2015

# Visuospatial deficits, walking dynamics and effects of visual cues on gait regulation in Parkinson's disease (PD)

BOSTON UNIVERSITY

SARGENT COLLEGE OF HEALTH AND REHABILITATION SCIENCES

Dissertation

# VISUOSPATIAL DEFICITS, WALKING DYNAMICS AND EFFECTS OF VISUAL CUES ON GAIT REGULATION IN PARKINSON'S DISEASE (PD)

by

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Submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

2015

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## DEDICATION

I dedicate my dissertation work to my family and many friends. Without their support, this dissertation would not have been completed.

## ACKNOWLEDGMENTS

*"Do the best you can until you know better. Then when you know better, do better." – Dr. Maya Angelou*

First and foremost, my entire family who has been standing by me with endless love all these years.

I would like to express my deepest gratitude to Dr. Alice Cronin-Golomb who undertook to act as my advisor despite her many other academic and professional commitments. Her wisdom, knowledge, patience and commitment to the highest standards motivated me tremendously.

I am extremely thankful to Dr. Sandy Neargarder who provided valuable guidance on the data analysis. Her kindness and encouragement inspired my final effort to get through the great loads of work.

I am also grateful for Robert Salazar who collaborated with me on this project. His diligent work and excellent executive skills were key in getting through the data collection and analysis process.

My sincere thank you to my committee, Dr. Serge Roy, Dr. Terry Ellis and Dr. Elliot Saltzman who guided my research throughout all these years. I am indebted to them for sharing expertise, supports and encouragement extended to me.

I take this opportunity to express my gratitude to the Department for the Dudley Allen Sargent Research Fund granted to me and their help on logistics, budget, and provide the research laboratory. Without their supports, this work could not be possibly carried out and finished.

The recruitment efforts were supported, with my gratitude, by Marie Saint-Hilaire, MD and Cathi Thomas, RN, MSN, of Boston Medical Center Neurology Associates, and by the Michael J. Fox Foundation Trial Finder. I sincerely thank Laura Pistorino, who assisted in participant recruitment; Tim Dorr, Olivier Barthelemy, Noor Toraif, and Norick Bowers for assistance with data collection; and Abhishek Jaywant for helpful discussions. I am deeply grateful to all of the individuals who participated in this study.

I cannot neglect to mention all the doctoral students and my friends who stood by me and gave tremendous encouragements. Rich Vartanian, Kendra Liljenquist were the best classmates that I could ask for. Dr. Cheng-Chieh Lin patiently guided me in the lab when I first came into the program. Megan and Gerhard Van De Linde walked with me steadfastly despite the tremendous work pressures we were facing together.

Finally, I dedicate this dissertation to the memory of my father and Dr. Robert Wagenaar who were the most influential persons in my life. I hope I have lived up to their trust in me.

**VISUOSPATIAL DEFICITS, WALKING DYNAMICS AND EFFECTS OF VISUAL CUES ON GAIT REGULATION IN PARKINSON'S DISEASE (PD)**

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ABSTRACT

Individuals with Parkinson's disease (PD) present with motor and non-motor symptoms, including in the visuospatial domain. Correction of walking abnormalities through application of visual cues in the environment has been reported in PD, but the mechanisms of action are poorly understood. The present project examined competing explanations of the effects of visual guidance on multiple aspects of gait in PD. Comfortable over-ground walking was performed by 9 participants with left-side motor onset (LPD), 11 with right-side motor onset (RPD), and 13 age-matched normal control participants (NC). Study 1 examined whether veering in PD is predominantly induced by asymmetrical perception of the visual environment or by motor asymmetry between relatively affected and relatively non-affected body side. Walking conditions were eyes-open, vision-occluded, and egocentric reference point (walk toward the perceived center of a distant target). The visual hypothesis predicted that LPD, with a known tendency toward left spatial hemineglect, would veer rightward, whereas RPD would veer leftward. The motor hypothesis predicted the opposite pattern of results because the more affected body side has shorter step length. The results supported the visual hypothesis.

In Study 2, visually-cued gait was examined to establish whether the key variable to improvement is attention to pattern rhythmicity, or instead if improvement may arise from perception of dynamic flow. Floor patterns included transverse lines (attention; 3 frequencies) and randomly-placed squares (dynamic; 3 densities). Relative to baseline, both transverse lines and random squares, especially at higher frequency/density, resulted in gait improvements and induced more stable interlimb coordination, especially for LPD, the subgroup known to have greater visual dependence. Effects lasted after the cues were removed. The success of the random-squares cuing indicates that the mechanism of improvement may be dynamic flow of visual texture rather than attention, and further suggests that vision-based interventions need not be restricted to transverse lines.

Taken together, the studies lay the foundation for the development of treatments for walking disturbances in PD by addressing critical issues that could influence the outcomes of therapeutic interventions, including the role of visual input and the differential effects on PD subgroups.

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STUDY 2: Effects of Visual Cues on the Regulation of Gait and Interlimb Coordination during Walking in Parkinson's Disease

## LIST OF ABBREVIATIONS

BAI – Beck Anxiety Inventory

BDI-II – Beck Depression Inventory

ECRP – Egocentric reference point

EO – Eyes open condition

RP - Relative Phase

H & Y – Hoehn and Yahr scale

IREDS – Infrared light emitting diodes

LARA – Relative phase between left and right arm swing

LED – Levodopa equivalent dosage

LLLA – Relative phase between left leg and arm swing

LLRL – Relative phase between left and right leg swing

LPD – Parkinson's disease patients with predominantly left-sided motor symptoms or with initial motor symptoms on left body side

MMSE – Modified Mini-Mental State Exam

NC – Healthy normal control adults, age-matched to individuals with Parkinson's disease

$P_1$ – The power in the arm swing angle at the stride frequency

$P_2$ – The power in the arm swing angle in the step frequency

PD – Parkinson's disease

PERP – Point estimate of relative phase

PSD – Power spectral density

RLRA – Relative phase between right leg and arm swing

RPD – Parkinson's disease patients with predominantly right-sided motor symptoms or with initial motor symptoms on right body side

RPI – Relative power index

SD – Standard deviation

SF – Stride frequency

SL – Stride length

UPDRS – Unified Parkinson's Disease Rating Scale

WS – Walking speed

YC – Healthy younger control adults

# GENERAL INTRODUCTION

This introduction lays out the rationale leading to the two main purposes of the dissertation project. One was to achieve insights into the factors that contribute to the difficulty in navigation experienced by individuals with Parkinson's disease (PD) that may arise primarily from motor deficits, visuospatial and perceptual deficits, or both. First, I hypothesized that we would find distinct profiles of navigational veering between people with PD who had motor symptom onset on the left body side (LPD) and those whose motor onset was on the right body side (RPD). I further hypothesized that veering under visual guidance would be in the direction predicted by visuospatial deficits rather than by the motoric asymmetry between the relatively affected and relatively non-affected body side. The second main aim of the project was to examine the effects of visual cues on regulating gait and coordination patterns during over-ground walking in people with PD. Two types of external visual cues were employed in order to assess competing theories in the literature on the mechanism underlying visually-controlled locomotion: attentional strategy on foot stepping over each provided spatially rhythmic cue vs. visual flow generated by self-motion. The visual cues on the walkway were equally-spaced transverse lines (spatially rhythmic) and randomly placed small squares. The random squares condition was used to highlight the role of dynamic visual cues in altering locomotive behavior by minimizing the attention drawn to foot placement and eliminating the rhythmic pattern of the cues. For both conditions, I hypothesized that the gait patterns of PD would be regulated at a level comparable to that of a healthy age-matched control group, and LPD and RPD groups would differ in their response to the

visual cues.

PD was documented in 1817 by James Parkinson (Parkinson 2002) with an emphasis on its evident motor symptoms. With increasing recognition and understanding of its negative impact on people's daily living, it has become a target of much neurological research. The etiology of the disease is still not clear but one of the well-known identifiers is the deficiency of the dopamine amacrine cells in the substantia nigra pars compacta in the midbrain (Kempster et al., 1989). Dopamine has important roles at several anatomical sites, and any interference with this neurotransmitter could result in abnormal function in multiple domains. For example, typical motor symptoms of the disease include resting tremor, bradykinesia, postural instability, gait freezing, shuffling gait pattern, rigidity in the trunk and limbs, reduced pelvis rotation and lack of arm swing, all of which put people with PD at a high risk of falling (Wood, Bliclough et al. 2002; Schaafsma, Balash et al. 2003; Schaafsma, Giladi et al. 2003). The symptoms almost always first emerge on one side of the body and then progress to bilateral involvement.

This asymmetry of motor symptoms in PD affects locomotive dynamics. Shorter stride length on the more affected side compared to the less affected side, and asymmetrical interlimb coordination, exist commonly among people with PD and these motor characteristics are strongly associated with impairments in postural stability, turning behavior and continuity of gait (Plotnik, Giladi et al. 2005; Yogev, Plotnik et al. 2007; Boonstra, van der Kooij et al. 2008; Nanhoe-Mahabier, Snijders et al. 2011; Frazzitta, Pezzoli et al. 2013; Lin, Wagenaar et al. 2014).

Reduced dopamine may not only be responsible for motor symptoms of PD but for non-motor perceptual impairments in contrast perception, motion discrimination, color discrimination and visuospatial perception (Bodis-Wollner et al., 1987; Bodis-Wollner 1990; Harris et al., 1990; Brandies, & Yehuda 2008). Higher-order visual processing and cognition may also be affected after the PD pathology develops further into central cortex (Berger et al. 1991; Davidsdottir et al., 2008). One role of vision in spatial navigation is perceiving the layout of the world, but a second that is equally important is controlling one's movement. Absence of proper visual input has been acknowledged as a critical risk factor for incidence of falls especially for people with visual impairment due to neurological disorders or ageing (Perrin, Jeandel et al. 1997; Hafström, Frasson et al. 2002; Lee and Scudds 2004.). Little is known about how visual impairments may affect movement in people with PD, however, because the disease was traditionally characterized as a motor disorder rather exclusively, and rehabilitation research has accordingly been directed mainly at interventions targeting the motor symptoms.

One aspect of spatial navigation is veering (lateral deviation along the medio-lateral axis). Veering abnormalities have been commonly reported among people with PD. Those who are more affected on the left side of body (LPD; initial right hemisphere pathology) tend to bump into objects more on the left side, whereas PD patients with right body-side onset (RPD; left hemisphere predominant pathology) show no particular bias (Davidsdottir, Cronin-Golomb et al. 2005). Hemi-specific errors in LPD and RPD have also been found on visuospatial testing, such as on horizontal line bisection (Lee,

Harris et al. 2001; Davidsdottir, Wagenaar et al. 2008; Laudate, Neargarder et al. 2013), copying and drawing tasks (Shelton, Bowers et al. 1990; Vallar 1998), self-report of daily visual function (Davidsdottir, Cronin-Golomb et al. 2005), reaching and grasping tasks (Rossit, McIntosh et al. 2012), body-scaled aperture estimation (Lee, Harris et al. 2001), and size perception comparison in two hemi-spaces (Milner and Harvey 1995; Harris, Atkinson et al. 2003). In general, LPD perceive stimuli in the left and upper quadrants of egocentric space as shorter or smaller than in the right and lower quadrants resulting in a rightward spatial bias, whereas RPD perceive visual stimuli more like healthy control adults. It has been suggested that damage to the right hemisphere contributes to more severe visuospatial impairments than damage to the left hemisphere, presumably because the right hemisphere mediates more visuospatial processing than the left (Cronin-Golomb 2010).

Whether veering in PD is more attributed to errors in visuospatial perception or to motoric asymmetry has not been addressed directly. Two potential mechanisms predict contradictory veering directions. The first goal of this dissertation research was to assess veering in individuals with LPD and RPD under conditions of visual guidance and vision occluded, and examine whether visuospatial bias or motor bias better account for lateral drift.

The second aim of this dissertation was to address the current debate over the mechanism underlying the effects of visual cues on gait regulation in PD, namely the attentional strategy hypothesis vs. the dynamic visual flow hypothesis. Because some pharmacological or surgical treatments of motor symptoms have been shown to evoke

unpredicted adverse effects (Appleby et al. 2007), the need for alternative therapeutic approaches that are effective and less harmful is imperative. One such approach is modification of the visual environment. Studies have shown that normal gait dynamics can be elicited in PD using external visual cues. The most commonly used is placing transverse lines along a walking pathway. Positive effects have been reported consistently in promoting more stable gait kinematics with better step length and increased walking speed (Jiang, Norman 2006; Azulay et al. 1996; Azulay et al. 1999; Azulay et al. 2006; Morris et al. 1996; Vitorio et al. 2014; Lewis et al. 2000; Almeida, Bhatt 2012; Sidaway et al. 2006; Suteerawattananon et al. 2004; Rubinstein et al. 2002; Wegen et al. 2006). Some investigators have suggested that the spatially rhythmic visual cues caused the walkers to focus their attention on stepping over each of the sequential transverse lines on the floor (Lewis et al. 2000; Lebold and Almeida 2011), whereas others believe it is the dynamic flow information that is important in movement control. This latter view was first raised by Azulay et al. (1999), and is consistent with the Gibsonian view (Gibson 1966) that visual information in the environment provides direct guidance for action. If dynamic visual flow is impeded experimentally, no improvement of gait is obtained (Azulay et al. 1999; Lebold and Almeida 2011). Recently, the attentional focus on foot positioning over each cue was challenged by the finding that increase of stride length and walking speed was still achieved even if information from lower extremities was not available (Vitorio et al. 2014). The assertion of the important role of embedded specific patterns of visual cues in gait regulation accords with Gibson's theory about visually controlled locomotion (Gibson 1966), which inspired some researchers to re-examine the

role of attention and start to investigate the effect of dynamic visual cues on walking pattern regulation in PD (Schubert et al. 2005; Young et al. 2010; Lin et al. 2014), though the number of related studies is still quite limited. Further, most of the studies were not conducted during over-ground walking but rather treadmill walking, which may affect the outcomes of kinematic measures of gait (Pearce et al. 1983; Stolze et al. 1997; Bello et al. 2010; Almeida, Bhatt 2012).

In order to address the aims of the second study, two types of visual cues were employed and systematically manipulated: the distance between lines and texture density of random squares. The latter was used based on the assumption that it is less likely to draw the walker's attention to foot placement compared to the equally spaced transverse lines. Therefore, changes in locomotive patterns that occur in the random squares condition would support the hypothesis that gait improvement in PD is attributable to the dynamic flow properties of the visual patterns, rather than use of an attentional strategy.

## STUDY 1: Veering in Hemi-Parkinson's Disease: Primacy of Visual over Motor Contributions


### ABSTRACT

The inability to maintain a straight trajectory while walking is often reported in individuals with Parkinson's disease (PD). It is as yet unclear as to whether the mechanism underlying veering, or lateral drift, is predominantly vision-based (asymmetrical perception of the visual environment) or motoric (asymmetry between relatively affected body side and relatively non-affected body side). We examined the competing visual and motor hypotheses by assessing veering in 20 non-demented individuals with PD and 13 matched normal control participants (NC). The PD group included 9 with initial/current predominant left-side onset of motor symptoms (LPD) and 11 with right-side onset (RPD). Participants walked in a corridor under three conditions: eyes-open, vision-occluded, and Egocentric Reference Point (ECRP; walk toward a subjectively perceived center of a target at the end of the corridor). Kinematic data were collected. The visual hypothesis predicted that LPD, with a known tendency toward mild left spatial hemineglect, would veer *rightward*, in line with their perception of the visual target as right of center, whereas RPD would show *leftward* veering. The motor hypothesis predicted the opposite pattern of results: LPD would veer *leftward* because their left (more affected) body side had shorter step length than the right (less affected) body side, and RPD, for the same reason, would veer *rightward*. Results supported the visual hypothesis. On both the eyes-open and ECRP conditions, RPD lateral drift significantly differed from NC, with RPD veering leftward despite a shorter stride length

on the right body side and LPD veering rightward despite a shorter stride length on the left body side, though the LPD-NC difference was not significant. The results also revealed significantly reduced rightward veering and stride length asymmetry in LPD when they walked in ECRP condition than in eyes-open condition. The findings suggest that interventions to correct walking abnormalities such as veering in PD should incorporate vision-based strategies rather than solely addressing motor asymmetries, and should be tailored to the distinctive navigational profiles of LPD and RPD.

## INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder first described in 1817 by James Parkinson (Parkinson 2002). Typical motor symptoms of the disease include resting tremor, bradykinesia, postural instability, freezing of gait, shuffling gait pattern, rigidity in the trunk and limbs, reduced pelvis rotation and lack of arm swing, all of which put people with PD at a high risk of falling (Bloem, Boers et al. 2001; Wood, Bilclough et al. 2002; Schaafsma, Balash et al. 2003; Schaafsma, Giladi et al. 2003). Non-motor features of the disease have also been identified. In the visual domain, these include changes in basic visual functions such as contrast sensitivity, motion perception, color discrimination and visuospatial perception (Bodis-Wollner, Marx et al. 1987; Bodis-Wollner 1990; Harris, Calvert et al. 1990; Davidsdottir, Cronin-Golomb et al. 2005; Uc, Rizzo et al. 2005; Brandies and Yehuda 2008; Archibald, Clarke et al. 2011).

A current view is that the role of vision in spatial navigation includes not only perceiving the layout of the world, but also, importantly, controlling one's movement. Absence of proper visual inputs has been acknowledged as a critical risk factor for falls especially for people with visual impairment due to neurological disorders or normal aging (Perrin, Jeandel et al. 1997; Hafström, Fransson et al. 2002 ; Lee and Scudds 2003). This proposition has not typically been applied to PD, because the disease was traditionally characterized as a motor disorder rather exclusively, with the focus of rehabilitation research directed at interventions targeting the motor symptoms. Davidsdottir and colleagues reported that visual and visuospatial impairments were prevalent in a sample of 81 individuals with PD, with visual hallucinations, double vision

and contrast sensitivity deficits being strongly associated with freezing of gait (Davidsdottir, Cronin-Golomb et al. 2005). Although visual processing is impaired, there is increased dependence on vision in PD for postural control (Azulay, Mesure et al. 2002) and gait regulation while walking (Morris, Iansek et al. 2005). Therefore, advancing our understanding of the non-motor symptoms of PD such as deficits in visuospatial processing, as well as their potential contribution to locomotive disability, is a pressing need in the field.

PD almost always has unilateral onset due to the underlying hemispheric dopamine asymmetry, and this laterality is reflected in the difficulties that people with PD commonly endorse in regard to navigating in space (Davidsdottir, Cronin-Golomb et al. 2005). PD patients with an initial left body-side onset of motor symptoms (LPD; right hemisphere predominant pathology) tend to bump into objects more on the left than right side, whereas PD patients with a right body-side onset (RPD; left hemisphere predominant pathology) show no particular bias. A mild visual neglect or disturbed object detection for the hemispace on the side of motor onset has been suggested to account for these phenomena. During spatial navigation tasks, veering (lateral deviation from a straight or intended path) in PD has been measured quantitatively; persons with LPD veered rightward in the presence of visual input, whereas persons with RPD veered leftward (Davidsdottir, Wagenaar et al. 2008; Young, Wagenaar et al. 2010). This finding echoes the different profiles that LPD and RPD display on visual perception tasks, including horizontal line bisection (Lee, Harris et al. 2001; Davidsdottir, Wagenaar et al. 2008; Laudate, Neargarder et al. 2013), copying and drawing tasks (Shelton, Bowers et

al. 1990; Vallar 1998), self-report of daily visual function (Davidsdottir, Cronin-Golomb et al. 2005), reaching and grasping tasks (Rossit, McIntosh et al. 2012), body-scaled aperture estimation (Lee, Harris et al. 2001), and size perception comparison in two hemi-spaces (Milner and Harvey 1995; Harris, Atkinson et al. 2003). Overall, individuals with LPD exhibit a rightward spatial bias, perceiving stimuli as shorter or smaller on the left than the right, whereas individuals with RPD perceive visual stimuli more like healthy control adults—for example, bisecting lines slightly to the left ("pseudoneglect") (Jewell and McCourt 2000). It appears that the consequences of right hemisphere damage (LPD) contribute to more severe visuospatial impairments than damage to the left hemisphere (RPD), as the right hemisphere mediates more visuospatial processing than the left in the general population and also in PD (Cronin-Golomb 2010).

Asymmetry of symptoms also influences the dynamics of sensorimotor coordination, which significantly influences postural stability, turning behavior, and continuity of gait. (Plotnik, Giladi et al. 2005; Yogev, Plotnik et al. 2007; Boonstra, van der Kooij et al. 2008; Nanhoe-Mahabier, Snijders et al. 2011; Frazzitta, Pezzoli et al. 2013; Lin, Wagenaar et al. 2014). Individuals with PD typically have less stable and more asymmetric inter-limb coordination patterns during locomotion, e.g., shorter stride length on the initially affected body side than on the secondarily affected body side (Plotnik, Giladi et al. 2005; Young, Wagenaar et al. 2010; Lin, Wagenaar et al. 2014). Although no conclusive association has been drawn between motor asymmetry and veering, the difference in stride length between body sides has been offered as an explanation (Guth and Laduke 1994). Moreover, there were consistent trends shown in

previous veering studies that LPD persons veered rightward, whereas RPD persons veered leftward during normal walking, corresponding to the hemisphere with presumed lower dopamine levels (Davidsdottir, Wagenaar et al. 2008; Young, Wagenaar et al. 2010).

Whether the source of veering in PD is more attributed to errors in visuospatial perception or to asymmetry of motor features has not been addressed directly. These two potential mechanisms provide contradictory predictions for veering direction. If veering is primarily driven by asymmetrical walking patterns expected in PD between the relatively affected and relatively non-affected body side, a tendency to veer towards the side of body that has relatively shorter step length would be observed regardless of whether they walked with eyes open or vision occluded, i.e., LPD would veer leftward, whereas RPD would veer rightward. On the other hand, if veering is driven by visuospatial bias (as seen in mild hemineglect), veering should be shifted in the opposite direction, with LPD veering rightward and RPD veering leftward. The visuospatial bias might be observed especially when participants were asked to walk towards the self-perceived center of a horizontal line placed at the end of the corridor. The resulting visuospatial shift of the egocentric midline in PD would come into play: LPD would generate rightward error on perceiving the center of the bar, resulting in a rightward veering trajectory, and a similar (but leftward) effect would be expected in RPD, although the size of the bias would be expected to be smaller because the influence of right hemisphere dysfunction on visuospatial perception is greater than that of the left.

Our goal was to assess directly whether visuospatial bias or motor bias accounts better for lateral drift in individuals with LPD and RPD.

## METHODS

### Participants

The study included 20 non-demented individuals who had been diagnosed with idiopathic PD (11 men, 9 women) and 13 normal control adults (NC; 4 men, 9 women) (Table 1). The distribution of men and women did not differ between the PD and NC groups ($\chi^2 = 1.87$, $p = 0.17$). The PD participants were recruited from the Parkinson's Disease Clinic at the Boston Medical Center and from the Michael J. Fox Foundation Trial Finder. The NC group was recruited from the Fox Trial Finder and the local community. All participants underwent health history screening prior to taking part in the study. Exclusion criteria included the inability to ambulate independently or history of musculoskeletal impairments or pain condition; lower extremity impairments that prevented the individual from moving freely; use of walking assistive devices; coexistence of serious chronic medical illness; history of traumatic brain injury or stroke; psychiatric or neurological diagnoses (besides PD, in the PD group); surgery affecting the thalamus, basal ganglia, or other brain regions; history of alcoholism or other drug abuse; use of psychoactive medication except antidepressants or anxiolytics in the PD group; use of any psychoactive medication in the control group; presence of clinically significant eye disease, or corrected binocular acuity poorer than 20/40. Participants were screened

for acuity binocularly at a distance of 10 feet using a Snellen chart; Snellen scores were converted to logMAR scores for the analysis. Mean acuity was -0.01 (20/16 Snellen) (SD = 0.07) for the PD group, and -0.09 (20/16 Snellen) (SD = 0.03) for the NC group. There was a significant group difference with NC showing better acuity (t[26.1] = 4.21, $p$ = 0.001, $\eta^2$ = 0.29) but is probably not of clinical significance, as both groups' acuity was very good. Although we considered including acuity as a covariate, because the results showed no effect of acuity on veering, it was not considered in further analyses.

All participants were right handed except three of the PD group and one of the NC group, all of whom were left handed. We conducted separate veering analyses with and without individuals who were left handed and found that the results were not affected; therefore handedness was not considered further in the analyses. All participants were native English speakers. All were non-demented as indexed by their scores on the modified Mini-Mental State Exam (mMMSE; Stern, Sano, Paulson & Mayeux, 1987), each obtaining 26.45 or better on conversion to standard MMSE scoring.

The PD group reflected mild to moderate stages of the disorder (stages 1-3 on the Hoehn and Yahr scale) (Hoehn and Yahr, 1967) (Table 1). Disease severity was determined with the use of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987). The PD group had a mean UPDRS total of 35.5 (SD = 14.5) denoting mild-moderate disease severity. The LPD group had a mean UPDRS total of 36.7 (SD = 12.5), and the RPD group had a mean UPDRS total of 34.5 (SD = 16.5). There was no significant difference between the LPD and RPD groups ($t$[18] = 0.33, $p$ = 0.75). All participants were taking medication for their parkinsonian symptoms and at the time of

testing were in their "on" period. Levodopa equivalent dosage (LED) mean was 457.7 (SD = 335.5) mg/day for LPD, 486.4 (SD = 318.4) mg/day for RPD. There was no significant difference in LED between these groups ($t[18] = 0.20$, $p = 0.85$).

The PD group was further characterized by side of motor symptom onset: nine with LPD (6 men and 3 women) and 11 with RPD (5 men and 6 women) (Table 1). The distribution of men and women did not differ between the two groups ($\chi^2 = 0.9$, $p = 0.34$). The LPD group included one in stage 1.5, five in stage 2, two in stage 2.5 and one in stage 3 (median 2, range 1.5 – 3). The RPD group included one in stage 1, six in stage 2, one in stage 2.5 and three in stage 3 (median 2, range 1 – 3). The distribution across stages did not differ between the two groups ($\chi^2 = 3.26$, $p = 0.52$). The initial side of onset was identified using self-report and through review of neurology records. The current side and extent of motor severity were assessed using the UPDRS. The extent of motor asymmetry was calculated based on the UPDRS motor severity score of left body side and of right body side, $[(Right\ score - Left\ score)/(Right\ score + Left\ score)]$. This asymmetry index ranges from -1 to 1, where scores closer to 1 indicate more extensive and severe symptoms on the right side of the body and scores closer to -1 indicate more extensive and severe symptoms on the left side of the body. The group means for LPD and RPD were -0.3 (SD = 0.3) and 0.3 (SD = 0.4), respectively. The difference was significant ($t[18] = 3.25$, $p = 0.004$, $\eta^2 = 0.37$). Although most individuals did not display strong and obvious motor asymmetry at the time of the study, there is evidence that the hemispheric asymmetry of brain lesions in PD remains well after motor symptoms have progressed from unilateral to bilateral (Rinne, Laihinen

et al. 1993). Hence, we would expect the impact of the hemispheric asymmetry on veering to be maintained in our sample.

We compared the LPD, RPD, and NC groups on demographic and other characteristics potentially pertinent to the study. Mean age, number of years of education, and MMSE score for each group were as follows: LPD age 67.3 years (SD = 7.6), education 17.0 years (SD = 2.4), MMSE 28.2 (SD = 1.1); RPD age 66.9 (SD = 5.8), education 17.9 (SD = 1.5), MMSE 28.9 (SD = 1.0); NC age 62.3 (SD = 5.5), education 17.8 (SD = 2.3), MMSE 29.0 (SD = 0.9). There was no significant difference between groups in age, $F(2,30) = 2.34$, $p = 0.11$, education, $F(2,30) = 0.53$, $p = 0.60$, or MMSE $F(2,30) = 1.65$, $p = 0.21$. Mood was assessed for all participants using the Beck Depression Inventory II (BDI-II) and Beck Anxiety Inventory (BAI) (Beck & Steer, 1993; Beck, Steer, & Brown, 1996). There were no group differences on the BDI-II ($F[2, 30] = 1.10$, $p = 0.35$). There was a significant effect of group on the BAI ($F[2, 30] = 5.24$, $p = 0.01$, $\eta^2 = 0.26$). Specifically, the RPD group had a significantly higher mean BAI than did the NC group ($p = 0.01$). There was no significant difference on BAI between the RPD and LPD groups ($p = 0.69$) or between the LPD and NC groups ($p = 0.11$). We used BAI as a covariate in the veering analyses and found that it did not affect any of the results; therefore it was not considered further in the analyses.

(Table 1 about here)

**Apparatus**

The over-ground walking assessment was implemented in a corridor (3.7m wide, 2.6m high, 10.4m long) constructed in the laboratory using black curtains on both sides.

The room was well lit and the sounds from surroundings were strictly controlled. Participants were allowed to take a break between walks along the corridor as needed. An experimenter was immediately behind the participant at all times to ensure safety.

*Three-dimensional kinematics*

Three-dimensional kinematic data were collected using an Optotrak 3020 System (Northern Digital Inc., Waterloo, ON, Canada), with a spatial resolution of 0.1 mm. Three position sensors were placed at the end of the walkway in left, right and middle positions facing the participant's direction of walking. The placement allows for an environmental reference plane to capture bilateral locomotor movements for at least four strides. The sensors were calibrated and the mean error was accepted when the value was 0.7 mm or less. Infrared light-emitting diodes (IREDs) were applied as position markers on the participant's chin (lower mandible) and bilaterally on the ankle (lateral calcaneus), knee (patella), hip (anterior superior iliac spine), wrist (radiocarpal joint), shoulder (humeral head), cheek (2 cm below zygomatic arch). The instantaneous position of each IRED was sampled during walking trials at a rate of 100 Hz and stored to disk for further analysis.

**Procedure**

Participants started each trial by aligning each foot with a marker placed at the center of, and perpendicular to the edge of the corridor's start line. A practice session was provided to each of the participants to enable them to become acclimated to the walking environment and choose their preferred walking speed. After the practice session, the

actual data collection began. No feedback on walking speed was provided. Participants were first asked to walk a straight line down the middle of the walkway with eyes open, at a comfortable speed, until they reached the end (eyes-open condition) (3 trials). Then they were instructed to repeat the task wearing a blindfold, which was similar to a sleeping mask with an elastic band (3 trials). The experimenter told them to stop either when they reached the end or were about to bump into the side of the walkway. The lights in the room were turned off during this condition, then put back on for the rest of the session. In the third condition, which assessed veering behavior in relation to visuospatial bias, a 0.05m wide and 1.53m long rectangle ("line") colored in bright yellow was placed horizontally at eye level on the wall at the end of the walkway. The examiner stood next to the line and moved a crossbar along it slowly from one end to the other (randomized direction across participants). The participants were instructed to stand straight facing forward and stated when the crossbar fell in the perceived center of the horizontal line. Lateral deviation of the judgment of the center of the horizontal line was recorded and the crossbar was removed afterwards. This test is similar to the Landmark test of line bisection, which has been used to detect lateral biases in allocentric spatial perception in PD (Lee, Harris et al. 2001; Davidsdottir, Wagenaar et al. 2008; Laudate, Neargarder et al. 2013), but at a longer viewing distance. The participants were then instructed to walk towards their self-perceived center of the horizontal line (egocentric reference point condition, ECRP) (3 trials). The line was not used in the other conditions. We expected that if there were a visuospatial bias, PD participants would perceive the

center of the line as off true center, compared to NC, and consequentially would engage in veering in the direction dictated by the bias.

## Data Reduction

The kinematic data were filtered using a zero-lag, fourth order Butterworth low-pass filter with a cut-off frequency of 5 Hz. Angular positions of the arms and legs in the sagittal plane were defined by the orientations of vectors from shoulder to wrist markers and from hip to ankle markers, respectively, measured relative to laboratory vertical (i.e., to the gravity axis). Positive angle values indicate forward wrist or ankle positions. Stride cycles for each leg were identified by two consecutive maxima from the angular position data of the corresponding leg. All the gait variables were computed using MatLab (MathWorks, Inc., Natick, MA) employing only the middle strides (approximately six strides excluding the first and last strides in the approximately viewing volume of eight strides) in order to avoid acceleration and deceleration variations at the beginning and at the end of the distance walked.

## Dependent Variables

### *Veering*

The midpoint between left and right hip position data was calculated, and veering was defined for each trial as the difference in medio-lateral position of this midpoint between the beginning and the end of the middle strides during walking. Positive drift values indicate rightward veering and negative values indicate leftward veering. Since, as

noted in the literature, veering could be accounted for by undetected body orientation errors at the starting point (Guth and Laduke 1994; Kallie, Schrater et al. 2007), we calculated the hip angle relative to the starting line using left and right hip positional data in the anteroposterior and mediolateral direction, $\tan^{-1}\{(R_{AP} - L_{AP})|(R_{ML} - L_{ML})\}$, then tested whether there was any misalignment before initiating walking and its relation with veering. Analysis of variance (ANOVA) showed that there were no significant differences in hip angle by group or condition (all $p$>.16), meaning that initial body orientation would not account for any group differences in veering.

*Stride Parameters*

Participants walked a total of 10.4 meters. Data from only the middle strides were analyzed for each leg, as the first stride reflected reaching a comfortable walking pattern, and the last stride slowing down and stopping at the end of the corridor. In this study, the number of consecutive strides of the left and right legs that were covered ranged from four to six. The following stride parameters were computed for each of the middle strides and then averaged across strides: walking speed, stride length, and stride asymmetry (calculated as the difference in the average stride lengths between the left and right legs), all of which may impact veering behavior (Guth and Laduke 1994). For example, higher walking speeds have been associated with smaller amounts of veering (Cicinelli 1989; Klatzky, Loomis et al. 1990). Additionally, if veering in PD is driven only by the motoric factor of stride length asymmetry (one of our hypotheses to be tested), the direction of veering should be toward the body side with the shorter stride length.

Average walking speed (m/s) was determined by dividing the linear displacement of the chin marker (between the times of left heel strike that began the first stride and ended the last stride) by the time elapsed between these heel strike events. The chin marker displacement was calculated according to:

$$D_T^2 = D_{AP}^2 + D_{ML}^2$$

where $D_T$ represents the total linear displacement (Euclidean distance) of the chin marker, and $D_{AP}$ and $D_{ML}$ are its displacements in the anteroposterior and mediolateral directions, respectively. Stride lengths (in meters) of the left and right legs were calculated for each trial by the anteroposterior displacements over the middle strides by the left and right ankle markers, respectively, divided by the number of the middle strides. Considering that variation in leg lengths among participants might have an impact on the results, we normalized stride lengths of each leg by dividing them by the individual's leg length, measured as the distance between hip and ankle markers on the side of the respective leg. These normalized stride lengths were used in the data analysis.

**Data Analysis**

Statistical analyses were performed using SPSS 18.0 (SPSS, Inc., Chicago, IL). An analysis of variance (ANOVA) was conducted to examine whether the three groups (LPD, RPD, and NC) differed in walking speed across conditions, as this could impact veering behavior. Results revealed significant group differences in walking speed ($F$[2, 30] = 6.23, $p$ = 0.005, $\eta^2$ = 0.29), with the LPD and RPD groups each walking significantly more slowly than the NC group based on Tukey's *post hoc* test (LPD vs.

NC: $p = 0.021$; RPD vs. NC: $p = 0.011$). Walking speed did not significantly affect the results on veering, however, so it was not considered further. Separate mixed design ANOVAs were performed to examine the effects of group (LPD, RPD and NC) and condition (eyes-open, vision-occluded and egocentric reference point [ECRP]) on veering and the stride parameters of normalized stride length and stride asymmetry. The analyses for all of the parameters were based on the average of three trials per condition. We used age as a covariate in the stride length analyses because even though the three groups did not significantly differ in age, previous literature suggests that there are age-related changes in gait for stride length (Himann, Cunningham et al. 1988; Prince, Corriveau et al. 1997).

A series of *a priori* between groups *t*-tests (or ANOVAs if a covariate was included), were performed to examine the differences between LPD and RPD, LPD and NC, and RPD and NC under each vision condition. *A priori* within groups *t*-tests were used to examine differences on the eyes-open and vision-occluded conditions, eyes-open and ECRP conditions, and vision-occluded and ECRP conditions within each group. In addition, we used Spearman correlations to examine the relation between veering (direction and extent) and stride asymmetry during walking in each condition for each group. We predicted that those individuals in each group with higher stride asymmetry scores would demonstrate more veering. We used one-tailed tests to examine these directional hypotheses.

## RESULTS

### *Veering*

A mixed design ANOVA on veering showed no significant effects of group ($F$[2,30] = 1.16, $p$ = 0.33), condition ($F$[1.1,33.3] = 0.53, $p$ = 0.49), or interaction between group and condition ($F$[2.2,33.3] = 1.26, $p$ = 0.30).

*Between-groups comparisons*

A series of *a priori* between groups t-tests revealed a significant group difference between RPD (leftward veering) and NC (rightward veering) in the eyes-open condition ($t$[22] = 3.67, $p$ = 0.001, $\eta^2$ = 0.38) and in the ECRP condition ($t$[22] = 2.66, $p$ = 0.014, $\eta^2$ = 0.24) (Fig. 1). These two groups did not differ in veering in the vision-occluded condition ($t$[22] = 0.11, $p$ = 0.88). There was no significant difference between the LPD group and either the RPD or NC group in any of the conditions (all $p$'s > 0.12).

*Within-groups comparisons*

A series of *a priori* within group t-tests revealed that for the LPD group, there was significantly less veering in the ECRP condition than in the eyes-open condition, with rightward veering in both conditions, $t$(8) = 2.32, $p$ = 0.049, $\eta^2$ = 0.40 (Fig. 1). With vision occluded, mean veering was leftward but the difference between veering under this condition and under either the eyes-open condition or the ECRP condition was not significant (all $p$'s > 0.26). The NC group on average showed rightward veering in all walking conditions. Like the LPD group, the NC group showed significantly less veering in the ECRP condition than in the eyes-open condition $t$(12) = 2.19, $p$ = 0.049, $\eta^2$ = 0.29; no other conditions significantly differed (all $p$'s > 0.37). For the RPD group, on average

veering was leftward in both the eyes-open and ECRP conditions and rightward in the vision-occluded condition, but the differences between conditions were not significant (all $p$'s> 0.24).

(Figure 1 about here)

***Normalized stride length***

A preliminary ANOVA was conducted and showed no differences between the normalized stride length computed based on the left leg time series and that computed based on the right leg time series ($F$[1,30] = 0.06, $p$ = 0.80); therefore the normalized stride length based on the left leg time series was utilized in further analyses. An ANOVA with age included as a covariate revealed a trend for the main effect of group ($F$[2,29] = 3.03, $p$ = 0.06, $\eta^2$ = 0.17), a significant main effect of condition ($F$[1.3,40.0] = 109.33, $p$ = 0.001, $\eta^2$ = 0.79), and no interaction between group and condition ($F$[2.7,40.0] = 1.76, $p$ = 0.18). Age was a significant covariate ($F$[1,30]= 8.10, $p$ = 0.008, $\eta^2$ = 0.21) in the analysis.

*Between-groups comparison*

A series of *a priori* t-tests and/or univariate ANOVAs (when age was a significant covariate) demonstrated that compared to the NC group, the LPD group exhibited significantly shorter stride length in the eyes-open condition ($t$[20] = 2.70, $p$ = 0.014, $\eta^2$ = 0.27) and in the vision-occluded condition ($F$[1,19] = 8.42, $p$ = 0.009, $\eta^2$ = 0.31). In the latter, age was a significant covariate ($F$[1,19] = 5.62, $p$ = 0.029, $\eta^2$ = 0.23) (Fig. 2). The difference between these two groups was not significant but had a trend in the ECRP condition ($t$[20] = 1.78, $p$ = 0.09, $\eta^2$ = 0.14). RPD had significantly shorter stride length

than NC in the vision-occluded condition ($t$[13.5] = 2.96, $p$ = 0.011, $\eta^2$ = 0.31); however, groups did not differ in the eyes-open condition ($F$[1,21] = 1.00, $p$ = 0.33) or the ECRP condition ($F$[1,21] = 2.21, $p$ = 0.15). Age was a significant covariate in the two latter comparisons ($F$[1,21] = 5.46, $p$ = 0.029, $\eta^2$ = 0.21 and $F$[1,21] = 4.38, $p$ = 0.049, $\eta^2$ = 0.17, respectively). There were no significant differences between the LPD and RPD groups in any of the conditions (all $p$'s > 0.38), with age as a significant covariate (all $p$'s < 0.036).

*Within-groups comparison*

A series of *a priori* within group t-tests showed that stride length was significantly shorter for all groups when walking with vision occluded than either with eyes open or in the ECRP condition (Fig. 2). For LPD, eyes-open vs. vision-occluded: $t$(8) = 6.55, $p$ = 0.001, $\eta^2$ = 0.84; vision-occluded vs. ECRP: $t$(8) = 5.71, $p$ = 0.001, $\eta^2$ = 0.80. For RPD, eyes-open vs. vision-occluded: $t$(10) = 7.10, $p$ = 0.001, $\eta^2$ = 0.83; vision-occluded vs. ECRP: $t$(10) = 6.79, $p$ = 0.001, $\eta^2$ = 0.82. For NC, eyes-open vs. vision-occluded: $t$(12) = 6.12, $p$ = 0.001, $\eta^2$ = 0.76; vision-occluded vs. ECRP: $t$(12) = 5.39, $p$ = 0.001, $\eta^2$ = 0.71). There was a trend for stride length to be longer in the ECRP condition than in eyes-open condition for LPD ($t$[8] = 1.95, $p$ = 0.087, $\eta^2$ = 0.32), and for RPD ($t$[10] = 2.08, $p$ = 0.064, $\eta^2$ = 0.30), but not for NC ($t$[12] = 0.49, $p$ = 0.64).

***Stride Asymmetry***

In regard to stride asymmetry, calculated as the difference in stride lengths between the left and right legs, an ANOVA revealed no significant main effects of group,

$F(2,30) = 0.20$, $p = 0.82$, or condition, $F(2,60) = 0.61$, $p = 0.55$, or interaction between group and condition, $F(4,60) = 0.58$, $p = 0.68$.

*Between-groups comparison*

A series of *a priori* between group t-tests showed that there was a significant group difference, as expected, between LPD and RPD in the eyes-open condition, $t(18) = 3.37$, $p = 0.003$, $\eta^2 = 0.39$, with LPD showing shorter stride length on the left body side and RPD showing shorter stride length on the right body side (see Fig. 3). The two groups did not differ in the other two conditions (all $p$'s > 0.14). Neither the LPD nor RPD group's stride asymmetry was significantly different from that of NC in any of the conditions (all $p$'s > 0.45).

*Within-groups comparison*

Stride asymmetry in the LPD group was significantly less in the ECRP condition, in which participants walked towards a self-perceived center of the horizontal line in front of them, than in the baseline eyes-open condition ($t[8] = 2.34$, $p = 0.048$, $\eta^2 = 0.41$). There was also a trend for stride asymmetry to be less in the vision-occluded condition than in the eyes-open condition ($t[8] = 1.94$, $p = 0.089$, $\eta^2 = 0.32$) (see Fig. 3), and there was no difference between the vision-occluded and ECRP conditions ($t[8] = 1.34$, $p = 0.22$). For neither RPD nor NC were any significant differences observed between any two of the conditions (all $p$'s > 0.17).

(Figures 2 and 3 about here)

### *Correlations*

We examined correlations between veering (direction and extent) and stride length asymmetry. A negative veering value indicates leftward drift (positive indicating rightward) and a negative value of stride asymmetry indicates shorter strides with the left leg (positive indicating shorter right-leg strides).

A significant correlation between less leftward veering and less stride length asymmetry (shorter strides with left leg) was found for the LPD group in the ECRP condition, $\rho = 0.61$, $p = 0.04$, and a trend in the same direction was found for the vision-occluded condition, $\rho = -0.54$, $p = 0.07$. There was no correlation for the eyes-open condition, $\rho = 0.47$, $p = 0.10$. For the RPD group, the correlation between veering and stride length asymmetry was not significant for any of the conditions (all $\rho's < 0.07$, $p's > 0.42$). For the NC group, there was a trend for a correlation between veering and stride asymmetry for the eyes-open condition ($\rho = 0.40$, $p = 0.09$). There were no significant correlations for the NC group for either the vision-occluded condition or the ECRP condition (all $\rho's < 0.12$, $p's > 0.35$).

## DISCUSSION

The results of the present study support the hypothesis that visual dysfunction, rather than motor dysfunction, is the predominant driver of veering in PD. This study also provides quantitative evidence for the existence of distinct patterns of veering and stride asymmetry that are specific to side of motor symptom onset in PD, under conditions with

visual input.

LPD have been reported to have a tendency toward mild left spatial hemineglect that produces a rightward shift of egocentric midline, whereas RPD tend to have (if any bias) a slight right spatial hemineglect that produces a leftward shift of egocentric midline (Lee, Harris et al. 2001; Lee, Harris et al. 2002; Harris, Atkinson et al. 2003; Davidsdottir, Cronin-Golomb et al. 2005). Based on the findings of previous visuospatial studies (Davidsdottir et al., 2008; Young et al., 2010), one would expect people with PD to veer in the direction of the lateral shift of the egocentric midline. By contrast, from a biomechanics point of view, PD veering should be influenced by motoric asymmetry between the relatively more affected body side and the relatively less affected body side. This would predict results opposite to those based on the visuospatial hypothesis: individuals with PD should veer towards the side with a shorter stride length.

Our findings mainly support the former visuospatial prediction under conditions of visual guidance. When participants were instructed to walk straight ahead in the eyes-open condition, LPD veered rightward and RPD veered leftward, consistent with our earlier studies on veering (Davidsdottir, Wagenaar et al. 2008; Young, Wagenaar et al. 2010), despite shorter stride length on the more affected body side (i.e., on the left side for LPD and on the right side for RPD). In the ECRP condition, when participants were asked to walk toward a subjectively perceived center of a target at the end of the corridor (reflecting their egocentric reference point), they veered in the same direction as seen in baseline eyes-open condition. When the task was performed with vision occluded, group differences were not significant, though it should be noted that the direction was in fact

opposite that seen under visual guidance; that is, the direction predicted by biomechanics alone: LPD veered to the left, corresponding to the body side with shorter stride length, and RPD veered to the right, likewise corresponding to the body side with shorter stride length. We conclude that under conditions of visual guidance that mirror everyday life, the mechanism underlying veering is predominantly vision-based instead of motoric.

Comparing our results to those of other studies reveals some inconsistencies in regard to the vision-occluded condition. As noted above, we found that RPD and NC veered to the body side that had shorter stride length, which was the right side; for the same reason, LPD veered to the left. In the study by Young and colleagues (Young, Wagenaar et al. 2010), the expected stride asymmetry was found between the initially-affected side and secondarily-affected side for PD, with LPD having a shorter stride length on the left and RPD on the right; NC had shorter stride length on the left than right. Despite the different directions of stride asymmetry between groups, all participants showed leftward veering in the vision-occluded condition. A possible explanation for the difference across studies was in regard to body orientation upon onset of walking. As the initial orientation of the body could be responsible for the trajectory of veering (Guth and Laduke 1994; Kallie, Schrater et al. 2007), it is important to guarantee that the alignment of the body axis relative to the true midline of the walkway is consistent across groups throughout the experiment. In the present study we tested body alignment using the angle between left and right hip markers before walking was initiated and showed that there were no significant differences in hip angle across all groups and conditions. Hence, we were able to rule out the possibility that initial body

orientation could account for group differences in the direction of veering. This information was not provided in the previous studies, leaving open this possibility in accounting for the different results reported.

Our findings underscore the dominant role of vision in controlling the direction of veering, but we also found evidence for the influence of certain motor characteristics of PD. There was a significant correlation of veering with stride asymmetry for LPD, under the ECRP condition. Although LPD veering and stride asymmetry were minimal in the ECRP condition, the correlation between the two variables was significant in a positive direction, meaning that the less the asymmetry in stride length (caused by shorter strides on the left than the right body side), the less leftward veering. We expect that the asymmetry of motor symptoms may have some impact on veering in PD, though it may not be powerful enough to overrule the effect of vision. Further study with larger samples and a wider range of disease severity will be required to examine this possibility.

It is noteworthy that age seemed to have no impact on the observed group differences in veering and stride asymmetry, in contrast to age being a significant covariate for group differences in stride length. As aging has been associated with reduced stride length (Prince, Corriveau et al. 1997), examining a range of age groups to further examine the effect of age on veering and stride asymmetry would be of interest as a future research direction.

It is well accepted that visual cues are critical for gait improvement for people with PD (Morris, Iansek et al. 1994; Azulay, Mesure et al. 1999; Lewis, Byblow et al. 2000; Lebold and Almeida 2011; Spaulding, Barber et al. 2013; Vitorio, Lirani-Silva et

al. 2014). These studies used traditional cueing methods such as stripes placed on the ground. Recently, Vitorio and colleagues reported that participants with PD could regulate stride length regardless of whether or not they were looking at their lower limbs while walking—that is, exproprioceptive information (from the lower limbs) is not crucial for gait improvements generated by visual cues (Vitorio, Lirani-Silva et al. 2014). The ECRP condition in the present study is similar in that participants gazed at the self-perceived center of the horizontal line at eye level, and accordingly did not focus on their lower limbs' movement during walking. Longer stride length was observed in the ECRP condition than in the baseline eyes-open condition, which was consistent with the findings of longer stride lengths achieved with visual cues reported by Vitorio et al. We also found less veering and decreased stride asymmetry under the ECRP condition compared to the eyes-open condition. LPD benefited more than RPD from cuing; the effects of the visual cue were significant for LPD but not for RPD. We have reported that individuals with LPD appear to be more visually dependent than those with RPD (Davidsdottir et al., 2008), which may explain the greater ability of LPD to benefit from conditions that provide visual cuing. These findings point to a potential role of explicit visual landmarks to guide locomotion in PD. It would be interesting for future research to examine other gait characteristics, such as stride-to-stride adjustments/corrections in body orientation angles that might be associated with veering during walking with a target present in front.

Our results suggest that individuals with LPD, with presumed predominant right hemisphere pathology, demonstrated patterns of gait disturbances that were visually

influenced, as shown by differences in the extent of veering between the eyes-open and ECRP conditions. Within this subgroup, common parkinsonian gait disturbances such as veering, stride asymmetry, and to some extent stride length were amenable to amelioration by visual guidance, mainly focusing on self-perceived center (ECRP condition). The effect of directing attention to perceived center at eye-level had significant effects on navigating the environment, raising the possibility of attentional or environmental strategies for intervention. Targeting visual attention and related aspects of cognition presents a potential but to date underexamined avenue of treatment (Sinforiani, Banchieri et al. 2004; Paris, Saleta et al. 2011; Doruk, Gray et al. 2014). These interventions hold promise particularly when combined with action observation-based (internal) strategies for intervention that have been shown to improve gait and walking in PD (Pelosin, Avanzino et al. 2010; Pelosin, Bove et al. 2013). Interventions to improve visual attention may prove to be a reasonable strategy to improve locomotion in PD, especially for individuals with left-side onset of symptoms. A further possibility suggested by the almost complete lack of veering in the ECRP condition is that distortion of visuospatial processing in hemiPD may be corrected by the use of objective environmentally-anchored landmarks, which may serve as targets to provide appropriate locomotion paths and guide locomotor trajectories.

In conclusion, the existence of the distinct directions of veering for LPD and RPD observed in this study supports the primacy of the visual control of navigation over the role of motor function as measured by kinematic data. This finding suggests that information on veering may be of importance in the management of PD. In particular,

interventions for gait disorders in PD should emphasize vision, visual attention, and environmental modification as means to rehabilitate veering problems, as this strategy may be more effective than focusing solely on motor symptoms as targets for treatment.

Table 1. Participant Characteristics

| Measure | LPD | RPD | NC | Significance |
|---|---|---|---|---|
| Sample size | 9 | 11 | 13 | NS |
| Age (years) | 67.3 (7.6) | 66.9 (5.8) | 62.3 (5.5) | NS |
| Education (years) | 17.0 (2.4) | 17.9 (1.5) | 17.8 (2.3) | NS |
| Gender (M:F) | 6:3 | 5:6 | 4:9 | NS |
| UPDRS motor asymmetry score | -0.3 (0.3) | 0.3 (0.4) | NA | $p = 0.004$ |
| UPDRS total score | 36.7 (12.5) | 34.5 (16.5) | NA | NS |
| BDI-II | 4.6 (2.4) | 6.1 (4.7) | 3.5 (4.7) | NS |
| BAI | 4.8 (3.5) | 6.3 (6.0) | 1.2 (1.5) | $p = 0.01$ |
| H & Y | 2 (1.5-3) | 2 (1-3) | NA | NS |
| LED | 457.7 (335.5) | 486.4 (318.4) | NA | NS |

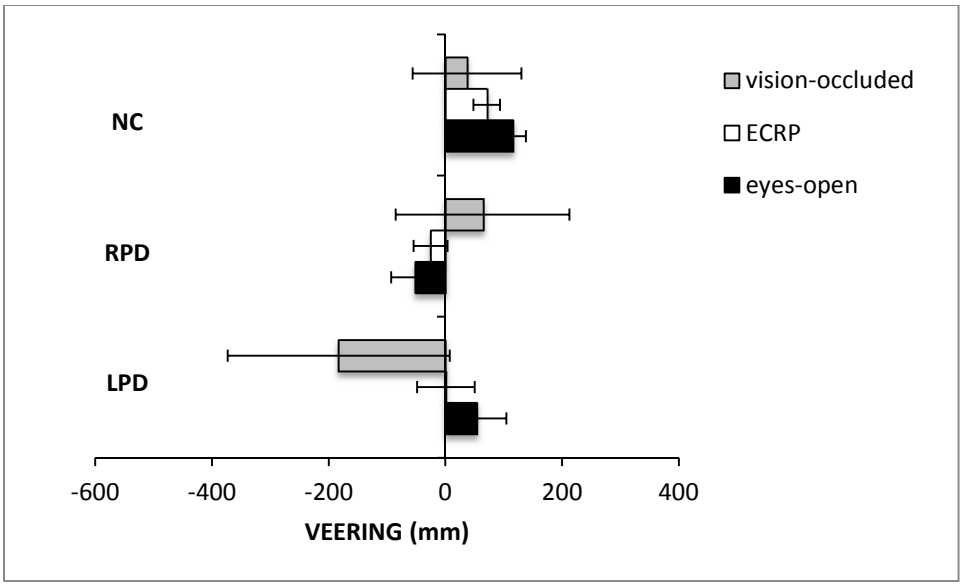
*Note*. Univariate Analysis of Variance tests were conducted comparing LPD (left-onset Parkinson's disease), RPD (right-onset Parkinson's disease) and NC groups (normal control). UPDRS = Unified Parkinson's Disease Rating Scale; H & Y = Hoehn & Yahr stage; BDI-II = Beck Depression Inventory – II; BAI = Beck Anxiety Inventory; LED = levodopa equivalent dosage. Values presented are means (standard deviations) except for Hoehn and Yahr, which is median and range. *p* value reflects results including the four participants who had less consistent laterality.

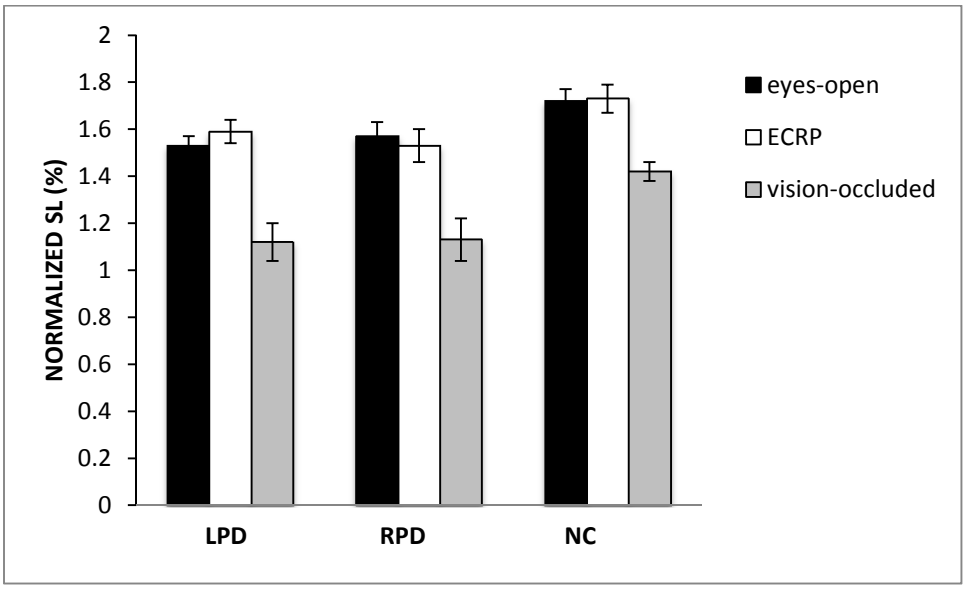
**Figure Legends**

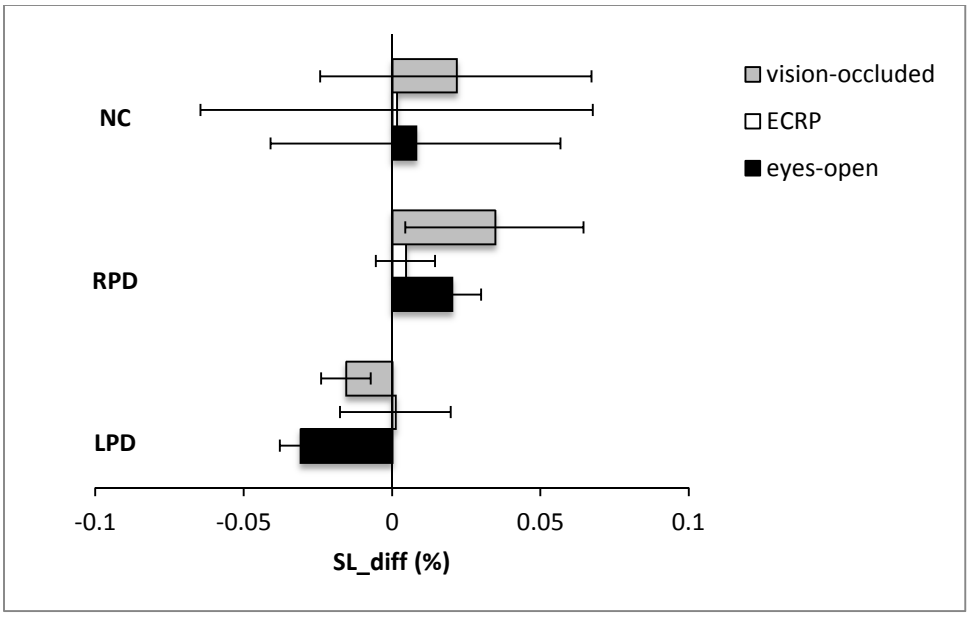
**Fig. 1.** Veering (in mm) during walking under three conditions: eyes-open, vision-occluded and ECRP. 9 LPD, 11 RPD and 13 NC. *Negative values* represent veering toward the left whereas *positive values* represent veering toward the right. Horizontal lines represent standard error of the mean.

**Fig. 2.** Normalized stride length (SL) on the left leg under three walking conditions: eyes-open, vision-occluded and ECRP. 9 LPD, 11 RPD and 13 NC. Vertical lines represent standard error of the mean. The unit is in percentage as the values are the stride length after normalization by individual's leg length.

**Fig. 3.** Difference in stride length between left and right body side (SL_diff) under three walking conditions: eyes-open, vision-occluded and ECRP. 9 LPD, 11 RPD and 13 NC. *Negative values* represent shorter stride length on the left body side whereas *positive values* represent shorter stride length on the right body side. Vertical lines represent standard error of the mean. The unit is in percentage as the values are the stride length after normalization by individual's leg length.


NC
RPD
LPD
vision-occluded
ECRP
eyes-open
-600
-400
-200
0
200
400
VEERING (mm)


NORMALIZED SL (%)
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
LPD
RPD
NC
eyes-open
ECRP
vision-occluded


vision-occluded
ECRP
eyes-open
NC
RPD
LPD
-0.1
-0.05
0
0.05
0.1
SL_diff (%)

## STUDY 2: Effects of Visual Cues on Regulation of Gait and Interlimb Coordination during Walking in Parkinson's disease


### ABSTRACT

Impairments in gait and the inability to maintain stable interlimb coordination while walking are often observed in individuals with Parkinson's disease (PD). Providing external visual cues with a spatially rhythmic pattern has shown positive rehabilitative effects, but it is unknown if the key variable is pattern rhythmicity, suggesting that attention to the placement of the foot in relation to the cue underlies improvement, or instead if it may be density or mere presence of pattern elements, suggesting that the mechanism of improvement may be perception of dynamic flow. A second potential variable to consider is side of disease onset, as individuals with left-side onset of motor symptoms (LPD) tend to have more visuospatial dysfunction and visual dependence than those with right-side onset of motor symptoms (RPD). We assessed 20 non-demented individuals with PD (9 LPD, 11 RPD) and 14 matched normal control participants (NC). Participants walked along a corridor under the following conditions: plain surface (baseline), surface with random squares of three densities, surface with transverse lines of three spatial frequencies, and plain surface again (post-intervention). Kinematic data were collected. With visual cues, especially of higher density/frequency but regardless of whether they were transverse lines or random squares, there was an overall improvement in walking speed with longer stride length and more stable interlimb coordination in PD and NC. The effects of the visual cues were stronger for LPD than RPD. The findings indicate that visual cues need not be restricted to traditional transverse lines but rather

could comprise random patterns in order to serve as interventions to correct walking abnormalities in PD, suggesting that the mechanism of improvement is based on dynamic flow of visual texture rather than on attention.

## INTRODUCTION

Parkinson's disease (PD) is characterized by a variety of motor symptoms including resting tremor, postural instability, disturbed gait pattern, and rigidity of the trunk and limbs with lack of arm swing (Blin et al., 1990; Bowes et al., 1992; Morris et al., 2001; Hausdorff 2009; Garcia-Ruiz 2011), all of which may lead to serious consequences such as falling (Wood et al., 2002; Schaafsma et al., 2003). Besides the motor symptoms, non-motor symptoms such as disturbances of basic vision and higher-order visuospatial perception and cognition are also common in this disorder (Bodis-Wollner, Marx et al. 1987; Bodis-Wollner 1990; Harris, Calvert et al. 1990; Davidsdottir, Cronin-Golomb et al. 2005; Uc, Rizzo et al. 2005; Brandies and Yehuda 2008; Archibald, Clarke et al. 2011). Vision is important not only for perceiving the layout of the world, but also for controlling one's movement. In PD there is a history of applying interventions that target deficits in visual perception in order to rehabilitate locomotive abnormalities, mainly slow walking speed and short stride length. Approaches have focused on improving gait kinematics to promote symmetry as well as increased step length and walking speed (Azulay et al. 1996; Morris et al. 1996; Azulay et al. 1999; Lewis et al. 2000; Rubinstein et al. 2002; Suteerawattananon et al. 2004; Azulay et al. 2006; Jiang, Norman 2006; Wegen et al. 2006; Sidaway et al. 2006; Almeida, Bhatt 2012; Vitorio et al. 2014).

The mechanism underlying visually-controlled gait dynamics has been debated, with some investigators attributing improvement to the enhancement of attentional strategies. For example, rhythmic visual cues, such as transverse lines on the floor, may

help walkers to focus their attention on stepping over each of the sequential lines, which results in better regulation of step length (Lewis et al. 2000; Lebold and Almeida 2011). Alternatively, improvement may be afforded by the presence of dynamic flow information produced by self-motion during walking (Azulay et al. 1999). Consistent with this Gibsonian view (Gibson 1966) is that visual information in the environment provides direct opportunity for action. If dynamic visual flow is impeded experimentally, no improvement of gait is obtained (Azulay et al. 1999; Lebold and Almeida 2011). Recently, the focus of attention on stepping over rhythmic visual line cues has been shown not to be critical for individuals with PD to achieve improvement in gait (Vitorio et al. 2014). The number of relevant studies supporting either view is limited, and most of the studies were not conducted during over-ground walking but rather with treadmill walking, which may affect the outcomes of kinematic measures of gait (Pearce et al. 1983; Stolze et al. 1997; Bello et al. 2010; Almeida, Bhatt 2012). Moreover, most of the studies used only lines, without consideration of the potential of other patterns to improve gait.

In the present study, we directly compared the attentional strategy and dynamic visual flow hypotheses as competing explanations for improvement of gait in PD following from vision-based interventions. We carried out systematic manipulations of the distance between lines and also provided conditions using random-squares pattern of various densities. The random-squares patterns were assumed to be less likely than evenly-spaced transverse lines to draw the individual's attention to foot placement. Gait improvement under the random-squares condition would support the hypothesis that the

dynamic pattern of the visual cues, rather than or in addition to attentional strategy, is a main contributor to gait regulation in individuals with PD. To provide a more detailed picture of walking improvement, we did not limit our investigation to the examination of standard gait parameters such as walking speed, stride length, and stride frequency, but also included the measurement of interlimb coordination.

Upper and lower limb coordination was quantified by the relative power index (RPI; indicating frequency inter-relations) and relative phase (indicating phase inter-relations) between the arms and legs. From the biomechanics point of view, individuals with PD are able to adjust their interlimb coordination pattern corresponding to changes in walking speed (van Emmerik et al. 1996; Wagenaar, van Emmerik 2000; Donker et al. 2001). A reduced standard deviation (or variability from one stride cycle to another) of the relative phase between upper and lower limbs would emerge at a high walking speed representing a more stable coordination pattern. Therefore, if visual cues directly lead to changes in gait in PD, modulations in coordination patterns would be expected to occur simultaneously. There has been evidence of changes in walking speed as well as in RPI with manipulation of optic flow speed in a virtual hallway in younger and older healthy adults (Chou et al. 2009). In a study conducted with people with PD and age-matched healthy control adults, an association was found between a decrease in the density of random dots embedded in a virtual hallway and a decrease in walking speed, but there was no such relation between dot density and either relative phase or RPI (Lin et al. 2014). The participants in the study by Lin and colleagues were asked to walk at a specific speed and not at their preferred walking speed, which does not reflect a real-life

situation. In the present study, we assessed the effects of optic flow, as provided by a pattern of floor visual cues, on gait and interlimb coordination, eliminating any constraints on walking speed by letting participants walk over-ground at their preferred comfortable speed.

A final variable examined in the current study was side of PD onset. The initial motor symptoms of PD usually are unilateral, reflecting asymmetrical depletion of dopamine in the substantia nigra (Kempster et al., 1989) that appears to be maintained well after the disease has progressed from unilateral to bilateral (Antonini et al. 1995; Booij et al. 1997). Left-side motor onset (LPD) and right-side motor onset (RPD) have been associated with distinct functional profiles, including more visuospatial dysfunction and visual dependence in LPD than RPD (Davidsdottir et al., 2008; Cronin-Golomb 2010). On this basis, we hypothesized that individuals with LPD would be more sensitive to visual manipulations than RPD, operationalized as showing stronger improvement in walking upon application of the vision-based interventions.

## METHODS

### Participants

The study included 20 non-demented individuals diagnosed with idiopathic PD (11 men, 9 women) and 14 normal control adults (NC; 5 men, 9 women) (Table 2). The distribution of men and women did not differ between the PD and NC groups ($\chi^2 = 1.23$, $p = 0.27$). The PD participants were recruited from the Parkinson's Disease Clinic at the

Boston Medical Center and from the Michael J. Fox Foundation Trial Finder. The NC participants were recruited from the Fox Trial Finder and the local community. All participants underwent health history screening prior to taking part in the study. Exclusion criteria included the inability to ambulate independently or history of musculoskeletal impairments or pain conditions; lower extremity impairments that prevented the individual from moving freely; use of walking assistive devices; coexistence of serious chronic medical illness; history of traumatic brain injury or stroke; psychiatric or neurological diagnoses (besides PD, in the PD group); surgery affecting the thalamus, basal ganglia, or other brain regions; history of alcoholism or other drug abuse; use of psychoactive medication except antidepressants or anxiolytics in the PD group; use of any psychoactive medication in the control group; presence of clinically significant eye disease, or corrected binocular acuity poorer than 20/40. Participants were screened for acuity binocularly at a distance of 10 feet using a Snellen chart; Snellen scores were converted to logMAR scores for the analysis. Mean acuity was -0.02 (20/20 Snellen; SD = 0.07) for the PD group, and -0.09 (20/16 Snellen; SD = 0.03) for the NC group. There was a significant group difference with NC showing better acuity ($t[25.4] = 4.30$, $p = 0.001$, $\eta^2 = 0.30$) and accordingly acuity was included as a covariate in the statistical analyses, but the difference was presumably not of clinical significance, as both groups had good vision. All participants were right handed except three of the PD group and one of the NC group, all of whom were left handed. All participants were native English speakers. All were non-demented as indexed by their scores on the modified Mini-Mental

State Exam (mMMSE; Stern, Sano, Paulson & Mayeux, 1987), each obtaining an average value of 28.6 or better on conversion to standard MMSE scoring.

The PD group reflected mild to moderate stages of the disorder (stages 1-3 on the Hoehn and Yahr scale; Hoehn and Yahr, 1967) (Table 2). Disease severity was determined with the use of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987). The PD group had a mean UPDRS total of 35.5 (SD = 14.5) denoting mild-moderate disease severity. The LPD group had a mean UPDRS total of 36.7 (SD = 12.5), and the RPD group had a mean UPDRS total of 34.5 (SD = 16.5). There was no significant difference between the LPD and RPD groups ($t[18] = 0.33$, $p = 0.75$). All participants were taking medication for their parkinsonian symptoms and at the time of testing were in their "on" period. Levodopa equivalent dosage (LED) mean was 457.7 (SD = 335.5) mg/day for LPD, 486.4 (SD = 318.4) mg/day for RPD. There was no significant difference in LED between these groups ($t[18] = 0.20$, $p = 0.85$).

The PD group was further characterized by side of motor symptom onset: nine with LPD (6 men and 3 women) and 11 with RPD (5 men and 6 women) (Table 2). The distribution of men and women did not differ between the two groups ($\chi^2 = 0.9$, $p = 0.34$). The LPD group included one in stage 1.5, five in stage 2, two in stage 2.5 and one in stage 3 (median 2, range 1.5 – 3). The RPD group included one in stage 1, six in stage 2, one in stage 2.5 and three in stage 3 (median 2, range 1 – 3). The distribution across stages did not differ between the two groups ($\chi^2 = 3.26$, $p = 0.52$). The initial side of onset was identified using self-report. Although most individuals did not display strong and obvious motor asymmetry at the time of the study, there is evidence that the

hemispheric asymmetry of brain lesions in PD remains well after motor symptoms have progressed from unilateral to bilateral (Rinne, Laihinen et al. 1993). Hence, the impact of the hemispheric asymmetry might be maintained in our sample.

We compared the LPD, RPD, and NC groups on demographic and other characteristics potentially pertinent to the study. Mean age, number of years of education, and MMSE score for each group were as follows: LPD age 67.3 years (SD = 7.6), education 17.0 years (SD = 2.4), MMSE 28.2 (SD = 1.1); RPD age 66.9 (SD = 5.8), education 17.9 (SD = 1.5), MMSE 28.9 (SD = 1.0); NC age 62.1 (SD = 5.3), education 17.5 (SD = 2.4), MMSE 29.0 (SD = 0.9). There was no significant difference between groups in age, $F(2,31) = 2.69$, $p = 0.08$, education, $F(2,31) = 0.43$, $p = 0.65$, or MMSE $F(2,31) = 1.67$, $p = 0.20$. Mood was assessed for all participants using the Beck Depression Inventory II (BDI-II) and Beck Anxiety Inventory (BAI) (Beck & Steer, 1993; Beck, Steer, & Brown, 1996). There were no group differences on the BDI-II ($F[2, 31] = 1.38$, $p = 0.27$). There was a significant effect of group on the BAI ($F[2, 31] = 5.83$, $p = 0.01$, $\eta^2 = 0.27$). Specifically, the RPD group had a significantly higher mean BAI than did the NC group ($p = 0.01$). There was no significant difference on BAI between the RPD and LPD groups ($p = 0.68$) or between the LPD and NC groups ($p = 0.09$). We used BAI as a covariate in all the statistical analyses.

(Table 2 about here)

## Apparatus

The over-ground walking assessment was implemented in a corridor (3.7m wide, 2.6m high, 10.4m long) constructed in a laboratory using curtains in black on two sides. The lab was well lit and the sounds from surroundings were strictly controlled. Participants were allowed to take a break any time as needed during the experiment. An experimenter was immediately behind the participant at all times to ensure their safety.

*Textured surface with transverse lines and random squares*

Participants walked on a 3.7m by 10.4m carpeted surface of dark green color throughout the experiment. There was one plain surface used to serve as the baseline assessment, and six that were textured by the external cues in various conditions. There were two types of external cues: random squares followed by transverse lines. The lines (5cm×250cm) and the squares (5cm×5cm) were constructed of laminated white tape (InSite Solutions, LLC., Wake Forest, NC, USA) that was securely adhered to the walking surface to prevent tripping. The space between transverse lines was manipulated such that three different spatial frequencies were presented to participants: 65cm, 45cm, and 25cm (line1, line2, and line3). The density of the random squares was manipulated to produce densities of 1.3, 4.8, and 16.4 squares/ $m^2$ (random1, random2, and random3). The order of the conditions within each type of the visual cues was randomized. One carpeted surface was presented at a time (that is, unrolled and placed in position at the beginning of each condition; removed when the condition was finished).

*Three-dimensional kinematics*

Three-dimensional kinematic data were collected using an Optotrak 3020 System (Northern Digital Inc., Waterloo, ON, Canada), with a spatial resolution of 0.1 mm. Three position sensors were placed at the end of the walkway in left, right and middle positions facing the participant's direction of walking. The placement allows for an environmental reference plane to capture bilateral locomotor movements for at least four strides. The sensors were calibrated and the mean error was accepted when the value was 0.7 mm or less. Infrared light-emitting diodes (IREDs) were applied as position markers on the participant's chin (lower mandible) and bilaterally on the ankle (lateral calcaneus), knee (patella), hip (anterior superior iliac spine), wrist (radiocarpal joint), shoulder (humeral head), cheek (2 cm below zygomatic arch). The instantaneous position of each IRED was sampled during walking trials at a rate of 100 Hz and stored to disk for further analysis.

**Procedure**

A practice set of trials was provided to all participants to enable them to become acclimated to the walking environment before starting the experimental portion of the study. In the first experimental condition, participants were first asked to choose their preferred comfortable walking speed and to proceed down the middle of the walkway on the plain, carpeted surface three times (baseline condition). They then were instructed to walk straight ahead on the surfaces textured with random squares three times for each density condition, followed by the same procedure for transverse lines three times for

each frequency condition. The order of the condition (frequency of lines or density of squares) within each visual-cue type was randomly assigned. To examine whether the effects of cues would persist when they were absent, at the end of the experiment (post-intervention condition), the participants walked on the plain surface as in the baseline condition. Participants were instructed to face forward and walk at their preferred walking velocity for the duration of the experimental session. No feedback on walking speed was provided.

**Data Reduction**

The kinematic data were filtered using a zero-lag, fourth order Butterworth low-pass filter with a cut-off frequency of 5 Hz. Angular positions of the arms and legs in the sagittal plane were defined by the orientations of vectors from shoulder to wrist markers and from hip to ankle markers, respectively, measured relative to laboratory vertical (i.e., to the gravity axis). Positive angle values indicate forward wrist or ankle positions. Stride cycles for each leg were identified by two consecutive maxima from the angular position data of the corresponding leg. All the gait variables were computed using MatLab (MathWorks, Inc., Natick, MA) employing only the middle strides (excluding the first and last strides) to avoid acceleration and deceleration variations at the beginning and at the end of the distance walked.

## Dependent Variables

*Stride Parameters*

The stride parameters examined in the study included walking speed, normalized stride length and stride frequency. In the experiment, participants walked a total of 10 meters for each trial. Data from only the middle strides were analyzed, as the first strides reflected reaching a comfortable walking pattern, and the last strides reflected slowing down and stopping at the end of the corridor. The number of consecutive strides of the left and right legs ranged from four to six. Average walking speed (m/s) was determined by dividing the linear displacement of the chin marker (between the times of left heel strike that began the first stride and ended the last stride) by the time elapsed between these heel strike events. The linear displacement of the chin marker was calculated according to:

$$D_T^2 = D_{AP}^2 + D_{ML}^2 \qquad (1)$$

where $D_T$ represents the total linear displacement (Euclidean distance) of the chin marker, and $D_{AP}$ and $D_{ML}$ are its displacements in the anteroposterior and mediolateral directions, respectively. Stride lengths of the left and right legs were calculated for each trial by the anteroposterior displacements over the middle strides by the left and right ankle markers, respectively, divided by the number of the middle strides. Considering that variation in leg lengths among participants might have an impact on the results, we normalized the stride length by dividing it by the individual's leg length, measured as the distance

between hip and ankle markers on the side of the respective leg. This normalized stride length was used in the data analysis.

*Relative Power Index*

The frequency relations between ipsilateral arm and leg movements were represented by the relative power index (RPI) and derived from the angular displacements of the arm and leg. We used the same methods described by Lin and colleagues (Lin et al. 2014). Specific movement frequencies and corresponding power for the leg and arm movements were obtained by processing the respective time series via a power spectral density (PSD) function (Fast Fourier transform algorithm using the Welch method for power estimation and a Hanning window for smoothing) (Wagenaar & van Emmerik, 2000). The power of the arm movement at the stride and step frequencies (as twice the stride frequency) was identified using these two frequencies obtained from the PSD of the leg movements.

Inter-limb coordination represented by RPI was quantified by means of computing the frequency interrelationship between arm and leg as follows:

$$RPI = {}^{P_1 - P_2}/_{P_1 + P_2} \qquad (2)$$

where $P_1$ is the power of the stride frequency in the arm swing time-series and $P_2$ is the power of the step frequency in the arm swing time-series. Both $P_1$ and $P_2$ are greater than or equal to zero and RPI values range from -1 to 1. If RPI equals 1, it reveals a 1:1 frequency coupling between arm and leg. If RPI equals –1, it indicates a 2:1 coordination pattern between arm and leg.

*Relative Phase*

The relative phase (RP) equations used in this experiment were the same as those suggested by Sternad and colleagues (Sternad, Turvey, & Saltzman, 1999). We examined RPI and judged all frequency ratios to fall into the 1:1 pattern (Fig. 4); therefore, "ordinary" relative phase (i.e., 1*phase_1 – 1*phase_2) was used in all analyses. Generalized relative phase would have been calculated only in those cases where 1:2 frequency coupling was detected (Young et al. 2010). The angular position of the arm and leg data was used to calculate the relative phase between the following limb pairs: 1) left arm versus right arm (LARA), 2) left leg versus right leg (LLRL), 3) left leg versus left arm (LLLA), and 4) right leg versus right arm (RLRA). Values of RP range from 0° to 360°, with deviation of RP from 180° indicating detuning from a "perfect" out-of-phase interlimb coordination. In addition, a RP value between 0° and 180° denotes advance in RP relative to the reference limb, and between 180° and 360° denotes phase delay (Saltzman, Lofqvist, Kay, Kinsella-Shaw, & Rubin, 1998). The RP was calculated for each stride cycle identified by two consecutive maxima from the angular position data of the left and the right leg. Both mean and standard deviation (SD; variability) of RP of each trial were calculated by circular statistics, with the latter representing the stability of coordination patterns. The smaller the SD of RP indicates the more stable coordination pattern during walking.

**Data Analysis**

Statistical analyses were performed using SPSS 18.0 (SPSS, Inc., Chicago, IL). The analyses for each parameter were based on the average of three trials per condition.

A series of mixed design analyses of variance (ANOVAs) were carried out to examine the effects of group (LPD, RPD and NC), and either the effect of condition (baseline and post-intervention), levels of frequency of the lines (0 [baseline], 65 [line1], 45[line2], and 25 [line3] cm), or density of the random squares (0 [baseline], 1.3 [random1], 4.8 [random2], and 16.4 [random3] squares/$m^2$) on walking speed, normalized stride length, stride frequency, relative power index, and mean and variability of RP. Walking speed, normalized stride length and stride frequency were computed based on the left leg time series. We considered BAI, logMAR_acuity and age as covariates in each ANOVA because of noted differences between the three groups. We reported the results of these covariates only when they were significant. Follow-up analyses of significant interactions of interest were conducted using a series of within *a priori t*-tests and between *a priori t*-tests (or ANOVAs if a covariate was included) in order to examine the following: (1) differences between performance on a pair of conditions (i.e., baseline and line1, baseline and line2, baseline and line3, line1 and line2, line1 and line3, line2 and line3) within each group; (2) differences between LPD and RPD, LPD and NC, and RPD and NC under each condition. We used a Bonferroni correction of .017 for the between group comparisons (.05/3 levels of lines and/or squares) and .008 for the within group comparisons (.05/6 comparisons per group for lines and/or squares) to reduce the risk of making Type I errors. Two sets of comparisons between transverse lines and random squares were also performed, one comparing the least number of cues on the walkway (level one for both) and one comparing the most (level 3 for both).

## RESULTS

### Baseline and post-intervention

Results of the main ANOVAs are provided below for each dependent variable. All *a priori* comparisons are shown in Table 3 (between group comparisons) and Table 4 (within group comparisons).

*Walking speed.* Results of the mixed design ANOVA showed significant main effects of condition ($F$[1,31] = 13.73, $p$ = 0.001, $\eta^2$ = 0.31), group ($F$[2,31] = 4.68, $p$ = 0.017, $\eta^2$ = 0.23), and interaction between condition and group ($F$[2,31] = 3.59, $p$ = 0.04, $\eta^2$ = 0.19) (Fig. 5). Within-group $t$ tests demonstrated that walking speed of the LPD and NC groups increased after the intervention ($t$[8] = 2.70, $p$ = 0.027, $\eta^2$ = 0.48 for the LPD group, $t$[13] = 3.58, $p$ = 0.003, $\eta^2$ = 0.50 for the NC group), though no such increase was seen for the RPD group ($t$[10] = 0.034, $p$ = 0.97).

*Normalized stride length.* There was no significant main effect of group ($F$[2,29] = 0.63, $p$ = 0.54), or effect of condition ($F$[1,31] = 1.89, $p$ = 0.18), showing that groups did not differ in stride length across conditions. There was a trend for an interaction ($F$[2,31] = 3.03, $p$ = 0.063, $\eta^2$ = 0.16) (Fig. 6), indicating a potential difference in the extent to which stride length was impacted by the intervention across groups. This is further demonstrated in the follow-up within-group $t$ tests showing that only the LPD group had a significantly longer stride length at post-intervention compared to baseline ($t$[8] = 2.03, $p$ = 0.077, $\eta^2$ = 0.34). Age and logMAR_acuity were significant covariates (age: $F$[1,30] = 7.12, $p$ = 0.012, $\eta^2$ = 0.19 and logMAR_acuity: $F$[1,30] = 8.40, $p$ = 0.007, $\eta^2$ = 0.22).

*Stride frequency.* There was a significant main effect of condition in the overall ANOVA ($F$[1,31] = 5.22, $p$ = 0.029, $\eta^2$ = 0.12), but neither the main effect of group ($F$[2,30] = 1.30, $p$ = 0.29) nor the interaction $F$[2,31] = 2.07, $p$ = 0.14) was significant. The results indicated that there was an overall increase in stride frequency before and after intervention but there was no difference between groups.

*Relative Power Index.* No main effect of condition ($F$[1,31] = 1.71, $p$ = 0.20), or effect of group ($F$[2,31] = 0.13, $p$ = 0.88), or interaction ($F$[2,31] = 0.04, $p$ = 0.96) were found in the ANOVA for relative power index. The mean RPIs in both baseline and post-intervention conditions were above 0.86, indicating the overall distribution of RPI was confined to 1:1 frequency ratio of arm swing and leg swing.

*Relative Phase*. There was no significant main effect of condition or group × condition interaction for any of the RP parameters (all $p$'s > 0.10). There was significant main effect of group for LLRL_mean ($F$[2,30] = 8.85, $p$ = 0.001, $\eta^2$ = 0.37), with BAI showing as a significant covariate ($F$[1,30] = 5.82, $p$ = 0.022, $\eta^2$ = 0.16), and a trend for LLRL_SD ($F$[2,31] = 2.63, $p$ = 0.088, $\eta^2$ = 0.15) and RLRA_mean ($F$[2,31] = 3.00, $p$ = 0.06, $\eta^2$ = 0.16). *A priori t*-tests showed that with BAI as a covariate, the RPD group had significantly larger mean relative phase between left leg and right leg than the LPD and NC groups, in both the baseline condition (LPD vs. RPD: $F$[1,17] = 10.77, $p$ = 0.004, $\eta^2$ = 0.39; RPD vs. NC: $F$[1,22] = 11.85, $p$ = 0.002, $\eta^2$ = 0.35) and the post-intervention condition (LPD vs. RPD: $F$[1,17] = 6.84, $p$ = 0.018, $\eta^2$ = 0.29; RPD vs. NC: $F$[1,22] = 10.79, $p$ = 0.003, $\eta^2$ = 0.33). No difference between the LPD and the NC groups was found in either condition ($p$ > 0.42). For LLRL_std, the NC group showed less variability

of relative phase between left and right legs than the LPD group ($t$[21] = 3.05, $p$ = 0.006, $\eta^2$ = 0.31) and the RPD group ($t$[13.6] = 1.90, $p$ = 0.079, $\eta^2$ = 0.16) in the baseline condition, but not in the post-intervention condition ($p$ > 0.23). There was no difference between LPD and RPD for either condition ($p$ > 0.69). For RLRA_mean, the RPD group had significantly less relative phase between right leg and right arm than the NC group at the end of the experiment ($t$[13] = 2.40, $p$ = 0.032, $\eta^2$ = 0.23), which indicated that the RPD group did not benefit from the visual cues intervention in regard to interlimb coordination on the right body side (side of initial motor onset).

**Transverse lines and random squares manipulations**

Results of the main ANOVAs are provided below for each dependent variable. All *a priori* comparisons are shown in Table 3 (between group comparisons) and Table 4 (within group comparisons).

*Walking speed.* For transverse lines, there was a significant main effect of spatial frequency ($F$[1.6, 49.9] = 4.31, $p$ = 0.026, $\eta^2$ = 0.12), a main effect of group ($F$[2,31] = 4.48, $p$ = 0.02, $\eta^2$ = 0.22) and an interaction between frequency and group ($F$[3.2, 49.9] = 4.08, $p$ = 0.01, $\eta^2$ = 0.21). For random squares, there was a significant main effect of density ($F$[2.1,65.1] = 8.18, $p$ = 0.001, $\eta^2$ = 0.21), a main effect of group ($F$[2,31] = 3.98, $p$ = 0.029, $\eta^2$ = 0.20), and an interaction ($F$[4.2,65.1] = 2.79, $p$ = 0.031, $\eta^2$ = 0.15) (Fig. 5). The results indicated that the manipulations on both transverse lines and random squares had significant overall effects on walking speed across groups and that the effects differed between groups. Specifically, the RPD group walked significantly more slowly

than the NC group in each of the three line conditions (all $p$'s < 0.011) and the three random squares conditions (all $p$'s < 0.019). This was not found either between LPD and RPD or LPD and NC. There was a trend for an increased walking speed in the line2 condition relative to the line3 condition for RPD ($t$[10] = 2.42, $p$ = 0.036, $\eta^2$ = 0.37) and in each of the line conditions relative to the baseline condition for NC (all $p$'s < 0.033). Compared to baseline, there was a trend for LPD to have an increased walking speed in the random3 condition ($t$[8] = 3.14, $p$ = 0.014, $\eta^2$ = 0.56) and for NC in each of the random squares conditions (all $p$'s < 0.022).

*Normalized stride length.* For transverse lines, there was no main effect of frequency ($F$[2.1,64.6] = 0.27, $p$ = 0.78) or effect of group ($F$[2,29] = 1.30, $p$ = 0.29) but there was a significant interaction ($F$[4.2,64.6] = 3.65, $p$ = 0.009, $\eta^2$ = 0.19). Age ($F$[1,30] = 6.81, $p$ = 0.014, $\eta^2$ = 0.19) and logMAR_acuity ($F$[1,30] = 7.62, $p$ = 0.01, $\eta^2$ = 0.20) were significant covariates. For random squares, there were no main effects of density ($F$[2.7,82.3] = 0.70, $p$ = 0.54) or group ($F$[2,29] = 1.03, $p$ = 0.37) but there was a significant interaction between density and group ($F$[5.3,82.3] = 2.47, $p$ = 0.036, $\eta^2$ = 0.14) (Fig. 6). The results showed that there was a trend for LPD having an increased stride length in the random3 condition relative to the baseline condition ($t$[8] = 2.56, $p$ = 0.03, $\eta^2$ = 0.45) whereas no effects were found in the other two groups. Age ($F$[1,30] = 5.88, $p$ = 0.022, $\eta^2$ = 0.16) and logMAR_acuity ($F$[1,30] = 6.01, $p$ = 0.02, $\eta^2$ = 0.17) were significant covariates. The findings demonstrated that although neither the transverse lines nor random squares manipulations had overall effects in regard to frequency/density

or group, there was a significant difference with respect to the extent to which stride length was impacted by both types of visual cues across groups.

*Stride frequency.* For transverse lines, there was no significant main effect of group ($F$[2,31] = 0.75, $p$ = 0.48) or a significant interaction ($F$[2.2,34.8] = 2.11, $p$ = 0.14), but there was a trend for a main effect of spatial frequency ($F$[1.1,34.8] = 3.46, $p$ = 0.067, $\eta^2$ = 0.10). For random squares, there was a significant effect of density ($F$[1.1,34.6] = 4.06, $p$ = 0.047, $\eta^2$ = 0.12), but no significant effect of group ($F$[2,30] = 2.55, $p$ = 0.095, $\eta^2$ = 0.15), where logMAR_acuity showed as a significant covariate ($F$[1,30] = 4.56, $p$ = 0.04, $\eta^2$ = 0.13), or interaction ($F$[2.2.34.6] = 1.70, $p$ = 0.20, $\eta^2$ = 0.10). Overall, manipulations of both transverse lines and random squares had marked impact on stride frequency across the groups.

*Relative Power Index.* For transverse lines, there was no main effect of frequency ($F$[2.2,67.7] = 0.17, $p$ = 0.86), main effect of group ($F$[2,31] = 0.64, $p$ = 0.54) or interaction ($F$[4.4,67.7] = 0.57, $p$ = 0.57). For random squares, results showed no main effect of density ($F$[2.4,75.6] = 0.23, $p$ = 0.83), effect of group ($F$[2,30] = 1.09, $p$ = 0.35) or interaction ($F$[4.9,75.6] = 0.43, $p$ = 0.82). Age was a significant covariate ($F$[1,30] = 4.65, $p$ = 0.039, $\eta^2$ = 0.13). The mean RPIs in all cue conditions were positive (above 0.85), indicating that the overall distribution was primarily close to 1:1 frequency ratio.

*Relative Phase.* For transverse lines, based on separate mixed design ANOVAs, significant main effects of group were found for the LLRL_mean ($F$[2,31] = 4.16, $p$ = 0.025, $\eta^2$ = 0.21) and for the RLRA_mean ($F$[2,31] = 4.98, $p$ = 0.013, $\eta^2$ = 0.24); a significant main effect of spatial frequency for the RLRA_mean ($F$[2.0,61.5] = 5.60, $p$ =

0.006, $\eta^2$ = 0.15); and a significant interaction for the LLLA_SD ($F$[6,93] = 3.83, $p$ = 0.01, $\eta^2$ = 0.16), where age was a significant covariate ($F$[1,30] = 5.01, $p$ = 0.03, $\eta^2$ = 0.14). For random squares, separate mixed design ANOVAs showed a significant main effect of density for the RLRA_mean ($F$[2.3,72.6] = 3.15, $p$ = 0.04, $\eta^2$ = 0.09); significant main effects of group for the RLRA_mean ($F$[2,31] = 8.80, $p$ = 0.001, $\eta^2$ = 0.36) and the LLRL_mean ($F$[2,31] = 4.65, $p$ = 0.039, $\eta^2$ = 0.13); and a trend for the effect of group for the LLRL_SD ($F$[2,31] = 2.92, $p$ = 0.069, $\eta^2$ = 0.16). No interaction was found for any of the RP parameters (all $p$'s > 0.10). The findings indicated overall group differences and impact of the manipulations of both transverse lines and random squares on interlimb coordination pattern on the right body side (RLRA_mean) (Fig. 7). Specifically, the RPD group had smaller RLRA_mean in the line1, line3, and random3 conditions relative to the LPD group (line1: $t$[18] = 2.52, $p$ = 0.022, $\eta^2$ = 0.26; line3: $t$[18] = 2.54, $p$ = 0.02, $\eta^2$ = 0.26; $t$[12.2] = 2.15, $p$ = 0.05, $\eta^2$ = 0.18). Only the LPD group showed a within-group difference in RLRA_mean, with a greater amplitude in the line2 condition ($t$[8] = 2.73, $p$ = 0.026, $\eta^2$ = 0.48) and in the line3 condition ($t$[8] = 2.58, $p$ = 0.033, $\eta^2$ = 0.45) relative to baseline; in the line1 condition relative to the line3 condition ($t$[8] = 3.83, $p$ = 0.001, $\eta^2$ = 0.65); in the random3 condition relative to baseline($t$[8] = 2.64, $p$ = 0.03, $\eta^2$ = 0.47) and relative to the random2 condition ($t$[8] = 2.43, $p$ = 0.041, $\eta^2$ = 0.43).

**Transverse lines vs. Random squares**

Two sets of comparisons between transverse lines and random squares were also performed for each dependent variable: when there were the least number of cues on the

walkway (line1 and random1; comparison1), and when there were the most number of the cues (line3 and random3; comparison2). The overall ANOVA for comparison1 showed a significant main effect of type of cue ($F$[1,31] = 4.58, $p$ = 0.04, $\eta^2$ = 0.13) and interaction between type and group ($F$[2,31] = 6.82, $p$ = 0.004, $\eta^2$ = 0.31) only for the LLLA_mean For comparison2, there was a significant effect of type of cue on the RLRA_mean ($F$[1,31] = 4.68, $p$ = 0.038, $\eta^2$ = 0.13). No significant main effect of type of cue or interaction between type and group was found for any other dependent variables (all $p$'s > 0.06). See Table 5 for results of the follow-up $t$-tests.

(Insert Tables 3, 4, 5 about here)

In summary, as illustrated in Table 3, group differences were found mainly on walking speed, stride length, RP between legs, and RP between ipsilateral arm and leg. The differences between RPD and LPD were similar to those between RPD and NC in all conditions, except that RPD and LPD did not differ in walking speed in any of the conditions. Generally, RPD showed slower walking speed with shorter stride length, larger mean and variability of RP between legs, larger variability of RP between arm and leg on the left body side and smaller mean of RP between arm and leg on the right body side than the other two groups. LPD appeared to have slower walking speed with shorter stride length and larger variability of RP between legs at baseline than NC, but the differences disappeared in all cueing conditions and the post-intervention condition. The results of within group comparisons revealed how the basic gait parameters and

coordination patterns were affected across different conditions for each group. While the NC group's walking speed and stride length were affected by both transverse lines and random squares cues, the RPD group seemed to be affected solely by the transverse lines whereas the LPD group seemed to be affected by the random squares. Walking speed and stride length increased when the distance between lines increased (namely frequency decreased) for RPD and when the density of the random squares increased for LPD. The different trends in changes between LPD and RPD were also found in variability of RP between left leg and left arm during line conditions. When the distance of lines reached its maximum (lowest spatial frequency), RPD tended to have smaller variability whereas LPD tended to have larger variability than in the conditions with shorter distances of lines (higher frequencies). A further comparison between the transverse lines condition and the random squares condition was demonstrated in Table 5. No difference between these two types of visual cues was found on any of the gait variables for LPD and NC whereas RPD showed a more cautious walking dynamics with slower walking speed, shorter stride length and lower stride frequency in line3 condition compared to random3 condition.

## DISCUSSION

The main goal of the study was to examine the effects of transverse line frequency and randomly displayed square density as external cues manipulated in random orders on temporal gait regulation and interlimb coordination patterns during comfortable speed walking in people with PD. The results of this study confirm the role of vision in controlling locomotor behavior of people with PD and age-matched healthy adults, with

the effects lasting after the external cues were removed. This study also provides evidence of distinct profiles between PD with left motor onset and those with right motor onset in response to the vision manipulations.

We confirmed the long-standing positive effect of external visual cues on gait regulation previously reported in people with PD (Martin 1967; Azulay et al. 1996; Morris et al. 1996; Azulay et al. 1999; Lewis et al. 2000; Rubinstein et al. 2002; Suteerawattananon et al. 2004; Azulay et al. 2006; Sidaway et al. 2006; Jiang, Norman 2006; Wegen et al. 2006; Chou et al. 2009; Almeida, Bhatt 2012; Lin et al. 2014; Vitorio et al. 2014). Recently, Vitorio and colleagues asked participants with PD to walk on a lined walkway with the exproprioceptive information from the lower limbs occluded, and reported that they could still regulate stride length; that is, looking at their lower limbs while walking was not crucial for gait improvements generated by visual cues (Vitorio et al. 2014). In the current study, we investigated dynamic flow through external cueing with random squares on the walkway, in an attempt to eliminate the spatial rhythmicity of the cueing pattern. To our knowledge, this is the first study that has used random patterned cues on the floor while participants walked over-ground at their preferred comfortable speed. We found that significant alterations in gait characteristics and in interlimb coordination were obtained even in the absence of spatial rhythmic cuing. Similar to the NC group, participants with LPD experienced a considerable increase in walking speed along with stride length compared to baseline when the density of the random squares was highest. The mean of RP between leg and arm on the right body side became larger in the traverse-lines conditions, as expected, but also became larger with

increasing density of the random squares in the LPD group, which has not been reported in the literature.

When we compared the transverse lines condition to the random squares condition at either their lowest spatial frequency/density or at their highest spatial frequency/density, for the LPD group, no significant difference between these two conditions was found except in the following two respects: First, when the frequency/density was highest, individuals with LPD had a greater LLLA_SD (indicating a less stable coordination pattern between arm and leg on the left body side) while walking in the line condition than in the random square condition. Second, LPD had greater RLRA_means while walking in the line condition than in the random square condition at the lowest frequency/density, indicating a smaller detuning from the "perfect" out-of-phase coordination pattern between arm and leg on the right body side. For RPD, the gait dynamics seemed to be better while walking in the random square condition than in the line condition at the highest frequency/density, which was indicated by faster walking speed, longer stride length, higher stride frequency, greater LLLA_mean, smaller LLLA_SD and smaller RLRA_SD. The NC group was not affected by the type of cues, showing only smaller LLLA_mean in the line condition than in the random square condition at the highest frequency/density. The mechanism behind the changes is not clear. It seems that a restriction was brought about to interlimb phase relation on the left body side while walking in the random square condition at the highest density, and to interlimb phase relation on the right body side at the lowest density. As the majority of the dependent variables were not affected by the type of cues, our

conclusion is that in general, the cues in the random pattern were as effective as the cues in the transverse lines in regulating locomotion. Visual cues presented in the form of a random pattern on the floor precluded watching foot placement such as may be done when walking over equally-spaced lines. Despite this lack of information for regulating foot position, participants with PD as well as NC responded to the external visual cues and adjusted their walking pattern flexibly and to a comparable level. This finding is consistent with the study by Vitorio and colleagues that showed an increase of stride length and walking speed in people with PD in the condition without the provision of visual information from lower extremities (Vitorio et al. 2014).

Most of the significant effects of the interventions described here were obtained by individuals with LPD. One important finding in this study is the observed interactions between condition and group in the main comparisons on walking speed and stride length. This is an indication of distinctive locomotor adjustments in LPD and RPD in response to vision manipulations. Both PD subgroups had significantly slower walking speed than the NC group at baseline. After the intervention session, the LPD group, but not the RPD group, had increased its mean walking speed accompanied by longer stride length so that it was the same as the NC group for these aspects of gait. In regard to RPD, during the manipulations of transverse lines, there was a trend for this group, but not the LPD group, to increase its walking speed and have longer stride length when the distance between lines was greater (lower spatial frequency). Different LPD-RPD patterns were also found on one of the coordination parameters - the variability of RP between left leg and left arm (LLLA_SD). We found that the LPD group's LLLA_SD decreased at the

smallest line distance condition (line3) (highest spatial frequency) compared to baseline but increased when the line distance was larger (lower spatial frequency) (as shown in Fig. 8). By contrast, the RPD group's LLLA_SD continuously decreased with increasing line distance indicating greater stability of coordination pattern. During the random squares manipulations, the LPD group, like the NC group, improved in walking speed and stride length especially when the density of the random squares was highest (16.4 squares/$m^2$), whereas the RPD group showed no difference across conditions. In summary, the effects of the visual cues on gait regulation seemed to be more general for the LPD group, whereas for the RPD group there was a relatively specific effect of frequency for the transverse-lines condition.

The subgroup results of the effects of visual cues on gait accord with reported distinct profiles in the visuospatial processing domain, such as greater visual dependence in LPD than RPD (Davidsdottir et al. 2008), which may imply divergent capacities between LPD and RPD to use external visual cues in regulating locomotion. In light of these findings, although more investigations are required in order to gain a richer understanding of the mechanism, it is critical to distinguish LPD and RPD in research design and provide interventions taking their distinctive profiles of behavioral performances into consideration, which may foster better rehabilitative outcomes than would occur if collapsing them into a single PD group.

We did not find effects of visual cues either in transverse lines condition or random squares condition on the frequency relation of interlimb coordination (RPI) in any of the groups. We attributed this finding to the overall high walking speed among

participants, which may have limited the potential for improvement. There is evidence of changes in RPI in relation to direct manipulations of walking speed on a treadmill (Wagenaar and van Emmerik 2000) and manipulations of optic flow speed in a virtual hallway (Chou et al. 2009) in younger and older healthy adults. It has been suggested that a transition from one frequency state of interlimb coordination to another would emerge at a walking speed of about 0.8 m/s (Wagenaar and van Emmerik 2000), which is substantially slower than the mean walking speeds of our sample which was about 1.5 m/s.

The finding that visual cues are able to foster improved gait mechanics without the need for rhythmicity in the pattern has important clinical implications. First, unlike random-patterned cues, rhythmic visual cues (i.e. transverse lines) requires attention to stepping in spatial relation to the cues. That is, spatially random cues may induce less cognitive load than spatially rhythmic cues. This advantage of random patterned cues may especially helpful for those people with PD who show signs of compromised attentional resources. Second, random patterned cues might be a better rehabilitation approach than rhythmic visual cues in regard to ecological validity. The environment that we live in on a daily basis rarely provides rhythmic patterned texture but rather is characterized by randomly clustered patterns or objects. Therefore, random patterned cues may provide broader practical applications in daily living either at home, outside or at a clinic. Most previous research on the effects of visual cues on gait regulation has used only transverse lines on the floor that are equally spaced specific to individual stride length. This traditional approach did show positive effects in the lab, yet lacks

generalization to the overall parkinsonian population in natural settings. Future investigations are needed to look at how manipulating some of random cues components, for example contrast of the pattern texture against the floor surface or shape of the cues might affect gait regulation in people with PD. A further possibility is to apply random visual cues into wearable device technology in real time.

In summary, our findings point to the important role of explicit visual cues, which do not have to be presented in a spatially regular pattern, to guide locomotion in people with PD. Different patterns of performance for individuals with LPD and those with RPD in locomotive behavior emerged with the provision of visual cues. It would be valuable to conduct investigations of those with PD at a more advanced disease stage than described in the present study, in order to assess the generalizability of our findings. In our sample of individuals with mild to moderate motor severity, the ability to adjust walking patterns even when the cues on the floor were randomly arranged supported the role of the dynamic visual flow in gait alteration, instead of or in addition to an attentional strategy to adjust gait. This last finding may be encouraging for individuals with PD and their caregivers who are seeking therapeutic approaches that are effective and less invasive than some of the available pharmacological or surgical treatments for locomotor impairments (Appleby et al. 2007). Random patterned cues may prove useful as a means of rehabilitation, especially for those who are unable to make use of auditory cues or those with compromised attentional resources.

**Table Legends**

**Table. 2.** Participant Characteristics

**Table. 3.** Follow-up *t*-tests results of between group comparisons for each dependent variable.

**Table. 4.** Follow-up *t*-tests results of within group comparisons for each dependent variable.

**Table. 5.** Follow-up *t*-tests results of two sets of comparisons between transverse lines and random squares for each dependent variable at the least number of cues on the walkway (line1 and random1; comparison1), and at the most number of the cues (line3 and random3; comparison2).

Table 2. Participant Characteristics

| Measure | LPD | RPD | NC | Significance |
|---|---|---|---|---|
| Sample size | 9 | 11 | 14 | |
| Age (years) | 67.3 (7.6) | 66.9 (5.8) | 62.1 (5.3) | NS |
| Education (years) | 17.0 (2.4) | 17.9 (1.5) | 17.5 (2.4) | NS |
| Gender (M:F) | 6:3 | 5:6 | 5:9 | NS |
| UPDRS motor asymmetry score | -0.3 (0.3) | 0.3 (0.4) | NA | $p = 0.004$ |
| UPDRS total score | 36.7 (12.5) | 34.5 (16.5) | NA | NS |
| BDI-II | 4.6 (2.4) | 6.1 (4.7) | 3.3 (4.6) | NS |
| BAI | 4.8 (3.5) | 6.3 (6.0) | 1.1 (1.5) | $p = 0.01$ |
| H & Y | 2 (1.5-3) | 2 (1-3) | NA | NS |
| LED | 457.7 (335.5) | 486.4 (318.4) | NA | NS |

*Note*. Univariate analyses of variance were conducted comparing LPD (left-onset Parkinson's disease), RPD (right-onset Parkinson's disease) and NC groups (normal control). UPDRS = Unified Parkinson's Disease Rating Scale; H & Y = Hoehn & Yahr stage; BDI-II = Beck Depression Inventory – II; BAI = Beck Anxiety Inventory; LED = levodopa equivalent dosage. Values presented are means (standard deviations) except for Hoehn and Yahr, which is median and range.

Table 3. Follow-up *t*-tests results of between group comparisons for each dependent variable

| | | walking speed (m/s) | normalized stride length (%) | relative phase (degrees) LLRL_M | LLRL_SD | LLLA_SD | LLRA_M |
|---|---|---|---|---|---|---|---|
| LPD vs. RPD | | | | | | | |
| baseline | | | | LPD smaller*, b | | | |
| post-intervention | | | | LPD smaller* | | | |
| lines | 1 | | RPD shorter[t, a, l] | | | | RPD smaller[t] |
| | 2 | | | | | | |
| | 3 | | RPD shorter[t, a, l] | | | RPD larger* | RPD smaller[t] |
| random | 1 | | | LPD smaller[t] | RPD larger[t] | | |
| | 2 | | | LPD smaller* | | | |
| | 3 | | | LPD smaller[t] | | | RPD smaller[t] |
| LPD vs. NC | | | | | | | |
| baseline | | LPD slower* | LPD shorter* | | LPD larger* | | |
| RPD vs. NC | | | | | | | |
| baseline | | RPD slower[t] | RPD shorter* | NC smaller* | RPD larger[t] | | |
| post-intervention | | RPD slower* | RPD shorter* | NC smaller*,b | | | RPD smaller[t] |
| lines | 1 | RPD slower* | | | | | RPD smaller[t] |
| | 2 | RPD slower* | | | | | RPD smaller[t] |
| | 3 | RPD slower* | | NC smaller* | | RPD larger[t, a] | RPD smaller* |
| random | 1 | RPD slower* | RPD shorter[t] | NC smaller* | | | |
| | 2 | RPD slower* | | NC smaller* | | | RPD smaller[t] |
| | 3 | RPD slower[t] | | NC smaller* | RPD larger* | | |

*Note*. * $p \leq .017$; t = trend $p > .017$ and $< .05$; a = age covariate used in analysis; l = logMAR acuity covariate used in analysis; b = total BAI acuity covariate used in analysis. There were no findings from the between group comparisons for stride frequency, relative power index, LLLA_mean, RLRA_SD, LARA_mean or LARA_SD. There were no differences between the LPD and NC groups in any of the conditions except for baseline. Slower walking speed, shorter stride length, and larger RP SD indicate poorer performance.

Table 4. Follow-up *t*-tests results of within group comparisons for each dependent variable

| | | walking speed (m/s) | normalized stride length (%) | stride frequency (Hz) | relative phase (degrees) LLLA_SD | RLRA_M |
|---|---|---|---|---|---|---|
| RPD | | | | | | |
| baseline vs. post-intervention | | | | | | |
| lines | b vs. 1 | | 1 shorter[t] | | | |
| | b vs. 2 | | | | | |
| | b vs. 3 | | | | | |
| | 1 vs. 2 | | | | 2 larger[t] | |
| | 1 vs. 3 | | | | 3 larger[t] | |
| | 2 vs. 3 | 3 slower[t] | | | | |
| random | b vs. 1 | | | | | |
| | b vs. 2 | | | | | |
| | b vs. 3 | | | | | |
| | 1 vs. 2 | | | | | |
| | 1 vs. 3 | | | | | |
| | 2 vs. 3 | | | | | |
| LPD | | | | | | |
| baseline vs. post-intervention | | baseline slower* | baseline shorter[t] | | | |
| lines | b vs. 1 | | | | | b smaller[t] |
| | b vs. 2 | | | | | b smaller[t] |
| | b vs. 3 | | | | b larger[t] | |
| | 1 vs. 2 | | | 1 lower[t] | | |
| | 1 vs. 3 | | | | 1 larger[t] | 3 smaller* |
| | 2 vs. 3 | | | | | |
| random | b vs. 1 | | | | | |
| | b vs. 2 | | | | | |
| | b vs. 3 | b slower[t] | b shorter[t] | | | b smaller[t] |
| | 1 vs. 2 | | | | | |
| | 1 vs. 3 | | | | | |
| | 2 vs. 3 | | | | | 2 smaller[t] |
| NC | | | | | | |
| baseline vs. post-intervention | | baseline slower* | | baseline lower[t] | | |
| lines | b vs. 1 | b slower[t] | b shorter [t] | b lower[t] | | b smaller[t] |
| | b vs. 2 | b slower[t] | | b lower[t] | | |
| | b vs. 3 | b slower[t] | | b lower[t] | | |
| | 1 vs. 2 | | 2 shorter* | | | |
| | 1 vs. 3 | | | | | |
| | 2 vs. 3 | | | | | |
| random | b vs. 1 | b slower[t] | | b lower[t] | | |
| | b vs. 2 | b slower[t] | | b lower* | | |
| | b vs. 3 | b slower[t] | | b lower* | | |
| | 1 vs. 2 | | | | | |
| | 1 vs. 3 | | | | | |

*Note*. * $p \leq .008$; t = trend $p > .008$ and $< .05$. There were no findings from the within group comparisons for relative power index, LLRL_mean, LLRL_SD, LLLA_mean, RLRA_SD, LARA_mean or LARA_SD. There were no differences between the LPD and NC groups in any of the conditions except for baseline. Slower walking speed, shorter stride length, lower stride frequency, and larger RP SD indicate poorer performance.

Table 5. Follow-up *t*-tests results of two sets of comparisons between transverse lines and random squares for each dependent variable at the least number of cues on the walkway (line1 and random1; comparison1), and at the most number of the cues (line3 and random3; comparison2)

| | walking speed (m/s) | normalized stride length (%) | stride frequency (Hz) | relative phase (degrees) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | LLLA_M | LLLA_SD | RLRA M | RLRA_SD | LLRL_M |
| RPD | | | | | | | | |
| line1 vs. random1 (the least dense) | | | | | | | | 1ine1 smaller[t] |
| line3 vs. random3 (the most dense) | line3 slower* | line3 shorter[t] | line3 lower* | line3 smaller* | line3 larger* | | line3 larger* | |
| LPD | | | | | | | | |
| line1 vs. random1 (the least dense) | | | | | random1 larger[t] | random1 smaller* | | |
| line3 vs. random3 (the most dense) | | | | | line3 larger* | | | |
| NC | | | | | | | | |
| line1 vs. random1 (the least dense) | | | | | | | | |
| line3 vs. random3 (the most dense) | | | | line3 smaller* | | | | |

*Note*. * $p \leq .05$; t = trend $p > .05$ and $< .10$. There were no findings for relative power index, LLRL_SD, LARA_mean or LARA_SD. Slower walking speed, shorter stride length, lower stride frequency, and larger RP SD indicate poorer performance.

**Figure Legends**

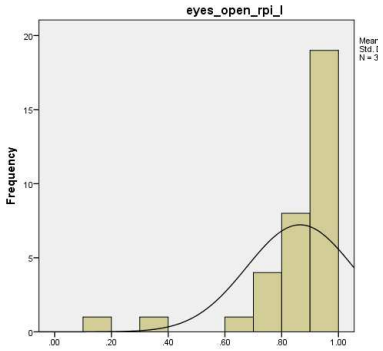
**Fig. 4.** Histogram of relative power index under baseline, transverse lines (3 frequencies), and random squares (3 densities) conditions. All values were well above zero (positive) which indicated 1:1 interlimb frequency coupling.

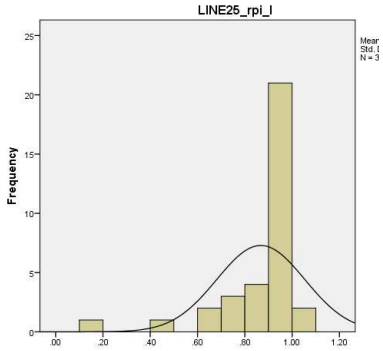
**Fig. 5.** Walking speed (in m/s) during walking under baseline, transverse lines (3 frequencies), random squares (3 densities) and post-intervention conditions. 9 LPD, 11 RPD and 14 NC. Vertical lines represent standard error of the mean. RPD walked more slowly than NC in all conditions (all $p$'s < 0.06), whereas LPD walked more slowly than NC only at baseline ($p = 0.012$).

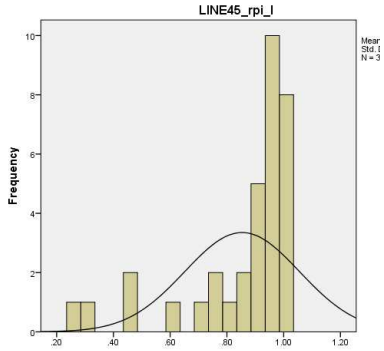
**Fig. 6.** Normalized stride length (SL; the individual's stride length divided by his/her leg length) on the left leg under all conditions: baseline, transverse lines (3 frequencies), random squares (3 densities) and post-intervention. 9 LPD, 11 RPD and 14 NC. Vertical lines represent standard error of the mean. The unit is in percentage as the values are the stride length after normalization by individual's leg length. RPD had shorter stride length than NC in both baseline and post-intervention conditions ($p < 0.04$), whereas LPD had shorter stride length than NC only at baseline ($p = 0.004$).

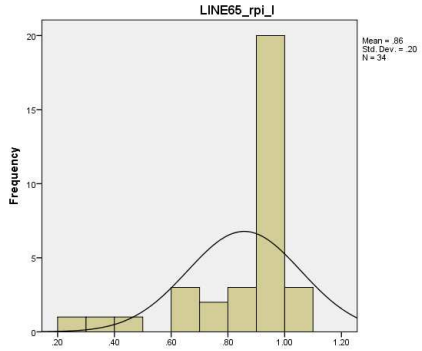
**Fig. 7.** Relative phase between right leg and right arm (RLRA_mean; degrees) during walking under all conditions: baseline, transverse lines (3 frequencies), random squares (3 densities) and post-intervention. 9 LPD, 11 RPD and 14 NC. Vertical lines represent standard error of the mean. There was an overall group difference and impact of the manipulations for both transverse lines and random squares.

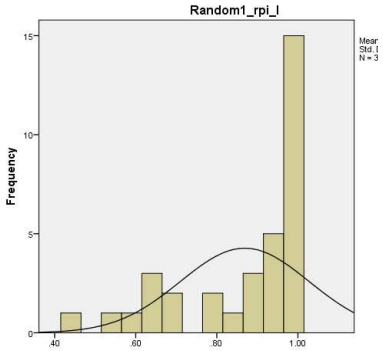
**Fig. 8.** Standard deviation of relative phase between left leg and left arm (LLLA_SD; degrees) during walking under transverse lines (3 frequencies) conditions. 9 LPD, 11 RPD and 14 NC. Vertical lines represent standard error of the mean. Different trends in changes between LPD and RPD were found during line conditions. When the distance of lines at its maximum (line1; lowest frequency), RPD tended to have smaller variability whereas LPD tended to have larger variability than the conditions with smaller distances of lines (higher frequencies) (LPD: line1 vs. line3, $p = 0.019$. RPD: line1 vs. line3, $p = 0.016$; line2 vs. line3, $p = 0.05$).

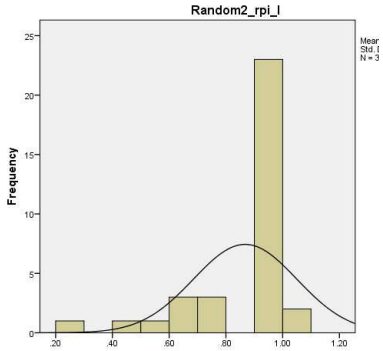

eyes_open_rpi_l
Frequency
Mean
Std. D
N = 3


LINE25_rpi_l
Frequency
Mean
Std. D
N = 3


LINE45_rpi_l
Frequency
Mean
Std. D
N = 3


LINE65_rpi_l
Frequency
Mean = .86
Std. Dev. = .20
N = 34


Random1_rpi_l
Frequency
Mean
Std. D
N = 3


Random2_rpi_l
Frequency
Mean
Std. D
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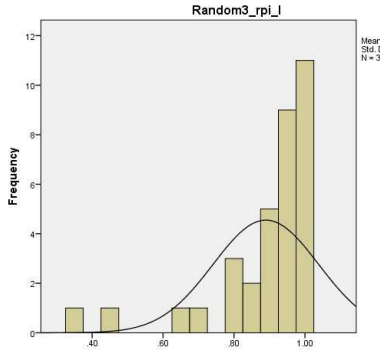
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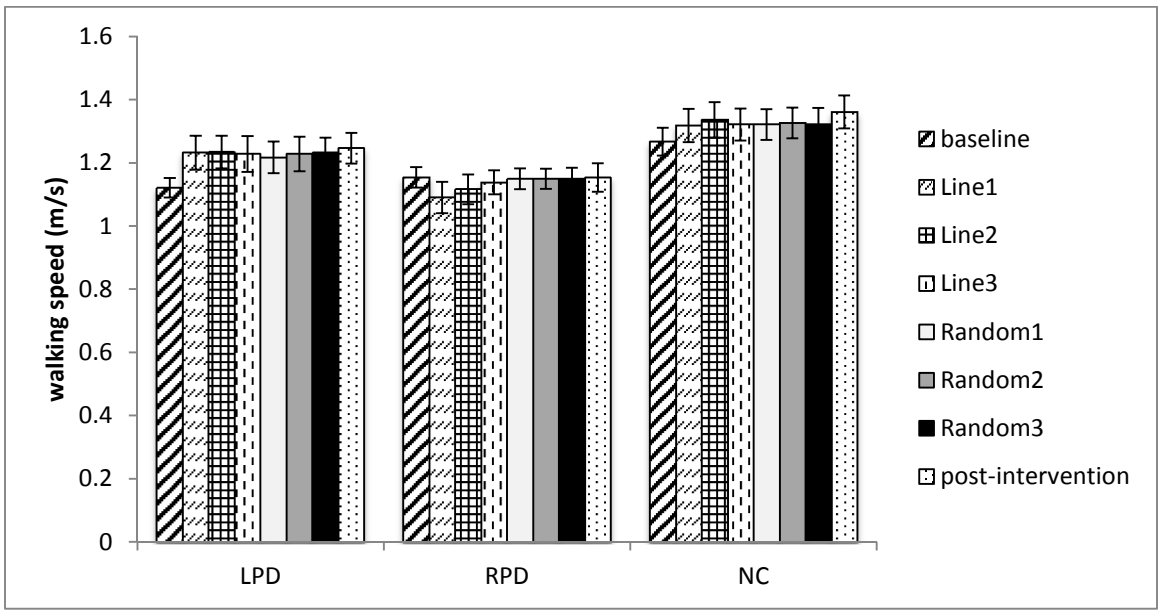
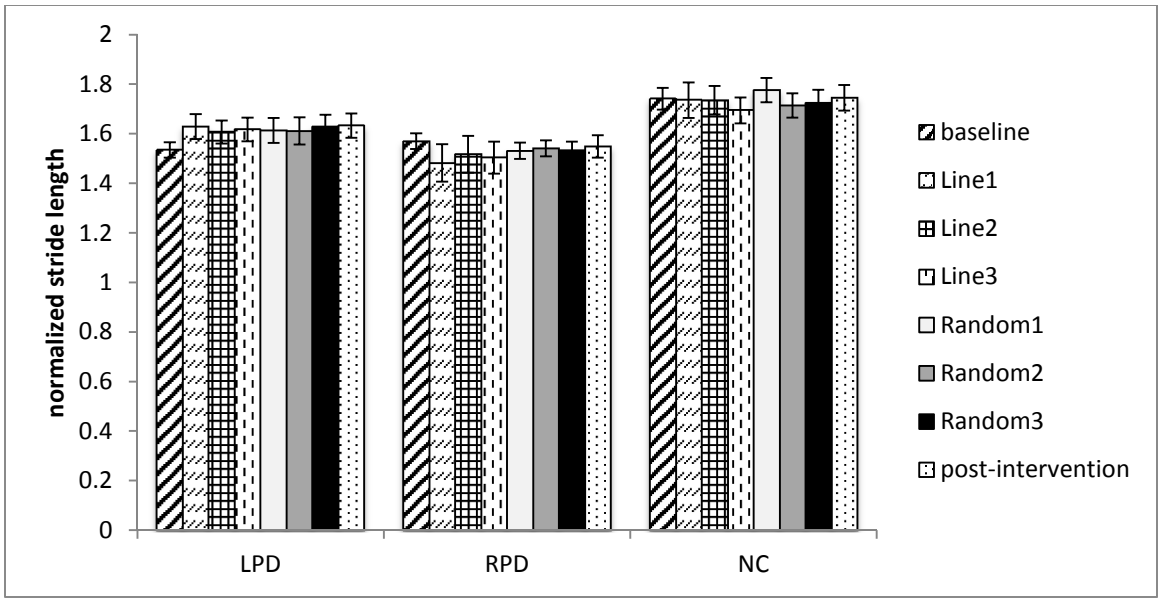
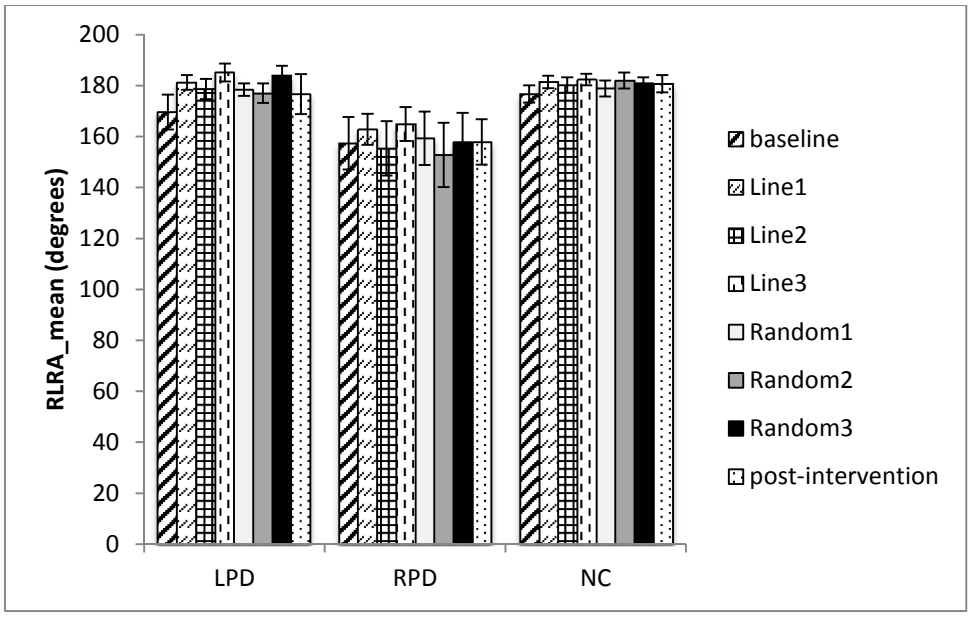
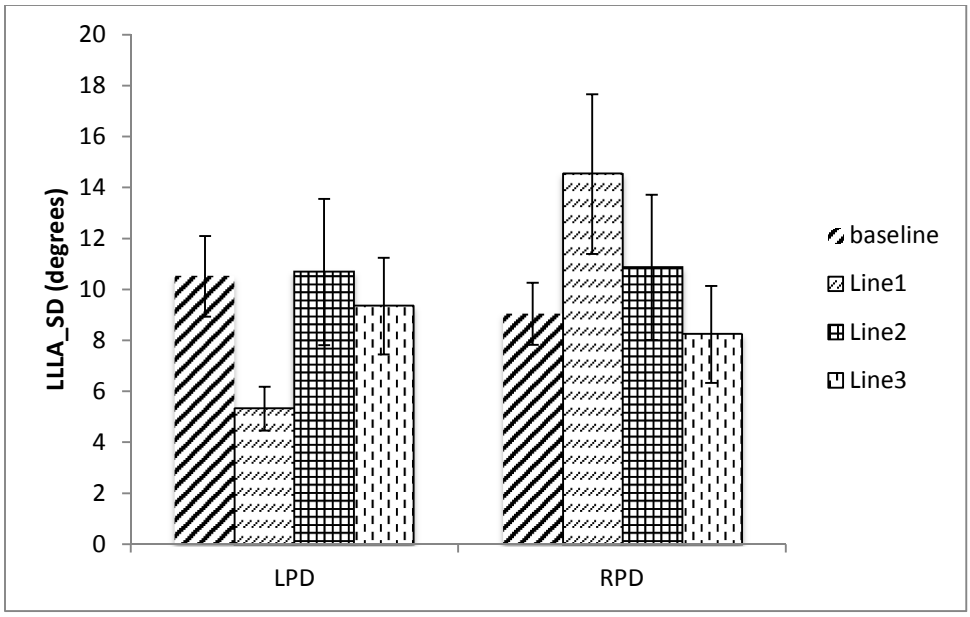
Frequency
Mean
Std. D
N = 3


1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
walking speed (m/s)
LPD
RPD
NC
baseline
Line1
Line2
Line3
Random1
Random2
Random3
post-intervention


normalized stride length
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
LPD
RPD
NC
baseline
Line1
Line2
Line3
Random1
Random2
Random3
post-intervention


RLRA_mean (degrees)
200
180
160
140
120
100
80
60
40
20
0
LPD
RPD
NC
baseline
Line1
Line2
Line3
Random1
Random2
Random3
post-intervention


20
18
16
14
12
10
8
6
4
2
0
LLLA_SD (degrees)
LPD
RPD
baseline
Line1
Line2
Line3

## GENERAL DISCUSSION

The results of the first study indicated that visual dysfunction is the predominant driver of veering in people with PD, rather than the motor dysfunction of the disease. Study 1 laid a foundation for Study 2, which assessed the effectiveness of visual cues in gait improvement in people with PD. For the first time, floor visual cues in random patterns were employed while the participants were asked to walk over-ground at their preferred comfortable speed. The positive effects observed during random cues trials as well as during the transverse lines condition suggested that rhythmic visual cueing is not the only or the necessary contributor to improved gait, but rather overall dynamic flow information produced by self-motion during walking is of significant importance. Moreover, the benefits obtained from the use of visual cues seemed to last after the cues were taken away. The two studies also provided quantitative evidence for the existence of distinct patterns of veering and stride asymmetry as well as of the changes in basic gait and interlimb coordination patterns in response to the visual cues that are specific to the initial side of the brain lesions in PD.

First, in Study 1, individuals with LPD veered rightward and those with RPD veered leftward when they walked in a corridor with eyes open, despite shorter stride length on the more affected body side (i.e., on the left side for LPD and on the right side for RPD). They veered in the same direction in the egocentric reference point (ECRP) condition when asked to walk toward a subjectively perceived center of a target at the end of the corridor. When vision was occluded, group differences were not significant, though it should be noted that the direction was in fact opposite that seen with visual

inputs, meaning in the direction predicted by motoric asymmetry alone: the LPD group veered to the left, corresponding to the body side with shorter stride length, and the RPD group veered to the right, corresponding to the body side with shorter stride length. These findings suggested that under conditions of visual inputs, the mechanism underlying veering is predominantly vision-based instead of motoric-based and the common parkinsonian gait disturbances such as veering, stride asymmetry, and to some extent stride length were amenable to amelioration by visual guidance, mainly focusing on self-perceived center (ECRP condition). No objective experimental evidence had been provided before this study in regard to whether known visuospatial deficits that produce a shift of egocentric midline in one direction, relative to motor impairments, had any association with veering in PD.

The findings from Study 2 provided better understanding of the mechanism underlying the positive rehabilitative results arising from the use of the explicit visual cues, which could further benefit people with PD practically in real life. Instead of or in addition to an attentional strategy, dynamic visual information also appears to play a strong role in gait adjustment. It is well known that people with PD rely heavily on attentional processes to modulate their stride length (Morris et al. 1996) and bilateral coordination of gait (Yogev et al. 2007). Gait asymmetry and regulation of gait variability and rhythmicity tend to get significantly worse when a concurrent task is introduced (Yogev et al. 2005). Hence, the method of transverse lines, dependent on rhythmicity, may fall short with cognitive or motor (dual-task) distraction. Further, in real-world environments, it is less likely to find walking surfaces with rhythmic than with

random patterns. The ability to adjust walking patterns observed in our sample even when the cues on the floor were randomly arranged may be an encouraging finding for individuals with PD and their caregivers who are seeking feasible therapeutic approaches that are effective as well as less potentially harmful than some of the available pharmacological or surgical treatments. This may be especially true for those with visual impairment that is significant enough to prevent them from perceiving rhythmic visual cues or those who have compromised attentional resources.

In contrast to previous investigations, in the present studies individuals' body alignment was tested before walking was initiated. As the initial orientation of the body could be responsible for the trajectory of veering (Guth and Laduke 1994; Kallie, Schrater et al. 2007), it is important to guarantee that the alignment of the body axis relative to the true midline of the walkway is consistent across groups throughout the experiment. We were able to rule out the possibility that initial body orientation could account for group differences in the direction of veering. Other factors that might affect study outcomes were also taken into account, such as age, anxiety levels, and visual acuity. For example, a finding of interest was the role of age in the group differences in normalized stride length in Study 2. Age was a significant covariate affecting the main effect of group in the main ANOVAs, even though the groups were age-matched.

A generally better result was observed in the LPD than the RPD group in the ECRP condition in Study 1 and during walking on a textured surface in Study 2. These findings suggest that the LPD group was better than RPD at using the objective environmentally-anchored landmark directly in front of them or on the floor surface in

order to adopt a more appropriate locomotion path and produce better locomotive patterns. Previous studies have shown a difference between LPD and RPD in visual dependence, which is the reduced ability to disregard visual environmental information (Cronin-Golomb, 2010). Greater visual dependence of LPD than RPD might translate to a greater ability of LPD to benefit from conditions that provide visual cuing.

Two limitations of the present studies should be acknowledged. First, the sample was not large, though it was similar to those seem in other studies of navigation in PD (e.g., Young et al., 2010; Lin et al., 2014). Second, because we examined only participants with mild to moderate PD, conclusions cannot be drawn about those with greater disease severity.

The findings from Study 2 provided better understanding of the mechanism underlying the positive rehabilitative results arising from the use of the explicit visual cues, which could further benefit people with PD practically in real life. Instead of or in addition to an attentional strategy, dynamic visual information also appears to play a strong role in gait adjustment. It is well known that people with PD rely heavily on attentional processes to modulate their stride length (Morris et al. 1996) and bilateral coordination of gait (Yogev et al. 2007). Gait asymmetry and regulation of gait variability and rhythmicity tend to get significantly worse when a concurrent task is introduced (Yogev et al. 2005). Hence, the use of transverse lines, dependent on attention to rhythmicity, may become less beneficial with cognitive or motor (dual-task) distraction. Further, in real-world environments, one is less likely to find walking surfaces with rhythmic than with random patterns. The ability to adjust walking patterns

that was observed in our sample even when the cues on the floor were randomly arranged may be an encouraging finding for individuals with PD and their caregivers who are seeking feasible therapeutic approaches that are effective as well as less potentially harmful than some of the available pharmacological or surgical treatments. This may be especially true for those with visual impairment that is significant enough to prevent them from perceiving rhythmic visual cues or those who have compromised attentional resources.

The observed improvements in veering as well as locomotive patterns induced by the presence of visual cues highlighted the primacy of the visual control of locomotion over motoric features and of dynamic visual flow over (or in additional to) attentional strategy. These findings provide insights that may be valuable for the development of interventions for gait disorders in PD that emphasize vision and environmental modification, rather than targeting solely motor symptoms. The existence of distinctive patterns of veering and gait regulation while using visual cues in people with LPD and RPD, observed in both studies, implies the potential importance of tailoring interventions to PD subgroups.

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**Publications**

Ren X, Salazar R, Neargarder S, Roy S, Ellis T, Saltzman E, Cronin-Golomb A (under review). Veering in hemi-Parkinson's disease: Primacy of visual over motor contributions.

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