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Freezing of Gait: Mechanisms, Mechanics, and Management

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

BAI = Beck Anxiety Inventory

BESTest = Balance Evaluation Systems Test

BOLD = blood oxygen-level dependent

Br = bias measure of Go-NoGo

BWD = backward walking trials

DT = dual-task forward walking trials

eTIV = estimated total intracranial volume

FOG = freezing of gait

FOG+ or Freezers = people with Parkinson disease with freezing of gait

FOG- or Non-Freezers = people with Parkinson disease without freezing of gait

FWD = forward walking trials

GNG = Go-NoGo task

IMG-BWD = motor imagery trials during which one imagines walking backward

IMG-FWD = motor imagery trials during which one imagines walking forward

KVIQ-20 = Kinesthetic and Visual Imagery Questionnaire

LBP = low back pain

M1 = primary motor cortex

MDS-UPDRS III = Movement Disorder Society Unified Parkinson Disease Rating Scale, motor symptom subscale

MI = motor imagery

MMSE = Mini Mental State Exam

Network 3 = cerebellar portion of the dorsal, cortical somatomotor network

Network 4 = cerebellar portion of the ventral, cortical somatomotor network

NFOG-Q = New Freezing of Gait Questionnaire

N-FOGQ = New Freezing of Gait Questionnaire

PCA = principal component analysis

PC = principal component

PD = Parkinson disease

Phonemic VF = phonemic section of verbal fluency task

PPN = pedunculopontine nucleus

Pr = discriminability measure of Go-NoGo task

ROI = region of interest

ROM = range of motion

ROSW = Revised Oswestry Disability Index

S1 = primary sensory cortex

Semantic VF = semantic section of verbal fluency task

SMN = somatomotor network

Stroop = difference in time to complete inhibition and color sections of Stroop task

SUIT = Spatially Unbiased Infratentorial

Switch accuracy VF = category switching section of verbal fluency task

Trails = difference in time to complete sections A and B of trail making task

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Dedicated to my parents, Moors and Tom Myers.

Abstract of the Dissertation

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Professor Gammon Earhart, Chair

Parkinson disease (PD) is a neurodegenerative disease with multiple motor and non-motor symptoms, including postural instability, gait impairments, and cognitive deficits. More than 50% of individuals with PD experience a symptom called freezing of gait (FOG), described as a transient inability to take another step forward. Individuals with PD who experience FOG (freezers) have further postural, gait, and cognitive impairments compared to individuals with PD without FOG (non-freezers). While degeneration of the dopaminergic neurons in the substantia nigra is accepted as the primary etiology of the disease, research shows that the disease has a global impact on the brain, accounting for the multiple symptoms displayed by people with PD.

People who experience freezing, in particular, show altered function of multiple neural networks. One theory on the mechanisms underlying FOG suggests that freezers have decreased attentional resources, and competing demands from motor and non-motor functions can exceed these limited attentional resources, leading to a freezing episode. Specifically, the theory, in conjunction with other research, proposes that the pedunculopontine nucleus (PPN) may be

involved in the mechanisms underlying FOG. Changes in PPN connections with the cerebellum and cortical regions in freezers suggest that the cerebellum may play an integral role in the pathogenesis of FOG. Not only does the cerebellum impact movement, but growing research shows its involvement with cognitive function. Therefore, this dissertation examines FOG through multiple lenses to better understand the potential role of the cerebellum in FOG pathogenesis. Based on prior research, we expected to find novel evidence of cerebellar structural and functional differences in freezers compared to non-freezers. Additionally, we hypothesized freezers would exhibit similar cognitive and motor characteristics as individuals with cerebellar damage (i.e., cerebellar patients), further supporting the theory of the cerebellum's involvement in the manifestation of FOG.

Three studies were conducted to investigate the mechanisms, mechanics, and management of FOG in PD, providing a broader understanding of the symptom and its impact. Study one (chapter 2) sought to compare cerebellar volumes in freezers and non-freezers, hypothesizing that freezers would have decreased volumes. We applied a spatially unbiased cerebellar atlas to anatomical MRI images of the cerebellum to get a reliable estimate of the individual volumes of the cerebellar lobules. Surprisingly, there were no volumetric differences between freezers and non-freezers. Study one also looked at relationships between cerebellar volumes and cognitive task performance, as cerebellar patients have associated cognitive deficits. We hypothesized volumes of the cerebellum would positively correlate with cognitive task performance. While freezers had decreased cognitive performance compared to non-freezers, volume and cognitive performance were negatively correlated in the non-freezers only.

Study two (chapter 3) examined the joint mechanics of freezers and non-freezers during multiple walking conditions. Freezers show greater spatiotemporal gait deficits (e.g., velocity and stride length) during forward, backward, and dual-task walking, suggesting that the way freezers move their joints during gait may be altered. To determine whether and how joint movements are altered in freezers, we used three-dimensional motion capture techniques to track the movements of the hip, knee, and ankle in various walking conditions, and conditions were compared between freezers and non-freezers. We hypothesized freezers would have greater amounts of single-joint, rather than multi-joint, movements during the gait cycle compared to non-freezers. We assessed single-joint movement by calculating a decomposition index between any two joints, giving a metric for how much one joint was held steady while the other joint moved. This analysis showed that freezers decompose their movement during gait more than non-freezers, particularly between the hip and both the knee and ankle. This increased movement decomposition echoes symptoms seen in cerebellar patients. We also hypothesized a principal component analysis on gait cycle variability would be able to differentiate freezers and non-freezers. While neither group significantly differed in variability from the other, backward gait had different sources of variability than forward or dual-task gait.

The third and final study (chapter 4) examined exercise as a means of managing symptoms in PD. Additionally, this study probed underlying neural changes associated with improvements in gait due to exercise. We collected functional MRI data before and after a 12-week exercise intervention from both freezers and non-freezers. During the MRI session, participants were asked to imagine themselves walking forward and backward. We used a region of interest analysis to examine activity in the parts of the somatomotor network while participants

performed the task. As backward gait is a more challenging and less familiar movement, we hypothesized that imagining backward gait would result in increased activity in regions of the somatomotor network. We also hypothesized freezers would have reduced activity in the cerebellum overall, providing evidence for cerebellar dysfunction in freezing of gait. Though there were no significant changes in either gait performance or functional MRI signal in any of the regions of interest, freezers consistently had decreased signal when imagining backward gait, particularly in the cerebellar region of the somatomotor network.

Together, these studies examined FOG from multiple angles. The results support potential cerebellar involvement in FOG, suggesting decreased recruitment of the somatomotor network and symptomatology that resembles that of cerebellar patients. The results may also inform rehabilitation for freezers and non-freezers. While response to exercise did not differ between the groups, the similarity of freezer symptoms with cerebellar patient symptoms may be important to consider when developing new interventions.

Chapter 1:
Introduction

1.1 Parkinson Disease

James Parkinson wrote about “the shaking palsy” in 1817, describing a condition where the individuals experienced

> [i]nvoluntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured. [1]

This is the first known description of a condition that became known as Parkinson disease (PD). Impressively, Dr. Parkinson was right about multiple aspects of the disease, differentiating his patients from other “shaking palsies”, noting the slow, progressive onset of symptoms, stooped posture, and shuffling gait. He even suggested that the disease may start in the medulla [1].

Over two centuries later, Dr. Parkinson’s work remains the foundation for PD research. It is now accepted that PD is a neurodegenerative disease characterized by four cardinal symptoms: tremor (trembling of the limbs and/or face), rigidity (joint stiffness), bradykinesia (slowness of movement), and postural instability (poor balance and coordination) [2]. While often discussed as a basal ganglia disorder with loss of dopaminergic neurons in the substantia nigra, PD likely starts with Lewy body accumulation in the medulla that progresses to more superior subcortical regions before infiltrating cortical regions [3]. These stages are described by Braak et al. [4] and explain why non-motor symptoms, such as loss of smell [5], may occur before motor symptoms in PD. Indeed, the Braak stages provide a framework for the progression of motor and non-motor

symptoms in PD, starting with autonomic dysregulation and progressing to motor and cognitive deficits [6].

Understanding and treatment of PD has advanced significantly since 1817; however many aspects of PD remain a mystery. With only 5-10% of know PD cases having monogenic, inherited forms of the disease [7], the pathogenesis of the disease remains predominantly unknown. The picture is further complicated with disease subcategorizations or phenotypes. For example, presence or absence of freezing of gait (FOG), i.e., temporary inability to take a step, is often used to classify people with PD. However we lack a strong understanding of this motor symptom. Given the strong link between FOG and risk of debilitating falls in people with PD [8], it is imperative to advance our understanding of the mechanisms, mechanics, and management of this PD symptom.

1.2 Freezing of Gait

Freezing of gait is a common motor symptom in people with PD, and is described as the temporary inability to take another step forward [9]. Some estimate up to 80% of individuals with advanced stages of PD experience FOG episodes (freezers) [10,11]. Freezing episodes can last for seconds up to minutes and can occur in a number of situations. Common situations for freezing include step initiation, turning, and walking through a narrow space [10]. Freezing can also be influenced by emotional wellness (stress, anxiety, depression) [12], and cognitive factors (attention, executive function) [13].

It is worth mentioning that while the symptom is called “freezing of gait”, there is substantial evidence to suggest that FOG is a global impairment involving multiple systems, both motor and non-motor. For example, freezing can occur during non-gait, non-lower limb activities. Upper

limb freezing is a well-recognized phenomenon [14–16] and presence of FOG symptoms impacts saccades, causing longer latencies [17]. Spatiotemporal gait characteristic in freezers compared to people with PD without FOG (non-freezers) show that freezers have significantly decreased velocity and stride lengths [18]. Further, not only does increased cognitive load increase the likelihood of inducing a freezing episode, but freezers also have increased cognitive deficits in domains such as set shifting and conflict resolution [13], suggestive of a freezing of thought processes. While it is clear that freezers have additional deficits compared to non-freezers, the pathogenesis and pathophysiology of FOG remain poorly understood.

Part of the difficulty with understanding FOG comes from its unpredictability, often manifesting during the person's daily activities but not during clinical or research assessments. Understandably, this makes study of the events leading up to a freezing episode challenging. Therefore, the research in this dissertation does not aim to directly study freezing episodes. Rather, it compares freezers and non-freezers in different contexts to understand how the symptom of FOG relates to other aspects of the person's function and behavior. For all the present research, freezers are classified using the New Freezing of Gait Questionnaire (NFOG-Q) [19]. Administration of this questionnaire begins with the patient watching a one-minute video of examples of freezing episodes, specifically in the lower limbs. Then the patient answers the question "Did you experience 'freezing episodes' over the past month?" If the patient answers 'yes' they are classified as a freezer, and if the patient answers 'no' they are classified as a non-freezer. Use of this classification allows for consistency across the present research studies and comparison with research from other groups.

1.2.1 Mechanisms

Multiple theories on the mechanisms of FOG have been proposed, each with their own set of data to support the theory [20]. One such model proposed by Plotnik et al. [21] suggests that FOG is caused by multiple gait impairments that contribute to motor fluctuations. During walking there is an accumulation of these motor fluctuations, culminating in a freezing episode. For example, the asymmetrically decreased step length and directional changes during a turn have an additive effect that exceeds a hypothetical neural threshold, resulting in a freeze. Another theory by Jacobs et al. [22] proposes a decoupling deficit in freezers, such that incongruence between a motor program and its response induces a freeze. This theory suggests that the trembling of the knees during a freeze is the result of multiple anticipatory postural adjustments that fail to properly couple with the forward step motor program. A third model by Lewis and Barker [23] notes that freezing episodes often occur when a secondary task is being performed concurrent with walking. This model suggests that freezers have low levels of neural processing reserves, so cognitive and limbic processing loads while walking cause a downstream inhibitory response, resulting in a freeze. A fourth and final model is put forward by Vandenbossche et al. [24] and expands upon Lewis and Barker's model [23]. This model proposes that freezers experience executive dysfunction and a loss of automaticity that results in a conflict-resolution deficit and a greater chance for incongruence that leads to a freezing episode.

While all four models propose good arguments and have strong data to support them, of interest here are the latter two by Lewis and Barker [23] and Vandenbossche et al. [24]. The inclusion of cognitive considerations into the model fits well with previous research [13], and Lewis and Barker suggest the pedunculopontine nucleus (PPN) as the convergence point for the multiple

processing streams. This is important because freezers show altered PPN connectivity between the cerebellum and other cortical regions [25]. Additionally, research shows the cerebellum may be involved in cognitive functions [26]. Investigation of potential cerebellar involvement in the manifestation of FOG is needed to build upon theories on the pathogenesis and pathophysiology of FOG.

Cerebellar networks

The cerebellum plays an integral role in movement coordination and balance [27], allowing one to recover from perturbations in one's motor program. Though small in volume, the cerebellum has a myriad of connections with the spinal cord and subcortical and cortical brain regions [28]. There are functional subdivisions of the cerebellum, including the cerebrocerebellum, spinocerebellum, and vestibulocerebellum [29], but the cerebellum can also be divided anatomically based on its fissures and folds [30]. These anatomical subdivisions are termed "lobules" and include lobules I-VI, crus I, crus II, and lobules VIII-X [28]. Each lobule has its own distinct connections with other regions of the nervous system. However, the lobules can grossly be divided into motor (lobules I-VI, VIII-X) and non-motor (crus I and crus II) groups based on their primary connections with the motor cortex and frontal cortex, respectively [31]. Further, the cerebellum has bidirectional connections with the basal ganglia through the PPN [32] and both regions connect with multiple cortical regions, forming a complex and integrated network. Additionally, with the cerebellum and basal ganglia at the center of the network, the inter-network connections can be topographically organized into motor, cognitive, and affective connections [33].

The network interconnections across motor and cognitive regions support the hypothesis that the cerebellum may play a significant role in the manifestation of FOG. Additionally, as theorized by Lewis and Barker [23], the PPN could also play a role in FOG. Not only do connections between the cerebellum and basal ganglia travel through the PPN, but research indicates that the PPN has altered structural connectivity in freezers compared to non-freezers [25,34], suggesting that the entire network in freezers may be altered. Perhaps the altered network function affects neural reserves in freezers, leading to the inhibitory burst from the PPN proposed by Lewis and Barker [23].

Cerebellar symptoms

As noted above, freezers have other deficits which separate them from non-freezers and suggest that FOG is a global symptom of PD rather than just a motor symptom. These symptoms share a high level of similarity with those experienced by individuals with cerebellar damage. Two commonalities among freezers and those with cerebellar damage are deficits in motor adaptation and cognition.

Motor adaptation is a well-documented phenomenon where an individual alters a movement pattern to accommodate an external perturbation. Healthy individuals show an adaptation period, during which there is error in their performance as they learn how to accommodate the perturbation. Over multiple trials, the error signal is reduced and performance improves, indicating that the person has adapted to the perturbation and has adequately adjusted their motor output. When the perturbation is removed, there is a de-adaptation period, similar but opposite in sign to the adaptation period, showing an adjustment period back to normal [35]. Individuals

with cerebellar damage are often unable to adapt fully such that during the period where a perturbation is present, they are constantly making movement errors. Their performance never fully accommodates the perturbation and when the perturbation is removed, cerebellar patients do not show a de-adaptation period but rather return immediately to their baseline performance [36,37]. Freezers show similar motor adaptation deficits [38,39].

Though the cerebellum is often considered to primarily contribute to motor functions, there is substantial evidence to suggest its involvement in cognitive processes as well. Functional network maps in the cortex [40] also map onto the cerebellum [41], including the somatomotor, dorsal attention, ventral attention, and frontoparietal networks. The cerebellum has at least two homotopic maps of the cerebral networks, suggesting that the cerebellum plays at least a minor role in cortical functions by virtue of its involvement in the network. More specifically, the topographical network between the cerebellum, basal ganglia, and cerebral cortex highlights the involvement of all these structures in cognitive processes [33].

A well-documented example of cerebellar-cognitive interactions comes from cerebellar patients who present with cognitive affective syndrome [42,43]. The deficits associated with this syndrome include deficits in executive function, visuospatial tasks, language processing, and affect dysregulation [43,44]. Freezers experience similar deficits [13]. In particular, freezers show executive function deficits when performing a Go-NoGo task [45] and the Stroop test [46], exhibiting decreased abilities in conflict resolution and inhibition [47–49]. Visuospatial deficits are evident in matrix reasoning and block design tasks [50], and some evidence suggests that the visual network is altered in freezers compared to non-freezers [51]. There is little work investigating language processing in PD, much less freezers and non-freezers; however some

freezers experience repetitive speech, where an individual will repeat syllables, words or phrases in succession. This symptom may be a speech equivalent of freezing of gait [52]. Finally, affective dysregulation in cerebellar patients includes a flattened affect [53], a symptom of PD in general [54]. Taken all together, it is clear that people with PD, and particularly freezers, have cognitive deficits that overlap those of cerebellar patients, suggesting the cerebellum's entanglement in the manifestation of FOG.

We chose to probe these potential relationships between the cerebellum and cognitive function in PD using MRI and cognitive task performance data from freezers and non-freezers. Chapter 2 asks whether the volumes of the cerebellar lobules differ between the two groups and examines potential relationships between the lobule volumes and cognitive performance. Prior research showed relationships between cortical volumes and cognitive performance [55,56], however this has not been thoroughly investigated in the cerebellum. We hypothesized freezers would have decreased volumes compared to non-freezers and that cerebellar volumes and cognitive task performance would positively correlate in freezers only.

1.2.2 Mechanics

Certainly the mechanisms of FOG are important to understand, but it is also crucial to know how the mechanisms manifest in behavior. The most distinct manifestation of FOG is a freezing episode; however the pathology is ever-present and may have subtle, non-intermittent expressions in one's overall movement. We know that as PD progresses, individuals adopt a more forward posture and shuffling gait. Undoubtedly these changes affect joint mechanics. Not only are there shifts in force distribution during gait, but also range of motion of joints becomes more limited and may impact fall risk in PD [57]. Freezers likely have even more altered joint

mechanics due to greater deficits in gait and balance compared to non-freezers, but there is surprisingly little kinematic research comparing joint mechanics between the two groups. By better understanding changes in joint mechanics, clinicians can develop rehabilitation protocols that are manageable for daily implementation and specific to deficits associated with PD.

Gait kinematics and kinetics

Gait impairment is one of the cardinal signs of PD [2], characterized by decreased step length, decreased velocity, and increased variability. While these deficits are well documented [58], there is surprisingly little research in joint mechanics during gait in PD, and thus little is understood about interactions between altered spatiotemporal gait characteristics and joint mechanics in people with PD. The research that has been done shows that people with PD have decreased joint movement in all planes during gait, and these reductions are further evident in the OFF-medication state [59]. Additionally, there is evidence showing that joint movement is inversely proportional to the disease severity [60], and unlike healthy older adults, the power at the hip and ankle are not related to velocity of forward movement [61]. Together, these results suggest a disconnect between central drive and peripheral output in people with PD [59,61].

The scaling of joint kinetics and kinematics was explored by Kuhman et al. [62] who found that people with PD exhibit an inability to adapt joint kinetics in response to different gait speeds. Kuhman et al. suggested that this is in keeping with the demonstration of postural inflexibility in people with PD, evidenced by an inability to adapt to perturbations and changes in support [63]. Perhaps people with PD exhibit global motor adaptation deficits, affecting their static and dynamic motor outputs. Again, this proposes a mismatch between central drive and peripheral

output, but it also highlights the relationship between gait and postural instability in people with PD.

Postural instability

As discussed above, gait and postural instability are of significant concern in people with PD due to their direct association with debilitating falls. One obvious time when postural stability is important is during postural transitions, whether that means coming from sitting to standing or changing directions in movement. An inability to properly maintain postural stability during these movements could result in a fall. Similar to the joint kinematics and kinetics during gait, people with PD may use different strategies than healthy adults to accomplish the task and maintain stability. When turning, people with PD not only take more steps to accomplish a turn, but the number of steps during the turn correlated with the degree of trunk flexion (sagittal plane). In healthy adults, the number of steps during a turn was correlated with lateral flexion (frontal plane) [67]. With freezers, this correlation may be even greater as postural control is further impaired [68] and trunk angle during standing is increased compared to non-freezers [69]. This is likely related to dysregulation of posture in the brainstem, specifically the pedunculopontine nucleus [70], which has altered connectivity in freezers [25,34].

Despite clear relationships between gait and postural instability and the increased risk of falls associated with FOG [8], little is known about gait mechanics in freezers compared to non-freezers. Therefore, chapter 3 of this dissertation probes how the joints of the lower limb move during gait in freezers and non-freezers We examined joint mechanics during forward, backward, and forward with dual-task gait conditions, as backward gait and dual-task gait are known to be

more impaired in freezers than non-freezers [64–66]. Additionally, in chapter 3 we continued to investigate potential cerebellar involvement in FOG by examining intralimb coordination. We hypothesized joint mechanics during backward and dual-task gait would differentiate freezers and non-freezers. Additionally, we expected freezers would have decreased intralimb coordination during the gait cycle compared to non-freezers.

1.2.3 Management

Unfortunately we are not close to a cure for PD. Our understanding of the disease processes is too limited, and technologies for neurogenesis and plasticity are hopeful but still too young to have realized their potential impact [71]. A recent review concluded that no clinically useful interventions have been developed to prevent or delay the progression of the disease [72]. But there is some reason for hope, as pharmacological and movement training interventions can mitigate symptoms and improve quality of life, and both methods are beneficial for freezers and non-freezers alike [72].

Pharmacological management

Motor symptoms can be treated with dopamine replacement therapy with high success for symptom reduction. Such pharmacological interventions likely have moderate, positive effects on quality of life [73]. Adjunct drug therapies can be included in one's daily medication regiment to boost effectiveness of dopamine agonists, such as catechol-O-methyl transferase (COMT) inhibitors [74]. Additionally, specific motor and non-motor symptoms can be targeted with other pharmacological interventions. For example, depression can be treated with Pramipexole and nortriptyline [75], and REM sleep behavior disorder can be treated with melatonin and clonazepam [76]. Unfortunately, disease progression and increased severity can lead to

resistance to antiparkinsonian medications [77], and not all symptoms respond well to pharmacological interventions [78]. In fact, gait impairments and postural instability are often medication-resistant. Also, prolonged use of levodopa, a dopamine precursor medication, can cause the development of dyskinesia [79], which necessitates further pharmacological or surgical interventions to reduce the dyskinesia to a manageable level [72].

FOG severity often, but not always, decreases with dopamine replacement therapy [80]; the complex pathophysiology of the symptom means that only dopamine dependent factors in the manifestation of FOG are affected [81]. Other, non-dopaminergic drugs have been tested [82–84] for effectiveness in treating FOG, but none have shown encouraging results. Therefore, due to FOG's resistance to drug therapy, non-pharmacological interventions may be necessary to mitigate the impact of freezing episodes on daily life.

Rehabilitation management

Regular physical activity, including physical therapy [85,86], group exercise [87–89], aerobic training [90–92], and resistance training [90,93,94] , is clinically useful for improving motor symptoms in people with PD [72]. For many, the physical activity may also improve measures of psychosocial well-being [95] and quality of life [96]. Whether a specific exercise is better than another is up for debate, but there is evidence to suggest that one needs a minimum of six months of training to expect clinically meaningful changes in motor symptomatology [97]. In fact, daily physical activity is recommended for older adults to reduce sedentary behavior [98], and particularly for people with PD, individuals should choose physical activities that they can incorporate into their daily routines [96], making it easier to accomplish activity goals.

Additionally, while choosing physical activities that fit well into a daily schedule is important, it is also important to choose “goal-based” activities (i.e., activities that train specific skills). People with PD show deficits in skill transfer [99], so general training may not significantly improve symptoms, but targeted training could. But what should the training focus on? A multitude of research examines gait and postural stability in PD and their relationships to risk of falls in people with PD [58,100,101]. Research on improving these symptoms is particularly important for freezers since gait [18,102] and balance impairments [68] are exacerbated in these individuals. While treadmill training [91,103,104], dance [89,105], and yoga [106–108] can significantly improve gait and balance in PD, the differential effects of exercise in freezers and non-freezers has not been explored well.

Therefore, chapter 4 examines differential effects of an exercise intervention on freezers and non-freezers. As noted above, physical activity is important and can improve symptoms in people with PD, however underlying neural mechanisms for this improvement are not well understood. Since movement in an MRI scanner must be kept to a minimum, we used motor imagery tasks to examine potential neural changes related to motor changes from an exercise intervention in freezers and non-freezers. We hypothesized motor imagery of backward gait would require greater neural activity compared to motor imagery of forward gait. We also hypothesized freezers would have reduced activity in the cerebellum overall, and differences in neural activity between freezers and non-freezers would diminish after an exercise intervention.

1.3 Summary

As we work towards a cure for Parkinson disease, the need for symptom management therapies grows stronger. Symptom management often requires a strong understanding of symptom cause.

Unfortunately, our understanding of freezing of gait is limited, and we lack effective treatments for this perplexing and devastating symptom. Therefore, scientists must examine freezing of gait from multiple angles to try to better understand the symptom and develop better treatment strategies.

Multiple models for the pathogenesis of freezing of gait have been proposed [20], but the most compelling model incorporates multiple systems, motor and non-motor. The changes in PPN connectivity and its connections with multiple areas of the cortex make the cerebellum a prime region of interest. The similarities in motor and non-motor deficits between freezers and cerebellar patients also incriminate the cerebellum for its involvement in the pathogenesis and pathophysiology of FOG.

Additionally, similarities in adaptation deficits between freezers and cerebellar patients add to the evidence suggesting cerebellar involvement in FOG. By studying the joint mechanics involved with gait, we can deepen our understanding of potential cerebellar involvement. Further, differences in gait mechanics in freezers and non-freezers, show that understanding mechanics in these subgroups of PD is important. This will not only illuminate what should be targeted in an intervention, but will also give researchers and clinicians quantitative outcomes to measure intervention efficacy.

As pharmacological interventions have a limited duration of efficacy, often accompanied by unpleasant side-effects such as dyskinesia, more non-pharmacological interventions need exploration for efficacy. People with PD benefit from daily physical activity, but research suggests that specificity is required to have the greatest impact on symptomatology. Because

postural instability and gait impairments are leading causes of falls in this population, interventions impacting these symptoms are in high demand.

This dissertation aims to take a multifaceted approach to studying freezing of gait. Cerebellar volume and function, gait mechanics, and exercise efficacy are explored in freezers and non-freezers. This work may inform future studies and perhaps encourage development of novel rehabilitation practices tailored to one's specific deficits, taking into account both mechanistic and mechanical deficits to enable more effective disease management.

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Chapter 2:
Cerebellar volume and executive function in Parkinson disease with and without freezing of gait

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2.1 Abstract

Background: Freezing of gait (FOG) affects approximately 50% of people with Parkinson Disease (PD), impacting quality of life and placing financial and emotional strain on the individual and caregivers. People with PD and FOG have similar deficits in motor adaptation and cognition as individuals with cerebellar lesions, indicating the cerebellum may play a role in FOG.

Objective: To examine potential differences in cerebellar volumes and their relationships with cognition between PD with (FOG+) and without FOG (FOG-).

Methods: Sixty-three participants were divided into two groups, FOG+ (n=25) and FOG- (n=38), based on the New Freezing of Gait Questionnaire. Cognitive assessment included Trail Making, Stroop, Verbal Fluency, and Go-NoGo executive function tasks. All participants completed structural T1- and T2-weighted MRI scans. Imaging data were processed with FreeSurfer and the Spatially Unbiased Infratentorial toolbox to segment the cerebellum into individual lobules.

Results: FOG+ performed significantly worse on phonemic verbal fluency ($F(1, 22)=7.06$, $p=0.01$) as well as the Go-NoGo task ($F(1, 22)=9.00$, $p=0.004$). We found no differences in cerebellar volumes between groups ($F(4, 55)=1.42$, $p=0.24$), but there were significant relationships between verbal fluency measures and lobule volumes in FOG-.

Conclusions: These findings underscore the need for longitudinal studies to better characterize potential changes in cerebellar volume, cognitive function, and functional connectivity between people with PD with and without FOG.

2.2 Introduction

Freezing of gait (FOG) affects approximately 50% of people with Parkinson disease (PD), with increasing prevalence as the disease progresses [1]. FOG is characterized by a temporary inability to make a step during walking or turning but can also affect upper limbs, speech, and eye movements. FOG increases the risk of falling, which can lead to serious health complications such as broken hips or wrists, placing financial and emotional strain on the individual and caregivers [2].

Although the underlying mechanisms of FOG remain unclear, the cerebellum has been implicated as a potential contributor to FOG. Recent research on cerebellar functional connectivity in PD with FOG (FOG+) showed altered connectivity between the cerebellum and other subcortical and cortical structures [3,4]. Notably, diffusion tensor imaging (DTI) research showed altered connectivity through the pedunculopontine nucleus (PPN) in FOG+ compared to PD without FOG (FOG-) and healthy controls [3]. FOG+ also show decreased after effects compared to FOG- following locomotor adaptation [5], indicating impaired retention of the learned adaptation. Individuals with cerebellar damage show similar deficits, displaying poor adaptation to, and retention after, removal of kinetic or visual perturbations [6]. While impaired retention of adaptation in FOG+ may relate to basal ganglia disruption, learning in these adaptation paradigms is relatively rapid and likely depends on the cerebellum. Therefore, deficits in rapid adaptation performance suggest FOG+ may have cerebellar impairment.

In addition to motor adaptation, growing evidence suggests that the cerebellum also has a role in cognition. For example, individuals with posterior cerebellar lesions display deficits in verbal fluency, spatial cognition, and working memory [7]. Anatomical studies [8] as well as functional

MRI studies [9] show that the posterior lobe of the cerebellum, particularly the crus I and crus II lobules, connects with the frontal cortex. Given this, the cerebellum may not only affect FOG in PD but could also affect cognition through its functional and anatomical connections with the frontal cortex.

People with PD develop cognitive impairment as the disease progresses, affecting set shifting, planning, and attention [10]. Deficits in executive function correlate with disruption of the fronto-striatal network [11]; however, dysfunction of the basal ganglia may also disrupt connections with the cerebellum, thereby affecting the fronto-cerebellar circuit. Further, FOG+ and FOG- differ in cognitive performance, including conflict resolution, response control, and verbal fluency [12]. Previous research suggests that dysfunction of the cognitive control network [13] may elicit freezing episodes. Specifically, FOG+ may fail to utilize frontal regions to respond to perturbations in gait, causing a freezing episode [14]. Therefore, research is needed to determine whether relationships exist between cognitive impairment and cerebellar structure and/or function in FOG+.

While several imaging studies examined relationships between cognition and cortical volume in PD [15], few studies included the cerebellum. Though one study showed decreased cognitive performance correlated with decreased overall cerebellar volume in PD [16], no studies examined potential differences in the individual cerebellar lobules between FOG+ and FOG- or their relationship to cognition. Each cerebellar lobule connects with distinct cortical regions and could therefore be affected by PD to different extents. Specifically, crus I and crus II anatomically connect to the prefrontal cortex [8], an area associated with executive function. Because FOG and cognition may relate to the cerebellum, and FOG+ have decreased cognitive

performance, we hypothesized that volumes of the crus I and II would be significantly decreased in FOG+ compared to FOG-. Additionally, we aimed to examine potential relationships between cerebellar lobule volumes and cognition. We hypothesized that crus I and II volumes in the FOG+ group would correlate with cognitive performance based on their anatomical connections with the frontal cortex.

2.3 Materials and Methods

2.3.1 Participants

All participants were part of a larger exercise intervention trial [17]. Study inclusion criteria were 1) clinical diagnosis of idiopathic PD, 2) clear benefit from levodopa, 3) Hoehn & Yahr stages I-IV, 4) ability to walk independently for at least three meters, and 5) score ≥ 24 on the Mini Mental State Exam (MMSE). For the present analyses, participants needed 1) T1- and T2-weighted structural MRI scans, 2) successful cortical and cerebellar segmentation with FreeSurfer software (v5.3.0, http://surfer.nmr.mgh.harvard.edu/) and the Spatially Unbiased Infratentorial (SUIT) toolbox [18] and 3) a complete cognitive dataset. Of the 120 participants, 63 participants met all inclusion criteria (Figure 2.1). Participants were divided into FOG+ and FOG-based on the New Freezing of Gait Questionnaire (N-FOGQ) [19]. A higher N-FOGQ score indicates a greater quantity and severity of freezing episodes in daily life and serves as a measure of freezing severity. Individuals who reported freezing episodes in the past month were categorized as FOG+ (n=25). All behavioral assessments and MRI scans were performed OFF medications, defined as ≥12-hours without anti-PD medications. This study was approved by the Human Research Protection Office of Washington University in St Louis, and all participants provided informed written consent.

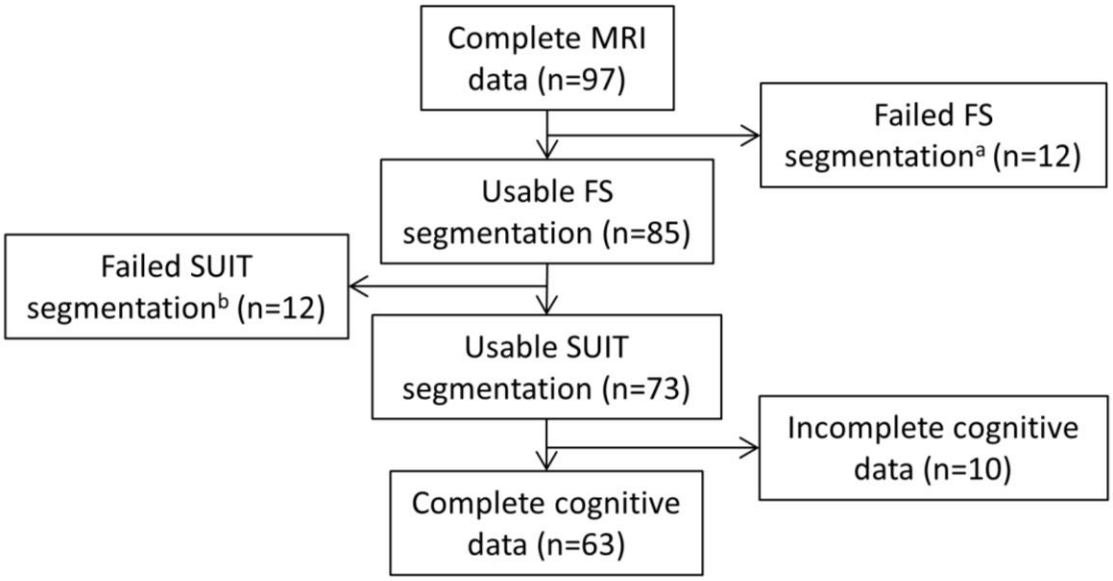

Figure 2.1. Participant Flow Diagram. Data for the present analyses came from a pool of participants who participated in a larger exercise intervention trial. Participants were included if 1) they had both a T1- and T2-weighted structural MRI scan; 2) FreeSurfer and the SUIT toolbox could properly segment the brain; and 3) they had a complete cognitive dataset.
[a]Failed FreeSurfer segmentation due to poor MRI quality or motion artifact.
[b]Failed SUIT segmentation defined as significant volume bleed into CSF or cortex, improper lobule segmentation, or exclusion of cerebellar cortex.

2.3.2 MRI acquisition and image processing

Participants completed MRI scans while OFF anti-PD medications on a Siemens TRIO 3T scanner (Erlangen, Germany) at Washington University School of Medicine. Participants completed whole brain structural T1-weighted (TR=2400ms, TI=1000ms, TE=3.16ms, FA=8°, 0.9mm^3 voxels, 8:09min) and T2-weighted (TR=3200ms, TE=455ms, 1.0mm^3 voxels, 4:43min) scans.

Structural scans were automatically segmented using FreeSurfer. After FreeSurfer processing, scans were visually inspected for proper segmentation and manually edited and reprocessed as

necessary. Manual edits failed to successfully segment scans from 12 participants (out of 97), removing them from further analysis (Figure 2.1).

The cerebellum's location puts it at risk for spatial warping during atlas normalization, making volume estimates of the cerebellum unreliable. To avoid this potential bias, we used the SUIT toolbox to segment the cerebellum into individual lobules, providing better estimates of the volume of each lobule (Figure 2.2). The SUIT toolbox provided volume measures for individual lobules (bilateral lobules I-IV, V, VI, crus I, crus II, VIIb, VIIIa, VIIIb, IX, and X) as well as total cerebellar volume. To optimize SUIT cerebellar segmentation for older adults, we applied FreeSurfer's cerebellar white matter mask from each participant's segmentation to remove white matter voxels, providing grey matter volumes for each lobule. In addition, we used the FreeSurfer-generated cortical ribbon and the T2-weighted CSF boundary to reduce inclusion of surrounding cortex and CSF during SUIT segmentation. Accurate SUIT segmentation was determined through visual inspection for each participant. Of the 85 participants' scans processed, SUIT failed to properly segment 12 scans, removing them from further analysis.

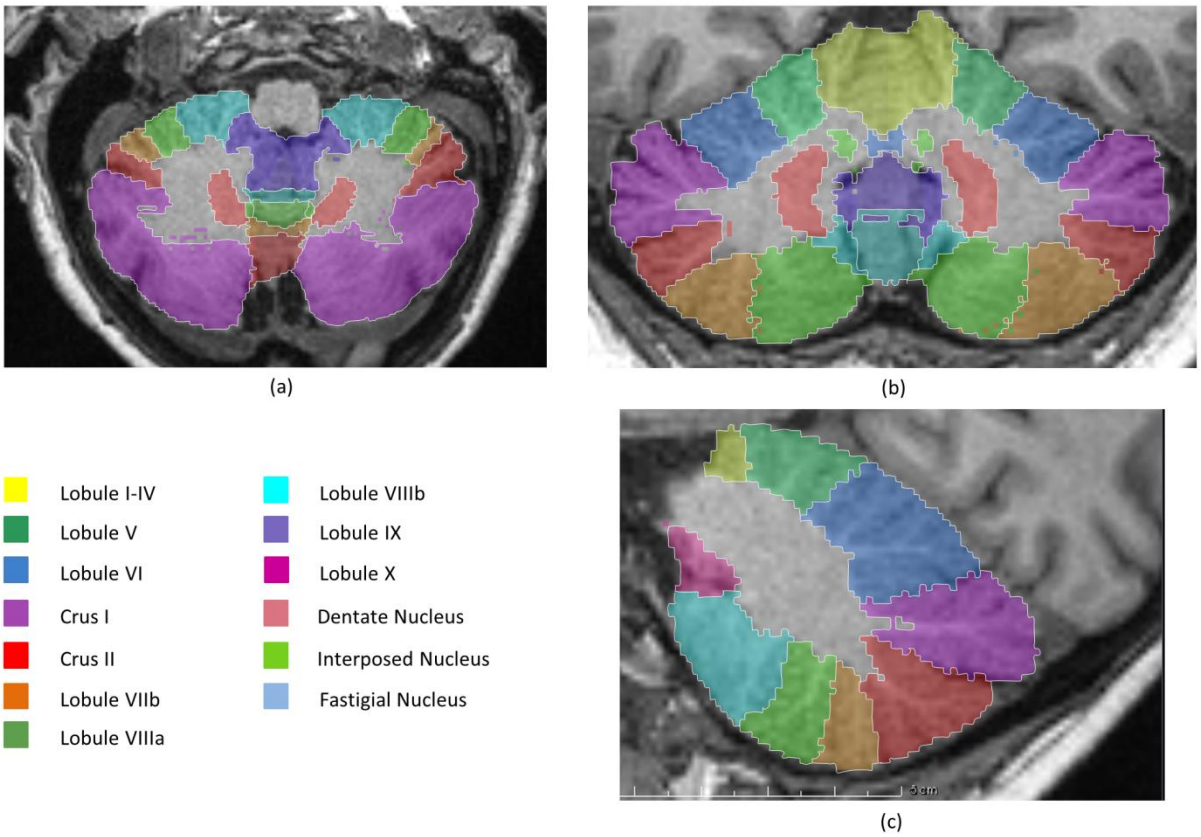

Figure 2.2. SUIT Segmentation of the Cerebellum. Lobules are bilateral with vermal portions in the middle. Lobules shown in (a) transverse, (b) coronal, and (c) sagittal views.

2.3.3 Cognitive assessment

Participants completed a short cognitive battery to assess executive function. Specific tests included Trail Making to measure attention and set-shifting [20], Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference test (i.e., Stroop) to measure attention and inhibition [21], and Verbal Fluency to measure response generation and flexibility [21]. As the primary dependent measures of cognitive performance, we computed the difference between Trails A and Trails B (Trails B time – Trails A time; Trails), the difference between the inhibition and color conditions of Stroop (Inhibition time – color time), and the total number of

correct responses for each section of Verbal Fluency (Phonemic VF, Semantic VF, and Switch Accuracy VF).

In addition to these standard neuropsychological measures, participants completed a computerized Go-NoGo (GNG) test of response inhibition. The GNG task requires participants to respond to certain stimuli (Go trials) while withholding responses to other stimuli (NoGo trials). We calculated discriminability (Pr) and bias (Br) scores as previously described [22] using an individual's hit and false alarm rates. Hit rate equals the number of correct responses divided by the total number of Go trials. False alarm rate equals the number of incorrect responses divided by the total number of NoGo trials. Discriminability measures the ability to differentiate between two trial types. A score of 0 indicates no discrimination and a score of 1 indicates perfect discrimination. Bias measures the likelihood to make one response over another response (i.e., does the participant make one response for all trials, regardless of trial type). A score of 0.5 indicates no bias, whereas a score >0.5 indicates a tendency towards responding to No-Go trials [22]. To avoid dividing by zero for the calculation of Pr and Br, hit rates of 1 were replaced with $(n_g - 0.5)/n_g$ and false alarm rates of 0 were replaced with $0.5/n_{ng}$, where n_g is the number of Go trials, and n_{ng} is the number of No-Go trials [23]. Of the 73 participants with successful FreeSurfer and SUIT segmentations, 10 had incomplete cognitive data and were removed from further analysis.

2.3.4 Statistical Analyses

Statistical analyses were performed with SPSS (IBM Analytics, version 24) with a statistical significance threshold of $\alpha<0.05$. Analyses included the omnibus, multivariate analysis of covariance (MANCOVA) as well as follow-up analysis of covariance (ANCOVA). Partial

correlations were used to control for demographics (age, education, disease duration) and estimated total intracranial volume (eTIV) when appropriate. Bonferroni correction was used when appropriate to correct for multiple comparisons. Participants with scores on any executive function task greater than 2.5 standard deviations above or below the grand mean were removed as outliers from analyses involving these data. This criterion excluded four participants from each group. To identify outliers in the lobule volumes, each participant's lobule volumes were normalized to the participant's total cerebellar volume. We set having ≥25% of normalized lobule volumes (7 lobules or more) being ±2.5 standard deviations from the normalized grand mean as our threshold for exclusion as an outlier. No participants met the exclusion criterion as no participant had more than 3 out of 28 lobules ±2.5 standard deviations from the normalized grand mean.

2.4 Results

The two groups were well-matched for demographics (Table 2.1), except for duration of PD diagnosis ($t(61)=-2.97$, $p=0.004$), indicating that FOG+ had a longer average disease duration. To control for this potential confound, analyses included a disease duration covariate when appropriate. As expected, the FOG+ group reported higher scores on the N-FOGQ compared to FOG- ($t(61)=-11.47$, $p<0.001$).

Table 2.1. Group demographic characteristics.

Demographics	FOG- (n=38)	FOG+ (n = 25)	p-value
Age (years)	63.9 (9.6)	66.7 (10.1)	0.27
Sex (# female)	18	11	1
MMSE (median, range)	29, 27 - 30	29, 24 - 30	0.16
Hoehn & Yahr (stage, n)	--	--	0.58
	I, 3	I, 1	
	II, 30	II, 19	
	III, 5	III, 4	
	IV, 0	IV, 1	
Duration of Diagnosis (years)	4.3 (3.2)	7.5 (5.2)	0.004*
Education (years)	16.3 (2.4)	15.4 (2.4)	0.14
N-FOGQ	0	9.8 (5.3)	<0.001*

Values denote mean (standard deviation), except where noted.
*statistically significant ($p<0.05$)

2.4.1 Cognitive Performance

After removing outliers for executive function, the omnibus MANCOVA with the raw scores for each cognitive test as dependent variables, age, education, and duration of PD diagnosis as covariates, and group (FOG- or FOG+) as a fixed factor, was significant ($F(7, 44)=3.35$, $p=0.006$). Follow-up univariate ANCOVAs showed significant differences in phonemic VF ($F(1, 22)=7.06$, $p=0.01$) and Pr ($F(1, 22)=9.00$, $p=0.004$) (Table 2.2).

Table 2.2. Cognitive performance measures.

ANCOVA Measure	FOG-, n=34	FOG+, n = 21	p-value
Trails (seconds)	60.5 (6.3)	71.4 (7.6)	0.21
Stroop (seconds)	32.1 (4.7)	33.8 (4.7)	0.58
Phonemic VF	42.6 (2.2)	33.8 (2.6)	0.01*
Semantic VF	39.7 (1.6)	37.1 (1.7)	0.68
Switch Accuracy VF	12.9 (0.5)	11 (0.6)	0.17
Pr	0.76 (0.03)	0.63 (0.04)	0.004*
Br	0.45 (0.007)	0.46 (0.007)	0.41

Values denote mean (standard deviation) after removing outliers based on cognitive performance.
*statistically significant ($p<0.05$)

2.4.2 Cerebellar Lobules

To test for grey matter volume differences in crus I and II between groups, we ran a MANCOVA with the SUIT grey matter volumes for crus I and II, bilaterally. The overall MANCOVA (covariates: age, disease duration, eTIV) showed no significant differences between groups ($F(4, 55)=1.42$, $p=0.24$). As an exploratory analysis, we ran a MANCOVA for differences in all lobules between groups (covariates: age, disease duration, eTIV), which showed a trend towards significance ($F(21, 38)=1.65$, $p=0.09$). Additional exploratory univariate ANCOVAs for each lobule, using an adjusted significance threshold of $\alpha < 0.01$, did not yield significant differences for any lobules (all $p>0.02$).

2.4.3 Relationships Between Cognition, Freezing Severity, and Cerebellar Volume

All participants

We first explored possible relationships between volume and cognitive performance within PD, regardless of freezing status. A third-order, partial correlation controlling for age, education, and eTIV showed a significant relationship between Trails and right crus II volume (partial $r=-0.30$, $p=0.03$). We also ran exploratory third-order, partial correlations for the other lobules controlling for age, education, and eTIV, with Bonferroni multiple comparisons correction ($\alpha<0.003$). This analysis showed significant correlations between Switch Accuracy VF and lobule I-IV (left: partial $r=-0.48$, $p<0.001$; right: partial $r=-0.44$, $p=0.001$), lobule V (left: partial $r=-0.54$, $p<0.001$; right: partial $r=-0.47$, $p=0.001$), and left lobule VI (partial $r=-0.53$, $p<0.001$). To ensure duration of PD diagnosis did not act as a confounder, we ran bivariate correlations between disease duration and age, education, measures of executive function, lobular and total cerebellar volumes, and NFOG-Q total (FOG+ only). No correlations reached significance (all $p\geq0.09$).

FOG+

Next, we ran the same third-order, partial correlations, using only FOG+ data. The third-order, partial correlation for cognitive measures and crus I and II volumes revealed a trend towards a relationship between Trails and right crus I (partial r=0.42, p=0.08) and between Stroop and left crus I (partial r=-0.43, p=0.07). The exploratory, third-order, partial correlation for cognitive performance and all lobule volumes showed no significant relationships (all p>0.005).

We also ran second-order, partial correlations on the FOG+ data, examining relationships between freezing severity, cognitive performance, and cerebellar lobule volumes. A second-order, partial correlation, controlling for age and education, showed a significant relationship between semantic VF and N-FOGQ score (partial r=-0.46, p=0.048).

A second-order, partial correlation, controlling for age and eTIV, found no significant relationships between crus I and II volumes and N-FOGQ score (all p>0.22). An exploratory second-order partial correlation between all lobules and N-FOGQ, controlling for age and eTIV and significant threshold set at $\alpha<0.003$ (Bonferroni correction for multiple comparisons) showed no significant relationships (all p>0.04).

FOG-

We ran the same third-order, partial correlations using only FOG- data. The partial correlation between cognitive performance and crus I and II volumes showed a significant relationship between Pr and crus II (right: partial r=-0.44, p=0.01; left: partial r=-0.33, p=0.07). In addition, Switch Accuracy VF significantly correlated with left lobule I-IV (partial r=-0.53, p=0.002), lobule V (left: partial r=-0.62, p<0.001; right: partial r=-0.54, p=0.002), and left lobule IV (partial r=-0.62, p<0.001).

2.5 Discussion

Based on multiple lines of research implicating the cerebellum in FOG, we investigated potential cerebellar volumetric differences between people with PD with and without FOG. Improved cerebellar segmentation methods revealed similar total cerebellar volume and individual lobular volumes between our groups of FOG+ and FOG-. PD with FOG did not have smaller cerebellar volumes, despite obvious motor deficits and impaired cognition. Further, no relationships between cerebellar volume and cognitive function or motor severity emerged for PD with FOG. These results suggest that in our sample cerebellar volume did not account for either the motor or cognitive deficits associated with FOG in PD.

Though FOG+ and FOG- did not differ in cerebellar volumes, the SUIT toolbox provided accurate volumes by using nonlinear normalization methods with a cerebellum-specific template rather than whole-brain alignment methods. Our methods prevented spatial warping that could bias volume calculations. Because cerebellar volume decreases with age [24], we defined the CSF boundary around the cerebellum using T2-weighted scans to optimize SUIT cerebellar segmentation for older adult brains. This optimized accuracy of segmentation, preventing inclusion of surrounding CSF and cortex into lobule volume calculations. Previous research examining volumetric differences in the cerebellum between FOG+ and FOG- reports conflicting results. Kostic et al. [25] did not find significant cerebellar volume differences between FOG+ and FOG-; however Herman et al. [26] found significantly lower cerebellar volume in FOG+ compared to FOG-. Our results may help clarify discrepancies in the current cerebellar volumetric literature in FOG+ and FOG-.

Although the present results suggest cerebellar volume is not associated with FOG in PD, it remains possible that other aspects of cerebellar pathology and function contribute to FOG in PD and its associated cognitive deficits. For example, cerebellar acetylcholinesterase activity was significantly reduced in PD compared to controls, which suggests disproportionate degeneration of cholinergic pathways compared to overall tissue degradation [27]. Cholinergic projections in the PPN are reduced in PD compared to controls [28], and DTI in FOG+ showed PPN connectivity with the cerebellum to be non-existent and corticopontine projections to be increased, suggesting an important function of the corticopontine-cerebellar pathways in the manifestation of FOG [3].

Further, reduced acetylcholine receptor density in the cerebellum may contribute to cognitive comorbidities in PD [29]. Importantly, dopaminergic replacement therapies have heterogeneous effects on cognition and the effects diminish over time [30], suggesting that the cholinergic system may also play a significant role in cognition and PD. Altogether, while volume of the cerebellum may not predict cognitive performance in FOG+, its involvement in freezing of gait requires further research, particularly in measures of cholinergic transmission and connectivity with the cerebral cortex

These findings raise the question of whether the tissue measured with structural MRI has the same functional integrity in FOG+ and FOG-. Indeed, FOG+ demonstrate reduced functional connectivity between the cerebellum and the supplementary motor area [31].Therefore, while grey matter volume measures may not capture cerebellar differences between FOG+ and FOG-, the pathophysiology of FOG may still involve the cerebellum.

Our results regarding executive dysfunction in FOG+ agree with previous research demonstrating cognitive differences between FOG+ and FOG-. Similar to our findings, Amboni et al. [32] also reported reduced verbal fluency for FOG+ compared to FOG-. PD with FOG also performed worse on the GNG task, consistent with previous reports of impaired performance compared to FOG- [33]. However, neither cognitive function nor severity of freezing symptoms correlated with cerebellar volume in our sample of PD with FOG. Further, duration of PD diagnosis did not correlate with executive function, indicating that disease duration was not a confounding factor in our analyses.

Interestingly, our results show FOG- have negative relationships between cerebellar lobule volumes and executive function, indicating decreased volume corresponded with better executive function. O'Callaghan et al. [34] found that smaller cerebellar volume correlated with increased functional connectivity between the cerebellum and the fronto-parietal network in PD compared to controls. Importantly, they used the SUIT toolbox to assess cerebellar volume. Combining across studies, these results suggest that better executive function may relate to greater functional connectivity between the cerebellum and the fronto-parietal network; conversely, worse executive function, as associated with FOG+, may relate to reduced functional connectivity between the cerebellum and the fronto-parietal network. Reduced connectivity could affect the ability to make corrective movements, requiring a higher degree of cognitive effort in order to successfully make necessary adjustments. This fits with the theory of "executive function overload" that proposes an inability of FOG+ to properly recruit frontal networks, particularly during dual-task conditions, leading to a freezing episode [14]. While speculative, this warrants

further research investigating cerebellar functional connectivity and its relationship with the motor and cognitive features associated with FOG in PD.

Our study may have limited generalizability due to inclusion of only mildly to moderately affected PD participants. While duration of PD diagnosis did not significantly correlate with cerebellar volume in our sample, cerebellar atrophy may occur later in the disease course or with greater disease severity. Future research should examine more severe PD participants. Further, the use of a cross-sectional design limits the ability to examine changes over time. Longitudinal studies that track PD participants over several years may clarify the cerebellum's role in disease progression and whether it influences the development of FOG. Additionally, studies may benefit from using a more comprehensive cognitive battery. Other aspects of cognition such as memory, attention, and visuospatial processing may also be affected in FOG and involve the cerebellum [12].

As freezing of gait can lead to falls and debilitating injuries that decrease a person's quality of life, greater understanding of the mechanisms behind FOG is needed. We used a novel approach for measuring cerebellar volumes in PD with and without FOG, examining whether individual cerebellar lobule volumes differed between the two groups and whether executive function relates to cerebellar volume in PD with FOG. We found no evidence of differences in cerebellar volumes between groups, despite having a well-differentiated sample. Instead, we found strong negative relationships between executive function and cerebellar volume in FOG- that may reflect functional connectivity differences between FOG+ and FOG-. By conducting longitudinal studies on volume, cognition, and functional connectivity in PD with FOG, the role of the cerebellum in the multifactorial mechanisms behind FOG can be ascertained.

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Chapter 3:
Backward, forward, and dual-task gait kinematics in people with Parkinson disease with and without freezing of gait

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3.1 Abstract

Background: People with Parkinson disease (PD) suffer from gait impairments such as gait variability, but the primary sources of variability are poorly understood. People with PD and freezing of gait (freezers) have greater gait impairments, particularly in backward and dual-task gait, compared to people with PD without freezing of gait (non-freezers). Increased variability in freezers may relate to cerebellar dysfunction.

Research question: Are the primary sources of variability in freezers different from non-freezers during backward, forward, and forward with dual-task gait conditions?

Methods: Freezers (n=13) and non-freezers (n=31) completed trials of backward, forward, and forward with dual-task (word listing) gait. Joint kinematics were measured using 3D motion capture. Sagittal joint angle waveforms were extracted for the hip, knee, and ankle. Decomposition index, a metric for how much one joint is held steady while another joint moves during gait, was calculated for the three joint combinations. Additionally, a principal component analysis (PCA) was used to extract independent sources of variance from the joint waveforms for each condition.

Results: Freezers had significantly greater decomposition indices between hip-ankle ($F(1,42)=5.1$, $p=.03$) and hip-knee ($F(1,42)=5.3$, $p=.03$). The PCA showed no differences between freezers and non-freezers; however, the primary variance sources differed between conditions. Primary variance during forward and forward with dual-task gait came from joint angle magnitude and timing of peak angles during the gait cycle. Backward gait showed primary variance from joint angle magnitude and range of motion.

Significance: The results show that freezers decompose movement more than non-freezers, further implicating cerebellar involvement in freezing of gait. Primary gait variance differs between gait conditions, suggesting gait interventions may affect gait conditions differently. Tailoring gait interventions to address sources of variability may improve intervention efficacy.

3.2 Introduction

Gait impairments are frequently observed in people with Parkinson disease (PD). These gait impairments increase the risk of debilitating falls in people with PD [1]. Further, gait impairments are not limited to forward gait and are often more pronounced during backward and dual-task gait [2–4]. Gait impairments during forward, backward, and dual-task walking are often greater among people with PD with freezing of gait (freezers) compared to people with PD without freezing of gait (non-freezers) [5,6]. While differences in spatiotemporal gait characteristics, including step length, velocity, and cadence, are well documented between freezers and non-freezers, joint kinematic differences are poorly understood. The cerebellum is integral to coordinating joints during movement [7], and current evidence suggests cerebellar involvement in freezing of gait (FOG) [8–10]. We hypothesized that impaired intralimb joint coordination in freezers may be related to cerebellar dysfunction and manifest similarly to that in patients with cerebellar damage [11]. One aim of this study was to determine if freezers demonstrate differences in interjoint coordination during various gait conditions, compared to non-freezers.

Joint coordination is related to gait variability, with enhanced coordination resulting in reduced variability [7]. While research indicates elevated gait variability in PD, particularly in freezers [2], interventions to reduce gait variability are limited [12]. This may be because primary sources of gait variability remain unclear. One method to better understand gait variability sources is principal component analysis (PCA), which separates total variance in the gait cycle into independent principal components (PCs). PCA is used with biomechanical data [13–15] to understand sources of variability during gait, allowing for comparison between conditions and

groups. To our knowledge, PCA has not been used to describe gait variability in freezers and non-freezers across different gait conditions.

Knowing the sources of variability during different gait conditions for freezers and non-freezers may allow for more targeted treatment options. Thus, the second aim of this study was to investigate potential kinematic differences in freezers and non-freezers using PCA. We hypothesized that forward (FWD), forward with dual-task (DT), and time-reversed backward (BWD) gait kinematics would show large sources of variability in sagittal joint angle trajectories at the hip, knee, and ankle. We also hypothesized that BWD and DT gait would be less similar to FWD gait in freezers, compared to non-freezers. These differences would be captured in the PCs as well as in a higher decomposition index [11,16], reflecting poorer intralimb joint coordination during BWD and DT compared to FWD.

3.3 Methods

3.3.1 Participants

All participants were part of a larger study, with the following inclusion criteria: 1) clinical diagnosis of idiopathic Parkinson disease, 2) able to stand independently for ≥30 minutes, 3) normal peripheral neurologic function, 4) no history of vestibular disease, and 5) Mini Mental State Exam (MMSE) score ≥24. Exclusion criteria were: 1) diagnosis of other major medical condition, 2) deep brain stimulation, 3) diagnosis of peripheral neuropathy, or 4) use of dopamine-blocking medications. For inclusion in the present analysis, participants also needed a body mass index (BMI) <30 and a complete set of usable 3D motion capture data. Of the 56 participants in the larger study, 44 met all inclusion criteria for this analysis.

All participants completed a behavioral assessment and 3D motion capture data collection. The behavioral assessment included the New Freezing of Gait Questionnaire (NFOG-Q) [17]. The first question of the NFOG-Q, "Did you experience freezing episodes in the past month?" was used to divide participants into freezers (n=13) and non-freezers (n=31). This sample size is comparable to prior gait research in freezers and non-freezers [5] and gait research using PCA [18]. Disease severity was measured using the Movement Disorder Society Unified Parkinson Disease Rating Scale, motor symptom subscale (MDS-UPDRS III) [18]. All participants provided written informed consent, and the Human Research Protection office of Washington University in St Louis approved this study.

Table 3.1. Demographic and Baseline Characteristics.

Characteristic/Measure	**Freezer (n=13)**	**Non-Freezer (n=31)**	**p-value**
Age$^{\tau}$ (years)	64.2 (6.6)	67.3 (9.2)	.28
Gender$^{\chi}$ (% female)	61.5	61.3	.99
BMI$^{\tau}$, mean (SD)	24.6 (3.0)	23.8 (2.7)	.35
MDS-UPDRS III$^{\eta}$, median (range)	26 (13, 48)	26 (3, 49)	.93
MMSE$^{\eta}$, median (range)	29 (27, 30)	29 (25, 30)	.91
BESTest$^{\eta}$, median (range)	84 (67, 96)	89 (63, 98)	.10
NFOG-Q$^{\eta}$, median (range)	13 (4, 21)	0	<.001
BWD velocity$^{\tau}$ (m/s), mean (SD)	0.66 (0.32)	0.74 (0.24)	.36
FWD velocity$^{\tau}$ (m/s), mean (SD)	1.12 (0.18)	1.21 (0.14)	.15
DT velocity$^{\tau}$ (m/s), mean (SD)	0.96 (0.19)	1.01 (0.24)	.52

Body mass index (BMI); Movement Disorder Society Unified Parkinson Disease Rating Scale, motor symptom subscale (MDS-UPDRS III); Mini Mental State Exam (MMSE); Balance Evaluation Systems Test (BESTest); New Freezing of Gait Questionnaire (NFOG-Q); Backward (BWD); Forward (FWD); Dual-task (DT).
$^{\tau}$Independent t-test
$^{\eta}$Mann-Whitney U Test
$^{\chi}$Chi-square

3.3.2 3D Motion capture

A Hawk Digital RealTime 8-camera system by Motion Analysis (Motion Analysis Corporation, Santa Rosa, CA, USA) was used with a 10'x10'x10' capture volume and camera capture rate of 100Hz. Participants wore fitted athletic clothing provided by the research team and their own shoes. Reflective markers (20mm diameter) were placed on T12, L5, and bilaterally on the PSIS, ASIS, iliac crest, greater trochanter, medial and lateral femoral condyles, tibial tuberosity, medial and lateral malleoli, 1st and 5th metatarsophalangeal joints, tip of the first toe, and 1" above the floor on the back of the shoe. Plates with four evenly spaced markers were placed 3.5" above the lateral condyle of the femur and 6" above the lateral malleolus of the distal fibula, providing tracking of the thigh and shank. A 5-second static trial was first collected where participants stood still with feet hip distance apart, arms straight and abducted to 45° with palms facing forward. The medial femoral condyle and medial tibial malleolus markers, as well as 1st metatarsal markers were then removed and an additional, 5-second static trial was collected. Next, participants walked diagonally across the capture volume in three gait conditions: FWD, BWD, and DT. Trials were grouped in blocks by condition (five trials per block), and blocks were randomized. For FWD trials, participants were instructed to walk forward at their comfortable pace. For BWD trials, participants were instructed to walk backward at their comfortable pace. For DT trials, participants were instructed to walk forward at their comfortable pace while listing as many different words as they could that begin with a specified letter, which changed for every trial. For safety, a research team member walked alongside participants.

3.3.3 Data Processing

Motion capture data were pre-processed in Cortex (version 1.1.4, Motion Analysis Corporation, Santa Rosa, CA, USA), exported as .c3d files, and imported into Visual3D (version 6, C-Motion,

Germantown, MD, USA). We used a low-pass, Butterworth 6Hz filter to smooth all kinematic data [5,13] and a custom MATLAB (version R2016a, MathWorks, Natick, MA, USA) pipeline to extract and process hip, knee, and ankle joint angles from each trial. BWD trials were time-reversed for comparison to FWD and DT trials [19]. Heel strikes were defined as the time points when the velocity of the heel marker changed from negative to positive. Each gait trial was segmented into right and left stride lengths, defined as heel strike of one foot to next heel strike of the same foot. Three complete, usable strides on the left and right leg were extracted for each condition and combined for a total of six strides per participant per condition. Range of motion (ROM) for each joint was calculated as the difference between maximum and minimum joint angles during the gait cycle. Timing of maximum and minimum angles were extracted as a percentage of the gait cycle.

3.3.4 Decomposition Index

To better understand how the joints moved relative to one another, a decomposition index was calculated [16] to denote the percentage of the gait cycle during which the movement of the joints was decomposed (i.e., where one joint was held fixed while another joint was moving). An angular velocity threshold of $<5^{\circ}$/sec was used to define a fixed joint [11].

3.3.5 Statistics

Right and left strides were combined for each walking condition for a total of six complete strides [20]. Joint trajectories were normalized to time and plotted over time (expressed as percent of gait cycle; Figure 3.1). Using IBM SPSS statistics (version 24, IBM, Armonk, NY, USA), repeated-measures analysis of variance (RM-ANOVA) were conducted with between-subject factor of freezing status (freezer, non-freezer) and within-subject factor of condition (BWD, FWD, DT). Significance was set at $\alpha<.05$. Sphericity was assessed using Mauchly's test

of sphericity, and Greenhouse-Geisser corrections were used when necessary. Residual outliers that were ≥ 3 interquartile ranges from the mean were winsorized to meet normality assumptions for RM-ANOVA. In the event of a significant main effect or interaction, post hoc analyses were conducted using Bonferroni corrections. Independent t-tests were used to compare PC scores between freezers and non-freezers. Bonferroni correction was used within each joint for the three gait conditions, resulting in a significance threshold of $\alpha \leq .016$.

3.3.6 Principal Component Analysis (PCA)

PCA reduces a large set of potentially related variables into a smaller number of orthogonal variables or principal components. All PCs are independent and have no shared variability with the other PCs [13]. Each PC is represented by an eigenvalue and a loading vector. The eigenvalue represents the percentage of variance the respective PC captures in the dataset. The loading vector indicates the source of the variability. Each participant receives an eigenfactor for each PC, which is a weighted factor for how far the participant is from the group mean.

Our PCA aimed to compare gait kinematics in freezers and non-freezers. Each gait condition was represented by a matrix where each row represented a participant (n=44) and each column represented 1% of the gait cycle. A 44x101 matrix was created for each gait condition and joint, nine matrices in total. PCA was applied to each matrix, and as many successive PCs as necessary to represent ≥90% of the total variance were extracted for further analysis [21]. Single component reconstruction was used to interpret the PCs for each analysis [13].

With kinematic data, three sources of variance are often present: a magnitude feature, a difference feature, and a phase shift. A magnitude feature refers to a vertical shift in the whole waveform and will be evident by a loading vector that is entirely positive or negative. A

difference feature refers to timing of maxima and minima being the same, but the magnitude relationship shifts between representative extremes. The loading vector for this kind of variability will have maxima and minima that coincide with maxima or minima in the mean waveform. A phase shift refers to variance in timing of local maxima and minima and will have a loading vector with a maximum and minimum on either side of a maximum or minimum in the mean waveform [13].

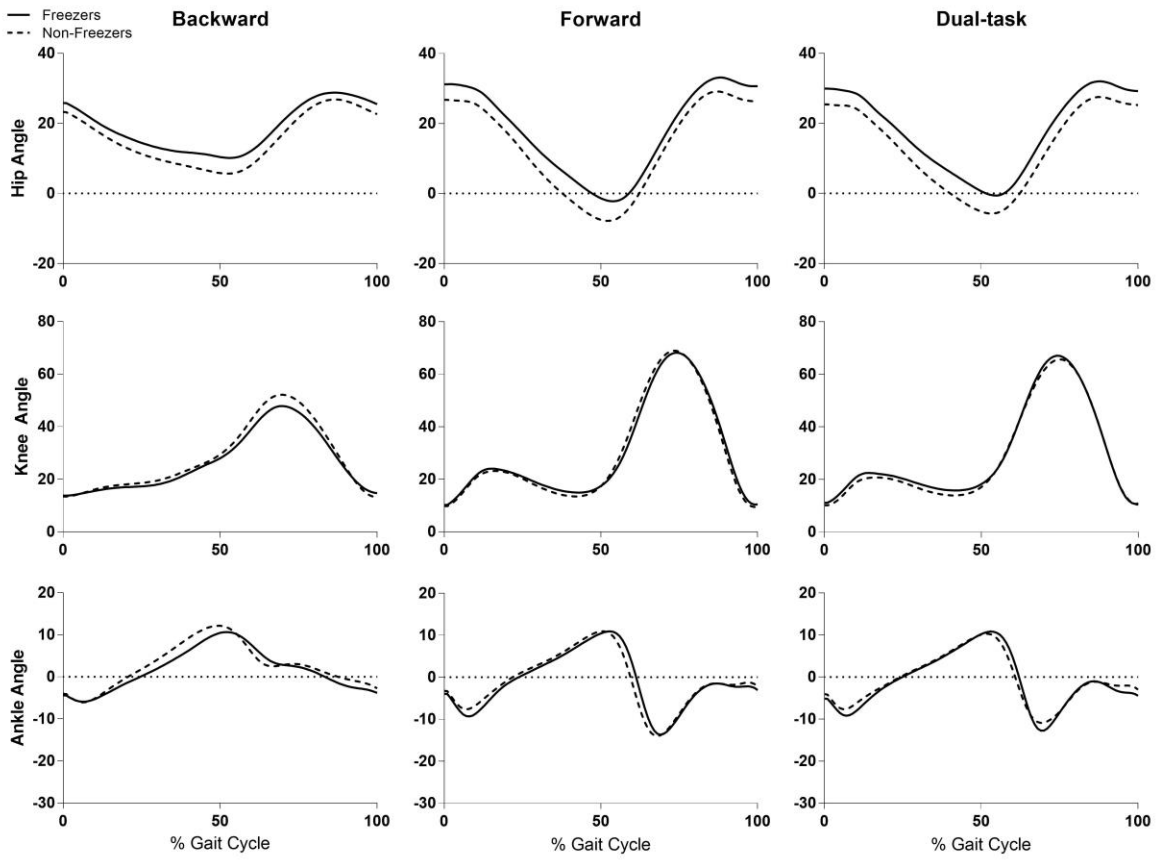

Figure 3.1. Average Joint Trajectories. Average joint trajectories across the gait cycle for freezers and non-freezers. At the hip, positive denotes flexion and negative denotes extension. At the knee, positive indicates flexion. At the ankle, positive denotes plantarflexion and negative denotes dorsiflexion.

3.4 Results

No FOG episodes occurred during motion capture.

3.4.1 Range of Motion

We conducted a RM-ANOVA for each joint. There was a significant main effect of condition for all joints (hip: $F(1.3,54.4)=224.0$, $p<.001$; knee: $F(1.2,49.3)=193.6$, $p<.001$; ankle: $F(1.2,49.8)=28.3$, $p<.001$). Post hoc analyses showed that hip, knee, and ankle ROM were significantly lower in BWD compared to both DT and FWD, and in DT compared to FWD. There was no main effect of freezing status, and no interaction between freezing status and gait condition (Table 3.2).

3.4.2 Timing of Minimum and Maximum Angles

We conducted a separate RM-ANOVA for each joint to compare timing of maximum and minimum angles. For timing of maximum angles, there were significant effects of condition for the hip ($F(1.3, 55.2)=4.4$, $p=.03$) and knee ($F(1.3, 53.4)=46.2$, $p<.001$), but not the ankle ($F(1.1, 48.1)=2.1$, $p=.15$). Post hoc analyses showed no significant difference between conditions at the hip. At the knee, the maximum angle in BWD occurred sooner in the gait cycle than both DT and FWD, with no difference between DT and FWD. There was no main effect of freezing status, and no interaction at any joint (Table 3.2).

For timing of minimum angles, there were significant condition effects at the hip ($F(1.2, 48.6)=4.9$, $p=.026$), knee ($F(2, 41)=9.1$, $p=.001$), and ankle ($F(1.2, 49.5)=280.9$, $p<.001$). Post hoc analyses for hip showed the minimum angle occurred earlier during BWD than DT and earlier during FWD compared to DT. At the knee, post hoc analyses showed the minimum angle occurred significantly earlier in BWD compared to DT and FWD, with no differences between DT and FWD. The minimum ankle angle occurred significantly later in BWD compared to DT

and FWD and later in DT compared to FWD. There was no main effect of freezing status and no interaction effect at the hip or knee. At the ankle, there was a significant effect of freezing status ($F(1,42)=4.3$, $p=.045$) such that minimum joint angles happened later in freezers. There was also a significant interaction at the ankle ($F(1.2,49.5)=6.4$, $p=.01$), indicating that minimum ankle angle during BWD in freezers happened later in the gait cycle compared to non-freezers (Table 3.2).

3.4.3 Decomposition Index

We conducted RM-ANOVAs on the decomposition indices for each joint pair. There was a significant main effect of condition for knee-ankle ($F(2,41)=7.4$, $p=.002$), hip-ankle ($F(1.7,70.9)=11.0$, $p<.001$), and hip-knee ($F(1.4, 59.7)=17.4$, $p<.001$), with BWD having higher decomposition compared to DT and FWD. Main effects of freezing status were present for hip-ankle ($F(1,42)=5.1$, $p=.03$) and hip-knee ($F(1,42)=5.3$, $p=.03$) indicating freezers had higher decomposition. All joint combinations showed a trend toward an interaction (knee-ankle: ($F(2, 41)=2.7$, $p=.08$); hip-ankle: ($F(1.7,70.9)=2.6$, $p=.09$); hip-knee: $F(1.4, 59.7)=4.0$, $p=.06$)), suggesting greater decomposition during BWD in freezers compared to non-freezers (Figure 3.2).

Table 3.2. Characterization of Gait

Range of Motion, degrees		**Hip***			**Knee***			**Ankle***		
	Condition	All	Freezers	Non-Freezers	All	Freezers	Non-Freezers	All	Freezers	Non-Freezers
	BWD	24.5 (5.9)	23.2 (6.8)	25.0 (5.5)	44.1 (9.7)	42.0 (9.6)	44.9 (9.7)	23.6 (5.0)	22.9 (5.7)	23.8 (4.7)
	FWD	39.0 (6.4)	37.2 (6.0)	39.7 (6.5)	63.9 (5.5)	60.9 (6.7)	65.1 (4.5)	29.4 (4.6)	28.1 (3.6)	29.9 (4.9)
	DT	36.2 (6.7)	34.4 (5.4)	37.0 (7.2)	61.5 (6.2)	59.4 (6.8)	62.4 (5.8)	28.3 (4.5)	27.8 (4.5)	28.6 (4.6)
Cycle Timing, % Gait Cycle		**Hip***			**Knee***			**Ankle**		
Max Timing	BWD	87.5 (5.3)	87.7 (6.2)	87.4 (5.0)	69.4 (4.2)	69.0 (3.7)	69.6 (4.5)	52.4 (6.1)	54.7 (8.4)	51.4 (4.6)
	FWD	89.4 (3.3)	90.1 (3.3)	89.1 (3.3)	74.2 (2.0)	75.2 (1.9)	73.9 (1.9)	53.5 (3.4)	54.3 (3.0)	53.1 (3.5)
	DT	89.8 (3.9)	88.9 (2.1)	90.2 (4.4)	75.3 (2.9)	75.1 (1.3)	75.4 (3.4)	55.0 (4.4)	54.9 (2.9)	55.0 (5.0)
		Hip*			**Knee***			**Ankle*ɣ+**		
Min Timing	BWD	53.3 (5.5)	52.8 (6.8)	53.5 (5.0)	47.8 (19.8)	39.7 (20.8)	51.1 (18.7)	90.3 (8.2)	95.2 (5.2)	88.3 (8.4)
	FWD	54.3 (3.2)	55.1 (2.1)	54.0 (3.5)	66.1 (26.7)	60.6 (27.5)	68.4 (26.5)	68.8 (2.9)	69.7 (2.5)	68.5 (3.0)
	DT	55.7 (4.2)	55.8 (2.0)	55.7 (4.8)	61.9 (27.4)	64.8 (28.6)	60.7 (27.3)	70.6 (4.4)	70.4 (3.0)	70.7 (4.9)
Decomposition Index		**Knee-Ankle***			**Hip-Ankle*ɣ**			**Hip-Knee*ɣ**		
	BWD	11.3 (6.8)	12.5 (4.8)	10.8 (7.5)	10.0 (5.8)	12.9 (8.2)	8.8 (4.1)	11.9 (7.5)	16.0 (8.3)	10.2 (6.5)
	FWD	7.1 (2.8)	7.8 (2.2)	6.8 (2.9)	7.0 (2.7)	7.5 (2.8)	6.8 (2.6)	6.7 (2.4)	7.2 (2.8)	6.4 (2.3)
	DT	7.9 (4.7)	6.1 (1.1)	8.6 (5.4)	6.9 (3.0)	7.1 (2.3)	6.8 (3.3)	8.3 (4.7)	9.1 (5.6)	8.0 (4.3)

Values represent mean (SD). Backward (BWD); Forward (FWD); Dual-task (DT).

*significant effect of condition, $p<.05$

ɣsignificant effect of freezing status, $p<.05$

+significant condition*freezing status effect, $p<.05$

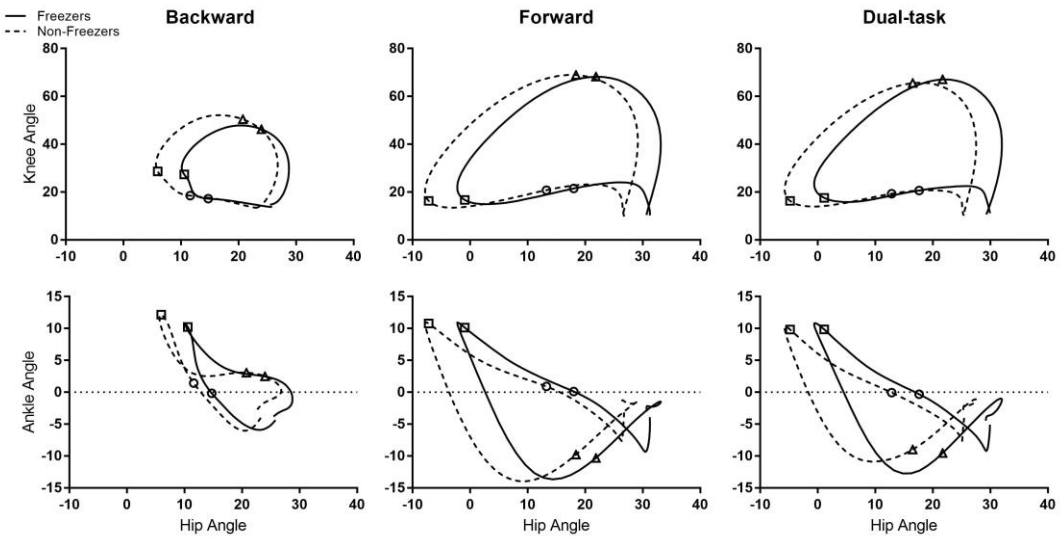

Figure 3.2. Angle-Angle Plots. These graphs depict how two angles are changing in relation to one another during the different gait conditions. The left column represents the backward gait condition; the middle column represents the forward gait condition; and the right column represents the dual-task gait condition. The top row represents the hip angle plotted against the knee angle. The bottom row represents the hip angle plotted against the ankle angle.
o indicates 25% of the gait cycle
□ indicates 50% of the gait cycle
Δ indicates 75% of the gait cycle

3.4.4 PCA

A set of nine PCAs were run to examine differences between freezers and non-freezers for each joint and condition separately (Table 3.3).

For the hip, each condition required the first two PCs to explain ≥90% (BWD: 95.6%; DT: 91.8%; FWD: 92.4%) of total variance. There were no significant differences in eigenfactors between groups for either PC. For the knee, BWD and DT required the first three PCs to explain ≥90% (BWD: 93.7%; DT: 90.1%) of total variance; FWD required the first four PCs (94.0%). There were no differences in eigenfactors for any PC between groups. For the ankle, four PCs were needed to explain ≥90% in BWD and DT (BWD: 95.2%; DT: 91.7%), and five PCs were

required to explain ≥90% variance threshold for FWD (FWD: 94.7%). None of the ankle PCs differentiated the two groups.

For all joints, the first PC primarily captured a magnitude feature (Figure 3.3 (hip); Figure 3.4 (knee); Figure 3.5 (ankle)). The second PC for FWD and DT captured a phase shift for all three joints. Range of motion for the two extreme waveforms were very similar; however, the minima and maxima were laterally shifted from one another. At the hip and knee, the second BWD PC showed a difference feature. The extreme waveforms were different in ROM magnitude, and maximum and minimum peaks in the loading vector align with maxima and minima in the mean waveforms. At the ankle, the second PC appeared to capture a difference feature and phase shift.

The knee and ankle required more PCs to explain ≥90% variance; eigenvectors and sources of variance becomes difficult to interpret after the first two PCs.

Table 3.3. Principal Component Eigenfactors

Joint	Principal Component	% Variance Explained	Freezers (mean (SD))	Non-Freezers (mean (SD))	Variance Type
Hip	BWD-PC1	84.3	23.4 (47.1)	-9.8 (82.3)	Magnitude Feature
	FWD-PC1	82.1	32.9 (53.2)	-13.8 (70.0)	Magnitude Feature
	DT-PC1	77.4	35.0 (54.6)	-14.7 (77.3)	Magnitude Feature
	BWD-PC2	11.3	0.40 (30.8)	-0.17 (26.3)	Difference Feature
	FWD-PC2	10.3	-6.9 (16.8)	2.9 (29.4)	Phase Shift
	DT-PC2	14.4	-2.4 (17.0)	1.0 (36.9)	Phase Shift
Knee	BWD-PC1	47.7	-15.2 (47.3)	6.4 (45.6)	Magnitude Feature
	FWD-PC1	49.2	-6.9 (29.5)	2.9 (53.7)	Magnitude Feature
	DT-PC1	57.7	4.8 (26.5)	-2.0 (64.6)	Magnitude Feature
	BWD-PC2	26.0	-4.6 (33.6)	1.9 (35.1)	Difference Feature
	FWD-PC2	30.8	8.8 (42.7)	-3.7 (35.6)	Phase Shift
	DT-PC2	24.1	5.7 (41.9)	-2.4 (33.8)	Phase Shift
Ankle	BWD-PC1	55.4	-4.6 (41.1)	1.9 (32.6)	Magnitude Feature
	FWD-PC1	39.1	2.5 (25.4)	-1.0 (28.6)	Magnitude Feature
	DT-PC1	40.4	2.3 (22.6)	-0.95 (33.9)	Magnitude Feature
	BWD-PC2	19.9	9.2 (21.4)	-3.9 (19.8)	Difference Feature
	FWD-PC2	31.6	8.9 (25.0)	-3.7 (24.0)	Phase Shift
	DT-PC2	29.1	-2.2 (28.3)	0.93 (25.6)	Phase Shift

Mean and SD of eigenfactors are for the first two principal components for each joint and each condition. Backward (BWD); Forward (FWD); Dual-task (DT); First principal component (PC1); Second principal component (PC2).

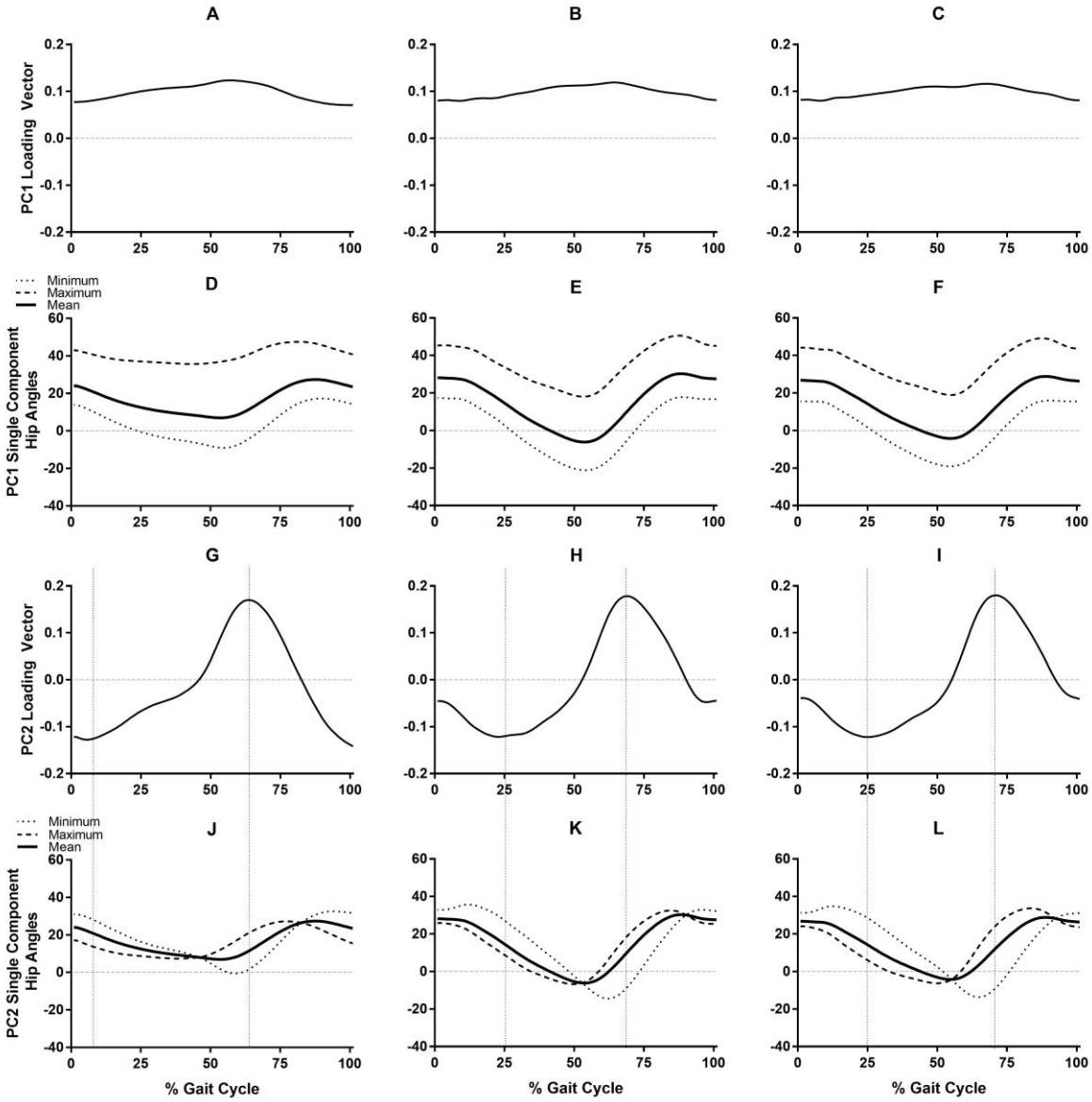

Figure 3.3. Hip Principal Components. Loading vectors for the first two principal components for the hip are shown, as are single component reconstructions for each PC. The left column (A, D, G, J) represents the backward gait condition; the middle column (B, E, H, K) represents the forward gait condition; and the right column (C, F, I, L) represents the dual-task condition. A-C represents the loading vector for the first principal component for each gait condition. D-F show the single component reconstructions based on maximum and minimum PC1 eigenfactors, as well as the sample mean. G-I depict the loading vector for the second principal component for each gait condition. J-L show the single component reconstructions for maximum and minimum PC2 eigenfactors, as well as the sample mean.

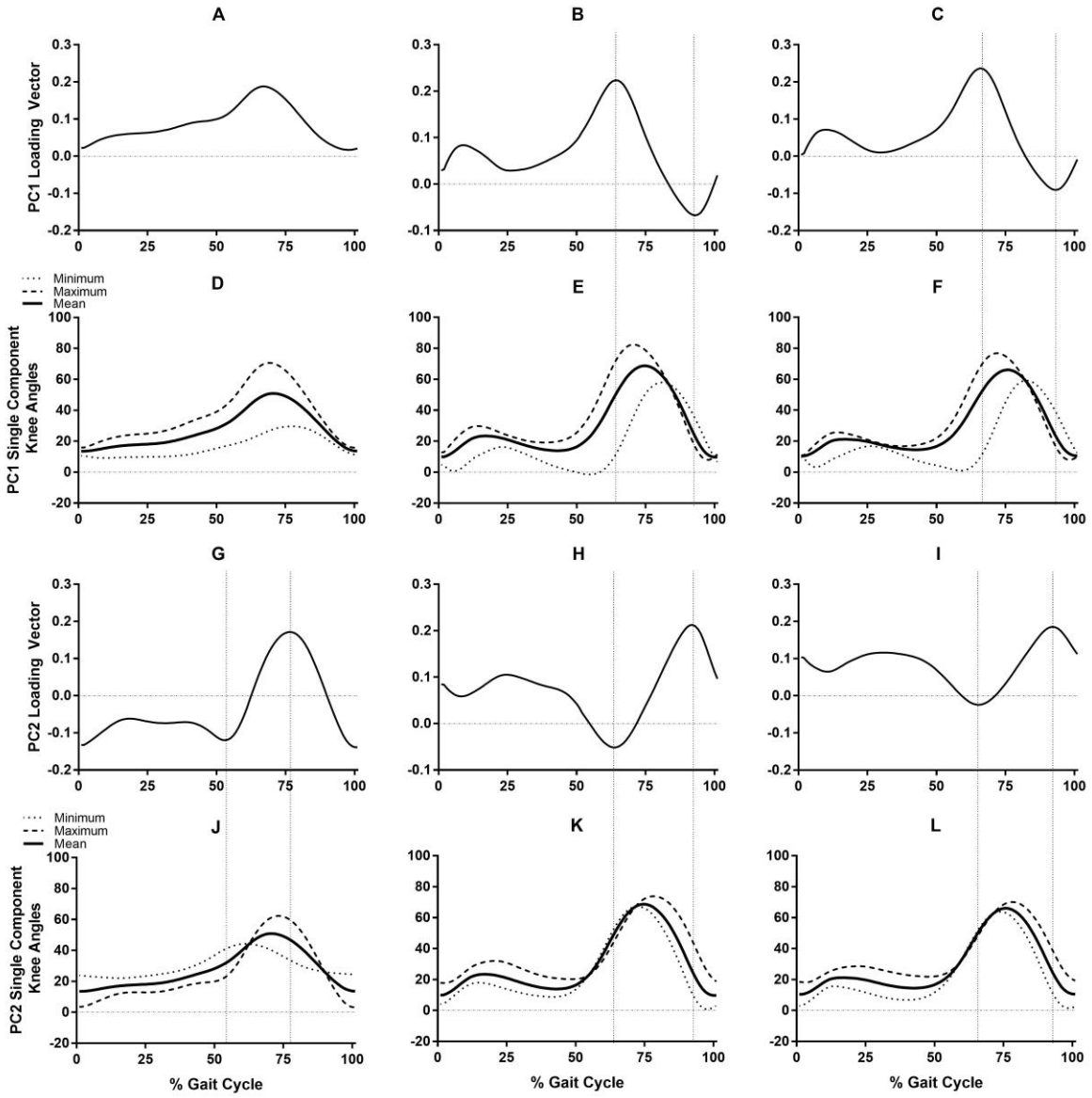

Figure 3.4. Knee Principal Components. Loading vectors for the first two principal components for the knee are shown, as are single component reconstructions for each PC. The left column (A, D, G, J) represents the backward gait condition; the middle column (B, E, H, K) represents the forward gait condition; and the right column (C, F, I, L) represents the dual-task condition. A-C represents the loading vector for the first principal component for each gait condition. D-F show the single component reconstructions based on maximum and minimum PC1 eigenfactors, as well as the sample mean. G-I depict the loading vector for the second principal component for each gait condition. J-L show the single component reconstructions for maximum and minimum PC2 eigenfactors, as well as the sample mean.

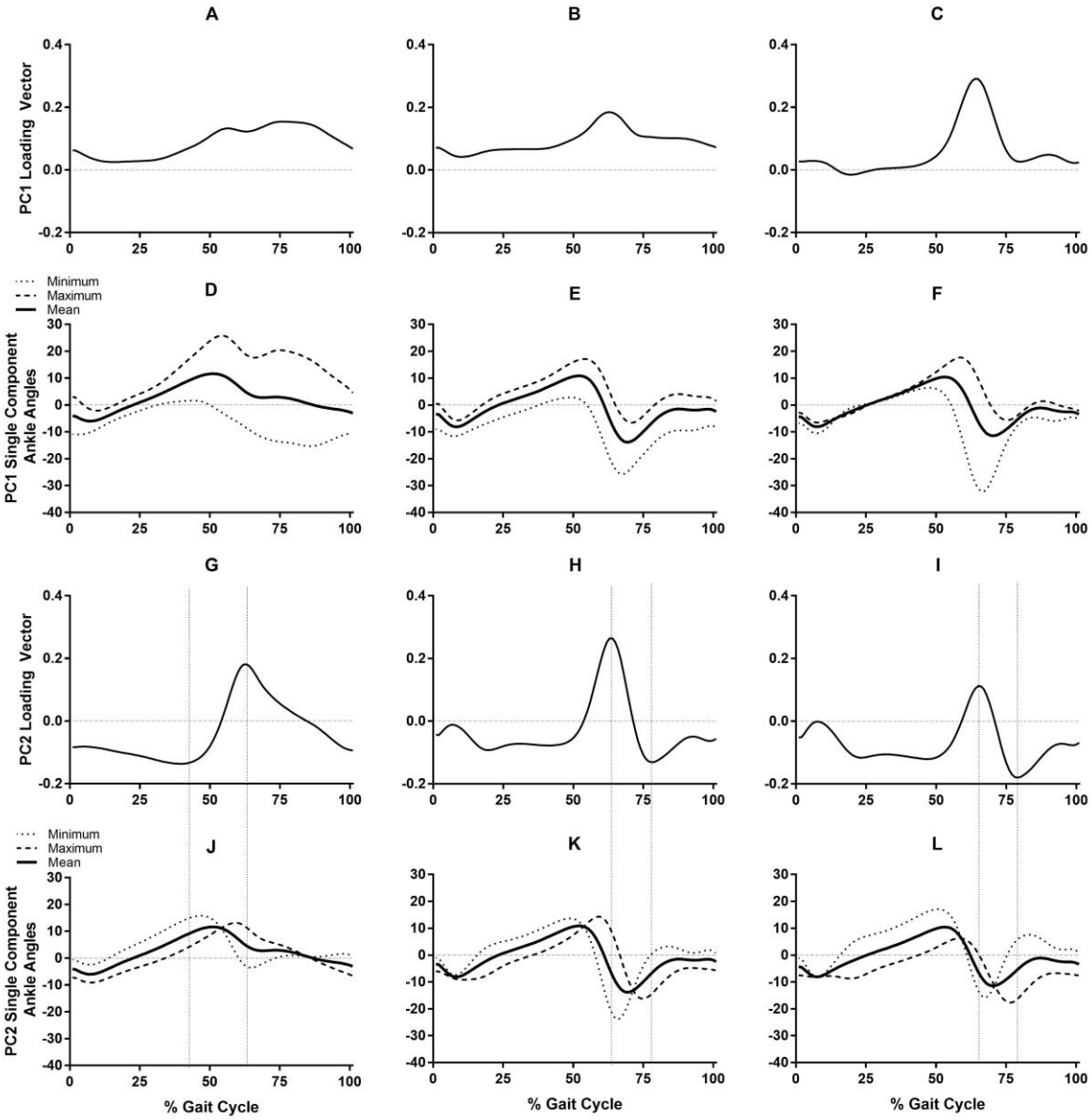

Figure 3.5. Ankle Principal Components. Loading vectors for the first two principal components for the ankle are shown, as are single component reconstructions for each PC. The left column (A, D, G, J) represents the backward gait condition; the middle column (B, E, H, K) represents the forward gait condition; and the right column (C, F, I, L) represents the dual-task condition. A-C represents the loading vector for the first principal component for each gait condition. D-F show the single component reconstructions based on maximum and minimum PC1 eigenfactors, as well as the sample mean. G-I depict the loading vector for the second principal component for each gait condition. J-L show the single component reconstructions for maximum and minimum PC2 eigenfactors, as well as the sample mean.
The dual-task PC2 was inverted for clarity.

3.5 Discussion

In this study, we examined differences in gait kinematics between freezers and non-freezers during forward, backward, and dual-task walking. Freezers had significantly greater decomposition indices for the hip-knee and hip-ankle compared to non-freezers. PCA showed that absolute magnitude of joint angles, but not overall joint ROM throughout the gait cycle, was the primary source of gait variance at all joints. The second largest source of variance differentiated the gait conditions. FWD and DT both showed distinct phase shifts for PC2. BWD was characterized as primarily having a difference feature at each joint rather than a phase shift. These results advance our understanding of gait mechanics and could provide an avenue to develop more targeted interventions to reduce gait variability and fall risk in PD.

The difference in the decomposition indices between freezers and non-freezers for the hip-knee and hip-ankle is particularly interesting as it relates to cerebellar involvement in FOG [8–10,22,23]. Freezers exhibit similar cognitive [24–26] and motor deficits [27,28] as cerebellar patients, and our results show that freezers also decompose walking movement more than non-freezers, similar to gait in people with cerebellar disease [11]. In patients with cerebellar dysfunction, decomposing multi-joint movement is a strategy to reduce movement variability [16]. Freezers may contend with increased gait variability related to PD as well as that associated with cerebellar dysfunction, resulting in increased overall variability and providing an impetus to decompose movement patterns to improve stability.

While PCA did not differentiate freezers and non-freezers, it highlighted differences in sources of variance between gait conditions. Our results suggest that BWD does not utilize the time-reversed FWD motor program as has been suggested previously [19]. Rather, BWD uses a

distinct motor program from FWD and DT [29,30]. The difference features seen in PC2 scores during BWD gait illustrate two distinct gait strategies. The BWD waveforms for individuals with the lowest PC2 scores resemble the FWD and DT waveforms. Individuals with higher PC2 scores had different joint mechanics. Specifically, higher PC2 scores at the hip were associated with less hip flexion at heel strike and little to no hip extension throughout the gait cycle. At the knee, higher PC2 scores meant full knee extension at heel strike and large knee flexion during 55-75% of the gait cycle. Finally, higher PC2 scores at the ankle were associated with more dorsiflexion at heel strike and nearly no dorsiflexion during 50-75% of the gait cycle. These results indicate that some individuals adopted a more forward flexed hip posture, presumably to stabilize during the backward movement. Others are able to maintain a more upright posture, allowing BWD to resemble FWD joint mechanics.

Our results are limited by a relatively small sample size, particularly for the freezer group; however, our joint angles are similar to previous studies [5] indicating our sample had representative spatiotemporal gait characteristics for PD. While velocity was not held constant across gait conditions, joint angles were normalized to percent gait cycle to reduce the influence of velocity. Our sample also had mild-moderate disease severity. Our results may not extend to more advanced PD.

Gait variability affects people with PD, particularly freezers, putting them at increased risk for falls. Many interventions target improving spatiotemporal gait characteristics [12]; however, the effects of interventions on variability are poorly understood. Here we showed that different gait conditions have different, independent sources of variability, so a given intervention may affect one gait condition differently than another. We also showed that freezers decompose gait more

than non-freezers, which may relate to growing evidence for cerebellar involvement in FOG; however, the mechanisms behind joint decomposition in freezers needs further study. A better understanding of freezing mechanisms and kinematic variability could lead to development of more effective interventions that address specific sources of gait variability, ultimately reducing risk of falls and improving quality of life.

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Chapter 4:
Effects of Exercise on Gait and Motor Imagery in People with Parkinson Disease and Freezing of Gait

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4.1 Abstract

Introduction: Exercise improves gait in Parkinson disease (PD), but whether exercise differentially affects people with PD with (freezers) and without freezing of gait (non-freezers) remains unclear. This study examines exercise's effects on gait performance, neural correlates related to these effects, and potential neural activation differences between freezers and non-freezers during motor imagery (MI) of gait.

Methods: Thirty-seven participants from a larger exercise intervention completed behavioral assessments and functional magnetic resonance imaging (fMRI) scans before and after a 12-week exercise intervention. Gait performance was characterized using gait velocity and stride length, and a region of interest (ROI) fMRI analysis examined task-based blood oxygen-level dependent (BOLD) signal changes of the somatomotor network (SMN) during MI of forward (IMG-FWD) and backward (IMG-BWD) gait.

Results: Velocity ($F(1,34)=55.04$, $p<0.001$) and stride length ($F(1,34)=77.58$, $p<0.001$) were significantly lower for backward versus forward walking in all participants. The ROI analysis showed freezers had lower BOLD signal compared to non-freezers in the cerebellum ($F(1,32)=7.01$, $p=0.01$), primary motor (left: $F(1,32)=7.09$, $p=0.01$; right: $F(1,32)=7.45$, $p=0.01$), and primary sensory (left: $F(1,32)=9.59$, $p=0.004$; right: $F(1,32)=8.18$, $p=0.007$) cortices during IMG-BWD only. The evidence suggests the exercise intervention did not affect gait or BOLD signal during MI.

Conclusion: While all participants had significantly slower and shorter backward velocity and stride length, respectively, the exercise intervention had no effect. Similarly, BOLD signal during MI did not change with exercise; however, freezers had significantly lower BOLD signal

during IMG-BWD compared to non-freezers. This suggests potential decreased recruitment of the SMN during MI of gait in freezers.

4.2 Introduction

Gait impairment is a common feature of Parkinson disease (PD) and is characterized by short, asymmetric steps and slow velocity. Gait decrements are evident in both forward and backward walking and are associated with an increase in debilitating falls [1]. In addition to the aforementioned gait impairments, approximately 50% of individuals with PD experience freezing of gait (FOG) at some point during the disease, with prevalence increasing with increased disease severity [2,3]. Individuals with PD and FOG (freezers) describe freezing episodes as feeling like their feet are stuck to the floor or as an inability to take another step forward [4]. Freezers have an even greater risk of falls and further gait decrements compared to people with PD without FOG (non-freezers) [1]. By addressing gait impairment in people with PD, we may be able to reduce fall risk and improve quality of life.

One approach to improving gait in PD is exercise. Many forms of exercise are associated with gait improvements in PD [5]; however, few studies have separated freezers and non-freezers to determine if exercise differentially affects gait performance in these populations. Further, we understand very little about how changes in gait relate to underlying brain activity and changes therein. To address these gaps, this study investigated how exercise affects gait, the neural correlates related to these effects, and potential differences in blood oxygen-level dependent (BOLD) signal changes between freezers and non-freezers.

We used a motor imagery (MI) paradigm during functional magnetic resonance imaging (fMRI) to investigate changes in brain activation after 12 weeks of exercise in people with PD, both freezers and non-freezers. Because multiple brain regions overlap between MI and motor execution [6], MI is a useful proxy to investigate how gait-related brain activity changes with

exercise. Previous work from our lab noted differences in cerebellar activity [7] but similar cerebellar volumes when comparing freezers and non-freezers [8]. In this paper, we further our examination of the role of the cerebellum in FOG and focus our analyses on the somatomotor network (SMN) [9,10]. The cerebellar component of the SMN is of particular interest because it includes areas known to be active during gait MI [6]. Further, these cerebellar regions are functionally related to primary motor (M1) and primary sensory (S1) cortices [11]. Prior research shows consistent involvement of S1 during MI, but debate over M1 involvement continues [6]. M1 is, however, part of the SMN [9]. While changes in gait are likely reflected in changes in M1 output during walking, whether similar changes occur during MI remains controversial. Therefore, we opted to explore regions of the SMN with known involvement in MI and functional connection to M1, while also examining M1 directly. We conducted a region of interest (ROI) analysis on cerebellar SMN areas, as well as S1 and M1 cortical regions. We hypothesized that, 1) the 12-week exercise intervention would improve gait performance in freezers more than non-freezers, 2) any improvement in gait performance would correspond with an increase in cerebellar BOLD signal, and 3) freezers would have significantly lower BOLD signal in cerebellar ROIs during MI, regardless of exercise.

4.3 Methods

4.3.3 Participants

All participants were part of a larger prospective, controlled exercise intervention study (ClinicalTrials.gov Identifier: NCT01768832) [12] where participants were recruited and assigned to the exercise intervention currently enrolling. Participants met the following inclusion criteria: 1) clinical diagnosis of idiopathic PD, 2) clear benefit from levodopa, 3) Hoehn & Yahr

stage I-IV, 4) ability to walk independently for at least three meters, and 5) score of ≥24 on the Mini Mental Status Exam (MMSE). Further, the present analyses required participants to have completed baseline and post-test behavioral assessments and MRI scans, and the MRI data needed to be of sufficient quality for successful cortical and cerebellar segmentation with FreeSurfer software (v5.3.0, http://surfer.nmr.mgh.harvard.edu/) and the Spatially Unbiased Infratentorial (SUIT) toolbox [13]. Of the 98 participants who completed the study, 37 participants met all inclusion criteria (Fig. 1).

Participants completed behavioral assessments and MRI scans while OFF medications, defined as being ≥12 hours since their last dose of anti-Parkinson medication. Freezers (n=13) and non-freezers (n=24) were differentiated using question one of the New Freezing of Gait Questionnaire (NFOG-Q), which asks whether an individual has experienced a freezing episode within the past month [14]. The Human Research Protection Office of Washington University in St Louis approved this study, and all participants provided written informed consent.

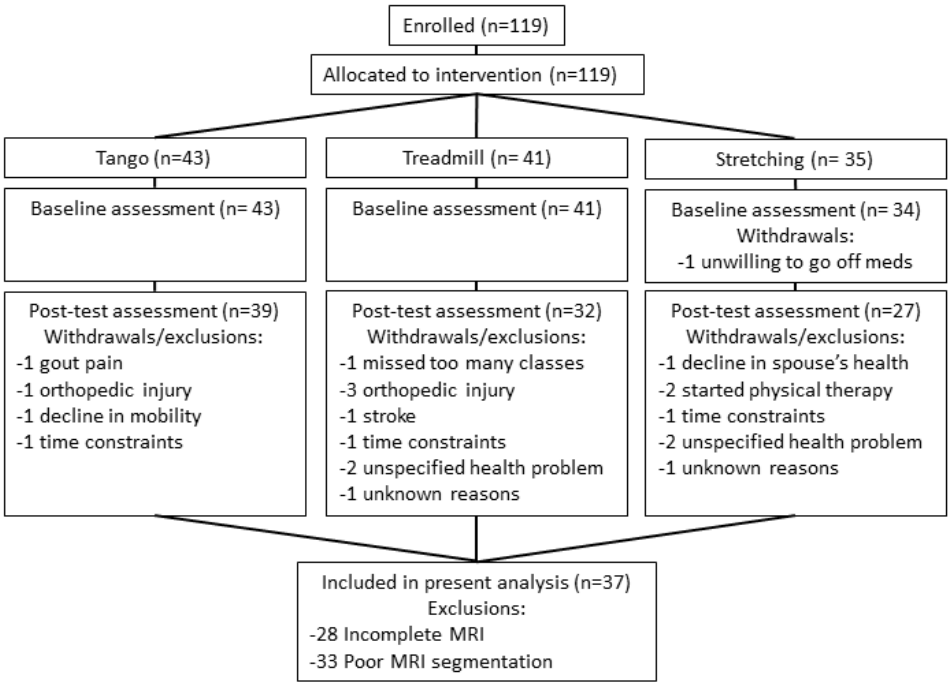

Figure 4.1. Consort Diagram.

4.3.2 Procedures

All participants completed a baseline behavioral assessment and MRI scan; participated in 12 weeks of treadmill walking (n=11), tango dance (n=13), or guided stretching (n=13); and completed a post-test evaluation comprised of the same behavioral assessment and MRI scan as at baseline. All assessments were performed within 5 weeks prior to starting and following completion of the exercise intervention (mean(SD): baseline:16.2(9.3) days; post-test:14.8(8.0) days). Participants were told to not change their regular exercise routine during the time between baseline evaluation and post-test evaluation, except for adding the exercise intervention provided as part of the study.

Behavioral assessments included gait analysis with an instrumented GAITRite walkway (CIR Systems, Franklin, NJ). Participants walked forward and backward across the GAITRite at a comfortable pace. Three trials of each gait direction were combined to calculate average forward and backward velocities and stride lengths. Participants were also assessed with the Movement Disorder Society Unified Parkinson's Disease Rating Scale Section III (MDS-UPDRS-III) [15]. The MDS-UPDRS-III was video recorded and scored by a rater blinded to treatment group and time point. Importantly, the un-blinded rater's score was used for the rigidity item (question 3.4) which could not be determined from the video.

Before the fMRI scan, participants practiced walking 15 and 30-foot long paths both forward and backward on level ground outside the scanner. Walking conditions were performed twice (8 total attempts). After two trials of a condition, participants sat in a chair with eyes closed and imagined performing the walking task just completed. Imagined tasks were performed twice and provided practice for the fMRI task. Additionally, prior to the MRI scan session, at baseline only, participants completed the full version of the Kinesthetic and Visual Imagery Questionnaire (KVIQ-20) [16], which is a validated measure of how well an individual is able to imagine performing movements with their body. This measure was only administered at baseline assessment as motor imagery training was not part of the interventions and was therefore expected to remain constant over the course of the study.

All fMRI scans were performed on a Siemens TRIO 3T scanner at Washington University in St. Louis School of Medicine. Participants completed T1-weighted (T1-W) structural scans (TR=2400ms, TI=1000ms, TE=3.16ms, FA=8°, 0.9mm^3 voxels, 8:09min), T2-weighted (T2-W)

structural scans (TR=3200ms, TE=455ms, 1.0mm^3 voxels, 4:43min), and BOLD sensitized eco-planar MRI scans (TR=2200ms, TE=27ms, 4mm voxels, FA=90°, 7:20min).

For the baseline and post-test MRI sessions, participants completed one T1-W, one T2-W, and two fMRI scans. During the fMRI scans, participants viewed task instructions from a screen projected onto a head coil-mounted mirror. Task instructions were presented using E-Prime (V2.0, Psychology Software Tools, Inc, Sharpsburg, PA), and an MRI-compatible eye tracker showed when eyes were open or closed. Trial direction (FWD or BWD) and length (15 or 30 feet) was displayed before each trial. Participants were told to close their eyes and imagine performing the instructed walking task, as they had previously outside the scanner. Participants indicated the start and end of task performance by pressing a button on an MRI compatible button box (Mag Design and Engineering, Redwood City, CA, USA). Rest periods lasted 15.4 seconds with eyes open, fixated on a crosshairs on the screen. Rests alternated with imagined walking trials of variable lengths dependent upon the participant's response. For the two fMRI scans, imagined forward (IMG-FWD) and imagined backward (IMG-BWD) walking conditions were intermixed, and each condition was presented 6 times (3 times per scan).

4.3.3 MRI Pre-processing

BrainVoyager QX (v2.8.2.2523**,** Brain Innovation, Maastricht, The Netherlands) was used to process fMRI data. For all imagine scans, the first two volumes were discarded. Sinc interpolation was used to correct for 3D head movement and slice-time correction. Scans with more than 2 degrees or 2 mm of movement were removed from further analyses. Temporal high-pass filtering was also used to account for signal drift. T1-W scans were transformed into Talaraich space [17], and all functional scans (baseline and post-test) were co-registered to the

participant-specific baseline T1-W scan. All tasks were modeled using an event-related design and the canonical hemodynamic response function.

Instructions in E-Prime were spaced at specific time intervals, but the length of each imagined walking trial was dictated by the time a participant took to imagine the instructed task (i.e. time between button presses). E-Prime allowed 19.8 seconds for any imagined walking trial; however, some participants' eyes remained closed for longer than the allotted time. In these instances, the imagined trial was included in analyses, but any subsequent tasks for which the instructions were missed due to the closed eyes were excluded from analyses. After removing the first two volumes from each scan, up to the next seven volumes of imagined task were included. This prevented inclusion of volumes with signal attenuation. As in previous research, trials of the same direction (forward, backward) but different distances (15ft, 30ft) were combined into IMG-FWD or IMG-BWD [7]. In order to have sufficient data for inclusion in this study, of the possible 12, 12, and 26 IMG-FWD, IMG-BWD, and Rest, respectively, participants needed at least half of each trial type to be included.

4.3.4 Region of Interest Analysis

We conducted an ROI analysis with a-priori defined regions for the SMN [9]. We focused on cerebellar regions associated with the SMN, as well as M1 and S1 cortical regions (Fig. 2) [10]. Baseline structural scans were automatically segmented using FreeSurfer and the SUIT toolbox as previously described [8]. Each participant's baseline scan was segmented with the SUIT toolbox using Buckner's 17 networks [10]. Only cerebellar regions associated with networks 3 and 4 were analyzed. The cerebellar ROI associated with network 3 corresponds to the dorsal, cortical SMN, and the cerebellar ROI associated with network 4 corresponds to the ventral,

cortical SMN. A custom MATLAB (R2016a, The MathWorks Inc., Natick, Massachusetts, USA) program converted the ROI coordinates from participant space to Talaraich space, using the Talaraich transform matrix generated by BrainVoyager.

Cortical regions were analyzed unilaterally (right-M1, left-M1, right-S1, left-S1) while cerebellar regions were not separated into left and right hemispheres. All cortical ROIs were traced by hand onto each participant's baseline T1-W scan. M1 consisted of the pre-central gyrus, extending from its most superior portion to the lateral sulcus [18,19]. Similarly, S1 consisted of the post-central gyrus, extending from the most superior portion of the gyrus to the lateral sulcus [18,19]. Both regions were traced bilaterally by individuals blinded to the demographics of the participants.

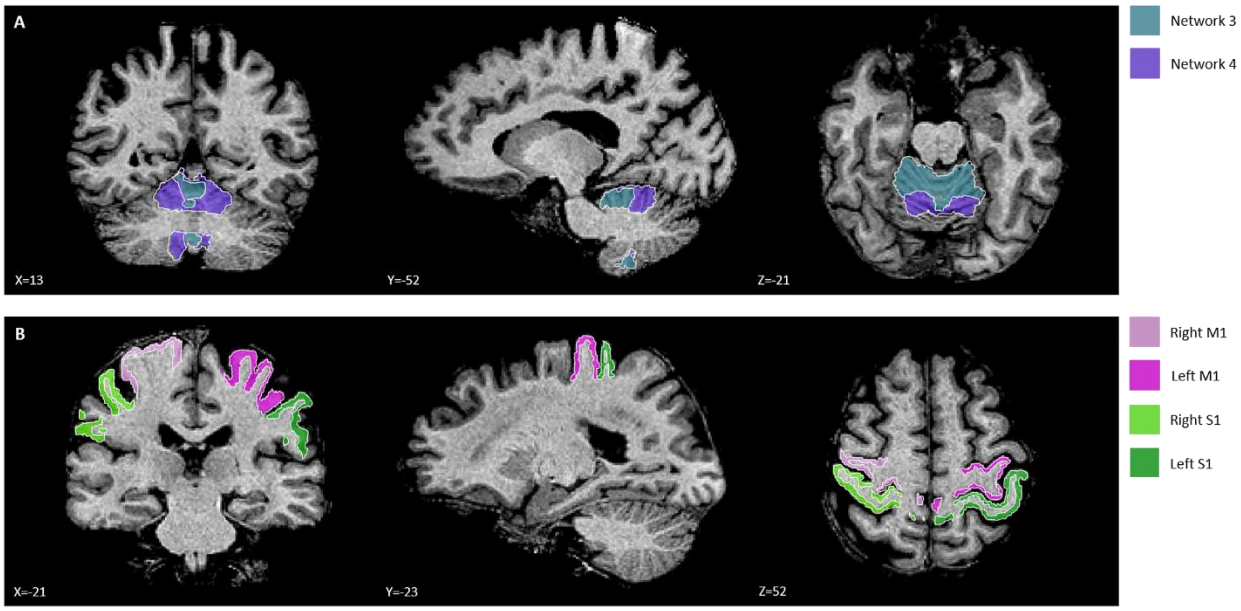

Figure 4.2. Regions of Interest. (a) Network 3 and network 4 in the cerebellum and (b) M1 and S1 in the cortex.

4.3.5 Statistics

Using BrainVoyager, average beta-weights per participant were extracted from each ROI for rest, IMG-FWD, and IMG-BWD. Baseline and post-test scan sessions were extracted separately. IMG-FWD and IMG-BWD beta-weights were normalized to rest by subtracting the average rest beta-weight from the respective scan session for each individual. Normalizing allowed for analysis of the change in beta-weight from rest associated with the imagery task. Specifically, a negative normalized beta-weight suggests a decrease in activity during the imagery task compared to rest, where as a positive beta-weight would indicate an increase in activity compared to rest. Repeated measures analyses of covariance (RM-ANCOVA) were conducted with within-subjects factors of time (baseline, post-test) and condition (forward, backward) and between-subjects factor of freezing status (freezer, non-freezer). Exercise group was used as a covariate to control for potential effects of the different exercise interventions. Residuals for gait characteristics and beta-weights were graphed with boxplots. Individuals with residuals ≥3 interquartile ranges away from the end of a box were investigated as potential outliers. Gait characteristics and beta-weights were analyzed separately. All statistics were performed using IBM-SPSS statistics (version 24, IBM Analytics, Armonk, New York, USA). Cortical and cerebellar analyses were treated as separate analyses. We used Bonferroni correction for multiple comparisons. Accordingly, for the cortical analyses we set significance at $\alpha \leq 0.01$, and for the gait characteristics and cerebellar analyses, we set significance at $\alpha \leq 0.02$.

4.4 Results

Freezers and non-freezers were matched well at baseline (Table 4.1). The two groups significantly differed on the NFOG-Q score as expected since non-freezers by definition score a 0 and freezers score ≥1. Freezers and non-freezers were similar in baseline LEDD, and there

were no differences in change in LEDD between freezers and non-freezers from baseline to post-test (t=0.10, p=.92).

Table 4.1 Baseline Demographics

Demographics	Freezers (n=13)	Non-Freezers (n=24)	p-value
Age, mean (SD)	65.13 (10.44)	65.81 (8.03)	0.83
Sex, % female	23	46	0.17
MDS-UPDRSIII$^{\surd}$, median (range)	36 (17-52)	34 (7-43)	0.4
MMSE$^{\surd}$, median (range)	29 (25-30)	29 (27-30)	0.52
Duration of diagnosis, mean (SD)	6.1 (5.0)	4.3 (4.3)	0.25
N-FOGQ, median (range)	10 (3-20)	0 (0)	<0.001 *
MRI Head Motion$^{\Omega}$, mean (SD)	1.05 (0.27)	1.08 (0.39)	0.82
Baseline LEDD$^{\surd\ddot{Y}}$, median (range)	600 (0, 1600)	600 (0, 2000)	0.62
KVIQ Visual, mean (SD)	34.8 (9.0)	38.1 (8.0)	0.27
KVIQ Kinesthetic, mean (SD)	34.8 (9.0)	38.1 (8.0)	0.27

*significant difference between freezers and non-freezers

$^{\Omega}$maximum head translation (X-, Y-, Z-plane) in mm or rotation (X-, Y-, Z-axis) in degrees

$^{\surd}$Mann-Whitney U test for non-parametric data

$^{\ddot{Y}}$LEDD measured in mg

We ran separate RM-ANCOVAs for velocity and stride length. For velocity, there was a main effect of condition ($F(1, 34)=55.04$, $p<0.001$) indicating that all participants had slower backward gait velocities compared to forward gait (Table 4.2). For stride length, there was a main effect of condition ($F(1, 34)=77.58$, $p<0.001$), indicating that both freezers and non-freezers took shorter steps during backward gait (Table 4.2). There was no significant effect of time, indicating that exercise did not significantly improve gait in either freezers or non-freezers. There were no extreme outliers.

Table 4.2 Gait Characteristics.

Gait Characteristic	Condition	Baseline		Post-test	
		Non-Freezer	Freezer	Non-Freezer	Freezer
Velocity (m/s)†	Forward	1.17 (0.18)	1.05 (0.19)	1.19 (0.19)	1.10 (0.16)
	Backward	0.70 (0.19)	0.63 (0.21)	0.80 (0.33)	0.75 (0.20)
Stride Length (m)†	Forward	1.30 (0.19)	1.20 (0.20)	1.33 (0.20)	1.23 (0.20)
	Backward	0.78 (0.19)	0.68 (0.24)	0.86 (0.26)	0.79 (0.23)

All values represent mean (SD) without removing outliers.

†significant condition effect, $p<0.001$

All participants had at least 13 usable Rest trials (range:13-26), 6 usable IMG-FWD trials (range: 8-12), and 6 usable IMG-BWD trials (range: 6-12) from the baseline and post-test MRI scans. Separate RM-ANCOVAs were run for network 3 and 4 cerebellar regions, and M1 and S1 (bilaterally). The RM-ANCOVA for network 3 showed a significant condition*freezing status interaction ($F(1,34)=5.60$, $p=0.02$), such that freezers had lower beta-weights during IMG-BWD compared to non-freezers. There were no significant effects for network 4. For M1 and S1, we noted a significant condition*freezing status interaction for left S1 only ($F(1,34)=8.90$, $p=0.005$), suggesting that freezers had significantly lower beta-weights during IMG-BWD compared to non-freezers. All other cortical ROIs showed trends towards significant condition*freezing status interactions (left M1: $F(1,34)=6.29$, $p=0.02$; right M1: $F(1,34)=5.56$, $p=0.02$; right S1: $F(1,34)=6.57$, $p=0.02$). No significant effect of time was seen for any ROI.

After removing two participants, one freezer and one non-freezer, as potential outliers, we repeated the ROI analyses. Both participants were outliers for ≥2 ROIs. Removing outliers did not affect the cerebellar ROI results (network 3: condition*freezing status- $F(1,32)=7.01$, $p=0.01$; network 4: no significant results); but the cortical ROI results were affected, such that all four ROIs had a significant condition*freezing status interaction (left M1: $F(1,32)=7.09$, $p=0.01$; right

M1: $F(1,32)=7.45$, $p=0.01$; left S1: $F(1,32)=9.59$, $p=0.004$; right S1: $F(1,32)=8.18$, $p=0.007$), again suggesting that freezers compared to non-freezers had lower beta-weights during IMG-BWD (Fig. 3).

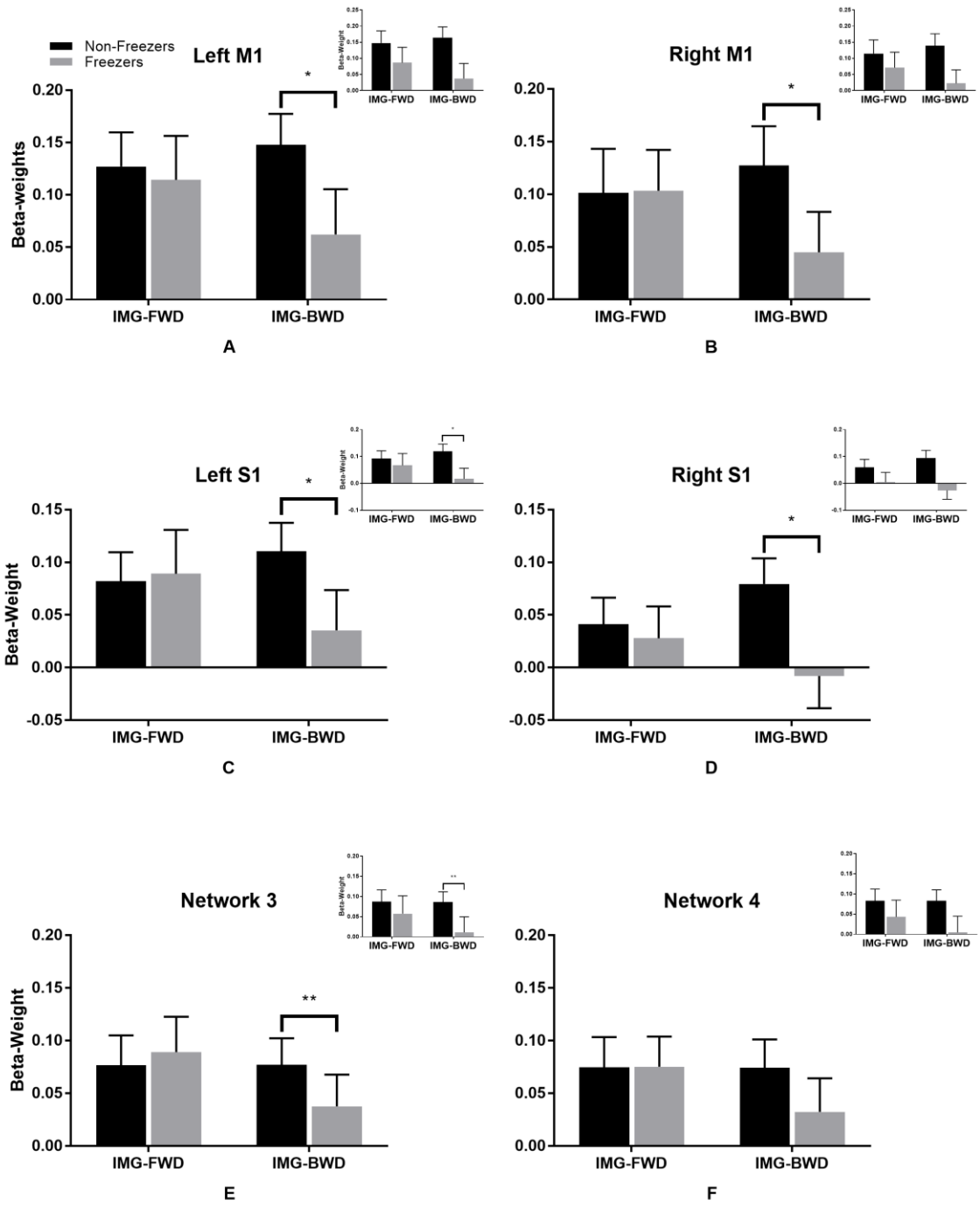

Figure 4.3. Beta-weights. Bars represent mean beta-weight for IMG-FWD and IMG-BWD, normalized to rest and collapsed across time for non-freezers and freezers, with two outliers removed. Error bars represent standard error of the mean. Plots represent results after removing one freezer and one non-freezers as potential outliers for a) left M1, b) right M1, c) left S1, d) right S1, e) network 3, and f) network 4. All insets show results with all participants included.
*p<0.012
**p<0.025

4.5 Discussion

This study examined differences in exercise response between freezers and non-freezers, both in BOLD signal and motor performance. Our data show condition*freezing status interactions across all cortical ROIs and cerebellar network 3 regions, as well as significant differences in forward and backward gait.

In line with our hypotheses, freezers compared to non-freezers showed lower beta-weights during IMG-BWD in all SMN ROIs except network 4. Our findings corroborate known sensorimotor processing deficits in freezers [20] that may be due to altered functional connectivity in cerebellar [21] and sensorimotor networks [22]. Surprisingly only IMG-BWD, not IMG-FWD, showed lower cerebellar BOLD signal in freezers. However, we believe our results may indicate the beginning of neural network changes specific to freezers because these differences were only apparent for the more difficult of the two walking tasks. Freezers with a longer duration of PD diagnosis (12.3 years) than our sample had significantly lower cerebellar activation during MI of all gait types [23]. The lower beta-weights during IMG-BWD in freezers suggests that there may be a progression of cerebellar activity reduction starting with more complicated gait tasks. In addition, cognitive deficits may impair freezers' ability to imagine walking backward. Though participants practiced the task outside the scanner, backward walking is challenging due to visuospatial constraints and lack of daily practice. Freezers' spatial processing deficits may compound the task's difficulty, forcing them to rely on other networks to perform the task. As PD progresses, freezers may use the cerebellum less as MI becomes progressively more challenging. In line with this idea, our results for M1 and S1 were similar to those for the cerebellum. Similar reductions in M1 activity for all imagined gait types [23] and

decreased interhemispheric connectivity of S1 in freezers [24] have been previously reported. The progressive reduction in cerebellar activity may reflect changes to the SMN as a whole.

We hypothesized there would be a time effect for both the ROI and gait performance analyses because research indicates that regular exercise affects resting-state networks [25]. Conversely, there were no significant changes in either gait performance or beta-weights. However, while not statistically significant, all participants improved backward gait velocity and stride length after exercise. On average, backward gait velocity increased by 0.11m/s, and stride length increased by 0.09m, regardless of freezing status. This corroborates findings on exercise benefits in people with PD [26] and suggests that these benefits occur regardless of freezing status. We note that forward gait did not show similar trends, likely because our participants had little room for improvement. Average forward gait velocity for healthy older adults falls between 0.9m/s and 1.2m/s [27-29], and our freezers and non-freezers were at 1.06m/s and 1.18m/s, respectively.

We chose to examine the SMN for neural correlates related to exercise-induced gait changes because the SMN likely contributes to motor output. Unfortunately, the trends of improvement during backward gait did not correspond with trends towards changes in beta-weights. This underscores the possibility of progressive decreased use of the SMN during MI for freezers as well as previous research showing exercise-induced gait changes correlating with changes in non-motor networks [25,30]. One possibility is that regular exercise improves movement self-confidence [31], allowing for decreased inhibition that results in performance improvements. Indeed, studies in older adults with mild cognitive impairment suggest that the fronto-executive network, known for involvement in learning and action-outcome associations, may be most

affected by exercise [25]. Exercise may weaken cognitive associations between backward walking and injury, allowing individuals to move with less fear and more confidence.

Our study is not without limitations. Our sample size is a potential limiting factor; however, our effects remain after Bonferroni correction for multiple comparisons. We also note that our sample was mild to moderate in disease severity, so the results of this study may not generalize to individuals with more severe PD. This was a necessary inclusion criterion as study assessments were performed OFF medications, and participants needed to fully participate in the exercise program. However, we propose that our results may represent early stages of neural network changes in freezers. Finally, we acknowledge that 12 weeks is a short amount of time for an exercise intervention and may not be long enough to induce measurable changes in gait or in the SMN.

Nevertheless, our results further understanding of freezing of gait in Parkinson disease. We provide evidence that may suggest possible progressive reduction in activity of regions associated with the SMN in freezers. Additionally, we note that changes in motor symptoms may not be directly related to changes in the somatomotor network. This highlights the fact that PD is not just a movement disorder. Rather, it affects multiple neural networks such that changes in one aspect of the disease may be related to a change in another disease aspect. Current treatment options for PD focus on mitigating symptoms; however, a more holistic approach could have greater effects on patient outcomes. Future research should focus on longitudinal analyses of Buckner's 17 networks in both freezers and non-freezers, over the span of years, to better characterize network changes associated with disease progression. This could help with early detection of potential freezers and help further understanding of how different aspects of the

disease are related to one another, providing a framework for development of more holistic treatment.

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Chapter 5:
Conclusion

5.1 Summary of Findings

Our knowledge and understanding of Parkinson disease (PD) remains limited, but research has come a long way since Dr. James Parkinson's original work, and the field continually moves forward. The research presented here focused on freezing of gait with the goal of examining the symptom and its effects from multiple angles. This allowed for investigation of 1) the role of the cerebellum in FOG, 2) gait mechanics in freezers versus non-freezers and whether joint mechanics hint at underlying mechanisms, and 3) how regular physical exercise impacts freezers and non-freezers, both in physical performance as well as neural function. Altogether, this dissertation advances our understanding of the pathogenesis of FOG and its management.

5.1.1 Chapter 2

Evidence for cerebellar involvement in the pathogenesis and pathophysiology of freezing continues to grow. Not only do freezers have altered cerebellar connectivity with the PPN [1–3], but freezers also exhibit similar cognitive deficits as those seen in cerebellar cognitive affective syndrome [4–6]. There is also evidence to show relationships between cortical volume and cognitive performance in PD [7,8]. Previous work reported changes in overall cerebellar volume [9–11], however the relationship with individual cerebellar lobules remained unclear, despite clear evidence that the lobules have distinct anatomical and functional connections [12,13]. Even less clear was whether freezers and non-freezers had different cerebellar lobule volumes and the nature of relationships between lobule volumes and cognitive performance. Prior research examining volume of the cerebellum suffered from spatial warping associated with anatomical

registration with cortical landmarks. The distance of the cerebellum from these registration points makes it susceptible to larger amounts of warping that impacts volumetric estimations. It has therefore been challenging to calculate a good estimate of cerebellar volume until recently with the development of the SUIT toolbox [14,15].

We endeavored to probe cerebellar lobule volumes and their relationships to freezing and cognition using the novel SUIT MRI analysis tool. The SUIT toolbox [14,15] provided a reliable estimate of the individual cerebellar lobule volumes, unbiased by spatial warping. Our primary results showed no significant differences in lobule volumes between freezers and non-freezers; however there were significant differences between these groups in performance on verbal fluency and Go-NoGo tasks. To our surprise, lobule volume and task performance were unrelated in freezers, but in non-freezers there was a significant relationship between lobule volume and task performance. In fact, in non-freezers, smaller lobule volumes were related to better task performance in direct opposition to our original hypothesis. Our results, in combination with research showing that cerebellar volume was negatively correlated with functional connectivity between the cerebellum and the fronto-parietal network [16], suggest that executive function may be more related to connectivity rather than volume.

5.1.2 Chapter 3

Freezing of gait clearly affects mobility as it manifests as a sudden arrest in stepping. The comorbidities associated with FOG, from cognitive deficits [17] to spatiotemporal gait deficits even outside of FOG episodes [18,19], suggest that freezing is a global impairment that may affect multiple aspects of an individual's experience [20]. In particular, the spatiotemporal gait

differences between freezers and non-freezers suggest joint mechanics during gait may be different between the two groups though this had not been systematically evaluated previously.

Chapter 3 of this dissertation addressed this gap, examining joint kinematics in freezers and non-freezers using traditional techniques as well as principal component analyses. A measure of particular interest was the decomposition index, which measures the extent to which the joints move together vs. individually during movement. The decomposition index may provide a window into cerebellar function, as the cerebellum is well known to be integral to joint coordination [21], and people with cerebellar damage often decompose a multi-joint movement into a series of single-joint movements [22]. This decomposition reduces the degrees of freedom during any single moment, perhaps giving the individual a higher probability of accomplishing the end goal of the movement. The analysis of movement decomposition was modeled after previous work in cerebellar patients [23]. The decomposition index between two joints represents the percentage of a movement during which one joint is moving and the other is held steady. Our results indicated that freezers had higher decomposition indices than non-freezers between the hip and ankle, as well as the hip and knee. This adds to the symptom similarities between freezers and cerebellar patients, further placing the cerebellum as a key player in the pathogenesis and pathophysiology of FOG. While likely unconscious, this movement pattern suggests freezers attempt to simplify movement to reduce the amount of neural resources required for successful execution of the movement. According to Lewis and Barker's theory [20], this would free up neural resources and reduce the probability of a freezing episode.

We also used principal component analysis to probe whether variability in sagittal movement of the hip, knee, and ankle joints differentiated between freezers and non-freezers. The main result

from this analysis showed that while freezers and non-freezers were not significantly different in their joint movements and that backward walking variability in both groups was significantly different from forward and dual-task walking. This adds to research suggesting that forward and backward walking are different motor programs [24,25] in addition to highlighting a difference in backward walking strategies. Some individuals adopted a forward lean position during backward walking, presumably to counteract their backward movement, while others maintained an upright trunk position.

5.1.3 Chapter 4

While researchers continue to investigate the mechanisms behind FOG, freezers continue to contend with the symptom and its comorbidities. Dopamine replacement therapy provides some symptom relief for freezers [26], but the relief for many is minimal and the side effects from prolonged use of the medications can be equally debilitating [27]. Thankfully, exercise can improve motor symptoms in people with PD [28], providing a non-pharmacological interventions to help manage disease symptoms.

Response to exercise in freezers and non-freezers has been minimally investigated, despite clear benefits in PD in general [29]. The multiple neural systems involved in freezing suggest that perhaps freezers would have altered responses. Involvement of the cerebellum alone could mean that freezers, despite multiple sessions of training, may have significant difficulty adapting movement, improving joint coordination or balance during movement. Chapter 4 of this dissertation sought to examine potential neural changes related to exercise by exposing freezers and non-freezers to 12 weeks of regular exercise. As people with PD are able to perform motor

imagery [30], a motor imagery and fMRI paradigm was used to assess changes in BOLD signal in regions of the somatomotor network that may relate to motor improvements due to exercise.

The primary results from this study showed that freezers had significantly less BOLD signal during motor imagery of backward walking compared to non-freezers. This was evident in the cerebellum, the primary sensory and primary motor cortices. Indeed, it seems that freezers recruit regions of the somatomotor network less during motor imagery compared to non-freezers. This decreased BOLD signal may be a reflection of the altered PPN connectivity observed in previous studies [1–3], and may also have some correlation with the decomposition of movement observed in freezers during backward walking. Interestingly, BOLD signal did not significantly change in either group after the exercise intervention; however there was also no change in velocity or stride length in forward or backward gait after the exercise program. As a whole, these results suggest that freezers and non-freezers may have similar responses to exercise. Despite the involvement of multiple neural systems in the pathogenesis of FOG, freezers remain capable of exercise participation and may benefit similarly to non-freezers though more work is warranted in this area.

5.2 Significant and Clinical Implications

This dissertation adds to the body of research on freezing of gait in Parkinson disease. A multifaceted approach was used to examine FOG, exploring neural mechanisms, biomechanics, and management of this problematic phenomenon. Much about the symptom remains unknown, but the present work builds upon the theory of Lewis and Barker [20] by showing relationships between FOG and the cerebellum. With a more comprehensive theory and understanding of FOG, it may be possible to improve clinical practices for better symptom management.

Lewis and Barker [20] postulated that freezing episodes are due to an inhibitory signal from the pedunculopontine nucleus, related to multiple neural inputs competing for depleted neural resources. The competing inputs could be motor or cognitive in nature, explaining why a simple change in direction could illicit a freeze as could a secondary cognitive task. This dissertation builds upon this theory, showing how the cognitive and motor functions of the cerebellum may be deficient in freezers. Importantly, causation remains unclear. While freezers have altered pedunculopontine connectivity [1–3], whether the cerebellar symptoms are due to poor connectivity or the poor connectivity is a response to cerebellar dysfunction has not been established. However a recent study noted changes in white matter structure in freezers compared to non-freezers, which one could interpret to mean freezers suffer from structural network degeneration [31]. But there is clearly a disruption in the functions of the cerebellum in freezers that has subtle manifestations other than freezing episodes.

This work showed similarities between freezers and non-freezers with regard to response to exercise and sources of gait variability. However, the decomposition index showed that freezers decompose gait more than non-freezers and prior research showed freezers have adaptation deficits [32].Therefore, it may be efficacious to tailor rehabilitation interventions to address joint coordination and/or adaptation in freezers, as freezers are more prone to falls than non-freezers [35]. These deficits in joint coordination and motor adaptation, while subtle and likely unnoticed by the person, could be affecting the ability to move effectively and adjust to changing environmental demands.

Placing these results into the larger picture of FOG, one wonders about the interactions between movement decomposition, cerebellar dysfunction, and attentional deficits. As stated earlier,

freezers may decompose movement to reduce attentional demands. It could also be that attentional capacity is reduced due to cerebellar dysfunction within the dorsal attention network. Research suggests that cueing helps freezers reduce the duration of a freeze [33,34], perhaps by providing a stimulus to focus their attention, relieving competition for attentional resources and allowing motor programs to run automatically and momentarily reducing movement decomposition. Therefore, it would be interesting to investigate joint mechanics and movement patterns preceding, during and following freezing episodes to probe the interactions between attention, movement decomposition, and cerebellar dysfunction.

Another potential target for rehabilitation for all people with PD may be gleaned from the backward gait mechanics, particularly the second principal component which showed that some individuals adopted a forward flexed posture. In general, as disease severity in PD progresses, the forward flexed posture becomes more severe and is related to postural instability and risk for falls. Identifying the propensity towards a flexed posture early on in the disease process by asking the participant to walk backward may allow clinicians to prescribe preventative physical therapy to mitigate complications later on.

Finally, it may be worth looking into whether cognitive training can improve symptoms of freezing. Recent research showed that freezers who received cognitive training reduced the amount of time they froze during a timed up and go task [36]. Frontal lobe areas associated with executive function have altered function in freezers compared to non-freezers [37,38]. Perhaps by strengthening the existing connections used during cognitive control of complex gait, the attentional load decreases, reducing the probability and duration of a freezing episode. The research presented in this dissertation looked at changes in BOLD signal after exercise without

significant results. Future work should not only look at changes in other regions of the brain in response to exercise, but it should also look at whether cognitive training can improve frontal lobe function, particularly during complex gait.

5.3 Limitations

Research always has limitations, and the study-specific limitations have been discussed in each chapter. Overarching limitations of the work include those inherent in the methods used as well as the selection criteria for inclusion in our studies. For example, there are limitations inherent in neuroimaging. While magnetic resonance imaging is a powerful tool for better understanding what areas of the brain are active at any given point in time, MRI is not an actual measure of neural activity. Rather, MRI measures the blood oxygen levels of brain areas, which are assumed to be a good proxy for neural activity. Additionally, the analysis of MRI data is still evolving and improving. A recent study found that a significant portion of MRI results may be false-positives due to errors in the analysis of the data [39]. Thankfully, the results in this dissertation are not affected by the errors presented in that study, but this underscores the dynamic and fluid nature of the field.

Motion capture techniques also have their limitations and are continuously improving. The recent incorporation into the commercial sector (i.e., use in the film industry, Microsoft Kinect) has made motion capture mainstream, but there is always a margin of error associated with these systems [40,41]. Thankfully, this margin of error is acceptable, and the signal filtering helps to smooth the signals such that the data are biologically relevant. However motion capture data require a lot of processing which, though based on multiple, well-founded assumptions, results in a processed signal that is quite removed from the original raw signal.

Research of the type presented here would not be possible without the participants; however the participants must meet certain criteria for participation which may limit the generalizability of any of the results. For example, participants were engaging in exercise intervention studies, which meant they needed to be able to participate in weekly exercise classes. This automatically excluded people with more severe PD. Additionally, our participant samples are a self-selecting group of people who want to be engaged in research and be involved in developing better, more effective therapies. Finally, the group sizes were relatively small. While statistical precautions were taken to best account for this, the chances of a type I error are higher with smaller sample sizes. Therefore, we encourage future researchers not only to build upon the findings presented here but also to replicate our studies with larger cohorts.

5.4 Future Directions

The significance of this dissertation as it applies to Parkinson disease research hopefully outweighs its limitations. Indeed, multiple avenues of research can branch off of the current work, helping to elucidate further the interconnected web of symptoms and mechanisms involved in freezing of gait. At the most general level, much larger cohorts and longer prospective studies are needed to try to piece together a clearer natural history of freezing of gait. The factors that may put one at risk for developing freezing of gait and at what stage of the disease are not established, but by knowing them, we may be able to better piece together FOG pathogenesis. Such understanding would also provide guidance as to what kinds of interventions may be most beneficial, for whom and at what point in the disease progression.

As hinted above, given the likelihood for cerebellar involvement in FOG, further examining the impacts of targeted trainings in freezers is needed. While freezers have increased decomposition

during gait, the actual spatiotemporal gait characteristics (i.e., velocity, stride length, etc.) were not significantly different between groups. What we do not know is whether 1) the decomposition index increases over time, and 2) whether an increased decomposition index is related to increased risk for falls. Depending on answers to these questions, it may also be worth exploring whether gait training during the mild/moderate disease severity stages impacts symptomatology as the disease progresses, particularly risk for fall in freezers.

In fact, applying the biomechanics and PCA techniques to fallers and non-fallers could open up an interesting vein of research. By probing the sources of movement variability in fallers and non-fallers, one may be able to understand the sequence of motor events that contribute to a fall. Alternatively, perhaps it would be more advantageous to understand the differences in the sequence of motor events that differentiate a fall from a near fall in response to the same external perturbation. These results may then be combined with the freezer/non-freezer results presented here, contributing to the overall picture of FOG and falls. Specifically, we found that some participants adopted a forward lean posture when walking backward. We hypothesized that this posture may have helped participants feel more stable during backward motion. Looking at whether backward walking posture predicts fallers and non-fallers could have clinical implications, particularly in prescribing preventative therapy for those at risk of becoming fallers. Additionally, it could be that variability in the frontal and transverse planes would be more interesting than the sagittal plane kinematics. We chose the sagittal plane because the participants were walking forward, however the side to side sway may be interesting, especially when thinking about faller/non-faller differences.

Finally, with many forms of physical activity showing benefits for people with PD to help their motor symptoms [30], maybe the question is not “what form of exercise should I do?” but rather “how much exercise should I do?” Some is better than none, but is tons better than some? Recent work with stroke patients showed that motor improvements were not related to the amount of rehabilitation participants received [42]. Though clearly a different population, the learning deficits associated with PD [43] beg the question of whether such a relationship exists in PD. Maybe frequency of physical training is more important than amount of work completed during each training session, allowing for frequent reminders on how to move rather than a short, intense period of movement that can quickly be forgotten.

PD patients are actively working to help researchers and clinicians discover therapies and interventions to improve their symptoms and slow the disease progression if not halt it altogether. All directions of research suggested here, as well as an infinite number more, could help propel the field forward toward more comprehensive understanding of the pathogenesis of FOG. While only a single symptom of the disease, freezing impacts over 75% of people with PD, and they are counting on clinicians and researchers to work with them in tackling this difficult problem.

5.5 References

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Appendix:
Yoga Improves Balance and Low Back Pain, but not Anxiety, in People with Parkinson Disease

A.1 Coversheet

The research included in the appendix comes from the intervention study described in chapter 3, which focused just on baseline data. This appendix uses the baseline and post-intervention data from the control and yoga groups. The purpose of this study was to examine potential effects of yoga on balance in people with PD. At its original conception, we hoped to integrate these analyses into the body of the dissertation as a fourth aim; however recruitment difficulties and low freezer recruitment rates shifted the analyses into a different research area than the other three aims. As such, the manuscript for this study is included as an appendix.

This study serves as pilot data for further investigation of the effects of yoga in people with PD. In particular, the results provide evidence for multiple therapeutic benefits of yoga for people with PD. Future research should expand upon these data to examine whether yoga effects freezers and non-freezers similarly. Also, given the many research studies and anecdotal stories suggesting non-motor, therapeutic benefits to yoga in general, a more thorough assessment of the effects of yoga on depression, anxiety, and quality of life among people with PD should be conducted.

This work has been submitted for publication and is currently under review.

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A.2 Abstract

Introduction: Individuals with Parkinson's disease (PD) experience postural instability, low back pain (LBP), and anxiety. These symptoms increase the risk of falls, as well as decrease quality of life. Research shows yoga improves balance and decreases LBP and anxiety in healthy adults, but its effects in PD are poorly understood.

Methods: All participants were part of a larger intervention study. Participants received pre-test and post-test evaluations, including completion of the Balance Evaluation Systems Test (BESTest), Beck Anxiety Inventory (BAI), and Revised Oswestry Disability Index (ROSW). Total scores for each measure, as well as individual balance system section scores from the BESTest (Biomechanical constraints, stability limits/verticality, transitions/anticipatory, reactive, sensory orientation, and stability in gait) were compared within group pre- to post-test. Participants in the yoga group (n=13) completed a twice weekly, 12-week yoga intervention, while controls (n=13) continued their usual routines for 12 weeks.

Results: Both the yoga (Z=-3.2, p=.001) and control (Z=-2.1, p=.04) group improved on the BESTest total score. The control group showed no changes in individual balance systems whereas the yoga group improved in stability limits/verticality (Z=-2.3, p=.02), transitions/anticipatory (Z=-2.5, p=.01), reactive (Z=-2.7, p=.008), and sensory orientation (-2.3, p=.02) systems. ROSW decreased in the yoga group only (Z=-2.1, p=.03). BAI did not change in either group.

Conclusions: Yoga is a non-pharmacological intervention that can improve balance and LBP in people with PD. This study demonstrated that yoga is feasible for people with PD, and participants reported high levels of enjoyment and intent to practice yoga after the study.

A.3 Introduction

People with Parkinson's disease (PD) suffer from balance and postural deficits, which increase the likelihood of debilitating falls [1]. Specifically, people with PD can have insufficient responses to external forces or perturbations, leading to loss of balance [2]. Limb stiffness [3] and a flexed posture [4] may also contribute to the risk of falls, and these symptoms become worse as the disease progresses. Additionally, increased flexed posture may contribute to low back pain (LBP), a symptom often untreated in PD [5]. Non-motor symptoms in people with PD are also present. Increased anxiety is a common non-motor symptom, which can affect up to 55% of individuals with PD [6]. The combination of increased motor disability [7] and anxiety negatively impacts the quality of life of individuals with PD [6]. While antiparkinsonian medications can decrease postural instability [8], the medications may also impact the pathogenesis of anxiety in PD [9], increasing symptomatology. Therefore, non-pharmacological interventions warrant exploration for long-term management of both motor and non-motor symptoms in PD.

Yoga has been explored in multiple populations [10–12], and it has been shown to improve balance [13]. Many yoga postures challenge balance by placing the individual's body in unstable positions, which cannot be maintained without the appropriate muscular activation to stabilize the joints [14]. Likely, individuals learn how to appropriately activate their muscles, resulting in balance improvements. In people with PD, yoga significantly improved measures of overall balance [15,16]. However, as assessed by the Balance Evaluation Systems Test (BESTest) [17], people with PD have deficits in all six systems of balance (biomechanical constraints, stability limits/verticality, transitions/anticipatory, reactive, sensory orientation, and stability in gait), and it is unclear which systems are most affected by yoga interventions. Yoga has other beneficial

effects, such as decreasing LBP [18] and anxiety [19] in non-PD populations. Improvements in LBP are likely related to physical aspects of yoga, while changes in anxiety could relate to both the breathing and meditative aspects of yoga [19–21]; however, these benefits have not been explored in PD.

The aims of this study, therefore, were to determine the effect of a 12-week yoga intervention on the specific systems of balance as well as LBP and anxiety. We developed a yoga program that incorporated breathing, meditation, and physical postures, with a focus on postural transitions, such as getting up and down from the floor. The design of our yoga program was intended to affect postural instability in people with PD by improving joint stability in static and dynamic positions. For this reason, our assessment of balance employed the full BESTest [17] to examine changes in each system of balance. We also used the Beck Anxiety Inventory (BAI) [22] to measure changes in anxiety and the Revised Oswestry Disability Index (ROSW) [23] for changes in LBP. We hypothesized that people with PD would show more improvements in BESTest, BAI, and ROSW scores after a yoga intervention than a control group receiving no intervention. Further, based on the transition-focused nature of the yoga program, we expected to see improvements in the biomechanical constraints, stability limits/verticality, and transitions/anticipatory systems of balance in the BESTest.

A.4 Methods

A.4.1 Participants

All participants were part of a larger intervention study with the following inclusion criteria: 1) clinical diagnosis of Parkinson's disease, 2) able to stand for at least 30 minutes, 3) normal peripheral function, 4) no history of vestibular disease, and 5) Mini Mental State Exam (MMSE)

score ≥24 [22]. Exclusion criteria included 1) diagnosis of any other major medical condition, 2) having deep brain stimulation or neural implants, 3) diagnosis of peripheral neuropathy, 4) use of neuroleptic or dopamine-blocking medications, and 5) has a current, regular yoga practice. Participants were randomized into one of three groups: controls, yoga, and an unrelated intervention. Only the control and yoga groups are included in the present study. All participants provided written informed consent, and this study was approved by the Human Research Protection office of Washington University in St Louis.

A.4.2 Evaluations

Participants received a pre-test evaluation consisting of a behavioral assessment and questionnaires, followed by a 12-week intervention or control period. Controls were asked to continue their usual daily routines during the 12 weeks, which began the day after their pre-test evaluation, and the yoga group participated in the yoga program for 12-weeks. Pre-test evaluations for the yoga group occurred within four weeks of starting the yoga program. All post-test evaluations occurred within two weeks of completing the yoga program or control period. The behavioral assessment included the full BESTest [17], which consists of 36 items, divided into six sections. Each section evaluates a different system of balance (biomechanical constraints, stability limits/verticality, transitions/anticipatory, reactive, sensory orientation, and stability in gait), and section scores add together for a total score. The individual section scores, as well as the total score, are valid for group comparisons [17] and were used here to evaluate changes in balance systems and overall balance in each group. Disease severity was measured using the Movement Disorder Society Unified Parkinson's disease Rating Scale, motor symptom subscale (MDS-UPDRS III) [23]. BESTest and MDS-UPDRS III were videotaped and scored by

a rater blinded to group. To minimize effects of medications, evaluation time remained consistent for both evaluations within each participant.

Participants received questionnaire packets electronically or through the mail one week before their scheduled evaluations and were asked to complete the entire packet before their evaluations. The packet of questionnaires included a demographics sheet, the BAI [24], and the ROSW [25]. The BAI is a self-report measure of anxiety that asks the participant to rate how much they are bothered by each of 21 items on a scale of 1 (not bothered at all) to 3 (severely, it bothered me a lot), for a maximum possible score of 63. The ROSW asks whether the participant experiences LBP chronically or when engaging in a list of ten different activities. Each activity has a possible answer of 0 (no disability) to 5 (severe disability), giving a maximum possible score of 50. ROSW scores are multiplied by two to provide a percentage of total disability. The BAI and ROSW were used to measure anxiety and LBP, respectively, before and after the intervention or control period. As part of the post-test questionnaire packet, participants in the yoga group also completed an exit questionnaire to evaluate their perceptions of the effectiveness of, and to elicit feedback on, the yoga program.

A.4.3 Yoga Intervention

Participants in the yoga intervention were assigned to one of two class sections (Monday/Wednesday mornings or Tuesday/Thursday afternoons) depending on their personal schedules. Classes had 7-9 participants, and 3-5 research team members, including two certified yoga instructors, were present at each class to assist participants when necessary. Instructors alternately taught classes to ensure all participants had equal exposure to both instructors, and the instructors discussed class format prior to the classes so that content and difficulty was

maintained across class sections. Participants were required to attend at least 20/24 classes for inclusion in the present analysis. Of the 15 enrolled participants, 13 completed enough classes for inclusion. Two participants discontinued participation in the study, one due to leg pain unrelated to the intervention and one due to employment conflicts.

All classes maintained the following format: 5 minutes introduction with relaxation and guided meditation, 10 minutes gentle spinal movements, 30-35 minutes standing poses, 5-10 minutes cool down, and 5 minutes rest and relaxation. Standing poses focused on balance and stability and included poses such as Warrior I and II, Crescent Lunge, Downward Dog, and Tree. Participants were encouraged to work on safely transitioning between poses, with or without assistance from research staff. The simplest, most accessible form of a pose was taught first, with more advanced variations offered as skill levels improved. During the final five minutes of every class, participants lay in savasana, a final resting pose where one lies supine on the floor with eyes closed in meditation. Instructors provided a brief leg or neck adjustment to maximize relaxation and comfort to all participants during this time. All participants were provided with a yoga mat (68x24in), high density foam blocks (9x6x4in), and a cloth strap (1x120in). Foam blocks and straps were used to assist participants in poses. Chairs were available upon request should a participant need to rest but were not part of the yoga class. There were no adverse events such as falls or muscular injuries during the classes.

A.4.4 Statistical Analyses

Statistical analyses were conducted using IBM SPSS statistics (version 24, IBM, Armonk, NY, USA). For the 13 yoga participants who completed the study, we used propensity score matching to identify 13 age-matched control participants. Analyses reported include the 13 yoga

completers and these 13 age-matched controls. Based on the smaller group sample sizes and data skewness, non-parametric tests were used. Mann-Whitney U tests were used to compare baseline performance for BESTest, BAI, and ROSW between groups. Wilcoxon signed rank tests were used to compare pre-test vs. post-test scores for BESTest, BAI, and ROSW within each group. Statistical significance was set at $\alpha<.05$.

A.5 Results

Participants in the yoga group attended an average of 22 classes, with a range of 20-24 classes. There were no significant demographic differences between groups at pre-test (Table A.1). Mann-Whitney U tests comparing pre-test performance for BESTest total, each BESTest section, BAI, and ROSW showed no significant differences between groups at pre-test.

Table A.1. Demographics

Demographic	Control (n=13)	Yoga (n=13)	p-value
Age, mean (SD)	65.0 (8.7)	70.5 (8.7)	.12
Sex, # female	5	6	.99
MMSE, median (range)	29 (25,30)	29 (27,30)	.73
UPDRS-III, median (range)	24 (18,42)	29 (10,49)	.74
H&Y, median (range)	2 (2,3)	2 (2,3)	.99

BESTest total score and the six section scores were compared for each group. In the control group, there was a significant improvement in overall score (Z=-2.1, p=.04) but not in any of the individual sections. The yoga group showed significant improvement in overall score (Z=-3.2, p=.001) as well as improvement in stability limits/verticality (Z=-2.3, p=.02), transitions/anticipatory (Z=-2.5, p=.01), reactive (Z=-2.7, p=.008), and sensory orientation (Z=-2.3, p=.02) sections. BAI scores at pre-test and post-test were compared for each group and showed no change in controls (Z=-.40, p=.69) or yoga (Z=-.04, p=.97). ROSW scores at pre-test

and post-test were compared for each group and showed no change for controls (Z=-.48, p=.63) but a significant decrease in disability for yoga (Z=-2.1, p=.03) (Table A.2; Figure A.1).

Table A.2. Outcome Measures

	Controls			Yoga		
BESTest	Pre-Test	Post-Test	**p-value**	Pre-Test	Post-Test	**p-value**
Biomechanical Constraints	10 (4,12)	11 (5,13)	.10	11 (7,14)	11 (9,15)	.81
Stability Limits/Verticality	18 (15,21)	19 (11,21)	.17	17 (12,20)	19 (16,21)	.02*
Transitions/Anticipatory	14 (10,18)	13 (11,18)	.39	15 (9,17)	16 (9,18)	.01*
Reactive	12(6,18)	13 (5,17)	.66	13 (6,14)	13 (7,18)	.008*
Sensory Orientation	13 (10,14)	13 (9,15)	.06	13 (11,14)	14 (11,15)	.02*
Stability in Gait	16 (10,19)	17 (13,20)	.11	16 (10,19)	15 (10,18)	.39
Total	84 (63,95)	86 (66,100)	.04*	87 (63,93)	90 (66,98)	.001*
Beck Anxiety Inventory	8 (0,14)	6 (1,14)	.69	8 (1,35)	7 (1,18)	.97
Revised Oswestry Disability Index	14 (0,40)	14 (0,40)	.63	14 (0,46)	2 (0,22)	.03*

All scores represent median (range). Wilcoxon signed rank test compared pre-test and post-test within each group, separately.

*significant at $\alpha<.05$

Twelve of the thirteen yoga participants completed an exit questionnaire. The overall response was positive, with ten participants noting the social aspect and sense of community as being beneficial for them. Eleven responded to the question “How effective was this exercise program? Please slide the bar along the scale” (0=not effective, 50=somewhat effective, 100=very effective). The average rating was 82.5, indicating participants thought the intervention was effective for them. Ten respondents answered the question “How would you rate the physical requirements of the class? Please slide the bar along the scale” (0=too easy, 50=just right, 100=too difficult). The mean answer was 62.2, indicating the class was challenging but not overly demanding for the participants. Four participants said driving distance to the class was difficult, and four indicated a printed document illustrating the yoga poses would have been

helpful. Eleven participants reported feeling physical benefits, such as improved balance, strength, and flexibility. Finally, ten participants said they planned on continuing yoga after the study, commenting that they enjoyed the program.

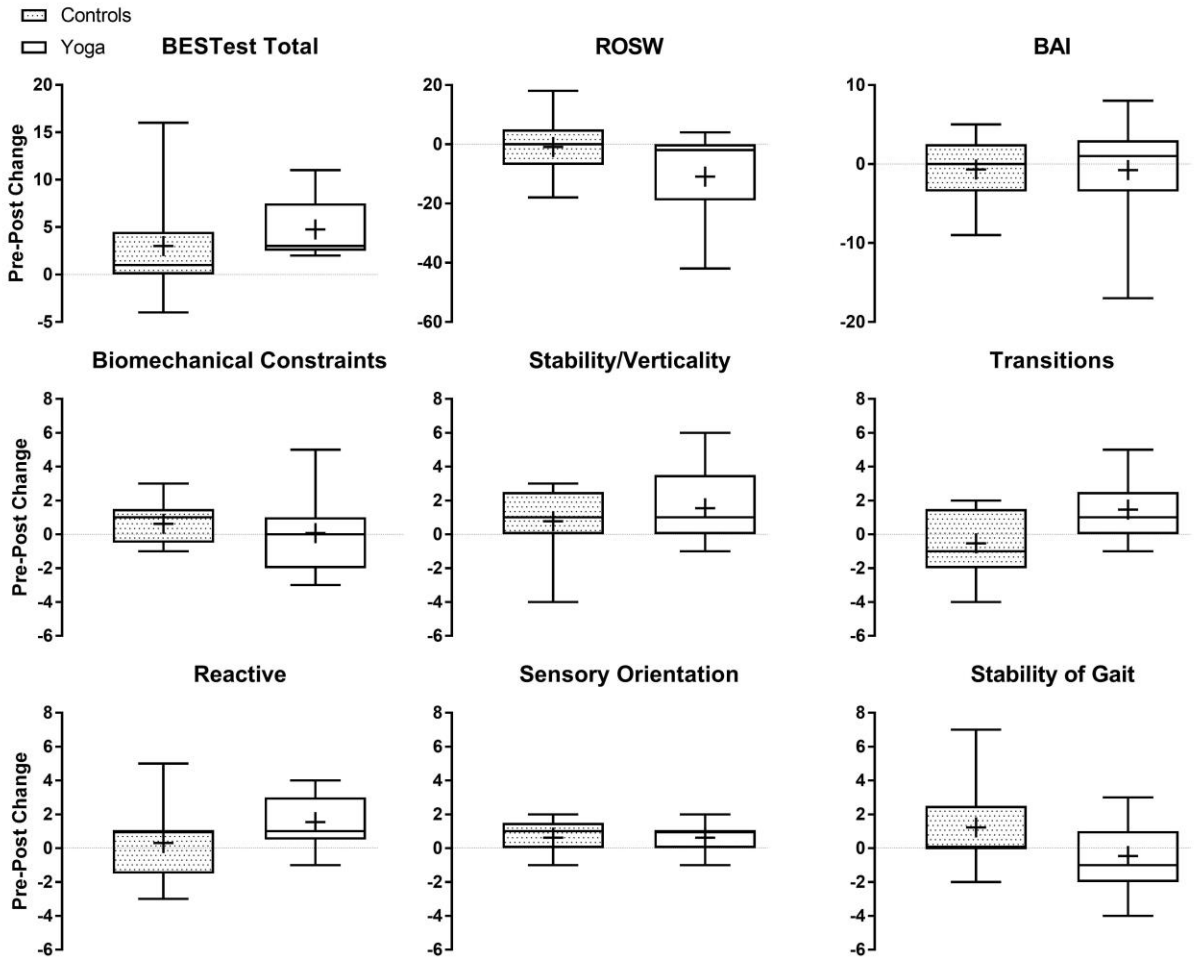

Figure A.1. Change Scores. Box and whisker plots for changes in outcomes from pre- to post-test. For the Balance Evaluation Systems Test (BESTest) and its system sections, a positive change denotes improvement. For Revised Oswestry Disability Index (ROSW), a negative change denotes reduced disability. For the Beck Anxiety Inventory (BAI), a negative change denotes reduced anxiety. The bottom two rows show the different balance systems within the BESTest.
+indicates mean value.

A.6 Discussion

Here we have shown that yoga can both improve balance and decrease LBP-related disability in people with PD. Specifically, our results indicate that after 12 weeks of yoga, people with PD were more stable and upright, better at transitions and anticipatory movements, more able to react quickly and appropriately to external stimuli, and better at sensory orientation. Additionally, people with PD reported significantly less LBP after the yoga intervention. On top of the quantitative evidence, qualitative feedback from the exit survey was highly positive with more than ¾ of the participants intending to continue yoga after the research study.

The BESTest results illuminate which specific systems of balance changed over the course of the yoga intervention. Minimal clinically important differences for the BESTest, particularly for the individual balance systems, have not been established in PD. However, people in the yoga class did report feeling physical improvements after the intervention, which may have contributed to improved performance on the BESTest. The improvement in the transitions/anticipatory balance system suggests a yoga program emphasizing transitions is effective for targeted improvements in this system of balance. Additionally, the program helped people with PD improve their responses to external perturbations (i.e., postural instability). As people with PD are highly prone to debilitating falls due to increased limb stiffness and poorly directed arm movements [3], significantly improving these balance systems may help reduce fall risk. Further, the stability limits/verticality balance system improved in the yoga group, suggesting yoga may have been able to mitigate the tendency towards the flexed trunk associated with increased disease severity [4].

The yoga group results stand in contrast to control group performance. While the controls improved in the BESTest total score, none of the individual systems significantly changed. This indicates the control group improved performance overall but improvement was random with no systematic change leading to this result. Additionally, controls were asked to continue their normal routines of physical activity, so changes in total BESTest score may be due to improvements associated with outside routines or with a practice effect from pre-test to post-test.

The LBP improvements are noteworthy as little research has been conducted looking at LBP treatment in PD. Exercises to address stooped posture and motor function are often given as the treatment for LBP [5], and the multiple motor and non-motor symptoms associated with PD may impact traditional LBP treatment efficacy. Here, we show the yoga group reported both significantly reduced LBP after the yoga intervention and they enjoyed the class overall. Previous research on LBP [26] suggests a reduction of 10% for the ROSW is clinically meaningful. Due to our smaller sample size, it cannot be determined whether this threshold was truly met, but our data do suggest the mean change in ROSW for the yoga group was around 10% (Figure A.1).

Participant enjoyment of an activity is important for activity adherence [27], and group exercise increases participant enjoyment [28]. Not only did the yoga group report enjoying the classes, but ten of the thirteen participants said they planned to continue practicing yoga after the study. This suggests the benefits of the yoga class went beyond quantifiable changes in balance and LBP. A regular yoga class would promote activity and provide a social support system, both of which are important among people with PD [29].

Surprisingly, we did not see a significant decrease in BAI in the yoga group, but this may have been due to participants reporting low anxiety at baseline with all pre-test scores less than 21, except for one participant in the yoga group [24]. That participant went from a pre-test BAI score of 35 to a post-test BAI score of 18. Additionally, while relaxation and guided meditation was offered at the beginning and end of each class, our yoga program did not focus on meditation.

Though this study's sample size was small, groups were similar at pre-test, and significant differences were detected from pre- to post-test. Additionally, we showed that a transition-focused yoga program is feasible, having had no adverse events during class; and most individuals who completed the program intended to continue to practice yoga after the study because of perceived physical benefits from the intervention. It is important to note, however, that a significant amount of assistance from research team members was needed to ensure the safety of participants. The ratio of research staff to participants was never more than 1:3. This may suggest this yoga program would not be as safe and effective for individuals with more severe PD. During classes, some participants used the foam blocks to adapt poses based on their flexibility or increase stability. This introduces variability in the received intervention, but it is standard in any yoga class to provide each participant with the necessary tools to fully participate during class in a safe and effective manner. Importantly, this yoga program did not use chairs, encouraging participants to challenge themselves and learn strategies for safe postural transitions.

Overall, our study shows that yoga is potentially beneficial for people with PD and warrants further examination. While we have shown improvements in specific systems of balance, future research should examine whether these improvements are due to improved muscle strength,

changes in muscle activation patterns, or other factors. Future work may also provide further insight into why yoga impacted LBP and its relationship to different systems of balance. Additionally, yoga's impact on fall risk requires further research. While we report balance improvements, whether that translates to fall reduction is beyond the scope of this study. Nevertheless, yoga offers a non-pharmacological treatment for balance deficits in people with PD, as well as other physical and social benefits, which are important for maintaining high quality of life.

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