Vestibular Function in People with Parkinson Disease and the Effects of Dopaminergic Medication

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Abstract

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There is growing evidence suggesting that Parkinson disease (PD) affects the vestibular system, which senses head accelerations including gravity. People with PD report symptoms consistent with vestibular dysfunction that may begin prior to their PD diagnosis. Vestibular dysfunction may also contribute to postural instability which is common with disease progression. In addition to the otolithic and semicircular canal (SCC) end organs in the periphery, the vestibular system has broad sub-cortical and cortical connectivity leading to multiple potential routes for PD pathology to affect vestibular function. However, it is unclear if vestibular dysfunction in PD is disease-specific, age-related, or both. Furthermore, it is unknown how dopaminergic medications used to treat PD may affect vestibular function. Due to the

distributed nature of vestibular connections and the inability to record from the end organs directly, localization of vestibular pathology in humans requires a comprehensive examination. The overarching objective of this dissertation is to understand how Parkinson disease and dopaminergic medications used to treat PD affect peripheral and central vestibular function in people with PD. This objective was met through the completion of two projects: a retrospective review of vestibular test records, and a prospective comparison of comprehensive vestibular testing in healthy controls and participants with PD, off-medication and on-medication.

First, a retrospective records review was performed to examine the results of comprehensive vestibular testing completed by people with PD at the University of Washington Dizziness and Balance Center. The record review aimed to characterize vestibular function in people with PD referred for vestibular testing compared to adults without PD who also completed testing at the center. It was hypothesized based on prior literature that vestibular test results would show specifically otolithic dysfunction in the periphery and a pattern of central vestibular involvement across disease stages. Records that included a diagnosis of PD were categorized based on the timing of the PD diagnosis relative to the date of vestibular testing as prodromal (vestibular assessment before PD diagnosis) or clinical (vestibular assessment within one year of or any time after PD diagnosis). Age and gender matching of PD records to non-PD control group (CG) records at a 1:2 ratio was then performed. The primary comparison was to determine if there were significant differences in vestibular test results between PD and CG, based on the presence of a diagnosis of PD. Secondary comparisons determined if there were differences based on disease severity. Comparisons were made for CG and prodromal PD, CG and clinical PD, and between the two PD groups. Results were partially aligned with the expected outcome. Unlike expectations, there were no differences between CG and PD records

for otolithic function. Consistent with expectations, central signs were present for the PD groups suggesting vestibulo-cerebellar dysfunction in all 3 three comparisons where sufficient data was available. All groups showed poor postural control performance. These findings suggest that peripheral otolithic dysfunction may not be more prevalent in PD than in typical aging, but central vestibular dysfunction that includes the cerebellum may be present in PD even at early disease stages.

Second, a prospective study used comprehensive vestibular testing to determine if vestibular function in PD is different from healthy older adults and to examine the effects of dopaminergic medication on vestibular function in PD. For the first aim, it was anticipated that, compared to healthy controls (HC), people with PD would have abnormalities in otolithic function, vestibular nucleus complex (VNC) functions, and vestibular sensory integration. For the second aim, it was anticipated that dopaminergic medication would improve otolithic function and inhibit central functions. To test this, 15 HC and 15 participants with PD completed comprehensive vestibular testing. Participants with PD completed testing when functionally off their dopaminergic medications for PD (OFF), and while on-medication (ON). Both aims used the same primary variables representing otolithic function, SCC function, VNC function, and vestibular sensory integration for postural control. Secondary variables were also collected and compared to provide context to interpret primary test results. To test for PD-specific vestibular deficits without any potential medication effects, vestibular test results for participants with PD, OFF, were compared to HC. It was expected that otolithic function would be abnormal in PD, however, the comparison found that otolithic function in PD was not significantly different from HC. Instead, there was evidence for reduced SCC function. The primary central function variables were not significantly different in PD. However, for secondary variables, there were

significant signs of dysfunction of the VNC and cerebellum, abnormal visual verticality perception, and well-known saccadic eye movement abnormalities.

The second aim of the prospective project, to determine the effects of dopaminergic medication on vestibular function in PD, used a quasi-experimental design. The results of participants with PD, OFF, were compared to ON. It was anticipated that medication would improve otolithic function and impair central vestibular functions. The results of comparisons showed no effect of medication on either peripheral or central vestibular function. However, there was a high prevalence of abnormal test results both OFF and ON. These findings indicate that there may be disease-specific VNC, cerebellar, and cortical vestibular processing abnormalities in PD affecting non-dopaminergic pathways.

In conclusion, the work of this dissertation demonstrates that disease-related central vestibular dysfunction may exist in people with PD, potentially at early disease stages. Additionally, the evidence that vestibular dysfunction in PD is not responsive to dopaminergic medications indicates potential non-dopaminergic pathway involvement in PD. Further research is needed to determine if this vestibular dysfunction is related to postural control and gait deficits, or non-motor symptoms in PD. Finally, examination and individualized treatment using established vestibular rehabilitation techniques and the development of novel interventions targeting vestibular function should be considered for people with PD.

Plain Language Summary

Parkinson disease (PD) is the second most common neurodegenerative disorder worldwide. People with PD often have problems with how their bodies move which can make walking and balance difficult. Other symptoms in PD are not related to movement, and these may include problems with vestibular function. The disease process of PD is believed to begin in the brainstem and later causes neurons that produce dopamine to die. The loss of dopamine is what causes many of the symptoms of PD. The vestibular system is a special sensory system that plays a key role in balance and keeping our eyes stable. The vestibular system can be divided into two components. One is peripheral, in the inner ear, and senses head movement and the pull of gravity. The other is central, in the brainstem, with multiple connections to other parts of the brain. There is growing evidence that problems with peripheral and central vestibular function occur in people with PD. These problems may even happen before a person receives a diagnosis of PD. However, what we don't know is if vestibular problems in people with PD are because of PD, a result of normal aging, or both. Also, it is not clear how medications used to treat the loss of dopamine in PD affect vestibular function. The overall aim of this dissertation was to understand how PD and the medications used to treat PD may impact peripheral and central vestibular functions. This objective was achieved through the completion of two studies.

The first study was to see if peripheral or central vestibular function in people with dizziness and balance complaints is different in people with PD compared to people of the same age. It was also to see if these differences in vestibular function showed up on the tests before or after people had a diagnosis of PD. In this study, we looked back at medical records for people who were tested in a clinic to see if they had vestibular problems. These people had testing because they had symptoms that might be caused by abnormal vestibular function. The records

of people with PD who had vestibular testing were compared to the testing of people without PD who were the same age and sex. People with PD did not appear to have peripheral vestibular problems. We found differences in people with PD that showed they had problems with some parts of the central part of the vestibular system. Some of these problems seemed to be happening both before and after people were diagnosed with PD.

In the second study, we tested whether people with PD and healthy people have differences in vestibular function. We also tested if medications taken to treat PD had any effect on vestibular function. Healthy participants completed vestibular testing once. Participants with PD completed testing twice, once before taking their usual dose of medication, and another time when taking their medication as usual. We compared the results of tests that participants with PD completed before they took medication to the tests of healthy participants. We found that people with PD may have changes in some peripheral vestibular functions and some changes in central vestibular functions.

Next, we checked to see if medications for PD change vestibular function. The test results collected when participants with PD were tested before taking their medication were compared to test results collected when they were taking their medication as usual. We saw that people with PD had problems with the central part of their vestibular system. Medication for PD did not improve any of the vestibular problems they had before taking their medication.

Together, these studies show that parts of the vestibular system are probably affected by PD, even before people with PD have other symptoms that lead to a diagnosis. They also show that the medications used to treat PD do not improve vestibular function. This means that PD could affect parts of the brain for vestibular function that do not use dopamine. Healthcare

providers and people with PD should know that the vestibular system could be affected by PD. Treatments for vestibular function could be a helpful addition for people with PD.

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Thank you, also, to my mentor, Valerie Kelly, for reminding me that no research is perfect. There will always be mistakes to learn from and improve next time. Not only have you been an academic mentor, but you were there for me when I had great need.

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Dedication

For Dr. George Danny Brodsky. You would have been proud, Dad.

Human Subjects Statement

This research was conducted with the approval of the Human Subjects Division

of the

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CHAPTER 1 – INTRODUCTION

1.1 Vestibular Function and Parkinson Disease

There is growing evidence suggesting that Parkinson disease (PD) affects the vestibular system, which senses head accelerations including gravity (Cui et al., 2022; Smith, 2018). People with PD report visual disturbance and dizziness consistent with vestibular dysfunction that may begin prior to PD diagnosis (Berliner et al., 2020; Mahajan et al., 2021). A predominant feature of PD with disease progression is postural instability (Bloem et al., 2021), which may result from a combination of motor control dysfunction and deficits in sensory function. It has been suggested that vestibular system involvement in PD contributes to the presence of postural instability with disease progression (Bohnen, Kanel, van Emde Boas, et al., 2022; J. H. Park et al., 2022). The vestibular system has broad sub-cortical and cortical connectivity leading to multiple possible routes for PD pathology to affect vestibular function. However, it is unclear if the vestibular changes observed in PD reflect changes that occur with typical aging. Furthermore, little is known about the role of dopamine in the human vestibular system, and the use of dopaminergic medications as a primary treatment for PD may impact vestibular function. The overall aim of this dissertation is to understand how PD and the dopaminergic medications used to treat PD may impact peripheral and central vestibular functions. Before exploring the existing evidence of vestibular dysfunction in PD, it is first important to have a background understanding of PD and current vestibular testing techniques.

1.2 Overview of Parkinson Disease

1.2.1 Prevalence and Impact on the Health Care System

Parkinson disease is the second most common neurodegenerative disorder, affecting approximately 106 out of every 100,000 adults worldwide (Ou et al., 2021) and 572 per 100,000 adults aged 45 years and older in North America (Marras et al., 2018). The prevalence of PD is increasing and is projected to result in a global financial burden of $17.5 million by 2030 (Dorsey et al., 2018; Ou et al., 2021; W. Yang et al., 2020). Morbidity and mortality in PD are highly associated with falls (Kalilani et al., 2016), and people with PD account for 2.5% of fall-related hospitalizations in the United States (Paul et al., 2017). Unfortunately, current interventions for PD do not fully ameliorate disease-related symptoms (Fabbri et al., 2016; Rosqvist et al., 2018; Schrag et al., 2020) or significantly reduce fall rates (Ashburn et al., 2019; M. E. Morris et al., 2017). An improved understanding of contributors to motor and non-motor features of PD could inform the application of existing treatments and the development of novel treatments to improve balance and mobility and reduce falls in people with PD.

1.2.2 Pathological Process and Disease Progression

The primary pathological definition of PD relies on the death of neurons in the substantia-nigra pars compacta and the presence of misfolded α-synuclein proteins in the form of Lewy bodies and Lewy neurites (Hughes et al., 1992). The substantia nigra is part of the basal ganglia located in the midbrain and is responsible for dopamine production. Other components of the basal ganglia are the nucleus accumbens, subthalamic nucleus, globus pallidus, and striatum. Progression of PD is understood to be due to the continued loss of dopaminergic neurons in the

substantia nigra and the spreading pathology of Lewy bodies and neurites from the brainstem to other sub-cortical and cortical areas (Braak et al., 2004; Ferreira et al., 2021; Seidel et al., 2015).

More recently, involvement of non-dopaminergic systems in the brain has been recognized in PD. Pathology in various cholinergic areas in the forebrain, basal ganglia, cerebellum, and brainstem appear to be associated with both motor and non-motor symptoms in PD (Bohnen, Kanel, Roytman, et al., 2022; Pasquini et al., 2021). Evidence for cholinergic involvement in PD includes imaging that demonstrates cholinergic pathway deficits related to postural control and vestibular integration in humans with PD (Bohnen, Kanel, Roytman, et al., 2022).

There are currently no tests that can be performed to confirm the pathology of PD in living humans. Research on biomarkers for PD has made significant progress in recent years but is not yet able to definitively diagnose PD (Mollenhauer, 2023). Instead, a clinical diagnosis of PD is based on symptom reporting, physical examination, and a positive response to levodopa therapy (Postuma et al., 2015). Non-invasive imagining techniques such as dopamine transporter scanning can be used in conjunction with clinical findings to give support to a probable diagnosis of PD (Bloem et al., 2021).

1.2.3 Motor Manifestations

Standing Balance Changes

The clinical diagnosis of PD is based on the cardinal motor signs of tremor, rigidity (muscle stiffness), and bradykinesia (small and slowed movement) (Postuma et al., 2015). These motor signs are attributed to loss of dopamine in the basal ganglia and are therefore treated using dopaminergic medications that increase the availability of dopamine in the brain (Bloem et al.,

2021). In addition to the cardinal signs, impaired balance and abnormal gait have long been documented in PD, and worsen with disease progression (Doherty et al., 2011; Samii et al., 2004).

Disease-related impacts on standing balance in PD include changes in steady state, reactive, and anticipatory postural control. Changes to steady state postural control in PD include postural changes such as Pisa syndrome (marked lateral flexion of the trunk), anticollis (forward flexion of the neck and head), and capticormia (excessive forward flexion of the trunk) (Barone et al., 2016; Doherty et al., 2011). The cause of these postural changes is still not clearly understood. They may be due to drug-induced dyskinesia, increased muscle rigidity, sensory impairment, or sensory integration deficits (Barone et al., 2016; Doherty et al., 2011; Huh et al., 2022; Lazzaro et al., 2018; Sasaki et al., 2022; Scocco et al., 2014). In addition to postural alignment impacts, standing postural sway also appears affected in people with PD. People with PD who are taking dopaminergic medications appear to have similar or greater sway area and velocity in standing when compared to older adults (Curtze et al., 2015; Doná et al., 2016; Horak et al., 2016; Workman & Thrasher, 2019). However, when people with PD are functionally off their medication (defined as medications withheld overnight for at least 12 hours), they appear to have decreased sway standing compared to healthy older adults (Curtze et al., 2015; Horak et al., 2016; Workman & Thrasher, 2019). Increased disease severity is associated with an increase in postural sway when on or off anti-parkinsonian medication (Dewey et al., 2014; Frenklach et al., 2009). These alterations in sway with medication may be a result of changes in rigidity. However, changes in sensory function or integration may also impact postural control in people with PD. When the ability to use visual or somatosensory inputs is altered for people with PD, they demonstrate poorer balance performance than healthy older adults (Colnat-Coulbois et al.,

2011; Doná et al., 2016; Feller et al., 2019; Frenklach et al., 2009; Harro et al., 2018). These findings suggest that people with PD rely more on visual information than vestibular or somatosensory inputs to maintain static postural control.

Altered reactive postural control is used in the evaluation of motor impairments and staging of PD progression. Postural stability is assessed using the pull-test – a sudden, unexpected pull in the posterior direction (Goetz et al., 2004, 2008). Specific changes to reactive postural control in PD include changes in response strategies (hip, ankle, and step), increased latency or decreased intensity of response to a perturbation, and decreased limits of stability (Schoneburg et al., 2013). The limit of stability is the maximum displacement of a person's center of mass in any direction before they fall or must take a step (Horak, 2006; Jacobson, Shepard, et al., 2021). People with PD appear to rely more on hip strategies and less on ankle strategies to adjust sway and maintain balance on an unstable surface (Colnat-Coulbois et al., 2011; Pantall et al., 2018). They also take smaller and slower steps in response to exceeding their limits of stability (Feller et al., 2019; Jacobs & Horak, 2006; Schoneburg et al., 2013). Possible causes for decreased reactive postural control in PD include postural alterations of the center of mass, rigidity and bradykinesia interfering with response timing and amplitude, and sensory impairments (Mileti et al., 2020; Schoneburg et al., 2013). Although medications can improve rigidity and bradykinesia, on- and off-medication comparisons for step response performance and muscle synergies do not appear to improve (Mileti et al., 2020).

Anticipatory postural control is also affected in people with PD (Bonora et al., 2017; Curtze et al., 2015; Delval et al., 2014; Schoneburg et al., 2013). Anticipatory postural control maintains postural equilibrium with planned movements such as reaching or initiation of walking (Horak, 2006). In people with PD, changes in anticipatory postural control may be due to

bradykinesia, or a dysfunction in the coordination of cognitive planning for a postural change and postural control mechanisms (Giladi & Nieuwboer, 2008; Schoneburg et al., 2013). Dopaminergic medications used to treat PD appear to improve anticipatory postural adjustments for gait initiation (Delval et al., 2014; Schoneburg et al., 2013) but not to the level of healthy older adults (Curtze et al., 2015).

Gait Dysfunction

Changes in gait are common in PD and are linked to an increased risk for falls (Lindholm et al., 2021). Early gait changes are often unilateral with progression to bilateral involvement (Mirelman et al., 2019; Schoneburg et al., 2013). Subtle gait alterations may even occur before diagnosis with PD, including decreased arm swing, trunk rotation, stride length and foot clearance during swing along with increased variability in stance width, stance time and swing time (Del Din et al., 2019; Marković et al., 2022; Mirelman et al., 2019; Wilson et al., 2020). These changes may not be easily perceptible on visual examination but can be quantified using inertial sensors and other motion capture tools (Di Biase et al., 2020; S. Lord, Galna, Verghese, et al., 2013). More complex gait activities, such as performing a concurrent task and turning, can also be affected in early stages of PD (Di Biase et al., 2020; S. Lord, Galna, & Rochester, 2013).

Some gait characteristics change in PD at similar rates to those in healthy aging adults; namely, slowed step velocity, shortened swing time, and increased step width (Wilson et al., 2020). However, PD-specific declines in gait speed and step length, greater variability of gait characteristics, greater step width, and shorter swing time have been documented (Marković et al., 2022; Mirelman et al., 2019; Wilson et al., 2020). In later disease stages, freezing of gait emerges and appears to affect approximately 23-50% of people with PD worldwide (Amboni et al., 2015; Zhang et al., 2021). Freezing of gait is the phenomena of “an episodic…inability to

generate effective stepping" (Giladi & Nieuwboer, 2008) during gait initiation, while walking, or turning (Schoneburg et al., 2013). People with freezing report several environmental and psychological triggers that can include turning, nearing a destination, passing through narrow spaces, navigating crowded spaces, when under stress, or when performing a concurrent task while walking (de Souza Fortaleza et al., 2017; S. R. Lord et al., 2020; Mirelman et al., 2019). Medication state can also be associated with freezing. Some people with PD have medication-induced freezing, while the majority have freezing associated with wearing off their medication (Amboni et al., 2015). Freezing has also been found to have associations with sensory system or sensory processing deficits in PD (Bohnen, Kanel, van Emde Boas, et al., 2022; Huh et al., 2016; S. R. Lord et al., 2020).

1.2.4 Non-motor Disease Impacts

In addition to the motor signs of PD, non-motor changes are also present and can impact the health and quality of life of people with PD (Amboni et al., 2015; Bloem et al., 2021; Mahajan et al., 2021; Rodriguez-Blazquez et al., 2021). Non-motor functions affected by PD can include sensory, cognitive, psychological, and autonomic changes. Anosmia, the loss of sense of smell, is common in PD and may be a prodromal symptom that can occur years prior to diagnosis (Bloem et al., 2021). There are also documented changes in the sensory systems that are important for postural control: vision, somatosensation, and vestibular function (Cui et al., 2022; José Luvizutto et al., 2020; Smith, 2018). Disease-related retinal changes have been known to affect vision in PD, and altered ocular motion function is also well-documented (Nieto-Escamez et al., 2023). Peripheral neuropathy affecting somatosensory inputs is more common in people with PD compared to their healthy peers (D. A. Paul et al., 2020). A growing body of research is demonstrating that vestibular function is impacted in PD and is associated with other

non-motor and motor symptoms (Kwon et al., 2022; Shalash et al., 2017; Smith, 2018), as will be covered in more detail later in this chapter. In addition to sensory end-organ dysfunction, changes to central processing and integration of sensory inputs have been observed in PD. Disease-related alterations in sensory integration in PD may be associated with loss of dopamine in the striatum (Cham et al., 2007) or changes to cholinergic or other non-dopaminergic pathways involved in sensory processing and integration (Bohnen, Kanel, Roytman, et al., 2022; Bohnen, Kanel, van Emde Boas, et al., 2022; Müller et al., 2013).

The pathology of PD can also contribute to cognitive and psychological changes. Cognitive changes have long been known to occur in PD, typically worsening with disease progression (Bloem et al., 2021). Impaired cognition is associated with an increased risk of falls in the aging population (Bayot et al., 2018) and in people with PD (Lindholm et al., 2021; Pelicioni et al., 2019). This may be due to cognitive impairment interfering with safe mobility, such as dual-tasking while walking (Kelly et al., 2012; Raffegeau et al., 2019). Psychological complaints are also common in people with PD, including increased risk for depression, anxiety, and psychosis (Bloem et al., 2021; Rodriguez-Blazquez et al., 2021).

Finally, autonomic dysfunction is also common in PD, causing a wide range of symptoms (Bloem et al., 2021; Z. Chen et al., 2020; Rodriguez-Blazquez et al., 2021). Autonomic functions are largely driven by the vagal nucleus and other brainstem nuclei. Changes to autonomic function often occur in the prodromal phase of PD (Bloem et al., 2021). This is likely due to of pathology of PD affecting nonmotor brainstem centers before sufficient loss of dopaminergic neurons in the substantia nigra leads to the motor signs used for clinical diagnosis (Braak et al., 2004). Common autonomic symptoms in PD include constipation, urinary dysfunction, sexual dysfunction, increased saliva production and drooling, and orthostatic hypotension (a drop in

blood pressure with a change in position from a lower level to a higher level) (Bloem et al., 2021; Z. Chen et al., 2020).

1.2.5 Current Treatments for Parkinson Disease

Currently, there are no treatments that can reverse or halt the pathology of PD. Instead, treatment for PD focuses on symptom management and slowing of functional declines through medication, surgical interventions, physical rehabilitation, and exercise (Armstrong & Okun, 2020; Bloem et al., 2021; Samii et al., 2004). The most common medications for PD act to increase dopamine levels in the brain (Armstrong & Okun, 2020). These dopaminergic medications are typically effective at reducing the cardinal motor signs of PD - tremor, rigidity, and bradykinesia - but do not fully ameliorate balance and gait dysfunction (Samii et al., 2004; Smulders et al., 2016; Workman & Thrasher, 2019). This may be due to non-dopaminergic involvement in PD affecting pathways involved in gait and postural control (Bohnen, Kanel, Roytman, et al., 2022; R. Morris, Martini, et al., 2019; Müller et al., 2013; Roytman et al., 2023). Recognition of potential non-dopaminergic involvement in PD has led to an expansion in medications to manage cognitive, autonomic, and psychological symptoms in PD (Bloem et al., 2021).

Surgical interventions for PD symptoms include deep brain stimulation and selective lesioning. Deep brain stimulation requires the placement of electrodes in the brain within or near areas of the basal ganglia and uses electrical stimulation to regulate neuronal activity (Bloem et al., 2021). Selective lesioning of the thalamus is typically used to reduce tremor, and deep brain stimulation can be effective for symptoms that also respond to dopaminergic medications (Armstrong & Okun, 2020). While deep brain stimulation may improve motor and non-motor

changes in PD, it also does not fully ameliorate PD symptoms (Armstrong & Okun, 2020; Bloem et al., 2021). Furthermore, the risks associated with intracranial neurosurgery mean that not all people with PD may be willing or eligible to undergo lesioning or deep brain stimulation procedures.

Exercise and physical rehabilitation can reduce the functional impacts of PD and may even slow disease progression (King et al., 2020; LaHue et al., 2016; Petzinger et al., 2013; Qian et al., 2023; Schenkman et al., 2018). Physical activity levels have been identified as a modifiable risk factor for the development of PD (Shih et al., 2016), and participation in moderate to high-intensity exercise appears to reduce the progression of motor symptoms in PD (Landers et al., 2019a; Schenkman et al., 2018). While the mechanism for the protective effects of exercise in PD is not clear, it likely is due to the apparent increase of neuroprotective factors with aerobic exercise (Landers et al., 2019b; O'Callaghan et al., 2020). Rehabilitation approaches to PD includes targeted physical therapy to address impairments of strength, flexibility, balance, and gait (Bloem et al., 2021; Osborne et al., 2022).

Overall, treatment for PD targets the signs and symptoms of the disease, but current interventions are unable to modify the pathology of PD. Typically, various combinations of pharmacological, surgical, exercise, and rehabilitation treatments are used to address the unique needs of each person with PD (Bloem et al., 2021; Samii et al., 2004). However, even combination treatments are unable to ameliorate all motor and non-motor PD symptoms in many people with PD.

In summary, PD is a clinical syndrome believed to be due to a spreading neuropathology of dopaminergic and non-dopaminergic pathways, characterized by the cardinal signs of tremor, rigidity, and bradykinesia (Postuma et al., 2015). Postural instability, gait impairment, and non-

motor symptoms are also common in PD, at times preceding clinical diagnosis (Bloem et al., 2021). There is evidence that disease-related motor, cognitive, and sensory impairments could all contribute to abnormal balance and gait in PD. Treatment for PD is currently unable to alter the neuropathology but instead focuses on the management of symptoms through medications, surgical interventions, exercise, and rehabilitation. Unfortunately, current treatments are unable to fully ameliorate the motor and non-motor symptoms in PD. Poor recognition of vestibular dysfunction in people with PD may also lead to these impairments going untreated (Berliner et al., 2020; Smith, 2018).

1.3 The Vestibular System

The overall role of the vestibular system is to sense head motion through the detection of angular and linear head acceleration. Vestibular responses to acceleration are integral to gaze stability for image clarity on the fovea and contribute to postural control. The vestibular system also appears to contribute to spatial memory and various autonomic functions (Bogle et al., 2022; Guidetti et al., 2020; Smith, 2017). To better understand how the vestibular system may be impacted in PD, it is necessary to first have a basic knowledge of vestibular anatomy, physiology, and techniques used for quantification of vestibular function.

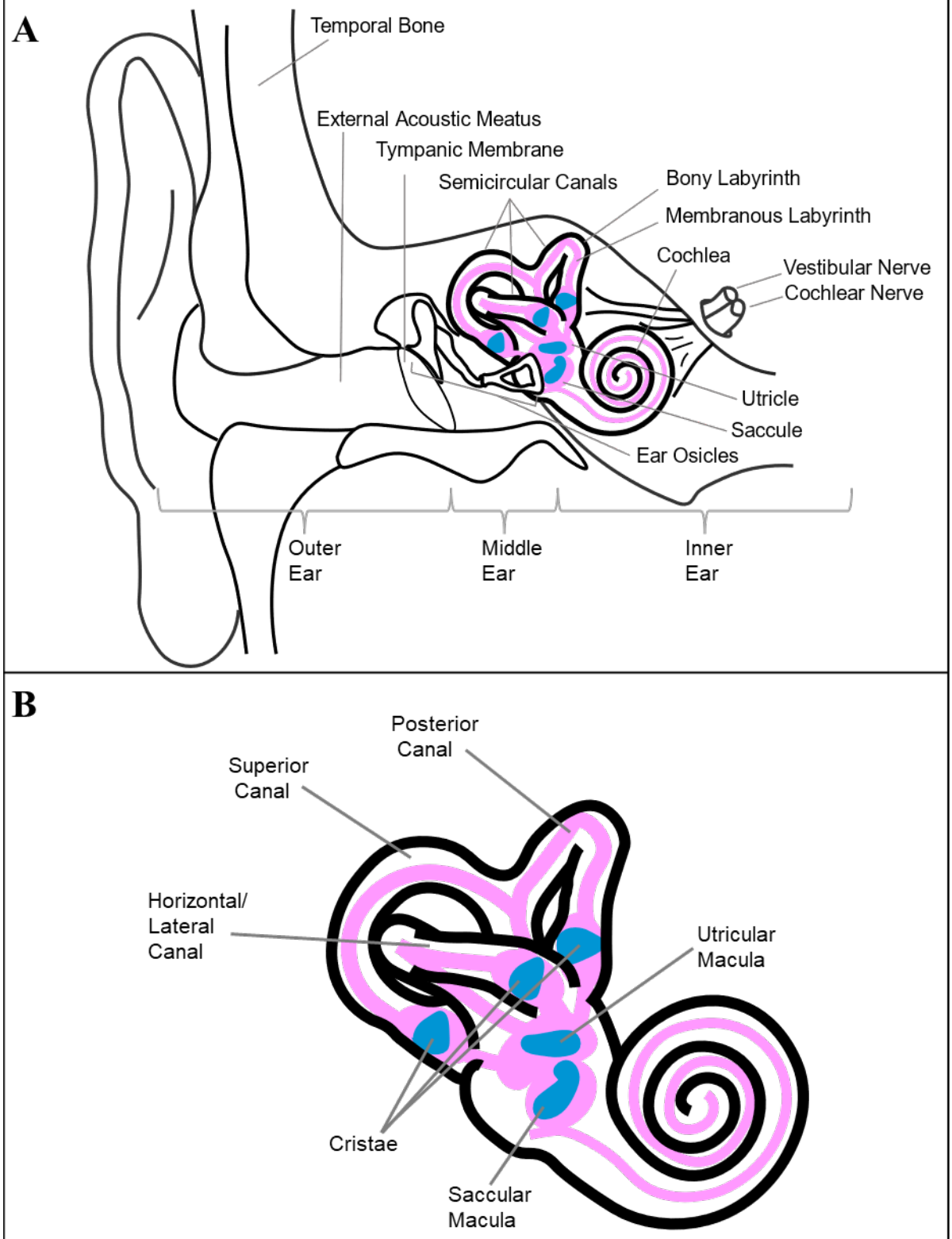
1.3.3 The Peripheral Vestibular System

The vestibular labyrinth is part of the inner ear, located in the temporal bone of the skull. As shown in **Figure 1.1**, the labyrinth includes the cochlea, which is the hearing organ, the vestibule, and three orthogonally oriented semicircular canals (SCCs). The SCCs are named for their anatomical positions: superior, posterior, and horizontal (or lateral). Within the bony

labyrinth is the membranous labyrinth, surrounded by perilymph and filled with endolymph. Together the vestibule and SCCs compose the vestibular labyrinth.

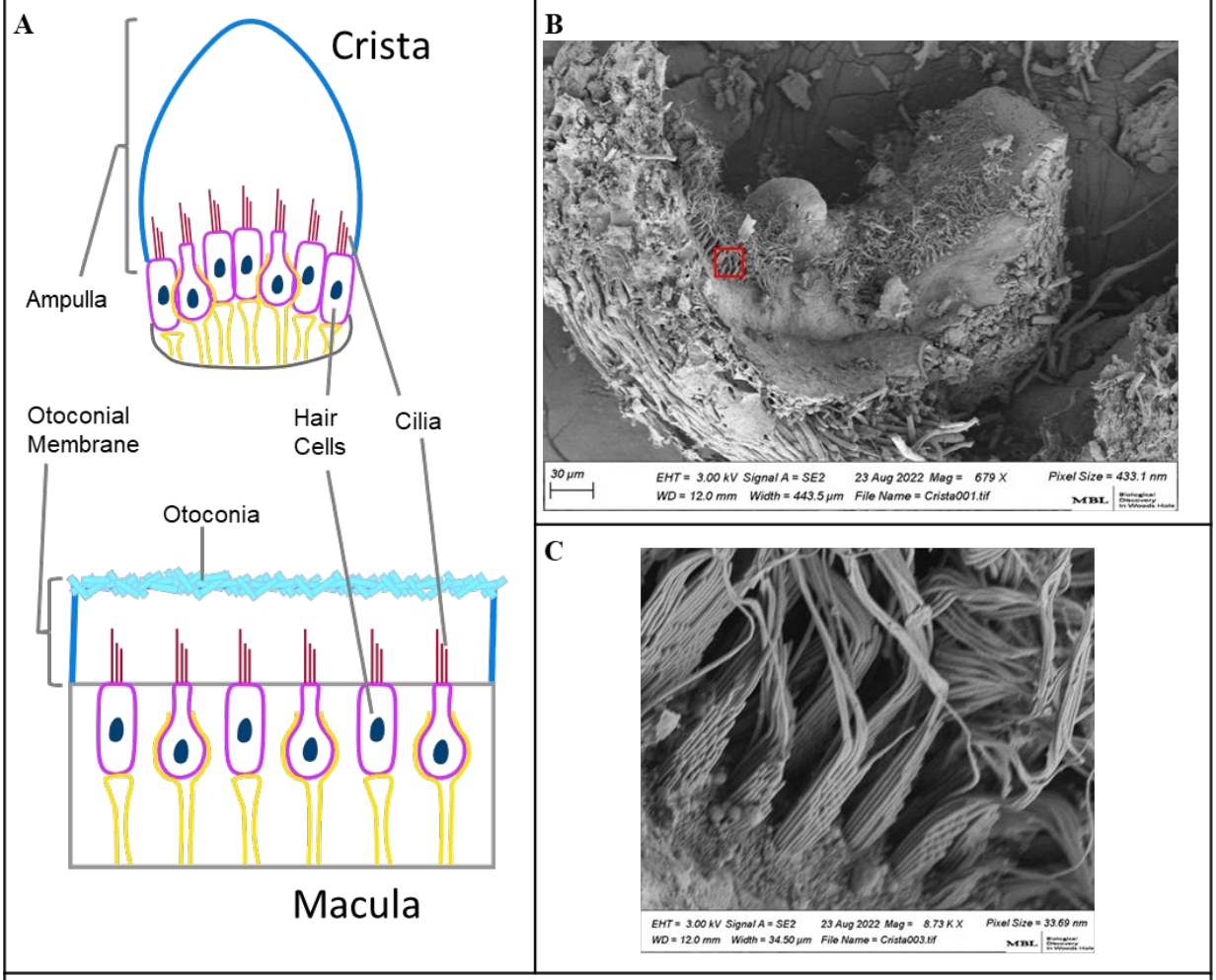
In mammals, there are two different types of sensory end-organs composed of patches of hair cells within the vestibular labyrinth (Goldberg et al., 2012). As shown in **Figure 1.1**, these sensory organs include two otolithic maculae in the vestibule and the cristae at the end of each SCC. The otolithic maculae are oriented at roughly 90 degrees to each other in the horizontal (utricle) and parasagittal (saccule) planes. Sensory hair cells in the end organs have stepped stereocilia and a longer kinocilium that are covered by a gelatinous membrane, as shown in **Figure 1.2**. In the maculae, calcium carbonate crystals called otoconia, are embedded in the surface of this membrane. The mass of the otoconia allows inertial deflection of the membrane with the embedded cilia for the detection of linear acceleration, including gravity. For the cristae of the SCCs, the gel membrane is called the ampulla and extends fully across the diameter of the canal. Endolymph fluid flow during rotational acceleration distends the ampulla, deflecting the embedded cilia and detecting rotational acceleration.

Figure 1.1 Ear and peripheral vestibular anatomy



Note. A. Structures of the outer, middle, and inner ear. **B.** Structures of the vestibular labyrinth.

Figure 1.2 Structure of the vestibular end organs

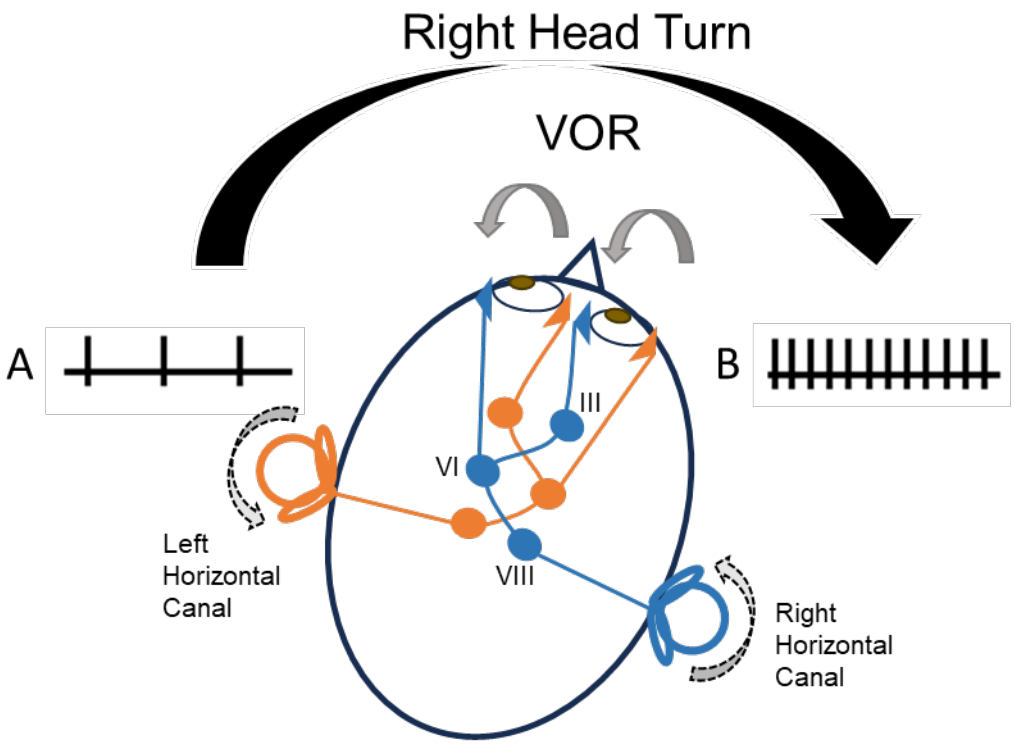


Note. A. Stylized structures of the cristae and macula. **B.** Electron microscopy image of a mouse crista without gel membrane at 679 times magnification. **C.** Area in B denoted by the red box at 8.73 K times magnification showing the cilia of vestibular hair cells. Images acquired by Amanda Ciani-Berlingeri and used with permission.

Physiologically, signaling from vestibular hair cells depends on the baseline firing rate of their associated afferent neurons and left-right pairing of the end organs. This baseline firing rate allows for a wider range of acceleration detection due to the ability to excite (increase) and inhibit (decrease) the firing rate. The SCCs are oriented in the ears as co-planar pairs, as shown in **Figure 1.3**. The direction of angular acceleration is detected through the combination of excitation and inhibition between coplanar pairs. For example, in the horizontal SCCs head rotation (yaw) to the right will excite the right horizontal canal and inhibit the left canal (Goldberg et al., 2012; Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021). The inequality of firing rates between pairs is then interpreted centrally as movement (velocity or acceleration) to the right.

The vestibular nerve is also considered part of the peripheral vestibular system and is a portion of cranial nerve eight. It is composed of two nerves, the inferior and superior vestibular nerve, with their cell bodies in two separate vestibular ganglia (Scarpa's ganglia). Peripheral to the vestibular ganglion, it splits into the superior and inferior vestibular nerves. The superior vestibular ganglion receives input from nerves innervating the utricle and a portion of the saccule, the superior canal, and the horizontal canal. The inferior vestibular ganglion receives input from nerves innervating the bulk of the saccule and the posterior canal. Collectively, the vestibular ganglia house the cell bodies of bipolar vestibular afferent neurons, which project to the brainstem and cerebellum primarily using glutamate as their neurotransmitter. Efferent modulation also travels from cholinergic neuron cell bodies in the brainstem via the vestibular nerves to the vestibular end organs (Mathews et al., 2017).

Figure 1.3 Co-planar pairing of semicircular canals to detect head acceleration



Note. VOR, vestibulo-ocular reflex; III, oculomotor nucleus; VI, abducens nucleus; VIII, vestibular nucleus complex. **A.** Representation of decreased firing rate for left lateral canal. **B.** Representation of increased firing rate for right lateral canal. Large solid black arrow denotes a head turn to the right. Dashed arrows indicate direction of endolymph flow. Orange and blue lines represent signal pathways for a horizontal VOR. Small grey arrows represent the opposite (leftward) rotation of the eyes in response to the VOR.

1.3.2 Central Vestibular System

The central vestibular system is highly interconnected with other subcortical and cortical systems for modulation of reflexive and voluntary responses to position and movement of the head (Goldberg et al., 2012; Kirsch et al., 2016). The primary vestibular area in the brainstem is the vestibular nuclear complex (VNC). The VNC includes four functionally and morphologically distinct areas mirrored on each side of midline (Goldberg et al., 2012). In addition to

interventricular neurons that connect the VNCs, there are multiple connections to subcortical and cortical areas including to the cerebellum, ocular motor nuclei, spinal motor and proprioception tracts, autonomic nuclei in the pons, and the thalamus for relay to the basal ganglia, limbic structures, and other cortical areas (Smith, 2022). The cerebellum also receives direct afferent input from the peripheral end organs via the 8th cranial nerve. Central vestibular connections result in reflexive and voluntary motor responses, autonomic responses, and contribute to spatial memory.

Motor reflexes from the VNC have two primary functions: maintenance of eye and head position for visual clarity and upright posture. Afferent signals from the vestibular end organs to the VNC are processed in combination with visual and somatosensory inputs and bidirectional cerebellar connections to produce reflexive outputs (Goldberg et al., 2012; Jacobson, Shephard, et al., 2021). Eye position is maintained using the vestibulo-ocular reflex (VOR) causing eye motion in the opposite direction of head motion to prevent retinal slip of a visual image (Goldberg et al., 2012; Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021). In its simplest form, the VOR occurs through a three-neuron pathway from the vestibular end organ afferents to the eye muscles (vestibular ganglia neurons to VNC to brainstem ocular motion nuclei which control extraocular muscles). Maintenance of upright posture occurs through vestibulo-spinal and vestibulo-collic reflexes acting to stabilize the head, and body relative to gravity and during position changes (Goldberg et al., 2012; Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021).

Other subcortical connections to the VNC influence reflexive and autonomic responses. Cerebellar links to the VNC also regulate the VOR, velocity storage, non-vestibular eye movements, and voluntary motor control responses (Bogle, 2022; Cullen, 2019; Magnani et al.,

2021). The VNC has connections in the pons to several autonomic centers. These centers are influenced by vestibular inputs for the regulation of cardiovascular responses, sweating, nausea, and vomiting (Bogle et al., 2022).

Ascending signals from the VNC pass through the thalamus to higher cortical centers including the basal ganglia. During this transit, the thalamus likely also participates in multisensory processing for regulation of motor control, conscious awareness of position, and spatial memory (Beylergil, Gupta, et al., 2022; Indovina et al., 2020). One destination for the thalamic relay of vestibular signals is the basal ganglia. Animal models have demonstrated that peripheral vestibular stimulation results in activity in the thalamus and various areas of the striatum (Sabzevar et al., 2023; Smith, 2022; Stiles et al., 2018; Stiles & Smith, 2015). In addition to the basal ganglia, vestibular signals have been demonstrated to activate areas in the hippocampus (Smith, 2022) and insular cortex (Frank et al., 2018). Human studies have also found sensitivity to vestibular inputs in portions of the cingulate, frontal, partial, and somatosensory cortices (Frank et al., 2018). This widespread distribution of vestibular information is likely due to its integration with visual and somatosensory signals for positional and spatial awareness.

1.3.3 Vestibular Testing Techniques

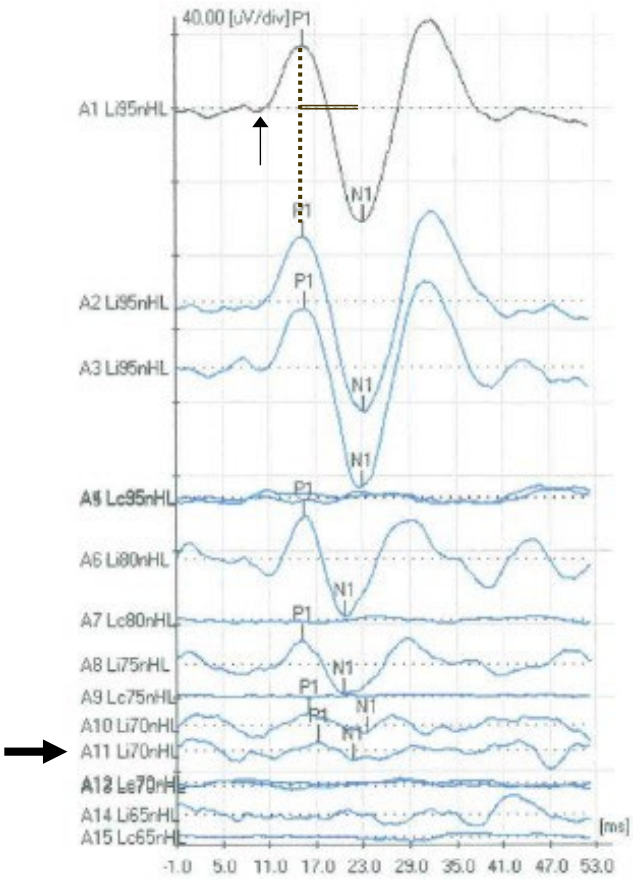
To test the integrity of the vestibular system, it is necessary to complete a comprehensive examination of peripheral and central vestibular functions (Agrawal et al., 2019; Filippopulos et al., 2022; Fracica et al., 2022). This is due to the inability to directly access the end organs within the labyrinth, and the numerous central pathways that are involved in vestibular reflexes and processing. The descriptions of tests below are categorized as assessing primarily peripheral

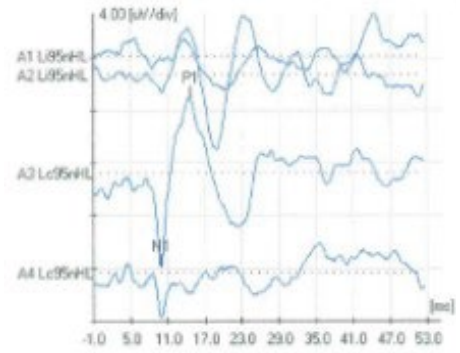
otolithic or SCC function, or central aspects of vestibular processing. If a test yields primarily peripheral function assessment with some central components, the test is listed by the peripheral organ it assesses. Detailed descriptions of vestibular examination and assessment can be found in various texts and are summarized here (Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021; Schubert, 2019).

Otolithic Function Tests

The most utilized test for otolithic function is the vestibular evoked myogenic potential (VEMP). In humans, VEMPs are performed with an air conducted auditory or bone conducted stimulus used to elicit a reflex response from the otolithic organs and responses are quantified using surface electromyography (EMG) (Taylor et al., 2020). Cervical VEMPs (cVEMPs) measure inhibition of the ipsilateral sternocleidomastoid muscle in response to primarily saccular vestibulospinal reflexes via the inferior vestibular nerve (Frank et al., 2018). Ocular VEMPs (oVEMPs) measure VOR activation of the inferior oblique for the contralateral eye primarily from the utricle and superior vestibular nerve. Auditory VEMPs typically use a tone-burst at 500 Hz, at anywhere from 85-105 decibels normal hearing level (dB nHL) which appears to have the best responsiveness (Jacobson, Shepard, et al., 2021; H. J. Park et al., 2010). Bone conducted VEMPs use a vibratory or mechanical stimulus of 100-500 Hz, typically at the midline forehead using a mechanical shaker or a specialized hammer. Both air and bone conducted VEMPs are often applied at a stimulus rate of 5 per second. Muscle response recordings are filtered and usually averaged over a sample of 100-200 accepted responses (Jacobson, Shepard, et al., 2021). Examples of VEMP tracings are shown in **Figure 1.4**, where the cVEMP shows the positive inhibitory peak (P1) followed by a negative excitatory peak (N1; **Figure 1.4 A**), and the oVEMP has the reverse pattern due to excitation (**Figure 1.4 B**).

Figure 1.4 Sample tracings of vestibular evoked myogenic potentials





Note. Stimulus volume is to the left of each tracing. **A**. Sample of cervical VEMP tracings from threshold testing. Markers are on the inhibitory P1 and excitatory N1 peaks. Tracings for cVEMPs are often inverted from this configuration when presented in the literature. Stimulus volume is to the left of each tracing. Thewide arrow indicates the response threshold at 70 dB nHL. The small arrow indicates the onset latency. The dashed line indicateds the interpeak amplitude. The double line indicates the interpeak latency **B**. Sample ocular VEMP with excitatory N1 and inhibitory P2 peaks.

Variables gathered from VEMP testing include the interpeak amplitude of the response (μV), onset latency of the first peak (ms), interpeak latency, and the response threshold to progressively decreasing intensity of the stimulus (e.g. volume of auditory stimulus, dB NHL). The interpeak amplitude represents the strength of the reflex response. However, in cVEMPs there is high intersubject variability of amplitudes due to several factors, including the level of tonic muscle contraction and electrode placement. Multiple methods can be used to reduce the effect of differences in tonic muscle activity: calculating the relative asymmetry of responses between ears, maximizing muscle contraction of the sternocleidomastoid, or biofeedback to

maintain equal levels of muscle contraction when sampling each side. The relative amplitude is calculated by taking the relative difference between ears: ((right ear amplitude – left ear amplitude/right ear amplitude + left ear amplitude) x 100). Two testing positions have been described as demonstrating effective muscle contraction, either reclined semi-supine with the head lifted and rotated contralateral to the tested ear, or supine with the head lifted at midline (Shahnaz & David, 2021). Finally, biofeedback can be utilized to provide the participant with a goal of maintaining contraction through visualization of EMG output or maintaining a pressure level by pushing their head against a blood pressure cuff (Alghadir & Anwer, 2018; Jacobson, Shepard, et al., 2021). Latency is reflective of the timing of the reflex following the stimulus, while the threshold is the point below which there is no recognizable response shown by the thick arrow in **Figure 1.4 A**. Peripherally, smaller amplitudes or higher thresholds can indicate decreased function of the otolithic organs (Taylor et al., 2020). However, a threshold that is lower than expected for age can indicate a dehiscence in the bony covering of the superior SCC (Taylor et al., 2020). Latency is reflective of nerve conduction velocity, and a prolonged latency may indicate a peripheral or central demyelinating pathology (C. Li, Zuniga, et al., 2014; Venhovens, Meulstee, & Verhagen, 2016). Bilaterally reduced amplitudes or absent VEMPs may be indicative of a central pathology, when other central signs are present (Taylor et al., 2020; Venhovens, Meulstee, & Verhagen, 2016).

There are several drawbacks to VEMP testing. First, there is no standard for electrode placement during VEMP testing, and even small inter- and intratester differences in electrode placement can affect amplitude or threshold (Shahnaz & David, 2021). Second, cVEMP testing requires adequate neck range of motion and strength for a person to hold their head and neck in a sustained position of flexion and rotation to generate optimal sternocleidomastoid contraction.

(Frank et al., 2018) Finally, oVEMPs can be difficult to record due to the small size of the inferior oblique and are less likely to be elicited as age increases (C. Li, Zuniga, et al., 2014; Shahnaz & David, 2021).

More recently, otolithic function has been clinically measured using video eye tracking to record the ocular counter roll (torsion) response to an en bloc head and body tilt (Sadeghpour et al., 2021). However, this test is only specific to the side of otolithic loss during the acute stage and appears to be abnormal with tilt in both directions once vestibular loss is chronic (Sadeghpour et al., 2021; Y. Yang et al., 2023). Some researchers have used the perception of linear acceleration with vision occluded as a measure of otolithic function (Agrawal et al., 2013). This test could be reflective of end organ function, but also relies on central vestibular processing for perception of movement. It also requires large, expensive equipment and dedicated space to perform the testing.

Semicircular Canal Function Tests

The bulk of available vestibular testing assesses the function of the SCCs across a range of stimulus frequencies. These include video head impulse testing (vHIT), bithermal caloric irrigation (calorics), head shake test, positioning tests, static positional testing, and many aspects of rotational chair testing (Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021). The ease of obtaining motion in canal plane for the horizontal canals has led to most canal function tests interrogating only this function. The exception to this is the vHIT, which has the potential to measure superior and posterior canal function at high frequencies. The vHIT assesses VOR function for gaze stability through passive, small, high velocity (200-400°/s), rapid acceleration head rotations, or “impulses” in the planes of canal pairs while maintaining gaze at a fixed target (L. Chen & Halmagyi, 2020; Jacobson, Shepard, et al., 2021). Because the rotations are

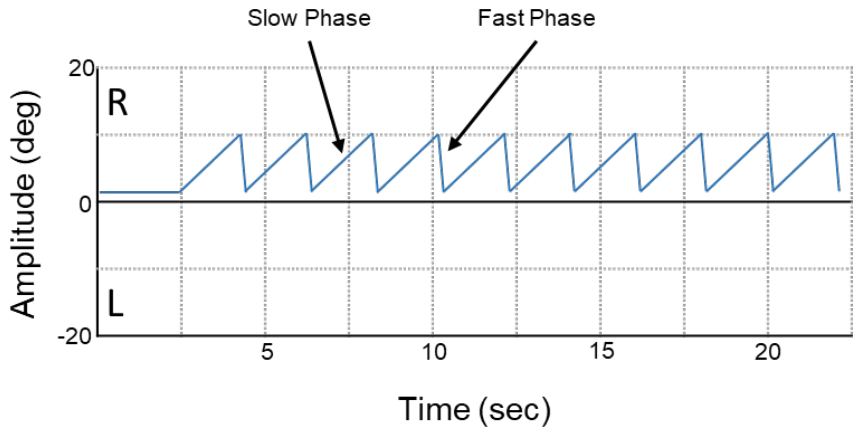
performed head on neck and are small, in addition to yaw rotation, rotations can also be performed in the planes of superior-posterior canal pairs. A head mounted system with an eye tracking camera and accelerometer is used to calculate the VOR gain. In vHIT the gain may be calculated by comparing the area under the curve for head velocity over time to eye velocity over time (Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021). The resultant calculation for gain with normal vestibular function using vHIT should be near 1.0, indicating equal and opposite reflexive eye motion in response to the head impulse. Other variables gathered during vHIT include the presence of small, high velocity eye movements called saccades during or after the head rotation. Saccades could occur following the impulse, typically indicating a dysfunctional VOR, or during head motion, indicating peripheral loss of VOR function and central compensation.

While central disruptions to ocular motion or the VOR pathway can impact vHIT testing, it is generally considered a peripheral-only assessment (Jacobson, Shepard, et al., 2021). The ability to measure superior and posterior canal function and equipment portability is an advantage of the vHIT, but it has several drawbacks. The test requires passive head movement by the examiner, which can be difficult to achieve if the patient or participant does not have adequate range of motion in the cervical spine, is unable to adequately relax their neck muscles, or has increased tone of neck musculature (Woo et al., 2024). The impulses themselves require practice to achieve the correct size and velocity of rotation with a rapid stop without a rebound. This is more difficult to achieve while maintaining the superior-posterior canal planes, due to the need for a pitch (flexion/extension) motion that is performed while maintaining 30-40° head rotation away from the target.

Bithermal caloric irrigation is considered a "gold standard" for peripheral vestibular testing (Halmagyi & Curthoys, 1988; Herdman & Clendaniel, 2014). Caloric testing assesses the function of each horizontal canal independently with a low frequency stimulus. This is achieved through warm and cool stimulus (water or air) irrigation in each ear canal to cause a temperature gradient across the temporal bone and thus the horizontal canal. The temperature gradient causes flow of the endolymph with deflection of the cupula, eliciting a VOR response (Halmagyi & Curthoys, 1988). With the ability for visual fixation removed, the VOR response causes nystagmus: a repeated rotation of the eyes away from the perceived direction of head motion due to the VOR followed by a rapid resetting return toward center (Eggers et al., 2019). As shown in **Figure 1.5**, the VOR response portion of nystagmus is termed the slow phase, with the rapid resetting motion termed the fast phase of nystagmus. The VOR is assessed by measuring the velocity (deg/s) of the slow phase using videonystagmography (VNG) with eye tracking software and specialized goggles that contain high speed infrared cameras (Ganança et al., 2009). Several variables can be collected during caloric testing including asymmetry of response between ears, the summed peak slow phase velocities, and directional preponderance (Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021)]. Asymmetry is calculated using the responses to each irrigation using Jongkee's Formula ((right warm + right cold – left warm – left cold)/ (right warm + right cold + left warm + left cold)) X 100) and is used to determine if there is a peripheral unilateral weakness (Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021). Summed peak slow phase velocities (PSPV) is the sum of peak velocities for all four irrigations and represents the overall horizontal canal response to all four irrigations. The summed PSPV is important if there is a bilaterally reduced response that is not significantly asymmetrical. Directional preponderance is a measure of if there is a stronger nystagmus in one direction,

rather than for one ear. Directional preponderance is calculated by comparing the PSPV of right beating to left beating nystagmus: ((right warm + left cold – left warm – right cold)/ (right warm + left cold + left warm + right cold)) X 100) (Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021). A directional preponderance could be caused by either an acute peripheral dysfunction or central involvement (Jacobson, Shepard, et al., 2021). Cutoff values for normal responses are typically provided with VNG software. However, due to differences in equipment and administration techniques, it is recommended that each testing location develop its own normative data.

Figure 1.5 Graphical representation of a VNG tracing of nystagmus



Note. VNG, videonystagmography. The slow phase of nystagmus is the eye rotation in the opposite direction of perceived head rotation as a result of the vestibulo-ocular reflex. The fast phase of nystagmus is the "reset" of the eye toward primary gaze position.

Positioning testing was developed to assess for vestibular dysfunction in any of the canals due to benign paroxysmal positional vertigo – a disorder caused by free floating otoconia traveling into the canals excessively stimulating the cupula during normal head movements (Bhattacharyya et al., 2008). This is tested by moving the patient or participant's head within

canal planes and monitoring immediately after the maneuver for a nystagmus response. The most common positioning tests include the Dix-Hallpike test (Dix & Hallpike, 1952) for posterior and anterior canal involvement and the supine roll test (Mcclure & London, 1985) for horizontal canal involvement. The average slow phase velocity of any nystagmus can be measured using VNG and is determined to be significant based on published or locally derived cutoff scores. Latency, duration, and direction of nystagmus assist the differential diagnosis of benign paroxysmal positional vertigo or suspicion of other central or peripheral vestibular dysfunction (Bhattacharyya et al., 2017). Static positional testing is often combined with positioning testing to record the presence, velocity, and direction of spontaneous nystagmus while in various static positions. When the head is statically positioned, nystagmus can indicate an acute unilateral peripheral dysfunction or central vestibular system dysfunction. Duration, direction, waveform, and velocity of nystagmus contribute to differential diagnosis (Eggers et al., 2019; Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021).

Central Vestibular Tests

When peripheral vestibular testing is normal or ambiguous there are additional tests that can provide information on central vestibular functioning such as tests of subjective visual vertical (SVV), dynamic visual acuity, sensory organization for postural control, and visual suppression or enhancement of the VOR (Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021). Enhancement and suppression testing will be described in the section on rotational chair testing later in this chapter. Subjective visual vertical testing measures the ability to use vestibular graviception in the absence of visual references to determine verticality (Friedmann, 1970). The SVV test is performed in a fully darkened room. A light bar is presented at various angles off from vertical, and the individual then remotely adjusts the light bar to their perceived

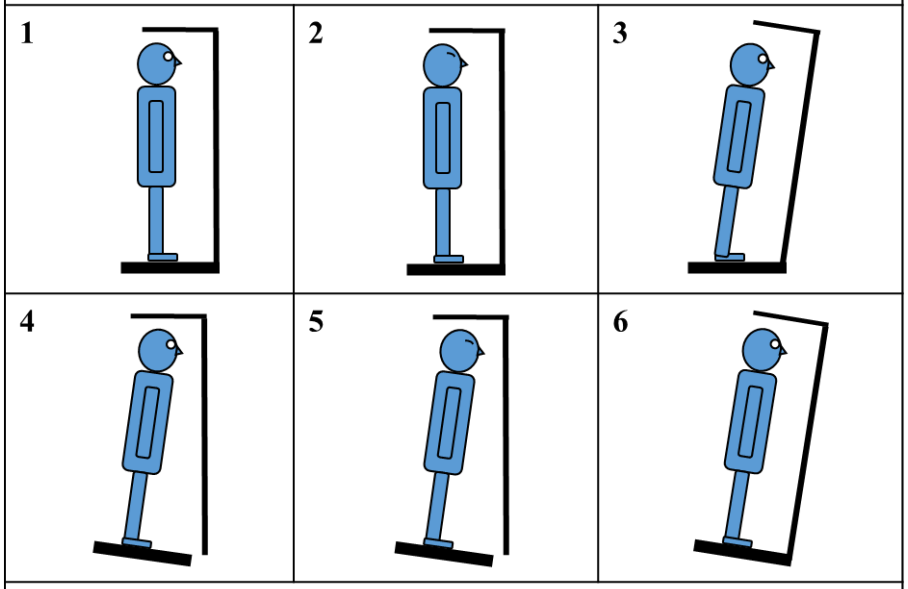
vertical. Accuracy of verticality perception is quantified as the mean degrees of deviation from gravitational vertical. Subjective visual horizontal can be assessed similarly but is not used as frequently. Acute peripheral otolithic loss may cause abnormal SVV; however, when otolithic function is normal SVV may be altered due to disruption in subcortical or cortical vestibular processing through acute or degenerative lesions (Friedmann, 1970; Gandor et al., 2016).

Like SVV, dynamic visual acuity (DVA) can give insight into central vestibular processing function if peripheral testing is normal. The DVA test assesses the effectiveness of the VOR in maintaining visual stability during active or passive head rotations by taking the difference of visual acuity during head shaking from when the head is static (C. Li, Beaumont, et al., 2014). Head shakes must be performed with an amplitude of no more than 20 degrees total arc at a frequency of 2 Hz to ensure optimal conditions to elicit a VOR. Visual acuity is measured as logarithmic Minimum Angle of Resolution (logMAR). A score of 0 logMAR indicates standard visual acuity, with better visual acuity represented as positive values, and worse visual acuity as negative values (Bailey & Lovie, 1976). Computerized DVA can be used to ensure that the visual stimulus is only presented when head velocity is adequate to require VOR to maintain stable gaze. The computerized system is also able to assess reaction time, which may affect results if central deficits are present. A drawback to DVA testing is the need for adequate non-painful neck rotation, overall visual acuity, and attention to complete the task.

The Sensory Organization Test (SOT) measures central sensory integration through postural responses when the ability to use visual and somatosensory cues is altered (Pedalini et al., 2009). **Figure 1.6** illustrates how a mobile force plate and visual surround are used to manipulate the sensory strategies available to an individual for maintaining postural control. There are a total of six conditions in the SOT during which visual input is manipulated by

allowing vision, closing the eyes, or tilting the visual surround in reference to postural sway. For each of these visual conditions, there is first a fixed force plate (conditions 1-3) allowing effective use of somatosensory responses, then the force plate tilts in reference to the individual's anterior-posterior sway (conditions 4-6). Changes to the center of pressure due to postural sway are quantified with the force plate and in combination with shear used to derive angles of sway to calculate an equilibrium score for each condition (Grove et al., 2021). The equilibrium score is a ratio of the maximum excursion of sway angles over the assumed angular limits of anterior-posterior stability. Equilibrium scores are then used to calculate a weighted composite score and sensory ratio scores, which are compared to age normative values (Pedalini et al., 2009; Pletcher et al., 2017). The Composite score provides a general quantification of balance performance. However, the sensory ratio scores represent performance patterns across the conditions and can be useful to differentiate types of sensorimotor impairments. The conditions most sensitive to detecting vestibular dysfunction are conditions 5 and 6 which alter somatosensory and visual input (Pedalini et al., 2009). However, in isolation, the SOT is unable to differentiate between peripheral and central vestibular dysfunction and should be combined with other peripheral and central integrity measures.

Figure 1.6 The Sensory Organization Test



Note. 1. Eyes open, fixed platform and surround. **2.** Eyes closed, fixed platform. **3.** Eyes open, fixed platform, sway-referenced surround. **4.** Eyes open, sway referenced platform, fixed surround. **5.** Eyes closed, sway referenced platform. **6.** Eyes open, sway referenced platform and surround.

Computerized dynamic posturography protocols often combine the SOT with testing for motor control and adaptation. Motor control testing assesses the muscle afferent stretch-based postural reflexes mediated through the brainstem, cerebellum, and basal ganglia using translational perturbations of the force platform (Jacobson, Shepard, et al., 2021; Nashner & Peters, 1990). Motor adaptation testing examines proactive postural control in responses to predictable and identical toes up/toes down perturbations of the platform. Adaptation testing is performed following motor control testing and assesses a person's ability to adapt postural corrective response through cortical and subcortical processing (Jacobson, Shepard, et al., 2021). Latency of responses for motor control and adaptation testing are based on the torque of the feet on the platform. The strength of the response is also measured for each leg, as is the amplitude scaling of responses relative to the displacement of the platform (Nashner & Peters, 1990).

Rotational Chair Testing of Peripheral and Central Vestibular Function

Rotational chair testing measures peripheral and central vestibular function through a variety of test conditions. Seated rotation is used to elicit nystagmus and measured with VNG to quantify the VOR. Typically, yaw rotations are used with an earth vertical axis that is centered between the vestibular organs to stimulate the horizontal canals (Arriaga et al., 2005; Baloh et al., 1979). Unilateral centrifugation centered on the untested utricle or tilted rotations (off vertical axis) are possible to stimulate the otolithic organs or vertical canals, respectively (Janky & Shepard, 2010; Wetzig et al., 1990). However, these are not used often due to the nauseating effects of the stimulus (Janky & Shepard, 2010). The most common rotational tests are sinusoidal acceleration, where the direction of rotations is reversed when peak amplitude is obtained, and step acceleration, where there is a sudden acceleration to a constant velocity, followed by sudden deceleration and an interval of static (i.e. 0 velocity) position (Arriaga et al., 2005; Baloh et al., 1979). When completed in darkness, rotations elicit a VOR driven nystagmus. Visual enhancement of the VOR by the visual-ocular reflex can be assessed by the presentation of earth-fixed visual stimuli during sinusoidal rotations. Visual suppression of the VOR is assessed by having the participant visually fixate on a target that moves in tandem with the chair (Jacobson, Shepard, et al., 2021).

During rotational chair testing, peripheral vestibular integrity is quantified by the gain of the VOR during sinusoidal and step testing in darkness, and the symmetry of response between rightward and leftward rotations (Arriaga et al., 2005; Baloh et al., 1979). Gain of the VOR during sinusoidal testing is calculated by fitting the slow phase velocities to a sinusoidal waveform and comparing this to the velocity waveform of the sinusoidal chair rotations (Jacobson, Shepard, et al., 2021). The pattern of gain reduction in context with the lead or lag of

the VOR in relation to chair accelerations (phase) can help differentiate between a peripheral and central vestibular dysfunction. Central involvement is implicated by abnormalities in suppression and enhancement of the VOR, which typically indicate dysfunction of the cerebellum or other central areas involved in smooth pursuit, saccadic, or visual-vestibular integration pathways (Jacobson, Shepard, et al., 2021). In step testing, slow phase eye velocity is fit with an exponential. The time it takes for the eye velocity to reduce to 37% of its peak slow phase velocity response following the onset or offset of rotations is the time constant. Prolonged time constants typically indicate dysfunctional inhibition of velocity storage. Shortened time constants with normal gain indicate dysfunctional velocity storage. Shortened time constants accompanied by low gain can indicate decreased SCC responses (Arriaga et al., 2005). Asymmetry of step testing gain can be used to calculate unilateral weakness with a formula similar to caloric irrigation.

Oculomotor testing

Oculomotor testing should be completed with vestibular testing because non-vestibular eye motion abnormalities can cause dizziness, interfere with the production of nystagmus by the VOR, or indicate involvement of central structures near to or sharing vestibular pathways (Filippopulos et al., 2022). Testing visually elicited eye movements for gaze stability, smooth pursuit, saccades, and optokinetic nystagmus (OKN) provides context for the interpretation of vestibular generated eye movements. Gaze stability testing uses VNG to measure any abnormal eye motions that occur during visual fixation and when fixation is removed. A jerk nystagmus with fast and slow phases with a fixed direction and velocity is typically indicative of a unilateral peripheral lesion. Pendular nystagmus with only slow phases, nystagmus that changes direction with gaze and does not follow a canal pattern (e.g. rightward gaze causing horizontal nystagmus

to become vertical), or static head position indicates central involvement (e.g. downward beating nystagmus during supine with the head turned to the right) (Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021). Square wave jerks are non-nystagmus, saccadic movements away from and returning to the point of gaze, and are an indication of central dysfunction of saccadic gating by the cerebellum (Barmack, 2003). Smooth pursuit and saccade testing are performed using VNG with the head still and the participant seated at a known and standardized distance from the visual stimulus. The system is calibrated using fixation on horizontal and vertical targets subtending known visual angles, and then the movement amplitude in video pixels can be converted to visual angle. Smooth pursuits are low velocity eye movements generated by multiple central areas with signals synapsing in the VNC before they reach cranial nerve nuclei III and IV to drive eye movements. Diagnostically, pursuit is typically tested using sinusoidal movements of a visual target. Smooth pursuit is quantified by the gain of the eye angle relative to the target position, phase of eye movements relative to the target, and presence of saccadic intrusions or overlay of nystagmus (Jacobson, Shepard, et al., 2021). Volitional saccades are high velocity eye movements created by burst generator neurons in the brainstem to change fixation between targets (Goldberg et al., 2012). Volitional, visually guided saccades are clinically tested by presenting visual targets in unpredictable positions during VNG recording. Typical variables produced from saccadic testing include the latency of eye movement onset (ms), mean or peak velocity (deg/s) versus saccade amplitude, and accuracy of initial and final eye position relative to the target. Increased saccadic latency may indicate poor nerve conduction or excessive inhibition of burst neurons, and low velocity indicates disruption of burst generator neurons in the brainstem (Goldberg et al., 2012; Jacobson, Shepard, et al., 2021). Poor saccadic accuracy with undershooting (hypometria) or overshooting (hypermetria) of a visual target can

indicate cerebellar or basal ganglia involvement (Herdman & Clendaniel, 2014; Jacobson, Shepard, et al., 2021).

The visual-ocular reflex that generates a smooth eye movement in response to retinal slip of the visual world is tested by eliciting nystagmus using a moving full field, high contrast visual stimulus. This is called the optokinetic response (Goldberg et al., 2012; Jacobson, Shepard, et al., 2021). When measured by VNG, optokinetic nystagmus (OKN) testing provides the gain and phase of the nystagmus slow phase relative to stimulus, and asymmetry in response to stimulus direction (%) (Jacobson, Shepard, et al., 2021). Generation of slow phase eye movements for OKN requires a synapse in the VNC, and the fast phase relies on adequate function of the saccadic burst generator. Therefore, OKN testing alone is not a useful tool in localizing potential central dysfunction. Results from the above ocular motion testing provide context for vestibular test results for differential diagnosis of potential peripheral or central vestibular dysfunction. Unlike smooth pursuit testing, which is voluntary, the OKN is reflexive and therefore a more robust measure.

Clinical vestibular assessment

In clinical settings where instrumented vestibular testing is not available, observation with or without video or Frenzel goggles can be used to subjectively assess for the presence and direction of nystagmus during head impulse, head shake, positioning, and positional testing (Filippopulos et al., 2022; Strupp et al., 2020). Gaze evoked nystagmus, smooth pursuit, saccades, and optokinetic testing can also be completed as part of a bedside exam (Filippopulos et al., 2022; Strupp et al., 2020). The modified Clinical Test of Sensory Integration and Balance (mCTSIB) is a clinical adaptation of the SOT measuring time without loss of balance using only four conditions: eyes open or closed and standing on floor or foam (Cohen et al., 1993). The

Functional Gait Assessment (Wrisley et al., 2004; Wrisley & Kumar, 2010) is a subjectively rated ten-item walking balance test designed and validated for use in populations with vestibular disorders including cutoff scores indicating increased fall risk (Eldeeb & Abdelraheem, 2021; Wrisley & Kumar, 2010). The impacts of vestibular disorders can be reported using the Dizziness Handicap Inventory (DHI) (Jacobson & Newman, 1990). The DHI is a 25-item questionnaire that includes questions about the physical, emotional, and functional impacts of dizziness or imbalance.

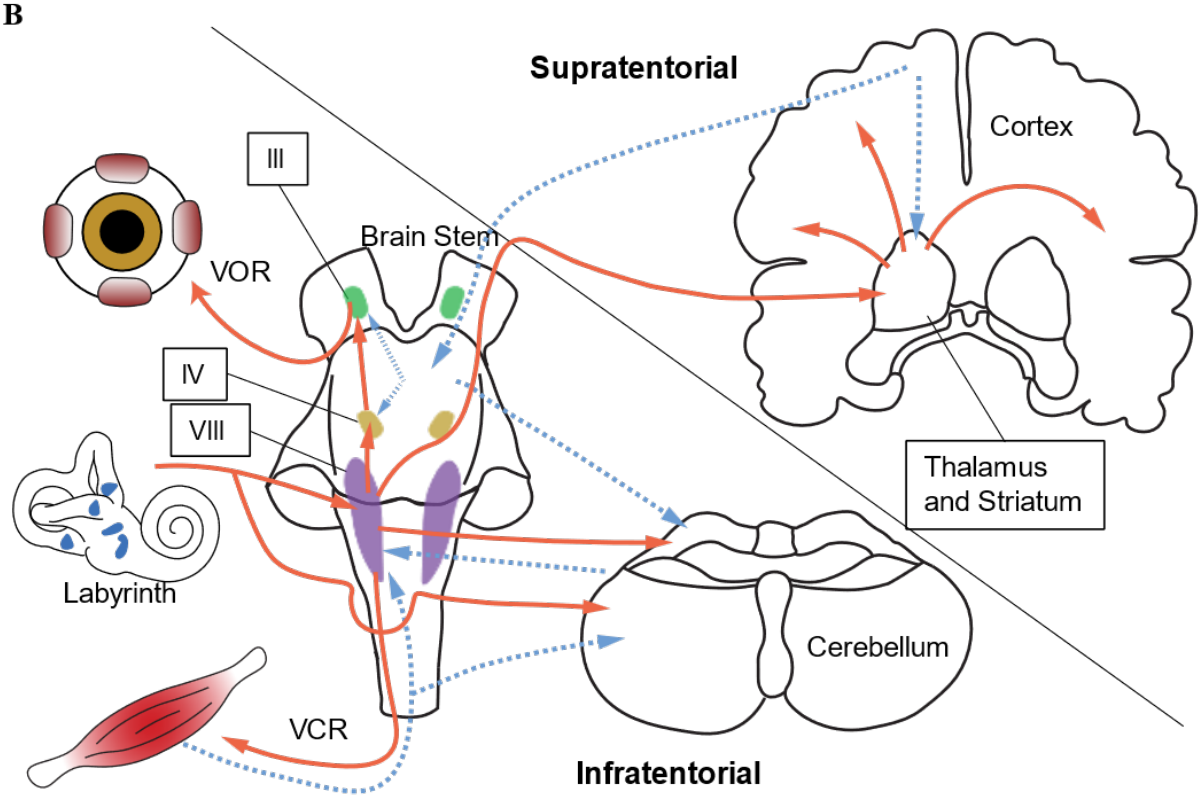
It is important in research and clinical practice to recognize that there is no single test of peripheral or central vestibular function. Instead, comprehensive vestibular testing is necessary to discern patterns of responses to a variety of stimuli that indicate dysfunction of the otolithic organs, SCCs, or vestibular nerve in the periphery, or centrally at the VNC, cerebellum, or other subcortical or cortical pathways. Ocular motion testing in combination with vestibular testing illuminates whether central or peripheral impairments in eye movement may be altering vestibular-driven nystagmus. Specific oculomotor dysfunctions may also help in localizing central dysfunctions. When instrumented vestibular testing is not available, clinical examination of many test procedures can be used to subjectively identify abnormal responses. **Figure 1.7** illustrates how the various vestibular tests described here provide information about the different peripheral and central aspects of vestibular function. Taken together, results of comprehensive vestibular and ocular motion testing can reveal a constellation of findings that may indicate disease-specific vestibular dysfunction.

Figure 1.7 Vestibular tests by function assessed and basic vestibular pathways

A

Test	Otoliths	Canals	VNC	Other Brainstem	Cerebellum	Supra-tentorial
VEMP	■		■	■		
Caloric		■	■			
VOR Suppression			■	■	■	
VOR Enhancement			■	■	■	
RCT Sinusoidal		■	■	■	■	
RCT Step		■	■	■	■	
Positioning		■	■			
Positional	■	■	■	■	■	
SVV	■		■	■	■	■
SOT	■		■	■	■	■
Motor Control				■	■	■
Adaptation				■	■	■
Gaze Stability			■	■	■	
OKN			■	■	■	■
Saccades				■	■	■
Smooth Pursuit			■	■	■	■

B



Note. A. Filled cells in the table indicate that the test in the first column provides information about function of the anatomical area listed in the first row. **B.** Simplified figure of vestibular neural pathways. Solid orange lines represent vestibular input from the periphery. Square dashed blue lines represent modulatory information. Narrow dashed lines represent saccadic generator input to the ocular muscle nuclei. III, oculomotor nucleus. IV, abducens nucleus. VII vestibular nucleus.

1.4 Current Evidence of Vestibular Involvement in Parkinson Disease

Available evidence suggests the presence of peripheral and central vestibular dysfunction in PD which may contribute to disease-related motor, cognitive, and autonomic impairments (Bloem et al., 2021; Bogle et al., 2022; Jacob et al., 2020; Smith, 2018, 2022). However, age-related vestibular deficits are common, and many studies did not include older adult control groups (Agrawal et al., 2019). In addition, the effects of dopaminergic medications taken by people with PD on vestibular function are unclear. The potential involvement of non-dopaminergic pathways in PD may also disrupt vestibular function. As a result, it is difficult to disentangle age related changes and effects of medication from vestibular changes due specifically to PD pathology.

Pathologic processes in PD may impact dopaminergic and non-dopaminergic neurotransmitter pathways important to the vestibular system. These include the VNC and vestibular ganglion, the pedunculopontine nucleus, and pre-cerebellar nuclei(Ferreira et al., 2021; Seidel et al., 2015; Wellings et al., 2017). In addition to evidence of prodromal changes in motor, cognitive, autonomic, and sensory functions (Berliner et al., 2020; Chastan et al., 2019; Mahajan et al., 2021; Schrag et al., 2020), recent evidence suggests early PD pathology in brainstem areas could also impact vestibular function (Cui et al., 2022; Smith, 2022).

Evidence for peripheral vestibular dysfunction in PD is mixed, with more evidence of otolithic than SCC dysfunction. Some studies demonstrate that people with PD have absent VEMPs - indicating lost otolithic function - more often than similar aged controls without PD (Lazzaro et al., 2018; Shalash et al., 2017; Venhovens, Meulstee, Bloem, et al., 2016). However, these findings are inconsistent in which VEMP is more affected, and most studies did not control

for medication state (Cui et al., 2022). The evidence for changes in SCC function measured by bithermal caloric responses and vHIT in people with PD is mixed (Hawkins et al., 2022; Hong et al., 2024; Lv et al., 2017; Vitale et al., 2011; Zhou et al., 2024). More recent and robust studies support a lack of association between PD status and reduced canal function (Hawkins et al., 2022; Hong et al., 2024). Abnormal calorics may be more specific to a subset of people with PD who have lateral trunk flexion (Pisa syndrome) (Huh et al., 2022; Vitale et al., 2011). However, none of these studies controlled for medication state, and in several studies, not all participants with PD were taking medication. In summary, evidence is strongest for otolithic versus SCC dysfunction in PD, but gaps remain in our understanding of disease-specific and medication-related effects on the peripheral vestibular system.

Evidence of central vestibular dysfunction in people with PD includes lack of nystagmus suppression with visual fixation and abnormal optokinetic nystagmus in response to a moving visual field (Cipparrone et al., 1988; Venhovens, Meulstee, Bloem, et al., 2016; Zhou et al., 2024). Both indicate that central integration in areas such as the VNC, cerebellum, and possibly the basal ganglia could be impaired. The Human Connectome Project has found structural connections between the VNC and the putamen in the striatum (Indovina et al., 2020). Disease-related changes in the striatum or the VNC may affect vestibular integration. Studies of vestibular sensory integration involving subcortical and cortical processing in PD have mixed results when assessing subjective verticality (Huh et al., 2022; José Luvizutto et al., 2020; Vitale et al., 2011), heading (determining the direction of externally driven motion) (Beylergil et al., 2019; Yakubovich et al., 2020), and postural control (Bohnen, Roytman, et al., 2022; Feller et al., 2019; Huh et al., 2016). However, this may be due to a lack of consistency in medication state between studies. Suppression of the VOR by the cerebellum appears to be affected in PD during

vHIT, caloric, and rotational chair testing (Cipparrone et al., 1988; Hawkins, Rey-Martinez, et al., 2021; Venhovens, Meulstee, Bloem, et al., 2016; White, Saint-Cyr, et al., 1983). Oculomotor abnormalities in PD have more robust documentation, with known changes to smooth pursuit and saccades with disease progression (Frei, 2021; Zhou et al., 2024). Changes to saccades may even be an early marker of brainstem involvement in PD (W. Ma et al., 2022).

There is growing evidence of non-dopaminergic pathway disruption in vestibular contributions to postural control in people with PD (Bohnen, Kanel, Roytman, et al., 2022; Gallea et al., 2017; Müller et al., 2013). Imaging studies have demonstrated that cholinergic deficits in the vestibular-thalamo-cortical system are associated with postural control and vestibular sensory integration dysfunction in older adults and people with PD (Bohnen, Kanel, Roytman, et al., 2022). The pedunculopontine nucleus has connections to the VNC and uses glutamatergic and cholinergic connections that play a role in movement control. Histopathological changes and decreased connectivity of the pedunculopontine nucleus have been seen in people with PD (Gallea et al., 2017; Seidel et al., 2015). Poor VOR cancellation and abnormal saccades support growing evidence of cerebellar dysfunction in PD (Cipparrone et al., 1988; Frei, 2021; Hawkins et al., 2022; Venhovens, Meulstee, Bloem, et al., 2016; White, Saint-Cyr, et al., 1983; Zhou et al., 2024). Taken together, studies of central vestibular and ocular motion function indicate that non-dopaminergic vestibular pathways may be disrupted due to PD pathology.

Evidence suggests the nonphysiologic effects of dopaminergic medication used for treating PD may not be uniformly beneficial for vestibular function. This could be due to receptivity for dopamine at peripheral end-organs, signal regulation or integration in the VNC, or non-dopaminergic pathway involvement in PD. Peripherally, there may be dopamine sensitive

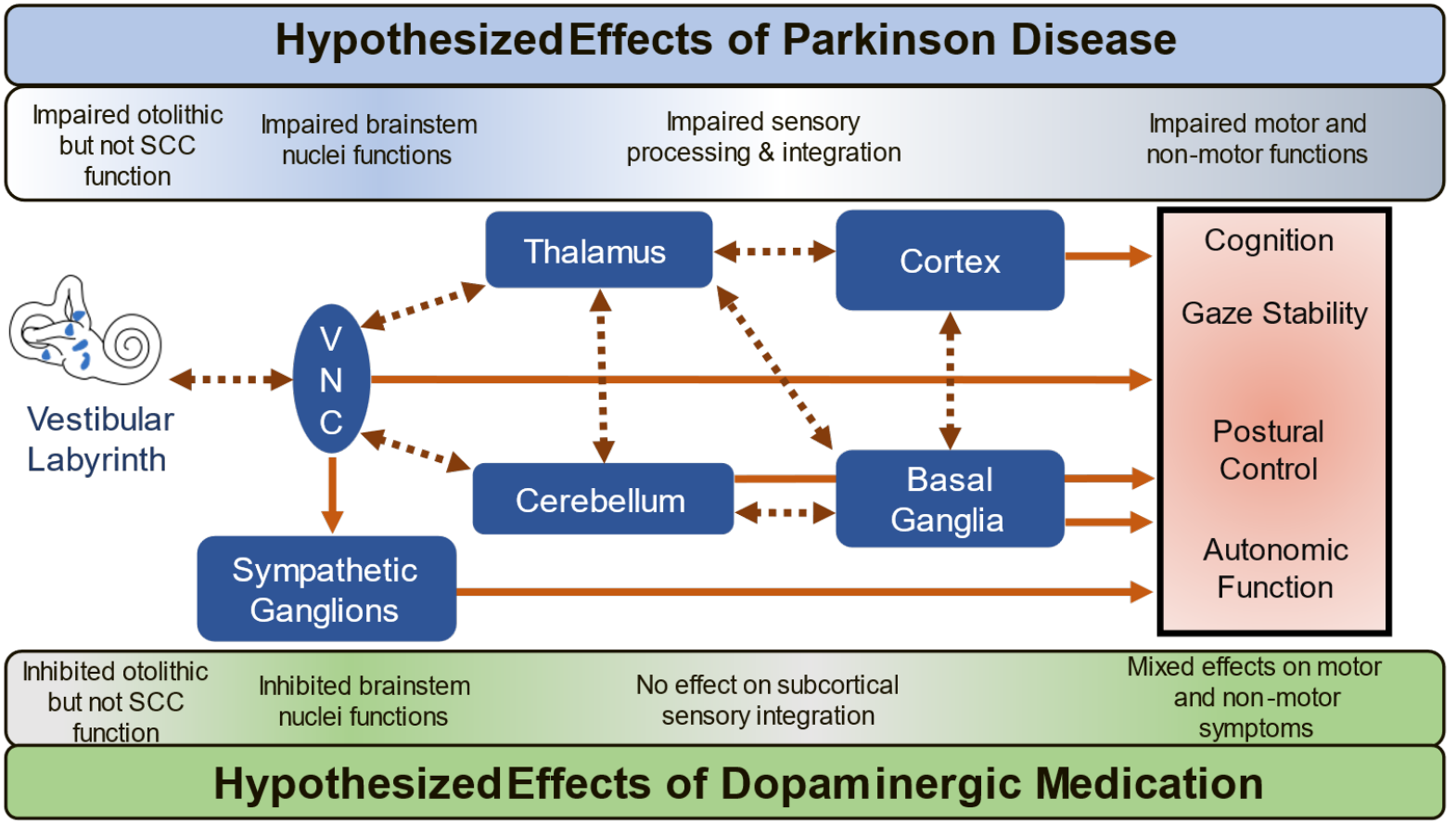
afferents or hair cells in the otolithic organs responsive to medication. Non-human mammal models suggest that dopamine is excitatory in the vestibular periphery at the otolithic organs or SCCs (Drescher et al., 2010; Meredith & Rennie, 2021). However, in people with PD, vestibular firing rates in response to motion measured by electrovestibulography decreased with dopaminergic medications (Lithgow & Shoushtarian, 2015). Evidence of dopaminergic medication effects on VEMPs indicates either increased amplitudes or no change with medication (Pötter-Nerger et al., 2012; Potter-Nerger et al., 2014), but it is unclear if the potential effects of dopamine are central or peripheral in origin. Only one study has assessed caloric function in PD while controlling for medication state and found no effect (Reichert et al., 1982). However, this was a comparison of an off-medication group who were newly diagnosed and not yet taking medications for PD, and an on-medication group who were taking prescribed medications that did not control for disease severity (Reichert et al., 1982). No studies of vHIT or rotational chair appear to have been conducted to assess possible peripheral effects of dopaminergic medications.

Centrally, dopaminergic medications may affect vestibular perception or integration in subcortical or cortical areas. Non-human animal studies suggest that dopamine could play a regulatory role at the VNC (Andrianov et al., 2009; Drescher et al., 2010). Pharmacological evidence in humans suggests that dopaminergic medications may have an inhibitory effect on the VNC (C. Lee & Jones, 2017; Soto & Vega, 2010). Dopaminergic medications are often found to increase standing postural sway and to worsen SOT Composite scores for sensory integration in people with PD (Bronte-Stewart et al., 2002; Curtze et al., 2015), though this may be due to increased dyskinesia with medication. However, in studies on verticality and heading perception

in PD, no changes were seen between on and off-medication states (Scocco et al., 2014; Yakubovich et al., 2020).

There is growing evidence from epidemiologic and intervention studies that vestibular deficits are associated with a variety of motor and non-motor symptoms that impact safety and quality of life in people with PD. The possible impacts of PD and dopaminergic medications to treat PD on peripheral and central vestibular functions are summarized in **Figure 1.8**. Motor associations with vestibular dysfunction in PD include an association between absent VEMPs or reduced caloric responses and the presence of postural abnormalities such as Pisa syndrome (Huh et al., 2022; Lazzaro et al., 2018; Tang et al., 2021; Vitale et al., 2011). Autonomic dysfunction, which may have vestibular contributions (Bogle et al., 2022), is related to falls in PD (Fanciulli et al., 2020; Romagnolo et al., 2019), and people with PD who have absent cVEMP responses are more likely to fall (Venhovens et al., 2020). Subjectively, people with PD report visual disturbance and dizziness consistent with vestibular dysfunction (Berliner et al., 2020; Mahajan et al., 2021). Finally, novel techniques to apply vestibular stimulation through caloric or galvanic stimulation appear to reduce motor and non-motor symptoms of PD in rodent models of PD and people with PD (Abasi et al., 2020; Kataoka et al., 2016; S. Lee et al., 2021; Narayanam et al., 2022; Samoudi et al., 2012; Wilkinson et al., 2019).

Figure 1.8 Hypothesized effects of Parkinson disease and dopaminergic medication on vestibular function



Note. VNC, vestibular nucleus complex. Double headed dashed arrows represent reciprocal connections between structures; solid single headed arrows represent influence on postural stability.

In summary, the potential impacts of PD and dopaminergic medications for PD on vestibular function are increasingly recognized. Advancements in vestibular testing techniques allow a comprehensive and robust assessment of vestibular function. Existing vestibular testing in people with PD has mixed results, with evidence of otolithic dysfunction, disruption of VNC-thalamic-basal ganglia loops, and abnormal sensory integration through dopaminergic or non-dopaminergic vestibulo-cerebellar and vestibulo-cortical pathways. Vestibular dysfunctions may explain some of the heterogeneity seen in PD presentation, such as abnormal peripheral function and subjective visual vertical having strong associations with Pisa syndrome. However, the bulk of existing research uses isolated vestibular tests, and most are limited by small sample sizes, lack comparisons to healthy older adults, or do not account for medication state that may affect test responses due to possible non-physiological effects of dopaminergic medications used to treat PD. Therefore, the proposed research addresses several important gaps in the existing literature. There is a need for research that utilizes a full suite of vestibular testing for contextual interpretation of results. Incorporating a comparison group of older adults without PD can allow for a clearer discrimination of age-related versus disease-related impacts on vestibular function. Finally, examining the effect of dopaminergic medication on vestibular physiological responses has the potential to inform our understanding of the role of dopaminergic and non-dopaminergic pathways in vestibular function. This research has important implications for clinical care. A better understanding of vestibular dysfunction in PD could guide clinical assessment and support individualized application of vestibular interventions, including those for gaze stability and postural control for people with PD.

1.5 Aims & Organization of This Dissertation

The overarching objective of this dissertation is to understand how disease and dopaminergic medications used to treat PD affect peripheral and central vestibular function in people with PD. Results of the research aimed at meeting this objective will be presented in three chapters. **Chapter 2** aims to characterize vestibular function in people with PD who were referred for vestibular testing compared to adults without PD using a review of comprehensive vestibular testing records. **Chapter 3** aims to determine disease-related vestibular impairments in people with PD by comparing vestibular testing of people with PD while off-medication to healthy similar-aged adults. **Chapter 4** aims to determine the effects of dopaminergic medications on central and peripheral vestibular function in people with PD through a comparison of off- and on-medication vestibular testing. **Chapter 5** discusses the results of these studies in context with the existing literature, proposes clinical implications for the findings, and suggests critical areas for future research.

CHAPTER 2: A RETROSPECTIVE REVIEW OF VESTIBULAR TESTING IN PRODROMAL AND CLINICAL PARKINSON DISEASE

2.1 Abstract

Background: Vestibular dysfunction may be present in Parkinson disease (PD), potentially developing in the prodromal disease stage, prior to a clinical diagnosis of PD. However, it is unclear if vestibular dysfunction in PD is disease-specific, due to typical aging, or both. The objective of this study was to compare vestibular functions in people diagnosed with PD and a matched control group (CG) of individuals without PD. It was hypothesized based on the existing literature that there would be a pattern of central vestibular involvement and peripheral otolithic dysfunction in PD, regardless of disease stage, and that semicircular canal function would be normal.

Methods: A retrospective review was completed of comprehensive vestibular testing records from people seen for diagnostic vestibular testing at the University of Washington Dizziness and Balance Center. Initial records were included if they had a diagnosis of PD at any time and did not have other audiovestibular or neurological diagnoses that could impact vestibular function. Records with PD were categorized based on the timing of the PD diagnosis relative to vestibular testing as prodromal (PD-prodromal) or clinical PD (PD-clinical). Age and sex matching to non-PD control records at a 1:2 ratio was then performed. Vestibular test results extracted from the records included vestibular-evoked myogenic potentials; caloric testing; dynamic positioning and static positional testing; optokinetic nystagmus testing; vestibulo-ocular reflex (VOR) enhancement and suppression; sinusoidal and step rotational chair testing; and oculomotor testing for gaze stability, smooth pursuits, and saccades; and computerized dynamic posturography including the Sensory Organization Test (SOT). The primary comparisons were

made between PD records and CG using permutation with a mixed effects model for continuous variables. Secondary comparisons of continuous variables between PD records based on PD diagnosis were compared using permutation with unpaired statistics. Fisher's exact test was used to compare categorical variables for all comparisons.

Results: Of the 7,809 available records, 40 had a diagnosis of PD and met all inclusion criteria. Following 1:2 matching, 80 CG records were used for comparison. Most notably, for the primary comparison, when all PD records were compared to CG, PD records had significantly worse VOR suppression gain (PD 0.34 (0.18); CG 0.23 (0.11; $p = 0.01$)). Significantly worse VOR suppression was also seen in comparisons of PD-clinical to CG (PD-clinical 0.40 (0.18); CG 0.25 (0.19); $p = 0.03$) and for PD-clinical (0.40 (0.18)) compared to PD-prodromal (0.23 (0.09); $p = 0.04$). Other significant findings were greater prevalence of positioning nystagmus in CG compared to combined PD ($p < 0.001$) and PD-prodromal ($p = 0.006$) records, better motor control latency for PD-prodromal compared to CG during computerized dynamic posturography ($p = 0.02$), and higher step test gains for PD-clinical compared to CG ($p = 0.04$). Finally, when comparing PD records based on diagnosis timing, PD-clinical had significantly worse OKN gain ($p = 0.04$), worse postural control SOT Composite scores ($p = 0.01$), and worse postural control SOT condition 5 equilibrium scores ($p = 0.02$) than those with prodromal-PD.

Discussion: When comparing records of people with any history of PD to matched GC records, there was no difference in otolithic function. Centrally, there was significantly reduced VOR suppression in the combined PD records compared to CG, PD-clinical compared to CG, and PD-clinical compared to PD-prodromal. All records, regardless of group had abnormal Composite scores on the SOT. However, SOT scores were only significantly different between the PD groups, where matching did not occur. Although not statistically significant, the PD-clinical

group was older than the PD-prodromal group. This age difference between PD groups where SOT differed, and the lack of difference with age-matched CG suggests that postural control declines with age. Gain for OKN was also only significantly worse in PD-clinical compared to PD-prodromal, suggesting that OKN also declines with age. Together, these findings suggest that central, but not peripheral vestibular dysfunction is affected differently in people with PD than same-aged adults, and that central vestibular dysfunction may be present in the prodromal stage of PD. These conclusions should take into consideration the fact that test records were available due to referrals for diagnostic testing, and this population may not represent typical people with PD or older adults. Comparisons in this study were limited by records having only partial vestibular testing, preventing comparison for several variables including measures of otolithic function.

Conclusions: Deficits in central vestibular function may occur even early in PD, with specific deficits in VOR suppression beyond those seen in age-matched peers without PD. Vestibular testing and appropriate existing vestibular treatments should be considered for people with PD who have symptoms of vestibular dysfunction.

2.2 Introduction

Vestibular dysfunction may be present in Parkinson disease (PD) (Smith, 2018), potentially during the prodromal disease stage, before clinical diagnosis (Mahajan et al., 2021; Schrag et al., 2019). Non-motor dysfunctions such as anosmia, sleep disorders, and depression are known to be prodromal symptoms of PD and vestibular dysfunction may also appear early, before the motor signs that are used for clinical diagnosis (Mahajan et al., 2021; Schrag et al., 2019). People with PD have complaints consistent with vestibular and oculomotor deficits (Berliner et al., 2020). Vestibular abnormalities in PD may be associated with PD-specific postural abnormalities (Tang et al., 2021; Vitale et al., 2011) and oculomotor abnormalities in PD could be a marker of disease progression (Cipparrone et al., 1988; Helmchen et al., 2012; Waldthaler et al., 2019; White, Saint-cyr, et al., 1983; Zhou et al., 2024). However, it is not clear if vestibular abnormalities seen in PD are due to disease-specific degenerative processes affecting peripheral or central vestibular function that are unrelated to normal aging.

Potential peripheral vestibular dysfunction may exist in the otolithic organs, which have been shown in animal models to be sensitive to dopamine (Meredith & Rennie, 2021; Toro et al., 2015) and dopamine receptors appear to exist in the human saccule (Eberhard et al., 2022). Dizziness in PD appears associated with dysfunction of the utricle (J. H. Park & Kang, 2021), and multiple abnormalities have been seen in the assessment of saccular function (Cui et al., 2022). However, few studies of otolithic function have performed comparisons with control groups to account for age-related vestibular declines. Semicircular canal (SCC) function is likely not affected by PD (Cicekli et al., 2019; Hawkins et al., 2022), although there is evidence that central suppression of the vestibular-ocular reflex is altered (Hawkins, Rey-Martinez, et al., 2021; Venhovens, Meulstee, Bloem, et al., 2016). There is also evidence of central vestibular

processing deficits in people with PD. People with PD appear to have abnormalities in motion perception to detect tilt and heading (Beylergil et al., 2019; Sasaki et al., 2022; Yakubovich et al., 2020), and use of vestibular inputs for standing postural control (Beylergil et al., 2021; Bohnen, Kanel, van Emde Boas, et al., 2022; Bohnen, Roytman, et al., 2022; Huh et al., 2022). However, none of these studies assessed participants for peripheral vestibular loss.

It is currently unknown if vestibular deficits found in prior research are related to neurodegeneration in PD, a result of normal age-related changes to vestibular function, or a combination of the two. Prior work has identified vestibular deficits in the general population of PD, but investigations of peripheral and central aspects of vestibular function and test procedures are inconsistent across studies (Cicekli et al., 2019; Cui et al., 2022; Smith, 2018). Few current studies included a control group of healthy age-matched adults. A comprehensive vestibular assessment including vestibular, postural control, and oculomotor measures is needed to determine if dysfunction is due to peripheral, central, or mixed vestibular impairment (Filippopulos et al., 2022; Fracica et al., 2022). A comprehensive profile of vestibular dysfunction in PD could inform physical therapy treatment for people with PD by incorporating established vestibular rehabilitation strategies with known best practices for PD treatment to improve postural control and gaze stabilization and reduce fall risk.

This retrospective study used records from comprehensive vestibular testing to compare vestibular function in people diagnosed with PD and a control group of individuals without PD. A secondary purpose was to examine vestibular function in people with PD categorized by the timing of vestibular assessment relative to PD diagnosis. It was expected that vestibular test results would show patterns of central involvement and peripheral otolithic dysfunction in PD, regardless of disease stage, and that semicircular canal function would be normal.

2.3 Methods

This retrospective analysis examined records from people seen for vestibular testing at an outpatient clinical center in a quaternary care hospital. Diagnosis and demographic searches used the Leaf cohort discovery tool (Dobbins et al., 2020). Import and export of data was managed using Research Electronic Data Capture (REDCap) (Harris et al., 2009). Vestibular records were available in a data repository with access approved by an institutional review board for research use. Access to patient data in electronic health records conformed to the ethical conduct of research on human subjects and was approved by an institutional review board.

2.3.1 Participants

Record inclusion criteria for both groups were the completion of vestibular testing, no history of neurological disorders (other than PD, for the PD group) that would affect vestibular function, oculomotor function, or postural control, and no recorded diagnosis of ototoxicity-induced loss of auditory or vestibular function. The PD group was defined by a diagnosis of idiopathic PD at any time without diagnosis of other movement disorders (e.g., supranuclear palsy, multiple system atrophy). Diagnosis of PD was verified manually in the electronic health record (EHR) using International Classification of Diseases codes and notes attached to recorded health care provider visits. If a diagnosis of PD could not be confirmed, the record was excluded. If there were multiple records of vestibular testing, the most recent test record was selected. Exclusion criteria were applied based on the timing of the exclusion diagnosis IDC-10 code appearing in the medical record. If an exclusion diagnosis that was not a degenerative disorder (e.g. stroke, brain injury) occurred following vestibular testing, and for the PD group diagnosis of PD, it was not considered exclusionary. The exception to this was diagnoses that may have

been reached due to vestibular testing (e.g. PICA stroke, brain tumor). If this diagnosis was entered in the record less than 6 months following vestibular testing the EHR was manually reviewed, and the case was included only if the diagnosis was not related to vestibular testing. For records with a history of transient ischemic attack before vestibular testing, the EHR was reviewed manually, and none appeared to have lasting effects on vestibular function so were included.

Subgroups were identified for those with PD based on the timing of PD diagnosis relative to vestibular testing: individuals diagnosed with PD one year or more after vestibular testing (PD-prodromal), and individuals with a recorded diagnosis of PD before or within one year after vestibular testing (PD-clinical). The one-year threshold was chosen based on the typical time of 1-2 years from the onset of initial motor symptoms to the clinical diagnosis of PD (Virameteekul et al., 2023). Control participants were identified from the database as those with no known PD diagnosis.

2.3.2 Data Extraction

Demographic information extracted included age at the time of vestibular testing, sex, race, and ethnicity.

Instrumented vestibular testing assessed peripheral and central vestibular function, postural control, and oculomotor functions. Assessment of peripheral function included tests of the otolithic organs (saccule and utricle) and semicircular canals. Otolithic function was assessed for saccule-generated vestibulo-spinal reflex at the ipsilateral sternocleidomastoid and utricle-generated vestibulo-ocular reflex (VOR) at the contralateral inferior oblique. Vestibular evoked myogenic potential (VEMP) testing of saccular (cervical or cVEMP) and utricular (ocular or oVEMP) reflexes used surface electromyography to measure the activity of the relevant muscles

in response to clicks or 500 Hz tone bursts in each ear. For detailed descriptions of VEMP testing, see Ch 1.3.3. Variables reflecting otolithic function were the presence or absence of cVEMP or oVEMP response for each ear at the highest stimulus volume tested (90-100 dB normal hearing level (NHL)).

Assessment of semicircular canal function included bithermal caloric irrigation, rotational chair testing (RCT), and dynamic positioning testing. The VOR response during these tests was quantified using videonystagmography (VNG) to measure the slow phase velocity of any elicited nystagmus. The combination of multiple tests allows for the assessment of canal functioning across a range of stimulus frequencies. Caloric testing is considered the gold standard for the assessment of horizontal canal function and uses a low-frequency stimulus (Halmagyi & Curthoys, 1988; Strupp et al., 2020) through cool and warm stimulus (water or air) irrigation in each ear canal. The resultant temperature change of endolymph in the horizontal canal causes fluid motion and a nystagmus response. Variables available from caloric testing included unilateral vestibular weakness (%), the directional preponderance of nystagmus (%), and the sum of peak slow phase velocities (PSPV) for all four irrigations (see Ch 1.3.3).

Rotational chair testing examined the vestibular response to low-moderate frequency stimuli. During rotational chair testing, the patient is seated in a chair and rotated while in total darkness to elicit a nystagmus response (Arriaga et al., 2005; Baloh et al., 1979). Sinusoidal accelerations were performed across a progression of frequencies to interrogate the vestibular response. Step testing assessed peripheral vestibular response and central velocity storage through sudden acceleration to a constant velocity followed by deceleration to a static position. The VOR gain is collected for both types of chair tests using separate calculations described in Ch 1.3.3. Sinusoidal testing also records the phase (deg) of the VOR response to the chair motion

and asymmetry (%) of gain for each rotational direction (see Ch 1.3.3). Sinusoidal testing gain, phase, and asymmetry were coded as normal or abnormal if there were at least two adjacent frequencies with results outside of normal ranges. Normal ranges were determined based on clinic-based normal cutoffs (unpublished data). Step testing gain and time constant were averaged across rotational directions. The asymmetry (%) of step rotation gains represented the weakness of right or left horizontal canal response based on the direction of rotation (see Ch 1.3.3 for details).

Additional assessment of canal function included positioning testing for benign paroxysmal positional vertigo and static positional testing. Positioning tests included the Dix-Hallpike and supine roll tests (Bhattacharyya et al., 2017; Dix & Hallpike, 1952; McClure & London, 1985). Positional tests for nystagmus were performed in seated upright, seated head hanging, and in supine with face-up, right, and left ear down to assess for peripheral- or central-caused positional nystagmus (Bhattacharyya et al., 2017). Positioning and positional testing results were coded as normal/abnormal based on clinical normative cutoff values for nystagmus using average slow phase velocities ≥ 6 deg/s in one position or ≥ 4 deg/s in multiple positions.

Central vestibular function was assessed through enhancement and suppression of the VOR, rotational chair step testing decay time, and computerized platform posturography, combined with oculomotor testing. Enhancement of the VOR was tested during sinusoidal chair rotations with an earth-fixed visual stimulus to determine the ability of central integration to increase the slow phase gain through the addition of the visual-ocular reflex (Arriaga et al., 2005). Suppression testing assesses the integrity of cerebellar inhibition of the VOR using a visual target that moves in tandem with the individual and is represented by overall gain. Decay time (s) during step testing assesses central velocity storage and cerebellar inhibition. The decay

time is defined as the time until the slow phase nystagmus velocity is reduced to 37% of its peak response (see Ch 1.3.3 for calculation details) and was averaged across all rotations (Arriaga et al., 2005).

Computerized dynamic posturography (CDP) was used to interrogate sensory pathways that may contribute to decreased postural control using the Sensory Organization Test (SOT) (Mirka & Black, 1990; Pedalini et al., 2009), motor control test, and adaptation test. During CDP testing the patient stands on a mobile force plate and sway is calculated through changes in center of pressure to produce an "equilibrium score" for each trial (see Ch 1.3.3 for details). The SOT uses six conditions that manipulate the ability to use visual and somatosensory input for postural control. A Composite score is calculated from all six conditions (see Ch 1.3.3), representing overall sensory integration for balance. The equilibrium score based on sway during condition 5 (eyes closed, sway-referenced platform) was used here to represent the effectiveness of vestibular function in maintaining balance. The ratios for somatosensory, visual, vestibular, and visual preference were represented as normal/abnormal based on the graphical output generated from the test system using manufacturer-provided age-related norm values. The motor control test measures the somatosensory reflex to maintain balance when perturbed by anterior-posterior translation of the force platform, represented by the average latency of motor response (ms) to medium and large translations (Harro et al., 2018). Adaptation testing uses repeated, predictable rotational translations of the force platform to assess motor learning following the motor control test and was categorized as normal/abnormal based on a reduction in the provided adaptation score between the first and last perturbation (Rossi-Izquierdo et al., 2016).

Subjective visual vertical (SVV) assesses otolithic function and central vestibular processing through the ability to determine the gravitational vertical of a light bar when deprived

of visual input (Friedmann, 1970). SVV performance is quantified as the mean error from the vertical (deg) of the final light bar position.

Oculomotor testing was performed to aid in the differential diagnosis of dizziness and assess whether oculomotor abnormalities may interfere with vestibular-generated eye movements (Filippopulos et al., 2022; Fracica et al., 2022). Eye movements were quantified using VNG for gaze stability, saccades, smooth pursuit, and optokinetic nystagmus. Gaze stability testing assesses the presence of nystagmus or other abnormal eye motions during eccentric gaze with a target. For this study, gaze stability was categorized as normal/abnormal based on the presence of at least 3 beats of nystagmus with an average slow phase velocity > 6 deg/sec. Saccades data were only available for the PD group due to changes in data provided in test printouts over time. Saccades testing assessed rapid eye movements generated in the brainstem to fixate visual targets, quantified as the accuracy of saccadic eye movements to acquire on the target without overshoot or undershoot (%), and latency (ms) of eye movement initiation. For some VNG testing, vertical saccadic measures were related to the vertical component of diagonal eye motions, not pure vertical saccades. Due to differences in stimulus paradigm over time, velocity measures were not comparable between all records and therefore were not included in the analysis. Smooth pursuit assessed the ability to visually track a low-velocity moving target at different frequencies quantified as the average gain of the eye velocity relative to the target velocity (see Ch 1.3.3). Optokinetic nystagmus (OKN) testing assessed central functions including velocity storage through a visual-ocular reflex response to a moving full field visual stimulus during static sitting. Due to differences in stimulus paradigm over time, OKN was quantified as the average gain of nystagmus responses (see Ch 1.3.3) to all available stimulus frequencies and directions (Dix, 1980).

2.3.3 Statistical methods

Statistical analyses were performed using R v 4.4.0 (R Core Team (2023)). Control matching was performed using a regression method (MatchIt package in R v4.4.0 (Ho et al., 2011)) to match for nearest age and exact sex at a 6:1 ratio. To reduce the time needed to extract data from scanned test results, inclusion criteria were then applied to the control-matched records (CG) to achieve a final 2:1 matching after the exclusion of missing test records.

Patient demographic and clinical characteristics were described using percentages or means and standard deviations (SD). Demographic and clinical characteristics were compared between CG and PD combined and for each subset using unpaired t-tests for continuous variables and Fisher's exact test for categorical variables. Significance was set at $p < 0.05$.

To determine if there were differences in the pattern of vestibular dysfunction in people with PD compared to CG, continuous variables were tested using permutation of a mixed-effects model to account for possible deviation from normality of the smaller samples available for each test and any within-group effects of the matched groupings. Fisher's Exact Test was used for categorical variables. Sub-group analyses were performed to compare PD-prodromal, and PD-clinical groups to their respectively matched CG. Due to concerns of non-normality following histogram inspection for the sub-groups, the comparison of continuous variables used permutation on unpaired statistics to detect p-values, and Fisher's Exact Test was used for categorical variables.

For a secondary analysis, the PD-clinical and PD-prodromal groups were compared to determine any differences in vestibular characteristics based on disease stage. To compare means of continuous variables, a permutation test to detect p-values was used on unpaired statistics due

to concerns of non-normality in the smaller sample size. Fisher's Exact Test was used for categorical variables.

For all analyses, significance was set at $p < 0.05$. Correction for multiple comparisons was not performed due to the exploratory nature of this study. However, with 29 variables used for comparisons, we would expect a false rejection of the null by chance alone for 1.45 tests if no effects are present. Because not all records had complete vestibular testing, if there were fewer than 10 records in either group, results were compared descriptively, but no significance test was conducted.

2.3.4 Role of Funding Source

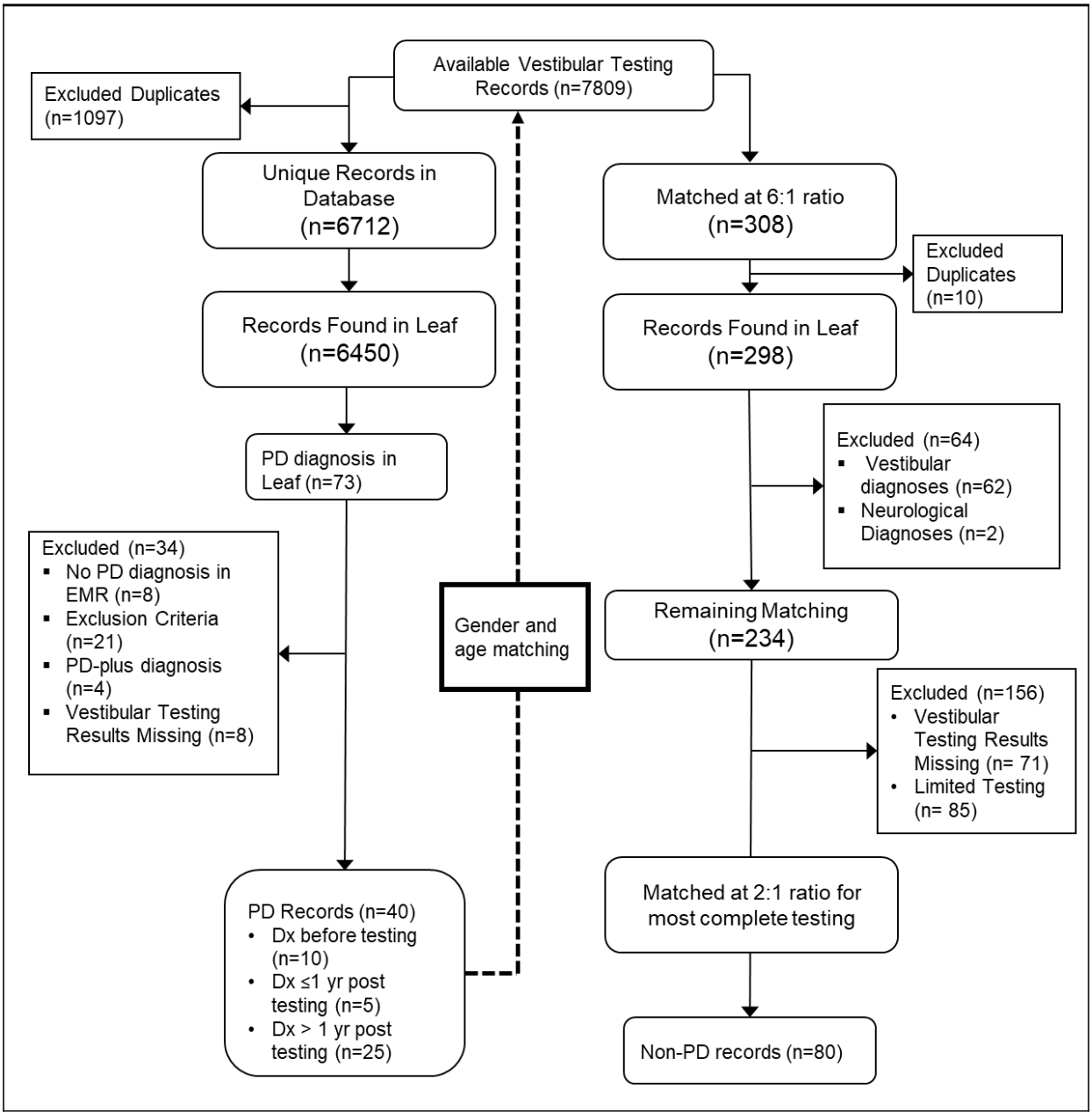
Funding for this research was provided by the Foundation for Physical Therapy Research, the University of Washington Auditory Neuroscience Training Program (NIH T32DC005361), the Walter C. and Anita C. Stolov Research Fund, and the University of Washington Retirement Association. The funders had no part in the design, conduct, or dissemination of this work.

2.4 Results

Of the 7,809 available records, 6,712 were for unique individuals (excluding duplicates due to repeated testing) and 6,450 were searchable in Leaf (**Figure 2.1**). A Leaf search identified 73 individuals with a diagnosis of PD entered in their medical records at any time. Eight individuals had a PD diagnosis in Leaf that could not be confirmed in their EHR, 25 had exclusionary diagnoses (including other parkinsonian disorders), and 8 did not have vestibular test record results available. This resulted in a final sample of 40 records divided into 25 PD-prodromal and 15 PD-clinical records. Due to added testing capacity over time, and some clinical testing limited to specific assessments based on referral, several vestibular test variables had

insufficient samples for comparison. For these variables, mean (SD) for continuous variables, or count (%) for categorical variables will be presented for descriptive purposes.

Figure 2.1 Identification and matching of Parkinson disease and control records



Demographic characteristics can be seen for each group in **Table 2.1**. The mean (SD) age for the entire PD group was 70.8 (9.7) years and for the CG was 70.7 (9.6). There were 28 (70%) females in the PD group and 54 (68%) in the CG. PD-prodromal mean age was 69.6 (10.2) years

with 17 (68%) females and PD-clinical age was 72.7 (8.7) years and 11 (73.3%) females. All groups were predominantly white and non-Hispanic.

Table 2.1 Demographic characteristics of control and PD records by group.

	Control Group	**PD-Combined**	**PD-Prodromal**	**PD-Clinical**	
Characteristic	N = 80	N = 40	N = 25	N = 15	p
Age [a]	70.7 (9.6)	70.8 (9.7)	69.6 (10.2)	72.7 (8.7)	0.3 [b]
range	50.8, 88.9	50.8, 88.6	50.8, 88.6	56.8, 85.0	
Sex (female)	54 (68%)	28 (70%)	17 (68%)	17 (68%)	>0.9 [c]
Race					0.2 [c]
Asian	5 (6.3%)	1 (2.5%)	1 (4.0%)	0 (0%)	
Black or African-American	3 (3.8%)	0 (0%)	0 (0%)	0 (0%)	
Unknown	17 (21%)	8 (20%)	3 (12%)	5 (33%)	
White	55 (69%)	31 (78%)	21 (84%)	10 (67%)	
Ethnicity					0.3 [c]
Hispanic or Latino/a	4 (5.0%)	1 (2.5%)	0 (0%)	1 (6.7%)	
Non-Hispanic or Latino/a	50 (63%)	26 (65%)	18 (72%)	8 (53%)	
Unknown	26 (33%)	13 (33%)	7 (28%)	6 (40%)	
Dx time since testing [a]	--	--	-6.5 (4.1)	1.7 (2.9)	**<0.001** [b]
range	--	--	-17.6, -1.5	-0.7, 10.0	

Note. PD, Parkinson disease. Dx time since testing is the number of years between documented diagnosis of PD and the date of vestibular testing with negative values indicating years prior to vestibular testing. Age and sex matching only occurred for the PD-combined group and control group. P-value indicates comparison of PD-prodromal and PD-clinical groups. All values indicate counts (percentages) unless otherwise noted.
[a] mean (SD)
[b] t-test
[c] Fisher's exact test
Bold indicates a p-value < 0.05.

As shown in **Table 2.2**, when the CG was compared to PD-combined using 2:1 matching, significant differences were seen in VOR suppression and positioning testing. The PD-combined group had worse VOR suppression with a gain of 0.34 (0.18), compared to the control mean gain of 0.23 (0.11) (p=0.01). A VOR suppression gain is considered abnormal if it is greater than 0.25, based on clinically established norms with high gain indicating potential dysfunction of vestibulo-cerebellar regulation of the VOR. During positioning testing, nystagmus was present

significantly less in PD cases with only 3 (8%) of PD cases having nystagmus compared to 29 (36%) of control cases ($p < 0.001$). Nystagmus on positioning testing without nystagmus on positional testing is most commonly an indicator of canalithiasis, a form of SCC dysfunction. No other significant differences were found between PD-combined and control records. In tests of otolithic function, 19% of PD records and 20% of control records had unilaterally absent cVEMPs ($p >0.9$), and 25% of PD and 36% of controls had a bilateral absence of responses ($p = 0.51$) indicating potential otolithic deficits. There were insufficient records that included oVEMP testing to make comparisons. Of the oVEMP results available neither group demonstrated unilateral absence, and bilateral absence occurred in 3 of the 5 records for both groups. In both groups, the SOT Composite score was abnormally low (PD 58 (18); CG 56 (18); $p = 0.57$) indicating poor overall postural control for balance. Condition 5 equilibrium scores were also low overall (PD 36 (27); CG 33 (27); $p= 0.61$) indicating poor balance under conditions requiring effective use of vestibular information. Subjective visual vertical was abnormal for both groups (PD 3.34 (2.55) deg; CG 3.91 (3.62) deg; $p =0.64$) indicating potential acute otolithic dysfunction or central dysfunction.

Results of a subgroup analysis of PD-prodromal and their corresponding CG records can be found in **Table 2.3**. There was insufficient sample to perform comparisons for VEMP, rotational chair step testing, VOR enhancement, VOR suppression, and SVV. For other variables, the analysis found a significant difference between the groups in the positioning testing for nystagmus and motor control test latency. During positioning testing, nystagmus was present significantly less often in PD-prodromal cases with only 2 (8.0%) of PD cases having nystagmus compared to 19 (38%) of CG cases ($p = 0.006$). Latency on the motor control test was in the normal range for both groups and was better in the PD-prodromal group, with shorter

response times (138.71 (8.43) ms), compared to CG (146 (14) ms; p = 0.02). A prolonged response time could indicate disruption of non-vestibular long-loop postural control pathways. No other significant differences were found between PD-prodromal and CG records. Qualitatively, Composite scores on the SOT were also below normal for both groups in this comparison (PD-prodromal 66 (11); CG 57 (17); p = 0.06). Condition 5 SOT equilibrium scores were also low for both groups without a significant difference (PD-prodromal 47 (24); CG 323 (27); p =0.10). Although there was insufficient data for comparison, average SVV was normal for PD-prodromal (2.69 (1.79) deg) and abnormal for CG (3.92 (2.74) deg).

Table 2.2 Comparison of vestibular test results for control and combined PD records

	Control Group		PD-Combined		
Vestibular Test	n	(N = 80)	n	(N = 40)	p
cVEMP unilateral absent [a]	25	5 (20%)	16	3 (19%)	>0.9
cVEMP bilateral absent [a]	25	9 (36%)	16	4 (25%)	0.51
cVEMP unilateral absent [a]	5	0 (0%)	5	0 (0%)	NA
oVEMP bilateral absent [a]	5	3 (60%)	5	3 (60%)	NA
Caloric unilateral weakness (%)	73	21 (20)	38	20 (19)	0.80
Caloric bilateral weakness [a]	73	4 (5%)	38	4 (11%)	0.44
Caloric directional preponderance (%)	73	13 (14)	38	13 (10)	0.99
RCT step test gain	33	0.58 (0.16)	19	0.64 (0.2)	0.26
RCT step test time constant (s)	33	11.88 (5.36)	19	10.87 (5.69)	0.51
RCT step test asymmetry (%)	33	8.26 (8.42)	19	6.06 (7.92)	0.35
RCT sinusoidal gain [a]	35	5 (14%)	22	4 (18%)	0.72
RCT sinusoidal phase [a]	28	15 (54%)	20	11 (55%)	>0.9
RCT sinusoidal asymmetry [a]	33	2 (6%)	21	0 (0%)	0.52
RCT VOR enhancement gain	28	0.93 (0.12)	16	0.94 (0.12)	0.83
RCT VOR suppression gain	27	0.23 (0.11)	16	0.34 (0.18)	**0.01**
Positioning [a]	80	29 (36%)	40	3 (8%)	**<0.001**
Positional [a]	80	8 (10%)	40	3 (8%)	0.74
Smooth pursuit gain	66	0.88 (0.20)	34	0.90 (0.13)	0.55
Optokinetic nystagmus gain	65	0.65 (0.17)	35	0.61 (0.17)	0.32
Subjective visual vertical (deg)	13	3.91 (3.62)	11	3.34 (2.55)	0.64
Gaze [a]	66	1 (2%)	34	0 (0%)	>0.9
SOT Composite	53	56 (18)	29	58 (18)	0.57
SOT Condition 5	54	33(27)	29	36 (27)	0.61
SOT somatosensory ratio [a]	53	6 (12%)	34	1 (3%)	0.41
SOT visual ratio [a]	53	25 (47%)	29	11 (38%)	0.5
SOT vestibular ratio [a]	53	36 (68 %)	29	17 (59%)	0.47
SOT visual preference ratio [a]	51	12 (24%)	28	3 (11%)	0.23
Motor control latency (ms)	53	144 (15)	29	141 (11)	0.32
Motor adaptation [a]	52	11 (21%)	29	4 (14%)	0.27

Note: c/oVEMP, cervical/ocular vestibular myogenic potential; Gaze, gaze stability testing; RCT, rotational chair test; SOT, Sensory Organization Test; VOR, vestibulo-ocular reflex.

[a] count (%) abnormal test results, Fisher's Exact Test. All values indicate counts (percentages) unless otherwise noted.

n = the number of cases with tests available for comparison on both groups.

Bold indicates a p-value < 0.05.

Table 2.3 Comparison of vestibular test results for control and prodromal PD groups

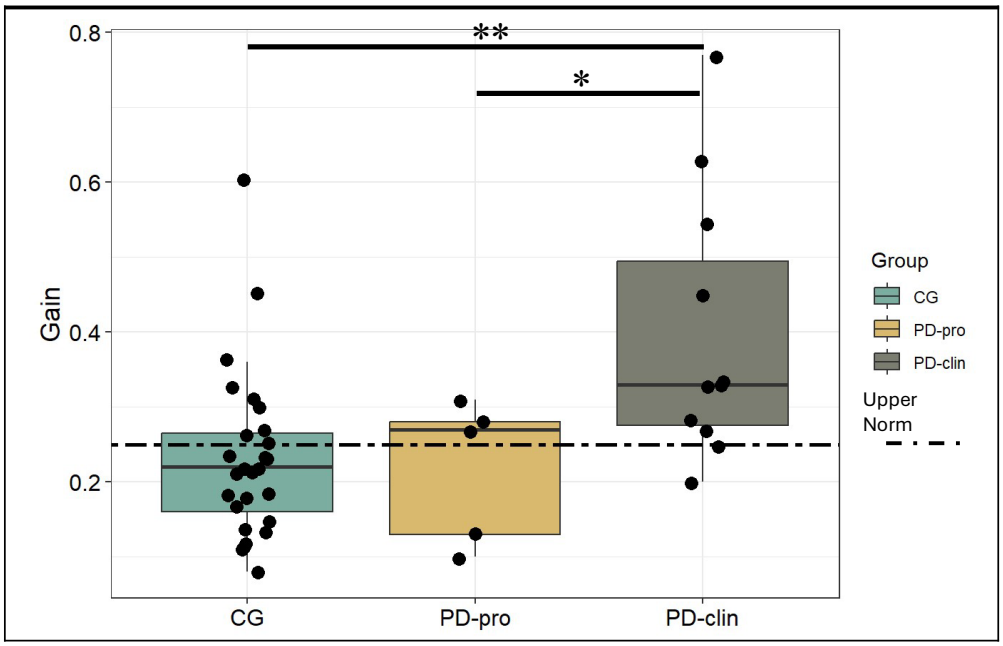
	Controls		**PD-Prodromal**		
Vestibular Test	n	(N = 50)	n	(N = 25)	p
cVEMP unilateral absent [a]	13	1 (8%)	9	2 (22%)	NA
cVEMP bilateral absent [a]	13	6 (46%)	9	2 (22%)	NA
oVEMP unilateral absent [a]	2	0 (0%)	2	1 (50%)	NA
oVEMP bilateral absent [a]	2	0 (0%)	2	0 (0%)	NA
Caloric unilateral weakness (%)	44	19 (20)	23	18 (22)	0.80
Caloric bilateral weakness [a]	44	1 (2%)	23	2 (9%)	0.27
Caloric directional preponderance (%)	44	12 (15)	23	13 (11)	0.81
RCT step test gain	11	0.71 (0.11)	7	0.62 (0.21)	NA
RCT step test time constant (s)	11	11.63 (4.45)	7	10.09 (5.35)	NA
RCT step test asymmetry (%)	11	6.23 (6.79)	7	6.10 (6.24)	NA
RCT sinusoidal gain [a]	15	1 (7%)	10	2 (20%)	0.54
RCT sinusoidal phase [a]	14	8 (57%)	10	6(60%)	>0.9
RCT sinusoidal asymmetry [a]	15	0 (0%)	10	0 (0%)	NA
RCT VOR enhancement gain	9	0.97 (0.14)	5	0.92 (0.08)	NA
RCT VOR suppression gain	8	0.30 (0.13)	5	0.22 (0.10)	NA
Positioning [a]	50	19 (38%)	25	2 (8%)	**0.006**
Positional [a]	50	5 (10%)	25	1 (4%)	0.66
Smooth pursuit gain	36	0.86 (0.23)	19	0.93 (0.07)	0.07
Optokinetic nystagmus gain	36	0.65 (0.16)	20	0.66 (0.14)	0.79
Subjective visual vertical (deg)	5	3.92 (2.74)	5	2.69 (1.79)	NA
Gaze [a]	36	1 (3%)	19	0 (0%)	>0.9
SOT Composite	31	57 (17)	17	66 (11)	0.06
SOT Condition 5	31	33 (27)	17	46 (24)	0.10
SOT somatosensory ratio [a]	31	1 (3%)	17	0 (0%)	>0.9
SOT visual ratio [a]	31	15 (48%)	17	5 (29%)	0.24
SOT vestibular ratio [a]	31	19 (61%)	17	8 (47%)	0.38
SOT visual preference ratio [a]	31	7 (23%)	17	2 (12%)	0.46
Motor control latency (ms)	31	146 (15)	17	138 (8)	**0.02**
Motor adaptation [a]	30	6 (20%)	17	2 (12%)	0.69

Note: c/oVEMP, cervical/ocular vestibular myogenic potential; Gaze, gaze stability testing; RCT, rotational chair test; SOT, Sensory Organization Test; VOR, vestibulo-ocular reflex.
[a] count (%) abnormal test results, Fisher's Exact Test. All values indicate mean (SD) unless otherwise noted.
Bold indicates a p-value < 0.05.

As shown in **Table 2.4** a subgroup analysis of PD-clinical and their corresponding CG records had insufficient records to perform comparisons for cVEMPs, oVEMPs, and SVV. For the remaining tests, there was a significant difference in step testing average gain and VOR suppression gain. The PD-clinical group averaged a step test gain of 0.65 (0.21) compared to the

CG group average step test gain of 0.52 (0.15); p = 0.04). Both step gain values are in the normal range. Low step gains can indicate peripheral or central disruption of the VOR response. The PD-clinical group VOR suppression gain was 0.40 (0.18), compared to the CG average suppression gain of 0.25 (0.19; p = 0.03). The differences in VOR suppression gain between CG and PD-clinical records can be seen in **Figure 2.2**. No other vestibular tests were significantly different between PD-clinical and CG records. Both groups had abnormally low SOT Composite scores (PD-clinical 48 (22); CG 55 (20); p =0.35) and low SOT condition 5 average equilibrium scores (PD-clinical 22 (26); CG 34 (27); p = 0.23). Although there was insufficient data to make comparisons, both groups were in the abnormal range for SVV (PD-clinical 3.88 (3.1) deg; CG 3.90 (4.27) deg).

Figure 2.2 VOR suppression gain for controls, PD-prodromal, and PD-clinical records



Note. CG, control group; PD-clin, clinical PD group; PD-pro, prodromal PD group; VOR, vestibulo-ocular reflex.
* p < 0.05, ** p < 0.01

Table 2.4 Comparison of vestibular test results for controls and clinical PD groups

	Controls		PD-Clinical		
Vestibular Test	n	mean (SD) N = 30	n	mean (SD) N = 15	p
cVEMP unilateral absent [a]	12	4 (33%)	7	1 (14%)	NA
cVEMP bilateral absent [a]	12	3 (25%)	7	2 (29%)	NA
oVEMP unilateral absent [a]	7	1 (14%)	5	0 (0%)	NA
oVEMP bilateral absent [a]	3	3 (100%)	3	2(67%)	NA
Caloric unilateral weakness (%)	29	24 (21)	15	24 (14)	0.92
Caloric bilateral weakness [a]	29	3 (10%)	15	2 (13%)	>0.9
Caloric directional preponderance (%)	29	14 (12)	15	13 (7)	0.71
RCT step test gain	22	0.52 (0.15)	12	0.65 (0.21)	**0.04**
RCT step test time constant (s)	22	12 (5.85)	12	11.32 (6.06)	0.77
RCT step test asymmetry (%)	22	9.27 (9.10)	12	6.03 (9.02)	0.33
RCT sinusoidal gain	20	4 (20%)	12	2 (17%)	>0.9
RCT sinusoidal phase	14	7 (50%)	10	5 (50%)	>0.9
RCT sinusoidal asymmetry	17	2 (12%)	10	0 (0%)	0.52
RCT VOR enhancement gain	19	0.91 (0.11)	11	0.95 (0.14)	0.44
RCT VOR suppression gain	19	0.20 (0.09)	11	0.40 (0.18)	**0.001**
Positioning [a]	30	10 (33%)	15	1(67%)	0.07
Positional [a]	30	3 (10%)	15	2 (13%)	>0.9
Smooth pursuit gain	30	0.92 (0.16)	15	0.87 (0.18)	0.33
Optokinetic nystagmus gain	29	0.64 (0.18)	15	0.54 (0.19)	0.12
Subjective visual vertical (deg)	8	3.9 (4.27)	6	3.88 (3.1)	NA
Gaze [a]	34	0 (0%)	12	0 (0%)	NA
SOT Composite	22	55 (19)	12	48 (22)	0.35
SOT Condition 5	23	33 (26)	12	22. (26)	0.23
SOT somatosensory ratio [a]	22	5 (23%)	12	1 (8%)	0.39
SOT visual ratio [a]	22	10 (45%)	12	6 (50%)	>0.9
SOT vestibular ratio [a]	22	17 (77%)	12	9 (75%)	>0.9
SOT visual preference ratio [a]	20	5 (25%)	11	1 (9%)	0.38
Motor control latency (ms)	22	143 (16)	12	146 (13)	0.62
Motor adaptation [a]	22	5 (23%)	12	2 (17%)	>0.9

Note: c/oVEMP, cervical/ocular vestibular myogenic potential; Gaze, gaze stability testing; RCT, rotational chair test; SOT, Sensory Organization Test; VOR, vestibulo-ocular reflex.
[a] count (%) abnormal test results, Fisher's Exact Test.
Bold indicates a p-value < 0.05.

As seen in **Table 2.5**, when comparing PD groups based on diagnosis timing, the PD-clinical group had significantly poorer VOR suppression with a mean gain of 0.40 (0.18), compared to the PD-prodromal group mean gain of 0.23 (0.09; p = 0.001). Oculomotor tests found significant differences between disease stages for OKN gain (PD-clinical 0.54 (0.19); PD-

prodromal 0.66 (0.14); p = 0.04). Due to averaging gain scores across stimulus velocities, normal cutoff scores are not available. However, lower OKN gain typically indicates a central vestibular or oculomotor pathway disruption. Postural control differences were seen in SOT Composite between the disease stage groups (PD-clinical 48 (22); PD-prodromal 66 (11); p = 0.01) and SOT condition 5 average (PD-clinical 22 (26); PD-prodromal 46 (24); p = 0.02). No other vestibular tests were significantly different between the groups based on PD diagnosis timing.

Table 2.5 Comparison of vestibular test results for prodromal and clinical PD groups

	PD-Prodromal		PD-Clinical		
Vestibular Test	n	(N = 25)	n	(N = 15)	p
cVEMP unilateral weakness [a]	10	2 (20%)	7	1 (14%)	>0.9
cVEMP bilateral weakness [a]	10	2 (20%)	7	2 (29%)	>0.9
cVEMP unilateral weakness [a]	3	0 (0%)	6	0 (0%)	NA
oVEMP bilateral weakness [a]	3	1 (33%)	6	3 (50%)	>0.9
Caloric unilateral weakness (%)	23	2 (8.7%)	15	2 (13%)	0.39
Caloric bilateral weakness [a]	23	18 (22)	15	24 (13)	>0.9
Caloric directional preponderance (%)	23	13 (11)	15	13 (7)	0.90
RCT step test gain	7	0.62 (0.21)	12	0.65 (0.21)	0.71
RCT step test time constant (s)	7	10.1 (5.4)	12	11.3 (6.1)	0.67
RCT step test asymmetry (%)	7	10.8 (10.0)	12	6.7 (5.7)	0.29
RCT sinusoidal gain	11	2 (18%)	13	2 (15%)	>0.9
RCT sinusoidal phase	10	6 (60%)	12	7 (58%)	>0.9
RCT sinusoidal asymmetry (%)	11	0 (0%)	13	0 (0%)	NA
RCT VOR enhancement gain	5	0.92 (0.08)	11	0.95 (0.14)	0.73
RCT VOR suppression gain	6	0.23 (0.09)	11	0.40 (0.18)	**0.04**
Positioning [a]	25	2 (8.0%)	15	1 (6.7%)	>0.9
Positional [a]	25	1 (4.0%)	15	2 (13%)	>0.9
Smooth pursuit gain	19	0.93 (0.07)	15	0.87 (0.18)	0.14
Saccades horizontal accuracy (%)	14	83 (28)	12	113 (65)	0.10
Saccades vertical accuracy (%)	13	81 (20)	12	83 (23)	0.76
Saccades horizontal latency (ms)	14	294 (75)	12	281 (65)	0.64
Saccades vertical latency (ms)	14	259 (69)	12	248 (103)	0.75
Optokinetic nystagmus gain	20	0.66 (0.14)	15	0.54 (0.19)	**0.04**
Subjective visual vertical (deg)	6	2.31 (1.86)	7	4.49 (3.27)	0.19
Gaze [a]	19	0 (0%)	15	0 (0%)	NA
SOT Composite	17	66 (11)	12	48 (22)	**0.01**
SOT Condition 5	17	46 (24)	12	22 (26)	**0.01**
SOT somatosensory ratio [a]	17	0 (0%)	12	1 (8.3%)	0.4
SOT visual ratio [a]	17	5 (29%)	12	6 (50%)	0.4
SOT vestibular ratio [a]	17	8 (47%)	12	9 (75%)	0.3
SOT visual preference ratio [a]	17	2 (12%)	11	1 (9.1%)	>0.9
Motor control latency (ms)	17	139 (8)	12	146 (13)	0.07
Motor adaptation [a]	17	2 (12%)	12	2 (17%)	>0.9

Note: c/oVEMP, cervical/ocular vestibular myogenic potential; Gaze, gaze stability testing; RCT, rotational chair test; SOT, Sensory Organization Test; VOR, vestibulo-ocular reflex.
[a] count (%) abnormal test results, Fisher's Exact Test. All values indicate mean (SD) unless otherwise noted.
Bold indicates a p-value < 0.05.

2.5 Discussion

The objective of this study was to characterize vestibular test results of people with PD compared to age-matched CG records and to determine differences in vestibular testing results at different disease stages of PD. Contrary to expectations and prior research (Cui et al., 2022), when comparing records of people with a history of PD to age and sex-matched CG records, there was no difference in otolithic dysfunction seen for cVEMP testing. Centrally, there was significantly reduced VOR suppression in the combined PD records compared to CG, clinical PD records compared to CG, and clinical PD compared to prodromal PD.

Prior literature suggests that otolithic function is abnormal in PD, with a higher prevalence of absent cVEMP and oVEMP responses than in healthy older adults (Berkiten et al., 2022; Cui et al., 2022). However, when comparing the combined PD records with CG, there was not a significant difference between groups. This could indicate that, once controlling for age, otolithic function is similar in PD and non-PD adults. There is support in existing literature for more subtle differences in VEMPs such as increased interpeak latencies and decreased amplitude that were not captured here due to the changes in testing equipment and protocols over time. A meta-analysis of existing VEMP studies in PD found that absent VEMPs are significantly different only in more severe PD when compared to controls (Cui et al., 2022). In this study, the PD-clinical group had only 5 out of 15 records with a diagnosis of PD that predated vestibular testing. It may be that vestibular dysfunction in PD leading to VEMP abnormalities does not occur until later disease stages. Finally, because all records came from individuals referred for testing due to potential vestibular complaints, it is also possible the CG had higher levels of otolithic dysfunction than the general population.

Existing literature examining SCC function in PD primarily utilizes video Head Impulse Testing with results indicating that SCC function is normal in PD (Hawkins et al., 2022; Lv et al., 2017). None of the PD records included video Head Impulse Testing so comparisons could not be performed to verify this pattern. However, no differences indicating worse SCC function in PD were seen between any groups for caloric or rotational chair testing. Nystagmus on positioning testing was significantly more prevalent in CG compared to combined and prodromal PD. It is possible that the exclusion criteria eliminating potential CG with neurological causes of vestibular dysfunction (e.g. stroke, multiple sclerosis) biased the sample. This may have led to a greater number of records with testing related to benign paroxysmal positional vertigo or other peripheral vestibular disorders such as canal paresis.

In central vestibular testing, abnormal VOR suppression may be associated with PD at later disease stages. Prior literature has demonstrated abnormal VOR suppression in PD (Hawkins, Rey-Martinez, et al., 2021; Venhovens, Meulstee, Bloem, et al., 2016; White, Saint-Cyr, et al., 1983). Comparisons with CG suggest that VOR suppression abnormalities occur in PD and appear to be related to disease stage rather than aging. Control and prodromal PD records had normal VOR suppression, on average, while clinical PD records had abnormally high VOR suppression gains, that were significantly worse than age-matched controls. Although the prodromal PD records could not be compared to CG due to insufficient data, VOR suppression was within a normal range for the PD-prodromal group. Visual suppression of the VOR is regulated by the vestibulo-cerebellum, and decreased VOR suppression in clinical, but not prodromal PD is supportive evidence that cerebellar functions are affected by PD in later disease stages (T. Li et al., 2023).

Postural control deficits and decreased balance are common in vestibular disorders, in PD, and with normal aging (Doná et al., 2016; Harro et al., 2018; Horak, 2006; Pedalini et al., 2009). Abnormal postural control was seen across all groups of records examined, with abnormal SOT Composite scores for the PD and CG. Equilibrium scores for Condition 5 of the SOT, which requires adequate peripheral vestibular input along with central integration, were also low and did not significantly differ between groups. This is unsurprising, given that imbalance is a likely reason to seek vestibular diagnostic testing.

Other significant differences were higher step testing gains and shorter motor control latency in the PD-prodromal group compared to CG indicating better function on these tests. This could be due to a sample bias of the control records leading to an atypical control group, as discussed above. Additionally, both the step gains and motor control latencies were in the normal range and did not demonstrate any significance in the other comparisons. Based on the anticipated false-positive rate of 1.45 significant tests for each set of comparisons, differences in step testing gain and motor control latency could also be due to chance.

In summary, these findings support existing evidence that vestibular deficits occur in people with PD, but with some central and peripheral deficits having a similar prevalence to same-age peers (J. H. Park & Kang, 2021). Centrally, abnormal VOR suppression may indicate vestibulo-cerebellar involvement in PD with disease progression (Barmack, 2003; Friedmann, 1970; T. Li et al., 2023). These findings should be verified through comprehensive vestibular testing in people with PD and healthy adults who do not specifically have dizziness or balance complaints.

2.5.1 Limitations

The primary limitation of this study is that all records are from patients referred to vestibular testing due to balance or dizziness complaints. Therefore, interpretation is limited to comparisons of people with PD to same-aged adults who require diagnostic vestibular testing. Systemic disorders that might affect vestibular or postural control function (e.g. diabetes, autoimmune disorders other than multiple sclerosis) were not excluded and could have influenced test results. Due to exclusion criteria, a relatively small final sample size of PD records was analyzed, limiting the power of the analysis. Increased testing capability of the clinical center over time, and specific testing completed based on referrals meant that many records did not have comprehensive vestibular test results available. Furthermore, updates to equipment and testing protocols resulted in an inability to make direct comparisons of many test results such as VEMPs, and subtle differences may have been overlooked due to the need to use coded rather than continuous comparisons.

2.5.2 Conclusion & Clinical Implications

Deficits in vestibular function may occur even early in PD, with specific central deficits in VOR suppression beyond those seen in age-matched peers without PD occurring at later disease stages. This may indicate disease-related vestibulo-cerebellar involvement in PD. Vestibular dysfunction should not be discounted in people with PD who have dizziness and balance complaints. Unrecognized vestibular dysfunction may contribute to postural control impairments or falls in PD. Vestibular testing and targeted vestibular treatments should be considered for people with PD who have symptoms of vestibular dysfunction.

CHAPTER 3: COMPARING VESTIBULAR FUNCTION IN PARKINSON DISEASE AND HEALTHY ADULTS

3.1 Abstract

Background: There is emerging evidence that peripheral and central vestibular dysfunction is present in Parkinson disease (PD) (Cui et al., 2022; Smith, 2018); however, it is unclear if this dysfunction is disease-related, age-related, or both. The objective of this study was to determine disease-related vestibular impairments in people with PD compared to healthy, similar-aged adults (HC). It was hypothesized that, compared to HC, people with PD would have a reduction in otolithic, vestibular nucleus complex, and vestibular sensory integration function, but no differences in semicircular canal function.

Methods: Fifteen people with PD, off-medication, and 15 HC completed comprehensive vestibular testing. Primary outcome variables were cervical vestibular evoked myogenic potentials (cVEMP) for otolithic function, the caloric testing sum of peak slow phase velocities (PSPV) for semicircular canal function (SCC), optokinetic nystagmus (OKN) for vestibular nucleus complex (VNC) function, and the Sensory Organization Test (SOT) vestibular ratio for sensory integration. Secondary outcome variables were collected for ocular VEMPs, rotational chair testing, vestibulo-ocular reflex (VOR) enhancement and suppression, subjective visual vertical, and videonystagmography for positional testing and oculomotor testing (gaze, saccades, smooth pursuit). Results were compared between the groups using unpaired permutation testing for continuous variables and Fisher's Exact test for categorical variables.

Results: For primary variables, participants with PD had significantly lower summed PSPV compared to HC ($p = 0.01$). There was no difference between PD and HC in cVEMP amplitudes

for either ear (left cVEMP $p = 0.24$; right cVEMP $p = 0.11$), OKN gain ($p = 0.13$), or SOT vestibular ratio scores ($p = 0.62$). For secondary variables, there was a significant difference between participants with PD and HC with lower sinusoidal rotational chair gain ($p < 0.01$), greater sinusoidal rotational chair asymmetry ($p = 0.01$), lower vestibulo-ocular reflex suppression gain ($p = 0.01$), shortened step rotational testing time constants ($p = 0.02$), more abnormal, SVV ($p < 0.01$), and more hypometric saccades ($p= 0.01$).

Discussion: It was expected that otolithic function, VNC function, and vestibular sensory integration would be altered in PD based on existing literature. However, there was no difference in otolithic function in PD compared to HC. There was evidence for reduced semicircular canal function in participants with PD compared to HC based on a decreased overall response to caloric irrigation. Centrally, participants with PD demonstrated abnormalities with rotational chair testing including signs of impaired velocity storage with shortened time constants on step testing and lower gain on sinusoidal rotational testing at higher frequencies. Both PD and HC showed low gain on OKN responses that did not significantly differ. Participants with PD also had significantly poorer and abnormal SVV estimation compared to HC. Saccades were hypometric compared to HC, but on average within a normal range. This study was limited by the small sample size and heterogeneity of results in the participants with PD.

Conclusions: People with PD may have a range of vestibular deficits beyond those expected due to aging, including impairments in peripheral semicircular canal function and non-dopaminergic central vestibular and oculomotor pathways. Vestibular testing should be considered for people with PD including tests of peripheral and central vestibular responses, and individualized treatment provided using established vestibular rehabilitation techniques.

3.2 Introduction

There is emerging evidence that vestibular dysfunction is present in PD (Cui et al., 2022; Smith, 2018). However, it is unclear whether vestibular changes in PD are disease-specific, a result of typical aging, or both. The bulk of existing literature examining vestibular function in PD uses isolated testing of peripheral responses without also examining central function that may influence testing or relies on postural responses as a proxy for vestibular function (Berkiten et al., 2022; Bohnen, Roytman, et al., 2022; Cicekli et al., 2019; Hawkins et al., 2022). In addition, comprehensive vestibular testing is needed to differentiate peripheral and central vestibular function (Eggers et al., 2019; Fracica et al., 2022), but little current literature exists that includes vestibular function assessment across a range of peripheral and central responses (Cipparrone et al., 1988; Scarpa et al., 2020; Venhovens et al., 2016; Vitale et al., 2011).

The peripheral vestibular system senses head accelerations through the deflection of hair cells at the five end organs in each ear. This deflection results in reflexive gaze and postural stabilization responses and, through sensory integration, awareness of movement and position. The cristae within the three semicircular canals (SCC) sense angular acceleration, and the two otolithic organs – the saccule and utricle – sense linear acceleration, and orientation in gravity. The most common test of vestibular function in the literature on PD is vestibular evoked myogenic potential (VEMP) testing. The VEMP test assesses otolithic function through sound- or vibration-induced stimulation of the otolithic organs and has shown abnormalities that could indicate end-organ or central pathway changes in PD (Berkiten et al., 2022; Cui et al., 2022; Park & Kang, 2021). However, few of these studies included other central or peripheral vestibular tests to differentiate the location of the dysfunction (Berkiten et al., 2022; Cicekli et al., 2019; Venhovens et al., 2016). More recent literature has included healthy control groups when

examining VEMPs in PD, however procedures and findings are not consistent (Cui et al., 2022). There is evidence that SCC response to a high-velocity stimulus using video Head Impulse Testing is spared in PD (Cicekli et al., 2019; Hawkins, Chiarovano, et al., 2021; Lv et al., 2017). However, studies of SCC function in PD at lower accelerations using caloric testing or rotational chair testing that included healthy controls have mixed results, with some studies showing impaired SCC function in PD, and others indicating that SCC function is intact (Cicekli et al., 2019; Cipparrone et al., 1988; Venhovens et al., 2016).

Centrally, vestibular processing may also be affected in PD. Evidence for central vestibular involvement in PD includes impairment of vestibulo-cerebellar visual enhancement or suppression of the vestibulo-ocular reflex (Cipparrone et al., 1988; Hawkins, Rey-Martinez, et al., 2021; Venhovens et al., 2016), abnormalities in oculomotor functions that are subserved by processing in the vestibular nucleus complex (VNC) such as optokinetic nystagmus (OKN) and smooth pursuit (Cipparrone et al., 1988; Venhovens et al., 2016; Zhou et al., 2024) and impaired vestibular sensory integration (Bohnen, Kanel, van Emde Boas, et al., 2022; Bohnen, Roytman, et al., 2022; Halperin et al., 2021; Harro et al., 2018). Vestibular sensory integration in PD has been assessed by measuring postural control tasks under conditions where visual and somatosensory functions are unavailable or inaccurate (Bohnen, Kanel, van Emde Boas, et al., 2022; Bohnen, Roytman, et al., 2022; Harro et al., 2018), or through heading tasks where the participant must estimate the direction of a real or perceived motion (Halperin et al., 2021). However, the majority of these studies did not complete other vestibular testing to rule out potential peripheral dysfunction contributions to altered performance under vestibular sensory demands.

Little of the current literature has examined the effects of dopaminergic medication on vestibular function in PD, and the effect of dopaminergic medications on vestibular function is unclear (Pötter-Nerger et al., 2012; Potter-Nerger et al., 2014; Scocco et al., 2014; Shalash et al., 2017). Evidence of dopamine-sensitive cells has been seen in the human saccule (Eberhard et al., 2022), but dopamine sensitivity in human SCCs has not been explored. Dopamine appears to play a role in the VNC or even the cerebellum (Canton-Josh et al., 2022; Soto & Vega, 2010; Vibert et al., 1995). It is also possible that central vestibular function changes seen in PD are related to non-dopaminergic pathway involvement (Bohnen, Kanel, Roytman, et al., 2022). Despite these unknowns, none of the current literature includes studies that have completed comprehensive vestibular testing in people with PD who are off dopaminergic medication (Bohnen, Kanel, Roytman, et al., 2022; Pötter-Nerger et al., 2012; Scocco et al., 2014). A better understanding of differences between disease-related and age-related changes in vestibular function could inform vestibular assessment and the use of existing and novel treatments for vestibular dysfunction in people with PD.

There is a critical gap in understanding whether vestibular function in PD is disease-related, age-related, or both. Furthermore, the role of dopamine in the vestibular system is not well understood and lack of control for the effects of dopaminergic medications used to treat PD may contribute to some of the inconsistencies seen in current literature on vestibular function in PD. The objective of this study was to determine disease-related vestibular impairments in people with PD compared to healthy, similar-aged adults. It was hypothesized that, compared to HC, people with PD would have a reduction in otolithic, VNC, and vestibular sensory integration functions, but no differences in semicircular canal function.

3.3 Methods

This cross-sectional observational study included people with PD and healthy controls (HC). The study was approved by the University of Washington Institutional Review Board, and all study procedures complied with the Ethical Principles and Guidelines for Research Involving Human Subjects. All participants completed informed consent before participating in any study procedures. Participants completed a demographic and clinical assessment, balance and gait testing, and vestibular testing. Data were collected over 1-4 sessions based on participant preference, need for cerumen removal, and equipment availability. For testing that occurred over multiple sessions, the maximum time between the first and last testing session was 9 weeks for people with PD and 18 weeks for HC.

3.3.1 Participants

Participants with PD and HC participants were recruited through the Washington State Parkinson Disease Registry, university websites, and local PD support and exercise groups. Eligibility criteria were: 1) age between 40-90 years; 2) no previous history of other diagnosed vestibular or auditory disorders; 3) ability to stand and walk for at least 2 minutes with or without an assistive device; 4) no history of other neurological disorders that would affect vestibular, oculomotor, or postural control functions; 5) no prior or ongoing exposure to drugs affecting audiovestibular function (e.g. ototoxic medications); 6) no major musculoskeletal or peripheral disorders that could significantly affect balance or gait. Additional eligibility criteria for the PD group included: 7) a diagnosis of PD without dementia; 8) current stable use of dopaminergic medications for at least 3 months; 9) no use of cholinergic medications to treat PD; and 10) no history of neurosurgical interventions for PD (e.g. deep brain stimulator placement).

Participants with PD were tested in the off-medication state, at least 8 hours after their last dose of PD medications.

3.3.2 Demographic and Clinical Assessment

A focused history was used to ascertain demographic information, including age, sex and gender, race and ethnicity, and highest level of education. Global cognition was screened using the Montreal Cognitive Assessment (Nasreddine et al., 2005). Medical co-morbidities were assessed with the Charlston Comorbidity Index (Quan et al., 2011). Any history of falls over the past three months was assessed with a custom questionnaire including frequency, circumstances, cause, and resultant injuries, if any. Impacts of dizziness or imbalance were reported using the Dizziness Handicap Inventory (DHI) (Jacobson & Newman, 1990). Balance confidence was assessed using the Activities-specific Balance Confidence Scale (ABC) (Powell & Myers, 1995). Orthostatic hypotension was tested by monitoring blood pressure for a drop ≥ 20 mmHg systolic or ≥ 10 mmHg diastolic when moving from supine to sitting and sitting to standing (National Institute for Health and Care Excellence [NICE], 2019). Otoscopy was performed to ensure that participants had an intact tympanic membrane and that excessive cerumen would not interfere with test procedures. Participants with excessive cerumen (where cerumen would interfere) returned to complete tests following cerumen removal using over-the-counter peroxide-based cleaning drops at home or after visiting their healthcare provider for cerumen removal.

For both groups, the severity of any motor symptoms of PD was assessed using the Movement Disorders Society Sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part 3 - Motor Examination. For people with PD, medication fluctuations, dyskinesia, and dystonia were rated using the MDS-UPDRS Part 4 – Motor Complications (Goetz et al.,

2008). Presence and severity of freezing of gait were reported using the new Freezing of Gait Questionnaire (nFoG) without video (Nieuwboer et al., 2009).

For both groups, the Functional Gait Assessment (FGA) was used as a clinical measure of postural stability while walking (Wrisley & Kumar, 2010). Inertial sensors (Opal by APDM, Inc., Portland, OR) were used to characterize postural control during the modified Clinical Test of Sensory Integration for Balance (mCTSIB) (Freeman et al., 2018) as well as gait and turning during a 2-minute walking test (Morris et al., 2019). A sensor at the waist was used to quantify postural control during the four conditions of the mCTSIB and 180 degree turns while walking. Sensors on the feet and waist were used to quantify gait speed during walking.

3.3.3 Vestibular Function Assessments

Vestibular testing included measures of otolithic, SCC, VNC, and central vestibular integration function. The function of the otolithic organs, which detect linear acceleration and gravity, was assessed using cervical VEMP (cVEMP, saccular function) and ocular VEMP (oVEMP, utricular function). The stimulus parameters were air conducted 500 Hz tone bursts, Blackman ramped with a 1 ms rise/fall and 2 ms plateau, at a rate of 5/s. The stimulus was set at 95dB normal hearing level and delivered through insert earphones using a BioLogic Navigator Pro (Natus Medical Inc., San Carlos, CA). Reflex responses were amplified and recorded with surface electromyography for the cVEMP at the ipsilateral sternocleidomastoid, bandpass filtered from 30-5000 Hz, and for the oVEMP at the contralateral inferior oblique, bandpass filtered from 3-1000 Hz. Impedance was kept below 6 Ω. The primary measure of otolithic function was quantified as the P1-N1 interpeak amplitudes (μV) of cVEMP responses, with higher values representing better function. The N1-P1 amplitudes of oVEMP responses for each ear, the

percentage difference in amplitudes between ears for cVEMP and oVEMP, and the presence or absence of cVEMP and oVEMP responses were collected as secondary variables.

The function of the semicircular canals (SCC) was measured using bithermal caloric irrigation. Caloric irrigation used cool (24° C) and warm (47° C) air irrigation in one ear canal at a time while the participant is supine with their head at 30 degrees flexion to position the horizontal SCC parallel to gravity. Irrigation results in cooling and warming of endolymph in the horizontal SCC, which is parallel to gravity, with a resultant fluid flow that deflects the cupula and generates a nystagmus response. Velocity (deg/s) of the slow phase of nystagmus was measured using infrared videonystagmography (VNG; Micromedical VisualEyes, Spectrum 8.10) and represents the VOR response for each horizontal canal. The primary variable representing SCC function was summed peak slow phase velocities (PSPV, deg/s) for all four irrigations. A smaller summed PSPV indicates a worse overall SCC function. Additional caloric measures collected were asymmetry in response between ears (%) and directional preponderance of nystagmus (%) (see Ch 1.3.3 for formulas).

Function of the VNC was assessed using optokinetic nystagmus (OKN) testing using a Neuro Kinetics I-Portal rotational chair system (I-Portal Neuro-Otologic Test Center, Neuro Kinetics Inc., Pittsburgh, PA). Eye movements of the OKN response are generated due to the retinal slip of a full field visual image. The OKN test used a moving full-field random dot visual pattern rotating at 20, 30, and 45 Hz bidirectionally to elicit nystagmus. Nystagmus was quantified using VNG, and the primary OKN variable was the gain of the nystagmus slow phase (see Ch 1.3.3). Complete data for all stimuli was not available because of postural changes, dystonia, or eye closure, so the average of gains for available data was used. Lower OKN gain can indicate dysfunction in central pathways for velocity storage and smooth pursuit eye

movement generation through an obligatory synapse in the VNC. Abnormalities in saccadic generation can also affect OKN.

Central sensory integration for balance was assessed with computerized posturography for the Sensory Organization Test (SOT) using a Neurocom Equitest system (Natus Medical, Middleton, WI) (Pedalini et al., 2009). The SOT interrogates the ability to use somatosensory, visual, and vestibular inputs to maintain postural control through postural responses under six conditions that alter the ability to use visual and somatosensory inputs. A full description of the SOT protocol can be found in Ch 1.3.3. When peripheral otolithic function or vestibular integration is impaired, performance will be abnormal under conditions 5 and 6. The primary central vestibular integration measure was the vestibular score, which is the ratio of the averaged equilibrium scores for condition 5 (eyes closed, sway-referenced platform) over condition 1 (eyes open, fixed platform). This was selected to account for any differences in baseline sway (condition 1) due to possible tremor or dyskinesia in the PD group. Lower SOT vestibular ratio scores indicate poorer use of vestibular inputs to maintain postural stability. Findings were interpreted in context with otolithic function testing and performance on other SOT conditions. Additional SOT variables were the SOT Composite score, normal/abnormal sensory ratios for somatosensation and vision, and normal/abnormal visual preference scores.

Additional vestibular assessments were completed to provide context for the primary measures. This included rotational chair testing of horizontal canal function to assess VOR gain and phase at different rates of acceleration using sinusoidal rotations at 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, and 0.64 Hz in darkness (I-Portal Neuro-Otologic Test Center, Neuro Kinetics Inc., Pittsburgh, PA). The pattern of gain, phase, and asymmetry responses to sinusoidal rotations can indicate peripheral or central dysfunction (see Ch 1.3.3 for details). The ability of central

function to visually enhance and suppress the VOR was tested during sinusoidal rotations at 0.80 Hz and 0.64 Hz, respectively. Step testing assessed central velocity storage and unilateral weakness of canal responses during rapid acceleration to constant velocity rotations and deceleration to static sitting. During step testing, central velocity storage was represented by the time constant (reduction in slow phase velocity to 37% of the peak slow phase velocity) of nystagmus (s). A shorter time constant indicates worse velocity storage, whereas a prolonged time constant can indicate dysfunction in cerebellar inhibition of velocity storage. Step testing gain was also measured. Reduced gain on three or more rotation conditions can indicate decreased bilateral SCC function. Unilateral weakness was measured by the gain asymmetry (%) for right and left rotational stimuli. A more complete description of step testing and calculation of variables can be found in Ch 1.3.3. Vestibular gravitational perception was measured using subjective visual vertical (SVV) using a light bar in the rotational chair booth and quantified as the mean error (deg) from vertical and variability of error (SD). A deviation greater than 3 deg from vertical in either direction was considered abnormal based on clinic-derived norm cutoffs (unpublished data).

Oculomotor assessment and VNG were performed using infrared video eye tracking to provide additional context for the primary vestibular measures. Oculomotor function was assessed for gaze stability with and without visual fixation, horizontal saccades latency (ms) and accuracy (%), and horizontal smooth pursuit at 0.1, 0.3, and 0.5 Hz stimulus frequency for gain, phase, and asymmetry (%). Additional VNG testing included post-head shake and static positional testing for the presence of nystagmus. Abnormal nystagmus was considered to be present if there were 3 or more beats with an average slow phase velocity ≥ 6 deg/s in one position or ≥ 4 deg/s in multiple positions based on clinic-established criteria.

3.3.4 Statistical Analysis

Demographic and clinical variables were described using mean and standard deviation or count and percentages. Normality of continuous variable distribution was determined using histogram inspection and the Shapiro-Wilk test. Differences between demographic and clinical variables of people with PD and HC were determined using t-test for normally distributed variables, chi-squared tests for categorical variables, and Fisher's Exact test for binary variables. Differences between the people with PD and HC for the primary outcome variables of cVEMP amplitude, caloric PSPV sum, average OKN gain, and SOT vestibular score were determined using permutation for unpaired statistics to determine p-values due to concerns regarding normality of variable distribution. Bonferroni correction was applied to the four primary measures to preserve the family-wise Type 1 error rate, resulting in a significance level of $p < 0.0125$.

Additional analyses were performed to describe trends observed in people with PD and HC for secondary variables. Secondary otolithic variables were the presence/absence of cVEMP and oVEMP in either ear and oVEMP amplitudes, when present. Secondary semicircular canal variables were caloric asymmetry, and pattern of sinusoidal chair testing phase, gain, and asymmetry. Secondary central function variables were caloric directional preponderance, step testing time constant, VOR enhancement, suppression gain, and change in gain with suppression (%), SVV error (deg), SOT Composite scores, presence of nystagmus during any gaze stability test, horizontal saccades accuracy and latency, and horizontal smooth pursuit gain, and phase. Differences in means for continuous variables were compared using permutation of unpaired statistics due to concerns about the normality of variable distributions following visual inspection of histograms. Fisher's exact test was used to compare differences between groups for

categorical variables. Significance was set at $p < 0.05$. Due to the exploratory nature of this secondary analysis, corrections for multiple comparisons were not made. However, at the given cutoff for significance and 30 comparisons performed, 1.5 comparisons could be expected to have a significant result by chance alone.

Due to limited tolerance for vestibular tests, and limited tolerance for the off-medication condition, full testing was not completed for all participants. The number of participants with available data for each test is included in the results reporting.

3.3.5 Role of Funding Source

This project was supported by funding from the Foundation for Physical Therapy Research, the University of Washington Auditory Neuroscience Training Program (NIH T32DC005361), the Walter C. and Anita C. Stolov Research Fund, the University of Washington Retirement Association, and the Virginia Merrill Bloedel Hearing Research Center. The funders played no role in the design, conduct, or reporting of this study.

3.4 Results

Testing was completed for 15 participants with PD and 15 HC participants. Demographic and clinical characteristics for each group are described in **Table 3.1** and **Table 3.2** using mean and standard deviation (SD) or count and percentage. There was no significant difference in age (PD 71.9 (6.7); HC 69.5 (6.8); $p = 0.3$) or sex (female PD 6 (40.0%); female HC 8 (53.3%); $p = 0.7$) between groups. People with PD had mild to moderate PD motor severity range as reflected by the MDS-UPDRS motor examination, (21.7 (13.5); range 0-51) and Hoehn and Yahr stage (2.0 (range 0-3)). Participants with PD had an average disease duration of 7.3 (range 1.2-14.0) years and few motor complications on the MDS-UPDRS-4 (2.8 (1.8)). Two participants with PD

(13.3%) reported freezing of gait. Participants with PD had a higher impact of dizziness or imbalance symptoms (DHI: PD 20.1 (14.5); HC 1.6 (3.2); p = 0.046) with no difference in balance confidence (ABC: PD 90.1 (11.4); HC 95.8 (4.9); p = 0. 4). Compared to HC, people with PD had significantly slower gait speed (PD 1.0 (0.1) m/s; HC 1.2 (0.2) m/s; p = 0.012), and lower turn velocity (PD 150.2 (27.8) deg/s; HC 198.2 (49.1) deg/s; p = 0.003). There were no significant differences between people with PD and HC for frequency of falls, the MoCA, FGA, or any conditions of the mCTSIB.

Table 3.1 Demographic characteristics of controls and participants with PD

	HC		**PD**		
Characteristic	mean (SD)	range	mean (SD)	range	p [b]
Age	69.5 (6.8)	57-84	71.9 (6.7)	59-82	0.3
Sex (female)[a]	8 (53.3%)		6 (40.0%)		0.7
Race[a]					0.5
Other	2 (13.3%)		0 (0%)		
White	13 (86.7%)		15 (100%)		
Ethnicity [a]					>0.9
Hispanic/Latinx	1 (6.7%)		0 (0.0%)		
Non-Hispanic/Latinx	14 (93.3%)		15 (100%)		
Education [a]					0.14
Some High School	0		0		
High School/GED	0		0		
Some College	3 (20.0%)		0 (0%)		
Bachelor's	4 (26.7%)		8 (53.3%)		
Graduate	8 (53.3%)		7 (46.7%)		

[a] count (%)
[b] Welch Two Sample t-test for normally distributed continuous variables; Fisher's exact test for binary variables; Pearson's Chi-squared test for categorical
Bold indicates a p-value < 0.05.

Table 3.2 Clinical, balance, and gait characteristics of controls and participants with PD

	HC		PD		
	mean (SD)	range	mean (SD)	range	p [b]
Clinical					
PD Duration	--	--	7.3 (4.0)	1.2-14.0	
Falls [a]					>0.9
No falls	9 (60.0%)		8 (53.3%)		
< 1/mo	6 (40.0%)		6 (40.0%)		
1-3/mo	0 (0%)		1 (6.7%)		
Dizziness Handicap Inventory	1.6 (3.2)	0-10	20.1 (14.5)	2-46	**0.046**
ABC	95.8 (4.9)	80.6-100	90.1 (11.4)	67.5-100	0.4
MDS-UPDRS-3	2.8 (1.8)	0-6	21.7 (13.5)	0-51	**<0.001**
MDS-UPDRS-4	--	--	5.2 (3.2)	0-11	
Hoehn & Yarh	--	--	2.0 (0.4)	1-3	
Freezing of Gait	--	--	2 (13.3%)		
MoCA	26.9 (2.1)	23-30	27.2 (2.7)	19-30	0.8
Balance and Gait					
Functional Gait Assessment	27.7 (2.9)	21.0-30.0	24.7 (4.8)	16-30	0.05
mCTSIB Sway					
1 Eyes open, floor	0.12 (0.04)	0.06-0.16	0.07-0.24	0.12 (0.04)	0.6
2 Eyes closed, floor	0.11 (0.04)	0.05-0.22	0.06-0.20	0.11 (0.04)	>0.9
3 Eyes open, foam	0.19 (0.08)	0.10-0.38	0.09-0.28	0.19 (0.08)	0.4
4 Eyes closed, foam	0.20 (0.09)	0.10-0.41	0.11-0.38	0.20 (0.09)	0.8
Gait Speed	1.2 (0.2)	0.9-1.8	1.0 (0.1)	0.7-1.2	**0.012**
Turn Velocity	198 (49)	150-354	150 (28)	115-207	**0.003**

ABC, Activity-specific Balance Confidence Scale; FGA; mCTSIB, Modified Clinical Test of Sensory Integration and Balance; MDS-UPDRS-3/4, Movement Disorders Society-sponsored Unified Parkinson's Disease Rating Scale, Part 3 – Motor Examination/ Part-4, Motor Complications; PD Duration, years since diagnosis with Parkinson disease.

[a] count (%)

[b] Welch Two Sample t-test for normally distributed continuous variables; Fisher's exact test for binary variables; Pearson's Chi-squared test for categorical variables.

Bold indicates a p-value < 0.05.

As shown in **Table 3.3**, for the primary peripheral vestibular function measures, cVEMPS was available for 14 participants with PD and 15 HC, and caloric testing was available for 12 participants with PD and 11 HC. For otolithic function, there was unilateral absence of a cVEMP in 4 (29%) participants with PD, and 1 (6.7%) HC. Bilateral cVEMP absence was seen in 2 (14%) participants with PD and none of the HC. There was no difference in left or right cVEMP

amplitudes between people with PD and HC (left cVEMP p = 0.24; right cVEMP p = 0.11). The mean summed PSPV for both groups was in a normal range. **Figure 3.1** shows that participants with PD had significantly smaller summed PSPV (90 (52)) deg/s compared to HC (155 (50) deg/s; p = 0.01).

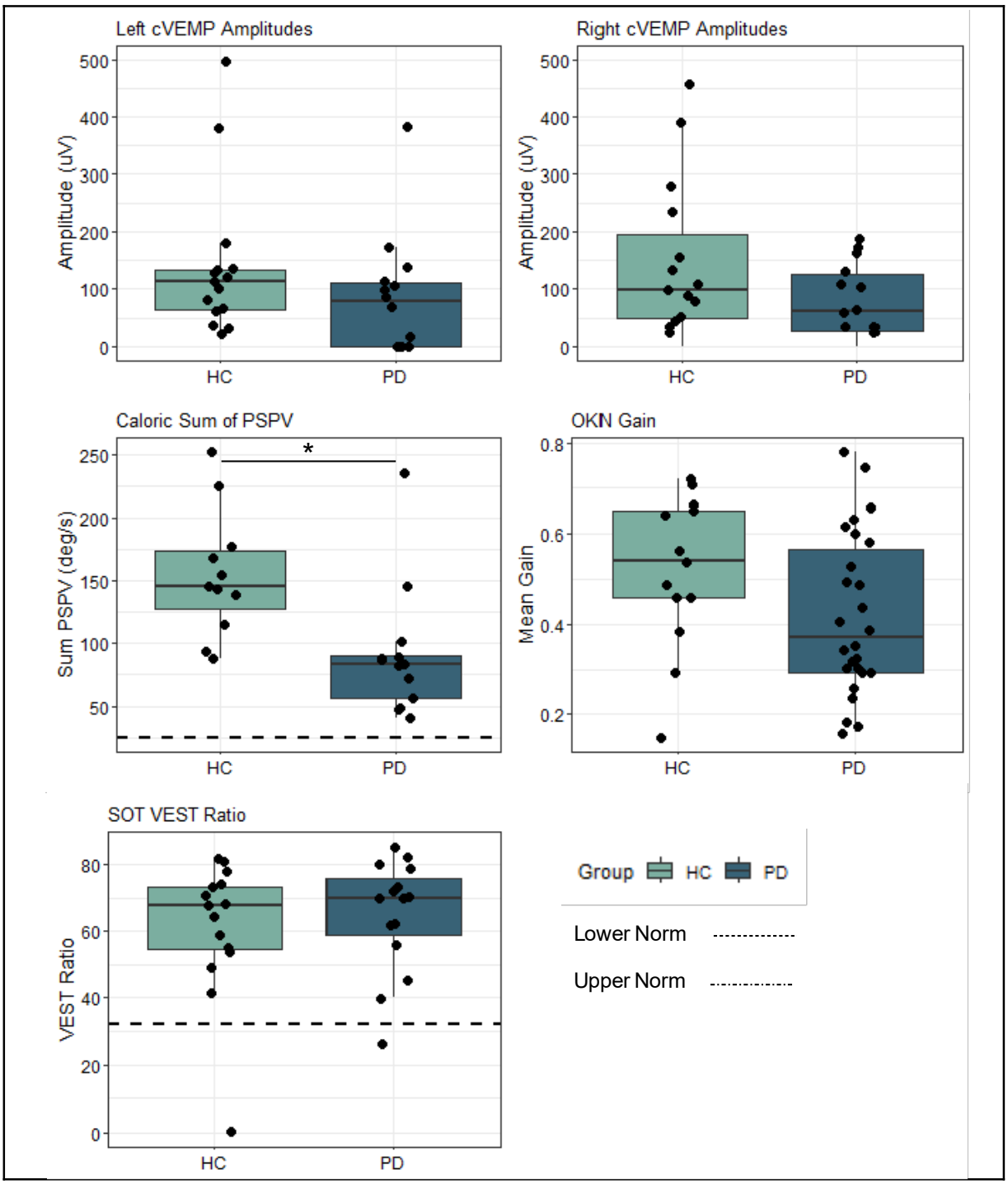
Table 3.3 Comparison of primary variables for controls and participants with PD

	Controls			PD			
Vestibular Test	n	mean (SD)	range	n	mean (SD)	range	p
Left cVEMP amplitude (uV)	15	139 (131)	22-497	14	85 (105)	0-384	0.24
Right cVEMP amplitude (uV)	15	146 (137)	0-459	14	77 (67)	0-188	0.11
Caloric PSPV Sum (deg/s)	11	155 (50)	88-252	12	90 (52)	40-235	**0.010**
OKN gain	13	0.52 (0.17)	0.15-0.72	13	0.41 (0.17)	0.16-0.66	0.13
SOT vestibular ratio	15	61 (21)	0-82	15	65 (17)	26-85	0.62

Note: c/oVEMP, cervical/ocular vestibular myogenic potential; PSPV sum, the sum of peak slow phase velocities for all irrigations; OKN, optokinetic nystagmus; SOT, Sensory Organization Test.
Bold indicates a p-value < 0.0125.

The results of comparisons for secondary measures of peripheral vestibular function are shown in **Table 3.4**. Ocular VEMPs were available for 11 participants with PD and 13 HC. There was unilateral absence of oVEMP in 1 (10%) participant with PD and none of the HC. Bilateral oVEMP absence was seen in 5 (50%) of participants with PD, and 3 (25%) HC. There were no significant differences between groups in any of the oVEMP measures. Caloric unilateral weakness was in an abnormal range for 2 (15%) participants with PD and 3 (27%) HC and was not significantly different between the groups (p = 0.63).

Figure 3.1 Primary vestibular test variables for healthy controls and participants with PD



Note. c/oVEMP, cervical/ocular vestibular evoked myogenic potential; HC, healthy controls; PD, participants with PD; PSPV, peak slow phase velocities; SOT, Sensory Organization Test; VEST vestibular ratio. Cutoff score for SOT VEST based on healthy control mean -2SD from Harro et al. 2018. * $p < 0.05$

For primary central vestibular function measures, OKN was available for 13 participants with PD and 13 HC participants and SOT was available for all 15 participants in both groups. Averaged OKN gain was below normal for both groups and did not significantly differ between PD and HC (PD 0.47 (0.17); HC 0.52 (0.17); $p = 0.13$). The SOT vestibular ratio did not significantly differ between PD and HC (PD 65 (17); HC 61 (21); $p = 0.62$) and appeared comparable to normal healthy ranges reported in similar aged groups (Harro et al., 2018). As shown in **Figure 3.2**, secondary central vestibular function testing found that on VOR suppression, gains were higher in the HC group, and above the normal cutoff range (PD 0.19 (0.07); HC 0.26 (0.07); $p = 0.01$). SVV was significantly more inaccurate in the PD group (PD 5.7 (4.9) deg; HC 1.6 (1.4) deg; $p = 0.01$).

Table 3.4 Comparison of secondary variables for controls and participants with PD

	Controls			PD			
Vestibular Test	n	mean (SD)	range	n	mean (SD)	range	p
L oVEMP amplitude (uV)	13	2.87 (2.64)	0.00-7.00	10	1.58 (2.02)	0.00-5.50	0.21
R oVEMP amplitude (uV)	12	3.7 (4.9)	0.0-12.7	11	1.7 (2.7)	0.00-7.87	0.26
cVEMP uni weak (%)	14	28 (26)	7-100	12	50 (39)	5-100	0.09
oVEMP uni weak (%)	9	48 (40)	8-100	5	33 (38)	8-100	0.47
cVEMP unilateral absent [a]	12	1 (6.7%)	--	10	4 (29%)	--	0.17
cVEMP bilateral absent [a]	15	0 (0%)	--	14	2 (14%)	--	0.22
oVEMP unilateral absent [a]	12	0 (0%)	--	10	1 (10%)	--	NA
oVEMP bilateral absent [a]	12	3 (25%)	--	10	5 (50%)	--	0.38
Caloric uni weak (%)	11	17 (16)	0-46	13	14 (12)	0-35	0.63
Caloric DP (%)	11	24 (35)	2-119	13	13 (8)	3-32	0.35
Positional horizontal n. [a]	15	0 (0%)	--	15	2 (13%)	--	0.48
Positional vertical n. [a]	15	1 (6.7%)	--	15	0 (0%)	--	>0.9
RCT sin gain [a]	15	0 (0%)	--	14	3 (21%)	--	0.10
RCT sin phase [a]	15	1 (6.7%)	--	14	2 (14%)	--	0.60
RCT sin asymmetry (%) [a]	15	0 (0%)	--	14	1 (7.1%)	--	0.60
VOR enhancement gain	14	0.94 (0.24)	0.38-1.27	13	0.83 (0.25)	0.41-1.25	0.28
VOR suppression gain	14	0.26 (0.07)	0.16-0.43	13	0.19 (0.07)	0.04-0.29	**0.01**
VOR suppression change (%)	13	63 (9)	45-74	12	58 (16)	39-82	0.31
RCT step gain	14	0.65 (0.13)	0.41-0.86	13	0.63 (0.15)	0.32-0.86	0.78
RCT step TC (s)	14	13.6 (5.4)	4.8-21.9	12	8.9 (4.0)	3.2-15.3	**0.02**
RCT step asymmetry (%)	14	5.0 (4.0)	0-11	13	9.0 (13.2)	0-49	0.36
SOT Composite	15	72 (10)	44-81	15	72 (10)	49-83	0.96
SOT visual ratio	15	81 (7)	68.0-95.0	15	80 (11)	51-94	0.76
SOT somatosensory ratio	15	97 (3)	92-104	15	97 (4)	84-102	0.89
SOT visual preference	15	94 (10)	67-106	15	93 (9)	72-104	0.71
Subjective Visual Vertical	14	1.6 (1.4)	0.02-5.06	14	5.7 (4.9)	0.8-16.9	**<0.01**
Oculomotor Test							
Pursuit gain	15	0.80 (0.17)	0.37-0.96	13	0.89 (0.10)	0.71-0.99	0.12
Pursuit phase	15	5.7 (3.7)	-1.8-11.3	13	5.3 (7.9)	-18.5-15.7	0.88
Saccade accuracy (%)	14	96 (4)	89-102	14	90 (7)	77.0-100.5	**0.01**
Saccade latency (ms)	14	224 (30)	168-269	14	218 (31)	181-271	0.60

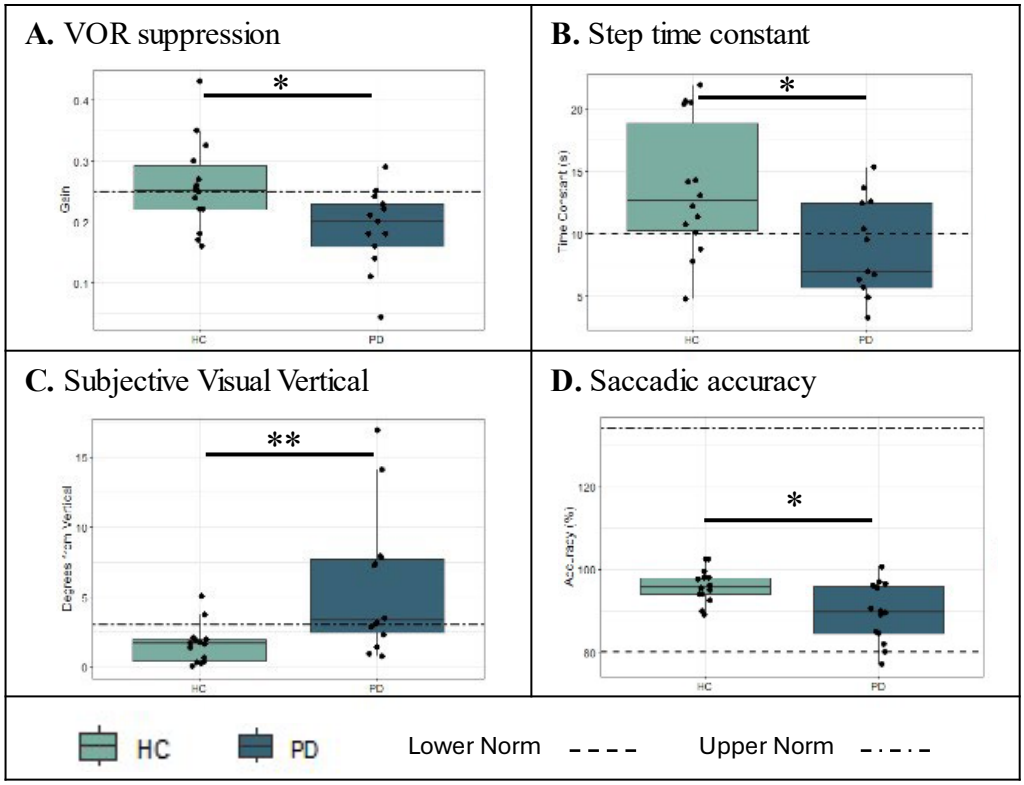
Note: c/oVEMP, cervical/ocular vestibular myogenic potential; DP, directional Preponderance; L, left; n., nystagmus; R, right; RCT, rotational chair test; uni weak, unilateral weakness; VOR, vestibulo-ocular reflex.

[a] count (%)

[b] Permutation test for continuous variables; Fisher's exact test for categorical variables.

Bold indicates a p-value < 0.05.

Figure 3.2 Differences between participants with PD and HC for significant secondary variables

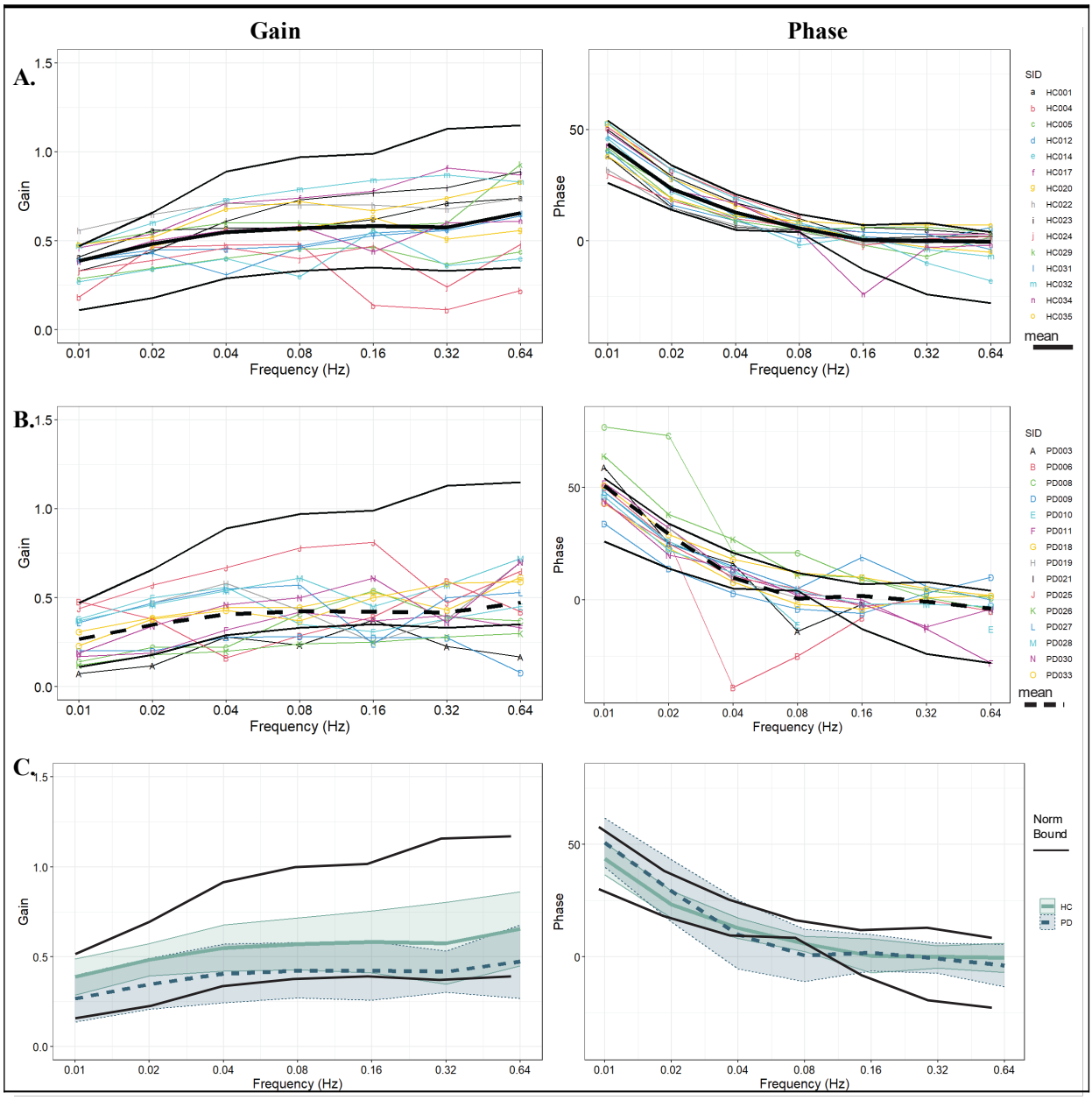


Note.HC, healthy controls. PD, participants with Parkinson disease.
* $p < 0.05$, ** $p < 0.01$

Sinusoidal rotational chair testing was completed on 14 participants with PD and 15 HC. As seen in **Figure 3.3**, the average sinusoidal gain for the PD group was lower than the HC group (PD 0.40 (0.12) HC 0.54 (0.14); $p < 0.01$). A pattern of clinically abnormal gain was seen in 4 (29%) of participants with PD and 1 (6.7%) HC. The average sinusoidal asymmetry was significantly higher in the PD group compared to HC (PD 9.94 (5.68)%; HC 5.89 (2.30)%; $p = 0.01$), and only 1 participant with PD and no HC had clinically abnormal asymmetry. The average sinusoidal phase was not significantly different between PD and HC. A pattern of clinically abnormal phase was seen in 4 (29%) of participants with PD and none of the HC participants. No other peripheral vestibular test results were different between groups. Rotational chair step testing was available for 13 participants with PD and 14 HC. On-average step testing

gain was normal for both groups and not significantly different between participants with PD and HC. Qualitatively, a unilateral weakness pattern on step gains was seen in 3 (15%) of participants with PD and none of the HC. Abnormal gains in 3 or more step conditions indicating bilateral weakness were seen in 1 (6.7%) of participants with PD and none of the HC. Participants with PD demonstrated time constants that were lower than HC (PD 8.9 (4.0) s; HC 13.6 (5.4) s; $p = 0.02$) and on average in an abnormal range. Specifically, below normal time constants were seen in 3 or more conditions for 8 (53%) participants with PD and 4 (26%) HC.

Figure 3.3 Sinusoidal rotational chair gain and phase for HC and PD.



Note. HC, healthy controls; PD, participants with Parkinson disease. **A.** Gain and phase for each HC. **B.** Gain and phase value for each participant with PD. **C.** Mean and 1 standard deviation for each group for gain and phase.

Significant oculomotor testing results can be seen in **Figure 3.2.** The PD group had decreased average left and right saccadic accuracy with hypometric saccades compared to HC (PD 90 (7)%; HC 96 (4)%; p = 0.01). No other central vestibular or oculomotor function

measures were different between groups. Qualitatively, there were saccadic intrusions present during smooth pursuit in both groups, with the greatest number of participants in each group having saccadic intrusions at 0.5 Hz stimulus. Saccadic components during 0.5 Hz pursuit were present in 11/14 (79%) participants with PD cases, and 7/15 (47%) HC.

3.5 Discussion

This study aimed to determine differences in vestibular function between people with PD, off medication, and healthy controls through comprehensive peripheral and central vestibular testing. When comparing means, there was evidence for reduced semicircular canal function in participants with PD compared to HC based on a decreased overall response to caloric irrigation. Centrally, participants with PD demonstrated abnormalities in rotational chair testing including signs of impaired velocity storage with shortened time constants on step testing and lower gain on sinusoidal rotational testing at higher frequencies. Both PD and HC showed low gain on OKN responses that did not significantly differ. Participants with PD also had significantly poorer and abnormal SVV estimation. Saccades were hypometric compared to controls, but on average within a normal range.

Peripheral vestibular test findings were converse to expectations. Unlike prior literature, this study found no difference in VEMP measures between people with PD and HC (Berkiten et al., 2022; Lazzaro et al., 2018; Shalash et al., 2017). Prior literature examining medication effects on VEMPs has shown no effect, or an improvement in amplitudes (Pötter-Nerger et al., 2012; Potter-Nerger et al., 2014). However, peripheral vestibular firing rates in response to tilt may be reduced when on-medication (Lithgow & Shoushtarian, 2015). It is possible that evidence for otolithic dysfunction in PD is a result of dopaminergic suppression of otolithic function. There

are known limitations in VEMP testing that relies on amplitude comparisons between individuals due to low inter-rater and intra-rater reliability of the test (Shahnaz & David, 2021). To account for this, the presence and absence of cVEMP and oVEMP responses as well as inter-ear differences were included in the secondary analysis. Although not significantly different, 29% of participants with PD had unilateral cVEMP loss compared to 6.7% of HC. Additionally, there were 50% of people with PD who lacked bilateral oVEMP responses, compared to 25% of HC. This higher prevalence of absent VEMP responses does trend toward findings in prior research (Cui et al., 2022). Because this study was exploratory, the sample size was small and both groups had a wide range of responses. The small sample and large variability could potentially mask smaller differences between the groups in the VEMP measures. The lack of significant difference in VEMPs between groups in the current study could also be due to the participants with PD having lower disease severity because of inclusion criteria for balance and walking tests. A meta-analysis by Cui et al. found that when stratified by disease severity, differences in VEMP testing between PD and controls were only significant for the more affected PD group based on Hoehn &Yahr stage (Cui et al., 2022). Qualitatively, no trend was seen for a higher prevalence of absent VEMPs for participants with more severe disease based on MDS-UPDRS-3 scores, which ranged from 0-51.

The results of lower response to caloric testing in participants with PD were also unexpected based on prior research (Cicekli et al., 2019; Venhovens, Meulstee, Bloem, et al., 2016). On average, the summed PSPV caloric response for both groups was within clinic-based normal ranges (unpublished data). Few studies have used caloric irrigation to assess SCC function in response to a low-frequency stimulus in PD (Cicekli et al., 2019; Reichert et al., 1982; Venhovens, Meulstee, Bloem, et al., 2016). In comparison, high-frequency stimulus testing

of the SCC using the video head impulse test has shown that SCC function is normal in PD (Berkiten et al., 2022; Hawkins et al., 2022). Like the cochlea that has a sensitivity to a range of sound frequencies, where loss can occur in specific ranges, the vestibular system may also be affected in the detection of only some frequencies of acceleration. There may be differences in lower frequency SCC responsiveness in PD that are not detected in tests utilizing higher frequency stimuli such as video head impulse testing. Low-frequency stimuli should be considered in future work examining SCC function in people with PD to ensure that the full range of SCC sensitivity is assessed.

Primary central test findings did not demonstrate differences in function on tests for OKN or for sensory integration functions on the SOT. Prior research has shown abnormal or decreased responses during OKN in people with PD (Cipparrone et al., 1988; Venhovens, Meulstee, Bloem, et al., 2016; Zhou et al., 2024). Given this, the lack of difference in OKN is unexpected but may be due to participants with PD in this study demonstrating milder disease than in prior studies. In both groups, the average eye gains were below normal. This could indicate that OKN velocity decreases with age because the normative cutoff values available were not adjusted for age. It is also possible that the contrast of the projected dot pattern stimulus in the test system used was not sufficiently compelling to drive full OKN responses in either group of older participants.

Prior research indicates that vestibular integration in PD may be affected; however, that was not seen in the results of the SOT here (Bohnen, Roytman, et al., 2022; Doná et al., 2016; Harro et al., 2018; Huh et al., 2016). Existing studies describing abnormalities of vestibular integration in PD have used different measures of integration including stimuli with greater visual-vestibular conflict such as optokinetic stimuli, or a concurrent saccade task (Doná et al., 2016; Harro et al., 2018). The testing protocol completed in this study used the standard visual

surround, with no concurrent task. Other work only found differences in people with PD who had specific motor impairments such as freezing of gait (Bohnen, Roytman, et al., 2022; Huh et al., 2016). This may indicate that vestibular integration abnormalities become evident only in later disease stages when motor impairments such as freezing often appear.

There were secondary findings that indicate central vestibular deficits in PD, including significant differences in some measures on sinusoidal chair testing, step testing, and abnormal SVV. Rotational chair testing assesses vestibular function at low to moderate frequency stimuli and has rarely been used to interrogate vestibular function in PD (Venhovens, Meulstee, Bloem, et al., 2016; White, Saint-Cyr, et al., 1983). This study found evidence of reduced velocity storage function with lower gains on sinusoidal testing with more asymmetrical responses, and reduced time constants on step testing. Participants with PD, on average, had normal phase. With central compensation following a unilateral peripheral loss, sinusoidal testing shows a pattern of phase advance in the presence of normal gain and asymmetry values (Maes et al., 2008). **Figure 3.3** shows that not all participants with PD who had clinically low gains had a corresponding phase advance that would be expected in a well-compensated unilateral peripheral hypofunction. Shortened time constants on step testing were also seen in participants with PD. Only one other study was available with rotational step testing in people with PD for comparison, with no abnormal findings reported (Venhovens, Meulstee, Bloem, et al., 2016). Typically, shortened time constants on rotational testing are accompanied by decreased gain in peripheral lesions while lesions in the areas of the vestibulo-cerebellum lead to prolonged time constants (Arriaga et al., 2005). Taken together results of rotational chair testing point toward possible velocity storage deficits in the VNC or cerebellum in people with PD. Reduced caloric PSPV, could indicate peripheral SCC dysfunction, or central dysfunction of nystagmus generation. Further

research is needed to determine if people with PD consistently demonstrate signs of abnormal velocity storage and to rule out possible low-velocity deficits of peripheral SCC function.

Decreased VOR suppression in PD has been seen in prior research (Hawkins, Rey-Martinez, et al., 2021; Naito et al., 2024; Venhovens, Meulstee, Bloem, et al., 2016; White, Saint-Cyr, et al., 1983). In a vestibular examination, poor VOR suppression is associated with cerebellar dysfunction (Beh et al., 2017). In this group, participants with PD demonstrated significantly lower gains during VOR suppression, which could indicate better suppression than HC. However, participants with PD also had lower overall gain without suppression at the same stimulus frequency (0.64 Hz), and a smaller change in VOR with suppression. Because of the lower unsuppressed gain, this finding should be interpreted with caution. In fact, a greater number of HC had abnormal VOR suppression, which supports existing evidence of age-related declines in cerebellar function (Arleo et al., 2024).

Oculomotor testing was consistent with existing literature relative to the finding that saccades were hypometric in participants with PD compared to HC (Zhou et al., 2024). Although there were no differences between the two groups for smooth pursuit phase or gain, participants with PD had a more frequent presence of saccadic intrusions on smooth pursuit (79% PD and 47% HC at 0.5 Hz). This trend is consistent with the current understanding of oculomotor impairments in PD, which may be due to disease-related non-dopaminergic pathway involvement (Frei, 2021; W. Ma et al., 2022; Waldthaler et al., 2019).

Finally, this study found larger SVV deviations in participants with PD that are consistent with previous reports of altered visuospatial orientation in people with PD (Artusi et al., 2022; José Luvizutto et al., 2020; Scocco et al., 2014). Altered SVV with normal otolithic function may indicate an underlying ocular torsion (rotation of the eye) due to central or peripheral lesions, or

a central processing disruption of cortical or subcortical areas involved in the judgment of verticality (Saj et al., 2019). Following the acute phase of otolithic loss, SVV typically approaches normal due to central compensation. In other studies, altered SVV, decreased otolithic function, and decreased caloric responses each appear to be associated with trunk lateroflexion in PD (Artusi et al., 2022; Gandor et al., 2016; Huh et al., 2016; Lazzaro et al., 2018; Sasaki et al., 2022). Although not explored here, this could indicate that poorly compensated peripheral dysfunction or central vestibular processing deficits may contribute to postural abnormalities in PD.

3.5.1 Limitations

Limitations in this study include the small sample size leading to underpowered comparisons for secondary vestibular variables. This study was conducted at a single site, and the demographic characteristics of the groups did not reflect the racial and ethnic proportions of the local population. Interpretation of results is therefore limited to the population studied. Due to the length and extent of testing, multiple participants were not able to complete all planned testing, further reducing the sample size for some variables. Additionally, the participants with PD had relatively mild disease severity, which could explain the lack of expected significant differences in VEMP and OKN between groups. These limitations could be addressed in future research utilizing a longitudinal cohort approach to determine if there are associations between disease progression and specific dysfunction through targeted caloric and rotational chair testing. Two HC participants had a family history of PD, and the potential prodromal manifestation of vestibular or oculomotor could have confounded group comparisons. To reduce the possibility of control participants with undiagnosed PD, future inclusion criteria could eliminate control participants with a family history of PD.

3.5.2 Conclusion & Clinical Implications

People with PD may have a range of vestibular deficits beyond those expected due to aging, including impairments in peripheral semicircular canal function and non-dopaminergic central vestibular and oculomotor pathways. Vestibular testing should be considered for people with PD including tests of low-frequency vestibular responses, and individualized treatment provided using established vestibular rehabilitation techniques. If testing indicates VOR suppression pathway involvement, limiting the ability for VOR adaptation, treatment should focus on compensatory strategies. Additional research is needed to verify potential velocity storage deficits in PD, what effects dopaminergic medications for PD have on vestibular impairments, and to determine if vestibular rehabilitation is effective for people with PD.

CHAPTER 4: DOPAMINERGIC MEDICATION EFFECTS ON VESTIBULAR FUNCTION IN PARKINSON DISEASE

4.1 Abstract

Background: Parkinson disease (PD) results in a variety of progressive motor and non-motor features, and current literature suggests that vestibular dysfunction may be a non-motor feature of PD (Cui et al., 2022; Smith, 2018). However, little is known about the role of dopamine in peripheral and central vestibular functions (Canton-Josh et al., 2022; Stiles & Smith, 2015). It is possible that there is non-dopaminergic involvement of the vestibular system in PD (Bohnen, Kanel, Roytman, et al., 2022; Frei, 2021; Hawkins, Rey-Martinez, et al., 2021). The objective of this research is to determine the effects of dopaminergic medication on peripheral and central vestibular function through a comparison of comprehensive vestibular assessments in people with PD.

Methods: Fifteen people with PD were tested while OFF and ON medication using comprehensive, instrumented vestibular assessment. Primary outcome variables for peripheral vestibular function were cervical vestibular-evoked myogenic potentials (cVEMP) for otolithic function, caloric testing sum of peak slow phase velocities (PSPV) for semicircular canal function (SCC), and optokinetic nystagmus (OKN) gain for vestibular nuclear complex and related nuclei function, and the vestibular ratio of the Sensory Organization Test (SOT) for vestibular sensory integration. Secondary outcome variables included ocular VEMPs, rotational chair sinusoidal and step testing, vestibulo-ocular reflex suppression and enhancement, subjective visual vertical (SVV), videonystagmography for positional testing, post-head shake nystagmus test, and oculomotor testing for gaze stability, smooth pursuit, and saccades. Additionally, test results were classified as normal or abnormal based on clinical criteria.

Permutation of paired statistics was used for continuous variables and Fisher's exact test was used for categorical variables.

Results: There were no significant differences for any primary or secondary vestibular test between off- and on-medication conditions. Qualitatively, participants had a variety of abnormal test results when off medication. These include unilateral weakness on cVEMP, low OKN gain, shortened step testing time constants, abnormal SVV, and saccadic components during smooth pursuit.

Discussion: The results seen here support that dopaminergic medications do not impact peripheral or central vestibular function as measured by VEMPs, caloric, and rotational chair testing. Abnormal results of vestibular testing may indicate central vestibular involvement in PD. The lack of medication response implies that vestibular dysfunction in PD may be due to the non-dopaminergic impacts of PD. This study was limited by a small sample size and reduced tolerance by some participants for vestibular testing when off medication.

Conclusions: Vestibular dysfunction is present in PD and does not appear responsive to dopaminergic medications. Assessment and treatment using established and novel vestibular interventions may be useful in managing PD-associated vestibular dysfunction.

4.2 Introduction

Parkinson disease (PD) results in a variety of progressive motor and non-motor features, and there is current literature suggesting that vestibular dysfunction may be a non-motor feature of PD (Cui et al., 2022; Smith, 2018). The vestibular system primarily uses glutamatergic and cholinergic signaling, however little is known about the role of dopamine in peripheral and central vestibular functions (Canton-Josh et al., 2022; Stiles & Smith, 2015). Current literature examining vestibular function in PD has rarely accounted for the use of dopaminergic medications in people with PD (Beylergil, Noecker, et al., 2022; Pötter-Nerger et al., 2012; Potter-Nerger et al., 2014; Scocco et al., 2014). Additionally, no existing studies have assessed the effect of medication in PD using comprehensive vestibular testing to examine both peripheral and central functions.

There is evidence from non-human animal models that dopamine may play an excitatory role in the otolithic organs or semicircular canals (SCC) of the vestibular periphery (Andrianov et al., 2009; Drescher et al., 2010; Toro et al., 2015). Dopamine receptors and dopamine have been found in the human saccule (Eberhard et al., 2022), however, it is unknown if dopamine has an excitatory or inhibitory function in the human peripheral vestibular system. Peripheral vestibular function of the otolithic organs of people with PD appears to be either improved or unchanged in response to medication (Pötter-Nerger et al., 2012; Potter-Nerger et al., 2014). Only one study has assessed semicircular canal responses related to medication (Reichert et al., 1982). However, the comparison was between medication naïve participants and participants with more advanced PD.

Centrally there is evidence that dopamine may play an inhibitory role in the regulation of vestibular processing in the vestibular nucleus complex (VNC) or related structures (Andrianov et al., 2009; Drescher et al., 2010; C. Lee & Jones, 2017). Dopaminergic medications appear to increase postural sway in people with PD, however, this is likely due to changes in rigidity or increased dyskinesias (Bronte-Stewart et al., 2002; Curtze et al., 2015). However, abnormalities in subjective visual vertical (SVV) and vestibular heading performance do not appear to improve in people with PD when on compared to off medication (Scocco et al., 2014; Yakubovich et al., 2020).

There may be non-dopaminergic involvement of the vestibular system in PD (Bohnen, Kanel, Roytman, et al., 2022; Frei, 2021; Hawkins, Rey-Martinez, et al., 2021). Impaired use of vestibular inputs during postural control tasks appears to be associated with cholinergic deficits in PD (Bohnen, Kanel, Roytman, et al., 2022). Known impairments in oculomotor function in PD may be due to disease impacts on shared brainstem and vestibulo-cerebellar pathways (Frei, 2021; Hawkins, Rey-Martinez, et al., 2021). There is a need for comprehensive vestibular testing to assess the potential impacts of dopaminergic medication on peripheral and central vestibular function in PD. Understanding the impacts of dopaminergic medications on vestibular functions in PD could give insight into the role of dopamine in the vestibular system and potential non-dopaminergic vestibular pathway involvement in PD. These insights could guide considerations for the treatment of vestibular dysfunction in PD, and potential novel approaches to address non-dopaminergic impacts of PD.

This study aimed to address the gaps in our understanding of medication impacts on vestibular function in PD and potential non-dopaminergic vestibular involvement. The objective of this research was to determine the effects of dopaminergic medication on peripheral and

central vestibular function through a comparison of comprehensive vestibular assessments in people with PD while functionally off medication (OFF; medications withheld at least 8 hours) to their testing when on their typical medications (ON). Based on the existing literature, it was hypothesized that peripherally, dopaminergic medications will improve otolithic but not SCC function, while centrally medications will inhibit VNC functions for ocular motion and central vestibular integration for postural control.

4.3 Methods

People with PD participated in a quasi-experimental study to determine the effects of dopaminergic medication on comprehensive vestibular testing results. This study was approved by the University of Washington Institutional Review Board, and all participants gave informed consent before participating in study visits.

4.3.1 Participants

We recruited participants with PD from the greater Seattle, WA area. Recruitment was through the Washington State Parkinson Disease Registry, local PD exercise and support groups, university webpage advertisements, and snowball recruitment. Eligibility criteria were: 1) age between 40-90 years old; 2) a diagnosis of PD without dementia; 3) current stable use of dopaminergic medications for at least 3 months; 4) no use of cholinergic medications to treat PD; 5) no history of neurosurgical interventions for PD (e.g. deep brain stimulator placement); 6) no history of other neurological disorders that would affect vestibular, oculomotor, or postural control functions; 7) no previous history of other diagnosed vestibular or auditory disorders; 8) no prior or ongoing exposure to drugs affecting audiovestibular function (e.g. ototoxic medications); 9) ability to stand and walk for at least 2 minutes with or without an assistive

device; and 10) no major musculoskeletal or peripheral disorders that could significantly affect balance or gait.

4.3.2 Clinical and Demographic Data Collection

Participants completed custom questionnaires and a focused interview to obtain age, sex and gender, race and ethnicity, level of education, and duration of PD. Co-existing medical conditions were ascertained using the Charlston Comorbidity Index (Quan et al., 2011). The Montreal Cognitive Assessment (MoCA) was used to assess global cognition (Nasreddine et al., 2005). The Dizziness Handicap Inventory (DHI) (Jacobson & Newman, 1990) was used to assess the impact of any dizziness or imbalance symptoms. Motor complications of PD were measured using the Movement Disorders Society Sponsored Unified Parkinson Disease Rating Scale (MDS-UPDRS) Part 4 – Motor Complications (Goetz et al., 2008), and the new Freezing of Gait Questionnaire (nFoG) without video (Nieuwboer et al., 2009). Balance ability was reported with the Activities-specific Balance Confidence Scale (ABC) (Powell & Myers, 1995).

The remaining tests were completed both OFF and ON. The first three participants were tested while ON during their first visit to gauge tolerance for participants with PD to complete comprehensive testing in a single visit. Remaining OFF and ON testing was randomized and blinded to the researcher performing recruiting until each participant was screened and accepted into the study. Researchers completing data collection and analysis were not blinded to medication state. The maximum time between the first and last testing sessions was 12 weeks. All remaining clinical, balance, gait, and vestibular tests were completed with the same protocol described in Ch 3.3, where additional details are provided.

Testing each session consisted of clinical examination, gait and balance measures, and vestibular testing. Orthostatic hypotension testing was performed to determine if a drop in blood pressure with position changes could contribute to any reported dizziness (NICE, 2019). Motor symptoms were assessed during OFF and ON visits using the MDS-UPDRS Part 3 - Motor Examination (Goetz et al., 2008). Clinical balance during gait was assessed using the Functional Gait Assessment (FGA), (Wrisley & Kumar, 2010) a clinical test consisting of ten walking activities, such as walking with head turns, narrow base walking, and climbing stairs. Additional balance and gait testing was conducted using inertial sensors (Opal by APDM, Inc., Portland, OR) at the wrist, feet, waist (lumbar), and sternum to quantify spatiotemporal variables. Participants performed the modified Clinical Test of Sensory Integration for Balance (Freeman et al., 2018) by standing with eyes open and closed on a firm floor and then a foam surface. Sway area during each condition was quantified as the root mean square (RMS, m/s^2) of sway using the lumbar sensor. A 2-minute walking task with turns was also completed to obtain gait speed (m/s) and turn velocity (deg/s) (R. Morris, Stuart, et al., 2019). Balance and gait variables were calculated using Mobility Lab software.

Otoscopy was completed during all visits to ensure that the tympanic membrane was intact, and that cerumen did not interfere with vestibular testing procedures. If excessive cerumen was present, participants completed all tests except those where cerumen would interfere. Participants were asked to return to complete the remaining tests following ear cleaning at home using over-the-counter peroxide-based cleaning drops.

4.3.3. Vestibular Function Assessments

Assessments were completed for otolithic, semicircular canal, and central vestibular functions. The primary measure of otolithic function was cervical vestibular evoked myogenic potentials (cVEMP), representing saccular function. Vibrations of the saccule were induced through 500 Hz tone bursts at 95dB normal hearing level (NHL) in each ear to elicit reflexive responses. Surface electromyography recorded saccular-driven vestibulo-spinal reflex inhibition at the ipsilateral sternocleidomastoid while contracted (BioLogic Navigator Pro, Natus Medical Inc., San Carlos, CA). Further details of VEMP parameters can be found in Ch 3.3.3. Saccular function was quantified as the P1-N1 interpeak amplitude (μV). The utricle-driven VOR was also measured using ocular VEMP (oVEMP) for each ear with the same stimulus parameters while recording activation of the contralateral inferior oblique. Utricular function was quantified as N1-P1 interpeak amplitude. The relative difference in amplitudes between ears was calculated for both cVEMP and oVEMP (see Ch1.3.3).

The primary test of semicircular canal function was bithermal caloric irrigation. Caloric testing used cool (24° C) and warm (47° C) air irrigation in each ear canal to cause temperature-induced endolymph flow in the horizontal semicircular canal of each ear with resultant cupular deflection and a nystagmus response. The slow phase of nystagmus representing the VOR was measured by videonystagmography (VNG) which used an infrared camera and eye tracking software to record eye movements (Micromedical VisualEyes, Spectrum 8.10). The primary variable was the sum of peak slow phase velocity (PSPV, deg/s) for all irrigations. Asymmetry in response between ears (%) was calculated using Jongkee's Formula and directional preponderance of nystagmus (%) data was also collected (see Ch1.3.3 for formulas).

The primary measure of the integrity of the VNC was horizontal optokinetic nystagmus (OKN). Optokinetic nystagmus is driven by retinal slip of a moving visual stimulus and eye movements are believed to be generated primarily through the VNC. Testing for OKN used a full-field stimulus at frequencies of 20, 30, and 45 Hz while the participant was seated in a fully darkened room and recorded using VNG (I-Portal Neuro-Otologic Test Center, Neuro Kinetics Inc., Pittsburgh, PA). Quantification of OKN used the mean gain (see Ch 1.1.3 for definition) of responses to all stimuli. For some participants, OKN could not be recorded at all stimulus frequencies due to eye closure from somnolence, dystonia, or inattention during testing. Phase and symmetry (%) of OKN were also recorded as secondary variables.

The primary measure of central vestibular sensory integration was the Sensory Organization Test (SOT) vestibular score (Pedalini et al., 2009). The SOT uses a mobile force plate and visual surround to assess the ability of the participant to use vestibular, visual, and somatosensory inputs to maintain postural stability and to re-weight sensory strategies under conditions of sensory conflict (Neurocom Equitest, Natus Medical, Middleton, WI). The SOT has six conditions, which are: 1) eyes open, 2) eyes closed, 3) sway-referenced surround all with a stable support surface, then 4) eyes open, 5) eyes closed, and 6) sway-referenced surround all with a sway referenced surface. Performance on each trial is represented by an equilibrium score, sensory ratio scores, and a Composite score. For details of how equilibrium scores are calculated see Ch 1.3.3. When peripheral vestibular testing is normal, poor postural control during conditions 5 and 6 are believed to represent abnormal central vestibular integration (Nashner & Peters, 1990; Voorhees, 1990). Participants completed three trials of each condition. The SOT vestibular score is the ratio of the average equilibrium scores for condition 5, which relies on vestibular input, to condition 1 where all sensory information is available and accurate (Nashner

& Peters, 1990). The vestibular score was selected to account for differences in sway during testing OFF and ON that may have been due to the presence of tremors or dyskinesia that could be detected during condition 1.

Additional vestibular assessments were completed to provide context for interpretation of the primary outcome measures. These included VNG testing for gaze-evoked nystagmus, positional testing, and post-head shake nystagmus. Static positional testing was performed seated with the head in neutral and head hanging forward, supine, and side-lying right and left positions to determine the presence of positional nystagmus. Nystagmus was considered present if there were more than three beats of nystagmus during positional testing with an average slow phase velocity greater than 6 deg/s. Passive and active head shake testing was used to assess for the presence or absence of any post-head shake nystagmus. Rotational chair testing of horizontal canal function was performed using the same Neurokinetics I-portal system as OKN testing. Rotational chair testing included sinusoidal testing, VOR enhancement, VOR suppression, and step testing (see Ch 1.3.3 for full descriptions). Sinusoidal testing was completed with rotations at 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, and 0.64 Hz in darkness to evoke a VOR response across a range of accelerations closer to natural vestibular stimuli. Central vestibular function of cerebellar and smooth pursuit pathways was tested using VOR enhancement at 0.8 Hz and suppression during 0.64 Hz sinusoidal rotations. Gain, phase, and asymmetry were collected for sinusoidal rotations as described in Ch 1.3.3. Step testing assessed the VOR peak gain and asymmetry (%) of gain at a constant velocity of 100 deg/s and immediately after stopping rotations. Central velocity storage was also assessed during step testing for the timing of nystagmus decay through the VOR time constant (s) (see Ch 1.3.3 for more complete descriptions of step testing variable definitions). Vestibular gravitational perception relying on

otolithic function and central integration was measured using subjective visual vertical at the end of rotational chair testing. Subjective visual vertical was quantified by the mean error from earth vertical (deg) when the participant was asked to adjust a projected bar into a vertical position while in an environment devoid of visual cues.

Oculomotor function was tested to assess the involvement of eye movement-related central pathways and to ensure that oculomotor abnormalities did not interfere with eye movements during vestibular testing. This included horizontal smooth pursuit at 0.1, 0.3, and 0.5 Hz stimulus frequency and horizontal saccades. Smooth pursuit was quantified as gain and phase for each stimulus velocity (see Ch 1.3.3). The presence of saccadic eye movements during pursuit testing was noted. Saccades testing was quantified by the latency (ms) and accuracy (%) of visually-driven saccades (see Ch 1.3.3).

4.3.4 Statistical Analysis

Demographic and clinical variables were described using mean and standard deviation or percentages. Normality of continuous variable distribution was determined using histogram inspection and the Shapiro-Wilk test for all vestibular, balance, and gait variables. To determine the effect of dopaminergic medication on motor examination and clinical balance and gait variables, a paired t-test was used. To determine the effect of medication on primary vestibular variables, cVEMP amplitude, caloric summed PSPV, OKN gain, and SOT vestibular ratios were compared between OFF and ON conditions. Continuous variables were inspected using histograms. Due to concerns regarding the normality of variable distribution permutation of paired statistics were used to determine the significance of differences between medication states. Significance was set at $p < 0.0125$.

Additional analyses were performed to describe differences between OFF and ON for secondary vestibular, balance, and gait variables using permutation of paired statistics for continuous variables, and Chi-squared test for categorical variables. Significance was set at $p < 0.05$. Due to differences in laboratory techniques and equipment compared to other studies, descriptive determinations of normal or abnormal responses use clinical-based normative values (unpublished data) for cutoff criteria when available. If clinical normative cutoff data were not available, manufacturer-supplied cutoffs were used.

Due to the exploratory nature of this secondary analysis, correction for multiple comparisons was not made. However, given the cutoff for significance at $p < 0.05$ and 30 comparisons performed, 1.5 significant results could be expected by chance alone.

4.3.5 Role of Funding Source

This project was supported by funding from the University of Washington Auditory Neuroscience Training Program (T32DC005361), the Foundation for Physical Therapy Research, the Walter C. and Anita C. Stolov Research Fund, the University of Washington Retirement Association, and the Virginia Merril Bloedel Hearing Research Center. The funders played no role in the design, conduct, or reporting of this study.

4.4 Results

Testing was completed for 15 participants with PD both OFF and ON. Demographic characteristics are shown in **Table 4.1.** Clinical characteristics are shown in **Table 4.2**. Demographic and clinical variables are described using mean and standard deviation (SD) or count and percentage. The average age of participants was 71.9 (range 59.0-82.0) years, and 6 (40%) participants were female. Average disease duration was 7.3 (range 1.2-14.0) years since

diagnosis. The average levodopa equivalent daily dose for participants was 720.6 (359.6) mg. Participants generally had mild to moderate motor signs of PD based on MDS-UPDSR-3 scores when OFF with mean scores of 21.7 (13.5), ranging from 0-51. Motor exam improved when ON to 16.1 (10.2; range 2-40, $p < 0.01$). Reported impact of dizziness or imbalance symptoms on the DHI was 20.1 (14.5) and average balance confidence on the ABC scale was 90.1 (11.4). On clinical balance testing, the average FGA scores were above the cutoff for increased risk for falls and did not significantly change between OFF and ON (OFF 24.7 (4.8); 25.2 (5.6), $p = 0.59$). There was a significant difference for mCTSIB Condition 2 RMS sway from 0.11 (0.05) m/s^2 OFF, increasing to 0.15 (0.06) m/s^2 when ON ($p < 0.01$). No other mCTSIB measures were significantly different based on medication state. Gait speed significantly improved from OFF to ON (OFF = 1.0 (0.1) m/s; ON = 1.1 (0.1) m/s; $p = 0.03$). There was no significant difference in turn velocity based on medication state ($p = 0.16$).

Table 4.1 Demographic characteristics

	mean (SD)	range
Age	71.9 (6.7)	59.0-82.0
Sex (female) [a]	6 (40%)	
Race [a]		
Other	0 (0%)	
White	15 (100%)	
Ethnicity [a]		
Hispanic/Latinx	0 (0%)	
Non-Hispanic/Latinx	15 (100%)	
Education [a]		
Some High School	0 (0%)	
High School/GED	0 (0%)	
Bachelor's	8 (53.3%)	
Graduate	7 (46.7%)	

Note: [a] count (%)

Table 4.2 Clinical, balance, and gait characteristics

	OFF		ON		
Clinical	mean (SD)	range	mean (SD)	range	p [a]
PD Duration	7.3 (4.0)	1.2-14.0	--	--	
Falls [b]					
No falls	8 (53.3%)		--	--	
< 1/mo	6 (40.0%)		--	--	
1-3/mo	1 (6.7%)		--	--	
DHI	20.1 (14.5)	2-46	--	--	
ABC	90.1 (11.4)	67.5-100	--	--	
MDS-UPDRS-3	21.7 (13.5)	0-51	16.1(10.2)	2-40	**<0.01**
MDS-UPDRS-4	5.2 (3.2)	0-11	--	--	
nFoG	1.7 (4.8)	0-17	--	--	
Hoehn & Yarh	2.0 (0.4)	1-3	--	--	
MoCA	27.2 (2.7)	19-30	--	--	
LED	720.6 (359.6)	300-1,514	--	--	
Balance and Gait					
FGA	24.7 (4.8)	16-30	25.2 (5.6)	11-30	0.59
mCTSIB					
1 Eyes open, floor	0.12 (0.05)	0.07-0.24	0.14 (0.07)	0.07-0.31	0.17
2 Eyes closed, floor	0.11 (0.05)	0.06-0.20	0.15 (0.06)	0.06-0.26	**<0.01**
3 Eyes open, foam [c]	0.17(0.05)	0.09-0.28	0.22 (0.12)	0.10-0.56	0.10
4 Eyes closed, foam [c]	0.19 (0.09)	0.11-0.38	0.20 (0.07)	0.12-0.37	0.18
Fall during test [b]	6 (30%)	--	6 (30%)	--	NA
Gait Speed	1.0 (0.1)	0.7-1.2	1.1 (0.1)	0.8-1.3	**0.03**
Turn Velocity	150.2 (27.8)	114.5-206.6	162.6 (20.2)	121.9-200.8	0.16

Note: ABC, Activity-specific Balance Confidence Scale; DHI, Dizziness Handicap Inventory, FGA, Functional Gait Assessment; LED, levodopa equivalent dose (mg); mCTSIB, Modified Clinical Test of Sensory Integration and Balance; MDS-UPDRS-3/4, Movement Disorders Society-sponsored Unified Parkinson's Disease Rating Scale, Part 3 – Motor Examination/ Part-4, Motor Complications; nFoG, New Freezing of Gait questionnaire; PD Duration, years since diagnosis with Parkinson disease.

[a] Paired t-test

[b] count (%)

[c] Due to participant falls during testing sway data was not compared for all OFF and ON resulting in n=11 for eyes open, foam, and n=12 for eyes closed, foam.

Bold indicates a p-value < 0.05.

Due to limitations in tolerance for testing for OFF medication status, or equipment issues, full testing was unable to be completed for some participants. The results of comparisons for primary outcome measures can be seen in **Table 4.3**. There were no significant differences in comparisons of medication state for any primary variables. Ratings of OFF testing for each participant as normal or abnormal are shown in **Figure 4.1.** For otolithic function, cVEMP testing was available for 14 participants OFF and 15 participants ON. Unilateral cVEMP absence was seen in 4 (29%) of participants when OFF, and 3 (20%) when ON. Bilateral cVEMP absence was seen in 2 (14%) of participants when OFF, and 2 (13%) when ON. The mean amplitudes for cVEMP when OFF were 85 (105) μV for the left ear and 77 (67) μV for the right ear. When ON the mean amplitudes were 69 (86) μV for the left ear ($p = 0.69$) and 71 (68) μV for the right ear ($p = 0.83$). Caloric testing was completed for 13 participants when OFF, and 15 participants ON. The summed caloric PSPV was in a normal range without a difference between OFF (19 (52 deg/s) and ON (87 (49) deg/s; $p = 1.86$). For central vestibular testing, OKN was completed for 13 participants OFF and 13 ON. When OFF, OKN gain was below normal (0.47 (0.16)) and was not significantly different when ON (0.46 (0.19); $p = 0.82$). The SOT was completed with all 15 participants both OFF and ON. One participant completed all conditions except condition 6 when ON and all conditions when OFF. All other participants were able to complete testing for every condition. The SOT vestibular ratio was 65 (17) when OFF and was not significantly different when ON (63 (23); $p = 0.82$). These scores were similar to those seen in healthy similar-aged adults in prior literature (Harro et al., 2018). Multiple participants had falls during OFF or ON SOT testing during the SOT in conditions 4, 5, and 6. During condition 4, two (13%) participants had falls when OFF and 1 (6.7%) when ON. During condition 5, three (20%) participants had

falls when OFF and 4 (27%) when ON. During condition 6, six (40%) participants had falls when OFF, and 3 (21%) had falls when ON.

Table 4.3 Comparison of primary variables for off and on medication

	OFF			ON			
Vestibular Test	n	mean (SD)	range	n	mean (SD)	range	p
Left cVEMP amplitude (μV)	14	85 (105)	0-384	15	69 (86)	0-334	0.67
Right cVEMP amplitude (μV)	14	77 (67)	0-188	15	71 (68)	0-222	0.82
Caloric PSPV Sum (deg/s)	13	90 (52)	40-235	15	87 (49)	20-166	0.86
OKN gain	13	0.47 (0.16)	0.16-0.66	13	0.46 (0.19)	0.18-0.78	0.82
SOT vestibular ratio	15	65 (17)	26-85	15	63 (23)	0-83	0.82

Note: c/oVEMP, cervical/ocular vestibular myogenic potential; PSPV sum, the sum of peak slow phase velocities for all irrigations; OKN, optokinetic nystagmus; SOT, Sensory Organization Test.

Secondary vestibular and oculomotor measures can be seen in **Table 4.4**. There was no significant difference between OFF and ON for any of the test variables. Cervical VEMP unilateral weakness was 50 (39)% OFF and 45 (35)% ON. This is considered abnormal during both medication conditions based on a clinical normative cutoff value of 40% weakness. Due to equipment malfunction, there were fewer oVEMPs available for OFF and ON. For OFF, there was data for 10 participant right ears and 11 participant left ears. For ON there was data for both ears for 14 participants. Of the data available, unilateral absence of oVEMPs was seen in 1 (10%) participant when OFF, and 3 (21%) participants when on. Bilateral absence of oVEMP was seen in 5 (50%) of participants OFF and 7 (50%) ON. When OFF the mean amplitude for the left ear was 1.58 (2.02) μV, and for the right ear was 1.74 (2.67) μV. Unilateral weakness of oVEMP was clinically normal OFF (33 (38)%) and was abnormal when ON (49 (49)%); however, the difference was not statistically significant ($p = 0.55$).

Figure 4.1 Abnormal and normal test results for participants OFF medication

	Participant														
Test	**03**	**06**	**08**	**09**	**10**	**11**	**18**	**19**	**21**	**25**	**26**	**27**	**28**	**30**	**33**
UPDRS-3	34	22	51	15	32	28	8	31	34	17	21	18	11	4	0
cVEMP unilateral absent	o		o	**A**	o	o	o	o	o	o	**A**	**A**	**A**	o	o
cVEMP bilateral absent	o		o	o	o	**A**	o	o	**A**	o	o	o	o	o	o
oVEMP unilateral absent	**A**			o	o	o				o	o	o	o	o	o
oVEMP bilateral absent	o			**A**	o	**A**				o	**A**	**A**	**A**	o	o
cVEMP uni weak	o		o	**A**	o		o	o		o	o	**A**	**A**	o	o
oVEMP uni weak	o				o					o				o	o
Caloric PSPV Sum			o	o	o	o	o	o		o	o	o	o	o	o
Caloric uni weak	**A**		o	o	o	o	o	o		o	o	o	**A**	o	o
OKN gain	**A**	**A**	**A**		**A**	**A**	**A**	**A**		o	**A**	**A**	**A**	**A**	**A**
SOT composite score	o	o	**A**	o	o	**A**	o	o	**A**	o	**A**	o	o	**A**	o
SOT fall	**A**	o	**A**	**A**	o	**A**	o	o	**A**	o	**A**	o	o	**A**	o
RCT sin gain	**A**	**A**	o	**A**	o	o	o	o		o	**A**	o	o	o	o
RCT sin phase advance	o	o	**A**	o	o	o	o	o		o	**A**	o	o	o	o
RCT sin phase lag	o	**A**	o	**A**	o	o	o	o		o	o	o	o	o	o
RCT sin asymmetry	o	o	o	**A**	o	o	o	o		o	o	o	o	o	o
RCT step gain	o	o	o	o	o	o	o	o	o	o	**A**	o	o	o	o
RCT step asymmetry	o	o	o		o	**A**	o	**A**		o	o	o	o	o	o
RCT step time constant	**A**	**A**	**A**		o	**A**	o	o	o	o	**A**	**A**	o	**A**	**A**
VOR suppression	o	o	o	o		o	**A**	o		o	o	**A**	o	o	o
VOR enhancement	**A**	o	o		o	**A**	o	o		o	**A**	o	o	o	o
Subjective Visual Vertical	**A**	o	**A**	**A**	**A**	**A**	o	**A**		o	**A**	o	**A**	o	**A**
Positional nystagmus	o	**A**	o	o	o	o	o	o	o	o	o	o	o	o	**A**
Head shake nystagmus	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Saccade accuracy	o	o	o	o	o	o	o	o		o	o	o	o	o	o
Saccade latency	o	o	o	o	o	o	o	o		**A**	o	o	o	**A**	o
Pursuit gain	o	**A**	**A**	o	o	o	o	o		o	**A**	o	o	o	o
Pursuit saccadic 0.1 Hz	o		**A**	o	**A**	o	**A**	**A**		o	**A**	o	**A**	**A**	**A**
Pursuit saccadic 0.3 Hz	o	o	**A**	o	**A**	**A**	**A**	**A**		o	**A**	o	**A**	**A**	**A**
Pursuit saccadic 0.5 Hz	**A**	**A**	**A**	o	**A**	**A**	**A**	**A**		o	**A**	o	**A**	**A**	**A**
Square Wave Jerks	o	o	**A**	**A**	**A**	o	o	**A**		**A**	o	o	o	**A**	o

Note: Orange boxes with "**A**" indicate an abnormal test result, light blue boxes with "o" indicate a normal test result. Grey boxes indicate testing was not completed or no data was available. c/oVEMP, cervical/ocular vestibular myogenic potential; L, left; R, right; RCT, rotational chair test; sin, sinusoidal; SOT, Sensory Organization Test; uni weak, unilateral weakness; UPDRS-3, Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale, Part 3; VOR, vestibulo-ocular reflex.

Table 4.4 Comparison of secondary variables for off and on medication

	OFF			ON			
Vestibular Test	n	mean (SD)	range	n	mean (SD)	range	p
L oVEMP amplitude (μV)	10	1.58 (2.02)	0.00-5.50	14	1.82 (2.64)	0.00-7.10	0.83
R oVEMP amplitude (μV)	11	1.74 (2.67)	0.00-7.87	14	1.49 (2.61)	0.00-7.90	0.81
cVEMP uni weak (%)	12	50 (39)	5-100	13	45 (35)	14-100	0.69
oVEMP uni weak (%)	5	33 (38)	8-100	7	49 (49)	2-100	0.55
cVEMP unilateral absent [a]	10	1 (10%)	--	14	3 (21%)	--	0.68
cVEMP bilateral absent [a]	14	2 (14%)	--	15	2 (13%)	--	>0.9
oVEMP unilateral absent [a]	10	5 (50%)	--	14	7 (50%)	--	>0.9
oVEMP bilateral absent [a]	10	14 (12)	--	14	23 (18)	--	0.15
Caloric uni weak (%)	13	14 (12)	0-35	15	23 (18)	0-51	0.63
Caloric DP (%)	13	13 (8)	3-32	15	24 (21)	2-74	0.09
Positional horizontal nys [a]	15	2 (13%)	--	15	0 (0%)	--	0.48
Positional vertical nys [a]	15	0 (0%)	--	15	0 (0%)	--	NA
RCT sin gain [a]	14	3 (21%)	--	15	3 (20%)	--	>0.9
RCT sin phase [a]	14	2 (14%)	--	15	4 (27%)	--	0.65
RCT sin asymmetry (%) [a]	14	1 (7.1%)	--	15	1 (6.7%)	--	>0.9
VOR enhancement gain	13	0.83 (0.25)	0.41-1.25	15	0.85 (0.21)	0.43-1.18	0.79
VOR suppression gain	13	0.19 (0.07)	0.04-0.29	15	0.22 (0.08)	0.05-0.36	0.27
VOR suppression change (%)	12	58 (16)	39-82	15	54 (22)	1-84	0.58
RCT step gain	13	0.63 (0.15)	0.32-0.86	15	0.59 (0.17)	0.33-0.81	0.55
RCT step TC (s)	12	8.7 (3.9)	3.2-15.3	15	10.0 (3.8)	4.9-17.3	0.37
RCT step asymmetry (%)	13	9 (13)	0-49	15	7 (6)	1.3-21.9	0.71
SOT Composite	15	72 (10)	49-83	14	72 (11)	47-87	0.92
SOT visual ratio	15	80 (11)	51-94	15	79 (17)	28-94	0.79
SOT somatosensory ratio	15	96.80 (4.02)	84-102	15	95.93 (2.28)	91-100	0.55
SOT visual preference	15	93 (9)	72-104	14	97 (10)	74-118	0.28
Subjective Visual Vertical	14	5.7 (4.9)	0.8-16.9	15	5.9 (5.4)	0.7-18.6	0.90
Oculomotor Test							
Pursuit gain	13	0.89 (0.10)	0.71-0.99	15	0.84 (0.17)	0.41-1.01	0.38
Pursuit phase	13	5.3 (7.9)	-18.5-15.7	12	4.9 (3.1)	-2.21-8.93	0.90
Saccade accuracy (%)	14	89.5 (7.1)	77.0-100.5	15	88.1 (6.3)	73.5-96.5	0.58
Saccade latency (ms)	14	218 (31)	181-271	15	233 (38)	176-309	0.27

Note: c/oVEMP, cervical/ocular vestibular myogenic potential; DP, directional preponderance; L, left; nys, nystagmus; R, right; RCT, rotational chair test; sin, sinusoidal; SOT, Sensory Organization Test; uni weak, unilateral weakness; VOR, vestibulo-ocular reflex.

[a] count (%)

[b] Paired permutation test for continuous variables; Fisher's exact test for categorical variables.

Other secondary test results that were abnormal are shown in **Figure 4.1**, including shortened step testing time constant (OFF 8.7 (3.9) s; ON 10.0 (3.8); p = 0.55) and poor accuracy on SVV (OFF 5.3 (7.9) deg; 5.9 (5.4); p =0.90). Step testing time constant was abnormal for 8 (53%) of participants OFF, and 6 (40%) ON. For sinusoidal rotational chair testing, testing was completed for 14 participants OFF and 15 participants ON. For sinusoidal gain, 4 (29%) participants had low gains OFF, and 3 (20%) had low gains ON. For sinusoidal phase OFF, 2 (14%) had phase lag and 2 (13%) had phase advance. During sinusoidal testing ON 6 (40%) had phase advance, while 2 (14%) had phase lag. Asymmetry on sinusoidal testing was seen in 1 (7.1%) participant OFF, and 4 (27%) participants ON.

Oculomotor testing results were within normal for saccade accuracy and latency, and smooth pursuit gain and phase. However, abnormal saccadic components were present during smooth pursuits. This was most evident at a stimulus of 0.5 Hz, where there were saccadic intrusions or only saccadic eye movements in 11 (79%) participants when OFF, and 12 (80%) when ON. On gaze stability testing, when vision was occluded 6 (43%) participants OFF had square wave jerk eye movements, and 5 (36%) of participants ON.

4.5 Discussion

The purpose of this study was to determine the effects of dopaminergic medication on vestibular function in people with PD by comparing the results of comprehensive vestibular testing of participants with PD when OFF and ON medication. There were no significant changes in vestibular function between OFF and ON. Participants with PD demonstrated abnormalities in OKN, velocity storage, SVV, and oculomotor function.

This is the first study to assess the effects of medication on vestibular function in people with PD using comprehensive vestibular testing. Current evidence for the effect of medication on peripheral vestibular function in PD is contradictory. Motion-induced vestibular firing rates appear to decrease in response to dopaminergic medications (Lithgow & Shoushtarian, 2015), while amplitudes of vestibular evoked myogenic potentials for otolithic function increased or did not change (Beylergil, Noecker, et al., 2022; Pötter-Nerger et al., 2012; Potter-Nerger et al., 2014). There are no current studies on SCC function responses to dopaminergic medications (Smith, 2018, 2022). The results seen here support that dopaminergic medications do not impact peripheral vestibular function as measured by VEMPs, caloric, and rotational chair testing.

Central vestibular functions related to velocity storage, perception, and oculomotor control appear to be affected in PD (Artusi et al., 2022; Beylergil et al., 2021; Frei, 2021; W. Ma et al., 2022; Waldthaler et al., 2019). Abnormal central findings were seen in participants both OFF and ON including shortened time constants and abnormal subjective visual vertical. Decreased time constants on rotational chair testing when other indicators of semicircular canal function are normal (e.g. caloric testing, gain on sinusoidal and step rotational chair testing) typically indicate potential abnormalities in velocity storage. Central velocity storage is a function of the VNC, the nucleus prespositus hyperglossi for horizontal velocities, and the cerebellum, with primarily glutamatergic and cholinergic transmission (Barmack, 2003). Qualitatively, disease severity based on the MDS-UPDRS-3 did not appear associated with an abnormal time constant. However, participants in this study were primarily in the mild-moderate range of disease severity, and statistical analysis of associations was not completed. This suggests that velocity storage may be affected even in early disease stages of PD.

Oculomotor abnormalities seen here have been shown previously to exist in PD (Frei, 2021; W. Ma et al., 2022; Waldthaler et al., 2019). Oculomotor abnormalities including low OKN gain and the presence of saccadic components during smooth pursuit are consistent with existing literature (Wu & Hallett, 2013; Zhou et al., 2024). Optokinetic nystagmus responses could be affected by abnormalities in smooth pursuit, velocity storage, or saccadic pathways (Barmack, 2003). The lack of response to medication indicates that non-dopaminergic functions for OKN are affected in PD, potentially within the VNC or cerebellum (Wu & Hallett, 2013).

Subjective visual vertical was also abnormal in this group of participants. Central processing for SVV appears to involve the VNC, cerebellum, and areas of the temporal and parietal cortex (Saj et al., 2019; Tae-Ho Yang et al., 2014). Prior literature suggests abnormal SVV can exist in early disease stages and is associated with postural control and gait deficits (Artusi et al., 2022). However, ocular torsion can also cause abnormal SVV, and subtle ocular torsion may have been missed during testing in this and other studies. Consistent with prior research no effect of medication on SVV was seen here (Scocco et al., 2014).

Overall, signs for central vestibular dysfunction in the VNC, cerebellum, or related brainstem areas did not change with dopaminergic medication. This suggests that vestibular pathway involvement in PD is non-dopaminergic and adds to existing evidence that there are non-dopaminergic pathway deficits in PD (Roytman et al., 2023). Non-dopaminergic vestibular pathway involvement could potentially contribute to disease-related abnormalities in postural control and gait (Bohnen, Kanel, Roytman, et al., 2022; R. Morris, Martini, et al., 2019).

4.5.1 Limitations

Interpretation of this study is limited by the off-medication state being a functional, but not true OFF state. The sample size was small and suffered further loss of data available for analysis in part due to the length of testing procedures not being well tolerated by all participants, particularly when OFF. Dystonia and abnormal posture also caused interference in the capture of eye tracking data for some participants. Participant disease severity was mild-moderate, likely limited by inclusion criteria for walking and balance testing. Based on the results that medication did not affect vestibular function, it is cautiously reasonable to conduct future research with participants on their typical dopaminergic medications. This could allow better tolerance for testing, and potential testing of vestibular function in people with PD at later disease stages.

4.5.2 Conclusion & Clinical Implications

Central vestibular deficits appear to occur in PD, even at early disease stages (Berliner et al., 2020; Mahajan et al., 2021), and are not responsive to dopaminergic medications. There is the potential to explore whether existing and novel vestibular treatment could address postural control and gait deficits that do not respond to dopaminergic medications. Assessment and treatment using established vestibular interventions should be considered in managing PD-associated vestibular dysfunction.

CHAPTER 5: CONCLUSIONS

The overall goal of this dissertation was to understand how Parkinson disease (PD) and dopaminergic medications used to treat PD affect peripheral and central vestibular function. This was achieved through retrospective and prospective studies using comprehensive vestibular testing to compare people with PD to controls and comparing people with PD off and on dopaminergic medications.

The results of this work support the evidence that vestibular dysfunction may exist early in the disease process in PD (Berliner et al., 2020; Mahajan et al., 2021; Schrag et al., 2019). **Chapter 2** retrospectively examined records of comprehensive vestibular testing in people with a diagnosis of PD at any point in time and compared these results with those of age-matched controls without a diagnosis of PD or other neurological disorders that could affect vestibular function. Vestibular dysfunction was present in recorded test results of people with PD and controls. There were minimal differences between people with PD and controls who were referred to vestibular testing. However, comparisons of records with clinical PD and controls and between clinical and prodromal PD showed some evidence that there is unique central vestibular dysfunction in PD at later disease stages (Dewey et al., 2014; Hawkins, Rey-Martinez, et al., 2021; White, Saint-Cyr, et al., 1983; Zhou et al., 2024). The retrospective comparisons in **Chapter 2** were limited by potential selection bias since vestibular testing occurred due to a referral-generating complaint suspicious of vestibular dysfunction, which may have underrepresented vestibular dysfunction in the PD groups related to healthy adults. Furthermore, the review was not able to address the question of medication effects on vestibular function. **Chapter 3** compared participants with PD who had mild to moderate motor disease severity to healthy similar-aged adults using the results of comprehensive vestibular testing.

In **Chapter 3**, when comparing healthy controls to people with PD who were off dopaminergic medication, participants with PD were found to have worse overall semicircular (SCC) function, decreased velocity storage, abnormal subjective visual vertical (SVV), and increased saccadic latency compared to controls. There is less prior evidence of abnormal SCC function in PD, however, this may be due to the use of testing that assesses high-frequency vestibular responses (Berkiten et al., 2022; Hawkins et al., 2022). This work adds to the literature using low-frequency stimuli to assess vestibular function in PD and importantly includes a control group (Cicekli et al., 2019; Venhovens, Meulstee, Bloem, et al., 2016). There is only one existing study that examines vestibular function using step rotational chair testing (Venhovens et al., 2020). Unlike that work, the comparison with healthy controls in **Chapter 3** found that participants with PD had abnormal velocity storage and that this was significantly different than controls. This indicates that rotary chair testing may be a useful tool in future research examining vestibular function in PD. Differences between healthy controls and people with PD in SVV and saccades were consistent with existing literature (José Luvizutto et al., 2020; L. Ma et al., 2022; Zhou et al., 2024). In addition to differences in vestibular function seen between controls and people with PD, in both the retrospective and prospective studies otolithic dysfunction and signs of central vestibular deficits were present regardless of group. This supports literature suggesting that vestibular dysfunction is present in PD (Cipparrone et al., 1988; Venhovens, Meulstee, Bloem, et al., 2016; Zhou et al., 2024), although it may not be greater than age-related changes in function (Agrawal et al., 2012, 2016).

The absence of a distinct vestibular profile of people with PD seen in **Chapters 2** and **3** was unexpected, specifically for the lack of difference in vestibular evoked myogenic potentials (VEMPs) (Berkiten et al., 2022; Cui et al., 2022). In **Chapter 3** participants with PD did

demonstrate a larger mean cervical VEMP inter-ear difference of 50% unilateral weakness, compared to controls with 28% weakness. Additionally, 29% of participants with PD had a unilateral cervical VEMP absence, compared to 6.7% of controls. However, these differences did not reach statistical significance, potentially due to the small sample size and heterogeneity of VEMP response profiles in people with PD. This heterogeneity was mirrored in the overall vestibular dysfunction profiles of participants with PD, which are shown in **Chapter 4**. There was also evidence of potential abnormal sinusoidal rotational chair testing, with a trend toward lower gains in people with PD. However, the number of participants with abnormal sinusoidal results for gain between groups was not significant. Rotary chair testing has been underutilized in the assessment of vestibular function in PD and may be useful in identifying disease-related changes that have not been seen in other tests of vestibular function (Arriaga et al., 2005).

In **Chapter 4**, the effects of dopamine on vestibular function in PD were examined. Participants with PD who completed comprehensive vestibular testing while off for comparison to controls in **Chapter 3** also completed the same testing while on their typical dopaminergic medication. The results of testing for each participant with PD were then compared based on medication state. These comparisons found no significant differences for any vestibular measures between off and on-medication testing. The current literature is contradictory, but these results support studies that indicate there is no effect of dopamine on vestibular function in PD (Beylergil, Noecker, et al., 2022; Pötter-Nerger et al., 2012; Potter-Nerger et al., 2014; Scocco et al., 2014). The lack of effect from dopaminergic medications supports that vestibular dysfunction in people with PD is likely due to non-dopaminergic pathway involvement in the disease process (Bohnen, Kanel, Roytman, et al., 2022; R. Morris, Martini, et al., 2019; Roytman et al., 2023).

In summary, the work of this dissertation indicates that vestibular dysfunction is present in people with PD, with potential central vestibular dysfunction that is beyond typical age-related changes. Disease-related changes in vestibular function may occur early in the disease but are not significantly greater than other age-related vestibular dysfunction. Some difficulties were encountered during the prospective study that may have affected test results. First, for participants with PD, there was more frequent artifact and loss of data during the measurement of nystagmus responses for caloric, OKN, and rotational chair testing due to eye closure. Participants with PD also had greater difficulty tolerating the required head position for cervical VEMP recording, and some participants were not able to complete full testing procedures due to discomfort while off medication. This limited the comparisons available for participants with greater disease severity and further underpowered the analyses. Overall, vestibular dysfunction appears to be present in PD, with potential disease-specific central vestibular impairment. Furthermore, vestibular dysfunction in PD does not appear to respond to dopaminergic medications, indicating that vestibular dysfunction in PD is potentially related to non-dopaminergic disease effects. Clinically, testing and individualized treatment for vestibular dysfunction should be considered in people with PD who present with complaints of dizziness or imbalance. Given the findings indicating disruption of VOR regulation pathways, strategies focused on non-vestibular sensory compensation may be a more effective rehabilitation approach.

Future Directions

There is evidence that vestibular dysfunction in PD is associated with disease severity (Beylergil et al., 2021; Hawkins, Rey-Martinez, et al., 2021; Nieuwhof et al., 2017) and specific postural and gait abnormalities (Bohnen, Kanel, van Emde Boas, et al., 2022; Lazzaro et al.,

2018). Future exploratory analyses with the data from these studies are planned to determine if there are individual profiles of vestibular dysfunction in PD or associations between disease severity and VEMPs, caloric weakness, rotational chair tests for sinusoidal gain, phase, vestibulo-ocular reflex cancellation, or step testing time constant. Results of these analyses could guide future research with targeted vestibular testing and larger cohorts to identify if vestibular dysfunction has associations with disease progression and specific postural or gait disturbances and if these associations are affected by established or novel vestibular rehabilitation techniques.

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