Saccade frequency response to visual cues during gait in Parkinson's disease: the selective role of attention

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Abstract

Gait impairment is a core feature of Parkinson's disease (PD) with implications for falls risk. Visual cues improve gait in PD but the underlying mechanisms are unclear. Evidence suggests that attention and vision play an important role however the relative contribution from each is unclear. Measurement of visual exploration (specifically saccade frequency) during gait allows for real-time measurement of attention and vision. Understanding how visual cues influence visual exploration may allow inferences of the underlying mechanisms to response which could help to develop effective therapeutics. This study aimed to examine saccade frequency during gait in response to a visual cue in PD and older adults, and investigate the roles of attention and vision in visual cue response in PD. A mobile eye-tracker measured saccade frequency during gait in 55 people with PD and 32 age-matched controls. Participants walked in a straight line with and without a visual cue (50cm transverse lines) presented under single and dual-task (concurrent digit span recall). Saccade frequency was reduced when walking in PD compared to controls, however visual cues ameliorated saccadic deficit. Visual cues significantly increased saccade frequency in both PD and controls under both single and dual-task. Attention rather than visual function was central to saccade frequency and gait response to visual cues in PD. In conclusion, this study highlights the impact of visual cues on visual exploration when walking and the important role of attention in PD. Understanding these complex features will help inform intervention development.

Keywords: Parkinson's disease, gait, saccades, visual cues, vision, attention

Introduction

Gait impairments, such as reduced speed, step length and increased double support time, are a common and early feature of Parkinson's disease (PD) (Lord *et al.*, 2014; Galna *et al.*, 2015) that are associated with reduced mobility and increased falls risk. Dopaminergic medication has limited effect on gait deficits in PD (Sethi, 2008) and despite recent cholinergic therapy showing promise (Henderson *et al.*, 2016), evidence for pharma-logical intervention for gait impairment remains limited. Clinical implementation of non-pharmalogical treatments such as cueing can help to ameliorate gait deficits and reduce falls risk (Canning *et al.*, 2014; Morris *et al.*, 2017). Visual cues (transverse lines to step over) are thought to exploit visual (Azulay *et al.*, 2006) and attentional (Yogev *et al.*, 2005) reliance for gait control in PD to overcome deficits (Keus *et al.*, 2014). Visual cues provide spatial stimuli related to the initiation or ongoing facilitation of gait (Nieuwboer *et al.*, 2007), which can improve gait characteristics (e.g. longer step length (Azulay *et al.*, 1999; Lewis *et al.*, 2000; Suteerawattananon *et al.*, 2004; Lee *et al.*, 2012) and better gait initiation (Jiang & Norman, 2006)). However, the mechanisms underlying cue response are poorly understood, which has led to reports of variable intervention response (Suteerawattananon *et al.*, 2004) and selective short-term gait characteristic improvement (Morris *et al.*, 2010).

Underlying attentional (Morris *et al.*, 1996) and visual (Graci *et al.*, 2010; Almeida & Bhatt, 2012) mechanisms have been implicated in visual cue response in PD (Vitorio *et al.*, 2014). Real-world environments are visually complex (i.e. full of visual distractions) and visual cues may alleviate the attentional burden of visual processing by focusing visual and attentional resources on task goals (i.e. stepping over the lines), which could facilitate gait. It is therefore likely that cue response relates to both attentional and visual processes, however previous studies have limited investigation to their independent contribution. Simultaneous measurement of visual and attentional processing is possible through the real-time monitoring

of saccadic (fast) eye-movements (Stuart *et al.*, 2016c). Saccades, particularly saccade frequency, form the basis of visual exploration and are influenced by both visual and attentional neural processes (Kimmig *et al.*, 2001), which provides a means to examine the mechanisms underlying response to visual cues. Our recent work has shown that people with PD make significantly fewer saccades when walking than age-matched older adults particularly under a dual-task (Galna *et al.*, 2012), with attentional mechanisms underpinning saccadic and gait impairment in PD (Stuart *et al.*, 2017b). A visual cue intervention may ameliorate deficits by prompting more frequent saccades, as recent studies have shown that cues increase visual exploration (fixation number) during gait in PD (Vitorio *et al.*, 2014; Beck *et al.*, 2015), but the underlying mechanisms remain unclear. Therefore, greater understanding of saccade frequency response to visual cues, as well as relationships between visual, attentional, saccadic and gait with cue application will help identify the mechanisms involved and allow for targeted intervention development.

This study aimed to: 1) examine the effect of visual cues on saccade frequency during gait in older adults and PD; and 2) evaluate the contribution of attention and visual function to visual cue response in PD. To do this we examined changes in saccade frequency in response to visual cues during gait in older adults and PD, evaluated the effect of attention on cued saccade frequency under dual-task conditions; and finally explored relationships between attention, visual function, saccades and gait (speed, step length and double support time) with a visual cue. We hypothesised that a visual cue would increase saccade frequency in both PD and older adults; that saccade frequency would be reduced in both groups under dual-task regardless of a visual cue; and changes in saccade frequency would be associated with cued gait and underpinned by attention rather than visual function. An *a priori* model from our previous literature review guided data analysis (Stuart *et al.*, 2016c).

Materials and Methods

Participants

This study was a part of the larger "Vision and gait in Parkinson's" study and the methodology has been detailed within our published protocol; Stuart *et al.* (2016b) (ClinicalTrials.gov NCT02610634). The study involved a convenience sample of 55 people with PD and 32 age-matched healthy older adult controls. Due to the exploratory nature of this study there were no specific previous cueing examples available to guide sample-size requirements, therefore previous eye-tracking research during walking was used to base our sample-size on (Galna *et al.*, 2012; Stuart *et al.*, 2014a; Stuart *et al.*, 2017b). The study adhered to the Declaration of Helsinki and was approved by the '*Newcastle and North Tyneside NHS Research Ethics Committee 1*' (Ref: 13/NE/0128). All participants provided signed informed consent prior to participation. PD participants were recruited if they had been diagnosed with PD by a movement disorders specialist using UK Brain Bank criteria. PD participants had to be non-demented (≥21 on MoCA) and healthy controls had to have cognitively intact (≥26 on MoCA) (Dalrymple-Alford *et al.*, 2010). All participants were aged ≥50years old, with no diagnosed visual (i.e. patient report and medical records screened for history of glaucoma, macular degeneration, cataracts etc.) or mood or other neurological condition, and were able to walk independently without an aid. All testing took place while 'ON' medication, which was taken ~1 hour before.

Demographic and clinical assessments

Age, sex, height and weight were reported. Disease severity was measured using the Movement Disorder Society (MDS-revised) Parkinson's disease rating scale (UPDRS) (Goetz *et al.*, 2008). Fear of falling was measured using the Falls Efficacy Scale (International version; FES-I), depression with the Geriatric Depression Scale (GDS-15), and retrospective falls from

patient interview and medical notes. Levodopa Equivalent Dose (LED) scores were calculated (Tomlinson *et al.*, 2010).

Cognitive and visual assessments

The Montreal Cognitive Assessment (MoCA) and Addenbrookes cognitive examination (ACE-R) measured global cognition. Specific cognitive domains were also assessed which included attention, executive function, working memory and visuo-spatial ability. Attention was examined using the computerised Cognitive Drug Research (CDR) battery (Corani *et al.*, 2006; Molloy *et al.*, 2006), which included simple reaction-time, choice reaction-time and digit vigilance. From these tests we derived composite measures of power of attention (PoA) (calculated as the sum of the means from each test) and fluctuating attention (FA) (calculated as the sum the coefficient of variation (CV%) from each test) (Allcock *et al.*, 2009; Lord *et al.*, 2014). Executive function was assessed using clock drawing (Royall's CLOX 1) (Royall *et al.*, 1998). Working memory was assessed using forward digit span from the Wechsler adult intelligence scale (Wechsler, 1945). Visuo-spatial ability was measured using judgement of line orientation (JLO), clock copying (Royall's CLOX 2) and subsections of the visual, object and space perception (VOSP) battery; incomplete letters, dot counting and position discrimination. Visual functions (i.e. basic visual processes) of visual acuity (VA; LogMar) and contrast sensitivity (CS; Mars Perceptrix) were assessed using standardised charts.

Study design

Protocol

A brief summary of the protocol follows, as full details of the testing procedures have been described elsewhere (Stuart *et al.*, 2016b). All participants walked straight for ~7m at a self-selected pace under different walking conditions (Figure 1(A)). The conditions were designed

to manipulate visual and attentional complexity of real-time walking with visual cues and dual-tasking. Walking conditions included:

Single task:

1) Straight walk (WALK) (3 trials)
2) Straight walk with a visual cue (black tape lines, placed 50cm apart and transverse to the start point) (WALK-CUE) (3 trials)

Dual-task:

1) Dual-task (maximal forward digit span) and straight walk (DUAL) (3 trials)
2) Dual-task (maximal forward digit span) and straight walk with a visual cue (DUAL-CUE) (3 trials)

The straight walking conditions (WALK) were always performed first to ensure participants could achieve the walk safely and to provide an unbiased baseline, this was followed by the cued conditions (WALK-CUE). The visual cue consisted of five transverse lines to step over, placed apart approximately a 'normal' step length (50cm). A standardised visual cue line distance was used as the primary focus of this study was the effect of visual cues on visual exploration (saccade frequency), and the distance was in line with previous research (Lewis *et al.*, 2000; de Melo Roiz *et al.*, 2011). Three trials of each condition were collected and averages for all outcomes calculated. Participants completed the walks under single and dual-task (randomised order). The dual-task involved the Wechsler forward digit span repetition while walking (Wechsler, 1945), which was normalised to each individuals maximum determined in sitting prior to walking. Participants had to listen to strings of numbers (digits) played over loud-speaker while walking and repeat back the strings in the same order as played. Incorrect

recall (dual-task errors) of the digit strings were recorded and analysed as percentage (%) of errors made.

<<Insert Figure 1 here>>

Outcomes Measures

The primary outcome was saccade frequency (number of fast eye movements per second) during gait. Raw data was processed using our validated algorithms for mobile eye-tracking (vertical and horizontal saccades) and electrooculography (EOG) (horizontal saccades only) (Stuart *et al.*, 2014b; Stuart *et al.*, 2017a). 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). Saccade frequency (calculated as number of saccades divided by the walk duration) was evaluated rather than pure number of saccades during walking, as this controlled for the differences in walking speeds between individual participants and groups.

Saccade frequency was reported as absolute (WALK, DUAL, WALK-CUE, DUAL-CUE) and change score (Δ) values. Change score showed the response of saccade frequency to visual cues when walking under single (WALK-CUE – WALK = ΔCUE) and dual-task (DUAL-CUE –DUAL = ΔCUE-DUAL). Change score was used in further analysis to overcome eye-tracker measurement limitations (detailed within Stuart *et al.* (2016a)), which allowed each participant to act as their own control. In brief, mobile eye-trackers are limited due to technological (i.e. lower sampling frequency than static devices) and physiological issues, such as flickers or refraction due to eye-lashes, eye-lids, dark skin and corrective lenses (e.g. glasses or contact lenses).

Secondary outcomes included gait characteristics of velocity, step length and double support-time, as these features have been shown to be influenced by visual cues in previous Parkinson's research (Morris *et al.*, 1996; Rubinstein *et al.*, 2002).

Equipment

A mobile infra-red eye-tracker (Dikablis, Ergoneers, Germany; 50Hz) and bi-temporal EOG (Zerowire, Aurion, Italy; 1000Hz) were used to record saccades while walking (Stuart *et al.*, 2016a). The mobile eye-tracker (displayed in Figure 1(B)) consisted of a head-unit and a backpack containing a transmitter (~1kg). A 3-dimensional motion capture system (Vicon, Oxford, UK; 100Hz) was used to measure gait characteristics within the walking conditions. All of these devices automatically synchronised and recorded simultaneous eye and body movement.

Data analysis and statistics

Descriptive data

Data analysis was performed with SPSS (IBM, Chicago, Il., USA, v.21). Normality assessment ensured data met criteria for parametric analysis (Field, 2013). Descriptive statistics were calculated and tabulated (i.e. means and standard deviations (SD)). Pearson chi-square (X^2) compared frequency data between groups. Due to the exploratory nature of the study $p<0.05$ was considered significant for the purposes of statistical interpretation.

Step 1: Saccade frequency during gait

To examine our first aim, we used a repeat measures ANOVA compared effect of visual cue (WALK, CUE) and dual-task (single, dual) on saccade frequency, with group (PD, control) as a between subject factor and partial eta-squared (η^2) determined effect size. The same analysis was performed for reported gait characteristics (velocity, step length and double support-time), with height entered as a co-variate.

Step 2: Determinants of saccade frequency and their relationship with cued-gait

To determine our second aim, we first examined independent cognitive or visual determinants of saccade frequency response to a visual cue (ΔCUE, ΔCUE-DUAL) through hierarchical multiple-regression. 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. One significantly different variable between the groups in univariate analysis represented each cognitive domain and visual function to avoid over-fitting. As PoA and FA were highly correlated in the PD group ($r=.76$, $p<.001$), 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). Poorer FA has also been shown to be a stronger predictor of falls than PoA (Allcock *et al.*, 2009) and has domain specific gait relationships(Lord *et al.*, 2014). Regression normality, co-linearity and independent errors were determined.

Secondly, a structural equation model (SEM) was created in SPSS AMOS (v22) to examine the direct and indirect relationship between saccade frequency and gait with a visual cue in PD, while including hypothesised cognitive and visual relationships (Stuart *et al.*, 2016c). SEM analysis was conducted in line with current recommendations (Xiong *et al.*, 2015) (described in detail within our protocol paper (Stuart *et al.*, 2016b)). The initial model used the same variables as multiple regression analysis (Figure 3(A)). The final SEM provided direct and indirect relationships between attention (represented by FA) and visual functions (represented by VA and CS), saccade frequency (represented by ΔCUE) and gait (represented by velocity with a visual cue) in PD.

Results

Participants

Demographic, cognitive, visual and clinical features of the participants are displayed in Table 1. PD and controls were matched for age, education and gender. The PD participants were a heterogeneous group (Median disease duration, ~60, Inter-quartile range 24 to 90 months) who had moderate disease severity (UPDRS III, ~37 ± 14). Global cognitive ability, domains of attention, executive function, visuo-spatial ability, working memory and visual function were all significantly impaired in PD compared to controls. With respect to gait, people with PD walked significantly slower, with shorter steps and increased double support-time for all walking conditions (with or without a visual cue) (Supplementary Table 1).

Saccade frequency during gait: effect of visual cues

Both visual cue and dual-task conditions had significant effects on saccade frequency during gait ($F(1,85)$=117.42, p<.001 [η^2=.494]; $F(1,85)$=11.97, p=.003 [η^2=.098], respectively). Both groups made significantly more saccades with a visual cue, compared to non-cued gait. Under dual-task conditions, both groups made significantly less saccades compared to single-task (Figure 2).

There was a near significant interaction between the visual cue and dual-task conditions (WALK-CUE x DUAL-CUE; $F(1,85)$=3.72, p=.057 [η^2=.042]), demonstrating that both groups maintained their saccade frequency under a dual-task (i.e. similar frequency to single-task) when using a visual cue. Despite reduction in un-cued saccade frequency in PD compared to controls (WALK, DUAL, Figure 2), overall there were no significant differences in saccade frequency between PD and controls (main effect: $F(1,85)$=.983, p=.324 [η^2=.011]).

Dual-task performance was improved in both groups with a visual cue, with significant improvement in PD. For example; older adult (WALK: 22.9 ± 23.1%, WALK-CUE: 15.7 ± 21.9%, *p*=.080) and PD (WALK: 27.6 ± 29.1%, WALK-CUE: 16.7 ± 18.9%, *p*=.003) participants made less errors on the digit span recall with a visual cue compared to non-cued gait.

<<Insert Figure 2 here>>

Independent determinants of saccade frequency response to visual cues

Both attention (FA; ß=-.35, *p*=.035) and visual function (CS; ß=-.45, *p*=.033) were associated with change in saccade frequency with a visual cue (ΔCUE) in PD independent of demographics (Table 2). Results indicated better attention and CS related to increased saccade frequency with a visual cue. There were no significant independent associations for controls.

Saccade frequency relationship with visually cued-gait in Parkinson's disease

Few significant associations were found between cued-gait and saccade frequency in PD and no significant associations for controls (Supplementary Table 2). The only findings were that faster gait velocity related to more frequent saccades with a cue (DUAL-CUE, ΔCUE-DUAL) in PD. Therefore, an SEM that included the independent relationships with cognition and visual function, was developed to further examine relationships between cued saccade frequency and gait in PD. Initially several SEMs were constructed, however due to limited quality indicators (factor loadings <.70) and associations within dual-task and control models, analysis was confined to single-task cued-gait in PD. Standardised regression coefficients (ß) for associations between each variable in the model are shown next to each arrow in Figure 3. Model explained variances (r^2) are provided in bold above appropriate variables. After trimming, hypothesised relationships between one latent (visual function) and three observed

variables (ΔCUE, FA, cued-gait velocity). Three non-significant pathways were trimmed (Figure 3(a) & 3(b)) and an overall fit of $X^2 = 2.3$ (d.f. = 5, $p = .806$), GFI (0.984) and RMSEA (0.000), which indicated acceptable goodness-of-fit. The final SEM explained 7% of the variance in saccade frequency (ΔCUE) and 13% variance in gait velocity with a visual cue (Post-hoc observed statistical power; 0.64 (Rosner, 2015)).

Attention (specifically FA) was central to direct and indirect relationships between visual function, saccade frequency response and cued-gait in PD. Better attention was directly related with greater change (increase) in saccade frequency (ΔCUE; ß = -.27, $p = .037$, Table 3) and faster gait (ß = -.37, p = .036, Table 3) with a cue. Better attention shared a direct relationship with better visual function (ß = .46, $p = .028$, Table 3). No other direct effects were found. However, there were significant indirect effects of visual function (ß = .17, $p = .005$, Table 3) and saccade frequency (ß = .10, $p = .031$, Table 3) on cued-gait, which were underpinned by attention. For example; poorer visual function and less increase in saccade frequency with a visual cue led to slower cued-gait velocity, but only through their relationship with poorer attention.

<<Insert Figure 3 here>>

Discussion

To our knowledge, this is the first study to investigate the influence of visual cues on saccade frequency during gait in PD. Increased saccade frequency in response to visual cues when walking in both PD and older adults supports our first hypothesis. In line with our second hypothesis, performance of a dual-task reduced saccade frequency compared to single task conditions in both groups regardless of the use of visual cues, although a higher saccade frequency was still maintained within all of the cued conditions compared to un-cued conditions. Contrary to our hypothesis, there was little relationship between cued saccade

frequency and gait in PD or controls. Instead, structural modelling demonstrated that increased saccade frequency with a visual cue (and better visual function) indirectly influenced cued-gait velocity, with relationships underpinned by attention. Attention had direct impact on cued-gait, saccade frequency response to cues and visual function, which highlighted a central role for attention in the response to visual cues in PD.

Saccade frequency when walking: response to visual cues

Visual cues increased saccade frequency during gait in both PD and controls, and this was even seen under dual-task conditions where attention was distracted from gait. Manual inspection of the eye-tracker videos confirmed that participants were looking at the visual cues. To rule out a simple learning effect of repeated trials we assessed the saccadic frequency over consecutive (n=3) straight line walking trials and found that saccades did not increase due to task familiarity (Repeated measures ANOVA; F=.152, p=.697). These findings agree with previous research demonstrating highly salient targets and specific task goals improve saccadic activity in PD during static tasks (Horowitz *et al.*, 2006). Methodological differences limit comparison to previous gait studies that have only examined fixation related outcomes when using visual cues (60-65cm transverse lines) (Vitorio *et al.*, 2014; Beck *et al.*, 2015). Vitorio *et al.* (2014) demonstrated a non-significant increase in fixation number with a visual cue within a small cohort of PD and controls. Similarly, Beck *et al.* (2015) investigated fixation durations in a small cohort of PD with freezing of gait and found that freezers made longer fixations than non-freezers with a visual cue, which was maintained under dual-task. However these results should be interpreted with caution due to the lack of a validated algorithm to derive fixation outcomes, and the low sampling frequency (30Hz) of the eye-tracking devices involved, which are not adequate to accurately derive the exact start and end of fixations (i.e. ≥200Hz is required for this (Stuart *et al.*, 2014a)). Due to saccades and fixations being coupled

(i.e. saccades are movements between fixations), these previous studies may have recorded an increase in saccade frequency with a visual cue, however limited eye-tracker resolution did not allow this analysis.

Saccade frequency was reduced in both PD and controls with a dual-task irrespective of the use of visual cues (Figure 2), although frequency was always higher with visual cues compared to without cues regardless of single or dual-task conditions. Indeed, saccade frequency with a cue had only minor reduction under dual-task compared to single-task conditions in both groups, which indicated maintenance of cue response although this was non-significant (p=.06). Improved maintenance of saccade frequency with a visual cue under dual-task possibly relates to a combination of resource allocation away from attentional control to the secondary task and the influence of the external stimuli (taped lines) on saccade initiation. For example, visual cues likely trigger more reflexive (bottom-up or automatic) rather than voluntary (top-down or cognitive) saccades in both older adults and PD, as these groups are known to have deficits in suppression of reflexive saccades to external visual stimuli (Butler *et al.*, 1999; Chan *et al.*, 2005). More reflexive saccadic initiation would free attentional resources to be applied to other concurrent tasks (i.e. cognitive or gait task). This theory is supported within this study as both groups improved on the secondary cognitive task (dual-task) when using a cue with greater response in PD, which is comparable to previous cueing research (van Wegen *et al.*, 2006; Baker *et al.*, 2007; Rochester *et al.*, 2007; Mak *et al.*, 2013).

Direct and indirect saccade frequency determinants and relationship with cued-gait

We examined the underlying determinants of saccade frequency when walking with a visual cue and their relationship with cued-gait. All participants increased their saccade frequency and adapted their gait strategy with a visual cue. However, limited association was found between cued saccade frequency and gait in PD and controls. Therefore an SEM was developed

to understand the complex relationship involved in PD. SEM included hypothesised relationships entered between cognition, visual function, saccade frequency cue response and cued-gait (Stuart *et al.*, 2016c). Overall the level of explained variance (13% gait impairment, 7% saccade frequency) and the relationship with attention are similar to previous saccadic (Buhmann *et al.*, 2015) and gait research in PD (Lord *et al.*, 2010) and older adults (MacAulay *et al.*, 2014). Our results highlighted that saccade frequency and gait with a visual cue were underpinned by attention rather than visual functions in PD.

Initial regression analysis showed that attention (FA) and visual function (CS) were found to be independent determinants of saccade frequency response to cues (ΔCUE) in PD. There were no determinants found in controls, which was despite the response in saccade frequency to visual cues being the same for both groups. The reasons for this remain unclear but one possibility is that our control group were cognitively intact (MoCA ≥26) unlike the PD participants (MoCA ≥21), which may have impacted results. Despite both attention and visual function being related to saccade frequency response to a visual cue in PD, this may have been predominantly driven by attention. Increased saccade frequency with a visual cue related to better attention and CS, however, when attention was restricted under dual-task there were no relationships between saccade frequency and attention or CS, which supported our assertion.

Our SEM findings supported a central role for attention in visual cue response, which agrees with previous theories (Morris *et al.*, 1996). Attention (specifically FA) directly related to visual function, saccade frequency response and cued-gait in PD, and underpinned indirect relationships between these features. For example, those with PD who had better attention, also had better visual function, increased their saccade frequency more with a visual cue and had faster cued-gait. Attention was likely required due to the goal-orientated instructions to step over the transverse lines while walking (Macdonald & Tatler, 2013). However the specific attentional mechanisms underpinning saccade frequency remain unclear, which is primarily

due to difficulty in determining whether top-down (frontal, cognitive or voluntary) or bottom-up (parietal, automatic or reflexive) attentional control drives saccades during walking (N'Guyen *et al.*, 2014). This is further compounded by the fact that people with PD rely on attention to drive both gait (Redgrave *et al.*, 2010) and saccadic control (Baluch & Itti, 2011), which may over burden the limited attentional resources available, particularly under dual-task. However, increased saccade frequency under dual-task with a visual cue indicates that cues may guide visual exploration and free attentional resources by stimulating more reflexive saccadic behaviour (i.e. an artificial driver for saccades while walking) that does not require cognitive input. Similarly, reduced secondary cognitive task errors with visual cues in both PD and controls further supports the notion of attentional unburdening with cues.

Attention may also be required to compensate for motor or visual deficits that accompany PD. For example, increased saccade frequency with a visual cue may reflect compensation for visual deficits, as previous studies have reported increased saccade frequency during visual search tasks in those with visual impairments (Barraga, 1964; Hawelka & Wimmer, 2005). Visual cue saliency would be reduced with visual impairment in PD and therefore attention may stimulate increased saccade frequency to filter the visual scene to distinguish the transverse lines from the floor (Horowitz *et al.*, 2006). However, the compensatory role of attention is complicated by attentional dysfunction in PD, which may impact visual, saccadic and gait especially in later disease.

Clinical Implications

Visual exploration (saccade frequency) significantly increased with the implementation of visual cues and this was maintained when participants were distracted with a secondary task. Attention is central to visual cue response in PD, therefore targeting attention deficits with therapeutic interventions, such as pharmacological manipulation, may further improve visual

exploration and gait response to visual cues. Ultimately, greater visual exploration would increase the amount of visual information available for gait control, with implication for safe and effective navigation and reduced falls risk.

Study Limitations

Gait characteristics were not the primary focus of this study and therefore a set distance (50cm) visual cue was used. This distance has been used in previous cueing research (Lewis *et al.*, 2000; de Melo Roiz *et al.*, 2011) as it represents average step length in PD obtained from free-living (Del Din *et al.*, 2016) and large-scale cueing trials (Nieuwboer *et al.*, 2007). Consequently, gait characteristics were not improved with the cue in every participant (Supplementary Table 1) (i.e. those with step length >50cm adapted their gait with a cue by shortening their step to ~50cm). Future studies should consider tailoring the visual cue to each individual (e.g. distance 20% larger than participant baseline step length). The study also involved limited range of vision assessments, as only basic visual functions were included due to their use within clinical settings. Future studies should include other more complex vision measures (i.e. depth perception or motion perception) or a full ophthalmic battery, as other visual outcomes may have a greater role in visual cue response. Finally, the correlational nature of the study does not determine causation of response.

Conclusions

This study provides important insights into visual cue response when walking in PD, which may influence safe mobility and reduce falls risk. Saccade frequency is reduced when walking in PD compared to older adults, however visual cues ameliorated saccadic deficits. Visual cues significantly increased saccade frequency, even when attention was distracted with a concurrent dual-task. Increased saccade frequency and faster gait with a visual cue was

underpinned by attention rather than visual function in PD. Future research investigating visual cues in PD should consider the underlying role of attention.

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Conflicts of Interest

The authors have no conflicts 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., S.L., B.G. 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.

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Figure Captions

Figure 1 - 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 2 - Saccade frequency during gait *[Mean and standard deviation]*

Figure 3 - Structural equation model of gait in Parkinson's disease 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, correlations are represent by bi-directional arrows. Latent variables are represented via circles and Observed variables via rectangles]*