by bottom-up target salience and top-down information', *Neuropsychologia*, 44(10), pp. 1962-77.

Hoyle, R.H. and Gottfredson, N.C. (2014) 'Sample Size Considerations in Prevention Research Applications of Multilevel Modeling and Structural Equation Modeling', *Prevention Science*, 16(7), pp. 987-996.

Huang, W.N., VanSwearingen, J.M. and Brach, J.S. (2008) 'Gait variability in older adults: observational rating validated by comparison with a computerized walkway gold standard', *Phys Ther*, 88(10), pp. 1146-53.

Huestegge, L. and Koch, I. (2009) 'Dual-task crosstalk between saccades and manual responses', *J Exp Psychol Hum Percept Perform*, 35(2), pp. 352-62.

Huestegge, L. and Koch, I. (2012) 'Eye movements as a gatekeeper for memorization: evidence for the persistence of attentional sets in visual memory search', *Psychological research*, 76(3), pp. 270-279.

Hughes, A.J., Daniel, S.E., Kilford, L. and Lees, A.J. (1992) 'Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases', *Journal of Neurology, Neurosurgery & Psychiatry*, 55(3), pp. 181-184.

Hull, R., Martin, R.C., Beier, M.E., Lane, D. and Hamilton, A.C. (2008) 'Executive function in older adults: A structural equation modeling approach', *Neuropsychology*, 22(4), pp. 508-522.

Hylan, J.P. (1898) 'Review of The Fluctuation of Attention', *Psychological Review*, 5(4), pp. 439-441.

Iaboni, A. and Flint, A.J. (2013) 'The complex interplay of depression and falls in older adults: a clinical review', *The American Journal of Geriatric Psychiatry*, 21(5), pp. 484-492.

Iansek, R., Danoudis, M. and Bradfield, N. (2013) 'Gait and cognition in Parkinson's disease: implications for rehabilitation', *Reviews in the Neurosciences*, 24(3), pp. 293-300.

Iersel, M.B.v., Kessels, R.P.C., Bloem, B.R., Verbeek, A.L.M. and Olde Rikkert, M.G.M. (2008) 'Executive Functions Are Associated With Gait and Balance in Community-Living Elderly People', *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 63(12), pp. 1344-1349.

Inzelberg, R., Schechtman, E. and Hocherman, S. (2008) 'Visuo-motor coordination deficits and motor impairments in Parkinson's disease', *PLoS ONE*, 3(11), p. e3663.

Irwin, D.E. and Andrews, R.V. (1996) 'Integration and accumulation of information across saccadic eye movements', in Inui, T. and McClelland, J.L. (eds.) *Attention and performance XVI: Information integration in perception and communication*. Cambridge, Massachusetts: The MIT Press, pp. 125-155.

Ishigaki, H. and Miyao, M. (1994) 'IMPLICATIONS FOR DYNAMIC VISUAL ACUITY WITH CHANGES IN AGE AND SEX', *Perceptual and Motor Skills*, 78(2), pp. 363-369.

Itti, L. (2005) 'Models of bottom-up attention and saliency', in Itti, L., Rees, G. and Tsotsos, J.K. (eds.) *Neurobiology of attention*. San Diego, CA: Elsevier, pp. 1-11.

Itti, L. and Koch, C. (2001) 'Computational modelling of visual attention', *Nat Rev Neurosci*, 2(3), pp. 194-203.

Jackson, S.R., Jackson, G.M. and Rosicky, J. (1995) 'Are non-relevant objects represented in working memory? The effect of non-target objects on reach and grasp kinematics', *Experimental Brain Research*, 102(3), pp. 519-530.

Jackson, S.R., Marrocco, R. and Posner, M.I. (1994) 'Networks of anatomical areas controlling visuospatial attention', *Neural Networks*, 7(6–7), pp. 925-944.

Jahanshahi, M. (2013) 'Effects of deep brain stimulation of the subthalamic nucleus on inhibitory and executive control over prepotent responses in Parkinson's disease', *Frontiers in Systems Neuroscience*, 7(118), pp. 1-20.

Jahanshahi, M., Obeso, I., Baunez, C., Alegre, M. and Krack, P. (2015) 'Parkinson's Disease, the Subthalamic Nucleus, Inhibition, and Impulsivity', *Movement Disorders*, 30(2), pp. 128-140.

Jankovic, J. (2008) 'Parkinson’s disease: clinical features and diagnosis', *Journal of Neurology, Neurosurgery & Psychiatry*, 79(4), pp. 368-376.

Javaid, M.A., Amassian, V., Glazman, S., Fesharaki, A., Stefanov, D. and Bodis-Wollner, I. (2012) 'Cortical control of voluntary saccades in Parkinson's disease and pre-emptive perception', *Parkinsonism & Related Disorders*, 18(Suppl 1), pp. S100-S103.

Jazbec, S., McClure, E., Hardin, M., Pine, D.S. and Ernst, M. (2005) 'Cognitive Control Under Contingencies in Anxious and Depressed Adolescents: An Antisaccade Task', *Biological Psychiatry*, 58(8), pp. 632-639.

Jellinger, K.A. (2014) 'The pathomechanisms underlying Parkinson's disease', *Expert Review of Neurotherapeutics*, 14(2), pp. 199-215.

Jenkins, L., Myerson, J., Joerding, J.A. and Hale, S. (2000) 'Converging evidence that visuospatial cognition is more age-sensitive than verbal cognition', *Psychology and Aging*, 15(1), pp. 157-175.

Jha, M., Jhunjhunwala, K., Sankara, B.B., Saini, J., Kumar, J.K., Yadav, R. and Pal, P.K. (2015) 'Neuropsychological and imaging profile of patients with Parkinson's disease and freezing of gait', *Parkinsonism & related disorders*, 21(10), pp. 1184-1190.

Jiang, Y. and Norman, K.E. (2006) 'Effects of visual and auditory cues on gait initiation in people with Parkinson's disease', *Clinical Rehabilitation*, 20(1), pp. 36-45.

Jokinen, P., Karrasch, M., Bruck, A., Johansson, J., Bergman, J. and Rinne, J.O. (2013) 'Cognitive slowing in Parkinson's disease is related to frontostriatal dopaminergic dysfunction', *J Neurol Sci*, 329(1-2), pp. 23-8.

Jones, R.D., Donaldson, I.M. and Timmings, P.L. (1992) 'Impairment of High-Contrast Visual Acuity in Parkinson's Disease', *Movement Disorders*, 7(3), pp. 232-238.

Joti, P., Kulashekhar, S., Behari, M. and Murthy, A. (2007) 'Impaired inhibitory oculomotor control in patients with Parkinson's disease', *Exp Brain Res*, 177(4), pp. 447-57.

Kaas, J.H. (2008) 'The evolution of the complex sensory and motor systems of the human brain', *Brain Research Bulletin*, 75(2–4), pp. 384-390.

Kaiser, P.K. (2009) 'Prospective Evaluation of Visual Acuity Assessment: A Comparison of Snellen Versus ETDRS Charts in Clinical Practice (An AOS Thesis)', *Transactions of the American Ophthalmological Society*, 107(1), pp. 311-324.

Kane, M. and Engle, R. (2002) 'The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective', *Psychonomic Bulletin & Review*, 9(4), pp. 637-671.

Kane, M.J., Conway, A.R.A., Hambrick, D.Z. and Engle, R.W. (2007) 'Variation in working memory capacity as variation in executive attention and control', *Variation in working memory*, 1, pp. 21-48.

Kane, M.J., Poole, B.J., Tuholski, S.W. and Engle, R.W. (2006) 'Working memory capacity and the top-down control of visual search: Exploring the boundaries of "executive attention"', *J Exp Psychol Learn Mem Cogn*, 32(4), pp. 749-77.

Kaplan, R.L., Van Damme, I. and Levine, L.J. (2012) 'Motivation Matters: Differing Effects of Pre-Goal and Post-Goal Emotions on Attention and Memory', *Frontiers in Psychology*, 3(404), pp. 1-9.

Karachi, C., Grabli, D., Bernard, F.A., Tande, D., Wattiez, N., Belaid, H., Bardinet, E., Prigent, A., Nothacker, H.P., Hunot, S., Hartmann, A., Lehericy, S., Hirsch, E.C. and Francois, C. (2010) 'Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease', *J Clin Invest*, 120(8), pp. 2745-54.

Karádi, K., Lucza, T., Aschermann, Z., Komoly, S., Deli, G., Bosnyák, E., Ács, P., Horváth, R., Janszky, J. and Kovács, N. (2015) 'Visuospatial impairment in Parkinson's disease: The role of laterality', *Laterality: Asymmetries of Body, Brain and Cognition*, 20(1), pp. 112-127.

Kavanagh, J.J., Barrett, R.S. and Morrison, S. (2004) 'Upper body accelerations during walking in healthy young and elderly men', *Gait & Posture*, 20(3), pp. 291-298.

Kavanagh, J.J. and Menz, H.B. (2008) 'Accelerometry: a technique for quantifying movement patterns during walking', *Gait Posture*, 28(1), pp. 1-15.

Kavanagh, J.J., Morrison, S. and Barrett, R.S. (2005) 'Coordination of head and trunk accelerations during walking', *European Journal of Applied Physiology*, 94(4), pp. 468-475.

Kelly, J.W., Loomis, J.M. and Beall, A.C. (2005) 'The importance of perceived relative motion in the control of posture', *Experimental Brain Research*, 161(3), pp. 285-292.

Kelly, V.E., Eusterbrock, A.J. and Shumway-Cook, A. (2012a) 'The Effects of Instructions on Dual-Task Walking and Cognitive Task Performance in People with Parkinson's Disease', *Parkinson's Disease*, 1(2012), pp. 1-9.

Kelly, V.E., Eusterbrock, A.J. and Shumway-Cook, A. (2012b) 'A review of dual-task walking deficits in people with Parkinson's disease: motor and cognitive contributions, mechanisms, and clinical implications', *Parkinsons Dis*, 1(2012), pp. 1-14.

Kelly, V.E., Johnson, C.O., McGough, E.L., Shumway-Cook, A., Horak, F.B., Chung, K.A., Espay, A.J., Revilla, F.J., Devoto, J. and Wood-Siverio, C. (2015) 'Association of cognitive domains with postural instability/gait disturbance in Parkinson's disease', *Parkinsonism & related disorders*, 21(7), pp. 692-697.

Kempster, P.A., Hurwitz, B. and Lees, A.J. (2007) 'A new look at James Parkinson's Essay on the Shaking Palsy', *Neurology*, 69(5), pp. 482-485.

Keus, S.H.J., Bloem, B.R., Hendriks, E.J.M., Bredero-Cohen, A.B. and Munneke, M. (2007) 'Evidence-based analysis of physical therapy in Parkinson's disease with recommendations for practice and research', *Movement Disorders*, 22(4), pp. 451-460.

Kevin O'Regan, J., Deubel, H., Clark, J.J. and Rensink, R.A. (2000) 'Picture Changes During Blinks: Looking Without Seeing and Seeing Without Looking', *Visual Cognition*, 7(1-3), pp. 191-211.

Khattab, A., Docherty, S., Bagust, J., Willington, R., Thomas, P. and Amar, K. (2012) 'Subjective visual vertical perception and sense of smell in Parkinson disease', *The Journal of Rehabilitation Research and Development*, 49(6), p. 961.

Kim, S.-H., Park, J.-H., Kim, Y.H. and Koh, S.-B. (2011) 'Stereopsis in drug naive Parkinson's disease patients', *The Canadian Journal of Neurological Sciences*, 38(02), pp. 299-302.

Kim, S. and Rehder, B. (2011) 'How prior knowledge affects selective attention during category learning: An eyetracking study', *Memory & Cognition*, 39(4), pp. 649-665.

Kimmig, H., Haußmann, K., Mergner, T. and Lücking, C.H. (2002) 'What is pathological with gaze shift fragmentation in Parkinson's disease?', *Journal of Neurology*, 249(6), pp. 683-692.

Klein, B.E.K., Moss, S.E., Klein, R., Lee, K.E. and Cruickshanks, K.J. (2003) 'Associations of visual function with physical outcomes and limitations 5 years later in an older population: The Beaver Dam eye study', *Ophthalmology*, 110(4), pp. 644-650.

Klein, C. and Fischer, B. (2005) 'Instrumental and test-retest reliability of saccadic measures', *Biol Psychol*, 68(3), pp. 201-13.

Klein, R.M. (2000) 'Inhibition of return', *Trends in Cognitive Sciences*, 4(4), pp. 138-147.

Klencklen, G., Despres, O. and Dufour, A. (2012) 'What do we know about aging and spatial cognition? Reviews and perspectives', *Ageing Res Rev*, 11(1), pp. 123-35.

Kline, R.B. (2011) *Principles and Practice of Structural Equation Modelling*. 3rd edn. New York: Guildford Publishing Group.

Klockgether, T. and Dichgans, J. (1994) 'Visual control of arm movement in Parkinson's disease', *Movement Disorders*, 9(1), pp. 48-56.

Knudsen, E.I. (2007) 'Fundamental components of attention', *Annu. Rev. Neurosci.*, 30(1), pp. 57-78.

Ko, H.-k., Poletti, M. and Rucci, M. (2010) 'Microsaccades precisely relocate gaze in a high visual acuity task', *Nat Neurosci*, 13(12), pp. 1549-1553.

Koh, S.B., Suh, S.I., Kim, S.H. and Kim, J.H. (2013) 'Stereopsis and extrastriate cortical atrophy in Parkinson's disease: a voxel-based morphometric study', *Neuroreport*, 24(5), pp. 229-32.

Kravitz, D.J., Saleem, K.S., Baker, C.I. and Mishkin, M. (2011) 'A new neural framework for visuospatial processing', *Nature Reviews. Neuroscience*, 12(4), pp. 217-230.

Kudlicka, A., Clare, L. and Hindle, J.V. (2011) 'Executive functions in Parkinson's disease: Systematic review and meta-analysis', *Movement Disorders*, 26(13), pp. 2305-2315.

Kuechenmeister, C.A., Linton, P.H., Mueller, T.V. and White, H.B. (1977) 'Eye tracking in relation to age, sex, and illness', *Archives of General Psychiatry*, 34(5), pp. 578-579.

Kulikowski, J.J. (1971) 'Effect of eye movements on the contrast sensitivity of spatio-temporal patterns', *Vision Research*, 11(3), pp. 261-273.

Land, M.F. (2006) 'Eye movements and the control of actions in everyday life', *Prog Retin Eye Res*, 25(3), pp. 296-324.

Lawrence, A.D., Watkins, L.H.A., Sahakian, B.J., Hodges, J.R. and Robbins, T.W. (2000) 'Visual object and visuospatial cognition in Huntington's disease: implications for information processing in corticostriatal circuits', *Brain*, 123(7), pp. 1349-1364.

Le Heron, C.J., MacAskill, M.R. and Anderson, T.J. (2005) 'Memory-guided saccades in Parkinson's disease: long delays can improve performance', *Exp Brain Res*, 161(3), pp. 293-8.

Lebold, C.A. and Almeida, Q.J. (2010) 'Evaluating the contributions of dynamic flow to freezing of gait in Parkinson's disease', *Parkinsons Dis*, 1(2010), pp. 1-7.

Lebold, C.A. and Almeida, Q.J. (2011) 'An evaluation of mechanisms underlying the influence of step cues on gait in Parkinson's disease', *J Clin Neurosci*, 18(6), pp. 798-802.

Lee, C.-N., Ko, D., Suh, Y.-W. and Park, K.-W. (2015) 'Cognitive Functions and Stereopsis in Patients with Parkinson's Disease and Alzheimer's Disease Using 3-Dimensional Television: A Case Controlled Trial', *PLoS ONE*, 10(3), p. e0123229.

Lee, C. (1999) 'Eye and head coordination in reading: roles of head movement and cognitive control', *Vision Research*, 39(22), pp. 3761-3768.

Lee, C., Grossman, M., Morris, J., Stern, M.B. and Hurtig, H.I. (2003) 'Attentional resource and processing speed limitations during sentence processing in Parkinson's disease', *Brain and Language*, 85(3), pp. 347-356.

Lee, D.R., Taylor, J.-P. and Thomas, A.J. (2012a) 'Assessment of cognitive fluctuation in dementia: a systematic review of the literature', *International Journal of Geriatric Psychiatry*, 27(10), pp. 989-998.

Lee, H.C., Yanting Chee, D., Selander, H. and Falkmer, T. (2012b) 'Is it reliable to assess visual attention of drivers affected by Parkinson's disease from the backseat?-a simulator study', *Emerg Health Threats J*, 5(1), pp. 1-8.

Legters, K. (2002) 'Fear of Falling', *Physical Therapy*, 82(3), pp. 264-272.

Leigh, R.J. and Kennard, C. (2004) 'Using saccades as a research tool in the clinical neurosciences', *Brain*, 127(Pt 3), pp. 460-77.

Leisman, G., Braun-Benjamin, O. and Melillo, R. (2014) 'Cognitive-motor interactions of the basal ganglia in development', *Frontiers in Systems Neuroscience*, 8(16), pp. 1-18.

Lemos, J., Pereira, D., Almendra, L., Rebelo, D., Castelhano, J., Cunha, G., Januario, C., Goncalves, A., Cunha, L. and Castelo-Branco, M. (2015) 'Saccadic eye movements in Parkinson's disease: an eye-tracking and fMRI study (P1.321)', *Neurology*, 84(14 Supplement).

Lewis, G.N., Byblow, W.D. and Walt, S.E. (2000) 'Stride length regulation in Parkinson's disease: the use of extrinsic, visual cues', *Brain*, 123(10), pp. 2077-2090.

Lewis, S.J., Cools, R., Robbins, T.W., Dove, A., Barker, R.A. and Owen, A.M. (2003) 'Using executive heterogeneity to explore the nature of working memory deficits in Parkinson's disease', *Neuropsychologia*, 41(6), pp. 645-54.

Li, F., Munn, S. and Pelz, J. (2008) 'A model-based approach to video-based eye tracking', *Journal of Modern Optics*, 55(4-5), pp. 503-531.

Liddell, H.S. (1919) 'Eye-Movement during Fluctuation of Attention', *The American Journal of Psychology*, 30(3), pp. 241-252.

Lin, C.-C., Wagenaar, R., Young, D., Saltzman, E., Ren, X., Neargarder, S. and Cronin-Golomb, A. (2014) 'Effects of Parkinson's disease on optic flow perception for heading direction during navigation', *Experimental Brain Research*, 232(4), pp. 1343-1355.

Lin, M.Y., Gutierrez, P.R., Stone, K.L., Yaffe, K., Ensrud, K.E., Fink, H.A., Sarkisian, C.A., Coleman, A.L. and Mangione, C.M. (2004) 'Vision Impairment and Combined Vision and Hearing Impairment Predict Cognitive and Functional Decline in Older Women', *Journal of the American Geriatrics Society*, 52(12), pp. 1996-2002.

Litvan, I., Goldman, J.G., Tröster, A.I., Schmand, B.A., Weintraub, D., Petersen, R.C., Mollenhauer, B., Adler, C.H., Marder, K., Williams-Gray, C.H., Aarsland, D., Kulisevsky, J., Rodriguez-Oroz, M.C., Burn, D.J., Barker, R.A. and Emre, M. (2012) 'Diagnostic Criteria for Mild Cognitive Impairment in Parkinson's Disease: Movement Disorder Society Task Force Guidelines', *Movement disorders : official journal of the Movement Disorder Society*, 27(3), pp. 349-356.

Liu-Ambrose, T., Davis, J., Nagamatsu, L., Hsu, L., Katarynych, L. and Khan, K. (2010) 'Changes in executive functions and self-efficacy are independently associated with improved usual gait speed in older women', *BMC Geriatrics*, 10(1), pp. 1-8.

Liversedge, S.P. and Findlay, J.M. (2000) 'Saccadic eye movements and cognition', *Trends in Cognitive Sciences*, 4(1), pp. 6-14.

Lohnes, C.A. and Earhart, G.M. (2011) 'Saccadic Eye Movements Are Related to Turning Performance in Parkinson Disease', *J Parkinsons Dis*, 1(1), pp. 109-118.

Lohnes, C.A. and Earhart, G.M. (2012a) 'Effect of subthalamic deep brain stimulation on turning kinematics and related saccadic eye movements in Parkinson disease', *Exp Neurol*, 236(2), pp. 389-94.

Lohnes, C.A. and Earhart, G.M. (2012b) 'Movement orientation switching with the eyes and lower limb in Parkinson disease', *Parkinsonism Relat Disord*, 18(5), pp. 462-8.

Long, G.M. and Crambert, R.F. (1990) 'The nature and basis of age-related changes in dynamic visual acuity', *Psychol Aging*, 5(1), pp. 138-43.

Lopes, M.d.S., Melo, A.d.S. and Nóbrega, A.C. (2014) 'Delayed latencies of auditory evoked potential P300 are associated with the severity of Parkinson's disease in older patients', *Arquivos de Neuro-Psiquiatria*, 72, pp. 296-300.

Lord, S., Archibald, N., Mosimann, U., Burn, D. and Rochester, L. (2012) 'Dorsal rather than ventral visual pathways discriminate freezing status in Parkinson's disease', *Parkinsonism & Related Disorders*, 18(10), pp. 1094-1096.

Lord, S., Galna, B., Coleman, S., Burn, D. and Rochester, L. (2013a) 'Mild depressive symptoms are associated with gait impairment in early Parkinson's disease', *Movement Disorders*, 28(5), pp. 634-639.

Lord, S., Galna, B., Coleman, S., Yarnall, A., Burn, D. and Rochester, L. (2014) 'Cognition and gait show a selective pattern of association dominated by phenotype in incident Parkinson's disease', *Frontiers in Aging Neuroscience*, 6(249), pp. 1-9.

Lord, S., Galna, B. and Rochester, L. (2013b) 'Moving forward on gait measurement: toward a more refined approach', *Movement Disorders*, 28(11), pp. 1534-1543.

Lord, S., Rochester, L., Hetherington, V., Allcock, L.M. and Burn, D. (2010) 'Executive dysfunction and attention contribute to gait interference in 'off' state Parkinson's Disease', *Gait Posture*, 31(2), pp. 169-74.

Lord, S.R., Dayhew, J., Sc, B.A. and Howland, A. (2002) 'Multifocal Glasses Impair Edge-Contrast Sensitivity and Depth Perception and Increase the Risk of Falls in Older People', *Journal of the American Geriatrics Society*, 50(11), pp. 1760-1766.

Lotharius, J. and Brundin, P. (2002) 'Pathogenesis of Parkinson's disease: dopamine, vesicles and α-synuclein', *Nature Reviews Neuroscience*, 3(12), pp. 932-942.

Luck, S.J. and Vogel, E.K. (1997) 'The capacity of visual working memory for features and conjunctions', *Nature*, 390(6657), pp. 279-281.

Lückmann, H.C., Jacobs, H.I.L. and Sack, A.T. (2014) 'The cross-functional role of frontoparietal regions in cognition: internal attention as the overarching mechanism', *Progress in Neurobiology*, 116, pp. 66-86.

Lueck, C.J., Tanyeri, S., Crawford, T.J., Henderson, L. and Kennard, C. (1990) 'Antisaccades and remembered saccades in Parkinson's disease', *Journal of Neurology, Neurosurgery & Psychiatry*, 53(4), pp. 284-288.

Macaskill, M.R., Graham, C.F., Pitcher, T.L., Myall, D.J., Livingston, L., van Stockum, S., Dalrymple-Alford, J.C. and Anderson, T.J. (2012) 'The influence of motor and cognitive impairment upon visually-guided saccades in Parkinson's disease', *Neuropsychologia*, 50(14), pp. 3338-47.

MacAulay, R.K., Brouillette, R.M., Foil, H.C., Bruce-Keller, A.J. and Keller, J.N. (2014) 'A Longitudinal Study on Dual-Tasking Effects on Gait: Cognitive Change Predicts Gait Variance in the Elderly', *PLoS ONE*, 9(6), p. e99436.

Macdonald, R.G. and Tatler, B.W. (2013) 'Do as eye say: Gaze cueing and language in a real-world social interaction', *Journal of Vision*, 13(4).

MacHner, B., Klein, C., Sprenger, A., Baumbach, P., Pramstaller, P.P., Helmchen, C. and Heide, W. (2010) 'Eye movement disorders are different in Parkin-linked and idiopathic early-onset PD', *Neurology*, 75(2), pp. 125-128.

Mactier, K., Lord, S., Godfrey, A., Burn, D. and Rochester, L. (2015) 'The relationship between real world ambulatory activity and falls in incident Parkinson's disease: Influence of classification scheme', *Parkinsonism & related disorders*, 21(3), pp. 236-242.

Mahoney, J.R., Holtzer, R., Izzetoglu, M., Zemon, V., Verghese, J. and Allali, G. (2015) 'The role of prefrontal cortex during postural control in Parkinsonian syndromes a functional near-infrared spectroscopy study', *Brain Research*, 1633(1), pp. 126–138.

Maidan, I., Bernad-Elazari, H., Gazit, E., Giladi, N., Hausdorff, J.M. and Mirelman, A. (2015) 'Changes in oxygenated hemoglobin link freezing of gait to frontal activation in patients with Parkinson disease: an fNIRS study of transient motor-cognitive failures', *Journal of neurology*, 262(4), pp. 899-908.

Maillet, A., Pollak, P. and Debû, B. (2012) 'Imaging gait disorders in parkinsonism: a review', *Journal of Neurology, Neurosurgery & Psychiatry*, 83(10), pp. 986-993.

Mak, M.K., Yu, L. and Hui-Chan, C.W. (2013) 'The immediate effect of a novel audio-visual cueing strategy (simulated traffic lights) on dual-task walking in people with Parkinson's disease', *Eur J Phys Rehabil Med*, 49(2), pp. 153-9.

Maltz, M. and Shinar, D. (1999) 'Eye Movements of Younger and Older Drivers', *Human Factors: The Journal of the Human Factors and Ergonomics Society*, 41(1), pp. 15-25.

Mannan, S.K., Hodgson, T.L., Husain, M. and Kennard, C. (2008) 'Eye movements in visual search indicate impaired saliency processing in Parkinson's disease', 171, pp. 559-562.

Manyam, B.V. (1990) 'Paralysis agitans and levodopa in “Ayurveda”: Ancient Indian medical treatise', *Movement Disorders*, 5(1), pp. 47-48.

Marigold, D.S. and Patla, A.E. (2007) 'Gaze Fixation Patterns for Negotiating Complex Ground Terrain', *Neuroscience*, 144(1), pp. 302-313.

Marino, S., Sessa, E., Di Lorenzo, G., Lanzafame, P., Scullica, G., Bramanti, A., La Rosa, F., Iannizzotto, G., Bramanti, P. and Di Bella, P. (2007) 'Quantitative analysis of pursuit ocular movements in Parkinson's disease by using a video-based eye tracking system', *European Neurology*, 58(4), pp. 193-197.

Martin, K.L., Blizzard, L., Wood, A.G., Srikanth, V., Thomson, R., Sanders, L.M. and Callisaya, M.L. (2013) 'Cognitive Function, Gait, and Gait Variability in Older People: A Population-Based Study', *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 68(6), pp. 726-732.

Marx, S., Respondek, G., Stamelou, M., Dowiasch, S., Stoll, J., Bremmer, F., Oertel, W.H., Hoglinger, G.U. and Einhauser, W. (2012) 'Validation of mobile eye-tracking as novel and efficient means for differentiating progressive supranuclear palsy from Parkinson's disease', *Front Behav Neurosci*, 6(88), pp. 1-11.

Matsumoto, H., Terao, Y., Furubayashi, T., Yugeta, A., Fukuda, H., Emoto, M., Hanajima, R. and Ugawa, Y. (2011) 'Small saccades restrict visual scanning area in Parkinson's disease', *Mov Disord*, 26(9), pp. 1619-26.

Matsumoto, H., Terao, Y., Furubayashi, T., Yugeta, A., Fukuda, H., Emoto, M., Hanajima, R. and Ugawa, Y. (2012) 'Basal ganglia dysfunction reduces saccade amplitude during visual scanning in Parkinson’s disease', *Basal Ganglia*, 2(2), pp. 73-78.

Matsuoka, T., Narumoto, J., Shibata, K., Okamura, A., Nakamura, K., Nakamae, T., Yamada, K., Nishimura, T. and Fukui, K. (2011) 'Neural correlates of performance on the different scoring systems of the clock drawing test', *Neuroscience Letters*, 487(3), pp. 421-425.

Matthis, J.S. and Fajen, B.R. (2014) 'Visual control of foot placement when walking over complex terrain', *J Exp Psychol Hum Percept Perform*, 40(1), pp. 106-15.

Maurer, C., Mergner, T., Lucking, C.H. and Becker, W. (2001) 'Adaptive changes of saccadic eye–head coordination resulting from altered head posture in torticollis spasmodicus', *Brain*, 124, pp. 413–426.

Mazer, J.A. (2011) 'Spatial attention, feature-based attention, and saccades: three sides of one coin?', *Biol Psychiatry*, 69(12), pp. 1147-52.

McKeith, I.G. (2000) 'Spectrum of Parkinson's disease, Parkinson's dementia, and Lewy body dementia', *Neurol Clin*, 18(4), pp. 865-902.

McNab, F. and Klingberg, T. (2008) 'Prefrontal cortex and basal ganglia control access to working memory', *Nature Neuroscience*, 11, pp. 103-107.

McPeek, R.M., Skavenski, A.A. and Nakayama, K. (2000) 'Concurrent processing of saccades in visual search', *Vision Research*, 40(18), pp. 2499-2516.

Meara, J., Mitchelmore, E. and Hobson, P. (1999) 'Use of the GDS-15 geriatric depression scale as a screening instrument for depressive symptomatology in patients with Parkinson's disease and their carers in the community', *Age and Ageing*, 28(1), pp. 35-38.

Mele, M.L. and Federici, S. (2012) 'A psychotechnological review on eye-tracking systems: towards user experience', *Disabil Rehabil Assist Technol*, 7(4), pp. 261-81.

Melton, L.J., Leibson, C.L., Achenbach, S.J., Bower, J.H., Maraganore, D.M., Oberg, A.L. and Rocca, W.A. (2006) 'Fracture risk after the diagnosis of Parkinson's disease: influence of concomitant dementia', *Movement Disorders*, 21(9), pp. 1361-1367.

Menant, J.C., St George, R.J., Fitzpatrick, R.C. and Lord, S.R. (2010) 'Impaired depth perception and restricted pitch head movement increase obstacle contacts when dual-tasking in older people', *J Gerontol A Biol Sci Med Sci*, 65(7), pp. 751-7.

Menant, J.C., Sturnieks, D.L., Brodie, M.A.D., Smith, S.T. and Lord, S.R. (2014) 'Visuospatial Tasks Affect Locomotor Control More than Nonspatial Tasks in Older People', *PLoS ONE*, 9(10), p. e109802.

Menz, H.B., Lord, S.R. and Fitzpatrick, R.C. (2007) 'A structural equation model relating impaired sensorimotor function, fear of falling and gait patterns in older people', *Gait Posture*, 25(2), pp. 243-9.

Meppelink, A.M., de Jong, B.M., Renken, R., Leenders, K.L., Cornelissen, F.W. and van Laar, T. (2009) 'Impaired visual processing preceding image recognition in Parkinson's disease patients with visual hallucinations', *Brain*, 132(11), pp. 2980-2993.

Mestre, D., Blin, O., Serratrice, G. and Pailhous, J. (1990) 'Spatiotemporal contrast sensitivity differs in normal aging and Parkinson's disease', *Neurology*, 40(11), p. 1710.

Mesulam, M.M. (1990) 'Large scale neurocognitive networks and distributed processing for attention', *Annals of neurology*, 28(5), pp. 597-613.

Mesulam, M.M. (1999) 'Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events', *Philosophical Transactions of the Royal Society B: Biological Sciences*, 354(1387), pp. 1325-1346.

Mitchell, J.P., Macrae, C.N. and Gilchrist, I.D. (2002) 'Working memory and the suppression of reflexive saccades', *Journal of Cognitive Neuroscience*, 14(1), pp. 95-103.

Moehler, T. and Fiehler, K. (2014) 'Effects of spatial congruency on saccade and visual discrimination performance in a dual-task paradigm', *Vision Research*, 105, pp. 100-111.

Moes, E. and Lombardi, K.M. (2009) 'The relationship between contrast sensitivity, gait, and reading speed in Parkinson's disease', *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*, 16(2), pp. 121-32.

Mohammadi, F., Bruijn, S.M., Vervoort, G., van Wegen, E.E., Kwakkel, G., Verschueren, S. and Nieuwboer, A. (2015) 'Motor switching and motor adaptation deficits contribute to freezing of gait in Parkinson's disease', *Neurorehabilitation and neural repair*, 29(2), pp. 132-142.

Moher, D., Liberati, A., Tetzlaff, J. and Altman, D.G. (2009) 'Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement', *PLoS Med*, 6(7), p. e1000097.

Molloy, S.A., Rowan, E.N., O'Brien, J.T., McKeith, I.G., Wesnes, K. and Burn, D.J. (2006) 'Effect of levodopa on cognitive function in Parkinson's disease with and without dementia and dementia with Lewy bodies', *Journal of Neurology, Neurosurgery & Psychiatry*, 77(12), pp. 1323-1328.

Moore, S.T., MacDougall, H.G. and Ondo, W.G. (2008) 'Ambulatory monitoring of freezing of gait in Parkinson's disease', *Journal of neuroscience methods*, 167(2), pp. 340-348.

Morris, M., Iansek, R., McGinley, J., Matyas, T. and Huxham, F. (2005) 'Three-dimensional gait biomechanics in Parkinson's disease: Evidence for a centrally mediated amplitude regulation disorder', *Movement Disorders*, 20(1), pp. 40-50.

Morris, M.E., Huxham, F., McGinley, J., Dodd, K. and Iansek, R. (2001) 'The biomechanics and motor control of gait in Parkinson disease', *Clinical Biomechanics*, 16(6), pp. 459-470.

Morris, M.E., Iansek, R., Matyas, T.A. and Summers, J.J. (1994a) 'Ability to modulate walking cadence remains intact in Parkinson's disease', *Journal of Neurology, Neurosurgery & Psychiatry*, 57(12), pp. 1532-1534.

Morris, M.E., Iansek, R., Matyas, T.A. and Summers, J.J. (1994b) 'The pathogenesis of gait hypokinesia in Parkinson's disease', *Brain*, 117(5), pp. 1169-1181.

Morris, M.E., Iansek, R., Matyas, T.A. and Summers, J.J. (1996) 'Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms', *Brain*, 119 (Pt 2), pp. 551-68.

Morris, M.E., Martin, C.L. and Schenkman, M.L. (2010) 'Striding out with Parkinson disease: evidence-based physical therapy for gait disorders', *Phys Ther*, 90(2), pp. 280-8.

Mosimann, U.P., Mather, G., Wesnes, K.A., O'Brien, J.T., Burn, D.J. and McKeith, I.G. (2004) 'Visual perception in Parkinson disease dementia and dementia with Lewy bodies', *Neurology*, 63(11), pp. 2091-2096.

Mosimann, U.P., Müri, R.M., Burn, D.J., Felblinger, J., O'Brien, J.T. and McKeith, I.G. (2005) 'Saccadic eye movement changes in Parkinson's disease dementia and dementia with Lewy bodies', *Brain*, 128(6), pp. 1267-1276.

Mueller, R.O. and Hancock, G.R. (2008) 'Best practices in structural equation modeling', in Osborne, J.W.E. (ed.) *Best practices in quantitative methods*. Thousand Oaks, CA.: Sage, pp. 488-508.

Muilwijk, D., Verheij, S., Pel, J.J., Boon, A.J. and van der Steen, J. (2013) 'Changes in Timing and kinematics of goal directed eye-hand movements in early-stage Parkinson's disease', *Transl Neurodegener*, 2(1), p. 1.

Munakata, Y., Herd, S.A., Chatham, C.H., Depue, B.E., Banich, M.T. and O'Reilly, R.C. (2011) 'A unified framework for inhibitory control', *Trends in Cognitive Sciences*, 15(10), pp. 453-459.

Munoz-Hellin, E., Cano-de-la-Cuerda, R. and Miangolarra-Page, J.C. (2013) '[Visual cues as a therapeutic tool in Parkinson's disease. A systematic review]', *Rev Esp Geriatr Gerontol*, 48(4), pp. 190-7.

Munoz, D.P., Broughton, J.R., Goldring, J.E. and Armstrong, I.T. (1998) 'Age-related performance of human subjects on saccadic eye movement tasks', *Exp Brain Res*, 121, pp. 391-400.

Muralidharan, V., Balasubramani, P.P., Chakravarthy, V.S., Lewis, S.J.G. and Moustafa, A.A. (2013) 'A computational model of altered gait patterns in parkinson's disease patients negotiating narrow doorways', *Frontiers in Computational Neuroscience*, 7(190), pp. 1-16.

Musil, C.M., Jones, S.L. and Warner, C.D. (1998) 'Structural equation modeling and its relationship to multiple regression and factor analysis', *Research in Nursing & Health*, 21(3), pp. 271-281.

Muslimović, D., Post, B., Speelman, J.D., Schmand, B., de Haan, R.J. and For the, C.S.G. (2008) 'Determinants of disability and quality of life in mild to moderate Parkinson disease', *Neurology*, 70(23), pp. 2241-2247.

N'Guyen, S., Thurat, C. and Girard, B. (2014) 'Saccade learning with concurrent cortical and subcortical basal ganglia loops', *Frontiers in Computational Neuroscience*, 8(48), pp. 1-17.

Nadkarni, N.K., Zabjek, K., Lee, B., McIlroy, W.E. and Black, S.E. (2010) 'Effect of Working Memory and Spatial Attention Tasks on Gait in Healthy Young and Older Adults', *Motor control*, 14(2), pp. 195-210.

Nantel, J., McDonald, J.C., Tan, S. and Bronte-Stewart, H. (2012) 'Deficits in visuospatial processing contribute to quantitative measures of freezing of gait in Parkinson's disease', *Neuroscience*, 221, pp. 151-6.

Nasreddine, Z.S., Phillips, N.A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L. and Chertkow, H. (2005) 'The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment', *J Am Geriatr Soc*, 53(4), pp. 695-9.

Naushahi, M.J., Ah-Kye, L.A., Lee, P.Y., Anastasopoulos, D., Pavese, N., Bain, P.G., Bronstein, A.M. and Nandi, D. (2012) 'Efficacy of chronic bilateral STN-DBS on altered eye-to-foot co-ordination in standing advanced parkinsonian patients during large gaze and whole-body reorientations', *Parkinsonism and Related Disorders*, 18(Suppl 2), p. S148.

Nevalainen, S. and Sajaniemi, J. (2004) 'Comparison of three eye tracking devices in psychology of programming research', *Proceedings of the 16th Annual Workshop of the Psychology of Programming Interest Group (PPIG)*. Carlow, Ireland, April 2004. PPIG, pp. 151-158.

Nieuwboer, A. (2008) 'Cueing for freezing of gait in patients with Parkinson's disease: a rehabilitation perspective', *Mov Disord*, 23 Suppl 2, pp. S475-81.

Nieuwboer, A., Baker, K., Willems, A.M., Jones, D., Spildooren, J., Lim, I., Kwakkel, G., Van Wegen, E. and Rochester, L. (2009) 'The short-term effects of different cueing modalities on turn speed in people with Parkinson's disease', *Neurorehabil Neural Repair*, 23(8), pp. 831-6.

Noudoost, B., Chang, M.H., Steinmetz, N.A. and Moore, T. (2010) 'Top-down control of visual attention', *Curr Opin Neurobiol*, 20(2), pp. 183-90.

Noudoost, B. and Moore, T. (2011) 'The role of neuromodulators in selective attention', *Trends in Cognitive Sciences*, 15(12), pp. 585-591.

Nutt, J.G., Bloem, B.R., Giladi, N., Hallett, M., Horak, F.B. and Nieuwboer, A. (2011) 'Freezing of gait: moving forward on a mysterious clinical phenomenon', *The Lancet Neurology*, 10(8), pp. 734-744.

Nystrom, M., Andersson, R., Holmqvist, K. and van de Weijer, J. (2013) 'The influence of calibration method and eye physiology on eyetracking data quality', *Behav Res Methods*, 45(1), pp. 272-88.

Nystrom, M. and Holmqvist, K. (2010) 'An adaptive algorithm for fixation, saccade, and glissade detection in eyetracking data', *Behav Res Methods*, 42(1), pp. 188-204.

O'Callaghan, C., Naismith, S.L., Hodges, J.R., Lewis, S.J.G. and Hornberger, M. (2013) 'Fronto-striatal atrophy correlates of inhibitory dysfunction in Parkinson's disease versus behavioural variant frontotemporal dementia', *Cortex*, 49(7), pp. 1833-1843.

O'Connor, D.H., Fukui, M.M., Pinsk, M.A. and Kastner, S. (2002) 'Attention modulates responses in the human lateral geniculate nucleus', *Nature neuroscience*, 5(11), pp. 1203-1209.

Oatley, K., Parrott, W.G., Smith, C. and Watts, F. (2011) 'Cognition and Emotion over twenty-five years', *Cognition and Emotion*, 25(8), pp. 1341-1348.

Obeso, I., Wilkinson, L., Casabona, E., Bringas, M., Álvarez, M., Álvarez, L., Pavón, N., Rodríguez-Oroz, M.-C., Macías, R., Obeso, J. and Jahanshahi, M. (2011a) 'Deficits in inhibitory control and conflict resolution on cognitive and motor tasks in Parkinson's disease', *Experimental Brain Research*, 212(3), pp. 371-384.

Obeso, I., Wilkinson, L. and Jahanshahi, M. (2011b) 'Levodopa medication does not influence motor inhibition or conflict resolution in a conditional stop-signal task in Parkinson's disease', *Experimental brain research*, 213(4), pp. 435-445.

Obeso, J.A., Marin, C., Rodriguez-Oroz, C., Blesa, J., Benitez-Temiño, B., Mena-Segovia, J., Rodríguez, M. and Olanow, C.W. (2008a) 'The basal ganglia in Parkinson's disease: current concepts and unexplained observations', *Annals of neurology*, 64(S2), pp. S30-S46.

Obeso, J.A., Rodríguez-Oroz, M.C., Benitez-Temino, B., Blesa, F.J., Guridi, J., Marin, C. and Rodriguez, M. (2008b) 'Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease', *Movement Disorders*, 23(S3), pp. S548-S559.

Okuma, Y. (2006) 'Freezing of gait in Parkinson's disease', *J Neurol*, 253 Suppl 7, pp. VII27-32.

Olesen, J. and Leonardi, M. (2003) 'The burden of brain diseases in Europe', *European Journal of Neurology*, 10(5), pp. 471-477.

Omoto, S., Kuroiwa, Y., Otsuka, S., Baba, Y., Wang, C., Li, M., Mizuki, N., Ueda, N., Koyano, S. and Suzuki, Y. (2010) 'P1 and P2 components of human visual evoked potentials are modulated by depth perception of 3-dimensional images', *Clinical Neurophysiology*, 121(3), pp. 386-391.

Onu, M., Badea, L., Roceanu, A., Tivarus, M. and Bajenaru, O. (2015) 'Increased connectivity between sensorimotor and attentional areas in Parkinson's disease', *Neuroradiology*, 57(9), pp. 957-968.

Ottosson, J., Lavesson, L., Pinzke, S. and Grahn, P. (2015) 'The Significance of Experiences of Nature for People with Parkinson's Disease, with Special Focus on Freezing of Gait—The Necessity for a Biophilic Environment. A Multi-Method Single Subject Study', *International Journal of Environmental Research and Public Health*, 12(7), pp. 7274-7299.

Owen, A.M. (2004) 'Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry', *Neuroscientist*, 10(6), pp. 525-37.

Owsley, C. (2011) 'Aging and vision', *Vision Res*, 51(13), pp. 1610-22.

Pagonabarraga, J. and Kulisevsky, J. (2012) 'Cognitive impairment and dementia in Parkinson's disease', *Neurobiology of disease*, 46(3), pp. 590-596.

Pahapill, P.A. and Lozano, A.M. (2000) 'The pedunculopontine nucleus and Parkinson's disease', *Brain*, 123(9), pp. 1767-1783.

Palavra, N.C., Naismith, S.L. and Lewis, S.J.G. (2013) 'Mild Cognitive Impairment in Parkinson's Disease: A Review of Current Concepts', *Neurology Research International*, 1(2013), pp. 1-8.

Parker, K.L., Lamichhane, D., Caetano, M.S. and Narayanan, N.S. (2013) 'Executive dysfunction in Parkinson's disease and timing deficits', *Frontiers in Integrative Neuroscience*, 7(75), pp. 1-9.

Parkinson, J. (2002) 'An Essay on the Shaking Palsy', *The Journal of Neuropsychiatry and Clinical Neurosciences*, 14(2), pp. 223-236.

Pashler, H., Carrier, M. and Hoffman, J. (1993) 'Saccadic eye movements and dual-task interference', *Q J Exp Psychol A*, 46(1), pp. 51-82.

Patla, A.E. (1998) 'How Is Human Gait Controlled by Vision', *Ecological Psychology*, 10(3-4), pp. 287-302.

Patla, A.E. and Greig, M. (2006) 'Any way you look at it, successful obstacle negotiation needs visually guided on-line foot placement regulation during the approach phase', *Neuroscience Letters*, 397(1-2), pp. 110-114.

Paul, S.S., Allen, N.E., Sherrington, C., Heller, G., Fung, V.S., Close, J.C., Lord, S.R. and Canning, C.G. (2014) 'Risk factors for frequent falls in people with Parkinson's disease', *J Parkinsons Dis*, 4(4), pp. 699-703.

Pearson, D. and Sahraie, A. (2003) 'Oculomotor control and the maintenance of spatially and temporally distributed events in visuo-spatial working memory', *The Quarterly Journal of Experimental Psychology: Section A*, 56(7), pp. 1089-1111.

Pedrotti, M., Lei, S., Dzaack, J. and Rotting, M. (2011) 'A data-driven algorithm for offline pupil signal preprocessing and eyeblink detection in low-speed eye-tracking protocols', *Behav Res Methods*, 43(2), pp. 372-83.

Peltsch, A., Hemraj, A., Garcia, A. and Munoz, D.P. (2011) 'Age-related trends in saccade characteristics among the elderly', *Neurobiol Aging*, 32(4), pp. 669-79.

Pelz, J., Hayhoe, M. and Loeber, R. (2001) 'The coordination of eye, head, and hand movements in a natural task', *Experimental Brain Research*, 139(3), pp. 266-277.

Pelz , J.B. and Canosa, R. (2001) 'Oculomotor behavior and perceptual strategies in complex tasks', *Vision Research*, 41(25-26), pp. 3587-96.

Peraza, L.R., Kaiser, M., Firbank, M., Graziadio, S., Bonanni, L., Onofrj, M., Colloby, S.J., Blamire, A., O'Brien, J. and Taylor, J.-P. (2014) 'fMRI resting state networks and their association with cognitive fluctuations in dementia with Lewy bodies', *NeuroImage: Clinical*, 4, pp. 558-565.

Pereira, J.B., Junque, C., Marti, M.J., Ramirez-Ruiz, B., Bargallo, N. and Tolosa, E. (2009) 'Neuroanatomical substrate of visuospatial and visuoperceptual impairment in Parkinson's disease', *Mov Disord*, 24(8), pp. 1193-9.

Perneczky, R., Ghosh, B.C.P., Hughes, L., Carpenter, R.H.S., Barker, R.A. and Rowe, J.B. (2011) 'Saccadic latency in Parkinson's disease correlates with executive function and brain atrophy, but not motor severity', *Neurobiology of Disease*, 43(1), pp. 79-85.

Pestilli, F. and Carrasco, M. (2005) 'Attention enhances contrast sensitivity at cued and impairs it at uncued locations', *Vision Research*, 45(14), pp. 1867-1875.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G. and Kokmen, E. (1999) 'Mild cognitive impairment: Clinical characterization and outcome', *Archives of Neurology*, 56(3), pp. 303-308.

Petersen, S.E. and Posner, M.I. (2012) 'The Attention System of the Human Brain: 20 Years After', *Annual review of neuroscience*, 35(1), pp. 73-89.

Peterson, D.S., Pickett, K.A., Duncan, R., Perlmutter, J. and Earhart, G.M. (2014) 'Gait-Related Brain Activity in People with Parkinson Disease with Freezing of Gait', *PLoS ONE*, 9(3), p. e90634.

Peterson, D.S. and Smulders, K. (2015) 'Cues and attention in Parkinsonian gait: Potential mechanisms and future directions', *Frontiers in Neurology*, 6(255), pp. 1-5.

Pfeiffer, H.C.V., Løkkegaard, A., Zoetmulder, M., Friberg, L. and Werdelin, L. (2014) 'Cognitive impairment in early-stage non-demented Parkinson's disease patients', *Acta Neurologica Scandinavica*, 129(5), pp. 307-318.

Pierrot-Deseilligny, C., Milea, D. and Müri, R.M. (2004) 'Eye movement control by the cerebral cortex', *Current Opinion in Neurology*, 17(1), pp. 17-25.

Pieruccini-Faria, F., Martens, K.A., Silveira, C., Jones, J.A. and Almeida, Q.J. (2014) 'Interactions between cognitive and sensory load while planning and controlling complex gait adaptations in Parkinson's disease', *BMC Neurol*, 14(1), p. 250.

Pinnock, R.A., McGivern, R.C., Forbes, R. and Gibson, J.M. (2010) 'An exploration of ocular fixation in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy', *Journal of Neurology*, 257(4), pp. 533-539.

Plotnik, M., Dagan, Y., Gurevich, T., Giladi, N. and Hausdorff, J.M. (2011) 'Effects of cognitive function on gait and dual tasking abilities in patients with Parkinson's disease suffering from motor response fluctuations', *Experimental brain research*, 208(2), pp. 169-179.

Plotnik, M., Giladi, N. and Hausdorff, J.M. (2009) 'Bilateral coordination of gait and Parkinson's disease: the effects of dual tasking', *J Neurol Neurosurg Psychiatry*, 80(3), pp. 347-50.

Porterfield, W. (1752) 'An essay concerning the motions of our eyes. Part II, Of their internal motions', in *Medical essays and observations*. Edinburgh: Hamilton, Balfour & Neill.

Posner, M.I. and Boies, S.J. (1971) 'Components of attention', *Psychological review*, 78(5), p. 391.

Posner, M.I. and Petersen, S.E. (1990) 'The attention system of the human brain', *Annu Rev Neurosci*, 13(1), pp. 25-42.

Posner, M.I. and Raichle, M.E. (1996) *Images of mind (revised)*. New York.

Posner, M.I. and Rothbart, M.K. (2007) 'Research on attention networks as a model for the integration of psychological science', *Annu Rev Psychol*, 58(1), pp. 1-23.

Possin, K.L. (2010) 'Visual spatial cognition in neurodegenerative disease', *Neurocase*, 16(6), pp. 466-87.

Possin, K.L., Filoteo, J.V., Song, D.D. and Salmon, D.P. (2008) 'Spatial and object working memory deficits in Parkinson's disease are due to impairment in different underlying processes', *Neuropsychology*, 22(5), pp. 585-595.

Poujois, A., Vidailhet, M., Trocello, J.M., Bourdain, F., Gaymard, B. and Rivaud-Péchoux, S. (2007) 'Effect of gabapentin on oculomotor control and parkinsonism in patients with progressive supranuclear palsy', *European Journal of Neurology*, 14(9), pp. 1060-1062.

Praamstra, P., Stegeman, D.F., Cools, A.R. and Horstink, M.W. (1998) 'Reliance on external cues for movement initiation in Parkinson's disease. Evidence from movement-related potentials', *Brain*, 121(Pt 1), pp. 167-77.

Preacher, K.J. (2006) 'Quantifying parsimony in structural equation modeling', *Multivariate Behavioral Research*, 41(3), pp. 227-259.

Price, M.J., Feldman, R.G., Adelberg, D. and Kayne, H. (1992) 'Abnormalities in color vision and contrast sensitivity in Parkinson's disease', *Neurology*, 42(4), p. 887.

Proudlock, F.A., Shekhar, H. and Gottlob, I. (2004) 'Age-related changes in head and eye coordination', *Neurobiol Aging*, 25(10), pp. 1377-85.

Putcha, D., Ross, R.S., Rosen, M.L., Norton, D.J., Cronin-Golomb, A., Somers, D.C. and Stern, C.E. (2014) 'Functional correlates of optic flow motion processing in Parkinson's disease', *Front Integr Neurosci*, 8(57), pp. 1-7.

Rae, C.L., Hughes, L.E., Anderson, M.C. and Rowe, J.B. (2015) 'The Prefrontal Cortex Achieves Inhibitory Control by Facilitating Subcortical Motor Pathway Connectivity', *The Journal of Neuroscience*, 35(2), pp. 786-794.

Rand, M.K., Lemay, M., Squire, L.M., Shimansky, Y.P. and Stelmach, G.E. (2010) 'Control of aperture closure initiation during reach-to-grasp movements under manipulations of visual feedback and trunk involvement in Parkinson's disease', *Exp Brain Res*, 201(3), pp. 509-25.

Rapport, L.J., Millis, S.R. and Bonello, P.J. (1998) 'Validation of the Warrington theory of visual processing and the Visual Object and Space Perception Battery', *J Clin Exp Neuropsychol*, 20(2), pp. 211-20.

Rascol, O., Sabatini, U., Chollet, F., Celsis, P., Montastruc, J.-L., Marc-Vergnes, J.-P. and Rascol, A. (1992) 'Supplementary and primary sensory motor area activity in Parkinson's disease: regional cerebral blood flow changes during finger movements and effects of apomorphine', *Archives of neurology*, 49(2), pp. 144-148.

Redgrave, P., Rodriguez, M., Smith, Y., Rodriguez-Oroz, M.C., Lehericy, S., Bergman, H., Agid, Y., DeLong, M.R. and Obeso, J.A. (2010) 'Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease', *Nature reviews. Neuroscience*, 11(11), pp. 760-772.

Reed-Jones, R.J., Solis, G.R., Lawson, K.A., Loya, A.M., Cude-Islas, D. and Berger, C.S. (2013) 'Vision and falls: A multidisciplinary review of the contributions of visual impairment to falls among older adults', *Maturitas*, 75(1), pp. 22-28.

Reingold, E.M. and Stampe, D.M. (2002) 'Saccadic Inhibition in Voluntary and Reflexive Saccades', *Journal of Cognitive Neuroscience*, 14(3), pp. 371-388.

Rektorova, I., Biundo, R., Marecek, R., Weis, L., Aarsland, D. and Antonini, A. (2014) 'Grey Matter Changes in Cognitively Impaired Parkinson's Disease Patients', *PLoS ONE*, 9(1), p. e85595.

Reynolds, J.H., Pasternak, T. and Desimone, R. (2000) 'Attention Increases Sensitivity of V4 Neurons', *Neuron*, 26(3), pp. 703-714.

Ricciardi, L., Bloem, B.R., Snijders, A.H., Daniele, A., Quaranta, D., Bentivoglio, A.R. and Fasano, A. (2014) 'Freezing of gait in Parkinson's disease: The paradoxical interplay between gait and cognition', *Parkinsonism & Related Disorders*, 20(8), pp. 824-829.

Richards, M., Cote, L.J. and Stern, Y. (1993) 'The relationship between visuospatial ability and perceptual motor function in Parkinson's disease', *Journal of Neurology, Neurosurgery & Psychiatry*, 56(4), pp. 400-406.

Ridderinkhof, K.R. and Wijnen, J.G. (2011) 'More than meets the eye: age differences in the capture and suppression of oculomotor action', *Front Psychol*, 2(267), pp. 1-8.

Rittman, T., Ghosh, B.C., McColgan, P., Breen, D.P., Evans, J., Williams-Gray, C.H., Barker, R.A. and Rowe, J.B. (2013) 'The Addenbrooke's Cognitive Examination for the differential diagnosis and longitudinal assessment of patients with parkinsonian disorders', *J Neurol Neurosurg Psychiatry*, 84(5), pp. 544-51.

Robbins, T.W. and Cools, R. (2014) 'Cognitive deficits in Parkinson's disease: A cognitive neuroscience perspective', *Movement Disorders*, 29(5), pp. 597-607.

Robinson, F.R., Straube, A. and Fuchs, A.F. (1993) 'Role of the caudal fastigial nucleus in saccade generation. II. Effects of muscimol inactivation', *Journal of Neurophysiology*, 70(5), pp. 1741-1758.

Rochester, L., Baker, K., Hetherington, V., Jones, D., Willems, A.-M., Kwakkel, G., Van Wegen, E., Lim, I. and Nieuwboer, A. (2010) 'Evidence for motor learning in Parkinson's disease: Acquisition, automaticity and retention of cued gait performance after training with external rhythmical cues', *Brain Research*, 1319(0), pp. 103-111.

Rochester, L., Chastin, S.F.M., Lord, S., Baker, K. and Burn, D.J. (2012a) 'Understanding the impact of deep brain stimulation on ambulatory activity in advanced Parkinson's disease', *Journal of neurology*, 259(6), pp. 1081-1086.

Rochester, L., Galna, B., Lord, S. and Burn, D. (2014) 'The nature of dual-task interference during gait in incident Parkinson's disease', *Neuroscience*, 265, pp. 83-94.

Rochester, L., Hetherington, V., Jones, D., Nieuwboer, A., Willems, A.-M., Kwakkel, G. and Van Wegen, E. (2004) 'Attending to the task: Interference effects of functional tasks on walking in Parkinson's disease and the roles of cognition, depression, fatigue, and balance', *Archives of Physical Medicine and Rehabilitation*, 85(10), pp. 1578-1585.

Rochester, L., Hetherington, V., Jones, D., Nieuwboer, A., Willems, A.-M., Kwakkel, G. and Van Wegen, E. (2005) 'The Effect of External Rhythmic Cues (Auditory and Visual) on Walking During a Functional Task in Homes of People With Parkinson's Disease', *Archives of Physical Medicine and Rehabilitation*, 86(5), pp. 999-1006.

Rochester, L., Nieuwboer, A., Baker, K., Hetherington, V., Willems, A.M., Chavret, F., Kwakkel, G., Van Wegen, E., Lim, I. and Jones, D. (2007) 'The attentional cost of external rhythmical cues and their impact on gait in Parkinson's disease: effect of cue modality and task complexity', *J Neural Transm*, 114(10), pp. 1243-8.

Rochester, L., Nieuwboer, A., Baker, K., Hetherington, V., Willems, A.M., Kwakkel, G., Van Wegen, E., Lim, I. and Jones, D. (2008) 'Walking speed during single and dual tasks in Parkinson's disease: which characteristics are important?', *Mov Disord*, 23(16), pp. 2312-8.

Rochester, L., Nieuwboer, A. and Lord, S. (2011) 'Physiotherapy for Parkinson's disease: defining evidence within a framework for intervention', *Neurodegenerative Disease Management*, 1(1), pp. 57-65.

Rochester, L., Yarnall, A.J., Baker, M.R., David, R.V., Lord, S., Galna, B. and Burn, D.J. (2012b) 'Cholinergic dysfunction contributes to gait disturbance in early Parkinson's disease', *Brain*, 135(9), pp. 2779-2788.

Roemmich, R.T., Hack, N., Akbar, U. and Hass, C.J. (2014) 'Effects of dopaminergic therapy on locomotor adaptation and adaptive learning in persons with Parkinson's disease', *Behavioural Brain Research*, 268, pp. 31-39.

Rosenberg-Katz, K., Herman, T., Jacob, Y., Giladi, N., Hendler, T. and Hausdorff, J.M. (2013) 'Gray matter atrophy distinguishes between Parkinson disease motor subtypes', *Neurology*, 80(16), pp. 1476-1484.

Rosner, B.A. (2006) *Fundamentals of Biostatistics*. illustrated edn. Boston, USA: Thomson-Brooks/Cole.

Ross, J.E., Bron, A.J. and Clarke, D.D. (1984) 'Contrast sensitivity and visual disability in chronic simple glaucoma', *Br J Ophthalmol*, 68(11), pp. 821-7.

Royall, D.R., Cordes, J.A. and Polk, M. (1998) 'CLOX: an executive clock drawing task', *J Neurol Neurosurg Psychiatry*, 64(5), pp. 588-94.

Royall, D.R., Espino, D.V., Polk, M.J., Verdeja, R., Vale, S., Gonzales, H., Palmer, R.R. and Markides, K.P. (2003) 'Validation of a Spanish translation of the CLOX for use in Hispanic samples: the Hispanic EPESE study', *International Journal of Geriatric Psychiatry*, 18(2), pp. 135-141.

Rubinstein, T.C., Giladi, N. and Hausdorff, J.M. (2002) 'The power of cueing to circumvent dopamine deficits: a review of physical therapy treatment of gait disturbances in Parkinson's disease', *Mov Disord*, 17(6), pp. 1148-60.

Sacrey, L.A., Clark, C.A. and Whishaw, I.Q. (2009) 'Music attenuates excessive visual guidance of skilled reaching in advanced but not mild Parkinson's disease', *PLoS ONE [Electronic Resource]*, 4(8), p. e6841.

Sacrey, L.A., Travis, S.G. and Whishaw, I.Q. (2011) 'Drug treatment and familiar music aids an attention shift from vision to somatosensation in Parkinson's disease on the reach-to-eat task', *Behav Brain Res*, 217(2), pp. 391-8.

Salthouse, T.A. (1996) 'The processing-speed theory of adult age differences in cognition', *Psychol Rev*, 103(3), pp. 403-28.

Salthouse, T.A. (2005) 'Relations Between Cognitive Abilities and Measures of Executive Functioning', *Neuropsychology*, 19(4), pp. 532-545.

Salvucci, D.D. and Anderson, J.R. (2001) 'Automated Eye-Movement Protocol Analysis', *HUMAN-COMPUTER INTERACTION*, 16, pp. 39–86.

Salvucci, D.D. and Goldberg, J.H. (2000) 'Identifying Fixations and Saccades in Eye-Tracking Protocols', *Eye Tracking Research & Applications Symposium*. Palm Beach Gardens, FL, USA. pp. 71-78.

Sampaio, J., Bobrowicz-Campos, E., Andre, R., Almeida, I., Faria, P., Januario, C., Freire, A. and Castelo-Branco, M. (2011) 'Specific impairment of visual spatial covert attention mechanisms in Parkinson's disease', *Neuropsychologia*, 49(1), pp. 34-42.

Sarasso, E., Agosta, F., Canu, E., Volontè, M.A., Sarro, L., Galantucci, S., Gatti, R., Falini, A., Comi, G. and Filippi, M. (2015) 'Brain structural and functional abnormalities in Parkinson’s disease patients with freezing of gait (I3-2B)', *Neurology*, 84(14. Supplement I3-2B).

Sauerbier, A. and Ray Chaudhuri, K. (2013) 'Parkinson's disease and vision', *Basal Ganglia*, 3(3), pp. 159–163.

Sawaguchi, T. and Goldman-Rakic, P.S. (1991) 'D1 dopamine receptors in prefrontal cortex: involvement in working memory', *Science*, 251(4996), pp. 947-950.

Schettino, L.F., Adamovich, S.V., Hening, W., Tunik, E., Sage, J. and Poizner, H. (2006) 'Hand preshaping in Parkinson's disease: effects of visual feedback and medication state', *Exp Brain Res*, 168(1-2), pp. 186-202.

Schwed, M.A., Getrost, T., Schmidtbleicher, D. and Haas, C.T. (2013) 'Biomechanical Analysis of Gait Adaptability in Parkinson's Disease', *Open Rehabilitation Journal*, 6, pp. 49-58.

Seichepine, D.R., Neargarder, S., Davidsdottir, S., Reynolds, G.O. and Cronin-Golomb, A. (2015) 'Side and type of initial motor symptom influences visuospatial functioning in Parkinson's disease', *J Parkinsons Dis*, 5(1), pp. 75-83.

Seidler, R.D., Bernard, J.A., Burutolu, T.B., Fling, B.W., Gordon, M.T., Gwin, J.T., Kwak, Y. and Lipps, D.B. (2010) 'Motor control and aging: Links to age-related brain structural, functional, and biochemical effects', *Neuroscience & Biobehavioral Reviews*, 34(5), pp. 721-733.

Seidlits, S.K., Reza, T., Briand, K.A. and Sereno, A.B. (2003) 'Voluntary spatial attention has different effects on voluntary and reflexive saccades', *ScientificWorldJournal*, 3, pp. 881-902.

Seiss, E. and Praamstra, P. (2004) 'The basal ganglia and inhibitory mechanisms in response selection: evidence from subliminal priming of motor responses in Parkinson's disease', *Brain*, 127(2), pp. 330-339.

Serchi, V., Peruzzi, A., Cereatti, A. and Della Croce, U. (2014a) 'Tracking gaze while walking on a treadmill: Spatial accuracy and limits of use of a stationary remote eye-tracker', *Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE*. Chicago, IL, 26-30 Aug. 2014. IEEE, pp. 3727-3730.

Serchi, V., Peruzzi, V., Cereatti, A. and Della Croce, U. (2014b) 'Performance of a remote eye-tracker in measuring gaze during walking', *20th IMEKO TC4 International Symposium and 18th International Workshop on ADC Modelling and Testing Research on Electric and Electronic Measurement for the Economic Upturn*. Benevento, Italy, September 15-17. IEEE, pp. 770-774.

Shafiq-Antonacci, R., Maruff, P., Whyte, S., Tyler, P., Dudgeon, P. and Currie, J. (1999) 'The effects of age and mood on saccadic function in older individuals', *J Gerontol B Psychol Sci Soc Sci*, 54(6), pp. P361-8.

Shaikh, A.G., Wong, A.L., Zee, D.S. and Jinnah, H.A. (2013) 'Keeping your head on target', *J Neurosci*, 33(27), pp. 11281-95.

Shibasaki, H., Tsuji, S. and Kuroiwa, Y. (1979) 'Oculomotor abnormalities in Parkinson's disease', *Archives of Neurology*, 36(6), pp. 360-364.

Shimizu, N., Naito, M. and Yoshida, M. (1981) 'Eye-head co-ordination in patients with Parkinsonism and cerebellar ataxia', *Journal of Neurology, Neurosurgery & Psychiatry*, 44(6), pp. 509-515.

Shin, S.-s., An, D.-h. and Yoo, W.-g. (2015) 'Comparison of gait velocity and center of mass acceleration under conditions of disrupted somatosensory input from the feet during the navigation of obstacles in older adults with good and poor visual acuity', *European Geriatric Medicine*, 6(3), pp. 208-213.

Shine, J.M., Matar, E., Ward, P.B., Bolitho, S.J., Pearson, M., Naismith, S.L. and Lewis, S.J.G. (2013a) 'Differential Neural Activation Patterns in Patients with Parkinson's

Disease and Freezing of Gait in Response to Concurrent Cognitive and Motor Load', *PLoS ONE*, 8(1), p. e52602.

Shine, J.M., Matar, E., Ward, P.B., Frank, M.J., Moustafa, A.A., Pearson, M., Naismith, S.L. and Lewis, S.J.G. (2013b) 'Freezing of gait in Parkinson's disease is associated with functional decoupling between the cognitive control network and the basal ganglia', *Brain*, 136(Pt 12), pp. 3671-81.

Shine, J.M., Moustafa, A.A., Matar, E., Frank, M.J. and Lewis, S.J.G. (2013c) 'The role of frontostriatal impairment in freezing of gait in Parkinson's disease', *Frontiers in Systems Neuroscience*, 7, p. 61.

Simpson, W.A. (1993) 'Optic Flow and Depth Perception', *Spatial Vision*, 7(1), pp. 35-75.

Simuni, T. and Sethi, K. (2008) 'Nonmotor manifestations of Parkinson's disease', *Ann Neurol*, 64 Suppl 2, pp. S65-80.

Sjostrand, J., Laatikainen, L., Hirvela, H., Popovic, Z. and Jonsson, R. (2011) 'The decline in visual acuity in elderly people with healthy eyes or eyes with early age-related maculopathy in two Scandinavian population samples', *Acta Ophthalmol*, 89(2), pp. 116-23.

Sloane, M.E., Owsley, C. and Jackson, C.A. (1988) 'Aging and luminance-adaptation effects on spatial contrast sensitivity', *JOSA A*, 5(12), pp. 2181-2190.

Smith, T., Gildeh, N. and Holmes, C. (2007) 'The Montreal Cognitive Assessment: validity and utility in a memory clinic setting', *Can J Psychiatry*, 52(5), pp. 329-32.

Snijders, A.H., Leunissen, I., Bakker, M., Overeem, S., Helmich, R.C., Bloem, B.R. and Toni, I. (2011) 'Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait', *Brain*, 134(Pt 1), pp. 59-72.

Soumare, A., Tavernier, B., Alperovitch, A., Tzourio, C. and Elbaz, A. (2009) 'A cross-sectional and longitudinal study of the relationship between walking speed and cognitive function in community-dwelling elderly people', *Journals of Gerontology Series A-Biological Sciences & Medical Sciences*, 64(10), pp. 1058-65.

Spaulding, S.J., Patla, A.E., Elliott, D.B., Flanagan, J., Rietdyk, S. and Brown, S. (1994) 'Waterloo Vision and Mobility Study: Gait Adaptations to Altered Surfaces in Individuals with Age-Related Maculopathy', *Optometry & Vision Science*, 71(12), pp. 770-777.

Sperling, G. (1960) 'The information available in brief visual presentations', *Psychological monographs: General and applied*, 74(11), p. 1.

Springer, S., Giladi, N., Peretz, C., Yogev, G., Simon, E.S. and Hausdorff, J.M. (2006) 'Dual-tasking effects on gait variability: the role of aging, falls, and executive function', *Mov Disord*, 21(7), pp. 950-7.

Srivastava, A., Sharma, R., Sood, S.K., Shukla, G., Goyal, V. and Behari, M. (2014) 'Saccadic eye movements in Parkinson's disease', *Indian Journal of Ophthalmology*, 62(5), pp. 538-544.

Stamenović, J., Đurić, S., Jolić, M., Živadinović, B. and Đurić, V. (2004) 'Examination of cognitive functions in patients with Parkinsons disease', *Facta Universitatis*, 11(2), pp. 80-86.

Stegemoller, E.L., Wilson, J.P., Hazamy, A., Shelley, M.C., Okun, M.S., Altmann, L.J. and Hass, C.J. (2014) 'Associations between cognitive and gait performance during single- and dual-task walking in people with Parkinson disease', *Phys Ther*, 94(6), pp. 757-66.

Stoerig, P. and Cowey, A. (1997) 'Blindsight in man and monkey', *Brain*, 120(3), pp. 535-559.

Stuart, S., Alcock, L., Galna, B., Lord, S. and Rochester, L. (2014a) 'The measurement of visual sampling during real-world activity in Parkinson's disease and healthy controls: A structured literature review', *J Neurosci Methods*, 222, pp. 175-88.

Stuart, S., Galna, B., Lord, S., Rochester, L. and Godfrey, A. (2014b) 'Quantifying Saccades While Walking: Validity of a Novel Velocity-Based Algorithm for Mobile Eye Tracking', *Engineering in Medicine and Biology Society, (EMBC) 2014. 36th Annual International Conference of the IEEE*. Chicago, Illinois, USA, 26-30 Aug. 2014. IEEE, pp. 5739 - 5742.

Suna, S., Tahir Kurtulus, Y. and Nese Gungor, Y. (2014) 'Evaluation of cognitive functions in Parkinson’s patients without dementia with auditory event related potential (P300)', *Düþünen Adam*, 27(2), pp. 132-137.

Svenningsson, P., Westman, E., Ballard, C. and Aarsland, D. (2012) 'Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment', *Lancet Neurol*, 11(8), pp. 697-707.

Sweeney, J.A., Rosano, C., Berman, R.A. and Luna, B. (2001) 'Inhibitory control of attention declines more than working memory during normal aging', *Neurobiology of Aging*, 22(1), pp. 39-47.

Sweeney, J.A., Strojwas, M.H., Mann, J.J. and Thase, M.E. (1998) 'Prefrontal and Cerebellar Abnormalities in Major Depression: Evidence from Oculomotor Studies', *Biological Psychiatry*, 43(8), pp. 584-594.

Swigler, C., Martin, A., Milice, F., Walley, M., LaPointe, L.L., Maitland, G. and Saunders, C. (2012) 'Contrast sensitivity visual acuity is deficient in Parkinson's disease and degrades motor performance', *Parkinsonism and Related Disorders*, 18(Supplement 2 (2.113)), pp. S104-S105.

t Hart, B.M., Schmidt, H.C.E.F., Klein-Harmeyer, I. and Einhäuser, W. (2013) 'Attention in natural scenes: contrast affects rapid visual processing and fixations alike', *Philos Trans R Soc Lond B*, 368(1628), pp. 1-10.

Takakusaki, K. (2013) 'Neurophysiology of gait: from the spinal cord to the frontal lobe', *Mov Disord*, 28(11), pp. 1483-91.

Tang, H., Huang, J., Nie, K., Gan, R., Wang, L., Zhao, J., Huang, Z., Zhang, Y. and Wang, L. (2015) 'Cognitive profile of Parkinson's disease patients: a comparative study between early-onset and late-onset Parkinson's disease', *International Journal of Neuroscience*, 126(3), pp. 1-8.

Tanguma, J. (2001) 'Effects of Sample Size on the Distribution of Selected Fit Indices: A Graphical Approach', *Educational and Psychological Measurement*, 61(5), pp. 759-776.

Taweekarn, P., Emasithi, A. and Jariengprasert, C. (2009) 'Impairment of the dynamic visual acuity in patients with Parkinson's disease', *Parkinsonism and Related Disorders*, 15, p. S190.

Taylor, J.-P., Colloby, S.J., McKeith, I.G. and O'Brien, J.T. (2013) 'Covariant perfusion patterns provide clues to the origin of cognitive fluctuations and attentional dysfunction in Dementia with Lewy bodies', *International Psychogeriatrics*, 25(12), pp. 1917-1928.

Taylor, J.P., Rowan, E.N., Lett, D., O'Brien, J.T., McKeith, I.G. and Burn, D.J. (2008) 'Poor attentional function predicts cognitive decline in patients with non-demented Parkinson's disease independent of motor phenotype', *Journal of Neurology, Neurosurgery & Psychiatry*, 79(12), pp. 1318-1323.

Temel, Y., Visser-Vandewalle, V. and Carpenter, R.H.S. (2008) 'Saccadic latency during electrical stimulation of the human subthalamic nucleus', *Current Biology*, 18(10), pp. R412-R414.

Temel, Y., Visser-Vandewalle, V. and Carpenter, R.H.S. (2009) 'Saccadometry: A novel clinical tool for quantification of the motor effects of subthalamic nucleus stimulation in Parkinson's disease', *Experimental Neurology*, 216(2), pp. 481-489.

Terao, Y., Fukuda, H., Ugawa, Y. and Hikosaka, O. (2013) 'New perspectives on the pathophysiology of Parkinson's disease as assessed by saccade performance: A clinical review', *Clin Neurophysiol*, 124(8), pp. 1491-1506.

Terao, Y., Fukuda, H., Yugeta, A., Hikosaka, O., Nomura, Y., Segawa, M., Hanajima, R., Tsuji, S. and Ugawa, Y. (2011) 'Initiation and inhibitory control of saccades with the progression of Parkinson's disease - changes in three major drives converging on the superior colliculus', *Neuropsychologia*, 49(7), pp. 1794-806.

Tessitore, A., Amboni, M., Esposito, F., Russo, A., Picillo, M., Marcuccio, L., Pellecchia, M.T., Vitale, C., Cirillo, M., Tedeschi, G. and Barone, P. (2012) 'Resting-state brain connectivity in patients with Parkinson's disease and freezing of gait', *Parkinsonism & Related Disorders*, 18(6), pp. 781-787.

Theeuwes, J. (2010) 'Top-down and bottom-up control of visual selection', *Acta Psychol (Amst)*, 135(2), pp. 77-99.

Tombu, M. and Jolicoeur, P. (2003) 'A central capacity sharing model of dual-task performance', *J Exp Psychol Hum Percept Perform*, 29(1), pp. 3-18.

Tomlinson, C.L., Stowe, R., Patel, S., Rick, C., Gray, R. and Clarke, C.E. (2010) 'Systematic review of levodopa dose equivalency reporting in Parkinson's disease', *Mov Disord*, 25(15), pp. 2649-53.

Tommasi, G., Fiorio, M., Yelnik, J., Krack, P., Sala, F., Schmitt, E., Fraix, V., Bertolasi, L., Le Bas, J.F., Ricciardi, G.K., Fiaschi, A., Theeuwes, J., Pollak, P. and Chelazzi, L. (2015) 'Disentangling the role of cortico-Basal Ganglia loops in top-down and bottom-up visual attention: an investigation of attention deficits in Parkinson disease', *J Cogn Neurosci*, 27(6), pp. 1215-37.

Toner, C.K., Reese, B.E., Neargarder, S., Riedel, T.M., Gilmore, G.C. and Cronin-Golomb, A. (2012) 'Vision-Fair Neuropsychological Assessment in Normal Aging, Parkinson's Disease and Alzheimer's Disease', *Psychology and aging*, 27(3), pp. 785-790.

Trachsel, M., Hermann, H. and Biller-Andorno, N. (2015) 'Cognitive Fluctuations as a Challenge for the Assessment of Decision-Making Capacity in Patients With Dementia', *American Journal of Alzheimer's Disease and Other Dementias*, 30(4), pp. 360-363.

Trick, G.L., Kaskie, B. and Steinman, S.B. (1994) 'Visual impairment in Parkinson's disease: deficits in orientation and motion discrimination', *Optom Vis Sci*, 71(4), pp. 242-5.

Trick, G.L. and Silverman, S.E. (1991) 'Visual sensitivity to motion: age-related changes and deficits in senile dementia of the Alzheimer type', *Neurology*, 41(9), pp. 1437-40.

Tropini, G., Chiang, J., Wang, Z.J., Ty, E. and McKeown, M.J. (2011) 'Altered directional connectivity in Parkinson's disease during performance of a visually guided task', *Neuroimage*, 56(4), pp. 2144-56.

Turano, K.A., Geruschat, D.R. and Baker, F.H. (2002) 'Fixation behavior while walking: persons with central visual field loss', *Vision Research*, 42(23), pp. 2635-2644.

Uc, E., Rizzo, M., Anderson, S., Shi, Q. and Dawson, J. (2005a) 'Driver Identification of Landmarks and Traffic Signs After a Stroke', *Transportation Research Record: Journal of the Transportation Research Board*, 1922(1), pp. 9-14.

Uc, E.Y., Rizzo, M., Anderson, S.W., Qian, S., Rodnitzky, R.L. and Dawson, J.D. (2005b) 'Visual dysfunction in Parkinson disease without dementia', *Neurology*, 65(12), pp. 1907-1913.

Uc, E.Y., Rizzo, M., Anderson, S.W., Sparks, J., Rodnitzky, R.L. and Dawson, J.D. (2006) 'Impaired visual search in drivers with Parkinson's disease', *Annals of Neurology*, 60(4), pp. 407-13.

Uc, E.Y., Tippin, J., Chou, K.L., Erickson, B.A., Doerschug, K.C. and Jimmeh Fletcher, D.M. (2011) 'Non-motor Symptoms in Parkinson's Disease', *US Neurology*, 7(2), pp. 113-119.

Uiga, L., Cheng, K.C., Wilson, M.R., Masters, R.S.W. and Capio, C.M. (2015) 'Acquiring visual information for locomotion by older adults: A systematic review', *Ageing Research Reviews*, 20(0), pp. 24-34.

Urwyler, P., Nef, T., Killen, A., Collerton, D., Thomas, A., Burn, D., McKeith, I. and Mosimann, U.P. (2013) 'Visual complaints and visual hallucinations in Parkinson's disease', *Parkinsonism Relat Disord*, 20(3), pp. 318-22.

Vaillancourt, D.E., Slifkin, A.B. and Newell, K.M. (2001a) 'Intermittency in the visual control of force in Parkinson's disease', *Experimental Brain Research*, 138(1), pp. 118-127.

Vaillancourt, D.E., Slifkin, A.B. and Newell, K.M. (2001b) 'Visual control of isometric force in Parkinson's disease', *Neuropsychologia*, 39(13), pp. 1410-1418.

van den Wildenberg, W., van Boxtel, G., van der Molen, M., Bosch, D., Speelman, J. and Brunia, C. (2006) 'Stimulation of the Subthalamic Region Facilitates the Selection and Inhibition of Motor Responses in Parkinson's Disease', *Cognitive Neuroscience, Journal of*, 18(4), pp. 626-636.

van der Hoorn, A., Renken, R.J., Leenders, K.L. and de Jong, B.M. (2014) 'Parkinson-related changes of activation in visuomotor brain regions during perceived forward self-motion', *PLoS One*, 9(4), p. e95861.

van Haastregt, J.C.M., Zijlstra, G.A.R., van Rossum, E., van Eijk, J.T.M. and Kempen, G.I.J.M. (2008) 'Feelings of anxiety and symptoms of depression in community-living older persons who avoid activity for fear of falling', *The American Journal of Geriatric Psychiatry*, 16(3), pp. 186-193.

van Iersel, M.B., Kessels, R.P., Bloem, B.R., Verbeek, A.L. and Olde Rikkert, M.G. (2008) 'Executive functions are associated with gait and balance in community-living elderly people', *Journals of Gerontology Series A-Biological Sciences & Medical Sciences*, 63(12), pp. 1344-9.

van Koningsbruggen, M.G., Pender, T., Machado, L. and Rafal, R.D. (2009) 'Impaired control of the oculomotor reflexes in Parkinson's disease', *Neuropsychologia*, 47(13), pp. 2909-15.

van Stockum, S., MacAskill, M., Anderson, T. and Dalrymple-Alford, J. (2008) 'Don't look now or look away: two sources of saccadic disinhibition in Parkinson's disease?', *Neuropsychologia*, 46(13), pp. 3108-15.

van Stockum, S., Macaskill, M.R. and Anderson, T.J. (2011a) 'Bottom-up effects modulate saccadic latencies in well-known eye movement paradigm', *Psychol Res*, 75(4), pp. 272-8.

van Stockum, S., MacAskill, M.R. and Anderson, T.J. (2012) 'Impairment of voluntary saccades and facilitation of reflexive saccades do not co-occur in Parkinson's disease', *J Clin Neurosci*, 19(8), pp. 1119-24.

van Stockum, S., Macaskill, M.R., Myall, D. and Anderson, T.J. (2011b) 'A perceptual discrimination task abnormally facilitates reflexive saccades in Parkinson's disease', *Eur J Neurosci*, 33(11), pp. 2091-100.

van Stockum, S., MacAskill, M.R., Myall, D. and Anderson, T.J. (2013) 'A perceptual discrimination task results in greater facilitation of voluntary saccades in Parkinson's disease patients', *Eur J Neurosci*, 37(1), pp. 163-72.

van Wegen, E., de Goede, C., Lim, I., Rietberg, M., Nieuwboer, A., Willems, A., Jones, D., Rochester, L., Hetherington, V., Berendse, H., Zijlmans, J., Wolters, E. and Kwakkel, G. (2006) 'The effect of rhythmic somatosensory cueing on gait in patients with Parkinson's disease', *J Neurol Sci*, 248(1-2), pp. 210-4.

Velasques, B., Machado, S., Portella, C.E., Silva, J.G., Basile, L.F., Cagy, M., Piedade, R. and Ribeiro, P. (2007) 'Electrophysiological analysis of a sensorimotor integration task', *Neurosci Lett*, 426(3), pp. 155-9.

Velik, R., Hoffmann, U., Zabaleta, H., Marti Masso, J.F. and Keller, T. (2012) *Engineering in Medicine and Biology Society, (EMBC) 2012. 34th Annual International Conference of the IEEE*. San Diego, CA, 2012. IEEE.

Velu, P.D., Mullen, T., Noh, E., Valdivia, M.C., Poizner, H., Baram, Y. and de Sa, V.R. (2013) 'Effect of visual feedback on the occipital-parietal-motor network in Parkinson's disease with freezing of gait', *Frontiers in neurology*, 4(209), pp. 1-6.

Ventre-Dominey, J., Dominey, P.F. and Broussolle, E. (2002) 'Dissociable processing of temporal structure in repetitive eye-hand movements in Parkinson's disease', *Neuropsychologia*, 40(8), pp. 1407-1418.

Ventre-Dominey, J., Ford Dominey, P. and Broussolle, E. (2001) 'Asymmetric influences of pointing on saccade latency in hemi-Parkinson's disease', *Neuropsychologia*, 39(5), pp. 470-7.

Vercruysse, S., Devos, H., Munks, L., Spildooren, J., Vandenbossche, J., Vandenberghe, W., Nieuwboer, A. and Heremans, E. (2012) 'Explaining freezing of gait in Parkinson's disease: motor and cognitive determinants', *Mov Disord*, 27(13), pp. 1644-51.

Verghese, J., Kuslansky, G., Holtzer, R., Katz, M., Xue, X., Buschke, H. and Pahor, M. (2007a) 'Walking While Talking: Effect of Task Prioritization in the Elderly', *Archives of Physical Medicine and Rehabilitation*, 88(1), pp. 50-53.

Verghese, J., Robbins, M., Holtzer, R., Zimmerman, M., Wang, C., Xue, X. and Lipton, R.B. (2008) 'Gait Dysfunction in Mild Cognitive Impairment Syndromes', *Journal of the American Geriatrics Society*, 56(7), pp. 1244-1251.

Verghese, J., Wang, C., Lipton, R.B., Holtzer, R. and Xue, X. (2007b) 'Quantitative gait dysfunction and risk of cognitive decline and dementia', *Journal of Neurology, Neurosurgery & Psychiatry*, 78(9), pp. 929-935.

Verleger, R., Koerbs, A., Graf, J., Śmigasiewicz, K., Schroll, H. and Hamker, F.H. (2014) 'Patients with Parkinson's disease are less affected than healthy persons by relevant response-unrelated features in visual search', *Neuropsychologia*, 62, pp. 38-47.

Versino, M., Zavanone, C., Colnaghi, S., Beltrami, G., Pacchetti, C., Zangaglia, R. and Cosi, V. (2005) 'Binocular control of saccades in idiopathic Parkinson's disease', *Ann N Y Acad Sci*, 1039, pp. 588-92.

Vervoort, G., Bengevoord, A., Nackaerts, E., Heremans, E., Vandenberghe, W. and Nieuwboer, A. (2015) 'Distal motor deficit contributions to postural instability and gait disorder in Parkinson's disease', *Behavioural brain research*, 1(287), pp. 1-7.

Vitorio, R., Lirani-Silva, E., Barbieri, F.A., Raile, V., Batistela, R.A., Stella, F. and Gobbi, L.T. (2012) 'The role of vision in Parkinson's disease locomotion control: free walking task', *Gait Posture*, 35(2), pp. 175-9.

Vitorio, R., Lirani-Silva, E., Barbieri, F.A., Raile, V., Stella, F. and Gobbi, L.T. (2013) 'Influence of visual feedback sampling on obstacle crossing behavior in people with Parkinson's disease', *Gait Posture*, 38(2), pp. 330-4.

Vitorio, R., Lirani-Silva, E., Pieruccini-Faria, F., Moraes, R., Gobbi, L.T. and Almeida, Q.J. (2014) 'Visual cues and gait improvement in Parkinson's disease: which piece of information is really important?', *Neuroscience*, 277, pp. 273-80.

Vogel, E.K., Woodman, G.F. and Luck, S.J. (2001) 'Storage of features, conjunctions, and objects in visual working memory', *Journal of Experimental Psychology: Human Perception and Performance*, 27(1), p. 92.

von Noorden, G.K. and Preziosi, T.J. (1966) 'Eye movement recordings in neurological disorders', *Archives of Ophthalmology*, 76(2), pp. 162-171.

Wai, Y.-Y., Wang, J.-J., Weng, Y.-H., Lin, W.-Y., Ma, H.-K., Ng, S.-H., Wan, Y.-L. and Wang, C.-H. (2012) 'Cortical involvement in a gait-related imagery task: comparison between Parkinson's disease and normal aging', *Parkinsonism & related disorders*, 18(5), pp. 537-542.

Walker, M.P., Ayre, G.A., Cummings, J.L., Wesnes, K., McKeith, I.G., O'Brien, J.T. and Ballard, C.G. (2000) 'Quantifying fluctuation in dementia with Lewy bodies, Alzheimer's disease, and vascular dementia', *Neurology*, 54(8), pp. 1616-1625.

Walton, C.C., Shine, J.M., Mowszowski, L., Gilat, M., Hall, J.M., O'Callaghan, C., Naismith, S.L. and Lewis, S.J.G. (2015) 'Impaired cognitive control in Parkinson's disease patients with freezing of gait in response to cognitive load', *Journal of Neural Transmission*, 122(5), pp. 653-660.

Wang, J., Tian, J., Wang, R. and Benson, V. (2013) 'Increased attentional focus modulates eye movements in a mixed antisaccade task for younger and older adults', *PLoS One*, 8(4), p. e61566.

Wang, M.Y., Rousseau, J., Boisjoly, H., Schmaltz, H., Kergoat, M.-J., Moghadaszadeh, S., Djafari, F. and Freeman, E.E. (2012) 'Activity Limitation due to a Fear of Falling in Older Adults with Eye DiseaseEye Disease and Activity Limitation', *Investigative Ophthalmology & Visual Science*, 53(13), pp. 7967-7972.

Wass, S.V., Smith, T.J. and Johnson, M.H. (2013) 'Parsing eye-tracking data of variable quality to provide accurate fixation duration estimates in infants and adults', *Behav Res Methods*, 45(1), pp. 229-50.

Wechsler, D. (1945) 'A standardized memory scale for clinical use', *The Journal of Psychology*, 19(1), pp. 87-95.

Weinrich, M. and Bhatia, R. (1986) 'Abnormal eye-head coordination in Parkinson's disease patients after administration of levodopa: a possible substrate of levodopa-induced dyskinesia', *Journal of Neurology, Neurosurgery & Psychiatry*, 49(7), pp. 785-790.

Weintraub, D., Moberg, P.J., Culbertson, W.C., Duda, J.E., Katz, I.R. and Stern, M.B. (2005) 'Dimensions of Executive Function in Parkinson's Disease', *Dementia and Geriatric Cognitive Disorders*, 20(2-3), pp. 140-144.

Weiss, P.H., Herzog, J., Potter-Nerger, M., Falk, D., Herzog, H., Deuschl, G., Volkmann, J. and Fink, G.R. (2015) 'Subthalamic nucleus stimulation improves Parkinsonian gait via brainstem locomotor centers', *Mov Disord*, 30(8), pp. 1121-5.

Wesnes, K.A., McKeith, I., Edgar, C., Emre, M. and Lane, R. (2005) 'Benefits of rivastigmine on attention in dementia associated with Parkinson disease', *Neurology*, 65(10), pp. 1654-1656.

West, G.L., Al-Aidroos, N., Susskind, J. and Pratt, J. (2011) 'Emotion and action: the effect of fear on saccadic performance', *Experimental brain research*, 209(1), pp. 153-158.

West, R. and Alain, C. (2000a) 'Age-related decline in inhibitory control contributes to the increased Stroop effect observed in older adults', *Psychophysiology*, 37(2), pp. 179-189.

West, R. and Alain, C. (2000b) 'Effects of task context and fluctuations of attention on neural activity supporting performance of the Stroop task', *Brain Research*, 873(1), pp. 102-111.

White, B.J., Marino, R.A., Boehnke, S.E., Itti, L., Theeuwes, J. and Munoz, D.P. (2013) 'Competitive Integration of Visual and Goal-related Signals on Neuronal Accumulation Rate: A Correlate of Oculomotor Capture in the Superior Colliculus', *J Cogn Neurosci*, 25(10), pp. 1754-65.

Wilde, N.J., Strauss, E. and Tulsky, D.S. (2004) 'Memory Span on the Wechsler Scales', *Journal of Clinical and Experimental Neuropsychology*, 26(4), pp. 539-549.

Wilson, S.J., Glue, P., Ball, D. and Nutt, D.J. (1992) 'Saccadic eye movement parameters in normal subjects', *Electroencephalography and clinical Neurophysiology*, 86(1), pp. 69-74.

Winogrodzka, A., Wagenaar, R.C., Booij, J. and Wolters, E.C. (2005) 'Rigidity and bradykinesia reduce interlimb coordination in Parkinsonian gait', *Archives of physical medicine and rehabilitation*, 86(2), pp. 183-189.

Wolfe, J. (1994) 'Guided Search 2.0 A revised model of visual search', *Psychonomic Bulletin & Review*, 1(2), pp. 202-238.

Wood, J.M., Lacherez, P.F., Black, A.A., Cole, M.H., Boon, M.Y. and Kerr, G.K. (2009) 'Postural Stability and Gait among Older Adults with Age-Related Maculopathy', *Investigative Ophthalmology & Visual Science*, 50(1), pp. 482-487.

Woollacott, M. and Shumway-Cook, A. (2002) 'Attention and the control of posture and gait: a review of an emerging area of research', *Gait & Posture*, 16(1), pp. 1-14.

Wright, L.A. and Wormald, R.P. (1992) 'Stereopsis and ageing', *Eye (Lond)*, 6 (Pt 5), pp. 473-6.

Wright, W.G., Gurfinkel, V.S., King, L.A., Nutt, J.G., Cordo, P.J. and Horak, F.B. (2010) 'Axial kinesthesia is impaired in Parkinson's disease: Effects of levodopa', *Experimental Neurology*, 225(1), pp. 202-209.

Wu, T. and Hallett, M. (2013) 'The cerebellum in Parkinson’s disease', *Brain*, 136(3), pp. 696-709.

Wurtz, R.H., Sommer, M.A., Pare, M. and Ferraina, S. (2001) 'Signal transformations from cerebral cortex to superior colliculus for the generation of saccades', *Vision Res*, 41(25-26), pp. 3399-412.

Xiong, B., Skitmore, M. and Xia, B. (2015) 'A critical review of structural equation modeling applications in construction research', *Automation in Construction*, 49(Part A), pp. 59-70.

Yamaji, S., Demura, S. and Sugiura, H. (2011) ' Influence of degraded visual acuity from light-scattering goggles on obstacle gait. ', *Healthy*, 3, pp. 99-105.

Yardley, L., Beyer, N., Hauer, K., Kempen, G., Piot-Ziegler, C. and Todd, C. (2005) 'Development and initial validation of the Falls Efficacy Scale-International (FES-I)', *Age Ageing*, 34(6), pp. 614-9.

Yarnall, A., Rochester, L. and Burn, D.J. (2011) 'The interplay of cholinergic function, attention, and falls in Parkinson's disease', *Movement Disorders*, 26(14), pp. 2496-2503.

Yarnall, A.J., Breen, D.P., Duncan, G.W., Khoo, T.K., Coleman, S.Y., Firbank, M.J., Nombela, C., Winder-Rhodes, S., Evans, J.R., Rowe, J.B., Mollenhauer, B., Kruse, N., Hudson, G., Chinnery, P.F., O'Brien, J.T., Robbins, T.W., Wesnes, K., Brooks, D.J., Barker, R.A., Burn, D.J. and On behalf of the, I.-P.D.S.G. (2014) 'Characterizing mild cognitive impairment in incident Parkinson disease: The ICICLE-PD Study', *Neurology*, 82(4), pp. 308-316.

Ye, Z., Altena, E., Nombela, C., Housden, C.R., Maxwell, H., Rittman, T., Huddleston, C., Rae, C.L., Regenthal, R., Sahakian, B.J., Barker, R.A., Robbins, T.W. and Rowe, J.B. (2015) 'Improving Response Inhibition in Parkinson's Disease with Atomoxetine', *Biological Psychiatry*, 77(8), pp. 740-748.

Yesavage, J.A. and Sheikh, J.I. (1986) 'Geriatric Depression Scale (GDS)', *Clinical Gerontologist*, 5(1-2), pp. 165-173.

Yeshurun, Y. and Carrasco, M. (1998) 'Attention improves or impairs visual performance by enhancing spatial resolution', *Nature*, 396(6706), pp. 72-75

Yogev-Seligmann, G., Hausdorff, J.M. and Giladi, N. (2008) 'The role of executive function and attention in gait', *Mov Disord*, 23(3), pp. 329-42; quiz 472.

Yogev, G., Giladi, N., Peretz, C., Springer, S., Simon, E.S. and Hausdorff, J.M. (2005) 'Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding?', *Eur J Neurosci*, 22(5), pp. 1248-56.

Yoshida, T., Warabi, T., Kato, M., Kiriyama, K. and Yanagisawa, N. (2005) 'Visuomotor dependency on an initial fixation target involved in the disorder of visually-guided manual movement in Parkinson's disease', *Neurosci Res*, 51(2), pp. 167-73.

Young, D.E., Wagenaar, R.C., Lin, C.C., Chou, Y.H., Davidsdottir, S., Saltzman, E. and Cronin-Golomb, A. (2010) 'Visuospatial perception and navigation in Parkinson's disease', *Vision Res*, 50(23), pp. 2495-504.

Young, W.R. and Hollands, M.A. (2012) 'Newly acquired fear of falling leads to altered eye movement patterns and reduced stepping safety: a case study', *PLoS One*, 7(11), p. e49765.

Yugeta, A., Terao, Y., Fukuda, H., Hikosaka, O., Yokochi, F., Okiyama, R., Taniguchi, M., Takahashi, H., Hamada, I., Hanajima, R. and Ugawa, Y. (2010) 'Effects of STN stimulation on the initiation and inhibition of saccade in Parkinson disease', *Neurology*, 74(9), pp. 743-748.

Zampieri, C. and Di Fabio, R.P. (2008) 'Balance and eye movement training to improve gait in people with progressive supranuclear palsy: quasi-randomized clinical trial', *Phys Ther*, 88(12), pp. 1460-73.

Zgaljardic, D.J., Borod, J.C., Foldi, N.S., Mattis, P.J., Gordon, M.F., Feigin, A. and Eidelberg, D. (2006) 'An Examination of Executive Dysfunction Associated with Frontostriatal Circuitry in Parkinson's Disease', *Journal of clinical and experimental neuropsychology*, 28(7), pp. 1127-1144.

Zhiwei, Z. and Qiang, J. (2007) 'Novel Eye Gaze Tracking Techniques Under Natural Head Movement', *Biomedical Engineering, IEEE Transactions on*, 54(12), pp. 2246-2260.

Zuverza-Chavarria, V. and Tsanadis, J. (2011) 'Measurement properties of the CLOX Executive Clock Drawing Task in an inpatient stroke rehabilitation setting', *Rehabilitation Psychology*, 56(2), pp. 138-144.

Zweig, R.M., Jankel, W.R., Hedreen, J.C., Mayeux, R. and Price, D.L. (1989) 'The pedunculopontine nucleus in Parkinson's disease', *Ann Neurol*, 26(1), pp. 41-6.