Published in final edited form as:

Parkinsonism Relat Disord. 2012 June ; 18(5): 462–468. doi:10.1016/j.parkreldis.2012.01.002.

Movement Orientation Switching with the Eyes and Lower Limb in Parkinson Disease

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Abstract

Difficulty switching between motor programs is a proposed cause of motor blocks in Parkinson disease (PD). Switching from one movement to another has been studied in the upper extremity and during postural control tasks, but not yet in the eyes and lower limb in PD. The purpose of this study was to compare movement orientation switching ability between people with PD and age-matched controls (CON) and to determine if switching ability is correlated between the eyes and lower limb. Twenty-six persons with PD and 19 age-matched controls participated. Movement orientation switching was studied in a seated position with the head fixed in a chinrest. In response to a randomly generated tone, participants switched from a continuous back-and-forth movement in either the horizontal or vertical orientation to the opposite orientation as quickly as possible. Lower limb movements were performed with the great toe pointing back and forth between targets positioned on a 45° angled floor platform. Eye movements were back and forth between the same targets. Eye and lower limb switch time was reduced in PD ($p < 0.01$), but after normalizing switch time to movement velocity, no differences existed between PD and CON. Eye and lower limb switch times were correlated in PD ($r = 0.513$, $p < 0.01$) but not in CON. In PD, switch time and movement velocity of the lower limb, but not the eyes, correlated with bradykinesia and postural instability/gait. Our results suggest that individuals with PD experience movement switching deficits with both the eyes and lower limb, perhaps driven by overall bradykinesia.

Keywords

Parkinson's disease; eye movements; basal ganglia

1. Introduction

Many persons with Parkinson disease (PD) experience bradykinesia and akinesia that often lead to functional decline including decreased mobility, freezing of gait, and a higher risk of fall-related injuries. According to the center-surround hypothesis, basal ganglia dysfunction in PD may lead to excessive inhibition of desired and undesired movements [1], leading to

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difficulty with selection and execution of the desired movement. This difficulty has been cited as a mechanism underlying problems with changing from one motor program to another [2–4], with extreme difficulties in switching motor programs perhaps contributing to the freezing phenomenon [5]. As freezing of gait is quite often triggered by turning, we hypothesize that difficulties in switching between motor patterns in order to change direction of movement may underlie the turning difficulties noted in many individuals with PD. Such impairments related to switching movement direction have been reported for upper extremity movements and postural control tasks [4, 6, 7]. Pfann et al. [7] even noted pauses, perhaps analogous to the freezing of gait sometimes triggered by turning, at the points of direction change during upper extremity movements. Specific impairments related to changing directions have also been hypothesized to contribute to difficulties with sit to stand movements in individuals with PD [8].

When considering direction changes, particularly during locomotion, one should not overlook the role of eye movements. Saccadic eye movements play an important role in locomotion as they provide a shift in gaze toward the direction of travel and initiate the top-down rotation sequence characteristic of a normal turning pattern [9–11]. Saccadic eye movements, however, are impaired in PD, as evidenced by a large body of evidence. Early work in persons with PD showed prolonged fixation times, bradykinesia, and akinesia during rapid alternating gaze shifts between two fixed targets [12]. Several more recent studies have demonstrated that people with PD make slower and smaller voluntary saccades than control subjects [13–15]. The basal ganglia (BG) circuitry may be particularly important for changing saccade direction [16], and saccade dysfunction is associated with turning difficulty in persons with PD [17]. During both 90 and 180 degree turns, the saccade initiating the turn is hypometric and displays altered timing relative to turn onset when compared with healthy controls.

To our knowledge, deficits in ability to change movement directions of the eyes and lower limbs have yet to be examined in the same individuals with PD. Therefore, the purpose of this investigation was to confirm whether individuals with PD have difficulty switching between two movement orientations with the eyes and lower limbs, and to determine if the ability to switch movement orientation with the eyes is correlated with switching ability in the lower limb. We hypothesized that deficits in the ability to change movement orientation with the eyes and lower limbs would be noted in individuals with PD, and that the deficits in the eyes and limbs would correlate with one another, indicating a similar amount of decline in orientation switch ability across different body parts. Confirmation of our hypotheses would support an overlap between oculomotor and lower limb control in the dysfunctional BG and provide important insights into the nature of eye and limb control in PD.

2. Methods

2.1 Participants

Twenty-six individuals with idiopathic PD (17 men, 9 women; age = 70.2 ± 10.5 ; PD duration 8.4 ± 6.0 years, Hoehn & Yahr stage = 2.3 ± 0.4 ; MDS-UPDRS III score = 41.0 ± 11.1) and 19 age- and gender-matched controls (11 men, 8 women; age = 67.7 ± 10.6 years) participated. Sample size was based on a-priori power analysis using switch time pilot data; 20 subjects per group would provide 87% power to detect a 0.7 effect size using a two-tailed, 2-way ANOVA ($p = 0.05$). Individuals with PD were recruited from Washington University School of Medicine's (WUSM) Movement Disorders Center. Controls were recruited from the Volunteers for Health Database, posted flyers, and other WUSM volunteer databases. All subjects met the following inclusion criteria: aged 30 years or older, normal central (except for PD in the PD group) and peripheral neurological function, able to stand independently for at least 30 minutes and walk independently without an assistive

device, no history of vestibular disease and no evidence or history of dementia. Exclusionary criteria included: serious medical condition other than PD, use of neuroleptic or other dopamine-blocking drug, use of drug that might affect balance such as benzodiazepines, evidence of abnormality on brain imaging (previously done for clinical evaluations-not part of this research), history or evidence of other neurological deficit, and history or evidence of orthopedic, muscular, or psychological problem that may affect task performance. Additionally, participants with PD were included based on a diagnosis of “definite PD” by a board certified neurologist, as previously described by Racette et al. [24] based upon established criteria [25, 26] and were excluded if they had received surgical management of PD (e.g. deep brain stimulation). All subjects gave informed consent to perform experimental procedures approved by the Human Research Protection Office at WUSM.

2.2 Experimental procedures

All procedures were performed in the Locomotor Control Laboratory at WUSM. Participants with PD were tested OFF medication, i.e. after a 12-hour withdrawal of all anti-Parkinson medications. Before testing procedures commenced, the Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Motor Subscale III was administered according to Goetz et al. [27] by a trained rater. The MDS-UPDRS-III is a measure of severity of PD motor symptoms, as well as physical disability, and includes measures of rigidity, gait, tremor, hand/arm and leg movements (bradykinesia), speech, and facial expressions. The modified Hoehn and Yahr scale was used to evaluate disease severity in PD [28]. FOG was assessed using the Freezing of Gait Questionnaire (FOG-Q) [29], with total FOG-Q score representing overall FOG severity, and freezers identified as those who reported freezing of gait at least once per week on item three of the questionnaire.

During the protocol, each participant performed eye and lower limb movement tasks while in a seated position. Lower extremity tasks were performed with the dominant limb. For all movement tasks, four white targets were placed on a black angled platform (45° relative to the floor) located on the floor in front of the subject. Targets were positioned 20 centimeters apart such that eye movements between targets would be approximately 25 degrees (Figure 1). Each subject was seated with his head resting in a chinrest to minimize head movement and angled downward such that the platform was positioned in the center of the visual field. The platform was centered in front of the subject at a distance that allowed for comfortable movement of the lower limb. To investigate the ability to switch movement orientation (switch task), participants began the task by moving either their eyes or lower limb (pointing with the big toe) back and forth as quickly as possible between two targets (either horizontally or vertically). Upon hearing an auditory tone, participants were instructed to switch movement orientation as quickly as possible and continue moving back and forth in the new orientation. Multiple orientation switches, including both horizontal-to-vertical (HV) and vertical-to-horizontal (VH) switches, were performed at random times during each trial with 4–6 orientation switches per 30 second trial. Auditory cues were triggered by the first author by pressing a button which sounded the signal. Throughout each trial, the interval between switches was random as that the tester did not time the interval between switch cues and made an effort to vary the time interval from switch to switch.

To control for differences in reaction time between PD and CON, simple reaction times (RT) of the lower limb and eyes were tested. Each participant began with eyes fixated or great toe positioned on a target centered between the 4 peripheral targets used for the switch task. Upon hearing a tone, the participant reacted as quickly as possible to move either left, right, up, or down, as instructed prior to each trial. To control for differences in movement velocity between PD and CON, participants also performed three 10 second trials of back and forth movements of the eyes or lower limb, moving as quickly as possible between the horizontal targets without switching orientations so that average movement velocity could

be determined. For all tasks, participants were given the opportunity to practice the task and data collection commenced when the participant was comfortable performing the task.

2.3 Data collection and processing

Lower limb movements were captured using an eight camera, passive marker, 3-dimensional, high-resolution motion capture system sampling at 100 Hz in Cortex software (Motion Analysis Corporation, Santa Rosa, CA). One retro-reflective marker was positioned at the base of the great toe. The motion capture system was calibrated both statically (calibration frame) and dynamically (wand) prior to each data collection session. Oculomotor data were captured using a head-mounted infrared binocular eye tracking system (Applied Sciences Laboratory, Bedford, MA) and electrooculography (EOG). Oculomotor data were captured synchronously at 1000Hz on the same PC workstation with kinematic data in Cortex software. The infrared eye tracking system was calibrated for each participant using a two step process. First, a nine-point relative points methods was used to calibrate the eye tracking system. Then, participants performed saccades of known amplitudes in four directions (up, down, left, right) to allow conversion of analog data (millivolts) into angle data (degrees).

Lower limb marker data and analog data were filtered using 4th order low-pass Butterworth filters. Marker data were filtered in Cortex with a cut-off frequency of 6 Hz while analog data were filtered in MotionMonitor (Innsport, Chicago, IL) with a cut-off frequency of 20 Hz. A global coordinate system was defined in MotionMonitor with the positive X-axis pointing anteriorly, positive Y-axis pointing to the left and positive Z-axis pointing upward vertically. Toe marker kinematic data and filtered analog data were exported for further processing in custom written MATLAB software (The Mathworks, Inc, Natick, MA).

For the orientation switch task, switch time was defined as the time interval between the auditory tone and the beginning of first full amplitude movement in the new orientation. As each trial contained multiple VH and HV switches, VH and HV switches were measured separately and an average switch time was determined for each switch orientation. For the RT tasks, RT was defined as the time interval between auditory tone and movement onset (lower limb movement exceeding 5 mm from origin and eye movements exceeding 0.5 degrees from origin). For the movement velocity task, movement velocity was calculated as the number of back and forth cycles completed during a measured time period multiplied by the average movement amplitude across all of the cycles within the trail. Finally, to control for the effect of movement velocity, switch times were normalized to movement velocity by multiplying the two measures. Individual trials were excluded from analysis if artifacts in oculomotor data due to blinks, prolonged closure of eyelids, or other factors precluded measurement. Remaining trials within a condition were averaged to obtain a single data point for each subject for each task.

2.4 Data Analysis

Independent Student's t-tests were used to compare between-group differences in movement velocity, movement amplitude, and normalized switch time for both the eyes and lower limb, and a bonferroni correction was used to control for multiple comparisons, bringing the level of significance for the t-tests to $p < 0.0045$. A mixed model was used to test the effect of group, segment (eye vs. lower limb), and the group-segment interaction on switch time and RT. Segment was treated as a repeated measure. Pearson's correlation coefficients were used to test the correlation between eye and lower limb switch times as well as the correlation between switch time and movement velocity. Spearman's rank order correlations were used to examine correlations between movement parameters (amplitude, velocity,

switch time) and FOG and the MDS-UPDRS III. The criterion for statistical significance was set at $p < 0.05$ for all analyses.

3. Results

Eye movements in the vertical plane could not be captured for a number of participants (13 PD and 2 CON). Therefore, only movement tasks in the horizontal plane and VH orientation switches are reported. Age did not differ between PD and CON ($t = .799$, $p = 0.429$), nor did RT ($F = 1.703$, $p = 0.199$), although RT was slower in the lower limb ($F = 28.343$, $p < 0.001$). Movement velocity was not statistically different between PD and CON for the eyes ($t = 1.505$, $p = 0.140$), but was decreased in PD for the lower limb ($t = 3.710$, $p = 0.001$). There was a significant group effect for switch time ($F = 20.99$, $p < 0.001$), but neither the main effect of segment nor the group-segment interaction were significant ($F = 2.386$, $p = 0.130$; $F = 0.143$, $p = 0.707$, respectively). Although switch time was significantly different between groups, normalized switch time did not differ significantly between groups for the eyes ($t = 1.683$, $p = 0.100$) or lower limb ($t = 1.138$, $p = 0.261$). During the movement velocity task, average lower limb and eye movement amplitudes closely approximated the expected values based on target placement (20 cm/ 25 degrees apart), and there were no group differences for the eyes ($t = 0.453$, $p = 0.653$) or lower limb ($t = 1.949$, $p = 0.058$). Eye and lower limb performance data are displayed in Table 1.

Across all participants, switch times of the eyes and lower limb were significantly correlated ($r = 0.425$, $p = 0.004$), but normalized switch times of the eyes and lower limb were not significantly correlated ($r = 0.257$, $p = 0.088$). Within PD, eye and lower limb switch time did not correlate significantly ($r = 0.286$, $p = 0.186$) but normalized switch times correlated significantly ($r = 0.513$, $p = 0.007$). Within CON, neither correlation was significant (switch time, $r = 0.089$, $p = 0.719$; normalized switch time, $r = -0.058$, $p = 0.812$) (Figure 2). In PD, FOG was correlated with lower limb velocity ($\rho = -.483$, $p = 0.013$), amplitude ($\rho = -0.552$, $p = 0.007$), and switch time ($\rho = 0.503$, $p = 0.009$). Total MDS-UPDRS-III scores correlated with lower limb switch time ($\rho = 0.502$, $p = 0.009$), velocity ($\rho = 0.551$, $p = 0.004$), and amplitude ($\rho = -0.606$, $p = 0.001$). MDS-UPDRS-III scores were also divided into sub-scores reflecting tremor (items 3.15 – 3.18), rigidity (item 3.3), bradykinesia (items 3.4 – 3.8), and postural stability and gait (PIGD, items 3.9 – 3.13). PIGD correlated with lower limb switch time ($\rho = 0.558$, $p = 0.003$), velocity ($\rho = -0.617$, $p = 0.001$) and amplitude ($\rho = -0.430$, $p = 0.032$). Bradykinesia correlated with lower limb switch time ($\rho = 0.412$, $p = 0.036$) and velocity ($\rho = -0.493$, $p = 0.010$). Eye switch time and velocity did not correlate significantly with any of the MDS UPDRS III subscores. These correlations are shown in Figure 3. Finally, switch time and movement velocity were significantly correlated in the eyes ($r = -0.587$, $p < 0.001$) and in the lower limb ($r = -0.749$, $p < 0.001$) across all participants.

Comparing freezers and non-freezers, groups did not differ in terms of movement velocity (eye, $t = 1.045$, $p = 0.306$; lower limb, $t = 1.134$, $p = 0.268$) or amplitude (eye, $t = 0.007$, $p = 0.995$; lower limb, $t = 0.852$, $p = 0.403$). The main effect of eye vs. lower limb was significant for RT ($F = 21.248$, $p < 0.001$) with RT being slower in the lower limb. Both the main effect of group ($F = 0.039$, $p = 0.845$) and the interaction ($F = 1.343$, $p = 0.258$) were not significant for RT. Switch time main effect of group ($F = 1.081$, $p = 0.309$), eye vs. lower limb ($F = 1.936$, $p = 0.177$), and the interaction ($F = 3.247$, $p = 0.084$) were all non-significant.

4. Discussion

This study sought to determine whether the ability to switch movement orientation with the eyes and lower limbs is impaired in PD and whether orientation switch ability is similar between the eyes and lower limbs. In summary, persons with PD took longer to switch movement orientation with both the eyes and lower limb, and displayed a reduction in lower limb movement velocity. When normalizing switch time to movement velocity, the significant group effects of switch time were negated. Across both PD and CON, eye switch time correlated significantly with lower limb switch time, and in persons with PD, FOG, UPDRS, PIGD, and bradykinesia correlated significantly with lower limb function, while oculomotor function did not correlate with these measures. There were no differences between PD freezers and non-freezers in terms of switch time, movement velocity, or movement amplitude.

Our hypothesis was supported in that persons with PD required 37% and 41% more time to switch orientation with their eyes and lower limb, respectively, compared to controls. However, since eye and lower limb movement velocities were slower in PD compared with CON, we normalized orientation switch times to movement velocity. In doing so, we noted that normalized switch times were similar between PD and controls, indicating that if PD were to move at the same velocity as the controls, their orientation switch ability may be comparable for both the eyes and lower limbs. As hypothesized, normalized lower limb switch times explained 26% of the variance in normalized eye switch times in PD, but this relationship did not hold true for controls.

Our finding of prolonged switch times in PD corroborates previous research. In the upper extremity, Almeida et al.[30] observed delays in switching between two coordination patterns in the upper extremity, while Plotnik et al.[6] showed that people with PD respond poorly to movement modifications. To our knowledge, this is the first study to report such findings in the lower extremity and eyes. Further, previous studies in the upper extremity did not account for movement velocity. Herein, we demonstrate that accounting for movement velocity negates the group differences in orientation switch ability. Thus, observed deficits in the ability to switch movement direction/orientation in our study and others, indicative of a deficit in motor program switching, may be simply a function of global bradykinesia. Regardless, it is clear that the overall time required to change from one movement paradigm to another in response to an external stimulus is greater in PD. This difficulty may contribute to FOG which is often triggered by a change in movement, such as switching from straight walking to turning. The modest delay in switching between simple motor programs observed in the present study may manifest in a much longer delay or freeze when the motor programs are more complicated (i.e. gait). A delay in switching could also be a contributing factor in falls, as a delay in selecting and executing the proper motor response to an unanticipated perturbation or change in body position may not allow enough time to catch oneself before a point of no return. Finally, our study supports previous work showing deficits in oculomotor function in PD. Visual information plays an important role in gait and people with PD show deficits in saccade performance that relate to impaired turning performance [17] and may contribute to FOG and falls.

While the basal ganglia are often described as having distinct loops for oculomotor and motor control, evidence suggests that the subthalamic nucleus (STN) may play key roles in the control of both eye and limb movements, indicating overlap of the oculomotor and motor loops. Some neurons within the STN respond to voluntary saccades as well as limb movements [18]. The timing and characteristics of saccade-related potentials in STN suggest that these cells are responsible for broad non-specific inhibitory output to inhibit unwanted motor programs, whether for the eyes or the limbs [19]. Disruption of this inhibitory output

from the STN could account for impairments in voluntary saccades [20] and limb movements. Abnormal STN output may also contribute to difficulty turning that can trigger FOG, as evidenced by the fact that STN deep brain stimulation can alleviate off-period freezing [21–23]. The apparent overlap between oculomotor and motor control in the basal ganglia provides a potential anatomical substrate where a pathophysiological disruption could contribute to impaired eye and limb movements and also to turning difficulties. Our data suggest that eye and lower limb switching are mildly correlated, supporting the potential for overlap between oculomotor and lower limb control by the basal ganglia and a global bradykinesia that appears to influence eye and limb movements similarly. In line with a center surround hypothesis [1], the common bradykinesia of the eyes and lower limbs may be due to over-activity of the subthalamic nucleus leading to excessive inhibitory output from the basal ganglia. In support of a global bradykinetic cause for delays in switching movement orientation in the tasks we studied, our global bradykinesia score obtained from the MDS-UPDRS-III correlated with lower limb orientation switch times, as did the PIGD score.

While we conclude that differences in switch time between PD and CON are driven by bradykinesia, it is important to consider alternative hypotheses. Since the switch task involved reacting to an auditory stimulus, differences in switch times could be attributed to differences in RT between PD and CON. However, RT did not differ between groups for either the lower limb or eyes, thus RT is unlikely to have contributed to group differences in switch time. An alternative hypothesis to our bradykinesia explanation is that PD suffer from a deficit in the ability to select and execute a new or different motor program, and that this deficit is at least partially independent of bradykinesia. If this were the case, we would expect group differences in switch time to remain even after controlling for movement velocity (normalized switch times), indicated that bradykinesia does not fully explain the effect of group on switch time. However, this was not the case as normalized switch times were very similar between PD and CON for both the eyes and lower limb. Further support for our bradykinesia hypothesis is that movement velocity and switch time were highly correlated in both the eyes and lower limb across all subjects, and that there were no differences between freezers and non-freezers in the ability to switch movement orientation.

4.1 Limitations

During the movement velocity and orientation switch tasks, participants were provided with visual cues in the form of targets. A large body of existing literature supports the use of various types of visual cueing strategies for improving movement in PD. Therefore, it is possible that movement amplitude and switching ability were enhanced in PD by the presence of targets. Additionally, the lower limb and eye movements required for the tasks herein were of relatively small amplitude (20cm for the lower limb and 25 degrees for the eyes). Since the performance of those with PD compared well with controls in terms of movement amplitude, it is possible that the inter-target distance chosen was too small to elicit hypokinetic movement in PD.

4.2 Conclusions and future directions

Switching between movement contexts is impaired in PD and affects not only upper and lower limb movements, but eye movements as well, and the severity of dysfunction is similar between eyes and lower limb. It appears that global bradykinesia may be a factor affecting switching ability in PD. Future work should explore movement switching ability of the lower limbs during more complex and functionally relevant tasks, such as during locomotion.

Acknowledgments

We thank Marie McNeely and Ryan Duncan for assistance with data collection, Brian Morrell for assistance with data processing, and Dr. Richard Abrams for assistance with project design and pilot testing. This publication was made possible by NIH grant R01 HD056015, the Barnes Jewish Hospital Foundation, and Grant Number UL1 RR024992 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Additional support came from the St. Louis Chapter of the American Parkinson Disease Association (APDA) and the APDA Advanced Center for PD Research at Washington University in St. Louis.

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A

B

C

Figure 1.

Experimental set-up. (A) Participants were seated in a chair with their head positioned in a chinrest to minimize head movement and with their head tilted downward. A binocular head-mounted eye tracking device was secured to their head in this position. A black platform was positioned on the floor in front of the subjects. The platform was angled 45 degrees to the floor with round white targets positioned on the face of the platform. (B) Configuration of targets for the orientation switch task. (C) Configuration of targets for the reaction time task.

Figure 2.
Correlation between eye and lower limb switch times for CON (top) and PD (bottom).

Figure 3. Correlations of lower limb switch time (left column) and movement velocity (right column) with MDS-UPDRS III, Bradykinesia, PIGD, and FOG in subject with PD only.

Table 1

Eye and lower limb performance data.

Measure	PD	(n)	Controls	(n)
Eye RT (sec)	0.293 ± 0.061	26	0.286 ± 0.034	18
Foot RT (sec)	0.360 ± 0.064	26	0.336 ± 0.062	19
Eye Velocity (degrees/sec)	48.05 ± 15.9	26	54.84 ± 13.5	19
Foot Velocity (cm/sec)	34.40 ± 12.6	25	[†] 47.89 ± 11.2	19
Eye Amplitude (degrees)	24.8 ± 4.2	26	25.1 ± 0.9	19
Foot Amplitude (cm)	18.5 ± 0.01	25	19.3 ± 0.01	19
Eye Switch Time (sec)	1.00 ± 0.294	26	[†] 0.731 ± 0.134	19
Foot Switch Time (sec)	1.11 ± 0.366	26	[†] 0.789 ± 0.126	19
Normalized Eye Switch Time ^a	45.25 ± 12.42	26	39.56 ± 9.26	19
Normalized Foot Switch Time ^b	34.46 ± 7.34	26	36.96 ± 7.17	19

Values are means ± standard deviations.

^{a,b} Arbitrary units^{*} Significantly group effect, $p < 0.05$ [†] Significantly group effect, $p < 0.01$