Study Title: Vestibulopathy, imbalance and gait disturbances in Parkinson disease

PI: Fay Pongmala, PhD

Study ID: HUM00192613

NCT#: NCT05446194

Protocol Version IRB Approval Date: 5/15/2025

Vestibulopathy, imbalance and gait disturbances in Parkinson disease

Principal Investigator: Nicolaas Bohnen, MD, PhD and Fay Pongmala, PhD

Funding Agency: VA - Rehabilitation R&D

Abstract

Parkinson disease (PD) is a progressive neurodegenerative disorder characterized by resting tremor, slowness of movement, rigidity as well as postural instability and gait difficulties (PIGD) motor features. Nigrostriatal dopaminergic denervation is a key pathological factor in PD. Advancing PD is associated with disabling PIGD motor features, in particular freezing of gait (FoG) (3, 4). Progressive Supranuclear Palsy (PSP) is a neurodegenerative disorder that is characterized by increased falls, postural instability, FOG, and vertical ocular motor dysfunction. FoG is an important trigger for falls and resulting in reduced functional abilities and that greatly affects quality of life in people with PD and PSP. This is further complicated by fear of falling resulting in pervasive sedentariness where avoidance of physical activity leads to deconditioning, thereby aggravating a downward functional spiral. Effective management of FoG represents an unmet clinical need (gap in clinical practice). The dopaminergic medication-refractory nature of PIGD motor features in advancing PD implicates non-dopaminergic brain pathologies.

We have novel preliminary data showing that non-acute vestibulopathy may be another important factor contributing to PIGD motor features, in particular FoG in PD and PSP. Unlike sporadic intermittent vestibular disorders with a more acute onset, chronic bilateral vestibular dysfunction of older age (recently defined by the Bárány Society as presbyvestibulopathy, PVP) is also common in PD (5-7). Our preliminary data suggest that PVP may be a critical determinant of FoG in PD (scientific premise). Furthermore, we found that absence of PVP was associated with a very low frequency of FoG suggesting a specific effect of PVP on FoG in PD. However, these preliminary observations need to be confirmed in a larger study using more dedicated assessment methods (knowledge gap). Closing this gap is important because of the potentially high clinical translational impact if our preliminary findings can be verified. The overarching goal of this study is to test the hypothesis that the presence of PVP is an important risk factor for FoG in subjects with PD and PSP while accounting for nigrostriatal dopaminergic denervation.

Contents

Protocol Title:

1.0 Study Personnel

Principal Investigators:

University of Michigan: Fay Pongmala, PhD 734-998-8400
Ann Arbor VA: Nicolaas Bohnen, MD, PhD 734-998-8400

2.0 Introduction

i) Motor impairments, dopamine responsive and progression in PD: The hallmark pathology of PD is loss of dopamine in the striatum secondary to progressive degeneration of dopaminergic cells in the substantia nigra pars compacta, due to the formation of Lewy bodies (8). A variable combination of tremor, rigidity, and bradykinesia symptoms may present along with PIGD motor features. Because of primary involvement of the basal ganglia in PD, it has often been asserted that these motor features are mainly attributable to nigrostriatal dopaminergic losses. A study by Vu et al., however, showed that L-DOPA potency was lowest for PIGD motor features compared to other cardinal motor features in PD (4). In the Sydney Multicenter Study of PD, patients were followed for about two decades. Results of this study indicate that dopamine non-responsive problems dominate 15 years after initial assessments and include frequent falls occurring in 81% of patients (9). Similar findings were reported by López et al. after following de novo PD patients for 10 years (3). López et al. reported good responses to dopaminergic treatment in the first year with a progressive decline becoming more manifest after 3 years of treatment. Significant PIGD motor disabilities arose at 10 years in 71% of patients that were mainly caused by non-dopamine-responsive features, such as FoG (3). FoG is usually manifested as transient but abrupt cessation or reduced of leg movement during walking leading to episodic experience of being ‘frozen’ or ‘glued’ to the ground often resulting in falling. This phenomenon may occur during gait, gait initiation, or most frequently during turning. FoG and falls are major contributors to decreased quality of life and impaired functional abilities in people with PD(10-12). Dopaminergic medication-resistance of

parkinsonian PIGD motor features has been proposed to result from the extension of the degenerative process to extra-striatal regions (13).

ii) Vestibular functions in PD and PSP: Appropriate postural control is essential for the coordinated control of locomotion. Peripheral sensory feedback from the vestibular, somatosensory (i.e., proprioception), and visual systems is centrally integrated and evaluated to prepare for an appropriate reactive motor response when postural instability may occur. There is increasing evidence that impaired integration of sensory feedback contributes to PIGD motor features in PD (14). Vestibular system function is multi-faceted and can be defined as the integration of both peripheral vestibular labyrinth and central vestibular system functions. For decades it has been speculated that PD is associated with dysfunction of the vestibular system (esp., given that postural instability is one of the major symptoms of this disorder) but clear evidence of such a connection has been slow to emerge (see Smith, 2018, for review (15)). Studies examining the specific contribution of vestibular sensory functions to PIGD motor features in PD are, however, inconsistent. For example, Reichert et al. carried out bithermal caloric tests and electronystagmography in PD patients and controls (16). Results showed that significantly more PD patients had reduced or absent vestibular responses than controls. Importantly, decreased or absent vestibular responses in patients with PD were associated with postural instability. More recent research by de Natale et al., found that vestibular-evoked myogenic potentials (VEMPs) were significantly altered in PD patients and with the severity of these alterations progressively increasing with disease severity (17, 18). These alterations in VEMPs were correlated with greater postural instability, suggesting that impaired vestibular activity may play an important role in postural instability in PD (17). However, there are also conflicting reports. For example, findings by Pastor et al. concluded that vestibular dysfunction could not clearly explain postural deficits in PD patients (19). A study by Chong et al. examined sensory processing function in PD patients and compared this to age-matched normal controls (20). Results of their study suggested that there was no difference in sensory processing efficacy between these two groups. Results of their study also showed no difference in parameters of vestibulo-ocular (VOR) and optokinetic nystagmus (OKN) reflexes between the control and PD group. **It should be noted, however, that key short-comings of the existing literature on the effects of vestibulopathy on motor impairments in PD is the absence of adjustment for the degree of nigrostriatal dopaminergic denervation, the key pathobiology in PD (knowledge gap).** We propose to assess vestibular dysfunction as it relates to FoG in subjects with PD while taking into account the severity of nigrostriatal dopaminergic denervation.

Disturbance of gaze is a distinct clinical feature in PSP which is often characterized by slower vertical saccades and an inability to utilize linear vestibular ocular reflex (tVOR) to determine distance (66-68). These clinical features of PSP negatively impact the ability to integrate visual stimuli which may contribute to postural instability (67). Loss of vestibular nuclei and impairment of central otolithic pathways inhibit tVOR, which in turn may explain postural instability and increased fall rates in PSP (67,68). Individuals with PSP experience higher fall rates and FOG rates compared to idiopathic PD (69). Rezvanian et al. found that 45.6% out of 349 PSP patients experience FOG further demonstrating the prevalence of FOG in PSP (69). Rezvanian et al. also distinguishes FOG is present during the early stages of PSP disease progression with severity increasing over time compared to PD (69). The research findings suggest that falls and FOG are clinically significant features of PSP which may require targeted treatment options.

Age-associated vestibular impairment is a significant contributor to imbalance and falls in older US adults. Unlike sporadic intermittent vestibular disorders with a more acute onset, chronic bilateral vestibular dysfunction of older age is common in the elderly (recently defined by the Bárány Society as presbyvestibulopathy, PVP). For example, about 50% of community-dwelling older adults were found to have evidence of PVP resulting in higher risk of imbalance and gait disturbances (1). Even older individuals without a history of dizziness but who

had abnormal findings on the clinical PVP test (i.e., the modified Romberg test, a postural control test with sensory conflict) also had significantly increased risk of falling (21). This suggests that the age-associated sub-clinical vestibular dysfunction is clinically relevant. **PD predominantly affects the older population and, expectedly, more chronic bilateral vestibular dysfunction of older age is also common in PD** (5-7) **and lack of PVP assessment in controls may explain some of the inconsistencies in studies of vestibular differences between PD and older controls**. Although the prior literature has been inconclusive about group differences in the frequency of vestibular changes between PD and older non-PD adults (see (15) for review), the possibility of intrinsic PD-related vestibular changes exists. However, if these may be present these would further augment the effects of age-associated vestibulopathy and thereby lower the symptomatic threshold for symptomatic presentation. Therefore, any presence of PD-specific vestibular changes beyond age-associated changes would further emphasize the potential therapeutic importance of pursuing vestibular rehabilitation strategies in the PD population suffering from treatment-refractory PIGD motor features.

iii) Vestibular sensory processing changes in FoG in PD: The inability to integrate postural sensory inputs may play a role in the pathophysiology of FoG (22). For example, FoG can be provoked under sensory conflict situations that challenges postural control but can also be alleviated by various sensory cues (23). Prior studies using postural sensory conflict tasks, such as the sensory organization test, have demonstrated that postural sensory deficits involving specific sensory modalities are strongly associated with FoG in PD and PSP (24). A common example is visual sensory processing where providing visual cues may help to attenuate freezing motor behaviors (23). However, there is limited literature on vestibular sensory processing in FoG (25). A recent study using a sensory conflict testing paradigm found that PD freezers had greater difficulties processing vestibular sensory information than non-freezers (24). **Importantly, relative effects of vestibular processing were greater than visual and somatosensory effects.** These data show that the inability to integrate vestibular information may be highly relevant for PD patients with PIGD motor features. Vestibular feedback becomes even more critical when initiating walking or turning (26). Gait initiation and turning are motor activities where visual and somatosensory feedback becomes more unreliable and thereby resulting in higher reliance on effective vestibular processing for postural control (27). This is also consistent with the clinical observations that gait initiation and turning are well-known risk factors for FoG and consequently these triggers are used clinically to provoke motor freezing (23). **Assessment of postural vestibular sensory deficits in PDpatients with FoG may provide a better understanding of pathomechanisms of FoG and may accurately identify suitable patients for rehabilitative interventions.**

INNOVATION

Our approach and subject cohort are unique in several ways by investigating new concepts. First, there are no prior published studies of vestibular dysfunction in PD that have also assessed the degree of dopaminergic nigrostriatal denervation with in vivo dopaminergic nerve terminal brain PET or SPECT imaging. Second, there are no published studies on the relationship between PVP and FoG in PD.

SIGNIFICANCE

The significance of this project is that it addresses an unmet need in clinical practice, i.e. there is currently no effective treatment for FoG in advancing PD or in PSP. Our preliminary data suggest that PVP may be a critical determinant of FoG. Assessment of postural

vestibular sensory deficits in PD patients with FoG and patients with PSP may provide a better understanding of pathomechanisms of FoG that may inform therapeutic management.

IMPACT & FUTURE DIRECTIONS
New knowledge from this project may provide important clues about the pathophysiology of motor freezing behaviors and associated risk of falls in PD. Such clues may inform novel therapeutic interventions for this unmet clinical need. Falls and postural instability are a major clinical dilemma in patients with PD. These issues get progressively worse and more difficult to treat as the disease progresses. New therapies to reduce FoG and imbalance in patients with PD and PSP may reduce fall risk and drastically improve functional abilities and quality of life of these patients.

Preliminary Studies

We present novel preliminary findings of a significant association between presence of FoG and PVP clinical status and evidence of an independent relationship between abnormal VOR function, PIGD motor features and postural control that cannot be explained by other PD specific features such as bradykinesia or rigidity.

i) **Association between clinical presence of FoG and PVP in persons with PD**. We investigated the relationship between the clinical presence of FoG and PVP in persons with PD. Methods: 92 patients with PD (M70/F22; mean age 67.6±7.4 years, mean motor disease duration 6.0±4.6 years, mean Hoehn and Yahr stage 2.4±0.6) completed detailed clinical assessment. FoG status was defined by direct observation of motor freezing behavior by an experienced neurologist while performing the UPDRS motor examination. Clinical screening for PVP was performed using the modified Romberg sensory conflict test (1). A time to fall < 20 seconds while standing on foam surface with eyes closed was used for the presence of PVP as previously reported (1), and validated in a prior study of patients with vestibular disorders (34). **Our findings showed a substantially higher frequency of FoG in PD persons with PVP (33%) compared to PD persons without PVP (3.3%; Likelihood ratio χ^2=15.6; P<0.0001), see table 1. Furthermore, PVP was present in the majority (84.6%) of PD persons with FoG.**
[^{11}C]DTBZ dopaminergic brain PET imaging was available in 29 patients. Logistic regression analysis of this subset showed that **the PVP effect remained highly significant (Likelihood ratio χ^2=10.3; P=0.0013) independent from the degree of nigrostriatal dopaminergic losses**. Similar independent significant effects for the PVP effect (Likelihood ratio χ^2=7.1; P=0.0070) was seen when adjusting the model for effects of age or the severity of parkinsonian motor impairments. These preliminary data suggest that PVP may be an important factor contributing to FoG independent of the degree of disease-specific confounders.

Table 1. Contingency table of FoG vs. clinical PVP status in PD (Likelihood ratio χ^2=15.6; P<0.0001)

	No PVP	PVP	Total
No FoG	57	22	79
FoG	2*	11**	13
Total	59	33	92

*FoG was present in 3.3% in PD persons without PVP
**PVP was present in 84.6% of PD freezers

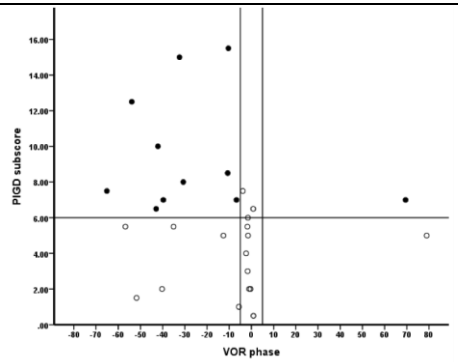
ii) VOR and PIGD features in PD and PSP. VOR was assessed in 29 PD patients (9 female, 67.8 ± 6.9 years of age, 5.9 ± 3.2 years of motor disease duration) using the active head rotation (AHR) protocol of the VORTEQ™ module of the VisualEyes™ VNG system. The two main outcome parameters were gain (ratio of slow component eye velocity and head velocity) and phase (offset in eye movement time relative to the head movement). All subjects underwent the MDS-UPDRS clinical examination for assessing PD severity. Separate sub-scores were calculated for PIGD, bradykinesia, tremor, and rigidity features. We dichotomized phase into "normal" and "abnormal", with -5° ≤ normal phase ≤ 5°. PIGD sub-score was dichotomized into "low" and "high" based on a median split (score of 6). Chi-square analysis was performed to test for difference in proportion normal/abnormal phase between the two PIGD groups (see **Table 2**). Near significant analysis (χ^2=3.1, p=0.077) showed that there were disproportionally more PD subjects with abnormal VOR phase in the group with high PIGD sub-scores (see also **Figure 1**).

Linear VOR has been assessed in PSP to determine whether abnormal VOR contributes to frequent falls. Liao et al. analyzed linear VOR in 9 individuals with PSP and 9 age-matched controls (66). The findings revealed individuals with PSP were unable to utilize linear VOR to adjust vergence on near objects. In the same study, VEMPs were measured from 10 PSP participants, which revealed decreased VEMP responses, suggesting abnormalities in otolith-spinal reflexes. The research suggests that a combination of abnormal linear VOR and otolith-spinal reflexes may contribute to increased falls and PIGD symptoms.

Table 2. Contingency table for the dichotomized PIGD sub-score ("low" and "high") and "normal" and "abnormal" VOR phase

Figure 1. Scatterplot of VOR phase versus MDS-UPDRS PIGD sub-score. PD patients with "abnormal" phase (≤ -5° or ≥ 5°) and "high" PIGD sub-score are in solid black dots. Subjects within the boundaries of the two vertical lines (around phase 0°) have a normal phase. Subjects above the horizontal line (median PIGD sub-score split) have high

			PGD sub-scores.
	Low PIGD sub-score	*High PIGD sub-score*	
Normal VOR phase	*8*	*3*	
Abnormal VOR phase	*7*	*11*	



We performed additional binary logistic regression to examine whether other PD motor features such as bradykinesia or rigidity or any other parkinsonian motor feature as captured by the total motor disease duration variable had a confounding effect on VOR phase. The near significant model (χ^2=9.3, p=0.053) showed independent prediction of VOR phase for the PIGD sub-score (Wald = 4.6, p = 0.032), while controlling for bradykinesia, rigidity, or motor disease duration (all n.s.). **These preliminary findings provide supportive evidence that abnormal VOR phase is associated with PIGD features in PD and cannot be explained by other features such as overall slowness of movement (bradykinesia) or rigidity (e.g. stiffness of the neck musculature).**

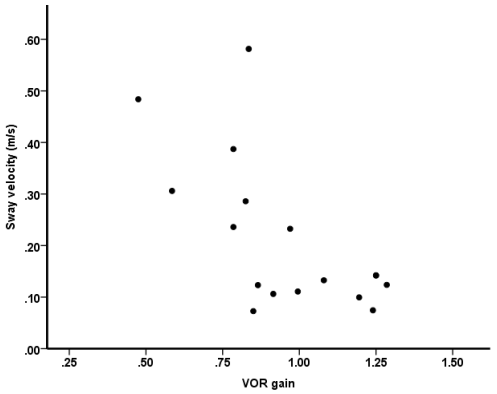


Figure 2. Scatterplot of VOR gain versus sway velocity during quiet stance with eyes open.

iii) VOR and biomechanical parameters of posture. In an exploratory manner we correlated the VOR parameters and biomechanical parameters of posture. Biomechanical data was available for a subgroup (n=17) of the same PD subjects described above. Posture was assessed using 6 OPAL accelerometer sensors (APDM Mobility Lab™) during normal stance with eyes open. Results showed that VOR gain correlated in a linear fashion with sway velocity (Spearman r = -0.587, p = .013), a measure of overall sway (**Figure 2**). We performed post-hoc linear regression analysis to examine the independent prediction of VOR gain on sway velocity while accounting for bradykinesia, rigidity and total motor disease duration. Near significant regression ($F_{(4,12)} = 2.50$, p=0.098) showed significant effect of VOR gain on (t=-3.0, p=0.011) sway velocity, however, not of bradykinesia, rigidity, or disease duration. **These preliminary findings provide supportive evidence that there is an independent relationship between VOR and postural control that cannot be explained by other PD specific features such as bradykinesia or rigidity.**

3.0 Objectives

Specific Aim: To perform detailed clinical assessments and dopamine transporter (DAT) [^{11}C]PE2I brain PET imaging in subjects with PD.

Hypothesis: The prevalence of FoG is higher in subjects with PD and PSP who also have evidence of PVP compared to those without PVP independent of nigrostriatal dopaminergic losses.

Exploratory Aim: To complete follow-up assessment with PD subjects to determine whether vestibular dysfunction is progressive in PD.

Exploratory hypothesis: Follow-up assessments will demonstrate progressive vestibular dysfunction in PD subjects.

Long-term goals: Finding will help to answer the current knowledge gap regarding whether vestibular dysfunction is progressive in this population. This is relevant as it may inform future treatments for people with PD and PIGD motor features.

4.0 Study Procedures

4.1 Study Design

Approach: The overarching goal of this study is to test the hypothesis that the presence of PVP is an important risk factor for FoG in subjects with PD and PSP while accounting for nigrostriatal dopaminergic denervation. For the main aim of the study, subjects with PD (gross recruitment n=64) and PSP (n= up to 20) will undergo brain DAT PET and MR imaging, followed by a baseline clinical test day. All participants will complete a 6-month prospective fall diary. PD subjects will be asked to return for optional visits at 3 years (±1 year) from their last visit and again 2 years (±1 year) after the previous follow-up for a limited test battery.

Design & subjects: Our main aim will be a cross-sectional study in 84 subjects (gross recruitment) with 64 subjects with a PD diagnosis following the UK Parkinson's Disease Society Brain Bank Research Center (UKPDSBRC) criteria (35) and presence of abnormal striatal denervation pattern on DAT PET scan and up to 20 subjects with a PSP diagnosis following the Movement Disorder Society Revised 2017 diagnostic criteria for PSP across a spectrum of severity of disease (modified Hoehn & Yahr stages 1-4*)* (69). Participants meeting the diagnostic criteria for probable PSP, as determined by a clinician, will be eligible. Our second exploratory aim will be to complete follow-up assessments to explore the progressive nature of vestibular dysfunction. PD subjects that previously participated in the study will be asked to return for a limited test battery at 3 years (± 1 year) from their last visit. A second follow-up visit for this exploratory aim will occur 2 years (± 1 year) from the previous visit.

General methods

After obtaining informed consent and screening for study eligibility, study participants will undergo DAT PET and MRI imaging, followed by a baseline clinical evaluation day. The clinical testing will consist of a clinical test battery (see **table 3** below). The motor component of the test battery will be performed in the dopaminergic medication 'off' state in the morning after overnight withholding of their dopaminergic medications. The remainder of the test battery will be performed in the medication 'on' state. Qualified personnel who have been trained in the use of the instruments and have undergone inter-rater reliability evaluations will perform the assessments. The DAT PET study will also be performed in the dopaminergic medication 'off' state in the morning.

Table 3: Components of the clinical test battery		
Limited motor test battery*	Main outcome parameter:	Administration time:
Parkinsonian ratings: Movement Disorder Society-revised Unified PD Rating Scale (MDS-UPDRS) (36)	UPDRS parkinsonian PIGD motor sub-score	15 min

FoG: Freezing of gait clinical provocation protocol (37)	Examiner-based FoG assessment	15 min
Clinical PVP test: Modified Romberg test (1)* Clinical PVP: Modified Romberg test (1) (ON)	Time to fall < 20 seconds when standing on foam with eyes closed (For participants taking oral dopamine replacement therapies, will be done both OFF and ON dopaminergic medication)	10 min
[Optional[APDM sensor-based walking and postural tests (iTUG, iWalk, iSAW, iSWAY)]	Sensor-based outcomes	15 min
(Optional) Mini-BESTtest dynamic balance test	Total scores	15 min
		Total motor: **35-65 min**
Non-motor tests		
Ankle sensation: Biothesiometer (Bio-Medical Instrument Co., Newbury, OH, USA) (38).	Vibration perception threshold at the medial malleoli	5 min
Motion Sickness Susceptibility Questionnaire	Total score 10 items	10 minutes
FoG rating: New Freezing of Gait Questionnaire (NFOG-Q) (39).	Sum of part II & III questions	5 min
Cognition: The PD Cognitive Rating Scale (40).	Total PDCRS score	20 min
Function: The PD Cognitive Functional Rating Scale (41)	Total PDCFRS score	10 min
Quality of life scale: Short Form 36 health survey questionnaire: SF-36 (42)	Total SF-36 scores	10 min
Dizziness & vertigo: Dizziness Handicap Inventory (43), Vertigo Symptom Scale (44)	Total score (25 items)	8-10 min
Vestibular testing: Video head impulse test, OVRT-C *, rotary chair, calorics	Bárány Society diagnostic criteria	45 min

	for PVP (45)	
		Total non-motor: **105 min**
Measures to be collected at home by the participants		
Fall diary (6 months)	Number of falls during 6 months	mail with biweekly monitoring phone call
		Total: 155 min

*Will be performed in the dopaminergic medication 'off' state

General clinical assessment**:** Clinical assessment will consist of a general medical and neurological examination, the measurement of visual acuity, orthostatic vital signs, general hearing assessment, weight and height in all subjects. General clinical information, such as duration of disease, age of onset, and medication use will be recorded. L-DOPA equivalent dose (LED) of dopaminergic medications will be calculated (51). We will use the Dizziness Handicap Inventory and Vertigo Symptom Scale to assess self-perceived handicap as a result of vestibular system disease (43, 44).

Determination of imbalance and FoG status: Imbalance will be defined as abnormal performance on the retropulsion test, presence of falls or FoG or subjective loss of balance functions. FoG classification will be based on the New Freezing of Gait Questionnaire, NFOG-Q (39) and/or direct observation of obvious FoG episode with ineffective stepping (52) by experienced clinicians during the Snijders et al. FoG provocation protocol. For example, non-FoG PD subjects (based on the NFOG-Q) who show specific evidence of FoG during the FoG provocation protocol will be reclassified as FoG (37). The gait assessment will be videotaped and FoG episodes will be scored by an unaffiliated VA movement disorders neurologist for blinded clinical judgment.

Presbyvestibulopathy (PVP) status assessment: Clinical testing for PVP will be performed using the modified Romberg test (1, 53). The modified Romberg Test is designed to test vestibular function exclusively where participants have to maintain balance on a foam-padded surface (to obscure proprioceptive input) with their eyes closed (to eliminate visual input). A time to fall < 20 seconds while standing on foam surface with eyes closed will be defined as clinical evidence of PVP (1), as previously validated in a prior study of patients with vestibular disorders (34). The modified Romberg test is similar to the Sensory Organization Test (SOT) where falls on the modified Romberg test corresponds to falls on the SOT5 subtest, which has been found to have high sensitivity (80%) and high specificity (80%) to diagnose a vestibular disorder (54).

Fall assessment: All subjects will participate in a prospective study assessing the risk of (near-) falls over a 6-month fall diary study. We will define a fall according to ICD criteria (ICD 9: E880A-E889A) as an unexpected event where a person falls to the ground from an upper level or the same level. We will define a near-fall as an occasion on which an individual felt that they were going to fall but did not actually fall (55). Falls and near-falls during follow-up will be ascertained with a set of monthly fall diaries, where subjects will be asked to fill out incidents of (near-) falls each week and document the circumstances (esp. indoor vs. outdoor and turn or not turn related) and consequences using standardized scoring forms (56). Monthly calendars will be returned by mail at the end of each month. Subjects will be called every 2 weeks to maintain compliance.

Dedicated vestibular testing: This will be based on evaluation of VOR based on a) air or water caloric irrigator (Air Fx (AFX), Aquastim, Micromedical Technologies, Inc. Chatham, IL), b) rotary chair (System 2000, Micromedical Technologies, Inc. Chatham, IL), and c) Video Head Impulse Testing (VORTEQ, Micromedical Technologies, Inc. Chatham, IL). All eye movements will be recorded with the VisualEyes Video Nystagmograph system (Micromedical Technologies, Inc. Chatham, IL). This device has lightweight high-speed binocular video goggles (110Hz) that allow for analysis of VOR in addition to pursuit tracking, saccade and optokinetic oculomotor tests. Vestibular response will be assessed utilizing patterns of oculomotor, vestibular, reaction time and cognitive (OVRT-C) functions in patients with PD and PSP. Participants will use a non-invasive FDA-cleared device, the Neurolign Dx 100, which will administer an OVRT-C test battery to evaluate visual and neurological deficits in patients with PD. Subjects with excessive earwax build up will be referred to their primary care physician for removal of the earwax prior to assessment. Our neuro-otology co-investigator Dr. Kevin Kerber will be in charge of the vestibular testing protocol.

Magnetic resonance imaging (MRI) will be performed on a 3 Tesla Philips Achieva system (Philips, Best, The Netherlands). A 3D inversion recovery-prepared turbo-field-echo was performed in the sagittal plane using TR/TE/TI=9.8/4.6/1041ms; turbo factor=200; single average; FOV=240x200x160mm; acquired Matrix = 240x200x160 slices and reconstructed to 1mm isotropic resolution.

PET imaging will be performed in 3D imaging mode on a Biograph 6 TruPoint PET/CT scanner (Siemens Molecular Imaging, Inc., Knoxville, TN), which acquire 63 transaxial slices (slice thickness: 2.4 mm) over a 15.2 cm axial field-of-view. Images were corrected for scatter and motion. Subjects will be scanned in the dopaminergic medication 'off' state. [^{11}C]PE2I will be prepared as described previously (50).
[^{11}C]PE2I PET imaging will be obtained using a 70-min dynamic imaging acquisition following a 15 mCi i.v. tracer injection. [^{11}C]PE2I PET imaging will be analyzed using a Logan plot and using the cerebellar hemisphere as reference region.
The PET imaging frames will be spatially coregistered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session (57). Statistical parametric mapping (SPM) software (SPM12; Wellcome Trust Centre for Neuroimaging, University College, London, England will be used for PET-MRI registration using the cropped T1-weighted MR volumetric scan. Freesurfer software will be used to define cortical and subcortical MR gray volumes-of-interest (VOI).

MRI-based PET partial volume correction: We will use the Müller-Gärtner partial volume correction technique, which is based on the assumption that white matter uptake is homogeneous and uses gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) to correct the partial volume effect in GM tissues (58). Using the segmented images and the assumed PET resolution, the method calculates the spill-out from WM to GM and subsequently subtracts it from the GM. Similarly, it also calculates the spill-out from the GM to the surrounding tissues and compensates for the difference to the GM. The result is a grey matter image with corrected activity values in all voxels.

4.2 Recruitment Methods

PD subjects will be recruited from the University of Michigan (U-M) Movement Disorder Center (MDC), which follows a population of about 2,000 clinically well-defined patients with PD. An additional source of subjects will be the VAAAHS Movement Disorders Clinic (directed by Dr. Bohnen). This clinic follows over 240 Veterans with idiopathic PD and this clinic serves as a tertiary referral center for more advanced PD subjects coming from the tri-state area (MI, north-western Ohio and eastern Indiana) resulting in a larger than average referral of new patients. PD and PSP subjects from previous studies who have indicated interest (initials in informed consent form) in new studies at our laboratory will also be contacted. In case of unforeseen need, additional recruitment of subjects is possible via local Parkinson support groups and the Michigan Parkinson Foundation. Data Direct (https://datadirect.med.umich.edu/) will be used to recruit patients at Michigan Medicine to be study participants. A flyer will also be used to recruit subjects.

Screening script: Screening script will be used if subjects do not wish to discuss the study further with a staff member or consent to the study in the clinic. In the past, subjects have expressed interest and discussed the study with staff members. However, they don't want to consent at that time and wish to go home and think about it. Study team members will follow-up with these subjects and use the screening script before subject comes in, to prevent wasted travel and time of the subject. Also, subjects recruited via other methods will be screened using the screening script.

Timetable: The main study, to be conducted over a 4-year period, will include a gross total of n=64 patients with PD (allowing for a net recruitment of n=56 given possible attrition (10-12%)), due to imaging claustrophobia, unexpected brain imaging findings etc. 16 subjects will be enrolled annually. Up to 20 PSP participants will be enrolled over the 4-year period to participate The study will continue after the main study portion is complete to allow for the collection of limited follow-up data at 3 years (±1 year) from last study visit and then again at 2 years (±1 year) post the previous follow-up visit.

Compensation: Subjects will not be charged for their participation in this study. Subjects will receive $100 for the completed PET scan and $100 for the MRI scan. Payment for completion of the Screening/Baseline Visit will be $200. Subjects that participate in the additional optional follow-ups for the exploratory aim will receive $25 for each follow-up visit. Subjects will be

financially compensated for lost time and effort. We estimate that about 2/3 of PD/PSP patients will also need one night of overnight lodging to accommodate for “off state” requirements. Cost for overnight lodging and meals are estimated at $280 per night (3 nights per person). Subjects will receive a voucher for valet parking at the University Hospital. Parking at Domino's Farms is free. Subjects will be paid after their last study visit or, in case they decide to withdraw from the study, they will be paid for the parts that they have completed.

4.3 Informed Consent Procedures

Prior to any research procedures, IRB-approved written informed consent will be obtained from each subject followed by initial study eligibility screening. A study team member will obtain consent in a private location at the Functional Neuroimaging, Cognitive, and Mobility Lab, or Ann Arbor VA Movement disorders clinic. Remote electronic consent may be obtained using SignNow to reduce physical interaction between study staff and subjects.

4.4 Inclusion/Exclusion Criteria

Eligibility criteria:

1. Diagnosis:
    - PD based on the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Research Criteria (n=64, gross; M/F, age 45 years or older), with duration of disease > 5 years and/or Hoehn & Yahr stages 1.5-4 and able to ambulate independently.
    - PSP following the Movement Disorder Society Revised 2017 diagnostic criteria for PSP across a spectrum of severity of disease (modified Hoehn & Yahr stages 1-4) (n=up to 20). PSP diagnosis will be verified by a clinician using the PSP-RS and other clinical information collected from the medical history. Participants meeting the diagnostic criteria for probable PSP, as determined by a clinician, will be eligible. (Investigator discretion).
2. Dementia will be excluded by cognitive screening assessment and assessment of instrumental activities of daily living (PDCFRS).

Exclusion criteria:

1. History of Meniere disease or recent onset of acute vestibular dysfunction, such as otolith disorders (BBPV etc).

2. Other disorders which may resemble PD, vascular dementia, normal pressure hydrocephalus, multiple system atrophy (MSA), corticobasal ganglionic degeneration, or toxic causes of parkinsonism. Prototypical cases have distinctive clinical profiles, like early and severe dysautonomia (MSA) or appendicular apraxia, which may differentiate them from idiopathic PD and PSP. The use of the UKPDSBRC clinical diagnostic criteria for PD will mitigate the inclusion of subjects with atypical parkinsonism.

3. Evidence of a stroke or mass lesion on structural brain imaging (MRI).

4. Participants in whom MRI is contraindicated including, but not limited to, those with a pacemaker, presence of metallic fragments near the eyes or spinal cord, or cochlear implant.

5. Severe claustrophobia precluding MR or PET imaging.

6. Subjects limited by participation in research procedures involving ionizing radiation.

7. Pregnancy (test within 48 hours of each PET session) or breastfeeding.

8. Subjects with active and unstable mood or anxiety disorders

9. Subjects with active ear infections or perforated eardrums

4.5 Study Evaluations

Table 4. Clinical test protocol for Participants:				
	Screening	**Imaging**	**Follow-up #1- OPTIONAL[4]**	**Follow-up #2- OPTIONAL [4]**
Visit No. [1]	**V1**	**V1**	**V2**	**V3**

Visit description	SCR [1] OFF state for motor testing	Imaging OFF state for PET	Optional 3 years (±1 year) follow up	Optional 2 year (±1 year) after follow-up #1
Informed Consent	X			
DAT PET[2]		X		
MRI[2]		X		
Demography	X		X*	X*
Medical History	X		X*	X*
MRI Screening Q.	X			
PD/PSP History	X			
Incl/Excl	X			
Physical Exam[3]	X		X	X
Motor Testing/ UPDRS Pt III (dopaminergic medication 'OFF' state)	X		X	X

UPDRS Pt I, II, IV	X		X	X
Modified Hoehn and Yahr (OFF)	X			
Modified Romberg Test (OFF)	X			
Modified Romberg Test (ON) (For individuals on dopaminergic medications)	X			
Freezing of Gait Provocation Protocol (FOG) (OFF)	X			
Optional: Postural Photograph	X			
Optional: MiniBESTest (OFF)	X		X	X
APDM iTUG, iWalk, iSAW, iSWAY) (OFF)	X			
Biothesiometer	X			

New-FOGQ	X			
Short Form 36 health survey questionnaire: SF-36	X			
Motion Sickness Susceptibility Questionnaire	X			
PD-CFRS	X			
PD-CRS	X			
DEXA Scan				
Dizziness Handicap Inventory	X			
Vertigo Symptom Scale	X			
VHIT vestibular testing	X			
Oculovestibular/ Rotary Chair vestibular testing	X			

Caloric vestibular testing	X			
OVRT-C Neurolign (OFF)	X		X	X
Ear exam	X			
6-months Fall Diary	X			

Foot notes

[1] order of assessments is flexible as long as “on” and “off” state requirement for assessments for each visit are followed.

[2] PET scan and MRI are considered part of V1 and can be done in any order with other assessments after informed consent is obtained.

[3] Physical Exam can be brief or focused on neurological (MDS-UPDRS Part III) depending on clinician’s determination, patient symptoms, and medical history.

[4]The visit and/or individual test components are optional.

*Abbreviated medical history and demographics forms will be used to assess changes since participants last study visit.

Assessments that are unable to be obtained during visits will not be deemed protocol deviations unless they affect the data integrity/validity of the study.

4.6 Data Analysis

Primary outcome measures and scientific rigor: Our primary outcome measure for Hypothesis 1 will be the New Freezing of Gait Questionnaire (NFOG-Q) (39). The NFOG-Q is the current gold standard for assessment of FoG in PD research and clinical trials (46-48). The diagnosis of PVP will be based on abnormal performance on the modified Romberg test (1). The modified Romberg test has high test-retest interrater reliability (each R=0.99) and has been validated in patients with vestibulopathy (34). The [^{11}C]PE2I PET radioligand has the highest affinity and selectivity among DAT PET ligands that are currently in human use (49, 50).

We propose to test the overall hypothesis that the prevalence of FoG is higher in subjects with PD and PSP who also have evidence of PVP compared to those without vestibulopathy independent of nigrostriatal dopaminergic losses. We will begin by calculating summary statistics (mean, median, SD, range, etc.) as well as plots of all data. This will allow us to examine the distribution of the data to ensure that assumptions of statistical models will be respected. All analysis will be performed using the R statistical software package. We predict that the prevalence of freezers will be higher in the PVP group compared to the non-PVP group. We will recruit a PD population enriched for the presence of FoG by requiring at motor disease duration of at least 5 years and exclude participants with early-stage Hoehn & Yahr disease. Given the prevalence of FoG in about 50% of patients in this group we expect to recruit about even groups of freezers and non-freezers. Our preliminary data showed that PVP was present in p1= 84.6% of PD freezers and p2=27.8% in non-freezers. Given our net recruitment target of n=56 (half of whom will be freezers) PVP will be present in just over half of the total study population (56.2%). We plan to build a predictive model, such as logistic or probit, that links the binary FoG response to PVP (a binary variable) and the DAT PET scan (linear variable). Power is set at 0.8 with a significance level of 0.05 and the rejection region is one sided: p1 > p2. Sample size for PD is estimated based on preliminary data that yield estimates for p1 and p2 (as outlined above), and using the R-module statmod and calling the function power.fisher.test which simulates data sets – in our case we set its parameter nsim=1000 data sets -- to generate required sample sizes for given power and including the dopamine PET scan preliminary findings. We will recruit up to 20 PSP participants to ensure an adequate sample size is used and to account for possible attrition.

Specifically, we used the R command > power.fisher.test(.7,.3,24,24,nsim=1000,alternative="greater"), yielding a power .82 or greater. [Note n1=n2=24 is a conservative estimate in the sense that 0.7 - 0.3 < 0.84 - 0.28 (obtained in our preliminary data), and in that 0.7 and 0.3 are symmetrically placed around 0.5]. Given these parameters and power simulations, the study requires a minimum sample of n=48 participants (about half freezers and half non-freezers) to achieve the stated goals, which is well within our recruitment target.

If we find a significant association between the presence of PVP and FoG then we will perform a post-hoc confounder variables analysis using parkinsonian motor severity, cognition, age, gender, dizziness ratings or ankle sensation variables to investigate the

specificity of the main result in both the PD and PSP subjects. As FoG is an important risk factor for falls we will also evaluate whether the presence of FoG at baseline may predict subsequent fall risk prospectively in a secondary analysis.

Missing data. Multiple imputation vs. single imputation via the mean, addresses the uncertainty in the missing values

Pitfalls, problems and alternative strategies

Possible scenario of falsification of primary hypothesis: If we fail to verify our primary hypotheses that vestibular dysfunction is a key determinant of FoG this would not preclude the possibility that a vestibular intervention may help to alleviate this mobility disturbance. For example, vestibular cerebellar compensation may play a role in PD to attenuate the effects of dopaminergic denervation on motor impairments, including gait functions (60, 61). Furthermore, prior vestibular stimulation studies have found physiological effects across different brain regions, including the brainstem and basal ganglia (62, 63) that are relevant for PD pathophysiology. The recently published portable TNM^{TM} intervention study also found positive clinical treatment effects in PD patients despite absence of screening for vestibulopathy in PD patients (64).

Ineligibility and attrition rate: During the eligibility screening and course of the study we anticipate overall subject combined exclusion and attrition rate of approximately 10-15% (gross target n=64 and net target n=56). This is based on a typical 5% exclusion rate as the DAT PET scan may not confirm the diagnosis of idiopathic PD, either on absence of nigrostriatal denervation or evidence of atypical parkinsonism such as multiple system atrophy (MSA) based on the inspection of the PET post-injection K_1 flow delivery images. There is also a small risk of withdrawal of subjects due to claustrophobia for the scanner despite appropriate pre-imaging screening and instructions. We will keep close documentation to register any missing data points, drop-outs and reasons for it.

Medication use: Changes in dopaminergic medication use will be monitored throughout the study for post-hoc analysis when needed.

Milestones of success:

- IRB approval during the first 2 months of year 1.
- A recruitment and completion target of 16 participants per year for the main aim
- Interim data processing and analysis on a yearly basis to identify and correct potential dilemma early in the course of the study.

The PI and the study coordinator will be in charge of the day-to-day operations of the study, oversee recruitment and monitor study completion to ensure successful accomplishment of the key milestones of this project.

4.7 Withdrawal of Subjects

Subjects can withdraw their participation in this protocol at any time.

5.0 Reporting

Ann Arbor VA IRB standard reporting guidelines will be followed.

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users, or other persons, whether or not related to the study AEs will be collected starting from the time the participant signs informed consent until their participation is completed.

A Serious Adverse Event (SAE) is an AE that has

- Led to death,
- Led to serious deterioration in the health of the participant, that either resulted in
  1.A life-threatening illness or injury, or
  2.A permanent impairment of a body structure or a body function, or
  3.In-patient or prolonged hospitalization, or
  4.Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

All AEs will be recorded in the participants' source documentation. For all AEs, sufficient information will be obtained as to 1) determine the severity of the event; 2) assess the casual relationship between the adverse event and the study; and 3) determine the outcome of the event. AEs will be followed until the event (or its sequelae) resolves or stabilizes at a level acceptable to the investigator.

The investigator will promptly review documented AEs to determine 1) if there is a reasonable possibility that the adverse event was caused by the study and 2) if the adverse event meets the criteria for "serious." If the investigator's final determination of causality is "possible or probable relationship to the study," the adverse effect will be classified as associated with the study for reporting purposes. If the investigator's final determination of causality is "not related to the study," this determination and the rationale for the determination will be documented.

6.0 Privacy and Confidentiality

All data collected under this research protocol will be coded data. The data linking file is stored on the Ann Arbor VA protected server. Only specific users with a login can access this file, and this file is password protected. PII information collected for recruitment are maintained in a file on the VA server. PHI information is reviewed for eligibility, and current medications may be acquired from medical records and become part of the research data.

One participant will be tested at a time to protect the privacy of participants. If study participant sessions were to overlap then participants will be managed in separate rooms with the doors closed to protect the privacy of participants. VA data will be collected in paper workbooks. This data will be entered into a file maintained on the VA server and then a copy will be sent to the University of Michigan following a DUA. This data will be entered into electronic files maintained on the VA server and transferred to the University of Michigan using a VA approved USB storage device.

The possibility of unintended disclosure of medical or research data is minimal, but not entirely impossible. We will employ stringent safeguards against unintended and inappropriate discovery and dissemination of personal medical and research data in our subjects by a multi-layered approach. All data bearing potential subject identifiers will reside securely on the VA server. Original data collection documents will be maintained in secure files under the control of the investigators and maintained at the Ann Arbor VA. Entries regarding details of the research project and its results will not be submitted to clinical medical databases. Data will be entered into an electronic database that will reside on the VA server. Electronic databases in the project will employ subject codes that cannot be linked directly to participants without a “key”, possessed only by the study investigators on the VA server, and maintained separately from the research data. Personal information that would directly identify study subjects will not be used in any publications or presentations resulting from this research study, unless separate written permission is given by the subject (or proxy). The data will be shared with the University of Michigan following the execution of a DUA.

7.0 Communication Plan

Science dissemination and communication plan. The current project aims to generate novel scientific insights into the comorbid presence of vestibular dysfunction and FoG in PD. Primarily, we aim to publish our results in top-level international clinically-oriented neuroscience journals (e.g., Annals of Neurology, Neurology, or Brain). This ensures that clinicians will take note of our results. Furthermore, we will present our results at (inter)-national conferences and symposia. We also envision that the results of this project will generate new knowledge on a new rehabilitation strategies to improve FoG and decrease fall risk in subjects with PD. We will communicate the project outcomes also in specialization courses for physical therapists involved in the Parkinson Care network. Direct communication to caregivers, patients and therapists by means of an information session on the outcome of this project will be organized in our lab for this purpose. In this way, participants will have the opportunity to be informed about the results of the ongoing studies and to discuss them with the researchers. Finally, we are already actively collaborating with Michigan Parkinson Foundation, a patient association that is committed to people afflicted with PD. This will give us the opportunity to inform a broader PD audience through their website, magazine, symposia and other organized activities.

8.0 References

1. Agrawal Y, Davalos-Bichara M, Zuniga MG, Carey JP. Head impulse test abnormalities and influence on gait speed and falls in older individuals. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology. 2013;34(9):1729-35. Epub 2013/08/10. doi: 10.1097/MAO.0b013e318295313c. PubMed PMID: 23928523.

3. Lopez IC, Ruiz PJ, Del Pozo SV, Bernardos VS. Motor complications in Parkinson's disease: ten year follow-up study. Mov Disord. 2010;25(16):2735-9. Epub 2010/10/12. doi: 10.1002/mds.23219. PubMed PMID: 20931632.

4. Vu TC, Nutt JG, Holford NH. Progression of motor and nonmotor features of Parkinson's disease and their response to treatment. British journal of clinical pharmacology. 2012;74(2):267-83. Epub 2012/01/31. doi: 10.1111/j.1365-2125.2012.04192.x. PubMed PMID: 22283961; PMCID: 3630747.

5. Venhovens J, Meulstee J, Bloem BR, Verhagen WI. Neurovestibular analysis and falls in Parkinson's disease and atypical parkinsonism. The European journal of neuroscience. 2016;43(12):1636-46. Epub 2016/04/12. doi: 10.1111/ejn.13253. PubMed PMID: 27062368.

6. van Wensen E, van Leeuwen RB, van der Zaag-Loonen HJ, Masius-Olthof S, Bloem BR. Benign paroxysmal positional vertigo in Parkinson's disease. Parkinsonism Relat Disord. 2013;19(12):1110-2. Epub 2013/08/21. doi: 10.1016/j.parkreldis.2013.07.024. PubMed PMID: 23948517.

7. Becker-Bense S, Wittmann C, van Wensen E, van Leeuwen RB, Bloem B, Dieterich M. Prevalence of Parkinson symptoms in patients with different peripheral vestibular disorders. Journal of neurology. 2017;264(6):1287-9. Epub 2017/04/02. doi: 10.1007/s00415-017-8470-7. PubMed PMID: 28364298.

8. Hughes AJ, Daniel SE, Blankson S, Lees AJ. A clinicopathologic study of 100 cases of Parkinson's disease. Arch Neurol. 1993;50:140-8.

9. Hely MA, Morris JG, Reid WG, Trafficante R. Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord. 2005;20(2):190-9. PubMed PMID: 15551331.

10. Giladi N, McDermott MP, Fahn S, Przedborski S, Jankovic J, Stern M, Tanner C. Freezing of gait in PD: prospective assessment in the DATATOP cohort. Neurology. 2001;56(12):1712-21. Epub 2001/06/27. PubMed PMID: 11425939.

11. Ferraye MU, Debu B, Pollak P. Deep brain stimulation effect on freezing of gait. Mov Disord. 2008;23 Suppl 2:S489-94. Epub 2008/08/01. doi: 10.1002/mds.21975. PubMed PMID: 18668617.

12. Devos D, Defebvre L, Bordet R. Dopaminergic and non-dopaminergic pharmacological hypotheses for gait disorders in Parkinson's disease. Fundam Clin Pharmacol. 2010;24(4):407-21. Epub 2010/02/19. doi: 10.1111/j.1472-8206.2009.00798.x
FCP798 [pii]. PubMed PMID: 20163480.

13. Maillet A, Pollak P, Debu B. Imaging gait disorders in parkinsonism: a review. Journal of neurology, neurosurgery, and psychiatry. 2012;83(10):986-93. Epub 2012/07/10. doi: 10.1136/jnnp-2012-302461
jnnp-2012-302461 [pii]. PubMed PMID: 22773859.

14. Muller ML, Albin RL, Kotagal V, Koeppe RA, Scott PJ, Frey KA, Bohnen NI. Thalamic cholinergic innervation and postural sensory integration function in Parkinson's disease. Brain : a journal of neurology. 2013;136(Pt 11):3282-9. Epub 2013/09/24. doi: 10.1093/brain/awt247
awt247 [pii]. PubMed PMID: 24056537.

15. Smith PF. Vestibular Functions and Parkinson's Disease. Frontiers in neurology. 2018;9:1085. Epub 2019/01/09. doi: 10.3389/fneur.2018.01085. PubMed PMID: 30619045; PMCID: PMC6297246.

16. Reichert WH, Doolittle J, McDowell FH. Vestibular dysfunction in Parkinson disease. Neurology. 1982;32(10):1133-8. Epub 1982/10/01. PubMed PMID: 6981783.

17. de Natale ER, Ginatempo F, Paulus KS, Manca A, Mercante B, Pes GM, Agnetti V, Tolu E, Deriu F. Paired neurophysiological and clinical study of the brainstem at different stages of Parkinson's Disease. Clin Neurophysiol. 2015;126(10):1871-8. doi: 10.1016/j.clinph.2014.12.017. PubMed PMID: 25622530.

18. de Natale ER, Ginatempo F, Paulus KS, Pes GM, Manca A, Tolu E, Agnetti V, Deriu F. Abnormalities of vestibular-evoked myogenic potentials in idiopathic Parkinson's disease are associated with clinical evidence of brainstem involvement. Neurol Sci. 2015;36(6):995-1001. doi: 10.1007/s10072-014-2054-4. PubMed PMID: 25567081.

19. Pastor MA, Day BL, Marsden CD. Vestibular induced postural responses in Parkinson's disease. Brain : a journal of neurology. 1993;116 (Pt 5):1177-90. Epub 1993/10/01. PubMed PMID: 8221054.

20. Chong RK, Horak FB, Frank J, Kaye J. Sensory organization for balance: specific deficits in Alzheimer's but not in Parkinson's disease. J Gerontol A Biol Sci Med Sci. 1999;54(3):M122-M8.

21. Agrawal Y, Carey JP, Della Santina CC, Schubert MC, Minor LB. Disorders of balance and vestibular function in US adults: data from the National Health and Nutrition Examination Survey, 2001-2004. Archives of internal medicine. 2009;169(10):938-44. Epub 2009/05/27. doi: 10.1001/archinternmed.2009.66. PubMed PMID: 19468085.

22. Takakusaki K. Neurophysiology of gait: from the spinal cord to the frontal lobe. Mov Disord. 2013;28(11):1483-91. Epub 2013/10/18. doi: 10.1002/mds.25669. PubMed PMID: 24132836.

23. Nieuwboer A, Giladi N. Characterizing freezing of gait in Parkinson's disease: models of an episodic phenomenon. Mov Disord. 2013;28(11):1509-19. Epub 2013/10/18. doi: 10.1002/mds.25683. PubMed PMID: 24132839.

24. Huh YE, Hwang S, Kim K, Chung WH, Youn J, Cho JW. Postural sensory correlates of freezing of gait in Parkinson's disease. Parkinsonism Relat Disord. 2016;25:72-7. Epub 2016/02/18. doi: 10.1016/j.parkreldis.2016.02.004. PubMed PMID: 26883663.

25. Vervoort G, Nackaerts E, Mohammadi F, Heremans E, Verschueren S, Nieuwboer A, Vercruysse S. Which Aspects of Postural Control Differentiate between Patients with Parkinson's Disease with and without Freezing of Gait? Parkinsons Dis. 2013;2013:971480. Epub 2013/08/13. doi: 10.1155/2013/971480. PubMed PMID: 23936729; PMCID: PMC3712240.

26. Kennedy PM, Cressman EK, Carlsen AN, Chua R. Assessing vestibular contributions during changes in gait trajectory. Neuroreport. 2005;16(10):1097-100. Epub 2005/06/24. doi: 10.1097/00001756-200507130-00013. PubMed PMID: 15973155.

27. Huh YE, Hwang S, Kim K, Chung WH, Youn J, Cho JW. Reply to letter: The association of postural sensory deficit with freezing of gait in Parkinson's disease. Parkinsonism Relat Disord. 2016;31:141-2. Epub 2016/06/20. doi: 10.1016/j.parkreldis.2016.06.006. PubMed PMID: 27318705.

33. Salerno J. The role of primary care in Alzheimer's disease. In: Primary care of Alzheimer's disease: a multidisciplinary challenge. Federal Practitioner. 1996(Suppl.):5-6.

34. Cohen H, Blatchly CA, Gombash LL. A study of the clinical test of sensory interaction and balance. Physical therapy. 1993;73(6):346-51; discussion 51-4. Epub 1993/06/01. doi: 10.1093/ptj/73.6.346. PubMed PMID: 8497509.

35. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. Journal of neurology, neurosurgery, and psychiatry. 1992;55(3):181-4. Epub 1992/03/01. PubMed PMID: 1564476; PMCID: 1014720.

36. Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, Stern MB, Tilley BC, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, Lewitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, Van Hilten JJ, Lapelle N. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. Mov Disord. 2007;22:41-7. PubMed PMID: 17115387.

37. Snijders AH, Haaxma CA, Hagen YJ, Munneke M, Bloem BR. Freezer or non-freezer: clinical assessment of freezing of gait. Parkinsonism Relat Disord. 2012;18(2):149-54. Epub 2011/10/05. doi: 10.1016/j.parkreldis.2011.09.006S1353-8020(11)00303-8 [pii]. PubMed PMID: 21968033.

38. Beaulieu ML, Muller M, Bohnen NI. Peripheral neuropathy is associated with more frequent falls in Parkinson's disease. Parkinsonism Relat Disord. 2018;54:46-50. Epub 2018/04/08. doi: 10.1016/j.parkreldis.2018.04.006. PubMed PMID: 29625874; PMCID: PMC6163065.

39. Nieuwboer A, Rochester L, Herman T, Vandenberghe W, Emil GE, Thomaes T, Giladi N. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. Gait & posture. 2009;30(4):459-63. Epub 2009/08/08. doi: 10.1016/j.gaitpost.2009.07.108S0966-6362(09)00200-8 [pii]. PubMed PMID: 19660949.

40. Pagonabarraga J, Kulisevsky J, Llebaria G, Garcia-Sanchez C, Pascual-Sedano B, Gironell A. Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. Mov Disord. 2008;23(7):998-1005. Epub 2008/04/03. doi: 10.1002/mds.22007. PubMed PMID: 18381647.

41. Kulisevsky J, Fernandez de Bobadilla R, Pagonabarraga J, Martinez-Horta S, Campolongo A, Garcia-Sanchez C, Pascual-Sedano B, Ribosa-Nogue R, Villa-Bonomo C. Measuring functional impact of cognitive impairment: validation of the Parkinson's disease cognitive functional rating scale. Parkinsonism Relat Disord. 2013;19(9):812-7. doi: 10.1016/j.parkreldis.2013.05.007. PubMed PMID: 23773412.

42. Jenkinson C, Peto V, Fitzpatrick R, Greenhall R. Self-reported functioning and well-being in patients with Parkinson's disease: comparison of the short-form health survey (SF-36) and the Parkinson's Disease Questionnaire (PDQ-39). Age and ageing. 1995;24:505-9.

43. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. Archives of otolaryngology--head & neck surgery. 1990;116(4):424-7. Epub 1990/04/01. PubMed PMID: 2317323.

44. Yardley L, Masson E, Verschuur C, Haacke N, Luxon L. Symptoms, anxiety and handicap in dizzy patients: development of the vertigo symptom scale. Journal of psychosomatic research. 1992;36(8):731-41. Epub 1992/12/01. doi: 10.1016/0022-3999(92)90131-k. PubMed PMID: 1432863.

45. Agrawal Y, Van de Berg R, Wuyts F, Walther L, Magnusson M, Oh E, Sharpe M, Strupp M. Presbyvestibulopathy: Diagnostic criteria Consensus document of the classification committee of the Barany Society. Journal of vestibular research : equilibrium & orientation. 2019;29(4):161-70. Epub 2019/07/16. doi: 10.3233/ves-190672. PubMed PMID: 31306146.

46. Pelosin E, Barella R, Bet C, Magioncalda E, Putzolu M, Di Biasio F, Cerulli C, Casaleggio M, Abbruzzese G, Avanzino L. Effect of Group-Based Rehabilitation Combining Action Observation with Physiotherapy on Freezing of Gait in Parkinson's Disease. Neural Plast. 2018;2018:4897276. Epub 2018/07/07. doi: 10.1155/2018/4897276. PubMed PMID: 29977280; PMCID: PMC5994277.

47. Iijima M, Orimo S, Terashi H, Suzuki M, Hayashi A, Shimura H, Mitoma H, Kitagawa K, Okuma Y. Efficacy of istradefylline for gait disorders with freezing of gait in Parkinson's disease: A single-arm, open-label, prospective, multicenter study. Expert Opin Pharmacother. 2019;20(11):1405-11. Epub 2019/05/02. doi: 10.1080/14656566.2019.1614167. PubMed PMID: 31039621.

48. Capecci M, Pournajaf S, Galafate D, Sale P, Le Pera D, Goffredo M, De Pandis MF, Andrenelli E, Pennacchioni M, Ceravolo MG, Franceschini M. Clinical effects of robot-assisted gait training and treadmill training for Parkinson's disease. A randomized controlled trial. Ann Phys Rehabil Med. 2019;62(5):303-12. Epub 2019/08/05. doi: 10.1016/j.rehab.2019.06.016. PubMed PMID: 31377382.

49. Sasaki T, Ito H, Kimura Y, Arakawa R, Takano H, Seki C, Kodaka F, Fujie S, Takahata K, Nogami T, Suzuki M, Fujiwara H, Takahashi H, Nakao R, Fukumura T, Varrone A, Halldin C, Nishikawa T, Suhara T. Quantification of dopamine transporter in human

brain using PET with 18F-FE-PE2I. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2012;53(7):1065-73. Epub 2012/06/13. doi: 10.2967/jnumed.111.101626. PubMed PMID: 22689927.

50. Varrone A, Halldin C. New developments of dopaminergic imaging in Parkinson's disease. Q J Nucl Med Mol Imaging. 2012;56(1):68-82. Epub 2012/03/31. PubMed PMID: 22460161.

51. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010;25(15):2649-53. Epub 2010/11/12. doi: 10.1002/mds.23429. PubMed PMID: 21069833.

52. Giladi N, Nieuwboer A. Understanding and treating freezing of gait in parkinsonism, proposed working definition, and setting the stage. Mov Disord. 2008;23 Suppl 2:S423-5. Epub 2008/08/01. doi: 10.1002/mds.21927. PubMed PMID: 18668629.

53. Shumway-Cook A, Horak FB. Assessing the influence of sensory interaction of balance. Suggestion from the field. Physical therapy. 1986;66(10):1548-50. Epub 1986/10/01. PubMed PMID: 3763708.

54. Cohen HS, Kimball KT. Usefulness of some current balance tests for identifying individuals with disequilibrium due to vestibular impairments. Journal of vestibular research : equilibrium & orientation. 2008;18(5-6):295-303. Epub 2008/01/01. PubMed PMID: 19542603; PMCID: PMC2819299.

55. Stack E, Ashburn A. Fall events described by people with Parkinson's disease: Implications for clinical interviewing and research agenda. Physiol Res Int. 1999;4/3:190-200.

56. Cumming RG, Salkeld G, Thomas M, Szonyi G. Prospective study of the impact of fear of falling on activities of daily living, SF-36 scores, and nursing home admission. J Gerontol: Med Sci. 2000;55A(M299-M305).

57. Minoshima S, Koeppe RA, Fessler JA, Mintun MA, Berger KL, Taylor SF, Kuhl DE. Integrated and automated data analysis method for neuronal activation studying using O^{15} water PET. In: Uemura K, Lassen NA, Jones T, Kanno I, editors. Quantification of brain function to tracer kinetics and image analysis in brain PET. Tokyo: Excerpta Medica; 1993. p. 409-18.

58. Muller-Gartner H, Links J, Prince J, Bryan R, McVeigh E, Leal J, Davatzikos C, Frost J. Measurement of radiotracer concentration in brain gray matter using positron emission tomography: MRI based correction of partial volume effects. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 1992;12:571-83.

60. Deveze A, Bernard-Demanze L, Xavier F, Lavieille JP, Elziere M. Vestibular compensation and vestibular rehabilitation. Current concepts and new trends. Neurophysiol Clin. 2014;44(1):49-57. Epub 2014/02/08. doi: 10.1016/j.neucli.2013.10.138. PubMed PMID: 24502905.

61. Gilat M, Dijkstra BW, D'Cruz N, Nieuwboer A, Lewis SJG. Functional MRI to Study Gait Impairment in Parkinson's Disease: a Systematic Review and Exploratory ALE Meta-Analysis. Curr Neurol Neurosci Rep. 2019;19(8):49. Epub 2019/06/20. doi: 10.1007/s11910-019-0967-2. PubMed PMID: 31214901.

62. Cai J, Lee S, Ba F, Garg S, Kim LJ, Liu A, Kim D, Wang ZJ, McKeown MJ. Galvanic Vestibular Stimulation (GVS) Augments Deficient Pedunculopontine Nucleus (PPN) Connectivity in Mild Parkinson's Disease: fMRI Effects of Different Stimuli. Front Neurosci. 2018;12:101. Epub 2018/03/16. doi: 10.3389/fnins.2018.00101. PubMed PMID: 29541016; PMCID: PMC5835530.

63. Black RD, Rogers LL, Ade KK, Nicoletto HA, Adkins HD, Laskowitz DT. Non-Invasive Neuromodulation Using Time-Varying Caloric Vestibular Stimulation. IEEE journal of translational engineering in health and medicine. 2016;4:2000310. Epub 2016/10/26. doi: 10.1109/jtehm.2016.2615899. PubMed PMID: 27777829; PMCID: PMC5074346.

64. Jenkins IH, Bain PG, Colebatch JG, Thompson PD, Findley LJ, Frackowiak RS, Marsden CD, Brooks DJ. A positron emission tomography study of essential tremor: evidence for overactivity of cerebellar connections. Annals of neurology. 1993;34:82-90.

65. Wilkinson D, Podlewska A, Banducci SE, Pellat-Higgins T, Slade M, Bodani M, Sakel M, Smith L, LeWitt P, Ade K. Caloric vestibular stimulation for the management of motor and non-motor symptoms in parkinson's disease: Intention-to-treat data. Data in brief. 2019;25:104228. Epub 2019/08/07. doi: 10.1016/j.dib.2019.104228. PubMed PMID: 31384641; PMCID: PMC6661455.

66. Liao K, Wagner J, Joshi A, Estrovich I, Walker MF, Strupp M, et al. Why do patients with PSP fall? Evidence for abnormal otolith responses. Neurology. 2008; 70:802–9. doi:10.1212/01.wnl.0000304134.33380.1e

67. Cronin T, Qadeer A, Barry S. Vestibular deficits in neurodegenerative disorders: balance, dizziness, and spatial disorientation. Frontiers in Neurology. 2017; 8: 1664-2295. doi: 10.3389/fneur.2017.00538

68. Carpinelli S, Valko Philipp O., Waldvogel D, Buffone E, Baumann C., Straumann D, Werth E, Bockisch C., Weber K., Valko Y. Distinct Vestibular Evoked Myogenic Potentials in Patients With Parkinson Disease and Progressive Supranuclear Palsy. Frontiers in Neurology. 2021; 11:1164-2295. doi: 10.3389/fneur.2020.598763

69. Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, Mollenhauer B, Müller U, Nilsson C, Whitwell JL, Arzberger T, Englund E, Gelpi E, Giese A, Irwin DJ, Meissner WG, Pantelyat A, Rajput A, van Swieten JC, Troakes C, Antonini A,

Bhatia KP, Bordelon Y, Compta Y, Corvol JC, Colosimo C, Dickson DW, Dodel R, Ferguson L, Grossman M, Kassubek J, Krismer F, Levin J, Lorenzl S, Morris HR, Nestor P, Oertel WH, Poewe W, Rabinovici G, Rowe JB, Schellenberg GD, Seppi K, van Eimeren T, Wenning GK, Boxer AL, Golbe LI, Litvan I; Movement Disorder Society-endorsed PSP Study Group. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord. 2017 Jun;32(6):853-864. doi: 10.1002/mds.26987. Epub 2017 May 3. PMID: 28467028; PMCID: PMC5516529