Vestibular Sensory Conflict During Postural Control, Freezing of Gait, and Falls in Parkinson's Disease

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ABSTRACT: Background: The vestibular system has been implicated in the pathophysiology of episodic motor impairments in Parkinson's disease (PD), but specific evidence remains lacking.
Objective: We investigated the relationship between the presence of freezing of gait and falls and postural failure during the performance on Romberg test condition 4 in patients with PD.
Methods: Modified Romberg sensory conflict test, fall, and freezing-of-gait assessments were performed in 92 patients with PD (70 males/22 females; mean age, 67.6 ± 7.4 years; Hoehn and Yahr stage, 2.4 ± 0.6; mean Montreal Cognitive Assessment, 26.4 ± 2.8).
Results: Failure during Romberg condition 4 was present in 33 patients (35.9%). Patients who failed the Romberg condition 4 were older and had more severe motor and cognitive impairments than those without. About 84.6% of all patients with freezing of gait had failure during Romberg condition 4, whereas 13.4% of patients with freezing of gait had normal performance ($\chi^2 = 15.6$; $P < 0.0001$). Multiple logistic regression analysis showed that the regressor effect of Romberg condition 4 test failure for the presence of freezing of gait (Wald $\chi^2 = 5.0$; $P = 0.026$) remained significant after accounting for the degree of severity of parkinsonian motor ratings (Wald $\chi^2 = 6.2$; $P = 0.013$), age (Wald $\chi^2 = 0.3$; $P = 0.59$), and cognition (Wald $\chi^2 = 0.3$; $P = 0.75$; total model: Wald $\chi^2 = 16.1$; $P < 0.0001$). Patients with PD who failed the Romberg condition 4 (45.5%) did not have a statistically significant difference in frequency of patients with falls compared with patients with PD without abnormal performance (30.5%; $\chi^2 = 2.1$; $P = 0.15$).
Conclusions: The presence of deficient vestibular processing may have specific pathophysiological relevance for freezing of gait, but not falls, in PD. © 2022 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: falls; freezing of gait; modified Romberg test; Parkinson's disease; vestibular efficacy

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by resting tremor, slowness of movement, rigidity, and postural instability and gait difficulties (PIGD). For decades it has been speculated that PD is associated with dysfunction of the vestibular system (especially given that postural instability is one of the major symptoms of PD), but clear evidence of such a connection has been slow to emerge.[1] Vestibular impairment, particularly chronic bilateral vestibular dysfunction, is a significant contributor to imbalance and falls in otherwise healthy older adults.[2] Abnormal findings on the modified sensory conflict Romberg test in older adults with deficient vestibular efficacy result in significantly increased odds of falling even in the absence of an overt history of

dizziness.[2] This finding suggests that the age-associated subclinical vestibular dysfunction captured by sensory conflict postural tests is clinically relevant. Abnormal vestibular efficacy is also common in PD.[3-5] Turning is a common trigger for falls and one of the most effective maneuvers to elicit freezing of gait (FoG) in PD.[6] In terms of multisensory integration for effective postural and gait control, vestibular feedback becomes more critical when initiating turning,[7] where visual and somatosensory feedback become more unreliable.[8] These findings suggest that vestibular efficacy is implicated in turning-associated PIGD motor features in PD, such as falls and FoG. We have conceptually defined vestibular efficacy as the ability of the central nervous system to process and integrate vestibular sensory information into downstream neural pathways. Although it may in part result from it, it is not the same as (peripheral) vestibular dysfunction. The primary goal of this study was to test the hypothesis that abnormal performance on the modified sensory conflict Romberg test condition 4, which increases vestibular burden during postural control, is an important risk factor for falls and FoG in patients with PD.

Subjects and Methods

Subjects

This cross-sectional study involved 92 patients with PD: 70 males/22 females; mean age, 67.6 ± 7.4 years; and mean motor disease duration, 6.0 ± 4.6 years. Subjects with PD met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria.[9] Patients in Hoehn & Yahr stage 5 or with dementia were not eligible for the study. Mean Montreal Cognitive Assessment (MoCa) score was 26.4 ± 2.8.[10] Most subjects had moderate severity of disease: 6 subjects in stage 1, 3 in stage 1.5, 20 in stage 2, 40 in stage 2.5, 20 in stage 3, and 3 in stage 4 of the modified Hoehn and Yahr classification with mean stage of 2.5 ± 0.6. Our rationale for including patients with (at least clinically defined) normal balance is that postural imbalance is not always an essential component of FoG.[11,12] Thirty-one subjects with PD were taking a combination of dopamine agonist and carbidopa-levodopa medications, 45 were using carbidopa-levodopa alone, 10 were taking dopamine agonists alone, and 6 were not receiving dopaminergic drugs. Subjects with evidence of large-vessel stroke or other intracranial lesions on anatomic imaging were excluded.

Clinical Assessment

The Movement Disorder Society–revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor examination was performed in the morning in the dopaminergic medication *off* state. The mean motor examination score on the MDS-UPDRS was 35.5 ± 14.2.[13] Participants were asked about a history of falling, even a single fall. A fall was defined as an unexpected event during which a person falls to the ground. We did not exclude falls as a result of a specific etiology. FoG status was defined by direct observation of motor freezing behavior by an experienced neurologist while performing the MDS-UPDRS motor examination in the dopamine (DA) medication *off* state (ie, score on MDS-UPDRS item 3.11 > 0) and in the setting of patient self-reported FoG. Fall status was determined as presence or absence of any reported falls within the prior year.

Modified Romberg 1–4 tests evaluate standing balance on firm and compliant support surfaces.[14,15] The modified Romberg test is similar to the Sensory Organization Test (SOT), where the Romberg 4 subtest corresponds to falls on the SOT5 subtest, which has been found to have a sensitivity of 80% and specificity of 80% to diagnose a vestibular disorder.[16] The modified Romberg test examines the ability to stand unassisted using four test conditions designed specifically to test the sensory inputs that contribute to balance—the vestibular system, vision, and proprioception.[17] The different conditions are: condition 1, standing on firm surface with eyes open while depending on visual, proprioceptive, and vestibular input; condition 2, standing on firm surface with eyes closed while depending on proprioceptive and vestibular input; and condition 3, standing on compliant surface with eyes open while depending on visual and vestibular input. The fourth test condition is designed to focus more specifically on vestibular function: 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 s on the Romberg 4 test (standing on foam surface with eyes closed) in the absence of falling on subtests 1–3 was defined as abnormal condition 4 test performance[15] and as previously validated in a prior study of patients with vestibular disorders.[18] Participants had a single attempt per condition unless the participant did not properly understand or follow the instructions. A research assistant was standing at arm's length to protect the participant in case of a fall.

This study (ClinicalTrials.gov Identifiers: NCT02458430 and NCT01754168) was approved by the Institutional Review Boards of the University of Michigan School of Medicine and Veterans Affairs Ann Arbor Healthcare System. Written informed consent was obtained from all subjects. Findings of episodic and nonepisodic mobility disturbances (ie, FoG and falls) and neurotransmitter brain PET changes obtained in a subset of the same cohort of patients in this study have been and will be published elsewhere.[19,20]

Statistical Analysis

Standard pooled-variance t or Satterthwaite's method of approximate t tests (t_{approx}) were used for group comparisons. The 2×2 contingency χ^2 testing was performed

TABLE 1 *Mean (±SD) values of demographic and clinical variables in the patients with versus without failure during Romberg condition 4*

Demographic and clinical variables	PD with failure during Romberg condition 4 (n = 33)	PD without failure during Romberg condition 4 (n = 59)	Group comparison (significance)
Age (y)	71.7 ± 7.5	66.2 ± 6.3	$t = 4.40$, $P < 0.0001$
Gender (male/female)	25/6	45/14	$\chi^2 = 0.003$, $P = 0.96$
Duration of motor PD (y)	6.4 ± 3.8	5.8 ± 4.9	$t = 0.64$, $P = 0.53$
MDS-UPDRS total motor score	37.4 ± 14.5	33.1 ± 12.1	$t = 3.73$, $P = 0.0004$
MoCa	25.6 ± 3.1	26.9 ± 2.5	$t = 2.21$, $P = 0.03$
LED	675 ± 331	629 ± 430	$t = 0.52$, $P = 0.60$

Gender distribution is presented as proportions. Standard pooled-variance t or Satterthwaite's method of approximate t tests (t_{approx}) was used for group comparisons. Levels of statistical difference between groups are presented in the last column.
PD, Parkinson's disease; MDS-UPDRS, Movement Disorder Society–revised Unified Parkinson's Disease Rating Scale; MoCa, Montreal Cognitive Assessment; LED, levodopa equivalent dose.

for comparison of proportions of fall status (0 falls vs. ≥1 fall) and FoG (no freeze vs. freeze) between the two Romberg test groups (Romberg condition 4 pass vs. fail while passing conditions 1–3). Multiple logistic regression was performed using FoG status as the outcome parameters while accounting for confounder variables (age, total motor UPDRS motor scores, and MoCa) that were shown to be different between the two Romberg test groups. Statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Selective Test Failure on Romberg Condition 4

Failure during Romberg condition 4 was present in 33 patients (35.9%). Table 1 lists mean (±SD) values of demographic and clinical variables in the patients with versus without failure during Romberg condition 4. Patients with PD with failure during Romberg condition 4 were older, had more severe motor impairments, and had lower cognitive performance compared with

patients with nonfailure during Romberg condition 4 (Table 1). For example, the frequency of failure during Romberg condition 4 was 10.3% in stages 1 and 2, 37.5% in stage 2.5, 65% in stage 3, and 66.7% in stage 4 of the modified Hoehn and Yahr scale.

Failure During Romberg Condition 4 and FoG

About 84.6% of all subjects with FoG had abnormal vestibular efficacy, while 13.4% of subjects with FoG had normal vestibular efficacy (likelihood ratio $\chi^2 = 15.6$; $P < 0.0001$; Table 2).

Confounder Analysis for Association Between Failure During Romberg Condition 4 and FoG

Multiple logistic regression analyses showed that the regressor effect of failure during Romberg condition 4 for the presence of FoG (Wald $\chi^2 = 5.0$; $P = 0.026$; odds ratio, estimate 7.96 with 5–95% CI: 1.28–49.4) remained significantly independent from the degree of severity of MDS-UPDRS Part III motor ratings (Wald $\chi^2 = 6.2$; $P = 0.013$; odds ratio, estimate 1.10 with 5–95% CI: 1.02–1.19), age (Wald $\chi^2 = 0.3$; $P = 0.59$),

TABLE 2 *Two-by-two contingency tables for the proportional association between Romberg test condition 4 performance and FoG Status*

FoG status	No failure during Romberg condition 4	Failure during Romberg condition 4	Total
No FoG	57	22	79
FoG	2[a]	11[b]	13
Total	59	33	92

Contingency table of FoG versus Romberg test condition 4 performance status in PD (likelihood ratio $\chi^2 = 15.6$; $P < 0.0001$).
[a]FoG was present in 3.3% of subjects with PD without failure during Romberg condition 4.
[b]Failure during Romberg condition 4 was present in 84.6% of subjects with PD with FoG.
FoG, freezing of gait; PD, Parkinson's disease.

TABLE 3 *Two-by-two contingency tables for the proportional association between Romberg condition 4 test performance and fall status*

Fall status	No failure during Romberg condition 4	Failure during Romberg condition 4	Total
No fall history	41	18	59
Fall history	18[a]	15[b]	33
Total	59	33	92

Contingency table of fall history versus clinical deficient vestibular efficacy status in Parkinson's disease (PD; likelihood ratio $\chi^2 = 2.1$; $P = 0.15$).
[a]Fall history present in 30.5% of patients with PD without failure during Romberg condition 4.
[b]Failure during Romberg condition 4 present in 45.5% of patients with PD with falls.

and MoCa (Wald $\chi^2 = 0.3$; $P = 0.75$; total model: Wald $\chi^2 = 16.1$; $P < 0.0001$; Somers' $D = 0.81$; concordance ratio = 90.7%).

Failure During Romberg Condition 4 and Falls

The frequency of patients with PD with falls was higher in patients with PD with failure during Romberg condition 4 (45.5%) compared with patients with PD with nonfailure during Romberg condition 4 (30.5%), but this was not statistically significant (likelihood ratio $\chi^2 = 2.1$; $P = 0.15$; Table 3).

Discussion

Our findings suggest that selective failure during Romberg condition 4 may be a specific independent contributor to FoG, but not falls, in patients with PD. During normal locomotion, sensory signals from visual, vestibular, and somatosensory systems are integrated via central neural networks and provide real-time information used as references for cognitive, emotional, and automatic locomotor processes.[21] Therefore, the inability to integrate postural sensory inputs may play a role in the pathophysiology of FoG.[21] For example, FoG can be provoked under sensory conflicting situations in which balance is challenged, but in different circumstances sensory cues may alleviate motor freezing behaviors.[6] Prior studies using postural sensory conflict tasks, such as the SOT, have demonstrated that postural sensory deficits involving specific sensory modalities are strongly associated with FoG in PD.[22] However, there is limited literature on vestibular sensory processing in FoG.[23] A recent study using a SOT testing paradigm found that patients with PD with FoG had greater difficulties processing vestibular sensory information than PD patients without FoG.[22] Interestingly, relative effects of vestibular processing were greater than visual and somatosensory effects. These data show that the inability to integrate vestibular information for postural control may be an important contributor to FoG. Vestibular feedback becomes especially critical when initiating walking or turning,[7] where visual and somatosensory feedback become more unreliable.[8] This is consistent with the observation that gait initiation and turning are well-known risk factors for FoG provocation.[6] With respect to turning, a prior study investigated the effects of galvanic vestibular stimulation (GVS) triggered at either gait initiation, a step before the potential turn, or at the time of appearance of the visual cue to make a turn.[7] Although the visual and vestibular perturbations significantly altered gait trajectory, the greatest interaction occurred when galvanic stimulation was triggered one step before the target appeared. This implies an increase in the weighting of vestibular inputs just before turning to prepare for the change in direction. These observations may explain why vestibular sensory processing deficits, such as seen in deficient vestibular efficacy, may play a role in FoG but do not provide insights for the lack of association with falls. However, falls may represent a more complex and more heterogenous episodic motor disturbance,[24] because of a plethora of fall-triggering factors not limited to gait initiation or falls (eg, inattention, neuropathy, musculoskeletal discomfort, deconditioning, frailty, mechanical slips, environmental obstacles, poor lighting, poor vision, side effects of anticholinergic or sedative drugs, bladder urgency, or any combinations of these, etc.). Furthermore, falls represent stochastic or more random events and may also be affected by emotional factors because of fear of falling. It is also possible that the absence of a significant fall status effect was due to our limited assessment based on patient's reporting a history of a prior fall. We believe that some of the less forceful but purely mechanical triggered falls represent a mechanical perturbation of postural control that will invoke a vestibular signal that in the case of a subsequent fall has been a failed attempt to initiate a postural recovery program that is of clinical relevance in PD. However, falls not related to a neurological etiology of falls may be one of the reasons for the lack of association between impaired vestibular efficacy and falls in this study. There may also be recall bias with false negative reporting of falls. However, this would be predicted to dilute rather than strengthen the findings in this study. Nevertheless, a recent prospective 1-year follow-up study found that the presence of neurovestibular dysfunction (as defined by abnormal vestibular-evoked myogenic potential) may predict the risk for future fall incidents in PD with postural imbalance.[25] Lastly, it is possible that our study sample size was underpowered to identify a deficient vestibular efficacy-associated component of falls.

Our findings demonstrated that a subset of patients with failure during Romberg condition 4 did not have FoG. The modified Romberg, as specified in our study, may be a good and easy clinical screening test but may have about an 80% diagnostic accuracy to diagnose vestibular deficits.[18] Therefore, performance of Romberg condition 4 predominantly, but not exclusively, may reflect vestibular efficacy. It could be possible that more stringent cutoff criteria for abnormalcy on the Modified Romberg test, such as a shorter time to fall, may result in a more accurate assessment of (significant) vestibular changes, but further research is needed. A dynamic visual reading test (ie, accuracy of reading during head movements) may potentially be another vestibular screening test that may deserve further studies.[26,27]

A primary premise of this work is that a loss of balance in task 4 of the Romberg test (balancing on a compliant surface with eyes closed) reflects "deficient vestibular efficacy." However, test 4 is very nonspecific in terms of potential neuropathology and could include vestibular,

proprioceptive, or cerebellar deficits. Although the Romberg 4 has relatively good sensitivity and specificity when comparing people with vestibular disorders versus matched controls, this test does not discriminate well between pathologies that could lead to a higher incidence of falls. Furthermore, it should be noted that pure isolation of a vestibular component in the modified Romberg test may be an elusive goal because test interpretation then should be based on differences between the different conditions of the Romberg that involve more versus less sensory integration.[22]

Furthermore, effective postural control will be the end result of multisensory, cognitive, and even emotional integration component of motor programs. The relative selectivity of failing Romberg condition 4 while passing conditions 1–3 is likely the result of limited capacity processing of these heteromodal functions where abnormal vestibular efficacy may be a critical factor imposed on nonvestibular components such that the final common pathway of sensorimotor, cognitive and emotional integratin may result in failure of the postural control system. Therefore, our study does not exclude that other sensory, such as proprioceptive, deficits also may play a role in FoG in PD.[28]

Unlike falls where we previously showed a cholinergic, but not a nigrostriatal dopaminergic, nerve terminal association, FoG can be dopaminergic medication responsive, at least in early-stage disease. Therefore, possible dopamine medication-responsive effects on multisensory integration in the legs may play a mechanistic role in performance on the modified Romberg test.

Some of the reported falls in this study may have happened during DA medication *on* state. However, for the type of patients with PD who have PIGD motor features (falls, FoG), these patients are likely also to suffer from motor fluctuations and in the absence of documentation of whether a fall happened in an *on* versus *off* state, it will be difficult to shed light on this. Furthermore, our prior falls studies found that falls were related to cholinergic hypofunction, but not to the degree of nigrostriatal losses.[29] However, it could be possible that there may be some components of DA-responsive postural control functions that could have resulted in possible disparity of our analysis because the Romberg 4 testing was performed in a DA medication *off* state.

Our findings may augur novel vestibular treatment approaches to treat FoG in PD. Caloric vestibular stimulation is a widely used technique that is commonly used to diagnose balance disorders or confirm absence of brainstem function. However, caloric stimulation may also have the potential to be used for therapeutic purposes. For example, the modulation of various networks and nuclei in the brain by caloric vestibular stimulation, including the basal ganglia, cerebellum, brainstem, insula, hypothalamus, thalamus, hippocampus, and prefrontal cortex, suggests significant potential for caloric vestibular stimulation to modulate both motor and nonmotor

functions.[30] Recent development of portable caloric vestibular stimulation devices has shown promise in treatment of PD. A recent example is the portable self-administered in-home thermoneuromodulation approach that was successfully applied in the PD population.[31] Preliminary findings showed significantly improved motor and nonmotor functions in PD in the home situation.[31,32] Other methods include traditional vestibular physical therapy or GVS. For example, a functional magnetic resonance imaging study found evidence that GVS can enhance deficient PPN connectivity and improve visual-cerebellar subnetwork interaction in PD in a stimulus-dependent manner.[33,34] This may provide a mechanism through which GVS may improve balance and related risk for FoG in PD.

A limitation of the study was that no objective vestibular testing was performed to confirm that failure during Romberg condition 4 is mainly driven by abnormal vestibular efficacy. Other limitations of the study include the lack of FoG subtyping because distinct subtypes of freezing motor behaviors may differ in pathophysiology mechanisms. Intuitively, vestibular mechanisms may play a more direct role in FoG that are caused by turning-induced events. However, there is also a link between vestibular dysfunction and anxiety, implicating that vestibular processing deficits may also play a role in freezing episodes triggered by anxiety spells.[35] Similarly, vestibular deficits may coexist with abnormal cognitive functions, suggesting that vestibular changes may also play a role in freezing induced by cognitive-motor dual tasking or other conditions with cognitive overload.[36,37]

The rationale for this study focused on the fact that FoG occurs frequently during tasks such as turning, where dynamic balance is needed, yet the modified Romberg test is performed under a static balance condition. However, it may be difficult to perform a SOT task under walking conditions on compliant surfaces with eyes closed because of safety concerns.

Another limitation of the study is the low frequency of female patients to determine whether gender effects may play a role in vestibular deficits in PD. This is of relevance because our study found there is an equal proportion (75.8% males in the deficient and 76.3% males in the nondeficient vestibular efficacy groups), while there is evidence of a higher risk for vestibular dysfunction in women.[38]

In conclusion, the selective failure during Romberg test condition 4 in patients with PD may contribute to the pathophysiology of FoG in PD independent from clinical confounder variables. Furthermore, we found that absence of condition 4 test failure was associated with a very low frequency of FoG, suggesting a specific effect of deficient vestibular efficacy on FoG in PD. Findings may augur vestibular therapy as a novel treatment for FoG in PD. The lack of a specific association between failure during Romberg condition 4 and falls in PD may reflect the more multifactorial and

stochastic chance effects of falls in PD or may be a result of our limited assessment of fall status in this study. ■

Data Availability Statement

Data may be available by qualified requests.

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