DOI: 10.1111/ejn.13589

Direct and indirect effects of attention and visual function on gait impairment in Parkinson's disease: influence of task and turning

Samuel Stuart[1], Brook Galna[1], Louise S Delicato[1,2], Sue Lord[1] and Lynn Rochester[1]*

[1]Institute of Neuroscience/Newcastle University Institute of Ageing, Clinical Ageing Research Unit, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, NE4 5PL, United Kingdom

[2]School of Psychology, Shackleton House, University of Sunderland, Sunderland, SR1 3QR, United Kingdom

***Correspondence to:**

Lynn Rochester, PhD

Professor of Human Movement Science

Institute of Neuroscience

Newcastle University Institute of Ageing

Newcastle University

Clinical Ageing Research Unit

Campus for Ageing and Vitality

Newcastle upon Tyne

NE4 5PL

Tel: +44191 208 1291

Fax: +44191 208 1290

Email: lynn.rochester@newcastle.ac.uk

Running Title: Effects of attention and vision on gait in Parkinson's

Journal Section: Clinical and Translational Neuroscience

Word Count: Abstract (250): 237

Article (Excluding abstract): 6317

Pages: 40

Figures: 4

Tables: 4

Supplementary Material: 3

KEYWORDS: Parkinson's disease, gait, saccades, attention, vision

Abstract

Gait impairment is a core feature of Parkinson's disease (PD) which has been linked to cognitive and visual deficits, but interactions between these features are poorly understood. Monitoring saccades allows investigation of real-time cognitive and visual processes and their impact on gait when walking. This study explored; 1) saccade frequency when walking under different attentional manipulations of turning and dual-task; and 2) direct and indirect relationships between saccades, gait impairment, vision and attention. Saccade frequency (number of fast eye-movements per-second) was measured during gait in 60 PD and 40 age-matched control participants using a mobile eye-tracker. Saccade frequency was significantly reduced in PD compared to controls during all conditions. However, saccade frequency increased with a turn and decreased under dual-task for both groups. Poorer attention directly related to saccade frequency, visual function and gait impairment in PD, but not controls. Saccade frequency did not directly relate to gait in PD, but did in controls. Instead, saccade frequency and visual function deficit indirectly impacted gait impairment in PD, which was underpinned by their relationship with attention. In conclusion, our results suggest a vital role for attention with direct and indirect influences on gait impairment in PD. Attention directly impacted saccade frequency, visual function and gait impairment in PD, with connotations for falls. It also underpinned indirect impact of visual and saccadic impairment on gait. Attention therefore represents a key therapeutic target that should be considered in future research.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised by cardinal motor symptoms of rigidity, bradykinesia, tremor, postural instability and gait deficit. Gait impairments present early (Galna *et al.*, 2015) and are difficult to treat due to their refractory nature to dopaminergic treatment (Sethi, 2008). Deficits lead to significant disability and increased falls risk (Lord *et al.*, 2016). While the motor contributions to gait are well studied, considerable non-motor contributions are increasingly becoming evidence especially the role of cognition and vision.

Cognitive deficits in PD are common, early features and include impaired executive function, visuo-spatial ability, working memory and attention, with features such as language less affected (Yarnall *et al.*, 2014; Barker & Williams-Gray, 2015). Attention is a key contributor to gait control and gait impairment even in very early PD (Galna *et al.*, 2015) supported by studies showing a strong association between them (Lord *et al.*, 2014), as well as the effect of dual-task protocols on gait (Kelly *et al.*, 2012; Rochester *et al.*, 2014). Visual deficits are also common in PD and range from impaired visual functions such as visual acuity (VA) and contrast sensitivity (CS) to more complex processes such as depth or motion perception (Weil *et al.*, 2016). Emerging evidence has also shown that visual dysfunction is associated with gait impairment (Spaulding *et al.*, 1994; Swigler *et al.*, 2012; Shin *et al.*, 2015) and manipulation of vision through environmental changes negatively impacts gait in PD (Azulay *et al.*, 1999; Davidsdottir *et al.*, 2008; Cowie *et al.*, 2010; Lebold & Almeida, 2010).

The relationship between attention, visual function and gait impairment in PD has been studied independently of each other therefore interactions between these features remain poorly understood (Stuart *et al.*, 2016c). Relationships between vision, cognition and gait are complex, but attention likely has a central role in gait and saccadic control (Stuart *et al.*, 2016c). During

goal-oriented tasks (e.g. gait) attention mediates visual processing of environmental information at multiple sites in the central nervous system (Borji *et al.*, 2011); from initial visual target selection for safe navigation to high level executive processes (Baluch & Itti, 2011). Early attentional biasing of visual information (Bar *et al.*, 2006) indicates that even though vision and cognition interact, they are possibly underpinned by attention (Borji *et al.*, 2011). However the neural mechanisms underlying attention are transient in nature and tend to fluctuate in efficiency over time (West & Alain, 2000). Decline in attentional function and increased attentional fluctuations become prominent with ageing (Salthouse, 1996), and even more so with PD – especially with progression to dementia (Ballard *et al.*, 2002; Emre, 2003). Attention may therefore play a greater role in saccadic (Rieger *et al.*, 2008a) and gait impairment (Lord *et al.*, 2014) in PD than in older adults. Establishing the relationships between attention, visual function and saccades when walking, and their impact on gait impairment in PD is central to understanding gait impairments as well as informing effective therapeutic interventions.

Saccades are fast eye movements between areas of interest within the environment that allow vital visual information to be processed, and they are influenced by both attentional (Mazer, 2011) and visual processes (Bridgeman *et al.*, 1981; Hernandez *et al.*, 2008). Monitoring of saccades using a mobile eye-tracker provides a methodology to investigate the influence of attention and vision during walking (Stuart *et al.*, 2014a). Saccades allow visual information to be acquired which is then integrated into motor circuits involved in gait via attentional projections (Macaluso, 2006; Kravitz *et al.*, 2011). Dysfunctional saccadic control (as a result of cognitive or visual impairment) could contribute to gait impairment in PD (Figure 1(D)) however to date this has not been tested. Dysfunctional saccades with PD have been noted within both static and dynamic tasks, although visuomotor research has primarily focussed on static computer-based assessments rather than monitoring during walking. Static testing has

demonstrated that people with PD make hypometric (particularly in vertical direction), slower and less frequent saccades than controls during visual search paradigms (Horowitz *et al.*, 2006; Uc *et al.*, 2006; Mannan *et al.*, 2008; Nys *et al.*, 2010; Verleger *et al.*, 2014). Dynamic testing has demonstrated significant reduction in saccade frequency during gait in older compared to younger adults (Dowiasch *et al.*, 2015), and non-significant reduction has been found in PD compared to older adults (Galna *et al.*, 2012; Vitorio *et al.*, 2012). However previous studies in PD have not robustly examined saccadic behaviour and have been limited by small sample sizes, which may have impacted results (Stuart *et al.*, 2014a). Similarly, no previous studies have examined the underlying relationships between saccades, attention, vision or gait in PD (Stuart *et al.*, 2014a; Stuart *et al.*, 2016c). Reduction in saccade frequency may relate to deficits in high-level cognition that determines which areas of interest to fixate on (Yarbus, 1967; Nelson *et al.*, 2004), and also low-level visual functions which impact the saliency or visibility of objects/areas (i.e. salient areas draw saccades) (Findlay, 1997; Zelinsky *et al.*, 1997). Ultimately, reduction in saccade frequency would reduce the visual input to be used for guidance of walking (Patla *et al.*, 1996), which may lead to mobility impairment and increased falls risk.

This study aimed to; 1) explore saccades during walking in PD compared to age matched controls and the influence of attentional manipulation (through turning and dual-tasking); and 2) explore the direct and indirect relationships between saccades, gait impairment, attention and vision using univariate and structural equation modelling. We hypothesised that saccade frequency during gait would be significantly reduced in PD compared to older adults and changes in saccade frequency and their relationship with gait would be related to attentional rather than visual impairment in PD. An *a priori* model was used to guide data analysis (Figure 1), which emerged from our previous literature review; Stuart et al. (2016c).

<<Insert Figure 1 here>>

Methods

The following is a brief overview of the study methodology, for detailed information please see the published protocol; Stuart *et al.* (2016b) (ClinicalTrials.gov NCT02610634).

Participants

This study involved 60 people with PD and 40 age-matched older adult controls who were ≥50 years old, able to walk independently, had no marked diagnosed visual, significant mood or other neurological disorder. PD was diagnosed by a movement disorder specialist according to UK Brain Bank criteria. PD participants without severe cognitive impairment were recruited (Montreal Cognitive Assessment (MoCA) ≥21) and testing took place one hour after medication intake. Four PD participants were excluded from analysis, as they were unable to adequately complete the study assessments. Controls were excluded if they presented with mild cognitive impairment or dementia (MoCA <26) (Dalrymple-Alford *et al.*, 2010). The study was approved by the Newcastle and North Tyneside NHS Research Ethics Committee (Ref: 13/NE/0128) and all participants gave informed consent.

Demographic and clinical assessment

Demographics of age, sex, height and weight were recorded (see Table 1). Disease severity was measured using the Movement Disorder Society (MDS-revised) Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz *et al.*, 2008). Fear of falling was measured using the Falls Efficacy Scale (International version; FES-I) (Yardley *et al.*, 2005), depression with the geriatric depression scale (GDS-15) (Yesavage & Sheikh, 1986), and retrospective falls from patient interview and medical notes. Levodopa equivalent dose (LED) scores were calculated according to standardised methods (Tomlinson *et al.*, 2010).

Cognition

Five cognitive domains were assessed:

Global cognition; measured with the Montreal Cognitive Assessment (MoCA) and Addenbrookes cognitive examination (ACE-R) (Mioshi *et al.*, 2006; Dalrymple-Alford *et al.*, 2010).

Attention was assessed using the computerised cognitive drug research battery, including simple reaction-time, choice reaction-time and digit vigilance. Power of attention (PoA) was calculated as the sum of the means and fluctuating attention (FA) was calculated as the sum the coefficient of variation (CV%) from each test (Allcock *et al.*, 2009; Lord *et al.*, 2014).

Executive function was measured with clock drawing (Royall's CLOX 1) (Royall *et al.*, 1998).

Visuo-spatial function was measured using judgement of line orientation (JLO) (Montse *et al.*, 2001), clock copying (Royall's CLOX 2) and subsections of the visual, object and space perception (VOSP) battery (i.e. incomplete letters, dot counting and position discrimination) (Rapport *et al.*, 1998).

Working memory was assessed using the maximal seated forward digit span from the Wechsler adult intelligence scale (Wechsler, 1945).

Visual function

Visual acuity (VA) and *contrast sensitivity* (CS) were assessed binocularly using standardised charts (LogMar and MarsCS) (Lovie-Kitchin, 1988).

Experimental design

Equipment

Saccades were measured using a head-mounted infra-red monocular mobile eye-tracker (Dikablis, Ergoneers, Germany; 50Hz) and bi-temporal electrooculography (EOG; Zerowire, Aurion, Italy; 1000Hz) (Stuart *et al.*, 2016a) (Figure 2(B)). The mobile eye-tracker consisted of a head-unit and a transmitter, which was contained within a backpack (~1kg). Participants all wore their usual corrective eye-wear that they would wear during walking in everyday life. The infra-red eye-tracker's eye-camera was positioned so that refraction from the lower section of bi/vari-focal glasses was not possible (i.e. above or lateral to this section of the glasses, or underneath the glasses altogether).

Gait was measured using a Vicon 3D motion capture system (Oxford, UK; 100Hz), with reflective markers placed on the feet, pelvis, shoulders, head and eye-tracker. These devices automatically synchronised and recorded simultaneous eye and body movement recording for the trial duration. Full details of the testing procedures are described elsewhere (Stuart *et al.*, 2016b).

Protocol

Saccades were measured as participants walked at a self-selected pace for ~7m under different conditions (Figure 2(A)). The conditions were designed to influence eye movements through attentional manipulation due to turning and dual-tasking when walking ('real-time') as follows;

- Straight line walking ($Walk_{Straight}$) (3 trials)
- Straight line walking through a doorway (80cm wide, placed 2.5m from start point) ($Walk_{Door}$) (3 trials)

- Turning to cue: walk and turn 40° left or right to a white target on the floor ($Turn_{Left}$ and $Turn_{Right}$) (3 trials in each direction)
- Dual task straight line walking ($Walk_{Straight}$) (3 trials)
- Dual task + straight line walking through a doorway (80cm wide, placed 2.5m from start point) ($Walk_{Door}$) (3 trials)
- Dual task + turning to cue: walk and turn 40° left or right to a white target on the floor ($Turn_{Left}$ and $Turn_{Right}$) (3 trials in each direction)

Dual task involved the Wechsler forward digit span repetition while walking (Wilde *et al.*, 2004), normalised to each individual's maximal digit span level which was determined in sitting prior to walking tests. Participants were required to listen to random strings of numbers (digits) played over a loud speaker while walking and repeat back the strings of digits in the same order they were played at the end of the walk. This ensured that artefacts from muscle and movement activity related to talking did not influence saccadic data.

Three trials for each condition were averaged. To ensure all participants eyes started in the same position, they were asked to look straight ahead at a camera at the end of the room for three seconds prior to walking and could look wherever they wanted once told to walk.

Outcome Measures

The primary behavioural outcome of this study was saccade frequency (number of saccades per second) during gait, obtained from the raw mobile eye-tracker data (Figure 2(C)) using a previously validated algorithm (Stuart *et al.*, 2014b). Only saccades with ≥5° amplitude (≥240°/sec) were analysed to account for vestibular-ocular reflex or micro-saccade data intrusion (Galna *et al.*, 2012; Stuart *et al.*, 2014b), and a maximal velocity threshold of ≥1000°/sec was used to rule out flickers or other spurious movements. Saccade frequency was calculated as the number of saccades made within a walk divided by the duration of the walk,

which controlled for the different walking speeds between participants in the same manner as previous research (Galna *et al.*, 2012).

Saccade frequency was monitored as it forms the basis for visual exploration when walking, which is a measure of how often an individual observes or samples their environment and the visual demand of the task (Patla *et al.*, 1996). Saccades are a robust, quantifiable outcome (Becker, 1989; Gorges *et al.*, 2014) that are mapped to underlying neural networks and processes (Kimmig *et al.*, 2001) to a greater extent than fixations or more generic measures of visual exploration (e.g. gaze or scan paths). Fixations are coupled to saccades (i.e. they are pauses between these movements) and are also influenced by cognitive and visual processes (Just & Carpenter, 1980). However, it is difficult to know exactly when a fixation starts and ends (Salvucci & Goldberg, 2000) due to mobile eye-tracker sampling frequency (i.e. need >200Hz for accurate fixation detection) (Stuart *et al.*, 2014a), as well as variable velocity (e.g. <30-100°/sec) and duration (e.g. 80-200ms) thresholds within the literature (Holmqvist & Nystrom, 2011), which have been shown to differ between static and dynamic tasks (Manor & Gordon, 2003). Gaze and scan paths also require time-consuming manual frame-by-frame analysis of eye-tracker videos (Vitório *et al.*, 2014; Beck *et al.*, 2015; Vitório *et al.*, 2016), which is subjective as algorithms that quantify eye movement are not used to determine saccades or fixations.

Although there was an increase in saccade frequency with a door compared to straight walking (from $Walk_{Straight}$ to $Walk_{Door}$) under single and dual task in both groups (Supplementary Material 1), there were no significant differences between straight walking and door conditions ($Walk_{Straight}$, $Walk_{Door}$), or between the two turning conditions ($Turn_{Left}$, $Turn_{Right}$). Therefore data were collapsed into walking (Walk) and turning (Turn) variables (Figure 2(A)) respectively to avoid type 1 error within our initial analysis. Saccade frequency data were reported as absolute (Walk, Turn) and change score (ΔDoor, ΔTurn) values. Change scores

were used in further analysis to overcome eye-tracker measurement limitations (Stuart *et al.*, 2016a), which allowed each participant to act as their own control. Change scores were created using set formula (see below; 1 and 2) and showed the influence of environmental stimuli (a door) and turning on saccade frequency when walking under single and dual task.

(1) $\Delta Door = Walk_{Door} - Walk_{Straight}$

(2) $\Delta Turn = Turn - Walk_{Straight}$

Secondary outcomes were five gait characteristics of velocity, step length, step time, double support and single support time under single and dual task conditions.

<<Insert Figure 2 here>>

Statistical Analysis

Descriptive data

Data were analysed using SPSS (v21, IBM, Chicago, Il., USA) and assessed for normality, meeting criteria for parametric analysis (Field, 2013). Descriptive statistics (means and standard deviations (SD)) were calculated for continuous variables. Pearson chi-square (X^2) test was used for comparison of frequency data. Statistical tests were two-tailed with a p-value of $p<.05$ considered significant and control for multiple comparisons was not performed due to the experimental nature of the study. We present our findings as a two-stage process in which we:

1) Describe the effect of attentional (turning and dual-task) manipulation on saccade frequency in PD and controls
2) Explore the direct and indirect relationships between saccade frequency, attention, visual function, and gait characteristics based on an *a priori* model (Figure 1).

Step 1: Saccade frequency while walking

Repeated measures ANOVAs were used to compare the effect of turning (Walk, Turn) and dual task (single, dual) on saccade frequency, with group (PD, control) as a between subject factor. The same analysis was performed for reported gait characteristics (velocity, step length, step time, double and single support time).

Step 2: Direct and indirect determinants of saccade frequency and their relationship with gait impairment

Following preliminary Pearson's correlations, independent cognitive or visual determinants of saccade frequency were examined through hierarchical multiple-regression analysis. Saccade frequency change scores (ΔDoor, ΔTurn) were used due to their consistent association with independent variables (Allison, 1990). Demographic features were entered into the first step (Age, MoCA, UPDRS-III, GDS-15), cognitive (FA, CLOX, JLO, Digit Span) and visual functions (VA, CS) in separate steps, and a final combined model is presented. FES-I was not entered due to the known interaction with depression/anxiety (van Haastregt *et al.*, 2008) and a lack of pathological cause limiting interpretation (Legters, 2002). Variables that were significantly different between PD and controls in the univariate analysis were selected to represent independent cognitive domains and visual functions. Only one variable was selected for each cognitive domain to avoid over-fitting. As PoA and FA were highly correlated ($r=.70$, $p<.001$), FA was chosen to represent attention as it is sensitive to age-related cognitive decline (Salthouse, 1996) and is characteristic of PD dementia (Emre, 2003; Burn & Yarnall, 2014). Poorer FA has also been associated with increased fall frequency in PD and is a stronger predictor of falls than PoA (Allcock *et al.*, 2009). Regression normality (histograms and P-P plots), co-linearity (tolerance and variance inflation factor) and independent errors (Durbin-Watson) were examined, which indicated that data were normal.

Structural equation modelling (SEM) was then used to examine the direct and indirect relationship between saccade frequency and gait impairment in PD, while including

hypothesised cognitive and visual relationships (Figure 1). SEM is statistically valid with modest sample sizes (5-20 cases per independent variable) that are realistic for observational research studies (Bentler & Chou, 1987; Tanguma, 2001; Menz *et al.*, 2007; Christopher Westland, 2010; Byrne, 2013; Wolf *et al.*, 2013; Hoyle & Gottfredson, 2014; Xiong *et al.*, 2015). The model was created in SPSS AMOS (v22).

SEM analysis was conducted in line with current recommendations (Kline, 2011; Byrne, 2013; Xiong *et al.*, 2015) which were applied in four separate steps. Figure 4(A) shows that we first created latent variables for cognition, visual function, saccade frequency and gait impairment from the same observed variables used within our multiple regression analysis. Significantly reduced step length, velocity and increased double support time represented gait impairment in PD compared to controls within univariate analysis. Second, poor latent variable representations were removed (i.e. standardised factor loading of <0.70). Third, any observed variables with 'perfect fit' (i.e. standardised factor loading ≥1.00) were used in place of the latent variable to avoid overfitting. Finally, model trimming and effect calculation were performed, which involved removal of non-significant associations (connection arrows / paths), and calculation of direct and indirect effects (i.e. for indirect effects the coefficients for each path were multiplied (Menz *et al.*, 2007)). The final SEM provided direct and indirect relationships between attention and visual functions, saccade frequency and gait velocity in PD (Figure 4(B) and Table 4).

Results

Participants

Participant demographic, cognitive, visual and clinical features are summarised in Table 1. PD and controls were well matched for age (p=.605) and corrective eye-wear (p=.184) but were significantly different in terms of gender (p=.036) and education (p=.023). Males were over

represented in the PD group and the PD group had fewer years of education. The PD cohort was a heterogeneous group (Median disease duration; ~60 months) with moderate disease severity (UPDRS III, ~37 ± 14) and impaired global cognition (MoCA, ACE-R*; p*<.001). This was expected as the PD group involved participants with mild cognitive impairment (MoCA ≥21) while the control group did not (MoCA ≥26). Attention (PoA and FA, p<.001), executive function (CLOX 1, p=.002), visuo-spatial ability (JLO, p=.029) and working memory (Digit span, p<.001) were all significantly impaired in PD compared to controls. Basic visual functions of VA (p=.005) and CS (p<.001) were also significantly impaired in PD compared to controls.

People with PD walked significantly slower (F=14.9, d.f.=1, p<.001), with shorter steps (F=9.7, d.f.=1, p=.002) and increased double support time (F= 0.20, d.f.=1, p=.003) than controls for all walking conditions (Table 2). Step time (F=2.87, d.f.=1, p=.094) and single support time (F=0.02, d.f.=1, p=.890) were not significantly different between the groups.

Saccade frequency while walking: effect of PD and attentional manipulation

Saccade frequency (Walk, Turn) was lower in PD participants than controls in all conditions (main effect; F=9.9, d.f.=1, p=.002) (Figure 3). There was a main effect of turning and dual-task on saccade frequency irrespective of participant group, where saccade frequency increased under the Turn condition compared to Walk (F=159.1, d.f.=1, p<.001) and decreased under the dual-task condition compared to single-task (dual-task; F=28.7, d.f.=1, p<.001) (Figure 3 and Supplementary Material 1).

<<Insert Figure 3 here>>

Direct and indirect determinants of saccade frequency and their relationship with gait impairment

Saccade frequency determinants

Under single task, regression analysis demonstrated that better attention (FA) was associated with a greater increase in saccade frequency during $Walk_{Door}$ and Turn conditions compared to $Walk_{Straight}$ in PD (ΔDoor *ß*=-.45, *p*=.009, ΔTurn *ß*=-.36, *p*=.041, Table 3), independent of demographic or visual function (VA and CS). Under dual task conditions poorer working memory was associated with a greater increase in saccade frequency in PD for the Turn condition only (ΔTurn *ß*=-.34, *p*=.018). There were no significant associations for control participants (as shown in Table 3).

Saccade frequency relationship with gait characteristics

There were no significant associations between saccade frequency and gait characteristics in PD (Supplementary Material 3). However, in control participants, increased saccade frequency in the Turn condition was related to increased velocity (*r*=.35, *p*=.026) and longer steps (*r*=.33, *p*=.038) under both single and dual task respectively (Supplementary Material 3).

Saccade frequency relationship with gait impairment in Parkinson's disease

SEM analysis was used to explore direct and indirect relationships between saccade frequency and gait in PD (see Figure 4 and Table 4). Gait outcomes under single task walking conditions in PD were used for the final model because this was the only condition in which a significant relationship was observed. It was not possible to formulate a SEM for controls due to limited quality of indicators (factor loadings <.70).

Standardised regression coefficients (ß) are shown for associations between each variable in the model (next to each arrow) and amount of variance explained (r^2) by the model is provided

in bold above appropriate variables (Figure 4(B)). After appropriate trimming, hypothesised relationships were examined between two latent (visual function and saccade frequency (ΔDoor, ΔTurn)) and two observed variables (FA and gait velocity). Three non-significant paths (represented by dashed lines within Figure 4(B)) were trimmed and the overall fit of the model was confirmed with $X^2 = 4.0$ (d.f.=8, p=.853), Goodness of Fit Index (GFI) (.977) and Root Mean Square Error of Approximation (RMSEA) (0.00), which indicated acceptable model fit. The final model explained 18% of the variance in saccade frequency (ΔDoor, ΔTurn) and 10% of the variance in gait velocity in PD.

Attention (FA) played a central role in all hypothesised relationships in PD. Attention also shared a significant relationship with visual function (ß=.46, p=.014), where better visual function (lower score is better) related to better attention in PD (Figure 4(B)), consistent with correlational analysis (Supplementary Material 2). There was a significant direct effect of attention on both saccade frequency (ß=-.42, p=.011) and gait velocity (ß=-.32, p=.012) in PD. This demonstrated that poorer attention directly related to poorer visual function, dysfunctional saccade frequency and slower velocity. Visual function was not associated with saccade frequency (ß=.13, p=.482) or gait velocity (ß=-.10, p=.531), nor was saccade frequency and gait velocity (ß=.04, p=.756). Instead, there were significant indirect relationships between these features with visual function (ß=-.15, p=.008) and saccade frequency (ß=.13, p=.011) demonstrating a significant indirect effect on gait velocity, which was underpinned by their relationship with attention. For example; poorer visual function and dysfunctional saccades related to gait impairment in PD because of the impact of attentional deficit on all of these features.

<<Insert Figure 4 here>>

Discussion

To our knowledge, this is the first study to explore and explain saccade frequency during walking in PD and older adults and its relationship to gait impairment. The evidence presented suggests that attention is central to gait and visual impairment in PD. In line with our hypothesis, saccade frequency while walking was reduced in PD compared to older adults in all conditions. However both groups responded in a similar manner to turning and attentional load. Our findings support a key role for attention in gait impairment in PD, which differs from age-matched controls. Attention directly impacted gait, saccade frequency and visual function in PD. Alternatively, contrary to our hypothesis saccade frequency was not directly related to gait in PD, but was in controls. Instead, visual function and saccade frequency had an indirect influence on gait impairment in PD, which was underpinned by their relationship with attention. Therefore, attention was central to direct and indirect impact on gait impairment in PD.

Saccade frequency while walking: effect of PD and attentional manipulation

In line with our hypothesis, saccade frequency was lower in PD when walking compared to controls, but changed in a similar manner to controls in response to turning and dual task manipulation. Gait was also significantly impaired in PD compared to age-matched controls, which was expected with deficits in three of five gait characteristics (slower velocity, shorter step length and increased double support time).

We found an increase in saccade frequency in both groups when performing a turn. This agrees in part with previous work which demonstrated an increase in horizontal saccade frequency during turns in PD (Galna *et al.*, 2012). Methodological differences however, limit comparison to other turning studies which report saccades when turning while standing in place rather than walking (Anastasopoulos *et al.*, 2011; Lohnes & Earhart, 2011). In contrast their findings show

that saccade frequency increases in PD compared to controls when turning. A possible explanation for this difference could be that impaired smooth pursuit with catch up saccades results in a higher number of saccades during a turn in place (Stuart *et al.*, 2014a). The reasons for an increased saccade frequency strategy with turns are speculative but older adults and people with PD have been shown to rely more on visual rather than proprioceptive or vestibular input for appropriate motor control when walking (Azulay *et al.*, 1999; Hollands *et al.*, 2017). Therefore greater visual information may have been required when performing a turn which lead to greater saccade frequency. Increased visual feedback may be required to stabilise various body segments (head, trunk etc.) and augment the vestibular or proprioceptive feedback mechanisms involved in critical challenges of turning (i.e. balance, trajectory and stepping maintenance) (Land, 2004), which have only partially been examined (Guitton *et al.*, 1986). Alternatively, our external visual cue (a line on the floor to turn towards) may also have enabled the pre-motor cortex to bypass the supplementary motor area and BG deficits in PD (Morris *et al.*, 1996; Morris, 2000; Morris *et al.*, 2001), which would allow greater movement (i.e. saccade frequency or gait). These explanations have obvious links to gait control and falls risk due to visual impairments but also implicate attention.

Turning performance may require attentional activation of various structures at many levels of information processing, with projections underpinned by dopaminergic and cholinergic systems (Calabresi *et al.*, 2006). Redgrave *et al.* (2010) highlighted that motor control impairment occurs early in PD and requires attentional effort to overcome the loss of automatic movement, particularly when performing complex motor tasks (i.e. a turn when walking). Age-related studies have demonstrated a tendency to focus visual exploration and attention on task goals when walking (Pelz *et al.*, 2001; Hayhoe *et al.*, 2003; Mennie *et al.*, 2007; Hayhoe *et al.*, 2009), which indicates that attention, saccadic and body movements are inter-related (Beurskens & Bock, 2012). Therefore a possible explanation for the increase in saccade

frequency due to turning in our study could be due to increased attention in response to the goal-directed cued turning task, which implicates the systems theory of motor control (Bernstein, 1967; Shumway-Cook & Woollacott, 2007). Goal-directed attentional drive of more frequent saccades with a turn would enable further visual information to be integrated into forward planning and initiation of walking trajectory changes (Reed-Jones *et al.*, 2009), which may be required to compensate for age or Parkinson's related sensorimotor deficits (Rieger *et al.*, 2008b; Gilat *et al.*, 2015).

The influence of dual-tasks on saccade frequency further supports the attentional control of saccades during gait. Saccade frequency reduced in both groups under walk and turn conditions in response to a dual-task where attention was distracted from walking. Attention has been implicated in saccadic initiation and control in previous dual-task research (Stuyven *et al.*, 2000). Reduced saccade frequency under dual-task suggests that cognitive, particularly attentional processes underpin saccade frequency during gait, comparable to previous research (Hoffman & Subramaniam, 1995). Previous studies of saccades during motor tasks such as reaching (Pashler *et al.*, 1993) or button pressing (Huestegge & Koch, 2009) have also shown similar change under dual-task conditions (e.g. slower, reduced or inappropriate saccades). Dual-task gait performance has also been extensively associated with attention in both PD (Yogev *et al.*, 2005) and older adults (Yogev-Seligmann *et al.*, 2008), which indicates that within the current study attentional resources were divided between gait, saccades and cognition. Therefore under dual-task, attentional resources become saturated in response to competing task goals (Moehler & Fiehler, 2014), which may result in preferential allocation of resource to gait control (Lee *et al.*, 2003) or the secondary cognitive task when walking rather than saccadic initiation. As a consequence this may impact attentional control of saccades, particularly in PD where attention is impaired and resources are limited.

Attentional control of saccades involves the pre-frontal cortex (PFC) and its complex interaction with the basal ganglia (BG) and brain stem (Javaid *et al.*, 2012; Matsumoto *et al.*, 2012). Brain stem saccade mechanisms are reportedly unaffected in PD (Gorges *et al.*, 2014), which implicates PFC and BG impairment in saccadic deficits (Gorges *et al.*, 2015). Attentional projections from the PFC, via the BG, inhibit the superior colliculus to facilitate initiation of voluntary and inhibit reflexive saccades (Terao *et al.*, 2011). Dopamine depletion in the striatum in PD impacts cortico-BG loops (Deijen *et al.*, 2006; Tommasi *et al.*, 2015), which may be one reason for the overall reduction in saccade frequency in PD compared to controls.

Direct and indirect determinants of saccade frequency and their relationship with gait impairment

We were interested to understand the determinants of saccade frequency when walking and to examine their relationship with gait. Our results demonstrate that even though there is a relationship between cognitive and visual function (Supplementary Material 2), attentional rather than visual deficits underpin gait impairment and saccade frequency when walking in PD.

Attention (specifically FA) was a consistent determinant of saccade frequency (ΔDoor, ΔTurn) independent of demographic and visual functions in PD, but not controls. This was despite the response to environmental manipulation (a doorway) or turning and dual-task on saccade frequency being the same for both groups, and the reasons for this are unclear. We controlled for age, depression and global cognition, but a lack of cognitive impairment (MoCA <26) in control participants may have had an impact (Peltsch *et al.*, 2014). Numerous other factors may also determine saccade frequency, such as colour properties or saliency of the environment; level of fatigue (Faber *et al.*, 2012); motivation (Kaplan *et al.*, 2012); and emotional state

(Oatley *et al.*, 2011). These features may therefore play a greater role in controls compared to PD where attentional impairment dominates.

Environmental (a doorway), turning and dual-task manipulation suggested that saccade frequency was driven predominantly by attention in PD, which indicates that saccade frequency may be a proxy measure of attention in PD. This agrees with previous research that has suggested attention plays a vital role in the execution of saccades (Hoffman & Subramaniam, 1995; Liversedge & Findlay, 2000). Under single task conditions, when participants performed a turn a greater increase in saccade frequency was related to better attention. However, when distracted under dual-task conditions there was no relationship between attention and saccade frequency. This suggests that when attention is constrained under dual-task it cannot drive saccades. Despite a lack of attentional association, we identified a relationship between working memory (digit span) and saccade frequency under dual-task in PD. Earlier work has implicated working memory in the attentional control of saccades (Kane *et al.*, 2006) with poorer working memory related to reduced saccades under dual-task conditions (Mitchell *et al.*, 2002). However poorer working memory related to increased saccade frequency with turns under dual-task, which may demonstrate a lack of saccadic control with attentional impairment and distraction in PD. However the specific attentional mechanisms remain unclear, as it is difficult to tease out whether top-down (frontal or cognitive, voluntary control) or bottom-up (parietal or automatic, reflexive control) attentional control drives saccade frequency when walking under different conditions in PD (N'Guyen *et al.*, 2014).

To understand the relationship between saccade frequency (ΔDoor, ΔTurn) and gait impairment in PD, we developed an SEM based on hypothesised relationships between cognition, vision, saccades and gait impairment in PD (Figure 1) (Stuart *et al.*, 2016c). Contrary to our hypothesis reduced saccade frequency did not directly influence gait in PD, but it did in controls. Lack of direct association was unexpected but highlights the complexity of the

underlying mechanisms involved in PD. Attention (specifically FA) shared a direct relationship with visual function, which indicated that these features influence each other. For example; poor visual function would directly impact attention, as visual information is integrated into subsequent higher-level cognitive processing (Archibald *et al.*, 2009; Hajee *et al.*, 2009; Bodis-Wollner *et al.*, 2013). Alternatively, attentional impairment would directly influence visual processing from an early stage, as attention is involved in initial selection of visual stimuli (Baluch & Itti, 2011) and influences stimulus appearance (Carrasco *et al.*, 2004), contrast (Carrasco *et al.*, 2000), resolution (Carrasco *et al.*, 2002) and salience (by up to 51%) (Reynolds *et al.*, 2000). Despite the inter-related nature of visual function and attention the early biasing of visual input and subsequent influence on visual processing would denote that attention likely underpins visual function (Stuart *et al.*, 2016c). Attention also directly related to saccade frequency and gait impairment in PD, and underpinned indirect relationships between all of the other model features, which suggests an over-arching or dominant role of attention in gait impairment in PD (Lord *et al.*, 2014; Lückmann *et al.*, 2014). For example, people with PD who had poorer attention, also had poorer visual function, increased their saccade frequency to a lesser extent in response to a door or turn, and had slower gait. These findings highlight the pivotal role that attentional dysfunction plays in visual, saccadic and gait impairment in PD, and are comparable to the extensive literature regarding relationship between attention and gait in PD (Lord *et al.*, 2014; Morris *et al.*, 2016).

Previous studies have shown that visual function deficits impact gait in older adults and PD (Spaulding *et al.*, 1994; Geldmacher, 2003; Hallemans *et al.*, 2010; Swigler *et al.*, 2012; Elliott, 2014; Shin *et al.*, 2015). However such studies tend to alter the visual environment (e.g. low lighting or walk in darkness) and have not accounted for the role of attention (Stuart *et al.*, 2016c), which provides only partial insight into the underlying mechanisms of gait impairment in PD. When hypothesised relationships between visual function, attention, saccades and gait

were entered into SEM analysis, attention rather than visual function was found to primarily contribute to saccadic and gait performance in PD. Visual function only indirectly influenced these features, which was underpinned by attention. Levels of explained variance (10% gait impairment, 18% saccade frequency) and the relationship with attention concur with earlier saccadic (Buhmann *et al.*, 2015) and gait research in PD (Lord *et al.*, 2010) and older adults (Liu-Ambrose *et al.*, 2010; MacAulay *et al.*, 2014). The remaining variance of both gait and saccade frequency may be due to numerous influences on these complex behavioural outcomes, such as; fatigue (Faber *et al.*, 2012), motivation (Kaplan *et al.*, 2012), prior knowledge of testing procedures (learning effect between walks) (Kim & Rehder, 2011), emotional state (Oatley *et al.*, 2011), colour properties of the visual scene (Amano *et al.*, 2012) and saliency of objects (i.e. doorway) (t Hart *et al.*, 2013). It is not possible to control or assess all of the influences on these outcomes, but the explained variance is functionally relevant because attentional impairment is central to PD (Taylor *et al.*, 2008) and is linked to gait deficit and falls risk (Allcock *et al.*, 2009; Lord *et al.*, 2014; Lord *et al.*, 2016).

A possible explanation for these findings are that attention may be required to compensate for underlying visual or motor (gait) deficits in PD, which has been discussed in previous work (Stuart *et al.*, 2016c). For example; those with better attention have more neural resources available to compensate for the dysfunctional BG (Rubinstein *et al.*, 2002; Tombu & Jolicoeur, 2003; Heuninckx *et al.*, 2008; Yogev-Seligmann *et al.*, 2008) or enhance vision (Carrasco & McElree, 2001; Carrasco *et al.*, 2004; Carrasco, 2006). However visual, saccadic and gait deficits persist despite attentional compensation. Compensation is most likely constrained by attentional, particularly FA impairment with PD progression (Ballard *et al.*, 2002), which has been linked to cholinergic dysfunction (Emre *et al.*, 2004; Molloy *et al.*, 2006). Increased cholinergic burden with PD has been related to gait impairment (Bohnen & Albin, 2011; Rochester *et al.*, 2012), cognitive dysfunction (Burn *et al.*, 2006), and falls (Yarnall *et al.*, 2011;

Henderson *et al.*, 2016). Therefore impaired FA as a result of progressive cholinergic burden with PD would lead to deficits in visual functions, saccadic activity and gait, with implication for increased trips and falls.

Clinical Implications

Our findings suggest that impaired attention, which is a common and early problem in PD, negatively impacts gait directly and indirectly through reduced visual observation which in turn impairs gait. Visual observation is critical to effective and safe gait, and impairment may lead to trips and falls, and overall reduced mobility. Greater awareness of the need for visual observation during gait, particularly how frequently an individual scans their environment as they move through it may therefore be important to improve overall safety. Targeting attention directly and through saccadic deficits with specific attentional therapeutic interventions (e.g. visual cues), rehabilitation (e.g. eye movement training (Zampieri & Di Fabio, 2008)) or pharmacological manipulation (e.g. rivastigmine (Henderson *et al.*, 2016)) may improve saccade frequency and gait in PD, which could reduce falls risk. Further research is required to understand the specific attentional mechanisms driving saccades during gait in PD in order to inform the most appropriate method of intervention.

Study Strengths and Limitations

A key strength of this hypothesis driven observational study was the use of SEM analysis and a clear *a priori* model to guide analysis (Figure 1). SEM allowed for examination of hypothesised relationships between cognition, vision, change in saccade frequency and gait, and uncovered important direct and indirect relationships.

A limitation of this study was the range of vision assessments performed, as we only used basic chart measures typically performed in clinic. Other vision measures such as depth or motion perception, or ideally a full neuro-ophthalmic battery should be performed in future studies.

These features may alter the contribution of vision within our model, or may highlight further interactions between visual and cognitive functions.

Conclusions

Our findings highlight important effects of attention on saccade frequency and gait when walking in PD. Attention has a central role in saccadic and gait impairment in PD. It had direct impact on visual observation of the environment when walking (reduced saccades) which in turn may influence safe navigation and avoidance of trip hazards. In addition, attention also shared a direct relationship with visual function which will influence visual observation when walking. Attention therefore represents a key target for therapeutics. Future research examining gait and vision in PD must consider the role of attention within visual, saccadic and gait impairment.

Acknowledgements

This research is supported by the National Institute for Health Research (NIHR) Newcastle Biomedical Research Unit (BRU) and centre (BRC) based at Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University. The research was also supported by NIHR Newcastle CRF Infrastructure funding. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

The authors would like to acknowledge Dr Alan Godfrey (Research Associate, Newcastle University), Aodhán Hickey (Research Technician, Newcastle University) and Henry King (Master's student) for their assistance with data collection and processing, and Dr Shirley Coleman (Senior Statistician, Newcastle University) for her advice regarding data analysis. Finally we thank all of the participants involved in the study for their time and input.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

S.S., B.G., S.L., L.R designed the study. S.S. and B.G. collected and analysed the data. S.S. wrote the first draft of the manuscript. S.S., B.G., L.S.D, S.L. and L.R. edited and revised the manuscript. L.R. conceived the experiment and directed the work.

Data Accessibility Statement

Data reported within this article is available at ClinicalTrials.gov (Reference NCT02610634 at https://clinicaltrials.gov/ct2/show/NCT02610634) and can be requested from the corresponding author.

Abbreviations

PD: Parkinson's disease, EOG: electrooculography, SEM: Structural equation model, BG: Basal ganglia, PFC: Pre-frontal cortex, FA: Fluctuation of attention, PoA: Power of attention, MoCA: Montreal cognitive assessment, ACE-R: Addenbrookes cognitive examination, JLO: Judgement of line orientation, VA: visual acuity, CS: contrast sensitivity, GDS-15: Geriatric depression scale (short form), UPDRS: unified Parkinson's disease rating scale, LED: Levodopa equivalent dosage.

References

Allcock, L.M., Rowan, E.N., Steen, I.N., Wesnes, K., Kenny, R.A. & Burn, D.J. (2009) Impaired attention predicts falling in Parkinson's disease. *Parkinsonism & related disorders*, **15**, 110-115.

Allison, P.D. (1990) Change scores as dependent variables in regression analysis. *Sociological methodology*, **20**, 93-114.

Amano, K., Foster, D.H., Mould, M.S. & Oakley, J.P. (2012) Visual search in natural scenes explained by local color properties. *Journal of the Optical Society of America. A, Optics, image science, and vision*, **29**, A194-199.

Anastasopoulos, D., Ziavra, N., Savvidou, E., Bain, P. & Bronstein, A.M. (2011) Altered eye-to-foot coordination in standing parkinsonian patients during large gaze and whole-body reorientations. *Movement disorders : official journal of the Movement Disorder Society*, **26**, 2201-2211.

Archibald, N.K., Clarke, M.P., Mosimann, U.P. & Burn, D.J. (2009) The retina in Parkinson's disease. *Brain*, **132**, 1128-1145.

Azulay, J.P., Mesure, S., Amblard, B., Blin, O., Sangla, I. & Pouget, J. (1999) Visual control of locomotion in Parkinson's disease. *Brain*, **122**, 111-120.

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. & Tovee, M. (2002) Fluctuations in attention: PD dementia vs DLB with parkinsonism. *Neurology*, **59**, 1714-1720.

Baluch, F. & Itti, L. (2011) Mechanisms of top-down attention. *Trends in neurosciences*, **34**, 210-224.

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. & Halgren, E. (2006) Top-down facilitation of visual recognition. *Proceedings of the National Academy of Sciences of the United States of America*, **103**, 449-454.

Barker, R.A. & Williams-Gray, C.H. (2015) Mild Cognitive Impairment and Parkinson's Disease-Something to Remember. *Journal of Parkinson's disease*, **4**, 651-656.

Beck, E.N., Ehgoetz Martens, K.A. & Almeida, Q.J. (2015) Freezing of Gait in Parkinson's Disease: An Overload Problem? *PLoS ONE*, **10**, e0144986.

Becker, W. (1989) The neurobiology of saccadic eye movements. Metrics. *Reviews of oculomotor research*, **3**, 13-67.

Bentler, P.M. & Chou, C.-P. (1987) Practical Issues in Structural Modeling. *Sociological Methods & Research*, **16**, 78-117.

Bernstein, N. (1967) *The co-ordination and regulation of movements*. Pergamon, Oxford, UK.

Beurskens, R. & Bock, O. (2012) Age-Related Deficits of Dual-Task Walking: A Review. *Neural Plasticity*, **1**, 1-9.

Bodis-Wollner, I., Glazman, S. & Yerram, S. (2013) Fovea and foveation in Parkinson's disease. *Behavioral neuroscience*, **127**, 139-150.

Bohnen, N.I. & Albin, R.L. (2011) The cholinergic system and Parkinson disease. *Behav Brain Res*, **221**, 564-573.

Borji, A., Sihite, D. & Itti, L. (2011) Computational Modeling of Top-down Visual Attention in Interactive Environments. In Hoey, J., McKenna, S., Trucco, E. (eds) *Proceedings of the British Machine Vision Conference*. BMVA Press, pp. 85.81-85.12.

Bridgeman, B., Kirch, M. & Sperling, A. (1981) Segregation of cognitive and motor aspects of visual function using induced motion. *Perception & Psychophysics*, **29**, 336-342.

Buhmann, C., Kraft, S., Hinkelmann, K., Krause, S., Gerloff, C. & Zangemeister, W.H. (2015) Visual Attention and Saccadic Oculomotor Control in Parkinson's Disease. *European Neurology*, **73**, 283-293.

Burn, D.J., Rowan, E.N., Allan, L.M., Molloy, S., O'Brien, J.T. & McKeith, I.G. (2006) Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. *Journal of neurology, neurosurgery, and psychiatry*, **77**, 585-589.

Burn, D.J. & Yarnall, A.J. (2014) Dementia in Parkinson's disease. In Chaudhuri, K.R., Tolosa, E., Schapira, A.H.V., Poewe, W. (eds) *Non-motor Symptoms of Parkinsons Disease*. Oxford University Press, Oxford, UK., pp. 158-171.

Byrne, B.M. (2013) *Structural equation modeling with AMOS: Basic concepts, applications, and programming*. Routledge: Taylor and Francis Group.

Calabresi, P., Picconi, B., Parnetti, L. & Di Filippo, M. (2006) A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine–acetylcholine synaptic balance. *The Lancet Neurology*, **5**, 974-983.

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., Tse, P.U. (eds) *Progress in Brain Research*. Elsevier, New York, pp. 33-70.

Carrasco, M., Ling, S. & Read, S. (2004) Attention alters appearance. *Nature Neuroscience*, **7**, 308-313.

Carrasco, M. & McElree, B. (2001) Covert attention accelerates the rate of visual information processing. *Proceedings of the National Academy of Sciences*, **98**, 5363-5367.

Carrasco, M., Penpeci-Talgar, C. & Eckstein, M. (2000) Spatial covert attention increases contrast sensitivity across the CSF: support for signal enhancement. *Vision research*, **40**, 1203-1215.

Carrasco, M., Williams, P.E. & Yeshurun, Y. (2002) Covert attention increases spatial resolution with or without masks: Support for signal enhancement. *Journal of Vision*, **2**, 467-479.

Christopher Westland, J. (2010) Lower bounds on sample size in structural equation modeling. *Electronic Commerce Research and Applications*, **9**, 476-487.

Cowie, D., Limousin, P., Peters, A. & Day, B.L. (2010) Insights into the neural control of locomotion from walking through doorways in Parkinson's disease. *Neuropsychologia*, **48**, 2750-2757.

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. & Anderson, T.J. (2010) The MoCA: well-suited screen for cognitive impairment in Parkinson disease. *Neurology*, **75**, 1717-1725.

Davidsdottir, S., Wagenaar, R., Young, D. & Cronin-Golomb, A. (2008) Impact of optic flow perception and egocentric coordinates on veering in Parkinson's disease. *Brain*, **131**, 2882-2893.

Deijen, J.B., Stoffers, D., Berendse, H.W., Wolters, E. & Theeuwes, J. (2006) Abnormal susceptibility to distracters hinders perception in early stage Parkinson's disease: a controlled study. *BMC neurology*, **6**, 1-9.

Dowiasch, S., Marx, S., Einhäuser, W. & Bremmer, F. (2015) Effects of aging on eye movements in the real world. *Frontiers in human neuroscience*, **9**, 1-12.

Elliott, D.B. (2014) The Glenn A. Fry award lecture 2013: blurred vision, spectacle correction, and falls in older adults. *Optometry and vision science : official publication of the American Academy of Optometry*, **91**, 593-601.

Emre, M. (2003) Dementia associated with Parkinson's disease. *The Lancet. Neurology*, **2**, 229-237.

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. & Lane, R. (2004) Rivastigmine for dementia associated with Parkinson's disease. *The New England journal of medicine*, **351**, 2509-2518.

Faber, L.G., Maurits, N.M. & Lorist, M.M. (2012) Mental Fatigue Affects Visual Selective Attention. *PloS one*, **7**, e48073.

Field, A. (2013) *Discovering statistics using IBM SPSS statistics*. Sage, London, UK.

Findlay, J.M. (1997) Saccade target selection during visual search. *Vision research*, **37**, 617-631.

Galna, B., Lord, S., Burn, D.J. & Rochester, L. (2015) Progression of gait dysfunction in incident Parkinson's disease: Impact of medication and phenotype. *Movement Disorders*, **30**, 359-367.

Galna, B., Lord, S., Daud, D., Archibald, N., Burn, D. & Rochester, L. (2012) Visual sampling during walking in people with Parkinson's disease and the influence of environment and dual-task. *Brain research*, **1473**, 35-43.

Geldmacher, D.S. (2003) Visuospatial dysfunction in the neurodegenerative diseases. *Frontiers in Bioscience*, **8**, e428-436.

Gilat, M., Shine, J.M., Walton, C.C., O'Callaghan, C., Hall, J.M. & Lewis, S.J.G. (2015) Brain activation underlying turning in Parkinson's disease patients with and without freezing of gait: a virtual reality fMRI study. *npj Parkinson's Disease*, **1**, 15020.

Goetz, C.G., Tilley, B.C., Shaftman, S.R., Stebbins, G.T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M.B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A.E., Lees, A., Leurgans, S., LeWitt, P.A., Nyenhuis, D., Olanow, C.W., Rascol, O., Schrag, A., Teresi, J.A., van Hilten, J.J. & LaPelle, N. (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*, **23**, 2129-2170.

Gorges, M., Müller, H.-P., Lulé, D., Pinkhardt, E., Ludolph, A. & 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**, 1-13.

Gorges, M., Pinkhardt, E.H. & Kassubek, J. (2014) Alterations of Eye Movement Control in Neurodegenerative Movement Disorders. *Journal of Ophthalmology*, **1**, 1-11.

Guitton, D., Kearney, R.E., Wereley, N. & Peterson, B.W. (1986) Visual, vestibular and voluntary contributions to human head stabilization. *Experimental brain research*, **64**, 59-69.

Hajee, M.E., March, W.F., Lazzaro, D.R., Wolintz, A.H., Shrier, E.M., Glazman, S. & Bodis-Wollner, I.G. (2009) Inner retinal layer thinning in Parkinson disease. *Archives of ophthalmology*, **127**, 737-741.

Hallemans, A., Ortibus, E., Meire, F. & Aerts, P. (2010) Low vision affects dynamic stability of gait. *Gait & posture*, **32**, 547-551.

Hayhoe, M., Gillam, B., Chajka, K. & Vecellio, E. (2009) The role of binocular vision in walking. *Visual neuroscience*, **26**, 73-80.

Hayhoe, M.M., Shrivastava, A., Mruczek, R. & Pelz, J.B. (2003) Visual memory and motor planning in a natural task. *Journal of Vision*, **3**, 6-6.

Henderson, E.J., Lord, S.R., Brodie, M.A., Gaunt, D.M., Lawrence, A.D., Close, J.C.T., Whone, A.L. & Ben-Shlomo, Y. (2016) Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet Neurology*, **15**, 249-258.

Hernandez, T.D., Levitan, C.A., Banks, M.S. & Schor, C.M. (2008) How does saccade adaptation affect visual perception? *Journal of Vision*, **8**, 3-3.

Heuninckx, S., Wenderoth, N. & Swinnen, S.P. (2008) Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, **28**, 91-99.

Hoffman, J.E. & Subramaniam, B. (1995) The role of visual attention in saccadic eye movements. *Perception & Psychophysics*, **57**, 787-795.

Hollands, M., Hollands, K. & Rietdyk, S. (2017) Visual Control of Adaptive Locomotion and Changes Due to Natural Ageing. In Barbieri, F.A., Vitório, R. (eds) *Locomotion and Posture in Older Adults: The Role of Aging and Movement Disorders*. Springer International Publishing, Cham, pp. 55-72.

Holmqvist, K. & Nystrom, M. (2011) *Eye tracking: A comprehensive guide to methods and measures*. Oxford University Press, Oxford, UK.

Horowitz, T.S., Choi, W.Y., Horvitz, J.C., Cote, L.J. & Mangels, J.A. (2006) Visual search deficits in Parkinson's disease are attenuated by bottom-up target salience and top-down information. *Neuropsychologia*, **44**, 1962-1977.

Hoyle, R.H. & Gottfredson, N.C. (2014) Sample Size Considerations in Prevention Research Applications of Multilevel Modeling and Structural Equation Modeling. *Prev Sci*, **16**, 987-996.

Huestegge, L. & Koch, I. (2009) Dual-task crosstalk between saccades and manual responses. *Journal of experimental psychology. Human perception and performance*, **35**, 352-362.

Javaid, M.A., Amassian, V., Glazman, S., Fesharaki, A., Stefanov, D. & Bodis-Wollner, I. (2012) Cortical control of voluntary saccades in Parkinson's disease and pre-emptive perception. *Parkinsonism & related disorders*, **18**, S100-S103.

Just, M.A. & Carpenter, P.A. (1980) A theory of reading: From eye fixations to comprehension. *Psychological review*, **87**, 329.

Kane, M.J., Poole, B.J., Tuholski, S.W. & 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**, 749-777.

Kaplan, R.L., Van Damme, I. & Levine, L.J. (2012) Motivation Matters: Differing Effects of Pre-Goal and Post-Goal Emotions on Attention and Memory. *Frontiers in psychology*, **3**, 1-9.

Kelly, V.E., Eusterbrock, A.J. & Shumway-Cook, A. (2012) A review of dual-task walking deficits in people with Parkinson's disease: motor and cognitive contributions, mechanisms, and clinical implications. *Parkinson's disease*, **1**, 1-14.

Kim, S. & Rehder, B. (2011) How prior knowledge affects selective attention during category learning: An eyetracking study. *Mem Cogn*, **39**, 649-665.

Kimmig, H., Greenlee, M., Gondan, M., Schira, M., Kassubek, J. & Mergner, T. (2001) Relationship between saccadic eye movements and cortical activity as measured by fMRI: quantitative and qualitative aspects. *Experimental brain research*, **141**, 184-194.

Kline, R.B. (2011) *Principles and Practice of Structural Equation Modelling*. Guildford Publishing Group, New York.

Kravitz, D.J., Saleem, K.S., Baker, C.I. & Mishkin, M. (2011) A new neural framework for visuospatial processing. *Nature Reviews. Neuroscience*, **12**, 217-230.

Land, M.F. (2004) The coordination of rotations of the eyes, head and trunk in saccadic turns produced in natural situations. *Experimental brain research*, **159**, 151-160.

Lebold, C.A. & Almeida, Q.J. (2010) Evaluating the contributions of dynamic flow to freezing of gait in Parkinson's disease. *Parkinson's disease*, **1**, 1-7.

Lee, C., Grossman, M., Morris, J., Stern, M.B. & Hurtig, H.I. (2003) Attentional resource and processing speed limitations during sentence processing in Parkinson's disease. *Brain and Language*, **85**, 347-356.

Legters, K. (2002) Fear of Falling. *Physical Therapy*, **82**, 264-272.

Liu-Ambrose, T., Davis, J., Nagamatsu, L., Hsu, L., Katarynych, L. & Khan, K. (2010) Changes in executive functions and self-efficacy are independently associated with improved usual gait speed in older women. *BMC Geriatr*, **10**, 1-8.

Liversedge, S.P. & Findlay, J.M. (2000) Saccadic eye movements and cognition. *Trends in cognitive sciences*, **4**, 6-14.

Lohnes, C.A. & Earhart, G.M. (2011) Saccadic Eye Movements Are Related to Turning Performance in Parkinson Disease. *J Parkinsons Dis*, **1**, 109-118.

Lord, S., Galna, B., Coleman, S., Yarnall, A., Burn, D. & 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**, 1-9.

Lord, S., Galna, B., Yarnall, A.J., Coleman, S., Burn, D. & Rochester, L. (2016) Predicting first fall in newly diagnosed Parkinson's disease: Insights from a fall-naive cohort. *Movement disorders : official journal of the Movement Disorder Society*.

Lord, S., Rochester, L., Hetherington, V., Allcock, L.M. & Burn, D. (2010) Executive dysfunction and attention contribute to gait interference in 'off' state Parkinson's Disease. *Gait & posture*, **31**, 169-174.

Lovie-Kitchin, J.E. (1988) Validity and reliability of viscual acuity measurements. *Ophthalmic and Physiological Optics*, **8**, 363-370.

Lückmann, H.C., Jacobs, H.I.L. & Sack, A.T. (2014) The cross-functional role of frontoparietal regions in cognition: internal attention as the overarching mechanism. *Progress in Neurobiology*, **116**, 66-86.

Macaluso, E. (2006) Multisensory Processing in Sensory-Specific Cortical Areas. *The Neuroscientist*, **12**, 327-338.

MacAulay, R.K., Brouillette, R.M., Foil, H.C., Bruce-Keller, A.J. & Keller, J.N. (2014) A Longitudinal Study on Dual-Tasking Effects on Gait: Cognitive Change Predicts Gait Variance in the Elderly. *PloS one*, **9**, e99436.

Mannan, S.K., Hodgson, T.L., Husain, M. & Kennard, C. (2008) Eye movements in visual search indicate impaired saliency processing in Parkinson's disease. **171**, 559-562.

Manor, B.R. & Gordon, E. (2003) Defining the temporal threshold for ocular fixation in free-viewing visuocognitive tasks. *Journal of neuroscience methods*, **128**, 85-93.

Matsumoto, H., Terao, Y., Furubayashi, T., Yugeta, A., Fukuda, H., Emoto, M., Hanajima, R. & Ugawa, Y. (2012) Basal ganglia dysfunction reduces saccade amplitude during visual scanning in Parkinson's disease. *Basal Ganglia*, **2**, 73-78.

Mazer, J.A. (2011) Spatial attention, feature-based attention, and saccades: three sides of one coin? *Biological psychiatry*, **69**, 1147-1152.

Mennie, N., Hayhoe, M. & Sullivan, B. (2007) Look-ahead fixations: anticipatory eye movements in natural tasks. *Experimental brain research*, **179**, 427-442.

Menz, H.B., Lord, S.R. & Fitzpatrick, R.C. (2007) A structural equation model relating impaired sensorimotor function, fear of falling and gait patterns in older people. *Gait & posture*, **25**, 243-249.

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R. & Hodges, J.R. (2006) The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry*, **21**, 1078-1085.

Mitchell, J.P., Macrae, C.N. & Gilchrist, I.D. (2002) Working memory and the suppression of reflexive saccades. *Journal of cognitive neuroscience*, **14**, 95-103.

Moehler, T. & Fiehler, K. (2014) Effects of spatial congruency on saccade and visual discrimination performance in a dual-task paradigm. *Vision research*, **105**, 100-111.

Molloy, S.A., Rowan, E.N., O'Brien, J.T., McKeith, I.G., Wesnes, K. & 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**, 1323-1328.

Montse, A., Pere, V., Carme, J., Francesc, V. & Eduardo, T. (2001) Visuospatial deficits in Parkinson's disease assessed by judgment of line orientation test: error analyses and practice effects. *Journal of clinical and experimental neuropsychology*, **23**, 592-598.

Morris, M.E. (2000) Movement disorders in people with Parkinson disease: a model for physical therapy. *Phys Ther*, **80**, 578-597.

Morris, M.E., Huxham, F., McGinley, J., Dodd, K. & Iansek, R. (2001) The biomechanics and motor control of gait in Parkinson disease. *Clinical Biomechanics*, **16**, 459-470.

Morris, M.E., Iansek, R., Matyas, T.A. & Summers, J.J. (1996) Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. *Brain*, **119 (Pt 2)**, 551-568.

Morris, R., Lord, S., Bunce, J., Burn, D. & Rochester, L. (2016) Gait and cognition: Mapping the global and discrete relationships in ageing and neurodegenerative disease. *Neuroscience & Biobehavioral Reviews*, **64**, 326-345.

N'Guyen, S., Thurat, C. & Girard, B. (2014) Saccade learning with concurrent cortical and subcortical basal ganglia loops. *Frontiers in Computational Neuroscience*, **8**, 1-17.

Nelson, J.D., Cottrell, G.W., Movellan, J.R. & Sereno, M.I. (2004) Yarbus lives: a foveated exploration of how task influences saccadic eye movement. *Journal of Vision*, **4**, 741-741.

Nys, G.M., Santens, P. & Vingerhoets, G. (2010) Horizontal and vertical attentional orienting in Parkinson's disease. *Brain and cognition*, **74**, 179-185.

Oatley, K., Parrott, W.G., Smith, C. & Watts, F. (2011) Cognition and Emotion over twenty-five years. *Cognition and Emotion*, **25**, 1341-1348.

Pashler, H., Carrier, M. & Hoffman, J. (1993) Saccadic eye movements and dual-task interference. *The Quarterly journal of experimental psychology. A, Human experimental psychology*, **46**, 51-82.

Patla, A., Adkin, A., Martin, C., Holden, R. & Prentice, S. (1996) Characteristics of voluntary visual sampling of the environment for safe locomotion over different terrains. *Experimental brain research*, **112**, 513-522.

Peltsch, A., Hemraj, A., Garcia, A. & Munoz, D.P. (2014) Saccade deficits in amnestic mild cognitive impairment resemble mild Alzheimer's disease. *The European journal of neuroscience*, **39**, 2000-2013.

Pelz, J., Hayhoe, M. & Loeber, R. (2001) The coordination of eye, head, and hand movements in a natural task. *Experimental brain research*, **139**, 266-277.

Rapport, L.J., Millis, S.R. & Bonello, P.J. (1998) Validation of the Warrington theory of visual processing and the Visual Object and Space Perception Battery. *Journal of clinical and experimental neuropsychology*, **20**, 211-220.

Redgrave, P., Rodriguez, M., Smith, Y., Rodriguez-Oroz, M.C., Lehericy, S., Bergman, H., Agid, Y., DeLong, M.R. & Obeso, J.A. (2010) Goal-directed and habitual control in the basal ganglia: implications for Parkinson’s disease. *Nature reviews. Neuroscience*, **11**, 760-772.

Reed-Jones, R., Reed-Jones, J., Vallis, L.A. & Hollands, M. (2009) The effects of constraining eye movements on visually evoked steering responses during walking in a virtual environment. *Experimental brain research*, **197**, 357-367.

Reynolds, J.H., Pasternak, T. & Desimone, R. (2000) Attention Increases Sensitivity of V4 Neurons. *Neuron*, **26**, 703-714.

Rieger, J.W., Kim, A., Argyelan, M., Farber, M., Glazman, S., Liebeskind, M., Meyer, T. & Bodis-Wollner, I. (2008a) Cortical Functional Anatomy of Voluntary Saccades in Parkinson Disease. *Clinical EEG and neuroscience*, **39**, 169-174.

Rieger, J.W., Kim, A., Argyelan, M., Farber, M., Glazman, S., Liebeskind, M., Meyer, T. & Bodis-Wollner, I. (2008b) Cortical functional anatomy of voluntary saccades in Parkinson disease. *Clinical EEG and neuroscience*, **39**, 169-174.

Rochester, L., Galna, B., Lord, S. & Burn, D. (2014) The nature of dual-task interference during gait in incident Parkinson's disease. *Neuroscience*, **265**, 83-94.

Rochester, L., Yarnall, A.J., Baker, M.R., David, R.V., Lord, S., Galna, B. & Burn, D.J. (2012) Cholinergic dysfunction contributes to gait disturbance in early Parkinson's disease. *Brain*, **135**, 2779-2788.

Royall, D.R., Cordes, J.A. & Polk, M. (1998) CLOX: an executive clock drawing task. *Journal of neurology, neurosurgery, and psychiatry*, **64**, 588-594.

Rubinstein, T.C., Giladi, N. & 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. *Movement disorders : official journal of the Movement Disorder Society*, **17**, 1148-1160.

Salthouse, T.A. (1996) The processing-speed theory of adult age differences in cognition. *Psychol Rev*, **103**, 403-428.

Salvucci, D.D. & 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.

Sethi, K. (2008) Levodopa unresponsive symptoms in Parkinson disease. *Movement disorders : official journal of the Movement Disorder Society*, **23 Suppl 3**, S521-533.

Shin, S.-s., An, D.-h. & 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**, 208-213.

Shumway-Cook, A. & Woollacott, M.H. (2007) *Motor control: translating research into clinical practice*. Lippincott Williams & Wilkins.

Spaulding, S.J., Patla, A.E., Elliott, D.B., Flanagan, J., Rietdyk, S. & Brown, S. (1994) Waterloo Vision and Mobility Study: Gait Adaptations to Altered Surfaces in Individuals with Age-Related Maculopathy. *Optometry & Vision Science*, **71**, 770-777.

Stuart, S., Alcock, L., Galna, B., Lord, S. & Rochester, L. (2014a) 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**, 175-188.

Stuart, S., Alcock, L., Godfrey, A., Lord, S., Rochester, L. & Galna, B. (2016a) Accuracy and re-test reliability of mobile eye-tracking in Parkinson's disease and older adults. *Medical Engineering and Physics*, **38**, 308–315.

Stuart, S., Galna, B., Lord, S. & Rochester, L. (2016b) A protocol to examine vision and gait in Parkinson's disease: impact of cognition and response to visual cues [version 2; referees: 2 approved]. *F1000Research*, **4**, 1379.

Stuart, S., Galna, B., Lord, S., Rochester, L. & 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*. IEEE, Chicago, Illinois, USA, pp. 5739 - 5742.

Stuart, S., Lord, S., Hill, E. & Rochester, L. (2016c) Gait in Parkinson's disease: A visuo-cognitive challenge. *Neuroscience & Biobehavioral Reviews*, **62**, 76-88.

Stuyven, E., Van der Goten, K., Vandierendonck, A., Claeys, K. & Crevits, L. (2000) The effect of cognitive load on saccadic eye movements. *Acta psychologica*, **104**, 69-85.

Swigler, C., Martin, A., Milice, F., Walley, M., LaPointe, L.L., Maitland, G. & Saunders, C. (2012) Contrast sensitivity visual acuity is deficient in Parkinson's disease and degrades motor performance. *Parkinsonism and Related Disorders*, **18**, S104-S105.

t Hart, B.M., Schmidt, H.C.E.F., Klein-Harmeyer, I. & Einhäuser, W. (2013) Attention in natural scenes: contrast affects rapid visual processing and fixations alike. *Philos Trans R Soc Lond B*, **368**, 1-10.

Tanguma, J. (2001) Effects of Sample Size on the Distribution of Selected Fit Indices: A Graphical Approach. *Educational and Psychological Measurement*, **61**, 759-776.

Taylor, J.P., Rowan, E.N., Lett, D., O'Brien, J.T., McKeith, I.G. & 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**, 1318-1323.

Terao, Y., Fukuda, H., Yugeta, A., Hikosaka, O., Nomura, Y., Segawa, M., Hanajima, R., Tsuji, S. & 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**, 1794-1806.

Tombu, M. & Jolicoeur, P. (2003) A central capacity sharing model of dual-task performance. *Journal of experimental psychology. Human perception and performance*, **29**, 3-18.

Tomlinson, C.L., Stowe, R., Patel, S., Rick, C., Gray, R. & Clarke, C.E. (2010) Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*, **25**, 2649-2653.

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. & 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. *Journal of cognitive neuroscience*, **27**, 1215-1237.

Uc, E.Y., Rizzo, M., Anderson, S.W., Sparks, J., Rodnitzky, R.L. & Dawson, J.D. (2006) Impaired visual search in drivers with Parkinson's disease. *Ann Neurol*, **60**, 407-413.

van Haastregt, J.C.M., Zijlstra, G.A.R., van Rossum, E., van Eijk, J.T.M. & 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**, 186-193.

Verleger, R., Koerbs, A., Graf, J., Śmigasiewicz, K., Schroll, H. & 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**, 38-47.

Vitório, R., Gobbi, L.T.B., Lirani-Silva, E., Moraes, R. & Almeida, Q.J. (2016) Synchrony of gaze and stepping patterns in people with Parkinson's disease. *Behavioural Brain Research*, **307**, 159-164.

Vitorio, R., Lirani-Silva, E., Barbieri, F.A., Raile, V., Batistela, R.A., Stella, F. & Gobbi, L.T. (2012) The role of vision in Parkinson's disease locomotion control: free walking task. *Gait & posture*, **35**, 175-179.

Vitório, R., Lirani-Silva, E., Pieruccini-Faria, F., Moraes, R., Gobbi, L.T.B. & Almeida, Q.J. (2014) Visual cues and gait improvement in Parkinson's disease: Which piece of information is really important? *Neuroscience*, **277**, 273-280.

Wechsler, D. (1945) A standardized memory scale for clinical use. *The Journal of Psychology*, **19**, 87-95.

Weil, R.S., Schrag, A.E., Warren, J.D., Crutch, S.J., Lees, A.J. & Morris, H.R. (2016) Visual dysfunction in Parkinson's disease. *Brain*.

West, R. & Alain, C. (2000) Effects of task context and fluctuations of attention on neural activity supporting performance of the Stroop task. *Brain research*, **873**, 102-111.

Wilde, N.J., Strauss, E. & Tulsky, D.S. (2004) Memory Span on the Wechsler Scales. *Journal of clinical and experimental neuropsychology*, **26**, 539-549.

Wolf, E.J., Harrington, K.M., Clark, S.L. & Miller, M.W. (2013) Sample Size Requirements for Structural Equation Models: An Evaluation of Power, Bias, and Solution Propriety. *Educational and psychological measurement*, **76**, 913-934.

Xiong, B., Skitmore, M. & Xia, B. (2015) A critical review of structural equation modeling applications in construction research. *Automation in Construction*, **49**, 59-70.

Yarbus, A.L. (1967) *Eye movements during perception of complex objects*. Springer.

Yardley, L., Beyer, N., Hauer, K., Kempen, G., Piot-Ziegler, C. & Todd, C. (2005) Development and initial validation of the Falls Efficacy Scale-International (FES-I). *Age Ageing*, **34**, 614-619.

Yarnall, A., Rochester, L. & Burn, D.J. (2011) The interplay of cholinergic function, attention, and falls in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*, **26**, 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. & On behalf of the, I.-P.D.S.G. (2014) Characterizing mild cognitive impairment in incident Parkinson disease: The ICICLE-PD Study. *Neurology*, **82**, 308-316.

Yesavage, J.A. & Sheikh, J.I. (1986) Geriatric Depression Scale (GDS). *Clinical Gerontologist*, **5**, 165-173.

Yogev-Seligmann, G., Hausdorff, J.M. & Giladi, N. (2008) The role of executive function and attention in gait. *Movement disorders : official journal of the Movement Disorder Society*, **23**, 329-342; quiz 472.

Yogev, G., Giladi, N., Peretz, C., Springer, S., Simon, E.S. & Hausdorff, J.M. (2005) Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *The European journal of neuroscience*, **22**, 1248-1256.

Zampieri, C. & 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**, 1460-1473.

Zelinsky, G.J., Rao, R.P.N., Hayhoe, M.M. & Ballard, D.H. (1997) Eye movements reveal the spatiotemporal dynamics of visual search. *Psychological Science*, **8**, 448-453.

Figure Legends:

Figure 1 - Theoretical Model of Cognitive and Visual Contribution to Gait Impairment in Parkinson's disease [Six pathways are involved; A) Cognition and gait, B) Vision and gait, C) Interaction between cognitive and visual functions, D) Saccades and gait, E) Cognition and saccades, and F) Vision and saccades]

Figure 2 - Study Protocol: A) Walking conditions, B) Dikablis mobile infra-red eye-tracker and electrooculography (EOG) placement, C) Mobile eye-tracker raw data [an example of a saccade occurrence has been marked on each x axis at the point when detected]

Figure 3 - Saccade frequency during gait [Mean and standard deviation (SD) results for single and dual task walking are displayed]

Figure 4 – Structural equation model of cognitive and visual contributions to gait impairment in Parkinson's disease [*significance level $p<.05$, dashed lines are non-significant pathways, indirect pathways are represented by faded block arrows underlying direct pathways, solid arrows are direct pathways, double-headed arrows represent correlations or shared relationships, latent variables are represented via circles/ovals and observed variables via rectangles]

Table 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†**
	Corrective eye-wear	Correction 31 / None 9	Correction 36 / None 20	.184†
	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)	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***
	Fluctuating attention (FA)	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) *[median and range]*	-	60.00 (4 - 444)	-
	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)	-
	Freezing of gait questionnaire (FOGQ)	-	3.52 (6.24)	-
	Levodopa equivalent daily dosage (LED)	-	599.87 (402.56)	-

[*significance level p<.05, SD = standard deviation, VOSP= visual object and spatial perception battery, † = X^2]

Table 2 – Gait characteristics

			Gait		
Group	**Task**	**Environment**	**Velocity (m/sec) Mean (SD)**	**Step length (m) Mean (SD)**	**Double support (sec) Mean (SD)**
PD	Single	Walk	1.07 (0.19)	0.62 (0.10)	0.31 (0.09)
		Turn	0.95 (0.17)	0.54 (0.09)	0.34 (0.12)
	Dual	Walk	0.99 (0.19)	0.59 (0.08)	0.33 (0.08)
		Turn	0.90 (0.16)	0.54 (0.09)	0.34 (0.08)
Control	Single	Walk	1.26 (0.18)	0.70 (0.09)	0.26 (0.06)
		Turn	1.09 (0.15)	0.60 (0.08)	0.28 (0.06)
	Dual	Walk	1.09 (0.20)	0.64 (0.08)	0.30 (0.07)
		Turn	0.99 (0.16)	0.57 (0.07)	0.31 (0.06)
Group Main Effect *F* (*p*)			**14.9 (<0.001)***	**9.7 (0.002)***	**0.2 (0.003)***

[sec = seconds, m = meters, SD = standard deviation]

Table 3 - Demographic, cognitive and visual function association with saccade frequency

Task	Change in Saccade Frequency (ΔSacc/sec)		PD		Control	
			ß	***p***	**ß**	***p***
Single	ΔDoor	Age	-.244	.156	-.259	.248
		UPDRS III	-.061	.737	-	-
		MoCA	-.166	.358	-.210	.275
		GDS-15	.019	.906	-.021	.904
		FA	**-.449**	**.009***	.077	.731
		JLO	-.096	.550	-.179	.429
		CLOX 1	.220	.177	-.074	.765
		Digit span	.049	.725	.174	.410
		VA	-.182	.310	.118	.591
		CS	-.365	.089	-.129	.544
	ΔTurn	Age	-.154	.382	-.253	.234
		UPDRS III	-.210	.268	-	-
		MoCA	-.280	.137	-.277	.132
		GDS-15	-.059	.724	-.193	.249
		FA	**-.359**	**.041***	.006	.978
		JLO	.092	.580	.052	.807
		CLOX 1	.028	.868	.071	.764
		Digit span	-.043	.767	.115	.566
		VA	.071	.699	-.064	.757
		CS	-.255	.246	-.009	.966
Dual	ΔDoor	Age	-.029	.865	-.057	.790
		UPDRS III	.333	.074	-	-
		MoCA	.275	.134	-.099	.593
		GDS-15	-.053	.744	.310	.075
		FA	-.160	.341	.076	.723
		JLO	.234	.151	-.141	.518
		CLOX 1	-.031	.846	-.144	.550
		Digit span	-.277	.055	-.129	.527
		VA	-.002	.990	-.114	.591
		CS	.112	.600	.080	.697
	ΔTurn	Age	.106	.533	.145	.504
		UPDRS III	-.015	.936	-	-
		MoCA	.249	.169	-.135	.471
		GDS-15	.142	.377	.223	.198
		FA	-.164	.325	-.339	.126
		JLO	.052	.745	.237	.285
		CLOX 1	-.049	.759	.025	.919
		Digit span	**-.343**	**.018***	-.157	.447
		VA	.247	.169	-.098	.646
		CS	.146	.488	.086	.679

[*significance level p<0.05, UPDRS III = Unified Parkinson's disease rating scale – motor section, GDS-15 = Geriatric depress scale, MoCA = Montreal cognitive assessment, FA = Fluctuating attention, CLOX 1 = Royalls clock drawing, JLO = judgement of line orientation, Digit Span = Maximal forward digit span, VA = visual acuity, CS = contrast sensitivity]

Table 4 - Structural equation model direct, indirect and total effects

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 $p<.05$, Direct effect pathway = path between Outcome and Predictor, Indirect effect pathways = path between Outcome and Predictor through relationship with *x* (where *x* represents either cognition, visual function or saccade frequency), Total effect = sum of all direct and indirect effects, ß = standardised coefficient]

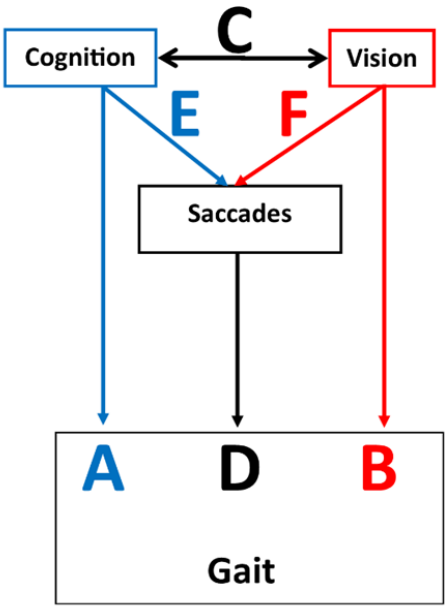


Figure 1 - Theoretical Model of Cognitive and Visual Contribution to Gait Impairment in Parkinson's disease *[Six pathways are involved; A) Cognition and gait, B) Vision and gait, C) Interaction between cognitive and visual functions, D) Saccades and gait, E) Cognition and saccades, and F) Vision and saccades]*

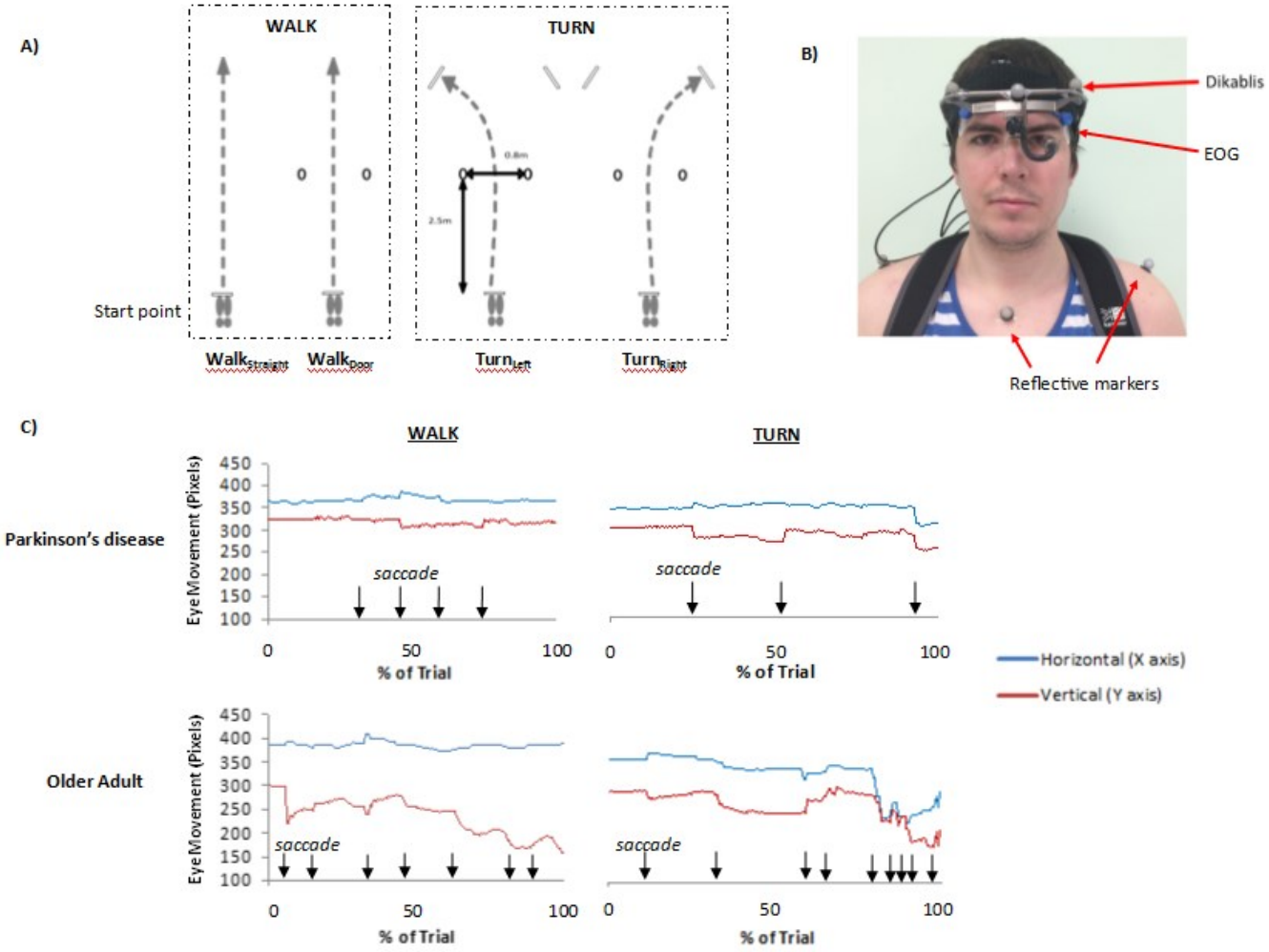


Figure 2 - Study Protocol: A) Walking conditions, B) Dikablis mobile infra-red eye-tracker and electrooculography (EOG) placement, C) Mobile eye-tracker raw data *[examples of saccade occurrences has been marked on each x axis at the point when detected]*

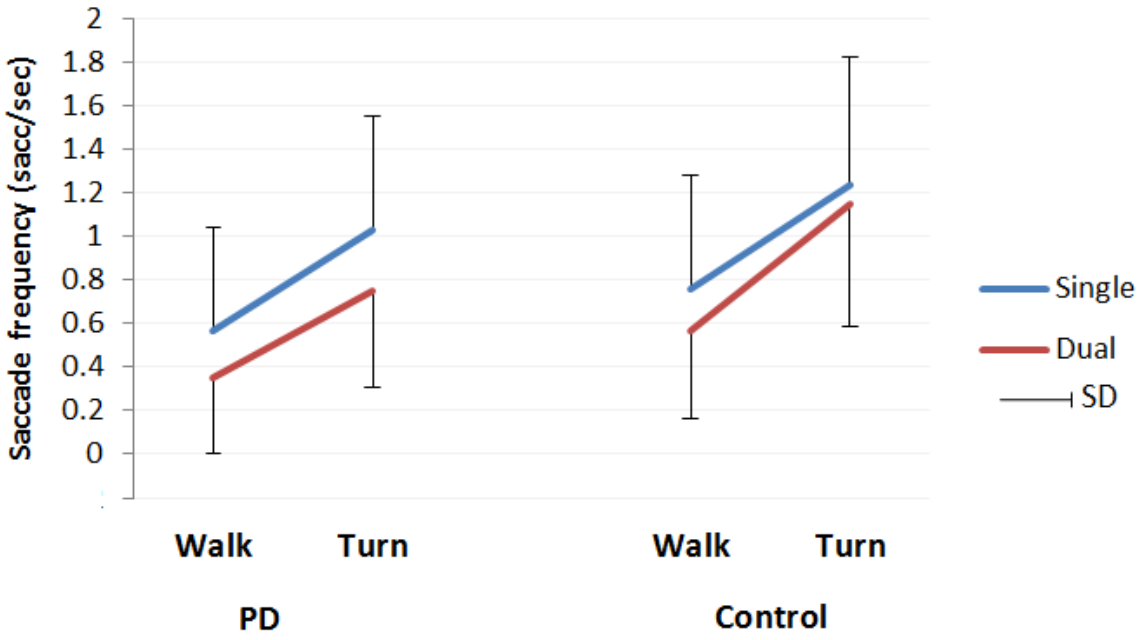
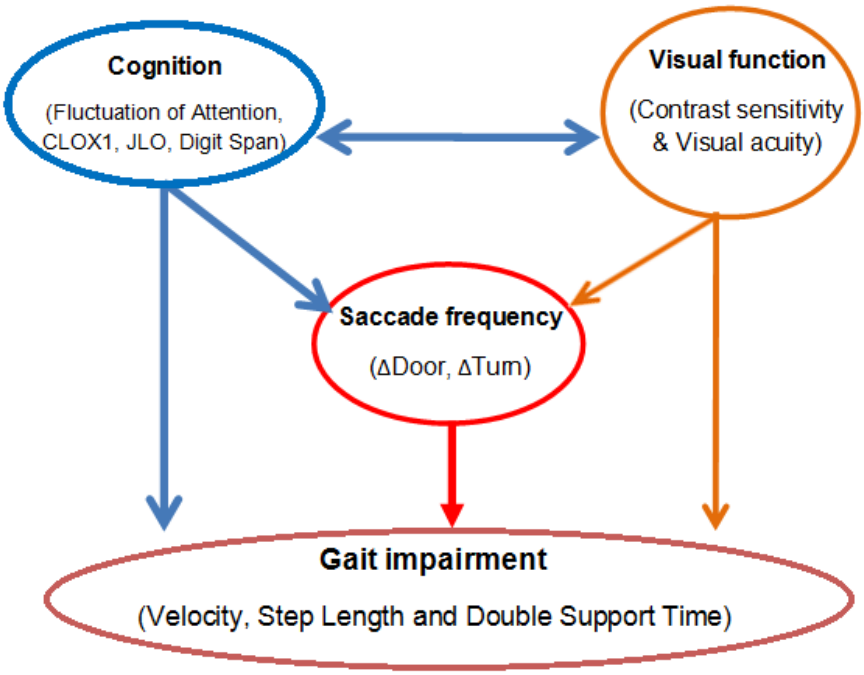


Figure 3 - Saccade frequency during gait *[Mean and standard deviation (SD) results for single and dual task walking are displayed]*

A) Initial Structural equation model



B) Final Structural Equation Model

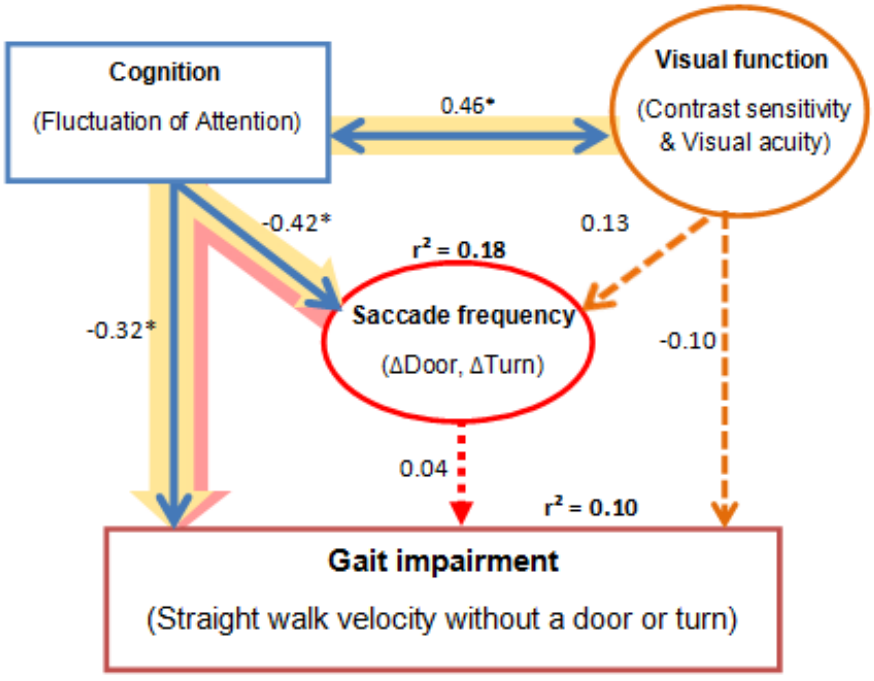


Figure 4 – Structural equation model of cognitive and visual contributions to gait impairment in Parkinson's disease *[*significance level p<.05, dashed lines are non-significant pathways, indirect pathways are represented by faded block arrows underlying direct pathways, solid arrows are direct pathways, double-headed arrows represent correlations or shared relationships, latent variables are represented via circles/ovals and observed variables via rectangles]*