



Vestibular Deficits in Neurodegenerative Disorders: Balance, Dizziness, and Spatial Disorientation

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The vestibular system consists of the peripheral vestibular organs in the inner ear and the associated extensive central nervous system projections—from the cerebellum and brainstem to the thalamic relays to cortical projections. This system is important for spatial orientation and balance, both of critical ecological importance, particularly for successful navigation in our environment. Balance disorders and spatial disorientation are common presenting features of neurodegenerative diseases; however, little is known regarding central vestibular processing in these diseases. A ubiquitous aspect of central vestibular processing is its promiscuity given that vestibular signals are commonly found in combination with other sensory signals. This review discusses how impaired central processing of vestibular signals—typically in combination with other sensory and motor systems—may account for the impaired balance and spatial disorientation in common neurodegenerative conditions. Such an understanding may provide for new diagnostic tests, potentially useful in detecting early disease while a mechanistic understanding of imbalance and spatial disorientation in these patients may enable a vestibular-targeted therapy for such problems in neurodegenerative diseases. Studies with state of the art central vestibular testing are now much needed to tackle this important topic.

Keywords: vestibular system, vestibular perception, neurodegeneration, spatial disorientation, balance

INTRODUCTION

The peripheral vestibular apparatus transduces head acceleration, both angular and linear acceleration (including gravity being equivalent to a physical linear acceleration), and functionally speaking plays an important role in the control of eye movement, posture, gait, and egocentric perception. The vestibular end-organ consists of the otolith organs—which transduce linear acceleration; and the semi-circular canals which transduce angular acceleration. From there the signal pass to the vestibular nerve, the brainstem and cerebellar circuits, vestibular thalamic projections, vestibulospinal projections, and finally the vestibular cortical network. Functionally, the vestibular system senses self-motion (“am I moving”) and spatial orientation (“where am I now”), with the neuroanatomical correlates mediating these vestibular sensations being distinct.

Vestibular, visual, and proprioceptive sensory input is integrated in the brain and used to subsequently adjust the outgoing motor response to maintain balance, posture, and gaze stabilization. Vestibular dysfunction—arising from peripheral or central components of the vestibular

system—may manifest as illusory self-motion (dizziness/vertigo) and spatial disorientation, which in turn can impair balance.

The overall prevalence of vestibular dysfunction in adults aged over 40 in the USA is 35%, representing 69 million individuals (1). Specifically, patients with vestibular dysfunction are at significantly greater risk of falls, involving both symptomatic and asymptomatic patient groups (1). Resultantly, vestibular dysfunction has a major impact on mortality, morbidity, health-care resources (1), and socioeconomic productivity (2).

The vestibular system is phylogenetically one of the oldest of all of the sensory systems (3) and the earliest to mature during development (4) and, thus, presents a potentially pertinent area of study in the context of neurodegeneration. For instance, work in Alzheimer's disease (AD) demonstrates areas of neuronal degeneration in phylogenetically older neurones (5).

With an aging population, we are facing a rise of both vestibular disorders and neurodegenerative conditions. Dizziness and imbalance are important in neurodegenerative disease due to their association with falls. In addition, detection of dizziness and imbalance, and specific vestibular testing may have a potential role in the identification of neurodegeneration, especially in the initial stages of the disease process. For future treatments in neurodegenerative disorders to be most effective, earlier detection is likely to be vital to restrict neuronal loss.

In this review, we will focus on dizziness, imbalance, and spatial disorientation in relation to the neurodegenerative conditions of AD, progressive supranuclear palsy (PSP), frontotemporal dementia (FTD), motor neurone disease (MND), multiple system atrophy (MSA), and Parkinson's disease (PD). In doing so, we demonstrate how detecting central and even peripheral vestibular pathology is important for the diagnosis and management of these conditions.

ALZHEIMER'S DISEASE

Alzheimer's disease is a form of dementia that typically presents with memory disturbance. It is characterized by beta-amyloid deposition in the brain, neurofibrillary tangles, and neuronal death. Imbalance is a little recognized feature of AD (6, 7), despite the condition carrying a high risk of falls (8) and gait abnormalities (9). Up to third of newly diagnosed AD patients complain of spatial disorientation (10), with wandering, for instance, a frequent symptom of AD (11).

Patients with AD are also three times more likely to experience a fracture compared to age-matched controls (12), and 47% have been observed to fall over the course of 1 year (13). Moreover, falls have been suggested to precede detectable cognitive changes in AD patients. A prospective study of presumptive preclinical AD patients found a higher rate of falls compared to aged-matched controls (14).

Nakamagoe et al. evaluated balance in individuals with AD and healthy aged-matched controls, using an eyes-closed stepping test. They reported that AD subjects were significantly more likely to move and turn than stay in the same position after 50 steps (7). Furthermore, stabilometry (objective study of body sway during quiet standing) testing has been demonstrated

to be significantly altered in AD patients across measures of antero-posterior sway, latero-lateral sway, and area of confidence ellipsis, worsening in each parameter when eyes were closed. In particular, the authors identified a strong correlation between impairment in the anterior-posterior sway component for the AD subjects and reduced cognitive scores (6). This has led some researchers to suggest balance disturbance is the leading cause of falls in patients with AD (7).

Further insights into the cause of falls in AD patients have been identified by provoking compensatory postural adjustments through virtual reality (15). Patients with AD demonstrated slower response times to adjusting body position in response to changing visual stimuli, with this effect pronounced in the AD group with a history of falls. The AD faller group was also shown to have abnormal postural correction, reflecting worse inherent postural stability. Postural control was also related to higher cognitive processing, with the authors concluding that falls may result in AD patients from insufficient cognitive resources to control posture. Indeed, dual-task gait testing (assessing gait while performing a challenging cognitive task) in patients with mild cognitive impairment who went on to develop dementia showed a reduced gait performance relative to those who did not (16), with future study addressing this paradigm in other neurodegenerative disorders (17).

This follows from work performed by Barra and colleagues that used spatial and verbal tasks in conjunction with a balance task performed in young healthy adults which found an increase incidence of falls during spatial-task performance. The authors concluded that cognitive performance was maintained at the expense of balance, transgressing the "posture first" principle (18). Note, other studies have suggested a principle of "posture first" in older adults and "cognition first" in younger adults (19); however, exactly why, when, and what causes this change in strategy remains obscure.

A core brain area implicated in spatial orientation is the hippocampus (20), with this area being among the earliest regions to degenerate during the course of AD (21). Aside from a few studies within humans (22, 23), the evidence for a major role of the vestibular system in hippocampal function has come from animal studies involving vestibular stimulation or lesions (24–27). Further, in a study by Brandt et al., they demonstrated that in patients with bilateral vestibular loss, major atrophy of the hippocampus that correlated with impairments on spatial memory tasks (23). This association has led some to speculate on causal relationship between peripheral vestibular loss and AD (28, 29). Namely, anterograde degeneration, in which destruction of lower structures, i.e., peripheral vestibular apparatus, leads to degeneration of their higher projection zones, i.e., vestibular projections and the hippocampus (28). However, there is no empirical epidemiological evidence to support peripheral vestibular loss as a risk factor for AD.

A related but distinct question is the role of the hippocampus in vestibular cortical processing. Over the last four decades, animal experimentalists have demonstrated the remarkable properties of a group of cells in the hippocampus—place cells—that effectively indicate the position of the animal within its

environment (30). These cells' indication of spatial position are updated by vestibular input, especially in the dark, and indeed, vestibular ablation renders these cellular systems permanently dysfunctional (31), indicating that the integrity of the peripheral vestibular system is obligatory for these spatial guidance systems.

A key concept in place cell functions (and head direction cells that provide a compass like indication of head angular orientation) is the conversion of inertial signals of motion to position—a function called path integration (30). Two recent human lesion studies, however, found no effect of hippocampal lesions upon path integration function (32, 33). Instead, lesions, due to stroke, in the temporoparietal junction (TPJ) (33) have been shown to impair vestibular-guided spatial orientation. It follows that AD may affect spatial orientation by its effect on vestibular cortical regions such as the TPJ.

Perhaps more important is the impact upon cortical networks with multimodal imaging studies showing a consistent disruption in AD (34). Given the evidence of a widespread vestibular brain network involved in the vestibular perception of self-motion (35, 36), it can be expected that pathological changes associated with AD are likely to impact upon this neural system.

PROGRESSIVE SUPRANUCLEAR PALSY

PSP is a pathologically defined disease underpinned by the accumulation of hyperphosphorylated tau throughout the brain, as well as in distinctive regions. Its clinical phenotype is however variable. PSP often presents with falls early in the course of the disease (37, 38). The midbrain is affected early on in the disease course (39). Although the vestibular nuclei (primarily in the pontomedullary junction) show loss of neurones at autopsy (40), the angular VOR (dependent on the semi-circular canal system and producing eye rotations to compensate for head angular rotation) is relatively maintained until later stages of the disease course (41), inferring preserved canalicular projections. In contrast, failure of saccular projections to the vestibular nuclei result (39) in markedly impaired linear (translational) VOR—a function reliant upon the otolithic sacculus and utriculus (42). This otolithic dysfunction corresponds clinically with the impaired ability of PSP patients' convergence and near viewing of a target, and may also reflect damage to the interstitial nucleus of Cajal (43, 39).

The hypothesis of saccular projection impairment is further supported by vestibular-evoked myogenic potentials (VEMPs) testing in patients with PSP. cVEMPs consist of inhibitory potentials recorded from the sternocleidomastoid (“cervical” VEMP—cVEMP) in response to loud sounds, and are used in the testing of vestibulospinal reflexes. During movement, otolithic inputs are integral for producing the vestibulospinal reflexes that adjust muscle tone so that stable posture can be maintained. Depending on bone or air sound conduction, saccular afferents can be preferentially activated through cVEMPs, with this being the case in the latter conduction (44). In contrast, oVEMPs uses the inferior oblique muscle of the eye (“ocular” VEMP—oVEMP) to measure utricular function (45). Liao and colleagues found a significant reduction of cVEMP

amplitude in PSP patients compared to age-matched healthy control group, with air sound conduction, inferring impaired function of the saccular pathways (42). They concluded that since the pathways mediating cVEMPs synapse in the lateral vestibular nuclei, this was not necessarily an inevitable feature of degenerative brainstem disease, but rather a specific sign in PSP.

Accordingly, the impaired ability to adjust vestibular reflexes for translational motion through the environment may be one component in the postural defect in PSP (42). However, how much this contributes to postural instability and falls in comparison to other factors is yet to be elucidated. Indeed, findings of impaired proprioceptive sensory inputs in PSP indicate it is likely to be an abnormality in central sensory integration, rather than a sole vestibular deficit (46). Dale et al. performed postural stability tasks on PSP patients versus healthy controls, finding patients with PSP had an inability to perceive backward tilt of the surface or body. Proposals for future study are focusing on the association between the VOR, postural deficits and falls in PSP (47).

Chen et al. have related this possible PSP pathogenesis ecologically to the bipedal upright locomotion (39). They proposed that PSP may owe its selective set of disturbances of eye movements and balance due to restricted involvement of a recently developed neural system that deals with erect permanent bipedal locomotion, the main components of which lie in the midbrain. Nevertheless, a distinct neural system for bipedalism is contentious, and furthermore, permanent bipedalism can be considered an adaptation of what is common—intermittent bipedalism, and whether a neural system between these states is distinct would be a further level of speculation. It is unclear whether PSP affects primates, although recent neuropathological analysis of cynomolgus monkeys found the cytopathology and distribution of tau deposits resemble those of PSP (48).

Additional vestibular mechanisms that may contribute to postural instability in PSP may include the vestibulo-colic reflex, which stabilizes the head on the body. PSP patients often show head turns opposite to the direction of intended gait due to over activity of the vestibulocollic reflex (49), which has been notionally attributed to the involvement of the brainstem reticular nuclei (50).

Computerized posturography testing can differentiate early PSP from early PD (51) and age-matched controls (52). Ondo and colleagues utilized the sensory organization test (SOT), where subjects are asked to stand still under a variety of altered sensory conditions (51). The SOT parameter that best differentiated PSP and PD was when both visual and proprioceptive inputs were deprived, leading the authors to conclude there was a vestibular pattern of dysfunction.

The limit of stability test (LOS) was also found to be abnormal in PSP (51, 52). LOS measures path sway, time, and distance traveled by the patient's center of gravity from an initial starting point to eight different points (51). The backward direction score was identified as being most severely affected, which is consistent with the higher frequency of falls in the backward direction in PSP patients (52). Of note, preservation in scores for the left (non-dominant side—with testing being performed on right

sided dominant individuals) and forward-left (non-dominant forward diagonal) directions were reported (52) and may reflect the distribution of central PSP pathology.

This backward fall phenomenon may draw comparison with “Tumarkin” drop attacks (“otolithic crises”) found in a subset of Meniere’s disease patients. Tumarkin falls occur without warning and without loss of consciousness, with a stereotyped direction, bearing similarities to falls in PSP. The pathophysiology of Tumarkin drop attacks is felt to be caused by a burst of neural impulses from the otolithic organs to the vestibulospinal pathways, triggering the fall (53). Indeed, cVEMP testing in Tumarkin patients has demonstrated which were more likely to be elevated or absent thresholds compared to the patient’s unaffected ear, implicating the involvement of the saccule in these patients (54). Similarly, as mentioned earlier, cVEMP measurements are also found to be abnormal in PSP (42), although this is likely to implicate saccular projections, rather than peripheral dysfunction as in Tumarkin attacks. Furthermore, falls in PSP are likely to be multifactorial, with axial rigidity also likely contributing to the nature of PSP falls (55).

Studied techniques to improve balance in PSP have involved audio-biofeedback (56). This consists of adding artificial sensory information that informs the brain about actual body posture and movements. In a study of eight patients with PSP, significant improvements in the Berg Balance Scale (which involves 14 different balance tasks) were observed after 6 weeks.

FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia is characteristically a pre-senile dementia that presents with a progression deterioration of personality, social interaction, and cognition. Studied measures of gait and balance have been found to be abnormal in FTD when compared with controls (57). The limit of stability and dynamic balance testing were impaired in patients with FTD. In comparison, spatial orientation has been found to be relatively intact in FTD individuals (58). Tu and colleagues investigated spatial orientation using a novel virtual supermarket task to compare patients with AD and FTD. Subjects watched a sequence of videos from a first-person perspective moving through a virtual supermarket and were commanded to preserve orientation to an initial starting point. Analyses revealed significantly impaired spatial orientation in AD, compared to FTD patient groups, and was able to discriminate the two groups to a high degree at presentation.

Voxel-based morphometry, a neuroimaging analysis technique to investigate focal differences in brain anatomy, was also performed on the subjects, identifying significantly greater atrophy in medial parietal and retrosplenial regions for AD patients compared to FTD patients. The authors went on to speculate that the retrosplenial region plays a crucial role in spatial orientation (58).

Nakamagoe et al. performed caloric and visual suppression testing on 14 patients with FTD (59). In healthy subjects, vestibular-nystagmus induced by the caloric test can be suppressed by visual fixation (i.e., visual suppression) and impaired visual fixation is typically indicative of a central pathology (i.e., cerebellum, brainstem and cerebral cortex). It was found that

FTD participants typically had an impaired visual suppression compared to controls. Further analysis was performed according to clinical features of the FTD patients, indicating that visual suppression of the VOR was significantly more altered in FTD patients with gait disturbance. The authors concluded that damage to the vestibular cortex, which they related to the inferior parietal lobule, might be responsible for the impairment of visual suppression in FTD patients. However, one caveat to this interpretation would be the identification of a discrete vestibular cortex, rather than the notion of distributed central projections of vestibular information in various cortical networks (60, 61).

MOTOR NEURONE DISEASE

Motor neurone disease is a progressive disorder in which degeneration of the upper and lower motor neurons leads to progressive weakness of bulbar, limb, and trunk muscles. As a result, falls are common in patients with MND, with a prospective longitudinal cohort study of MND patients showing an annual incidence of 64% (62). Interestingly, a study of head and other physical trauma injury in patients with MND, demonstrated a higher risk of injury compared to controls in the first year after diagnosis that subsequently reverted back to the level in the control group 1 year after diagnosis (63). In addition, with many MND patients reporting unsteadiness and fear of falling early in the course of the disease (64), this may suggest other factors as well muscle weakness may be contributing to falls in MND.

Sanjak et al. used SOT in computerized posturography to assess vestibular deficits in patients who were ambulatory with MND compared to healthy controls (64). They found that MND subjects in the normative range in clinical mobility displayed distinct impairment in equilibrium testing and an increased number of falls during conditions of altered support surface, when vision was absent or sway-referenced, in comparison with healthy controls, suggesting a vestibular pattern of impairment. The authors hypothesized that cerebellar involvement in MND may result in this particular pattern of vestibular deficit since the peripheral function was preserved in these patients. Nonetheless, caution is required on the interpretation of SOT in such patients, when factors such as inherent muscle weakness and spasticity may also lead to postural instability and increased body sway, independent of vestibular dysfunction.

Vestibular-evoked myogenic potential measurement has also been performed on patients with MND, showing no abnormalities in patients in the early stages of the disease (65). Additional assessment of the vestibular system in MND has found abnormalities in visual suppression (66) and caloric testing (67). Ohki et al. found abnormalities of visual suppression in two out of nine patients with early stages of MND (66), which is indicative of cerebellum pathology.

MULTIPLE SYSTEM ATROPHY

Multiple system atrophy is an oligodendroglionopathy characterized by prominent alpha-synuclein inclusions, resulting in neuronal death, which manifests clinically with autonomic failure, ataxia, and parkinsonism. Balance and gait are also frequently

found to be disturbed in MSA (68), and symptom assessment scales focusing on these parameters are important for the evaluation of patients in early stages of MSA (69).

It is typically classified into a cerebellar predominant (MSA-C) and parkinsonism predominant (MSA-P) subtypes. Lee and Koh retrospectively identified the clinical features of 20 MSA-C patients, with disequilibrium (50%) and dizziness (15%) the most common initial presentation (38). For 21 MSA-P patients, tremor was the most frequent symptom (19%), while dizziness was found in 10%. Similarly, Sakakibara and Hirumab found 60% (9/15) of patients with MSA-C reported dizziness on head-turning (70).

Falls are frequent in MSA (71), and abnormalities in VEMPs for MSA patients have been associated with an increased risk of falling (72).

It is important to note, however, due to the frequent finding of orthostatic hypotension, identifying vestibular-related dizziness and balance impairment can be a challenge (73, 74). Nevertheless, vestibular function testing in MSA is abnormal (72, 75), pathological studies at autopsy show neuronal loss in the vestibular nuclei (76) and neuroimaging demonstrate degeneration in flocculus and nodulus in the cerebellum of MSA patients (70).

Impaired VOR suppression on visual fixation has also been identified in MSA (70, 77, 78). Indeed, its use as has been put forward as a method of distinguishing PD from MSA (78). Despite this assertion, abnormalities have been found in the cerebellum of PD patients (79), and impaired VOR suppression has been documented in such patients (80).

PARKINSON'S DISEASE

Parkinson's disease is broadly classified as a "movement disorder" but encompasses a wide variety of motor and non-motor symptoms, which results from the irreversible loss of dopaminergic neurones. Postural instability is one of the most disabling features in PD. Using computerized posturography integrated with a virtual reality system to analyze LOS, patients with PD were found to have a reduced LOS area and greater postural sway compared with healthy subjects (81). The deterioration in postural control was significantly associated with major risk of falls. Additionally, the manipulation of sensory input on the subjects was suggestive of reduced use of vestibular information to maintain postural control. Moreover, computerized posturography using SOT in patients with PD also demonstrated impaired processing of vestibular information (82, 83), with additional study indicating this was independent from the stage of the disease (84).

Perturbation of proprioceptive information in PD patients found no reweighting of vestibular inputs (85), which contrasts when performed in healthy subjects (86), with authors concluding that the issue of postural control in PD lay not in the ability to generate movement but the inability to perceive movement. However, this conclusion, neglects the issue of impaired anticipatory postural adjustments found in PD, while the sensory evaluation performed was limited to visual, vestibular, and proprioceptive stimulation.

Functional neuroimaging of PD patients has demonstrated reduced neuronal activity in the cingulate sulcus visual area (87), where vestibular and optic inputs are integrated (88), as

well as showing reduced activation of this area is associated with increased disease severity (87). Therefore, a deficit of central sensory processing in PD is implied.

Vestibular-evoked myogenic potential responses in PD patients have been linked to the motor and non-motor symptoms (89). Specifically, impaired cVEMP testing in PD patients has been shown to be correlated significantly to contralateral rigidity, bradykinesia severity, ipsilateral dyskinesia scores, as well as sleep, mood, and memory impairment. Indeed, cVEMP testing in PD patients compared to aged-matched controls has been frequently found to be abnormal (72, 90, 91). This reflects potential brainstem pathology among PD patients, which links previous study of pathological changes in the vestibular nuclei of PD patients (92), and disrupted connections between vestibular nuclei and the dorsal raphe nuclei (93). Additional mechanisms for this may include the reduced effect of dopamine on the excitability of vestibular nuclei found in PD patients (94).

Peripheral ipsilateral vestibular paresis has been associated with lateral trunk deviation (Pisa syndrome) in patients with PD (95). In addition, the perception of the subjective visual vertical (the ability of a person to perceive earth-vertical with respect to gravity) has been demonstrated to be deviated in PD patients with lateral trunk flexion (96). Gandor and colleagues produced a similar finding in PD patients, and discussed that altered verticality perception in PD may reflect a central vestibular processing deficit (97).

The symptom of freezing of gait (FOG) in PD has also been related to the vestibular system. Huh et al. evaluated PD patients with FOG, PD patients without FOG, and aged-matched healthy controls using the SOT (98). PD patients with FOG showed worse postural sensory processing compared to those without FOG and a particular inability to use vestibular information. The authors attributed this with abnormal central processing of vestibular signals in PD. However, a causal relationship between FOG and impaired vestibular processing based on these results cannot yet be established until future research analyzing the imaging correlates of postural sensory deficits in PD patients with FOG is undertaken.

The brain area implicated in FOG is the pedunculopontine nucleus (PPN) (99). Direct projections to the PPN from vestibular nuclei have been confirmed in primates (100), and vestibular stimuli in macaque monkeys enhance the activity of the PPN neurones (101). PPN deep brain stimulation (DBS) in PD reduces falls (102). We showed that PPN DBS in PD patients showed improved vestibular perceptual thresholds (103). Paradoxically, PPN stimulation worsened sway in these patient in the dark. Although this could imply worse postural control, a strategy of increased postural movement to improve sensory feedback could provide additional information to the vestibular system to help control balance. The recent developments in new DBS targets in improving balance control in PD provide a fertile ground for future study and therapeutic approaches, e.g., recently studies of PPN stimulation in PSP patients has showed promising results (104).

Similarly, targeted vestibular rehabilitation and therapy in PD has received attention, demonstrating improved postural control and balance performance (105–108). Stimulation of the

vestibulospinal tract through proprioceptive disturbance and visual suppression improved double stance gait performance in patients with PD compared to those receiving standard physiotherapy (109). Moreover, in a single patient study, repeated caloric stimulation produced improvement in assessment scores for motor and non-motor symptoms of PD, which was sustained at 5-month follow-up (110). Yet, vestibular rehabilitation tended to represent different techniques in different studies illustrating it as a potentially disparate practice. Furthermore, small number studies and frequent lack of randomization and comparator impair meaningful results.

Galvanic vestibular stimulation, involving transcranial direct current stimulation, can stimulate and inhibit vestibular afferents. Its use in PD patients has demonstrated improvement of postural instability (111, 112) and motor performance (113, 114). Similarly, stochastic vestibular stimulation, which uses subthreshold electrical noise has demonstrated improvements in postural control for PD patients (115, 116). These are, however, small number studies with limited follow-up of patients.

CONCLUSION

This review highlights the role of vestibular function and dysfunction, in a number of neurodegenerative diseases, with a particular focus on the central vestibular system. Permanent bipedal locomotion is a hallmark of the human species, and is critically dependent upon the integration and processing of multiple sensory information (i.e., visual proprioceptive

and vestibular sensory inputs), notwithstanding the requisite peripheral function. As a result, only limited neurodegeneration in central vestibular areas may result in significant clinical manifestations, especially imbalance and falls. Some of the disease areas discussed illustrate genuine advances in our understanding of neurodegenerative conditions, which can aid diagnostic and treatment strategies. A deeper mechanistic understanding of the role of the dysfunction of central vestibular systems in neurodegenerative disease is, therefore, much warranted.

Presently vestibular testing in neurodegenerative disease all too often focuses on peripheral (i.e., canal and otolith) function. Rather, testing should explore additional deficits in the central vestibular circuits. Indeed, state of the art exploration of central vestibular deficits is much warranted to provide a deeper mechanistic understanding of how balance and spatial disorientation so frequently arises in neurodegenerative disease.

AUTHOR CONTRIBUTIONS

All authors listed have made substantial, direct, and intellectual contribution to the work and approved it for publication.

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REFERENCES

- 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. *Arch Intern Med* (2009) 169(10):938-44. doi:10.1001/archinternmed.2009.66
- Bronstein AM, Golding JF, Gresty MA, Mandala M, Nuti D, Shetye A, et al. The social impact of dizziness in London and Siena. *J Neurol* (2010) 257:183-90. doi:10.1007/s00415-009-5287-z
- Romer AS. *The Vertebrate Body*. London: WB Saunders Company (1950).
- Nandi R, Luxon LM. Development and assessment of the vestibular system. *Int J Audiol* (2008) 47(9):566-77. doi:10.1080/14992020802324540
- Lyness SA, Zarow C, Chui HC. Neuron loss in key cholinergic and aminergic nuclei in Alzheimer disease: a meta-analysis. *Neurobiol Aging* (2003) 24(1):1-23. doi:10.1016/S0197-4580(02)00057-X
- Leandri M, Cammisuli S, Cammarata S, Baratto L, Campbell J, Simonini M, et al. Balance features in Alzheimer's disease and amnesic mild cognitive impairment. *J Alzheimer Dis* (2009) 16(1):113-20. doi:10.3233/JAD-2009-0928
- Nakamagoe K, Fujimiya S, Koganezawa T, Kadono K, Shimizu K, Fujizuka N, et al. Vestibular function impairment in Alzheimer's disease. *J Alzheimer Dis* (2015) 47(1):185-96. doi:10.3233/JAD-142646
- Perttinen NM, Öhman H, Strandberg TE, Kautiainen H, Raivio M, Laakkonen ML, et al. How do community-dwelling persons with Alzheimer disease fall falls in the FINALEX study. *Dement Geriatr Cogn Dis Extra* (2017) 7(2):195-203. doi:10.1159/000477394
- Annweiler C, Beauchet O, Bartha R, Wells JL, Borrie MJ, Hachinski V, et al. Motor cortex and gait in mild cognitive impairment: a magnetic resonance spectroscopy and volumetric imaging study. *Brain* (2013) 136(3):859-71. doi:10.1093/brain/aw373
- Guariglia CC, Nitrini R. Topographical disorientation in Alzheimer's disease. *Arq Neuropsiquiatr* (2009) 67(4):967-72. doi:10.1590/S0004-282X2009000600001
- Alzheimer's Association. 2016 Alzheimer's disease facts and figures. *Alzheimer Dement* (2016) 12(4):459-509. doi:10.1016/j.jalz.2016.03.001
- Buchner DM, Larson EB. Falls and fractures in patients with Alzheimer-type dementia. *JAMA* (1987) 257:1492-5. doi:10.1001/jama.1987.03390110068028
- Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of falls in dementia: a prospective study in older people. *PLoS One* (2009) 4:e5521. doi:10.1371/journal.pone.0005521
- Stark SL, Roe CM, Grant EA, Hollingsworth H, Benzinger TL, Fagan AM, et al. Preclinical Alzheimer disease and risk of falls. *Neurology* (2013) 81(5):437-43. doi:10.1212/WNL.0b013e31829d8599
- Gago MF, Yelshyna D, Bicho E, Silva HD, Rocha L, Lurdes Rodrigues M, et al. Compensatory postural adjustments in an oculus virtual reality environment and the risk of falling in Alzheimer's disease. *Dement Geriatr Cogn Dis Extra* (2016) 6(2):252-67. doi:10.1159/000447124
- Montero-Odasso MM, Sarquis-Adamson Y, Speechley M, Borrie MJ, Hachinski VC, Wells J, et al. Association of dual-task gait with incident dementia in mild cognitive impairment: results from the gait and brain study. *JAMA Neurol* (2017). doi:10.1001/jamaneurol.2017.0643
- Montero-Odasso M, Pieruccini-Faria F, Bartha R, Black SE, Finger E, Freedman M, et al. Motor phenotype in neurodegenerative disorders: gait and balance platform study design protocol for the ontario neurodegenerative research initiative (ONDRI). *J Alzheimer Dis* (2017):1-5. doi:10.3233/JAD-170149
- Barra J, Bray A, Sahni V, Golding JF, Gresty MA. Increasing cognitive load with increasing balance challenge: recipe for catastrophe. *Exp Brain Res* (2006) 174(4):734-45. doi:10.1007/s00221-006-0519-2
- Berger L, Bernard-Demanze L. Age-related effects of a memorizing spatial task in the adults and elderly postural control. *Gait Posture* (2011) 33:300-2. doi:10.1016/j.gaitpost.2010.10.082
- Maguire EA, Frackowiak RS, Frith CD. Recalling routes around London: activation of the right hippocampus in taxi drivers. *J Neurosci* (1997) 17(18):7103-10.
- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* (1991) 82(4):239-59. doi:10.1007/BF00308809

22. Vitte E, Derosier C, Caritu Y, Berthoz A, Hasboun D, Soulie D. Activation of the hippocampal formation by vestibular stimulation: a functional magnetic resonance imaging study. *Exp Brain Res* (1996) 112(3):523–6. doi:10.1007/BF00227958
23. Brandt T, Schautzer F, Hamilton DA, Brüning R, Markowitsch HJ, Kalla R, et al. Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans. *Brain* (2005) 128(11):2732–41. doi:10.1093/brain/awh617
24. Horii A, Takeda N, Mochizuki T, Okakura-Mochizuki K, Yamamoto Y, Yamatodani A. Effects of vestibular stimulation on acetylcholine release from rat hippocampus: an in vivo microdialysis study. *J Neurophysiol* (1994) 72:605–11.
25. Sharp PE, Blair HT, Etkin D, Tzvetanos DB. Influences of vestibular and visual motion information on the spatial firing patterns of hippocampal place cells. *J Neurosci* (1995) 15(Pt 1):173–89.
26. Russell NA, Horii A, Smith PF, Darlington CL, Bilkey DK. Lesions of the vestibular system disrupt hippocampal theta rhythm in the rat. *J Neurophysiol* (2006) 96(4–14):10. doi:10.1152/jn.00953.2005
27. Tai SK, Ma J, Ossenkopp KP, Leung LS. Activation of immobility-related hippocampal theta by cholinergic septohippocampal neurons during vestibular stimulation. *Hippocampus* (2012) 22(4):914–25. doi:10.1002/hipo.20955
28. Previc FH. Vestibular loss as a contributor to Alzheimer's disease. *Med Hypotheses* (2013) 80:360–7. doi:10.1016/j.mehy.2012.12.023
29. Harun A, Oh ES, Bigelow RT, Studenski S, Agrawal Y. Vestibular impairment in dementia. *Otol Neurotol* (2016) 37(8):1137–42. doi:10.1097/MAO.0000000000001157
30. Eichenbaum H, Dudchenko P, Wood E, Shapiro M, Tanila H. The hippocampus, memory, and place cells: is it spatial memory or a memory space? *Neuron* (1999) 23:209–26. doi:10.1016/S0896-6273(00)80773-4
31. Stackman RW, Clark AS, Taube JS. Hippocampal spatial representations require vestibular input. *Hippocampus* (2002) 12(3):291–303. doi:10.1002/hipo.1112
32. Kim S, Sapiurka M, Clark RE, Squire LR. Contrasting effects on path integration after hippocampal damage in humans and rats. *Proc Natl Acad Sci U S A* (2013) 110(12):4732–7. doi:10.1073/pnas.1300869110
33. Kaski D, Quadir S, Nigmatullina Y, Malhotra P, Bronstein AM, Seemungal BM. Temporoparietal encoding of space and time during vestibular-guided orientation. *Brain* (2016) 139(Pt 2):392–403. doi:10.1093/brain/awv370
34. Zhao X, Liu Y, Wang X, Liu B, Xi Q, Guo Q, et al. Disrupted small-world brain networks in moderate Alzheimer's disease: a resting-state fMRI study. *PLoS One* (2012) 7(2012):e33540. doi:10.1371/journal.pone.0033540
35. Seemungal BM. The cognitive neurology of the vestibular system. *Curr Opin Neurol* (2014) 27(1):125–32. doi:10.1097/WCO.0000000000000060
36. Nigmatullina Y, Hellyer PJ, Nachev P, Sharp DJ, Seemungal BM. The neuroanatomical correlates of training-related perceptuo-reflex uncoupling in dancers. *Cereb Cortex* (2015) 25(2):554–62. doi:10.1093/cercor/bht266
37. Cherchi M. Infrequent causes of disequilibrium in the adult. *Otolaryngol Clin North Am* (2011) 44:405–14. doi:10.1016/j.otc.2011.01.011
38. Lee SW, Koh SB. Clinical features and disability milestones in multiple system atrophy and progressive supranuclear palsy. *J Mov Disord* (2012) 5(2):42–7. doi:10.14802/jmd.12010
39. Chen AL, Riley DE, King SA, Joshi AC, Serra A, Liao K, et al. The disturbance of gaze in progressive supranuclear palsy: implications for pathogenesis. *Front Neurol* (2010) 1:147. doi:10.3389/fneur.2010.00147
40. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. *Arch Neurol* (1964) 10:333–59. doi:10.1001/archneur.1964.00460160003001
41. Das VE, Leigh RJ. Visual-vestibular interaction in progressive supranuclear palsy. *Vision Res* (2000) 40:2077–208110. doi:10.1016/S0042-6989(00)00046-8
42. 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
43. Kokkoroyannis T, Scudder CA, Balaban CD, Highstein SM, Moschovakis AK. Anatomy and physiology of the primate interstitial nucleus of Cajal. 1. Efferent projections. *J Neurophysiol* (1996) 75:725–73.
44. Rosengren SM, Welgampola MS, Colebatch JG. Vestibular evoked myogenic potentials: past, present and future. *Clin Neurophysiol* (2010) 121:636–51. doi:10.1016/j.clinph.2009.10.016
45. Welgampola MS, Carey JP. Waiting for the evidence: VEMP testing and the ability to differentiate utricular versus saccular function. *Otolaryngol Head Neck Surg* (2010) 143(2):281. doi:10.1016/j.otohns.2010.05.024
46. Dale ML, Horak FB, Wright WG, Schoneburg BM, Nutt JG, Mancini M. Impaired perception of surface tilt in progressive supranuclear palsy. *PLoS One* (2017) 12(3):e0173351. doi:10.1371/journal.pone.0173351
47. Srulijes K, Mack DJ, Klenk J, Schwickert L, Ihlen EA, Schwenk M, et al. Association between vestibulo-ocular reflex suppression, balance, gait, and fall risk in ageing and neurodegenerative disease: protocol of a one-year prospective follow-up study. *BMC Neurol* (2015) 15:192. doi:10.1186/s12883-015-0447-5
48. Uchihara T, Endo K, Kondo H, Okabayashi S, Shimozawa N, Yasutomi Y, et al. Tau pathology in aged cynomolgus monkeys is progressive supranuclear palsy/corticobasal degeneration-but not Alzheimer disease-like -Ultrastructural mapping of tau by EDX. *Acta Neuropathol Commun* (2016) 4:118. doi:10.1186/s40478-016-0385-5
49. Bisdorff AR, Bronstein AM, Wolsley C, Lees AJ. Torticollis due to disinhibition of the vestibulo-colic reflex in a patient with Steele-Richardson-Olszewski syndrome. *Mov Disord* (1997) 12:328–36. doi:10.1002/mds.870120311
50. Murdin L, Bronstein AM. Head deviation in progressive supranuclear palsy: enhanced vestibulo-colic reflex or loss of resetting head movements? *J Neurol* (2009) 256:1143–5. doi:10.1007/s00415-009-5090-x
51. Ondo W, Warrior D, Overby A, Calmes J, Hendersen N, Olson S, et al. Computerized posturography analysis of progressive supranuclear palsy: a case-control comparison with Parkinson's disease and healthy controls. *Arch Neurol* (2000) 57:1464–9. doi:10.1001/archneur.57.10.1464
52. Ganesan M, Pasha SA, Pal PK, Yadav R, Gupta Direction A. specific preserved limits of stability in early progressive supranuclear palsy: a dynamic posturographic study. *Gait Posture* (2012) 35:625–9. doi:10.1016/j.gaitpost.2011.12.012
53. Ishiyama G, Ishiyama A, Baloh RW. Drop attacks and vertigo secondary to a non-Menièrè otologic cause. *Arch Neurol* (2003) 60(1):71–5. doi:10.1001/archneur.60.1.71
54. Timmer FC, Zhou G, Guinan JJ, Kujawa SG, Herrmann BS, Rauch SD. Vestibular evoked myogenic potential (VEMP) in patients with Ménière's disease with drop attacks. *Laryngoscope* (2006) 116(5):776–9. doi:10.1097/01.mlg.0000205129.78600.27
55. Tarnutzer AA, Newman-Toker DE. Fits, faints, funny turns, and falls in the differential diagnosis of the dizzy patient. In: Bronstein A, editor. *Oxford Textbook of Vertigo and Imbalance*. Oxford University Press (2013). 321 p.
56. Nicolai S, Mirelmann A, Herman T, Zijlstra A, Mancini M, Becker C, et al. Improvement of balance after audio-biofeedback. A 6-week intervention study in patients with progressive supranuclear palsy. *Z Gerontol Geriatr* (2010) 43(4):224–8. doi:10.1007/s00391-010-0125-6
57. Velayutham SG, Chandra SR, Bharath S, Shankar RG. Quantitative balance and gait measurement in patients with frontotemporal dementia and Alzheimer diseases: a pilot study. *Indian J Psychol Med* (2017) 39(2):176–82. doi:10.4103/0253-7176.203132
58. Tu S, Wong S, Hodges JR, Irish M, Piguet O, Hornberger M. in spatial translation – a novel tool to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia. *Cortex* (2015) 67:83–94. doi:10.1016/j.cortex.2015.03.016
59. Nakamagoe K, Kadono K, Koganezawa T, Takiguchi M, Terada M, Yamamoto F, et al. Vestibular impairment in frontotemporal dementia syndrome. *Dement Geriatr Cogn Dis Extra* (2016) 6(2):194–204. doi:10.1159/000445870
60. Brandt T, Dieterich M. The vestibular cortex: its locations, functions, and disorders. *Ann N Y Acad Sci* (1999) 871(1):293–312. doi:10.1111/j.1749-6632.1999.tb09193.x
61. Guldin WO, Akbarian S, Grüsser OJ. Cortico-cortical connections and cytoarchitectonics of the primate vestibular cortex: a study in squirrel monkeys (*Saimiri sciureus*). *J Comp Neurol* (1992) 326(3):375–401. doi:10.1002/cne.903260306
62. Brooks BR, Li J, Huang W, Anderson FA, Miller RG, Mitsumoto H. Epidemiology of falls in amyotrophic lateral sclerosis patients: analysis of cross-sectional and prospective cohorts in the ALS CARE registry. *Annals of Neurology*; (Vol. 62). 2007 Jan 1; Hoboken, NJ, USA: Wiley-Liss (2007). p. S23–4.
63. Turner MR, Abisgold J, Yeates DGR, Talbot K, Goldacre MJ. Head and other physical trauma requiring hospitalization is not a significant risk factor

- in the development of ALS. *J Neurol Sci* (2010) 288:45–8. doi:10.1016/j.jns.2009.10.010
64. Sanjak M, Hirsch MA, Bravver EK, Bockenek WL, Norton HJ, Brooks BR. Vestibular deficits leading to disequilibrium and falls in ambulatory amyotrophic lateral sclerosis. *Arch Phys Med Rehabil* (2014) 95:1933–9. doi:10.1016/j.apmr.2014.05.024
 65. Kilic S, Gazioglu S, Serap-Zengin K, Dübüş HÜ, Boz C. Cervical vestibular evoked myogenic potential to air-conducted sound in early amyotrophic lateral sclerosis. *Clin Neurophysiol* (2012) 42:119–23. doi:10.1016/j.neucli.2012.01.001
 66. Ohki M, Kanayama R, Nakamura T, Okuyama T, Kimura Y, Koike Y. Ocular abnormalities in amyotrophic lateral sclerosis. *Acta Otolaryngol Suppl* (1994) 511:138–42. doi:10.3109/00016489409128318
 67. Steinmetz EF, Lebo CP, Norris FH Jr. Electronystagmographic findings in motor neuron disease. *Laryngoscope* (1974) 84:281–9. doi:10.1288/00005537-197402000-00010
 68. Geser F, Seppi K, Stampfer-Kountchev M, Köllensperger M, Diem A, Ndayisaba JP, et al. The European multiple system atrophy-study group (EMSA-SG). *J Neural Transm* (2005) 112:1677–86. doi:10.1007/s00702-005-0328-y
 69. Matsushima M, Yabe I, Oba K, Sakushima K, Mito Y, Takei A, et al. Comparison of different symptom assessment scales for multiple system atrophy. *Cerebellum* (2016) 15:190–200. doi:10.1007/s12311-015-0686-4
 70. Sakakibara R, Hirumab K, Uchiyama T, Hattori T. Head-turning dizziness in multiple system atrophy. *Parkinsonism Relat Disord* (2004) 10(4):255–6. doi:10.1016/j.parkreldis.2004.02.005
 71. Abdo WF, Borm GF, Munneke M, Verbeek MM, Esselink RAJ, Bloem BR. Ten steps to identify atypical parkinsonism. *J Neurol Neurosurg Psychiatry* (2006) 77(12):1367–9. doi:10.1136/jnnp.2006.091322
 72. Venhovens J, Meulstee J, Bloem BR, Verhagen WIM. Neurovestibular analysis and falls in Parkinson's disease and atypical parkinsonism. *Eur J Neurosci* (2016) 43:1636–46. doi:10.1111/ejn.13253
 73. Drachman DA. A 69-year-old man with chronic dizziness. *JAMA* (1998) 280:2111–8. doi:10.1001/jama.280.24.2111
 74. Mathias CJ, Mallipeddi R, Bleasdale-Barr K. Symptoms associated with orthostatic hypotension in pure autonomic failure and multiple system atrophy. *J Neurol* (1999) 246:893–8. doi:10.1007/s004150050479
 75. Wang SR, Young YH. Multiple system atrophy manifested as dizziness and imbalance: a report of two cases. *Eur Arch Otorhinolaryngol* (2003) 260:404–7. doi:10.1007/s00405-003-0595-x
 76. Wenning GK, Tison F, Ben Shlomo Y, Daniel SE, Quinn NP. Multiple system atrophy: a review of 203 pathologically proven cases. *Mov Disord* (1997) 12:133–47. doi:10.1002/mds.870120203
 77. Anderson T, Luxon L, Quinn N, Daniel S, Marsden CD, Bronstein A. Oculomotor function in multiple system atrophy: clinical and laboratory features in 30 patients. *Mov Disord* (2008) 23:977–84. doi:10.1002/mds.21999
 78. Rascol O, Sabatini U, Fabre N, Senard JM, Simonetta-Moreau M, Montastruc JL, et al. Abnormal vestibuloocular reflex cancellation in multiple system atrophy and progressive supranuclear palsy but not in Parkinson's disease. *Mov Disord* (1995) 10:163–70.
 79. Wu T, Hallett M. The cerebellum in Parkinson's disease. *Brain* (2013) 136(3):696–709. doi:10.1093/brain/awt360
 80. Halmagyi GM, Gresty MA. Clinical signs of visual-vestibular interaction. *J Neurol Neurosurg Psychiatry* (1979) 42(10):934–9. doi:10.1136/jnnp.42.10.934
 81. Doná F, Aquino CC, Gazzola JM, Borges V, Silva SM, Ganança FF, et al. Changes in postural control in patients with Parkinson's disease: a posturographic study. *Physiotherapy* (2016) 102:272–9. doi:10.1016/j.physio.2015.08.009
 82. Rossi-Izquierdo M, Basta D, Rubio-Rodríguez JP, Santos-Pérez S, Ernst A, Sesar-Ignacio Á, et al. Is posturography able to identify fallers in patients with Parkinson's disease? *Gait Posture* (2014) 40:53–7. doi:10.1016/j.gaitpost.2014.02.003
 83. Colnat-Coulbois S, Gauchard GC, Maillard L, Barroche G, Vespignani H, Auque J, et al. Management of postural sensory conflict and dynamic balance control in late-stage Parkinson's disease. *Neuroscience* (2011) 193:363–9. doi:10.1016/j.neuroscience.2011.04.043
 84. Rossi M, Soto A, Santos S, Sesar A, Labella T. A prospective study of alterations in balance among patients with Parkinson's disease. Protocol of the postural evaluation. *Eur Neurol* (2009) 61:171–6. doi:10.1159/000189270
 85. Hwang S, Agada P, Grill S, Kiemel T, Jeka JJ. A central processing sensory deficit with Parkinson's disease. *Exp Brain Res* (2016) 234:2369–79. doi:10.1007/s00221-016-4642-4
 86. Hwang S, Agada P, Kiemel T, Jeka JJ. Dynamic reweighting of three modalities for sensor fusion. *PLoS One* (2014) 9:e88132. doi:10.1371/journal.pone.0088132
 87. Putcha D, Ross RS, Rosen ML, Norton DJ, Cronin-Golomb A, Somers DC, et al. Functional correlates of optic flow motion processing in Parkinson's disease. *Front Integr Neurosci* (2014) 8:57. doi:10.3389/fnint.2014.00057
 88. Cardin V, Smith AT. Sensitivity of human visual and vestibular cortical regions to egomotion-compatible visual stimulation. *Cerebral Cortex* (2010) 20(8):1964–73. doi:10.1093/cercor/bhp268
 89. Shalash AS, Hassan DM, Elrassas HH, Salama MM, Méndez-Hernández E, Salas-Pacheco JM, et al. Auditory- and vestibular-evoked potentials correlate with motor and non-motor features of Parkinson's disease. *Front Neurol* (2017) 8:55. doi:10.3389/fneur.2017.00055
 90. Pollak L, Prohorov T, Kushnir M, Rabey M. Vestibulocervical reflexes in idiopathic Parkinson disease. *Neurophysiol Clin* (2009) 39:235–40. doi:10.1016/j.neucli.2009.07.001
 91. de Natale ER, Ginatempo F, Paulus KS, Manca A, Mercante B, Pes GM, et al. Paired neurophysiological and clinical study of the brainstem at different stages of Parkinson's Disease. *Clin Neurophysiol* (2015) 126:1871–8. doi:10.1016/j.clinph.2014.12.017
 92. Seidel K, Mahlke J, Siswanto S, Kruger R, Heinsen H, Auburger G, et al. The brainstem pathologies of Parkinson's disease and dementia with Lewy bodies. *Brain Pathol* (2015) 25:121–35. doi:10.1111/bpa.12168
 93. Halberstadt AL, Balaban CD. Selective anterograde tracing of the individual serotonergic and nonserotonergic components of the dorsal raphe nucleus projection to the vestibular nuclei. *Neuroscience* (2007) 147:207–23. doi:10.1016/j.neuroscience.2007.03.049
 94. Pötter-Nerger M, Reich MM, Colebatch JG, Deuschl G, Volkman J. Differential effect of DOPA and subthalamic stimulation on vestibular activity in Parkinson's disease. *Mov Disord* (2012) 27:1268–75. doi:10.1002/mds.25061
 95. Vitale C, Marcelli V, Furia T, Santangelo G, Cozzolino A, Longo K, et al. Vestibular impairment and adaptive postural imbalance in parkinsonian patients with lateral trunk flexion. *Mov Disord* (2011) 26:1458–63. doi:10.1002/mds.23657
 96. Scocco DH, Wagner JN, Racosta J, Chade A, Gershanik OS. Subjective visual vertical in Pisa syndrome. *Parkinsonism Relat Disord* (2014) 20(8):878–83. doi:10.1016/j.parkreldis.2014.04.030
 97. Gandor F, Basta D, Gruber D, Poewe W, Ebersbach G. Subjective visual vertical in PD patients with lateral trunk flexion. *Parkinsons Dis* (2016) 2016:7489105. doi:10.1155/2016/7489105
 98. 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. doi:10.1016/j.parkreldis.2016.02.004
 99. Fling BW, Cohen RG, Mancini M, Nutt JG, Fair DA, Horak FB. Asymmetric pedunculopontine network connectivity in parkinsonian patients with freezing of gait. *Brain* (2013) 136:2405–18. doi:10.1093/brain/awt172
 100. Hazrati LN, Parent A. Projection from the deep cerebellar nuclei to the pedunculopontine nucleus in the squirrel monkey. *Brain Res* (1992) 585:267–71. doi:10.1016/0006-8993(92)91216-2
 101. Aravamuthan BR, Angelaki DE. Vestibular responses in the macaque pedunculopontine nucleus and central mesencephalic reticular formation. *Neuroscience* (2012) 223:183–99. doi:10.1016/j.neuroscience.2012.07.054
 102. Moro E, Hamani C, Poon Y-Y, Al-Khairallah T, Dostrovsky JO, Hutchison WD, et al. Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. *Brain* (2010) 133(1):215–24. doi:10.1093/brain/awp261
 103. Yousif N, Bhatt H, Bain PG, Nandi D, Seemungal BM. The effect of pedunculopontine nucleus deep brain stimulation on postural sway and vestibular perception. *Eur J Neurol* (2016) 23(3):668–70. doi:10.1111/ene.12947
 104. Rowe J, Khan A, Romanowski C, Isaac C, Khan S, Mair R, et al. Clinical experience with pedunculopontine nucleus stimulation in conditions with nigrostriatal disconnection. *World Neurosurg* (2016) 89:9–18. doi:10.1016/j.wneu.2015.11.054
 105. Acarer A, Karapolat H, Celebisoy N, Ozgen G, Colakoglu Z. Is customized vestibular rehabilitation effective in patients with Parkinson's? *NeuroRehabilitation* (2015) 37(2):255–62. doi:10.3233/NRE-151258

106. Basta D. Efficacy of a vibrotactile neurofeedback training in stance and gait conditions for the treatment of balance deficits: a double-blind, placebo-controlled multicenter study. *Otol Neurotol* (2011) 32:1492–9. doi:10.1097/MAO.0b013e31823827ec
107. Zeigelboim BS, Klagenberg KE, Teive HA, Munhoz RP, Martins-Bassetto J. Vestibular rehabilitation: clinical benefits to patients with Parkinson disease. *Arq Neuropsiquiatr* (2009) 67(2A):219–23. doi:10.1590/S0004-282X2009000200009
108. Rossi-Izquierdo M, Soto-Varela A, Santos-Perez S, Sesar-Ignacio A, Labella-Caballero T, Rossi-Izquierdo M, et al. Vestibular rehabilitation with computerised dynamic posturography in patients with Parkinson's disease: improving balance impairment. *Disabil Rehabil* (2009) 31(23):1907–16. doi:10.1080/09638280902846384
109. Tramontano M, Bonni S, Martino Cinnera A, Giacomo K, Cinnera MA, Tramontano M, et al. Blindfolded balance training in patients with Parkinson's disease: a sensory-motor strategy to improve the gait. *Parkinsons Dis* (2016) 2016:7536862.
110. Wilkinson D, Podlowska A, Sakel M. A durable gain in motor and non-motor symptoms of Parkinson's disease following repeated caloric vestibular stimulation: a single-case study. *NeuroRehabilitation* (2016) 38(2):179–82. doi:10.3233/NRE-161308
111. Kataoka H, Okada Y, Kiriya T, Kita Y, Nakamura J, Morioka S, et al. Can postural instability respond to galvanic vestibular stimulation in patients with Parkinson's disease? *J Mov Disord* (2016) 9(1):40–3. doi:10.14802/jmd.15030
112. Okada Y, Kita Y, Nakamura J, Kataoka H, Kiriya T, Ueno S, et al. Galvanic vestibular stimulation may improve anterior bending posture in Parkinson's disease. *Neuroreport* (2015) 26:405–10. doi:10.1097/WNR.0000000000000360
113. Lee S, Kim DJ, Svenkeson D, Parras G, Oishi MMK, McKeown MJ. Multifaceted effects of noisy galvanic vestibular stimulation on manual tracking behavior in Parkinson's disease. *Front Syst Neurosci* (2015) 9:5. doi:10.3389/fnsys.2015.00005
114. Pan W, Soma R, Kwak S, Yamamoto Y. Improvement of motor functions by noisy vestibular stimulation in central neurodegenerative disorders. *J Neurol* (2008) 255:1657–61. doi:10.1007/s00415-008-0950-3
115. Samoudi G, Jivegård M, Mulavara AP, Bergquist F. Effects of stochastic vestibular galvanic stimulation and LDOPA on balance and motor symptoms in patients with Parkinson's disease. *Brain Stimulat* (2015) 8(3):474–80. doi:10.1016/j.brs.2014.11.019
116. Pal S, Rosengren SM, Colebatch JG. Stochastic galvanic vestibular stimulation produces a small reduction in sway in Parkinson's disease. *J Vestib Res* (2009) 19:137–42. doi:10.3233/VES-2009-0360

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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