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Occulomotor Function and Locomotion in Parkinson's Disease

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by

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A**bstract of the Dissertation**

Many persons with Parkinson's disease (PD) experience difficulty turning that can lead to freezing of gait, falls, and an increased risk of fall-related injuries. We hypothesized, based on previous literature, that turning difficulty and freezing during turning may be related to deficits in the ability to switch from one motor pattern to another (Chapter 2). We further hypothesized that deficits in oculomotor control, particularly in the case of voluntary saccades, also contribute to the pathogenesis of turning difficulty since turning is normally initiated with an eye movement (Chapter 3). Finally, we hypothesized that current treatment approaches including pharmacological and surgical interventions would improve turning performance and oculomotor performance in individuals with PD (Chapter 4).

To determine whether individuals with PD have trouble switching motor patterns with the eyes and whether they experience similar deficits in the lower limb, we tested healthy controls and persons with PD during an orientation switch task. The PD group delayed orientation switching that was attributable to bradykinesia, and there was a correlation in the amount of impairment across body parts. These results suggest that while individuals with PD may take longer to switch from one motor pattern to another, bradykinesia may be the driving factor as opposed to an internal deficit in the ability to switch motor programs. Regardless of mechanism, delays in switching motor patterns may play a role in freezing and turning difficulty.

To determine if oculomotor function is abnormal in PD during turning and whether this contributes to turning difficulty, participants with PD and healthy controls performed in-place 90º and 180° turns. Turn performance was worse in PD (i.e., longer

time to turn, more steps) and those with PD made more saccades during the turns. Further, the saccade initiating the turn was smaller, slower, and exhibited altered timing relative to the first step of the turn in those with PD compared with controls. Finally, saccade performance was correlated with turn performance in those with PD. Our results suggest that the oculomotor strategy used by those with PD is altered and less efficient as compared with controls, and that oculomotor dysfunction may be a contributing factor in turning difficulty.

To determine if therapeutic interventions could improve oculomotor function and related turning performance, we tested individuals with PD and deep brain stimulation (DBS) of the subthalamic nucleus. Gait parameters and turn duration improved with both levodopa therapy and DBS, but only DBS was successful in improving concurrent oculomotor function. The amplitude and velocity of the first saccade improved with DBS, while the latency of the first saccade decreased relative to the onset of head rotation and the first step.

Taken together, these studies corroborate previous knowledge that voluntary saccades are dysfunctional in PD. Further, these studies relate oculomotor impairment to a functional task and give insight into the role of therapeutic interventions for improving turning difficulty in PD. These results also provide support for using visual cueing to improve turning performance and therefore, future research should examine the efficacy of such cues on turning performance.

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Chapter 1: Introduction

Parkinson's disease (PD) is a progressive neurodegenerative condition that affects nearly 1.5 million people in the U.S. PD is primarily a disease of the basal ganglia with pathophysiology characterized by selective degeneration of dopaminergic neurons in the substantia nigra pars compacta and accumulation of alpha-synuclein "Lewy bodies" throughout the brain. While the disease also presents with non-motor symptoms, the four cardinal motor symptoms of tremor, rigidity, postural instability, and bradykinesia combine in a motor disorder that can severely limit mobility, activities of daily living, and quality of life. Among the myriad motor disturbances associated with PD, impairments in gait are the most common cause of disability. Forward walking is impaired through a reduction in gait velocity and stride length, while gait transitions such as initiation, navigating obstacles, and turning elicit further dysfunction. Turning difficulty (TD) is extremely problematic as turning is very common during locomotion and activities of daily living but is a primary trigger for freezing of gait (FOG), often leading to falls [1]. This is significant as falls that occur during turning are eight times more likely to result in a hip fracture than falls during straight line walking [2], contributing to a 3.2 fold greater risk of hip fractures in PD compared with age-matched individuals without PD [3]. It is clear that addressing TD in individuals with PD would offer lower risk for injury and improved function, yet the underlying causes of TD are not well understood, limiting our ability to offer therapeutic strategies to those affected.

Eye and Limb Control in PD

According to Mink's center-surround hypothesis of basal ganglia function,[4] decreased availability of dopamine and overactivity of the sub-thalamic nucleus (STN) in

PD lead to excessive inhibition of desired and undesired movements. Bradykinesia, hypokinesia, and in severe cases, akinesia result and can be observed during limb movements, functional tasks, and even during eye movements. For example, hypokinesia can include undershooting targets during reaching tasks,[5] micrographia,[6] and reduced stride length during gait. Bradykinesia is evident during a multitude of movements including gait, large amplitude ballistic movements, tasks requiring accuracy, and object tracking tasks.[7] The oculomotor system is similarly affected, albeit differentially depending on the nature of the task. Reflexive, or visually guided saccades, are largely unaffected in the early stages of PD,[8] but show reduced gain and increased latency during later disease stages.[9,10] Deficits in smooth pursuit can be observed in milder patients during tasks where the subject is required to follow a slowly oscillating target.[11] Finally, voluntary saccades, defined as eye movements that are internally generated as opposed to eye movements in response to an external visual stimulus, appear to be the most affected as deficits can be measured in early stages of PD and are observed before deficits in reflexive saccades.[12] In summary, voluntary saccades in people with PD are slower and smaller than those of control subjects.[8,12-15]

Motor Pattern Switching in PD

Beyond the aforementioned impairments, individuals with PD also experience difficulty in selecting and executing new motor patterns[16,17] along with difficulty planning and performing sequential[18] and simultaneous motor acts.[19] It is hypothesized that FOG may be a manifestation of such difficulties in switching between motor programs, and we suggest that TD and related freezing episodes are examples of this. Multiple studies have reported motor switching difficulty in the upper extremity. Plotnik

et al.[20] found that patients with PD have impaired ability to process motor responses to successive stimuli, while Inzelberg et al.[21] confirmed this with a similar upper extremity task and also showed that motor switching deficits were not correlated with mental switching deficits, hypothesizing separate mechanisms. During upper extremity point-to-point and reversal movement tasks, muscle activation, kinetics, and kinematics were affected in subjects with PD.[22] In a study by Leis et al.[23], when persons with PD were required to change a planned action they showed substantially pronounced decrements in movement performance, such as slowness and greater variability, indicating that modifying a planned action affects subsequent motor execution. Difficulty changing motor patterns has also been noted beyond the upper extremity. In studying the sit-to-stand task in PD and controls, Mak and Hui-Chan [24] propose that slowness in PD patients could be attributed to difficulties in switching direction from flexion to extension at the bottom of task. Finally, in a study of oculomotor switching, the ability to respond to unanticipated changes in target amplitude was well maintained in PD, probably due to the benefits of external cueing associated with this type of tasks, but the ability to respond to unanticipated changes in target direction was decreased, characterized by greater variability in latency and in accuracy. This study suggests that changes in saccade direction may rely on the basal ganglia. Overall, there is a large body of literature supporting deficits in the ability to modify and switch between motor plans, but none of these studies have been performed in the lower extremity specifically or with the eyes.

Turning in Healthy Controls and PD

Visual information plays a key role in locomotion and therefore impairments in visual processing increase locomotor dysfunction. It has been shown that older adults

with visual impairments (i.e., loss in visual acuity) fall more frequently than those without visual impairments,[25-27] and clear differences in gaze behavior have been demonstrated between older adult fallers and non-fallers during obstacle navigation tasks.[28] Visual information is important for turning as well. During turns, studies on healthy controls show that a top-down rotation sequence is used whereby the eyes are the first to rotate. This initial saccade, combined with a subsequent head turn, provides a shift of gaze to a position aligned with the direction of travel. This initial change in gaze is then followed by rotation of the head, trunk, and feet. [29-32] This sequence is thought to provide the central nervous system with an external, or global, reference frame that is used to control body movement in space such that one goes where one is looking.[31,33]

While turning has been well described in healthy controls, few studies have focused on turning in PD. In a case report, Morris et al.[34] noted that their subject used an increased number of steps and a narrower base of support compared to a control subject. He also displayed reduced movement of the pelvis and upper trunk during turning. Stack et al.[35] noted that individuals with a history of freezing or falls used a greater number of steps to turn and appeared unstable during turns. Recent work has demonstrated that subjects with PD tend to turn en bloc, i.e. rotating the head and trunk simultaneously rather than in sequence, and require greater time to turn.[36-38] The work of Crenna et al.[36] is particularly interesting because it reveals that turning deficits are present even in individuals with mild PD who as of yet have no alteration or impairment in their straight walking. This suggests that turning difficulty may affect individuals with PD even from a very early stage of the disease when other symptoms are not yet apparent. Although oculomotor control is found to be dysfunctional in PD during isolated saccade tasks, no

research has been done to date to characterize how this translates to turning and impacts turning kinematics.

Therapeutic interventions

Multiple studies have examined the effect of interventions on oculomotor function in persons with PD. The efficacy of levodopa, the most commonly prescribed medication for PD, in improving saccade function is still a matter of debate. Saccade amplitude appears to be largely unaffected by levodopa,[39,40] while saccade latency decreases during voluntary saccades [41,42] and increases during reflexive saccades.[42,43] On the other hand, deep brain stimulation (DBS) has proven very beneficial for improving saccade function in PD. Improvements in gain and latency during both voluntary and reflexive saccades have been measured when STN DBS is turned on vs. off.[44-47] The effect of therapeutic interventions on turning has not been as widely studied.

Scope of Thesis

This research was designed to understand the contribution of oculomotor impairments to locomotor dysfunction in PD. In summary, chapter 2 examines the correlation between oculomotor and lower limb impairments in PD, chapter 3 describes the impact of oculomotor dysfunction on turning in both PD and controls, and chapter 4 studies the effect of interventions on turning performance and related oculomotor control in PD.

Specific Aim 1: (Chapter 2)

To determine whether individuals with PD have difficulty switching movement direction during movements of the eyes and lower limbs.

Hypothesis 1a: Individuals with PD will display deficits in the ability to change movement orientation with the eyes and lower limbs as compared with healthy controls.

Hypothesis 1b: Deficits in the ability to change movement orientation of the eyes will be related to ability to change movement orientation of the lower limb, indicative of a similar level of impairment across different body parts.

Specific Aim 2: (Chapter 3)

To determine whether eye movements during turning are impaired in individuals with PD who have difficulty turning during walking, and to determine whether characteristics of the saccade that initiates a turn are predictive of ensuing turn performance.

Hypothesis 2a**:** Individuals with PD will demonstrate slower, smaller saccades at turn initiation and will make more saccades during the turn compared to controls.

Hypothesis 2b**:** The amplitude, velocity, and latency of the saccade initiating a turn will be predictive of the time required to execute the turn. We expect turns that are initiated with slower, smaller, and later saccades will take longer to complete.

Specific Aim 3: (Chapter 4)

To determine the independent and combined effects of medication and DBS of the STN on saccadic eye movements during turning and turning performance in persons with PD.

Hypothesis 3a**:** Both anti-Parkinson medication and STN DBS will independently improve the amplitude and timing of the saccade initiating turns and turning performance, but STN DBS will result in greater improvements than medication.

Hypothesis 3b**:** Improvements in saccade performance during turning with DBS will be additive with the effects of medication.

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Chapter 2: Movement orientation switching with the eyes and lower limb in Parkinson's Disease

This chapter is in press:

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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 45º 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.

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 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 saccadesthan 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.[18] based upon established criteria[19,20] 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.[21] 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.[22] FOG was assessed using the Freezing of Gait Questionnaire (FOG-Q), [23] 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 or 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 (45º 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. Ocuolmotor 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 (ρ = -.483, p = 0.013), amplitude (ρ = -0.552, p = 0.007), and switch time (ρ = 0.503, p = 0.009). Total MDS-UPDRS-III scores correlated with lower limb switch time (ρ = 0.502, p=0.009), velocity (ρ = 0.551, p = 0.004), and amplitude (ρ = -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 (ρ = 0.558, 0.003), velocity (ρ = -0.617, p = 0.001) and amplitude (ρ = -0.430, p = 0.032). Bradykinesia correlated with lower limb switch time (ρ = 0.412, p = 0.036) and velocity (ρ = -0.493, p = 0.010). Eye switch time and velocity did not correlate significantly with any of the MDS UPDRS III sub-scores. 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.[24] 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 to 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.[25] 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.[26] Disruption of this inhibitory output from the STN could account for impairments in voluntary saccades[27] 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.[28-30] 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 persons with 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.

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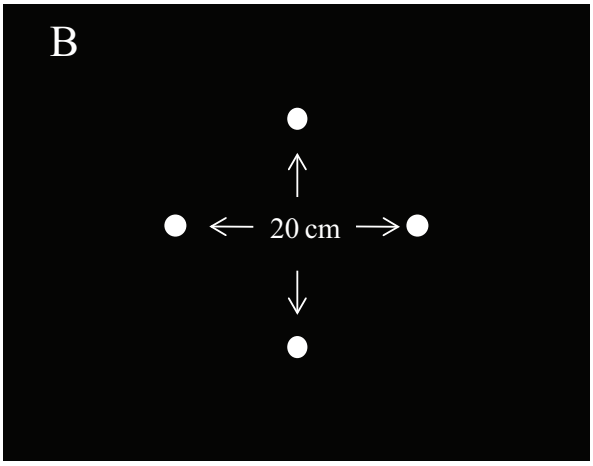
Figure 1:

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.

A



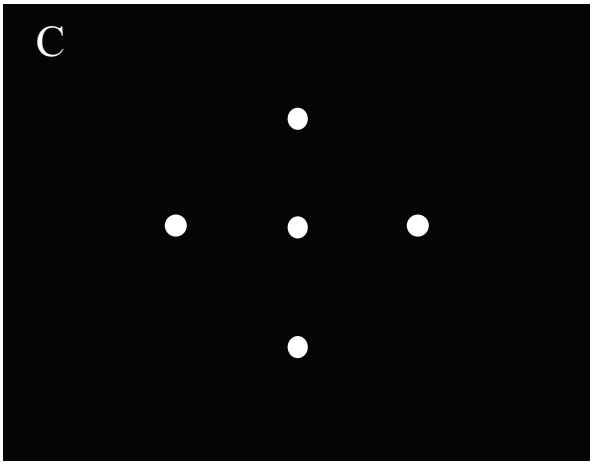
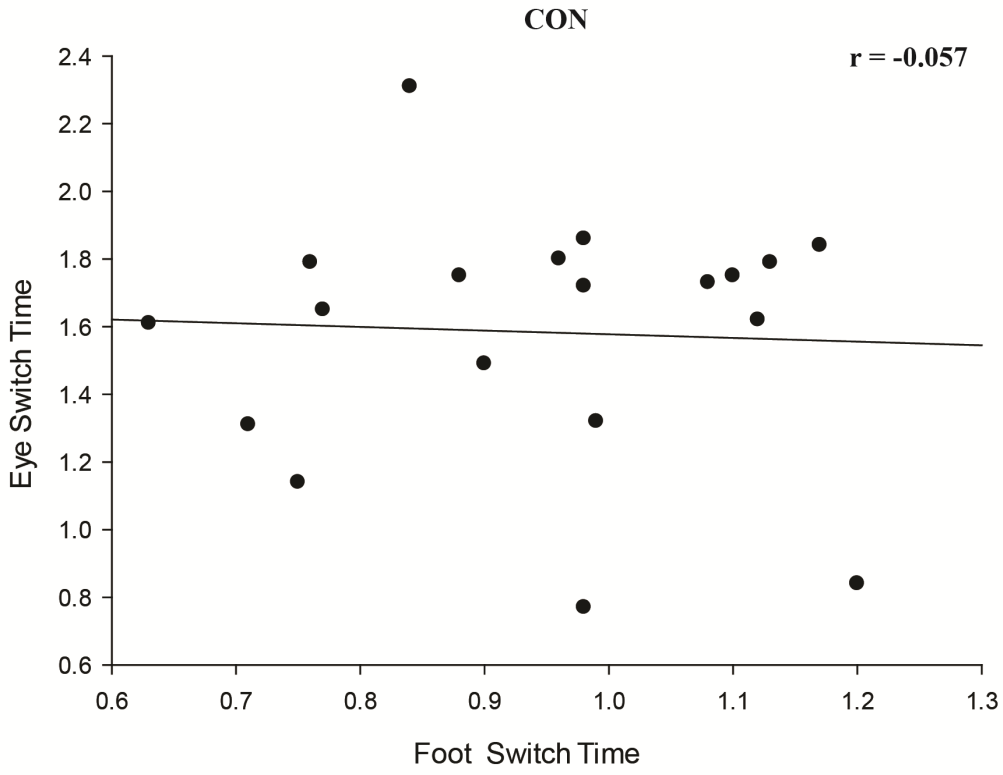


Figure 2:

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


CON
r = -0.057
Eye Switch Time
Foot Switch Time
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3

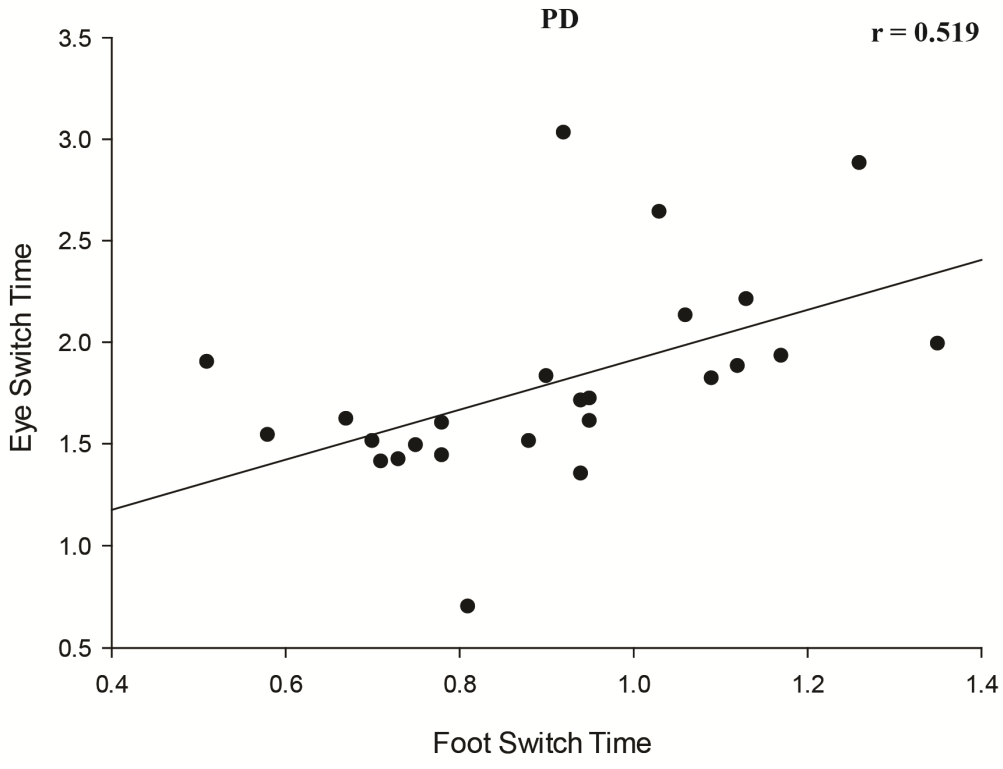
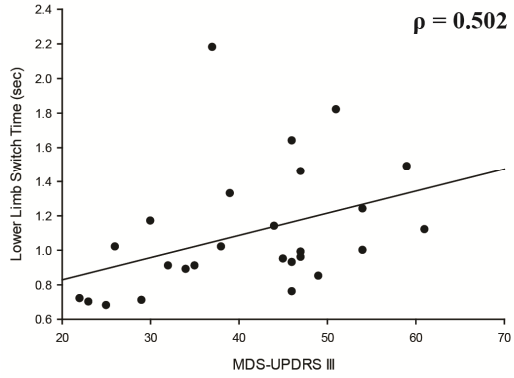
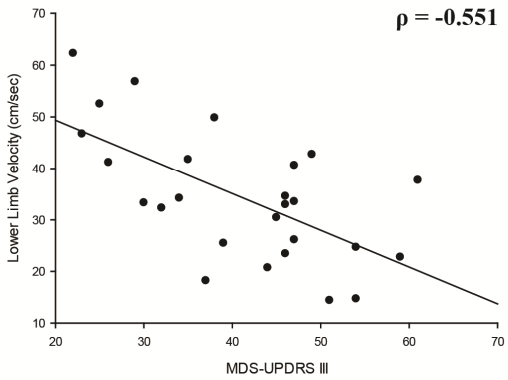
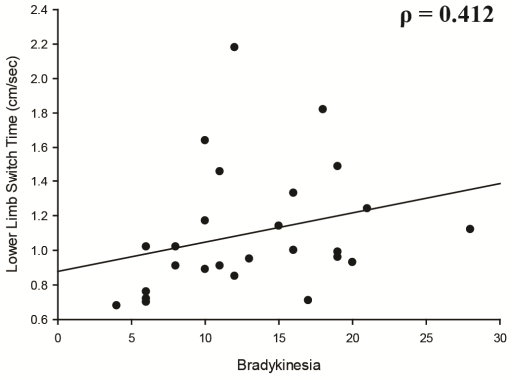
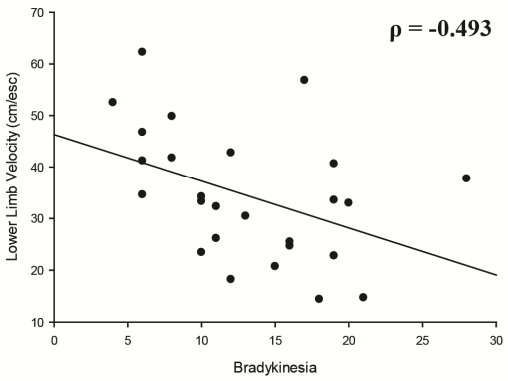

PD
r = 0.519
Eye Switch Time
Foot Switch Time
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.4
0.6
0.8
1.0
1.2
1.4

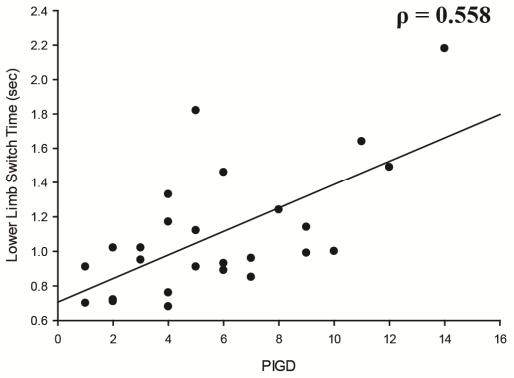
Figure 3: Correlations of lower limb switch time (left column) and movement velocity (right column) with MDS-UPDRS III, Bradykinesia, PIGD, and FOG in subject with PD only.

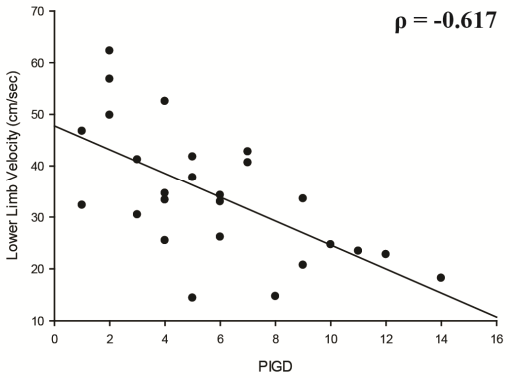

ρ = 0.502
Lower Limb Switch Time (sec)
MDS-UPDRS III

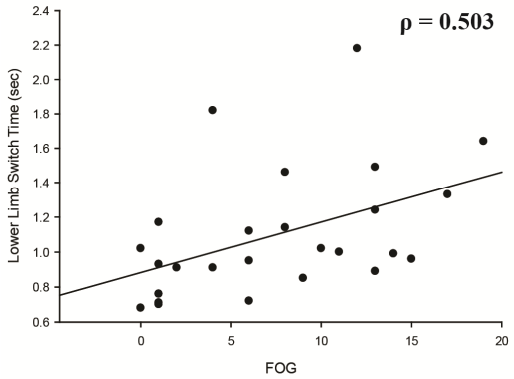

ρ = -0.551
Lower Limb Velocity (cm/sec)
MDS-UPDRS III


ρ = 0.412
Lower Limb Switch Time (cm/sec)
Bradykinesia


ρ = -0.493
Lower Limb Velocity (cm/esc)
Bradykinesia


ρ = 0.558
Lower Limb Switch Time (sec)
PIGD


ρ = -0.617
Lower Limb Velocity (cm/sec)
PIGD


ρ = 0.503
Lower Limb Switch Time (sec)
FOG

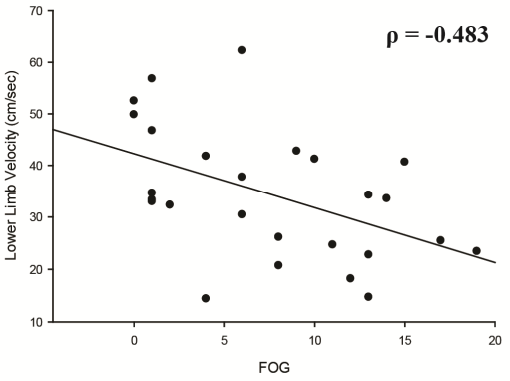

ρ = -0.483
Lower Limb Velocity (cm/sec)
FOG

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

* Significant group effect, $p < 0.05$

† Significant group effect, $p < 0.01$

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Chapter 3: Saccadic eye movements are related to turning performance in Parkinson's disease

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Lohnes CA, Earhart GM. Saccadic eye movements are related to turning performance in Parkinson's disease. *Journal of Parkinson's Disease*. 2011; 1(1):109-118.

Abstract

Background. Persons with Parkinson's disease (PD) experience difficulty turning, leading to freezing of gait and falls. We hypothesized that saccade dysfunction may relate to turning impairments, as turns are normally initiated with a saccade. *Objective.* Determine whether saccades are impaired during turns in PD and if characteristics of the turn-initiating saccade are predictive of ensuing turn performance. *Methods*. 23 persons with PD off medication and 19 controls performed 90 and 180 degree in-place turns to the right and left. Body segment rotations were measured using 3-D motion capture and oculomotor data were captured using a head-mounted eye tracking system and electrooculography. Total number of saccades and the amplitude, velocity, and timing of the first saccade were determined. *Results*. Turn performance (turn duration, number of steps to turn) was impaired in PD ($p<0.05$). PD performed more saccades, and the velocity and timing of the first saccade was impaired for both turn amplitudes ($p<0.05$). Amplitude of the first saccade was decreased in PD during 180 degree turns. Turn duration correlated with oculomotor function. Characteristics of the first saccade explained 48% and 58% of the variance in turn duration for 90 and 180 degree turns, respectively. *Conclusions*. Turning performance is impaired in PD and may be influenced by saccade dysfunction. An association between saccade function and turning performance may be indicative of the key role of saccades in initiating proper turning kinematics. Future work should focus on improving saccade performance during functional tasks and testing the effects of therapeutic interventions on related outcomes.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease that is associated with a reduction in mobility, with problems that include difficulty turning. Turning difficulties can lead to freezing of gait (FOG), falls, fear of falling, and social withdrawal.[1-3] Falls that occur during turning are eight times more likely to result in hip fracture than falls during straight line walking.[4] Furthermore, individuals with PD have a 3.2 fold greater risk of hip fracture than age-matched individuals without PD.[5] In addition to the large personal cost of turning difficulties, hip fractures represent a substantial financial burden to society, with the cost of hip fracture care in individuals with PD totaling approximately $192 million per year in the United States.[5,6]

Studies focusing on turning have noted that individuals with PD require more steps and take longer to complete a turn than healthy controls.[7-11] Those with PD who report turning difficulty also have a higher incidence of freezing of gait and falls.[10,12] Furthermore, the timing of segmental rotations during turn initiation is altered in PD. This has been termed "en bloc" turning and is characterized by the near simultaneous rotation of the head, trunk, and pelvis and reduced relative rotations between adjacent segments.[9,13-15] Other measures of poor turn quality have been observed in those with PD including a wider turn arc[16], narrowed step width[11,16,17], and higher variation in step duration compared with controls.[16]

It is evident that visual information plays an important role in the control of locomotion and turning. Clear differences in gaze behavior and stepping performance have been demonstrated between older adult fallers and non-fallers.[18] In addition, training of eye movements has been shown to improve locomotor performance in

individuals with cerebellar damage.[19] Several studies in healthy individuals have shown that the eyes participate in a top-down rotation sequence such that the eyes are the first to turn, followed by the head, trunk, and then the feet.[20-23] The initial saccade during a turn, in combination with subsequent head movements, provides a shift of gaze to a position aligned with the direction of travel. Gaze shifts precede shifts in center of mass (COM) trajectory during turning and unexpected perturbations of gaze cause delays in COM movement to steer the body along the desired trajectory.[24]

While eye movements have been measured in healthy adults during turning tasks, it is unclear how eye movements relate to turning performance in individuals with PD. During head-fixed tasks, saccadic eye movements have been shown to be abnormal in those with PD, including prolonged fixation times, bradykinesia, and akinesia during rapid alternating gaze shifts between two fixed targets.[25] Several more recent studies have demonstrated deficits in control of voluntary saccades in people with PD, consistently noting that saccades are slower and smaller than those of control subjects.[26-30] Briand et al[29] reviewed a series of 15 studies of voluntary saccades and noted that all but one of these studies reported voluntary saccade performance inferior to that of control subjects in individuals with PD. Therefore, we hypothesize that saccadic eye movements performed during turns are also likely abnormal and may contribute to impaired turn performance. A disruption of the normal top-down rotation sequence by poor saccade timing or decreased saccade amplitude may contribute to the altered turning kinematics reported in those with PD. Hence, the purposes of this study were to determine whether saccadic eye movements during turning are impaired in individuals with PD and to

determine if characteristics of the saccade that initiates a turn are predictive of ensuing turn performance.

METHODS

Participants

Twenty-three individuals with idiopathic PD and 19 age- and gender-matched controls participated in this investigation. Individuals with PD were recruited from a database of patients from Washington University School of Medicine's (WUSM) Movement Disorders Center. Control participants were recruited from the Volunteers for Health Database, posted flyers, and other healthy volunteer databases associated with WUSM. 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: any 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, such as previous stroke or muscle disease, and history or evidence of orthopedic, muscular, or psychological problem that may affect task performance during the study. 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. (1999) based upon established criteria (Calne et al. 1992, Hughes et al. 1992) and were excluded if they had received surgical management of PD (e.g. pallidotomy or deep brain

stimulation). All subjects gave informed consent to perform experimental procedures approved by the Human Research Protection Office at WUSM.

Experimental Procedures

All study 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[31] 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 also was used to evaluate disease severity in PD.[32]

During the experimental protocol, participants completed in-place turns of 90 degrees and 180 degrees amplitude. Instructions were given to perform the turns in a comfortable and normal fashion. No specific auditory or visual cues were provided to cue turn onset or completion other than directing subjects to "turn 90 degrees to face the wall beside you" or "turn 180 degrees to face the wall behind you", accordingly. Participants were instructed to begin the movement anytime after receiving the turn direction instruction of left or right for the given trial. Turns were completed to both the right and left in randomized order and all 90° turns were completed prior to beginning the block of 180° turns. Participants completed a minimum of 5 turns in each direction. Data quality was visually monitored in real time and additional turns were completed as needed to insure an adequate number of quality trials for analysis.

Full body kinematic data were captured using an eight camera, passive marker, 3-dimensional, high –resolution motion capture system (Motion Analysis Corporation, Santa Rosa, CA) sampling at 100 Hz in Cortex software (Motion Analysis Corporation, Santa Rosa, CA). Thirty-eight retro-reflective markers were positioned on the head (top of head, back of head, left ear, right ear), trunk (left and right acromion, right scapula, sternal notch, xyphoid process, 7^{th} cervical vertebra, 12^{th} thoracic vertebra), pelvis (left and right anterior superior iliac spine, left and right posterior superior iliac spine, sacrum), both legs (greater trochanter, anterior thigh, medial and lateral femoral condyle, tibial tuberosity, front of shank, medial and lateral malleolus) and both feet (calcaneus, navicular, distal 2^{nd} metatarsal). Ocuolmotor 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.

Data Processing

Individual kinematic 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. Global and segment coordinate systems were defined in MotionMonitor with the positive X-axis pointing anteriorly, positive Y-axis pointing to the left, and positive Z-axis pointing upward vertically. Rotations of the head, trunk, pelvis, and feet about global Z were extracted using a Z-X-Y Euler sequence. Subsequently, kinematic angle data and filtered analog data were exported for further processing in custom written MATLAB software (The Mathworks, Inc, Natick, MA).

Time of onset for segment rotations (relative to the global coordinate system) was determined by identifying the first frame at which the rotation reached five degrees above baseline. Similar criteria were used to identify turn offset, defined as the frame at which the rotation came within five degrees of maximal, final position. Eye tracker and EOG data were used to identify and measure saccades occurring just prior to and during turn performance. Saccades were identified visually and later confirmed to be true saccades if the maximum velocity of the eye movement exceeded 30 degrees/sec.[33,34] Onsets and offsets of the first saccade associated with each turn were identified visually. Using these time points, saccade amplitude, peak velocity, and timing of the first saccade relative to head and foot rotations were calculated. Example trials are shown for an individual with PD and a control in Figure 4.

Individual trials were excluded from analysis if eye position or body segment rotations about the global Z-axis were not static for at least 1000ms prior to turn onset. Trials were also excluded if artifacts in oculomotor data due to blinks, prolonged closure of eyelids, or other factors precluded measurement of the initial saccade. Remaining trials within a condition (90 or 180 degrees) were averaged to obtain a single data point for each subject. Left and right turns were combined for analysis as turn performance did not differ between leftward and rightward turns.

Data Analysis

Independent Student's t-tests were used to compare between-group differences in turn performance and oculomotor performance during both 90 and 180 degree turns. Our primary variables of interest were the amplitude and velocity of the saccade initiating the turn, the total number of saccades performed during the turn, and the timing of the first

saccade relative to onsets of head and foot rotations. The latencies between the first saccade and head/foot rotations were normalized to the duration of the first gait cycle and are reported as a percentage of the first gait cycle time. We also employed a linear regression model with turn duration as the dependent variable and number of saccades, initial saccade velocity and normalized timing of the saccade relative to turn onset as the independent variables to identify the amount of variance in turn performance accounted for by characteristics the saccade initiating the turn. Saccade amplitude and the normalized timing of the saccade relative to head rotation onset were not included in the model as they were highly correlated with the included variables. The criterion for statistical significance was set at $p<0.05$.

RESULTS

Demographic data are displayed in Table 1. Data from three participants included in the 90 degree turn analysis could not be included in the analysis for the 180 degree turn due to poor oculomotor data quality. Conversely, one participant was included in the 180 turn analysis but omitted from the 90 degree analysis for similar reasons. Regardless of turn type, age did not differ between PD and controls.

Turn performance was impaired in PD compared with controls, with both 90 and 180 degree turns requiring more steps ($p<0.05$) and a greater time to complete ($p<0.01$). PD also performed a greater number of saccades during their turns, and the peak velocity of the initial saccade was slower in PD for both 90 and 180 degree turns ($p<0.01$). The amplitude of the initial saccade was less in PD than in controls for 90 degree turns only ($p<0.01$). The normalized latency between start of the first saccade and start of the first

step (Norm E-F Index) was different between groups, with PD performing the first saccade earlier relative to the onset of foot rotation (<0.05, Table 2).

The number of saccades, initial saccade amplitude, initial saccade velocity, and Norm E-F Index were all significantly correlated with turn duration (Figure 5). Turn duration, which was highly correlated with the number of steps required to turn, was used as the dependent variable representing turn performance in our regression analysis. The linear regression model, which included both PD and controls, explained a significant amount of the variance in turn duration for both 90 degree (R^2 = .481, F(3,27)=11.4, p < .001) and 180 degree (R^2 = .578, F(3,25) = 16.0, p < .001) turns. Table 3 reports the unstandardized (B) and standardized (β) regression coefficients for these models.

Comparing freezers and non-freezers, turn duration and number of steps were greater in subjects who reported freezing of gait at least once per week on item 3 of the FOG questionnaire (p<0.05). Mean values for initial saccade velocity and Norm E-F Index differed between freezers and non-freezers, but these comparisons did not reach statistical significance. Despite the lack of statistical significance, the effect sizes, measured using Cohen's *d*, were moderate to large. Effect size for saccade velocity between freezers and non-freezers equaled 0.91 for 90 degree turns and 0.52 for 180 degree turns. Norm E-F Index effect sizes were 0.8 for 90 degrees turns and 0.86 for 180 degree turns. Number of saccades and initial saccade amplitude were similar between freezers and non-freezers. Data comparing freezers and non-freezers is presented in Table 4.

DISCUSSION

This study sought to determine whether saccadic eye movements performed during turning are impaired in individuals with PD and to determine if characteristics of the saccade that initiates a turn are predictive of ensuing turn performance. In confirmation of our hypotheses, saccadic eye movements were impaired during turning in persons with PD and these impairments were related to turning dysfunction. Individuals with PD used a greater number of saccades to complete both 90 and 180 degree turns, the initial saccade was both smaller (180 degrees only) and slower than that of controls, and the timing of the initial saccade relative to the turn onset was altered in those with PD. Furthermore, turn performance was impaired in persons with PD and approximately 50% of the variance in turn performance was explained by saccade performance across all participants. Differences in saccade performance between the 90 and 180 degree turns were largely predictable. The 180 degree turns required approximately twice as many saccades as the 90 degree turns and the amplitude of the initial saccade was similar between turn magnitudes for both groups. This suggests that the size of the turn-initiating saccade is constant for turns of 90 degrees and larger, and that simply more saccades are performed for large turns. Similarly, the delay between the first saccade and turn onset did not differ between the two turn magnitudes.

Previous research widely demonstrates that voluntary saccade performance is impaired in persons with PD.[25-30] These studies, however, have focused only on simple head-fixed tasks or on saccades performed in conjunction with head movements from a seated position. Studying the oculomotor system using simple saccade paradigms has allowed researchers to better understand basal ganglia disorders using a simple, predictable, and well understood motor system. However, little information has been

gathered from such studies regarding the implications of oculomotor impairments on functional activities in those with PD. To the best of our knowledge, this is the first study to report saccade performance during a more complex, functional task in people with PD. Our novel findings support previous work that voluntary saccades are impaired in PD and lend support to the idea that the eyes play a key role in turning. The turning sequence has been characterized in healthy controls and consists of a top-down rotation sequence led by the eyes and followed by rotations of the head, trunk, pelvis, and feet.[20-23] In individuals with PD this sequence is impaired, characterized by smaller intersegmental rotations and altered timing of segment rotations.[9,13,14] The present study reveals that the turning sequence in PD is also characterized by a longer than normal delay between the first saccade and the initiation of the gait cycle, as well as a smaller and slower saccade at the beginning of the turn. Functionally, this manifests in reduced turn performance. As evidenced by the strong correlations between saccade performance (the number of saccades, saccade velocity, and saccade timing) and turn performance (number of steps and turn duration), the degree of oculomotor impairment may impact turn quality.

Our finding of a greater delay between the initial saccade and the rest of the turning sequence in the PD group is contrary to our hypothesis. Expanding the PD en-bloc turning phenomenon to include eye movements, one would expect the eyes to rotate more in sync with the head, trunk and feet, as opposed to our observation of a longer latency between the eyes and feet. Our PD group actually performed the first saccade much earlier in the rotation sequence than did the controls, and the longer latencies were unexpectedly associated with a longer turn duration and more steps. This finding may be explained by a generalized bradykinesia that affects both the motor and oculomotor

systems. While the basal ganglia are often described as having distinct loops for oculomotor and motor control, recent evidence suggests an overlap in control of both eye and limb movements by the subthalamic nucleus (STN), as neurons in the STN respond to both voluntary saccades and limb movements.[35] Therefore, the greater delay between eye movement and turn onset seen in PD may be the result of a dysfunctional common motor pathway responsible for an overall bradykinetic turn sequence. Based on this, deep brain stimulation (DBS) may prove beneficial for improving turn performance in PD by enhancing both eye and limb movements. Levodopa therapy, the most common treatment for those with PD, provides minimal improvement in both turn performance and voluntary saccade performance.[36,37] However, DBS of the STN in persons with PD has shown considerable efficacy in improving motor performance, including gait and performance of voluntary and reflexive saccades.[38-40]. However, no studies to date have examined the effect of DBS on turn performance, nor the effect of DBS on saccade function during functional tasks. Therefore, future work should target the effects of STN-DBS on turn performance and associated oculomotor performance.

Studies extending beyond PD corroborate a relationship between oculomotor dysfunction and gait impairments; a relationship that appears to be related to risk of falling in a range of populations. In a study comparing elderly individuals who were at high risk for falling with those at low risk for falling, a longer delay between horizontal saccade initiation and initiation of footlift was observed in the high-risk group during a precise walking task.[41] Differences in gaze behavior have also been shown between adult fallers and non-fallers.[18] In patients with progressive supranuclear palsy (PSP), those with more severe gaze palsy displayed an altered stepping pattern when navigating

obstacles, placing them at higher risk for trips and falls.[42] In our study, subjects who reported FOG at least once per week displayed turn performance deficits and altered saccade timing and velocity, although the comparison of oculomotor measures failed to reach statistical significance, possible due to the small group sizes. Disease severity (MDS-UPDRS III) and duration were not different between freezers and non-freezers, illustrating that FOG is a specific pathology not present in all PD patients regardless of disease stage or severity.[2] While we did not obtain fall history records in this study, FOG has been shown to be a risk factor for falling, and thus the freezers in our study likely represent a sample of patients at higher risk for falls and fall-related injuries. Taken together, our study and those of other pathological populations suggest a relationship between fall risk and gait/oculomotor function. Therefore, rehabilitation strategies aimed at decreasing the risk of falls during ambulation, and in particular during turning, are important.

Cueing has received considerable attention over the past decade as a means of improving temporal and spatial parameters of gait in persons with PD. Rhythmic auditory, visual, and attentional cues have been shown to improve stride length and gait velocity during straight walking.[43-46] However, the ability of cues to improve turning performance is less well understood. When rhythmic auditory cues were used during a U-turn task, only step time variability was improved among a number of turn performance parameters.[16] In contrast, another study found that rhythmic auditory and somatosensory cues improved turn time in a functional task (carrying a tray).[47] Clearly, more work is necessary to determine the effect of cues on turning, and based on the

importance of oculomotor function during turning, using cues to promote a more appropriate oculomotor strategy during turns should be of interest.

Limitations

One limitation of this study is that saccades were measured using two separate measurement systems. The infrared binocular eye tracking system served as our primary measurement tool, with EOG serving a secondary role. Due to the technical nature of measuring pupil and corneal reflections using the infrared system, quality infrared data could not be obtained from all participants. In such cases, EOG data were used for analysis. To verify agreement between these two measurement systems, infrared and EOG data were compared using data from participants for whom we had both data sets. When comparing the timing, amplitude, and velocity of the initial saccade, values obtained from the two systems compared exceptionally well. Therefore, the authors felt confident in pooling data obtained from either measurement system. Another limitation of this study is that measurement occurred in a laboratory setting and thus participants were aware that their performance was being monitored. Hence, it is possible that participants' oculomotor and turning performance may have differed from their usual performance in a more natural setting. The authors think, however, that such effects are minimal and would have been experienced similarly by both groups, thus not detracting for our findings.

Conclusions and Future Directions

It is evident that turning difficulty is a primary trigger for freezing and falls in PD, and our study indicates that impaired voluntary saccades may contribute significantly to this problem. Rehabilitative strategies might consider focusing on cueing persons with

PD to initiate turns with a more appropriate top-down rotation sequence, initiated by a large amplitude saccade prior to commencing the gait cycle. Accordingly, future research should be directed towards studying the effects of cueing and practice on the ability to improve saccade performance during turns, and whether such improvements offer meaningful improvements in turn performance and related fall risk. Additionally, future work may assess the effects of therapeutic interventions (e.g. deep brain stimulation) on such variables.

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Figure 4. Representative data from individual turn trials showing eye, head, and foot rotations in the horizontal plane.

Panel A: Representative 90 degree turn performed by an individual with PD. The subject performed 8 saccades of varying amplitudes during the turn, and required 3 steps to complete the turn. Panel B: Representative 90 degree turn performed by a healthy control. The subject performed only 5 saccades during the turn and required only 2 steps and less time to complete the turn than the individual with PD. Panel C: Representative 180 degree turn performed by an individual with PD. The subject performed 15 saccades of varying amplitudes during the turn, and required 5 steps to complete the turn. Panel D: Representative 180 degree turn performed by a healthy control. The subject performed 8 saccades of more consistent amplitude than those performed by the individual with PD, and required only 4 steps and less time to complete the turn than the individual with PD.

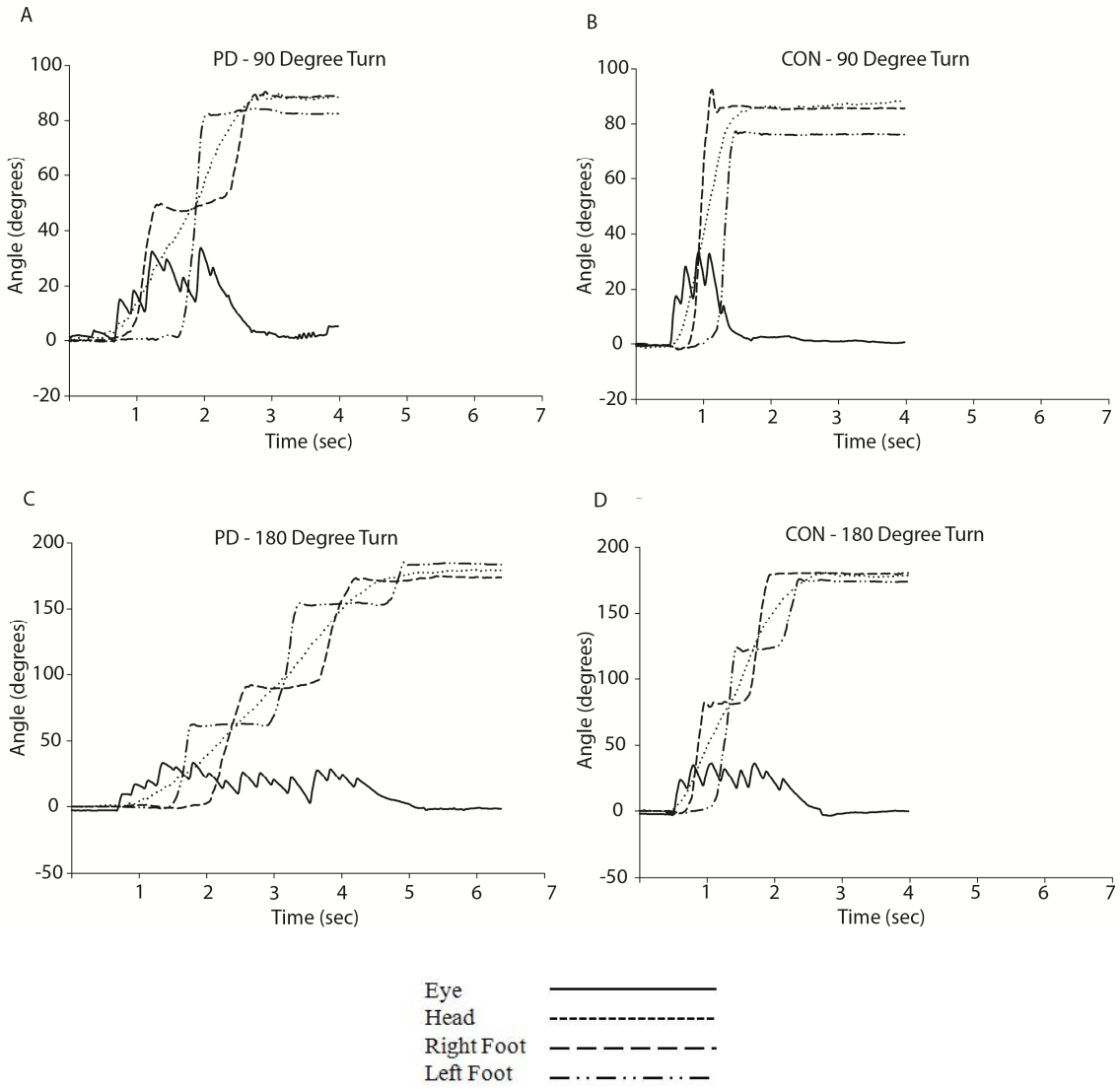
A
PD - 90 Degree Turn
Angle (degrees)
Time (sec)
B
CON - 90 Degree Turn
Angle (degrees)
Time (sec)
C
PD - 180 Degree Turn
Angle (degrees)
Time (sec)
D
CON - 180 Degree Turn
Angle (degrees)
Time (sec)
Eye
Head
Right Foot
Left Foot

Figure 5. Correlations between turn duration and various parameters of saccade performance.

Correlations include all subjects from both the PD and control groups, with Pearson correlation coefficients shown in top right of each panel. The left column shows correlations of saccade number (A), amplitude of the first saccade (B), velocity of the first saccade (C), and normalized timing of the first saccade relative to the first step (D) for 90 degree turns. The right column (E-H) shows the same correlations for 180 degree turns.

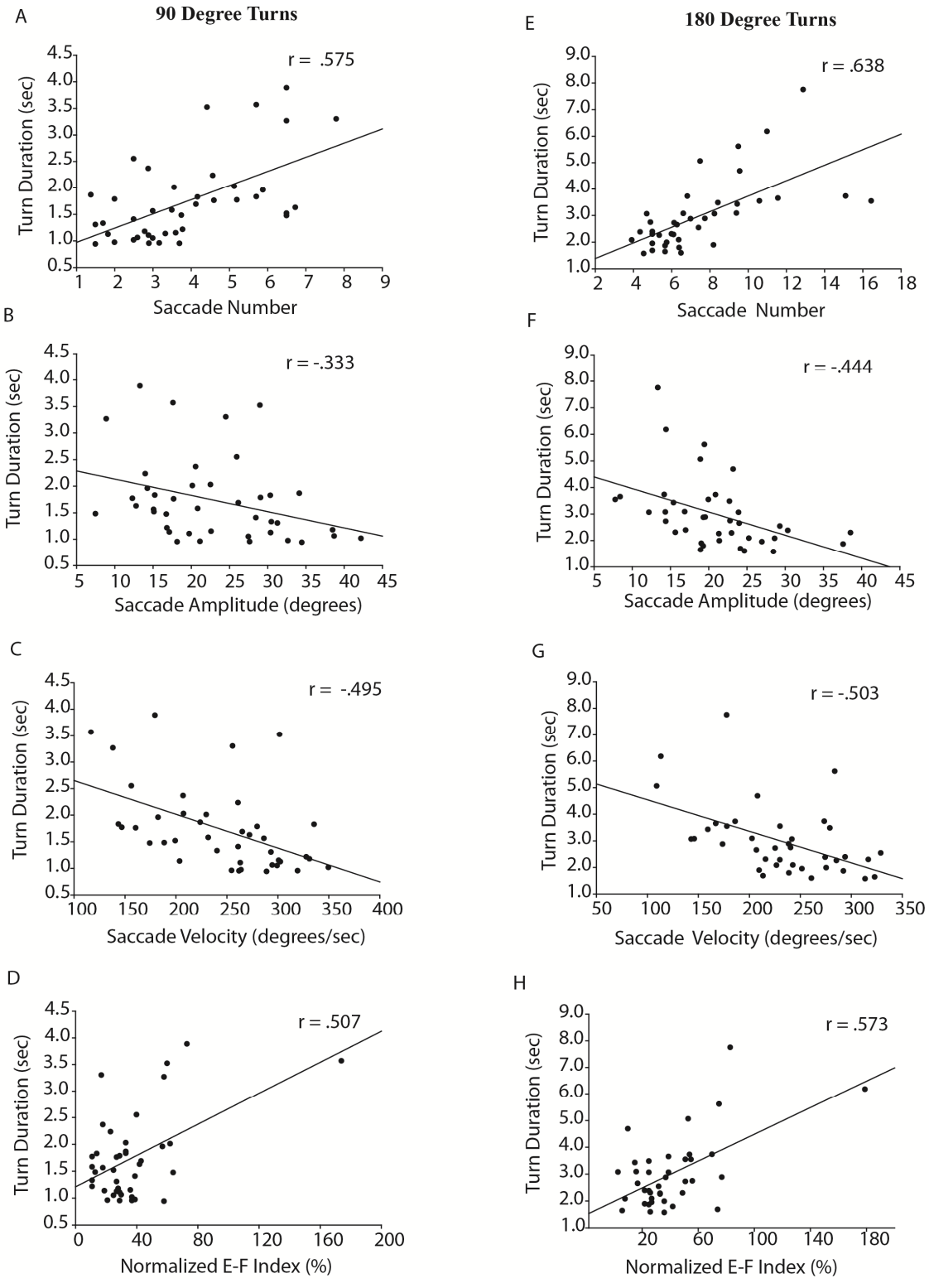
A
90 Degree Turns
r = .575
Turn Duration (sec)
Saccade Number
B
r = -.333
Turn Duration (sec)
Saccade Amplitude (degrees)
C
r = -.495
Turn Duration (sec)
Saccade Velocity (degrees/sec)
D
r = .507
Turn Duration (sec)
Normalized E-F Index (%)
E
180 Degree Turns
r = .638
Turn Duration (sec)
Saccade Number
F
r = -.444
Turn Duration (sec)
Saccade Amplitude (degrees)
G
r = -.503
Turn Duration (sec)
Saccade Velocity (degrees/sec)
H
r = .573
Turn Duration (sec)
Normalized E-F Index (%)

Table 1. Subject Demographics

	PD (90° turns)	PD (180° turns)	Controls
Age (years)	68.7 ±10.2	68.6 ±10.8	68.8 ± 11.4
Male/Female	14/8	13/7	11/8
PD Characteristics			
Disease Duration (years)	7.4 ± 5.8	6.8 ± 5.6	
Hoehn & Yahr Stage	2.3 ± 0.4	2.3 ± 0.4	
(# in each stage)	Stage 1 = 1	Stage 1 = 1	
	Stage 2= 9	Stage 2= 7	
	Stage 2.5 = 10	Stage 2.5 = 10	
	Stage 3 = 2	Stage 3 = 2	
Freezing of Gait Score	5.7 ± 4.8	5.8 ± 5.0	
No. Freezers (FOG 3 ≥ 2)	8	8	
MDS-UPDRS III Score	40.1 ± 11.9	38.7 ± 11.5	

Values are means ± standard deviations.

Table 2. Turn Performance and Oculomotor Performance During 90 and 180 Degree Turns

	90° Turns			180° Turns		
Measure	PD		Controls	PD		Controls
# of Steps	4.3 ± 2.6	*	2.7 ± 0.8	7.7 ± 5.1	*	4.5 ± 0.9
Turn Duration (seconds)	2.1 ± 0.8	†	1.4 ± 0.5	3.6 ± 1.5	†	2.4 ± 0.7
# of Saccades	4.5 ± 1.7	†	3.1 ± 1.4	8.9 ± 3.2	†	6.0 ± 1.5
First Saccade Amplitude (degrees)	20.6 ± 8.1		25.7 ± 8.4	17.4 ± 4.6	†	24.7 ± 6.7
First Saccade Velocity (deg/sec)	219.0 ± 65.6	†	273.1 ± 41.1	206.7 ± 61.2	†	255.3 ± 39.5
Norm E-H Index (% of 1st gait cycle)	19.4 ± 19.3		11.5 ± 6.1	26.8 ± 25.0	*	13.4 ± 7.2
Norm E-F Index (% of 1st gait cycle)	45.4 ± 33.9	*	25.4 ± 9.7	52.3 ± 38.1	*	28.1 ± 11.5

Values are means ± standard deviations.

* Significantly different between groups, $p < 0.05$

† Significantly different between groups, $p < 0.01$

Table 3. Results of Linear Regression Analysis

		B	SE (B)	β	p
90° Turns	# Saccades	18.24	6.40	.392	.007
	Saccade Velocity	-.232	.18	-.180	.211
	Norm E-F Index	94.59	36.93	.329	.015
180 ° Turns	# Saccades	18.72	5.79	.407	.003
	Saccade Velocity	-.283	.28	-.248	.048
	Norm E-F Index	147.01	53.01	.337	.009

90° Turns, R^2 = .481

180° Turns, R^2 = .578

Table 4. Comparison of Freezers and Non-Freezers

	90° Turns			180° Turns		
	Freezers (n=8)		Non-Freezers (n=14)	Freezers (n=8)		Non-Freezers (n=12)
Disease Duration	8.6 ± 7.0		6.7 ± 5.2	8.3 ± 6.7		5.8 ± 4.8
MDS-UPDRS III Score	40.1 ± 13.1		40.1 ± 11.7	39.9 ± 12.9		37.8 ± 11.0
# Saccades	4.5 ± 2.0		4.6 ± 1.6	9.1 ± 2.6		8.8 ± 3.7
Saccade Amplitude (degrees)	20.6 ± 8.5		20.7 ± 8.2	18.2 ± 3.4		16.9 ± 5.4
Saccade Velocity (deg/sec)	183.8 ± 59.8		239.2 ± 61.7	187.7 ± 61.5		219.4 ± 60.2
Norm E-F Index	61.1 ± 49.0		36.4 ± 18.2	70.8 ± 48.1		40.0 ± 24.8
Total Steps	6.4 ± 3.6	*	3.1 ± 0.5	11.1 ± 6.7	*	5.4 ± 1.1
Turn Duration (seconds)	2.8 ± 8.1	†	1.6 ± 0.4	4.7 ±1.7	*	2.8 ± .77

Values are means ± standard deviations.

*Significantly different between groups, $p < 0.05$

†Significantly different between groups, $p < 0.05$

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Chapter 4: Effect of Subthalamic Deep Brain Stimulation and Levodopa on Turning Kinematics and Related Saccadic Eye Movements in Parkinson's Disease

This chapter has been submitted:

Lohnes CA, Earhart GM. (In Review, *Experimental Neurology*) Effect of Subthalamic Deep Brain Stimulation and Levodopa on Turning Kinematics and Related Saccadic Eye Movements in Parkinson's Disease

Abstract

Background: Persons with Parkinson's disease (PD) experience turning difficulty, often leading to freezing of gait and falls. Visual information plays a significant role in locomotion and turning, and while the effects of medication and deep brain stimulation (DBS) on oculomotor function have been well documented, the effects of each on oculomotor function during turning and on turning itself have yet to be fully elucidated. *Objective: T*o determine the separate and combined effects of levodopa and STN DBS on turning performance and related oculomotor performance in PD. *Methods:* Eleven subjects with PD and DBS of the subthalamic nucleus performed a seated voluntary saccade task and standing 180° turns. Oculomotor data were captured using an infrared eye tracking system while segment rotations were measured using 3-D motion capture. *Results:* During the seated saccade task, neither medication nor DBS improved saccade amplitude or latency, while DBS alone improved gait velocity and stride length during forward walking. During turning, both medication and DBS improved turn performance (turn duration) and reduced the number of saccades performed during the turns. DBS increased the amplitude and velocity of the saccade initiating the turn while medication had no effect. DBS decreased the intersegmental latencies (eye-head, eye-foot, and head-trunk) but this effect was lost for eye-head and eye-foot after controlling for the duration of the first gait cycle. *Conclusions:* DBS significantly improves turn performance and related oculomotor performance while medication has a minimal effect. These findings add to the growing list of therapeutic benefits offered by DBS.

INTRODUCTION

Turning during gait is common and required during normal ambulation and activities of daily living. Individuals with Parkinson's disease (PD), however, experience difficulty turning, leading to freezing of gait (FOG), falls, and fear of falling.[1-3] Falls during turns are eight times more likely to result in hip fracture than falls during straight line walking, and individuals with PD have a 3.2 fold greater risk of hip fracture than age-matched individuals without PD.[4] Hip fractures represent a substantial financial burden to society, with the cost of hip fracture care in individuals with PD totaling approximately $192 million per year in the United States.[5]

Recent studies have attempted to elucidate the cause of turning difficulty in PD in order to develop strategies to overcome the issue. Such studies have noted that persons with PD require more steps and take longer to complete a turn than healthy controls.[6-9] Additionally, individuals with PD show altered timing of segmental rotations during turn initiation, such that their turning strategy is more "en bloc" than healthy controls,[8,10-12] although this finding may not be observed in early PD stages.[13] It is also clear that visual information plays an integral role in this turning sequence. In healthy controls, the eyes participate in the top-down rotation sequence such that they eyes precede the sequential rotations of the head, trunk, and feet.[14] In subjects with PD, however, the amplitude of the initial saccade is smaller than in healthy controls, a greater number of smaller saccades are performed during the turn, and the timing of the initial saccade relative to the first step is altered.[9,13] These oculomotor deficits are consistent with a large body of literature supporting voluntary saccade dysfunction in PD. Prolonged fixation times, bradykinesia, and akinesia during rapid alternating gaze shifts have been observed in PD, and voluntary saccades are widely described as being smaller and slower in PD.[15] In

gaze re-orienting tasks where the eyes rotate in concert with the head to fixate on a lateral target, eye-head coordination is found to be abnormal such that both saccades[16] and head rotations [16,17] are delayed, hypometric, and slow.

Few studies have been done to determine the effects of interventions on turning in PD. While levodopa therapy was effective in improving MDS-UPDRS III scores and gait velocity in one study, congruent with previous research,[18] the effect on turn duration, steps to turn, and the timing of body segment rotations was minimal.[19] Similarly, the effects of anti-Parkinson medications on saccade function are mixed. While the amplitude of voluntary saccades appears to be resistant to levodopa therapy,[20,21] levodopa may have a beneficial effect on voluntary saccade latencies[22,23] but a negative effect on reflexive saccade latencies.[23,24] In contrast, the effects of subthalamic nucleus (STN) deep brain stimulation (DBS) on turning are more robust and in line with evidence showing that DBS improves gait velocity and stride length in PD.[25,26] The effects of DBS on saccade function are also well documented. Rivaud-Pechoux et al.[27] found a positive effect of STN DBS on saccade gain during a memory guided saccade task. Sauleau et al.[28] also reported improvements with STN DBS in gain and latency of both saccades and gaze during head fixed and head free reflexive saccade tasks, respectively. Finally, Temel et al.[29,30] found a marked improvement in saccade latency distributions with STN-DBS, whereas dopaminergic medication had a negative effect on saccade latency.

While the effects of anti-parkinson medication on turning and oculomotor function have been reported separately, as well as the effects of DBS on the latter, no studies have examined the effect of levodopa on both turning and oculomotor function in PD, and only one study has tested the effects of DBS on turning in PD.[31] Therefore, the

purpose of this study was to determine to separate and combined effects of levodopa and STN DBS on turning performance and related oculomotor performance in PD. Based on evidence that DBS improves both gait and oculomotor performance in PD, we hypothesized that turning performance (time to turn) would be improved with DBS, including an increase in initial saccade amplitude and alterations in the timing of the first saccade relative to turn onset. We also hypothesized that levodopa would improve turning and related oculomotor function, but to a lesser extent than DBS, and that the combination of the two therapies would have an additive effect on turning performance. We based the latter hypothesis on a study by Ferrarin et al.[26] who showed that levodopa and DBS provided an additive benefit in terms of gait speed, stride length, and intersegmental range of motion during gait.

METHODS

Participants

Eleven individuals with idiopathic PD participated in this investigation. Participants were recruited from a database of patients from Washington University School of Medicine's (WUSM) Movement Disorders Center. All participants met the following inclusion criteria: aged 30 years or older, bilateral STN DBS and a minimum of 3 months post implantation surgery, currently taking levodopa medication, 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: any 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, such as previous stroke or muscle disease, and history or evidence of orthopedic, muscular, or psychological problem that may affect task performance during the study. Idiopathic PD was based on a diagnosis of "definite PD" by a board certified neurologist, as previously described by Racette et al. [32] based upon established criteria.[33,34] All participants gave written informed consent to perform experimental procedures approved by the Human Research Protection Office at WUSM.

Experimental Procedures

All study procedures were performed in the Locomotor Control Laboratory at WUSM, which each participant visited on two separate days. Participants were tested in the "on" state of their anti-Parkinson' medication for the entirety of one of the visits and were in the "off" state for the entirety of the other visit (i.e. after a 12-hour withdrawal of all anti-Parkinson medications). The order of these visits was counterbalanced. Within each visit, the experimental protocol was performed twice; once with DBS stimulators turned on using clinical settings, and once with DBS stimulators turned off. Again, the order of these conditions was counterbalanced within the testing day. Prior to commencing each round of the experimental protocol, the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Motor Subscale III was administered according to Goetz et al.[35] 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 also was used to evaluate

disease severity in PD[36] and the FOG questionnaire (FOG-Q) was assessed to categorize freezers and non-freezers.[37]

Saccade Task

To evaluate simple voluntary saccade function during an eyes only task, participants performed saccades to targets positioned 20° to the left and right of a center target. The task was performed in a seated position with the participant's head positioned in a chin-rest to minimize head movement and rotation, and the square targets (2.5 cm X 2.5 cm) were located at eye level on a white wall in front of the subject. Upon hearing an auditory tone, subjects were instructed to react as quickly as possible by performing a saccade to one of the lateral targets. Within each block of trials, the order of left and right movements was randomized. Five trials were performed for each target.

Turning Protocol

Following the seated saccade task, participants completed in-place turns of 180° amplitude. Instructions were given to perform the turns in a comfortable and normal fashion. No specific auditory or visual cues were provided to cue turn onset or completion other than directing subjects to "turn 180 degrees to face the wall behind you." Participants were instructed to begin the movement anytime after receiving the turn direction instruction of left or right for the given trial. Turns were completed to both the right and left in randomized order. Participants completed a minimum of 5 turns in each direction. Data quality was visually monitored in real time and additional turns were completed as needed to ensure an adequate number of quality trials for analysis.

Full body kinematic data were captured using an eight camera, passive marker, 3-dimensional, high–resolution motion capture system (Motion Analysis Corporation,

Santa Rosa, CA) sampling at 100 Hz in Cortex software (Motion Analysis Corporation, Santa Rosa, CA). Thirty-four retro-reflective markers were positioned on the head (top of head, back of head, left ear, right ear), trunk (left and right acromion, right scapula, sternal notch, xyphoid process, 7^{th} cervical vertebra, 12^{th} thoracic vertebra), pelvis (left and right anterior superior iliac spine, left and right posterior superior iliac spine, sacrum), both legs (greater trochanter, anterior thigh, lateral femoral condyle, tibial tuberosity, front of shank, lateral malleolus) and both feet (calcaneus, navicular, distal 2^{nd} metatarsal). Ocuolmotor 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.

Walking Task

To confirm the clinical benefit of both the medication and DBS stimulation, subjects performed 3 trials of forward walking at a comfortable, self selected pace across a 5 m instrumented, computerized GAITRite walkway (CIR Systems, Inc., Havertown, PA). Gait velocity and stride length were used as measures of gait function.

Data Processing

Individual kinematic 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. Global and segment coordinate systems were defined in MotionMonitor with the positive X-axis pointing anteriorly, positive Y-axis pointing to the left, and positive Z-axis pointing upward vertically. For the turning task,

rotations of the head, trunk, pelvis, and feet about global Z were extracted using a Z-X-Y Euler sequence. Subsequently, kinematic angle data and filtered analog data were exported for further processing in custom written MATLAB software (The Mathworks, Inc., Natick, MA).

For the turning task, we characterized the timing of the rotation sequence by identifying the time of onset of each segment yaw rotation (relative to the global coordinate system). This was determined by identifying the first frame at which the yaw rotation reached five degrees above baseline. Similar criteria were used to identify turn offset, defined as the frame at which the yaw rotation came within five degrees of maximal, final position. Eye tracker and EOG data were used to identify and measure saccades occurring just prior to and during turn performance. Saccades were identified visually and later confirmed to be true saccades if the maximum velocity of the eye movement exceeded 30 degrees/sec.[38,39] Onsets and offsets of the first saccade associated with each turn were identified visually. Using these time points, saccade amplitude, peak velocity, and timing of the first saccade relative to head and foot rotations were calculated. Our primary variables of interest for the turning task were the amplitude and velocity of the saccade initiating the turn, the total number of saccades performed during the turn, turn duration, and the timing of the first saccade relative to the onset of the first step. Secondary variables of interest included the timing of the turning sequence, i.e. the timing of each body segment (head, trunk, pelvis) relative to the first step of the turn.

For the seated task, the first saccade following the auditory cue was measured in a similar manner. Variables of interest were the latency of saccade onset with respect to the auditory cue and saccade amplitude.

Individual trials were excluded from analysis if eye position or body segment rotations about the global Z-axis (during the turn task) were not static for at least 1000ms prior to turn onset. Trials were also excluded if artifacts in oculomotor data due to blinks, prolonged closure of eyelids, or other factors precluded measurement of the initial saccade. Remaining trials were averaged to obtain a single data point for each combination of medication and DBS state within each subject. For the turning and seated tasks, left and right trials were combined for analysis as performance did not differ between leftward and rightward trials.

Data Analysis

A two-way repeated measures ANOVA was used to evaluate the main effects of medication status and DBS status as well as the interaction between the two for all variables of interest. The criterion for statistical significance was set at $p<0.05$.

RESULTS

Demographic data are displayed in Table 1; performance data are displayed in Tables 2 and 3. The main effect of DBS on MDS-UPDRS III scores was significant ($F=23.4$, $p=0.001$), with DBS improving MDS-UPDRS III scores. Neither the main effect of medication status ($F=0.199$, $p=.665$) nor the interaction ($F=1.252$, $p=0.289$) were significant. DBS had a main effect on gait velocity ($F=5.44$, $p=0.042$) and stride length ($F=4.89$, $p=0.51$), as both improved with DBS turned on. The main effect of medication on gait velocity and stride length ($F=0.047$, $p=0.83$, $F=0.248$, $p=0.629$, respectively), as well as the interaction between medication and DBS for the same two gait variables ($F=0.006$, $p=0.94$, $F=0.085$, $p=0.78$, respectively), were not significant.

Both DBS and medication improved turn duration as the main effects of both were significant ($F=7.77$, $p=0.019$; $F=5.08$, $p=0.048$, respectively) while the interaction was not ($F=4.073$, $p=0.071$). Similarly, DBS and medication each lowered the number of saccades performed during turns (main effects: $F=24.932$, $p=0.001$; $F=12.71$, $p=0.005$, respectively) and the interaction of DBS and medication was significant for number of saccades (interaction $F=7.70$, $p=0.02$). For the amplitude of the first saccade performed during the turn, the main effect of DBS was significant ($F=36.515$, $p<0.001$) as DBS increased first saccade amplitude, while the main effect of medication ($F=0.823$, $p=0.386$) and the interaction ($F=0.725$, $p=0.414$) were not. The main effect of DBS on saccade velocity was significant ($F=9.803$, $p=0.011$) as DBS increased saccade velocity, while the main effect of medication ($F=1.551$, $p=0.241$) and the interaction ($F=0.593$, $p=0.459$) were not.

In characterizing the timing of the rotation sequence, there was a main effect of DBS for the eye-head ($F=6.416$, $p=0.03$), eye-foot ($F=10.435$, $p=0.009$), and head-trunk ($F=6.382$, $p=0.030$) latencies as DBS decreased the latencies between segment rotations. Neither the main effects of medication nor the interactions were significant. When dividing the latencies by the duration of the first gait cycle to obtain normalized latencies in order to control for turning speed, each of the above main effects of DBS were removed except for the normalized head-trunk latency ($F=12.039$, $p=0.006$). Finally, during the seated tasks, there were no significant effects of DBS ($F=1.224$, $p=0.297$; $F=1.653$, $p=.231$) or medication ($F=0.294$, $p=0.601$; $F=0.803$, $p=0.394$) in regards to saccade latency or amplitude, respectively.

DISCUSSION

The purpose of this study was to determine the independent and combined effects of levodopa and DBS on measures of turning performance and related oculomotor performance in PD. In summary, both DBS and levodopa had a profound effect on turning duration as well as the number of saccades performed during the turn. DBS also improved MDS-UPDRS III scores and gait parameters (velocity and stride length), while levodopa did not. Secondly, the amplitude and velocity of the first saccade performed during the turn was increased significantly by DBS but was not improved with levodopa. Finally, the inter-segmental latencies between the eyes, head, trunk, and feet were decreased by DBS but not by levodopa, however this effect was largely eliminated when we controlled for turning speed.

To the best of our knowledge, this is the first study to address the therapeutic effects of DBS on turning in PD as well as the first to measure the effects of DBS on oculomotor function during a functionally relevant task. Our findings are consistent with previous research that shows an improvement in motor symptoms, particularly gait, with DBS. DBS was effective in increasing gait velocity by approximately 13% and stride length by approximately 10% in our study. Our findings of improved turning duration and concomitant improvements in oculomotor performance during turns are novel yet anticipated based on the efficacy of DBS in improving saccade function and gait in previous studies. Previous work in our lab (Lohnes and Earhart, 2011) showed that persons with PD turn slower and with more steps than healthy, age-matched controls, and that turn performance is correlated with oculomotor function such that individuals who perform later, larger, faster, and fewer saccades turn better. Similarly, data herein suggest that improved oculomotor performance associated with DBS is correlated with

improved turn performance. Neither of these studies, however, address a cause-and-effect relationship between oculomotor and turn performance. Since the oculomotor system initiates the turning sequence, we hypothesize that saccades occurring before and early in the turn sequence may affect subsequent turning kinematics, but it is also plausible that improvements in oculomotor function (as measured herein) are driven by improved turn performance. For example, a decrease in the number of saccades performed during the turn may be an effect of shortened turn duration and increased turn speed. This is evidenced by the data in that the number of saccades performed per second was greater with DBS ON compared with DBS OFF (2.34 saccades/sec vs. 1.94 saccades/sec, respectively). Thus, if our subjects had turned for the same length of time with DBS both OFF and ON, they would have performed more saccades in the same timeframe with DBS ON. Beyond the role of the oculomotor system, other factors are also likely to contribute to the improved turn performance noted with DBS. DBS improved overall MDS-UPDRS-III scores as well as bradykinesia, rigidity, and PIGD, measures that are all independent from saccade function but could affect turn performance. DBS also produced a shortening of intersegmental latencies (eye-head, eye-foot, head-trunk). Again, while DBS-related improvements in saccade function could have contributed to this, the decreased intersegmental latencies are most likely due to the increased speed with which subjects were able to complete the turns during DBS stimulation, hence shortening all aspects of the turn sequence. This hypothesis is supported by the fact that intersegmental latencies were similar when we controlled for the duration of the first gait cycle.

Levodopa was not nearly as effective as DBS in improving gait and turning. Turning duration and the number of saccades performed during the turns were improved with medication, albeit to a lesser extent than with DBS, while gait velocity and stride length, saccade amplitude and velocity, and turn sequence variables were unaffected by levodopa. Subjects in this study did display a top-down rotation sequence in regards to the timing of rotation onset of the various segments (eye-head, head-trunk, trunk-foot), but it is possible that the turning sequence used herein is still more "en bloc" than the pattern utilized by healthy controls. The presence of a top-down rotation sequence in the current study is in contrast to Hong & Earhart[8,19] which reported en bloc timing in a group of non-DBS PD patients, and are in line with Anastasopoulos et al.[13] who observed a top-down rotation sequence in a sample of mild PD patients. On the other hand, our study was similar to Hong & Earhart[19] in that these timing characteristics did not change when levodopa was taken. Conclusions related to the effects of levodopa in the present study must be interpreted cautiously as these may be explained by a dosing issue, as MDS-UPDRS III scores also did not improve with levodopa. Although we used clinically prescribed doses of levodopa, these doses are most likely much less than the maximally effective dose, as is often the case with DBS patients. Following DBS implantation and resulting motor improvement, levodopa doses are often reduced significantly to limit dyskinesias. As a result, the failure of levodopa to improve many of the oculomotor and turning measures herein may be due to the limited doses used.

While DBS improved walking and turning performance, it did not improve saccade performance during the seated saccade task, which is contrary to previous research showing beneficial effects of DBS on saccade performance. There were,

however, some methodological differences between ours and previous studies. Previous studies examined the effects of DBS on both voluntary (memory guided saccades, anti-saccades) and reflexive saccades using protocols where the saccade was cued visually (either the appearance of a lateral target or the disappearance of the central target). In our study, we used an auditory cue to initiate the saccade. Furthermore, our targets were static in that they remained in view for the duration of the test. In contrast to memory-guided or anti-saccade paradigms where the subjects perform saccades to a target-less location, our subjects made saccades toward a static visual target which may have served as an external cue that facilitated performance.

Limitations

There are a few limitations related to this study. First, the use of clinical levodopa doses was intended to increase the external validity of our study, but it is possible that in doing so we missed potential therapeutic effects that would otherwise have been seen with a maximally effective dose. As such, the reported effects of medication on turn and oculomotor performance should be taken with caution and should not be extrapolated beyond persons with PD and STN-DBS. It is likely that levodopa dosing is higher in persons with PD but without DBS, and thus levodopa may have a more profound effect on turning and related oculomotor performance than reported herein. It is also possible that the effect of medication on persons with DBS differs from the effect of medication on those without DBS. Further, we used a 12 hour levodopa withdrawal period before OFF medication testing and a 45 minute rest period between DBS stimulator changes and data collection. A 12 hour medication withdrawal period may have only resulted in a partial off-medication state but due to the study design, a longer withdrawal period was

not practical as full washout can take multiple days. In regards to DBS, it has also been shown that 90% of changes in motor performance (UPDRS-III scores) occur within 45 minutes of DBS being turned off, and changes after DBS is turned on occur more quickly, with 90% of changes in motor performance occurring in 15-20 minutes.[41] While our washout periods may not have resulted in full OFF or ON states, we feel the resulting medication and DBS conditions are representative of clinical conditions. Another limitation of this study is that we did not consider specific electrode placement within the STN when selecting participants, resulting in some likely heterogeneity among subjects in regards to stimulation localization within the STN. While saccade-related neurons are clustered in the ventral STN,[41,42] PD motor symptoms such as gait and balance appear to respond similarly to dorsal and ventral STN DBS.[43] As such, functional tasks that significantly involve the oculomotor system (e.g. turning) may be best ameliorated by DBS in the ventral STN. Selecting sub-groups of patients based on electrode placement (i.e., dorsal vs. ventral STN) may offer further understanding of the effect of STN DBS on oculomotor function during turning, but cognitive function must be considered in such studies as response inhibition has been shown to decrease with ventral STN DBS.[44] Finally, during the seated saccade task, we used a novel paradigm with static targets and an auditory cue. This may explain the lack of effect of both DBS and medication on saccade amplitude and latency.

Conclusions/Implications

In conclusion, STN DBS is largely effective in improving both straight walking and turning performance in PD, including increases in saccade amplitude and a decreased number of saccades required to complete the turn. These results add to the growing

number of known benefits offered by DBS, and add to the functional applicability of previous research that has found beneficial effects of DBS on saccades and gaze during seated tasks. Future work may aim to define optimal DBS electrode placement for patients whose primary motor complications include freezing during turning, or a history of falls during turns.

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Figure 6. Representative data from individual turn trials showing eye-in-head, head-over-ground, and foot-over-ground rotations about the z (vertical) axis. Left column = DBS OFF; Right column = DBS ON; Top row = Meds OFF; Bottom row = Meds ON. All turns are to the right and are initiated with the right foot. Both DBS and levodopa improve turn duration and reduce the number of saccades required to complete the turn.

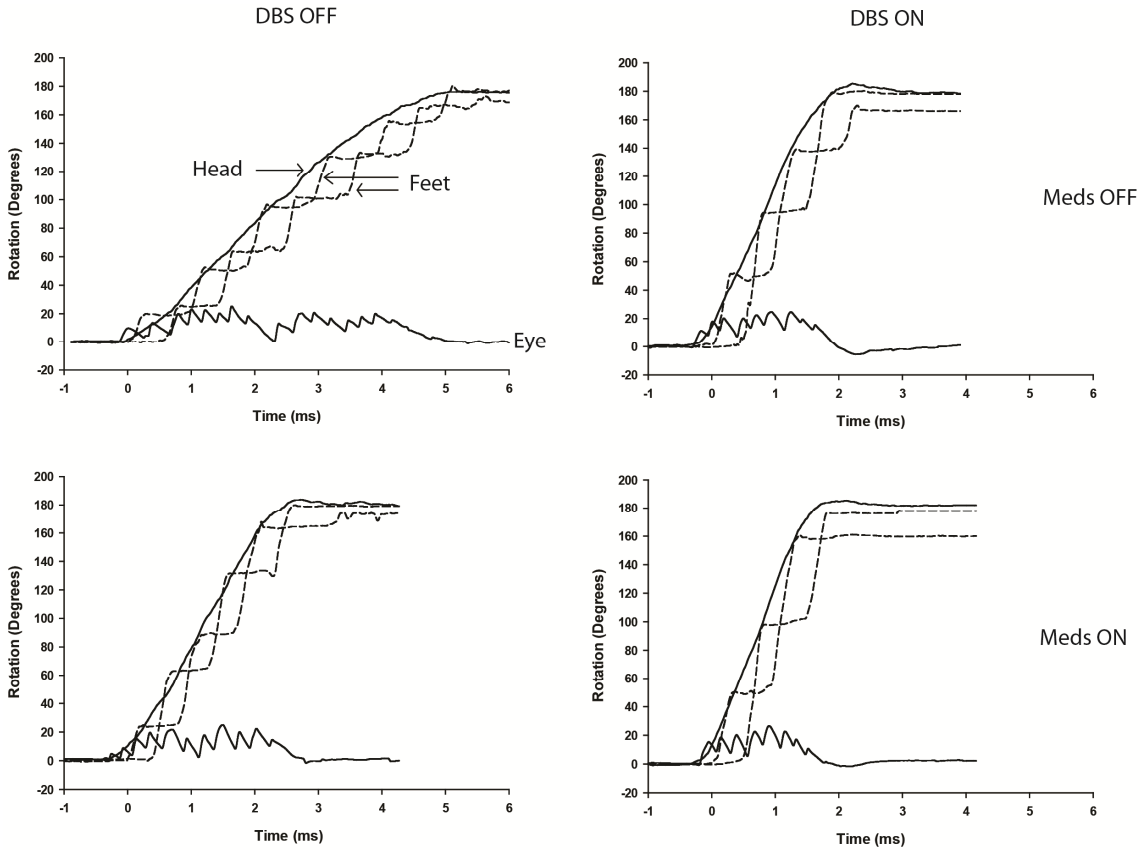
DBS OFF
DBS ON
Head
Feet
Eye
Meds OFF
Meds ON
Rotation (Degrees)
Time (ms)

Figure 7. Effects of DBS and levodopa on oculomotor performance during turns. *Significant main effect of DBS ($p<0.05$); † Significant main effect of Medication ($p<0.05$); ‡ Significant interaction between DBS and Medication ($p<0.05$)

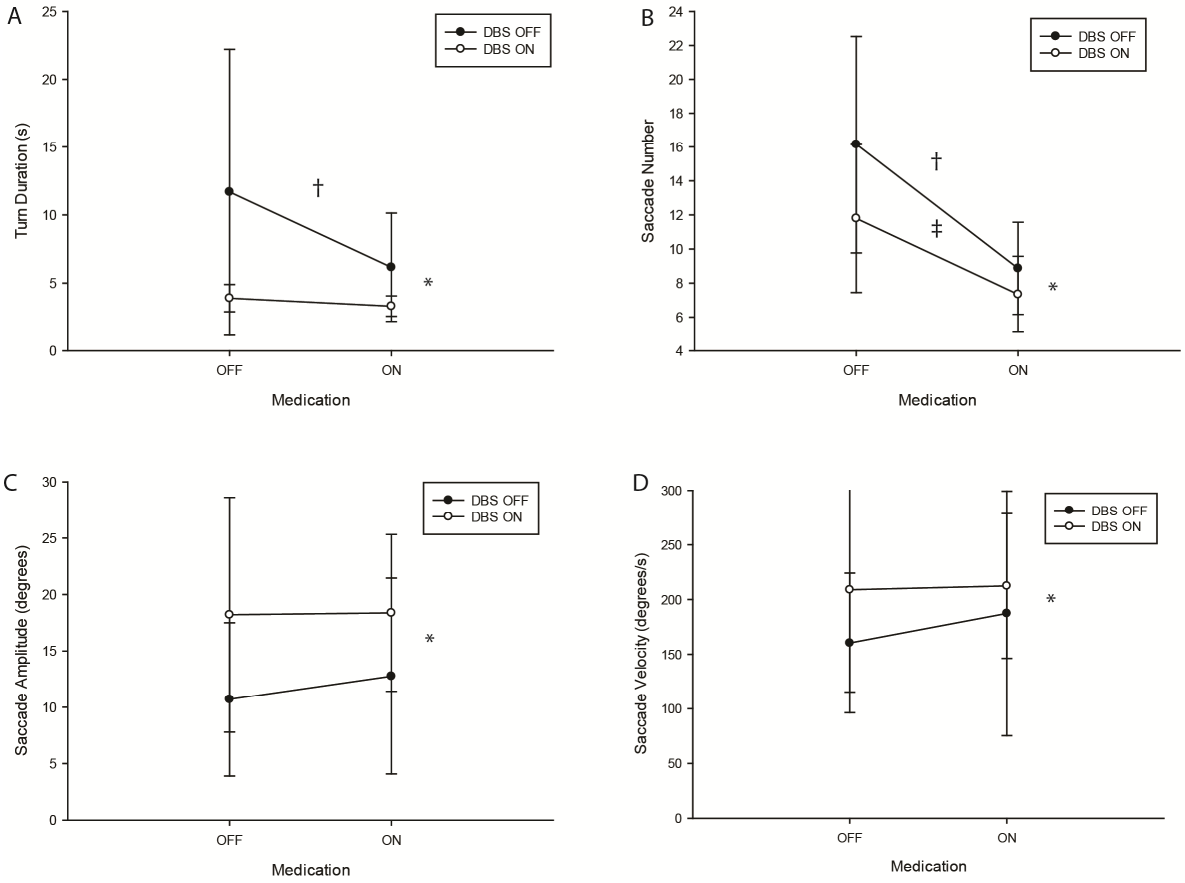
A
Turn Duration (s)
DBS OFF
DBS ON
†
*
OFF
ON
Medication
B
Saccade Number
DBS OFF
DBS ON
†
‡
*
OFF
ON
Medication
C
Saccade Amplitude (degrees)
DBS OFF
DBS ON
*
OFF
ON
Medication
D
Saccade Velocity (degrees/s)
DBS OFF
DBS ON
*
OFF
ON
Medication

Table 1. Subject Demographics

Age (years)	66.6 ±7.1			
Male/Female	8/3			
Disease Duration (years)	15.6 ± 6.6			
Hoehn & Yahr Stage (OFF/OFF)	2.6 ± 0.6			
Freezing of Gait Score	5.8 ± 4.4			
# of Freezers *	3			
Disease Severity	DBS OFF/ Meds OFF	DBS ON/ Meds OFF	DBS OFF/ Meds ON	DBS ON/ Meds ON
MDS-UPDRS III	45.81 ± 10.0	32.5 ± 8.8	43.0 ± 9.5	30.2 ± 6.0

Values are means ± standard deviations.

* Reported freezing at least once/week on item 3 of the FOG-Q.

Table 2. GAITRite and Seated Saccade Task Data

	DBS OFF		DBS ON	Mean ± SD
GAITRite Data				
Gait Velocity (cm/s)				
Meds OFF	94.9 ± 30.1		106.8 ± 20.5	**100.8 ± 25.3**
Meds ON	93.9 ± 23.6		106.5 ± 16.5	**100.2 ± 20.1**
Mean ± SD	**94.4 ± 26.9**	*****	**106.6 ± 18.5**	
Stride Length (cm)				
Meds OFF	103.8 ± 25.2		113.4 ± 17.9	**108.6 ± 21.6**
Meds ON	104.2 ± 20.4		115.7 ± 15.7	**110.0 ± 18.1**
Mean ± SD	**104.0 ± 22.8**	*****	**114.6 ± 16.8**	
Seated Saccade Task				
Saccade Latency (ms)				
Meds OFF	335.8 ± 98.0		335.0 ± 104.0	**335.4 ± 101.0**
Meds ON	335.3 ± 89.3		355.6 ± 95.5	**345.5 ± 92.4**
Mean ± SD	**335.5 ± 93.7**		**345.3 ± 99.8**	
Saccade Amplitude (°)				
Meds OFF	15.0 ± 2.1		16.0 ± 1.3	**15.49 ± 1.7**
Meds ON	15.8 ± 2.5		16.3 ± 3.2	**16.02 ± 5.7**
Mean ± SD	**15.4 ± 2.3**		**16.1 ± 2.2**	

Values are means ± standard deviations.

* Significant main effect of DBS ($p<0.05$)

Table 3. Kinematic Performance Data

	DBS OFF		DBS ON	Mean
Eye-Head Latency (ms)				
Meds OFF	320.3 ± 275.6		168.9 ± 133.6	**244.6 ± 204.6**
Meds ON	261.2 ± 143.5		151.9 ± 102.8	**206.6 ± 123.2**
Mean ± SD	**290.8 ± 209.6**	*****	**160.4 ± 118.2**	
Head-Trunk Latency (ms)				
Meds OFF	71.5 ± 115.1		11.8 ± 48.2	**41.7 ± 81.6**
Meds ON	55.7 ± 62.6		27.4 ± 62.7	**41.6 ± 62.6**
Mean ± SD	**63.6 ± 88.8**	*****	**19.6 ± 55.5**	
Eye-Foot Latency (ms)				
Meds OFF	667.2 ± 438.1		334.5 ± 289.8	**500.9 ± 364.0**
Meds ON	569.2 ± 527.3		248.7 ± 174.3	**409.0 ± 350.8**
Mean ± SD	**618.2 ± 482.7**	*****	**291.6 ± 232.1**	
N. Eye-Head Latency (% First Gait cycle)				
Meds OFF	306.8 ± 179.4		247.4 ± 277.4	**277.1 ± 228.4**
Meds ON	269.0 ± 96.4		190.2 ± 92.2	**229.6 ± 94.3**
Mean ± SD	**287.9 ± 137.7**		**218.8 ± 184.6**	
N. Eye-Foot Latency (% First Gait cycle)				
Meds OFF	48.8 ± 33.5		59.9 ± 76.7	**54.3 ± 55.1**
Meds ON	59.0 ± 47.0		33.2 ± 24.8	**46.1 ± 35.9**
Mean ± SD	**54.4 ± 40.3**		**46.51 ± 50.8**	
N. Head-Trunk Latency (% First Gait cycle)				
Meds OFF	7.5 ± 12.1		2.7 ± 6.6	**5.1 ± 9.3**
Meds ON	7.3 ± 8.0		3.6 ± 6.0	**5.5 ± 7.0**
Mean ± SD	**7.4 ± 10.0**	*****	**3.2 ± 6.3**	
N. Head-Foot Latency (% First Gait cycle)				
Meds OFF	18.2 ± 29.2		35.1 ± 49.9	**26.6 ± 39.6**
Meds ON	30.5 ± 40.4		15.7 ± 22.3	**23.1 ± 31.4**
Mean ± SD	**16.9 ± 35.0**		**22.3 ± 33.0**	

Values are means ± standard deviations.

* Significant main effect of DBS ($p<0.05$)

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Chapter 5: Conclusion

Summary of Findings

Previous research has shown that individuals with PD suffer from bradykinesia that affects both the limbs and eyes. Further, these patients also have difficulty switching between motor patterns which results in functional impairments such as turning difficulty and freezing of gait. Previous work also demonstrated direction switching impairments in the upper extremity and during postural control tasks, but not yet in the eyes and lower limb. In Chapter 2, we noted that the ability of individuals with PD to switch between movement orientations is in fact decreased during lower limb and oculomotor tasks, but that bradykinesia appears to be the underlying cause of this impairment. Further, switch times correlated between eyes and lower limb, suggesting parallel declines in switching ability in the eyes and lower limb.

It is well known that the turning difficulty experienced by persons with PD is characterized by a more "en bloc" turning sequence. However, it was previously unclear how eye movement function contributed to this impairment. In Chapter 3, we provided the first evidence that saccadic eye function is impaired in PD during turning and that the amount of oculomotor dysfunction is correlated with turn performance.

Improving turning in patients with PD may reduce the incidence of falls and injuries, yet the effect of interventions on turning is not understood. As levodopa has the potential to improve saccades and DBS is widely accepted to do so, it was hypothesized in chapter 4 that such interventions may improve turning as well since turns are initiated with a saccade. Indeed, our findings show that levodopa improves turning duration, but

not related oculomotor function, while DBS has a strong influence on turning performance and the related oculomotor strategy.

Significance and Clinical Implications

Taken together, these studies corroborate previous research that voluntary saccade function is impaired in PD, and expand on these finding by delineating how dysfunctional saccades affect a functional task (turning). Studying the oculomotor system and related dysfunction in PD has offered us a better understanding of basal ganglia function and dysfunction. As the oculomotor system is simple and largely understood, it is well suited for studying behavior in a controlled and systematic manner, free from many confounders often involved in the study of more complex motor symptoms. However, many conclusions drawn from oculomotor research lack apparent or immediate therapeutic relevance and may not have implications that will improve function and quality of life in persons with PD. In contrast, our findings bridge the gap between oculomotor impairments and systemic motor function and may have implications for clinical care.

One of the main implications of this research is that oculomotor dysfunction in PD correlates well with turning performance. While identifying a cause and effect relationship was beyond the scope of this work, our shown association between saccades and turning provides rationale for targeting the oculomotor system with therapeutic interventions and rehabilitation. For example, it is well known that both internally and externally generated cues can improve motor function in PD. Visual cues, such as lines on the floor, increase stride length and velocity during gait, and auditory cues have shown similar benefits.[1-5] Cues are also efficacious in ceasing episodes of freezing.[6] In light of this, and since saccade function is largely maintained in the presence of visual triggering,

the possibility of cueing the oculomotor system to improve turning performance is apparent. Since individuals with PD initiate the turn sequence with a smaller saccade than age-matched controls, a potential cueing strategy could include a large saccade to a lateral target before initiating the turn sequence. This may elicit a more-top down rotation sequence.

A second implication of this research relates to the importance of understanding how medications and DBS affect the whole spectrum of functional impairments in PD. This work adds to this understanding by providing insights into the effects of these two interventions on turning. While symptoms such as tremor, forward gait, and non-motor complications may dominate for some patients, FOG and TD may be chief complaints of others. The ability to tailor interventions on a patient-by-patient basis is paramount, but science is still working toward a full understanding of how each intervention affects PD, both positively and negatively. Our results add rationale for STN DBS as therapy for patients whose symptoms include TD. Further, our results suggest a potential mechanism for the observed improvements in turning through facilitation of saccades.

Limitations

One limitation of this work is that it is correlative in nature. While we have shown that saccade function relates to turning performance and that DBS improves both, our results do not tell us if oculomotor control independently controls turning performance nor whether improving oculomotor control improves turning independent of other factors. Secondly, turning in these studies was limited to in-place turns as opposed to turns during gait. It is possible that differences exist between in-placing turning and turning in the midst of walking. Finally, all observations were performed in a laboratory

environment and participants were aware they were being monitored. It is possible that motor strategies used outside the laboratory may differ from those measured within the laboratory.

Suggestions for Future Research

The influence of the oculomotor system on functional tasks is still poorly understood. While we demonstrate herein that saccade function is correlated with turn performance, we do not provide sufficient evidence to support causality. Therefore, future studies should aim to answer whether saccades that occur during turning do in fact affect turn performance. This may be achieved by manipulating the parameters of the initial saccade such as the amplitude or timing relative to turn onset. Further, locomotor tasks such as obstacle navigation, crossing barriers, and walking through narrow passages often invoke freezing in persons with PD. It is possible that the oculomotor strategy used during these situations differs in PD, perhaps by focusing attention on a different part of the environment or using a temporal scanning sequence that differs from controls. If such were the case, it would again be interesting to modify subjects' oculomotor strategy and measure subsequent changes in task performance.

Secondly, the effect of rehabilitative interventions, such as visual cueing, on turning has not yet been addressed. Since cueing has shown great promise in improving locomotion in PD, a study of the effects of oculomotor cueing on turning is warranted. This could include both externally generated visual cues as well as internally generated cues such as thinking about making a larger saccade prior to turning.

Finally, since neurons related to oculomotor function are largely sequestered in the ventral region of the STN, research into the differential effects of dorsal vs. ventral

stimulation of the STN on oculomotor performance and subsequent turning performance would be beneficial. Such data could provide additional rationale for specific electrode placement within the STN.

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