Summer 8-15-2016

Motor Adaptation and Automaticity in People with Parkinson's Disease and Freezing of Gait

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by

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A dissertation presented to the
Graduate School of Arts & Sciences
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

August 2016
St. Louis, Missouri

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Acknowledgments

The work in this dissertation was supported by a variety of sources. I was primarily supported by the Clinical Research Training Center TL1 pre-doctoral program, which is part of an institutional award from the National Institutes of Health (UL1TR00448, sub-award TL1TR000449). I was also awarded small grants for research and travel from the Parkinson's and Movement Disorders Foundation and Parkinson's Disease Foundation. Additional support came from the Program in Physical Therapy at Washington University, Health South Neurology, the Greater St. Louis Chapter of the American Parkinson's Disease Foundation (APDA), and the APDA Center for Advanced PD Research at Washington University. I am grateful for all the agencies and funding sources involved in this work.

I was fortunate to have had outstanding mentorship and guidance from Dr. Gammon Earhart throughout my doctoral education. Dr. Earhart was instrumental in introducing me to the field of Parkinson's disease research, helping me to design original research projects, and allowing me to conduct and carryout the work independently. Most importantly, Dr. Earhart has been an extremely attentive mentor and an advocate for me to maximize my training experience. I would also like to acknowledge the members of my committee who have devoted their time to and expertise to help improve this work, as well as the faculty of the Program in Physical Therapy for their roles in furthering my education.

The other members of the Locomotor Control Lab, both past and present, also deserve recognition for not only their contributions to helping me design and conduct these studies, but also for making the lab a rewarding place to come to work every day. To add, I thank my peers in the Movement Science Program who formed a positive and supportive network in which to share ideas and experiences.

Finally, I wish to recognize my parents, who always supported me in furthering my education, my wife Sarah, a fellow neuroscientist with whom I could always work through my struggles with research, and my newly born son Theodore, who is a constant reminder to slow down and enjoy the world around you.

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August 2016

Dedicated to Mom, Dad, Sarah, and Theodore.

Abstract

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Doctor of Philosophy in Movement Science

Washington University in St. Louis, 2016

Professor Gammon Earhart, Chair

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by cell death in the substantia nigra pars compacta, resulting in motor symptoms of tremor, rigidity, bradykinesia and gait impairment. Freezing of gait (FOG) is one serious gait disturbance, characterized by a transient inability produce effective stepping during walking and turning, and affects roughly half of people with PD at some point during their disease. Despite the ongoing research on the behavioral, neurological, and cognitive characteristics of people with FOG (PD+FOG), the mechanisms underlying freezing are still poorly understood. The overall aim of this work was to further investigate motor behavior in PD+FOG to provide insight into its potential mechanisms. The first experiment investigated possible cerebellar dysfunction in PD+FOG by examining visuomotor adaptation, a well-known cerebellar-dependent process. We found that there were no differences in reaching or walking adaptation between freezers and non-freezers, however non-freezers exhibited smaller after-effects compared to freezers and healthy older adults. Furthermore, adults with PD, as well as older and younger adults adapt walking patterns slower than reaching patterns, indicating walking is a more complex task

requiring greater sensorimotor processing to modify. Overall, this study showed that cerebellar function, in terms of its role in sensorimotor adaptation, is relatively preserved in PD and FOG.

In the second experiment, we examined motor automaticity of saccadic eye movements and reaching. Reduced automaticity is a likely motor-cognitive mechanism that contributes to freezing behavior, however automaticity in other motor systems has yet to fully described. Using an anti-saccade task, we found that PD+FOG participants were slower to respond to both automatic and non-automatic eye movements, and had increased saccade velocity variability compared to PD-FOG and controls. These changes were not related to disease severity or general cognition. In contrast, both PD groups were slower to execute (greater latency) reaching movements during both pro- and anti-reaching, but no freezer non-freezer differences were noted. PD+FOG reached with lower peak velocity compared to older adults but were similar to PD-FOG during both automatic and non-automatic conditions. These data show that changes in automaticity and control exist outside locomotor centers, indicating freezing may be a global motor disturbance. Altogether, the work in this dissertation furthers our knowledge on motor control in PD+FOG and provides additional evidence that freezing affects non-gait motor function.

Chapter 1: Background, rationale, and specific aims

1.1 Parkinson's disease

Affecting close to 1% of adults over the age of 65, Parkinson's disease (PD) is the second most common neurodegenerative disorder[1]. Degradation of neurons in the substantia nigra pars compacta (SNpc) is the neuropathological hallmark in PD, which leads to increased inhibitory outflow from the basal ganglia (BG) and significant motor dysfunction[2]. Other pathological indications of PD include aggregation of the brain protein α-synuclein as well as degradation of non-dopaminergic neurotransmitter systems, such as the cholinergic and serotonergic system[3,4]. Clinically, PD is characterized by primary motor signs of tremor, bradykinesia, rigidity, and postural instability/gait impairment, which worsen throughout the course of the disease. However, various combinations of underlying pathophysiologic changes may result in many different PD phenotypes, with a range of motor, cognitive, and autonomic problems. Overall, these changes lead to declines in mobility[5], increased risk of injury to due falling[6], and overall poorer quality of life[7,8]. In addition to the obvious burden endured by the patient[9] and any caregivers[10], the economic burden to the U.S. healthcare system was estimated to be eight billion dollars in 2010[1].

Parkinsonian gait is characterized by reduced stride length, wide base of support, flexed posture, and reduced arm swing[11,12]. Gait impairment is common among people with PD and is often reported at early in the disease[5]. Since gait and balance are strongly associated with proper mobility and function, they may represent not only the onset of disability in PD but also serve as an important locus of treatment and rehabilitation[5,13].

1.2 Freezing of gait

Freezing of gait (FOG), defined as a "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk"[14,15], is a serious gait disturbance in PD. The estimated prevalence of FOG in people with PD is variable, but a recent 12-year longitudinal study found that roughly half of the cohort experienced FOG at some point during the study time[16]. A typical freezing episode is characterized by small-amplitude, high-frequency sub-movements and can last anywhere from a few seconds to over a minute. Freezing can occur during straight-line walking, but is also common during more complex gait maneuvers such as turning, initiation, and walking through narrow spaces[14,17,18]. In general, freezers have more asymmetric gait, both with respect to cadence and step length, as compared to non-freezers, particularly during complex gait tasks such as turning[19-21]. These biomechanical alterations translate to situations that compromise balance and stability and lead to increased risk of falls[22,23], making FOG a very disturbing and disabling condition. Unfortunately, FOG is not adequately treated with dopaminergic medication[14,24] and deep brain stimulation (DBS) surgery[25]. Therefore, the overall goal of this dissertation was to study potential mechanisms associated with FOG in an attempt to contribute to the body of knowledge surrounding this poorly understood phenomenon (see Section 1.5 for additional rationale). Several hypotheses and mechanisms have been proposed to explain FOG, supported by both behavioral and neuroimaging evidence. This dissertation focuses on two potential mechanisms of FOG: 1) cerebellar dysfunction and 2) impaired automaticity.

One feature of FOG that has gained recent attention is that it is not exclusively localized to gait and is observable during other tasks. For instance, freezing of the upper-limb, which appears as small and variable amplitude movements of the hand and arm, is a well-documented feature in those who experience FOG and less common in those who don't experience FOG[26-29]. Festination and freezing has also been reported during speech tasks[30,31]. Taken together, these

studies support the notion that freezing may be a global feature of motor impairment in people with Parkinson's disease and does not simply affect walking. Therefore, an over-arching goal of this dissertation was to explore how freezing is associated with motor control in various effectors, such as the lower limbs (e.g. walking), upper limbs (e.g. reaching), and eye (e.g. saccades).

The role of the cerebellum in PD as both an area of dysfunction and compensation is becoming increasingly more appreciated. Based on many recent studies, it is understood that the cerebellum is implicated in the pathophysiology of many of the cardinal symptoms of PD (tremor, rigidity, akinesia, postural instability) and potentially non-motor symptoms as well[32]. However, these reports are taken from heterogeneous groups of PD, which may include both freezers and non-freezers. Recent neuroimaging studies showed that features of cerebellar structure and function may distinguish freezers from non-freezers [33-36]. For instance, Youn et al. found decreased structural connectivity (i.e. white matter tracts) between the cerebellum and the pedunculopontine nucleus (PPN) in a group of freezers compared to non-freezers[36]. Furthermore, Fling et al. found abnormal functional connectivity between the supplemental motor area (SMA) and the cerebellar locomotor region (CLR) at rest in freezers compared to non-freezers and healthy control counterparts[33]. Together, these data indicate the cerebellum may be specifically affected in freezers. However, these studies tended to focus on a small region, the CLR, which is located on the midline of the cerebellum near the fastigial nuclei[37]. One question that arises then is are freezers also impaired during other cerebellar-related tasks that would engage larger regions of the cerebellum? One way to test this would be to examine motor adaptation, a common laboratory task that is known to require healthy cerebellar function. Therefore, the objective of Aim 1 of this dissertation was to use motor adaptation tasks to assess cerebellar-dependent motor behavior in PD-FOG and PD+FOG compared to neurologically healthy adults.

1.3 Motor adaptation

Sensorimotor adaptation is a process by which a motor output is recalibrated on a trial-by-trial basis using error feedback[38,39]. The key features that distinguish adaptation from other types of motor learning are that it: 1) requires graded error feedback (magnitude and direction) and 2) is a transient phenomenon; the original motor pattern returns soon after the perturbation is removed. There are several ways to perturb the sensory environment to study adaptation in the laboratory, such as using prism lenses, force-fields, moving platforms (e.g. treadmills), and virtual environments. While there may be differences in the effect each perturbation has on specific attributes of adaptation, a similar pattern is observed across an array of studies: 1) large errors occur after introducing the perturbation, 2) movement errors are gradually reduced to normal performance after 10-15 trials, typically resembling an exponential decay function 3) large errors (after-effects) in the opposite direction occur following removal of the perturbation, indicating adaptation was stored in the nervous system, and 4) movement errors are gradually reduced until normal performance is regained in the absence of the perturbation. An example of typical motor adaptation performance is shown in Figure 1.1. Aim 1 of this dissertation focuses on visuomotor adaptation using prism lenses as a way to understand how the brain changes movements based on shifts in visual perception. It is worth noting that there is new evidence that people with PD do not adapt or retain newly learned locomotor patterns following walking on a split-belt treadmill[40]. Locomotor adaptation using a split-belt treadmill paradigm still represents a movement-by-movement change in motor pattern and therefore represents a parallel way to study motor adaptation in PD and FOG (see Chapter 5 and Appendix for further discussion).

Healthy individuals rapidly adapt upper limb[41-43], lower limb[44], and multi-limb movements like walking[45,46] to accommodate for visual perturbations using prism lenses. In contrast, people with cerebellar lesions neither adapt nor show any after-effects[41,46,47], showing the cerebellum is

intricately involved in adaptation and subsequent retention of newly adapted movement patterns in response to prism glass perturbations. The effects of PD on visuomotor adaptation are unfortunately equivocal. Different studies show normal adaptation and normal after-effects[48], normal adaptation but decreased after-effects[49], and slowed adaptation with decreased after-effects [47,50] in people with PD. It reasons that the basal ganglia would be involved in visuomotor adaptation, given their theoretical role in movement selection and inhibition[2,51]. In support of this idea, some neuroimaging data showed basal ganglia activation during the early phases of both adaptation and post-adaptation[52]. Two factors may explain these mixed results regarding the impact of PD on adaptation: 1) use of small and heterogeneous samples of PD and 2) inconsistent protocols across studies (e.g. throwing vs. reaching, various number of trials attempted). Overall, the relationship between PD and visuomotor adaptation remains unclear and requires further investigation.

In addition to neurological disease or injury, normal aging may impact visuomotor adaptation. Here, the data are clearer, showing that adaptation is slower but after-effects are normal or even larger than normal in older adults compared to younger adults[53-55]. It is therefore necessary to distinguish two phases of adaptation: strategic control and spatial recalibration. Strategic control refers to the first several trials after a perturbation is introduced during which the participant uses cognitive strategies to quickly reduce errors. After this is accomplished, spatial recalibration takes over during subsequent trials when errors are minimal[56]. Here, the new sensorimotor relationship is strengthened with each successful trial. The cerebellum is involved during both phases, however with distinct cerebellar regions participating in each phase [57-59]. During strategic calibration, the posterior lobules and dentate nucleus are activated, whereas both anterior and posterior lobules are activated during spatial recalibration. Thus based on performance during an adaptation task, one may make predictions about the location of cerebellar dysfunction in a given subject. Since we are unsure of the extent of cerebellar

impairment in PD+FOG, evidence of visuomotor adaptation may provide useful information to address this question. Therefore, in Aim 1, we sought to examine the relationship between FOG, PD and motor task on subsequent visuomotor adaptation.

Another way to study adaptation is to introduce mechanical perturbations that result in discordances in proprioceptive and kinesthetic feedback. A split-belt treadmill is one such apparatus that is widely used to understand locomotor adaptation. With this device, the experimenter can manipulate the speed of each belt (and thus each leg) independently, thus inducing asymmetries in walking step length and timing. Similar to visuomotor adaptation, healthy people can normalize their walking patterns and exhibit after-effects following adaptation[60]. There have been several studies investigating locomotor adaptation in people with PD, which all show that people with PD are also able to adapt similar to healthy older adults[61,62]. More refined comparisons of freezers and non-freezers demonstrate that freezers have greater variability[62] and may adapt at a slower rate[40] compared to non-freezers. Since the cerebellum is also strongly linked to locomotor adaptation[63], cerebellar dysfunction may also underlie locomotor adaptation impairment in PD+FOG.

Turning is a complex walking task that involves asymmetrical stepping, independent head control, and regulation of body center of mass[64]. Based on these constraints, freezing is much more common during such complex gait tasks[15,18]. A method to simulate turning in the laboratory is to walk on a stationary rotating surface, which will also induce an adaptive process within the locomotor system[65,66]. The interesting feature of this adaptation paradigm is the after-effect: following stepping on a rotating surface, the participant walks in curvilinear paths when attempting to walk in a straight line. This podokinetic system, referring to the relative position of the foot and trunk, has been studied to investigate how the nervous system retains newly learned locomotor patterns. Healthy older adults and people with PD show robust after-effects

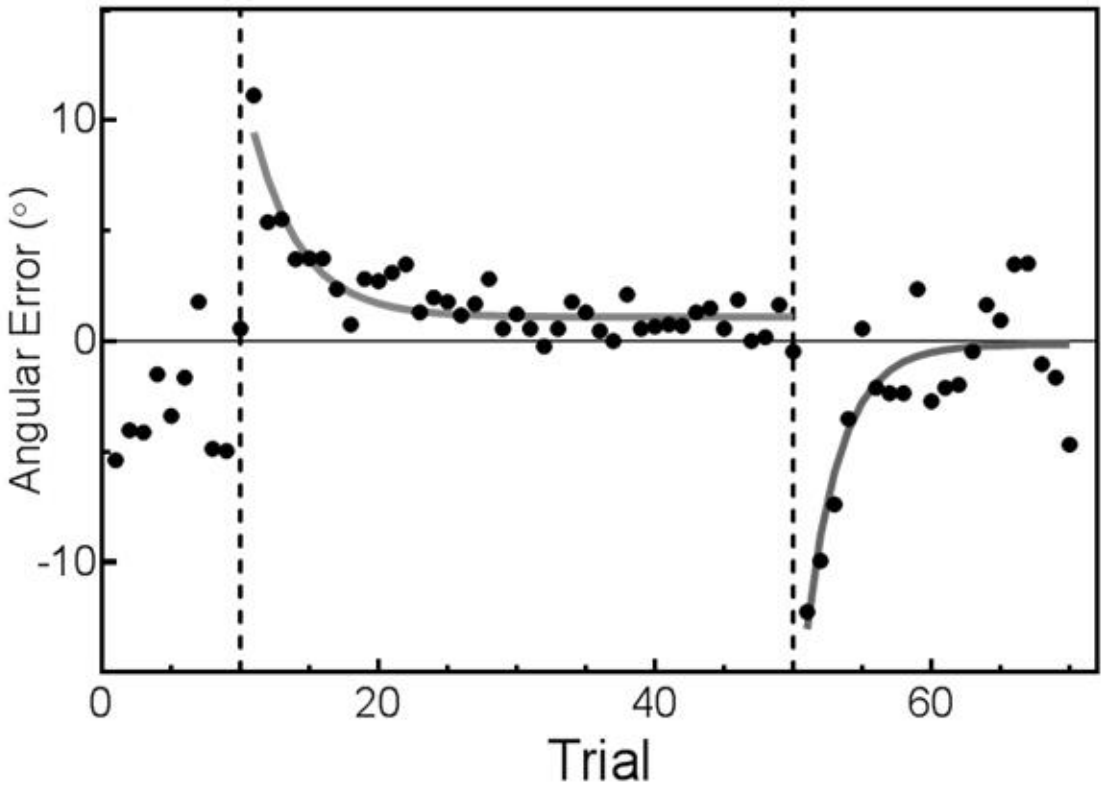
similar[67], however patients with cerebellar lesions exhibit reduced after-effects[68]. This study suggests the importance of cerebellar function in the retention of locomotor patterns. It remains to be determined if the potential cerebellar dysfunction in PD+FOG affects this type of locomotor retention. Therefore, the objective of the Appendix chapter was to determine if FOG was related to the storage of locomotor patterns following podokinetic adaptation.

1.4 Motor automaticity

The second domain of motor control addressed in this work is automaticity and how it relates to freezing. One current hypothesis to explain motor arrests during gait and other tasks is a lack of automaticity. Automaticity refers to the ability to execute learned actions without significant attentional control[69,70]. One simple and common way to evaluate automaticity is with a dual-task paradigm, where a subject performs a primary task (e.g. walking) alone and while performing a secondary cognitive or motor task. If performance on the primary task is similar in both conditions, it is likely automatized given that the second attention-demanding task did not alter it (i.e. cause interference). If automaticity is lost, higher-order brain (i.e. cortical) structures are required to take over function.

Automaticity has been studied in heterogeneous groups of PD using both dual-task experiments and neuroimaging. Many studies reliably demonstrate that dual-tasking significantly impairs performance during walking, upper limb, and cognitive tasks[71-74]. In addition, an fMRI study showed that participants with PD were able to learn and automatize a new motor sequence, but it required greater cortical activation compared to healthy adults[75]. Altogether, lack of motor automaticity appears to a key feature of motor control in PD, likely due to decreased function of basal ganglia circuits.

Figure 1.1. Example of pointing errors during visuomotor adaptation. Each data point represents a trial. Solid lines are exponential best-fits to the data. Vertical dashed lines separate baseline, adaptation, and post-adaptation phases, from left to right.



One potential confound of the aforementioned studies is that they included heterogeneous sample of people with PD, and thus combined freezers and non-freezers. Thus, it is unknown to what extent freezing contributed to these results. It is postulated that a freezing episode is due in part to "resource overload", by which cortical resources are overloaded with both cognitive and movement execution demands[76]. This theory is supported anecdotally by reports that freezing occurs frequently in more complex situations (e.g. crowded places) or gait tasks (e.g. turning[14,17]) and by evidence in the laboratory that dual-tasking is more difficult for freezers than for non-freezers[77]. While dual-task conditions appear to affect gait in all people with PD [72,73,78], there may be a substantial impairment in motor-cognitive processing that is present in freezers. Recent cognitive and neuroimaging data support this, showing that freezers have impaired executive function[79-81] and decreased coupling between cognitive-motor loops within the basal ganglia[82,83]. Decreased automaticity also may explain how freezing can occur during other tasks, as mentioned above, allowing for a possibility that freezing affects the entire motor system. One system that has not been described in freezers is the oculomotor system. Control of saccadic eye movements is essential for efficient visuomotor interaction and visual processing of the environment. As such, in Aim 2 of this dissertation, we ask how automaticity differs between freezers and non-freezers, and whether the oculomotor system is affected by such changes.

1.5 Oculomotor function in PD

Eye movement control has been extensively studied in both healthy adults and adults with neurological conditions. One appeal to studying the oculomotor system is that saccades are well-characterized, simple, and stereotyped movements[84,85]. In addition, the brain circuits underlying saccadic eye movement behavior are well-defined, allowing one to make specific predictions about the brain regions affected when saccades are abnormal[86]. One common method to study the oculomotor system is the comparison of pro-saccades and anti-saccades.

For these comparisons, participants must make saccades either toward a visual target (pro-saccades) or to a symmetrically opposite location from the target (anti-saccade). Such a paradigm provides information about visually-driven saccades and internally-driven saccades[87,88]. In PD, pro-saccade latency and velocity may be slower compared to older healthy adults[89-91], however more recent studies have shown no difference in pro-saccade performance in PD[92,93]. In contrast, anti-saccades are clearly impaired in PD, where PD groups are slower to respond, hypometric, and have decreased peak velocity [92-95] relative to healthy older adults. In addition, people with PD make more frequent incorrect pro-saccade errors when performing anti-saccades [92,93]. Thus, the effect of PD on oculomotor function involves both an inability to inhibit pro-saccades and impaired ability to generate non-visually guided saccades. These data support the traditional view that the basal ganglia are involved in applying and releasing inhibition on motor circuits, which accounts for the oculomotor behavior seen in PD. One caveat to these data is that they again involve heterogeneous groups of PD, likely consisting of both freezers and non-freezers.

One way to view the pro-saccade/anti-saccade task is that it requires two levels of movement automaticity. Pro-saccades are fast (150-250 ms latencies), reflexive movements elicited from a salient visual stimulus. Since most saccades are related to visual information and require less attention to perform[96], pro-saccades are considered automatic movements. In contrast, anti-saccades are slower, voluntary movements that require inhibition of the automatic pro-saccade and execution of a non-visually guided saccade. Thus, anti-saccades may be considered less automatic because they are a less commonly executed movement. Given the difference in level of automaticity of pro-saccades relative to anti-saccades, this paradigm provides a platform by which to study motor automaticity. Therefore, in Aim 2, we again examined the effects of FOG and PD on movement automaticity, using the oculomotor system as a model for movement control.

1.6 Rationale for studies

Freezing of gait remains a poorly addressed aspect of PD phenomenology, due in part to a lack of evidence on motor control in freezers. Thus, the primary goal of this work was to investigate two aspects of motor control to understand potential mechanisms underlying freezing. Because freezing is associated with non-gait movement, we also aimed to show how freezing affects movement in other effectors, some of which have yet to be described (e.g. eye movements). Overall this work addresses current gaps in the literature and may spur future studies to test surgical and rehabilitative interventions specific to freezing.

In the first experiment (Chapter 2), we examined two groups of people with PD, freezers and non-freezers, to compare both the effect of PD and FOG on visuomotor adaptation. We predicted that the freezer group would show slower adaptation and smaller after-effects due to impaired cerebellar function directly affecting adaptation. In contrast, we hypothesized the PD-specific effects, relative to healthy older adults, would be smaller after-effects but normal adaptation as shown by Fernandez-Ruiz et al, relating to the basal ganglia's role in storage and updating of novel sensorimotor patterns[49]. In a second similar experiment (Chapter 3), we explored how the motor task, in this case reaching or walking, would impact visuomotor adaptation in older and younger healthy adults. Based on limited previous work, it is apparent that healthy individuals can adapt walking patterns to prism glasses[45,46], but it is currently unknown if this adaptation and subsequent after-effects occur at a similar rate and magnitude as during reaching. This comparison provides information into how movements of various complexity are recalibrated by the nervous system.

Finally, in a third experiment (Chapter 4), we studied automatic and non-automatic saccadic eye movements in people with PD with and without FOG. Based on the rationale that motor

automaticity is impaired in PD+FOG, we anticipated that both types of saccades would be impaired in this group relative to PD-FOG. An additional goal of this experiment was to confirm previous reports of increased latency and decreased velocity of non-automatic (voluntary) saccades in people with PD compared to healthy adults. To explore potential similarities across motor effectors, we used the same anti-saccade paradigm but instead measured reaching movements in the same groups. Altogether, this experiment provides valuable information about how freezing affects non-gait motor systems and contribute to the hypothesis that freezing is related to deficits in automaticity.

1.7 Specific Aims

1.7.1 Specific Aim 1

Assess the relationship between PD, FOG, and motor task and visuomotor adaptation.

Aim 1a: Determine the impact of FOG on visuomotor adaptation.

Hypothesis 1a: The rate of adaptation during reaching and walking with prism glasses will be reduced and the magnitude of the after-effect (post-adaptation) will be smaller in PD+FOG relative to PD-FOG.

Aim 1b: Determine the impact of PD on visuomotor adaptation.

Hypothesis 1b: The rate of adaptation during reaching and walking with prism glasses in PD-FOG will be similar to CTRL. The after-effect magnitude will be smaller in PD-FOG compared to CTRL.

Aim 1c: Determine the effect of movement task on visuomotor adaptation.

Hypothesis 1c: The rate of adaptation will be greater during reaching compared to walking. In turn, the after-effect magnitude will be smaller during walking compared to reaching.

1.7.2 Specific Aim 2

Assess the relationship between PD, FOG, motor effector and motor automaticity.

Aim 2a: Determine how FOG impacts automatic and non-automatic movements.

Hypothesis 2a: PD+FOG will have longer latencies and decreased peak velocity relative to PD-FOG during automatic and non-automatic movements.

Aim 2b: Determine how PD impacts automatic and non-automatic movements.

Hypothesis 2b: PD-FOG group will have longer latencies and decreased peak velocity relative to CTRL during non-automatic movements only.

Aim 2c: Compare automatic and non-automatic movements across motor effectors

Hypothesis 2c: Saccade and reach latencies and velocities will be correlated across all groups for automatic movements (pro-saccades and pro-reaches). Saccade and reach latencies and velocities will not be related for non-automatic movements (anti-saccade and anti-reaches).

1.7.3 Specific Aim Appendix

Aim: Determine how FOG affects retention of podokinetic adaptation

Hypothesis: The peak velocity and rate of decay of after-rotation velocity following podokinetic stimulation will be reduced in PD+FOG compared to PD-FOG and controls.

Chapter 2: Prism adaptation in Parkinson disease: Comparing reaching to walking and freezers to non-freezers

This chapter was published in May 2015 in the journal Experimental Brain Research and reprinted with permission from the publisher.

Nemanich ST, Earhart GM. Prism adaptation in Parkinson disease: comparing reaching to walking and freezers to non-freezers. Exp Brain Res. 2015;233(8):2301-10.

2.1 Abstract

Visuomotor adaptation to gaze-shifting prism glasses requires recalibration of the relationship between sensory input and motor output. Healthy individuals flexibly adapt movement patterns to many external perturbations; however, individuals with cerebellar damage do not adapt movements to the same extent. People with Parkinson disease (PD) adapt normally, but exhibit reduced after-effects, which are negative movement errors following removal of the prism glasses and are indicative of true spatial realignment. Walking is particularly affected in PD, and many individuals experience freezing of gait (FOG), an episodic interruption in walking, that is thought to have a distinct pathophysiology. Here, we examined how individuals with PD with (PD+FOG) and without (PD-FOG) FOG, along with healthy older adults, adapted both reaching and walking patterns to prism glasses. Participants completed a visually-guided reaching and walking task with and without rightward-shifting prism glasses. All groups adapted at similar rates during reaching and during walking. However, overall walking adaptation rates were slower compared to reaching rates. The PD-FOG group showed smaller after-effects, particularly during walking, compared to PD+FOG, independent of adaptation magnitude. While FOG did not appear to affect characteristics of prism adaptation, these results support the idea that the distinct neural processes governing visuomotor adaptation and storage are differentially affected by basal ganglia dysfunction in PD.

2.2 Introduction

Motor adaptation while wearing prism glasses is a form of visuomotor learning in which the nervous system modifies the relationship between a visual input and motor output, resulting in a new movement pattern. Adaptation occurs after multiple trials, during which individuals minimize the error between predicted and actual sensory consequences of a movement. In healthy individuals, adaptation after-effects, defined as movement errors in the opposite

direction of initial errors made during adaptation, occur after the visual perturbation is removed[41,47]. After-effects indicate that the novel movement pattern was stored and retained. To return to baseline performance, individuals must "de-adapt" the new sensorimotor relationship in the same iterative fashion as during adaptation[39].

The cerebellum is a critical structure for normal visuomotor adaptation[39,41,47,97-99]. Individuals with cerebellar damage require more attempts to adapt, or never adapt their movements and demonstrate little to no after-effect following exposure to prism glasses. These consistent results demonstrate that the cerebellum is required not only to update motor commands based on sensory feedback errors, but also to store transient sensorimotor patterns.

In addition to the cerebellum, other brain regions including the basal ganglia are implicated in visuomotor adaptation. Parkinson disease (PD) is a neurodegenerative disorder that affects dopaminergic cells in the substantia nigra pars compacta, resulting in excessive output of the basal ganglia. Individuals with PD show diminished after-effects following adaptation compared to healthy older adults. This suggests that to some degree, the basal ganglia influence sensorimotor recalibration or spatial realignment[49,50]. While after-effect magnitude is reduced in PD, the adaptation process itself is relatively preserved such that adaptation rates are similar between PD and healthy controls[48,50]. Collectively, the data from individuals with PD or cerebellar damage suggest that the processes of adaptation and storage are likely controlled by distinct but interconnected neural processes.

Although several studies have compared adaptation in PD to healthy controls, it remains unclear whether individuals with particular PD phenotypes differ in terms of motor adaptation performance. One particularly interesting phenotype is characterized by the presence of freezing of gait (FOG). Defined as "a brief, episodic absence or marked reduction of forward

progression of the feet despite the intention to walk"[14], FOG is a disabling phenomenon that affects 20-60% of all individuals with advanced PD[17]. Because of the characteristic deficits in limb coordination during gait, and more recently observed differences in brain activity and connectivity, FOG may be considered a distinct phenotype of PD and not simply a result of more advanced or severe disease. Specifically, people with PD who experience freezing (PD+FOG) have difficulties regulating cadence and stride length during complex walking tasks compared to those who do not experience freezing (PD-FOG)[20,100,101]. Furthermore, decreased activity in regions of the cerebellum[34] and reduced connectivity in fronto-striatal[83,102] and visual networks[103] are reported in PD+FOG. Since these networks are important in not only executing voluntary movement but also visuomotor adaptation, PD+FOG may exhibit different behavior during prism adaptation tasks compared to PD-FOG, distinct from overall deficits in motor control. However, to our knowledge, no study has examined visuomotor adaptation in PD+FOG compared to PD-FOG and healthy older adults. This comparison may provide insight into distinct neural mechanisms that are perturbed by the presence of FOG.

In this study, we compared the rates and magnitudes of prism adaptation and after-effects during two tasks (reaching and walking) to determine the effect of PD and FOG on adaptation. We chose to examine not just reaching, but also walking because it is particularly affected in PD+FOG and as such may reveal differences between PD groups that are not apparent during reaching. Based on previous results, we expected smaller after-effects during both tasks in the two PD groups compared to healthy older adults. Furthermore, because cerebellar-specific deficits in PD+FOG may also affect visuomotor adaptation, we predicted the PD+FOG group would adapt slower and have smaller subsequent after-effects during walking compared to PD-FOG and healthy older adults.

2.3 Materials and Methods

2.3.1 Participants

Thirteen individuals with PD+FOG (age 68.2 ± 6.04, 13 right-handed), 13 with PD-FOG (age 67.4 ± 11.63, 12 right-handed), and 13 healthy older adults (CTRL; age 69.0 ± 4.03, 11 right-handed) participated. In the PD groups, FOG was assessed using the New Freezing of Gait Questionnaire (NFOGQ)[104]. Freezing status is determined by freezing activity in the past month; those who answer yes, indicating that they have experienced freezing in the past month, are asked additional questions about the frequency and severity of freezing to attain a composite NFOGQ score; those who answer no, indicating they have not experienced freezing in the past month, are given a score of zero. PD-FOG and PD+FOG groups were matched for age, sex and disease severity. PD participants were recruited from the Washington University School of Medicine Movement Disorders Clinic. Each PD participant had a confirmed diagnosis of idiopathic PD according to established criteria[105]. To avoid confounding effects of dopamine on visuomotor adaptation [106], participants with PD were studied off of any anti-Parkinson medication, defined as a minimum 12-hour withdrawal. Control participants were spouses of PD participants or were recruited from a volunteer database, matched to the age and sex of PD participants, and had normal central and peripheral neurological function. Inclusion criteria for all participants were: 1) visual acuity of 20/40 or better, 2) able to walk independently, 3) able to stand and walk for 30 minutes without rest, 4) normal somatosensory function, 5) no history of vestibular disease, and 6) no evidence of dementia (Mini-mental Status Examination, MMSE ≥ 26 [107]. Participants were excluded based on the following criteria: 1) serious medical problem, 2) use of neuroleptic or dopamine-blocking drug, 3) use of drug that may affect balance, 4) evidence of abnormality from brain imaging, 5) history of other neurological injury, 6) history of ocular disease, such as macular degeneration. Motor severity was assessed in the PD groups using the Movement Disorder Society-Unified Parkinson Disease Rating Scale motor subsection III (MDS-UPDRS III). Additionally, balance impairment was quantified using the Mini-Balance

Evaluation Systems Test (MiniBEST), a measure of dynamic balance control [108]. This study was approved by the Human Research Protection Office at Washington University and is in accord with all national and international policies concerning human subject research. All individuals gave written informed consent prior to participating in the study.

2.3.2 Tasks

Participants performed two tasks while wearing eyeglass frames containing 30-diopter laterally-displacing prism lenses (Fresnel Prism and Lens Co, Bloomington, MN): a reaching task requiring participants to reach and point to a visual target, and a walking task requiring participants to walk in a straight line to a visual target.

The goal of the reaching task was to reach forward and point to a visual target as accurately as possible. Participants stood 1.6 m in front of a large piece of parcel paper hung on a wall. A 5 cm x 5 cm crosshair positioned in the middle of the paper served as the reaching target, which was vertically aligned at the participant's shoulder height. Using a laser pointer, participants were asked to keep their eyes closed and flex the shoulder of the dominant arm as quickly as possible, push the button on the laser pointer, and hold this position (i.e. do not attempt to correct). A member of the research team marked the location of the reach-and-point on the paper to provide visual feedback of its endpoint. Participants completed 70 total reach-and-point movements in three separate phases: Baseline (10 trials), Adaptation (40 trials), Post-Adaptation (20 trials). During Baseline trials, participants reached with eyes closed. After each reach-and-point, they opened their eyes to assess performance and to prepare for any needed adjustments during the next movement. During Adaptation trials, participants wore prism glasses and another pair of modified goggles that secured the prism glasses to the head and obscured vision outside of the prism lenses. Here, participants reached with eyes open. Finally, during Post-Adaptation trials, visual input was again removed (eyes closed) during the reach. The primary reason for eliminating visual input was to minimize on-line movement

correction during reaching, which is common during upper-limb movements. While participants did have visual feedback during the Adaptation phase, modification of the prism glasses minimized viewing of the arm during the reach. Thus the majority of visual input during this phase was the target and the end pointing location. We also asked participants to reach as quickly as possible, reducing the potential to use proprioceptive feedback to alter arm trajectory.

The goal of the walking task was to walk forward in a straight trajectory, ending with one's feet on a target. A 3.0 x 0.7 m walkway was marked by tape on the floor, including target lines (0.3 m) located at each end of the path. While beginning at one end of the path, participants walked at a normal pace and stopped when the arches of their feet were directly on the target line. As in the Reaching task, 70 walking trials were performed in three phases. During the Baseline phase, participants walked to the target with eyes closed. Participants were discouraged from counting their steps while walking with eyes closed, but were encouraged to visualize walking to the target. At the end of each walking trial, participants opened their eyes to assess performance and make adjustments for subsequent trials. Then, a research team member positioned the participant at the center of the walking path before beginning the next trial.

During the Adaptation phase, walking was completed while wearing the same prism glasses and modified goggles as worn for the Reaching task. In addition, participants were fitted with a platform that rested on the shoulders and sat parallel to the horizontal plane, occluding vision of the ground and the lower half of the body while walking. Preliminary pilot data showed that the magnitude of adaptation was greatly diminished if participants were able to look down (and not through the prism glasses) and use the path lines as visual cues to complete the task. Therefore, we limited participants' ability to look at the ground or at their feet while walking and instead encouraged them to look straight ahead. The target line was visible over the platform at the start of each trial but would then be obscured as the participant proceeded on the path. At

the end the trial, a research team member temporarily moved the platform to allow view of the target line. In this way, we ensured participants were using visual information about their body position relative to the target to complete the task. Finally, in the Post-Adaptation phase, participants walked to the target with their eyes closed, similar to Baseline trials. Consecutive trials were performed in opposite walking directions thus using both ends of the path and minimizing any directional effect on performance.

2.3.3 Data collection and analysis

Performance during reaching was determined by manually measuring the horizontal distance from the end-point of the reach to the target position to the nearest 0.5 cm. Rightward errors were considered positive, indicating the direction of the prism shift. Lateral distance was converted to angular error using trigonometric calculations. Movement data during the Walking task were recorded at 100 Hz using an 8-camera motion capture system (Motion Analysis Inc, Santa Rosa, CA). Reflective markers were placed bilaterally on the greater trochanter and on the left scapula (offset) of each participant. Data in each movement trial were truncated at the trial stopping point, indicated by a trigger pressed when the participant stopped walking. All movement data were processed for discontinuities and digitally low-pass filtered using a Butterworth filter with cut-off of 6 Hz. The body's center position was defined as the midpoint of the two trochanter markers. The target line position was determined by the midpoint of two collinear markers set on either side of the walking path.

Analysis was conducted using custom-written Matlab (The Mathworks Inc., Natick, MA) scripts to determine the absolute end-point error and angular deviation. We defined the x-direction as the direction of walking and the y-direction as any left/right deviation in laboratory space. Therefore, angular deviation was calculated as the inverse tangent of the change in the y-direction of the body's midpoint divided by the change in x-direction of the body's midpoint.

Positive angular deviation angles represented rightward errors. Herein, we only report angular errors because they account for the initial position of the body at the start of a trial.

Mean performance during each task was determined for each group. The magnitude of adaptation (M_{Adap}) was defined as the difference between the error of the first trial and the average error of last five trials of the Adaptation phase. The magnitude of the after-effect (M_{Post}) was defined as the error first trial during Post-Adaptation [109]. To quantify individual rate of adaptation (Table 2.2) and group mean rate of adaptation and de-adaptation (Figure 2.1), trial-by-trial angular deviation data were fit to exponential functions using Matlab built-in data fitting functions. For both adaptation and Post-Adaptation phases, a monotonic decay function in the form $y=A*exp(-bt)+C$ was used, where t is the trial number, A is a scaling constant, b is the rate constant, and C is the horizontal asymptote. Since the value $1/b$ represents the time constant of the exponential function and thus an index of adaptation rate, we chose to limit the range of b to reflect the task conditions, such that the minimum adaptation rate is 1 trial and maximum rate is 40 trials. Therefore, upper and lower bounds for the parameter b were set at 1 and 0.025 respectively. Finally, we assessed the goodness of fit using the R^2 value of each curve. While an exact cut-off was not used to determine adequate fit, individual data were examined to assess each fit (see Table 2.2).

Differences in demographic data (age, MMSE, sex) were evaluated using appropriate comparisons (one-way ANOVA or chi-square test), and PD-specific variables were compared using independent t-tests (MDS-UPDRS III and MiniBEST) or Kruskal-Wallace tests (disease duration and NFOGQ). A repeated-measures ANOVA with between-subject effect of Group and within-subject effect of Task (Reaching/Walking) was used to determine differences in Adaptation Rate, M_{Adap}, and M_{Post}. Post-hoc comparisons between PD-FOG and PD+FOG were analyzed using Tukey's tests if main effects were found. In addition we calculated Pearson and

Spearman correlation coefficients to determine linear relationships between measures of adaptation and demographic variables age and MDS-UPDRS III. All statistical analyses were performed using SPSS, v. 21 (IBM, Chicago, IL). Statistics were considered significant when $p<0.05$.

2.4 Results

The PD+FOG group on average had greater, but not significantly different, motor symptom severity and duration of PD compared to PD-FOG (MDS-UPDRS III = 49.23±10.66 and 40.77±12.58 respectively), which is typical given that FOG occurs later in the disease progression[15]. MiniBEST scores were similar between the PD groups. Finally, groups did not significantly differ by age, sex, or MMSE (Table 2.1).

2.4.1 Summary or reaching and walking behavior

Mean angular errors for each trial and exponential fits during reaching and walking are shown in Figure 2.1. Overall, performance was consistent with other typical prism adaptation studies. On average, each group gradually decreased movement errors after successive trials during the Adaptation phase, eventually reaching a minimal error level. After removing the prisms, all groups showed significant after-effects on the first trial during the post-adaptation phase. Because recalibration is also required during Post-Adaptation, all groups gradually reduced after-effect errors and returned to baseline performance.

2.4.2 Adaptation Rate

We quantified adaptation rate during reaching and walking as the reciprocal of the time constant *b* derived from exponential fits of data during the Adaptation phase. Individual and group mean values for rate and model fit (R^2) are shown in Table 2.2. During reaching, adaptation rates were fast (CTRL = 1.90±0.37 trials; PD-FOG = 2.79±1.41 trials; PD+FOG = 7.50±4.01 trials) in

all groups. One participant in the PD+FOG group did not reduce reaching errors over the 40 trials allotted and thus was assigned the maximal rate of 40. Adaptation rates during walking were slower (CTRL = 16.38±4.03 trials; PD-FOG = 11.15±3.80 trials; PD+FOG = 15.41±4.16 trials) and more variable across groups. Several participants had maximal walking adaptation rates of 40 due to either not reducing walking errors or not reaching a steady state within the 40 trials allotted. We observed that walking errors were also subject to greater trial-to-trial variability, which led to several poor exponential fits (low R^2 values). Variability is illustrated in Figure 2.2 showing representative good and poor fits of walking adaptation data from each group. We included all data in the current analysis after confirming that results were unchanged even if participants with poor fits were removed. The ANOVA revealed a significant effect of Task such that walking adaptations rates were higher (slower) than reaching rates across groups ($F_{36,1}$ = 19.8, $p < 0.001$). However, group was not a significant effect in this model ($F_{36,2}$ = 1.34, p = 0.28). These data confirm that PD+FOG adapted at similar rates to PD-FOG and CTRL and that all groups adapted slower during walking.

2.4.3 Magnitude of adaptation and after-effects

Figure 2.3 shows the relationship between the M_{Adap} and M_{Post} during each task across groups. M_{Adap} represents the error difference between the first and average of last five trials after donning the prism glasses, while M_{Post} is the error on the first trial after removing the prism glasses. M_{Adap} was not different between tasks ($F_{36,1}$ =2.437, p=0.13) or between groups ($F_{36,2}$=0.345, p = 0.71), indicating the prism glasses produced similar error magnitudes across groups during both tasks. However, M_{Post} was significantly greater during reaching compared to walking ($F_{36,1}$=54.314, p<0.001). There was also a main group effect for M_{Post} ($F_{36,2}$ = 5.112, p = 0.011); M_{Post} was significantly less in PD-FOG compared to PD+FOG (post-hoc comparison, p=0.009).

2.4.4 Association between adaptation and demographic information

To determine if adaptation rates, M_{Adap} or M_{Post} were related to PD severity we performed linear Pearson (M_{Adap} and M_{Post}) or Spearman (Adaptation rates) correlations between experimental and demographic variables. There was a positive relationship between walking adaptation rate and MDS-UPRDS III ($\rho = 0.422$, $p = 0.032$), such that those with greater disease severity adapted slower during walking. Since age may also affect rate of visuomotor adaptation (Buch, Young et al. 2003), we then compared adaptation and after-effect measures with age for all participants. No significant relationships between age and these variables were noted, however, one correlation was trending toward significance (Age vs. Walking $M_{Adap,}$ $r = -0.285$, $p = 0.078$). Table 2.3 summarizes the results of the correlations.

2.5 Discussion

In this study, we noted similar rates of adaptation in PD+FOG and PD-FOG during both reaching and walking. The primary difference in the PD groups was the magnitude of after-effects, which overall was smaller in PD-FOG compared to PD+FOG. In addition, we noted that for all groups, adaption of walking was slower than adaptation of reaching, and after-effects were larger during reaching than during walking.

The rate of adaptation is associated with how quickly one reduces movement errors while wearing prisms, a process known to be regulated by the cerebellum (Martin, Keating et al. 1996). Previous studies indicate cerebellar-specific dysfunction in PD+FOG, which we predicted would also affect visuomotor adaptation. Using fMRI to study brain activity during gait. Peterson et al. report decreased activity in the cerebellum during standing in PD+FOG[34]. Furthermore, a resting-state fMRI study showed different connectivity patterns between the cerebellum and supplementary motor area in PD+FOG compared to PD-FOG[33]. Despite these data, we found no significant differences in adaptation rate during reaching or walking between

PD+FOG and PD-FOG. One reason for the lack of cerebellar findings in this study could be due to the anatomical specificity of walking control in the cerebellum. During normal walking, the cerebellar vermis regulates upright posture and flexor/extensor activation, while the lateral regions of the cerebellum control walking under external guidance[110,111]. Thus, adapting walking trajectory to prism glasses is primarily regulated by the lateral cerebellum. In contrast, the neuroimaging studies of PD+FOG mentioned above focused on the vermis (particularly the cerebellar locomotor region) and did not explore other cerebellar regions. Therefore, dysfunction localized in the vermis is unlikely to affect visuomotor adaptation, explaining the similarity in adaptation rates in the PD groups.

Furthermore, both PD groups adapted at similar rates to CTRL participants. These results align with previous reports of normal adaptation in PD[47-50]. In contrast, Contreras-Vidal and Buch noted that people with PD adapt pointing movements slower when exposed to a large kinematic distortion[112]. The conflicting results may be due to the magnitude of the visual perturbation, which for prism adaptation is small. Gradual perturbations may be controlled by primarily cerebellar mechanisms[113], whereas large perturbations may be corrected using fronto-striatal circuitry. Therefore, the similar adaptation rates in the PD groups relative to CTRLs is reasonable, showing that error correction mechanisms in the cerebellum appear on average to be unaffected by PD. However, we did observe a relationship between global motor function (MDS-UPDRS III) and adaptation rate such that those with worse motor impairment adapted walking trajectories slower. PD progression is associated with increased cerebellar dysfunction[32], which could explain the greater adaptation rates observed in the more impaired individuals. Additional comparisons using groups of PD participants of various motor impairment levels (e.g. mild vs. moderate) are thus needed to provide information on the relationship between adaptation and disease progression.

The novel result from this study was the difference in after-effect magnitude, independent of adaptation magnitude, in people with PD with and without FOG. The after-effect magnitude reflects the true spatial realignment achieved during adaptation[114]. Our results of smaller after-effects, particularly during walking, in PD confirmed previous studies[47,49,50], but only in the PD-FOG group. One possible explanation of smaller after-effects is smaller adaptation magnitudes[109]. However, we noted no difference in M_{Adap} between the groups or between tasks. Thus, the storage of new visuomotor relationships is reduced in PD, supporting the argument that spatial realignment is impaired in PD regardless of adaptation magnitude, providing a role for the basal ganglia in controlling prism adaptation.

The remaining question is why PD+FOG actually showed larger after-effects than PD-FOG, suggesting that PD+FOG achieved a greater level of spatial realignment. The difference in after-effect magnitude between PD+FOG and PD-FOG could be explained by compensatory mechanisms used by PD+FOG that are advantageous for the walking task. One hypothesis regarding walking dysfunction in PD+FOG is that in situations of uncertainty, PD+FOG use more cortical resources because they are unable to recruit automatic mechanisms for movement control[76]. In the novel environment created by wearing prism glasses, more cortical (i.e. voluntary) control of walking is required to successfully adapt to the visual perturbation and retain the new movement pattern. This strategy may selectively benefit the PD+FOG group, resulting in the observed larger after-effects. Evidence from other types of walking adaptation paradigms indirectly support this idea. For example, walking on a split-belt treadmill where one belt is driven faster than the other requires one to recalibrate the stride length and timing of both legs. PD+FOG are unable to regulate their gait while walking on a split-belt treadmill and instead increase their stride length variability compared to PD-FOG and controls[40,62,115]. Split-belt adaptation may be controlled automatically by subcortical structures including the mesencephalic locomotor region, another region known to be dysfunctional in PD+FOG[33,116].

Walking control targeted by split-belt treadmill walking differs from the prism adaptation walking task studied herein, for which more voluntary control is needed. Still, the reasons why the after-effect magnitude was actually enhanced by FOG during prism adaptation are unclear and require further investigation.

The results of this study should be interpreted in light of the following limitations. While we classified the PD group as having the presence or absence of FOG, we acknowledge that FOG exists on a continuum, where the severity of FOG varies between individuals. While our sample of PD participants had moderately high motor impairment (MDS-UPDRS III mean = 45), the severity of freezing in the PD+FOG group was relatively mild (mean NFOGQ = 11.31). To add, no PD+FOG participant experienced freezing while walking forward during the walking task (3 participants froze while turning after walking to the target). Perhaps including individuals with more severe FOG (i.e. greater NFOGQ score) than those in our sample would reveal greater differences, however those with more severe FOG would be unable to complete the task because of frequent freezing episodes, especially off medication. Overall, future studies of motor adaptation in PD and FOG should aim to include more severe PD+FOG to study the spectrum of both PD and FOG severity.

One unique finding reported here was that older adults with and without PD took longer to adapt their walking pattern than their reaching pattern while wearing rightward-shifting prism glasses. In turn, the after-effect magnitude was larger following reaching adaptation compared to walking. This result is not surprising given that the number of trials performed after full adaptation increases the magnitude of the after-effect, enriching the sensorimotor recalibration[109]. However, the reasons why walking adaptation rates were significantly greater than reaching are less clear. One possibility is the difference in task demands associated with both reaching and walking. For instance, balance and limb coordination require different levels

of control during walking than reaching. In addition, the sensory input guiding walking (visual/optic flow, proprioceptive and vestibular) is richer than during reaching. Therefore, there are considerably more parameters to reconcile during spatial realignment of walking compared to reaching, which may account for the slower adaptation rate. Further work should look to examine this distinction in healthy controls, providing insight into the intrinsic properties of the sensorimotor adaptation system (see model proposed by[43]).

We conclude that prism adaptation rate during reaching or walking is not affected by PD or presence of FOG. Despite similarities in adaptation, smaller after-effects were observed in the PD group during walking, particularly in PD-FOG. In addition, we observed that all participants adapted slower during walking, which suggests task-dependent effects for adaptation performance. Altogether, these results indicate that cerebellar-dependent deficits in PD+FOG have a minimal effect on visuomotor adaptation. In contrast, basal ganglia dysfunction in PD, without the confound of FOG, affects the storage of novel visuospatial relationships and overall spatial realignment.

Table 2.1

Participant demographics

	CTRL (n= 13)	PD-FOG (n=13)	PD+FOG (n=13)	p-value
Age (yr)	69.00±4.03	67.38±11.63	68.15±6.04	0.84
Sex (M/F)	7/6	7/6	6/7	1.00
MMSE (0-30)	28.46±1.39	27.88±1.51	28.38±1.50	0.98
Disease Duration (yr)	--	6.43±4.07	9.27±5.21	0.24
MDS-UPDRS III (0-132)	--	40.77±12.58	49.23±10.66	0.07
Mini-BEST (0-32)	--	21.00±3.01	20.00±3.80	0.29
NFOGQ (0-28)	--	0	11.31±2.35	<0.01

Data are Mean±SD;
Range of measures given in parentheses;
P-value obtained from one-way ANOVA for Age and MMSE, chi-square test for sex, Kruskal-Wallis test for disease duration and NFOGQ, and student's t-tests for MDS-UPDRS and Mini-BEST.
MMSE: Mini-mental status examination (lower scores indicate greater cognitive impairment), MDS-UPDRS III: Movement Disorder Society version of the Unified Parkinson Disease Rating Scale Subsection III (higher scores indicate greater severity), Mini-BEST: Mini-Balance Evaluation Systems Test (lower scores indicate poorer balance), NFOGQ: New Freezing of Gait Questionnaire (higher scores indicate greater severity)

Figure 2.1. Average trial-by-trial angular error during Reaching (A) and Walking (B) in all groups for Baseline, Adaptation, and Post-Adaptation phases. Continuous lines represent the exponential fit to data; vertical dashed lines distinguish the phase (Baseline, Adaptation, Post-Adaptation); horizontal dotted lines mark the location of the target edges. Error bars are ±SEM.

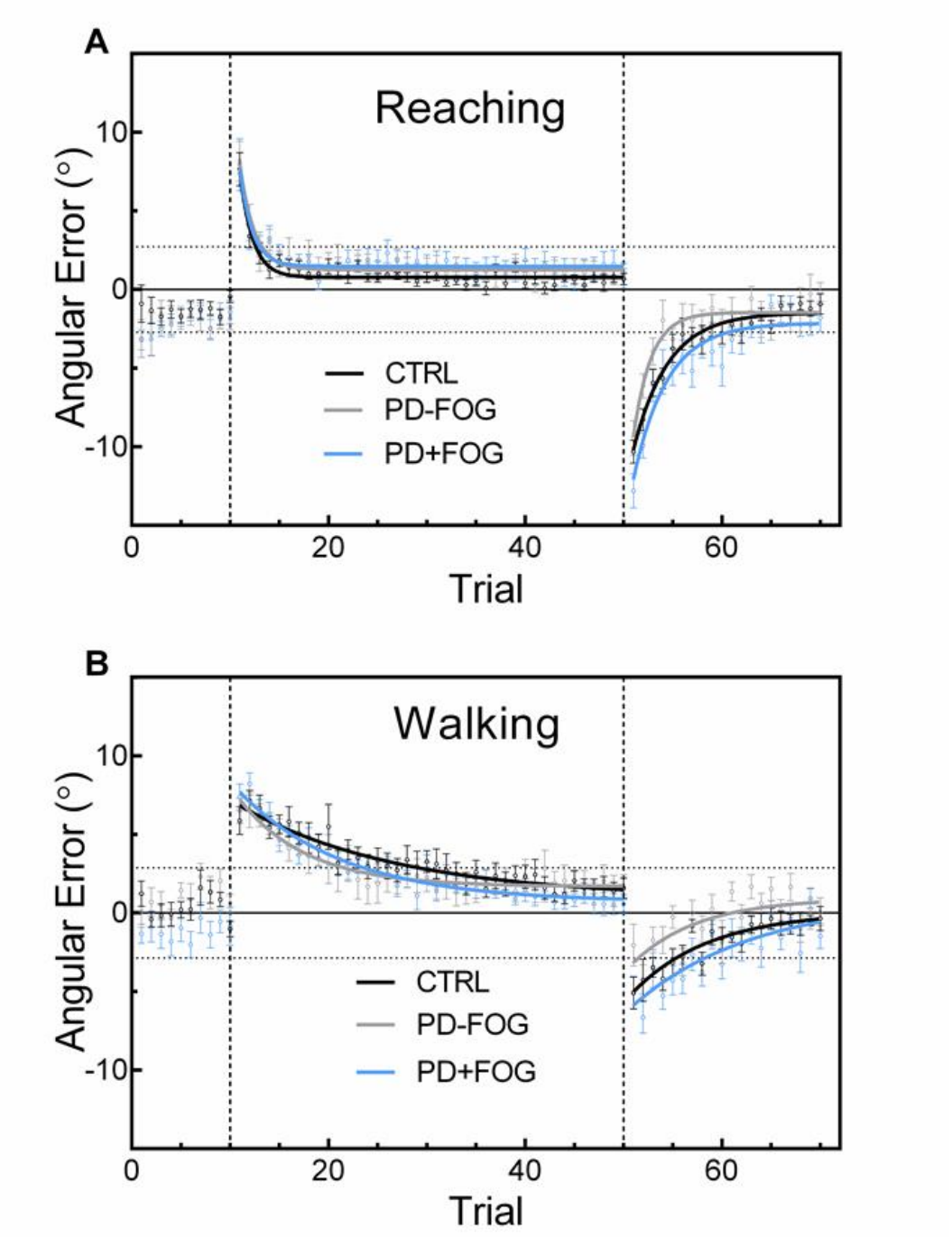


Table 2.2

Adaptation rates and model fits

Reaching	**CTRL**		**PD-FOG**		**PD+FOG**	
Participant	Rate	R^2	Rate	R^2	Rate	R^2
1	1.00	0.59	1.00	0.45	1.00	0.30
2	4.16	0.73	2.21	0.52	1.78	0.31
3	1.00*	0.18	3.99	0.60	1.00	0.41
4	1.00*	0.15	1.00	0.66	1.00	0.18
5	1.86	0.77	1.00	0.46	1.00	0.79
6	3.48	0.79	1.00*	0.11	1.27	0.46
7	2.26	0.49	1.00	0.77	40.0[#]	0.15
8	1.00	0.40	1.00	0.33	4.94*	0.08
9	1.23	0.53	19.46	0.46	1.68	0.49
10	1.00	0.60	1.00	0.51	1.48	0.80
11	1.00*	0.02	1.00	0.47	1.41	0.90
12	4.63	0.31	1.38*	0.21	1.00	0.69
13	1.12	0.70	1.25*	0.24	40.0[†]	0.00
Mean	**1.90**	**0.48**	**2.80**	**0.44**	**7.50**	**0.43**
SEM	**1.33**	**0.25**	**1.41**	**0.19**	**4.01**	**0.29**

Walking	**CTRL**		**PD-FOG**		**PD+FOG**	
Participant	Rate	R^2	Rate	R^2	Rate	R^2
1	40[#]	0.26	8.75	0.82	2.04	0.68
2	12.9	0.42	40.0*[†]	0.00	8.50*	0.25
3	1.44	0.42	1.39	0.25	3.51	0.41
4	12.0	0.87	1.90	0.37	6.09	0.73
5	3.73	0.54	14.4	0.61	6.47	0.77
6	14.9	0.83	15.9	0.80	40.0	0.51
7	15.9	0.45	1.49	0.41	40.0*[†]	0.09
8	40.0*[†]	0.01	1.41	0.40	16.2	0.83
9	40.0[#]	0.38	8.04	0.47	22.0	0.68
10	3.46	0.70	1.51	0.58	5.07	0.58
11	19.3	0.66	40.0[†]	0.01	4.86	0.77
12	4.99	0.43	4.52	0.94	5.70	0.50
13	4.43	0.47	5.61*	0.16	40.0	0.79
Mean	**16.4**	**0.49**	**11.1**	**0.45**	**15.4**	**0.58**
SEM	**4.03**	**0.23**	**3.79**	**0.30**	**4.16**	**0.23**

*High trial-trial variability; [#]Did not reach steady state; [†]Did not reduce errors

Figure 2.2 Representative walking adaptation data showing good (left column) and poor fits (right column) in CTRL (top row), PD-FOG (middle row) and PD+FOG (bottom row). Red continuous lines are monotonic exponential fits.

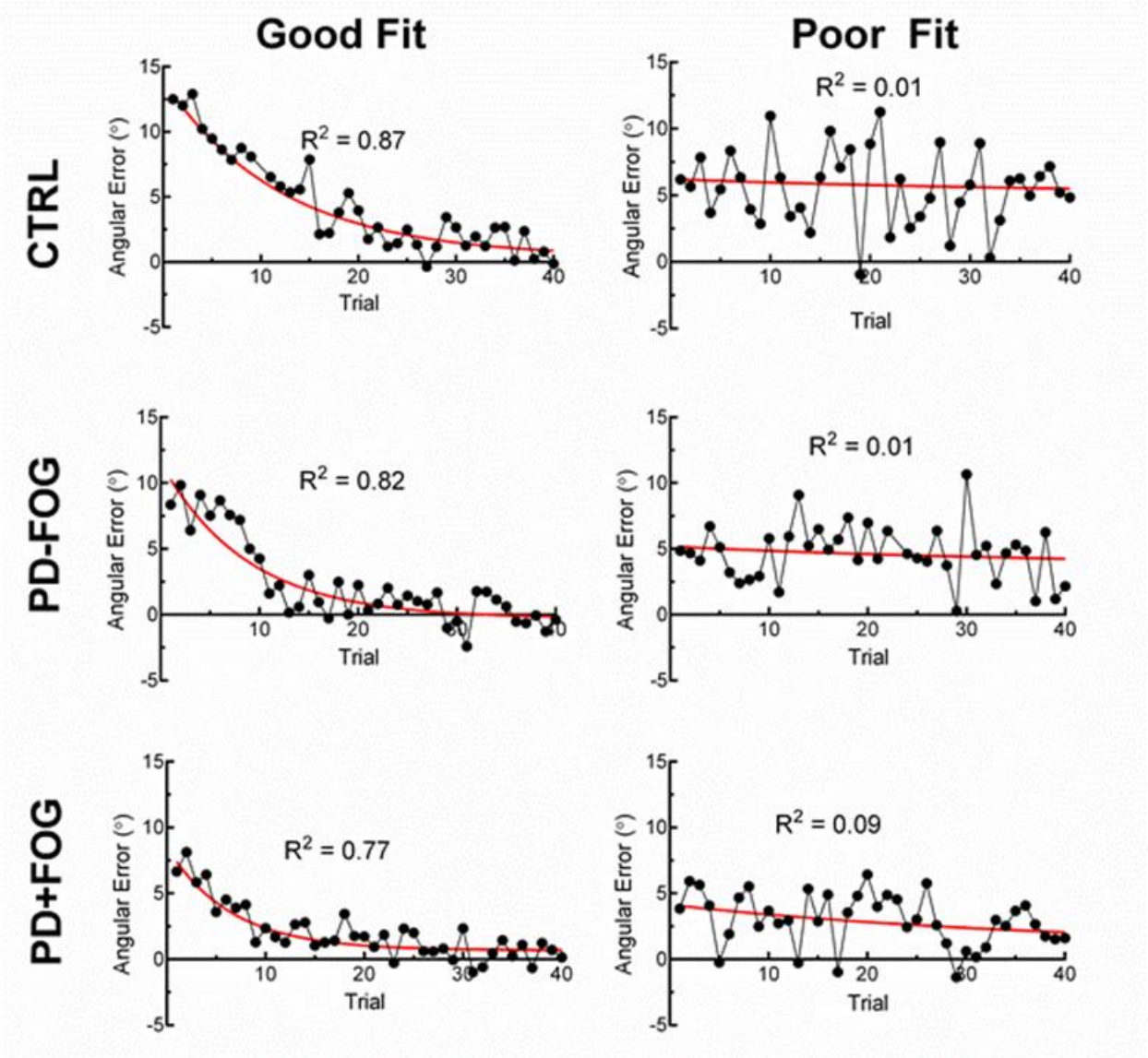


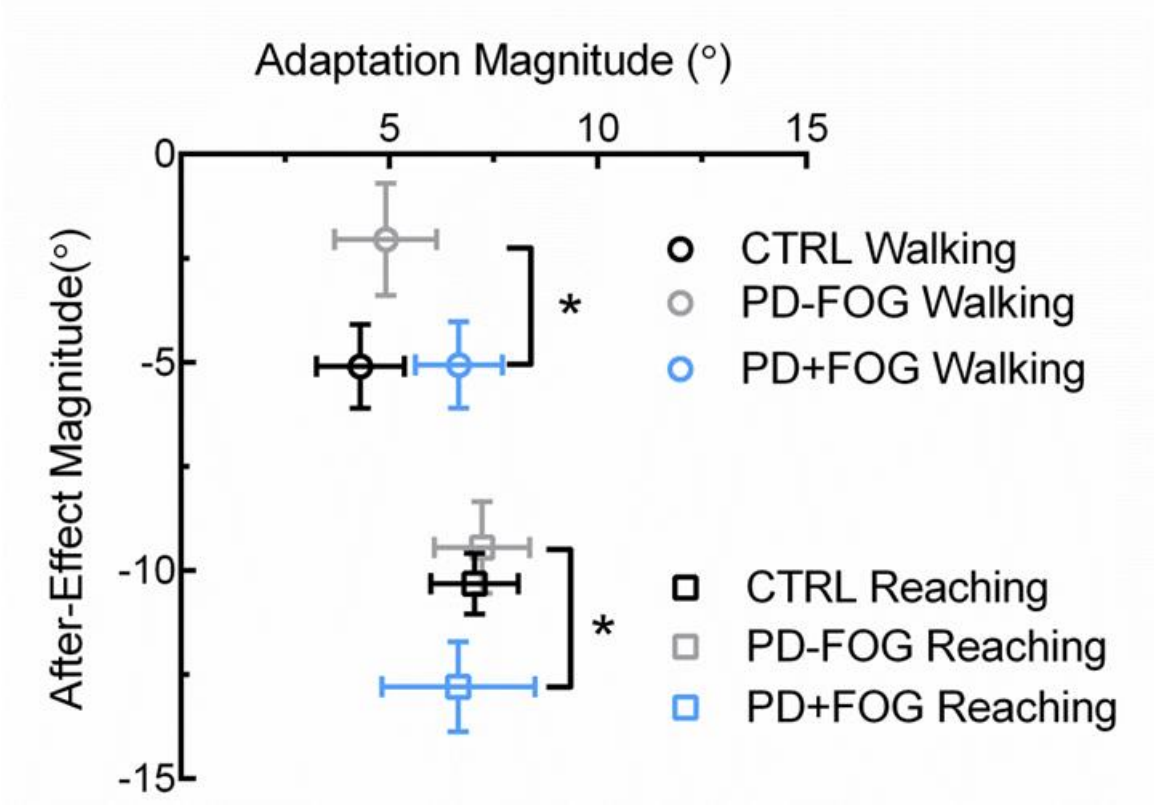
Table 2.3

Correlation analyses of demographic and experimental variables

Age vs.	r/ρ	p	UPDRS-III vs.	r/ρ	p
Reaching			*Reaching*		
#Adap Rate	0.208	0.204	#Adap Rate	0.204	0.317
M_{Adap}	-0.083	0.615	M_{Adap}	-0.338	0.091
M_{Post}	-0.144	0.381	M_{Post}	-0.273	0.178
Walking			*Walking*		
#Adap Rate	-0.113	0.492	#Adap Rate	0.422	**0.032**
M_{Adap}	-0.285	0.078	M_{Adap}	0.001	0.998
M_{Post}	0.008	0.958	M_{Post}	-0.185	0.367

r: Pearson correlation coefficient; ρ: Spearman correlation coefficient #Spearman correlation used. See text for definitions of variables.

Figure 2.3. Relationship between magnitude of adaptation (abscissa) and after-effect (ordinate) during reaching (squares) and walking (circles) adaptation. Error bars are ±SEM. *Significant post-hoc differences in M_{Post} between PD-FOG and PD+FOG (p=0.009). In addition, M_{Post} was significantly different across tasks (reaching>walking; $F_{36,1}$=54.314, p<0.001).



Chapter 3: How do age and nature of the motor task influence visuomotor adaptation?

This chapter was published in September 2015 in the journal Gait & Posture and reprinted with permission from the publisher.

Nemanich ST, Earhart GM. How do age and nature of the motor task influence visuomotor adaptation? Gait Posture. 2015;42(4):564-8. PMCID: 4651796.

3.1 Abstract

Visuomotor adaptation with prism glasses is a paradigm often used to understand how the motor system responds to visual perturbations. Both reaching and walking adaptation have been documented, but not directly compared. Because the sensorimotor environment and demands are different between reaching and walking, we hypothesized that characteristics of prism adaptation, namely rates and after-effects, would be different during walking compared to reaching. Furthermore, we aimed to determine the impact of age on motor adaptation. We studied healthy younger and older adults who performed visually-guided reaching and walking tasks with and without prism glasses. We noted age effects on visuomotor adaptation, such that older adults adapted and re-adapted slower compared to younger adults, in accord with previous studies of adaptation in older adults. Interestingly, we also noted that both groups adapted slower and showed smaller after-effects during walking prism adaptation compared to reaching. We propose that walking adaptation is slower because of the complex multi-effector and multi-sensory demands associated with walking. Altogether, these data suggest that humans can adapt various movement types but the rate and extent of adaptation is not the same across movement types nor across ages.

3.2 Introduction

A majority of daily walking involves navigation of complex environments and is highly dependent on visual guidance. Humans can flexibly adapt their walking patterns to visual distortions, which are easily created with gaze-shifting prism glasses. In this paradigm, individuals rapidly alter motor output based on trial-to-trial feedback, eventually establishing a new visuomotor mapping. While many studies of human prism adaptation focus on the upper extremity[41,99,109,117], adaptation is also observed during saccades[118,119], lower extremity movements[44] and walking[45,46,120]. Some have compared movement types in the context of generalization or how the type of movement or task generalizes to another[44-46]. However, no study has yet to

determine if adaptation is similar in rate and extent across different adapted tasks, or if the type of movement influences how it is adapted (e.g. upper limb movements are adapted faster than lower limb movements). It is obvious that the demands associated with upper extremity movements and walking are quite different. Based on the model of visuomotor coordination proposed by Redding and Wallace[114], we propose that walking adaptation involves many more subsystems than reaching adaptation, resulting in slower error-correction processes. The behavioral consequence of this is slower adaptation during walking. In order to support or refute this hypothesis, we herein compare adaptation of reaching to adaptation of walking.

A secondary aim of this paper was to determine the effects of aging on motor adaptation of reaching and walking. Normal aging involves a myriad of changes in the nervous system that affect visuomotor adaptation, including degradation of sensory receptors and atrophy of the frontal cortex and cerebellum[56,121]. Older adults respond poorly to changes in their environment, which may underlie the high incidence of falls and movement-related injuries in this population. Indeed, existing data indicate that older adults adapt slower to visual perturbations but show similar if not larger after-effects compared to younger adults[53,55]. Strategic control processes, which are important during adaptation but not for expression of after-effects, are thought to be impaired in older adults and account for slower adaptation. However, the available literature has focused primarily on upper-extremity adaptation in older adults. The additional challenges, mainly balance and coordination, during walking may further impair older adults' ability to adapt their walking pattern, but this has not been studied.

In this experiment, we evaluated visuomotor adaptation to prism glasses in healthy older and younger adults during reaching and walking. Our goal was to examine the effects of both age and motor task on the properties of visuomotor adaptation. In accord with previous studies, we predicted older adults would adapt slower but have similar after-effects compared to younger

adults during both tasks. Furthermore, we postulated that because walking is more demanding than reaching, adaptation rates during walking would be slower compared to reaching for all participants.

3.3 Materials and Methods

3.3.1 Participants

Young (n = 15, 7 male, mean age 25.0 ± 5.83 years) and old (n = 18, 9 male, mean age 70.1 ± 7.27 years) adults participated. Younger adults were recruited from the student cohort at the Washington University School of Medicine Program in Physical Therapy. Older adults were recruited using a volunteer database provided by the Department of Psychology at Washington University. All participants had normal neurological function, 20/40 vision or better without the aid of glasses, and were not cognitively impaired (Mini-mental status exam ≥ 26). Participants provided written consent before participation and were compensated for their time, travel, and effort. All procedures were approved by the Human Research Protection Office at Washington University School of Medicine in St. Louis.

3.3.2 Tasks and Procedures

Participants completed 70 visually-guided reaching and walking trials in the Locomotor Control Laboratory at Washington University School of Medicine in St. Louis. Each task was divided into three phases: Baseline (10 trials), Adaptation (40 trials), and Post-Adaptation (20 trials).

For the reaching task, participants reached and pointed to a visual target with their dominant arm as quickly as possible using a laser pointer. Participants stood 1.6 m from a large piece of paper hung on a wall. A 5 cm x 5 cm crosshair served as the target and was positioned at each participant's shoulder height. After each reach, the experimenter marked the position of the reach end-point on the paper to allow feedback regarding reach accuracy. During Baseline,

reaching occurred without vision of the target (eyes closed). During Adaptation, participants reached while wearing eyeglass frames containing 30-diopter rightward-shifting prism lenses (Fresnel Prism and Lens Co, Bloomington, MN). They also wore modified, lens-free safety goggles frames over the prisms to obscure peripheral vision and ensure gaze was directed through the prism lenses. Eyes remained open throughout Adaptation phase. For Post-Adaptation, prisms were removed and reaching was completed without vision. For all trials, participants viewed their performance after each reach before completing the next trial.

The walking task required participants to walk forward on a path to a visual target on the floor (white piece of tape, 0.3 m long). Participants were instructed to stop with the arches of their feet resting in the middle of the piece of tape. After each trial, the participant turned around and completed the next trial in the opposite direction. Walking was completed with the same phases and vision restrictions as in the reaching task. In addition, participants were fitted with a platform extending forward from the chest to limit vision of the feet and target during Adaptation. Participants were instructed to first look at the target then look straight ahead while walking. However, we ensured that each participant was able to view the position of the feet relative to the target after each Adaptation trial. Walking position was measured using an 8-camera motion capture system (Motion Analysis Corp, Santa Rosa, CA). Reflective markers were placed bilaterally on the greater trochanters and on the left scapula (offset marker). The midpoint of the pelvis markers was used to represent walking trajectory.

3.3.3 Data Analysis

Reaching errors were calculated by measuring the horizontal distance from reach end-point to center of the target. Absolute error was converted to an angular error using trigonometric calculations. Data measured using motion capture were processed for discontinuities and digitally low-pass Butterworth filtered (cut-off of 6 Hz). Walking errors were calculated from the

difference in walking trajectory endpoint and center of walking target. These distances were also converted to angular errors. We defined rightward errors as positive and leftward errors as negative.

Trial-to-trial angular error curves for each phase were plotted for each task, and then averaged across all participants. We analyzed four characteristics of prism adaptation: magnitude of the adaptation (M_{adap}), magnitude of the after-effect (M_{ae}), rate of adaptation (R_{adap}) and rate of Post-Adaptation (R_{post}). M_{adap} was defined as the difference in angular error between the first Adaptation trial and the average of the last five Adaptation trials. M_{ae} was defined as the angular error during the first Post-Adaptation trial (Fernandez-Ruiz and Diaz 1999). Although M_{ae} is simply a magnitude, we present it as negative to indicate direction of the error and not to confuse it with M_{adap}. Adaptation and Post-Adaptation curves were fitted by a monotonic exponential function, allowing for estimation of the curve decay constant. We used built-in Matlab (R2011b, Mathworks Inc., Natick, MA) data fitting functions to fit curves during Adaptation and Post-Adaptation phases to the form $y = A*exp(-b*t)+c$, where A is a scaling constant, b is the decay constant, t is the trial number, and c is the horizontal asymptote. R_{adap} and R_{post} were defined as $1/b$ for the exponential fit of Adaptation and Post-Adaptation curves, respectively. We limited the range of b to 0.025-1 for Adaptation fits and 0.05-1 for Post-Adaptation fits, which translates to a range of 1-40 for R_{adap} and 1-20 for R_{post}. These ranges reflect the minimum and maximum possible adaptation rates given the number of trials in each phase. Goodness-of-fit was determined by visual inspection in conjunction with R^2 values. Several fits from each group fit poorly to the exponential function, resulting in inaccurate parameter estimates. Specifically, three reaching Adaptation (1 old, 2 young), three walking Adaptation (1 old, 2 young), 1 reaching Post-Adaptation (old) and six walking Post-Adaptation (3 young, 3 old) were deemed poor fits. We excluded these from analysis of R_{adap} and $R_{post.}$ (Subsequent analyses showed their inclusion did not change interpretation of the data). Finally,

to quantify trial-to-trial variability, we calculated the standard deviation of the last five trials of each phase.

To examine the effects of age and task on the four adaptation variables, we used a mixed-effects ANOVA with between-groups effect of Group (Young vs. Old) and within-groups effect of Task (Reaching vs. Walking) using SPSS v21 (IBM Corp, Chicago IL). We also performed a 3-way ANOVA (Task-Phase-Group) to compare changes in variability across the experiment. If a main effect was present, post-hoc t-tests were used to compare group differences within each task. Statistics were considered significant if $p<0.05$.

3.4 Results

In this experiment, older and younger adults reached and walked to a visual target while wearing gaze-shifting prism glasses. Both groups exhibited normal prism adaptation curves and large negative after-effects following removal of the prisms, indicating participants achieved true spatial realignment. Figure 3.1 shows group mean trial-to-trial angular errors for each phase during reaching and walking. In both tasks, Baseline errors were similar across tasks and groups (mean Baseline error during reaching: Old = -1.08 ± 0.18°, Young = -0.64 ± 0.52°; during walking: Old = -0.12 ± 0.82°, Young = 1.48 ± 0.44°), and were within the target boundaries denoted by the horizontal dotted lines (± 2.8°).

Figure 3.2 shows individual and mean values for M_{adap} and M_{ae}. M_{adap} was similar between groups during reaching (Young = 7.72 ± 0.88°, Old = 6.90 ± 0.81°) but greater in the young group during walking (Young = 7.00 ± 0.63°, Old = 3.93 ± 0.84°) (Figure 3.2A). Table 3.1 summarizes the ANOVAs for all four adaptation measures. There were significant main effects of Task (Reaching > Walking) and Group (Young > Old) for M_{adap}. M_{ae} was slightly greater in the old group during reaching (Old = -10.36 ± 0.63°, Young = -8.39 ± 0.60) but similar between

groups during walking (Old = -4.73 ± 0.78°, Young = -4.08 ± 0.65°) (Figure 3.2B). Task was also a significant main effect in the ANOVA of M_{ae} (Reaching > Walking) however Group was not significant.

Decay rates of the Adaptation and Post-Adaptation curves revealed further differences between groups. Figure 3.3 shows the mean R_{adap} and R_{post} during both tasks. R_{adap} was similar between groups during reaching (Old = 2.51 ± 0.66 trials, Young = 2.33 ± 0.59 trials) but was greater in older adults during walking (Old = 14.23 ± 3.28 trials, Young = 6.38 ±1.68 trials) (Figure 3.3A). The ANOVA of R_{adap} showed a significant main effect of Task (Walking >Reaching) while Group and Task*Group interaction did not reach significance. Further differences were observed in the estimate of R_{post}. Older adults (8.67 ± 2.09 trials) had greater R_{post} compared to younger adults (2.66 ± 0.85 trials) during walking (Figure 3.3B). Here, the ANOVA showed significant effects of Task, Group and Group*Task interaction. Overall, younger adults de-adapted faster compared to older adults for both tasks, but this difference was pronounced during walking.

Movement variability (standard deviation) across the experimental phases is shown in Figure 3.4. Variability was greater during walking (1.67 ± 0.15°) compared to reaching (1.27 ± 0.07°), as indicated by a main effect of Task; $F(31,1) = 4.64$, $p = 0.04$) and was associated with the experimental phase ($F(31,2) = 10.2$, $p < 0.001$), such that Baseline and Post-Adaptation phases were more variable than the Adaptation phase. To add, older adults tended to have greater variability overall (Old = 1.73 ± 0.14°, Young = 1.16 ± 0.06°, main effect of Group; $F(31,1) = 9.44$, $p = 0.004$). In total, variability was significantly altered by task conditions and age of the participant.

3.5 Discussion

We observed age effects on prism adaptation during reaching and walking, where older adults adapted and re-adapted slower during both tasks. Numerous studies comparing older and younger adults show aging affects adaptation but not after-effects[53-55]. These results support the idea that two main processes regulate motor adaptation: strategic control and sensory recalibration. Strategic control is the ability to use cognitive strategies or prior knowledge to reduce movement errors, while sensory recalibration is an intrinsic property of the nervous system to respond to changes in one's environment[56,114]. For the prism adaptation paradigm used herein, sensory recalibration occurs during both Adaptation and Post-Adaptation and slowly reconciles motor output with visual and proprioceptive feedback. However, strategic control occurs only during the early phases of Adaptation and Post-Adaptation as participants seek to quickly reduce movement errors. As was thought previously, aging likely affects strategic control more so than sensory recalibration since older adults exhibit slower adaptation rates but normal after-effects. Our data support this and show that strategic control may also impact Post-Adaptation given the slower R_{post} observed in older adults. During Post-Adaptation, initial large errors drive similar adaptive processes as used during Adaptation. In this situation, strategic control is essential because vision was permitted only at the start and end of Post-Adaptation trials, requiring participants to use explicit information about their starting and ending positions to correct movements. Altogether, these results point to age-related slowing of visuomotor adaptation but no changes in total realignment during multiple motor tasks.

The novel result of this study was the task-specific effects on characteristics of prism adaptation. All four variables (M_{adap}, M_{ae}, R_{adap}, and R_{post}) were significantly different between reaching and walking. M_{adap} was smaller during walking, showing the visual perturbation caused greater errors during reaching compared to walking. This might be explained by the differences in movement duration between tasks; walking trials were considerably longer than

reaching trials. Participants may have had opportunity to adjust changing their trajectory mid-trial. Additionally, since walking was performed after reaching, more participants may have explicitly been aware of the effect of the prism glasses and could better predict the appropriate walking pattern needed to reach the target. While we did not measure walking trajectory directly, participants did adhere to the instruction given to walk in a straight line. The smaller M_{ae} observed during walking is not surprising, however, given all participants adapted reaching movements faster than walking. As a result, they performed more correctly adapted reaching movements during Adaptation. Previous work by Fernandez-Ruiz and Diaz showed that there was a positive correlation between number of trials performed after complete adaptation and M_{ae}[109]. Thus, the smaller after-effect observed during walking may be partly due to the fewer number of walking trials completed after complete adaptation.

There was also a difference in R_{adap} and R_{post} across tasks such that all participants adapted and de-adapted slower during walking compared to reaching. These changes were unlikely the result of performing the walking task second, as one would expect more efficient adaptation after repeated exposure to the prisms. Furthermore, because walking trial durations exceeded reaching durations, we would also expect within-trial adjustments to lead to faster adaptation rates. While this may have occurred on the first several trials, accounting for lower M_{adap} during walking, the overall error reduction rate was still significantly slower. Therefore, something inherent to the motor output during walking likely resulted in reduced sensory recalibration and strategic control processes that drive adaptation, particularly in older adults.

There are several potential explanations for this result that relate to the visuomotor system. The first is differences in sensory weighting during reaching and walking[122]. Prism adaptation causes a re-weighting of sensory input such that visual feedback dominates proprioceptive and/or vestibular feedback. While vestibular input is present during both tasks, it is much more

important for walking control than for reaching. The extra information provided by the vestibular system may have caused interference that slowed the sensory recalibration process during walking[123]. Another potential rationale is the contrast in motor demands between tasks. Walking requires dynamic control of balance and all four extremities, while reaching requires static control of balance and movement of one extremity. Based on Redding and Wallace's model of prism adaptation, the nervous system integrates signals from multiple sensory-motor subsystems to achieve spatial realignment[114]. During walking, there are many more active subsystems compared to reaching. Although they suggest that these subsystems are controlled in parallel, there may be some cost associated with operating many subsystems simultaneously. If the cost is time-related, it would result in more walking trials (i.e. slower R_{adap}) to reach accordance between visual input and motor output. This is slightly counter-intuitive, given that walking is usually assumed to be an automatic motor program. However, in our task, walking was probably under more voluntary control because participants walked with a goal in mind, and adjusted their walking accordingly. Overall, walking may require multiple effector-specific motor commands, resulting in prolonged adaptation rates.

Finally, the problem of trial-to-trial variability may partly account for some of the differences reported here. The mean within-participant variability of the last five trials during each phase was greater during walking. This shows that visual perturbation greatly affected walking since participants were inconsistently hitting the target even after complete adaptation or de-adaptation. Because the error signal is driving adaptation, transient increases in error between trials, which were more common during walking, would slow down the rate of return to baseline performance.

In this study, we show the effects of both age and motor task on properties of visuomotor adaptation to prism glasses. Similar to previous reports we found that older adults adapted

slower to visual perturbations. Despite these differences, the after-effect magnitude was similar between older and younger adults, suggesting that strategic control is more impacted by age than is sensory recalibration. Finally, while we show task-dependent effects on rates of adaptation and de-adaptation, additional work is needed to elucidate the relationship between the motor task and processes underlying visuomotor adaptation.

Figure 3.1. Mean trial-to-trial angular errors during reaching (A) and walking (B). Data points represent the mean error for a single trial across participants. Continuous lines are the exponential best fit to the mean data. Horizontal dotted lines indicate the boundaries of the reaching or walking target. Vertical dashed lines separate the phases of the task: Baseline-left, Adaptation-middle, Post-Adaptation-right. Error bars are ± SEM.

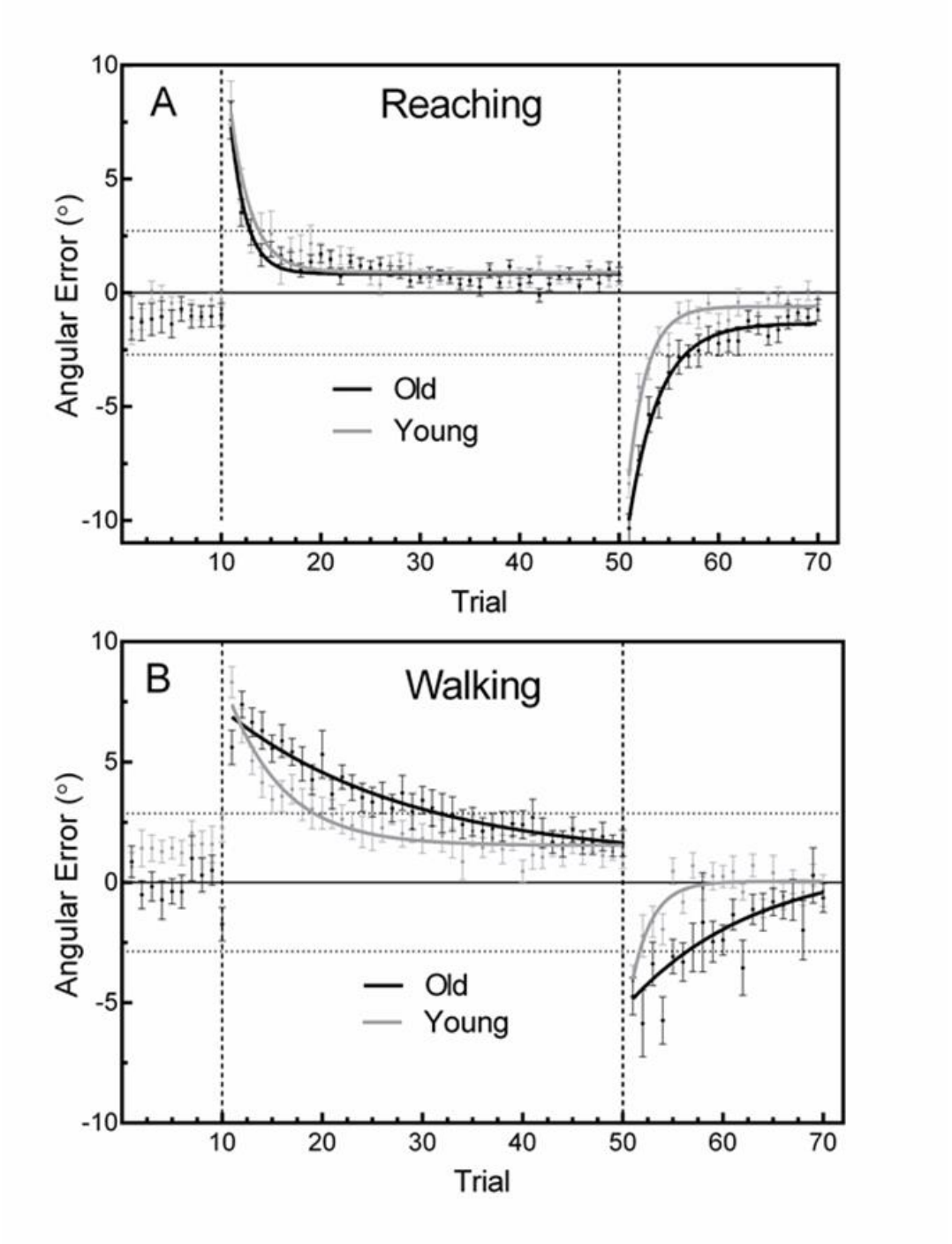


Table 3.1

ANOVA summary for adaptation variables

	Main Effects		Interaction	Post-hoc (Young vs. Old)	
Measure	Task	Group		Reach	Walk
M_{adap}	**5.29 (0.03)**	**5.69 (0.02)**	1.97 (0.17)	0.69 (0.50)	**2.82 (0.01)**
M_{ae}	**50.5 (<0.001)**	3.85 (0.06)	0.88 (0.36)	N/A	N/A
R_{adap}	**11.9 (0.002)**	3.06 (0.09)	3.81 (0.06)	N/A	N/A
R_{post}	**7.18 (0.01)**	**6.15 (0.02)**	**5.24 (0.03)**	1.36 (0.18)	**2.44 (0.02)**

Values are F-statistic from ANOVA model and t-statistic for post-hoc tests; p-values are given in parentheses
Bolded text indicates significance; N/A: Not applicable; no main effect present

Figure 3.2. Individual (circles) and mean (line) M_{adap} (A) and M_{ae} (B) during reaching and walking. M_{adap} was smaller during walking and in older adults, while M_{ae} was greater during walking compared to reaching. Error bars are ± SEM. See Table 1 for ANOVA results. P-values represent post-hoc comparisons.

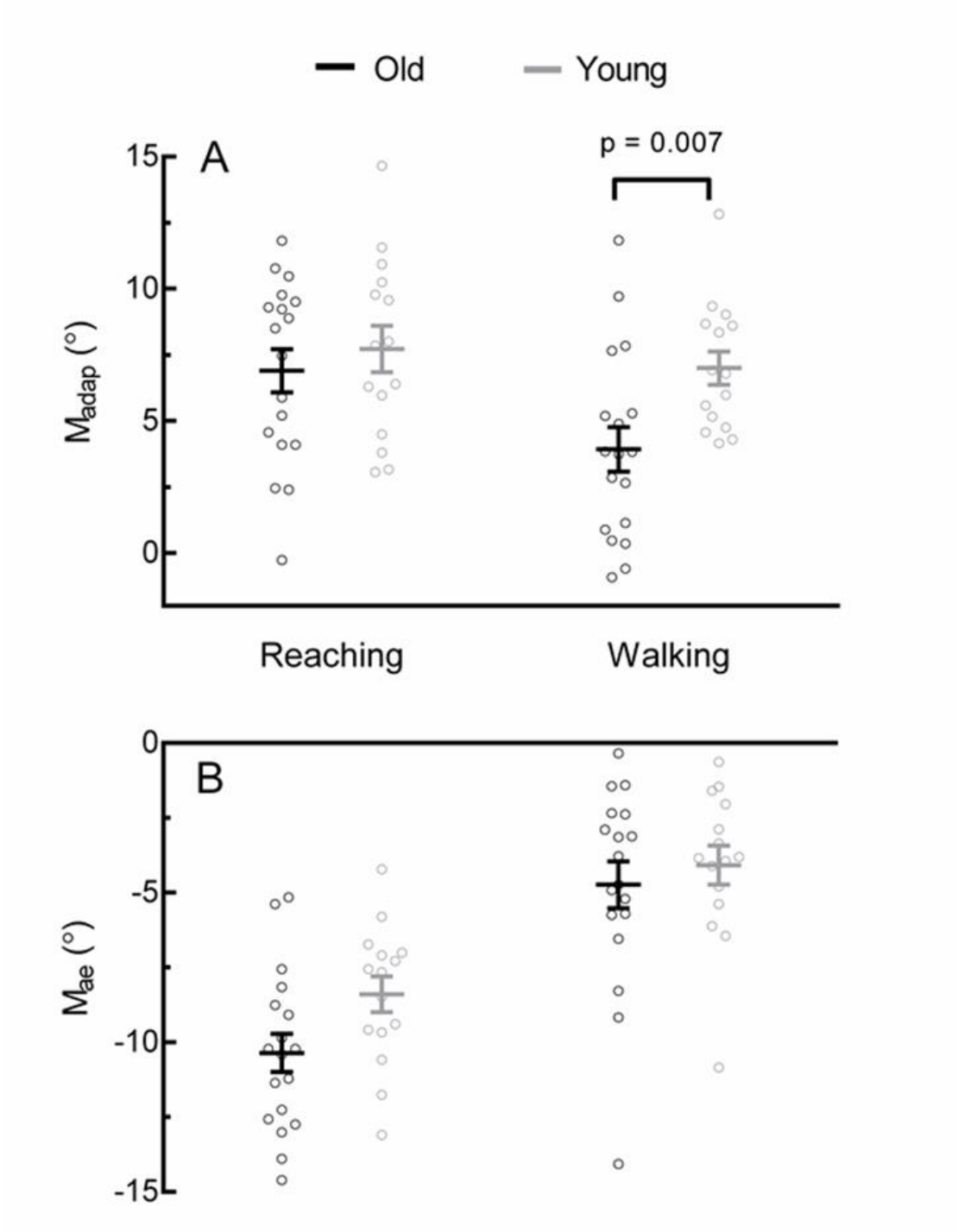


Figure 3.3 Mean estimated R_{adap} (A) and R_{post} (B) during reaching and walking. Both groups adapted (R_{adap}) slower during walking compared to reaching, and this difference was pronounced in older adults. R_{post} was slower on average during walking compared to reaching, and older adults re-adapted slower than younger adults, particularly during the walking task. Error bars are ± SEM. See Table 1 for ANOVA results. P-values represent post-hoc comparisons.

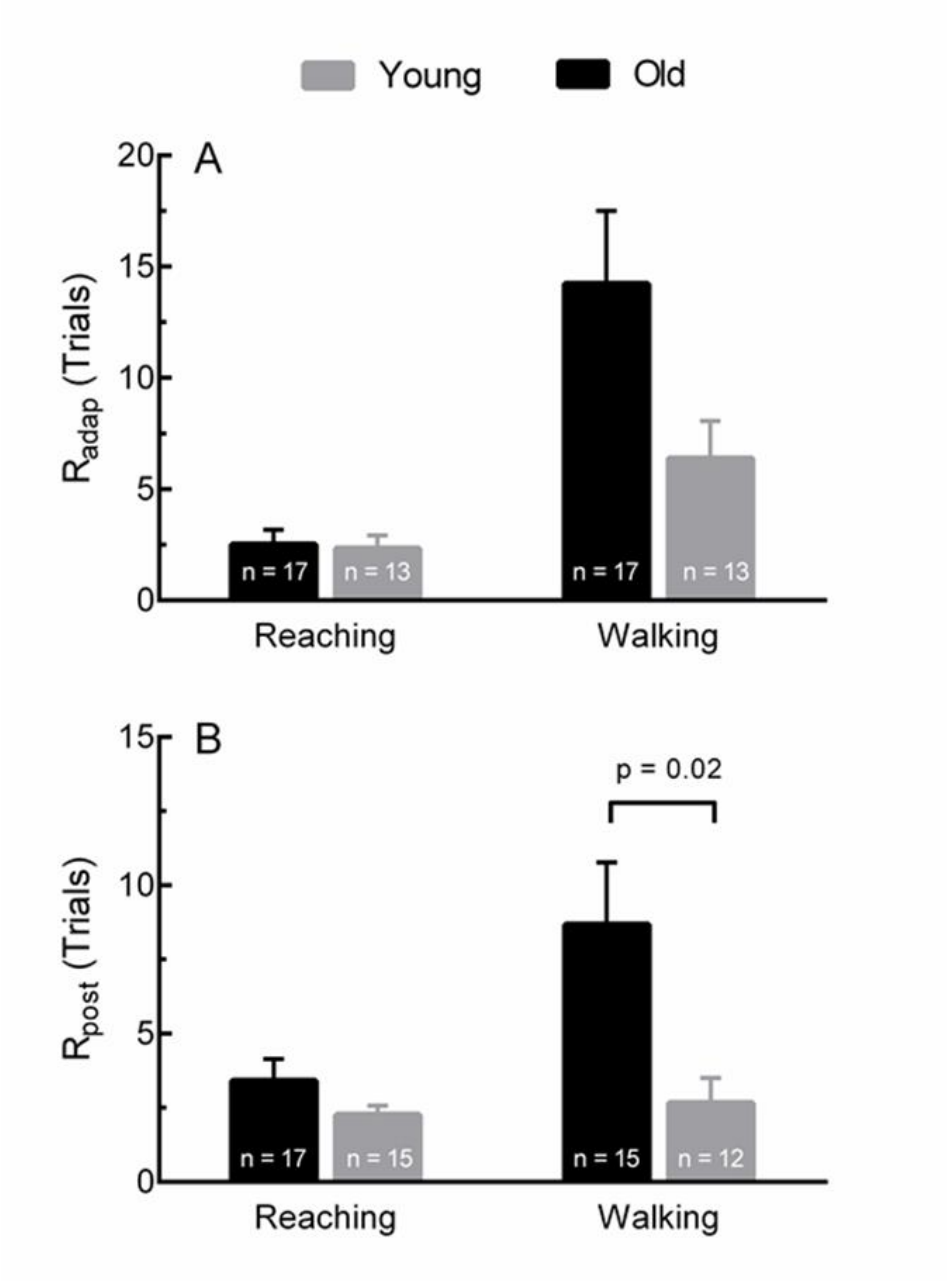
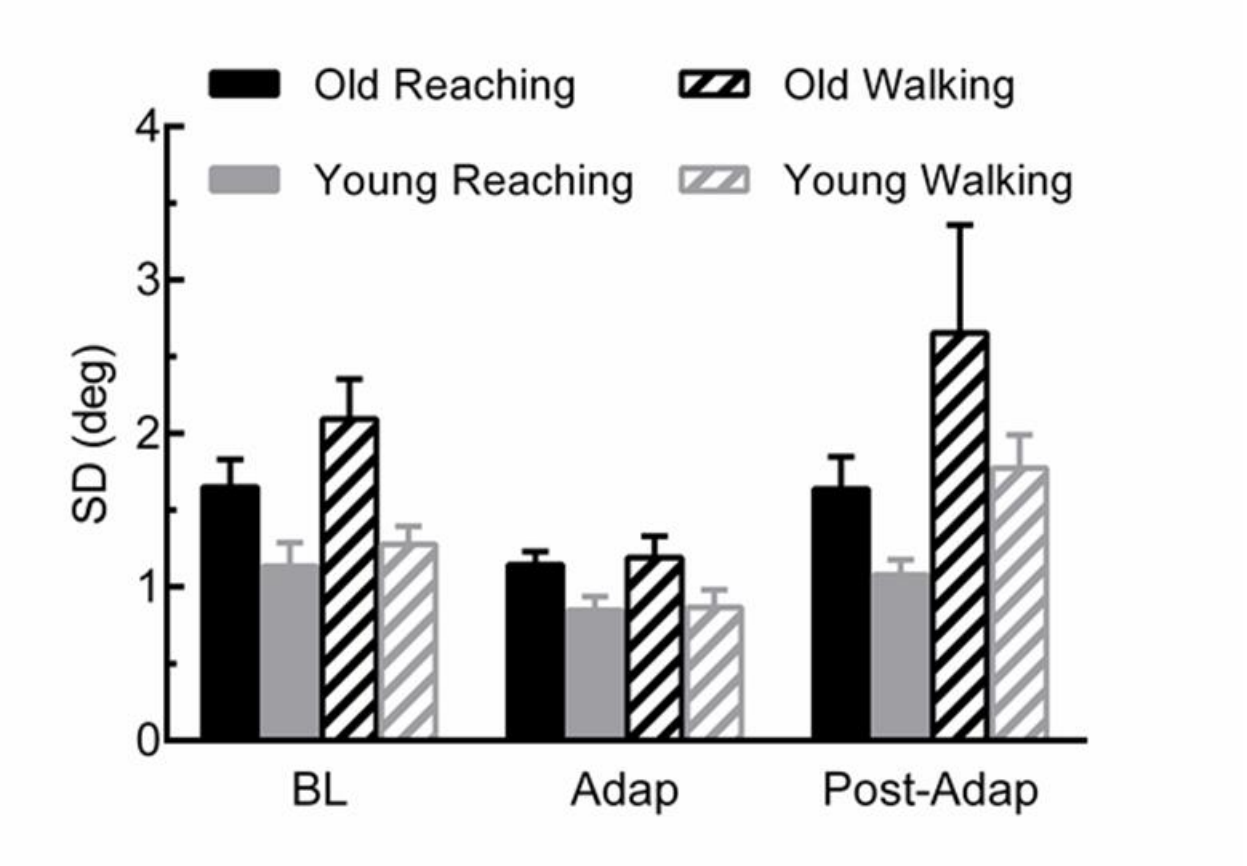


Figure 3.4. Mean standard deviation shown for each group, task, and across each experimental phase. SD represents the average standard deviation of the last five trials of the respective phase. Error bars are ± SEM. Main effects from ANOVA: Task ($p = 0.04$), Phase ($p < 0.001$) and Group ($p= 0.004$).



Chapter 4: Increased saccade latency and variability is associated with freezing of gait in Parkinson's disease

This chapter has been submitted as an original research article to *Clinical Neurophysiology* in January 2016 and is currently in review.

4.1 Abstract

Freezing of gait (FOG) is a locomotor disturbance in Parkinson disease (PD) related to impaired motor automaticity. In this study, we investigated the impact of freezing on automaticity in the oculomotor system using an anti-saccade paradigm. Subjects with PD with (PD+FOG, n=13) and without (PD-FOG n=13) FOG, and healthy age-matched controls (CTRL, n=12) completed automatic pro-saccades and non-automatic anti-saccades. Primary outcomes were saccade latency, velocity, and gain. PD+FOG (pro-saccade latency = 271 ms, anti-saccade latency = 412 ms) were slower to execute both types of saccades compared to PD-FOG (253 ms, 330 ms) and CTRL (246 ms, 327 ms). Saccade velocity and gain variability was also increased in PD+FOG. Saccade performance was affected in PD+FOG for both types of saccades, indicating differences in automaticity and control in the oculomotor system related to freezing. These results and others show that FOG impacts non-gait motor functions, suggesting global motor impairment in PD+FOG.

4.2 Introduction

Among the many gait difficulties in people with Parkinson's disease (PD), freezing of gait (FOG) is one of the most common, affecting over half of the PD population[16]. FOG manifests as episodic interruptions of the gait cycle during normal walking and other complex gait tasks like turning[14,17]. Additional research into the mechanisms of FOG showed that freezing is not limited to gait, but can also be observed in other motor tasks, such as upper limb movements and speech[28,30,124]. Altogether, these studies indicate that freezing may be a global phenomenon impacting not just gait but the entire motor system.

Many hypotheses explaining FOG phenomenology have been proposed[125], and two specifically relate FOG to impairments in cognitive-motor function. The interference model suggests

excessive overlap of activity in sensorimotor, associative, and limbic circuits of the basal ganglia leads to abnormal inhibition from the globus pallidus, leading to freezing episodes[126]. Additionally, the cognitive model proposes freezers have impaired conflict resolution and response automaticity in challenging environments, resulting in an increased reliance on cortical resources[76]. Evidence for this is seen in dual-task experiments, commonly used to assess automaticity, during which people with PD and FOG (PD+FOG) have poorer gait performance during dual-task tests compared to those who do not have FOG (PD-FOG)[77]. Recent neuroimaging data also support the cognitive model, showing increased activation and connectivity of cortical regions in PD+FOG[33,102]. Tying back into the interference model, increased activity may lead to resource "overloads", particularly during cognitively demanding tasks, inducing motor arrests observed during a freezing episode[83]. Given these hypotheses, it is reasonable to predict that impaired automaticity is a common feature of freezing that would affect all motor output.

Saccades are fast eye movements that allow us to quickly foveate objects of interest, and are mediated by both cortical (DLPFC, FEF, SEF) and subcortical (thalamus, basal ganglia, superior colliculus) circuits as well as oculomotor neurons in cranial nerves[86,127]. Saccadic output follows highly stereotyped patterns and is well-described in both healthy[84,128] adults and PD. These studies show that people with PD are generally slower to respond (i.e. increased latency) and make slower (i.e. decreased velocity) volitional saccades[92,129], supporting the traditional view that slowed voluntary movement is a result of increased inhibition of the basal ganglia[130].

The anti-saccade task is a common way to study a different aspect of oculomotor control[87]. In this task, participants make saccades either toward a visual target (the automatic pro-saccade) or to a mirrored position of a visual target (non-automatic anti-saccade). Anti-saccades require

inhibition of a visually-guided response as well as initiation of a non-visually guided saccade. As such, anti-saccade tasks are useful to assess both the cognitive and motor aspects of oculomotor control and have been used in both healthy individuals and patients with neurological conditions[131-133]. In addition, anti-saccade performance correlates well with other measures of executive function in adults[134,135]. Altogether, anti-saccades likely involve parallel processing of cognitive and motor commands mediated by the basal ganglia, and are a suitable approach to study cognitive-motor processing and its relationship to freezing. However to our knowledge only one recent study directly examined the impact of FOG on saccades. This study noted that PD+FOG made more anti-saccade errors, which were related to grey-matter loss in visual, frontal, and parietal regions[136]. Interestingly, no differences in pro- or anti-saccade latency were noted between freezer subgroups, suggesting the oculomotor impairment was specific to response inhibition and not selection. Since freezing is associated with a maladaptive response to increased cognitive-motor demand and impaired automaticity, the link between freezing and oculomotor function merits further investigation.

In this study, we investigated automaticity and control using an anti-saccade task in PD-FOG and PD+FOG relative to healthy adult controls. We hypothesized that PD+FOG would demonstrate impaired saccade automaticity, as evidenced by slowness of movements and prolonged response latency during both pro- and anti-saccades compared to PD-FOG and controls. In contrast, we predicted that PD-FOG would be slower and more variable during volitional anti-saccades compared only to controls. This work aimed to increase our knowledge of the oculomotor system in PD-FOG and PD+FOG in an effort to better understand the impact of freezing as a potential global motor disturbance and inform the development of treatment approaches to address freezing.

4.3 Materials and Methods

4.3.1 Participants

A sample of twenty six people with PD (13 PD-FOG and 13 PD+FOG) and twelve age-matched neurologically healthy older adults took part in the study. PD participants were recruited from the Movement Disorders Center at Washington University School of Medicine and had a diagnosis of idiopathic PD as defined by previous criteria[105]. Healthy older adults were recruited from a volunteer database managed by the Department of Psychological & Brain Sciences at Washington University. All subjects were free of other neurological conditions including dementia (Montreal cognitive assessment (MOCA) > 21[137]), and were able to walk independently with or without an assistive device. Additionally, PD participants were excluded if they were unable to tolerate medication withdrawal or had previous deep brain stimulation surgery. Given our sample size, the effect size was calculated to be 0.48, assuming 80% power and Type I error rate of 5%.

We classified the group of PD participants as freezers (PD+FOG) and non-freezers (PD-FOG) based on self-report of freezing episodes over the past month using the New Freezing of Gait Questionnaire (NFOGQ), a reliable instrument which uses both written and video descriptions of FOG to determine FOG severity[104]. If the participant reports s/he has not experienced any freezing episodes over the past month, s/he is classified as PD-FOG and given a score of zero. If the participant responds that s/he has experienced freezing over the past month, s/he is asked additional questions about the duration and frequency of episodes and a composite NFOGQ score ranging from 1- 28 is determined. PD participants were evaluated in the off state, defined as at least a 12-hour withdrawal from any anti-Parkinson medication, and clinically evaluated for descriptive purposes using the Movement Disorder Society version of the Unified Parkinson Disease Rating Scale (MDS-UPDRS). Sub-sections I (non-motor symptoms), II (motor aspects of daily living), and III (motor sign severity) were administered and scored by a

trained physical therapist. This protocol was approved by the Human Research Protection Office at Washington University School of Medicine. Participants provided informed consent before participating and were compensated for their time.

4.3.2 Saccade Tasks

We used a modified anti-saccade paradigm to study saccadic eye movements[87,88]. The task parameters were chosen based on previously published best practices for saccade testing in people with neurological conditions[88]. The tasks required participants to either make saccades toward (pro-saccade) or to a symmetrically-opposite location away from (anti-saccade) a visually presented target. Stimuli were presented on a 22'' LCD monitor and controlled by E-Prime v2.0 (Psychology Software Tools, Sharpsburg, PA) on a Dell E6440 Latitude laptop computer. Participants sat approximately 50 cm from the display, which was adjusted to eye level. A chin rest was used to minimize head movement. Participants performed one block of 50 pro-saccades and another block of 50 anti-saccades, the order of which was counter-balanced across participants. The number of trials was chosen both to minimize fatigue and to get reliable estimations of saccade parameters for each participant[88].

Each trial began with a blue or red fixation cross (2.6°) centered on a white background (see Figure 4.1). A blue cross indicated a pro-saccade should be made; a red cross indicated an anti-saccade should be made. Following a random delay period (750-2000 ms), the fixation cross was extinguished and a black circular target (diameter = 1.2°) was displayed randomly to the right or left at 15° eccentricity. Participants were instructed to make the appropriate eye movement as soon as the target appeared. After 1000 ms, the target was extinguished, leaving a white screen for 2500 ms (inter-trial interval). Participants completed 5-10 practice trials of each type before beginning the experiment.

4.3.3 Cognitive Tasks

Two neuropsychological tests, the Go-NoGo (GNG) and Trail-making tests (TMT), were administered to assess general cognitive function. The GNG task tests processing speed as well as response inhibition, and consisted of a string of letters or the number “5” presented individually for 750 ms (stimulus inter-stimulus interval = 1250 ms, total trials = 150). The GNG was administered with EPrime v2.0 on the same laptop computer as used during the saccade tasks. Participants were instructed to press the spacebar key as quickly as possible whenever a letter (target) appeared on the screen, but to not press the key when the number “5” (foil) appeared. Up to 10 practice trials were performed for familiarization. False alarm rate (number of responses to foils/total number of trials), miss rate (number of non-responses to targets/total number of trials), and reaction time (RT, correct responses only) were calculated. The TMT requires the participants to connect a series of numbers (TMT A) or alternate between numbers and letters (TMT B). To account for differences in visuomotor speed and to address task-set switching, the difference in completion time between TMT B and A was reported.

4.3.4 Data analysis

Eye movement data were collected using a binocular head-mounted videooculography system (Eye-Trac 6, Applied Science Laboratories, Bedford, MA). This system detects eye position using both pupil and corneal reflection and is accurate to < 1°. For each participant, the system was calibrated using a 9-point display and an array of 5 targets at known eccentricities (to convert voltage signal to angular position). Raw eye position from both eyes was measured at 120 Hz for 1000ms, beginning at target onset. All analyses were performed using custom written Matlab scripts and built-in functions (R2011b, The Mathworks Inc., Natick, MA). Raw position data were low-pass filtered at 30 Hz, and velocity and acceleration profiles were calculated based on position-time and velocity-time differentiation, respectively. Movement onset was determined when the first saccade following target onset exceeded 30°/s and 8000

°/s^2 [138]. Trials were labeled as invalid and excluded if no saccade was detected or if excessive blinking or eyelid drooping contaminated the signal. Saccade errors were defined as a measured saccade made in the incorrect direction; these trials were marked as errors and excluded from further analysis[139]. Our primary outcome variables were saccade latency, gain (saccade amplitude normalized to target amplitude), and peak velocity, which were calculated for all remaining trials (non-error valid trials). In addition, we calculated saccade error rate as the ratio of error trials to valid trials. There were no valid trials with latencies less than 100 ms, which represents the threshold for preparatory or anticipatory saccades[93], thus we did not exclude any saccades based on latency from our results.

4.3.5 Statistical analysis

Statistical procedures were carried out using SPSS v23 (IBM Corp, Armonk, NY) and Matlab v2011b. Baseline demographic and cognitive data were compared using one-way ANOVA (comparing all groups) and independent samples t-tests (comparing PD-FOG and PD+FOG) for continuous and normally distributed variables and Mann-Whitney U tests for categorical or non-normally distributed variables.

We examined saccade latency and velocity across all trials in each group (fixed-effects analysis) and at the group level (mixed-effects analysis). In the fixed-effects analysis, we computed cumulative distribution functions of latency, velocity, and gain and compared them using 2-sample Kolmogirov-Smirnov (K-S) tests. Since three comparisons were needed, we accounted for multiple comparisons by adjusting α as: α/n, where n is the number of K-S tests performed. In the mixed-effects analysis, an individual measure of central tendency and variability was calculated for each participant. Because of non-normal distributions, median and interquartile range (IQR) were used for latency while mean and standard deviation (SD) were used for velocity and gain. Then, a mixed-effects ANOVA model was used to compare the

between-subjects effect of group (CTRL/PD-FOG/PD+FOG) and within-subjects effect of task (pro-saccade/anti-saccade) in the block condition. Finally, we used bivariate Pearson correlations to explore the relationship between clinical and oculomotor variables separately in the two PD groups. We chose to examine clinical characteristics of PD (disease severity and levodopa equivalent daily dose (LEDD)) and cognitive function (MOCA) given their associations with oculomotor function[128,140]. For all tests, unless otherwise stated, the level of significance was set at $\alpha = 0.05$.

4.4 Results

Demographic and clinical characteristics of participants are shown in Table 4.1. Groups did not differ by age (p= 0.20) or cognitive function (MOCA score, p=0.68). PD+FOG participants had greater disease duration, took greater doses of dopaminergic medication and had worse non-motor disease severity (MDS-UPDRS I, p = 0.012). Motor aspects of daily living (MDS-UPDRS II, p = 0.085) and motor sign severity (MDS-UPDRS III, p = 0.35) did not significantly differ between the two PD groups. In the blocked condition, there was a floor effect such that median error rate for pro-saccade was zero in all groups. Thus, we analyzed error rate for just the anti-saccade task. PD-FOG groups committed more errors compared to CTRL (Table 4.1), however rates were similar between PD+FOG and PD-FOG (post-hoc, p=0.83) and PD+FOG and CTRL (post-hoc, p = 0.08). There were no significant differences in GNG RT, false alarm rate, miss rate, or TMT completion time.

4.4.1 Saccade latency

Group distributions and average data for block saccade latency are shown in Figure 4.2. PD+FOG distributions differed from both PD-FOG and CTRL for pro-saccades (2-sample K-S test; PD+FOG vs. PD-FOG: $p < 0.01$, PD+FOG vs. CTRL: $p < 0.01$) and anti-saccades (PD+FOG vs. PD-FOG: $p < 0.001$, PD+FOG vs. CTRL: $p < 0.001$), while the PD-FOG

distribution was not different than CTRL (pro-saccade: p = 0.60, anti-saccade: p = 0.81). Group average of individual median latencies showed significant main effects as expected for task (Figure 4.2C; anti-saccade > pro-saccade, F(35,1) = 145, p <0.001) as well as group (F(35,2) = 4.30, p= 0.02). Post-hoc t-tests revealed anti-saccade latency was greater in PD+FOG compared to CTRL (t = -3.36, p <0.01) and PD-FOG (t = -2.75, p = 0.01). No differences were noted between PD-FOG and CTRL. Across all trials, anti-saccade latency variability as measured by IQR was largest in PD+FOG (Figure 4.2B). Group mean of individual variability revealed only a significant task effect, confirming that latency variability increased during anti-saccades (Figure 4.2D; F(33,1) = 8.27, p = 0.01).

4.4.2 Saccade velocity

The group distribution of saccade velocity indicated that PD+FOG group made more frequent low-velocity saccades, particularly during the anti-saccade task (Figure 4.3A and B). When comparing both pro- and anti-saccade velocity distributions, significant differences were noted for each pairwise comparison of the three groups (2-sample K-S test, ps<0.001). However, average group data of peak velocity showed only a significant main task effect (Figure 4.3C; pro-saccade>anti-saccade, F(35,1) = 45.8, p<0.001). Analysis of individual velocity variability (SD) showed both a main task (Figure 4.3D; F = 12.8, p = 0.001) and group (F(33,2) = 4.48, p = 0.02) effect. Post-hoc testing showed that both PD groups had greater velocity variability for pro-saccades (PD-FOG vs. CTRL: t = -3.38, p < 0.01; PD+FOG vs. CTRL: t = -2.623, p= 0.02). PD+FOG was also more variable compared to CTRL (t = -2.02, p = 0.06) and PD-FOG (t = -2.01, p = 0.06), but these comparisons failed to reach significance.

4.4.3 Saccade gain

As expected based on saccade main sequence relationships, saccade gain showed similar patterns to the velocity data. Figures 4.4A and 4B show the group distribution of saccade gain

across groups. For pro-saccades, the CTRL distribution was significantly different than the PD-FOG ($p<0.001$) and PD+FOG ($p<0.001$), however there was no difference between the PD groups ($p = 0.35$). There were significant differences in gain distribution between all three groups for anti-saccades ($ps<0.001$). Mean individual gain depicted in Figure 4.4C showed non-significant task ($F(33,2) = 3.85$, $p = .06$) and group ($F(33,1) = 1.21$, $p = 0.31$) effects. There was a significant task effect for gain variability, as measured by the coefficient of variation ($F(33,2) = 36.6$, $p < 0.001$), indicating variability was greater during anti-saccades (Figure 4.4D). No group effect for gain variability was noted ($F(33,1) = 2.28$, $p = 0.12$).

4.4.4 Relationship of saccade parameters to clinical features

Disease severity (MDS-UPDRS III) was significantly related to pro-saccade velocity ($r = -0.55$, $p = 0.05$) and gain ($r = -0.62$, $p = 0.02$), anti-saccade latency ($r = 0.69$, $p = 0.01$) and error rate in PD-FOG ($r = 0.58$, $p = 0.04$). In addition, MOCA score was significantly related to anti-saccade error rate only in PD-FOG ($r = -0.59$, $p = 0.04$). The only significant correlation in PD+FOG was between LEDD and pro-saccade velocity ($r = -0.55$, $p = 0.05$).

4.5 Discussion

In this study, we investigated the automaticity of the oculomotor system in people with PD with and without FOG. Overall, PD+FOG were slower to initiate both automatic pro-saccades and non-automatic anti-saccades. Saccade velocity and gain were also impacted, as PD+FOG made more frequent slow, low amplitude saccades during both conditions compared to PD-FOG. This is the first study to our knowledge to demonstrate differences in timing and execution of saccadic eye movements between PD-FOG and PD+FOG.

4.5.1 Saccade performance and response automaticity

Several previous studies consistently show that PD participants commit more errors and are slower, both in terms of velocity and latency, during anti-saccades compared to pro-saccades[92,93,139]. This observation fits with general deficits in reflexive response inhibition and slowing of internally-generated motor responses in PD[141]. However, the association between freezing and cognitive-motor function of saccades has been less examined. We noted that PD+FOG were slower to respond during both saccade tasks when compared to PD-FOG and CTRL. It is noteworthy that we detected differences during pro-saccades, for which evidence regarding the effect of PD is mixed[89,92,93,142]. In prior studies, subgroups of freezers and non-freezers were not considered, which may have masked any differences and perhaps contributed to the varied results. Visually-elicited pro-saccades are thought to be automatic movements because they require little control from the frontal cortex and basal ganglia[86]. The increased latency in pro-saccades for the PD+FOG group may be related to increased cortical input needed to execute the movement. Despite the differences between gait and saccades, these data support the idea that there is a common deficit in automaticity unique to FOG, where performance of automatic movement requires additional control via the cerebral cortex[76].

Increased variability is also associated with less automatized movement and is characteristic of movement in PD[101] and PD+FOG[29]. There were clear differences in velocity and gain variability for PD+FOG, as seen in the elevated SD and near-linear shape of the distribution functions in Figures 4.3A and B and 4.4A and B. At the group level, both PD groups showed greater pro-saccade velocity variability relative to CTRL, while anti-saccade variability was also larger in PD+FOG. Together, these results show that the range of saccade velocities is wider both within and across PD+FOG participants. Surprisingly, average velocity and gain were not different across groups, primarily because PD groups made hypermetric and high velocity saccades that

shifted the mean closer to that of the CTRL group. In general, variability may be associated with the target amplitude of each saccade (15°), which was relatively large compared to other studies[92,93]. As such, participants may have produced large high-velocity saccades to compensate, thereby increasing variability. Another factor that may influence variability is fatigue, which is likely to be worse in the PD groups. We did not formally assess fatigue but required participants to complete a manageable number of consecutive trials and provided rest breaks in between sets to minimize fatigue. While these factors may contribute to some of the observed differences, velocity and gain variability was overall pronounced in PD+FOG, supporting further that automaticity of saccades may be impaired in this group.

Interestingly, PD+FOG anti-saccade error rates were similar if not slightly lower than PD-FOG (Table 4.1). This is in contrast to a recent study showing that error rates were elevated in PD+FOG during a similar anti-saccade task and were associated with grey matter loss in many cortical regions[136]. At minimum, there are two processes that need to occur for a successful anti-saccade: 1) inhibition of a pro-saccade and 2) execution of a non-visually guided saccade[86,143]. The Walton et al. study suggests that saccade inhibition is impaired in PD+FOG, related to a problem with cognitive control. It is unclear at the moment why we also did not see increased error rates in the PD+FOG group. The results from our GNG task also show that there were no significant differences in response inhibition between groups, which agrees with previous work[79]. Therefore, there is a distinction between the inhibitory control required for the cognitive and saccade tasks. One major difference between these tasks is that the GNG does not require an alternate motor response following inhibition of the automatic response. While there is likely an inhibitory control problem associated with PD, our data show that the difficulty unique to PD+FOG involves executing the anti-saccade, as seen in the large differences in anti-saccade latency compared to PD-FOG and CTRL (Figure 4.2B and 2C). The saccade velocity and gain data further support this idea given that the proportion of low velocity, low gain

saccades was greater in PD-FOG compared to PD-FOG and CTRL. The deficit of anti-saccade execution in PD+FOG may be due to an inability to release inhibition on the oculomotor circuit. Other studies examining the role of deep brain stimulation (DBS) on oculomotor function indicated that subthalamic nucleus DBS (STN-DBS) improves anti-saccade latency but does not improve error rates[144-146]. DBS stimulation may normalize the inhibitory drive of the substantia nigra pars reticulata on the oculomotor circuit, thereby allowing for more efficient saccade performance. Overall, additional research using saccade tasks that isolate response inhibition and execution in conjunction with neurophysiological techniques is needed to fully explore the impact of both PD and FOG on oculomotor and cognitive function.

Two potential confounds when examining the effects of FOG are disease severity and medication usage. Typically, PD+FOG occurs later in disease progression and thus is associated with greater disease severity[14]. Therefore, any FOG-specific differences may simply be due to worsened motor signs. Our PD groups were well matched for disease severity as measured by the MDS-UPDRS-III (Table 4.1). The correlation analysis also showed that latency, velocity, gain and error rates were significantly related to disease severity, but only in PD-FOG. This suggests that saccade performance may be less dependent on overall motor function in PD+FOG, further supporting the link between FOG phenotype and impaired oculomotor function. Participants were also tested off dopaminergic medication, thus controlling for effects of medication use on saccade output. Still, it is unclear how saccade performance would change if participants were then tested in a medicated state. Previous work showed dopaminergic medication led to increases in latency variability[142]. It is possible, then, that saccade variability would be increased in PD+FOG when on medication, as PD+FOG were on higher doses of medication compared to PD-FOG. In some cases, medication will alleviate gait freezing duration and frequency, while in other cases FOG episodes are worsened with

medication[15]. The relationships between non-gait freezing and medication use remain to be explored.

4.5.2 FOG represents a global motor dysfunction

Our results contribute to the growing body of evidence that freezing affects gait and non-gait movements alike[27-29,147]. Together, these studies suggest that the pathophysiology underlying FOG may be a common contributor to motor dysfunction. While festination or freezing of the upper limb and speech have been documented, pure oculomotor freezing has yet to be reliably reported. One study noted that during a rhythmic saccade task, some subjects "froze" between consecutive saccades[148]. In our data, some saccade traces showed features similar to gait freezing, such as increased frequency and small amplitude. However, it is difficult to directly compare saccades and gait freezing, given the differences in movement amplitude, rhythmicity, and velocity. While the current evidence shows a general deficit of cognitive-motor processing may underpin freezing, the actual manifestation of freezing may differ across various effectors. For instance, one recent experiment showed that upper-limb and lower-limb freezing co-occur in PD, but are not correlated[29]. Future studies that manipulate the timing of stimuli (e.g. rhythmic saccades) or the cognitive demand (e.g. difficult dual-tasks), may be helpful in directly comparing motor behavior across body parts or movement types. This may lead us toward approaching freezing as a global motor phenotype that reflects impairment not just of gait but of the entire motor system.

4.6 Conclusion

Latency, velocity, and gain of automatic and non-automatic saccades were different across groups of people with PD with and without FOG. Additional deficits in saccade automaticity were evidenced by increased velocity and gain variability across and within participants. Overall, our results support the idea that FOG is a distinct phenotype in PD with an underlying

pathophysiology related to impaired cognitive-motor control. Furthermore, this deficit impacts multiple effectors and it not limited to gait alone. Additional work is needed to fully elucidate how freezing impacts automaticity across motor systems.

Table 4.1

Table 1. Subject Demographics and Cognitive Task Data

Demographics	**CTRL (n= 12)**	**PD-FOG (n=13)**	**PD+FOG (n= 13)**
Age (yr)	72.3 ± 5.28	68.1 ± 7.04	68.7 ± 5.84
Sex (# male)	4	5	7
MOCA	26.4 ± 2.43	26.3 ± 2.78	25.6 ± 2.18
Years since diagnosis		4.73 ± 3.93	8.73 ± 5.93
LEDD (mg)		691 ± 734	1043 ± 684
MDS-UPDRS-I		7.23 ± 3.00	13.2 ± 7.06*
MDS-UPDRS-II		8.08 ± 5.35	11.9 ± 5.09
MDS-UPDRS-III		36.3 ± 13.3	40.4 ± 7.72
NFOGQ			10.9 ± 5.54
[a]Anti-saccade error rate (%)	15.8 ± 18.6	34.6 ± 37.8^	25.4 ± 42.6
Cognitive Tasks			
[a]GNG RT (ms)	400.0 ± 44.0	414.0 ± 43.5	392.0 ± 70.5
GNG False Alarm (%)	4.33 ± 3.86	3.49 ± 2.08	3.90 ± 2.69
GNG Misses (%)	0.72 ± 1.15	0.46 ± 0.69	1.23 ± 0.64
TMT B-A Completion Time (s)	46.4 ± 20.7	45.9 ± 19.7	68.6 ± 47.1

Values represent Mean ± SD; [a]Median ± IQR. MOCA: Montreal Cognitive Assessment; LEDD: Levodopa equivalent daily dose; MDS-UPRDS: Movement Disorder Society Unified Parkinson Disease Rating Scale I (Non-motor) II (Motor Aspects of Daily Living III (Motor Assessment), NFOGQ: New Freezing of Gait Questionnaire; GNG: Go-NoGo; RT: Reaction Time; TMT: Trail-making task. *Significantly greater than PD-FOG ($p<0.05$); ^Significantly greater than CTRL ($p<0.05$)

Figure 4.1. Anti-saccade paradigm. A blue fixation cross indicated a pro-saccade trial while a red cross indicated an anti-saccade trial. Fixation was maintained for a variable period (750-2000 ms, blue/red bar), and the target (black bar) appeared immediately after the fixation cross was removed. A correct saccade is shown in the gray trace.

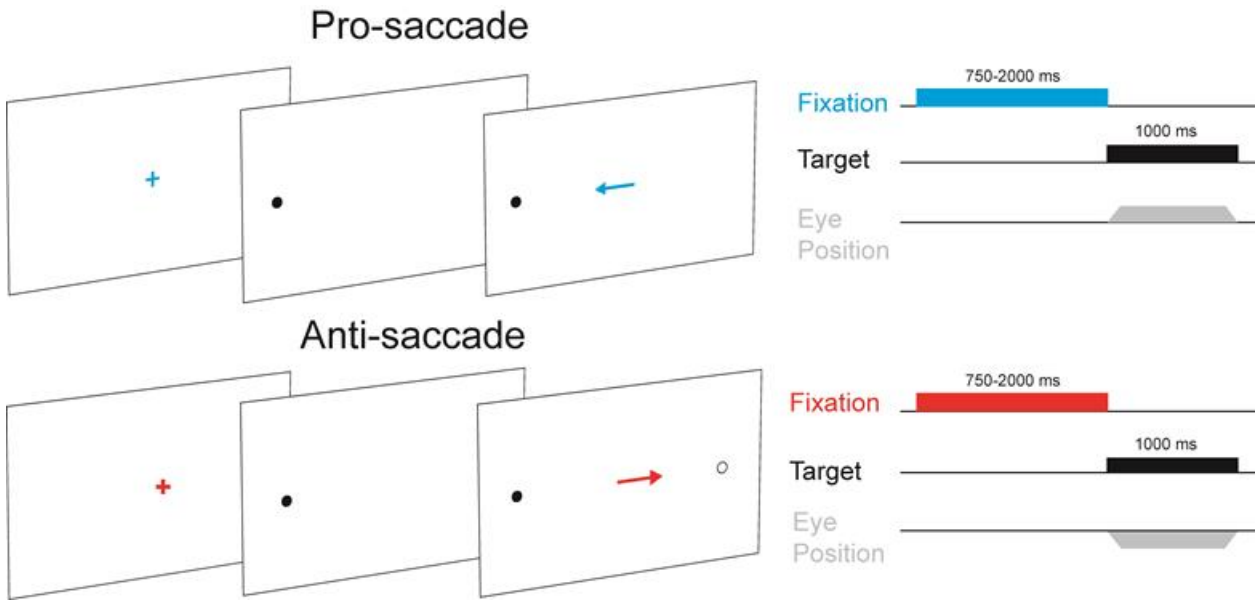


Figure 4.2. Saccade latency. ***Top row:*** **Latency distributions for pro-saccade (A) and anti-saccade (B).** ***Bottom row:*** **Group mean (C) and variability (D) of pro-saccade and anti-saccade latency across groups. Dotted lines in (A) and (B) represent 95% confidence bands. Error bars in (C) and (D) represent ± 1 SD. *p<0.05, **p<0.01 (between-subjects effect), #p<0.05 (within-subjects effect, anti-saccade > pro-saccade)**

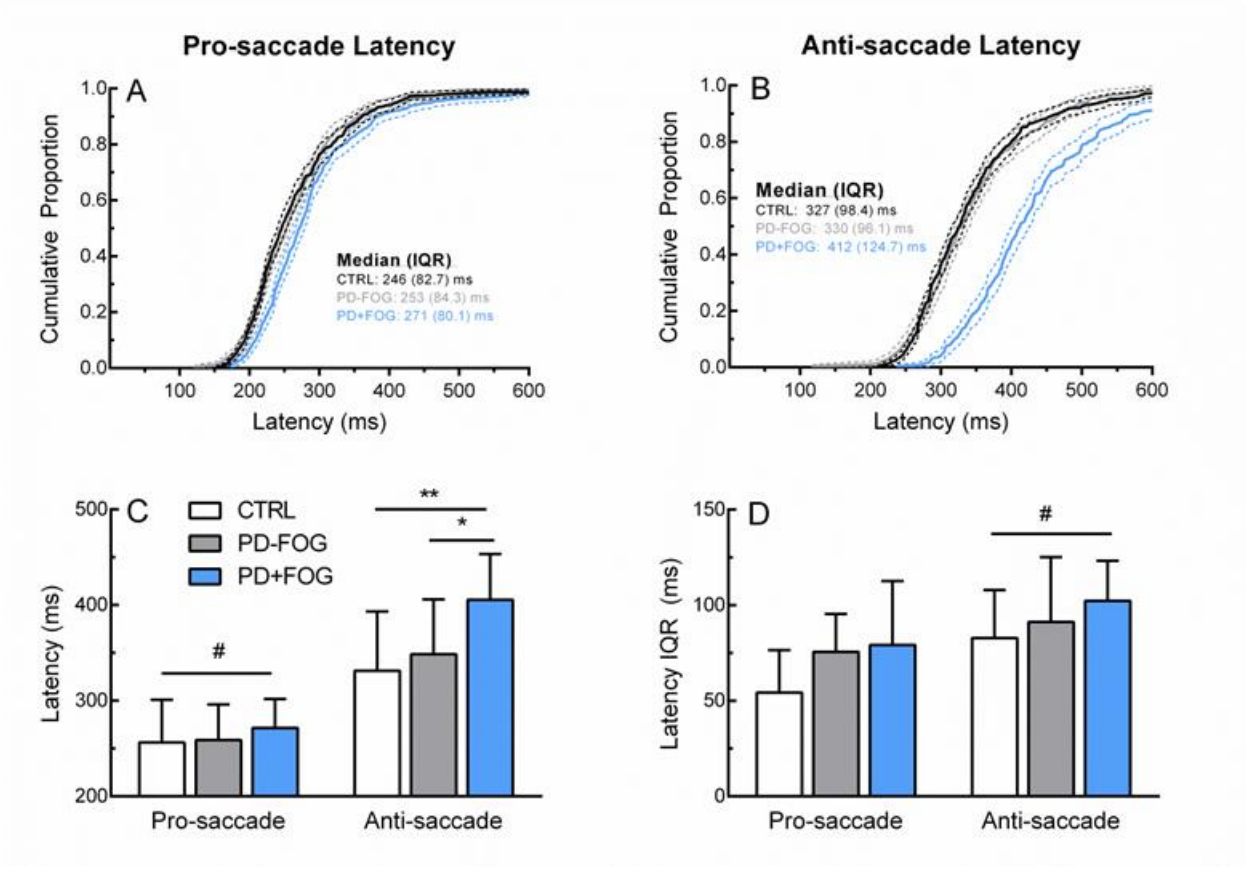


Figure 4.3. Saccade velocity. ***Top row:*** **Velocity distributions for pro-saccades (A) and anti-saccades (B).** ***Bottom row:*** **Group mean (C) and variability (D) of pro-saccade and anti-saccade velocity across groups. Dotted lines in (A) and (B) represent 95% confidence bands. Error bars in (C) and (D) represent ± 1 SD. *p<0.05, **p<0.01 (between-subjects effect), #p<0.05 (within-subjects effect)**

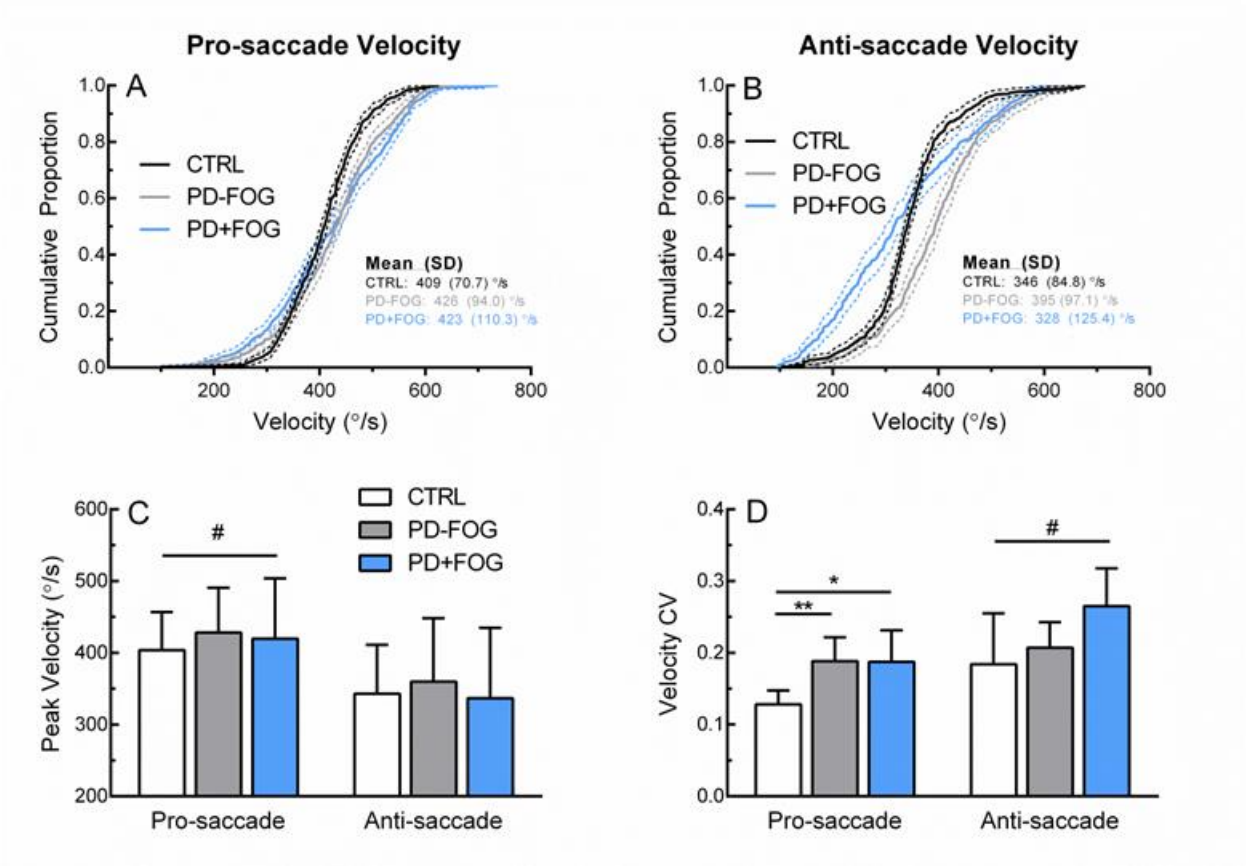
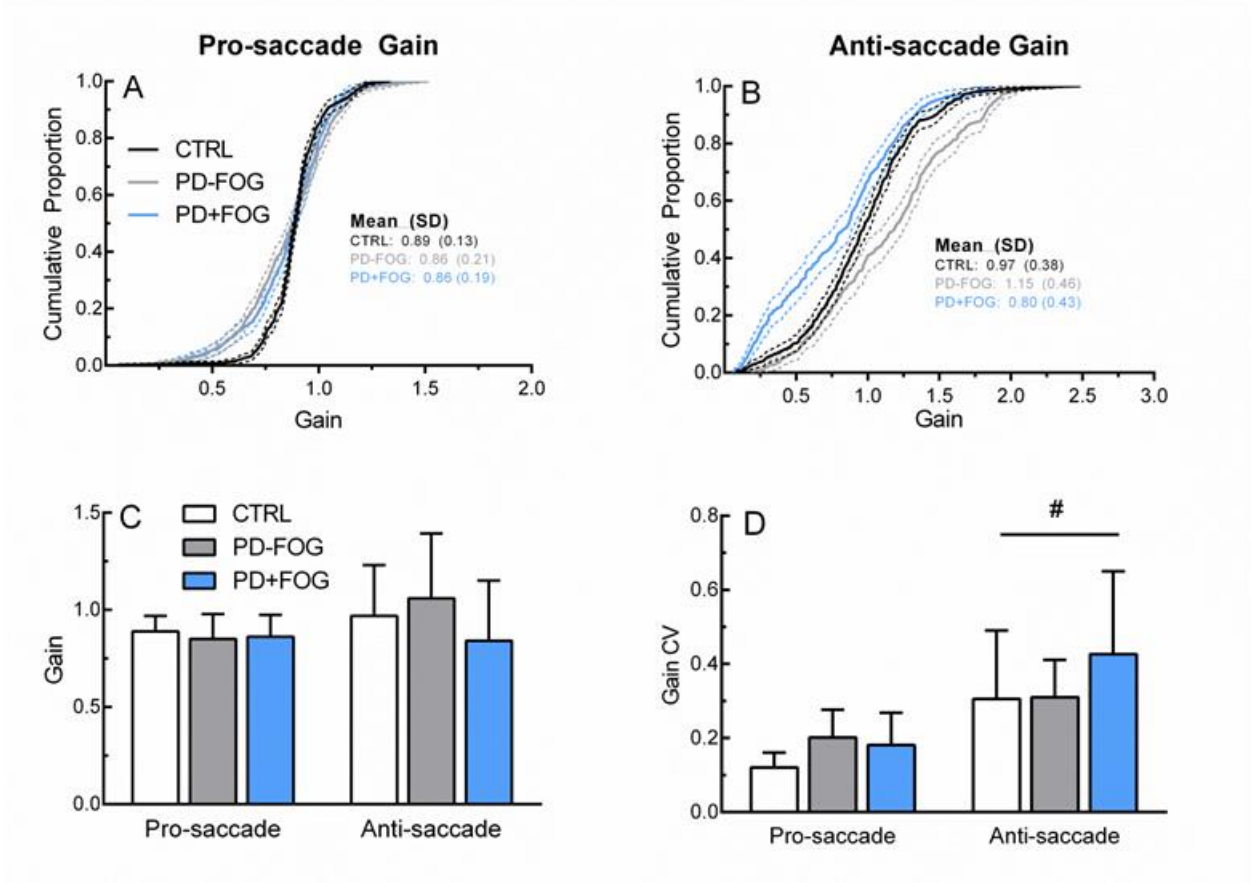


Figure 4.4 Saccade gain. ***Top row:*** **Gain distributions for pro-saccades (A) and anti-saccades (B).** ***Bottom row:*** **Group mean (C) and variability (D) of pro-saccade and anti-saccade gain across groups. Dotted lines in (A) and (B) represent 95% confidence bands. Error bars in (C) and (D) represent ± 1 SD.** $^{\#}$**p<0.05 (within-subjects effect).**



The same protocol and tasks outlined in Chapter 4 were used to study reaching movements in the same participants, but were not published in this manuscript. There were no significant relationships between reaching kinematics between groups or across tasks that were notable. Nevertheless, we report the data for the reaching experiment here. These figures are analogous to Figures 4.2-4.4.

Figure 4.5. Reaching latency. ***Top row:*** **Latency distributions for pro-reach (A) and anti-reach (B).** ***Bottom row:*** **Group mean (C) and variability (D) of pro-reach and anti-reach latency across groups. Dotted lines in (A) and (B) represent 95% confidence bands. Error bars in (C) and (D) represent ± 1 SD. *p<0.05, **p<0.01 (between-subjects effect), #p<0.05 (within-subjects effect, anti-reach > pro-reach)**

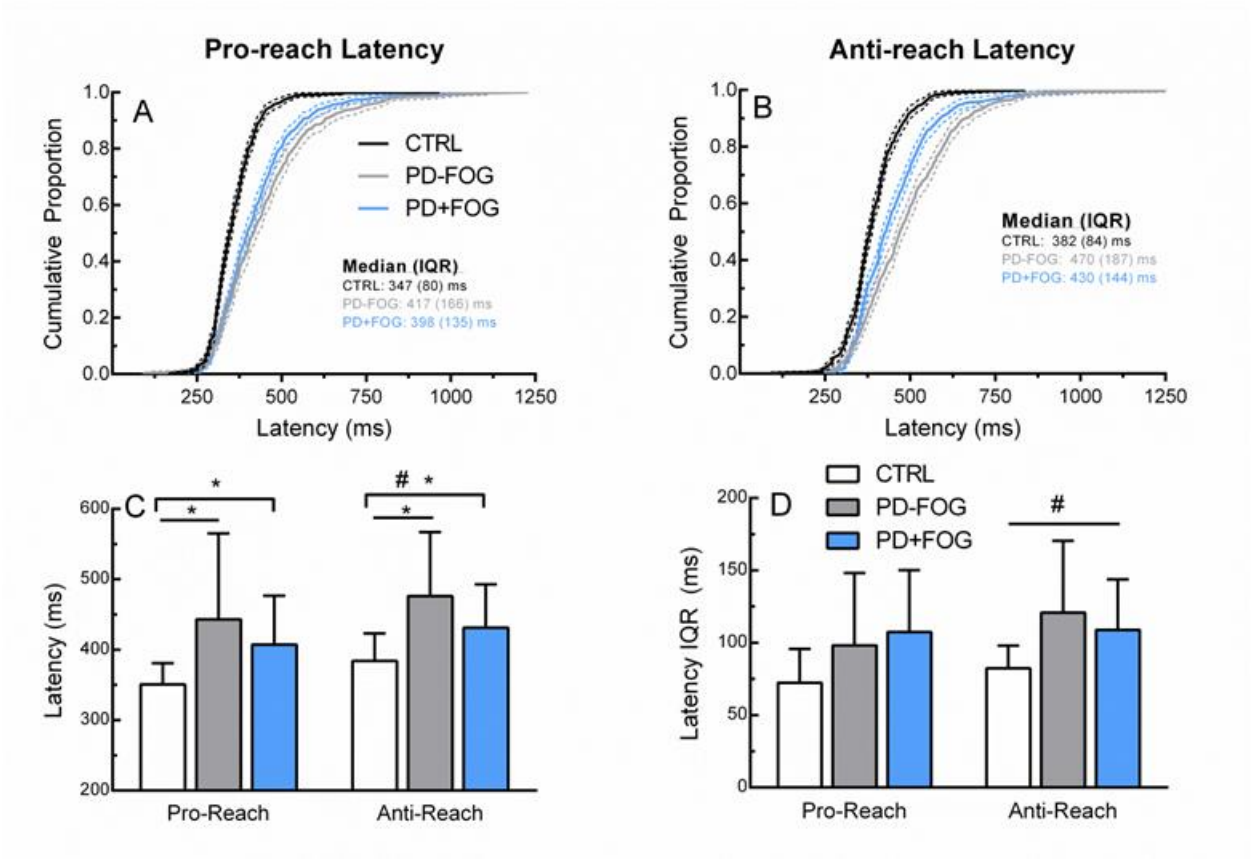


Figure 4.6. Reach velocity. ***Top row:*** **Velocity distributions for pro-reach (A) and anti-reach (B).** ***Bottom row:*** **Group mean (C) and variability (D) of pro-reach and anti-reach velocity across groups. Dotted lines in (A) and (B) represent 95% confidence bands. Error bars in (C) and (D) represent ± 1 SD. *p<0.05, **p<0.01 (between-subjects effect)**

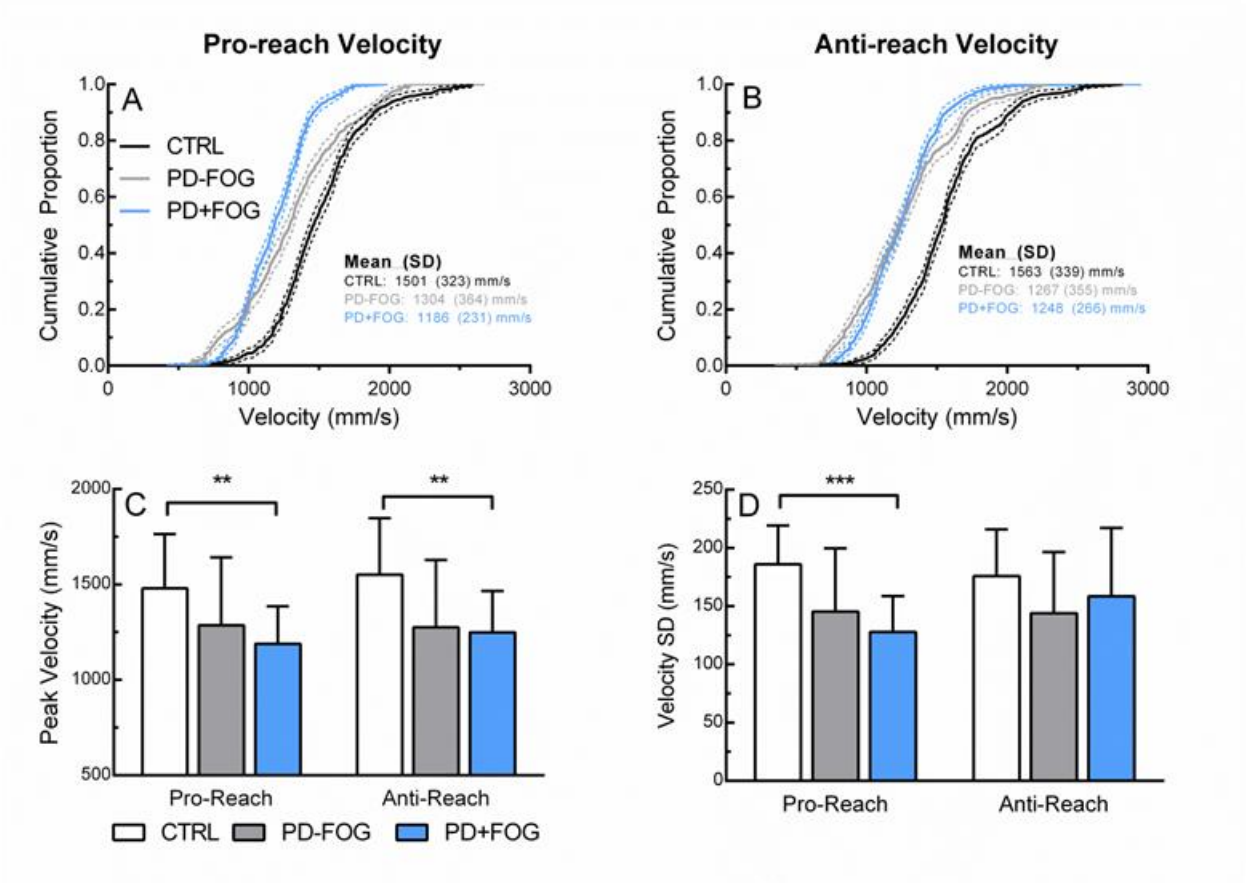


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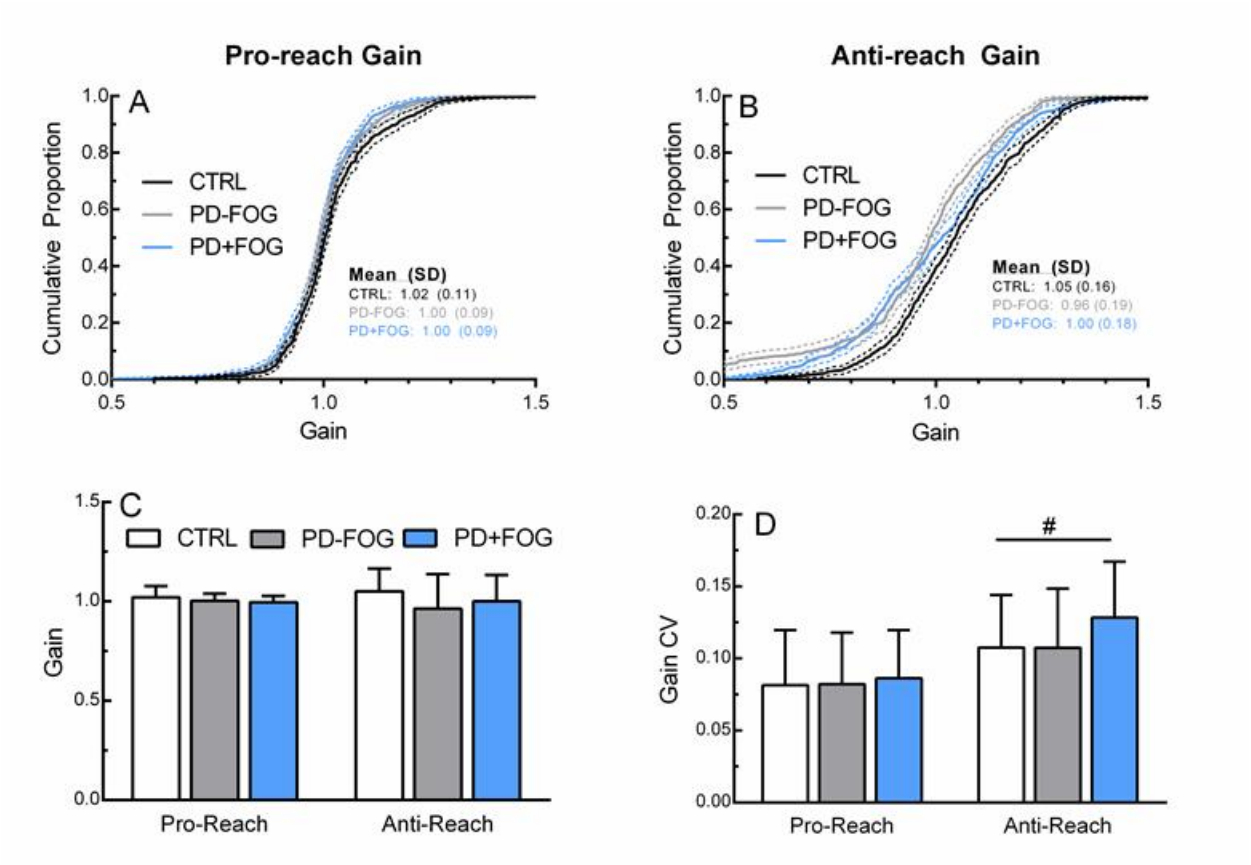
Figure 4.7. Reach gain. ***Top row:*** **Velocity distributions for pro-reach (A) and anti-reach (B).** ***Bottom row:*** **Group mean (C) and variability (D) of pro-reach and anti-reach gain across groups. Dotted lines in (A) and (B) represent 95% confidence bands. Error bars in (C) and (D) represent ± 1 SD.** [#]**Anti-reach > Pro-reach, p<0.01 (within-subjects effect)**



Chapter 5: General discussion, clinical implications, and future directions

5.1 Summary of findings

In this dissertation, we studied aspects of movement control in people with PD and freezing of gait in an effort to understand how this phenotype is related to ability to adapt movement and generate automatic movements. In this chapter we summarize the main findings of these experiments and how they support or challenge existing knowledge regarding motor control in both PD and PD+FOG.

5.1.1 Adaptation rate in PD and FOG

The objective of Chapter 2 was to determine if the cerebellum is differentially affected in PD+FOG by measuring motor adaptation, a process that strongly involves the cerebellum[41,46]. For reaching and walking tasks alike, the rate of adaptation was not different between freezers and non-freezers, nor was it different between the PD and healthy older adult groups. Furthermore, the magnitude of adaptation was similar across groups, indicating that the prism glasses elicited a similar amount of error in all participants. Previous data regarding adaptation rate in people with PD are fairly consistent. Two older studies noted that people with PD may have a modest reduction in adaptation rate, but overall their performance resembled that of older adults[47,50]. The suggestion that PD does not impact adaptation rate has been confirmed by more recent studies[48,49,149,150]. Our data align with these studies, and overall strengthen the argument that people with PD can adapt their movements to visual perturbations. In contrast, Contreras-Vidal and Buch noted that a group of people with PD exhibited greater errors during late adaptation, indicating they did not consistently reduce their errors, showing overall slower adaptation[112]. One important difference in this study is that the authors employed a large (90°) visual distortion via a monitor, rather than using prism glasses, which distort the visual field to a lesser extent (10-20°). This likely resulted in a greater reliance on explicit (i.e. cortico-striatal) rather than implicit (i.e. cortico-cerebellar) movement correction, thus revealing a PD-specific impairment[56,106]. To add, participants performed many more trials (~400) to reach full

adaptation, which may have resulted in fatigue in those with PD. In any case, the majority of data, including ours, point to the conclusion that PD does not impact visuomotor adaptation rate when perturbations are relatively small. Furthermore, our study also indicates that the FOG phenotype does not affect adaptation, suggesting that cerebellar function underlying prism adaptation is normal in those who experience FOG. Previous neuroimaging studies point to the cerebellum, particularly the CLR, as a locus of dysfunction in PD+FOG[33,34,36,151]. The fact that we did not find behavioral evidence of cerebellar impairment in PD+FOG during prism adaptation may be related to cerebellar anatomy. Visuomotor adaptation elicits widespread activation of the posterior cerebellum and is likely focused in the dentate nucleus[57,113,152]. Thus, it is plausible that the lateral regions of the cerebellum, which include the dentate nucleus, are functionally intact in PD-FOG and PD+FOG, resulting in normal visuomotor adaptation. We expected to see differences in walking adaptation, given that walking control is localized in the spinocerebellum, overlapping with the CLR[153]. Instead, walking adaptation was also normal, suggesting that visuomotor adaptation as a neural process is regulated in the lateral cerebellum regardless of the motor effectors involved. This idea is also supported by anatomical evidence of significant visual projections to regions in the lateral cerebellum[154].

Interestingly, locomotor adaptation on a split-belt treadmill is impaired in PD+FOG[40,62]. In the Appendix chapter we show that the storage of novel locomotor patterns may be blunted in freezers. These adaptation tasks sharply contrast the prism adaptation studies in that they involve spatiotemporal changes in gait rather than visually-induced transformations. Spatiotemporal control of gait is likely controlled by medial regions of the cerebellum including the CLR[110,111], supporting previous neuroimaging findings in PD+FOG as described above. Therefore, cerebellar dysfunction in PD+FOG may be specific to adaptation of the timing and placement of steps during gait rather than to adaptation of walking due to visual perturbations.

Other gait studies confirm this notion, noting impaired spatiotemporal properties of walking in PD+FOG[19,21,155].

5.1.2 After-effect magnitude in PD and FOG

The after-effect is an important feature of normal adaptation because it reveals how fully the new sensorimotor relationship is retained in the nervous system[50,109]. Typically, the after-effect is measured as the magnitude of error following removal of the sensory perturbation. There were significant differences in the after-effect magnitude during both reaching and walking adaptation between the groups in Chapter 2. Specifically, the non-freezer (PD-FOG) group showed the smallest after-effect compared to freezers and older adults. Surprisingly, however, the freezer group showed similar after-effects compared to older adults. These results both support previous findings and offer new data regarding the association between freezing and retention of visuomotor adaptation. In past studies of prism adaptation in PD, several papers noted differences in performance between PD and control groups during the Post-Adaptation phase. Stern et al. showed a faster decay of performance in a group of PD subjects, suggesting a relationship between PD and strength of newly learned sensorimotor memories[50]. In addition, Fernandez-Ruiz showed smaller initial after-effects following prism adaptation in PD subjects[49]. In healthy adults, the striatum is among the many structures showing increased activation during de-adaptation[52]. Taken together, these studies provide behavioral and neurophysiological evidence that the basal ganglia are involved in storage and/or retention of visuomotor adaptations. Our data of reduced after-effects in the PD-FOG group support this idea, however one would expect to also observe this in the PD+FOG group. One explanation for this disparity is the relationship between adaptation rate and magnitude of after-effect: if a subject adapts faster and thus performs more movements while fully adapted, the sensorimotor relationship is strengthened, leading to an increase in after-effect magnitude[109]. However, there were not significant differences in adaptation rates between PD-FOG and PD+FOG. In fact, we

did not observe any relationships in our data that would explain these findings and therefore can only speculate on what is driving this difference One possibility is the dynamic changes in brain network connectivity that occur in PD and FOG. FOG is hypothesized to be related to abnormal striato-frontal network activity characterized by hyper-activity in subcortical (i.e. basal ganglia) motor areas and hypo-activity in cortical regions during continuous movement[102,116]. While it remains to be determined if these are compensatory or dysfunctional changes, increased activity in the basal ganglia may help reinforce learned movement patterns, thus resulting in larger after-effect magnitudes in PD+FOG. In any case, our data confirm the role of the basal ganglia in the retention of newly learned motor patterns and demonstrate that differing pathophysiology, such as in PD+FOG, may lead to differences in motor behavior.

An important factor in many motor adaptation studies is at what time after adaptation the retention is measured. Thus far, we have defined retention as the immediate negative after-effect observed following removal of the sensory perturbation. Other studies have investigated the effect of PD on retention following a washout period or 24-48 hours following adaptation. In these studies, the premise is that if an individual retains any motor memories, he should show smaller errors and adapt faster when exposed to the sensory perturbation during a second session (i.e. greater “savings”). Several studies demonstrated people with PD having similar performance on adaptation tasks in consecutive sessions, indicating they retain little to none of the novel motor pattern from one session to the next[150,156]. While the after-effect magnitude may be influenced by both the cerebellum and basal ganglia, measures of savings are more strongly related to basal ganglia function[157,158] and indicate how the nervous system selects appropriate motor programs based on a set of environmental conditions. We did not test longer-term retention of prism adaptation, but it would be worth exploring differences in savings between PD-FOG and PD+FOG, which we would expect to diminished in both groups. This may help explain the differences in after-effects observed in our study.

5.1.3 Reaching versus walking adaptation

The experiment in Chapter 2 was the first to show that people with PD can properly adapt walking trajectories to prism glasses relative to older adults. One additional interesting result from this study was that all participants took longer (i.e. more trials) to adapt walking compared to reaching, as quantified by adaptation rate estimates. To further explore this effect, we examined the difference between walking and reaching adaptation in young and older healthy adults (Chapter 3). Based on previous literature describing differences in adaptation rate in older adults, we expected the older group to have slower adaptation rates for both reaching and walking tasks[53-55]. Our second hypothesis was that walking adaptation would be a slower process than reaching, regardless of age. Many studies previously showed that adults can easily adapt walking trajectories to prism glasses[45,46,159], however the direct comparison of adaptation between two tasks was unaddressed in the literature. Our data confirm previous reports of significant aging effects on visuomotor adaptation, although this effect was primarily due to large differences between age groups in the walking task rather than the reaching task. Interestingly, adaptation rates were indeed greater during the walking task in both groups, confirming our initial hypothesis. Therefore, the rate of prism adaptation appears to be related to both age and the motor task or effectors being recalibrated.

Theoretical models of visuomotor adaptation have defined two primary phases of adaptation: strategic control and spatial recalibration[114]. Strategic control is related to explicit knowledge of the movement errors occurring during adaptation, and the use of cognitive judgements to correct these errors[56,160]. Spatial recalibration, on the other hand, is an implicit nervous system process that reduces the discrepancy between sensory feedback and motor output (i.e. performance errors). These two phases, strategic control and spatial recalibration, occur at different time scales during adaptation. Strategic control is more active during the first several

trials of adaptation when errors are large; strategic control is less crucial later in adaptation. In contrast, spatial recalibration is active throughout adaptation, but may be more important during late adaptation when the new sensorimotor relationship is being strengthened. Finally, the neural substrates associated with the two processes are unique as well. The cerebellum is thought to process motor errors and continuously update the sensorimotor mappings between the parietal and motor cortices, thus underlying spatial calibration[57,58,152,161]. Strategic control is related to action selection and inhibition mediated by the dorsolateral prefrontal cortex (DLPFC) and basal ganglia[52,162,163]. Our data support this model since we noted effects of both age (related to declines in strategic control) and task (related to differences in spatial recalibration) on subsequent adaptation rate. The variation in spatial recalibration may be related to the amount brain dedicated to controlling upper limb and walking tasks. One would predict walking has a larger brain representation since it involves complex coordination all four limbs as well as postural muscles. An increase in time needed to recalibrate this more extensive and complex set of motor representations may explain the increased adaptation rate observed in our study. Overall, the processes underlying motor adaptation are similar regardless of what part of the body is adapted, however temporal costs related to the biomechanical "complexity" of the movement may also exist. This idea remains to be tested in various other experimental tasks (see Section 5.3).

5.1.4 Oculomotor function and automaticity in PD and FOG

In chapter 4, we explored another facet of motor control, automaticity, and how it relates to PD and FOG. This experiment focused on saccades, which are highly stereotyped eye movements. Because of the few degrees of freedom associated with saccades relative to other movements, there are predicatble saccade amplitude-velocity relationships[84]. In addition, the neural circuits underlying saccades are well-defined[86,127]. For these reasons, the oculomotor

system is ideal to study movement control and behavior in people with and without neurological injury and disease.

Pro-saccade/anti-saccade tasks have been used to study oculomotor function in many populations[87,92,131]. An advantage of this task is that it manipulates the relationship between stimulus location and motor response. In the pro-saccade condition, the location of the stimulus matches the direction of the required saccade; the spatial feature stimulus-response relationship is congruent. Conversely, during the anti-saccade condition, the stimulus-response pair is incongruent; the location of the required saccade is an inversion of the stimulus location[86]. Other common neuropsychological tests, such as the Stroop Task, elicit similar dissociations between stimulus-response pairing.

Based upon previous data, pro-saccade latency is unaffected (Briand 1999, Cameron 2010) or slightly elevated[89,90] in heterogeneous samples of PD. In contrast, the data regarding anti-saccades are unequivocal: participants with PD are slower to respond and exhibit slower peak velocity during anti-saccades. In Chapter 4, we predicted that FOG-related pathophysiology could also impact oculomotor control. The main finding in our experiment was that both automatic, pro-saccades and non-automatic, anti-saccades are slower and more variable in PD+FOG compared to PD-FOG and compared to older adults. The effect was small yet significant when comparing automatic pro-saccades, which may help explain why other studies using heterogeneous samples of PD reported mixed results: FOG helps explain some variability in saccade function. We were surprised to find the large effect of increased latency and variability in the anti-saccade data, which also showed no significant differences in mean saccade latency between PD-FOG and older adults. Thus, our data show that latency and variability of both automatic and, to a greater extent, non-automatic saccades are associated with FOG.

Automatic pro-saccades are thought to be executed via direct connections from parietal cortex to oculomotor circuits, thus requiring little control from prefrontal cortex and basal ganglia[86]. Under the "cognitive overload" hypothesis, excessive activity from prefrontal cortical regions leads to processing overloads and ultimately to freezing episodes[76]. Indeed, neuroimaging studies show that during freezing there is hyperactivity in prefrontal and motor cortical regions in PD+FOG compared to PD-FOG[102,164]. Given that the frontal cortex can have an inhibitory influence on saccade control[86], it is possible that increased activity in these regions underlies the slowness and variability of pro-saccades shown in our data.

We also noted a large difference in anti-saccade latency between PD+FOG and PD-FOG. Anti-saccades require an inhibitory response to suppress the automatic pro-saccade, as well as a voluntary motor response to execute a non-visually guided saccade. As such, movement preparation for an anti-saccade task is more complex relative to a pro-saccade task. During successful anti-saccades in healthy adults, increases in activity of the DLPFC are thought to reflect inhibitory signals that suppress the pro-saccade, thus representing a set of preparatory commands preceding the motor response[143]. If this signaling is dysfunctional in PD+FOG, we would expect to see an increase in error rate in this group. A recent report comparing oculomotor behavior in PD-FOG and PD+FOG noted more errors in PD+FOG[136]. However in our study, the error rates were greater in the PD groups compared to healthy older adults but similar between PD-FOG and PD+FOG. At the moment it unclear why our data did not match the previous finding, but it may be related to differences in participant samples, general cognition, and task instructions. Another explanation is that poor inhibitory control is a consequence of general PD pathophysiology, as shown in previous studies[79,92,93,141]. The impairment that is specific to PD+FOG may be related not just to applying inhibition but also to

an inability to appropriately release inhibition on oculomotor circuits, explaining the increased latency and variability in the anti-saccade data from PD+FOG.

Another current model of FOG similar to the automaticity or "cognitive" model posits that motor arrests arise from excessive and poor integration of motor, cognitive, and limbic signals, resulting in over-inhibition of subcortical targets (superior colliculus in the case of saccades) of the basal ganglia[126]. The overload in cortico-basal ganglia circuits is related to the demands of the task and environment. In the anti-saccade task, the goal of inhibiting a reflexive pro-saccade and generating a saccade to a mirrored location may have been sufficiently challenging and novel to reveal this dysfunction. The level of dopaminergic depletion may also play a role by modulating this circuit via direct and indirect pathways. While we tested participants off medication, the levodopa equivalent daily dose (LEDD) provides a total amount of dopaminergic medication an individual consumes and is associated with incidence of FOG[16,165]. Indeed, our PD+FOG group took larger daily doses of medication than PD-FOG. Interestingly, there was a significant relationship between LEDD and pro-saccade latency and velocity but no relationship between anti-saccade parameters (Appendix B, Figure B1 and B2). This suggests that the tonic inhibition on the oculomotor circuit may be related to dopaminergic depletion as measured by medication use. Because of the complex interaction between the basal ganglia signaling and dopaminergic medication, it is difficult to directly evaluate the link between these processes and subsequent oculomotor behavior in our study. Previous work noted that dopaminergic medication led to an overall increase in reflexive saccade latency, but there was substantial variability across "on" to "off" conditions[142]. It is unclear at the moment how saccade performance would change if participants were tested while optimally medicated, however one may predict saccade variability would overall be worsened while in the "on" state. By testing participants off medication, we instead measure behavior in the participant's overall

"worst" motor state, which is more closely related to the actual disease mechanisms and avoids medication confounds.

One expected result that was not observed in this experiment was decreased velocity and amplitude of anti-saccades in the PD groups. The group average data yielded no significant differences between groups, but when examining the distribution of velocity between groups, we noted that PD groups did in fact make more frequent low-velocity saccades and had a greater range of saccade velocity (i.e. greater variability). During testing, it was apparent that many participants did not make accurate anti-saccades on many trials. Instead, they made very large saccades that greatly overshot the intended target, perhaps adopting a strategy which minimized anti-saccade errors at the cost of saccade accuracy. This resulted in large amplitude, high-velocity saccades which may have biased the mean saccade velocity toward a value similar to that of older adult controls. Because no explicit instructions were given other than "look as quickly and accurately as possible", the participants likely adopted one strategy (speed or accuracy) over another, resulting in the increased variability. However, the data do align with more modern theories of motor control in PD, which posit that bradykinesia is not related to an inability to perform high-velocity movements, but rather an implicit decision to do so[166]. While we did not test this directly, it is clear that participants with PD are capable of making high-velocity saccades, but also made many low-velocity saccades. This contrasts sharply with older adults, who executed saccades more accurately and with a narrower velocity range[84] (Figure 4.3A/B). Scaling back the target eccentricity may solve this problem, as one review paper reported that people with PD are less hypometric for saccade amplitudes less than 10°[167]. Another way to address the problem of variability would be to provide on-line feedback during each trial, giving a measure of saccade error that would employ motor learning mechanisms. Using this paradigm, one could determine whether performance is improved with external feedback and whether feedback is more beneficial for PD-FOG or PD+FOG.

5.1.5 Comparison of saccades and reaching

While the main finding of the experiment in Chapter 4 pertained to saccade performance, we also aimed to examine motor function during reaching movements to compare two different effectors on the same task. The eye-hand system has been extensively studied because of the strong link reliance of object grasping/manipulation on visual feedback[168,169]. In our data, this relationship is decoupled, allowing us to examine the basic behavioral features, mainly latency and peak velocity, of each movement type. These quantities may reflect basic neural computation and information processing, allowing one to make predictions about how the brain is controlling each movement.

We noted that saccade latencies were consistently shorter than reach latencies (Figure 4.5), regardless of the task condition (pro-saccade/reach or anti-saccade/reach) or group. The difference between reaching and saccadic latency may be due in part to the shorter neural pathway in the oculomotor circuit and lower inertial constraints on eye musculature[85]. However, there was a strong relationship between saccade and reach latencies across participants during the pro-condition (Appendix B, Figure B5A). During the anti-condition however, there was a weaker correlation between the two latencies in the control group (Appendix B, Figure B5B) The correlation between latency measures indicates response time may be an individual property: if you are slow to initiate a saccade, you are likely slow to initiate a reach. This confirms a previous study showing correlation between manual and saccade latencies in PD[170]. In contrast, there were no relationships between saccade and reach peak velocity (Figure B6). Velocity is a parameter related to movement execution, and is tightly linked to movement amplitude in the oculomotor system[84,171]. This relationship however is not observed during upper limb movements, indicating that reach velocity is a flexible parameter that can be modified. This is supported by the variability data, showing reach velocity variability was greater

across participants compared to saccade variability (Figure 4.6). Participants were instructed to move as quickly as possible, maximizing speed over any other parameter. Under traditional speed-accuracy tradeoff logic, one may predict participants would subsequently have poorer accuracy, but this was not the case: almost all participants reached to the target with near-perfect accuracy (reach gain, Figure 4.7). Thus some other factor led to a shift in participants' reaching velocity, allowing for better accuracy. One explanation may be practice effects, given we did not manipulate the target location, allowing for maximization of both speed and accuracy. Overall, it appears that the reaching speed-accuracy relationship is much more flexible than the saccade main sequence relationship.

Interestingly, the large difference between pro-saccade and anti-saccade latency was absent in the reaching data. That is, within a group, latency and velocity were similar for pro-reaches and anti-reaches. The automaticity assumption underlying pro-saccades may therefore not hold for reaching movements. Pro- and anti-saccades have distinct properties related to the presence of visual stimuli, whereas pro and anti-reaches are similar in that they both require a voluntary visuomotor plan, irrespective of the final reach endpoint. Altogether, these results suggest that response latency is a more basic feature of movement that is consistent within individuals but varies across effectors. Movement velocity, on the other hand, is a more dynamic movement property that can be adjusted for an individual reach.

5.1.6 Common themes across Chapters 2-4

While the two main areas of study in this dissertation were treated as separate contributors to motor dysfunction in PD and FOG, there are some common themes across the experiments. First, the intrinsic process of adaptation may be considered "automatic" because, at least in healthy adults, adaptation requires no conscious effort or strategy. The initial phase, described

above as strategic calibration, may require cognitive skills to recognize motor errors, but the latter process of spatial recalibration occurs implicitly within the nervous system. There is some evidence that adaptation is impaired when performed with a difficult secondary task[172,173], suggesting that not all aspects of adaptation are truly "automatic". It is true that older adults, and adults with PD, require greater cortical resources to perform motor tasks in novel environments[75,174], which further complicates the situation. In the prism adaptation study, it is likely that strategic processes were minimal because the visual perturbation was constant and predictable throughout adaptation. Given this assumption, it is unlikely that the spatial recalibration aspect of motor adaptation is "automatic" in the sense that gait or pro-saccadic eye movements are automatic. One way to address this question would be to manipulate the cognitive load during adaptation to determine if there is a differential effect of cognitive load across the groups. Based on our de-automaticity hypothesis of FOG, we would expect adaptation rate in the presence of cognitive load would be slowed to the greatest extent in the PD+FOG group.

Both experiments (Chapter 2 and 4) addressing motor control in PD and FOG had specific roles of cognitive control that were needed for successful task completion. In the adaptation tasks, appropriate strategies to reduce error were needed (strategic control phase), whereas response inhibition was crucial for successful completion of the anti-saccade task. Cognitive impairments unique to PD+FOG include impairments in executive function[79], set-shifting[175], visuospatial processing[176], memory[177,178], and implicit sequence learning[179]. In Chapter 4, we conducted two standard tests of executive function (Go/No-Go) and set-shifting (Trail-making A/B). There were no significant differences in reaction time or errors between the freezer and non-freezer groups during the Go/No-Go task, which aligns with our finding in Chapter 4 which showed no differences in anti-saccade error rate. To add, the difference in completion time between Trail-making B and A was greater in the PD+FOG group, however this effect was driven primarily by

two outlier participants. Once removed, completion times were similar between groups. The fact that we failed to find differences in cognitive function in PD+FOG using either neuropsychological testing or anti-saccade tasks, but did find significant motor impairment in oculomotor tasks suggests the strong and complicated interaction between cognition and motor function.

Finally, a problem that is difficult to solve when studying individuals with neurological disease or damage is the role of compensation. It is thought that when one brain region experiences damage or is no longer functioning properly, another brain region will take over for lost function. Many neuroimaging studies show abnormal patterns of connectivity of various brain regions in heterogeneous samples of PD[180-182] and specifically in PD+FOG[33,83,103]. What is difficult to determine is whether these changes are related to pathophysiology of PD or are compensatory mechanisms that serve to maintain function.

The cerebellum has gained recent attention as an important locus of compensation in PD[32,180,183]. For instance some data indicate that cerebellar connectivity is greater in the akinetic-rigid relative to the tremor-dominant phenotype[183]. Since the akinietic-rigid phenotype is typically associated with greater disease duration and severity, cerebellar hyper-connectivity may in fact be compensatory rather than pathologic. How would these compensatory changes affect adaptation data? It is plausible that elevated cerebellar connectivity would lead to faster prism adaptation. Indeed, using non-invasive brain stimulation researchers showed that facilitating cerebellar activity results in enhanced adaptation[184,185]. Thus, increased cerebellar connectivity could serve to normalize adaptation in PD, explaining why there was no observed difference in adaptation rate.

There was a moderate positive relationship between disease severity (motor UPDRS score) and adaptation rate. We also compared adaptation rates by classifying the sample as tremor-dominant or akinetic-rigid dominant phenotype, and noted no differences between the phenotypes (6 tremor-dominant, 16 PIGD, 4 indeterminate). One would expect then that if compensation is related to increases in disease progression or severity, then there would be no or even an inverse relationship between UPRDS and adaptation rate. To add, if the cerebellum is hypoactive in the tremor-dominant phenotype, one would also anticipate impaired adaptation in this subgroup (although we had a very small number of this phenotype). Taken together, these results do not directly support the idea that compensation is related to declines in motor function (i.e. greater UPDRS) or improved adaptation performance. Since two studies showed that some people with PD exhibit impaired adaptation and after-effects[47,50] it is important to understand what neurological and demographic factors are strongly associated with adaptation behavior going forward.

5.2 Clinical significance

While these studies were designed to address unanswered basic questions regarding motor function and behavior in PD, the experimental results have potential clinical implications for future treatment and disease management for people with PD with and without FOG. First, motor adaptation and learning are fundamental processes underlying rehabilitation interventions. Whether using devices such as treadmills and robots, or specific exercise programs, therapists engage patients in adaptive processes that drive changes in the nervous system[38,39]. Therefore, it is essential to understand how individuals with and without neurological injury respond to such therapeutic approaches. Adaptation tasks allow one to first assess a person's capacity for future rehabilitation. The data from Chapter 2 showed that people with PD adapt both upper limb movement and walking normally in response to visual

perturbations. This is useful information since adaptation paradigms have been previously used for rehabilitation in other disorders such as hemispatial neglect[186] and stroke[187,188]. Prism glasses have also been used to improve gait initiation in PD[189], and may have clinical use for improving other gait asymmetries, such as veering[190].

Using treadmills to adapt and improve gait is another avenue for clinical use of adaptive capacity in PD. While split-belt treadmill adaptation is most likely unaffected in PD-FOG[61,101] and may be impaired exclusively in PD+FOG[40], no study has explored how this intervention may improve gait symmetry and speed in people with PD over time. One report investigated the impact of walking on a rotating treadmill to improving turning in PD, but noted no significant benefit after 5 days of training[191]. The results from the experiment in the Appendix chapter indicate that individuals with PD and FOG may have impaired retention of newly learned locomotor patterns, which could explain why training did not result in improvement.

A significant challenge when using any adaptation approach is the short duration of effects. In healthy adults, after-effects last on the order of tens of minutes. To create longer-lasting motor memories in healthy adults, repeated training sessions over many weeks are needed[39]. As demonstrated in this work and others, retention of newly adapted motor patterns in a single day and across several days is already limited in PD due to basal ganglia dysfunction. It reasons then that shorter-duration training may not be adequate to demonstrate significant effects. Optimizing the parameters for rehabilitation programs using motor adaptation paradigms should be addressed in future studies.

The data from Chapter 2 and the Appendix also provide more information regarding the neural substrates of gait impairment in PD and FOG. Because visuomotor adaptation was preserved but retention of adaptation was blunted in PD+FOG, the locomotor centers of the cerebellum

(vermis and fastigial nuclei) may be loci for intervention. Such intervention could involve non-invasive imaging techniques (transcranial magnetic stimulation (TMS) or direct current stimulation (DCS) to modulate cerebellar activity in these regions. Furthermore, while the cerebellum is not likely a realistic target for direct stimulation with DBS, this region may be worthwhile to explore using animal models of PD. This is an important avenue given that current DBS targets do not reliably alleviate freezing episodes[25,192]. Overall, further investigation of the cerebellar involvement in locomotor circuits using neurophysiological techniques may shed light on unknown mechanisms of FOG and offer new approaches to treat FOG.

The conclusions from Chapter 4 related to oculomotor function likewise have potential clinical use. Saccades are the most common type of eye movement and are crucial for natural visual sampling, reading, driving, and a host of other daily tasks. Therefore, saccade impairment may be linked to other more complex behaviors. For instance, delays in locating objects in the path ahead may underlie fall risk in people with PD. While the interaction between gaze and locomotion is complex[193,194], our data at minimum show that some reflexive (pro-saccade) and most voluntary (anti-saccades) gaze shifts are slower in PD+FOG, which could translate to a slower visual sampling of space during walking[195]. Precise location of objects in space is especially important when precise stepping is required, such as when climbing stairs or navigating cluttered hallways[196]. The idea of visual sampling during walking is beginning to be quantified in PD[197] in order to understand oculomotor-locomotor control and its potential relation to fall risk. However the exact link between oculomotor and locomotor behavior during a freezing episode remains to be determined.

Measuring saccade function also represents a potential simple yet powerful tool to track disease progression. The great amount of research dedicated to understanding the saccade system

has provided a wealth of behavioral, neurophysiological, and neuroanatomical data that has powerful potential for diagnosis and continual monitoring of neurological conditions[88,198]. In addition, saccadometry is a reliable, objective measure of motor function, in contrast to many rating scales of PD. Finally, since anti-saccade tasks are difficulty to administer in a clinical setting, an added benefit to such a laboratory-based task is that it provides information regarding cognitive function in addition to motor function[198]. Determining cognitive decline in patients with PD is important to verifying existing diagnosis (PD/PD+mild cognitive impairment/PD+dementia), and saccade assessment may complement existing neuropsychological testing involved in PD diagnosis.

5.3 Future directions

The experiments performed in this dissertation have revealed several potential avenues of future research. One limitation of these studies is that there is no neurophysiologic measure of function that can be correlated with behavior. Thus, the conclusions are limited to assumptions of the neurological function of people with PD-FOG and PD+FOG based upon animal and human studies of the nervous system. To remedy this, a follow-up study could implement a neurophysiologic technique, such as transcranial magnetic stimulation (TMS), direct current stimulation (DCS), or neuroimaging, in conjunction with behavioral tasks. Specifically, one study could employ a similar adaptation paradigm while using brain stimulation to either facilitate or inhibit cerebellar function to examine its effect on resulting adaptation across groups. This type of study would better sort out the common or distinct neural mechanisms at play in PD-FOG and PD+FOG and may also shed light on the issue of compensation in this disease. Similarly, it would be interesting to determine if cerebellar stimulation enhances walking and reaching adaptation to the same extent, or is arm adaptation facilitated to a greater extent than walking given the same stimulation.

While there is more of a link between saccade behavior and neural substrates, it would still be beneficial to use fMRI to determine the specific brain regions that are differentially activated in PD-FOG and PD+FOG during different saccade types. An anti-saccade task could easily be implemented in an MRI scanner, and is an ideal method to study sensorimotor function because saccades are less likely to elicit head movement compared to movement of the limbs.

Aside from a neurophysiological method, it would be interesting to modify the task conditions, particularly the cognitive load, for the saccade and reaching tasks in Chapter 4. One experiment could determine how saccade performance is impacted by increasing the difficulty of the secondary task (e.g. verbal fluency, serial 7s), and if this differs across groups. Another manipulation that would increase the difficulty of the anti-saccade task is implementation of a Go-NoGo format. On a subset of trials, there would be a stop cue instead of a peripheral target, which would signal the participant to not make any saccade and instead maintain fixation. This would introduce another level of inhibitory control, but one that does not also require a volitional saccade. Furthermore, this may increase the overall attention of participants to mitigate any effect boredom or fatigue may have had on the results. Overall, there are many variations of the anti-saccade task that can be used to probe various aspects of oculomotor control and would be useful to pursue in future studies of cognitive-motor function in PD and FOG.

One other area that future work should examine is the classification of freezers. The tool we used for classification, the New Freezing of Gait Questionnaire, is based on self-report of freezing episodes. While this tool does have good reliability and validity[104], the gold standard for FOG would be reliable replication of freezing in the laboratory. However, freezing is notoriously difficult to reproduce in this setting, which is why self-report measures are most frequently used. There are many reasons why freezing may be difficult to consistently observe: active suppression by the patient, freezing occurs only in certain environments, fluctuations in

medication levels, and presence or absence of cues to name a few[24]. A further limitation of this self-report measure of FOG is that it places someone who freezes only in certain situations (e.g. when entering an elevator) and someone who freezes multiple times during straight-walking, turning, etc. in the same broad category. From this example, it is readily apparent that freezing exists on a spectrum and is highly variable across people. This does not necessarily mean that the mechanisms underlying the severity of freezing are different, but is a good example of how complex freezing behavior can be. Going forward, the NFOGQ should still be administered as it takes into account the participant's perception of his own movement, which is an important factor in rehabilitation. In conjunction with this, a standardized movement battery of walking and upper extremity tasks should also be developed, validated and implemented to give objective measures of freezing frequency and duration. Together, these assessments of FOG would provide a more comprehensive determination of not only who is a freezer/non-freezer but how much they freeze and during which tasks.

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Appendix A: Reduced after-effects following podokinetic adaptation in people with Parkinson's disease and freezing of gait

This appendix was published in the journal *Parkinsonism and Related Disorders* in November 2015 and is reprinted with permission from the publisher. This project satisfied the thesis for the Master's of Science in Clinical Investigation awarded through the Clinical Research Training Center.

Nemanich ST, Earhart GM. Reduced after-effects following podokinetic adaptation in people with Parkinson's disease and freezing of gait. Parkinsonism & Related Disorders. 2016;22:93-7.

Abstract

Gait dysfunction is common in people with Parkinson's disease (PD). Freezing of gait (FOG) is one such gait disturbance that significantly impacts mobility and quality of life in PD. Recent evidence suggests that cerebellar connectivity may differ in people with PD and FOG (PD+FOG) relative to those without FOG (PD-FOG). Investigation of gait adaptation, or the ability to change gait patterns in response to external perturbations, is cerebellum-dependent, is a practical means of probing cerebellar integrity and may provide additional insights regarding the FOG phenomenon. In this study, we investigated gait adaptation in PD and FOG by measuring after-effects, namely whole-body rotation, following stepping on a rotating disc in PD+FOG compared to PD-FOG and older healthy adults. We refer to the period of stepping on the rotating disc as the podokinetic (PK) stimulation and after-effects as podokinetic after-rotation (PKAR). Our primary measure of adaptation was the magnitude and rate of decay of the after-effects. We noted that PKAR was diminished in PD+FOG compared to the other groups, indicating reduced storage of the adapted gait pattern in PD+FOG. In the PD groups, FOG explained about 20% of the variability in peak velocity. Furthermore, these differences were independent of stepping cadence or motor sign severity. Our results show that gait adaptation is impaired in PD+FOG, suggesting the cerebellum may be differentially impacted in PD+FOG compared to PD-FOG. This supports previous neuroimaging evidence of cerebellar dysfunction in PD+FOG. Overall, these data further our understanding of gait deficits in PD+FOG.

Introduction

Freezing of gait (FOG) is a disabling gait disturbance that affects more than half of individuals with Parkinson's disease[16] (PD). A recent consensus paper defined FOG as a "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk"[24].

Clinically, freezers (PD+FOG) are at greater risk for falls, fear of falling, and experience poorer quality of life compared to non-freezers[7,17,22] (PD-FOG).

Currently, there are many hypotheses regarding the underlying mechanisms of FOG, including lack of gait automaticity, frontal-executive dysfunction and gait asymmetry (for review see[14]). A recent study by Mohammadi et al. investigated how PD+FOG, compared to PD-FOG and healthy older adults, responded to imposed asymmetry and sudden gait switches using a split-belt treadmill paradigm. They noted that PD+FOG had maladaptive stepping patterns when one belt of the treadmill was suddenly driven faster. Furthermore, they showed significant differences in rates of adaptation to split belts and re-adaptation to tied belts, such that PD+FOG were slower to adapt and re-adapt compared to PD-FOG and healthy controls[40]. Because gait adaptation is regulated by the cerebellum[60], evidence of slower adaptation in PD+FOG supports growing information about differences in the cerebellum among PD+FOG and PD-FOG[33,34,151]. Despite this, there are few data describing differences in cerebellar-dependent motor tasks between PD+FOG and PD-FOG.

In adaptation paradigms, the after-effect is a measure of the extent to which a newly learned motor pattern was stored in the nervous system and reflects the true recalibration achieved during adaptation[39]. Another apparatus that induces gait adaptation and after-effects is a rotating treadmill. While stepping on a rotating surface, the stance foot rotates relative to the stationary trunk, inducing a new relationship between foot and trunk position during stepping[65]. Following exposure, individuals spontaneously rotate with respect to space when stepping on a stationary surface reflecting adaptation of the foot-trunk system, termed the podokinetic (PK) system. Experimentally, after-effects, or podokinetic after-rotation (PKAR), are induced in younger adults across a range of stimulus duration and amplitudes[66]. When studying people with PD, Hong et al. found no differences in PKAR between PD and neurologically healthy older

adults[199]. This null result may have been due to both small sample size, testing PD participants on dopaminergic medication, which may impact motor adaptation[106], and combining freezers and non-freezers into a single PD group. In contrast, participants with cerebellar damage exhibited reduced peak rotational velocity following PK stimulation, suggesting the cerebellum is associated with storage and expression of PKAR[68]. Based on the gait adaptation deficits during split-belt treadmill walking and differences in cerebellar connectivity in PD+FOG, we hypothesized that PD+FOG would also show reduced after-effects following PK stimulation. Therefore, the main goal of this study was to determine whether PKAR differs in PD+FOG relative to PD-FOG following stepping on a rotating treadmill. We predicted peak velocity of PKAR would be smallest and return to baseline more slowly in PD+FOG compared to PD-FOG and controls. A secondary goal was to determine whether PKAR differs in people with PD evaluated off medication as compared to older adults, since prior work only compared people with PD on medication to older adults. We predicted that peak PKAR velocity would be smaller in the PD-FOG and PD+FOG groups off medication compared to older adults.

Materials and Methods

Participants

A convenience sample of 12 healthy older adults, 11 PD-FOG, and 9 PD+FOG took part in the study. Older adult participants were neurologically healthy and recruited from the OIder Adult Volunteer database managed by the Department of Psychology at Washington University, or were spouses of PD participants. Participants with PD were recruited from the Movement Disorders Center at Washington University or from our laboratory database of those who had taken part in prior studies. All participants with PD had a diagnosis of idiopathic PD based on defined criteria[105]. FOG was classified using the New Freezing of Gait Questionnaire (NFOGQ[104]), which includes a video to illustrate the variety of ways in which freezing can occur. Each PD participant was asked if s/he had experienced freezing episodes over the past month.

If the answer was yes, then we denoted her/him as a freezer (PD+FOG) and proceeded with the NFOGQ to determine a composite score assessing the duration and severity of freezing. If the answer was "no", then we denoted her/him as a non-freezer (PD-FOG) with NFOGQ score of zero. Motor severity was assessed by a trained physical therapist using the Movement Disorder Society Unified PD Rating Scale subscale III (MDS-UPDRS III). The testing of PD participants occurred off of dopaminergic medication, defined as at least a 12-hour withdrawal from all anti-parkinsonian drugs; we excluded those who could not tolerate medication withdrawal. In addition, we excluded any individual with PD who had deep brain stimulation surgery. All participants were included if they could walk independently and stand for at least 15 minutes continuously. Further, they were excluded if they showed evidence of dementia (Mini-mental Status Exam (MMSE) <26[107], took medications that could affect balance (e.g. benzodiazepines) or had orthostatic hypotension. All procedures described were approved by the Human Research Protection Office at Washington University. Participants provided written informed consent before beginning the study and were compensated for their time and effort.

Task

Participants stepped in place for 15 minutes on a motor-driven rotating disc (NeuroKinetics Inc., Pittsburgh, PA) embedded in the floor of the laboratory. We chose an intermittent training schedule consisting of three 5-minute bouts of stepping on the disc interleaved with 5-minute rest breaks, during which participants sat in a chair (25 minute total training session). Previous data indicate that similar after-effects appear following both intermittent and continuous training[199]. During stepping, the disc rotated clockwise or counterclockwise (randomly chosen) at 45°/s. Participants stepped in place in the middle of the disc while maintaining a unidirectional heading. Vision and hearing were not modified during the training session, and participants were allowed to step at a self-selected cadence. Following the final 5 minutes of stepping, participants stepped in place on the disk for ten minutes continuously with the

treadmill turned off (after-effect phase). During this phase, participants wore a blindfold and earplugs to minimize sensory bias. A metronome attached to the participant at ear level and set at 120 beats/min was used to set cadence[200]. A frictionless wheel suspended from the ceiling, adjusted to each participant's height, was used for balance support and orientation while stepping during both phases.

Data acquisition and analysis

Kinematic data were collected at 100 Hz during the 10 minutes of PKAR using a high-resolution, 8-camera motion capture system (CMOS sensors, 307,200 pixels, 208 LEDs per Ringlight, Motion Analysis Inc., Santa Rosa, CA). After an initial calibration, reflective markers (19 mm diameter) were placed bilaterally on the anterior superior iliac spine to measure whole body rotation during PKAR. Additional markers were placed on the calcaneus, lateral malleolus, and first proximal phalanx of each foot to measure cadence. Raw marker data were examined for discontinuities and smoothed with a low-pass filter (Butterworth, 6 Hz cutoff). Final analysis was performed using custom Matlab (R2011b, Natick, MA) scripts. A moving average filter was applied, averaging the data over 5-second intervals. Angular position in the horizontal plane, a measurement confirmed to be reliable (accuracy = 0.98, unpublished data), was calculated using the hip markers over the total ten-minute time course. Finally, angular velocity was calculated as the derivative of angular position. A typical PKAR curve has a rising phase, normally lasting for the first two minutes, followed by a falling phase. The falling phase was identified manually by two assessors (one blinded and one unblinded) for each participant's curve and fit to a single monotonic exponential function in the form $y = A*exp(-b*t)+C$, where b is the decay constant, C is the horizontal *asymptote* and $A+C$ is the maximum value of the function (when t = 0), and t is time. We compared these three parameters across groups (parameter estimates were similar for each assessor). To validate that individuals adhered to a cadence of 120 steps/minute during PKAR, we also calculated the average cadence during 2-

minute windows of the ten-minute PKAR time-course. We used the rhythmic peaks in the vertical heel marker time series (z-direction) to determine footfall during stepping to measure cadence.

All statistical analyses were performed using SPSS (v21, IBM Corp, Chicago, IL). Appropriate parametric comparisons were made to examine differences in demographic variables (t-tests for two groups, ANOVA for more than two groups). We compared primary PKAR outcome variables peak velocity, decay rate, and asymptote using ANCOVA with group as a fixed effect and cadence as a covariate (Earhart 2004). If a main group effect was present, we performed post-hoc comparisons (Tukey) between PD+FOG/PD-FOG, PD+FOG/Old, and PD-FOG/Old. We also reported effect sizes (partial η^2) for each variable. Finally, to explore the relationship between PKAR and FOG, we performed a linear regression using data from the PD groups to model peak PKAR velocity. Potential predictor variables included age, disease severity (MDS-UPDRS III), disease duration, cadence, and FOG. Age, disease severity and duration were chosen to account for general changes in somatomotor function; cadence was chosen because of its potential impact on PKAR velocity[200]; FOG was chosen to explore its relationship to PKAR. Continuous variables (age, disease severity and duration, cadence) with significant ($p<0.1$) bivariate linear correlation with peak velocity or categorical variables (FOG) with significant ($p<0.1$) differences in peak velocity among the strata were included in the model. The final variables were forward-entered in separate blocks to determine the impact of each variable (change in model R^2). To assess potential collinearity among predictors, we examined the variance inflation factor, or how much an estimated coefficient is inflated based on collinearity, for all variables. For all other tests, the level of significance was set at $\alpha = 0.05$.

Results

Groups did not differ by age (one-way ANOVA: $F(28,2) = 0.62$, $p = 0.55$). Disease duration and motor sign severity were greater in the PD+FOG group compared to PD-FOG, but these differences were not statistically significant (t-tests; $p = 0.27$ for disease duration, $p = 0.08$ for MDS-UPDRS III). While we used a metronome to hold cadence fixed during PKAR, the cadence measured during PKAR differed between groups (one-way ANOVA; $F(28,2) = 3.35$, $p = 0.05$). As such, cadence was included as a covariate in our analyses. Three participants experienced FOG episodes lasting 2-13 s during PKAR, despite external cueing of cadence. These episodes all occurred after reaching peak velocity (i.e. all occurred after 5 minutes of stepping), and all time points were included in the analyses. Participant demographics are shown in Table A1.

Figure A1 shows representative PKAR velocity data and curve fits for one participant from each group. These plots illustrate the dynamics of a typical PKAR time-course: a rising phase lasting from minutes 0-2, followed by a falling phase from minutes 2-10. The equation of the exponential fit to the falling phase is shown for each curve. Peak velocity decreases by group such that Old>PD-FOG>PD+FOG. We noted a similar trend in the analysis of average group PKAR, also shown in Figure A1.

Curve fit parameters of PKAR velocity as well as post-hoc effect sizes are summarized in Table A2. Peak velocity was smallest in PD+FOG (7.17±3.86 °/s) and largest in the Old group (10.66±4.66 °/s). Statistical analysis showed that peak velocity was significantly different across groups ($F(28,2) = 4.78$, $p = 0.02$). Using post-hoc comparisons, we noted significant differences between PD+FOG /PD-FOG ($p = 0.03$) and PD+FOG/Old ($p = 0.03$). There were no differences in the estimates of decay rate ($F(28,2) = 0.674$, $p = 0.52$) or asymptote($F(28,2) =$

2.81, p = 0.08) between the groups. Given a total sample size of 32, we had 81% power to detect a difference in peak velocity between groups.

We collapsed the two PD groups into a single group to explore the relationship between peak velocity and other demographic variables. The final regression model including age, disease severity, and FOG status (Table 3) was significant ($F(16,3) = 5.77$, $R^2 = 0.52$, $p=0.007$). Age ($p = 0.01$) and freezing status ($p = 0.02$) were significant predictors of peak velocity in the final model (Table A3). The model's R^2 value increased by 0.19 when freezing status was added, indicating that freezing status accounted for about 20% of the overall variability in measured peak velocity after accounting for age and disease severity.

Discussion

In this study, we investigated how after-effects following stepping on a rotating treadmill were affected by PD and FOG. The main result was that individuals with PD+FOG exhibited the smallest peak velocity compared to the other groups. This result supports recent data showing locomotor adaptation is impaired in PD+FOG, and points to potential neurological mechanisms underlying this PD phenotype.

Previous work investigating locomotor adaptation in PD showed similar adaptation rate and after-effects between PD and healthy older adults. Using a split-belt treadmill paradigm, Roemmich et al. showed that people with PD adapted step length asymmetry and stored new walking patterns, as indicated by significant negative after-effects, despite increased gait asymmetry compared to controls[61]. The only study to our knowledge comparing PKAR in PD and older adults also found similar rate and magnitude of after-effects between groups[199]. In contrast, two other studies reported distinct differences in gait adaptation when separating PD+FOG and PD-FOG in comparison to healthy older adults. Nantel-Mahabier et al. noted that

PD+FOG have maladaptive responses to split-belt treadmill walking such that they increase rather than decrease stride and step asymmetry over time compared to PD-FOG and older adults [62]. Furthermore, Mohammadi et al. showed a similar maladaptive response during split-belt walking, noting a significantly slower adaptation rate in PD+FOG compared to PD-FOG and controls. Interestingly, this study also observed that PD+FOG actually had larger initial after-effects but returned to baseline more slowly during re-adaptation relative to PD-FOG[40]. A larger baseline asymmetry in PD+FOG may have accounted for the initially larger after-effects. Nevertheless, there is sufficient data to indicate locomotor adaptation and retention differences exist between PD+FOG and PD-FOG.

In the current study, we observed smaller peak PKAR velocity in PD+FOG, suggesting this group was unable to store the adapted locomotor pattern induced by the rotating treadmill to the same extent as PD-FOG or older adults. These results are similar to another study of PKAR in people with cerebellar lesions, which noted lower peak velocity but similar decay rate and asymptote compared to younger adults[68]. Together with the evidence of split-belt adaptation dysfunction in PD+FOG, these data indicate the cerebellum is associated with gait adaptation and retention and may contribute to gait dysfunction observed in PD+FOG. The cerebellum has recently received more attention as a major contributor to motor dysfunction in PD[32], however, we did not observe differences in PKAR between the PD-FOG and older adults. Emerging neuroimaging data show that the cerebellar locomotor region has abnormal activity at rest[33] and during imagined gait tasks[34] in PD+FOG relative to PD-FOG. This is likely one anatomical area that is involved in the pathogenesis of PD+FOG, however its role in gait adaptation has yet to be determined.

Potential explanations for results and study limitations

Three participants experienced FOG while stepping in place. While these brief periods of festination may have caused transient declines in PKAR, the fitted parameters reflect the entire PKAR time course and not isolated segments. Furthermore, freezing episodes did not occur during the first 2-3 minutes of PKAR; as such there were no pauses during the rising phase and FOG episodes therefore did not influence the peak velocity measure. We also tested participants with PD off dopaminergic medication, which affects not only global motor function, but motor adaptation[106] and cerebellar function[180]. However, medication may reduce after-effects following motor adaptation[106], and is associated with both increases and decreases in cerebellar connectivity[180]. Thus, the effects observed here are not likely related to freezing episodes or medication use, suggesting other factors are contributing to reduced after-effects.

One factor that has not been adequately explored in studies of PK adaptation is the influence of the vestibular and proprioceptive systems on PKAR expression. An interesting feature of PKAR is that it is not perceived by the participant. Thus, both vestibular and proprioceptive systems are remodeled during PK stimulation[66]. It is thought that during the first 1-2 minutes of PKAR, turning velocity is diminished because of vestibular suppression. While there were no differences in time to reach peak velocity across groups, some participants did peak earlier than others, perhaps indicating less or more vestibular influence on PKAR. A second possibility is that changes in proprioceptive adaptation accounted for reduced PKAR. It is well established that proprioception is impaired in PD[201,202], and such deficient processing of proprioceptive information could similarly inhibit the PKAR response. Altogether, central processing of multiple sensory inputs PD[203] likely contributes to PKAR expression. Probing multisensory integration during and after podokinetic adaptation is an area in need of additional research.

Our results should be considered in light of the following limitations. First, categorization of PD+FOG was based on self-report and not direct observation of freezing episodes. This may have caused misclassification of some PD participants. Second, we focused on sensorimotor rather than cognitive-motor differences between groups. We did not collect specific information on cognitive function in our sample, however previous studies show deficits in several cognitive domains (for review see[204]) in PD+FOG. It is possible that unmeasured differences in cognition contributed to the differences in PKAR. Finally, we did not determine the test-retest reliability of angular rotation or marker placement in our data. However, the reliability of similar marker placement has been established[205]. While the reliability of rotational position in the transverse plane is understudied, we have no reason to expect it would be different than in other planes of movement. We based our measurements on standard biomechanical formulae and thus do not expect major changes in measurement technique or marker placement to significantly change our results.

Conclusion

Overall, our results show that after-effects following locomotor adaptation are reduced in PD+FOG and add to current knowledge of the potential mechanisms underlying FOG. Gait adaptation paradigms have implications for physical rehabilitation in people with PD with and without FOG because they explore how individuals respond in novel environments or to external perturbations, and reflect capacity to retain adapted motor patterns.

Table A1

Participant Demographics

Characteristic	Old (n = 12)	PD-FOG (n = 11)	PD+FOG (n = 9)
Age (yr)	70.51 ± 8.28	69.26 ± 4.39	67.00 ± 7.19
Males n (%)	5 (42)	7 (64)	4 (44)
Disease Duration (yr)	—	5.36 ± 2.60	6.67 ± 3.69
MDS-UPDRS Part III	—	33.91 ± 12.24	46.00 ± 10.58
NFOGQ	—	0	14.33 ± 7.51*
Cadence (steps/min)	119.93 ± 4.13	125.27 ± 6.83	113.68 ± 16.67*

Values represent Mean ± SD

MDS-UPDRS Part III: Movement Disorder Society Unified Parkinson Disease Rating Scale Motor Subscale (0-132); NFOGQ: New Freezing of Gait Questionnaire (0-28); Cadence measured during PKAR

*Significantly different than PD-FOG ($p<0.05$)

Figure A1. Individual and group after-effects following stepping on the rotating treadmill. ***Top:*** **Representative PKAR velocity time course for each group (from left to right: Old, PD-FOG, PD+FOG). Continuous line is the exponential best fit of the falling phase of the curve with corresponding equation.** ***Bottom:*** **Group average PKAR time course. Error bars are ± SEM. Old: Older adult group; PD-FOG: Non-freezer Parkinson's disease group; PD+FOG: Freezer Parkinson's disease group.**

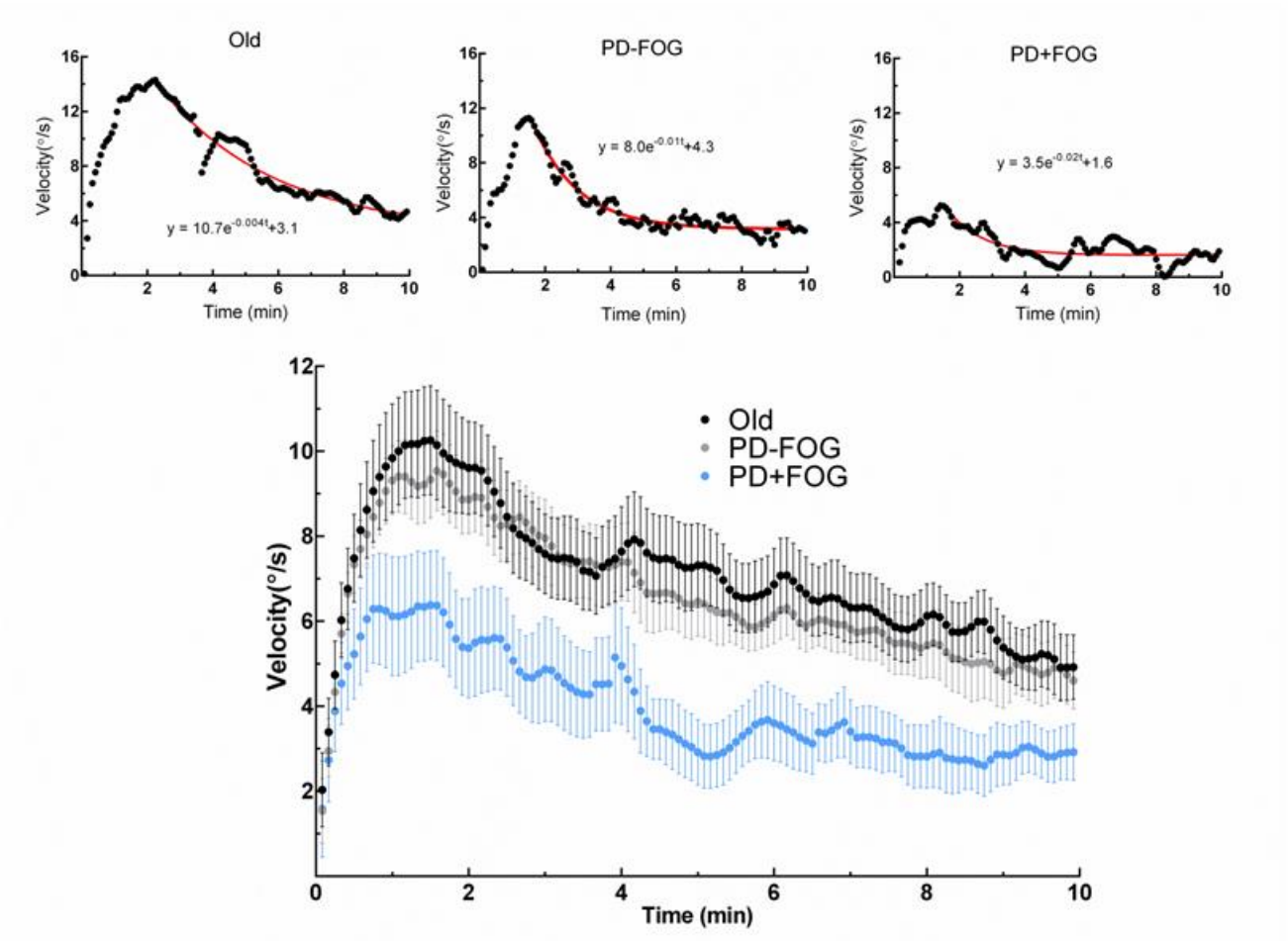


Table A2

PKAR exponential fit parameters

Parameter	Old	PD-FOG	PD+FOG	η^2
Peak Velocity (°/s)	10.66 ± 1.34*	10.42 ± 0.73*	7.17 ± 1.29	0.25
Decay Rate (min)	3.92 ± 1.11	2.85 ± 0.57	2.54 ± 0.69	0.05
Asymptote (°/s)	3.97 ± 0.94	4.46 ± 0.74	2.12 ± 0.60	0.17

Values are Mean±SEM

Peak Velocity = A+C;Decay Rate = 1/b (larger is slower decay); Asymptote = C, η^2 = Partial effect size

*Significantly different than PD+FOG ($p<0.05$, post-hoc)

Table A3

Linear regression model of peak velocity

Predictor	B	SE(B)	p	VIF
Step 1				
Age	-0.32	0.15	0.05	1.00
Step 2				
Age	-0.29	0.15	0.07	1.02
MDS-UPDRS III	-0.09	0.05	0.09	1.02
Step 3				
Age	-0.36	0.13	0.01	1.07
MDS-UPDRS III	-0.04	0.05	0.43	1.24
FOG	-3.36	1.32	0.02	1.25

Step 1 $\Delta R^2 = 0.20$, Step 2 $\Delta R^2 = 0.13$, Step 3 $\Delta R^2 = 0.19$ Overall model fit was as $R^2 = 0.52$ ($p < 0.01$). *VIF:* Variance inflation factor

Appendix B: Supplemental data

Figure B1. Correlation between LEDD and pro-saccade latency (A) and velocity (B). Data from experiments in Chapter 4.

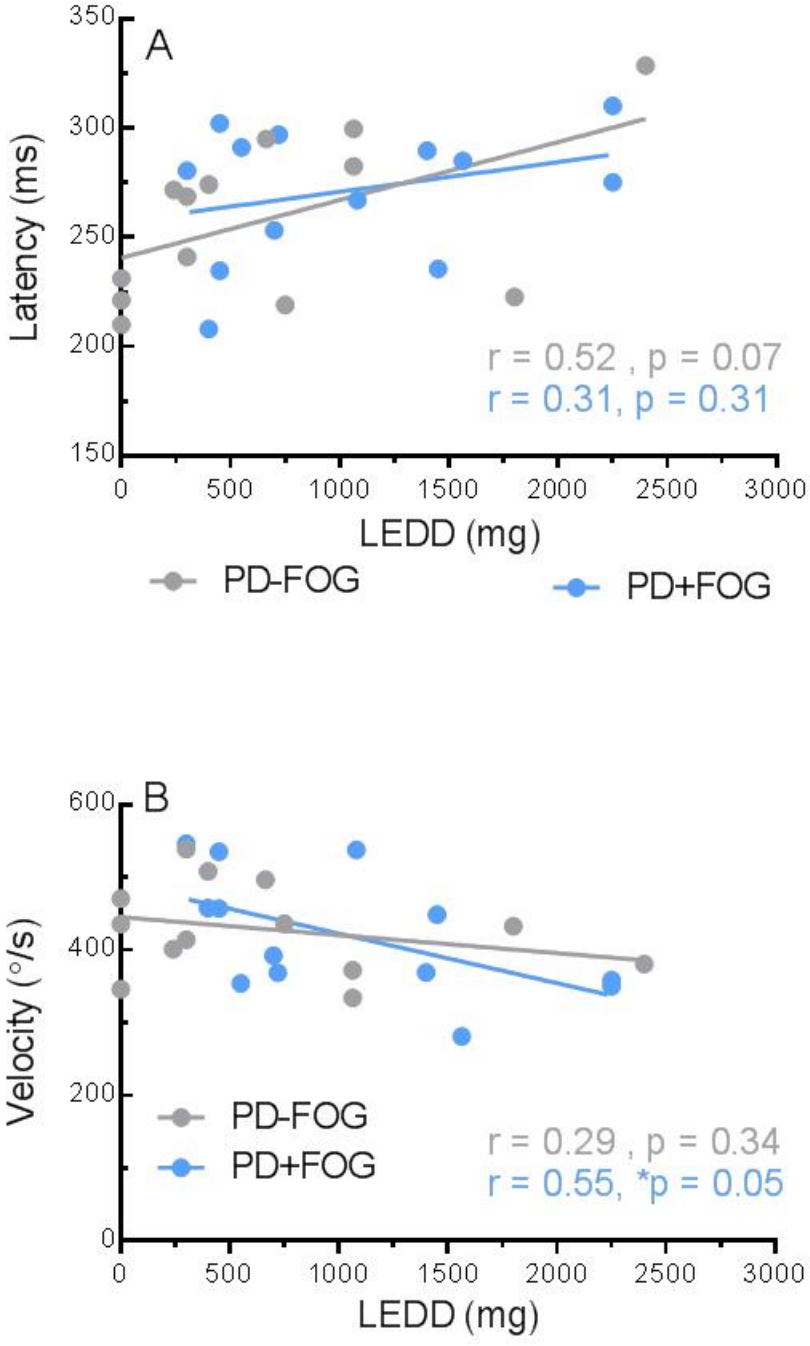
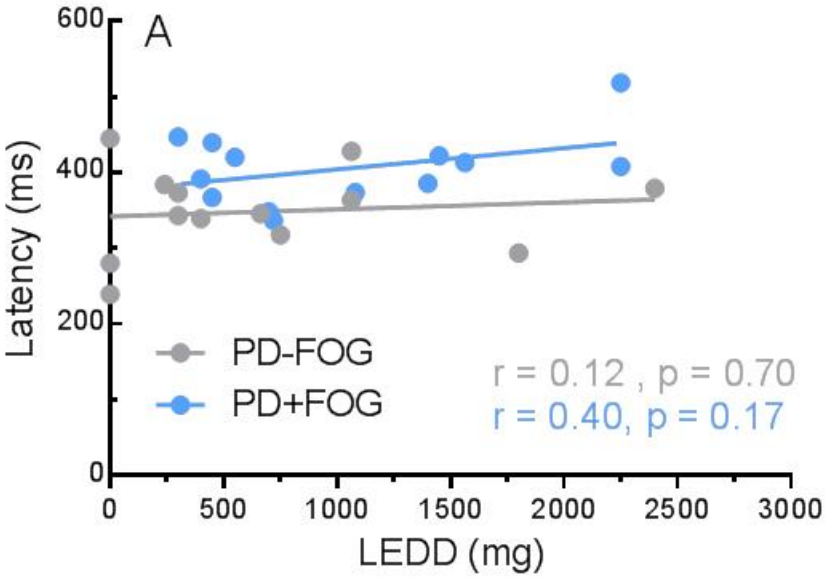


Figure B2. Correlation between LEDD and anti-saccade latency (A) and velocity (B). Data from experiments in Chapter 4.



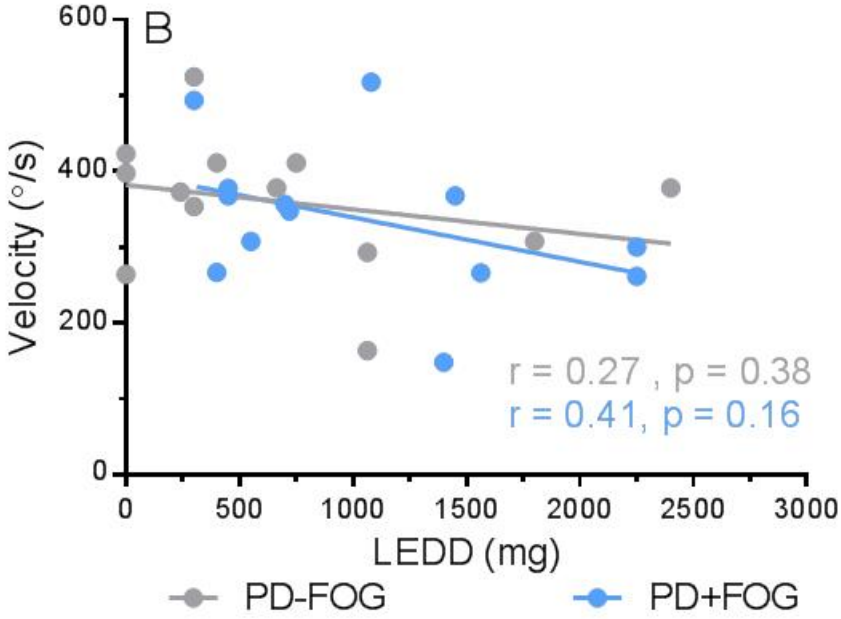


Figure B3. Dual-task condition for saccades. (A) Relationship between block and dual-task latency. Dotted line represents line of unity. (B) Group average of block and dual-task latency across groups. Error bars represent ± 1 SD.

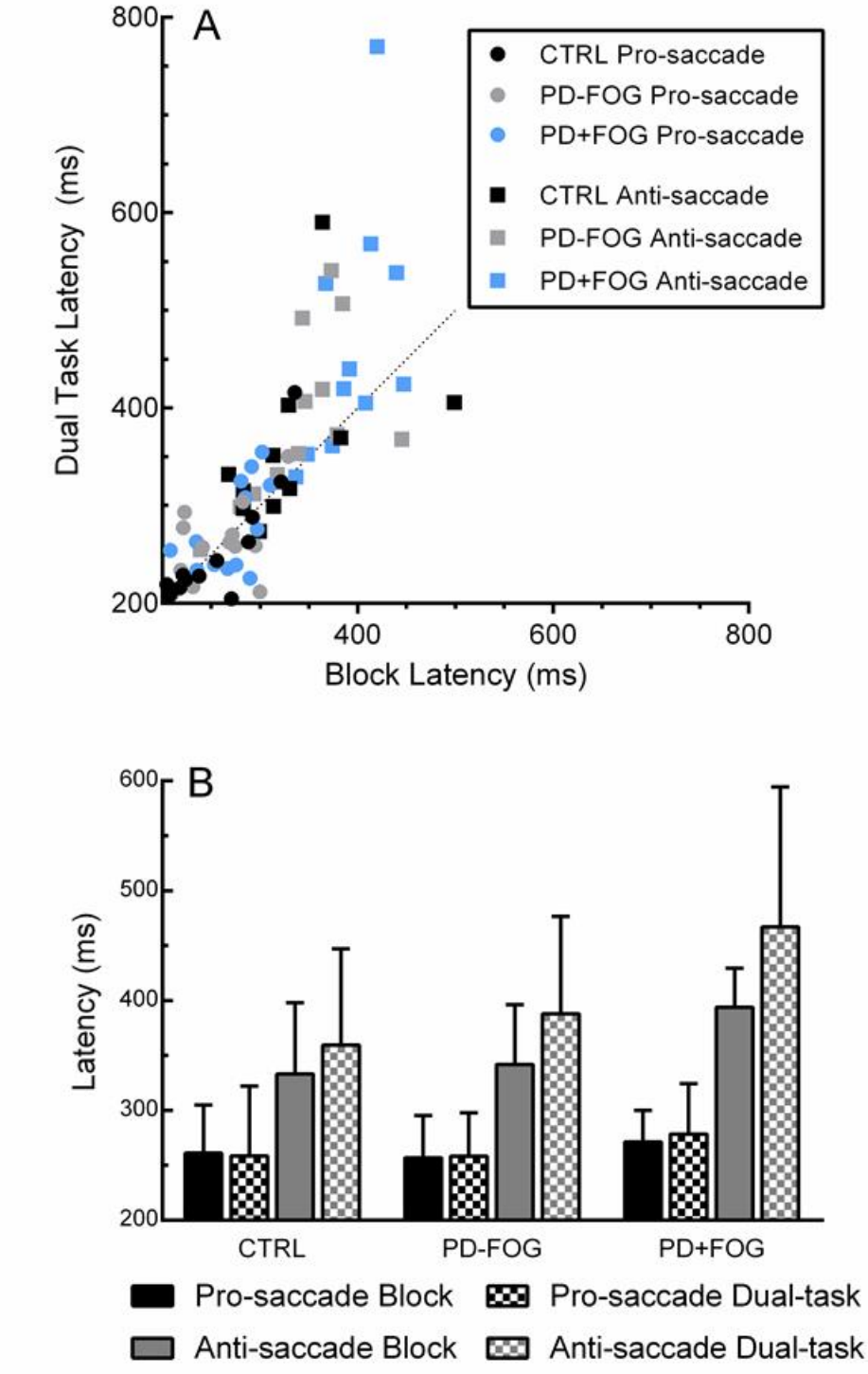


Figure B4. Dual-task condition for reaching. (A) Relationship between block and dual-task latency. Dotted line represents line of unity. (B) Group average of block and dual-task latency across groups. Error bars represent ± 1 SD.

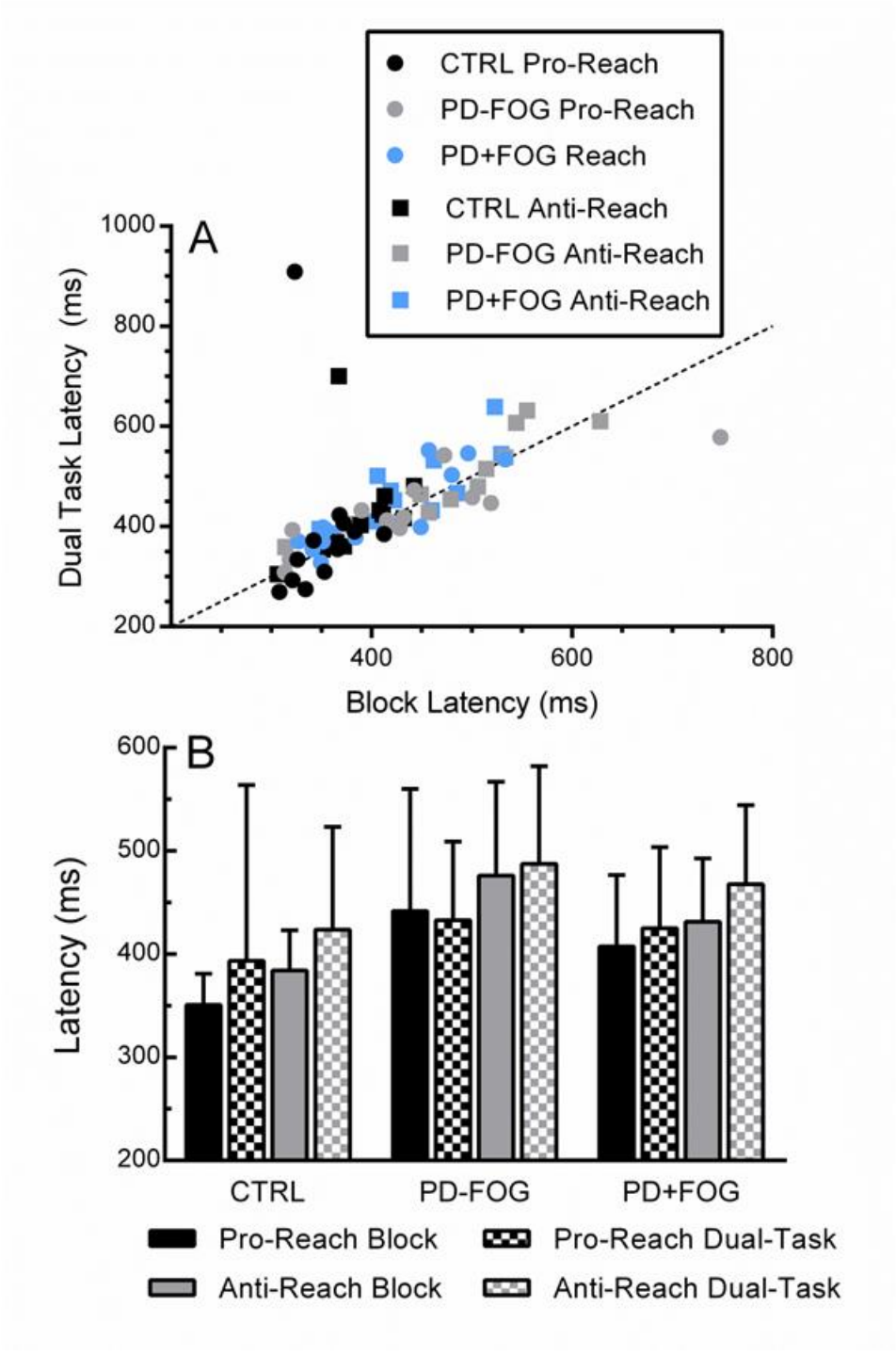


Figure B5. Relationship between saccade and reach latencies. (A) Pro-condition, (B) Anti-condition. Dotted lines represents line of unity (saccade latency = reach latency). Correlation coefficient (r) is shown.

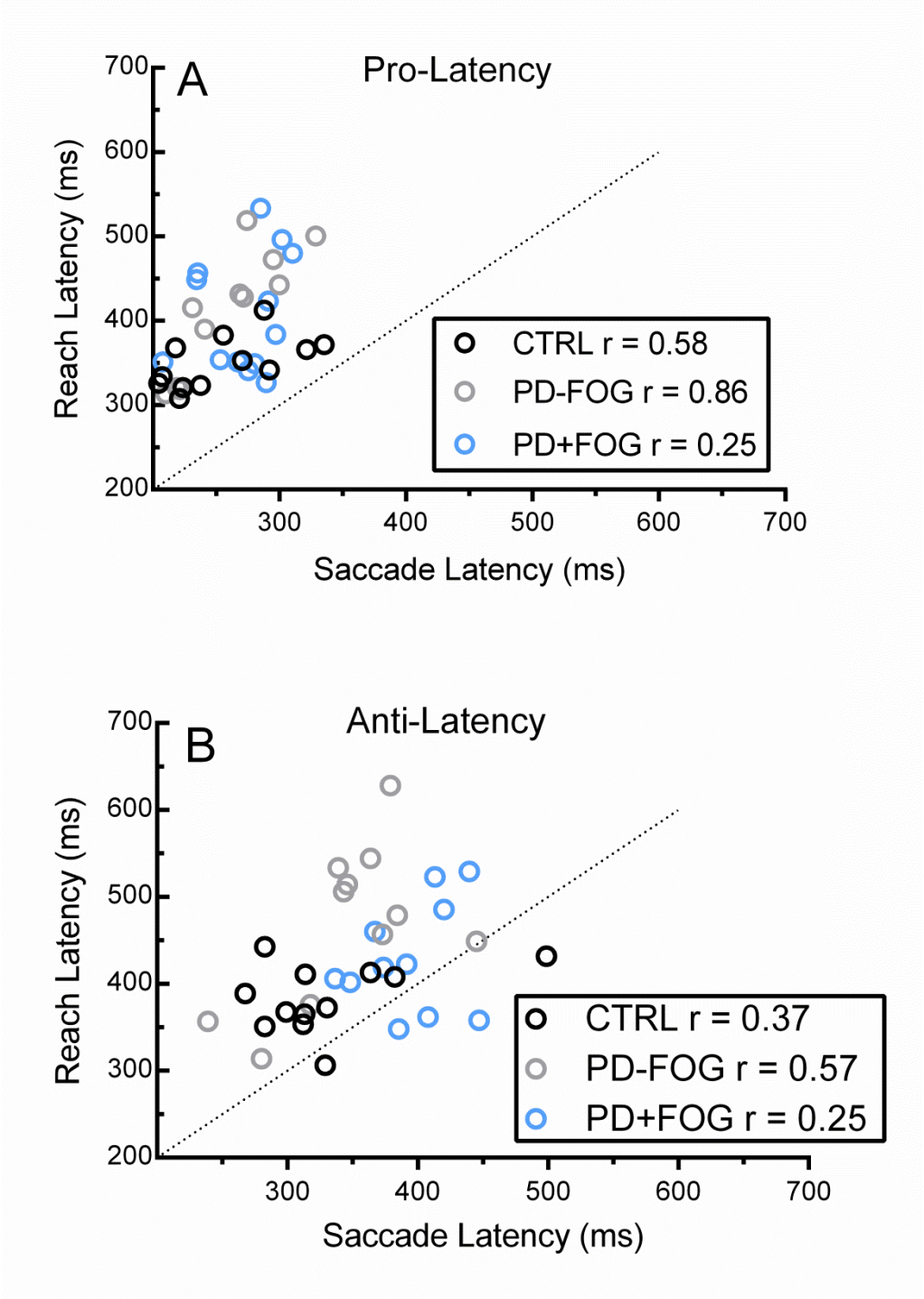


Figure B6. Relationship between saccade and reach velocity. (A) Pro-condition, (B) Anti-condition. Correlation coefficient (r) is shown.