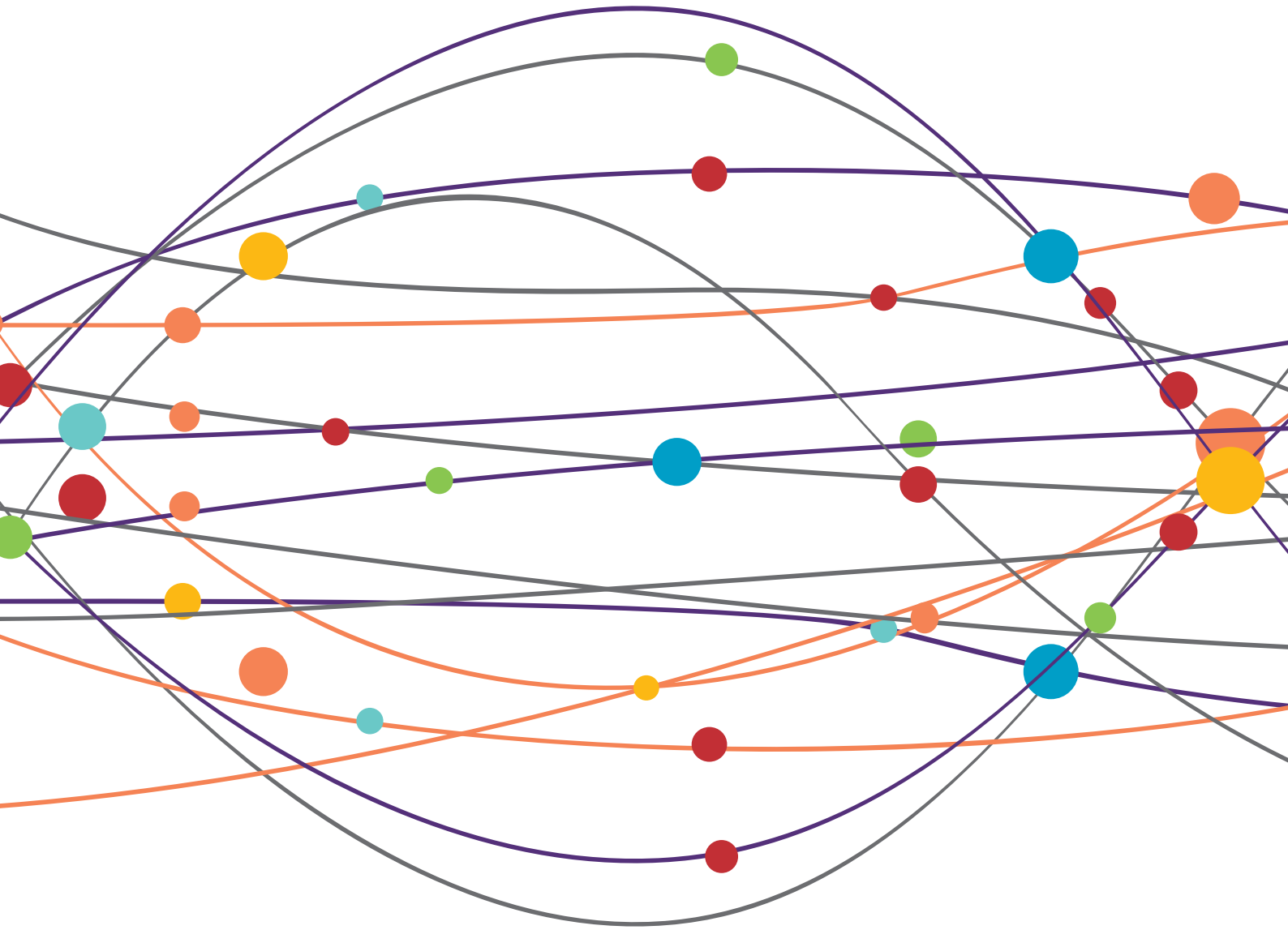
AGE-RELATED VESTIBULAR LOSS: CURRENT UNDERSTANDING AND FUTURE RESEARCH DIRECTIONS

EDITED BY: Yuri Agrawal and John Carey
PUBLISHED IN: Frontiers in Neurology



frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88945-300-9
DOI 10.3389/978-2-88945-300-9

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view.
By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: **researchtopics@frontiersin.org**

AGE-RELATED VESTIBULAR LOSS: CURRENT UNDERSTANDING AND FUTURE RESEARCH DIRECTIONS

Topic Editors:
Yuri Agrawal, Johns Hopkins University, United States
John Carey, Johns Hopkins University, United States

Citation: Agrawal, Y., Carey, J., eds. (2017). Age-Related Vestibular Loss: Current Understanding and Future Research Directions. Lausanne: Frontiers Media. doi: 10.3389/978-2-88945-300-9

Table of Contents

frontiers in Neurology

EDITORIAL
published: 30 August 2017
doi: 10.3389/fneur.2017.00443

Editorial: Age-Related Vestibular Loss: Current Understanding and Future Research Directions

*Yuri Agrawal**

Johns Hopkins University, Baltimore, MD, United States

Keywords: vestibular diseases, aging, vestibular function tests, falls, dizziness

Editorial on the Research Topic

Age-Related Vestibular Loss: Current Understanding and Future Research Directions

This Research Topic reflects the collective work of 44 authors from around the world yielding 11 thoughtful and provocative publications. Several themes have clearly emerged from this body of work, which help to establish where we are in understanding age-related vestibular loss and the fundamental research gaps that we must address. First and foremost, it is clear that we are dealing with a topic of tremendous public health significance. The global population is aging, and age-related degeneration of the vestibular system is a widespread phenomenon that occurs as part of the normal aging process. Older individuals disproportionately experience falls, which are a disastrous event associated with tremendous morbidity and early mortality. It is known that the vestibular system contributes to fall risk; however, the extent to which vestibular loss contributes to falls in older adults is not precisely known (and may differ across individuals). Moreover, although falls are highly common and age-related vestibular loss is widespread, vestibular therapies such as vestibular rehabilitation are seldom offered to the large number of older adults presenting with falls in the primary care setting. Much work needs to be done to provide a strong, quantitative evidence base for the causal relationship between vestibular loss and falls in older adults and the benefit of vestibular therapy.

A second theme that follows from the first is the clear need for efficient clinical tests that identify clinically meaningful vestibular loss in older adults. The vestibular system is a highly complex structure that encompasses five peripheral end-organs and widespread central connections through brainstem nuclei, the cerebellum, the thalamus, vestibular cortex, and hippocampus. The function of the vestibular system can be probed at many levels, based on anatomy (e.g., canal vs. otolith, peripheral vs. central), based on level of analysis (e.g., cellular neurotransmitters vs. cortical networks, reflex vs. perceptual testing), and based on functional behaviors (e.g., gait vs. spatial orientation). Moreover, in the context of aging, vestibular loss is typically one of the multiple concomitant deficits that may be occurring and contributing to a given clinical phenotype (e.g., dizziness, imbalance, and falls). Specifically, older adults may also have deficits in proprioception, vision, hearing, and muscle strength. Further, even if sensorimotor function is relatively intact, older adults may have deficits in central integration of these various sensory signals to generate a coherent motor output. Additionally, older individuals may compensate to varying degrees for their deficits, such that inadequacies of compensation may also contribute to the clinical picture. It is, therefore, critical for useful clinical tests to disambiguate the various layers of potential contributing factors (i.e., primary sensorimotor deficits, deficits in central integration, and deficits in compensation) within a given older adult, with the goal of providing "personalized" strategies to improve balance function.

The publications in this Issue highlight numerous vestibular assays that differentiate older from younger individuals. Chau et al. observed reduced vestibulo-ocular reflex responses to

OPEN ACCESS

Edited by:
Michael Strupp, Ludwig-Maximilians-Universität München, Germany

Reviewed by:
Shinichi Iwasaki, The University of Tokyo, Japan
Yi-Ho Young, National Taiwan University, Taiwan

***Correspondence:**
Yuri Agrawal
yagrawa1@jhmi.edu

Specialty section:
This article was submitted to Neuro-Otology, a section of the journal Frontiers in Neurology

Received: *07 July 2017*
Accepted: *11 August 2017*
Published: *30 August 2017*

Citation:
Agrawal Y (2017) Editorial: Age-Related Vestibular Loss: Current Understanding and Future Research Directions. Front. Neurol. 8:443. doi: 10.3389/fneur.2017.00443

rotational stimulation among older adults with dizziness. Bermúdez Rey et al. observed increasing vestibular perceptual thresholds beginning at the age of 40, and the authors also found that higher roll tilt thresholds were associated with poorer postural stability. Chiarovano et al. reported that older adults with postural instability did not experience a rotation perception during warm caloric irrigation. They termed this phenomenon "vestibular neglect," and suggested it arose from reduced central responsivity to peripheral stimulation. Maheu et al. provide a review of age-related differences in performance on the standard clinical vestibular tests. Several studies also considered how aging might lead to deficits in central vestibular processing. At a molecular level, Smith discussed the differences in neurotransmission occurring at the level of the vestibular nuclear complex in older vs. younger animals. Xie et al. showed poorer performance among older adults on a test of spatial navigation, the triangle completion task, relative to younger individuals. Arshad and Seemungal reviewed several recent studies that reported reduced connectivity of central vestibular networks associated with increased age. Two studies specifically evaluated whether compensation for vestibular loss differs between young and old adults. Vestibular compensation relies on central mechanisms (cerebellar, brainstem, striatal, etc.) and may thus be a measure of central nervous system rather than vestibular function. Scheltinga et al. reported that older adults with acute unilateral vestibular loss (aUVL) experienced greater balance impairments compared to younger individuals with aUVL. Moreover, the balance impairments in older individuals took longer to improve and were less likely to resolve. Anson et al. examined how age influenced the generation of compensatory saccades following horizontal head impulse testing. They observed that increased age was associated with larger compensatory saccade amplitude, even after accounting for underlying VOR gain.

These studies all assess vestibular function at a different level of analysis. However, the "holy grail" would be a test that provides a comprehensive snapshot of the extent to which the observed vestibular impairment contributes to the individual's symptoms relative to other impairments, and the individual's level of compensation. As stated by Fernández et al., "Reaching a complete, meaningful, and treatment-oriented diagnosis in elderly dizzy patients remains an important challenge for even the most experienced clinician." New techniques and assays will likely be needed to accomplish this task. For example, postural assessment is becoming increasingly powerful through frequency-based analyses and analyses of complexity. It is possible that a simple postural test can determine the source of an individual's sway (e.g., reduced proprioception vs. vestibular function) based on the sway frequencies observed. Moreover, as discussed by Anson and Jeka, assays that are more ecologically valid (e.g., accelerometry deployed during routine daily activities) may be more sensitive at detecting deficits that manifest dynamically during daily activities but that may not be evident in a clinical laboratory. Finally, assays that measure central vestibular processing and compensation may prove useful in understanding the clinical picture and also designing therapy. Currently, functional imaging studies provide insight into these processes, although other measures that can be more easily scaled may prove more useful in the clinical setting.

This research topic clearly highlights a growing awareness of age-related vestibular loss, and its potentially far-reaching impact on the public's health. Indeed, efforts are currently underway by the Barany Society's International Classification of Vestibular Diseases to codify diagnostic criteria for age-related vestibular loss. As discussed, age-related vestibular loss is a complex phenomenon to manage clinically and study scientifically, largely owing to the complexity of the vestibular system as well as the complexity of the aging process. This is both a challenge and an opportunity to harmonize our conceptual framework, standardize our assessment tools, and catalyze innovation and new developments in this field.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

FUNDING

This work was supported by NIH NIDCD K23 DC013056.

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

frontiers in Neurology

MINI REVIEW
published: 26 June 2015
doi: 10.3389/fneur.2015.00144

Vertigo and dizziness in the elderly

Lara Fernández[1], *Hayo A. Breinbauer*[2,3] *and Paul Hinckley Delano*[1,4]*

[1] Otolaryngology Department, Clinical Hospital of the University of Chile, Santiago, Chile, [2] Otolaryngology Department, San Juan de Dios Hospital, University of Chile, Santiago, Chile, [3] Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile, [4] Physiology and Biophysics Program, Institute of Biomedical Sciences (ICBM), Medicine Faculty, University of Chile, Santiago, Chile

The prevalence of vertigo and dizziness in people aged more than 60 years reaches 30%, and due to aging of world population, the number of patients is rapidly increasing. The presence of dizziness in the elderly is a strong predictor of falls, which is the leading cause of accidental death in people older than 65 years. Balance disorders in the elderly constitute a major public health problem, and require an adequate diagnosis and management by trained physicians. In the elderly, common causes of vertigo may manifest differently, as patients tend to report less rotatory vertigo and more non-specific dizziness and instability than younger patients, making diagnosis more complex. In this mini review, age-related degenerative processes that affect balance are presented. Diagnostic and therapeutic approaches oriented to the specific impaired system, including visual, proprioceptive, and vestibular pathways, are proposed. In addition, presbystasis – the loss of vestibular and balance functions associated with aging – benign paroxysmal positional vertigo, and stroke (in acute syndromes) should always be considered.

Keywords: dizziness, presbystasis, vertigo, falls, elderly, aging

OPEN ACCESS

Edited by:
Yuri Agrawal,
Johns Hopkins University, USA

Reviewed by:
Barry M. Seemungal,
Imperial College London, UK
Alejo Suarez,
British Hospital, Uruguay

***Correspondence:**
Paul Hinckley Delano,
Physiology and Biophysics Program, Otolaryngology Department, ICBM, University of Chile, Independencia 1027, Santiago 8380453, Chile
pdelano@med.uchile.cl

Specialty section:
This article was submitted to Neuro-otology, a section of the journal Frontiers in Neurology

Received: *23 March 2015*
Accepted: *12 June 2015*
Published: *26 June 2015*

Citation:
Fernández L, Breinbauer HA and Delano PH (2015) Vertigo and dizziness in the elderly. Front. Neurol. 6:144. doi: 10.3389/fneur.2015.00144

Introduction

The terms dizziness and vertigo cover a variety of symptoms regarding disorders of spatial orientation and motion perception, such as the illusion of rotatory motion (classical rotatory vertigo) or the feeling of unsteadiness, which can affect objectively the ability to achieve a stable gaze, posture, and gait (1). Altogether they represent a common and serious issue in the elderly, where its prevalence reaches 30% beyond 60 years of age (1, 2), while rising to 50% beyond 85 years (1).

The sole presence of dizziness in the elderly is a strong predictor of falls (3). Moreover, the presence of abnormal balance tests increases the risk of hip and wrist fractures (4). Injuries related to falls lead to mobility restriction and loss of independence, and increase the fear of falling, which also predicts subsequent falls (2). In addition, falls are the leading cause of accidental death in persons older than 65 years (5), while dizziness is one of the strongest contributors to the disability burden after age 65 (6).

Although the majority of these patients present benign balance disorders, (7–9), in the elderly, common causes of vertigo may manifest differently, with a more confusing constellation of symptoms, as patients tend to report less rotatory vertigo and more non-specific dizziness and instability than younger patients presenting with the same condition (9). Underlying this phenomenon is the progressive multimodal impairment of balance, including the loss of vestibular and proprioceptive functions, and the impairment of central integration of these and other sensory inputs associated with aging, which may also be called as presbystasis, presbyequilibrium, or multisensory dizziness (4, 7, 10). In addition, the skeletal muscle strength and mass are reduced with aging, increasing the risk of fall-related injuries in elderly patients (11).

On the other hand, a small number of patients harbor a serious and potentially life-threatening cause, mainly associated with stroke, and this risk of more serious diagnoses increases with age (12, 13). Altogether, vertigo, dizziness, and balance disorders in the elderly constitute a major public health issue, which needs adequate management by trained physicians. This mini review presents recent advances in the diagnosis and management of dizziness in elderly patients.

Pathophysiology of Balance in the Elderly

Age-related degeneration of different neural structures affects balance, including the vestibular receptors, central vestibular neurons, cerebellum, and visual and proprioceptive pathways. The number of hair cells in the vestibular organs and the number of fibers in the superior and inferior vestibular nerves decrease with age (14–16). From a functional perspective, age-related deficits appear to be larger on semicircular canals, followed by saccular function, while the utriculus remains less affected (17–19). A steady asymmetrical decrease in the ability of sensing angular rotation with age has been reported, as assessed by video head impulse testing (vHIT) of the vestibulo-ocular reflex (VOR) (4, 19, 20). This fact is associated with a loss of dynamic visual acuity due to the inability to compensate fast head rotations with corrective eye movements, thus assuring a steady image over the retina (21). However, while on the acute phase of vestibular loss, this may cause intense rotatory vertigo (due to a sudden vestibular asymmetry), on elderly patients the slow onset of these chronic impairments would not manifest with vertigo. Instead, they complain about movement intolerance, instability, and insecure gait, particularly when sudden turns are needed, as there is an incapability of processing these movements properly. This may also explain the observed lack of rotatory vertigo in elderly patients with benign paroxysmal positional vertigo (BPPV) (8).

Nevertheless, while "active" vestibular symptoms may be milder or shifted toward instability, functional balance performance and disequilibrium phenomena are actually more severe. The sole presence of VOR asymmetry (which may present in elderly patients without history of an acute vestibular syndrome, and rarely in the form of bilateral vestibulopathy) is a significant predictor of falling (4, 22). In addition, compensation phenomena after vestibular loss are weakened in elderly patients, for example, impairment after vestibular neuritis is harsher on the elderly (23). Behind this lies degeneration of multiple non-vestibular subsystems. For instance, the medial vestibular nucleus, important in vestibular compensation due to its commissural fibers, shows lower neuron density in healthy older adults (24). There is also a mean loss of cerebellum Purkinje cells of about 2.5% per decade (25). Vibration and touch thresholds, the ability to detect position and direction of joint movements, and muscle strength also deteriorate with age (2). Visual accommodation, depth perception, and the ability to suppress nystagmus by visual fixation is diminished due to aging of the oculomotor system with increased saccade latency, and reduced eye tracking velocity (2).

Similarly, elderly patients with chronic pathological asymmetric vestibular evoked myogenic potentials (VEMPs) or deviated subjective visual vertical (SVV) tests, do not report dizziness or vertigo as significant symptoms, which may relate to central compensation occurring from the beginning of this slow onset of vestibular function (18, 19, 26, 27). This scenario leads to no pathological symptoms at all. Therefore, it is still controversial whether presbystasis by itself should be always considered pathological or not.

In summary, in order to maintain balance, the brain uses all available sensorial cues from vestibular, visual, and proprioceptive inputs, which in turn are integrated by the central nervous system to execute adequate motor responses. In this manner, age-related balance deterioration does not appear to behave as a unique standardized phenomenon, but the opposite, it seems to be extremely variable from patient to patient (17, 18, 20, 27). Moreover, minor new or acute impairments can affect disproportionately their capacity to cope difficult equilibrium scenarios, as every sensory modality may already be partially deteriorated. Current knowledge is moving toward determining which abnormalities in balance testing relate to higher risk of falling, and toward a balance disorder "profile" of selective impairments, which, as we propose, may guide a target-specific treatment (28–30). While asymmetric, severe, and multimodal balance impairments due to aging are likely to cause symptomatology *per se*, the magnification and distortion of the symptom spectrum of specific pathologies by presbystasis is perhaps more common. All these factors should be taken into account in the diagnosis and management of elderly patients.

Diagnosis of Dizziness in the Elderly

Reaching a complete, meaningful, and treatment-oriented diagnosis in elderly dizzy patients remains an important challenge for even the most experienced clinician. Obtaining a good clinical history can be a tough task. It has been reported that more than half of elderly patients with balance disorders are vague, inconsistent, or contradictory in describing their symptoms (31). Besides, there is not a single symptom that can predict with specificity the underlying causes of dizziness, and most of the times, elderly patients have more than one cause of dizziness (32, 33). Moreover, caloric test responses depend on several factors that could be affected by age, such as ear canal volume, temporal bone thickness, and blood supply to the temporal bone (34). Several studies have found that caloric responses tend to increase in middle age with a peak between 50 and 70 years, and then decline modestly thereafter (35, 36).

A systematic assessment of balance should be achieved in this type of patient, for which recent technological developments are of great assistance. The impairment of each of the three semicircular canals can be examined by means of vHIT (37) procuring a reliable, objective, and quantitative value for VOR. Ocular and cervical VEMPs give equally reliable information over utricular and saccular function independently (38). The non-vestibular proprioceptive and visual sensory components of balance and their central integration in overall equilibrium performance can be thoroughly assessed by dynamic computed posturography (39). Altogether these tests provide an objective assessment of every component and subsystem of balance, allowing specific profiling of patients (40, 41).

Besides HIT, the SVV bucket test and modified Romberg and Fukuda tests represent low complexity alternatives for the same assessment, and may be used to develop simple, low cost, and quick screening procedures (20, 42). SVV by means of bucket test may even provide sensible assessment of utricular components beyond VEMP contributions (27). Head-shaking nystagmus and dynamic visual acuity testing among others constitute bedside, fast, inexpensive, and easy to interpret vestibular tests for VOR (4, 7, 18). Testing for postural hypotension, joint position sense, and gait disorders can also contribute to assess non-vestibular components in a bedside low-cost manner, contributing to designing an integral but component-specific treatment.

A particular scenario exists in acute onset of severe dizziness or vertigo; an acute vestibular syndrome, where ruling out stroke is critical, particularly in the elderly. The HINTS assessment protocol (head impulse test, nystagmus directionality, and test of skew) can be performed at the bedside, with high sensitivity and specificity to diagnose stroke in an acute vestibular syndrome (43). This three-step bedside oculomotor examination has shown better sensitivity than early magnetic resonance imaging (MRI). MRI can give a false negative result in vertebrobasilar stroke (44), and is not always readily available (45). A full description of the management of acute vertigo in the elderly is beyond the scope of this mini review, further readings can be obtained elsewhere (13, 46).

Also, of note is positional testing for BPPV. This clinical entity accounts for one in every three causes of dizziness in the elderly. With a simple diagnosis–treatment scheme (even in the absence of rotatory symptoms), testing should be performed routinely (8). Consequently, to seek a precise diagnosis, it seems to be mandatory to obtain a good clinical history and perform thorough neuro-otologic bedside examination, including postural testing, while the majority of patients may benefit from vestibular tests, and stroke assessment protocols for an acute balance disorder.

TABLE 1 | Etiology of dizziness and vertigo in the elderly.

Peripheral vestibular	Benign paroxysmal positional vertigo
	Vestibular neuritis
	Bilateral vestibular loss
	Late-onset Meniere's disease or decompensation (2)
	Labyrinthitis
	Occlusion of the anterior vestibular artery (48)
Central nervous system	Vestibular migraine (49)
	Transient ischemic attack of vertebrobasilar artery (50)
	Stroke
	Neurodegenerative disorders (51)
	Downbeat and upbeat nystagmus syndromes (51)
Cardiovascular (2)	Arrhythmia
	Postural hypotension
	Congestive heart failure
	Heart valve failure
Medications (52)	Antihypertensive
	Benzodiazepines
	Hypnotics
	Anxiolytics
	Antiepileptic
Multimodal balance disorder	Presbystasis (10)
Others	Primary and secondary neoplasia (breast and prostate) (53, 54)
	Somatoform vertigo and psychiatric dizziness (55)
	Musculoskeletal system disorders
	Proprioception and somatosensory loss

Etiology

The majority of diseases that cause dizziness in any age group become more prevalent in older individuals. This can be explained by the cumulative probability of exposure or by age-related changes that make the elderly more susceptible to these pathologies (47). A summary of the main causes of dizziness in the elderly is shown in **Table 1**.

Management of Elderly Patients with Dizziness

As with younger patients, disease-specific therapies should be provided, such as repositioning maneuvers for BPPV and rehabilitation exercises for vestibular hypofunction. Nevertheless, special consideration is needed for elderly. A flowchart for the management of these patients is proposed in **Figure 1**. A high level of suspicion for BPPV should be maintained. In dubious cases, treatment attempts should be preferred, given diminished symptomatology and the safety and simplicity of reposition maneuvers (56).

In acute syndromes, stroke should always be ruled out by HINTS. Vestibular suppressants should be tapered quickly due to their inhibitory effect on central compensation (57). Although steroids have been proven to diminish functional loss over time, they may not contribute to acute symptomatic relief (58). Steroids side effects should be carefully considered before administration, particularly on this age group.

Current knowledge advises the initiation of vestibular rehabilitation (VR) as soon as possible after an acute vestibular syndrome (29, 30). VR works as a catalyzer and enhancer of central compensation on the basis of three principles: adaptation (rearrangement of VOR networking), substitution (strengthening of non-vestibular components of balance), and habituation (increase of sensory thresholds).

Chronic dizziness derived from previously acquired vestibular loss (vestibular neuritis, bilateral vestibulopathy among others) has good results with VR, particularly in terms of independence and quality of life, although it may need longer and more intensive therapy (28, 59). Moreover, VR is indicated in presbystasis, whereas the objective is to reduce symptoms or decrease the risk of falling (29, 30, 60). In addition, if there are deficits in lower extremity muscle strength, specific therapies directed to locomotor dysfunctions should be indicated (61). Proper balance

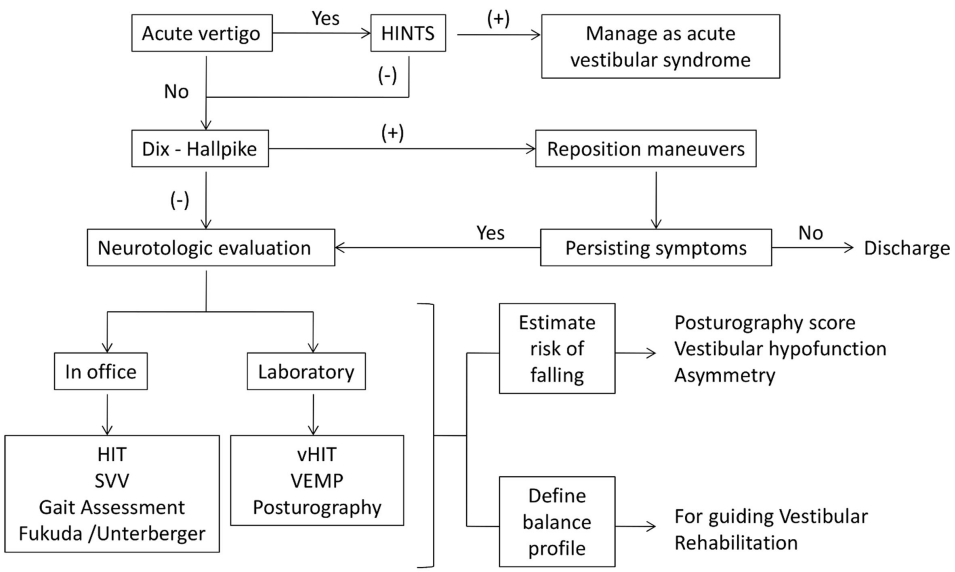


FIGURE 1 | Proposed flowchart for the management of dizziness in elderly patients. An accurate anamnesis and physical examination will determine further vestibular, neurological, or cardiovascular tests. Patients with chronic vertigo should be evaluated with Dix–Hallpike maneuvers. After that, and depending on the available resources, office or laboratory tests help to estimate the risk of falling and define the balance profile to guide the management of these patients. On the other hand, every acute patient should be evaluated with the HINTS protocol.

characterizations may help in designing more specific and efficient interventions. For instance, a patient lacking postural stability will require postural- and gait-focused therapy. Care should be taken in focusing therapy on ongoing symptoms rather than solely on testing abnormalities, as certain patients could require other treatments prior to benefit from VR, such as in the case of vestibular migraine, or visually induced dizziness, among others.

Importantly, spontaneous compensation strategies differ among patients (half of the population tend to rely on visual cues, while the other half rely on postural information), supporting the need for customized rehabilitation programs (30). Computerized dynamic posturography seems to allow such characterization, while being a reliable objective measurement of the "amount" of unbalance and risk of falling, and monitoring progress (30).

Initiatives using Internet resources and mobile devices to support adherence and the realization of rehabilitation exercises at home have been developed (60, 62). Other balance-improving treatments being currently explored include biofeedback devices worn all day, which give tactile or acoustic cues when the center of gravity is being lost, allowing the patient to react accordingly (63). In severe cases of bilateral VOR loss and inadequate compensation strategies, the role of vestibular implants (devices similar in their concept to cochlear implants) is beginning to be explored, and interventions have already been made in the first patients with satisfying functional outcomes (64).

Conclusion

Dizziness in the elderly remains a difficult subject, given the underlying factor of vestibular impairment due to aging in the form of presbystasis. The diagnostic and therapeutic approach must be multi-systemic and oriented to the visual, proprioceptive, and vestibular systems. BPPV and stroke (particularly in acute syndromes) should always be considered, given the frequency of the first and the severity of the latter.

Current vestibular testing allows a complete characterization of balance function and its deficits, and is becoming useful as a guide to planning treatment, where a cause-specific pathology is present, or presbystasis is the sole issue. Under this last condition, VR should be considered in the elderly where no other plausible balance disorder is suspected, in order to treat a probably symptomatic presbystasis. Here, resolution of symptomatology would confirm the assumed working hypothesis of presbystasis, while lack of progress would lead to further exploration of less common causes.

Future challenges on the subject include the further determination of vestibular impairment profiles and their specific VR alternatives, in order to achieve the shortest and most efficient therapy possible. However, research should also focus on preventive efforts to avoid falls. The threshold between what may be considered non-significant vestibular abnormalities and those correlating with a higher risk of falling should be better explored. This will inevitably lead to the establishment of a reasonable battery of (hopefully, bedside, low-cost, easy to interpret) examinations designed to rule out unacceptable risk for falling, in the fashion of the HINTS protocol for stroke.

Acknowledgments

Dr. PHD is funded by Fundación Guillermo Pulema.

References

1. Jonsson R, Sixt E, Landahl S, Rosenhall U. Prevalence of dizziness and vertigo in an urban elderly population. *J Vestib Res* (2004) **14**:47–52.
2. Barin K, Dodson EE. Dizziness in the elderly. *Otolaryngol Clin North Am* (2011) **44**:437–54. doi:10.1016/j.otc.2011.01.013
3. 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**:938–44. doi:10.1001/archinternmed.2009.66
4. Ekvall Hansson E, Magnusson M. Vestibular asymmetry predicts falls among elderly patients with multi-sensory dizziness. *BMC Geriatr* (2013) **13**:77. doi:10.1186/1471-2318-13-77
5. Kannus P, Parkkari J, Koskinen S, Niemi S, Palvanen M, Jarvinen M, et al. Fall-induced injuries and deaths among older adults. *JAMA* (1999) **281**:1895–9. doi:10.1001/jama.281.20.1895
6. Mueller M, Strobl R, Jahn K, Linkohr B, Peters A, Grill E. Burden of disability attributable to vertigo and dizziness in the aged: results from the KORA-Age study. *Eur J Public Health* (2014) **24**:802–7. doi:10.1093/eurpub/ckt171
7. Tuunainen E, Jantti P, Poe D, Rasku J, Toppila E, Pyykko I. Characterization of presbyequilibrium among institutionalized elderly persons. *Auris Nasus Larynx* (2012) **39**:577–82. doi:10.1016/j.anl.2011.12.004
8. Batuecas-Caletrio A, Trinidad-Ruiz G, Zschaeck C, Del Pozo De Dios JC, De Toro Gil L, Martin-Sanchez V, et al. Benign paroxysmal positional vertigo in the elderly. *Gerontology* (2013) **59**:408–12. doi:10.1159/000351204
9. Piker EG, Jacobson GP. Self-report symptoms differ between younger and older dizzy patients. *Otol Neurotol* (2014) **35**:873–9. doi:10.1097/MAO.0000000000000391
10. Tuunainen E, Poe D, Jantti P, Varpa K, Rasku J, Toppila E, et al. Presbyequilibrium in the oldest old, a combination of vestibular, oculomotor and postural deficits. *Aging Clin Exp Res* (2011) **23**:364–71. doi:10.3275/7623
11. Woo N, Kim SH. Sarcopenia influences fall-related injuries in community-dwelling older adults. *Geriatr Nurs* (2014) **35**:279–82. doi:10.1016/j.gerinurse.2014.03.001
12. Dagan E, Wolf M, Migirov LM. Why do geriatric patients attend otolaryngology emergency rooms? *Isr Med Assoc J* (2012) **14**:633–6.
13. Saber Tehrani AS, Kattah JC, Mantokoudis G, Pula JH, Nair D, Blitz A, et al. Small strokes causing severe vertigo: frequency of false-negative MRIs and nonlacunar mechanisms. *Neurology* (2014) **83**:169–73. doi:10.1212/wnl.0000000000000573
14. Johnsson LG. Degenerative changes and anomalies of the vestibular system in man. *Laryngoscope* (1971) **81**:1682–94. doi:10.1288/00005537-197110000-00016
15. Richter E. Quantitative study of human Scarpa's ganglion and vestibular sensory epithelia. *Acta Otolaryngol* (1980) **90**:199–208. doi:10.3109/00016488009131716
16. Merchant SN, Velazquez-Villasenor L, Tsuji K, Glynn RJ, Wall C III, Rauch SD. Temporal bone studies of the human peripheral vestibular system. Normative vestibular hair cell data. *Ann Otol Rhinol Laryngol Suppl* (2000) **181**:3–13.
17. Agrawal Y, Ward BK, Minor LB. Vestibular dysfunction: prevalence, impact and need for targeted treatment. *J Vestib Res* (2013) **23**:113–7. doi:10.3233/ves-130498
18. Davalos-Bichara M, Agrawal Y. Normative results of healthy older adults on standard clinical vestibular test. *Otol Neurotol* (2014) **35**:297–300. doi:10.1097/MAO.0b013e3182a09ca8
19. Li C, Layman AJ, Geary R, Anson E, Carey JP, Ferrucci L, et al. Epidemiology of vestibulo-ocular reflex function: data from the Baltimore longitudinal study of aging. *Otol Neurotol* (2015) **36**:267–72. doi:10.1097/MAO.0000000000000610
20. Agrawal Y, Davalos-Bichara M, Zuniga MG, Carey JP. Head impulse test abnormalities and influence on gait speed and falls in older individuals. *Otol Neurotol* (2013) **34**:1729–35. doi:10.1097/MAO.0b013e318295313c
21. Ishigaki H, Miyao M. Implications for dynamic visual acuity with changes in aged and sex. *Percept Mot Skills* (1994) **78**:363–9. doi:10.2466/pms.1994.78.2.363
22. Tuunainen E, Rasku J, Jantti P, Pyykko I. Risk factors of falls in community dwelling active elderly. *Auris Nasus Larynx* (2014) **41**:10–6. doi:10.1016/j.anl.2013.05.002
23. Fujimoto C, Egami N, Kinoshita M, Sugasawa K, Yamasoba T, Iwasaki S. Involvement of vestibular organs in idiopathic sudden hearing loss with vertigo: an analysis using oVEMP and cVEMP testing. *Clin Neurophysiol* (2015) **126**:1033–8. doi:10.1016/j.clinph.2014.07.028
24. Alvarez JC, Díaz C, Suárez C, Fernández JA, González del Rey C, Navarro A, et al. Neuronal loss in human medial vestibular nucleus. *Anat Rec* (1998) **251**:431–8. doi:10.1002/(SICI)1097-0185(199808)251:4<431::AID-AR2>3.3.CO;2-D
25. Yesmin T, Ara S, Umar BU, Rahman M, Afroz H, Sultana K, et al. Numbers of Purkinje cell with increasing age-a post mortem study. *Faridpur Med Coll J* (2011) **6**:92–4. doi:10.3329/fmcj.v6i2.9209
26. Tourtillott BM, Ferraro JA, Bani-Ahmed A, Almquist E, Deshpande N. Age-related changes in vestibular evoked myogenic potentials using a modified blood pressure manometer feedback method. *Am J Audiol* (2010) **19**:100–8. doi:10.1044/1059-0889(2010/10-0021)
27. Sun DQ, Zuniga MG, Davalos-Bichara M, Carey JP, Agrawal Y. Evaluation of a bedside test of utricular function – the bucket test – in older individuals. *Acta Otolaryngol* (2014) **134**:382–9. doi:10.3109/00016489.2013.867456
28. Alrwaily M, Whitney SL. Vestibular rehabilitation of older adults with dizziness. *Otolaryngol Clin North Am* (2011) **44**:473–96. doi:10.1016/j.otc.2011.01.015
29. Cabrera-Kang C, Tusa R. Vestibular rehabilitation: rationale and indications. *Semin Neurol* (2013) **33**:276–85. doi:10.1055/s-0033-1354593
30. 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**:49–57. doi:10.1016/j.neucli.2013.10.138
31. Newman-Toker DE, Cannon LM, Stofferahn ME, Rothman RE, Hsieh YH, Zee DS. Imprecision in patient reports of dizziness symptom quality: a cross-sectional study conducted in an acute care setting. *Mayo Clin Proc* (2007) **82**:1329–40. doi:10.4065/82.11.1329
32. Lawson J, Fitzgerald J, Birchall J, Aldren CP, Kenny RA. Diagnosis of geriatric patients with severe dizziness. *J Am Geriatr Soc* (1999) **47**:12–7. doi:10.1111/j.1532-5415.1999.tb01895.x
33. Kerber KA, Brown DL, Lisabeth LD, Smith MA, Morgenstern LB. Stroke among patients with dizziness, vertigo, and imbalance in the emergency department: a population-based study. *Stroke* (2006) **37**:2484–7. doi:10.1161/01.STR.0000240329.48263.0d
34. Enrietto JA, Jacobson KM, Baloh RW. Aging effects on auditory and vestibular responses: a longitudinal study. *Am J Otolaryngol* (1999) **20**:371–8. doi:10.1016/S0196-0709(99)90076-5
35. Bruner A, Norris TW. Age-related changes in caloric nystagmus. *Acta Otolaryngol Suppl* (1971) **282**:1–24.
36. Mulch G, Petermann W. Influence of age on results of vestibular function tests. Review of literature and presentation of caloric test results. *Ann Otol Rhinol Laryngol Suppl* (1979) **88**:1–17.
37. MacDougall H, Weber K, McGarvie LA, Halmagyi GM, Curthoys IS. The video head impulse test: diagnostic accuracy in peripheral vestibulopathy. *Neurology* (2009) **73**:1134–41. doi:10.1212/WNL.0b013e3181bacf85
38. Brantberg K. Vestibular evoked myogenic potentials (VEMPs): usefulness in clinical neurotology. *Semin Neurol* (2009) **29**:541–7. doi:10.1055/s-0029-1241042
39. Soto-Varela A, Faraldo-Garcia A, Rossi-Izquierdo M, Lirola-Delgado A, Vaamonde-Sanchez-Andrade I, Del-Rio-Valeiras M, et al. Can we predict the risk of falls in elderly patients with instability? *Auris Nasus Larynx* (2015) **42**(1):8–14. doi:10.1016/j.anl.2014.06.005
40. Curthoys I, Topple A, Halmagyi G. Unilateral vestibular deafferentation (UVD) causes permanent asymmetry in the gain of the yaw VOR to high acceleration head impulses in guinea pigs. *Acta Otolaryngol Suppl* (1995) **520**:59–61. doi:10.3109/00016489509125190
41. Curthoys I. The interpretation of clinical tests of peripheral vestibular function. *Laryngoscope* (2012) **122**:1342–52. doi:10.1002/lary.23258
42. Cohen HS, Mulavara AP, Peters BT, Sangi-Haghpeykar H, Bloomberg JJ. Standing balance tests for screening people with vestibular impairments. *Laryngoscope* (2014) **124**:545–50. doi:10.1002/lary.24314
43. Kattah JC, Talkad AV, Wang DZ, Hsieh YH, Newman-Toker DE. HINTS to diagnose stroke in the acute vestibular syndrome: three-step bedside oculomotor examination more sensitive than early MRI diffusion-weighted imaging. *Stroke* (2009) **40**:3504–10. doi:10.1161/STROKEAHA.109.551234

44. Oppenheim C, Stanescu R, Dormont D, Crozier S, Marro B, Samson Y, et al. False-negative diffusion-weighted MR findings in acute ischemic stroke. *AJNR Am J Neuroradiol* (2000) **21**:1434–40.
45. Edlow JA, Newman-Toker DE, Savitz SI. Diagnosis and initial management of cerebellar infarction. *Lancet Neurol* (2008) **7**:951–64. doi:10.1016/S1474-4422(08)70216-3
46. Newman-Toker D, Saber A, Mantokoudis G, Pula JH, Guede CI, Kerber KA, et al. Quantitative video-oculography to help diagnose stroke in acute vertigo and dizziness – toward an ECG for the eyes. *Stroke* (2013) **44**:1158–61. doi:10.1161/STROKEAHA.111.000033
47. Lo AX, Harada CN. Geriatric dizziness: evolving diagnostic and therapeutic approaches for the emergency department. *Clin Geriatr Med* (2013) **29**:181–204. doi:10.1016/j.cger.2012.10.004
48. Pardal Refoyo JL, Perez Plasencia D, Beltran Mateos LD. [Ischemia of the anterior vestibular artery (Lindsay-Hemenway syndrome). Review and comments]. *Acta Otorrinolaringol Esp* (1998) **49**:599–602.
49. Furman JM, Balaban CD. Vestibular migraine. *Ann N Y Acad Sci* (2015) **1343**:90–6. doi:10.1111/nyas.12645
50. Paul NLM, Simoni M, Rothwell PM. Transient isolated brainstem symptoms preceding posterior circulation stroke: a population-based study. *Lancet Neurol* (2013) **12**:65–71. doi:10.1016/s1474-4422(12)70299-5
51. Strupp M, Kremmyda O, Adamczyk C, Bottcher N, Muth C, Yip CW, et al. Central ocular motor disorders, including gaze palsy and nystagmus. *J Neurol* (2014) **261**(Suppl 2):S542–58. doi:10.1007/s00415-014-7385-9
52. Shoair OA, Nyandege AN, Slattum PW. Medication-related dizziness in the older adult. *Otolaryngol Clin North Am* (2011) **44**:455–71. doi:10.1016/j.otc.2011.01.014
53. Gloria-Cruz TI, Schachern PA, Paparella MM, Adams GL, Fulton SE. Metastases to temporal bones from primary nonsystemic malignant neoplasms. *Arch Otolaryngol Head Neck Surg* (2000) **126**:209–14. doi:10.1001/archotol.126.2.209
54. Alvo A, Miranda G, Delano PH. Imaging case of the month: metastatic prostate adenocarcinoma presenting as hearing loss and disequilibrium. *Otol Neurotol* (2012) **33**:e79–80. doi:10.1097/MAO.0b013e3182713c4a
55. Staab JP. Chronic dizziness: the interface between psychiatry and neuro-otology. *Curr Opin Neurol* (2006) **19**:41–8. doi:10.1097/01.wco.0000198102.95294.1f
56. Bhattacharyya N, Baugh RF, Orvidas L, Barrs D, Bronston LJ, Cass S, et al. Clinical practice guideline: benign paroxysmal positional vertigo. *Otolaryngol Head Neck Surg* (2008) **139**:S47–81. doi:10.1016/j.otohns.2008.08.022
57. Strupp M, Brandt T. Vestibular neuritis. *Semin Neurol* (2009) **29**:509–19. doi:10.1055/s-0029-1241040
58. Strupp M, Zingler V, Arbusow V, Nicklas D, Maag K, Dieterich M, et al. Methylprednisolone, valacyclovir or the combination for vestibular neuritis. *N Engl J Med* (2004) **351**:354–9. doi:10.1056/NEJMoa033280
59. Jung JY, Kim JS, Chung PS, Woo SH, Rhee CK. Effect of vestibular rehabilitation on dizziness in the elderly. *Am J Otolaryngol* (2009) **30**:295–9. doi:10.1016/j.amjoto.2008.06.013
60. Huang K, Sparto PJ, Kiesler S, Siewiorek DP, Smailagic A. iPod-based in-home system for monitoring gaze-stabilization exercise compliance of individuals with vestibular hypofunction. *J Neuroeng Rehabil* (2014) **11**:69. doi:10.1186/1743-0003-11-69
61. Howe TE, Rochester L, Neil F, Skelton DA, Ballinger C. Exercise for improving balance in older people. *Cochrane Database Syst Rev* (2011) **11**:CD004963. doi:10.1002/14651858.CD004963.pub3
62. Geraghty AW, Kirby S, Essery R, Little P, Bronstein A, Turner D, et al. Internet-based vestibular rehabilitation for adults aged 50 years and over: a protocol for a randomised controlled trial. *BMJ Open* (2014) **4**:e005871. doi:10.1136/bmjopen-2014-005871
63. Horak F, King L, Mancini M. Role of body-worn movement monitor technology for balance and gait rehabilitation. *Phys Ther* (2015) **95**:461–70. doi:10.2522/ptj.20140253
64. Pelizzone M, Fornos AP, Guinand N, Van De Berg R, Kos I, Stokroos R, et al. First functional rehabilitation via vestibular implants. *Cochlear Implants Int* (2014) **15**(Suppl 1):S62–4. doi:10.1179/1467010014z.000000000165

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.

frontiers in Neurology

MINI REVIEW
published: 22 September 2015
doi: 10.3389/fneur.2015.00205

The effects of aging on clinical vestibular evaluations

Maxime Maheu[1,2], *Marie-Soleil Houde*[1], *Simon P. Landry*[1,2] *and François Champoux*[1,2]*

[1] *École d'orthophonie et d'audiologie, Université de Montréal, Montréal, QC, Canada,* [2] *Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain (CRIR), Institut Raymond-Dewar (IRD), Montréal, QC, Canada*

Balance disorders are common issues for aging populations due to the effects of normal aging on peripheral vestibular structures. These changes affect the results of vestibular function evaluations and make the interpretation of these results more difficult. The objective of this article is to review the current state of knowledge of clinically relevant vestibular measures. We will first focus on otolith function assessment methods cervical-VEMP (cVEMP) and ocular-VEMP (oVEMP), then the caloric and video-head impulse test (vHIT) methods for semicircular canals assessment. cVEMP and oVEMP are useful methods, though research on the effects of age for some parameters are still inconclusive. vHIT results are largely independent of age as compared to caloric stimulation and should therefore be preferred for the evaluation of the semicircular canals function.

Keywords: VEMP, vHIT, caloric vestibular stimulation, vestibular function tests, aging

OPEN ACCESS

Edited by:
Yuri Agrawal,
Johns Hopkins University, USA

Reviewed by:
Americo Migliaccio,
Neuroscience Research Australia, Australia
Toshihisa Murofushi,
Teikyo University School of Medicine, Japan

***Correspondence:**
François Champoux,
École d'Orthophonie et d'Audiologie, Faculté de Médecine, Université de Montréal, C.P. 6128, Succursale Centre-Ville, Montréal, QC H3C 3J7, Canada
francois.champoux@umontreal.ca

Specialty section:
This article was submitted to Neuro-otology, a section of the journal Frontiers in Neurology

Received: *03 August 2015*
Accepted: *07 September 2015*
Published: *22 September 2015*

Citation:
Maheu M, Houde M-S, Landry SP and Champoux F (2015) The effects of aging on clinical vestibular evaluations. Front. Neurol. 6:205. doi: 10.3389/fneur.2015.00205

Introduction

With the accelerating aging of the global population, age-related health issues are becoming a growing concern (1). Increased risks of falls from loss of balance are among these health concerns (2) and are considered by the WHO as an important burden on both the health care system and health of the population (3). Vestibular information, which provides information related to static and dynamic position in space, is known to play a major role in balance (4). Better understanding of the effects of aging on the vestibular system can thus be beneficial in addressing risks of fall in an aging population.

The vestibular system is located in the inner ear and is composed of three semicircular canals (lateral, anterior, and posterior) that detect angular acceleration and two otolith organs (saccule and utricule) that detect gravity (5). Information from the saccule and the posterior semicircular canal projects to central vestibular pathways mostly through the inferior vestibular nerve. Information from the utricule, the lateral, and the anterior semicircular canals mostly projects through the superior vestibular nerve (5) and primarily reaches the vestibular nuclei (5).

The integrity of these vestibular structures is essential for normal balance. Investigations on the vestibular system and aging have revealed reductions in many vestibular structures, including otoconia in both otolith organs (6, 7), vestibular hair cells in the horizontal crista ampullaris (8), scarpa ganglion neurons (9–11), and vestibular nuclei neurons (12, 13).

The objective of this article is to review the current state of knowledge of clinically relevant vestibular measures part of a comprehensive assessment protocol. Indeed, with the aging population and the increasing data from scientific research, it is becoming crucial to take a critical look at the effects of aging on clinical test results to gain insight on best practices for clinical vestibular evaluation in an elderly population.

Comprehensive Assessment of the Vestibular System

Healthcare professionals such as audiologists frequently perform vestibular testing. These evaluations are done to detect vestibular deficits in order to improve vestibular compensation and to reduce both dizziness and unsteadiness. A comprehensive clinical test battery should include appropriate techniques to assess the otolith organs and the semicircular canals.

The vestibular-evoked myogenic potential (VEMP) is an electrophysiological technique used to assess otolith function and can be evoked using different stimuli, such as sounds, vibrations, and electrical stimulations (14–17). Two responses can be evoked using VEMP: ocular-VEMP (*oVEMP*) and cervical-VEMP (*cVEMP*).

The cVEMP is an inhibitory response measured from the ipsilateral sternocleidomastoïd muscle and originates from the saccule (16, 18). The inhibition response is measured from the first positive peak occurring around 13 ms (p13 or P1) followed by a negative peak around 23 ms (n23 or N1).

The oVEMP is an excitatory response of the inferior oblique eye muscle contralateral to the stimulated ear and is thought to originate from the utricle (18, 19). The oVEMP response is composed of a negative peak occurring at around 11–12 ms (N1) and positive peak occurring at around 18 ms (P1) (20). These responses have been found to be robust indicators of vestibular system integrity and are independent from hearing abilities (21, 22).

Caloric stimulation is a commonly used clinical vestibular evaluation method that induces a movement of the endolymph within the horizontal semicircular canal by applying either warm or cold water or air to the external ear canal (23). Despite its wide clinical use, the mechanisms underlying caloric stimulation are contested [for more details see Ref. (24)].

The video-head impulse test (vHIT) is a more recent technique for the functional assessment of all six semicircular canals (25). This latest vestibular clinical assessment tool uses an infrared camera designed to track pupillary movement and a patient-worn gyroscope mounted on goggles (26). Gain, the vHIT's output, is calculated by comparing eye and head velocity during fast head movements in each of the six semicircular canals' planes (25, 26). vHIT can provide useful information in the assessment of semicircular canal function through the vestibulo-ocular reflex (VOR) (25, 27). Measurement of the vertical canal function is based on the 2D modified HIT technique (28). This method yields higher gains for the vertical canals than the 3D HIT coil technique. vHIT is highly sensitive to calibration error. This can lead to erroneous calculation of gain magnitude and make comparison between studies difficult.

Effects of Aging and Vestibular Evaluation Techniques

Evaluation of Otolith Function

The effects of normal aging on VEMP responses have been analyzed for different parameters, such as peak-to-peak amplitude [the difference between both components (microvolt)], latency [time of occurrence of both components (millisecond)], thresholds [lowest intensity of a stimuli to trigger a response], response rate [prevalence of a VEMP response (%)], and asymmetry ratio [difference in amplitude between individual ears].

cVEMP and Aging

One of the most widely observed effects of aging with cVEMP is a decrease in recorded amplitude (15, 19, 29–35). Indeed, this decrease has been reported to happen at a rate of 0.14 μV per decade (31) and is independent of the stimulus used (35). On the other hand, cVEMP thresholds have been observed to remain steady up to 50 years of age (15) and then progressively increase (15, 19, 34). This increase has been reported for click and tone burst stimulations (12). Though the majority of studies report no significant effect of age on cVEMP latencies (19, 31, 33, 35), few authors have observed age-related increased latency on the p13 (15, 34) and n23 (9), while other have reported age-related decreases to n23 (24). cVEMP response rates are widely reported to decrease with age. However, the age at which this happens is still contested. Some report a response rate of 100% for participants <65 years old followed by a rapid decline (32), while others have observed a progressive decline starting at 50 years old (15).

oVEMP and Aging

Numerous studies have reported a decrease in oVEMP amplitude related to age (19, 29, 31, 33, 35–37). More specifically, oVEMP amplitude has been reported to decrease by 2.9 μV per decade, independent of the stimulus used (19, 29, 31, 33, 36, 37). Normal aging has been reported to increase oVEMP thresholds (12). Most studies report significant increases in oVEMP latency with age (19, 31, 33, 36, 37). This increase has been reported to be significant after 60 years of age (36) and at a rate of 0.12 ms per decade (31). Interestingly, it has been suggested that this increase is only significant in men (33). To the best of our knowledge, only one study did not report any significant difference in oVEMP latencies between age groups (35). oVEMP response rate has been shown to decrease with normal aging (36, 37) but can be dependent on the method of stimulus presentation used (36). A significant reduction in response rate for participants over 60 years of age can be measured when stimuli are presented by bone conduction though no significant differences in response rate were found for galvanic stimulation.

Evaluation of Semicircular Canal Function

Caloric and Aging

Caloric stimulation output is based on the slow-phase movement of the eyes during caloric evoked nystagmus. Few recent researches have looked at the effects of aging on caloric stimulation. Investigations on the effects of normal aging on caloric response found a significant increase in response for middle-aged groups followed by a slow decline with increasing age (32, 38, 39). However, this difference was only noted for the warm irrigation (32, 39). Despite these results suggesting an effect of aging on caloric responses, some investigations have failed to uncover any age-related differences (40, 41).

TABLE 1 | Effects of aging on clinical vestibular evaluation techniques.

Evaluation technique	Parameter	Effect of aging	Reference
cVEMP	Amplitude	Decrease	(15, 19, 29–35)
	Thresholds	Increase	(15, 19, 34)
	Latencies	Inconclusive	(15, 19, 31–35)
	Response rate	Inconclusive	(15, 32)
oVEMP	Amplitude	Decrease	(19, 29, 31, 33, 35–37)
	Thresholds	Increase	(19)
	Latencies	Increase[a]	(19, 31, 33, 36, 37)
	Response rate	Inconclusive	(36, 37)
Caloric	Slow-phase velocity	Inconclusive	(38–41, 47)
vHIT	Gain	No significant effect[b]	(32, 42–46)

[a] *Possible gender effect.*
[b] *Decrease at high rotary velocities.*

vHIT and Aging

Recent advances in eye-tracking technology have led to the development of the vHIT. Numerous methods exist to calculate vHIT gain. The studies described in this review divided the area under the eye velocity curve by the area under the head velocity curve (42). In healthy adults, gain is typically between 0.8 and 1.2 (26). Investigations on the effects of aging on vHIT gain have only suggested a minor effect (26, 42–44). However, a higher head rotation velocity can elicit significant differences after 70 years old (45, 46). The decline in gain per decade has been suggested to be 0.012 (45) and significant gain differences have only been found beginning at 90 years of age (45). Till now, research on the effects of aging on vHIT has primarily investigated the effect of aging on the horizontal semicircular canals. To the best of our knowledge, only one study assessed the effect of age on vertical canals (42). The authors found that age did not influence vHIT response for anterior canals and gain only slightly decreased with age for the posterior canals.

Discussion

Current clinical vestibular evaluation methods provide information on the integrity of the peripheral vestibular system. Understanding results from these evaluations in the context of normal aging is crucial to properly diagnosing vestibular disorders. Despite the well-known effects of aging on the peripheral vestibular system (6, 8), the effects of normal aging on vestibular evaluations, as highlighted by this review, is of yet a largely contested field (see **Table 1**). Understanding these effects has important clinical implications to help delineate various vestibular pathologies in an aging population.

From the existing research, it is possible to propose guidelines for the use of clinical vestibular evaluations in an aging population. For instance, cVEMP is a useful tool to evaluate saccule function and the inferior vestibular nerve for the elderly when used with precaution. Reduced amplitude is reported with aging but these parameters should still be considered valuable, especially as amplitude asymmetry ratios are shown to remain stable with age (31, 35). Despite their inconsistencies in research, latencies can also be valuable complementary parameters. In fact, as most studies report no significant change in cVEMP latencies parameters, a change in latency should not be attributed to aging and should draw the attention of the clinician (19, 31, 33, 35). Taken together, these last two parameters can allow clinicians to identify vestibular pathologies using cVEMP without significant age-related interference.

Ocular-VEMP can be a useful evaluation method for utricule function and superior vestibular nerve integrity if it is used attentively. Similarly to cVEMP, amplitude remains a valid parameter for oVEMP evaluation as there is no significant asymmetry despite a strong decrease (31). Latencies must be considered with caution as multiple investigations have reported significant age-related increases (19, 31, 33, 36, 37). It has also been suggested that this increase in latency is exclusive to men (33). We therefore propose the use of clinician-established evaluation norms taking age and gender into account.

On the other hand, caloric testing should be used with precaution for an aging population. Till now, there is debate surrounding the mechanisms underlying caloric responses (47). Therefore, non-vestibular factors beyond normal aging could influence the results (40). The lack of unanimity for caloric responses in relation to age, combined with the debate surrounding the mechanisms underlying this method (47), are indicators that caloric testing still requires investigation before conclusive opinions on the effects of aging can be drawn.

We propose that vHIT is the preferable method to evaluate the vestibular canals in an aging population, although some precaution is needed regarding neck stiffness to avoid neck injuries. Results from vHIT appear to be largely independent of normal aging (45, 46) as only the posterior semicircular canal demonstrates a slight decrease in gain with increasing age (42). Therefore, semicircular canal function of older patients should be evaluated using vHIT. However, further studies are needed to measure the effect of aging for vHIT on the vertical semicircular canals.

Conclusion

This review provided an overlook for the existing literature for the effects of aging on clinical vestibular evaluations. Of the most popular evaluation methods, vHIT is largely independent of age and should be preferred over caloric to evaluate semicircular function. This recommendation is due to a lack of understanding of the underlying mechanisms of caloric stimulation and the inconstant reported effects of aging. cVEMP and oVEMP are also useful methods, though it should be kept in mind that research on the effects of aging are still inconclusive for some parameters.

Funding

This work was supported by grants from the Fonds de Recherche du Québec – Santé (FRQS).

References

1. Lutz W, Sanderson W, Scherbov S. The coming acceleration of global population ageing. *Nature* (2008) **451**:716–9. doi:10.1038/nature06516
2. Iwasaki S, Yamasoba T. Dizziness and imbalance in the elderly: age-related decline in the vestibular system. *Aging Dis* (2014) **6**:38–47. doi:10.14336/AD.2014.0128
3. World Health Organization. *WHO Global Report on Falls Prevention in Older Age*. France: WHO Press (2007). 47 p.
4. Cullen KE. The vestibular system: multimodal intergration and encoding of self-motion for motor control. *Trends Neurosci* (2012) **35**:185–96. doi:10.1016/j.tins.2011.12.001
5. Baloh R, Honrubia V, Kerber KA. *Clinical Neurophysiology of the Vestibular System*. 4th ed. New York, NY: Oxford University Press (2011). 455 p.
6. Walther LE, Westhofen M. Presbyvertigo-aging of otoconia and vestibular sensory cells. *J Vestib Res* (2007) **17**:89–92.
7. Igarashi M, Saito R, Mizukoshi K, Alford BR. Otoconia in young and elderly persons: a temporal bone study. *Acta Otolaryngol Suppl* (1993) **504**:26–9. doi:10.3109/00016489309128117
8. Lopez I, Ishiyama G, Tang Y, Tokita J, Baloh RW, Ishiyama A. Regional estimates of hair cells and supporting cells in the human crista ampullaris. *J Neurosci Res* (2005) **82**:421–31. doi:10.1002/jnr.20652
9. Velázquez-Villaseñor L, Merchant SN, Tsuji K, Glynn RJ, Wall C III, Rauch SD. Temporal bone studies of the human peripheral vestibular system. Normative Scarpa's ganglion cell data. *Ann Otol Rhinol Laryngol Suppl* (2000) **181**:14–9.
10. Park JJ, Tang Y, Lopez I, Ishiyama A. Age-related change in the number of neurons in the human vestibular ganglion. *J Comp Neurol* (2001) **431**:437–43. doi:10.1002/1096-9861(20010319)431:4<437::AID-CNE1081>3.0.CO;2-P
11. Richter E. Quantitative study of human Scarpa's ganglion and vestibular sensory epithelia. *Acta Otolaryngol* (1980) **90**:199–208. doi:10.3109/00016488009131716
12. Alvarez JC, Díaz C, Suárez C, Fernández JA, González del Rey C, Navarro A, et al. Aging and the human vestibular nuclei: morphometric analysis. *Mech Ageing Dev* (2000) **114**:149–72. doi:10.1016/S0047-6374(00)00098-1
13. Lopez I, Honrubia V, Baloh RW. Aging and the human vestibular nucleus. *J Vestib Res* (1997) **7**:77–85. doi:10.1016/S0957-4271(96)00137-1
14. Zhou G, Kenna MA, Stevens K, Licameli G. Assessment of saccular function in children with sensorineural hearing loss. *Arch Otolaryngol Head Neck Surg* (2009) **135**:40–4. doi:10.1001/archoto.2008.508
15. Singh NK, Kashyap RS, Supreetha L, Sahana V. Characterization of age-related changes in sacculocolic response parameters assessed by cervical vestibular evoked myogenic potentials. *Eur Arch Otorhinolaryngol* (2014) **7**:1869–77. doi:10.1007/s00405-013-2672-0
16. 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
17. Papathanasiou ES, Murofushi T, Akin FW, Colebatch JG. International guidelines for the clinical application of cervical vestibular evoked myogenic potentials: an expert consensus report. *Clin Neurophysiol* (2014) **125**:658–66. doi:10.1016/j.clinph.2013.11.042
18. Curthoys IS. A critical review of the neurophysiological evidence underlying clinical vestibular testing using sound, vibration and galvanic stimuli. *Clin Neurophysiol* (2010) **121**:132–44. doi:10.1016/j.clinph.2009.09.027
19. Rosengren SM, Govender S, Colebatch JG. Ocular and cervical vestibular evoked myogenic potentials produced by air- and bone-conducted stimuli: comparative properties and effects of age. *Clin Neurophysiol* (2011) **122**:2282–9. doi:10.1016/j.clinph.2011.04.001
20. Welgampola MS, Colebatch JG. Characteristics and clinical applications of vestibular-evoked myogenic potentials. *Neurology* (2005) **24**:1682–8. doi:10.1212/01.WNL.0000161876.20552.AA
21. Colebatch JG, Halmagyi GM. Vestibular evoked potentials in human neck muscles before and after unilateral vestibular deafferentation. *Neurology* (1992) **42**:1635–6. doi:10.1212/WNL.42.8.1635
22. Colebatch JG, Halmagyi GM, Skuse NF. Myogenic potentials generated by a click-evoked vestibulocollic reflex. *J Neurol Neurosurg Psychiatry* (1994) **57**:190–7. doi:10.1136/jnnp.57.2.190
23. Gonçalves DU, Felipe L, Lima TM. Interpretation and use of caloric testing. *Braz J Otorhinolaryngol* (2008) **74**:440–6. doi:10.1590/S0034-72992008000300020
24. Stahle J. Controversies on the caloric response. From Bárány's theory to studies in microgravity. *Acta Otolaryngol* (1990) **109**:162–7. doi:10.3109/00016489009107430
25. Macdougall HG, McGarvie LA, Halmagyi GM, Curthoys IS, Weber KP. The video head impulse test (vHIT) detects vertical semicircular canal dysfunction. *PLoS One* (2013) **8**:e61488. doi:10.1371/journal.pone.0061488
26. Patterson JN, Bassett AM, Mollak CM, Honaker JA. Effects of hand placement technique on the video head impulse test (vHIT) in younger and older adults. *Otol Neurotol* (2015) **36**:1061–8. doi:10.1097/MAO.0000000000000749
27. Weber KP, MacDougall HG, Halmagyi GM, Curthoys IS. Impulsive testing of semicircular-canal function using video-oculography. *Ann N Y Acad Sci* (2009) **1164**:486–91. doi:10.1111/j.1749-6632.2008.03730.x
28. Migliaccio AA, Cremer PD. The 2D modified head impulse test: a 2D technique for measuring function in all six semi-circular canals. *J Vestib Res* (2011) **21**:227–34. doi:10.3233/VES-2011-0421
29. Agrawal Y, Zuniga MG, Davalos-Bichara M, Schubert MC, Walston JD, Hughes J, et al. Decline in semicircular canal and otolith function with age. *Otol Neurotol* (2012) **33**:832–9. doi:10.1097/MAO.0b013e3182545061
30. Akin FW, Murnane OD, Tampas JW, Clinard CG. The effect of age on the vestibular evoked myogenic potential and sternocleidomastoid muscle tonic electromyogram level. *Ear Hear* (2011) **32**:617–22. doi:10.1097/AUD.0b013e318213488e
31. Li C, Layman AJ, Carey JP, Agrawal Y. Epidemiology of vestibular evoked myogenic potentials: data from the Baltimore Longitudinal Study of Aging. *Clin Neurophysiol* (2015). doi:10.1016/j.clinph.2015.01.008
32. Maes L, Dhooge I, D'Haenens W, Bockstael A, Keppler H, Philips B, et al. The effect of age on the sinusoidal harmonic acceleration test, pseudo-random rotation test, velocity step test, caloric test, and vestibular-evoked myogenic potential test. *Ear Hear* (2010) **31**:84–94. doi:10.1097/AUD.0b013e3181b9640e
33. Layman AJ, Li C, Simonsick E, Ferrucci L, Carey JP, Agrawal Y. Association between saccular function and gait speed: data from the Baltimore Longitudinal Study of Aging. *Otol Neurotol* (2015) **36**:260–6. doi:10.1097/MAO.0000000000000544
34. Maleki M, Jafari Z, Zarrinkoob H, Akbarzadeh Baghban A. Effect of aging on saccular function. *Med J Islam Repub Iran* (2014) **28**:117.
35. Nguyen KD, Welgampola MS, Carey JP. Test-retest reliability and age-related characteristics of the ocular and cervical vestibular evoked myogenic potential tests. *Otol Neurotol* (2010) **31**:793–802. doi:10.1097/MAO.0b013e3181e3d60e
36. Chang CM, Young YH, Cheng PW. Age-related changes in ocular vestibular-evoked myogenic potentials via galvanic vestibular stimulation and bone-conducted vibration modes. *Acta Otolaryngol* (2012) **132**:1295–300. doi:10.3109/00016489.2012.708437
37. Tseng CL, Chou CH, Young YH. Aging effect on the ocular vestibular-evoked myogenic potentials. *Otol Neurotol* (2010) **31**:959–63. doi:10.1097/MAO.0b013e3181e8fb1a
38. van der Laan FL, Oosterveld WJ. Age and vestibular function. *Aerosp Med* (1974) **45**:540–7.
39. Bruner A, Norris TW. Age-related changes in caloric nystagmus. *Acta Otolaryngol Suppl* (1971) **282**:1–24.
40. Mallinson AI, Longridge NS. Caloric response does not decline with age. *J Vestib Res* (2004) **14**:393–6.
41. Zapala DA, Olsholt KF, Lundy LB. A comparison of water and air caloric responses and their ability to distinguish between patients with normal and impaired ears. *Ear Hear* (2008) **29**:585–600. doi:10.1097/AUD.0b013e3181734ed0
42. McGarvie LA, MacDougall HG, Halmagyi GM, Burgess AM, Weber KP, Curthoys IS. The video head impulse test (vHIT) of semicircular canal function – age-dependent normative values of VOR gain in healthy subjects. *Front Neurol* (2015) **6**:154. doi:10.3389/fneur.2015.00154
43. MacDougall HG, Weber KP, McGarvie LA, Halmagyi GM, Curthoys IS. The video head impulse test: diagnostic accuracy in peripheral vestibulopathy. *Neurology* (2009) **73**:1134–41. doi:10.1212/WNL.0b013e3181bacf85
44. Batuecas-Caletrio A, Klumpp M, Santacruz-Ruiz S, Gonzalez FB, Sánchez EG, Arriaga M. Vestibular function in cochlear implantation: correlating objectiveness and subjectiveness. *Laryngoscope* (2015). doi:10.1002/lary.25299

45. Matino-Soler E, Esteller-More E, Martin-Sanchez JC, Martinez-Sanchez JM, Perez-Fernandez N. Normative data on angular vestibulo-ocular responses in the yaw axis measured using the video head impulse test. *Otol Neurotol* (2015) **36**:466–71. doi:10.1097/MAO.0000000000000661
46. Mossman B, Mossman S, Purdie G, Schneider E. Age dependent normal horizontal VOR gain of head impulse test as measured with video-oculography. *J Otolaryngol Head Neck Surg* (2015) **44**:29. doi:10.1186/s40463-015-0081-7
47. Barin K. Interpretation and usefullness of caloric testing. 2nd ed. In: Jacobson G, Shepard N, editors. *Balance Function Assessment and Management*. San Diego: Plural Publishing (2014). p. 319–47.

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 24 December 2015
doi: 10.3389/fneur.2015.00268

Prevalence of Vestibular Disorder in Older People Who Experience Dizziness

*Allan T. Chau[1], Jasmine C. Menant[1], Patrick P. Hübner[1], Stephen R. Lord[1] and Americo A. Migliaccio[1,2]**

[1] Neuroscience Research Australia, University of New South Wales, Sydney, NSW, Australia, [2] Department of Otolaryngology – Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Dizziness and imbalance are clinically poorly defined terms, which affect ~30% of people over 65 years of age. In these people, it is often difficult to define the primary cause of dizziness, as it can stem from cardiovascular, vestibular, psychological, and neuromuscular causes. However, identification of the primary cause is vital in determining the most effective treatment strategy for a patient. Our aim is to accurately identify the prevalence of benign paroxysmal positional vertigo (BPPV), peripheral, and central vestibular hypofunction in people aged over 50 years who had experienced dizziness within the past year. Seventy-six participants aged 51–92 (mean ± SD = 69 ± 9.5 years) were tested using the head thrust dynamic visual acuity (htDVA) test, dizziness handicap inventory (DHI), as well as sinusoidal and unidirectional rotational chair testing, in order to obtain data for htDVA score, DHI score, sinusoidal (whole-body, 0.1–2 Hz with peak velocity at 30°/s) vestibulo-ocular reflex (VOR) gain and phase, transient (whole-body, acceleration at 150°/s^2 to a constant velocity rotation of 50°/s) VOR gain and time constant (TC), optokinetic nystagmus (OKN) gain, and TC (whole-body, constant velocity rotation at 50°/s). We found that BPPV, peripheral and central vestibular hypofunction were present in 38 and 1% of participants, respectively, suggesting a likely vestibular cause of dizziness in these people. Of those with a likely vestibular cause, 63% had BPPV; a figure higher than previously reported in dizziness clinics of ~25%. Our results indicate that htDVA, sinusoidal (particularly 0.5–1 Hz), and transient VOR testing were the most effective at detecting people with BPPV or vestibular hypofunction, whereas DHI and OKN were effective at only detecting non-BPPV vestibular hypofunction.

Keywords: aged, postural balance, vestibular function tests, benign paroxysmal positional vertigo, peripheral and central vestibular function

OPEN ACCESS

Edited by:
Sergio Carmona, Instituto de Neurociencias de Buenos Aires, Argentina

Reviewed by:
Nicolas Perez, University of Navarra, Spain
Giacinto Asprella-Libonati, Giovanni Paolo II Hospital ASM POLICORO, Italy

***Correspondence:**
Americo A. Migliaccio
a.migliaccio@neura.edu.au

Specialty section:
This article was submitted to Neuro-otology, a section of the journal Frontiers in Neurology

Received: *02 September 2015*
Accepted: *10 December 2015*
Published: *24 December 2015*

Citation:
Chau AT, Menant JC, Hübner PP, Lord SR and Migliaccio AA (2015) Prevalence of Vestibular Disorder in Older People Who Experience Dizziness. Front. Neurol. 6:268. doi: 10.3389/fneur.2015.00268

INTRODUCTION

The vestibular system detects and initiates responses to changes in sensations of equilibrium. Disorder in any part of this system, typically occurring due to aging or injury, results in dizziness and imbalance, which contributes to an increased risk of falls (1). Injury to the vestibular system due to trauma, disease, or ototoxic drugs is often localized, e.g., to the peripheral component, whereas injury through aging is thought to affect the vestibular system as a whole. While structural changes within the vestibular system as a whole have been observed due to aging, associations between these

changes and dizziness (visual stability), imbalance, gait disturbances, and falls has yet to be established (2), and it is not clear whether the prevalence of dizziness and imbalance in the elderly of ~30% (3) is primarily due to psychological, cardiovascular, muscular, or vestibular system degeneration.

One component of the vestibular system is the angular vestibulo-ocular reflex (VOR), which is responsible for stable vision during head motion by rotating the eyes in the opposite direction to head rotation to maintain gaze and images stationary on the retina. The cristae ampullaris of the semicircular canals, which sense angular head rotations, displays the most profound degeneration in the vestibular end organ, where there is a 40% decrease in hair cells for all canals by age 80 (4–6). Cristae type I hair cell loss with advancing age occurs at twice the rate of the macule, whereas for type II hair cells, it is at the same rate for all five sense organs – the decline is roughly linear with age for both types (5, 6). However, previous studies examining the effect of aging on the angular VOR have been conflicting in their findings. Upon stimulation of the VOR via sinusoidal rotation testing, gain values (gain = eye velocity/head velocity; the ideal gain of the VOR during typical viewing is equal to unity) were shown to decrease with age, whereas phase shift (the difference in time between ideal eye velocity for head movement compensation and actual eye velocity) (7) has generally been demonstrated to increase with age. However, the testing conditions under which these changes were observed were not the same, with differences being attributed to lower (<0.4 Hz) frequency stimuli (8–10) or higher (>2 Hz) frequency stimuli (11, 12). Age-related changes in the dominant time constant (TC) (time taken for eye velocity to decay to 63% of its peak velocity under constant velocity head rotation with unidirectional rotation testing of the VOR) have also been studied, again with conflicting findings. Some studies reporting decreasing TCs (from a mean of 15.1 s to a mean of 11.7 s) with age (12), while others report shorter TCs in younger participants (13), whereas others report no age-related changes to the physiological function of these three (gain, phase, and TC) parameters (14). Therefore, for those within the healthy population who do not experience balance problems, it is unclear whether the anatomical changes described in the literature relate functionally to older people. Research utilizing head thrust dynamic visual acuity (htDVA) has also suggested a link between htDVA scores and propensity to falls within older, community-dwelling populations (15). The rationale behind passive htDVA is that people with vestibular organ injury have problems stabilizing images as only the VOR can keep up with fast head movements, resulting in a decrease in visual acuity during head thrusts [i.e., a difference between static and dynamic visual acuity (DVA)] (16). However, while htDVA is a very specific test (90% unilateral peripheral hypofunction, 90% bilateral hypofunction), its sensitivity in detecting peripheral vestibular hypofunction is limited (23% unilateral peripheral hypofunction, 55% bilateral peripheral hypofunction), meaning that although a bad DVA score indicates a poor VOR, a good score may not always mean a well-functioning VOR (17).

Benign paroxysmal positional vertigo (BPPV) is a condition where the otoconia are dislodged from their usual position within the utricle and migrate into one of the semicircular canals (the posterior canal is most commonly affected due to its anatomical position). When the head is re-oriented relative to gravity, the gravity-dependent movement of the heavier otoconial debris within the affected semicircular canal causes pathological endolymph displacement and a resultant sensation of vertigo. BPPV is the most common form of positional vertigo, accounting for nearly one half of patients with peripheral vestibular disorder. Approximately 18% of people seen in dizziness clinics (18) and 25% of people sent for vestibular testing have BPPV (19). In a population-based survey of 1003 people, the prevalence of BPPV was 2.4% and the 1-year prevalence of BPPV increased with age such that it was seven times higher in those aged 60 years and older compared to those aged 18–39 years (20).

Additionally, research into the efficacy of treatments for dizziness, such as vestibular rehabilitation, has seemingly indicated benefit and improvements in the quality of life of patients suffering from dizziness and imbalance (21). Identification of these people is important so that they can receive rehabilitation treatment. Our aim is to identify accurately the prevalence of BPPV, peripheral and central vestibular hypofunction within people over the age of 50 who had experienced an episode of dizziness, self-reported or documented, within the last year. We sought a snapshot of this particular population because these were the people most likely to present to a physician with dizziness, while acknowledging that this approach would likely result in an over-estimate of the true numbers of people with vestibular disorders in this overall age group. We used the Dizziness Handicap Inventory Questionnaire, Dix–Hallpike test, clinical head impulse test (cHIT), htDVA test, as well as sinusoidal and unidirectional rotational chair testing in order to, respectively, obtain data for BPPV, presence of refixation saccades, DVA, sinusoidal VOR gain and phase (between 0.1 to 2 Hz), transient VOR gain and TC, and optokinetic nystagmus (OKN) gain and TC.

MATERIALS AND METHODS

Participants

We studied 76 people with self-reported dizziness who had experienced at least one dizziness episode within the past year; 44 females and 28 males, aged 51–92 years old (mean = 69 ± 9.5). Participants were recruited through advertisements and mail flyers, the Neuroscience Research Australia website and newsletter, existing clinical networks and by contacting residents of retirement villages. The inclusion criteria were aged 50 years and over, dizziness (self-reported or documented) not currently being treated, living independently in the community or retirement village and able to understand English. The exclusion criteria were presence of a degenerative neurological condition or cognitive impairment. Participants identified on assessment with conditions that required urgent treatment defined as suspected stroke, transient ischemic attack, or other undiagnosed neurological or acute cardiovascular condition, severe depressive symptoms, or severe anxiety symptoms were also excluded from the study and referred for appropriate treatment. No participant included had a history of hypotension, bradycardia, fainting, seizures, or vomiting/migraines due to motion sickness. All participants gave

written and informed consent prior to participating in the study. The experimental protocol was approved by the Human Research Ethics Committee at the University of New South Wales.

Testing Protocol

Baseline testing took 1 day to complete for each participant. No participant was treated on the same day as their testing. Participants completed the Jacobson and Newman dizziness handicap inventory (DHI) (22), followed by the tests below in the order presented.

Dix–Hallpike Test to Detect BPPV

Participants underwent the Dix–Hallpike test for vertical canal BPPV using Frenzel lens goggles with integrated video camera for eye image recording (23). With the head turned 45° to one side and extended about 20° backward, the participant was brought from a sitting position to a supine position. Once supine, the eyes were observed for 30 s. If no nystagmus ensued, the participant was brought back to the sitting position and kept stationary for 30 s, after which the other side was tested. Horizontal canal BPPV testing began with the body supine and the head inclined forward 30°. The head was then turned to either side, i.e., the supine roll test. The Epley or particle repositioning maneuver was *not* performed on participants to treat their BPPV during this baseline testing session.

Clinical Head Impulse Test

A head impulse consists of a unilateral transient head rotation with peak amplitude ~10°, peak velocity ~150°/s, and peak acceleration ~3000°/s^2 (16). Passive, five leftward and five rightward, head impulses were manually delivered while the subject fixated the examiner's nose. The examiner noted whether or not refixation saccades occurred, i.e., positive for cHIT, for each direction of rotation.

Dynamic Visual Acuity

Participants who normally wore glasses or contact lenses for distant viewing were instructed to wear them during all DVA tests. Participants were seated 2 m directly in front of a high-resolution (1920 × 1080) 18.1-viewable-inch monitor with a refresh rate of 85 Hz. Static visual acuity was measured first by repeatedly displaying a single optotype (the letter E, randomly rotated each trial by 0°, 90°, 180°, or 270°) on a computer monitor. Participants viewed five optotypes per acuity level (letter size), which decreased in visual acuity levels of 0.1 LogMAR (MAR, minimum angle resolved). The lower the LogMAR score, the better the visual acuity, with LogMAR = −0.3, 0, 0.3, 0.7, 1.0, and 1.3 corresponding to Snellen visual acuity of 20/10, 20/20, 20/40, 20/100, 20/200, and 20/400, respectively. Static visual acuity was determined when the participant failed to correctly identify five optotypes on an acuity level or reached the LogMAR score of 0.000 (Snellen equivalent of 20/20 acuity).

For the dynamic component of the test, two IDG500/ADXL33 IMU (2D gyroscopes) Analog Combo Boards, aligned in the right anterior and left posterior (RALP) and left anterior and right posterior (LARP) vestibular semicircular canal (SCC) planes attached to an adjustable head mount were positioned on the participants head to measure angular head velocity in the horizontal, LARP, and RALP planes. A head thrust (also known as a head impulse) is a manually delivered, unpredictable, unidirectional, rapid head rotation with peak amplitude ~10°, peak velocity ~150°/s, and peak acceleration ~3000°/s^2. Horizontal head thrusts to assess horizontal canal function were performed first, followed by RALP, and then LARP head thrusts. Each semicircular canal was assessed separately, with head thrusts delivered only in its particular orientation until DVA was determined (i.e., leftward head thrusts tested the left horizontal canal and the DVA score was determined, followed by right horizontal canal testing, and so on). One practice trial for a head thrust was performed before commencing dynamic head thrust DVA (htDVA) testing in each of the planes of the horizontal, superior, and posterior SCCs. During each head thrust, the optotype "E" randomly oriented in one of the four directions () was displayed on the monitor 2 m in front of the participant when head velocity, sensed by the IDG500/ADXL33 Analog Combo Board, was between 120 and 180°/s for more than 40 ms. The optotype was displayed on the monitor for no longer than 85 ms, during which time the head would have rotated 9°–13.5°. To account for loss of concentration or blinking, the participant was allowed to view each optotype a maximum of three times, at which point the participant was required to guess the orientation. Once the participant indicated a response, the next trial was started, with the test being terminated when the participant incorrectly identified five optotypes at one acuity level or the participant reached the LogMAR score of 0.000. The htDVA test score was calculated by subtracting the static visual acuity LogMAR score from the DVA LogMAR score. As an aid to data interpretation only, we classified the scores as normal [≤0.158, i.e., ≤2 SDs from normal mean, see Ref. (17)], borderline (>0.158 and ≤0.316, 2–4 SDs), and abnormal (>0.316).

Rotary Chair Testing

The movements of both eyes were recorded in two dimensions (horizontal and vertical) using video-oculography. Eye position was recorded at 30 fps with a small, light-weight, high speed video camera mounted onto a light-weight scuba mask with an adjustable rubber strap that sat tightly on the bridge of the nose and around the eye sockets to minimize movement of the camera relative to the head. Two infrared light-emitting diodes (LEDs) were directed toward the eyes. The image of the eye was reflected from a hot (infrared) mirror onto the camera, the camera and hot mirror were mounted rigidly onto the mask. Horizontal and vertical eye movements were calibrated *in vivo* by asking the participant to fixate sequentially on the center and then four tips of a cross projected from a mask-mounted cross-hair projector. Eye position was calculated by tracking the pupils in the video images.

The rotary chair consisted of a reinforced car seat with foot support, four point safety harness, and head holder brace, used to tightly secure the participant's head, torso, and feet to the chair, respectively. The chair sat on a freely rotating hollow shaft attached via gears and a tension controlled toothed-belt to a floor-mounted motor (Baldor SD55-15A1 brushed DC servo motor, USA). The hollow shaft had a position encoder (S2 Optical Kit, USA) to monitor chair position, and slip-ring so that electrical signals, including power supply, could connect with equipment attached

to the chair. For example, signals to and from the chair and video data acquisition laptop computer and angular velocity (rate) sensor (GyroPAK3, USA) that measured chair velocity. Chair position and velocity were precisely controlled using a motion controller (NI PCI-7342, USA) and LabVIEW program (National Instruments, USA) running on the control PC located outside of the testing room. Head (angular chair position and velocity) and eye (video-oculography, horizontal and vertical angular eye position, and velocity) data were synchronously sampled at 30 Hz by the acquisition laptop computer (DAQ NI-USB-6008, USA), which wirelessly transmitted these data to the control PC.

The VOR testing protocol consisted of four steps.

1. Each participant was examined for spontaneous nystagmus by asking them to fixate on a point (170 cm) directly in front of them at eye level, and to hold that same gaze position even after the lights were turned out and they were in complete darkness.
2. The visual vestibulo-ocular reflex (VVOR) was tested by sinusoidal horizontal whole-body rotations at a series of frequencies (0.1, 0.2, 0.4, 0.5, 0.8, 1, 1.6, and 2 Hz, all with peak velocity 30°/s). The participant was tested in light, with instructions to visually fixate on a room-fixed point (170 cm) directly in front of them at eye level.
3. The VOR was measured using the VVOR rotation protocol above, the only difference being that the participant was tested in complete darkness.
4. The horizontal VOR was tested during transient rotations (i.e., acceleration steps). From stationary, the chair (and participant) accelerated (~150°/s^2) up to a constant velocity of 50°/s lasting for 3 min and then de-accelerated (~150°/s^2) to stationary, remaining so for at least 1 min. Testing was in complete darkness, except for a 1 min period starting precisely 1 min after acceleration commenced. During this 1 min period, OKN was induced by optokinetic stimuli painted on the walls of the room (40° subtending black stripes to 8° subtending white stripes). Participants were told not to fixate on the stripes as they entered their view. The OKN gain and TC were measured using the data collected during this 1 min period in light, whereas the VOR gains and TCs were measured during the 1 min periods in complete darkness immediately post acceleration and de-acceleration. Responses were measured for both leftward and rightward transient rotations.

Participant Vestibular Rehabilitation Category

Each participant was assessed at a case conference that included a geriatrician, vestibular physiotherapist, applied neurologist, vestibular scientist, and psychologist. Each specialist evaluated the participant's medical history and performance on a range of depression and anxiety questionnaires as well as sensorimotor, balance, cardiovascular (data not presented here), and vestibular tests, including the tests outlined in this study. Each participant was categorized as having symptoms of dizziness due to vestibular hypofunction making them suitable for vestibular rehabilitation exercises ("Lesion" group), BPPV making them suitable for Epley maneuver treatment ("BPPV" group), or due to non-vestibular cause, e.g., cardiovascular, neuromuscular, or psychogenic condition ("non-vestibular" group). Only after all the testing was complete and participants categorized were they referred for later treatment.

Data Analysis

For sinusoidal data, cycles (a cycle equals one period) with quick phases (resetting eye movements that bring the eye back to center once they reach the edge of the oculomotor range) were removed, and the remaining (i.e., slow-phase vestibular eye movements) cycles were overlaid and averaged on a point-by-point basis. Gain and phase were computed using the horizontal eye and head velocities. Gain was defined as the eye/head quotient of amplitude for least-squares best-fit pure sinusoids approximating the eye and head velocity mean traces. Gain and phase were expressed with the convention that unity gain and zero phase imply a perfectly compensatory VOR; positive phase implies that eye movements lead head movements and negative phase implies that eye movements lag behind head movements. During testing at 1.6 and 2 Hz decoupling that sometimes occurred between the head and chair was detected by a large increase in phase shift and decrease in gain compared to the 1 Hz data. Decoupled data were not included in the analysis.

For unidirectional transient data (i.e., acceleration steps), the points in time where the absolute magnitude of eye velocity was maximal immediately after acceleration (P_{EXC}, excitatory stimulus) and after de-acceleration (P_{INH}, inhibitory stimulus) were determined and used to calculate the excitatory VOR gain (eye/head velocity at P_{EXC}) and the inhibitory VOR gain (at P_{INH}), respectively. Starting at time P_{EXC}, points on the eye velocity trace immediately before the start, and after the end, of quick phases (therefore, only selecting the slow-phase data) were manually chosen and an exponential curve was fitted to the data in order to calculate the excitatory TC. TC was defined as the time taken for eye velocity to decay to 63% of peak velocity under constant velocity rotation. An unusually long (>30 s) vestibular TC suggests a central vestibular disorder (24). The inhibitory TC was similarly calculated by fitting points after time P_{INH}. The OKN gain was calculated by selecting slow-phase eye velocity data points (i.e., excluding quick phase data points as per above) during the constant velocity rotation period with lights on. The average velocity of these points was calculated and divided by 50°/s (i.e., eye/head velocity) to calculate the OKN gain. The OKN TC was calculated by fitting an exponential curve to the slow-phase data during lights off, starting immediately after the period with lights on. The VOR and OKN, gains and TCs, calculations were identical for both leftward and rightward transient data.

Statistical Analysis

Statistical analysis was performed using Matlab 2008a (Mathworks, USA) and Excel 2007 (Microsoft, USA) software. We used a mixed-design repeated measures analysis of variance (ANOVA) with two-, three-, and four-factor interactions to analyze the data (25). Main and interaction effects of participant vestibular rehabilitation group (*group*: "lesion," "non-vestibular,"

or "BPPV"), test type (*test*: "VVOR" or "VOR"), eye used to calculate the gain or phase (*eye*: "left," "right"), and test frequency (*frequency*: 0.1, 0.2, 0.4, 0.5, 0.8, 1, 1.6, and 2 Hz) on sinusoidal VOR gain and phase were investigated. Main and interaction effects of "*group*," "*eye*," vestibular stimulus applied with respect to the lesion side (*sameside*: "yes" or "no") and vestibular stimulus type (*stimulus*: "excitatory," "inhibitory") on transient VOR gain and TC were investigated. Main and interaction effects of "*group*," "*eye*," and "*sameside*" on OKN gain and TC were investigated. Main and interaction effects of "*group*," "*sameside*," and canal (*canal*: "horizontal," "anterior," and "posterior") on DVA score were investigated. Main and interaction effects of "*group*" on total physical, total emotional, total functional, and grand total DHI scores were investigated. We report variables (or factors) with 95% confidence (i.e., 5% significance) as significant and those with 90% confidence (i.e., 5–10% significance) as trends. We also report the effect size η^2 for ANOVA, which was considered as small 0.005–0.05, medium 0.05–0.125, or large >0.125; and effect size Cohen-*d* for *z-test*, which was considered as small 0.15–0.45, medium 0.45–0.75, or large >0.75 (26).

RESULTS

Demographics

Ten participants (5 female, 5 male) were categorized into the lesion group, 19 (15 female, 4 male) into the BPPV group, and 47 (26 female, 21 male) into the non-vestibular group. There was no difference in mean ages between non-vestibular (68.3 ± 9.5 years), lesion (70 ± 11.8 years), and BPPV (70.1 ± 8.6 years) groups (ANOVA: "*group*" variable, $P = 0.749$, $\eta^2 = 0.008$).

We categorized the last dizzy episode for each participant into six time periods [test day (prior to testing), last week, last month, last 3 months, last 6 months, last year]. For the lesion group, three participants experienced a dizzy episode on the day, four in the last week, and three in the last month. For the BPPV group, five on the day, nine in the last week, three in the last month, one in the last 3 months, and one in the last year. For the non-vestibular group, 12 on the day, 10 in the last week, 16 in the last month, 5 in the last 3 months, and 4 in the last 6 months.

For the 19 BPPV patients during Dix–Hallpike testing; 8 had upbeat right torsional nystagmus during right posterior canal testing only; 5 upbeat left torsional nystagmus during left posterior canal testing only; and 6 had upbeat with left torsional nystagmus during left posterior canal testing and upbeat with right torsional nystagmus during right posterior canal testing. Fourteen out of the 19 BPPV participants described head movement as a clear trigger for their dizziness, which was predominantly a spinning sensation.

Clinical Head Impulse Test

The cHIT was performed in 68 out of the 76 participants. The remaining eight could not be tested due to difficulty with moving their head due to neck stiffness and or pain. The cHIT was positive in 8/42 in the non-vestibular group, 1/9 in the lesion group, and 4/17 in the BPPV group. There was no difference in these proportions between groups (*z*-test: lesion vs. non-vestibular, $P = 0.569$, Cohen-$d = -0.159$; BPPV vs. non-vestibular, $P = 0.697$. Cohen-$d = 0.101$; lesion vs. BPPV, $P = 0.447$, Cohen-$d = 0.303$).

Head Thrust Dynamic Visual Acuity

Table 1 shows the mean htDVA scores for non-vestibular, lesion, and BPPV groups as well as the proportion of participants classified as normal, borderline, and abnormal. For presentation of non-vestibular group data in **Table 1** only, ipsilesional is left and contralesional is right.

The factors which affected the htDVA score were the canal tested (ANOVA: *canal*, $P < 0.05$, $\eta^2 = 0.015$) and participant group (ANOVA: *group*, $P < 0.01$, $\eta^2 = 0.021$). There was a close to 5% significant difference between ipsilesional and contralesional rotations (ANOVA: *sameside*, $P = 0.0506$, $\eta^2 = 0.008$), and toward an interaction between *sameside* and *group* (ANOVA: $P = 0.0715$, $\eta^2 = 0.007$).

Sub-analysis comparing only non-vestibular and lesion group data showed a significant difference in htDVA score between rotations toward the ipsilesional and contralesional (both left and right sides were pooled for the non-vestibular group) sides (ANOVA: *sameside* variable, $P < 0.02$, $\eta^2 = 0.019$). Additionally, for the lesion group only, horizontal canal htDVA scores were significantly different between ipsilesional and contralesional sides (ANOVA: *sameside*, $P < 0.01$, $\eta^2 = 0.058$).

Sub-analysis comparing only BPPV and lesion group data showed a significant difference in htDVA score between groups (ANOVA: *group*, $P < 0.002$, $\eta^2 = 0.058$) as well as between canals (ANOVA: *canal*, $P < 0.01$, $\eta^2 = 0.068$) and between ipsilesional and contralesional sides (ANOVA: *sameside*, $P < 0.05$, $\eta^2 = 0.023$). There was a close to 5% significance interaction between group and lesion sides (ANOVA: $P = 0.0558$, $\eta^2 = 0.02$). Examination of the canals individually indicated that anterior canal htDVA scores were significantly different between BPPV and lesion groups (ANOVA: *group*, $P < 0.001$, $\eta^2 = 0.217$). Additionally, there was a trend toward a difference in posterior canal DVA scores between BPPV and lesion groups (ANOVA: *group*, $P = 0.0726$, $\eta^2 = 0.07$) as well as between ipsilesional and contralesional sides (ANOVA: *sameside*, $P = 0.0996$, $\eta^2 = 0.059$). There were no differences between non-vestibular and BPPV groups.

Dizziness Handicap Inventory

Table 2 shows the mean DHI scores for physical, emotional, and functional parts of the questionnaire as well as the mean grand total DHI scores for the non-vestibular, lesion, and BPPV groups.

There was a significant difference in the total emotional score between groups (ANOVA: *group,* $P < 0.01$, $\eta^2 = 0.138$). There was a close to 5% significant difference in grand total scores between groups (ANOVA: *group*, $P = 0.0643$, $\eta^2 = 0.072$).

Sub-analysis comparing only lesion and non-vestibular group data showed a significant difference in the total emotional (ANOVA: *group,* $P < 0.001$, $\eta^2 = 0.186$) and grand total scores (ANOVA: *group*, $P < 0.02$, $\eta^2 = 0.098$) as well as a trend toward a difference in total functional scores (ANOVA: *group*, $P = 0.0572$, $\eta^2 = 0.064$). There was a close to 5% significant difference in total emotional scores between lesion and BPPV groups (ANOVA: *group*, $P = 0.0504$, $\eta^2 = 0.135$). There was no difference in DHI scores between the BPPV and non-vestibular groups.

TABLE 1 | Summary of mean htDVA scores for non-vestibular, lesion (non-BPPV), and BPPV groups as well as the proportion of participants classified as normal, borderline, and abnormal (≤0.158, >0.158 and ≤0.316, and >0.316, respectively).

Side	Canal	Non-vestibular			Lesion (non-BPPV)			BPPV		
		Affected	No.	Mean ± SD	Affected	No.	Mean ± SD	Affected	No.	Mean ± SD
Ipsi.	Hor.	Normal	34/47	0.154 ± 0.131	Normal	3/15	0.300 ± 0.139	Normal	11/23	0.200 ± 0.131
		Borderline	8/47		Borderline	5/15		Borderline	9/23	
		Abnormal	5/47		Abnormal	7/15		Abnormal	3/23	
	Ant.	Normal	28/44	0.182 ± 0.180	Normal	5/15	0.237 ± 0.112	Normal	14/22	0.137 ± 0.065
		Borderline	8/44		Borderline	4/15		Borderline	8/22	
		Abnormal	8/44		Abnormal	6/15		Abnormal	0/22	
	Post.	Normal	18/40	0.189 ± 0.116	Normal	2/15	0.328 ± 0.151	Normal	5/20	0.249 ± 0.127
		Borderline	16/40		Borderline	5/15		Borderline	10/20	
		Abnormal	6/40		Abnormal	8/15		Abnormal	5/20	
Contra.	Hor.	Normal	31/45	0.160 ± 0.143	Normal	5/5	0.113 ± 0.041	Normal	8/13	0.211 ± 0.195
		Borderline	9/45		Borderline	0/5		Borderline	2/13	
		Abnormal	5/45		Abnormal	0/5		Abnormal	3/13	
	Ant.	Normal	20/43	0.208 ± 0.138	Normal	2/5	0.195 ± 0.081	Normal	8/12	0.135 ± 0.068
		Borderline	12/43		Borderline	2/5		Borderline	4/12	
		Abnormal	11/43		Abnormal	1/5		Abnormal	0/12	
	Post.	Normal	17/39	0.203 ± 0.115	Normal	3/5	0.245 ± 0.210	Normal	6/12	0.188 ± 0.096
		Borderline	15/39		Borderline	1/5		Borderline	4/12	
		Abnormal	7/39		Abnormal	1/5		Abnormal	2/12	

For the non-vestibular group, ipsilesional is left and contralesional is right.

TABLE 2 | Summary of mean DHI scores for physical, emotional, and functional parts of the questionnaire as well as the mean total DHI scores for non-vestibular, lesion, and BPPV groups.

DHI score	Non-vestibular (*n* = 47)	Lesion (non-BPPV) (*n* = 10)	BPPV (*n* = 19)
	Mean ± SD	Mean ± SD	Mean ± SD
Physical	10.1 ± 6.65	11.8 ± 6.76	11.4 ± 6.96
Emotional	4.85 ± 5.56	12.4 ± 8.42	6.42 ± 6.95
Functional	8.04 ± 7.48	13.2 ± 8.34	8.74 ± 8.17
Total	23.0 ± 16.5	37.4 ± 19.2	26.5 ± 18.8

Total scores of ≤39, ≥40 and ≤69, and ≥70 indicate low, moderate, and severe self-perception of handicap, respectively.

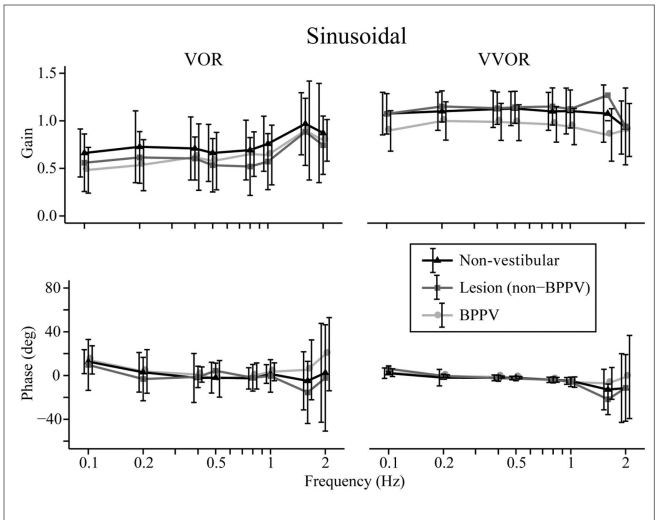


FIGURE 1 | Mean sinusoidal vestibulo-ocular reflex (VOR) and visual VOR (VVOR) gains and phases for non-vestibular, lesion, and BPPV groups over all frequencies.

Sinusoidal Horizontal VOR and VVOR Testing

The factors that affected the gain were the test protocol (VOR or VVOR; ANOVA: *test*, $P < 0.0001$, $\eta^2 = 0.275$), participant group (ANOVA: $P < 0.0001$, $\eta^2 = 0.026$), and testing frequency (ANOVA: $P < 0.0001$, $\eta^2 = 0.017$). There was a significant interaction between test protocol and frequency (ANOVA: $P < 0.0001$, $\eta^2 = 0.033$). As shown in **Figure 1**, the VOR gain increases at frequencies ≥1.6 Hz (ANOVA: *frequency*, $P < 0.0002$, $\eta^2 = 0.025$).

Sub-analysis comparing only lesion and non-vestibular group data showed the factors that affected gain were test protocol (ANOVA: $P < 0.001$, $\eta^2 = 0.297$), group (ANOVA: $P < 0.02$, $\eta^2 = 0.003$), and frequency (ANOVA: $P < 0.001$, $\eta^2 = 0.019$) particularly between 0.5 and 1 Hz where the mean lesion VOR gain was ~25% lower than the mean non-vestibular VOR gain. Phase was affected by test protocol (ANOVA: $P < 0.0001$, $\eta^2 = 0.022$) and frequency (ANOVA: $P < 0.0001$, $\eta^2 = 0.069$), and there was a significant interaction between test protocol and frequency (ANOVA: $P < 0.01$, $\eta^2 = 0.013$). The frequency significantly affected phase during VOR testing only when 0.1, 1.6, and 2 Hz were included in the analysis (when these frequencies were removed, frequency no longer became significant), whereas it significantly affected phase at all frequency ranges of VVOR testing (ANOVA: $P < 0.0001$, $\eta^2 = 0.156$).

Sub-analysis comparing only BPPV and non-vestibular group data showed the factors that affected gain were test protocol (ANOVA: $P < 0.001$, $\eta^2 = 0.238$), group (ANOVA: $P < 0.001$, $\eta^2 = 0.028$), and frequency (ANOVA: $P < 0.001$, $\eta^2 = 0.015$). Between 0.5 and 1 Hz, the mean BPPV VOR gain was ~13% lower than the mean non-vestibular VOR gain. Phase was affected by test protocol (ANOVA: $P < 0.0001$, $\eta^2 = 0.032$), group (ANOVA:

$P < 0.01$, $\eta^2 = 0.005$), and frequency (ANOVA: $P < 0.001$, $\eta^2 = 0.045$). There were significant interactions between test protocol and frequency (ANOVA: $P < 0.0001$, $\eta^2 = 0.022$) as well as group and frequency (ANOVA: $P < 0.002$, $\eta^2 = 0.012$). There was a VOR phase difference between BPPV and non-vestibular groups (ANOVA: $P < 0.02$, $\eta^2 = 0.007$), which was not significant during testing at <2 Hz ($P = 0.0871$, $\eta^2 = 0.004$). Frequency did not affect the VOR phase for frequencies >0.1 and <2 Hz. There was a difference between BPPV and non-vestibular groups for VVOR phase (ANOVA: $P < 0.05$, $\eta^2 = 0.005$), which was no longer significant during testing at <2 Hz ($P = 0.0627$, $\eta^2 = 0.003$). Frequency significantly affected the VVOR phase at all frequency ranges of VVOR testing (ANOVA: $P < 0.0001$, $\eta^2 = 0.085$).

Transient (Acceleration Steps) Horizontal VOR Testing

Figure 2 shows the means for VOR gain and TC for ipsilesional and contralesional transient unilateral rotations that were excitatory (during acceleration) and inhibitory (during de-acceleration) for the non-vestibular, lesion, and BPPV groups. For the non-vestibular group and **Figure 2** only, ipsilesional is left and contralesional is right. **Figure 3** shows the typical raw trace response in a participant from the non-vestibular group.

The factor which affected the acceleration step gain was whether the stimulus was excitatory or inhibitory (ANOVA: *stimulus*, $P < 0.05$, $\eta^2 = 0.019$). There was a close to 5% significant effect of group on the acceleration step gain (ANOVA: *group*, $P = 0.0624$, $\eta^2 = 0.021$) and TC (ANOVA: *group*, $P = 0.0926$, $\eta^2 = 0.018$).

Sub-analysis comparing only non-vestibular and lesions group data showed a trend toward a difference in acceleration step gain between ipsilesional and contralesional sides (both left and right sides were pooled for the non-vestibular group) (ANOVA: *sameside*, $P = 0.0798$, $\eta^2 = 0.017$). The acceleration step TC was not different (ANOVA: *group*, $P = 0.651$, $\eta^2 = 0.001$) between lesion and non-vestibular groups. Within the lesion group, there was a trend toward a difference in TC between ipsilesional and contralesional rotations (ANOVA: $P = 0.0809$, $\eta^2 = 0.095$).

Sub-analysis comparing only non-vestibular and BPPV group data showed a significant difference in acceleration step gain between groups (ANOVA: $P < 0.05$, $\eta^2 = 0.021$), especially during inhibition stimulation (ANOVA: $P < 0.05$, $\eta^2 = 0.038$). However, there were no significant factors which affected the TC.

Sub-analysis comparing only BPPV and lesion group data showed a significant difference in acceleration step gain between groups (ANOVA: $P < 0.05$, $\eta^2 = 0.053$). For inhibitory stimuli, there was a trend toward a difference in acceleration step gain between BPPV and lesion groups (ANOVA: $P = 0.0623$, $\eta^2 = 0.069$). There was also a significant difference in the TC between BPPV and lesion groups (ANOVA: $P < 0.05$, $\eta^2 = 0.06$), as well as a trend toward a difference in TC between ipsilesional and contralesional rotations (ANOVA: $P = 0.0796$, $\eta^2 = 0.029$). For excitatory stimuli, there was a difference in TC between BPPV and lesion groups (ANOVA: $P < 0.02$, $\eta^2 = 0.123$).

Transient VOR testing identified one participant with excitatory response, displayed in **Figure 4**, with exponential decay longer than normal duration.

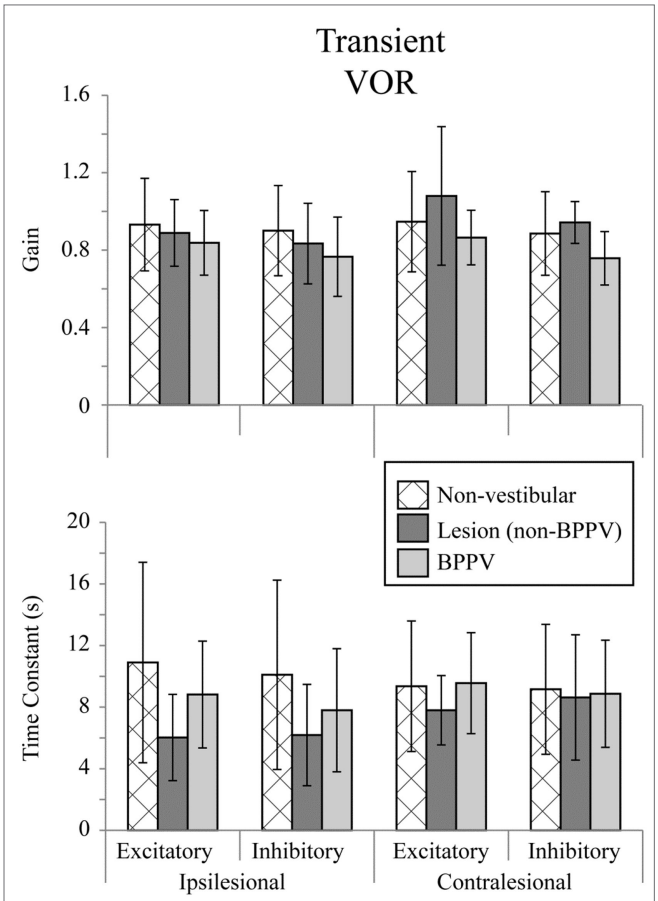


FIGURE 2 | Mean transient (acceleration step) VOR gains and time constants for ipsilesional and contralesional rotational stimuli that are excitatory (measured during acceleration) or inhibitory (measured during de-acceleration) for non-vestibular, lesion, and BPPV groups. For the non-vestibular group, ipsilesional is left and contralesional is right.

Optokinetic Testing (OKN)

Figure 5 shows the mean values for optokinetic gain and TC for the non-vestibular, lesion, and BPPV groups during ipsilateral and contralateral stimuli. For the non-vestibular group and **Figure 5** only, ipsilesional is left and contralesional is right.

The factor which affected the OKN TC was whether the stimulus was ipsilesional or contralesional (ANOVA: *same-side*, $P < 0.05$, $\eta^2 = 0.035$). No factors affected the OKN gain. Within the lesion group, the TC was significantly different between ipsilesional and contralesional rotations ($P < 0.01$, $\eta^2 = 0.467$).

DISCUSSION

Thirty-eight percent of participants had a detectable peripheral vestibular disorder (29/76) and 1% a central vestibular disorder (1/76), which was the likely cause of their dizziness. Of those with a vestibular cause, 63% (19/30) had BPPV, which is higher than the previously reported ~25% in dizziness clinic populations (18,

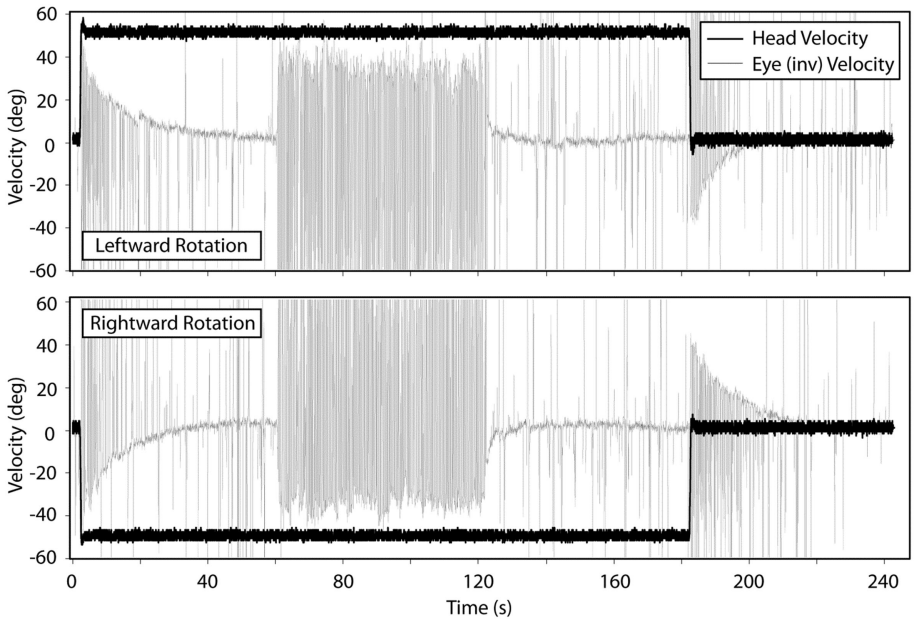


FIGURE 3 | Typical response from a participant in the non-vestibular group during transient VOR and OKN testing. Top panel shows responses during leftward rotations and bottom panel for rightward rotations.

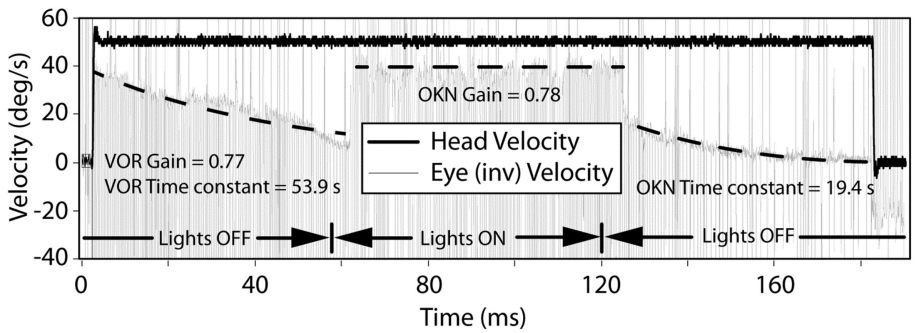


FIGURE 4 | The VOR and OKN response during leftward rotation in a participant with central vestibular dysfunction. The left and right dashed lines indicate exponential decay fits to the slow-phase component of the eye movement in darkness and are used to calculate the VOR gain, VOR, and OKN time constants. The middle dashed line indicates a linear fit to the slow-phase component of the eye movement in light and is used to calculate the OKN gain.

19). This 2.5 times larger prevalence can be explained by the fact that participants had experienced dizziness in the last year, which meant this population was biased toward having a vestibular disorder. However, it is also important to note that due to the difference in time between dizzy spell and assessment, for some of the participants, vestibular disorders may have resolved or progressed to chronic and well-compensated, which would have made detection less possible.

Head Thrust Dynamic Visual Acuity

For the non-vestibular group, htDVA scores were similar between left and right sides, whereas in the lesion group, there was a difference between ipsilesional and contralesional sides. For the BPPV group, the posterior canal htDVA score on the ipsilesional side was highest (worst).

The difference in lesion group horizontal htDVA scores between ipsilesional and contralesional head rotations is due to loss of vestibular function, as has been previously reported [e.g., Ref. (17)]. However, for all groups, there was a trend toward a difference in htDVA scores depending on the canal tested, i.e., horizontal, anterior, or posterior. In fact, within BPPV and lesion groups, this difference was significant. This finding is understandable for the BPPV group given that BPPV commonly occurs in the posterior canals (as was the case in all our participants) due to their anatomical position. The relationship between posterior canal htDVA score and BPPV has not been

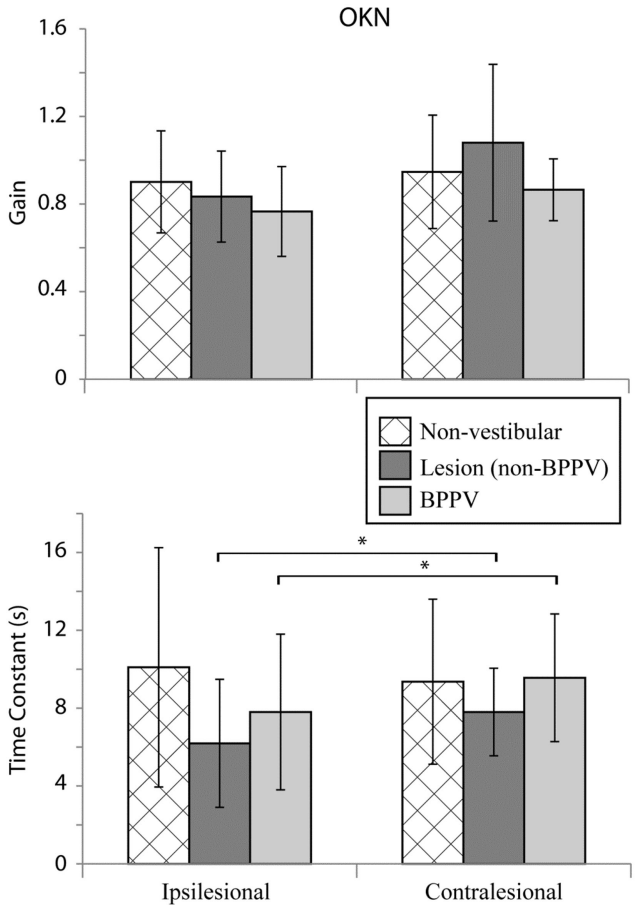


FIGURE 5 | Mean optokinetic nystagmus (OKN) gains and time constants for non-vestibular, lesion, and BPPV groups for ipsilesional and contralesional rotational stimuli. For the non-vestibular group, ipsilesional is left and contralesional is right. The * denotes significant difference.

previously reported. Our finding suggests that BPPV not only inappropriately persists a vestibular-evoked eye movement once the head has stopped rotating but also alters the VOR eye movement *during* the head movement (i.e., when the optotype is flashed) in a way that affects DVA. By contrast, for the lesion group, it is not clear why the posterior canal htDVA score was higher than the other canals when testing the contralesional side. During htDVA testing, it was noted that in our population ~59% (45/76) used bifocal or multifocal glasses. The vertical direction of the head thrusts during anterior and posterior canal testing is likely to have caused viewing lens crossover, which could have increased htDVA scores during the testing for those canals.

Dizziness Handicap Inventory Scores

In examining the DHI scores, it appears BPPV has less effect on emotional and functional quality of life than other vestibular conditions. Participants with BBPV perceived their handicap to be somewhere between lesion and non-vestibular participants and the difference in total scores was only statistically different between the lesion and non-vestibular groups.

Sinusoidal Horizontal VOR and VVOR

We found significant differences in gain and phase between BPPV and non-vestibular groups. Manifestation of BPPV usually occurs in the posterior canals, given their anatomical position, so presumably the horizontal VOR should not be affected by BPPV, yet our results suggest it is. Our findings show that the BPPV group sinusoidal horizontal VOR gain was between the lesion and non-vestibular group gains, especially between 0.5 and 1 Hz, which seems to be the critical point for detecting vestibular disorder during human rotary chair testing. Presumably, this is because the VOR contributes to vision stabilization starting at around 0.5 Hz. During higher-frequency chair rotations, decoupling can occur between the head and chair resulting in larger response variation and decreased sensitivity. Across all groups, the VOR gain increased at stimulus frequencies ≥1.6 Hz, whereas VVOR gain decreased at 2 Hz, which agrees with the findings of Li et al. (11) that suggested decreasing gain with increasing frequency. Our VOR phase analysis showed no significant difference between non-vestibular and lesion groups, whereas at higher frequencies (≥1.6 Hz), there were differences between non-vestibular and BPPV as well as BPPV and lesion groups.

Transient (Acceleration Steps) Horizontal VOR

With Transient VOR testing, differences were noted primarily between BPPV compared to non-vestibular and lesion groups, respectively. There was no difference in TC between non-vestibular and BPPV groups, whereas gain was shown to differ, especially during inhibitory stimulation. This finding is consistent with our sinusoidal VOR data, which also showed a difference between BPPV and non-vestibular groups. The largest (albeit not statistically significant) difference between ipsilesional vs. contralesional gain was observed in the lesion group during excitatory stimulation. Similarly, the largest difference between ipsilesional and contralesional TC was observed in the lesion group during inhibitory stimulation. Transient VOR testing identified one participant with likely central vestibular dysfunction.

Optokinetic Nystagmus

With regard to horizontal OKN testing, for the lesion and BPPV groups, there was a significant difference in TC between ipsilesional and contralesional rotations. No other significant results were obtained from any of the comparisons for TC or gain. This is a somewhat surprising result given that the OKN response is a mixture of optokinetic and smooth pursuit systems that should perfectly stabilize vision during 50°/s constant velocity head rotations in the light (24). A decrease in OKN gain or increase in TC would be indicative of central, most likely cerebellar, injury. In fact, in the case of the one participant with central vestibular dysfunction described above (see Results and **Figure 4**), the OKN TC was almost seven times the normal TC of about 3 s.

Technical Issues

There were some issues with the amount of viable data we were able to collect, especially with regard to transient VOR testing and OKN testing. This happened due to some participants blinking frequently (resulting in noisy data) and some participants closing their eyes during OKN testing to reduce nystagmus (leading to a lack of reinforcement of the reflex and consequently a lack of OKN response). During sinusoidal VOR testing, despite tight fitting head and body restraints and straps, decoupling between the head and chair, especially in larger participants, was unavoidable at high frequencies. This limitation reduced the amount of data included at these frequencies.

CONCLUSION

Overall, the results suggest that htDVA, DHI, sinusoidal VOR (particularly at 1 Hz), transient VOR, and OKN testing are all useful tools for detecting peripheral vestibular causes of dizziness in older people. Our most surprising finding was that BPPV and lesion groups had similarly low gains compared to the non-vestibular group during sinusoidal horizontal VOR testing. We also observed a possible relationship between BPPV and an isolated increase in the affected posterior canal htDVA score, which warrants further investigation.

AUTHOR CONTRIBUTIONS

AC collected DVA and rotary chair data, wrote thesis upon which this manuscript was drafted. JM helped conceive the study, recruited participants, and collected DHI, BPPV, and cHIT data, proofread manuscript. PH collected DVA and rotary chair data, wrote the processing data software. SL helped conceive the study, obtained ethics approval, and proofread the manuscript. AM helped conceive the study, analyzed (statistical, summary, and figures) the data, and wrote the draft and final manuscripts.

ACKNOWLEDGMENTS

This study was funded by the National Health and Medical Research Council of Australia (NHMRC) Project Grant APP1026726. AM was supported by The Garnett Passe and Rodney Williams Memorial Foundation Senior/Principal Research Fellowship in Otorhinolaryngology. PH was supported by a University of New South Wales (UNSW) International Research Scholarship and a Neuroscience Research Australia (NeuRA) supplementary scholarship. SL was supported by an NHMRC Research Fellowship. We would like to thank Mr. Georg Poller for his assistance with data collection and processing, Ms. Holly Hunter and Ms. Mayna Ratanapongleka for participant recruitment and Dix–Hallpike testing.

REFERENCES

1. Guyton AC, Hall JE. Vestibular sensations and maintenance of equilibrium. In: Guyton AC, editor. *Guyton and Hall Textbook of Medical Physiology*. Philadelphia, PA: Saunders; Elsevier (2011). p. 692–3.
2. Sloane PD, Baloh RW, Honrubia V. The vestibular system in the elderly: clinical implications. *Am J Otolaryngol* (1989) **10**(6):422–9. doi:10.1016/0196-0709(89)90038-0
3. Neuhauser HK, von Brevern M, Radtke A, Lezius F, Feldmann M, Ziese T, et al. Epidemiology of vestibular vertigo: a neurotologic survey of the general population. *Neurology* (2005) **65**(6):898–904. doi:10.1212/01.wnl.0000175987.59991.3d
4. Rosenhall U. Degenerative patterns in the aging human vestibular neuro-epithelia. *Acta Otolaryngol* (1973) **76**(2):208–20. doi:10.3109/00016487309121501
5. Merchant SN, Velázquez-Villaseñor L, Tsuji K, Glynn RJ, Wall C III, Rauch SD. Temporal bone studies of the human peripheral vestibular system. Normative vestibular hair cell data. *Ann Otol Rhinol Laryngol Suppl* (2000) **181**:3–13.
6. Rauch SD, Velazquez-Villaseñor L, Dimitri PS, Merchant SN. Decreasing hair cell counts in aging humans. Review. *Ann N Y Acad Sci* (2001) **942**:220–7. doi:10.1111/j.1749-6632.2001.tb03748.x
7. Goldberg JM, Wilson VJ, Cullen KE, Angelaki DE, Broussard DM, Büttner-Ennever JA, et al. *Vestibulo-Ocular Reflexes*. New York: Oxford University Press (2012).
8. Furman JM, Redfern MS. Effect of aging on the otolith-ocular reflex. *J Vestib Res* (2001) **11**(2):91–103.
9. Paige GD. Senescence of human visual-vestibular interactions. 1. Vestibulo-ocular reflex and adaptive plasticity with aging. *J Vestib Res* (1992) **2**(2):133–51.
10. Peterka RJ, Black FO, Schoenhoff MB. Age-related changes in human vestibulo-ocular reflexes: sinusoidal rotation and caloric tests. *J Vestib Res* (1990) **1**(1):49–59.
11. Li CW, Hooper RE, Cousins VC. Sinusoidal harmonic acceleration testing in normal humans. *Laryngoscope* (1991) **101**(2):192–6. doi:10.1288/00005537-199102000-00016
12. Baloh RW, Jacobson KM, Socotch TM. The effect of aging on visual-vestibuloocular responses. *Exp Brain Res* (1993) **95**(3):509–16. doi:10.1007/BF00227144
13. DiZio P, Lackner JR. Age differences in oculomotor responses to step changes in body velocity and visual surround velocity. *J Gerontol* (1990) **45**(3):M89–94. doi:10.1093/geronj/45.3.M89
14. Maes L, Dhooge I, D'Haenens W, Bockstael A, Keppler H, Philips B, et al. The effect of age on the sinusoidal harmonic acceleration test, pseudorandom rotation test, velocity step test, caloric test, and vestibular-evoked myogenic potential test. *Ear Hear* (2010) **31**(1):84–94. doi:10.1097/AUD.0b013e3181b9640e
15. Honaker JA, Shepard NT. Use of the dynamic visual acuity test as a screener for community-dwelling older adults who fall. *J Vestib Res* (2011) **21**(5):267–76. doi:10.3233/VES-2011-0427
16. Halmagyi G, Curthoys IS. A clinical sign of canal paresis. *Arch Neurol* (1988) **45**(7):737–9. doi:10.1001/archneur.1988.00520310043015
17. Schubert MC, Migliaccio AA, Della Santina CC. Dynamic visual acuity during passive head thrusts in canal planes. *J Assoc Res Otolaryngol* (2006) **7**(4):329–38. doi:10.1007/s10162-006-0047-6
18. Nedzelski JM, Barber HO, McIlmoyl L. Diagnoses in a dizziness unit. *J Otolaryngol* (1986) **15**(2):101–4.
19. Hughes CA, Proctor L. Benign paroxysmal positional vertigo. *Laryngoscope* (1997) **107**(5):607–13. doi:10.1097/00005537-199705000-00010
20. von Brevern M, Radtke A, Lezius F, Feldmann M, Ziese T, Lempert T, et al. Epidemiology of benign paroxysmal positional vertigo: a population based study. *J Neurol Neurosurg Psychiatry* (2007) **78**(7):710–5. doi:10.1136/jnnp.2006.100420
21. Hillier SL, McDonnell M. Vestibular rehabilitation for unilateral peripheral vestibular dysfunction. *Cochrane Database Syst Rev* (2011) (2):CD005397. doi:10.1002/14651858.CD005397.pub3
22. Jacobson GP, Newman CW. The development of the dizziness handicap inventory. *Arch Otolaryngol Head Neck Surg* (1990) **116**(4):424–7. doi:10.1001/archotol.1990.01870040046011
23. Dix MR, Hallpike CS. The pathology symptomatology and diagnosis of certain common disorders of the vestibular system. *Proc R Soc Med* (1952) **45**(6):341–54.
24. Leigh RJ, Zee DS. *The Neurology of Eye Movements*. 4th ed. New York, NY: Oxford University Press (1993).
25. Diggle PJ, Liang KY, Zeger SL. *Analysis of Longitudinal Data*. New York, NY: Oxford University Press (1994).

26. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Erlbaum (1988).

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.

frontiers in Neurology

PERSPECTIVE
published: 06 January 2016
doi: 10.3389/fneur.2015.00269

Perspectives on Aging Vestibular Function

Eric Anson[1]* *and John Jeka*[2,3]

[1] Department of Otolaryngology Head and Neck Surgery, Johns Hopkins Medical Institutes, Baltimore, MD, USA, [2] Department of Kinesiology, Temple University, Philadelphia, PA, USA, [3] Department of Bioengineering, Temple University, Philadelphia, PA, USA

Much is known about age-related anatomical changes in the vestibular system. Knowledge regarding how vestibular anatomical changes impact behavior for older adults continues to grow, in line with advancements in diagnostic testing. However, despite advancements in clinical diagnostics, much remains unknown about the functional impact that an aging vestibular system has on daily life activities such as standing and walking. Modern diagnostic tests are very good at characterizing neural activity of the isolated vestibular system, but the tests themselves are artificial and do not reflect the multisensory aspects of natural human behavior. Also, the majority of clinical diagnostic tests are passively applied because active behavior can enhance performance. In this perspective paper, we review anatomical and behavioral changes associated with an aging vestibular system and highlight several areas where a more functionally relevant perspective can be taken. For postural control, a multisensory perturbation approach could be used to bring balance rehabilitation into the arena of precision medicine. For walking and complex gaze stability, this may result in less physiologically specific impairments, but the trade-off would be a greater understanding of how the aging vestibular system truly impacts the daily life of older adults.

Keywords: aging, vestibular, VOR, balance, walking, functional testing

OPEN ACCESS

Edited by:
Susan J. Herdman, Emory University, USA

Reviewed by:
Jennifer Christy, University of Alabama at Birmingham, USA
John Allum, University Hospital Basel, Switzerland

***Correspondence:**
Eric Anson
eanson1@jhmi.edu

Specialty section:
This article was submitted to Neuro-otology, a section of the journal Frontiers in Neurology

Received: *01 November 2015*
Accepted: *14 December 2015*
Published: *06 January 2016*

Citation:
Anson E and Jeka J (2016) Perspectives on Aging Vestibular Function. Front. Neurol. 6:269. doi: 10.3389/fneur.2015.00269

AGING AND THE VESTIBULAR SYSTEM

Many systems in the human body are adversely affected by the aging process, including the vestibular system. It has long been known that the number of vestibular hair cells is reduced in older adults compared to younger adults, independent of vestibular disease (1–4). The decline in hair cells is not uniform throughout the vestibular periphery. The saccule and utricle experience approximately a 25% reduction in hair cells, whereas semi-circular canals (SCCs) lose approximately 40% of their hair cells with age (5). Moreover, type I hair cells die off at a higher rate in the SCCs compared to the saccule and utricle, whereas type II hair cells experience similar rates of degeneration in the SCCs and otolith organs (3, 6–8). Utricular hair cells are more susceptible to age-related degeneration than saccular hair cells (3).

The size and number of neurons that make up the vestibular nucleus decrease by 3% each decade beginning around age 40 (9). The number of vestibular nerve fibers also declines with increasing age (10). Fewer vestibular sensory cells and neural pathways result in an age-related reduction in vestibular afferent signals to the central nervous system. There is also an associated reduction in the number of cerebellar Purkinje cells that contribute to modulation of vestibular afferents (11).

Paralleling the anatomical changes, most behavioral experiments have demonstrated a decline in functional vestibular tests [e.g., decreased vestibulo-ocular reflex (VOR) with increased age] (12–16). Fewer sensory cells in the SCCs result in a reduced capacity for detecting rotational head movements. In addition to reduced VOR gain, older adults also have shorter VOR time constants (12). Reduction in the vestibular time constant suggests the neural integrator as a potential site of age-related degeneration (13, 17). Dependence of the VOR on age appears to be variable as not all experiments demonstrate age-related decline in VOR gain (18, 19). VOR function measured by head impulse testing was impaired more often than otolith function based on vestibular-evoked myogenic potential (VEMP) testing for adults over 70 (20).

The functional consequence of fewer sensory cells in the otolith organs includes reduced sensitivity to gravity and linear acceleration (21, 22). Consistent with the decreased sensitivity of the saccule, older adults have smaller amplitude ocular and cervical VEMPs (23–27). Cervical VEMP response latencies are also longer and depend on a greater extent on stimulus volume to generate an effective response in older adults (27, 28). The optimal frequency for air conducted VEMPS also changes with increased age (25). Older adults display less ocular counter roll during slow roll tilt and also in response to galvanic vestibular stimulation consistent with reduced utricular responsiveness (29, 30). Linear VOR responses to fore-aft accelerations were smaller in older adults than in younger adults (31), demonstrating that the otolith responses to movement and to sound/vibration show a similar pattern of decline with age. The linear VOR has been implicated in anticipatory eye movements and a decline in otolith function may contribute to abnormal gaze stability during repetitive behaviors such as walking (32).

FUNCTIONAL IMPACT OF THE AGING VESTIBULAR SYSTEM

It has been estimated that 30–35% of older adults suffers from vestibular dysfunction (33, 34). The most common type of vestibular disorder in the elderly is benign paroxysmal positional vertigo (BPPV) (35), likely due to fewer otoconia adhering to the saccule or utricle combined with alteration in calcium metabolism (22, 26, 36). Diagnosis of BPPV is based on stereotypical patterns of nystagmus and vertigo during positional testing, such as Hallpike–Dix testing (35, 37), supine head turns (38, 39), or deep head hanging (40). Routine medical screening for BPPV has been advocated for older adults due to the prevalence and ease of treatment (41).

Approximately one-third to one-half of the population over the age of 65 experiences an injurious fall annually (42, 43). Vestibular dysfunction results in balance impairments that frequently result in falls (44). Eighty percent of fallers in a recent study were found to have a vestibular impairment (45). Older adults experience more disequilibrium following nerve section associated with treatment of acoustic neuroma compared to younger adults (46). Persistent disequilibrium suggests that sensory reweighting may be more difficult with reduced vestibular input to the aging nervous system (47–49). Sensory reweighting involves prioritizing accurate and reliable sensory information over less reliable or less accurate sensory information for estimating body motion in space (50). Deviations in subjective visual vertical with age are consistent with reduced sensitivity of the otolith organs that lead to an increase in visual weighting to identify vertical (51, 52). Healthy older adults also demonstrate an increase in trunk sway velocity with age (53, 54). Older adults with abnormal utricular responses to whole body tilt have more variable medio-lateral sway relative to young adults, partly due to altered gravitational integration for postural control (29). Additionally, age-related changes in somatosensory function (reduced nerve conduction velocity), visual impairments, cognitive decline, and decreased strength may impact balance-related sensory integration for older adults who develop vestibular pathology (55–57).

Reduced capabilities in the aging vestibular system may impair the ability to rapidly detect changes in head acceleration and may contribute to slower walking as a self-protective strategy to prevent falls in older adults. Falls are known to occur most frequently during walking or transitions from sitting/standing to walking when head acceleration is higher (58). Abnormal SCC function [based on clinical head impulse test (HIT)] has been associated with slower gait speed and increased odds of falling in adults over 70 years old (59). By contrast, individuals with acute unilateral vestibular disease do not show a strong or consistent relationship between trunk velocity while walking and VOR gain (60). These inconsistencies may represent functional distinctions between VOR and vestibulo-spinal pathways despite neural convergence in the vestibular nuclei (61). Walking leg movement and trunk sway may receive different vestibular modulation as has been demonstrated for vision (62). Increased variability of double support time during walking has recently been reported for older female fallers with asymmetric responses to the post head shaking nystagmus test (63). Saccular function has also been shown to contribute to age-related changes in gait speed in healthy older adults (64). Slower gait speed may be a compensation related to postural abnormalities during a task when the base of support is dynamically changing (65), or to impaired visual stability at faster head speeds (66), or both. Differences in sample size, age, and pathology of vestibular dysfunction limit comparisons between these studies and highlight the need for additional studies to better understand the causal link between walking difficulties and age-related decline in SCC and otolith function.

The vestibular system has been linked to visuospatial function (67, 68), and individuals with vestibular loss experience difficulties with spatial navigation (69). Accurate spatial navigation depends on having a stable egocentric reference frame, and the vestibular system has been proposed as a source for that reference (70). Older fallers made significantly larger errors when performing a triangle walking task blindfolded, demonstrating a reduced ability to accurately perform spatial path integration (71, 72). Older adults have greater difficulty integrating multisensory cues for navigation than younger adults (73). Older adults are more likely to experience cognitive decline, and vestibular dysfunction mediates the decline in cognition associated with increased age (74). It is not clear to what extent age-related decline in spatial navigation measured when blindfolded relates to goal-oriented

walking since path direction is influenced by vision, vestibular, and proprioceptive input (75).

However, many older adults with degenerating vestibular systems do not report imbalance or dizziness (13). Symptom reports do not consistently relate to either physiological (i.e., VOR) or perceptual assessments of vestibular function such as dynamic visual acuity (76–80). Further complicating the mismatch between symptoms and physiology, older adults may have anxiety/depression/fear of falling that exacerbates or mimics symptoms from age-related vestibular dysfunction (81–84). Due to limitations in vestibular diagnostic testing, clinicians may not be able to detect residual vestibular function in older adults with vestibular loss confirmed by current diagnostic testing (20, 85). Among older adults with severe vestibular loss canal function was impaired in 100% of individuals, but approximately 60% of those individuals demonstrate some degree of preserved otolith function (86). However, canal function evaluated by HIT does not require complete absence of function in order to be identified as pathologic (87, 88); therefore, there may also be preserved canal function in adults with age-related decline in vestibular function based on HITs. In addition to partially preserved vestibular function, inconsistent subjective reports may also be due to anticipatory mechanisms (89, 90), changes in lifestyle behaviors (91), or changes in multisensory reweighting (92, 93).

FUTURE DIRECTIONS FOR FUNCTIONAL VESTIBULAR TESTING

Current vestibular assessments are very good at characterizing the reactivity of the peripheral vestibular sensory epithelium; however, they rely on artificial and unnatural stimuli to determine whether the vestibular system is working (79, 94, 95). The relevance of these artificial assessments to natural multisensory functional behavior is not always clear (96, 97). Even when there are associations between vestibular tests and functional activities, such as standing and walking, the direct causal link between walking and tests performed while sitting or lying down remains to be elucidated. Some tests such as calorics and clinical head impulse testing are very good at identifying abnormal vestibular function (88), but they may not be sensitive enough to identify slow decline in vestibular function associated with age (41). The range for clinically normal rotational VOR gain is 0.7–1.0, making it is unclear whether the measure of rotational VOR gain is adequate to capture age-related decline (14, 15, 98). Recently, more attention has been placed on corrective saccades resulting from head impulse testing as an additional method for identifying age-related change in vestibular-mediated gaze stability (99–101). Quantification of gaze stability based on compensatory saccades may prove to be more sensitive for identifying subtle age-related decline in vestibular function associated with aging. Since adaptive compensatory saccades contribute to gaze stability to a greater extent in response to vestibular pathology (102), new methods to quantify "global gaze stability" during natural behavior are needed that allow for multiple loci for neural control.

Current clinical balance assessments cannot specifically identify change in vestibular function as the primary contribution to balance problems for older adults. Perturbation-based evaluation of balance and sensory weighting allows for balance testing to move beyond descriptions of sway to mechanistic identification of abnormal multisensory integration (50, 103). This type of balance assessment has the potential to move beyond the standard approach to clinical balance assessment for older adults and bring balance rehabilitation closer to precision medicine. Major limitations to implement this level of precision diagnostics for balance include the expense of equipment, space for equipment, technical skills to perform the experiment, and interpret the experimental results. Additionally, the time needed to conduct these experiments may be clinically prohibitive. Future work in this field should focus on adapting perturbation style laboratory techniques for identifying mechanistic contributions to balance impairments into clinical settings (104), as well as controlled trials designed to target impaired balance mechanisms with rehabilitation strategies using a precision medicine approach. Clinical adaptations could include the use of body worn inertial sensors and head-mounted displays for visual stimulation to reduce equipment cost and space (105, 106). Electrical vestibular stimulation and tendon vibration could provide specific stimulation (103), rather than relying on non-specific effects encountered with foam surfaces. Demonstrating that equivalent results can be obtained in a shorter, more clinically friendly time frame is necessary before widespread clinical acceptance of this technique. Furthermore, task-specific balance assessment should not be restricted to standing balance. Body worn inertial sensors and smartphone technology can and should be leveraged to identify functional balance impairments during tasks, such as walking, obstacle crossing, and stair negotiation (60, 107, 108).

The ability to see clearly during head/body movement is important for many daily tasks, such as shopping, obstacle avoidance and manipulation, determining location/navigation by reading signs, and driving. The primary purpose of the VOR is to stabilize gaze during locomotion (109, 110). Oscillopsia, the apparent "jumping of objects … due to bobbing up and down of the head" degrades visual acuity during head motion making faces or reading signs/labels difficult or impossible to recognize (111–113). Oscillopsia can lead to reduced quality of life through reduction in activity participation, elevated economic burden, and self-imposed limitations on driving (86, 114). In contrast to seated tests of gaze stability, walking gaze stability depends on multiple sensory systems (vision, vestibular, and proprioception) for coordination of ocular muscles with postural muscles that control movement of the head (115–118). Characterizing overall gaze stability during walking would provide greater insight into actual functional problems experienced by older adults with reduced vestibular function. Overall gaze stability, despite being less physiologically specific, during a more natural behavior such as walking would be more informative about the daily life impact that vestibular decline has on older adults. In order to be more patient focused, future studies should move beyond the laboratory to evaluate functional gaze stability in natural settings during typical daily tasks. This is particularly relevant for studies attempting to link head impulse assessment of VOR gain to gaze stability during walking as peak head velocity during walking often exceeds the peak velocity of a head impulse (119). Portable

lightweight gaze analysis systems could be sent home to capture a "day in the life" of an older adult or individuals with vestibular dysfunction.

Despite associations between VEMP tests and functional behaviors such as gait speed, the directionality and causality of those links remain unclear. Functionally relevant methods to evaluate otolith contributions to vestibulo-spinal control during standing and walking are needed (120, 121). Including assessments when the postural control system is under real or apparent threat, for example at heights, will also be important as vestibulo-spinal gain and postural sway are different under those conditions (121–123). Treadmills paired with virtual reality or head-mounted displays should be leveraged to evaluate spatial navigation for older adults. Immersive technology will facilitate simultaneous measurement of balance and walking ability, gaze stability, and eye movement control, while also tasking aspects of cognition, fear/anxiety, and ability to navigate through space. As new methods are devised to probe functional vestibular behavior, they will need to incorporate physiologically relevant vestibular stimulation for the SCCs and otoliths while also capturing the multiple systems influenced by the vestibular system (119, 124). A comprehensive and integrative approach to the evaluation of vestibular function should concurrently address gaze stability and postural control during functionally relevant standing and walking tasks.

AUTHOR CONTRIBUTIONS

EA and JJ conceived of the work. EA drafted the work. EA and JJ critically revised the work. EA and JJ approved the final version.

FUNDING

Supported in part by NIDCD T32 DC000023.

REFERENCES

1. Lopez I, Ishiyama G, Tang Y, Tokita J, Baloh RW, Ishiyama A. Regional estimates of hair cells and supporting cells in the human crista ampullaris. *J Neurosci Res* (2005) **82**:421–31. doi:10.1002/jnr.20652
2. Rosenhall U, Rubin W. Degenerative changes in the human vestibular sensory epithelia. *Acta Otoaryngol* (1975) **79**:67–80. doi:10.3109/00016487509124657
3. Gleeson M, Felix H. A comparative study of the effect of age on the human cochlear and vestibular neuroepithelia. *Acta Otoaryngol Suppl* (1987) **436**:103–9. doi:10.3109/00016488709124982
4. Taylor RR, Jagger DJ, Saeed SR, Axon P, Donnelly N, Tysome J, et al. Characterizing human vestibular sensory epithelia for experimental studies: new hair bundles on old tissue and implications for therapeutic interventions in ageing. *Neurobiol Aging* (2015) **36**:2068–84. doi:10.1016/j.neurobiolaging.2015.02.013
5. Matheson AJ, Darlington CL, Smith PF. Dizziness in the elderly and age-related degeneration of the vestibular system. *NZ J Psychol* (1999) **28**:10–6.
6. Anniko M. The aging vestibular hair cell. *Am J Otolaryngol* (1983) **4**:151–60. doi:10.1016/S0196-0709(83)80037-4
7. Rosenhall U. Degenerative patterns in the aging human vestibular neuro-epithelia. *Acta Otolaryngol* (1973) **76**:208–20. doi:10.3109/00016487309121501
8. Rauch SD, Velazquez-Villaseñor L, Dimitri PS, Merchant SN. Decreasing hair cell counts in aging humans. *Ann N Y Acad Sci* (2001) **942**:220–7. doi:10.1111/j.1749-6632.2001.tb03748.x
9. Lopez I, Honrubia V, Baloh RW. Aging and the human vestibular nucleus. *J Vestib Res* (1997) **7**:77–85. doi:10.1016/S0957-4271(96)00137-1
10. Park JJ, Tang Y, Lopez I, Ishiyama A. Age-related change in the number of neurons in the human vestibular ganglion. *J Comp Neurol* (2001) **431**:437–43. doi:10.1002/1096-9861(20010319)431:4<437::AID-CNE1081>3.0.CO;2-P
11. Andersen BB, Gundersen HJG, Pakkenberg B. Aging of the human cerebellum: a stereological study. *J Comp Neurol* (2003) **466**:356–65. doi:10.1002/cne.10884
12. Baloh RW, Jacobson KM, Socotch TM. The effect of aging on visual-vestibuloocular responses. *Exp Brain Res* (1993) **95**:509–16. doi:10.1007/BF00227144
13. Baloh RW, Enrietto J, Jacobson KM, Lin A. Age-related changes in vestibular function: a longitudinal study. *Ann N Y Acad Sci* (2001) **942**:210–9. doi:10.1111/j.1749-6632.2001.tb03747.x
14. Li C, Layman AJ, Geary R, Anson E, Carey JP, Ferrucci L, et al. Epidemiology of vestibulo-ocular reflex function: data from the Baltimore Longitudinal Study of Aging. *Otol Neurotol* (2015) **36**:267–72. doi:10.1097/MAO.0000000000000610
15. McGarvie LA, MacDougall HG, Halmagyi GM, Burgess AM, Weber KP, Curthoys IS. The video head impulse test (vHIT) of semicircular canal function – age-dependent normative values of VOR gain in healthy subjects. *Front Neurol* (2015) **6**:1–11. doi:10.3389/fneur.2015.00154
16. Mossman B, Mossman S, Purdie G, Schneider E. Age dependent normal horizontal VOR gain of head impulse test as measured with video-oculography. *J Otolaryngol Head Neck Surg* (2015) **44**:29. doi:10.1186/s40463-015-0081-7
17. Enrietto JA, Jacobson KM, Baloh RW. Aging effects on auditory and vestibular responses: a longitudinal study. *Am J Otolaryngol* (1999) **20**:371–8. doi:10.1016/S0196-0709(99)90076-5
18. Furman JM, Redfern MS. Effect of aging on the otolith-ocular reflex. *J Vestib Res* (2001) **11**(2):91–103.
19. Maes L, Dhooge I, D'Haenens W, Bockstael A, Keppler H, Philips B, et al. The effect of age on the sinusoidal harmonic acceleration test, pseudorandom rotation test, velocity step test, caloric test, and vestibular-evoked myogenic potential test. *Ear Hear* (2010) **31**:84–94. doi:10.1097/AUD.0b013e3181b9640e
20. Agrawal Y, Zuniga MG, Davalos-Bichara M, Schubert MC, Walston JD, Hughes J, et al. Decline in semicircular canal and otolith function with age. *Otol Neurotol* (2012) **33**:832–9. doi:10.1097/MAO.0b013e3182545061
21. Walther LE, Westhofen M. Presbyvertigo-aging of otoconia and vestibular sensory cells. *J Vestib Res* (2007) **17**(2–3):89–92.
22. Igarashi M, Saito R, Mizukoshi K, Alford BR. Otoconia in young and elderly persons: a temporal bone study. *Acta Otolaryngol Suppl* (1993) **504**:26–9. doi:10.3109/00016489309128117
23. Akin FW, Murnane OD, Tampas JW, Clinard CG. The effect of age on the vestibular evoked myogenic potential and sternocleidomastoid muscle tonic electromyogram level. *Ear Hear* (2011) **32**:617–22. doi:10.1097/AUD.0b013e318213488e
24. Li C, Layman AJ, Carey JP, Agrawal Y. Epidemiology of vestibular evoked myogenic potentials: data from the Baltimore Longitudinal Study of Aging. *Clin Neurophysiol* (2015) **126**:2207–15. doi:10.1016/j.clinph.2015.01.008
25. Piker EG, Jacobson GP, Burkard RF, McCaslin DL, Hood LJ. Effects of age on the tuning of the cVEMP and oVEMP. *Ear Hear* (2013) **34**:e65–73. doi:10.1097/AUD.0b013e31828fc9f2
26. Ishiyama G. Imbalance and vertigo: the aging human vestibular periphery. *Semin Neurol* (2009) **29**:491–9. doi:10.1055/s-0029-1241039
27. Welgampola MS, Colebatch JG. Vestibulocollic reflexes: normal values and the effect of age. *Clin Neurophysiol* (2001) **112**:1971–9. doi:10.1016/S1388-2457(01)00645-9
28. Maleki M, Jafari Z, Zarrinkoob H, Akbarzadeh Baghban A. Effect of aging on saccular function. *Med J Islam Repub Iran* (2014) **28**:117.
29. Serrador JM, Lipsitz LA, Gopalakrishnan GS, Black FO, Wood SJ. Loss of otolith function with age is associated with increased postural sway measures. *Neurosci Lett* (2009) **465**:10–5. doi:10.1016/j.neulet.2009.08.057

30. Jahn K, Naessl A, Schneider E, Strupp M, Brandt T, Dieterich M. Inverse U-shaped curve for age dependency of torsional eye movement responses to galvanic vestibular stimulation. *Brain* (2003) **126**:1579–89. doi:10.1093/brain/awg163
31. Tian J, Mokuno E, Demer JL. Vestibulo-ocular reflex to transient surge translation: complex geometric response ablated by normal aging. *J Neurophysiol* (2006) **95**:2042–54. doi:10.1152/jn.00635.2005
32. Schneider R, Walker MF. Amplitude and frequency prediction in the translational vestibulo-ocular reflex. *J Vestib Res* (2014) **24**:357–64. doi:10.3233/VES-140528
33. 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**:938–44. doi:10.1001/archinternmed.2009.66
34. Neuhauser HK, Radtke A, von Brevern M, Lezius F, Feldmann M, Lempert T. Burden of dizziness and vertigo in the community. *Arch Intern Med* (2008) **168**:2118–24. doi:10.1001/archinte.168.19.2118
35. von Brevern M. Benign paroxysmal positional vertigo. *Semin Neurol* (2013) **33**:204–11. doi:10.1055/s-0033-1354590
36. Otsuka K, Suzuki M, Furuya M. Model experiment of benign paroxysmal positional vertigo mechanism using the whole membranous labyrinth. *Acta Otolaryngol* (2003) **123**:515–8. doi:10.1080/0036554021000028094
37. Dix MR, Hallpike CS. The pathology symptomatology and diagnosis of certain common disorders of the vestibular system. *Proc R Soc Med* (1952) **45**:341–54.
38. Fife TD. Recognition and management of horizontal canal benign positional vertigo. *Am J Otol* (1998) **19**:345–51.
39. Parnes LS, Agrawal SK, Atlas J. Diagnosis and management of benign paroxysmal positional vertigo (BPPV). *CMAJ* (2003) **169**(7):681–93.
40. Yacovino DA, Hain TC, Gualtieri F. New therapeutic maneuver for anterior canal benign paroxysmal positional vertigo. *J Neurol* (2009) **256**:1851–5. doi:10.1007/s00415-009-5208-1
41. Furman JM, Raz Y, Whitney SL. Geriatric vestibulopathy assessment and management. *Curr Opin Otolaryngol Head Neck Surg* (2010) **18**:386–91. doi:10.1097/MOO.0b013e32833ce5a6
42. Stevens JA, Mack KA, Paulozzi LJ, Ballesteros MF. Self-reported falls and fall-related injuries among persons aged >or=65 years – United States, 2006. *J Safety Res* (2008) **39**:345–9. doi:10.1016/j.jsr.2008.05.002
43. Alamgir H, Muazzam S, Nasrullah M. Unintentional falls mortality among elderly in the United States: time for action. *Injury* (2012) **43**:2065–71. doi:10.1016/j.injury.2011.12.001
44. Jáuregui-Renaud K, Gutierrez-Marquez A, Viveros-Rentería L, Ramos-Toledo V, Gómez-Alvarez F. Neurotology symptoms at referral to vestibular evaluation. *J Otolaryngol Head Neck Surg* (2013) **42**:55. doi:10.1186/1916-0216-42-55
45. Liston MB, Bamiou D-E, Martin F, Hopper A, Koohi N, Luxon L, et al. Peripheral vestibular dysfunction is prevalent in older adults experiencing multiple non-syncopal falls versus age-matched non-fallers: a pilot study. *Age Ageing* (2014) **43**:38–43. doi:10.1093/ageing/aft129
46. Driscoll CL, Lynn SG, Harner SG, Beatty CW, Atkinson EJ. Preoperative identification of patients at risk of developing persistent dysequilibrium after acoustic neuroma removal. *Am J Otol* (1998) **19**:491–5.
47. Guerraz M, Yardley L, Bertholon P, Pollak L, Rudge P, Gresty MA, et al. Visual vertigo: symptom assessment, spatial orientation and postural control. *Brain* (2001) **124**:1646–56. doi:10.1093/brain/124.8.1646
48. Borel L, Harlay F, Magnan J, Chays A, Lacour M. Deficits and recovery of head and trunk orientation and stabilization after unilateral vestibular loss. *Brain* (2002) **125**:880–94. doi:10.1093/brain/awf085
49. Assländer L, Hettich G, Mergner T. Visual contribution to human standing balance during support surface tilts. *Hum Mov Sci* (2015) **41**:147–64. doi:10.1016/j.humov.2015.02.010
50. Peterka RA. Sensorimotor integration in human postural control. *J Neurophysiol* (2002) **88**(3):1097–118. doi:10.1152/jn.00605.2001
51. Kobayashi H, Hayashi Y, Higashino K, Saito A, Kunihiro T, Kanzaki J, et al. Dynamic and static subjective visual vertical with aging. *Auris Nasus Larynx* (2002) **29**:325–8. doi:10.1016/S0385-8146(02)00058-5
52. Sun DQ, Zuniga MG, Davalos-Bichara M, Carey JP, Agrawal Y. Evaluation of a bedside test of utricular function – the bucket test – in older individuals. *Acta Otolaryngol* (2014) **134**:382–9. doi:10.3109/00016489.2013.867456
53. Gill J, Allum JH, Carpenter MG, Held-Ziolkowska M, Adkin AL, Honegger F, et al. Trunk sway measures of postural stability during clinical balance tests: effects of age. *J Gerontol A Biol Sci Med Sci* (2001) **56**:M438–47. doi:10.1093/gerona/56.7.M438
54. Hegeman J, Shapkova EY, Honegger F, Allum JHJ. Effect of age and height on trunk sway during stance and gait. *J Vestib Res* (2007) **17**(2–3):75–87.
55. Deveze A, Bernard-Demanze L, Xavier F, Lavieille J-P, Elziere M. Vestibular compensation and vestibular rehabilitation. Current concepts and new trends. *Neurophysiol Clin* (2014) **44**:49–57. doi:10.1016/j.neucli.2013.10.138
56. Redfern MS, Jennings JR, Martin C, Furman JM. Attention influences sensory integration for postural control in older adults. *Gait Posture* (2001) **14**:211–6. doi:10.1016/S0966-6362(01)00144-8
57. Iwasaki S, Yamasoba T. Dizziness and imbalance in the elderly: age-related decline in the vestibular system. *Aging Dis* (2015) **6**:38–47. doi:10.14336/AD.2014.0128
58. Robinovitch SN, Feldman F, Yang Y, Schonnop R, Leung PM, Sarraf T, et al. Video capture of the circumstances of falls in elderly people residing in long-term care: an observational study. *Lancet* (2013) **381**:47–54. doi:10.1016/S0140-6736(12)61263-X
59. Agrawal Y, Davalos-Bichara M, Zuniga MG, Carey JP. Head impulse test abnormalities and influence on gait speed and falls in older individuals. *Otol Neurotol* (2013) **34**:1729–35. doi:10.1097/MAO.0b013e318295313c
60. Allum JHJ, Honegger F. Relation between head impulse tests, rotating chair tests, and stance and gait posturography after an acute unilateral peripheral vestibular deficit. *Otol Neurotol* (2013) **34**:980–9. doi:10.1097/MAO.0b013e31829ce5ec
61. Carriot J, Jamali M, Brooks JX, Cullen KE. Integration of canal and otolith inputs by central vestibular neurons is subadditive for both active and passive self-motion: implication for perception. *J Neurosci* (2015) **35**:3555–65. doi:10.1523/JNEUROSCI.3540-14.2015
62. Logan D, Ivanenko YP, Kiemel T, Cappellini G, Sylos-Labini F, Lacquaniti F, et al. Function dictates the phase dependence of vision during human locomotion. *J Neurophysiol* (2014) **112**:165–80. doi:10.1152/jn.01062.2012
63. Larsson J, Ekvall Hansson E, Miller M. Increased double support variability in elderly female fallers with vestibular asymmetry. *Gait Posture* (2015) **41**:820–4. doi:10.1016/j.gaitpost.2015.02.019
64. Layman AJ, Li C, Simonsick E, Ferrucci L, Carey JP, Agrawal Y. Association between saccular function and gait speed: data from the Baltimore Longitudinal Study of Aging. *Otol Neurotol* (2015) **36**:260–6. doi:10.1097/MAO.0000000000000544
65. Novak AC, Deshpande N. Effects of aging on whole body and segmental control while obstacle crossing under impaired sensory conditions. *Hum Mov Sci* (2014) **35**:121–30. doi:10.1016/j.humov.2014.03.009
66. Honaker JA, Shepard NT. Age effect on the gaze stabilization test. *J Vestib Res* (2010) **20**(5):357–62. doi:10.3233/VES-2010-0365
67. Yoder RM, Taube JS. The vestibular contribution to the head direction signal and navigation. *Front Integr Neurosci* (2014) **8**:1–13. doi:10.3389/fnint.2014.00032
68. Bigelow RT, Semenov YR, Trevino C, Ferrucci L, Resnick SM, Simonsick EM, et al. Association between visuospatial ability and vestibular function in the Baltimore Longitudinal Study of Aging. *J Am Geriatr Soc* (2015) **63**:1837–44. doi:10.1111/jgs.13609
69. Jandl NM, Sprenger A, Wojak JF, Göttlich M, Münte TF, Krämer UM, et al. Dissociable cerebellar activity during spatial navigation and visual memory in bilateral vestibular failure. *Neuroscience* (2015) **305**:257–67. doi:10.1016/j.neuroscience.2015.07.089
70. Cohen HS. Vestibular disorders and impaired path integration along a linear trajectory. *J Vestib Res* (2000) **10**(1):7–15.
71. Barrett MM, Doheny EP, Setti A, Maguinness C, Foran TG, Kenny RA, et al. Reduced vision selectively impairs spatial updating in fall-prone older adults. *Multisens Res* (2013) **26**:69–94. doi:10.1163/22134808-00002412
72. Adamo DE, Briceño EM, Sindone JA, Alexander NB, Moffat SD. Age differences in virtual environment and real world path integration. *Front Aging Neurosci* (2012) **4**:26. doi:10.3389/fnagi.2012.00026

73. Bates SL, Wolbers T. How cognitive aging affects multisensory integration of navigational cues. *Neurobiol Aging* (2014) **35**:2761–9. doi:10.1016/j.neurobiolaging.2014.04.003
74. Semenov YR, Bigelow RT, Xue Q-L, Lac SD, Agrawal Y. Association between vestibular and cognitive function in U.S. adults: data from the National Health and Nutrition Examination Survey. *J Gerontol A Biol Sci Med Sci* (2015). doi:10.1093/gerona/glv069
75. Rossignol S, Dubuc R, Gossard J-P. Dynamic sensorimotor interactions in locomotion. *Physiol Rev* (2006) **86**:89–154. doi:10.1152/physrev.00028.2005
76. Bhansali SA, Stockwell CW, Bojrab DI. Oscilopsia in patients with loss of vestibular function. *Otolaryngol Head Neck Surg* (1993) **109**:120–5.
77. McGath JH, Barber HO, Stoyanoff S. Bilateral vestibular loss and oscillopsia. *J Otolaryngol* (1989) **18**:218–21.
78. Schubert MC, Herdman SJ, Tusa RJ. Vertical dynamic visual acuity in normal subjects and patients with vestibular hypofunction. *Otol Neurotol* (2002) **23**:372–7. doi:10.1097/00129492-200205000-00025
79. Badaracco C, Labini FS, Meli A, Tufarelli D. Oscillopsia in labyrinthine defective patients: comparison of objective and subjective measures. *Am J Otolaryngol Neck Med Surg* (2010) **31**:399–403. doi:10.1016/j.amjoto.2009.06.002
80. Guinand N, Pijnenburg M, Janssen M, Kingma H. Visual acuity while walking and oscillopsia severity in healthy subjects and patients with unilateral and bilateral vestibular function loss. *Arch Otolaryngol Head Neck Surg* (2012) **138**:301–6. doi:10.1001/archoto.2012.4
81. Marchetti GF, Whitney SL, Redfern MS, Furman JM. Factors associated with balance confidence in older adults with health conditions affecting the balance and vestibular system. *Arch Phys Med Rehabil* (2011) **92**:1884–91. doi:10.1016/j.apmr.2011.06.015
82. Hong SM, Kim B-G, Lee BC, Park S-K, Hong SK, Lee H-J, et al. Analysis of psychological distress after management of dizziness in old patients: multicenter study. *Eur Arch Otorhinolaryngol* (2012) **269**:39–43. doi:10.1007/s00405-011-1591-1
83. Zur O, Schoen G, Dickstein R, Feldman J, Berner Y, Dannenbaum E, et al. Anxiety among individuals with visual vertigo and vestibulopathy. *Disabil Rehabil* (2015) **37**:2197–202. doi:10.3109/09638288.2014.1002577
84. Jacobson GP, Piker EG, Watford KE, Gruenwald J, Wanna GB, Rivas A. Concordance and discordance in patient and provider perceptions of dizziness. *Am J Otolaryngol* (2014) **35**:779–83. doi:10.1016/j.amjoto.2014.05.003
85. Brantberg K, Löfqvist L. Preserved vestibular evoked myogenic potentials (VEMP) in some patients with walking-induced oscillopsia due to bilateral vestibulopathy. *J Vestib Res* (2007) **17**(1):33–8.
86. Agrawal Y, Ward BK, Minor LB. Vestibular dysfunction: prevalence, impact and need for targeted treatment. *J Vestib Res* (2013) **23**:113–7. doi:10.3233/VES-130498.Vestibular
87. Perez N, Rama-Lopez J. Head-impulse and caloric tests in patients with dizziness. *Otol Neurotol* (2003) **24**:913–7. doi:10.1097/00129492-200311000-00016
88. Cohen HS, Sangi-Haghpeykar H, Ricci NA, Kampangkaew J, Williamson RA. Utility of stepping, walking, and head impulses for screening patients for vestibular impairments. *Otolaryngol Head Neck Surg* (2014) **151**:131–6. doi:10.1177/0194599814527724
89. Schubert MC, Zee DS. Saccade and vestibular ocular motor adaptation. *Restor Neurol Neurosci* (2010) **28**:9–18. doi:10.3233/RNN-2010-0523.Saccade
90. Lehnen N, Ulrich B, Glasauer S. Head-free gaze control in humans with chronic loss of vestibular function. *Ann N Y Acad Sci* (2009) **1164**:409–12. doi:10.1111/j.1749-6632.2009.03774.x
91. Ward BK, Agrawal Y, Hoffman HJ, Carey JP, Della Santina CC. Prevalence and impact of bilateral vestibular hypofunction: results from the 2008 US National Health Interview Survey. *JAMA Otolaryngol Head Neck Surg* (2013) **139**:803–10. doi:10.1001/jamaoto.2013.3913
92. Jeka JJ, Allison LK, Kiemel T. The dynamics of visual reweighting in healthy and fall-prone older adults. *J Mot Behav* (2010) **42**:197–208. doi:10.1080/00222895.2010.481693
93. Franz JR, Francis CA, Allen MS, O'Connor SM, Thelen DG. Advanced age brings a greater reliance on visual feedback to maintain balance during walking. *Hum Mov Sci* (2015) **40**:381–92. doi:10.1016/j.humov.2015.01.012
94. Demer JL, Crane BT. Ocular compensation due to labyrinthine input during natural motion. *Ann N Y Acad Sci* (2001) **942**:148–61. doi:10.1111/j.1749-6632.2001.tb03742.x
95. Robinson DA. The oculomotor control system: a review. *Proc IEEE* (1968) **56**:1032–49. doi:10.1109/PROC.1968.6455
96. Grossman GE, Leigh RJ. Instability of gaze during walking in patients with deficient vestibular function. *Ann Neurol* (1990) **27**:528–32. doi:10.1002/ana.410270512
97. Dowiasch S, Marx S, Einhäuser W, Bremmer F. Effects of aging on eye movements in the real world. *Front Hum Neurosci* (2015) **9**:46. doi:10.3389/fnhum.2015.00046
98. MacDougall HG, McGarvie LA, Halmagyi GM, Curthoys IS, Weber KP. The video head impulse test (vHIT) detects vertical semicircular canal dysfunction. *PLoS One* (2013) **8**:e61488. doi:10.1371/journal.pone.0061488
99. Yang C, Lee JY, Kang BC, Lee HS, Yoo MH, Park HJ. Quantitative analysis of gains and catch-up saccades of video-head impulse testing by age in normal subjects. *Clin Otolaryngol* (2015). doi:10.1111/coa.12558
100. Perez-Fernandez N, Eza-Nuñez P. Normal gain of VOR with refixation saccades in patients with unilateral vestibulopathy. *J Int Adv Otol* (2015) **11**:133–7. doi:10.5152/iao.2015.1087
101. Matiño-Soler E, Esteller-More E, Martin-Sanchez J-C, Martinez-Sanchez J-M, Perez-Fernandez N. Normative data on angular vestibulo-ocular responses in the yaw axis measured using the video head impulse test. *Otol Neurotol* (2015) **36**:466–71. doi:10.1097/MAO.0000000000000661
102. Mantokoudis G, Schubert MC, Tehrani ASS, Wong AL, Agrawal Y. Early adaptation and compensation of clinical vestibular responses after unilateral vestibular deafferentation surgery. *Otol Neurotol* (2014) **35**:148–54. doi:10.1097/MAO.0b013e3182956196
103. Hwang S, Agada P, Kiemel T, Jeka JJ. Dynamic reweighting of three modalities for sensor fusion. *PLoS One* (2014) **9**:1–8. doi:10.1371/journal.pone.0088132
104. Engelhart D, Pasma JH, Schouten AC, Meskers CGM, Maier AB, Mergner T, et al. Impaired standing balance in elderly: a new engineering method helps to unravel causes and effects. *J Am Med Dir Assoc* (2014) **15**:.e1–6. doi:10.1016/j.jamda.2013.09.009
105. Alahmari KA, Marchetti GF, Sparto PJ, Furman JM, Whitney SL. Estimating postural control with the balance rehabilitation unit: measurement consistency, accuracy, validity, and comparison with dynamic posturography. *Arch Phys Med Rehabil* (2014) **95**:65–73. doi:10.1016/j.apmr.2013.09.011
106. Allum JHJ, Adkin AL. Improvements in trunk sway observed for stance and gait tasks during recovery from an acute unilateral peripheral vestibular deficit. *Audiol Neurootol* (2003) **8**:286–302. doi:10.1159/000071999
107. Salarian A, Horak FB, Zampieri C, Carlson-Kuhta P, Nutt JG, Aminian K. iTUG, a sensitive and reliable measure of mobility. *IEEE Trans Neural Syst Rehabil Eng* (2010) **18**:303–10. doi:10.1109/TNSRE.2010.2047606
108. Mellone S, Tacconi C, Chiari L. Validity of a smartphone-based instrumented timed up and go. *Gait Posture* (2012) **36**:163–5. doi:10.1016/j.gaitpost.2012.02.006
109. Grossman GE, Leigh RJ, Bruce EN, Huebner WP, Lanska DJ. Performance of the human vestibuloocular reflex during locomotion. *J Neurophysiol* (1989) **62**:264–72.
110. Leigh RJ, Brandt T. A reevaluation of the vestibulo-ocular reflex: new ideas of its purpose, properties, neural substrate, and disorders. *Neurology* (1993) **43**:1288–95. doi:10.1212/WNL.43.7.1288
111. Crawford J. Living without a balancing mechanism. *Br J Ophthalmol* (1964) **48**:357–60. doi:10.1136/bjo.48.7.357
112. Ford FR, Walsh FB. Clinical observations upon the importance of the vestibular reflexes in ocular movements. *Bull Johns Hopkins Hosp* (1936) **58**:80–8.
113. Wist ER, Brandt T, Krafczyk S. Oscillopsia and retinal slip evidence supporting a clinical test. *Brain* (1983) **106**:153–68. doi:10.1093/brain/106.1.153
114. Sun DQ, Ward BK, Semenov YR, Carey JP, Della Santina CC. Bilateral vestibular deficiency: quality of life and economic implications. *JAMA Otolaryngol Head Neck Surg* (2014) **140**:527–34. doi:10.1001/jamaoto.2014.490
115. DellaSantina CC, Cremer PD, Carey JP, Minor LB. Comparison of head thrust test with head autorotation test reveals that the vestibulo-ocular reflex is enhanced during voluntary head movements. *Arch Otolaryngol Head Neck Surg* (2002) **128**:1044–54. doi:10.1001/archotol.128.9.1044
116. Demer JL. Evaluation of vestibular and visual oculomotor function. *Otolaryngol Head Neck Surg* (1995) **112**:16–35. doi:10.1016/S0194-5998(95)70301-2
117. Pozzo T, Berthoz A, Lefort L, Vitte E. Head stabilization during various locomotor tasks in humans. II. Patients with bilateral peripheral vestibular deficits. *Exp Brain Res* (1991) **85**:208–17. doi:10.1007/BF00230002

118. Herdman SJ, Hall CD, Schubert MC, Das VE, Tusa RJ. Recovery of dynamic visual acuity in bilateral vestibular hypofunction. *Arch Otolaryngol Head Neck Surg* (2007) **133**:383–9. doi:10.1001/archotol.133.4.383
119. Allum JHJ. Recovery of vestibular ocular reflex function and balance control after a unilateral peripheral vestibular deficit. *Front Neurol* (2012) **3**:83. doi:10.3389/fneur.2012.00083
120. Laube R, Govender S, Colebatch JG. Vestibular-dependent spinal reflexes evoked by brief lateral accelerations of the heads of standing subjects. *J Appl Physiol* (2012) **112**:1906–14. doi:10.1152/japplphysiol.00007.2012
121. Naranjo EN, Allum JHJ, Inglis JT, Carpenter MG. Increased gain of vestibulospinal potentials evoked in neck and leg muscles when standing under height-induced postural threat. *Neuroscience* (2015) **293**:45–54. doi:10.1016/j.neuroscience.2015.02.026
122. Wuehr M, Kugler G, Schniepp R, Eckl M, Pradhan C, Jahn K, et al. Balance control and anti-gravity muscle activity during the experience of fear at heights. *Physiol Rep* (2014) **2**:e00232. doi:10.1002/phy2.232
123. Kugler G, Huppert D, Schneider E, Brandt T. Fear of heights freezes gaze to the horizon. *J Vestib Res* (2014) **24**:433–41. doi:10.3233/VES-140529
124. Hitier M, Besnard S, Smith PF. Vestibular pathways involved in cognition. *Front Integr Neurosci* (2014) **8**:59. doi:10.3389/fnint.2014.00059

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 25 January 2016
doi: 10.3389/fneur.2016.00004

Absence of Rotation Perception during Warm Water Caloric Irrigation in Some Seniors with Postural Instability

*Elodie Chiarovano[1,2], Pierre-Paul Vidal[1], Christophe Magnani[1], Georges Lamas[2], Ian S. Curthoys[3] and Catherine de Waele[1,2]**

[1] CNRS UMR 8257, Cognition and Action Group, Centre Universitaire des Saints-Pères, Université Paris Descartes, Paris, France, [2] ENT Department, Salpetriere Hospital, Paris, France, [3] Vestibular Research Laboratory, School of Psychology, University of Sydney, Sydney, NSW, Australia

Falls in seniors are a major public health problem. Falls lead to fear of falling, reduced mobility, and decreased quality of life. Vestibular dysfunction is one of the fall risk factors. The relationship between objective measures of vestibular responses and age has been studied. However, the effects of age on vestibular perception during caloric stimulation have not been studied. Twenty senior subjects were included in the study, and separated in two groups: 10 seniors reporting postural instability (PI) and exhibiting absence of vestibular perception when they tested with caloric stimulation and 10 sex- and age-matched seniors with no such problems (controls). We assessed vestibular perception on a binary rating scale during the warm irrigation of the caloric test. The function of the various vestibular receptors was assessed using video head impulse test (vHIT), caloric tests, and cervical and ocular vestibular-evoked myogenic potentials. The Equitest was used to evaluate balance. No horizontal canal dysfunction assessed using both caloric test and vHIT was detected in either group. No significant difference was detected between PI and control groups for the peak SPV of caloric-induced ocular nystagmus or for the HVOR gain. All the controls perceived rotation when the maximal SPV during warm irrigation was equal to or ≥15°/s. None of the subjects in the PI group perceived rotation even while the peak SPV exceeded 15°/s, providing objective evidence of normal peripheral horizontal canal function. All the PI group had abnormal Equitest results, particularly in the two last conditions. These investigations show for the first time that vestibular perception can be absent during a caloric test despite normal horizontal canal function. We call this as dissociation vestibular neglect. Patients with poor vestibular perception may not be aware of postural perturbations and so will not correct for them. Thus, falls in the elderly may result, among other factors, from a vestibular neglect due to an inappropriate central processing of normal vestibular peripheral inputs. That is, failure to perceive rotation during caloric testing when the SPV is >15°/s, should prompt the clinician to envisage preventive actions to avoid future falls such as rehabilitation.

Keywords: semicircular canal, otolith, seniors, balance, video head impulse test, vertigo, vestibular neglect

OPEN ACCESS

Edited by:
Yuri Agrawal, Johns Hopkins University, USA

Reviewed by:
Benjamin Thomas Crane, University of Rochester, USA
William Michael King, University of Michigan, USA

***Correspondence:**
Catherine de Waele
catherine.de-waele@parisdescartes.fr

Specialty section:
This article was submitted to Neuro-otology, a section of the journal Frontiers in Neurology

Received: *12 October 2015*
Accepted: *11 January 2016*
Published: *25 January 2016*

Citation:
Chiarovano E, Vidal P-P, Magnani C, Lamas G, Curthoys IS and de Waele C (2016) Absence of Rotation Perception during Warm Water Caloric Irrigation in Some Seniors with Postural Instability. Front. Neurol. 7:4. doi: 10.3389/fneur.2016.00004

INTRODUCTION

Falls in seniors are a major public health problem. In studies of the risk of falls, seniors frequently report dizziness when walking; also standing upright in the dark becomes difficult with age (1). Maintaining balance for 30 s on a foam pad with eyes closed was impossible for 68% of healthy individuals over 70 years old (2). More than one in three people older than 65 years fall at least once a year (3). Falls cause primary injuries such as fracture or head injury. These lead to fear of falling, reduced mobility, and decreased quality of life in the long term (4, 5).

Falls have numerous causes, including deformations of skeletal geometry, peripheral, hind limb neuropathy, peripheral, foveal visual deficits, and vestibular deficits. Risk factors of falling are well described in the literature. The risk of falling increases linearly with the number of risk factors (3). Vestibular dysfunction is one of these risk factors (6, 7).

At the peripheral level, vestibular function changes with age. Horizontal canal function, as assessed by caloric stimulation (8) or video-HIT (9), does not appear to decline with age, but some reports of response to head impulses suggest that it does (10–12). In contrast, the use of ocular and cervical vestibular-evoked myogenic potentials (VEMPs) has provided evidence that otolith utricular and saccular functions are affected by age (13–16).

At the central level, findings concerning the changes to vestibular perception with age are consistent: there is no effect of age on self-motion perception (17, 18), but there is an increase in the variability of the perception threshold (19). In that context, it is also interesting that there is a very large literature on canal-otolith interaction – demonstrating that modulating otolithic input modifies canal-induced nystagmus and also canal-induced subjective sensations (20, 21). The neural basis for that interaction is also well established – convergence of otolith neurons onto second order canal neurons (22, 23). Finally, age seems to decrease the activation of the cortical area activated by caloric stimulations such as the ipsilateral parieto-insular vestibular cortex (PIVC) (24, 25).

The relationship between objective measures of vestibular responses and age has been studied. However, to our knowledge, the effects of age on vestibular perception during caloric stimulation and on the relation between the absence of vestibular perception and falls in senior subjects have not been studied. We therefore studied these issues in two groups of senior subjects: one reporting unstable feelings and exhibiting absence of vestibular perception when they tested with caloric stimulation and the other (age-matched) group with no such problems. Patients with poor vestibular perception may not be aware of postural perturbations, and so will not correct for them; such individuals may be more likely than their age-matched peers to fall. Thus, falls in the elderly may result from a vestibular neglect due to an inappropriate central processing of normal vestibular peripheral inputs.

We assessed vestibular perception on a simple binary rating scale during the caloric test and more particularly during warm irrigation. The function of the various vestibular receptors was assessed using vHIT, caloric tests, and cervical and ocular VEMPs (26). The Equitest was used to evaluate balance.

MATERIALS AND METHODS

Twenty subjects were included in the study: ten patients and ten controls:

Ten senior patients (six females, four males; mean age 77 ± 8 years; min–max: 66–85) were selected using two criteria:

- First, they complained of postural instability (PI): these patients reported feeling unstable as if they had drunk too much but without having consumed alcohol. They had to walk close to a wall if they wanted to walk in a straight line and reported feeling as if they were on a rocking boat.
- Second, these patients with PI complaints also displayed an absence of rotatory perception during warm caloric nystagmus. As it turned out, they had objectively measured PI greater than age-matched controls.

Ten age- and sex-matched seniors (mean age of 74 ± 6 years; min–max: 67–85) were also investigated. They did not complain of PI (controls).

The inclusion criterion for both groups was that the peak of the slow-phase eye velocity of their caloric nystagmus during warm irrigation should exceed 15°/s, providing objective evidence of normal peripheral horizontal canal function. Subjects were not included if they experienced vertigo or if they had a chronic inner ear disease (such as Meniere's disease, positional vertigo, or vestibular neuritis), neurological problem, or abnormal MRI. All the patients were informed about the different vestibular and balance tests and gave written informed consent. The clinical Research Ethics Committee approved this work, registered at ANSM (ID RCB 2014-A00222-45).

Dizziness Handicap Inventory

The Dizziness Handicap Inventory (DHI) questionnaire developed by Jacobson and Newman (27) reports activity limitation and restriction resulting from dizziness and unsteadiness. All subjects completed the DHI.

Caloric Test

Caloric tests were performed using open-loop sequential bithermal external auditory conduct irrigations with water at 30 and 44°C and using video-nystagmography (Synapsis, France). The peak velocity of the slow phase of the induced-ocular nystagmus (peak SPV) was recorded for each warm and cold stimulation (30 s of irrigation) and for each ear. Percent canal paresis (CP) was calculated using Jongkees' formula (28): $CP = 100 \times [(LW + LC) - (RW + RC)]/LW + LC + RW + RC$, where LW, LC, RW,

Abbreviations: ACS, air-conducted sound; BCV, bone-conducted vibration; cVEMP, cervical vestibular-evoked myogenic potentials; DHI, Dizziness Handicap Inventory; H-VHIT, horizontal video head impulse test; HVOR gain, horizontal vestibulo-ocular reflex; NR, not responders to VEMPs; oVEMP, ocular vestibular-evoked myogenic potentials; PI, postural instability; PIVC, parieto-insular vestibular cortex; SCM, sterno-cleido-mastoideus; SOT, Sensory Organization Test; SPV, slow-phase velocity of the ocular nystagmus; STB, short tone burst; VEMPs, vestibular-evoked myogenic potentials; VHIT, video head impulse test; VOR, vestibulo-ocular reflex.

and RC are maximum velocity of the induced ocular nystagmus obtained on the left (L) and right (R) sides, with warm (W) and cold (C) water. A CP value above 25% was considered to indicate an abnormal response.

For vestibular perception, we asked the subject to report feelings of rotation and/or dizziness during the post-warm-irrigation period while the induced caloric nystagmus was present. Vestibular perception was scored 1 if there was perception of body rotation whose direction (to the right or the left) could be clearly given by the patient (**Figure 1A**) and 0 if there was no perception of body rotation (**Figure 1B**).

We assessed perception of rotation to warm irrigation only because, in our patients, warm irrigation induced more vigorous ocular nystagmus than cold irrigation. Also, the peak SPV needed to be ≥15°/s, the value which induced a perception of rotatory vertigo in 100% of the controls. Individuals with a poor ocular response (SPV <15°/s) to warm caloric stimulations were excluded from the study.

Video Head Impulse Test

Horizontal video-HIT (OtosuiteV®, GN Otometrics, Denmark) was used to test horizontal semicircular canal function (29). Approximately 20 horizontal head impulses were manually applied to each side with unpredictable timing and direction. Gain of HVOR was quantified at similar head acceleration in the both groups. The HVOR gain values were separated according to the direction (toward the right or left) of the head impulse. A significant difference between the two sides has been reported in healthy subjects (30). For the PI group, the mean peak head velocity was 195 ± 21°/s (mean peak head acceleration: 3957 ± 283°/s^2) for impulses toward the left side and was 189 ± 29°/s (mean peak head acceleration: 3841 ± 943°/s^2) for impulses toward the right side. For the control group, the mean peak head velocity was 189 ± 17°/s (mean peak head acceleration: 3709 ± 447°/s^2) for impulses toward the left side and was 188 ± 19°/s (mean peak head acceleration: 3658 ± 518°/s^2) for impulses toward the right side.

The VOR gain was calculated using two methods. First, the method described by MacDougall et al. (31): VOR gain was calculated as the area under the desaccaded eye velocity curve divided by the area under the head velocity curve. Second, a method developed in our laboratory using a linear regression (slope method). The linear regression was computed in MATLAB using linear polynomial curve fitting (polyfit) of the eye velocity from the start of the head movement to the peak of the head velocity. Noise was reduced by a rectangular low-pass filter using the discrete Fourier transform at 20 Hz for head velocity and at 38 Hz for eye velocity. Only data following almost perfectly a straight line were included in the analysis (linearity >98%). The difference between left and right sides was quantified as a gain asymmetry ratio: ratio = (L − R)/(L + R) × 100 where L and R are the mean gain values from the left and right head impulses, respectively.

Cervical and Ocular VEMPs

Vestibular-evoked myogenic potentials were recorded with a Nicolet Viking 4 apparatus (Nicolet Biomedical Inc., Madison, WI, USA) with a four-channel averaging capacity, as previously described (32–34).

Cervical vestibular-evoked myogenic potentials assess predominantly the function of the sacculo-spinal pathways (35). They were recorded from surface electrodes above the tensed sterno-cleido-mastoideus (SCM) muscle ipsilateral to the stimulated ear in response to air-conducted (AC) short tone burst (STB) stimuli: 500 Hz, 102 dB nHL, 128 dB SPL, rise/fall time 2 ms, plateau time 2 ms, presented through calibrated TDH39 headphones. EMG activity of the SCM was monitored

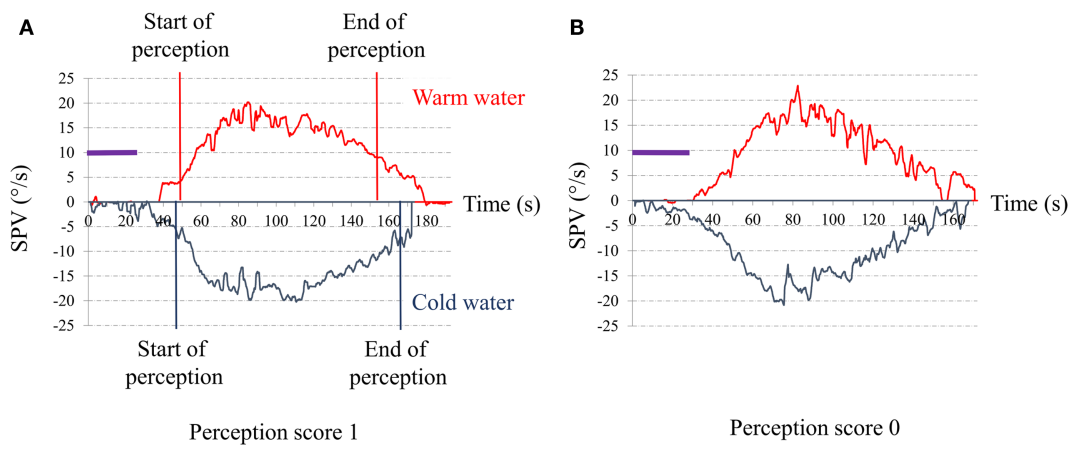


FIGURE 1 | Time series of the slow-phase velocity (SPV) of caloric nystagmus to warm and cold external canal ear irrigation. Abscissa: time in seconds from the beginning of irrigation; Ordinates: SPV of the induced ocular nystagmus in degree per second; purple bar: duration of the ear irrigation (30 s). **(A)** Typical response of a control senior. The red vertical lines indicate the start and the end of the perception of rotation for warm irrigation. The blue vertical lines indicate the start and the end of the perception of rotation for warm irrigation. The perception appeared when the SPV reached a value for SPV close to 5°/s (start) and disappears when SPV decline to or below 10°/s (end). **(B)** Typical response of one of our senior complaining for postural instability. Note that despite the high SPV (exceeding 15°/s) to both warm and cold irrigations, the patient did not report any rotation perception.

on a display to ensure that sufficient muscle activation was maintained (>150 μV).

Ocular vestibular-evoked myogenic potentials assess predominantly the function of the utriculo-ocular pathways (36). They were recorded from surface electrodes above the inferior oblique extraocular muscle contralateral to the stimulated ear in response to AC STB, and to bone-conducted vibration (BCV) at Fz, and to BCV stimulation at the mastoid. The AC STB (500 Hz, 110 dB nHL, 132 dB SPL, rise/fall time 2 ms, plateau time 2 ms) were presented through calibrated TDH39 headphones. BCV stimuli (500 Hz STB, 135 dB FL, rise/fall time = 2 ms and plateau time = 2 ms) were delivered by a hand-held Bruel and Kjaer (Naerum, Denmark) Mini-Shaker 4810.

Patients with no measurable response on either side were considered to be non-responders (NR).

Equitest

Equilibrium was assessed by the Sensory Organization Test (SOT) on the EquiTest® (37, 38). The SOT included six conditions. *Condition 1*: the subject was asked to stand upright while maintaining eyes open. *Condition 2*: the subject was asked to stand upright while maintaining eyes closed. *Condition 3*: the cabin moved adaptively following subject's movements. In this condition, the vision was sway-referenced. *Condition 4*: the support base moved adaptively following subject's movements while eyes were open: sway-referenced proprioception. *Condition 5*: same as condition 4, but with eyes closed. *Condition 6*: the support base and the cabin moved in a synchronized way: vision and proprioception are sway-referenced. According to the change of the body center of pressure for the six different conditions, a percentage somatosensory, visual, and vestibular score was calculated, a visual preference was estimated, and a composite score was obtained.

Vibration-Induced Nystagmus and Head-Shaking Nystagmus Test

Spontaneous nystagmus was tested using an infrared camera with the subject in a sitting and a supine position. Vibration-induced nystagmus was tested with a vibratory stimulation of 100 Hz applied to the mastoid (39–41). Head-shaking stimulation consisted of turning the head of the patient in the horizontal plane to the left and the right at 2 Hz for 20 s (42–44). The presence of nystagmus during one or more of these tests indicated asymmetry of vestibular function between the ears in the horizontal plane.

Audiometric Tests

Tympanometry and stapedial reflexes were carefully evaluated to exclude patients suffering from conductive hearing loss, which could lead to a misinterpretation of ACS VEMPs. The mean pure-tone threshold (PTA) for tones at 250 and 500 Hz and 1 and 2 kHz was used as indicator of hearing loss.

RESULTS

Dizziness Handicap Inventory

The DHI score 39 ± 11% was for the PI group and 14 ± 19% for the control group. In the control group, 3 individuals out of 10 with high score (20, 22, and 30), the remaining individuals had DHI score inferior or equal to 10. These three patients did not complain for instability (and did not fail on the Equitest). These high score was linked to high scores at questions related to their difficulty at performing head movement (French DHI, questions 1, 8, 11, 12, 13, 25), a current syndrome without objective deficits in seniors over 70 years old. This difference was significant (non-parametric Mann–Whitney test, $p = 0.002$).

Vestibular Horizontal Canal Receptor Function

Horizontal canal function was assessed using both video-nystagmoscopy and video-nystagmography. None of the study population (control or PI group) exhibited spontaneous nystagmus in darkness or ocular nystagmus induced by either head shaking or vibration.

Caloric Tests

No significant difference was detected between PI and control groups for the peak SPV of caloric ocular nystagmus induced either by warm or cold water irrigations (**Table 1**). No CP was detected in either group.

All of controls perceived rotation (score 1) (**Figure 2**) when the maximal SPV during warm irrigation was ≥15°/s. The direction of the perceived rotation was in all cases toward the side of the fast phase of the induced ocular nystagmus. The perception of rotation increased progressively to a maximum at the peak of the SPV and then progressively decreased in good agreement with the eye velocity of the induced caloric nystagmus. The perception disappeared when eye velocity fell to or below 10°/s. In most cases, the patient's head turned progressively in the direction of the slow component of caloric-induced eye nystagmus for both warm and cold irrigation.

None of the subjects in the PI group perceived rotation (score 0) (**Figure 2**) even while the peak SPV exceeded 15°/s. They all stated that did not feel anything: absolutely no sensation at all of head or body rotation.

Horizontal Video Head Impulse Test

There was no significant difference between the two groups in the mean HVOR gain calculated by either slope or area method (**Table 2**). The HVOR gain calculated using the slope method was similar to that using the area method, although the value obtained from the area was consistently greater that from the

TABLE 1 | Mean slow-phase peak velocity (SPV) of the induced ocular nystagmus obtained for warm and cold irrigations in PI and control senior groups.

SPV (°/s)	SPV left warm	SPV right warm	SPV left cold	SPV right cold
PI	25 ± 9.4 (15–40)	25 ± 5 (17–32)	13 ± 5 (7–19)	12 ± 4 (7–16)
Control	27 ± 8 (20–42)	24 ± 5 (15–33)	16 ± 5 (6–24)	15 ± 4 (11–23)

There was no significant difference between the two groups.

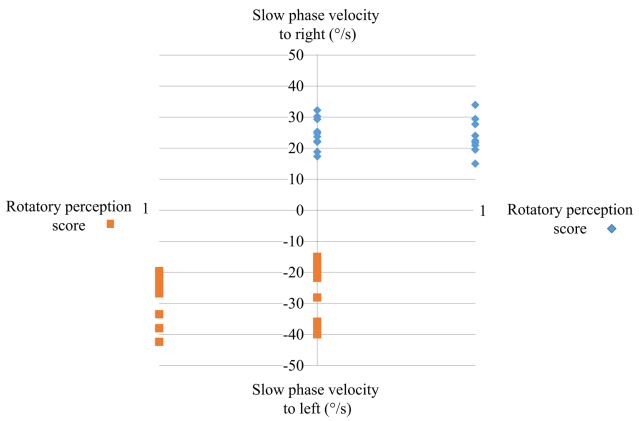


FIGURE 2 | The perception of rotation score during caloric testing as a function of the peak of the slow-phase velocity. Ordinates: peak SPV induced by warm water irrigation of the right or the left ear; abscissa: perception rotation score during irrigation. Note that the seniors with postural instability did not perceive any rotation (score 0) irrespective of whether the left or right ear was irrigated; all controls perceived rotation.

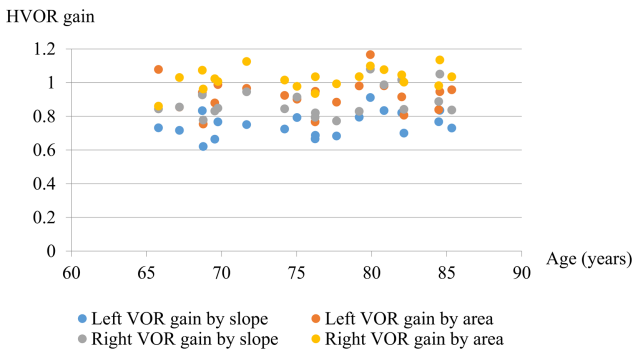


FIGURE 3 | Graph showing the gain of HVOR calculated by slope and area methods. There was no significant difference in HVOR gain with age between 65 and 86 years even for high accelerations (mean 3700 ± 550°/s²).

TABLE 2 | Mean HVOR gain calculated with slope and area methods in PI and control seniors groups.

hVOR gain	Left with slope	Left with area	Right with slope	Right with area
PI	0.76 ± 0.06	0.95 ± 0.11	0.90 ± 0.08	1.02 ± 0.07
Control	0.73 ± 0.08	0.90 ± 0.08	0.88 ± 0.09	1.02 ± 0.06

There was no significant difference between the two groups.

slope (**Figure 3**). The HVOR gain ratio for the PI group was: −8.3 ± 2.0 (min–max: −11.5 to −5.0), which was not significantly different from that for the control group: −8.9 ± 2.1 (min–max: −11.4 to −5.3).

These investigations show for the first time that vestibular perception can be absent during a caloric test despite objective measures of horizontal canal functioning suggesting that it is normal. We went on to test whether vestibular perception can be associated with PI.

Vestibular Otolithic (Utricular and Saccular) Receptor Function

None of our subjects exhibited conductive hearing loss. The mean PTA in the PI group was 30 ± 20 dB (min–max: 0–110 dB) and in the control group was 35 ± 25 dB (min–max: 5–110 dB).

Cervical VEMPs in Response to AC STB

The mean peak-to-peak (corrected and uncorrected) amplitudes of the early P13–N23 waves were not significantly different between the two groups (**Table 3**). The EMG activity of the SCM muscle was similar: 180 ± 42 for PI subjects versus 184 ± 70 for control subjects. No significant difference was found for the P13 and N23 latencies between the two groups. Forty percent of PI and 30% of the control group were NR.

TABLE 3 | Mean values of amplitude and latencies for cVEMPs and oVEMPs for PI senior and control senior groups in response to ACS and BCV at Fz and mastoid.

		Amplitude (μV)	P13/n1 latency (ms)	N23/p1 latency (ms)
ACS 102 dB cVEMPs	PI	Uncorrected: 79 ± 129 Corrected: 0.41 ± 0.67	15.3 ± 0.9	22.3 ± 2.0
	Control	Uncorrected: 85 ± 88 Corrected: 0.56 ± 0.45	15.0 ± 1.1	21.4 ± 1.5
ACS 110 dB oVEMPs	PI	2.1 ± 4.0*	11.4 ± 0.5	15.4 ± 1.0
	Control	5.9 ± 5.3	11.0 ± 0.4	14.6 ± 0.8
Fz BCV oVEMPs	PI	3.6 ± 5.0*	11.3 ± 0.8	15.6 ± 1.0
	Control	8.7 ± 7.7	11.0 ± 0.7	15.0 ± 0.8
Mastoid BCV oVEMPs	PI	7.7 ± 6.1	11.5 ± 1.0	15.7 ± 1.3
	Control	12.9 ± 9.8	10.8 ± 0.8	15.2 ± 0.8

**Non-parametric Mann–Whitney test, p = 0.001.*

Ocular VEMPs in Response to AC STB

The mean peak-to-peak n1–p1 amplitude was significantly lower in the PI group than the control group (**Table 3**). There was no significant difference for the n1 and p1 latencies between the two groups. Sixty percent of PI subjects and 30% of the control group were NR.

Ocular VEMPs in Response to BCV at the Fz Location

The mean peak-to-peak amplitude was significantly smaller in the PI group than the control group (**Table 3**). There was no significant difference between the groups for the n1 and p1 latencies. Sixty percent of PI subjects and 20% of controls were NR.

Ocular VEMPs in Response to BCV at Mastoid Location

The mean peak-to-peak amplitude was not significantly different between the PI and control groups (**Table 3**). The n1 and p1 latencies did not differ significantly between the two groups. Twenty percent of PI subjects and 10% of controls were NR.

Equitest

All members of the control group had normal Equitest results in all six conditions. All the PI group had abnormal Equitest results: 80% fell in conditions 5 and 6; and 20% had a low score in condition 5 and fell in condition 6. Subjects with no perception of vertigo during the caloric test could not maintain balance in condition 5 (eyes closed, sway-referenced platform), a condition which tests the contribution of the vestibular inputs to balance (**Figure 4**).

DISCUSSION

In this work, we report that a subset of patient complaining of PI, when submitted to caloric irrigation, displayed a lack of perception of ego motion, contrasting with a normal ocular nystagmic response. Such vestibular neglect appearing quite uncommon, we assessed their full vestibular and postural performances. We found that poor vestibular perception in these 10 PI patients was associated with an inadequate postural strategy to maintain balance in conditions 5 (eyes closed + sway-referenced platform) and condition 6 (vision-referenced + sway-referenced platform) of the Equitest. We hypothesized that the absence of perception of movement during caloric test may be a marker of risk of fall which has not been considered before.

Our results are consistent with a study by Diard et al. (45). They reported that despite normal caloric tests, some seniors failed to maintain balance in the conditions 5 and 6 of the Equitest, a syndrome they called a vestibular omission. They suggested that this phenomenon was due to misapplication of normal peripheral vestibular information. However, they did not report whether patients perceived rotation during caloric stimulation.

Ours is the first report of a clear dissociation between horizontal canal function and perception of rotation during caloric stimulation in elderly subjects. We propose to call this dissociation "vestibular neglect." Despite normal responses to warm caloric stimulation, the subjects have no perception of rotation and no perception of eye movements. The only similar report we are aware is by Takeda et al. (46), who describe a stroke patient with normal caloric responses and no perception of rotation during caloric stimulation. We found a relationship between vestibular neglect and PI. This result suggested a deficit of the central processing of vestibular information in patients exhibiting vestibular neglect. In summary, we suggest that a lack of egomotion perception during caloric test should draw the attention to PI and encourage measures to prevent falls. That said, it is clear that "vestibular neglect" may be one of the many causes of PI.

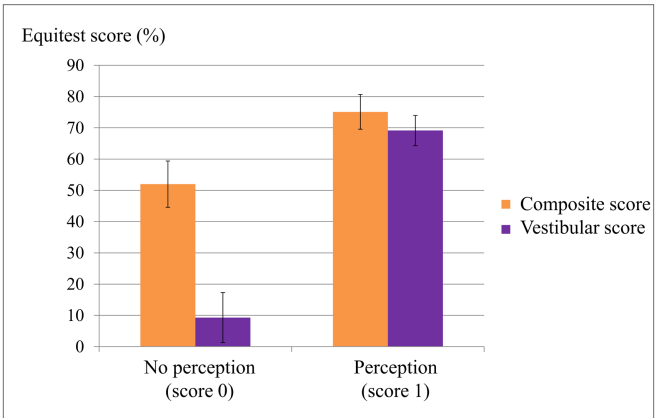


FIGURE 4 | Relation between composite and vestibular score on the Equitest and the perception score during caloric irrigation. Most patients with a low perception score had a poor vestibular score on the Equitest and a low composite score.

The effect on age on vestibular perception has been the subject of several studies. Roditi and Crane (17) used sinusoidal acceleration for surge (forward–backward), sway (left–right), heave (up–down), and yaw rotation. Only the thresholds for surge and sway for sinusoidal rotation at 0.5 and 1 Hz were found to be significantly higher in subjects >50 years old. Chang et al. (18) failed to detect any correlation between vestibular perception threshold, gain of VOR, and age using a rotational chair. A correlation has been found between horizontal perceptual threshold and oVEMP amplitude in the otolith system. In contrast, no significant association was detected for vertical perceptual thresholds and cVEMP amplitudes (10, 11). Therefore, vestibular perception is usually tested with more specific and quantified tests using rotatory chairs at various frequencies of head accelerations. In contrast, the caloric test imposes a large vestibular stimulation, activating all sensors at low frequencies. To our knowledge, such "brute force" was, rightly so, never employed to test vestibular perception. It may be useful to help to prevent fall but it cannot be considered as a bona fide test of vestibular perception.

The persistence of a normal HVOR in the PI group contrasted with the absence of perception of illusory movements during the caloric tests. Three non-mutually exclusive factors could be at play.

First, this dissociation can be explained by the differences between the vestibulo-ocular and the vestibulo-cortical and vestibulo-subcortical pathways. A trisynaptic pathway links the canal sensors to the extraocular motoneurons in 6 ms. In contrast, a polysynaptic, distributed network underlies self-motion perception: its first relay is in the vestibular nuclei, the second in the thalamus, and it includes several inter-connected cortical areas. These areas include the PIVC, temporal superior gyrus, inferior parietal lobe, and insula (47–49), where visual, vestibular, and proprioceptive inputs converge. A number of vestibular and cerebellum connections have been reported [for review see Ref. (50)] so a dysfunction of the cerebellum could be involved. Such complex circuitry may be more sensitive to the aging process that the three-neuronal arc of the VOR. Functional MRI during caloric stimulation may be informative and establish whether there is a link between the absence of perception of rotation and either a cognitive failure or abnormal activation of the areas devoted to integrate vestibular inputs at the subcortical level and/or the cortical network such as PIVC (48).

Second, the HVOR apparently does not decline with age as has been shown using calorics (8, 51) and vHIT: McGarvie et al. (9) failed to detect any significant decline of HVOR gain until age 90 years. Only a slight decrease of vertical VOR gain after age 80 years was found when head impulses were delivered in the plane of the posterior canal. These functional studies contrast

with morphological data. In humans, the number and the density of hair cells decrease with age in the cristae vestibular ampulla between 60 and 90 years (52–54). Moreover, there are morphological changes to the cristae hair cell cilia, including a reduction of the numbers, disarrangements, and formation of giant cilia (55, 56). Clearly, the vestibulo-ocular network displays sufficient plasticity to cope with these cellular alterations.

Third, an inappropriate integration of otolith and canal signals and central reweighting of sensory inputs related to motion detection could participate to vestibular neglect. In that regard, the finding of Agrawal et al. (10, 11) that perceptual thresholds for linear motion increased in subjects with utricular dysfunction is relevant. The occurrence of utricular dysfunction augmenting with age, and it would lead to inappropriate integration of otolith and canal signals at the second order vestibular neurons level and consequently to misperception of the canal information induced by the caloric irrigation. We intend to test the hypothesis of an inappropriate integration of otolith and canal signals and central valuing by comparing the perceptual thresholds for linear motion of patients with and without vestibular neglect.

CONCLUSION

We show that some seniors are unable to detect and report a subjective sensation of rotation during strong unilateral horizontal canal stimulation, despite objective evidence that these seniors have normal peripheral horizontal semicircular canal function. We suggest that this dissociation between perception and objective vestibular responses may be a determinant of PI, because it is these same seniors who demonstrate greater PI than age-matched controls. Therefore, failure to perceive rotation during caloric testing when the SPV is >15°/s should encourage the clinician to envisage preventive actions to avoid future falls such as rehabilitation. Further studies are needed to evaluate the proportion of PI seniors without vestibular perception, amongst a larger population of patients with complaints of PI.

AUTHOR CONTRIBUTIONS

CW and GL devised the protocol and wrote much of the paper; EC tested subjects, wrote much of the paper, and conducted the analyses; IC contributed to the redaction of the paper and consulted; CM made the Matlab program for vHIT data analysis; and P-PV reviewed the paper.

ACKNOWLEDGMENTS

We thank Barbara Rault for her participation of the caloric data recordings from the ENT department of the Salpetriere hospital.

REFERENCES

1. Norré ME, Forrez G, Beckers A. Vestibular dysfunction causing instability in aged patients. *Acta Otolaryngol* (1987) **104**(1–2):50–5. doi:10.3109/00016488709109046
2. Davalos-Bichara M, Agrawal Y. Normative results of healthy older adults on standard clinical vestibular tests. *Otol Neurotol* (2014) **35**(2):297–300. doi:10.1097/MAO.0b013e3182a09ca8
3. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med* (1988) **319**(26):1701–7. doi:10.1056/NEJM198812293192604
4. Chang JT, Morton SC, Rubenstein LZ, Mojica WA, Maglione M, Suttorp MJ, et al. Interventions for the prevention of falls in older adults: systematic review and meta-analysis of randomised clinical trials. *BMJ* (2004) **328**(7441):680. doi:10.1136/bmj.328.7441.680
5. Hartholt KA, van Beeck EF, Polinder S, van der Velde N, van Lieshout EMM, Panneman MJM, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. *J Trauma* (2011) **71**(3):748–53. doi:10.1097/TA.0b013e3181f6f5e5
6. 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
7. Ishiyama G. Imbalance and vertigo: the aging human vestibular periphery. *Semin Neurol* (2009) **29**(5):491–9. doi:10.1055/s-0029-1241039
8. Mallinson AI, Longridge NS. Caloric response does not decline with age. *J Vestib Res* (2004) **14**(5):393–6.
9. McGarvie LA, MacDougall HG, Halmagyi GM, Burgess AM, Weber KP, Curthoys IS. The video head impulse test (vHIT) of semicircular canal function – age-dependent normative values of VOR gain in healthy subjects. *Front Neurol* (2015) **6**:154. doi:10.3389/fneur.2015.00154
10. Agrawal Y, Bremova T, Kremmyda O, Strupp M, MacNeilage PR. Clinical testing of otolith function: perceptual thresholds and myogenic potentials. *J Assoc Res Otolaryngol* (2013) **14**(6):905–15. doi:10.1007/s10162-013-0416-x
11. Agrawal Y, Davalos-Bichara M, Zuniga MG, Carey JP. Head impulse test abnormalities and influence on gait speed and falls in older individuals. *Otol Neurotol* (2013) **34**(9):1729–35. doi:10.1097/MAO.0b013e318295313c
12. Mossman B, Mossman S, Purdie G, Schneider E. Age dependent normal horizontal VOR gain of head impulse test as measured with video-oculography. *J Otolaryngol Head Neck Surg* (2015) **44**(1):29. doi:10.1186/s40463-015-0081-7
13. Welgampola MS, Colebatch JG. Vestibulocollic reflexes: normal values and the effect of age. *Clin Neurophysiol* (2001) **112**(11):1971–9. doi:10.1016/S1388-2457(01)00645-9
14. Rosengren SM, Govender S, Colebatch JG. Ocular and cervical vestibular evoked myogenic potentials produced by air- and bone-conducted stimuli: comparative properties and effects of age. *Clin Neurophysiol* (2011) **122**(11):2282–9. doi:10.1016/j.clinph.2011.04.001
15. Kantner C, Gürkov R. Characteristics and clinical applications of ocular vestibular evoked myogenic potentials. *Hear Res* (2012) **294**(1–2):55–63. doi:10.1016/j.heares.2012.10.008
16. Zuniga MG, Dinkes RE, Davalos-Bichara M, Carey JP, Schubert MC, King WM, et al. Association between hearing loss and saccular dysfunction in older individuals. *Otol Neurotol* (2012) **33**(9):1586–92. doi:10.1097/MAO.0b013e31826bedbc
17. Roditi RE, Crane BT. Directional asymmetries and age effects in human self-motion perception. *J Assoc Res Otolaryngol* (2012) **13**(3):381–401. doi:10.1007/s10162-012-0318-3
18. Chang N-YN, Hiss MM, Sanders MC, Olomu OU, MacNeilage PR, Uchanski RM, et al. Vestibular perception and the vestibulo-ocular reflex in young and older adults. *Ear Hear* (2014) **35**(5):565–70. doi:10.1097/AUD.0000000000000052
19. Schweigart G, Chien R-D, Mergner T. Neck proprioception compensates for age-related deterioration of vestibular self-motion perception. *Exp Brain Res* (2002) **147**(1):89–97. doi:10.1007/s00221-002-1218-2
20. Lansberg MP, Guedry FE, Graybiel A. The effect of changing the resultant linear acceleration relative to the subject on nystagmus generated by angular acceleration. *Aeromed Acta* (1963) **9**:97–122.
21. Curthoys IS, Wearne SL, Dai M, Halmagyi GM, Holden JR. Linear acceleration modulates the nystagmus induced by angular acceleration stimulation of the horizontal canal. *Ann N Y Acad Sci* (1992) **656**:716–24. doi:10.1111/j.1749-6632.1992.tb25249.x
22. Curthoys IS, Markham CH. Convergence of labyrinthine influences on units in the vestibular nuclei of the cat. I. Natural stimulation. *Brain Res* (1971) **35**(2):469–90. doi:10.1016/0006-8993(71)90489-6

23. Straka H, Dieringer N. Basic organization principles of the VOR: lessons from frogs. *Prog Neurobiol* (2004) **73**(4):259–309. doi:10.1016/j.pneurobio.2004.05.003
24. Suzuki M, Kitano H, Ito R, Kitanishi T, Yazawa Y, Ogawa T, et al. Cortical and subcortical vestibular response to caloric stimulation detected by functional magnetic resonance imaging. *Brain Res Cogn Brain Res* (2001) **12**(3):441–9. doi:10.1016/S0926-6410(01)00080-5
25. Karim HT, Fuhrman SI, Furman JM, Huppert TJ. Neuroimaging to detect cortical projection of vestibular response to caloric stimulation in young and older adults using functional near-infrared spectroscopy (fNIRS). *Neuroimage* (2013) **76**:1–10. doi:10.1016/j.neuroimage.2013.02.061
26. Curthoys IS. The interpretation of clinical tests of peripheral vestibular function. *Laryngoscope* (2012) **122**(6):1342–52. doi:10.1002/lary.23258
27. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. *Arch Otolaryngol Head Neck Surg* (1990) **116**(4):424–7. doi:10.1001/archotol.1990.01870040046011
28. Jongkees LB, Maas JP, Philipszoon AJ. Clinical nystagmography. A detailed study of electro-nystagmography in 341 patients with vertigo. *Pract Otorhinolaryngol* (1962) **24**:65–93.
29. MacDougall HG, Weber KP, McGarvie LA, Halmagyi GM, Curthoys IS. The video head impulse test: diagnostic accuracy in peripheral vestibulopathy. *Neurology* (2009) **73**(14):1134–41. doi:10.1212/WNL.0b013e3181bacf85
30. Weber KP, Aw ST, Todd MJ, McGarvie LA, Pratap S, Curthoys IS, et al. Inter-ocular differences of the horizontal vestibulo-ocular reflex during impulsive testing. *Prog Brain Res* (2008) **171**:195–8. doi:10.1016/S0079-6123(08)00626-2
31. MacDougall HG, McGarvie LA, Halmagyi GM, Curthoys IS, Weber KP. The video head impulse test (vHIT) detects vertical semicircular canal dysfunction. *PLoS One* (2013) **8**(4):e61488. doi:10.1371/journal.pone.0061488
32. de Waele C, Huy PT, Diard JP, Freyss G, Vidal PP. Saccular dysfunction in Meniere's disease. *Am J Otol* (1999) **20**(2):223–32.
33. Chiarovano E, Zamith F, Vidal P-P, de Waele C. Ocular and cervical VEMPs: a study of 74 patients suffering from peripheral vestibular disorders. *Clin Neurophysiol* (2011) **122**(8):1650–9. doi:10.1016/j.clinph.2011.01.006
34. Chiarovano E, Darlington C, Vidal P-P, Lamas G, de Waele C. The role of cervical and ocular vestibular evoked myogenic potentials in the assessment of patients with vestibular schwannomas. *PLoS One* (2014) **9**(8):e105026. doi:10.1371/journal.pone.0105026
35. Colebatch JG, Halmagyi GM, Skuse NF. Myogenic potentials generated by a click-evoked vestibulocollic reflex. *J Neurol Neurosurg Psychiatry* (1994) **57**(2):190–7. doi:10.1136/jnnp.57.2.190
36. Curthoys IS, Iwasaki S, Chihara Y, Ushio M, McGarvie LA, Burgess AM. The ocular vestibular-evoked myogenic potential to air-conducted sound; probable superior vestibular nerve origin. *Clin Neurophysiol* (2011) **122**(3):611–6. doi:10.1016/j.clinph.2010.10.047
37. Nashner LM. A model describing vestibular detection of body sway motion. *Acta Otolaryngol* (1971) **72**(6):429–36. doi:10.3109/00016487109122504
38. Nashner LM, Black FO, Wall C. Adaptation to altered support and visual conditions during stance: patients with vestibular deficits. *J Neurosci* (1982) **2**(5):536–44.
39. Négrevergne M, Ribeiro S, Moraes CL, Maunsell R, Morata GC, Darrouzet V. [Video-nystagmography and vibration test in the diagnosis of vestibular schwannoma. Review of 100 cases]. *Rev Laryngol Otol Rhinol (Bord)* (2003) **124**(2):91–7.
40. Ohki M, Murofushi T, Nakahara H, Sugasawa K. Vibration-induced nystagmus in patients with vestibular disorders. *Otolaryngol Head Neck Surg* (2003) **129**(3):255–8. doi:10.1016/S0194-5998(03)00529-1
41. Hong SK, Koo J-W, Kim JS, Park M-H. Implication of vibration induced nystagmus in Meniere's disease. *Acta Otolaryngol Suppl* (2007) 1**27**(558):128–31. doi:10.1080/03655230701625019
42. Kamei T. Two types of head-shaking tests in vestibular examination. *Acta Otolaryngol Suppl* (1988) **458**:108–12. doi:10.3109/00016488809125112
43. Jacobson GP, Newman CW, Safadi I. Sensitivity and specificity of the head-shaking test for detecting vestibular system abnormalities. *Ann Otol Rhinol Laryngol* (1990) **99**(7 Pt 1):539–42. doi:10.1177/000348949009900708
44. Takahashi S, Fetter M, Koenig E, Dichgans J. The clinical significance of head-shaking nystagmus in the dizzy patient. *Acta Otolaryngol* (1990) **109**(1–2):8–14. doi:10.3109/00016489009107409
45. Diard JP, Vitte E, Semont A, Freyss G. Equilibre, instabilité et chutes du sujet vieillissant. *La Rev d'ONO* (1993) **19**:82–8.
46. Takeda N, Tanaka-Tsuji M, Sawada T, Koizuka I, Kubo T. Clinical investigation of the vestibular cortex. *Acta Otolaryngol Suppl* (1995) **520**(Pt 1):110–2. doi:10.3109/00016489509125203
47. de Waele C, Baudonnière PM, Lepecq JC, Tran Ba Huy P, Vidal PP. Vestibular projections in the human cortex. *Exp Brain Res* (2001) **141**(4):541–51. doi:10.1007/s00221-001-0894-7
48. Dieterich M, Brandt T. Functional brain imaging of peripheral and central vestibular disorders. *Brain* (2008) **131**(Pt 10):2538–52. doi:10.1093/brain/awn042
49. zu Eulenburg P, Caspers S, Roski C, Eickhoff SB. Meta-analytical definition and functional connectivity of the human vestibular cortex. *Neuroimage* (2012) **60**(1):162–9. doi:10.1016/j.neuroimage.2011.12.032
50. Barmack NH. Central vestibular system: vestibular nuclei and posterior cerebellum. *Brain Res Bull* (2003) **60**(5–6):511–41. doi:10.1016/S0361-9230(03)00055-8
51. Mulch G, Petermann W. Influence of age on results of vestibular function tests. Review of literature and presentation of caloric test results. *Ann Otol Rhinol Laryngol Suppl* (1979) **88**(2 Pt 2 Suppl 56):1–17. doi:10.1177/00034894790880S201
52. Merchant SN, Velázquez-Villaseñor L, Tsuji K, Glynn RJ, Wall C III, Rauch SD. Temporal bone studies of the human peripheral vestibular system. Normative vestibular hair cell data. *Ann Otol Rhinol Laryngol Suppl* (2000) **181**:3–13.
53. Lopez I, Ishiyama G, Tang Y, Tokita J, Baloh RW, Ishiyama A. Regional estimates of hair cells and supporting cells in the human crista ampullaris. *J Neurosci Res* (2005) **82**(3):421–31. doi:10.1002/jnr.20652
54. Taylor RR, Jagger DJ, Saeed SR, Axon P, Donnelly N, Tysome J, et al. Characterizing human vestibular sensory epithelia for experimental studies: new hair bundles on old tissue and implications for therapeutic interventions in ageing. *Neurobiol Aging* (2015) **36**(6):2068–84. doi:10.1016/j.neurobiolaging.2015.02.013
55. Rosenhall U, Rubin W. Degenerative changes in the human vestibular sensory epithelia. *Acta Otolaryngol* (1975) **79**(1–2):67–80. doi:10.3109/00016487509124657
56. Nakayama M, Helfert RH, Konrad HR, Caspary DM. Scanning electron microscopic evaluation of age-related changes in the rat vestibular epithelium. *Otolaryngol Head Neck Surg* (1994) **111**(6):799–806. doi:10.1016/S0194-5998(94)70571-2

Conflict of Interest Statement: Ian S. Curthoys is unpaid consultant to and has received funding for travel from GN Otometrics. The other co-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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 18 February 2016
doi: 10.3389/fneur.2016.00018

The Effect of Age on Improvements in Vestibulo-Ocular Reflexes and Balance Control after Acute Unilateral Peripheral Vestibular Loss

*Alja Scheltinga[1,2], Flurin Honegger[1], Dionne P. H. Timmermans[1,2] and John H. J. Allum[1]**

[1] Division of Audiology and Neurootology, Department of ORL, University Hospital of Basel, Basel, Switzerland, [2] Radboud University, Nijmegen, Netherlands

Background: An acute unilateral peripheral vestibular loss (aUVL) initially causes severe gaze and balance control problems. However, vestibulo-ocular reflexes (VOR) and balance control are nearly normal 3 months later as a result of peripheral recovery and/or central compensation. As pre-existing vestibular sensory loss is assumed to be greater in the healthy elderly, this study investigated whether improvements in VOR and balance function over time after aUVL are different for the elderly than for the young.

Methods: Thirty aUVL patients divided into three age-groups were studied (8 age range 23–35, 10 with range 43–58, and 12 with range 60–74 years). To measure VOR function eye movements were recorded during caloric irrigation, rotating chair (ROT), and head impulse tests. Balance control during stance and gait was recorded as lower trunk angular velocity in the pitch and roll planes. Measurements were taken at deficit onset, and 3, 6, and 13 weeks later.

Results: There was one difference in VOR improvements over time between the age-groups: Low acceleration ROT responses were less at onset in the elderly group. Deficit side VOR responses and asymmetries in each group improved to within ranges of healthy controls at 13 weeks. Trunk sway of the elderly was greater for stance and gait at onset when compared to healthy age-matched controls and the young and greater than that of the young and controls during gait tasks at 13 weeks. The sway of the young was not different from controls at either time point. Balance control for the elderly improved slower than for the young.

Conclusion: These results indicate that VOR improvement after an aUVL does not differ with age, except for low accelerations. Recovery rates are different between age-groups for balance control tests. Balance control in the elderly is more abnormal at aUVL onset for stance and gait tasks with the gait abnormalities remaining after 13 weeks. Thus, we conclude that balance control in the elderly is more affected by the UVL than for the young, and the young overcome balance deficits more rapidly. These differences with age should be taken into account when planning rehabilitation.

Keywords: vestibular loss, aging, vestibulo-ocular reflex, vestibulo-spinal reflex, balance control

Edited by:
Yuri Agrawal,
Johns Hopkins University, USA

Reviewed by:
Benjamin Thomas Crane,
University of Rochester, USA
Emily Keshner,
Temple University, USA

****Correspondence:***
John H. J. Allum
john.allum@usb.ch

Specialty section:
This article was submitted to Neuro-otology, a section of the journal Frontiers in Neurology

Received: *30 October 2015*
Accepted: *05 February 2016*
Published: *18 February 2016*

Citation:
Scheltinga A, Honegger F, Timmermans DPH and Allum JHJ (2016) The Effect of Age on Improvements in Vestibulo-Ocular Reflexes and Balance Control after Acute Unilateral Peripheral Vestibular Loss. Front. Neurol. 7:18. doi: 10.3389/fneur.2016.00018

INTRODUCTION

Because of its ability to detect linear and angular body accelerations, the vestibular system plays a crucial role in static and dynamic balance control (1). This role includes stabilizing the head and trunk, especially on unstable surfaces (2). Following acute unilateral vestibular loss (aUVL) due to acute vestibular neuritis or following eight nerve neurectomy, vestibular signals driving vestibulo-ocular reflexes (VOR) and vestibule-spinal reflexes (VSR) are inaccurate or absent causing postural instability (3, 4). Effects of aUVL on the VOR include spontaneous nystagmus, skew deviation, eye cyclotorsion, VOR gain reductions, and phase changes (1, 5, 6). VSR contributions to balance control are also affected. Head and body tilt and deviation of the locomotor trajectory toward the affected side as well as stance and gait instability have been observed as a result (5, 7, 8).

Patients with aUVL can regain normal gaze and balance control after an aUVL (7, 9–11) but the extent to which patients recover normal function can differ between patients (1) and between stance and gait tasks (4). Recovery of function can occur via peripheral vestibular recovery and/or central compensation (3). However, the recovery rates for VOR and VSR measures (as recorded during balance control tasks) differ. Furthermore, VOR and balance control measures are weakly correlated with one another (4, 11). Whether differences in recovery rates of VOR and balance measures differ with age is not known.

As with other sensory systems, e.g., hearing, the vestibular sensory system deteriorates with age (12–14). Because vestibular reflexes contribute to both the gaze and balance control, both functions are assumed to decline with age, too (12, 15). The elderly (those over 60 years of age) have greater trunk angular sway during stance and stance tasks compared to younger subjects (16–19). However, weak correlations between changes in VOR function and balance control as a result of subject age have been found (20). Thus, despite the decline in the numbers of hair cells in the peripheral vestibular system with age (21), VOR function does not decline with age to the same extent as the decline in balance control during stance (18, 22–24). Given this difference between how VOR and balance control declines with age the question arises if, with an aUVL, balance control is changed more compared to the VOR in the elderly than in the young. A difference would have important clinical implications, because clinically it is often assumed that VOR and balance control functions are correlated (9).

Currently it is not known if the improvements in VOR and VSR function (based on measures of balance control) over time following an aUVL are different between the elderly and the young. This study therefore focused on the extent to which age might affect improvement of VOR and VSR function in aUVL patients. This knowledge could be useful when establishing evidence-based therapy regimes appropriate for the young and elderly following an acute UVL.

MATERIALS AND METHODS

Subjects

Consecutively collected patient data from the University Hospital Basel was examined retrospectively for this study approved by the ethical committee of NW Switzerland (EKNZ). The 30 subjects (13 females and 16 males) with an aUVL diagnosed as presumably vestibular neuritis on the basis of a pathological canal paresis, the presence of a spontaneous nystagmus beating toward the healthy ear, nausea, and the constant presence of symptoms over hours were subdivided into the following three groups: young (<35 years), middle-aged (36 < years < 60), and elderly (>60 years). Patients were excluded from this study if they had a previous history of balance problems related to the inner ear or had concurrent neurological or orthopedic problems affecting balance. The young group consisted of four men and four women with a mean age of 28.1 years (range 23–35). The middle-aged group consisted of six men and four women with a mean age of 51.4 years (range 43–58). The elderly group consisted of six men and six women with a mean age of 65.7 years (range 60–74). Measurements were taken at acute onset of the UVL (within 2–5 days of the patient's entry into in-patient hospital care), and planned for 3, 6, and 12 weeks after onset. Average times were, however, 3, 6.2, and 13.1 weeks. Although all subjects were measured at onset, not every subject could be measured four times, which resulted in 27 subjects being measured at 3 weeks; 25 subjects at 6.2 weeks; and 25 subjects at 13 weeks. All patients were treated intravenously with methylprednisolone (125 mg Solumedrol™ per day) and then discharged 4 days after entry as an in-patient with oral medication. On discharge, patients were offered 10 sessions of balance-oriented physical therapy. Apart from comparisons between patient group means over time, group data was compared with that of an equal number of age-matched healthy controls recorded previously (6, 7, 18, 25). Written informed consent was obtained from the patients to use their data anonymously.

Measurement Systems

To measure VOR function in response to high accelerations (above 2000°/s^2), one of two video Head Impulse Test (vHIT) systems was used [ICS system from GN Otometrics and EyeSeeCam (ESC) from Interacoustics]. Both systems were used according to the protocol described by MacDougall et al. (26) with head velocities reaching 100–250°/s by 100 ms. At least 20 head rotations to each side were performed. During the head movements, the patient was seated and fixed gaze on a small target 3 m away. Sections of the data with covert saccades and artifacts are removed from the recordings prior to gain calculations by the vHIT manufacturer's software. Gains were calculated based on the quotient of the areas under the eye and head velocity impulse responses for the ICS system. The interval used started 100 ms prior to peak head velocity and ended when head velocity first crossed zero after the peak. For the ESC system, a regression between eye and head velocity was performed over the first 100 ms of data following the onset of head velocity defined as first exceeding 20°/s. As the ICS and ESC methods do not yield the same gain values (the regression fit yields lower gain values), we corrected ESC gain values to equivalent ICS gains based on quadratic fit between the gain values obtained from the two methods (27).

Rotating Chair tests (ROT) were performed according to the previous descriptions (25, 28). The ROT was performed with low accelerations of 20 and 5°/s^2. For these tests, horizontal whole body

rotation was performed in darkness using periods of constant acceleration reaching velocities of 120 and 200°/s, respectively. Subjects were seated in the rotating chair (Tönnies, Wurzburg) with the head fixed to the chair. A triangular velocity profile was used for the 20°/s^2 acceleration and slow phase eye velocity (SPV) amplitude of the nystagmic eye movements was measured at its peak just after the chair reached a velocity of 120°/s (28). For the constant 5°/s^2 acceleration over 40 s to a velocity of 200°/s the mean level of SPV between 30 and 40 s of acceleration was used as the VOR measure (25). Further details of these vHIT and ROT tests are described in Allum and Honegger (11).

A SwayStar™ system (Balance International Innovations, Switzerland) was used to measure balance control and thereby VSR contributions to balance control. This system was attached to the trunk at L1–3 using a converted motor-cycle belt. The gyroscopes systems measured angular velocity in the pitch and roll planes from which angular displacements were calculated with trapezoid integration on-line. The same standard protocol of 14 stance and gait tasks was used as described before to measure balance control (7). Tasks were performed by the participants without shoes. Stance tasks consisted of standing on one and two legs with eyes open and closed. All stance tasks were ended after 20 s or when the participant lost balance or the non-stance foot touched the ground. Standing on one leg trials were performed on the preferred leg. All stance tasks except the standing on one leg eyes closed trial were also repeated on a foam support surface (thickness 10 cm, width 50 cm, length 150 cm, and density 25 kg/m^2). A semi-stance gait-like task, walking eight tandem steps, was performed on a normal floor and on the foam support system with the participants observing their feet while walking. Five gait tasks were all performed at the subjects' preferred gait speed. Three consisted of walking 3 m with either eyes closed, while rotating the head left and right or while pitching the head up and down. The fourth gait task was to walk over four low barriers, each 24 cm high spaced 1 m apart. The final task was to walk up and down a set of stairs consisting of two up- and two downward steps, each 23 cm high. During all trials one or two spotters, as necessary, stood next to the participant to prevent a fall in case of loss of balance. The duration of each gait trial was the time needed to complete the task or to when the subject lost balance. As measures of balance control we used the peak-to-peak angular displacement and velocity in the roll and pitch directions (see lower right **Figure 2**) from each trial as well as trial durations.

Data Analysis

A Wilcoxon signed rank test was performed to determine if there were differences in VOR and balance measures over time. A Kruskall–Wallis test was performed with the age-group as grouping variable to calculate whether test results differed for different age-groups and to show if there was any effect of age on recovery between onset of the aUVL and at 13 weeks later.

The mean recovery time (as well as of the mean plus and minus the SEM) of balance measures was modeled by the following equation, $y = p_1 + p_2 \cdot e^{-p_3 t}$, where y is the measured mean at time, t, in weeks, p_1 the steady state mean value of the measure, p_2 the difference between onset and steady state means, and $1/p_3$ the exponential decay time constant of the mean between onset and steady state. The parameters of the exponential model function were estimated using MATLAB's *nlinfit* (non-linear least-squares regression) function. Further details may be obtained from Allum and Honegger (4).

RESULTS

Effect of Age on VOR at Onset of an aUVL and 13 Weeks Later

Most VOR measures were not different between the age-groups. For example, the level of spontaneous nystagmus as determined by its SPV was not different between the groups at onset of the aUVL or 13 weeks later. The mean levels for the young, middle-aged, and elderly were 7.4, 10.3, and 6.3°/s with SDs of 6.1, 5.7, and 3.1, respectively. At 13 weeks, the level of spontaneous nystagmus was 1.3, 1.9, and 0.8°/s with SDs of 1.7, 2.0 and 0.7°/s, respectively. There were slightly more deficits on the right side for young (61.5%) compared to the elderly (41.6%). The middle-aged had 40% of the deficits on the right. In addition, there were almost no significant differences between the age-groups for mean VOR responses after aUVL. At aUVL onset, VOR deficit side values were outside of the range of healthy normal as indicated by the 95% limits shown in **Figure 1**, and the statistics of **Table 1**; likewise for the corresponding asymmetries. The latter were greater than normal across all age-groups at aUVL onset. At 13 weeks, mean VOR responses for each group were in the normal range with the exception of the canal paresis values from the caloric test which remained, on average, greater than the normal upper limit of 30% for all groups.

Relatively more of the elderly had no improvement of peripheral vestibular function at 13 weeks (42% with a CP remaining greater than 90% compared with 25% young). However, the number of patients with full peripheral recovery (CP <30%) at 13 weeks was the same across the groups (50% of young, 40% of middle-aged, and 33% of elderly). **Figure 1** also shows that generally differences in deficit side responses between onset and 13 weeks were not present between the age-groups although there was a weak trend for decreases in VOR deficit side responses with age. This trend was only significant for normal ($p = 0.007$) and deficit side ($p = 0.031$) responses of the elderly with respect to the young for 5°/s ROT responses at aUVL onset (**Figure 1**). In keeping with this trend, a larger number of the elderly had ROT responses to the deficit side, which were not compensated to the lower 5% bound of normal levels (20.1°/s for 20°/s^2 and 11.5°/s for 5°/s^2 rotations at 13 weeks). That is 12% of the young, 0% of the middle-aged, but 33% of the elderly were not compensated for 20°/s^2 ROT at 13 weeks. The corresponding figures for 5°/s2 ROT were 12, 30, and 42%, respectively.

Effect of Age on Balance Tests at Onset of an aUVL and 13 Weeks Later

In contrast to the limited number of differences with age for VOR responses, we observed several differences for stance and gait tests, specifically for those balance tests typically pathological for aUVL patients (4, 7). **Figure 2** shows an example of the differences

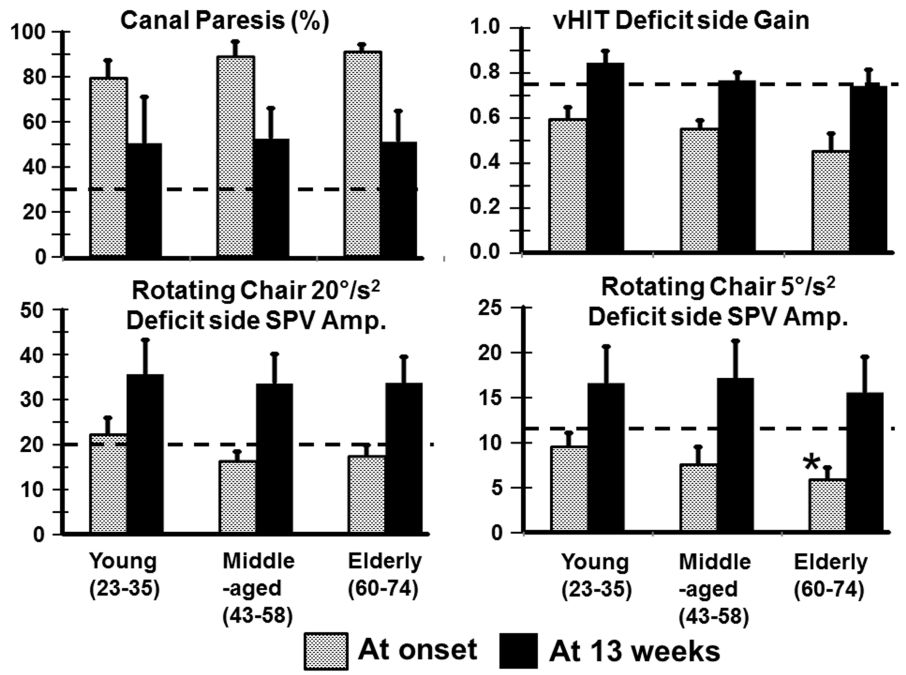


FIGURE 1 | Means of VOR values (and SEM) for young, middle-aged, and elderly patients recorded at onset and 13 weeks after an aUVL. The column heights represent the mean value and the vertical bars on the columns the SEM. The horizontal dashed line marks the upper (for canal paresis) and lower (for responses to heads rotation to the deficit side) 95% limits of healthy normal subjects. The asterisk marks a value for the elderly significantly different from the young ($p < 0.05$).

TABLE 1 | Significant (*p*) comparisons at onset of an aUVL and 13 weeks later with respect to twice the number of healthy age-matched normal subjects for young (23–35 years of age *N* = 8) and elderly (60–74 years of age, *N* = 12) UVL patients.

VOR test	Measure	Young at aUVL onset	Young after 13 weeks	Elderly at aUVL onset	Elderly after 13 weeks
Caloric	CP%	**0.000**	ns	**0.000**	**0.009**
vHIT	Def side	0.047	ns	0.013	ns
ROT 20°/s²	Def side	0.000	ns	0.000	ns
	Asymm	**0.001**	ns	**0.000**	ns
ROT 5°/s²	Def side	0.000	ns	0.000	ns
	Asymm	**0.000**	ns	**0.001**	ns
Balance Test	**Measure**	**Young at aUVL onset**	**Young after 13 weeks**	**Elderly at aUVL onset**	**Elderly after 13 weeks**
s2ecf	Pivel	ns	ns	**0.01**	ns
	Rovel	ns	ns	**0.019**	ns
w8tan	Pivel	ns	ns	**0.014**	ns
	Rovel	ns	ns	**0.000**	**0.000**
	Piang	ns	ns	**0.000**	0.056
	Roang	ns	ns	**0.000**	**0.006**
	Dur	ns	ns	**0.006**	ns
w3mhp	Pivel	ns	ns	**0.021**	ns
	Rovel	ns	ns	**0.004**	ns
	Piang	ns	ns	**0.048**	0.044
	Roang	ns	ns	**0.037**	ns
	Dur	ns	0.013	ns	0.011
w3mec	Pivel	ns	ns	**0.003**	ns
	Rovel	ns	ns	**0.026**	ns
	Piang	ns	ns	ns	ns
	Roang	ns	ns	**0.036**	**0.023**
	Dur	ns	0.006	ns	ns

Mean and SEM for the listed measures are provided in the figures.
In the upper part of the table of VOR measures CP stands for canal paresis; vHIT, video head impulse test; ROT 20°/s², rotating chair test with 20°/s² acceleration; ROT 5°/s², rotating chair test with 5°/s² acceleration. Def side stands for deficit side gain for vHIT and slow phase velocity peak amplitudes for the ROT test, Asymm for response asymmetry. In the lower part of the table listing balance tests s2ecf stands for standing on two legs on foam with eyes closed; w8tan, walking eight tandem steps; w3mhp, walking 3 m while pitching the head up and down; w3mec, walking 3 m with eyes closed. ns for not significant.
Values significantly greater than normal reference values are marked in black bold font, those less, in gray font and underlined.

for the stance test standing on two legs eyes closed on foam. In **Figure 2**, the original recordings are transformed into *x–y* (roll versus pitch) velocity plots, which depict the differences between the elderly and the young more clearly. Both patients in the figure had no peripheral vestibular recovery so that any improvement in balance function could only be due to central compensation. The appearance in **Figure 2** of the elderly having greater sway at aUVL onset and 13 weeks later is confirmed ($p < 0.03$) by the columns marked with asterisks in **Figure 3**. As also indicated by **Figure 3** and **Table 1**, pitch and roll velocity values were outside the normal range across all three age populations at onset except for pitch velocity values for the young. The greater sway at aUVL onset in the elderly was the main reason why the improvement in pitch velocity over 13 weeks was significantly greater ($p = 0.05$) in the elderly. That is, there was a greater possibility for improvement.

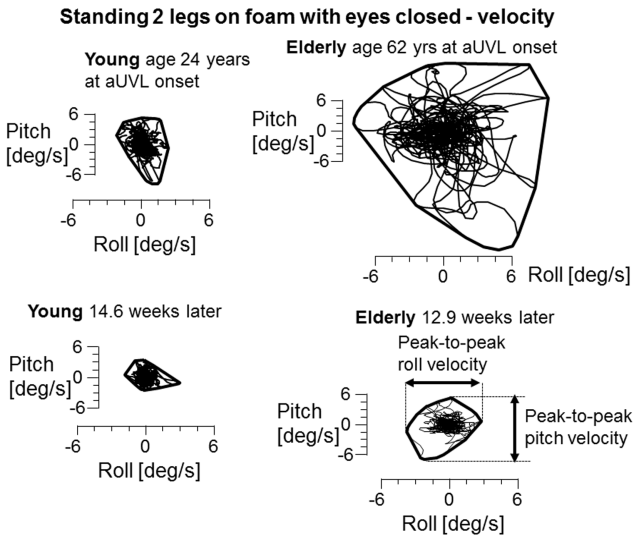


FIGURE 2 | *x–y* plots of trunk sway roll versus pitch angular velocity during the task of standing 2 legs on foam with eyes closed. Both the young and elderly patients in the plots had no peripheral vestibular recovery. CP changed from 84 to 92% for the elderly patient and from 85 to 95% for the young patient. A convex hull has been plotted around each set of traces to show the limits of sway. The measures used to calculate differences in angular velocities between the groups are marked in the lower right *x–y* diagram.

Recovery to the steady state level of stance balance control after aUVL was normally complete for all age-groups by 13 weeks (**Figure 4**). Recovery of the normal stance control was, however, slower in the elderly (as modeled by the exponential fit in **Figure 4**) taking approximately 10 weeks to reach within 10% of the steady state value. The middle-aged took less time, 3.7 weeks, to reach the 10% level. Recovery in the young was so rapid that an exponential fit to their time series data was not possible.

In contrast to stance, control of roll angle and angular velocity is more crucial than that of pitch when walking in tandem steps. The examples in **Figure 5** (again patients with no peripheral recovery) and the mean column plots of **Figure 6** indicate that these measures are significantly greater in the elderly than the young at onset and at 13 weeks (range of p values 0.007–0.045). In addition, the values for the elderly were significantly greater than values of healthy age-matched controls at onset and at 13 weeks ($p < 0.006$, see **Table 1**). There were no significant differences in balance improvement in the young and elderly between aUVL onset and 13 weeks for the tandem gait task (see differences in pairs of column plots in **Figure 6**).

We also examined the gait tasks walking 3 m while pitching the head up and down with eyes open, and walking without voluntary head movements but with eyes closed. The results for these tests were similar. The elderly had values outside of the range of healthy elderly at aUVL onset but generally not at 13 weeks (**Table 1**). Both pitch angle and velocity improvements were greater in the elderly (see **Figure 7**) for the walking eyes closed task when compared to the young (range of p values 0.004–0.03). This was due partly to the greater onset values of the elderly. However, this effect was partially counteracted by the slower recovery in

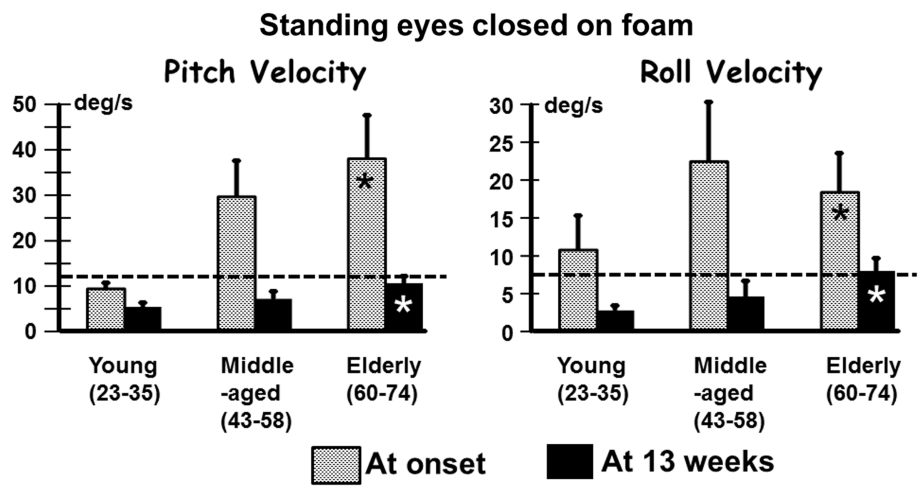


FIGURE 3 | Means (and SEMs) of pitch and roll velocity for the task of standing eyes closed on foam. The layout of the figure is identical to that of **Figure 1**.

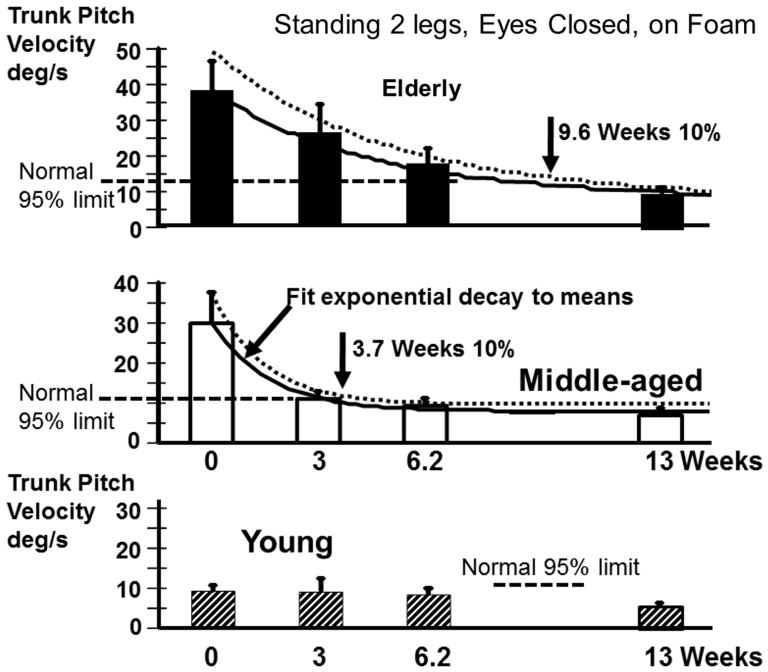


FIGURE 4 | **Recovery time courses of pitch velocity for the different age populations for the task standing eyes closed on foam**. The column heights indicate mean values at aUVL onset (0) and 3, 6.2, and 13 weeks after onset. The vertical bars on the columns represent the SEM. The thick line joining the means is an exponential fit (see Materials and Methods) to the change in the mean value over time. The dashed line above the full line is an exponential fit (same model form) to the means plus the SEM. The recovery times to 10% of steady state are marked by vertical arrows in the figure. The upper 95% limit of normal sway for the age-group is marked by a dashed horizontal line. Note the recovery of the young was so rapid that no model fit was possible.

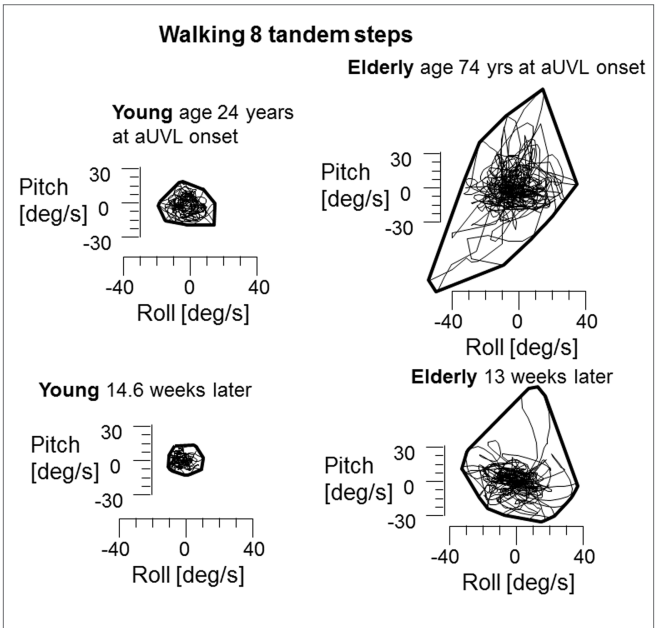


FIGURE 5 | **Plots of roll versus pitch velocity for the task of walking eight tandem steps**. The layout of the figure is identical to that of **Figure 2**. The young and elderly patients in this example had no peripheral vestibular recovery. CP young 85% at onset to 95% after 13 weeks, elderly person 74% at onset to 100% at 13 weeks. Note the significantly larger sway at onset and at 13 weeks for the elderly person.

the elderly. As shown in **Figure 8**, pitch velocity recovery was to within 10% of steady state at 15.2 weeks in the elderly and reached the same relative level at 11.3 weeks in the middle age. In contrast, the young increased pitch velocity over time for the eyes closed walking task. This was due to significant increase in gait speed (see **Table 1**). Both the young and the elderly had increased gait speed at 13 weeks for both of these gait tasks (**Table 1**).

DISCUSSION

Vestibular sensory inputs have a major influence on balance control even if this influence is not as powerful as that on the VOR (10, 11, 26, 29). Thus, it is to be expected that an aUVL initially has a profound effect on VOR and balance function. An intriguing point is that central compensation is able to restore VOR and balance function to nearly normal levels even when peripheral sensory recovery is absent (see **Figures 1**, **3** and **6**). That is, within 13 weeks after an aUVL VOR function and balance control improve to approximately normal values (6, 7, 11). As VOR function and balance control (in the form of trunk sway) deteriorate with age (12–14, 16, 17, 19, 22), we had expected that there would be a detrimental effect of age on the recovery of both functions after aUVL. Surprisingly we found that for balance tasks, but not for VOR tasks, the elderly were more detrimentally influenced by aUVL than young

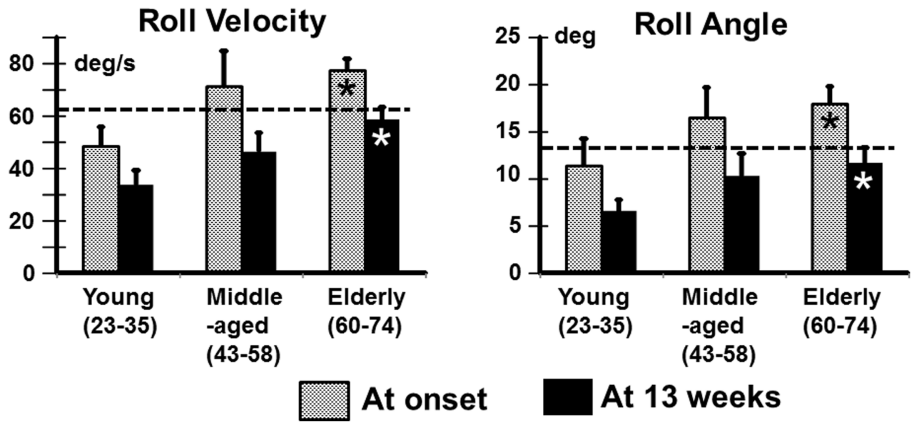


FIGURE 6 | Means and SEM of roll angular velocity and angle for the task of walking eight tandem steps in the different age-groups. The layout of the figure is identical to that of **Figure 1**.

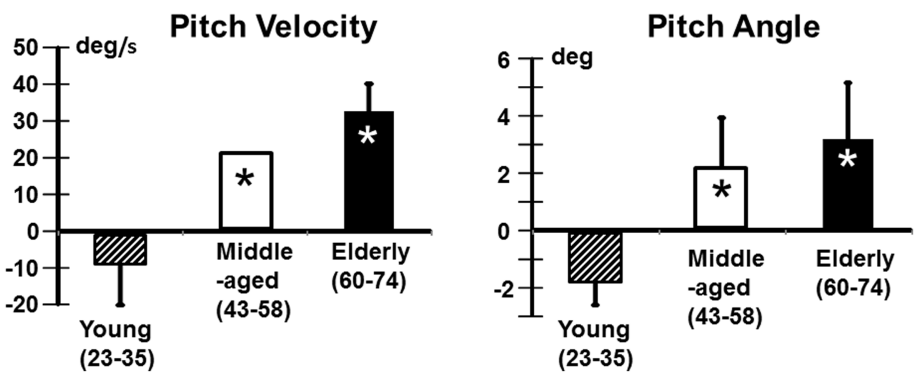


FIGURE 7 | Improvement in pitch angular velocity and pitch angle for the task of walking 3 m with eyes closed. As indicated by the asterisks the improvement in the middle-aged and elderly is significantly greater than that of the young ($p < 0.05$). However, as indicated in **Figure 8**, trunk sway measures of the young are weakly affected by the aUVL.

subjects. VOR tests with low accelerations were the exception with a greater influence on the elderly. That is, with this minor exception, the combined effect of central compensation and peripheral recovery within VOR pathways after an aUVL was similar for the young and elderly.

The question arises whether the slightly decreased VOR values we observed for the elderly (see **Figure 1**) were the results of differences in the number of left and right deficits in each age-group. For example, vHIT gains are 15% larger for head impulses to the right compared to the left when the right eye is measured (24, 30). The number of right deficits ears was greater in the young compared to the elderly (61.5 versus 41.6%) and this difference might have influenced the results in the direction of trend observed (see **Figure 1**). However, a similar trend for larger deficit side responses in the young was also noted for the ROT results (see **Figure 1**). Therefore, we considered the greater number of right side deficits in the young not to have influenced our results.

The greater effect of the aUVL on balance control of the elderly (and to a lesser extent for the middle-aged) was manifest as a greater divergence from normal reference values at onset (**Table 1**) and in the time course of recovery (see **Figures 4** and **8**). In other words, the aUVL had a greater absolute effect on the balance control in the elderly. Also in contrast to our expectations, when differences occurred, the recovery was greater in the elderly, because balance control in the young was hardly changed from normal. Another factor influencing the differences in balance control improvement was the rate of recovery which was slower for the elderly. Thus, the elderly remained with worse balance control than the young over a longer period of time. Differences in improvement were pronounced in balance tests

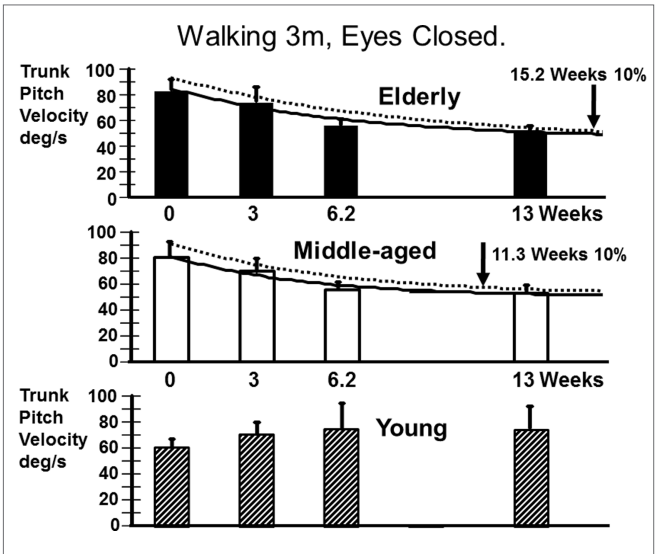


FIGURE 8 | Recovery time courses of pitch velocity for the different age populations for the task of walking 3 m with eyes closed. The layout of the figure is identical to that of **Figure 4**. Note that the data of the young cannot be fitted by an exponential decay model.

with vision absent, reinforcing data indicating that the visual influence on gait and stance is enhanced following vestibular loss (4, 11). Although proprioceptive influences are a major influence on balance control, these influences are not increased as much as visual influences following an aUVL (4).

When differences in recovery were present with age, more recovery was also seen in the pitch plane than in the roll plane. This supports the idea that trunk pitch and trunk roll control are controlled in a different way by the central nervous system (29). This finding also suggests that recovery within the pathways responsible for pitch plane control is faster and more effective than the recovery within the pathways for roll plane control (4). Another factor influencing the faster recovery in the pitch plane could be the larger number of degrees of freedom for the roll compared to pitch plane and the use of a stiffening strategy in the elderly (31). Stiffening leads to balance instability particularly in the roll plane (32).

There was not a systematic change in durations for gait trials in the young with respect to elderly subjects. All subjects reduced gait task durations (increased gait speed) in the weeks after aUVL onset. However, the young increased pitch trunk sway velocity as expected with increases in gait speed [see **Figure 8** (17)]. In contrast, the middle-aged and elderly decreased sway as gait speed increased over time. Thus, the presence of central compensation for a vestibular loss reducing trunk sway appears to counteract the normal increase in trunk sway with increased gait speed in those over 35 years of age. Therefore, it is an open question whether elderly subjects would have improved more if we had asked them to walk faster. Brandt et al. (5) showed that elderly aUVL subjects were better of running than walking following on aUVL.

Differences with age on the recovery of VOR function were basically not observed, except at very low accelerations during ROT tests at 5°/s^2 but major age-related differences in balance control were observed. These findings support our previous observations that VOR and balance test measures are either weakly or not correlated (4, 11). The strongest correlation is negative between the visual contribution to stance control and the deficit side response amplitude for 20°/s^2 ROT ($R = 0.48$). Other correlations are lower than $R = 0.4$ (4). It should be emphasized that peripheral recovery as shown by caloric testing did not show any difference between the age-groups. On average, recovery was much less than 100% in each age-group. CP values reduced from 87 to 52% (see **Figure 1**), on average, without differences between age-groups, even though more of the elderly had a lack of peripheral recovery and insufficient VOR compensation at 13 weeks. In general, both young and elderly had VOR measures that were equally different from those of healthy controls. These results support our previous findings that lack of VOR recovery does not imply that balance function has not recovered and, oppositely, the recovery in VOR measures does not imply a recovery in balance function (4, 11). Rather, the young whose VOR values were pathological after an aUVL had balance control that was hardly changed from normal by the UVL, whereas the elderly and to a lesser extent the middle-aged had ongoing stance and gait balance deficits for several weeks after an aUVL despite significant improvements in VOR measures.

Despite the lack of strong correlations noted above, it is possible that some similar processes underlie VOR and VSR recovery following an aUVL. For example, a lack of peripheral vestibular recovery (as indicated by the greater number of elderly patients with caloric CP values greater than 90% at 13 weeks) and reduced central compensation (as determined by ROT responses of the elderly) may have a correlated negative influence on the central compensation for balance deficits. To answer this question in detail, additional studies with larger numbers of patients are required. Regardless of the cause, the longer period of gait deficits after aUVL in the elderly implies that the physical therapy needs of the elderly should be focused initially on stance and gait balance control and then after 6–8 weeks primarily on gait balance control, even if ROT and vHIT VOR tests indicate a return to normal function during this period.

The elderly are presumably always adapting to the constant worsening in balance control with aging over the age of 60 years (18). Nonetheless, they were unable to cope with the sudden unstable balance caused by an aUVL. To improve their responses to an aUVL those with risk factors indicative of UVL [e.g., see Chuang et al. (33) could be treated with physical therapy ahead of a possible UVL just as has been employed prior to surgical removal of cerebellar pontine angle tumors (34)]. In fact, it is one of the weaknesses of the current study that we were not able to control the activity levels of the patients prior to an aUVL nor for their adherence to prescribed physical therapy post aUVL.

CONCLUSION

Our results indicate that aUVL due, presumably, to vestibular neuritis causes a relative worsening of stance and gait balance control in the elderly compared to the young. At acute onset, the elderly are more unstable than the young and take longer to reacquire the balance abilities of age-matched controls. VOR function

in the young may fail to improve to normal levels rapidly after aUVL onset; however, this appears not to prevent rapid recovery of normal balance control in the young.

AUTHOR CONTRIBUTIONS

JA conceived the experimental design, planned the data collection, constructed the figures, and rewrote drafts of the manuscript. AS helped collect data, worked on the statistics, and wrote the first drafts of the manuscript. DT also worked on early drafts of the paper and helped collect data. FH was involved in setting up the experimental design (clinical tests), conceived the modelling procedures, and worked on data analysis.

ACKNOWLEDGMENTS

This research was supported by a grant to JA from the Freiwillige Akademische Gesellschaft Basel. AS and DT were supported by the Nijmegen University Fund. The authors would like to thank Barbara Wenger for secretarial assistance.

REFERENCES

1. Lacour M. Restoration of vestibular function: basic aspects and practical advances for rehabilitation. *Curr Med Res Opin* (2006) **22**(9):1651–9. doi:10.1185/030079906X115694
2. Horak FB. Postural compensation for vestibular loss and implications for rehabilitation. *Restor Neurol Neurosci* (2010) **28**(1):57–68. doi:10.3233/RNN-2010-0515
3. Allum JH. Recovery of vestibular ocular reflex function and balance control after a unilateral peripheral vestibular deficit. *Front Neurol* (2012) **3**:83. doi:10.3389/fneur.2012.00083
4. Allum JHJ, Honegger F. Recovery times of stance and gait balance control after an acute unilateral peripheral vestibular deficit. *J Vestib Res* (2015) **25**:219–31.
5. Brandt T, Strupp M, Benson J. You are better off running than walking with acute vestibulopathy. *Lancet* (1999) **354**(9180):746. doi:10.1016/S0140-6736(99)03179-7
6. Allum JHJ, Ledin T. Recovery of vestibulo-ocular function in subjects with acute peripheral vestibular loss. *J Vestib Res* (1999) **9**:135–44.
7. Allum JH, Adkin AL. Improvements in trunk sway observed for stance and gait tasks during recovery from an acute unilateral peripheral vestibular deficit. *Audiol Neurootol* (2003) **8**(5):286–302. doi:10.1159/000071999
8. De Waele C, Graf W, Josset P, Vidal PP. A radiological analysis of the postural syndromes following hemilabyrinthectomy and selective canal and otolith lesions in the guinea pig. *Exp Brain Res* (1989) **77**(1):166–82. doi:10.1007/BF00250579
9. Halmagyi GM, Weber KP, Curthoys IS. Vestibular function after acute vestibular neuritis. *Restor Neurol Neurosci* (2010) **28**(1):37–46. doi:10.3233/RNN-2010-0533
10. MacDougall HG, Curthoys IS. Plasticity during vestibular compensation: the role of saccades. *Front Neurol* (2012) **3**:21. doi:10.3389/fneur.2012.00021
11. Allum JHJ, Honegger F. Relation between head impulse tests, rotating chair tests, and stance and gait posturography after an acute unilateral peripheral vestibular deficit. *Otol Neurootol* (2013) **34**(6):980–9. doi:10.1097/MAO.0b013e31829ce5ec
12. Iwasaki S, Yamasoba T. Dizziness and imbalance in the elderly: age-related decline in the vestibular system. *Aging Dis* (2015) **6**(1):38–47. doi:10.14336/AD.2014.0128
13. Baloh RW, Enrietto J, Jacobson KM, Lin A. Age-related changes in vestibular function: a longitudinal study. *Ann N Y Acad Sci* (2001) **942**:210–9. doi:10.1111/j.1749-6632.2001.tb03747.x
14. Barin K, Dodson EE. Dizziness in the elderly. *Otolaryngol Clin North Am* (2011) **44**(2):437–54,x. doi:10.1016/j.otc.2011.01.013
15. Hsieh LC, Lin HC, Lee GS. Aging of vestibular function evaluated using correlational vestibular autorotation test. *Clin Interv Aging* (2014) **9**:1463–9. doi:10.2147/CIA.S67720
16. Gill J, Allum JH, Carpenter MG, Held-Ziolkowska M, Adkin AL, Honegger F, et al. Trunk sway measures of postural stability during clinical balance tests: effects of age. *J Gerontol A Biol Sci Med Sci* (2001) **56**(7):M438–47. doi:10.1093/gerona/56.7.M438
17. Goutier KM, Jansen SL, Horlings CG, Kung UM, Allum JH. The influence of walking speed and gender on trunk sway for the healthy young and older adults. *Age Ageing* (2010) **39**(5):647–50. doi:10.1093/ageing/afq066
18. Hegeman J, Shapkova EY, Honegger F, Allum JHJ. Effect of age and height on trunk sway during stance and gait. *J Vestib Res* (2007) **17**(2–3):75–87.
19. Peterka RJ, Black FO. Age-related changes in human posture control: sensory organization tests. *J Vestib Res* (1990) **1**(1):73–85.
20. Baloh RW, Ying SH, Jacobson KM. A longitudinal study of gait and balance dysfunction in normal older people. *Arch Neurol* (2003) **60**(6):835–9. doi:10.1001/archneur.60.6.835
21. Rauch SD, Velazquez-Villaseñor L, Dimitri PS, Merchant SN. Decreasing hair cell counts in aging humans. *Ann N Y Acad Sci* (2001) **942**(1):220–7. doi:10.1111/j.1749-6632.2001.tb03748.x
22. Peterka RJ, Black FO, Schoenhoff MB. Age-related changes in human vestibulo-ocular reflexes: sinusoidal rotation and caloric tests. *J Vestib Res* (1990) **1**(1):49–59.
23. Mossman B, Mossman S, Purdie G, Schneider E. Age dependent normal horizontal VOR gain of head impulse test as measured with video-oculography. *J Otolaryngol Head Neck Surg* (2015) **44**(1):29. doi:10.1186/s40463-015-0081-7
24. McGarvie LA, MacDougall HG, Halmagyi GM, Burgess AM, Weber KP, Curthoys IS. The video head impulse test (vHIT) of semicircular canal function – age-dependent normative values of VOR gain in healthy subjects. *Front Neurol* (2015) **6**:154. doi:10.3389/fneur.2015.00154
25. Allum JHJ, Honegger F, Ura M. Documentation of the recovery course and deficit side localization of an acute unilateral vestibular deficit using four-quadrant diagrams of slow phase velocity. *Acta Otolaryngol Suppl* (1991) **481**:419–23. doi:10.3109/00016489109131436
26. MacDougall HG, Weber KP, McGarvie LA, Halmagyi GM, Curthoys IS. The video head impulse test: diagnostic accuracy in peripheral vestibulopathy. *Neurology* (2009) **73**(14):1134–41. doi:10.1212/WNL.0b013e3181bacf85
27. Cleworth T, Carpenter MG, Allum JHJ, editors. Differences in head impluse test results due to analysis techniques. *Abstract for ADANO Conference*; Bern (2015).
28. Allum JH, Ledin T. Recovery of vestibulo-ocular reflex-function in subjects with an acute unilateral peripheral vestibular deficit. *J Vestib Res* (1999) **9**(2):135–44.
29. Carpenter MG, Allum JH, Honegger F. Vestibular influences on human postural control in combinations of pitch and roll planes reveal differences in spatiotemporal processing. *Exp Brain Res* (2001) **140**(1):95–111. doi:10.1007/s002210100802
30. Weber KP, Aw ST, Todd MJ, McGarvie LA, Pratap S, Curthoys IS, et al. Chapter 3.7 – Inter-ocular differences of the horizontal vestibulo-ocular reflex during impulsive testing. In: Christopher K, Leigh RJ, editors. *Progress in Brain Research*. (Vol. **171**), Amsterdam: Elsevier (2008). p. 195–8. doi:10.1016/S0079-6123(08)00626-2
31. Allum JHJ, Carpenter MG, Honegger F, Adkin AL, Bloem BR. Age-dependent variations in the directional sensitivity of balance corrections and compensatory arm movements in man. *J Physiol* (2002) **542**(Pt 2):643–63. doi:10.1113/jphysiol.2001.015644
32. Grüneberg C, Bloem BR, Honegger F, Allum JHJ. The influence of artificially increased hip and trunk stiffness on balance control in man. *Exp Brain Res* (2004) **157**(4):472–85.
33. Chuang Y-M, Chern C-M, Liao W-H, Hsu L-C, Lien C-F, Lirng J-F, et al. Comorbid intracranial vertebral artery asymmetry as a risk factor for severe

vestibular neuronitis. *Otol Neurotol* (2011) **32**(3):478–82. doi:10.1097/MAO.0b013e31820e785c

34. Magnusson M, Karlberg M, Tjernström F. 'PREHAB': vestibular prehabilitation to ameliorate the effect of a sudden vestibular loss. *NeuroRehabilitation* (2011) **29**(2):153–6. doi:10.3233/NRE-2011-0689

Conflict of Interest Statement: The authors Flurin Honegger and John H. J. Allum declare a conflict of interest as they both worked as consultants for the company producing the SwayStar equipment used in this study. The remaining 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.

frontiers in Neurology

REVIEW
published: 03 March 2016
doi: 10.3389/fneur.2016.00020

Age-Related Neurochemical Changes in the Vestibular Nuclei

*Paul F. Smith**

Department of Pharmacology and Toxicology, School of Medical Sciences and Brain Health Research Centre, University of Otago, Dunedin, New Zealand

There is evidence that the normal aging process is associated with impaired vestibulo-ocular reflexes (VOR) and vestibulo-spinal reflexes, causing reduced visual acuity and postural instability. Nonetheless, the available evidence is not entirely consistent, especially with respect to the VOR. Some recent studies have reported that VOR gain can be intact even above 80 years of age. Similarly, although there is evidence for age-related hair cell loss and neuronal loss in Scarpa's ganglion and the vestibular nucleus complex (VNC), it is not entirely consistent. Whatever structural and functional changes occur in the VNC as a result of aging, either to cause vestibular impairment or to compensate for it, neurochemical changes must underlie them. However, the neurochemical changes that occur in the VNC with aging are poorly understood because the available literature is very limited. This review summarizes and critically evaluates the available evidence relating to the noradrenaline, serotonin, dopamine, glutamate, GABA, glycine, and nitric oxide neurotransmitter systems in the aging VNC. It is concluded that, at present, it is difficult, if not impossible, to relate the neurochemical changes observed to the function of specific VNC neurons and whether the observed changes are the cause of a functional deficit in the VNC or an effect of it. A better understanding of the neurochemical changes that occur during aging may be important for the development of potential drug treatments for age-related vestibular disorders. However, this will require the use of more sophisticated methodology such as *in vivo* microdialysis with single neuron recording and perhaps new technologies such as optogenetics.

Keywords: vestibular nucleus complex, aging, monoamines, glutamate, GABA, nitric oxide

OPEN ACCESS

Edited by:
Yuri Agrawal,
Johns Hopkins University, USA

Reviewed by:
Kathleen Cullen,
McGill University, Canada
Sascha Du Lac,
Johns Hopkins University, USA

***Correspondence:**
Paul F. Smith
paul.smith@otago.ac.nz

Specialty section:
This article was submitted to Neuro-otology, a section of the journal Frontiers in Neurology

Received: *02 November 2015*
Accepted: *09 February 2016*
Published: *03 March 2016*

Citation:
Smith PF (2016) Age-Related Neurochemical Changes in the Vestibular Nuclei. Front. Neurol. 7:20. doi: 10.3389/fneur.2016.00020

AGE-ASSOCIATED CHANGES IN VESTIBULAR FUNCTION

Aging in humans has been thought to be associated with an increasing impairment of the vestibulo-ocular reflexes (VOR) and vestibulo-spinal reflexes, which results in reduced visual acuity and postural instability (1–14). The prevalence of dizziness and vertigo has been estimated at 30% in people over the age of 60, and dizziness in the elderly is associated with a high risk of falls (15, 16). Nonetheless, there is disagreement about VOR impairment, in particular. A recent study of the VORs using the video head impulse test (vHIT) for all six semi-circular canals reported that,

Abbreviations: 5-HT, 5-hydroxy-tryptamine; AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; GABA, γ-aminobutyric acid; HPLC, high performance liquid chromatography; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; VNC, vestibular nucleus complex; VOR, vestibulo-ocular reflex.

although gain decreased with high head velocities, it was largely unaffected in healthy adults in the 80–89 years' age group (17). Similar results have recently been reported by Matiño-Soler et al. (18), who observed that the horizontal VOR gain was stable up until 90 years of age and then decreased thereafter. McGarvie et al. (17) suggested that cerebellar compensation, in the form of VOR plasticity, may be responsible for the preservation of VOR function despite aging. On the other hand, Li et al. (19) reported that horizontal VOR gain remained stable from 26 to 79 years of age and then significantly declined (people over the age of 80 had an approximately eightfold increase in the odds of having a VOR gain <0.80). Kim and Sharpe (20) also found that the vertical VOR was relatively preserved in the elderly, although vertical smooth pursuit eye movement, eye-head tracking, and VOR cancelation during intentional head movement, were impaired. Studies of perceptual threshold levels related to the horizontal VOR have suggested that there may be little difference between young and older adults (21), although some dynamic visual acuity studies suggest otherwise (22). Otolithic function, evaluated using ocular and cervical vestibular-evoked myogenic potentials (o- and c-VEMPs), has been reported to decline with age (19, 23–26). Vestibulo-sympathetic reflexes have also been reported to be impaired with increasing age, which can lead to an increase in orthostatic hypotension (27, 28).

There is increasing evidence that age-related changes in vestibular function result in cognitive deficits (29–31). Cyran et al. (31) studied the functional connectivity of a vestibular cortical network (i.e., the superior, middle, and inferior frontal and temporal gyri, the lingual gyrus, insula, superior and inferior parietal lobe, parietal operculum, posterior cingulate gyrus, cuneus, thalamus, and cerebellar tonsil) in relation to age, using a tensor independent component analysis of fMRI data acquired in response to galvanic vestibular stimulation. They found that the functional connectivity of the network decreased with age, which they suggested was due not to structural deterioration but to functional changes; the somatosensory sensory networks, on the other hand, remained relatively intact. Recently, several large epidemiological studies have implicated vestibular dysfunction in the development of cognitive deficits in elderly humans (29, 30, 32). Although these data are based on surveys and therefore necessarily correlational in nature, they are consistent with the results of clinical studies in humans [e.g., see Ref. (33, 34) for a review] and experimental studies in animals (35–40), which have shown that vestibular dysfunction results in cognitive impairment, especially related to spatial memory.

Age-related vestibular impairment has often been attributed to a degeneration of the peripheral vestibular receptor hair cells or to changes in the number of neurons in Scarpa's ganglion or the brainstem vestibular nucleus complex (VNC). Many studies have reported that the hair cells and their afferent connections decrease with age (41–50). Nonetheless, some studies have found no significant age-related differences in the number of hair cells in the crista ampullaris of aging gerbils (51) or the human utricle (52) and others have found no significant differences in the number of neurons in Scarpa's ganglion (53, 54). Neuronal loss has been reported in the human VNC (55–58) and in the VNCs of some animal species [e.g., Ref. (59)]. However, Fernandez et al. (60) could find no significant age-related decrease in the number of neurons in the golden hamster. Johnson and Miquel (61) analyzed the ultrastructure of the rat lateral vestibular nucleus at 4 weeks, 6–8 weeks, 6–8 months, and 18–20 months of age, and found a number of age-related changes that increased in frequency with increasing age, including nuclear membrane invaginations, disorganized endoplasmic reticulum, rod-like nuclear inclusions, and lipofuscin-like cytoplasmic dense bodies. In addition, the oldest age group exhibited axonal degeneration and dendritic swelling. Takeuchi et al. (62) have also reported dystrophic axon terminals in the VNC of 360-day-old gerbils. The cytoplasms were found to contain neurofilaments and vesicles with membranous granular substances. Therefore, it is possible that there is age-related structural deterioration in the VNC even without neuronal loss itself.

In summary, there is increasing evidence that the human VORs are largely intact, at least until approximately 80 years of age. Ocular and cervical vestibular-evoked myogenic potentials (o- and c-VEMPs), on the other hand, appear to decline more obviously with age, and there is epidemiological evidence at least to suggest that any decline in vestibular function with age is associated with cognitive deficits. The evidence relating to structural deterioration of the peripheral hair cells, and neuronal loss in Scarpa's ganglion and the VNC, is divided, although there may be morphological changes in the VNC irrespective of neuronal loss.

The apparent discrepancies between the results of the different functional and structural studies in aged animals and humans suggest considerable variability in the effects of aging on the vestibular system. One obvious explanation for this is species differences. Another possibility is that, even within a single species, some of this variability is the result of differences in a combination of genetic and environmental influences on the way that the vestibular system ages and the extent to which it is capable of adaptive plasticity in response to aging. In this respect, it is important to note that Radtke-Schuller et al. (63) have recently reported that the cholinergic vestibular efferent neurons, which provide feedback to the peripheral vestibular system, do not degenerate with age. By contrast, cochlear efferent neurons do degenerate with age.

It is reasonable to assume that functional changes in the vestibular nucleus that are associated with either vestibular impairment or plasticity that prevents it, would be the result of neurochemical changes and that these would constitute a neurochemical signature of the aged vestibular nucleus. The aim of this review is to summarize and critically evaluate what is currently known on this topic.

NEUROCHEMICAL CHANGES IN THE VESTIBULAR NUCLEUS WITH AGE

By contrast with the functional and neuroanatomical studies of the vestibular system, there are relatively few neurochemical studies of the VNC in relation to aging.

Monoamines

The VNC has been shown to receive noradrenergic inputs from the locus coeruleus and the response of VNC neurons to glutamate

appears to be modulated by noradrenaline (NA) via α_2 receptors [see Ref. (64, 65) for reviews]. NA also appears to modulate the response to GABA via α_2 receptors and β receptors (66). Likewise, the VNC receives serotonergic projections from the dorsal raphe nucleus and VNC neurons appear to have 5-hydroxytryptamine $(5\text{-HT})_{1A}$, 5-HT_{1B}, and 5-HT_2 receptors [see Ref. (64, 65) for reviews]. VNC neurons also respond to dopamine (DA) via "D_2-like" receptors (i.e., D_2, D_3, and D_4 receptors). There is evidence that DA depolarizes medial vestibular nucleus (MVN) neurons by acting on presynaptic "D_2-like" receptors to inhibit the release of GABA from inhibitory interneurons [see Ref. (65) for a review].

Cransac et al. (67) studied the levels of NA, 5-HT, and DA and their metabolites in the MVN of rats at 4, 21, and 24 months of age, using homogenized micropunch samples and high performance liquid chromatography (HPLC). They found a decrease in NA with age and an increase in the ratio of its metabolite, 3-methoxy, 4-hydroxyphenylglycol (MHPG), to NA. By contrast, 5-HT and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), increased in the MVN with age while DA and 3,4-dihydroxyphenylacetic acid (DOPAC) levels remained unchanged. Di Mauro et al. (66) have suggested that a decrease in the NA content of the VNC could be responsible for deterioration of vestibular function with age.

Amino Acids

The excitatory and inhibitory amino acids are among the most important neurotransmitters in shaping the response of VNC neurons. Every subtype of glutamate receptor is expressed in the VNC (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), *N*-methyl-D-aspartate (NMDA) and the metabotropic glutamate receptors), and glutamate is the primary neurotransmitter used in the synapses between the vestibular nerve and VNC neurons [see Ref. (64, 65) for reviews]. Similarly, many VNC neurons have γ-aminobutyric acid (GABA) receptors of both the $GABA_A$ and $GABA_B$ subtypes, and the $GABA_A$ receptor is thought to primarily mediate commissural inhibition between the bilateral VNCs. Glycine, acting on glycine receptors, is also important in inhibitory neurotransmission in the VNC [see Ref. (64, 65) for reviews].

Him et al. (68) reported that the responses of MVN neurons to NMDA and AMPA were similar in brainstem slices from young (3 months of age) and aged rats (24 months of age), suggesting no change in the sensitivity of these glutamate receptor subtypes. Liu et al. (69) compared glutamate levels in the VNCs of rats at 4 and 24 months of age, using homogenized samples and HPLC, and found that glutamate levels significantly decreased with age (see **Figure 1A**); by contrast, there was no such decrease in the cerebellum. Since Him et al. (68) measured only the response of MVN neurons to NMDA and AMPA, and Liu et al. (69) measured only the levels of glutamate, the results of these two studies are not necessarily incompatible. For example, it is possible that AMPA and NMDA receptors upregulated or increased their sensitivity to glutamate in response to a decrease in its availability, resulting in an approximately normal response to those agonists. However, neither of these studies allows the neurochemical changes to be attributed to any specific function within the VNC. Therefore, the functional significance of these results remains unclear.

Him et al. (70) reported that neurons in the MVN from aged (24 months old) rats exhibited an increased sensitivity to the $GABA_A$ receptor agonist, muscimol, which they suggested might be a compensatory change in response to a loss of neurons within the MVN. Giardino et al. (71) detected increased levels of glutamic acid decarboxylase (GAD) in the 24-month-old rat VNC, and concluded that this may reflect an increased synthesis of GABA in the aged VNC. However, Liu et al. (69), again using homogenized samples and HPLC, found no significant change in GABA levels in the VNC or cerebellum with aging in the rat (**Figure 1B**).

In the only study of age-related changes in glycine receptors in the VNC to date, Nakayama et al. (72) demonstrated a large

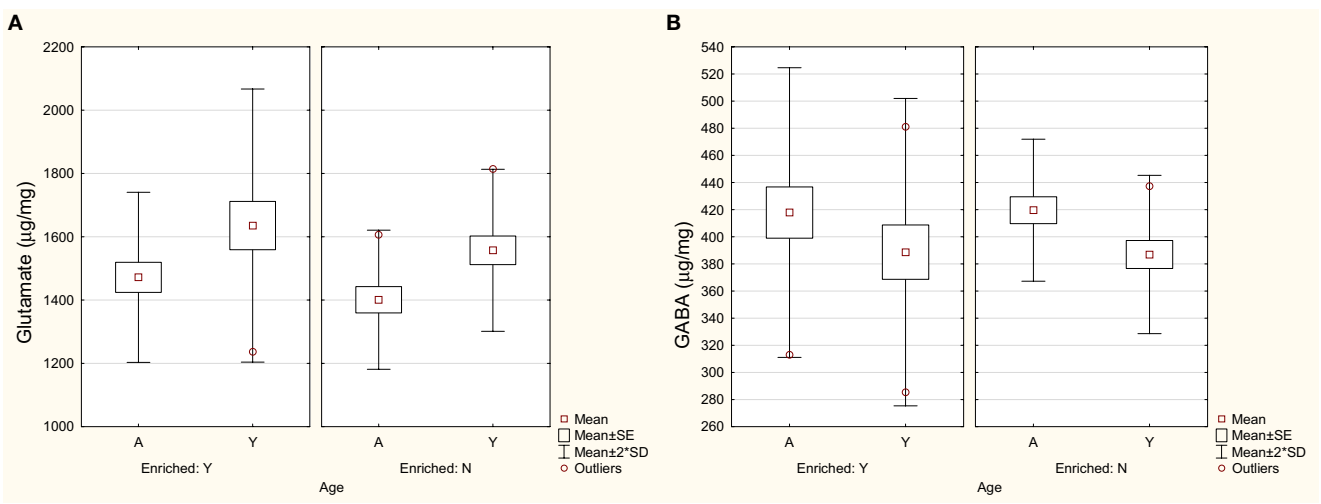


FIGURE 1 | Levels of glutamate (A) and GABA (B) in the VNC in aged (A) and young (Y) rats housed in either an enriched environment ("Y") or not ("N"). Symbols represent means with the SE and SD for the mean. Modified from Liu et al. (69).

decrease in strychnine binding in the VNC as a function of age (3, 18, and 26 months). The amount of strychnine binding in the 26-month-old rat was approximately 50% of that in the 3-month-old rat. Once again, the functional significance of these changes is unknown. However, Nakayama et al. (72) speculated that an increased glycine synthesis might occur in order to prevent such a large decrease in glycine receptors from causing functional impairment.

Other Neurochemical Changes with Age

Sulaiman and Dutia (73) showed that many MVN neurons in brainstem slices are inhibited by δ-opioid receptor agonists such as [D-Ala2, D-Leu5]-enkephalin (DADLE) and [D-Pen2, Pen5]-enkephalin (DPLPE), an effect that was blocked by the δ-receptor antagonist, naltrindole. Interestingly, they found that the inhibitory effects of DADLE increased with age, although the oldest animals used were only 160–180 g in weight.

Liu et al. (69) were interested in analyzing the L-arginine metabolic system in the VNC and cerebellum of aged (24 months old) and young (4 months old) rats. Some of the rats were housed in a standard environment, and others were housed in an enriched environment, with running wheels and toys. They employed homogenized samples, HPLC and liquid chromatography/mass spectrometry (LC/MS/MS) to quantify the concentrations of L-arginine, L-citrulline, L-ornithine, agmatine, putrescine, spermidine, spermine, as well as glutamate and GABA (the latter as previously mentioned). These neurochemicals are all related and part of the L-arginine metabolic pathway (see **Figure 2**). L-arginine is a semi-essential amino acid metabolized by nitric oxide synthase (NOS) in order to produce nitric oxide (NO) and L-citrulline (74). NO is non-conventional neurotransmitter that is important for synaptic plasticity and learning and memory; however, it is also a free radical, and therefore in excessive amounts it can be neurotoxic [see Ref. (75) for a review]. There is a great deal of evidence that NO is implicated in both the normal aging process and age-related neurodegenerative processes [(76, 77); see Ref. (78, 79) for reviews]. The polyamines putrescine, spermidine, and spermine are down-stream metabolites of L-arginine (see **Figure 2**).

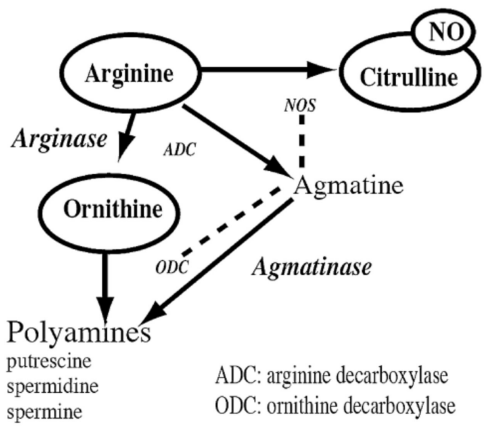


FIGURE 2 | The arginine metabolic pathway showing the conversion of L-arginine to the neurotransmitter, nitric oxide (NO), and L-citrulline, by nitric oxide synthase (NOS), of which there are three isoforms; the conversion of L-arginine to agmatine by arginine decarboxylase (ADC), which is then converted to polyamines such as putrescine, spermidine, and spermine by agmatinase and ornithine decarboxylase (ODC); and the conversion of L-arginine to L-ornithine by arginase, which is then converted to the same polyamines. Glutamate is one of the end products of L-arginine, and glutamate serves as a precursor for the synthesis of GABA. Reproduced from Smith et al. (82) with permission from Elsevier.

Liu et al. (69) found that in the VNC, putrescine, L-arginine, and L-citrulline increased significantly with age, while spermine and L-ornithine decreased (see **Figure 3**). In the cerebellum, spermidine and L-citrulline increased significantly with age, while spermine decreased. Linear discriminant analysis (LDA) was used to show that age could be predicted from a subset of these neurochemicals. For the VNC, the LDA could predict age with 100% accuracy from the levels of putrescine, spermidine, spermine, L-citrulline, glutamate, and GABA. For the cerebellum, age could be predicted with 93% accuracy from the levels of spermine and spermidine only.

L-citrulline (the coproduct of NO) was significantly higher in the aged VNC and cerebellum, which is consistent with the increase in NO in the aged cerebellum that has been reported previously (80). Mistry et al. (81) reported that L-arginine concentrations in the cerebellum were not significantly different between young (3–5 months old) and aged (18–22 months old) male rats, which is consistent with the results of Liu et al. (69).

In further analyses of the same data set, Smith et al. (82) used multiple linear regression in order to determine whether each variable could be predicted from the others. Age was a significant predictor variable for putrescine ($R^2 = 0.68$), spermidine ($R^2 = 0.93$), agmatine ($R^2 = 0.76$), and L-ornithine ($R^2 = 0.50$). Using cluster analyses, there were no large differences in the covariation of the different neurochemical variables between the young and aged animals, and glutamate and GABA covaried closely in both groups (see **Figure 4**).

In summary, there is evidence that, with aging, the levels of NA and glutamate decrease in the VNC, while those of 5-HT and NO increase (**Figure 5**). On the other hand, there is evidence that GABA and DA levels do not change significantly (**Figure 5**). The data relating to neuronal responsiveness are more difficult to interpret, since they may reflect receptor number, affinity or efficacy; however, the available data suggest that the response of VNC neurons to NMDA and AMPA receptor agonists does not change significantly, while $GABA_A$ receptor and δ-opioid receptor agonists have an increased effect. There is a significant downregulation of glycine receptors in the VNC with age.

CONCLUSION AND FUTURE DIRECTIONS

Although vertigo and dizziness are common complaints among the elderly (15, 16), there is some disagreement as to how much of this is due to VOR dysfunction. Some recent studies have suggested that the VOR remains relatively preserved even in people over the age of 80 [e.g., Ref. (17)]. There is, on the other hand, evidence for dysfunction of o- and c-VEMPs with advancing age [e.g., Ref. (19, 23–26)]. The evidence for age-related hair cell loss

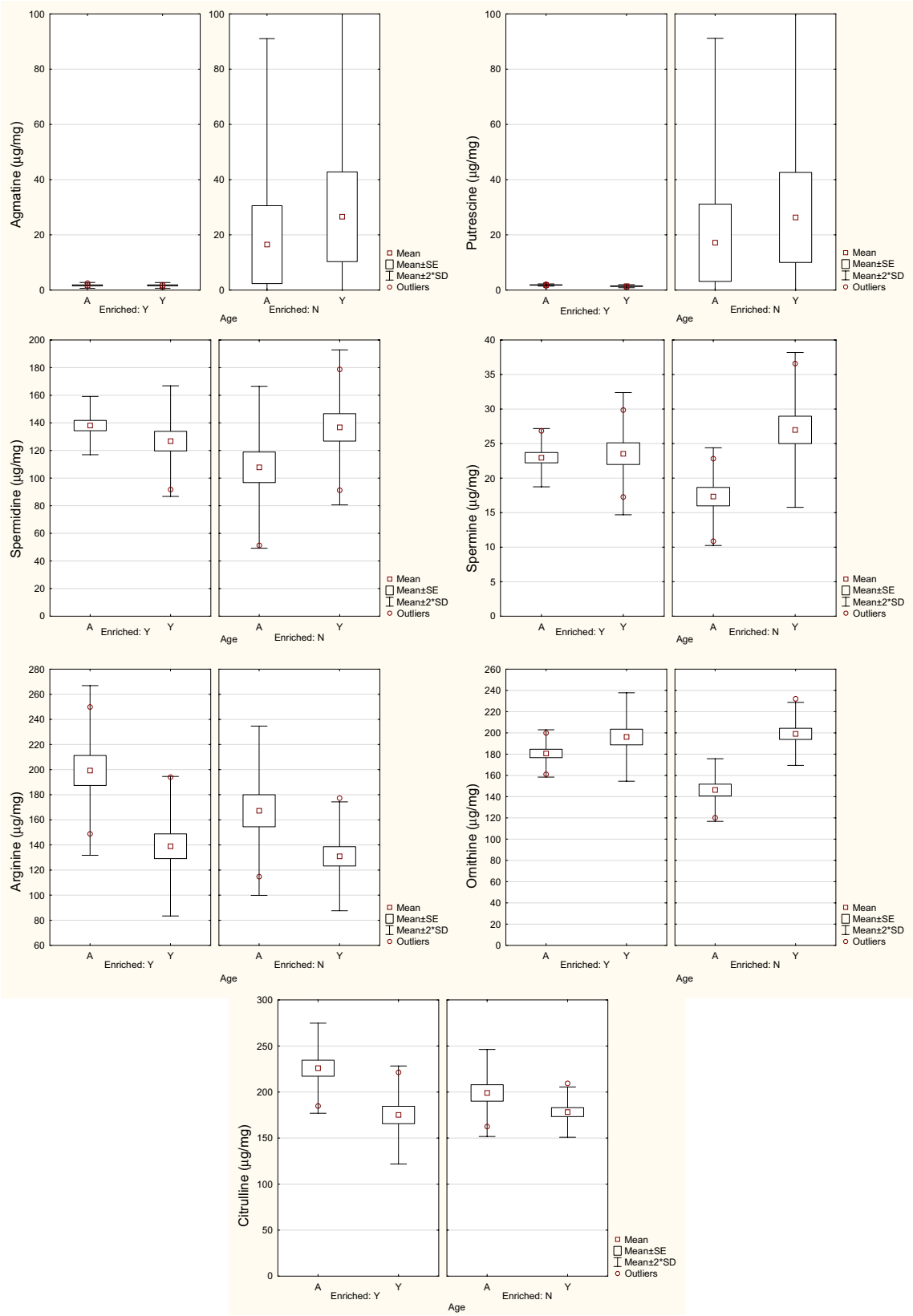


FIGURE 3 | Levels of agmatine, putrescine, spermidine, spermine, L-arginine, L-ornithine, and L-citrulline in the VNC in in aged (A) and young (Y) rats housed in either an enriched environment (Y) or not (N). Symbols represent means with the SE and SD for the mean. Modified from Liu et al. (69).

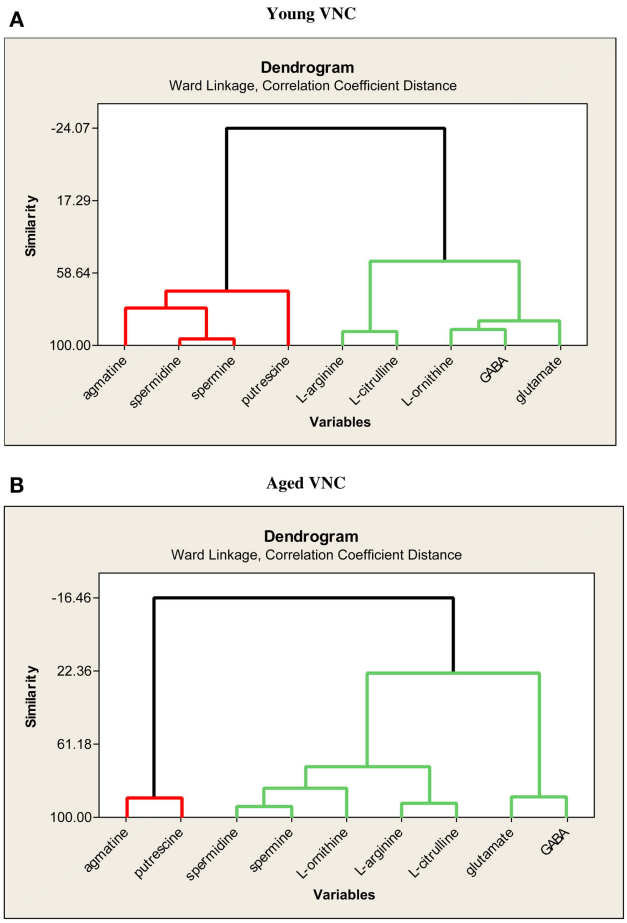


FIGURE 4 | Dendrograms showing the similarities in the degree of expression of the nine neurochemical variables in the VNC of young (A) and aged (B) rats. Reproduced from Liu et al. (69) with permission from Elsevier.

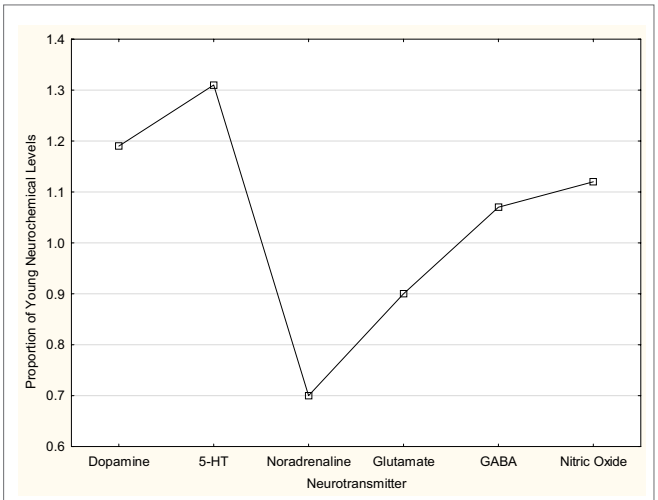


FIGURE 5 | Schematic diagram of changes in levels of dopamine, 5-HT, noradrenaline, glutamate, GABA and nitric oxide, with age. The data regarding dopamine and 5-HT are from Table 1 in Cransac et al. (67). The data regarding noradrenaline are estimated from **Figure 1** in the same paper. The data regarding glutamate and GABA are from Liu et al. (69). The nitric oxide levels are estimated from the levels of the coproduct L-citrulline (i.e., both are produced from the action of nitric oxide synthase on L-arginine), also from Liu et al. (69). In all cases, the young data are from rats at 3–4 months of age and the aged data from animals at 24 months of age. The data from Cransac et al. (67) are from the MVN whereas the data from Liu et al. (69) are from the VNC as a whole. In all cases, the aged data are expressed as a proportion of the mean values for the young data in each study, in order to make comparisons across studies possible. The changes in 5-HT, noradrenaline, glutamate, and nitric oxide were statistically significant.

and neuronal loss in Scarpa's ganglion and the VNC is divided; however, it may be that structural deterioration occurs even without neuronal loss. One possibility is that some of the changes that lead to increased vertigo and dizziness in the elderly are related not to peripheral degeneration or even degeneration in the VNC, but to deterioration in the vestibulo-limbic and vestibulo-cortical pathways. Recent studies have shown age-related changes in the vestibulo-cortical networks and epidemiological studies have increasingly linked vestibular impairment to cognitive deficits in the elderly (29–31).

Assuming that there are structural and functional changes in VNC neurons with age that contribute to vestibular impairment, it is almost certain that these will be dictated by neurochemical changes, either causing deterioration of function or perhaps caused by that deterioration; some of these changes may even be compensatory and may help to preserve vestibular function, up to a point. Unfortunately, at this time, there are relatively few quantitative studies that can shed light on this topic. Of the studies that have been published, there is evidence for a decrease in NA and an increase in 5-HT in the VNC, with no change in DA levels (67); a decrease in glutamate levels (69) with no change in the sensitivity of AMPA and NMDA receptors (68) (**Figure 5**). The evidence relating to GABA is contradictory, with Giardino et al. (71) reporting an increase in GAD, possibly reflecting an increased synthesis of GABA, while Liu et al. (69) found no significant change in GABA levels (**Figure 5**). On the other hand, Him et al. (70) reported an increased sensitivity of MVN neurons to a $GABA_A$ receptor agonist. There is evidence for a decrease in glycine receptors (72) and an increase in the sensitivity of MVN neurons to the inhibitory effects of δ opioid receptor agonists (73). Finally, Liu et al. (69) have reported complex changes in various neurochemicals that are part of the L-arginine metabolic pathway, some of which are implicated in the production of NO. Unfortunately, to completely understand the changes that are occurring in any particular neurotransmitter system, it is necessary to have information not only about neurotransmitter levels, preferably their release (see below), but also the number, affinity and efficacy of their receptors (i.e., the degree to which activation of the receptor by an agonist results in a change in neuronal function, for example, via influx of ions through linked ion channels or G protein mobilization). For example, it is possible to have no change in neurotransmitter release, no change in receptor number or affinity, however a change in efficacy. While neurotransmitter release can be measured using microdialysis *in vivo*, and receptor number can be measured using receptor binding, western blotting or

immunohistochemistical methods, affinity, with spatial information, is best measured using receptor autoradiography, and efficacy requires the use of patch clamping (for ion channel-linked receptors) or GTPase assays (to measure G protein mobilization for G protein-coupled receptors). The combination of all these methods is rarely used and therefore it can be difficult to interpret the functional meaning of a decrease or an increase in a neurotransmitter without knowing the number, affinity and efficacy of the receptors.

Aside from the many differences in species and methods, e.g., different types of HPLC to analyze neurochemical levels and electrophysiological versus binding techniques to analyze receptors, most of the available studies suffer from the limitation that it is difficult, if not impossible, to relate any neurochemical changes observed to the function of specific VNC neurons (other than attributing the changes to a specific subnucleus of the VNC such as the MVN, if only that subnucleus was dissected). Furthermore, it is impossible to determine whether any observed changes are the cause of a functional deficit in the VNC as opposed to an effect of it. In fact, there are few electrophysiological studies of VNC neuronal function in aged animals. One reason for this is that aged animals are expensive and difficult to maintain for the required length of time. Twenty-two months for a rat is equivalent to approximately 65 years for a human, and therefore some animals will not survive the desired length of time. A perennial limitation of HPLC studies is that they analyze the total concentrations of neurochemicals in brain tissue, not only the components related to their role as neurotransmitters, and therefore some of the changes may reflect energy metabolism and any apparent lack of change may be due to adjustments in the neurotransmitter/non-neurotransmitter components (69). Therefore, one important future direction will be to combine microdialysis, which can measure neurotransmitter release within the VNC, with electrophysiological recording from single neurons. This is a much more difficult method than using brain homogenate samples, but will yield more specific information. Another important new direction will be to exploit optogenetic techniques in order to selectively modulate neuronal subtypes via light-sensitive proteins that have been genetically inserted into the target neurons (83), while at the same time using microdialysis to measure neurotransmitter release and electrophysiology to record functional changes.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

ACKNOWLEDGMENTS

Some of the research reviewed here was supported by grants from the New Zealand Neurological Foundation and Lottery Health Board to Assoc. Prof. Ping Liu of the Department of Anatomy, University of Otago.

REFERENCES

1. Baloh RW. Dizziness in older people. *J Am Geriatr Soc* (1992) **40**:713–21. doi:10.1111/j.1532-5415.1992.tb01966.x
2. Baloh RW, Enrietto J, Jacobson KM, Lin A. Age-related changes in vestibular function: a longitudinal study. *Ann N Y Acad Sci* (2001) **942**:210–9. doi:10.1111/j.1749-6632.2001.tb03747.x
3. Baloh RW, Jacobson KM, Socotch TM. The effect of aging on visual-vestibuloocular responses. *Exp Brain Res* (1993) **95**:509–16. doi:10.1007/BF00227144
4. Baloh RW, Ying SH, Jacobson KM. A longitudinal study of gait and balance dysfunction in normal older people. *Arch Neurol* (2003) **60**:835–9. doi:10.1001/archneur.60.6.835
5. Paige GD. Senescence of human visual-vestibular interactions. 1. Vestibulo-ocular reflex and adaptive plasticity with aging. *J Vestib Res* (1992) **2**: 133–51.
6. Redfern MS, Jennings JR, Martin C, Furman JM. Attention influences sensory integration for postural control in older adults. *Gait Posture* (2001) **14**:211–6. doi:10.1016/S0966-6362(01)00144-8
7. Tian JR, Crane BT, Wiest G, Demer JL. Effect of aging on the human initial interaural linear vestibulo-ocular reflex. *Exp Brain Res* (2002) **145**:142–9. doi:10.1007/s00221-002-1111-z
8. Su HC, Huang TW, Young YH, Cheng PW. Aging effect on vestibular evoked myogenic potential. *Otol Neurotol* (2004) **25**:977–80. doi:10.1097/00129492-200411000-00019
9. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? *Age Ageing* (2006) **35**:ii7–11. doi:10.1093/ageing/afl077
10. Serrador JM, Lipsitz LA, Gopalakrishnan GS, Black FO, Wood SJ. Loss of otolith function with age is associated with increased postural sway measures. *Neurosci Lett* (2009) **465**(1):10–5. doi:10.1016/j.neulet.2009.08.057
11. Deshpande N, Patla AE. Visual-vestibular interaction during goal directed locomotion: effects of aging and blurring vision. *Exp Brain Res* (2007) **176**:43–53. doi:10.1007/s00221-006-0593-5
12. Agrawal Y, Davalos-Bichara M, Zuniga MG, Carey JP. Head impulse test abnormalities and influence on gait speed and falls in older individuals. *Otol Neurotol* (2013) **34**(9):1729–35. doi:10.1097/MAO.0b013e318295313c
13. Agrawal Y, Zuniga MG, Davalos-Bichara M, Schubert MC, Walston JD, Hughes J, et al. Decline in semicircular canal and otolith function with age. *Otol Neurotol* (2012) **33**(5):832–9. doi:10.1097/MAO.0b013e3182545061
14. Davalos-Bichara M, Agrawal Y. Normative results of healthy older adults on standard clinical vestibular tests. *Otol Neurotol* (2014) **35**(2):297–300. doi:10.1097/MAO.0b013e3182a09ca8
15. Iwasaki S, Yamasoba T. Dizziness and imbalance in the elderly: age-related decline in the vestibular system. *Aging Dis* (2014) **6**(1):38–47. doi:10.14336/AD.2014.0128
16. Fernández L, Breinbauer HA, Delano PH. Vertigo and dizziness in the elderly. *Front Neurol* (2015) **6**:144. doi:10.3389/fneur.2015.00144
17. McGarvie LA, MacDougall HG, Halmagyi GM, Burgess AM, Weber KP, Curthoys IS. The video head impulse test (vHIT) of semicircular canal function – age-dependent normative values of VOR gain in healthy subjects. *Front Neurol* (2015) **6**:154. doi:10.3389/fneur.2015.00154
18. Matiño-Soler E, Esteller-More E, Martin-Sanchez JC, Martinez-Sanchez JM, Perez-Fernandez N. Normative data on angular vestibulo-ocular responses in the yaw axis measured using the video head impulse test. *Otol Neurotol* (2015) **36**(3):466–71. doi:10.1097/MAO.0000000000000661
19. Li C, Layman AJ, Carey JP, Agrawal Y. Epidemiology of vestibular evoked myogenic potentials: data from the Baltimore longitudinal study of aging. *Clin Neurophysiol* (2015) **126**(11):2207–15. doi:10.1016/j.clinph.2015.01.008
20. Kim JS, Sharpe JA. The vertical vestibulo-ocular reflex, and its interaction with vision during active head motion: effects of aging. *J Vestib Res* (2001) **11**:3–12.
21. Chang NY, Hiss MM, Sanders MC, Olomu OU, MacNeilage PR, Uchanski RM, et al. Vestibular perception and the vestibulo-ocular reflex in young and older adults. *Ear Hear* (2014) **35**(5):565–70. doi:10.1097/AUD.0000000000000052
22. Deshpande N, Tourtillott BM, Peters BT, Bloomberg JJ. Dynamic visual acuity (DVA) during locomotion for targets at near and far distances: effects of aging,

walking speed and head-trunk coupling. *J Vestib Res* (2013) **23**(4–5):195–201. doi:10.3233/VES-130500
23. Janky KL, Shepard N. Vestibular evoked myogenic potential (VEMP) testing: normative threshold response curves and effects of age. *J Am Acad Audiol* (2009) **20**(8):514–22. doi:10.3766/jaaa.20.8.6
24. Akin FW, Murnane OD, Tampas JW, Clinard CG. The effect of age on the vestibular evoked myogenic potential and sternocleidomastoid muscle tonic electromyogram level. *Ear Hear* (2011) **32**(5):617–22. doi:10.1097/AUD.0b013e318213488e
25. Chang CM, Young YH, Cheng PW. Age-related changes in ocular vestibular-evoked myogenic potentials via galvanic vestibular stimulation and bone-conducted vibration modes. *Acta Otolaryngol* (2012) **132**(12):1295–300. doi:10.3109/00016489.2012.708437
26. Singh NK, Kashyap RS, Supreetha L, Sahana V. Characterization of age-related changes in sacculocolic response parameters assessed by cervical vestibular evoked myogenic potentials. *Eur Arch Otorhinolaryngol* (2014) **271**(7):1869–77. doi:10.1007/s00405-013-2672-0
27. Ray CA, Monahan KD. Aging attenuates the vestibulo-sympathetic reflex in humans. *Circulation* (2002) **105**:956–61. doi:10.1161/hc0802.104289
28. Kuipers NT, Sauder CL, Ray CA. Aging attenuates the vestibulo-respiratory reflex in humans. *J Physiol* (2003) **548**:955–61. doi:10.1113/jphysiol.2002.033357
29. Bigelow RT, Semenov YR, Trevino C, Ferrucci L, Resnick SM, Simonsick EM, et al. Association between visuospatial ability and vestibular function in the Baltimore longitudinal study of aging. *J Am Geriatr Soc* (2015) **63**(9):1837–44. doi:10.1111/jgs.13609
30. Semenov YR, Bigelow RT, Xue QL, Lac SD, Agrawal Y. Association between vestibular and cognitive function in U.S. adults: data from the national health and nutrition examination survey. *J Gerontol A Biol Sci Med Sci* (2015) **71**(2):243–50. doi:10.1093/gerona/glv069
31. Cyran CA, Boegle R, Stephan T, Dieterich M, Glasauer S. Age-related decline in functional connectivity of the vestibular cortical network. *Brain Struct Funct* (2016, in press).
32. 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
33. Brandt T, Schautzer F, Hamilton DA, Bruning R, Markowitsch H, Kalla R, et al. Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans. *Brain* (2005) **128**:2732–41. doi:10.1093/brain/awh617
34. Bigelow RT, Agrawal Y. Vestibular involvement in cognition: visuospatial ability, attention, executive function, and memory. *J Vestib Res* (2015) **25**(2):73–89. doi:10.3233/VES-150544
35. Wallace DG, Hines DJ, Pellis SM, Whishaw IQ. Vestibular information is required for dead reckoning in the rat. *J Neurosci* (2002) **22**(22):10009–17.
36. Zheng Y, Balabhadrapatruni S, Munn O, Masumura C, Darlington CL, Smith PF. Evidence for deficits in a 5 choice serial reaction time task in rats with bilateral vestibular deafferentation. *Behav Brain Res* (2009) **203**:113–7. doi:10.1016/j.bbr.2009.04.027
37. Zheng Y, Darlington CL, Smith PF. Impairment and recovery on a food foraging task following unilateral vestibular deafferentation in rat. *Hippocampus* (2006) **16**:368–78. doi:10.1002/hipo.20149
38. Zheng Y, Goddard M, Darlington CL, Smith PF. Bilateral vestibular deafferentation impairs performance in a spatial forced alternation task in rats. *Hippocampus* (2007) **17**:253–6. doi:10.1002/hipo.20266
39. Zheng Y, Goddard M, Darlington CL, Smith PF. Long-term deficits on a foraging task after bilateral vestibular deafferentation in rats. *Hippocampus* (2009) **19**:480–6. doi:10.1002/hipo.20533
40. Baek J-H, Zheng Y, Darlington CL, Smith PF. Evidence that spatial memory deficits in rats following bilateral vestibular loss are probably permanent. *Neurobiol Learn Mem* (2010) **94**:402–13. doi:10.1016/j.nlm.2010.08.007
41. Gleeson M, Felix H. A comparative study of the effect of age on the human cochlear and vestibular neuroepithelia. *Acta Otolaryngol Suppl* (1987) **436**:103–9. doi:10.3109/00016488709124982
42. Anniko M. The aging vestibular hair cell. *Am J Otolaryngol* (1983) **4**:151–60. doi:10.1016/S0196-0709(83)80037-4
43. Lyon MJ, King JM. Aging rat vestibular ganglion: II. Quantitative electron microscopic evaluation. *Ann Otol Rhinol Laryngol* (1997) **106**:753–8. doi:10.1177/000348949710600908
44. Merchant SN, Velazquez-Villasenor L, Tsuji K, Glynn RJ, Wall C III, Rauch SD. Temporal bone studies of the human peripheral vestibular system. Normative vestibular hair cell data. *Ann Otol Rhinol Laryngol* (2000) **181**:3–13.
45. Park JJ, Tang Y, Lopez I, Ishiyama A. Age-related change in the number of neurons in the human vestibular ganglion. *J Comp Neurol* (2001) **431**:437–43. doi:10.1002/1096-9861(20010319)431:4<437::AID-CNE1081>3.0.CO;2-P
46. Rauch SD, Velazquez-Villasenor L, Dimitri PS, Merchant SN. Decreasing hair cell counts in aging humans. *Ann N Y Acad Sci* (2001) **942**:220–7. doi:10.1111/j.1749-6632.2001.tb03748.x
47. Kevetter GA, Leonard RB. Decreased expression of calretinin and calbindin in the labyrinth of old gerbils. *Brain Res* (2002) **957**:362–5. doi:10.1016/S0006-8993(02)03668-5
48. Lopez I, Ishiyama G, Tang Y, Tokita J, Baloh RW, Ishiyama A. Regional estimates of hair cells and supporting cells in the human crista ampullaris. *J Neurosci Res* (2005) **82**:421–31. doi:10.1002/jnr.20652
49. Leonard RB, Kevetter GA. Structural and functional changes in the cristae ampullares of aged gerbils. *Neuroscience* (2007) **147**:794–802. doi:10.1016/j.neuroscience.2007.05.001
50. Taylor RR, Jagger DJ, Saeed SR, Axon P, Donnelly N, Tysome J, et al. Characterizing human vestibular sensory epithelia for experimental studies: new hair bundles on old tissue and implications for therapeutic interventions in ageing. *Neurobiol Aging* (2015) **36**(6):2068–84. doi:10.1016/j.neurobiolaging.2015.02.013
51. Kevetter GA, Zimmerman CL, Leonard RB. Hair cell numbers do not decrease in the crista ampullaris of geriatric gerbils. *J Neurosci Res* (2005) **80**:279–85. doi:10.1002/jnr.20451
52. Gopen Q, Lopez I, Ishiyama G, Baloh RW, Ishiyama A. Unbiased stereologic type I and type II hair cell counts in human utricular macula. *Laryngoscope* (2003) **113**(7):1132–8. doi:10.1097/00005537-200307000-00007
53. Alidina A, Lyon MJ. Aging rat vestibular ganglion: I. Quantitative light microscopic evaluation. *Am J Otolaryngol* (1990) **11**:174–81. doi:10.1016/0196-0709(90)90034-S
54. Fujii M, Goto N, Kikuchi K. Nerve fiber analysis and the aging process of the vestibulocochlear nerve. *Ann Otol Rhinol Laryngol* (1990) **99**:863–70. doi:10.1177/000348949009901103
55. Lopez I, Honrubia V, Baloh RW. Aging and the human vestibular nucleus. *J Vestib Res* (1997) **7**:77–85. doi:10.1016/S0957-4271(96)00137-1
56. Alvarez JC, Diaz C, Suarez C, Fernandez JA, Gonzalez del Rey C, Navarro A, et al. Neuronal loss in human medial vestibular nucleus. *Anat Rec* (1998) **251**:431–8. doi:10.1002/(SICI)1097-0185(199808)251:4<431::AID-AR2>3.3.CO;2-D
57. Alvarez JC, Diaz C, Suarez C, Fernandez JA, Gonzalez del Rey C, Navarro A, et al. Aging and the human vestibular nuclei: morphometric analysis. *Mech Ageing Dev* (2000) **114**:149–72. doi:10.1016/S0047-6374(00)00098-1
58. Tang Y, Lopez I, Baloh RW. Age-related change of the neuronal number in the human medial vestibular nucleus: a stereological investigation. *J Vestib Res* (2001) **11**:357–63.
59. Sturrock RR. Age related changes in neuron number in the mouse lateral vestibular nucleus. *J Anat* (1989) **166**:227–32.
60. Fernandez JA, Suarez C, Navarro A, Diaz C, Alvarez JC, Gonzalez del Rey C, et al. Aging in the vestibular nuclear complex of the male golden hamster (*Mesocricetus auratus*): anatomic and morphometric study. *Histol Histopathol* (2007) **22**:855–68.
61. Johnson JE Jr, Miquel J. Fine structural changes in the lateral vestibular nucleus of aging rats. *Mech Ageing Dev* (1974) **3**(3–4):203–24. doi:10.1016/0047-6374(74)90017-7
62. Takeuchi YK, Takeuchi IK, Murashima Y, Seto-Ohshima A. Age-related appearance of dystrophic axon terminals in cerebellar and vestibular nuclei of Mongolian gerbils. *Exp Anim* (1997) **46**(1):59–65. doi:10.1538/expanim.46.59
63. Radtke-Schuller S, Seeler S, Grothe B. Restricted loss of olivocochlear but not vestibular efferent neurons in the senescent gerbil (*Meriones unguiculatus*). *Front Aging Neurosci* (2015) **7**:4. doi:10.3389/fnagi.2015.00004
64. Smith PF, Darlington CL. Recent advances in the pharmacology of the vestibulo-ocular reflex system. *Trends Pharmacol Sci* (1996) **17**:421–7. doi:10.1016/S0165-6147(96)10050-X

65. Vidal PP, Cullen K, Curthoys IS, Du Lac S, Holstein G, Idoux E, et al. Chapter 28: the vestibular system. 4th ed. In: Paxinos G, editor. *The Rat Nervous System*. San Diego: Academic Press (2014). p. 805–64.
66. Di Mauro M, Bronzi D, Li Volsi G, Licata F, Lombardo P, Santangelo F. Noradrenaline modulates neuronal responses to GABA in vestibular nuclei. *Neuroscience* (2008) **153**(4):1320–31. doi:10.1016/j.neuroscience.2008.02.014
67. Cransac H, Peyrin L, Cottet-Emard JM, Farhat F, Pequiqot JM, Reber A. Aging effects on monoamines in rat medial vestibular and cochlear nuclei. *Hear Res* (1996) **100**:150–6. doi:10.1016/0378-5955(96)00116-5
68. Him A, Guneser R, Cenqiz N, Ozturk G. Glutamate responsiveness of medial vestibular nucleus neurons in aged rats. *Brain Res Bull* (2010) **81**:81–4. doi:10.1016/j.brainresbull.2009.07.008
69. Liu P, Zhang H, Devaraj R, Ganesalingam G, Smith PF. A multivariate analysis of the effects of aging on glutamate, GABA and arginine metabolites in the rat vestibular nucleus. *Hear Res* (2010) **269**:122–33. doi:10.1016/j.heares.2010.06.019
70. Him A, Johntson AR, Yau JL, Seckl J, Dutia MB. Tonic activity and GABA responsiveness of medial vestibular nucleus neurons in aged rats. *Neuroreport* (2001) **12**:3965–8. doi:10.1097/00001756-200112210-00022
71. Giardino L, Zanni M, Fernandez M, Battaglia A, Pignataro O, Calza L. Plasticity of GABA(a) system during ageing: focus on vestibular compensation and possible pharmacological intervention. *Brain Res* (2002) **929**:76–86. doi:10.1016/S0006-8993(01)03381-9
72. Nakayama M, Caspary DM, Konrad HR, Milbrandt JC, Helfert RH. Age-related changes in [3H]strychnine binding in the vestibular nuclei of rats. *Hear Res* (1999) **127**:103–7. doi:10.1016/S0378-5955(98)00177-4
73. Sulaiman MR, Dutia MB. Opioid inhibition of rat medial vestibular nucleus neurones in vitro and its dependence on age. *Exp Brain Res* (1998) **122**(2):196–202. doi:10.1007/s002210050507
74. Wu G, Morris SM Jr. Arginine metabolism: nitric oxide and beyond. *Biochem J* (1998) **336**:1–17. doi:10.1042/bj3360001
75. Garthwaite J. Concepts of neural nitric oxide-mediated transmission. *Eur J Neurosci* (2008) **27**:2783–802. doi:10.1111/j.1460-9568.2008.06285.x
76. Liu P, Smith PF, Appleton I, Darlington CL, Bilkey DK. Potential involvement of NOS and arginase in age-related behavioural impairments. *Exp Gerontol* (2004) **39**:1207–22. doi:10.1016/j.exger.2004.04.008
77. Liu P, Smith PF, Appleton I, Darlington CL, Bilkey DK. Hippocampal nitric oxide synthase and arginase and age-associated behavioral deficits. *Hippocampus* (2005) **15**:642–55. doi:10.1002/hipo.20085
78. Malinski T. Nitric oxide and nitroxidative stress in Alzheimer's disease. *J Alzheimers Dis* (2007) **11**:207–18.
79. McCann SM, Mastronardi C, de Laurentiis A, Rettori V. The nitric oxide theory of aging revisited. *Ann N Y Acad Sci* (2005) **1057**:64–84. doi:10.1196/annals.1356.064
80. Siles E, Martínez-Lara E, Cañuelo A, Sánchez M, Hernández R, López-Ramos JC, et al. Age-related changes of the nitric oxide system in the rat brain. *Brain Res* (2002) **956**:385–92. doi:10.1016/S0006-8993(02)03575-8
81. Mistry SK, Greenfeld Z, Morris SM Jr, Baylis C. The 'intestinal-renal' arginine biosynthetic axis in the aging rat. *Mech Ageing Dev* (2002) **123**(8):1159–65. doi:10.1016/S0047-6374(02)00003-9
82. Smith PF, Ganesh S, Liu P. A comparison of random forest regression and multiple linear regression for prediction in neuroscience. *J Neurosci Methods* (2013) **220**:85–91. doi:10.1016/j.jneumeth.2013.08.024
83. Packer AM, Roska B, Häusser M. Targeting neurons and photons for optogenetics. *Nat Neurosci* (2013) **16**:805–15. doi:10.1038/nn.3427

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

frontiers in Neurology

ORIGINAL RESEARCH
published: 18 July 2016
doi: 10.3389/fneur.2016.00113

Aging Increases Compensatory Saccade Amplitude in the Video Head Impulse Test

Eric R. Anson[1], Robin T. Bigelow[1], John P. Carey[1], Quan-Li Xue[2,3], Stephanie Studenski[4], Michael C. Schubert[1], Konrad P. Weber[5,6] and Yuri Agrawal[1]*

[1] Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2] Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [3] Center on Aging and Health, Johns Hopkins Medical Institutions, Baltimore, MD, USA, [4] Longitudinal Studies Section, National Institute on Aging, Baltimore, MD, USA, [5] Department of Neurology, University Hospital Zurich, University of Zurich, Zurich, Switzerland, [6] Department of Ophthalmology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

Objective: Rotational vestibular function declines with age resulting in saccades as a compensatory mechanism to improve impaired gaze stability. Small reductions in rotational vestibulo-ocular reflex (VOR) gain that would be considered clinically normal have been associated with compensatory saccades. We evaluated whether compensatory saccade characteristics varied as a function of age, independent of semicircular canal function as quantified by VOR gain.

Methods: Horizontal VOR gain was measured in 243 participants age 27–93 from the Baltimore Longitudinal Study of Aging using video head impulse testing. Latency and amplitude of the first saccade (either *covert* – occurring during head impulse, or *overt* – occurring following head impulse) were measured for head impulses with compensatory saccades (n = 2230 head impulses). The relationship between age and saccade latency, as well as the relationship between age and saccade amplitude, were evaluated using regression analyses adjusting for VOR gain, gender, and race.

Results: Older adults (mean age 75.9) made significantly larger compensatory saccades relative to younger adults (mean age 45.0). In analyses adjusted for VOR gain, there was a significant association between age and amplitude of the first compensatory covert saccade ($\beta = 0.015$, $p = 0.008$). In analyses adjusted for VOR gain, there was a significant association between age and amplitude of the first compensatory overt saccade ($\beta = 0.02$, $p < 0.001$). Compensatory saccade latencies did not vary significantly by age.

Conclusion: We observed that aging *increases* the compensatory catch-up saccade amplitude in healthy adults after controlling for VOR gain. Size of compensatory saccades may be useful in addition to VOR gain for characterizing vestibular function in aging adults.

Keywords: VOR, compensatory saccades, healthy aging, head impulse test, vestibular

OPEN ACCESS

Edited by:
Daniele Nuti,
University of Siena, Italy

Reviewed by:
Sergei B. Yakushin,
Mount Sinai School of Medicine, USA
Nicolas Perez,
University of Navarra, Spain

****Correspondence:***
Eric R. Anson
eanson1@jhmi.edu

Specialty section:
This article was submitted to Neuro-otology, a section of the journal Frontiers in Neurology

Received: *20 May 2016*
Accepted: *05 July 2016*
Published: *18 July 2016*

Citation:
Anson ER, Bigelow RT, Carey JP, Xue Q-L, Studenski S, Schubert MC, Weber KP and Agrawal Y (2016) Aging Increases Compensatory Saccade Amplitude in the Video Head Impulse Test. Front. Neurol. 7:113. doi: 10.3389/fneur.2016.00113

INTRODUCTION

Several studies have shown that rotational vestibular function declines with age (1–3). There is a reduction in the quantity of vestibular hair cells that occurs as a consequence of aging (4–7). This may result in alterations in vestibular function, characterized by reduced vestibulo-ocular reflex (VOR) gain and increased VOR gain variability with advancing age (1, 2, 8). Reduced function of the angular VOR results in generation of compensatory saccades (3, 9, 10). Studies have shown that compensatory saccades occur more frequently with increasing age (3, 11). Interestingly, compensatory saccades have been observed in older individuals even when VOR gain was clinically in the normal range (10, 11).

It is unclear whether the increased frequency and amplitude of compensatory saccades with age reflect greater VOR gain deficits in older individuals, which may be either clinical or subclinical (12, 13). Moreover, it is unclear whether saccade characteristics in older adults, such as saccade timing and amplitude, differ from saccades observed in younger individuals.

In this study, we investigate the relationship between age and compensatory saccade amplitude and latency in a cohort of healthy older adults within the Baltimore Longitudinal Study of Aging (BLSA). We used video head impulse testing (vHIT) to measure horizontal semicircular canal function (quantified as VOR gain) and to detect compensatory saccades. We considered both covert saccades (occurring during the head impulse) and overt saccades (occurring after the head impulse), separately (14–16). The goal of the study is to evaluate whether aging influences compensatory saccade latency and amplitude or whether the compensatory saccades observed in older individuals correlate only with reduced VOR function.

MATERIALS AND METHODS

Participants

The BLSA is an ongoing prospective cohort study initiated by the National Institute on Aging (NIA), in 1958. Participants are community-dwelling participants aged 20–103 who undergo a standardized array of tests over 3 days, every 1–4 years at the NIA. This study evaluated a cross-sectional sample of all BLSA participants between June 2014 and April 2015. During this time period, 243 participants completed vHIT testing. All participants provided written-informed consent, and the BLSA study protocol was approved by the Institutional Review Board at Harbor Hospital. Participants were asked to identify their race from the following options: White, Black or African-Americans, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, "Two or More Races," "Don't Know," or "Refused." Race-ethnicity was grouped as "white," "black," and "other," as the majority of participants were either white or black.

Video Head Impulse Testing

Vestibular function was measured for the horizontal VOR using vHIT. Methods to measure horizontal semicircular canal function have been published previously and validated in older adults (8, 17–19). In brief, participants wore the EyeSeeCam video-oculography system, a lightweight goggle frame with a built in camera to record right eye movements and an accelerometer to record head movement at a sampling frequency of 220 Hz (Interacoustics, Eden Prairie, MN, USA). Participants sat approximately 1.25 m from a visual fixation target on the wall. Trained examiners tilted the participant's head 30° below horizontal to bring the horizontal semicircular canal into the plane of head rotation and then performed 10–15 small amplitude (15–20°) "center-out" head impulses to the right and left, with peak velocity typically from 150 to 250°/s.

The EyeSeeCam software provides interpolated head impulse data at 1000 Hz in the exported MATLAB data file, which we used for subsequent *post hoc* analyses. During *post hoc* analysis, experienced evaluators examined individual head impulse traces using custom software (MATLAB, MathWorks) and rejected head impulses that had pupil tracking artifact during the head impulse or incorrectly performed head impulses (i.e., low peak head velocity, excessive head recoil, or overshoot) (20). Horizontal VOR gain was calculated as the ratio of the area under (AUC) the de-saccaded eye velocity curve over the area under the head velocity curve from the onset of the head impulse until head velocity returned to 0 (21). This method of gain calculation has been shown to be least susceptible to methodological errors (20). Saccades were initially identified by an automatic detection algorithm based on eye accelerations greater than 4000°/s^2 and visually verified by experienced examiners. Covert saccades were defined as any saccade starting before head velocity returns to 0, and overt saccades were defined as any saccade starting after head velocity returns to 0, see **Figure 1** (15). In order to simplify the regression analysis, head impulses without any saccades were excluded from analyses relating age to amplitude and latency of the first compensatory saccade and were not used to calculate VOR gain. Head impulses without saccades were included in the normalization of the cumulative saccade amplitude to reduce

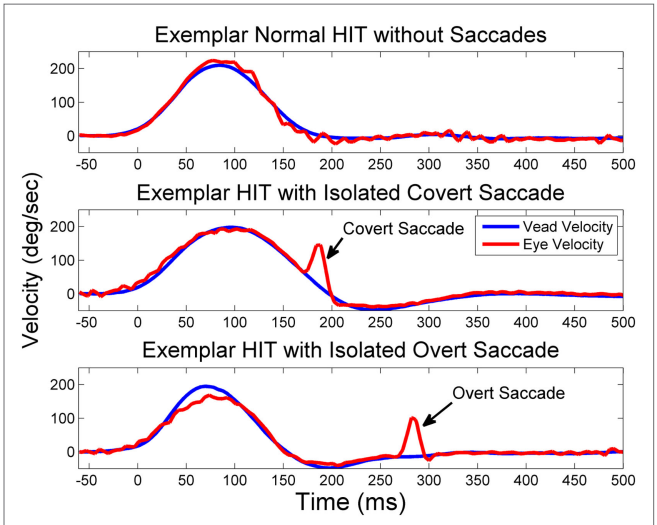


FIGURE 1 | Exemplar HITs with and without saccades. Exemplar vHITs showing the presence of a normal response without saccades (upper pane), an isolated covert compensatory saccade (middle pane), and an isolated overt saccade (lower pane). Saccades are indicated by arrows. Eye velocity (red) has been inverted and shown superimposed on head velocity (blue).

the potential for sample bias. Head impulses with bi-directional saccades were also excluded from these analyses.

To exclude volitional saccades (i.e., saccades not generated reflexively to compensate for a deficient VOR), we only analyzed saccades when the saccade latency was between 25 and 503 ms after head impulse testing (HIT) onset, defined as head velocity >20°/s (22). We chose 25 ms as the earliest that saccades may be present based on previously reported ranges for both active and passive HIT (23). To determine the latest time period for non-volitional compensatory saccades, we first estimated the population average HIT duration from our sample by bootstrapping 1000 new populations allowing for resampling, with 500 nested resamples for variance estimates (24). This resulted in a population average HIT duration of 253 ms. We identified 250 ms after the HIT ended (503 ms) as the criteria after which saccades could not be reliably attributed to the HIT stimulus based on reported values for volitional saccade latencies in older adults (25, 26). Saccade latency (time from the onset of the HIT until the onset of the saccade) and amplitude for the first compensatory saccade was determined for each HIT with a compensatory saccade. Covert saccade amplitude was adjusted such that the velocity of the VOR and the resultant position change of the eye due to the VOR were removed. Eye velocity was summed with head velocity to calculate the velocity of the eye in space (because both velocities followed the convention that movement to the right was positive, to the left was negative), see **Figure 2**. Amplitude for all saccades was calculated as the area under the curve for the saccade based on the eye-in-space velocity. This served to remove the VOR component from covert saccades, and the amplitudes were largely unchanged for overt saccades since the head was not moving during those saccades.

Data Analysis

We combined rightward and leftward HITs for a total sample of 486 ears, of which 452 had at least one head impulse that resulted in a compensatory saccade. We plotted cumulative saccade amplitude as a function of saccade latency across the cohort, to graphically represent the population of saccades observed in the cohort and differences between younger (<60 years, mean age 45.0) and older (≥60 years, mean age 75.9) age groups. Cumulative saccade amplitudes in latency bins of 10 ms were normalized to account for the number of individuals and head impulses with and without compensatory saccades in each bin. *T*-tests were used to compare mean saccade amplitude and latency between young and older adults, separately for overt and covert saccades. Analyses of saccade latency and amplitude were based on individual head impulses with compensatory saccades [$n = 2223$ (353 head impulses with covert saccades, 1870 head impulses with overt saccades), representing 227 participants]. All analyses accounted for clustering by individual using mixed effects regression models. Covert vs. overt compensatory saccades were evaluated in separate regression models. We evaluated the association between latency of the first saccade and age and the association between amplitude of the first saccade and age in multivariate analyses adjusted for VOR gain, gender, and race. We included the individual-specific mean head impulse

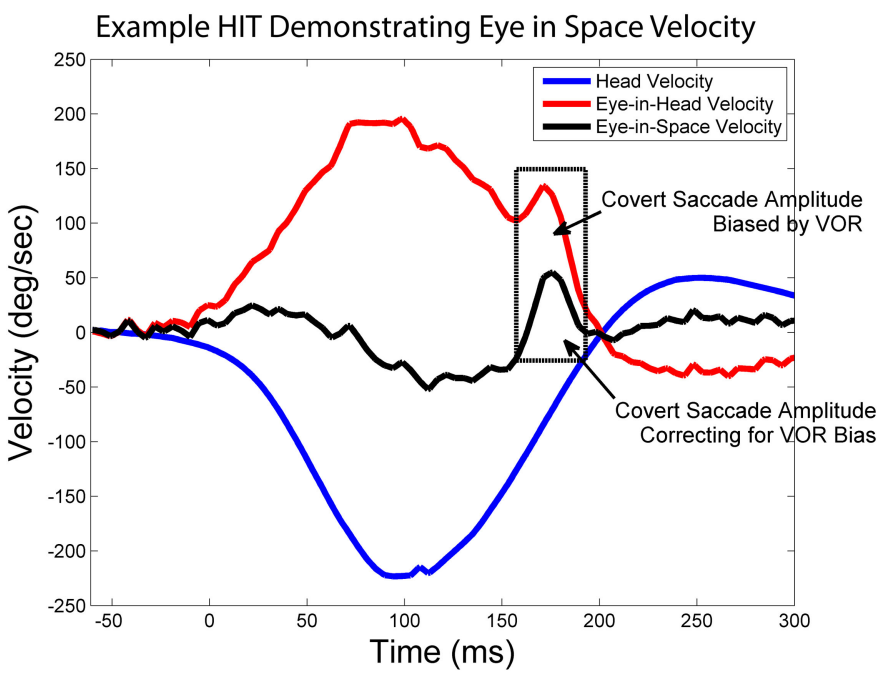


FIGURE 2 | Calculating eye-in-space velocity. Exemplar vHIT showing how the sum of head velocity (blue) and eye-in-head velocity (red) can be used to calculate eye-in-space velocity (black). The boxed in area highlights a covert saccade and demonstrates how using eye-in-space rather than eye-in-head velocity to calculate saccade amplitude removes the bias that results from VOR-mediated eye movement.

parameters (i.e., VOR gain, saccade latency, amplitude) as random effects to account for the within-individual correlation between the repeated head impulses. This results in valid statistical inference for the fixed effects (i.e., age, gender, and race). We estimated the model parameters *via* maximum likelihood using xtmixed in STATA. All mixed effects regression models were adjusted for age, gender, and race. We adjusted alpha levels within specific questions: for regression analyses $\alpha = 0.0125$ (applying a Bonferroni correction for four regressions), and an adjusted $\alpha = 0.0125$ (applying a Bonferroni correction for four comparisons) was used for *t*-test comparisons.

RESULTS

The mean age of participants was 72.3 (SD 16.4, range 27–93) and 52% of the participants were female. Sixty-two percent of the participants were white, 21% of the participants were black, and the remaining 17% were classified as other. One hundred seventy-four of 486 ears (35.8%) had at least one head impulse with a covert saccade, and 417 of 486 ears (85.8%) had at least one head impulse with an overt saccade. The mean peak head velocity during head impulses with saccades was 212.9°/s (SD 31.4°/s).

The normalized cumulative amplitude of overt and covert saccades as a function of saccade latency was plotted for younger ($n = 28$) adults (<60 years old) and older adults ($n = 199$; **Figure 3**). Mean amplitudes for overt saccades were significantly larger for older vs. younger adults (**Table 1**). Mean latencies were not significantly different for older vs. younger adults (**Table 1**).

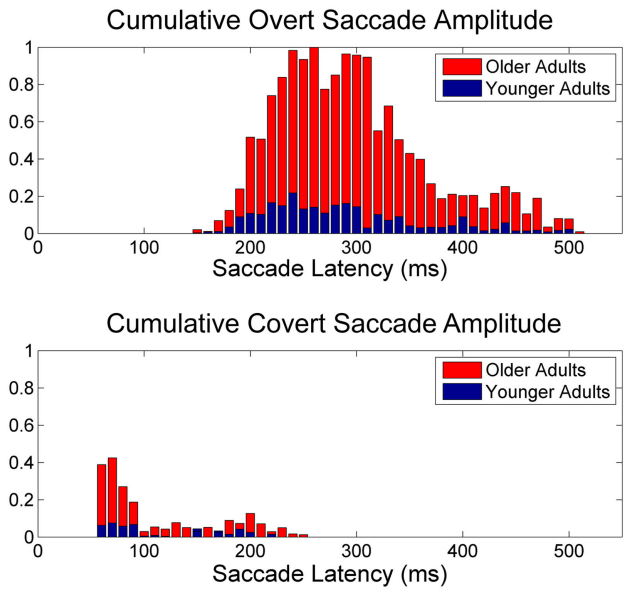


FIGURE 3 | Normalized saccade amplitude. Normalized cumulative saccade amplitude for overt (upper panel) and VOR corrected covert (lower panel) saccades as a function of latency following onset of head impulse. Note the normalized cumulative amplitude is larger for older adults (≥60 years) relative to younger adults (<60 years) and that overt saccades have larger amplitude compared to covert saccades after correcting for VOR eye velocity and amplitude.

Relationship between Saccade Metrics and Age

Covert Saccades

We evaluated whether the covert saccade amplitudes were correlated with differences in VOR gain between older and younger adults or whether age may be an independent contributor (**Table 2**). In multivariate analyses adjusting for VOR gain, we observed a persistent significant association between age and amplitude of the first compensatory covert saccade ($\beta = 0.015$, $p = 0.008$). This association corresponds to an increase in covert saccade amplitude of approximately 0.15° for every decade of life, while controlling for VOR gain. There was no significant association between age or VOR gain and latency of the first compensatory covert saccade (**Table 2**).

Overt Saccades

We next evaluated whether overt saccade amplitudes were correlated with differences in VOR gain between older and younger adults or whether age was an independent predictor (**Table 3**). In analyses adjusted for VOR gain, there was a significant association between age and amplitude of the first compensatory overt saccade ($\beta = 0.02$, $p < 0.001$). This association corresponds to an increase in overt saccade amplitude of approximately 0.2° for every decade of life, while controlling for VOR gain. There was no significant association between age and latency of the first compensatory overt saccade. Additionally, there was a significant association between VOR gain and amplitude of the

TABLE 1 | Mean (SD) compensatory (overt, covert) saccade latency and amplitude for younger and older adults.

	Younger adults (age 45.0, *N* = 28)	Older adults (age 75.9, *N* = 199)	*t*-test *p* value
Overt			
Mean latency (ms)	298.2 (86.1)	302.2 (74.3)	0.4834
Mean amplitude (deg)	1.2 (0.8)	1.7 (1.4)	0.0000*
Covert			
Mean latency (ms)	96.1 (52)	87.3 (49.5)	0.2949
Mean amplitude (deg)	1.1 (0.8)	1.4 (1.1)	0.1042

*Significant results indicated by * for p < 0.0125.*

TABLE 2 | Relationship between latency and amplitude of the first covert saccade and age controlling for VOR gain.

	Covert saccade latency			Covert saccade amplitude		
Predictor variables	**β**	***p***	**95% CI**	**β**	**p**	**95% CI**
Age	−0.03	0.942	(−0.75, 0.70)	0.015	0.008*	(0.004, 0.026)
VOR gain	34.04	0.055	(−0.79, 68.9)	0.47	0.237	(−0.31, −1.25)
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	−25.49	0.038	(−49.51, −1.47)	0.015	0.935	(−0.35, 0.38)
Other	−12.26	0.309	(−35.86, 11.34)	0.30	0.091	(−0.05, 0.65)
Gender						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	−23.43	0.014	(−42.11, −4.76)	−0.30	0.038	(−0.59, −0.017)

*Significant results indicated by * for p < 0.0125.*

TABLE 3 | Relationship between latency and amplitude of the first overt saccade and age controlling for VOR gain.

	Overt saccade latency			Overt saccade amplitude		
Predictor variables	**β**	***p***	**95% CI**	**β**	**p**	**95% CI**
Age	0.189	0.512	(−0.37, 0.76)	0.020	0.000*	(0.011, 0.028)
VOR gain	98.44	0.000*	(66.0, 130.89)	−4.03	0.000*	(−4.47, −3.58)
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	0.20	0.982	(−17.32, 17.72)	0.047	0.727	(−0.22, 0.31)
Other	−6.58	0.525	(−26.85, 13.69)	0.24	0.129	(−0.07, 0.55)
Gender						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.71	0.818	(−12.84, 16.26)	−0.15	0.197	(−0.37, 0.076)

*Significant results indicated by * for p < 0.0125.*

first compensatory overt saccade ($\beta = -4.03$, $p < 0.001$). This association corresponds to a decrease in overt saccade amplitude of approximately 0.4° for every 0.1 increase in VOR gain. We also observed a significant association between VOR gain and overt saccade latency ($\beta = 98.44$, $p < 0.001$). This corresponds to overt saccades happening 10 ms later for every 0.1 increase in VOR gain.

DISCUSSION

The current results demonstrate that healthy older adults make significantly larger covert and overt compensatory saccades relative to younger adults. Additionally, we found that the higher amplitude compensatory saccades in older individuals were not fully explained by reduced VOR function in this group: even after accounting for lower VOR gain, older adults made significantly larger saccades. There are several potential explanations for these findings. First, the most straight forward explanation is that slight reductions in VOR gain with age are sufficient to trigger compensatory saccades. Second, it is possible that the saccade-generating mechanism in older adults may be impaired relative to younger adults. Increased levels of cerebellar disinhibition in older adults may contribute to reduced VOR calibration and generation of over-compensatory saccades (27). Maladaptive interaction between the paramedian pontine reticular formation and the vestibular nuclei may also contribute to the relationship between VOR gain and saccade amplitude reported here (28, 29). Although saccades triggered by target-driven head free gaze shifts were observed to be smaller and slower in older adults (30), compensatory saccades triggered by retinal slip or position error due to VOR insufficiency may result from a different neural mechanism or behave differently in the context of aging. Alternatively, declines in peripheral vestibular function in the context of aging may result not only in decreases in VOR gain but might also affect gaze stabilization by other mechanisms. Peng et al. showed that, during HIT, humans demonstrate a range of corrective eye movements superimposed on the VOR (31). Some of these eye movements correct primarily gaze velocity (i.e., retinal slip) errors and some correct primarily gaze position (i.e., foveal displacement) errors. The distribution of these corrective eye movements were found to depend on the status of vestibular function and the degree of challenge of the stimulus. In particular, normal humans exposed to high acceleration head impulses in their study employed more saccades that corrected gaze position errors late in the course of the head impulse after gaze velocity error was minimized. Thus, gaze stabilization during head impulses appears to rely not only on the VOR but on eye movements that correct for gaze position errors as well. Whether the distribution of these eye movements changes with age will require further research, but it is clear that VOR gain is only a partial measure of gaze stabilization ability.

In this sample, there were approximately 6× more overt saccades than covert saccades. Individuals recovering from acute surgical unilateral vestibular loss quickly begin using compensatory saccades that, over a period of days, shift earlier in time, eventually becoming covert in their timing (32). Some authors have hypothesized that covert saccades are generated in response to a combination of vestibular signals, gaze velocity error, and gaze position error, while overt saccades are thought to be generated in response to gaze position error (given that the head is still, so head and eye velocity are both equal to 0) (16, 33, 34). It is possible that gaze velocity error during the head impulses did not exceed 2–4°/s, typically tolerated by healthy adults (35, 36). The majority of individuals in this study had VOR gain close to unity, which suggests only minimal retinal slip throughout the head impulse, despite the presence of compensatory saccades. Alternatively, the disproportionate number of overt saccades suggests that the individuals in this study may have reduced ability to detect or quickly respond to gaze velocity errors that would produce covert saccades. The higher percentage of overt saccades may also have been an artifact of the less predictable "center-out" head impulses employed in this study (37). It is not clear whether saccadic adaptation to age-related decline in vestibular function – which is typically incomplete and bilateral – is different from that which occurs following complete vestibular loss, which is typically complete and unilateral. Determining whether compensatory saccades in older adults are preferentially generated in response to retinal position vs. retinal velocity errors will have implications for vestibular rehabilitation (38–40).

The current findings did not support any relationship between compensatory saccade latency and age, in contrast with previous work on discrete saccadic eye movements (25). The lack of age dependence for compensatory saccade latency is consistent with previous research, suggesting that compensatory saccade timing is a stereotypic, learned behavior (41). Latency of saccades during head impulses decreases and becomes less variable over time, during recovery from loss of vestibular function (32). Unlike individuals recovering from unilateral vestibular loss, the cross-sectional population of older adults in this study may be at different stages in compensation/adaptation for age-related vestibular loss. Prospective longitudinal studies would be necessary to demonstrate whether adults with age-related decline in vestibular function follow a similar learning profile with respect to latency of compensatory saccades.

We observed that the saccade amplitude is larger for older adults in a cohort of healthy adults and that saccade amplitude is in part related to VOR gain. It is interesting to note that, in this

cohort, only 17 individuals had abnormally low VOR gain (VOR gain <0.68) as defined in previous studies (19). Future studies should determine whether saccade amplitude may provide a more complete picture of gaze stability in aging adults than VOR gain alone. Additionally, future studies should determine whether saccade amplitude is more strongly related to measures of functional mobility like balance and walking in older adults than VOR gain. Higher compensatory saccade amplitudes may contribute to gaze instability or oscillopsia with walking head motion, which may, in turn, result in slower walking speeds in older adults.

Limitations

These data are cross-sectional and cannot be used to support causal inferences between changes in age and changes in compensatory saccades or VOR gain. Moreover, we cannot determine from these data whether the larger compensatory saccades in healthy older adults observed in this study represent adaptive or perhaps maladaptive compensation to change in rotational VOR function. We could not precisely measure eye position relative to a world-fixed target using the video head impulse system, which would be needed to determine whether the compensatory saccades brought the eye back to, or potentially overshot, the target. Measurement systems capable of quantifying the target location relative to the head are needed to address this limitation. We also only considered horizontal VOR gain in this study and future studies will need to establish whether these relationships hold for the vertical canals as well. Finally, to simplify our analysis and to ensure that we were capturing saccades of vestibular origin, we only considered the first compensatory saccade. A number of head impulses resulted in mixed types of saccades, and their significance will require future characterization and study.

CONCLUSION

The size of compensatory saccades is larger for older adults compared to younger adults, even after accounting for level of similar rotational vestibular function as measured by VOR gain. The amplitude of compensatory saccades may be an additional indicator of decline in gaze stabilization ability in aging adults along with VOR gain.

AUTHOR CONTRIBUTIONS

EA and RB collected the data. EA, Q-LX, and YA drafted the manuscript. EA, Q-LX, and YA conducted the statistical analysis and interpreted the statistical analysis. EA, RB, JC, MS, SS, KW, and YA interpreted the data and critically edited the manuscript. YA designed the experiment. All authors approved the submitted version of the manuscript and are accountable for the accuracy and integrity of the work.

FUNDING

The study was supported in part by NIDCD K23 DC013056 and NIDCD T32 DC000023.

REFERENCES

1. Li C, Layman AJ, Geary R, Anson E, Carey JP, Ferrucci L, et al. Epidemiology of vestibulo-ocular reflex function: data from the Baltimore Longitudinal Study of Aging. *Otol Neurotol* (2015) 36:267–72. doi:10.1097/MAO.0000000000000610
2. Mossman B, Mossman S, Purdie G, Schneider E. Age dependent normal horizontal VOR gain of head impulse test as measured with video-oculography. *J Otolaryngol Head Neck Surg* (2015) 44:29. doi:10.1186/s40463-015-0081-7
3. Matiño-Soler E, Esteller-More E, Martin-Sanchez J-C, Martinez-Sanchez J-M, Perez-Fernandez N. Normative data on angular vestibulo-ocular responses in the yaw axis measured using the video head impulse test. *Otol Neurotol* (2015) 36:466–71. doi:10.1097/MAO.0000000000000661
4. Lopez I, Ishiyama G, Tang Y, Tokita J, Baloh RW, Ishiyama A. Regional estimates of hair cells and supporting cells in the human crista ampullaris. *J Neurosci Res* (2005) 82:421–31. doi:10.1002/jnr.20652
5. Rosenhall U, Rubin W. Degenerative changes in the human vestibular sensory epithelia. *Acta Otolaryngol* (1975) 79:67–80. doi:10.3109/00016487509124657
6. Gleeson M, Felix H. A comparative study of the effect of age on the human cochlear and vestibular neuroepithelia. *Acta Otolaryngol Suppl* (1987) 436:103–9. doi:10.3109/00016488709124982
7. Taylor RR, Jagger DJ, Saeed SR, Axon P, Donnelly N, Tysome J, et al. Characterizing human vestibular sensory epithelia for experimental studies: new hair bundles on old tissue and implications for therapeutic interventions in ageing. *Neurobiol Aging* (2015) 36:2068–84. doi:10.1016/j.neurobiolaging.2015.02.013
8. McGarvie LA, MacDougall HG, Halmagyi GM, Burgess AM, Weber KP, Curthoys IS. The video head impulse test (vHIT) of semicircular canal function – age-dependent normative values of VOR gain in healthy subjects. *Front Neurol* (2015) 6:154. doi:10.3389/fneur.2015.00154
9. Yang C, Lee JY, Kang BC, Lee HS, Yoo MH, Park HJ. Quantitative analysis of gains and catch-up saccades of video-head impulse testing by age in normal subjects. *Clin Otolaryngol* (2015). doi:10.1111/coa.12558
10. Perez-Fernandez N, Eza-Nuñez P. Normal gain of VOR with refixation saccades in patients with unilateral vestibulopathy. *J Int Adv Otol* (2015) 11:133–7. doi:10.5152/iao.2015.1087
11. Rambold HA. Age-related refixating saccades in the three-dimensional video-head-impulse test: source and dissociation from unilateral vestibular failure. *Otol Neurotol* (2016) 37:171–8. doi:10.1097/MAO.0000000000000947
12. Halmagyi GM, Curthoys IS. A clinical sign of canal paresis. *Arch Neurol* (1988) 45:737–9. doi:10.1001/archneur.1988.00520310043015
13. Petersen J, Straumann D, Weber KP. Clinical diagnosis of bilateral vestibular loss: three simple bedside tests. *Ther Adv Neurol Disord* (2013) 6:41–5. doi:10.1177/1756285612465920
14. Blödow A, Pannasch S, Walther LE. Detection of isolated covert saccades with the video head impulse test in peripheral vestibular disorders. *Auris Nasus Larynx* (2013) 40:348–51. doi:10.1016/j.anl.2012.11.002
15. Weber KP, Aw ST, Todd MJ, McGarvie LA, Curthoys IS, Halmagyi GM. Head impulse test in unilateral vestibular loss: vestibulo-ocular reflex and catch-up saccades. *Neurology* (2008) 70:454–63. doi:10.1212/01.wnl.0000299117.48935.2e
16. Tian J, Crane BT, Demer JL. Vestibular catch-up saccades in labyrinthine deficiency. *Exp Brain Res* (2000) 131:448–57. doi:10.1007/s002219900320
17. Agrawal Y, Schubert MC, Migliaccio AA, Zee DS, Schneider E, Lehnen N, et al. Evaluation of quantitative head impulse testing using search coils versus video-oculography in older individuals. *Otol Neurotol* (2014) 35:283–8. doi:10.1097/MAO.0b013e3182995227
18. Bartl K, Lehnen N, Kohlbecher S, Schneider E. Head impulse testing using video-oculography. *Ann N Y Acad Sci* (2009) 1164:331–3. doi:10.1111/j.1749-6632.2009.03850.x
19. MacDougall HG, Weber KP, McGarvie LA, Halmagyi GM, Curthoys IS. The video head impulse test: diagnostic accuracy in peripheral vestibulopathy. *Neurology* (2009) 73:1134–41. doi:10.1212/WNL.0b013e3181bacf85
20. Mantokoudis G, Saber Tehrani AS, Kattah JC, Eibenberger K, Guede CI, Zee DS, et al. Quantifying the vestibulo-ocular reflex with video-oculography: nature and frequency of artifacts. *Audiol Neurootol* (2015) 20:39–50. doi:10.1159/000362780

21. MacDougall HG, McGarvie LA, Halmagyi GM, Curthoys IS, Weber KP. The video head impulse test (vHIT) detects vertical semicircular canal dysfunction. *PLoS One* (2013) 8:e61488. doi:10.1371/journal.pone.0061488
22. Glasauer S, von Lindeiner H, Siebold C, Büttner U. Vertical vestibular responses to head impulses are symmetric in downbeat nystagmus. *Neurology* (2004) 63:621–5. doi:10.1212/01.WNL.0000135022.14937.A9
23. Tian JR, Crane BT, Ishiyama A, Demer JL. Three dimensional kinematics of rapid compensatory eye movements in humans with unilateral vestibular deafferentation. *Exp Brain Res* (2007) 182:143–55. doi:10.1007/s00221-007-0977-1
24. Zoubir A, Boashash B. The bootstrap and its application in signal processing. *IEEE Signal Process Mag* (1998) 15:56–76. doi:10.1109/79.647043
25. Abel LA, Troost BT, Dell'Osso LF. The effects of age on normal saccadic characteristics and their variability. *Vision Res* (1983) 23:33–7. doi:10.1016/0042-6989(83)90038-X
26. Warren DE, Thurtell MJ, Carroll JN, Wall M. Perimetric evaluation of saccadic latency, saccadic accuracy, and visual threshold for peripheral visual stimuli in young compared with older adults. *Invest Ophthalmol Vis Sci* (2013) 54:5778–87. doi:10.1167/iovs.13-12032
27. Walker MF, Zee DS. Asymmetry of the pitch vestibulo-ocular reflex in patients with cerebellar disease. *Ann N Y Acad Sci* (2005) 1039:349–58. doi:10.1196/annals.1325.033
28. Kang J-H, Sharpe JA. Dissociated palsy of vertical saccades: loss of voluntary and visually guided saccades with preservation of reflexive vestibular quick phases. *J Neuroophthalmol* (2008) 28:97–103. doi:10.1097/WNO.0b013e3181772647
29. Kato I, Nakamura T, Kanayama R, Aoyagi M. Slow saccades and quick phases of nystagmus after pontine lesions. *Acta Otolaryngol Suppl* (1994) 511:95–8. doi:10.3109/00016489409128309
30. Dowiasch S, Marx S, Einhäuser W, Bremmer F. Effects of aging on eye movements in the real world. *Front Hum Neurosci* (2015) 9:46. doi:10.3389/fnhum.2015.00046
31. Peng GCY, Zee DS, Minor LB. Phase-plane analysis of gaze stabilization to high acceleration head thrusts: a continuum across normal subjects and patients with loss of vestibular function. *J Neurophysiol* (2004) 91:1763–81. doi:10.1152/jn.00611.2002
32. Mantokoudis G, Schubert MC, Tehrani ASS, Wong AL, Agrawal Y. Early adaptation and compensation of clinical vestibular responses after unilateral vestibular deafferentation surgery. *Otol Neurotol* (2014) 35:148–54. doi:10.1097/MAO.0b013e3182956196
33. Eggers SDZ, De Pennington N, Walker MF, Shelhamer M, Zee DS. Short-term adaptation of the VOR: non-retinal-slip error signals and saccade substitution. *Ann N Y Acad Sci* (2003) 1004:94–110. doi:10.1196/annals.1303.010
34. Paige GD. Senescence of human visual-vestibular interactions: smooth pursuit, optokinetic, and vestibular control of eye movements with aging. *Exp Brain Res* (1994) 98:355–72. doi:10.1007/BF00228423
35. Demer JL, Honrubia V, Baloh RW. Dynamic visual acuity: a test for oscillopsia and vestibulo-ocular reflex function. *Am J Otol* (1994) 15:340–7.
36. Crane BT, Demer JL. Human gaze stabilization during natural activities: translation, rotation, magnification, and target distance effects. *J Neurophysiol* (1997) 78:2129–44.
37. Mantokoudis G, Agrawal Y, Newman-Toker DE, Xie L, Saber Tehrani AS, Wong A, et al. Compensatory saccades benefit from prediction during head impulse testing in early recovery from vestibular deafferentation. *Eur Arch Otorhinolaryngol* (2015) 273(6):1379–85. doi:10.1007/s00405-015-3685-7
38. Fadaee SB, Migliaccio AA. The effect of retinal image error update rate on human vestibulo-ocular reflex gain adaptation. *Exp Brain Res* (2016) 234:1085–94. doi:10.1007/s00221-015-4535-y
39. Schubert MC, Della Santina CC, Shelhamer M. Incremental angular vestibulo-ocular reflex adaptation to active head rotation. *Exp Brain Res* (2008) 191:435–46. doi:10.1007/s00221-008-1537-z
40. Schubert MC, Hall CD, Das V, Tusa RJ, Herdman SJ. Oculomotor strategies and their effect on reducing gaze position error. *Otol Neurotol* (2010) 31:228–31. doi:10.1097/MAO.0b013e3181c2dbae
41. Lee S-H, Newman-Toker DE, Zee DS, Schubert MC. Compensatory saccade differences between outward versus inward head impulses in chronic unilateral vestibular hypofunction. *J Clin Neurosci* (2014) 21:1744–9. doi:10.1016/j.jocn.2014.01.024

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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 03 October 2016
doi: 10.3389/fneur.2016.00162

Vestibular Perceptual Thresholds Increase above the Age of 40

*María Carolina Bermúdez Rey[1,2], Torin K. Clark[1,2,3], Wei Wang[1,4], Tania Leeder[2], Yong Bian[1,2] and Daniel M. Merfeld[1,2]**

[1] Harvard Medical School, Boston, MA, USA, [2] Jenks Vestibular Physiology Laboratory, MEEI, Boston, MA, USA, [3] University of Colorado at Boulder, Boulder, CO, USA, [4] Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

We measured vestibular perceptual thresholds in 105 healthy humans (54F/51M) ranging from 18 to 80 years of age. Direction-recognition thresholds were measured using standard methods. The motion consisted of single cycles of sinusoidal acceleration at 0.2 Hz for roll tilt and 1.0 Hz for yaw rotation about an earth-vertical axis, inter-aural earth-horizontal translation (*y*-translation), inferior–superior earth-vertical translation (*z*-translation), and roll tilt. A large subset of this population (99 of 105) also performed a modified Romberg test of standing balance. Despite the relatively large population (54F/51M), we found no difference between thresholds of male and female subjects. After pooling across sex, we found that thresholds increased above the age of 40 for all five motion directions investigated. The data were best modeled by a two-segment age model that yielded a constant baseline below an age cutoff of about 40 and a threshold increase above the age cutoff. For all subjects who passed all conditions of the balance test, the baseline thresholds were 0.97°/s for yaw rotation, 0.66°/s for 1-Hz roll tilt, 0.35°/s for 0.2-Hz roll tilt, 0.58 cm/s for *y*-translation, and 1.24 cm/s for *z*-translation. As a percentage of the baseline, the fitted slopes (indicating the threshold increase each decade above the age cutoff) were 83% for *z*-translation, 56% for 1-Hz roll tilt, 46% for *y*-translation, 32% for 0.2-Hz roll tilt, and 15% for yaw rotation. Even taking age and other factors into consideration, we found a significant correlation of balance test failures with increasing roll-tilt thresholds.

Keywords: vestibular, perception, thresholds, aging

OPEN ACCESS

Edited by:
Yuri Agrawal,
Johns Hopkins University, USA

Reviewed by:
Paul MacNeilage,
Ludwig Maximilian University of Munich, Germany
Benjamin Thomas Crane,
University of Rochester, USA

***Correspondence:**
Daniel M. Merfeld
dan_merfeld@meei.harvard.edu

Specialty section:
This article was submitted to Neuro-otology, a section of the journal Frontiers in Neurology

Received: *24 May 2016*
Accepted: *14 September 2016*
Published: *03 October 2016*

Citation:
Bermúdez Rey MC, Clark TK, Wang W, Leeder T, Bian Y and Merfeld DM (2016) Vestibular Perceptual Thresholds Increase above the Age of 40. Front. Neurol. 7:162. doi: 10.3389/fneur.2016.00162

INTRODUCTION

Data suggest that, on average, females and males have a significantly different number of vestibular afferent fibers (1) and that a significant difference in the size of the vestibular labyrinth exists (2). Such anatomical differences could contribute to behavioral differences, but studies utilizing standard clinical vestibular assays (3–8) have found no significant sex effects. Nonetheless, differences could exist. Wall and colleagues reported a very small, but significant, difference in the VOR phase at 0.005 Hz in a population of 25 males and 25 females (9). Benson reported perceptual translation thresholds (i.e., the smallest motion that can be reliably perceived as leftward or rightward) for females that were roughly 40% lower than for males for each of the three translation directions (7), but this difference was not statistically significant. Similarly, yaw rotation thresholds were reported to be about 20% lower in females than males (8), but again, this difference was not statistically significant. Given these data, we felt that a sex effect deserved study using a larger sample.

We chose to measure vestibular thresholds for a variety of reasons. (1) Threshold testing uses small motions that typically are well tolerated. (2) Like other threshold measures (e.g., auditory thresholds), vestibular thresholds have direct functional relevance. (3) Thresholds have been shown to be a sensitive measure of vestibular function that has been shown to identify specific peripheral vestibular deficits (10). (4) Thresholds have shown great promise to help diagnose central disorders such as vestibular migraine (11, 12), which may be the most prevalent vestibular disorder. (5) Unlike other vestibular responses such as the VOR, one previous study was unable to demonstrate adaptive perceptual threshold changes even following substantial training efforts (13) – possibly because the brain receives little information to drive adaptation during threshold-level motion. (6) Thresholds can provide a comprehensive assay of many aspects of vestibular function – including perception, all peripheral end organ pairs, central vestibular functions, etc. – that are straightforward to interpret and can be compared across motion types (i.e., translation, tilt, and rotation) relative to normal.

Earlier vestibular threshold studies have come to different conclusions regarding the effect of age on rotation thresholds and translation thresholds. One study (14) measured thresholds for yaw rotation in a group of 19 younger subjects, aged 20–26, and a group of 16 older subjects, aged 63–84, and found no significant effect of age. Similarly, Seemungal and colleagues (15) reported no difference in yaw rotation thresholds between a group of 14 young (mean age of 23) and 9 older (mean age of 63) normal subjects. Each of these reports is consistent with another study (16) of 24 normal subjects between the ages of 21 and 60 that found no effect of age on yaw rotation thresholds.

While published studies do not show a significant correlation of yaw rotation thresholds with age, there is evidence to suggest that translational thresholds do correlate with age. However, one of the studies that did not find a correlation of yaw rotation threshold with age (16) did report a correlation with age for thresholds measured using naso-occipital (*x*-axis) and inter-aural (*y*-axis) translations. Furthermore, Agrawal and colleagues (17) reported that thresholds of 42 normal subjects demonstrated a significant positive correlation with age for naso-occipital (*x*-axis) and inferior–superior (*z*-axis) translation but not for inter-aural (*y*-axis) translation, and another recent paper (18) reported that translation thresholds for 42 normal subjects were significantly correlated with age for naso-occipital (*x*-axis), inferior–superior (*z*-axis), and inter-aural (*y*-axis) translations. Finally, Kingma (19) reported that for a population of 28 healthy subjects between the ages of 22 and 60 (7 subjects/decade), thresholds increased linearly with age for naso-occipital (*x*-axis) translation but found no correlation for inter-aural (*y*-axis) translation thresholds.

Before proceeding, we also note that non-vestibular cues (e.g., somatosensory and proprioceptive) may contribute to these thresholds, but a previous study showed bilateral vestibular defective patients have significantly higher thresholds (20), suggesting a predominant influence of the vestibular cues.

Given the earlier findings, we decided to include a larger number of healthy normal subjects (54 females and 51 males) than reported in previous investigations. We specifically targeted our recruitment to obtain age- and gender-matched subjects for each decade spanning an age range between 18 and 80. We measured direction-recognition thresholds in the dark for (a) yaw rotations – transduced primarily by the lateral semicircular canals, (b) superior–inferior (*z*-axis) translations – transduced primarily by the saccular organs, (c) inter-aural (*y*-axis) translations – transduced primarily by the utricular organs, and (d) roll tilts – transduced primarily by the vertical canals and the utricular organs. We emphasize that this study is the first to look at age effects for roll-tilt thresholds; the importance of this is emphasized by recent reports of lowered thresholds in patients suffering vestibular migraine (11, 12).

MATERIALS AND METHODS

Perceptual thresholds were sampled in 105 subjects, 54 females and 51 males, between the ages of 18 and 80. All subjects filled out a general health questionnaire to confirm that they qualified to participate, including the absence of vestibular symptoms. Menstrual cycle status and diagnosis of migraine were determined *via* two separate questionnaires. A standing balance test was used to objectively evaluate balance function. Threshold data collection methods generally mimicked those used by Valko and colleagues (20), but data were collected for only a small subset of the frequencies sampled in that earlier study. Specifically, for each subject, yaw rotations were applied about an earth-vertical axis at 1 Hz, *y*-translations were applied along an earth-horizontal axis at 1 Hz, *z*-translations were applied along the earth-vertical axis at 1 Hz, and roll tilts about a head-centered earth-horizontal axis were applied at 0.2 and 1 Hz. Participation in the study took about 3 h including at least two breaks. Informed consent was obtained from all subjects as dictated by the Declaration of Helsinki, and the study was approved by the MEEI Human Use Committee.

Questionnaires

A short health questionnaire was administered to all subjects for screening purposes. History of current and previous diseases, with an emphasis in neurological, otologic, vestibular, and chronic uncontrolled diseases, and medications was obtained. Acting conservatively, subjects diagnosed with any major health problem or under medications that could potentially affect vestibular function or decision making were excluded, as were subjects with any history of vestibular symptoms. As just one example, subjects with vestibular migraine would typically have been excluded because of their occasional symptoms.

Women were asked to fill out a separate questionnaire to establish menstrual cycle status (premenopausal, postmenopausal, or other). For premenopausal women, length and regularity of cycles, start of current cycle (i.e., first day of menstrual bleeding), and current use of hormonal contraception was recorded.

Because prevalence of migraine is known to be higher in females (21), we considered migraine as a potential confounding factor for our analyses. The Migraine Screen Questionnaire (MS-Q) developed and validated by Láinez et al. (22, 23) was administered to confirm history of migraine and/or to detect hidden migraine. A MS-Q score ≥4 was considered positive.

Balance Testing

To assess balance function, the modified Romberg test of standing balance on firm and compliant support surfaces (24) was performed. This balance test consists of four steps. Each step must be passed in order to move to the next step. All steps are performed standing with feet together and arms crossed. To pass the first step, each participant had to stand on the floor for 15 s with eyes open. To pass the second step, they had to stand on the floor for 15 s with eyes closed. To pass the third step, they had to stand on memory foam with eyes open for 30 s. To pass the final step, they had to stand on the foam with eyes closed for 30 s. This final test condition primarily assesses vestibular function (24, 25), since visual contributions are eliminated and the foam makes kinesthetic cues unreliable. The balance test was scored on a pass/fail basis. Failure was defined as participants needing to open their eyes or arms or move their feet to maintain stability before the end of the trial. All subjects were allowed two trials at each step.

Motion Stimuli and Psychophysical Threshold Tests

The motion paradigms and psychophysical tests employed to measure perceptual thresholds for this study have been previously published in detail (26, 27), so are described briefly herein. Motion stimuli were generated with a Moog 6DOF motion platform. Motion stimuli were single cycles of sinusoidal acceleration (either linear acceleration or angular acceleration) [$a(t) = A\sin(2\pi ft) = A\sin\left(\frac{2\pi t}{T}\right)$, where A is the acceleration amplitude and f is the motion frequency]. We present thresholds using the peak velocity of each stimulus. As shown in earlier papers [e.g., Ref. (8, 26)], this yields bell-shaped velocity trajectories having a maximum velocity of $v_{max} = A/(\pi f)$.

Subjects were seated in an upright position, held *via* an adjustable five-point harness and a helmet. To minimize other sensory cues, motions were performed in the dark in a light-tight room, all skin surfaces except the face and hands were covered, and noise-canceling headphones played constant amplitude white noise during the motions to mask any auditory cues and to indicate the time period when each motion occurred.

A three-down/one-up (3D/1U) adaptive staircase was used to target stimuli near threshold (28, 29). To minimize training effects, suprathreshold practice trials were administered until each subject understood and was comfortable with the task before each set of trials. Each block consisted of 100 trials, where a single motion stimulus was provided per trial. One hundred trials was considered adequate because an earlier study (29) showed that 100 trials yielded methodological threshold variations of just 18% – much less than the intra-subject variations reported previously by Benson (7, 8). Furthermore, 200 trials, while roughly doubling test time, yielded just an incremental improvement in threshold precision (from 18 to 13%). Until the first mistake, the stimulus was halved after three correct responses at each level. From this point onward, the size of the change in stimulus magnitude was determined using parameter estimation by sequential testing (PEST) rules (30). For all conditions, initial stimuli were set at a level that was suprathreshold for the vast majority of subjects. Yaw rotations began at a $v_{max} = 4°/s$, y-translations at $v_{max} = 4$ cm/s, z-translations at $v_{max} = 16$ cm/s, and roll tilts at $v_{max} = 3°/s$ for 1-Hz stimuli and $v_{max} = 2°/s$ for 0.2 Hz. No feedback was provided as to the correctness of the responses after each trial. On only one test (1-Hz roll tilt) did the subject increase the stimulus amplitude beyond the motion device motion capabilities (1 out of more than 500 successful tests). When this occurred, since we thought that the subject may not have understood how to indicate the tilt direction, the subject was instructed again and given a second chance and then successfully completed the testing.

As a subtle enhancement to the published methods, all subjects used a two-stage task on an iPad to indicate responses. The iPad backlight illumination was off during all motion stimuli. Subjects were instructed to first tap the left (top) side of the screen if they perceived a leftward (upward) motion or to tap the right (bottom) side for rightward (downward) motion. Each tap was followed by feedback confirming the selection. Subjects were instructed that they must provide an answer. These instructions mimicked our earlier instructions, with the only difference as the use of an iPad instead of buttons to provide the binary indications. These standard binary data are used for all analyses presented herein.

After indicating perceived motion direction, subjects were instructed to indicate whether they were uncertain or not uncertain. If uncertain, subjects pressed the left and right sides of the iPad screen simultaneously. Otherwise, they pressed the same side of the screen again (e.g., right side twice for a right/certain response). These certainty/uncertainty data are not presented herein and are described here only to report our exact procedures.

As noted by others (13), testing at different frequencies could yield different results, especially since thresholds vary with frequency [e.g., Ref. (7, 8, 20, 26, 31–33)]. Roll tilts at 0.2 Hz were chosen to assess sensory integration between canal and otolith cues (34), but we chose 1-Hz stimuli for most testing because (1) subjects report that tasks using 1-Hz stimuli are easier than both (a) higher frequency (e.g., 5 Hz) stimuli that require high alertness to avoid missing brief stimuli and (b) lower frequency (e.g., 0.1 Hz) stimuli that require extended periods of attention and (2) they require just 1 s, so 100 trials can be accomplished in less than 10 min (including time for responses and pauses between trials).

Data Analysis

For all conditions, the threshold (σ, sometimes called the psychometric width parameter) was determined by fitting a psychometric curve to the binary (e.g., left/right) experimental data. Specifically, a Gaussian cumulative distribution psychometric function defined by the parameters σ and μ was fit using a maximum likelihood estimate *via* a bias-reduced generalized linear model (BRGLM) (35) and probit link function (36). Fits were performed in MATLAB using the Statistic Toolbox version 8.3.

Geometric means were calculated for across subject averages, because, consistent with earlier reports (7, 8), data demonstrated a lognormal distribution across subjects for all conditions (Kolmogorov–Smirnov goodness-of-fit for lognormal distribution, $p > 0.25$). Both non-parametric and parametric analyses (using data in logarithmic units) were used. Multiple logistic regression was used to estimate the odds of failing the balance

test associated with thresholds and age. A Pearson correlation was used to test for correlation between thresholds in different axes. Analyses were performed using SAS statistical software (SAS Institute Inc., Cary, NC, USA).

Data in other sensory domains [e.g., odor identification (37), visual acuity (38), and speech intelligibility (39)] suggest thresholds vary with age in a piecewise manner – with a flat plateau below an age cutoff and decreasing sensitivity above the same age cutoff. As our data shown in **Figure 1** also suggest a similar piecewise linear pattern, we hypothesize thresholds remain relatively constant (i.e., no effect of age) up until some age cutoff at which point they increase (for simplicity, we assume this increase is linear). For each motion condition, the following continuous, piecewise linear model was fit to each subject's threshold (σ_i) data with three parameters: (1) an "age cutoff" $\left(\hat{a}_{\text{cutoff}}\right)$, (2) a "baseline" level $\left(\hat{\sigma}_{\text{baseline}}\right)$ that represents the average threshold for ages less than the age cutoff, and (3) a "slope" $\left(\hat{m}\right)$ that represents the rate of threshold increase above the age cutoff, where a_i is each subject's age in years rounded to the nearest integer at the time of testing was (e.g., 38 years of age). We present slope per decade (i.e., 10 years) throughout, since decades provide a more meaningful timescale for such changes.

$$\sigma_i = f(a_i) = \begin{cases} \hat{\sigma}_{\text{baseline}} & \text{if } a_i \le \hat{a}_{\text{cutoff}} \\ \hat{m}\left(a_i - \hat{a}_{\text{cutoff}}\right) + \hat{\sigma}_{\text{baseline}} & \text{if } a_i > \hat{a}_{\text{cutoff}} \end{cases}$$

As previously discussed, the thresholds were lognormally distributed; thus, the threshold data were log transformed and then a log-transformed version of the above age model was fit using a least-squared Nelder–Mead non-linear minimization routine (MATLAB fminsearch.m). Residuals were analyzed to assess the appropriateness of the fits. A parametric bootstrap approach (41), with $M = 2{,}000$ simulated data sets, was used to estimate the 95% confidence intervals of each fit parameter.

As shown in **Figure 1**, the age cutoffs were found to be similar across motion conditions. To quantify a single overall age cutoff,

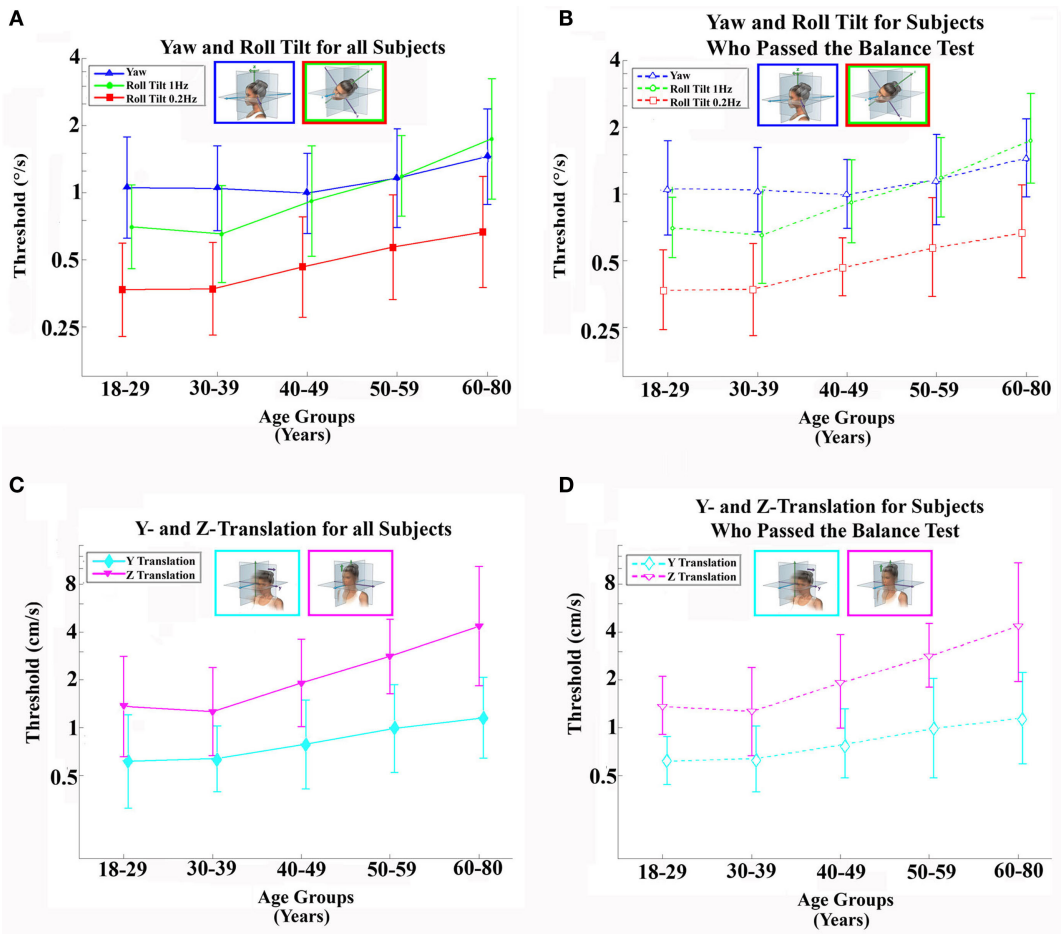


FIGURE 1 | Average (geometric mean) vestibular perceptual thresholds when grouped into five age ranges; error bars represent SD. (A,B) Top row shows thresholds for 1-Hz yaw rotation (blue triangle), 1-Hz roll tilt (green circle), 0.2-Hz roll tilt (red square); **(C,D)** bottom row shows thresholds for 1-Hz *z*-translation (magenta triangle) and 1-Hz *y*-translation (cyan diamond). **(A,C)** Left column, with solid lines and filled symbols, represents data from all 105 subjects. **(B,D)** Right column, with dashed lines and open symbols, represents data from 79 subjects who completed and passed all steps of the balance test. For clarity, data points are offset left/right slightly to minimize overlap. Inset cartoons indicating motion direction are reprinted with permission from Wolfe et al. (40).

a comprehensive model (same piecewise form as above) was fit to the thresholds across all motion conditions. The model consisted of 11 parameters: 1 overall age cutoff, 5 baseline levels, and 5 slopes (corresponding to each of the 5 motion conditions). Each individual threshold data point was first log transformed, then standardized by the motion condition using the respective mean and SD prior to fitting a log-transformed version of the linear age model described above to each of the five data sets simultaneously. The standardization and log transformation processes were reversed to present model fit parameters and curves in the original physical units. We used likelihood ratio tests and Bayesian information criteria (BIC) to assess goodness-of-fit for the proposed piecewise two-segment linear models compared to alternative simple linear and average models.

RESULTS

Thresholds

Our data do not suggest any threshold differences between males and females (**Table 1**). Statistical tests fail to demonstrate any significant effect of sex on thresholds. Even when we included migraine status, age, and balance test results as factors in multivariate analyses, no significant sex effect was found ($p > 0.4$, for each motion condition).

We also looked for a potential difference between premenopausal women under hormonal contraception and normal cycling women (**Table 2**). In all conditions, women taking hormonal birth control had higher thresholds. This difference did not appear significant except for yaw rotation thresholds (Wilcoxon rank sum, $p = 0.037$). Given multiple comparisons, we do not treat this difference as significant.

Furthermore, given that the association between hormonal contraception and yaw rotation thresholds could be explained by shared associations with other factors such as age, migraine status, or balance test results, we included all these factors in a multivariate analysis and found no significant effect of hormonal contraception on yaw rotation thresholds ($p = 0.68$) or for any of our other motion conditions.

In our sample, participants with migraine, defined as a MS-Q score of 4 or more (23), had lower thresholds for 4 of the 5 conditions – all but yaw rotation – than all other subjects. After correcting for multiple comparisons, that potential difference was not significant (**Table 3**). Because the sample size for migraine sufferers was so low ($N = 5$), this is noted as interesting but was not further explored herein.

Table 4 shows the velocity threshold geometric mean for each motion condition separated into five age groups. As previously reported (7), *z*-translation thresholds were significantly higher (typically ~2× higher) than *y*-translation thresholds (paired *t* test, $p < 0.0001$). Yaw rotation thresholds were higher than roll tilt 1-Hz thresholds (paired *t* test, $p = 0.0028$), and roll tilt 0.2-Hz thresholds were significantly lower than both yaw rotation and roll tilt 1-Hz thresholds (paired *t* test, $p < 0.0001$ each). All five motion conditions showed an increase of threshold (poorer direction-recognition performance) with age (**Figure 1**). We note that all five subplots show a relatively flat threshold plateau below the age of 40–49 and also show increasing thresholds above that same age cutoff.

When each of the five motion conditions was analyzed separately, this age effect was significant, even following multiple comparisons correction, for four of the five motions tested (Kruskal–Wallis, $p < 0.005$) – all but yaw rotation. A similar trend with age was evident in the yaw rotation data, but this trend was not statistically significant (Kruskal–Wallis, $p = 0.087$). **Figures 2** and **3** show these data.

Having established that there is an age effect that is independent of other factors, we evaluated whether there is an age cutoff above which threshold increases accumulate by fitting a two-piece linear model to the data. To minimize the impact of undiagnosed vestibular dysfunction, this model fit was first performed only on

TABLE 1 | Thresholds for males and females (95% CI) for each of the five motion conditions.

	Sex		Statistical analyses
	Male	Female	Wilcoxon rank sum
No. of participants	51	54	
Yaw rotation (°/s)	1.05 (0.91–1.20)	1.18 (1.04–1.35)	$p = 0.4474$
y-translation (cm/s)	0.79 (0.66–0.96)	0.77 (0.65–0.91)	$p = 0.8954$
z-translation (cm/s)	1.84 (1.48–2.31)	2.09 (1.68–2.60)	$p = 0.3992$
Roll tilt 0.2 Hz (°/s)	0.47 (0.40–0.54)	0.45 (0.39–0.53)	$p = 0.9463$
Roll tilt 1 Hz (°/s)	0.91 (0.78–1.08)	0.94 (0.80–1.11)	$p = 0.8450$

Data show no significant differences between sexes.

TABLE 2 | Thresholds for females who are and are not taking hormonal birth control for each of the five motion conditions.

	Hormonal birth control		Statistical analyses
	No	Yes	Wilcoxon rank sum
No. of participants	20	14	
Yaw rotation (°/s)	0.92 (0.75–1.14)	1.32 (1.00–1.74)	$p = 0.0373$
y-translation (cm/s)	0.56 (0.47–0.68)	0.80 (0.52–1.24)	$p = 0.1779$
z-translation (cm/s)	1.32 (1.03–1.69)	1.65 (1.09–2.52)	$p = 0.4732$
Roll tilt 0.2 Hz (°/s)	0.35 (0.29–0.43)	0.37 (0.28–0.48)	$p = 0.3303$
Roll tilt 1 Hz (°/s)	0.67 (0.55–0.82)	0.80 (0.65–0.98)	$p = 0.3359$

After multiple comparisons correction, no significant differences were found. 95% confidence intervals provided in parentheses.

TABLE 3 | Threshold dependent on migraine status (95% CI) for each of the five motion conditions.

	Migraine status		Statistical analyses
	No	Yes	Wilcoxon rank sum
No. of participants	100	5	
Yaw rotation (°/s)	1.11 (1.01–1.22)	1.16 (0.66–2.01)	$p = 0.9221$
y-translation (cm/s)	0.80 (0.71–0.91)	0.46 (0.34–0.62)	$p = 0.0462$
z-translation (cm/s)	2.03 (1.73–2.38)	1.05 (0.87–1–27)	$p = 0.0430$
Roll tilt 0.2 Hz (°/s)	0.47 (0.42–0.52)	0.31 (0.25–0.39)	$p = 0.0698$
Roll tilt 1 Hz (°/s)	0.94 (0.83–1.06)	0.76 (0.48–1.21)	$p = 0.4122$

Significant differences were suggested for z-translation and y-translation, but after multiple comparisons correction, no significant differences were found.

TABLE 4 | Mean threshold by age group for each of the motion conditions, with a 95% confidence interval.

Age (in years)	No. of subjects	Yaw rotation (°/s)	*y*-translation (cm/s)	*z*-translation (cm/s)	Roll tilt 0.2 Hz (°/s)	Roll tilt 1 Hz (°/s)
All	105	1.11 (1.01–1.23)	0.78 (0.69–0.89)	1.97 (1.68–2.30)	0.46 (0.41–0.51)	0.93 (0.83–1.04)
18–29	29	1.06 (0.87–1.28)	0.61 (0.48–0.79)	1.36 (1.04–1.77)	0.37 (0.31–0.44)	0.70 (0.60–0.82)
30–39	20	1.04 (0.86–1.26)	0.64 (0.52–0.78)	1.26 (0.96–1.67)	0.37 (0.30–0.46)	0.65 (0.52–0.81)
40–49	19	0.99 (0.83–1.19)	0.79 (0.59–1.05)	1.91 (1.44–2.53)	0.46 (0.37–0.59)	0.92 (0.71–1.18)
50–59	21	1.16 (0.94–1.44)	0.99 (0.75–1.29)	2.81 (2.23–3.53)	0.57 (0.45–0.72)	1.19 (1.00–1.42)
60–80	16	1.45 (1.14–1.84)	1.15 (0.87–1.53)	4.35 (2.86–6.60)	0.67 (0.51–0.88)	1.74 (1.29–2.35)
Passed balance	79	1.04 (0.94–1.16)	0.69 (0.61–0.79)	1.62 (1.38–1.91)	0.40 (0.36–0.45)	0.81 (0.72–0.91)
18–29	24	0.98 (0.79–1.21)	0.51 (0.43–0.60)	1.14 (0.93–1.40)	0.34 (0.29–0.41)	0.63 (0.55–0.73)
30–39	20	1.04 (0.86–1.26)	0.64 (0.52–0.79)	1.26 (0.95–1.67)	0.37 (0.30–0.46)	0.65 (0.52–0.81)
40–49	13	0.87 (0.70–1.09)	0.70 (0.52–0.95)	1.74 (1.17–2.62)	0.39 (0.32–0.47)	0.81 (0.62–1.06)
50–59	14	1.16 (0.91–1.48)	0.97 (0.66–1.42)	2.43 (1.83–3.21)	0.52 (0.38–0.70)	1.17 (0.94–1.46)
60–80	8	1.37 (1.02–1.85)	1.18 (0.75–1.85)	3.80 (1.91–7.59)	0.58 (0.39–0.85)	1.45 (0.98–2.14)

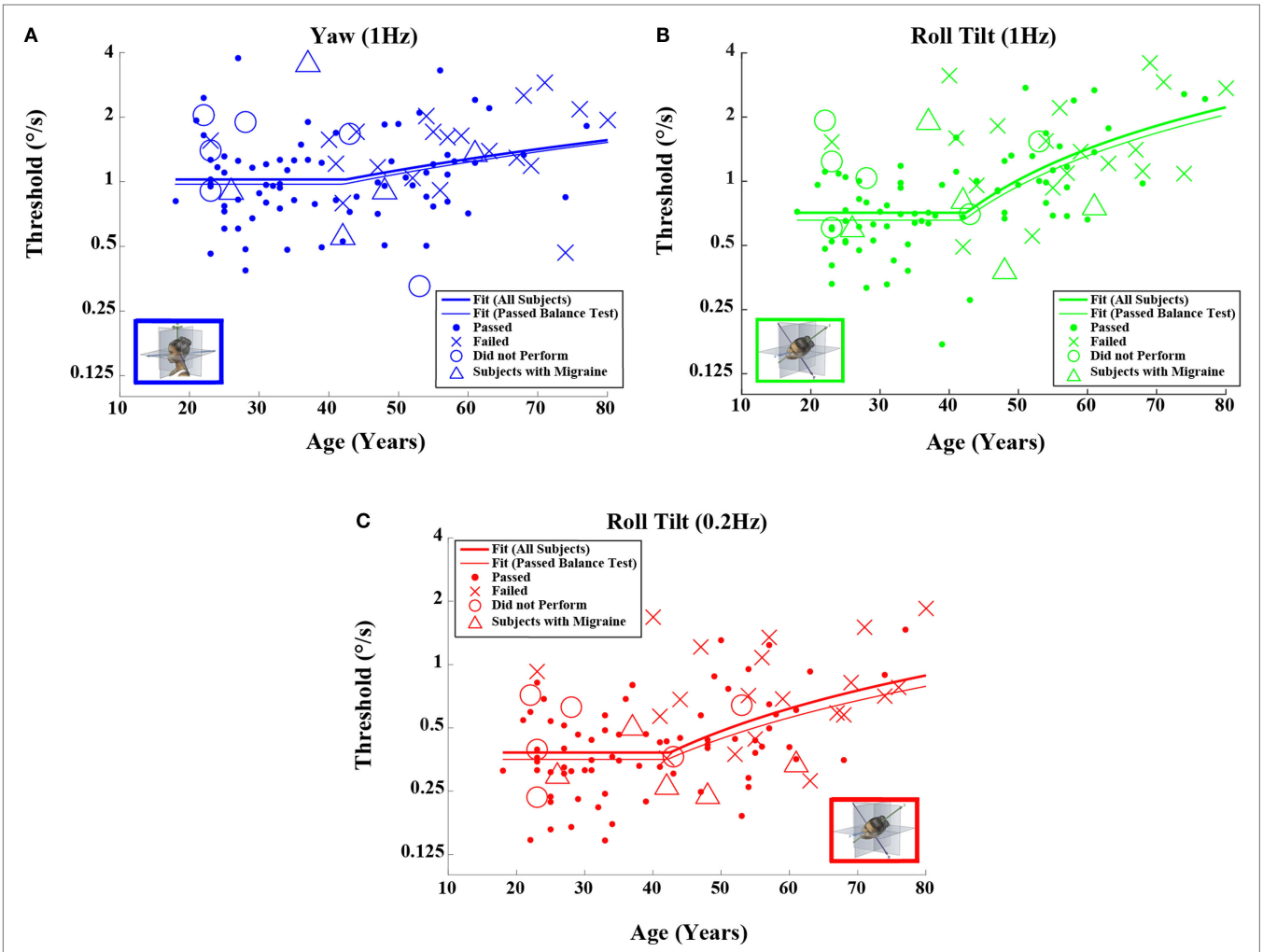


FIGURE 2 | Threshold data for all subjects are plotted versus age for (A) 1-Hz yaw rotation, (B) 1-Hz roll tilt, and (C) 0.2-Hz roll tilt. Closed circles (●) show data for subjects who passed the balance test. Cross mark (X) show data for 20 subjects who passed conditions 1–3 but did not pass condition 4 of the balance test. Open circles (○) show data for six subjects who did not attempt the balance test. Triangles (Δ) show data for five migraineurs. Inset cartoons indicating motion direction are reprinted with permission from Wolfe et al. (40).

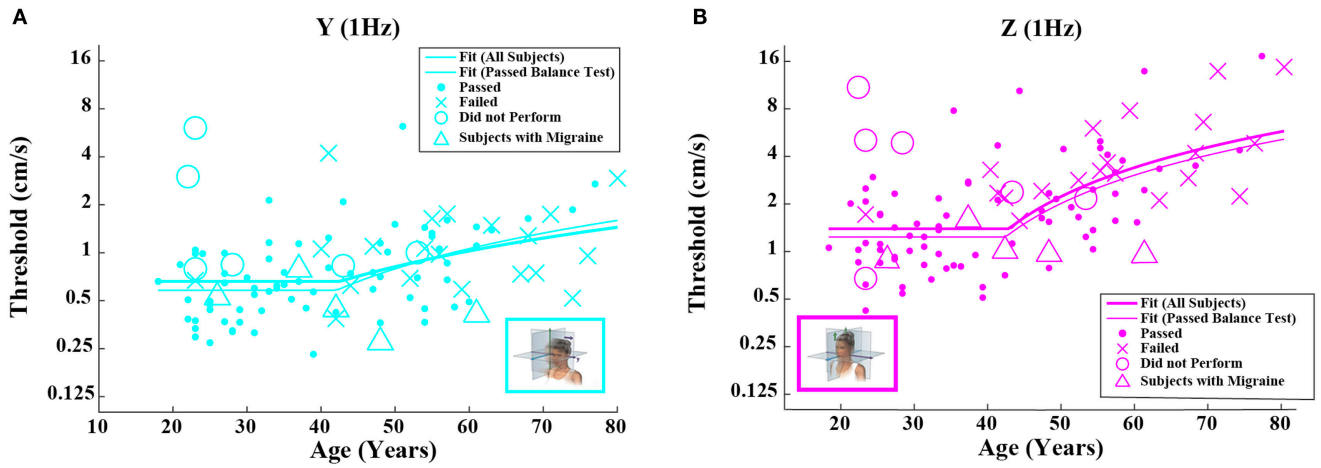


FIGURE 3 | Threshold data for all subjects are plotted versus age for (A) 1-Hz *y*-translation and (B) 1-Hz *z*-translation. Closed circles (●) show data for subjects who passed the balance test. Cross mark (X) show data for 20 subjects who passed condition 3 but did not pass condition 4 of the balance test. Open circles (○) show data for six subjects who did not attempt the balance test. Triangles (Δ) show data for five migraineurs. Inset cartoons indicating motion direction are reprinted with permission from Wolfe et al. (40).

TABLE 5 | Fit parameters determined by fitting each motion condition individually for subjects who passed the balance test.

Motion	Age cutoff (years)	Baseline	Slope (per decade)	Slope (% per decade)
Yaw rotation 1 Hz	46.2 (24.3–65.8)	0.98 (0.82–1.10) °/s	0.19 (0.04–0.94) °/s	19.56 (15.35–23.77)
Y-translation 1 Hz	39.0 (26.6–50.0)	0.57 (0.47–0.67) cm/s	0.23 (0.12–0.54) cm/s	40.33 (20.29–60.37)
Z-translation 1 Hz	42.0 (32.2–49.3)	1.24 (1.02–1.46) cm/s	1.02 (0.52–2.20) cm/s	82.80 (42.12–123.47)
Roll tilt 1 Hz	43.0 (32.2–49.7)	0.66 (0.57–0.74) °/s	0.39 (0.20–0.72) °/s	59.77 (28.42–91.11)
Roll tilt 0.2 Hz	42.6 (27.0–54.0)	0.35 (0.30–0.40) °/s	0.12 (0.05–0.33) °/s	33.32 (18.46–48.18)

95% confidence intervals provided for each parameter in parenthesis.

data from subjects who passed the balance test. Fitting this model to the data set for each motion individually (**Table 5**), we found an average age cutoff of 42.6 years. The residuals were consistent with a normal distribution (KS tests, $p > 0.4$).

Given that the fitted "age cutoff" was similar across the motion conditions, we also fit a model having 11 parameters that fit a single age cutoff across all 5 threshold data sets while simultaneously fitting 2 parameters (slope above cutoff age, baseline below cutoff age) to each of the 5 motion conditions. This fit was performed twice – once with all of the data and once with data obtained from subjects who passed the balance test. **Table 6** shows the results from this fit. As can be seen in **Figures 2** and **3** and **Table 6**, the two fits yielded similar curves. The overall age cutoff when fit simultaneously across all motion conditions was 42.1 years for all subjects and 42.7 years for all subjects who passed the balance test. Each of the slope values shown in **Table 6** was significantly greater than 0 ($p < 0.05$) corresponding to an increase in threshold (worse performance) with increasing age above ~40 years.

Table 7 shows fitted degrees of freedom (DOF), variance explained, $-2 \times \log(\text{likelihood})$, and BIC for each of the four different models presented: mean model, simple linear model, simultaneous two-segment linear model, and the independent two-segment linear model. To allow us to provide a single estimate of variance and BIC for each fitting method, we emphasize that each of the five data sets were standardized using customary calculations (i.e., the mean was subtracted from each data point and then divided by SD) described earlier in the methods, which yields two benefits. First, it makes all parameters dimensionless, which allows us to combine variance across different motion conditions. Second, it makes the variance for each of our five motion dimensions the same, which provides even weighting across the five measures (Otherwise, the variance could be dominated by the measure having the greatest variance).

As one would expect, more fit parameters (i.e., more DOF) yields variance reductions, but the 11-parameter 2-segment model explains roughly twice the variance of the 10-parameter model. In other words, adding a single age cutoff parameter to the linear regression model doubles the variance explained.

Likelihood ratio testing was used to test the nested models (mean, simultaneous two-segment, and independent two-segment) and showed that the proposed simultaneous two-segment linear model was significantly better than the mean model for both the full data set (χ^2 statistic = 121.8, DOF = 6, $p < 0.0001$) and the 79 subjects who passed the balance test (χ^2 statistic = 88.6, DOF = 6, $p < 0.0001$). Likelihood ratio testing also showed the simultaneous two-segment linear model is not significantly different from the independent two-segment linear model for both the full data set (χ^2 statistic = 0.9, DOF = 4, $p = 0.92$) and the 79

TABLE 6 | Fit parameters determined *via* single simultaneous fit of all threshold data.

Motion	Baseline	Slope (per decade)	Slope (% per decade)
All subjects			
Yaw rotation 1 Hz	1.02 (0.93–1.13) °/s	0.14 (0.04–0.27) °/s	14.0 (3.9–27.5)
Y-translation 1 Hz	0.66 (0.57–0.76) cm/s	0.21 (0.10–0.35) cm/s	31.6 (14.2–57.0)
Z-translation 1 Hz	1.39 (1.15–1.66) cm/s	1.17 (0.68–1.87) cm/s	84.1 (45.0–141.9)
Roll tilt 1 Hz	0.71 (0.61–0.81) °/s	0.40 (0.24–0.61) °/s	56.6 (32.9–90.1)
Roll tilt 0.2 Hz	0.38 (0.34–0.43) °/s	0.14 (0.07–0.21) °/s	35.4 (18.6–58.7)
Passed balance test			
Yaw rotation 1 Hz	0.97 (0.87–1.09) °/s	0.15 (0.02–0.31) °/s	14.9 (01.9–34.5)
Y-translation 1 Hz	0.58 (0.50–0.67) cm/s	0.27 (0.13–0.47) cm/s	46.0 (20.5–85.6)
Z-translation 1 Hz	1.24 (1.02–1.49) cm/s	1.03 (0.56–1.86) cm/s	83.2 (42.3–160.0)
Roll tilt 1 Hz	0.66 (0.57–0.74) °/s	0.37 (0.21–0.61) °/s	56.0 (30.5–95.3)
Roll tilt 0.2 Hz	0.35 (0.31–0.40) °/s	0.11 (0.05–0.20) °/s	32.4 (13.9–58.4)

95% confidence intervals provided for each parameter in parenthesis. Top half of the table shows fitted parameters when all data are fitted; fitted age cutoff was 42.5 (37.1–46.9). Bottom half shows fitted parameters for subjects who passed the balance test; fitted age cutoff was 42.1 (36.5–46.6).

TABLE 7 | Degrees of freedom (DOF), variance explained, −2 × log(likelihood) – which is sometimes called deviance and was calculated using the natural log – and Bayesian information criteria (BIC) scores are shown for the four different models presented herein.

Name	DOF	% variance explained	−2 log(*L*)	BIC
All subjects (*N* = 105)				
Mean	5	–	−4.02	27.29
Linear regression	10	12.10	−71.8	−9.21
Simultaneous 2-segment	11	20.70	−125.8	−56.95
Independent 2-segment	15	20.90	−126.7	−32.85
Passed balance test (*N* = 79)				
Mean	5	–	−4.03	25.86
Linear regression	10	7.20	−33.6	26.15
Simultaneous 2-segment	11	20.10	−92.6	−26.79
Independent 2-segment	15	20.30	−93.6	−3.92

*The simplest model simply calculates the mean (e.g., **Table 1**), ignoring age variations, and provides a standard statistical baseline for the three other models. The linear regression model (**Table 5**) has 10 fit parameters – a slope and intercept for each of the 5 motion directions. The independent 2-segment model has 15 fit parameters – a baseline, age cutoff, and slope for each of our 5 threshold measures reported herein. The simultaneous 2-segment model has 11 fit parameters – a single age cutoff as well as a baseline measure and slope for each of 5 threshold measures. The BIC was the smallest (best) for the 11-parameter model both for all subjects and for subjects who passed the balance test.*

subjects who passed the balance test (χ^2 statistic = 1.0, DOF = 4, $p = 0.91$).

Bayesian information criteria statistics showed that this model was substantially better than the other models considered, including the simple linear model. In fact, this analysis showed that the simultaneous two-segment model had the smallest BIC for both the full data set and for the 79 subjects who passed the balance test. The BIC for the 11-parameter 2-segment model was always more than 20 points lower than for any other model. For context, BIC differences greater than 10 are considered "very strong" evidence for the model with the lower BIC (42).

The two simple models – the mean and linear regression models – do not match our data well. The mean model cannot capture the fact that thresholds increase above the age of about 40, and the linear regression model cannot capture the fact that thresholds are relatively constant below the age of about 40 (e.g., **Figure 1**).

Bias

For our direction-recognition task, the fitted bias parameter represents the stimulus magnitude at which a subject is equally likely to respond right (up) or left (down) (43). It is poorly understood because it could originate from any of the three sources: (a) a bias in the information, (b) a bias in the placement of the decision boundary (43), or (c) a bias in the noise distribution. We evaluated bias and normalized bias; normalized bias is simply the fitted bias divided by the fitted threshold. This dimensionless parameter has the advantage that it is readily comparable across motion conditions.

Neither the mean value of the bias nor the mean value of normalized bias was significantly different from 0 for any of the 5 motion conditions. This was true across all 105 subjects as well as for the 79 subjects who passed the balance test (*t* test, $p > 0.05$ for all 20 conditions tested after correction for multiple comparisons).[1] Furthermore, correlation coefficients for either bias or normalized bias versus age were not significantly different from 0 for any of the 5 motion conditions. Again, this was true for all subjects as well as for those who passed the balance test (Kruskal–Wallis, $p > 0.1$ for all 20 conditions tested).

Figures 4 and **5** show scatterplots of the normalized bias values for all the motion conditions. Consistent with correlation analyses reported above, no significant or consistent trends are evident.

Relationship between Thresholds and Romberg Balance Testing

Given that vestibular information is a fundamental contributor to balance control, we looked for associations between thresholds

[1] Prior to multiple comparison correction, only the normalized *Z*-translation bias for subjects who passed the balance test suggested a statistically significant effect (*t*-test, $p = 0.0441$).

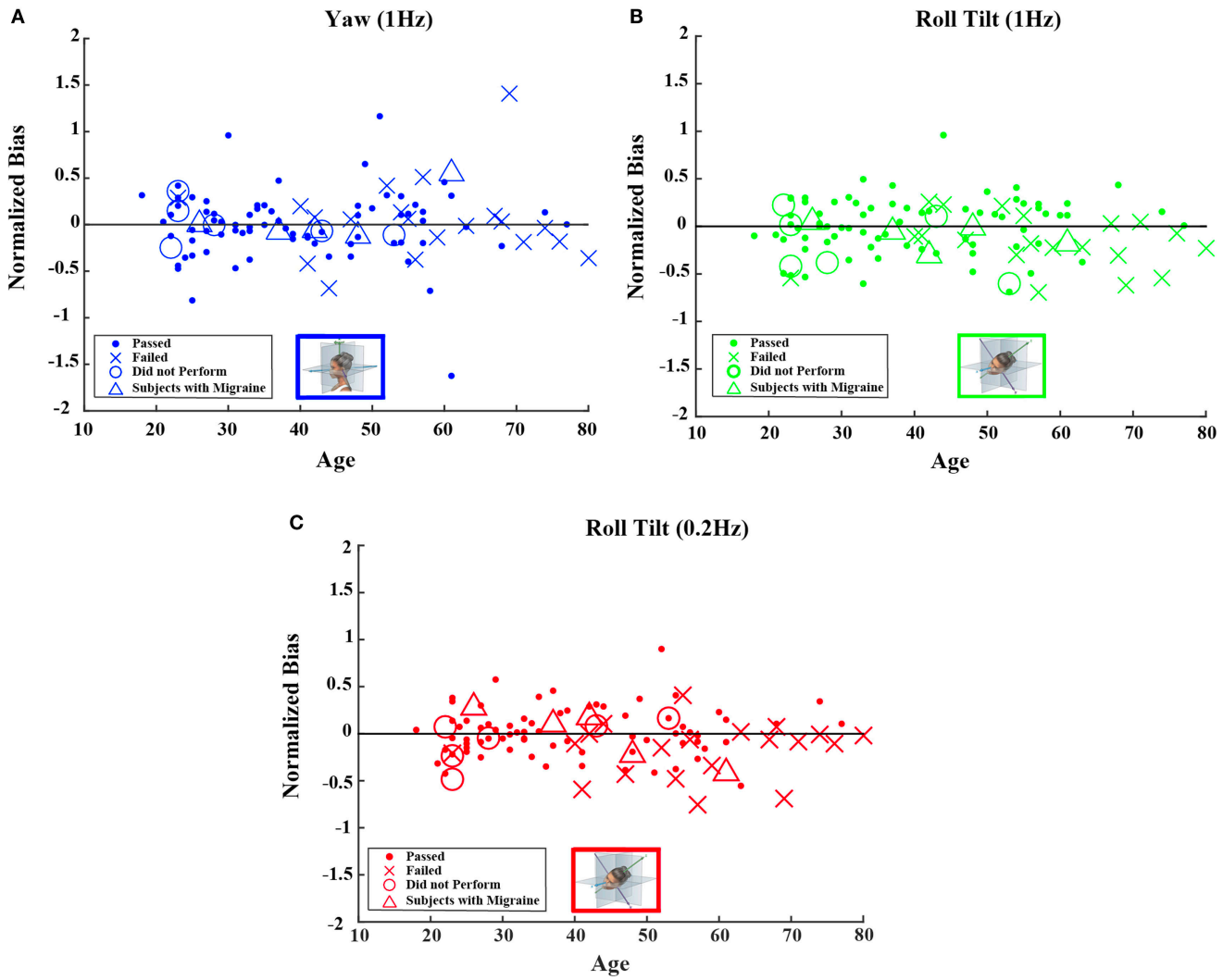


FIGURE 4 | Normalized bias data for all subjects are plotted versus age for (A) 1-Hz yaw rotation, (B) 1-Hz roll tilt, and (C) 0.2-Hz roll tilt. Closed circles (●) show data for subjects who passed the balance test. Cross mark (X) show data for 20 subjects who passed condition 3 but did not pass condition 4 of the balance test. Open circles (○) show data for six subjects who did not attempt the balance test. Triangles (Δ) show data for five migraineurs. Format mimics **Figure 2**.

and performance on the modified Romberg test. A subsample of 99 subjects performed the balance test. Not a single participant failed the test in conditions 1, 2, or 3, but 20% (20 of 99) failed in condition 4. Thresholds were significantly greater for participants who failed the final balance test condition (i.e., the Romberg test condition focused primarily on vestibular function) for all motion axes (**Table 8**).

Consistent with earlier findings (25), the proportion of balance test failures increased with age group (Fisher exact test, $p < 0.0001$). To test whether the observed difference between the pass and fail group may be due to an age effect or to the influence of other confounding factors, we adjusted for age, gender, and migraine using a mixed model. The significant association of balance test failure with increasing threshold remained persistent for roll tilt at both 0.2 and 1 Hz ($p = 0.003$ and $p = 0.02$, respectively) but was not significantly correlated for increasing yaw rotation ($p = 0.09$), y-translation ($p = 0.50$), and z-translation ($p = 0.09$) thresholds. The age effect was unchanged for all motion paradigms – remaining significant for y-translation, z-translation, and roll tilt at 1 Hz (each $p < 0.0001$) and roll tilt at 0.2 Hz ($p = 0.0007$) and not significant for yaw rotation ($p = 0.12$).

Odds of failing the balance test have been associated with significantly increased odds of falling, for American adults 40 years and older (25). Our data show that a 1 unit increase in roll-tilt thresholds at 0.2 Hz (following transformation in SAS using natural log) were associated with a 5.6-fold increase in the odds of failing the balance test (odds ratio, 5.6; 95% confidence interval, 1.6–18.9) in a multiple logistic regression adjusted for age. One-unit increase in roll-tilt thresholds at 1 Hz (log-transformed version) was associated with a 3.7-fold increase in the odds of balance testing failure (odds ratio, 3.7; 95% confidence interval, 1.1–12.9).

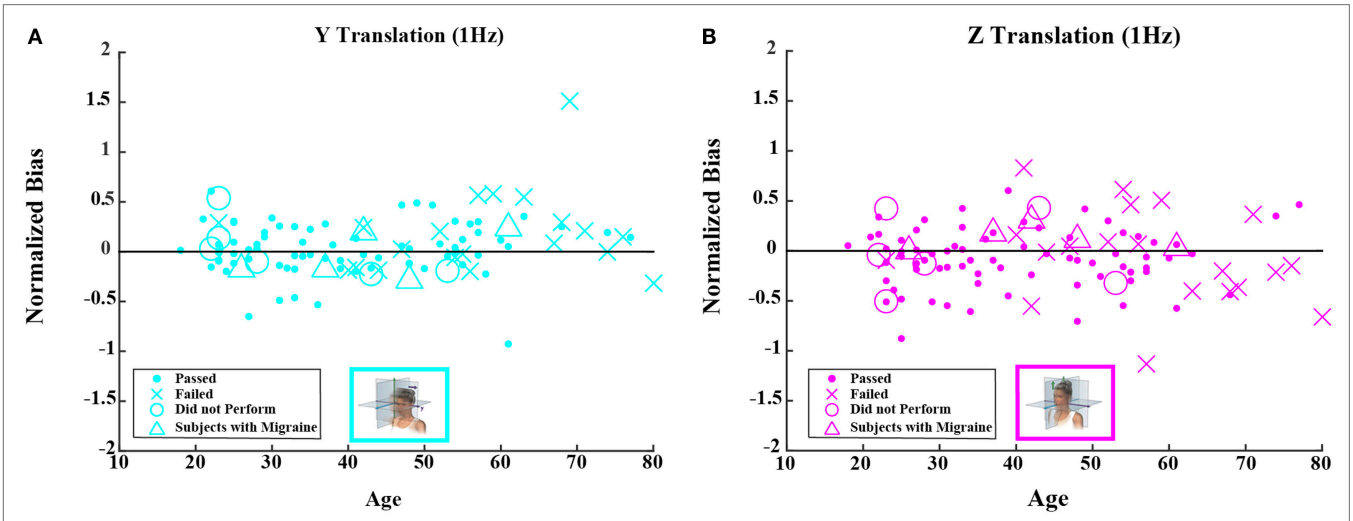


FIGURE 5 | Normalized bias data for all subjects are plotted versus age for (A) 1-Hz *y*-translation and (B) 1-Hz *z*-translation. Closed circles (●) show data for subjects who passed the balance test. Cross mark (X) show data for 20 subjects who passed condition 3 but did not pass condition 4 of the balance test. Open circles (○) show data for six subjects who did not attempt the balance test. Triangles (Δ) show data for five migraineurs. Format mimics **Figure 3**.

TABLE 8 | Mean thresholds for subjects who passed and failed the balance test.

	Balance test		Statistical analyses
	Pass	Fail	Wilcoxon rank sum
No. of participants	79	20	
Yaw rotation (°/s)	1.04 (0.94–1.16)	1.43 (1.19–1.71)	$p = 0.0030$
y-translation (cm/s)	0.69 (0.61–0.79)	1.05 (0.81–1.35)	$p = 0.0066$
z-translation (cm/s)	1.62 (1.37–1.91)	3.67 (2.79–4.84)	$p < 0.0001$
Roll tilt 0.2 Hz (°/s)	0.40 (0.36–0.45)	0.76 (0.60–0.95)	$p < 0.0001$
Roll tilt 1 Hz (°/s)	0.81 (0.72–0.91)	1.55 (1.18–2.03)	$p < 0.0001$

Significant differences were found for each of the motion conditions.

DISCUSSION

In this study, we attempted to determine whether sex or age affected perceptual thresholds of vestibular functioning. To do this, we asked subjects to indicate the direction of movement they perceived in 5 blocks of 100 trials each for the following motion conditions: yaw rotation, *y*-translation, *z*-translation, roll tilt at 1 Hz, and roll tilt also at 0.2 Hz. One primary finding was that thresholds increased with age for all motion directions above the age of about 40. This finding is consistent with a number of earlier threshold studies that had reported similar effects of age *x*-axis translation (16, 19) and *y*-axis translation (16) but inconsistent with a few earlier studies that reported no such age effects for yaw rotation (14–16). We note that the yaw rotation age effect was the smallest that we observed and our study had a larger total number of subjects than the earlier studies; these differences likely explain why we found a significant effect of aging in contrast to earlier studies.

We explicitly note that our finding of a statistically significant effect of age on yaw rotation thresholds required both our two-segment model and more than 50 subjects. Our translation threshold findings showed more substantial age effects. These findings are consistent with earlier findings that translation thresholds increase with age (16–19). No previous studies have examined roll-tilt thresholds, which is a focus of our study (i.e., 40% of the data reported).

The second primary finding was that increasing roll-tilt threshold was correlated with failure to complete the Romberg foam balance test. Since we know of no mechanism by which balance would impact vestibular thresholds, and since we know that balance depends on vestibular function [e.g., Ref. (44)] and that falls correlate with failure to complete the Romberg foam balance test (25), it is reasonable to suggest that this correlation shows that fall risk is substantially impacted by vestibular function. We emphasize that this was true even when measured in a healthy population chosen without any evidence of specific vestibular disorders.

Finally, while we did not report a full analysis of the within subject correlations between thresholds in different axes, our initial analyses showed that 9 of the 10 pairwise comparisons (all but the correlation of yaw rotation thresholds with *y*-translation thresholds) of the 5 threshold measurements were correlated ($p < 0.05$); we plan to make this topic the focus of a future manuscript as soon as we complete extensive analyses of these correlations. A more detailed discussion of our findings and the implications are presented below.

Sex Differences and Individual Differences

One goal when conducting this study was to determine whether there were sex differences in vestibular perceptual thresholds. According to our findings, there were no differences between males and females in their perceptual thresholds; this finding is in line with other studies comparing sex differences (8, 16, 17, 26).

Benson and colleagues previously published a pair of comprehensive threshold studies (7, 8). These studies looked at rotational thresholds (8) and translational thresholds (7). For the 4 motions

studied with 24 or more subjects, all demonstrated a range of thresholds with a ratio of roughly 10 for all 4 motions (i.e., the maximum threshold divided by the minimum threshold was about 10). In decibel units, Benson reported SDs of 4.40 (yaw rotation), 4.63 (*X*-translation), 3.98 (*Y*-translation), and 6.10 (*Z*-translation). When converted to decibels our experimental SDs were 4.11 (yaw rotation), 5.23 (*Y*-translation), 6.47 (*Z*-translation), 4.62 (1.0-Hz roll tilt), and 4.36 (0.2-Hz roll tilt), which appear similar to Benson's. These similar empiric variations reported by both studies are most likely due to intersubject differences since variations due to sampling and other methodological details have been shown to be an order of magnitude smaller for 100 binary forced-choice trials (29) than these empirical variations.

Motion Differences

Next, we looked at differences in perceptual thresholds for the various motion stimuli. We found differences in several of the motion thresholds that we tested. Namely, we found that the threshold for *y*-translation was less than the threshold for *z*-translation, by approximately a factor of 2. This finding is consistent with MacNeilage et al. who indicated that utricles may have a greater sensitivity to perceive horizontal motion compared to the saccules' sensitivity to perceive vertical motion (45). This suggestion carries more weight when we also consider that the utricles have a greater density of hair cells compared to the saccules (46). It is possible that the additional hair cells in the utricles could contribute to their sensitivity and therefore lower the *y*-threshold. Furthermore, Valko et al. suggest that earth-vertical movement is more difficult to discriminate as the otolith must determine whether the gravitational force increases or decreases, whereas for an earth-horizontal movement, the body and brain have access to a greater amount of non-vestibular cues to aid in determining the direction of a particular motion (20). Overall, there are many differences between earth-vertical and earth-horizontal movements; it is possible that the amount of information (e.g., tactile) available during earth-horizontal movement provides easier perception and recognition of the motion direction compared to the amount of information available when moving along the *z*-axis.

When we divided the data by age group, the threshold velocity for roll tilt at 0.2 Hz was less than the threshold velocity for 1-Hz roll tilt. This is consistent with Valko et al.'s study, where the researchers found that roll-tilt thresholds, expressed as peak velocity, decreased at lower frequencies in healthy subjects (20).

Furthermore, the threshold for roll tilt at 1 Hz was also lower than the yaw threshold. Because roll tilt is perceived by an integration of otolith and semicircular canals, the amount of information available to the vestibular system may facilitate the perception of motion compared to the yaw rotation which primarily relies on the semicircular canals.

Ages for Perceptual Cutoffs

Finally, because we saw that thresholds for each motion condition increased from decade to decade after about age 40, we thought it would be interesting to determine whether there was one specific age at which the perceptual thresholds began to increase for all five motion paradigms. By modeling the data we collected in this study, we found that we were able to separate vestibular thresholds into two categories, namely, "younger" and "older" adults, where younger adults' thresholds were stable until about 40 years of age, at which point "older" adult vestibular performance began to decline (i.e., thresholds began to increase) at a steady rate for each of the motion thresholds. Between this finding and findings from other studies (16, 18, 47), we can directly assert that changes in vestibular function occur with age. While increasing age above the age cutoff was associated with an increase in threshold in each motion condition, some conditions were impacted more than others: *z*-translation thresholds increased by ~83% of the baseline per decade after the age cutoff, roll tilt 1 Hz by 56%/decade, *y*-translation by 46%/decade, roll tilt 0.2 Hz 32%/decade, and yaw rotation 15%/decade. These rates of increased thresholds with aging are for the subset of subjects that passed the balance test, but the values when including all subjects are similar.

Vestibular System Aging

Vestibular functioning can decline for any number of reasons including neurodegenerative disease, peripheral loss, and even medications and their side effects. Age is an important factor that influences the vestibular system and vestibular function. While the mechanisms behind aging remain disputed, it is an important and relevant issue to address here. While others have considered the mechanisms of aging and its particular effect on the vestibular system (48), we would like to expand on what has previously been proposed by comparing age-related changes in the vestibular system to other systems, by discussing potential mechanisms, and consider why little or no threshold difference occur before the age of 40.

Comparison to Other Modalities

We report that – for five different tests of vestibular function – perceptual thresholds appeared constant between the ages of 20 and 40 and increased linearly above the age of 40. A roughly similar pattern has been reported for other sensory systems but with the functional performance plateau lasting until the age of 60. For example, average odor identification shows a plateau until about the age of 60 with functional declines evident above the age of 60 (37). As shown in **Figure 2** of Doty, visual acuity (38) and speech intelligibility (39) show similar patterns including declines above the age of about 60. It is interesting to note that the functional decline appears to begin about two decades earlier for vestibular function than for smell, vision, or speech intelligibility. This may indicate that vestibular function is preferentially targeted by whatever mechanism(s) causes functional sensory loss with age (e.g., vestibular threshold increases with age).

Mechanism

The threshold variations were qualitatively similar across all conditions; this suggests at least one shared common cause. The fact that the functional decline pattern (i.e., roughly linear threshold increase begins to occur around age 40 for all conditions) is about the same for all conditions tested weighs against an "overstimulation" cause like that reported for hearing loss (49–51), though

that certainly does not mean that hearing loss and functional vestibular loss cannot share another (or other) mechanism(s).

No explanation, including our common cause explanation, can explain the quantitative differences across motions (e.g., why do *z*-translation thresholds demonstrate a slope of more 80% while yaw rotation a 15% slope?) at this time. One simple explanation is that these do not share a common cause. Alternatively, these deficits could reflect a common cause with the quantitative differences due to (a) the amount of available redundancy, which may vary for different motions, (b) the baseline, which obviously impacts this relative slope measure, and/or (c) other mechanisms in addition to a cause common to all motions.

Several studies have reported human vestibular hair cell and vestibular afferent neuron counts as a function of age (46, 52). Vestibular hair cell loss has been reported to show a linear decline with age from birth through 100 years of age that does not directly match our threshold data, especially the constant threshold plateau we report below age 40. This argues against hair cell loss in isolation being a direct explanation of the threshold age pattern we report. Similarly, the loss of afferent neurons does not in isolation match the threshold age pattern we report.

Therefore, we will briefly consider another (possibly related) cause – the free radical theory of aging, which is probably the most persistent theory of aging and could explain why performance declines begin to be evident for vestibular thresholds around the age of 40 but later for some other sensory functions. Specifically, we note that in primates, the average firing rate of peripheral afferent neurons is nearly 100 spikes per second, with the resting rate reported as averaging 91.3 spikes per second for the semicircular canals (53) and 62.7 spikes per second for the otolith organs – 79.1 for superior nerve and 47.0 for inferior nerve (54). These resting rates average between 50 and 100 spikes per second across about 40,000 vestibular afferent neurons (40) and, hence, assert a substantial metabolic load. While the resting rate for individual neurons in the vestibular nuclei is a bit lower, the central vestibular system similarly asserts a substantial metabolic load [e.g., Ref. (55)].

A metabolic-related cascade that could lead to age-related vestibular threshold increases is sketched in the following paragraphs. The heavy metabolic load of the vestibular system – both central and peripheral vestibular systems – requires extensive ATP production *via* mitochondria. Since mitochondria are the biggest contributors of oxidative load (i.e., free radicals) to the body, this leads directly to a relatively large oxidative stress. Many of these free radicals are quenched. Others escape and cause damage distributed elsewhere. But some of these free radicals cause local damage. This local damage can lead to dysfunctional central and/or peripheral function. This proposed mechanism would be consistent with studies showing oxidative contributions to peripheral cochlear dysfunction [e.g., Ref. (56)]. When the vestibular functional loss (i.e., neuronal cell death and/or dysfunction) leads to more "signal" loss than "noise" loss, it would lead to increased perceptual thresholds.

A review of the evidence for/against the free radical theory of aging and other theories of aging is beyond the scope of this paper but can be found in various books/reviews [e.g., Ref. (57–59)] We simply note here that the most recent incarnation (60, 61) of the free radical theory of aging (59, 62, 63) would be consistent with the cascade described above. If the free radical theory of aging is the major contributor to the deficit observed in thresholds above the age of 40, this could make vestibular threshold changes a relatively simple, sensitive, non-invasive behavioral biomarker for aging in humans above the age of 40, especially, since, as noted earlier, the age effects for vestibular function appear earlier than for odor discrimination, visual acuity, or speech intelligibility.

Why Are No Threshold Changes Evident below the Age 40?

Small threshold changes below the age of 40 may be evident for an individual but were masked by intersubject variability, since our study was not longitudinal. Long-term longitudinal studies would likely show whether threshold changes occur in individual humans before the age of 40.

While speculative, the free radical mechanism described earlier could also be consistent with the relative threshold constancy before age 40. Let us assume that vestibular contributions are crucial and that oxidative neuronal cell loss due to cell death or neuronal dysfunction is inevitable. If true, one reasonable evolutionary strategy would be to have an excess of neurons at least till reproductive vigor started to wane. In other words, some neuronal cell loss occurs before age 40, but the available excess of vestibular neurons yields redundancy such that the incremental decrease in overall signal matches the incremental decrease in overall noise for each vestibular neuron lost due to dysfunction or death. But around age 40, the vestibular cell counts reduce to the point that each neuron loss causes more incremental signal loss than noise loss. If true, this would suggest that we have on the order of 40,000 vestibular afferent neurons to provide some redundancy to fend off functional impact of peripheral vestibular loss. Such peripheral redundancy could also explain why thresholds as a function of age do not match the aging patterns shown by vestibular afferent neuron counts (52, 64) or vestibular hair cell counts as a function of age (46, 64). Furthermore, this hypothesis could account for different quantitative aging patterns reported herein (i.e., *Z*-translation slope much greater than yaw rotation slope relative to baseline) for different movements.

Implications

Our threshold data showed that vestibular thresholds broadly increased with age above the age of 40 (by 15–83% per decade depending upon the motion condition, $p < 0.05$ for all five threshold measures). Furthermore, our data showed that balance test failures increased significantly as roll-tilt thresholds increased – even when age and other factors were fully considered by our mixed-model analysis. This latter finding is important because an earlier study showed that failure to complete the Romberg foam balance test correlates highly with falls (25). More specifically, data from a National Health and Nutrition Examination Survey (NHANES) were analyzed to show that 35.4% of American subjects above the age of 40 were unable to stand on foam with their eyes closed – the exact same failure that we showed to be significantly correlated with increasing roll-tilt thresholds. The earlier study (25) also reported increased odds of falling – an

odds ratio of 6.3 – for such individuals with subclinical vestibular dysfunction relative to those without dysfunction (i.e., individuals who were able to complete the balance testing successfully).

Given different definitions and different methods, these American findings are neither far from the findings of a German study that estimated prevalence of vertigo to be 22.9% (65) nor from self-reported vertigo prevalence rates of about 20% (66, 67). In fact, self-reported dizziness for the American study was 27.0% – certainly in line with the earlier estimates. For the fraction of such symptomatic individuals with measured vestibular dysfunction, the American study reported increased odds of falling – i.e., an odds ratio of 12.3. Our findings of a decrement in vestibular function – directly assessed *via* vestibular thresholds – above the age of 40 could certainly help explain why 35% of the NHANES population above the age of 40 demonstrated balance dysfunction.

Given the clear evidence presented herein that vestibular function declines with age above the age of 40 and given the relative consistency of the earlier estimates of vestibular and balance dysfunction (25, 65–67), it seems reasonable to try to make a conservative estimate of the number of people who might die each year due to vestibular dysfunction. For example, it seems likely that at least some of the transportation accidents (e.g., car crashes) that lead to the death of about 50,000 Americans each year (39) are due to vestibular dysfunction, but, unfortunately, we were unable to find enough relevant data at this time to estimate the contributions of vestibular dysfunction to motor vehicle accidents. On the other hand, available data do allow us to conservatively estimate the number of deaths each year caused by falls related to vestibular dysfunction. These calculations are provided in detail in Appendix A. **Table A1** in Appendix provides a range of estimates – some more conservative and some less so. The annual death estimates correlated with vestibular dysfunction range from 48,000 to 152,000.[2] While the largest estimate of nearly 152,000 deaths per year may prove inaccurate, it is worth noting that this would be placed third in the US behind only heart disease and cancer. Even the lowest estimate of ~48,000 deaths per year – which would place this as the tenth largest cause of death in the US – conveys the gravity of the problem.

We emphasize that estimating death rates was not a goal of our study but rather an implication of the finding – even after correcting for age effects – that the proportion of balance test failures increased with roll-tilt thresholds, especially at 0.2 Hz ($p = 0.0007$); 1 unit increase in roll-tilt thresholds (log-transformed version) corresponded to a 5.6-fold increase in the odds of failing the balance test. We further emphasize that extrapolating the current data to fall risk has limitations. Nonetheless, the range of estimated deaths potentially due to vestibular dysfunction (**Table A1** in Appendix) suggests the scope of the problem and highlights the need for broader epidemiologic studies focused on mortality associated with vestibular dysfunction.

We close this implications section by juxtaposing some facts discussed above. (1) Data showed that vestibular thresholds, including roll-tilt thresholds, broadly increased with age above the age of 40 (by 15–83% per decade depending upon the motion condition). (2) Analyses showed that balance test failures, which have previously been shown to correlate highly with falls (25), increased significantly as roll-tilt thresholds increased. (3) Calculations suggested that vestibular dysfunction could possibly be ranked somewhere between the third and tenth biggest killer of Americans. Even in isolation, this is alarming. But, given the rapid aging of the world's population [e.g., Ref. (68)], the problem will rapidly grow much worse unless existing efforts to improve vestibular screening, vestibular diagnoses, vestibular treatments, balance treatments, fall prediction, and fall prevention are accelerated.

Brief Summary

We measured vestibular perceptual thresholds in 105 healthy humans (54F/51M) ranging from 18 to 80 years of age. We found that thresholds significantly increased above the age of 40 for all five motion directions investigated. Even taking age and other factors into consideration, we found a significant correlation of balance test failures with increasing roll-tilt thresholds.

AUTHOR CONTRIBUTIONS

MB, TC, and DM designed the study and assisted in statistical analyses and interpretation and manuscript preparation. WW, YB, and TL also assisted in manuscript preparation, and statistical analyses and interpretation.

ACKNOWLEDGMENTS

This research was supported by NIH/NIDCD R01-DC01458 and R01-DC014924. We also thank Raquel Galvan-Garza, Wangsong Gong, Bob Grimes, Csilla Haburcakova, Faisal Karmali, Kristen Kirk, Rick Lewis, Koeun Lim, and Yongwoo Yi.

[2] A reviewer helpfully suggested that the paper might be better off without the appendix. After dialog engendered by the Frontier's process, this footnote has been added to specifically note that we all agree that (a) the estimated range is large because available data do not allow solid estimates, (b) the issue was too important to gloss over by ignoring it, (c) the only way to resolve the matter is to obtain better data, and (d) including these broad estimates is likely to encourage the acquisition and analysis of better data.

REFERENCES

1. Moriyama H, Itoh M, Shimada K, Otsuka N. Morphometric analysis of fibers of the human vestibular nerve: sex differences. *Eur Arch Otorhinolaryngol* (2007) 264(5):471–5. doi:10.1007/s00405-006-0197-5
2. Sato H, Sando I, Takahashi H. Computer-aided three-dimensional measurement of the human vestibular apparatus. *Otolaryngol Head Neck Surg* (1992) 107(3):405–9.
3. Peterka RJ, Black FO, Schoenhoff MB. Age-related changes in human vestibulo-ocular reflexes: sinusoidal rotation and caloric tests. *J Vestib Res* (1990) 1(1):49–59.
4. Peterka RJ, Black FO, Schoenhoff MB. Age-related changes in human vestibulo-ocular and optokinetic reflexes: pseudorandom rotation tests. *J Vestib Res* (1990) 1(1):61–71.
5. Peterka RJ, Black FO. Age-related changes in human posture control: sensory organization tests. *J Vestib Res* (1990) 1(1):73–85.

6. Peterka R, Black FO, Schoenhoff M. Age-related changes in human postural control: motor coordination tests. *J Vestib Res* (1990) 1:87–96.
7. Benson AJ, Spencer MB, Stott JR. Thresholds for the detection of the direction of whole-body, linear movement in the horizontal plane. *Aviat Space Environ Med* (1986) 57(11):1088–96.
8. Benson AJ, Hutt EC, Brown SF. Thresholds for the perception of whole body angular movement about a vertical axis. *Aviat Space Environ Med* (1989) 60(3):205–13.
9. Wall C III, Black FO, Hunt AE. Effects of age, sex and stimulus parameters upon vestibulo-ocular responses to sinusoidal rotation. *Acta Otolaryngol* (1984) 98(3–4):270–8. doi:10.3109/00016488409107563
10. Priesol AJ, Valko Y, Merfeld DM, Lewis RF. Motion perception in patients with idiopathic bilateral vestibular hypofunction. *Otolaryngol Head Neck Surg* (2014) 150(6):1040–2. doi:10.1177/0194599814526557
11. Lewis RF, Priesol AJ, Nicoucar K, Lim K, Merfeld DM. Abnormal motion perception in vestibular migraine. *Laryngoscope* (2011) 121(5):1124–5. doi:10.1002/lary.21723
12. Lewis RF, Priesol AJ, Nicoucar K, Lim K, Merfeld DM. Dynamic tilt thresholds are reduced in vestibular migraine. *J Vestib Res* (2011) 21(6):323–30. doi:10.3233/VES-2011-0422
13. Hartmann M, Furrer S, Herzog MH, Merfeld DM, Mast FW. Self-motion perception training: thresholds improve in the light but not in the dark. *Exp Brain Res* (2013) 226(2):231–40. doi:10.1007/s00221-013-3428-1
14. Chang NY, Hiss MM, Sanders MC, Olomu OU, MacNeilage PR, Uchanski RM, et al. Vestibular perception and the vestibulo-ocular reflex in young and older adults. *Ear Hear* (2014) 35(5):565–70. doi:10.1097/AUD.0000000000000052
15. Seemungal BM, Gunaratne IA, Fleming IO, Gresty MA, Bronstein AM. Perceptual and nystagmic thresholds of vestibular function in yaw. *J Vestib Res* (2004) 14(6):461–6.
16. Roditi RE, Crane BT. Directional asymmetries and age effects in human self-motion perception. *J Assoc Res Otolaryngol* (2012) 13(3):381–401. doi:10.1007/s10162-012-0318-3
17. Agrawal Y, Bremova T, Kremmyda O, Strupp M, MacNeilage PR. Clinical testing of otolith function: perceptual thresholds and myogenic potentials. *J Assoc Res Otolaryngol* (2013) 14(6):905–15. doi:10.1007/s10162-013-0416-x
18. Bremova TC, Caushaj A, Ertl M, Strobl R, Böttcher N, Strupp M, et al. Comparison of linear motion perception thresholds in vestibular migraine and Menière's disease. *Eur Arch Otorhinolaryngol* (2016) 273:2931–9. doi:10.1007/s00405-015-3835-y
19. Kingma H. Thresholds for perception of direction of linear acceleration as a possible evaluation of the otolith function. *BMC Ear Nose Throat Disord* (2005) 5(1):5. doi:10.1186/1472-6815-5-5
20. Valko Y, Lewis RF, Priesol AJ, Merfeld DM. Vestibular labyrinth contributions to human whole-body motion discrimination. *J Neurosci* (2012) 32(39):13537–42. doi:10.1523/JNEUROSCI.2157-12.2012
21. National Center for Health Statistics. *Health, United States, 2013: With Special Feature on Prescription Drugs*. Hyattsville, MD: Centers for Disease Control and Prevention (2014).
22. Láinez MJ, Dominguez M, Rejas J, Palacios G, Arriaza E, Garcia-Garcia M, et al. Development and validation of the Migraine Screen Questionnaire (MS-Q). *Headache* (2005) 45(10):1328–38. doi:10.1111/j.1526-4610.2005.00265.x
23. Láinez MJ, Castillo J, Dominguez M, Palacios G, Diaz S, Rejas J. New uses of the Migraine Screen Questionnaire (MS-Q): validation in the Primary Care setting and ability to detect hidden migraine. MS-Q in Primary Care. *BMC Neurol* (2010) 10:39. doi:10.1186/1471-2377-10-39
24. CDC. *Balance Procedures Manual*. Atlanta: Survey NHaNE (2003). p. 26.
25. 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
26. Grabherr L, Nicoucar K, Mast FW, Merfeld DM. Vestibular thresholds for yaw rotation about an earth-vertical axis as a function of frequency. *Exp Brain Res* (2008) 186(4):677–81. doi:10.1007/s00221-008-1350-8
27. Chaudhuri SE, Karmali F, Merfeld DM. Whole body motion-detection tasks can yield much lower thresholds than direction-recognition tasks: implications for the role of vibration. *J Neurophysiol* (2013) 110(12):2764–72. doi:10.1152/jn.00091.2013
28. Leek MR. Adaptive procedures in psychophysical research. *Percept Psychophys* (2001) 63(8):1279–92. doi:10.3758/BF03194543
29. Karmali F, Chaudhuri S, Yi Y, Merfeld D. Determining thresholds using adaptive procedures and psychometric fits: evaluating efficiency using theory, simulations, and human experiments. *Exp Brain Res* (2015) 234(3):773–89. doi:10.1007/s00221-015-4501-8
30. Taylor MM, Douglas Creelman C. PEST: efficient estimates on probability functions. *J Acoust Soc Am* (1967) 41:782–7. doi:10.1121/1.1910407
31. Karmali F, Lim K, Merfeld DM. Visual and vestibular perceptual thresholds each demonstrate better precision at specific frequencies and also exhibit optimal integration. *J Neurophysiol* (2014) 111(12):2393–403. doi:10.1152/jn.00332.2013
32. Soyka F, Robuffo Giordano P, Beykirch K, Bulthoff HH. Predicting direction detection thresholds for arbitrary translational acceleration profiles in the horizontal plane. *Exp Brain Res* (2011) 209(1):95–107. doi:10.1007/s00221-010-2523-9
33. Soyka F, Giordano PR, Barnett-Cowan M, Bulthoff HH. Modeling direction discrimination thresholds for yaw rotations around an earth-vertical axis for arbitrary motion profiles. *Exp Brain Res* (2012) 220(1):89–99. doi:10.1007/s00221-012-3120-x
34. Lim K, Karmali F, Nicoucar K, Merfeld DM, editors. *Whole-Body Tilt Thresholds Outperform Static Maximum-Likelihood Sensory Integration Program No. 825.02. 2014 Neuroscience Meeting Planner*. Washington, DC: Society for Neuroscience (2014).
35. Chaudhuri SE, Merfeld DM. Signal detection theory and vestibular perception: III. Estimating unbiased fit parameters for psychometric functions. *Exp Brain Res* (2013) 225(1):133–46. doi:10.1007/s00221-012-3354-7
36. McCullagh PNJA. *Generalized Linear Models*. 2nd ed. London: Chapman & Hall/CRC (1989). 532 p.
37. Doty RL, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L. Smell identification ability: changes with age. *Science* (1984) 226(4681):1441–3. doi:10.1126/science.6505700
38. Pitts DG. The effects of aging on selected visual functions: dark adaptation, visual acuity, stereopsis, and brightness contrast. In: Sekuler RK, Kline D, Diskmukes K, editors. *Aging and the Human Visual Function*. New York: Liss (1982). p. 131–59.
39. Jerger J. Audiological findings in aging. *Adv Otorhinolaryngol* (1973) 20:115–24. doi:10.1159/000393092
40. Wolfe JK, Levi K, Bartoshuk D, Herz L, Klatzky R, Lederman R, et al. *Sensation & Perception*. Sunderland, MA: Sinauer Associates, Inc. (2014).
41. Efron B. Better bootstrap confidence intervals. *J Am Stat Assoc* (1987) 82(397):171–85. doi:10.1080/01621459.1987.10478410
42. Kass RE, Raftery AE. Bayes factors. *J Am Stat Assoc* (1995) 90(430):773–95. doi:10.1080/01621459.1995.10476572
43. Merfeld DM. Signal detection theory and vestibular thresholds: I. Basic theory and practical considerations. *Exp Brain Res* (2011) 210(3–4):389–405. doi:10.1007/s00221-011-2557-7
44. Horak F, MacPherson J. Postural orientation and equilibrium. In: Rowell L, Sheperd J, editors. *Handbook of Physiology*. New York: Oxford University Press (1996). p. 254–92.
45. MacNeilage PR, Banks MS, DeAngelis GC, Angelaki DE. Vestibular heading discrimination and sensitivity to linear acceleration in head and world coordinates. *J Neurosci* (2010) 30(27):9084–94. doi:10.1523/JNEUROSCI.1304-10.2010
46. Merchant SN, Velázquez-Villaseñor L, Tsuji K, Glynn RJ, Wall C III, Rauch SD. Temporal bone studies of the human peripheral vestibular system. Normative vestibular hair cell data. *Ann Otol Rhinol Laryngol Suppl* (2000) 181:3–13.
47. Agrawal Y, Zuniga MG, Davalos-Bichara M, Schubert MC, Walston JD, Hughes J, et al. Decline in Semicircular canal and otolith function with age. *Otol Neurotol* (2012) 33(5):832–9. doi:10.1097/MAO.0b013e3182545061
48. Ishiyama G. Imbalance and vertigo: the aging human vestibular periphery. *Semin Neurol* (2009) 29(5):491–9. doi:10.1055/s-0029-1241039
49. Liberman MC, Beil DG. Hair cell condition and auditory nerve response in normal and noise-damaged cochleas. *Acta Otolaryngol* (1979) 88:161–76. doi:10.3109/00016487909137156

50. Patuzzi RB, Yates GK, Johnstone BM. Outer hair cell receptor current and sensorineural hearing loss. *Hear Res* (1989) 42:47–72. doi:10.1016/0378-5955(89)90117-2
51. Slepecky N. Overview of mechanical damage to the inner ear: noise as a tool to probe cochlear function. *Hear Res* (1986) 22:307–21. doi:10.1016/0378-5955(86)90107-3
52. Velázquez-Villaseñor L, Merchant SN, Tsuji K, Glynn RJ, Wall C III, Rauch SD. Temporal bone studies of the human peripheral vestibular system: normative Scarpa's ganglion cell data. *Ann Oto Rhinol Laryngo Suppl* (2000) 181:14–9.
53. Goldberg JM, Fernandez C. Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey: resting discharge and response to constant angular accelerations. *J Neurophysiol* (1971) 34:635–60.
54. Fernandez C, Goldberg JM, Abend WK. Response to static tilts of peripheral neurols innervating otolith organs of the squirrel monkey. *J Neurophysiol* (1972) 35:978–97.
55. Massot C, Chacron MJ, Cullen KE. Information transmission and detection thresholds in the vestibular nuclei: single neurons vs. population encoding. *J Neurophysiol* (2011) 105(4):1798–814. doi:10.1152/jn.00910.2010
56. Henderson D, Bielefeld EC, Harris KC, Hu BH. The role of oxidative stress in noise-induced hearing loss. *Ear Hear* (2006) 27:1–19. doi:10.1097/01.aud.0000191942.36672.f3
57. Arking R. *Biology of Aging: Observations and Principles*. New York: Oxford University Press (2006).
58. de Grey ADR, Rae M. *Ending Aging: The Rejuvenation Breakthroughs that Could Reverse Human Aging in Our Lifetime*. New York: Macmillan (2007).
59. Harman D. The biologic clock: the mitochondria? *J Am Geriatr Soc* (1972) 20(4):145–7. doi:10.1111/j.1532-5415.1972.tb00787.x
60. de Grey AD. A mechanism proposed to explain the rise in oxidative stress during aging. *J Anti Aging Med* (1998) 1:53–66.
61. de Grey AD. A proposed refinement of the mitochondrial free radical theory of aging. *Bioessays* (1997) 19:161–6. doi:10.1002/bies.950190211
62. Balaban RS, Nemoto S, Finkel T. Mitochondria, oxidants, and aging. *Cell* (2005) 120(4):483–95. doi:10.1016/j.cell.2005.02.001
63. Barja G. Rate of generation of oxidative stress-related damage and animal longevity. *Free Radic Biol Med* (2002) 33(9):1167–72. doi:10.1016/S0891-5849(02)00910-3
64. Richter E. Quantitative study of human Scarpa's ganglion and vestibular sensory epithelia. *Acta Otolaryngol* (1980) 90:199–208. doi:10.3109/00016488009131716
65. Neuhauser HK, Radtke A, von Brevern M, Lezius F, Feldmann M, Lempert T. Burden of dizziness and vertigo in the community. *Arch Intern Med* (2008) 168(19):2118–24. doi:10.1001/archinte.168.19.2118
66. Hannaford PC, Simpson JA, Bisset AF, Davis A, McKerrow W, Mills R. The prevalence of ear, nose and throat problems in the community: results from a national cross-sectional postal survey in Scotland. *Fam Pract* (2005) 22(3):227–33. doi:10.1093/fampra/cmi004
67. Yardley L, Owen N, Nazareth I, Luxon L. Prevalence and presentation of dizziness in a general practice community sample of working age people. *Br J Gen Pract* (1998) 48(429):1131–5.
68. He W, Goodkind D, Kowal P. *An Aging World: 2015*. Washington DC: US Census Bureau, US Government Publishing Office (2016).
69. CDC. *Web-Based Injury Statistics Query and Reporting System (WISQARS)*. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Available from: http://www.cdc.gov/injury/wisqars/leading_causes_death.html
70. Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. *National Vital Stat Rep* (2013) 61(4):1–118.
71. National Center for Health Statistics. *National Hospital Discharge Survey (NHDS)*. National Center for Health Statistics. Available from: http://205.207.175.93/hdi/ReportFolders/ReportFolders.aspx?IF_ActivePath=P,18
72. Parkkari J, Kannus P, Palvanen M, Natri A, Vainio J, Aho H, et al. Majority of hip fractures occur as a result of a fall and impact on the greater trochanter of the femur: a prospective controlled hip fracture study with 206 consecutive patients. *Calcif Tissue Int* (1999) 65(3):183–7. doi:10.1007/s002239900679
73. Panula J, Pihlajamaki H, Mattila VM, Jaatinen P, Vahlberg T, Aarnio P, et al. Mortality and cause of death in hip fracture patients aged 65 or older: a population-based study. *BMC Musculoskelet Disord* (2011) 12:105. doi:10.1186/1471-2474-12-105
74. Heron M. Deaths: leading causes for 2010. *Natl Vital Stat Rep* (2013) 62(6):1–96.

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.

APPENDIX

A. Estimating Annual Fatalities Related to Vestibular Dysfunction

According to the CDC online web-based injury statistics query and reporting (69), 26,734 persons over 40 years of age died in the US in 2011 as a direct result of unintentional falls. This is consistent with a National Vital Statistics Report (70) that stated that 26,009 persons died in the US in 2010 as a direct result of unintentional falls. Of course, only some of the 26,734 fall-related deaths were due to vestibular dysfunction. To provide this estimate of deaths related to vestibular dysfunction, some simple calculations are required. Such calculations require that we know (a) the prevalence of vestibular dysfunction and (b) the increased risk of fall due to vestibular dysfunction, both of which were discussed earlier. Specifically, we will use (a) the 35.4% estimate of prevalence provided by Agrawal et al. (25), because it is the most comprehensive broad assessment based on objective measures, and (b) the reported odds ratio of 6.3 for those individuals over the age of 40 defined as having vestibular dysfunction using the balance metric (25), because it arises from the same comprehensive data set. We note that using these estimates yield a smaller (i.e., more conservative) estimated death rate than if we used the 27% prevalence rate for vestibular dysfunction with clinical symptomology with the 12.3 odds ratio for falls in this population.

If the total pertinent population at a point in time is x, then 35.4% ($0.354x$) have vestibular dysfunction and 64.6% ($0.646x$) do not. Let us represent the risk of falling without vestibular dysfunction as w. Then, the risk of falling with vestibular dysfunction [as defined by Agrawal et al. (25)] is 6.3 times higher ($6.3w$). While it can be argued that the risk of a bad fall for those with vestibular dysfunction is likely higher than for those with normal function, we conservatively assume that the risk of death due to a fall is independent of vestibular status (y). The total number of US deaths directly due to falls (26734) equals the sum of deaths in those with vestibular dysfunction ($0.354 \times 6.3\ w\ x\ y = 2.23z$) and those without vestibular dysfunction ($0.646\ w\ x\ y = 0.646z$), where $z = w\ x\ y$, so $26{,}734 = 2.23z + 0.646z$. This can be solved for z, which equals 9296; therefore, $26{,}734 = 2.23(9296) + 0.646(9296)$; thus, we can estimate that 20,729 (2.23×9296) equals the number of fall deaths in those individuals with vestibular dysfunction. Of course, these individuals had a chance of falling independent of their vestibular status. By definition, this risk is the same as for individuals without vestibular dysfunction, so 3,291 (0.354×9296) of these would have fallen independent of their vestibular dysfunction, leaving an estimated 17,438 deaths directly attributable to falls due to vestibular dysfunction. These calculations suggest that 65% of deaths directly attributable to falls are related to vestibular dysfunction (We note that death due to falling is relatively rare; so, risk and odds here would be nearly equivalent).

But falls also indirectly lead to death. For example, falls cause hip fractures, among other injuries, and hip fracture has a high mortality rate following fracture. There were 306,000 hospital admissions for hip fractures in 2010 (71), and it has been estimated that more than 95% are due to falls (72). One study reported that the overall 1-year post-fracture mortality rate was 27.3% and further reported that mortality after hip fracture at the end of the follow-up was 79.0% (73). If we conservatively use the 1-year mortality rate of 27.3%, this suggests that more than 79,361 patients die each year following hospitalization for a hip fracture. Repeating the exact same calculations outlined in the previous paragraph, we estimate that there may be 51,767 deaths correlated with falls (i.e., following hip fracture) that are related to vestibular dysfunction. As for the calculations in the previous paragraph, some fraction of these deaths is unrelated to the fall and hip fracture. The same study reported an average death risk ratio of 3.26 in this hip fracture population relative to an age-matched population. Analogous to the above calculations, the total number of deaths equals those related to the hip fracture and those that would have occurred anyway ($51{,}767 = 3.26v + v$), yielding the estimated number of deaths related to the hip fracture as 39,615. Simply summing these two death estimate numbers (i.e., the number of fall deaths directly and indirectly related to vestibular dysfunction) yields an estimate that vestibular dysfunction contributes to 57,053 deaths each year.

Given the conservative nature of these estimates (using only 1-year hip fracture mortality, not including traffic and other non-fall accidents, using the lower odds ratio, etc.), these estimates suggest that vestibular dysfunction likely contributes to more than 57,000 deaths each year. If categorized this way, according to a national vital statistics report (74), this would rank number 10 on the list of leading causes of death in 2010 behind heart disease (598,000), cancer (575,000), chronic respiratory diseases (138,000), stroke (129,000), accidents (121,000), Alzheimer's (83,000), and diabetes (69,000). **Table A1** in Appendix provides a range of estimates – some more conservative and some less so. The annual death estimates correlated with vestibular dysfunction range from 48,000 to 152,000.

TABLE A1 | Deaths due to vestibular dysfunction under different assumptions.

Prevalence (%)	Falling odds ratio	Deaths	Fall death due to VD (%)	Fall death due to VD	Admissions for hip fractures	Percent fractures due to falls (%)	Hip fracture mortality rate (%)	Deaths indirectly attribute to fall related to VD	Death from hip fracture, indirectly related to VD	Total estimated deaths
35.4	6.3	26,734	65.23	17,438	306,000	95	27.3	79,361	39,615	57,053
27	12.3	26,734	75.31	20,133	306,000	95	27.3	79,361	45,732	65,865
22.9	6.3	26,734	54.83	14,657	306,000	95	27.3	79,361	33,297	47,954
35.4	6.3	26,734	65.23	17,361	306,000	95	79	229,653	114,637	131,998
27	12.3	26,734	75.31	20,133	306,000	95	79	229,653	132,090	152,223
22.9	6.3	26,734	54.83	14,657	306,000	95	79	229,653	96,355	111,012

The top row shows the values described in detail in the text. The second row changes only the prevalence for vestibular function accompanied by clinical symptomology and the matching odds ratio from the American study (25). The third row uses the prevalence reported in the German study (65) with the most conservative odds ratio of 6.3 from the American study (25). The next three rows repeat the calculations from the first three rows but now using the hip fracture mortality rate of 79% at the end of follow-up (73).

frontiers in Neurology

ORIGINAL RESEARCH
published: 27 April 2017
doi: 10.3389/fneur.2017.00173

Vestibular Loss in Older Adults Is Associated with Impaired Spatial Navigation: Data from the Triangle Completion Task

Yanjun Xie[1], Robin T. Bigelow[1], Scott F. Frankenthaler[1], Stephanie A. Studenski[2], Scott D. Moffat[3] and Yuri Agrawal[1]*

[1] Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2] Longitudinal Studies Section, Translational Gerontology Branch, National Institute on Aging, National Institute of Health, Baltimore, MD, USA, [3] Department of Cognition and Brain Science, Cognitive Aging, School of Psychology, Georgia Institute of Technology, Atlanta, GA, USA

Background: Vestibular inputs have been shown to play a critical role in spatial navigation. In this study, we sought to evaluate whether vestibular loss due to aging contributes to impaired spatial navigation as measured by the triangle completion task (TCT).

Materials and methods: We recruited three types of participants: young controls <55 years of age, older controls ≥55 years of age, and older patients from a Neurotology Clinic with evidence of vestibular physiologic impairment but who did not have any known vestibular disorder. We performed the cervical vestibular-evoked myogenic potential to evaluate saccular function and video head impulse testing to quantify horizontal semicircular canal vestibulo-ocular reflex gain. To assess spatial navigation ability, we administered the TCT, in which participants were conveyed along two segments of a pre-drawn triangular path and instructed to complete the final segment independently. We measured the angle (degrees) and distance (centimeters) of deviation from the correct trajectory. We evaluated the influence of vestibular inputs on TCT performance.

Results: Forty-eight adults participated in the study (mean age: 62.0 years; 52.1% females), including 9 young controls, 15 older controls, and 24 clinic patients. Clinic patients had the greatest distance of deviation (67.7 cm), followed by older controls (45.4 cm), then young controls (27.8 cm; $p < 0.01$). Similarly, clinic patients had greater rotational angles (22.1°) compared to older (13.3°) and younger controls (12.4°; $p < 0.01$). Following multivariate linear regression adjusting for demographic variables, loss of otolith function was associated with an 18.2 cm increase in distance of deviation (95% CI: 15.2–47.4) and a 9.2° increase in rotational angle (95% CI: 3.0–15.5). Abnormal semicircular canal function was associated with a 26.0 cm increase in distance of deviation (95% CI: 0.2–51.8) and a 10.8° increase in rotational angle (95% CI: 3.0–15.5). Participants with both otolith and canal abnormalities had a larger distance error ($\beta = 25.3$, 95% CI: 6.2–44.4) and angle of deviation ($\beta = 18.1$, 95% CI: 10.1–26.2) than with either condition alone.

OPEN ACCESS

Edited by:
Daniele Nuti,
University of Siena, Italy

Reviewed by:
Carlos R. Gordon,
Tel Aviv University, Israel
Alexander A. Tarnutzer,
University of Zurich, Switzerland

****Correspondence:***
Yanjun Xie
johnny@jhmi.edu

Specialty section:
This article was submitted to Neuro-otology, a section of the journal Frontiers in Neurology

Received: *23 December 2016*
Accepted: *12 April 2017*
Published: *27 April 2017*

Citation:
Xie Y, Bigelow RT, Frankenthaler SF, Studenski SA, Moffat SD and Agrawal Y (2017) Vestibular Loss in Older Adults Is Associated with Impaired Spatial Navigation: Data from the Triangle Completion Task. Front. Neurol. 8:173. doi: 10.3389/fneur.2017.00173

Conclusion: Vestibular loss in older adults was associated with poorer performance on a dynamic spatial navigation task relative to old and young controls.

Keywords: triangle completion task, path integration, spatial navigation, visuospatial cognition, vestibular system, aging

INTRODUCTION

Spatial navigation is a fundamental cognitive motor activity that humans rely on for survival. Navigation strategies can be allocentric, i.e., reliant on external visual landmarks and environmental cues, or egocentric, i.e., using a person-centered frame of reference. Navigation also involves path integration, i.e., the reliance on self-motion cues provided by the visual system through optic flow, the proprioceptive system through feedback from muscles, tendons, and joints, and the vestibular system through the semicircular canal and otolith organs which sense angular and linear head acceleration, respectively (1, 2). Decline in sensory function has been associated with deficits in egocentric navigation (3). Specifically, individuals with vestibular loss have been shown to have difficulty with spatial navigation tasks such as walking a memorized route without visual feedback (4, 5).

Vestibular function declines with normative aging (6, 7). Older individuals with reduced vestibular function have been shown to have poorer performance on neurocognitive tests of spatial cognition, such as mental rotation tests or visual image retention tests (8). However, whether vestibular loss in aging adults is associated with impaired performance on dynamic spatial navigation tasks that provide real-time vestibular inputs has to our knowledge not been explored.

In this study, we evaluated performance on the triangle completion task (TCT) in a cohort of older adults with vestibular loss. The TCT, in which blindfolded participants are conveyed along two segments of a pre-drawn triangular path and instructed to complete the final segment independently, has been widely used as a test of path integration (9, 10). We recruited older patients presenting to a Neurotology Clinic with evidence of vestibular physiologic impairment but who did not have any known vestibular disorder such as Menière's disease or acoustic neuroma. These individuals may have been particularly affected by vestibular loss risk factors that accumulate with age, such as ototoxic exposures, infections, and genetic predispositions (11). We compared the patients to two groups of controls: a healthy older control group and a young control group. We hypothesized that relative to young and older control participants, older individuals with reduced vestibular function will have greater impairment in path integration.

MATERIALS AND METHODS

Study Participants

Study participants were aged 55 years and older and presented to the Johns Hopkins Neuro-Otology Clinic for dizziness. They had objective evidence of unilateral or bilateral vestibular impairment on vestibular physiologic testing as detailed below, and these participants had a negative clinical work-up for other vestibular pathologies including benign paroxysmal positional vertigo, Menière's disease, acute or prior episodes of vestibular neuritis, superior canal dehiscence syndrome, acoustic neuroma, or an underlying neurologic disease that could cause dizziness. Thus, the Neurotology Clinic patients were considered to have aging-related decline in vestibular function (11, 12). Participants with unilateral vestibular loss also had a negative medical work-up (i.e., confirming no prior history of vestibular neuritis, superior canal dehiscence syndrome, or unilateral Menière's disease, etc.) and were considered to have a unilateral form of aging-related vestibular loss. Among these participants, the etiology of their vestibular aging may be attributed to exogenous exposure(for example, ototoxic medication, previous infections), changes in the otoconial and macular structures of the inner ear, or intrinsic genetic susceptibilities that accumulate with age (11, 13).

Two types of control participants were recruited. Young controls were recruited from clinic staff <55 years. Older controls were ≥55 years and were recruited from the Baltimore Longitudinal Study of Aging (BLSA). The BLSA is an ongoing prospective cohort study of the normative aging process supported by the Intramural Research Program (IRP) of the National Institute on Aging (NIA). The study assesses the health, cognitive, and functional status of a cohort of over 1,300 relatively healthy community-dwelling individuals every 1–4 years. The BLSA takes place at the NIA IRP Clinical Research Unit in Baltimore, MD, USA.

Potential subjects in all settings were excluded if they could not participate in testing procedures due to blindness, poor neck range of motion or cervical spine instability, inability to walk unassisted, or memory or cognitive impairment. Individuals with conductive hearing loss were also excluded from air-conducted cervical vestibular-evoked myogenic potential (cVEMP) testing. All participants provided written informed consent. The study was approved by the Johns Hopkins Hospital Institutional Review Board, and the BLSA protocol was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences in Research Triangle Park, NC, USA.

Vestibular Testing

All participants underwent air-conducted cVEMP testing to assess saccular function (14) and video head impulse testing (vHIT) to assess horizontal semicircular canal function (15, 16). Details of both vestibular physiologic tests have been published previously. In brief, during cVEMP testing, participants sat upright and were instructed to flex their neck to provide tonic background muscle activity. Air-conducted 500 Hz (125 dB SPL) tone bursts were delivered monoaurally *via* intra-auricular speakers. Responses were recorded from an electrode montage consisting of a non-inverting electrode placed at the midpoint of the ipsilateral sternocleidomastoid muscle belly, an inverting electrode placed

at the sternoclavicular junction, and a ground electrode placed on the manubrium sterni. Responses to 100 stimuli were averaged. The first positive and negative peaks that occurred between 13 and 23 ms after stimulus onset were designated p13 and n23. The raw peak-to-peak amplitude was calculated as the sum of the p13 and n23 amplitudes (in microvolts). The corrected peak-to-peak amplitude was calculated by dividing the raw amplitude by the rectified background EMG activity recorded during a 10-ms interval before the stimulus onset. The amplitude of the better-hearing ear was recorded for those with an intact cVEMP response. Individuals with no response above 100 dB acoustic clicks were considered to have absent function in the tested ear. In addition to recording continuous cVEMP amplitude measures, participants were categorized as having present, unilaterally absent, or bilaterally absent cVEMP response.

During the vHIT, participants removed their corrective spectacles and sat 1.25 m from a visual fixation target. They wore the EyeSeeCam video-oculography system consisting of a light-weight goggle frame with a built-in camera to record eye movements and an accelerometer to record head movements (Interacoustics USA, Eden Prairie, MN, USA). Right eye position was calibrated using projected targets from a glasses-mounted laser. A trained examiner tilted the participant's head 30° below the horizon to bring the horizontal semicircular canal into the rotational plane. The examiner then applied 10–15 low amplitude (15°–20°) horizontal head impulses to each side with unpredictable direction and timing. Certified examiners evaluated vHIT tracings using custom software (MATLAB, MathWorks, Natick, MA, USA) and rejected tests with pupil tracking artifact or incorrect performance (i.e., low peak velocity or excessive head recoil or overshoot) (17). vHIT tracings were reviewed by trained examiners following well-established procedures in the senior author's (YA) laboratory (7). Discrepancies and errors were adjudicated by the senior author. Peak head velocity ranged from 150°/s to 200°/s, and eye velocity was measured in the right eye from a two-point differentiator. Vestibulo-ocular reflex (VOR) gain was defined as the ratio of the area under the eye velocity curve to the head velocity curve from HIT onset until the head velocity returned to 0 (18). An abnormal VOR gain was defined as values <0.8 or >1.0. Participants were categorized as having normal, unilaterally abnormal, or bilaterally abnormal VOR gain. One BLSA participant had missing vHIT data, and four clinic patients had missing vHIT data. Vestibular physiologic impairment is defined by aberrant response in cVEMP testing or abnormal VOR gain in vHIT testing.

Triangle Completion Task

The TCT was designed based on published procedures by Adamo et al., whose study team had previously developed this path integration task (19). Participants walked four triangular paths on a 10 ft × 10 ft flat tile floor in the testing area with their shoes on. Each triangle (92.5 cm × 185.5 cm × 212 cm) contained a 30°–60°–90° configuration. Before each trial, participants were instructed to look at the triangle they were about to walk on to become familiarized with the path. They were encouraged to complete a trial run using one triangular path with their eyes open. Then, participants were blindfolded and a noise-reducing headphone was placed on both ears to remove auditory input. As such, participants only had access to vestibular, proprioceptive and motor efference cues to perform the navigation task. The examiner stood side-by-side with the participant and supported his or her torso by placing hands lightly on the participant's shoulders. In this fashion, participants were guided through two segments of the triangle and at the end of the second segment, they were asked to rotate on their own and walk along the hypotenuse back to the origin. Participants walked counterclockwise for the first two triangles and clockwise for the remaining two. For the first and third trials, participants started with the longer triangular limb (185.5 cm), and for the remaining trials, they started with the shorter triangular limb (92.5 cm). The midpoint that bisected the distance between two anterior tips of the feet was marked as the endpoint for each trial. The distance (in centimeters) that the participant deviated from the starting point (termed "*distance of deviation*") and the absolute value of an angle (in degrees) the participant made with respect to the correct triangular limb (termed "*angle of deviation*") were recorded with tape and retractable rulers.

Data Analysis

Demographic, vestibular function, and performance on the TCT were analyzed using descriptive statistics. We performed a parametric analysis of variance (ANOVA) to compare each characteristic between young controls, older controls from the BLSA, and Neuro-Otology Clinic patients with physiologic evidence of vestibular function loss. In comparing VOR gain across participant groups, VOR gain of the "better ear" was used. Next, we used multivariate linear regression modeling pooling all participants to evaluate the association between vestibular parameters and TCT performance, after adjusting for demographic characteristics (age, sex, and race). A p-value of less than 0.05 was considered statistically significant. STATA 13 statistical software was used for all analyses (StataCorp, College Station, TX, USA).

RESULTS

Forty-eight individuals participated in the study (52.1% females), including 9 young controls (mean age: 30.8 years, SD: 6.3), 15 older controls (mean age: 69.1 years, SD: 12.2), and 24 older patients with dizziness (mean age: 69.3 years, SD: 10.1). Consecutive clinic patients fulfilling these criteria (~7% of patients presenting with dizziness) were recruited between January 2015 and March 2016 at the Johns Hopkins Hospital. Demographic, vestibular testing, and TCT performance data are presented in **Table 1**. None of the young controls had evidence of vestibular physiologic impairment. Two (13%) of 15 BLSA controls had abnormal cVEMP testing (both had bilaterally absent cVEMP responses), and 8 (57%) of BLSA controls had VOR gain abnormalities (5 unilaterally abnormal, 3 bilaterally abnormal). Among clinic patients, all patients had abnormal cVEMP testing: 50% had unilaterally absent cVEMP response and the remainder had bilaterally absent cVEMP responses. All but one clinic patient had abnormal VOR gain (13 unilaterally abnormal, 6 bilaterally abnormal). vHIT data were not available in one BLSA controls and four clinic patients due to participant refusal or

TABLE 1 | Demographic, vestibular function, and triangle completion task results.[a]

	Young controls, $N = 9$	BLSA controls, $N = 15$	Neurotology Clinic patients, $N = 24$	p Value
Age (mean, SD)	30.8 (6.3)	69.1 (12.2)	69.3 (10.1)	**<0.01**
Sex (n, %)				
Male	3 (33.3)	9 (60.0)	11 (45.8)	
Female	6 (66.7)	6 (40.0)	13 (54.2)	0.45
Race (n, %)				
White	2 (22.2)	13 (86.7)	15 (62.5)	
African-American	3 (33.3)	1 (6.7)	5 (20.8)	
Other	4 (44.4)	1 (6.7)	4 (16.7)	**0.01**
Cervical VEMP (cVEMP) function category (n, %)				
Present	9 (100)	13 (86.7)	0	
Unilaterally absent	0	0	12 (50.0)	
Bilaterally absent	0	2 (13.3)	12 (50.0)	**<0.01**
cVEMP amplitude of the better ear (μV, SD)	3.4 (0.8)	1.4 (0.6)	0.6 (0.3)	**<0.01**
VOR gain category (n, %)				
Normal	8 (88.9)	6 (40.0)	1 (4.2)	
Unilaterally abnormal	1 (11.1)	5 (33.3)	13 (54.2)	
Bilaterally abnormal	0	3 (20.0)	6 (25.0)	0.15
VOR gain of the better ear (SD)	1.0 (0.0)	1.0 (0.1)	0.9 (0.3)	0.56
Distance of deviation (cm, SD)	27.8 (13.4)	45.4 (28.2)	67.7 (38.6)	**<0.01**
Angle of deviation (°, SD)	12.4 (4.5)	13.3 (12.9)	22.1 (13.1)	**0.04**

[a]*Young controls were <55 years old. Older controls were ≥55 years old from the Baltimore Longitudinal Study of Aging (BLSA). Dizzy patients were recruited from the Neurotology Clinic. Statistically significant results are bolded. For participants with unilaterally absent cVEMP response, cVEMP parameters from the remaining ear were included. Individuals with bilaterally absent cVEMP responses were excluded from the cVEMP amplitude calculations.*

cVEMP, cervical vestibular-evoked myogenic potential; VOR, vestibulo-ocular reflex.

exclusion criteria detailed in Section "Materials and Methods." cVEMP amplitude was highest in young controls at 3.4 μV (SD: 0.8 μV) followed by 1.4 μV (SD: 0.6 μV) in older controls from the BLSA and 0.6 μV (SD: 0.3 μV) in clinic patients ($p < 0.01$ for overall ANOVA F-test). The VOR gain of the "better ear" did not significantly differ between the three groups of participants ($p = 0.56$). Similarly, average VOR gain between the left and right ears also did not significantly differ between the three groups of participants ($p = 0.08$). Audiometric data were available in 21 of 24 Neuro-Otology Clinic patients. Most clinic patients presented with mild to moderate high-frequency sensorineural hearing loss consistent with presbycusis. No participant presented with conductive hearing loss, and one presented with low-frequency sensorineural loss (subsequent work-up for Meniere's disease was negative). The pure-tone average for these participants was 27.8 dB in the left ear and 32 dB in the right ear. In clinic patients, 8 of 11 patients with unilateral cVEMP abnormalities had bilateral high-frequency sensorineural hearing loss consistent with presbycusis (for the reminder, 1 participant had bilateral normal hearing and 2 had no audiometric data). Similarly, 7 of 13 patients with unilateral VOR gain abnormalities had bilateral high-frequency sensorineural hearing loss (for the remainder, 2 had bilateral normal hearing; 1 had unilateral low-frequency sensorineural loss in the contralateral ear and a negative work-up for Meniere's disease; 3 individuals had no available audiometric data).

In the TCT, we observed a stepwise increase in the distance of deviation between young controls (27.8 cm), older controls (45.4 cm), and older, dizzy patients (67.7 cm; $p < 0.01$ for ANOVA F-test). For the rotational angle, both young (12.4°) and older controls (13.3°) deviated less than clinic patients (22.1°; $p < 0.01$ for ANOVA F-test).

We further categorized all participants into groups according to whether they had normal, unilaterally abnormal, or bilaterally abnormal cVEMP and VOR gain responses (**Figures 1** and **2**). As such, control participants with vestibular impairment were categorized with clinic patients in the abnormal vestibular response groups. For cVEMP responses, we observed that as cVEMP function worsened, the distance and angle of deviation increased. For VOR gain, we observed a similar relationship such that as VOR gain function worsened, both the distance and angle of deviation became larger. *Post hoc* pairwise comparison tests were performed to further analyze these differences, and statistically significant results are represented in **Figures 1** and **2**.

Next, we used multivariate linear regression models to evaluate the association between vestibular function (cVEMP and VOR gain) and the distance and angle of deviation across all participants (**Table 2**). To simplify these analyses, we collapsed the unilaterally and bilaterally abnormal categories into a single abnormal category for both cVEMP and VOR gain responses. We also created a category of participants who had concurrent cVEMP and VOR abnormalities. In analyses adjusted for age, sex and race/ethnicity, we observed that an abnormal cVEMP was associated with an 18.2 cm increase in deviation distance [95% confidence interval (95% CI): 15.2–47.4] and a 9.2° increase in the rotational angle (95% CI: 3.0–15.5). The cVEMP amplitude was not associated with the distance or angles of deviation, although it should be noted that participants with absent cVEMP responses ($N = 14$) were not included in this analysis. Similarly, an abnormal VOR response was associated with a 26.0 cm increase in the distance of deviation (95% CI: 0.2, 51.8) and a 10.8° increase in the angle of deviation (95% CI: 3.0, 15.5). The VOR gain value was also not associated with the distance or angle of deviation. Of note, age was a significant independent predictor of distance

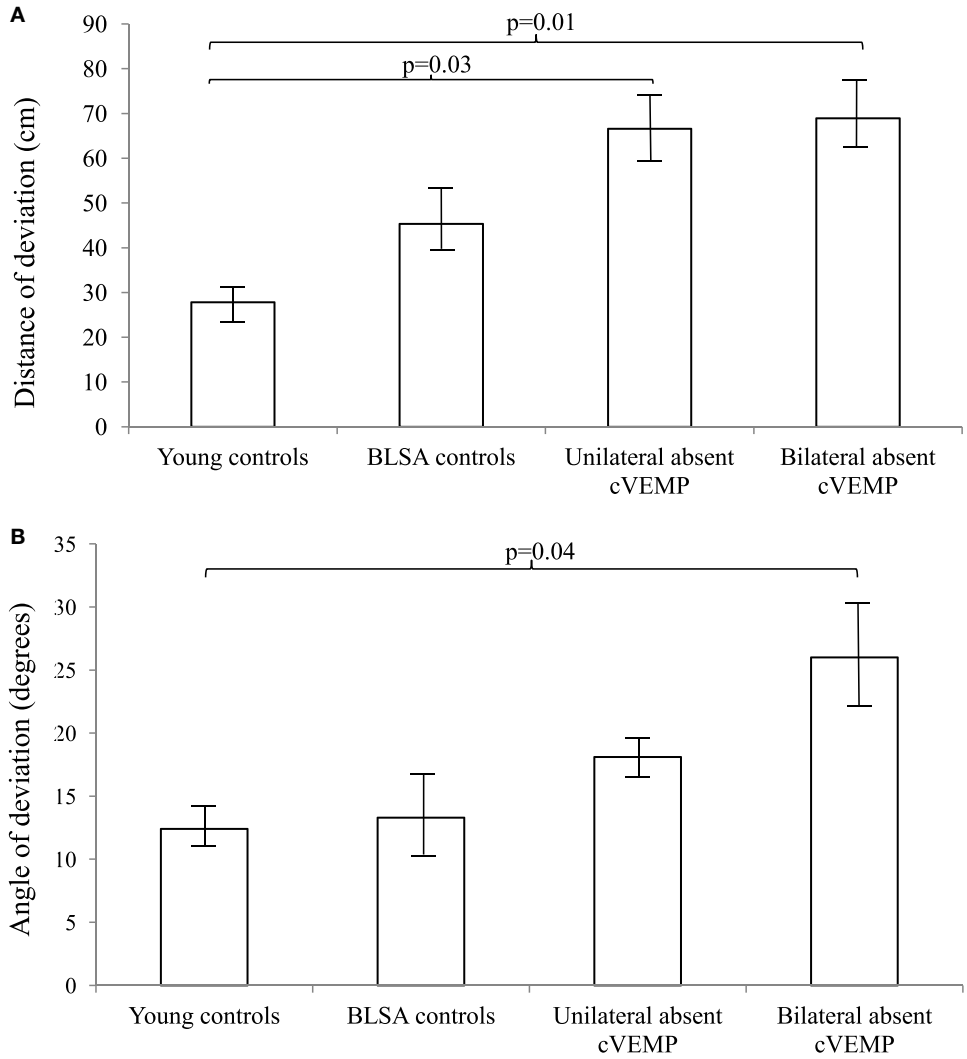


FIGURE 1 | **Distance (A) and angles (B) of deviation by cervical vestibular-evoked myogenic potential (cVEMP) response**. We included 9 young controls, 15 Baltimore Longitudinal Study of Aging (BLSA) controls, and 24 clinic patients (12 unilateral absent and 12 bilaterally absent cVEMP responses). An analysis of variance demonstrated significant differences in the distance and angles across cVEMP categories ($p < 0.01$). A pairwise *post hoc* analysis revealed differences that were indicated by the brackets. Error bars indicate the SEM.

but not angle of deviation (data not shown). Finally, participants with both cVEMP and VOR abnormalities ($N = 13$) on testing had a significantly larger distance of deviation ($\beta = 25.3$, 95% CI: 6.2–44.4) and rotational angle ($\beta = 18.1$, 95% CI: 10.1–26.2) than with either vestibular abnormality alone in adjusted analyses.

DISCUSSION

In this study, we found that older individuals with vestibular physiologic loss had impaired egocentric spatial navigation, as measured by the TCT. We evaluated three groups of participants: older clinic patients with vestibular loss, older controls from the BLSA, and young controls. We observed that both groups of older participants deviated more and made larger rotational angle errors compared to young controls. In addition, older clinic patients had greater impairment in the TCT relative to the older control cohort. Consistent with this finding, we found that absent cVEMP responses and abnormal VOR gain were significantly associated with larger distance error and greater angle of deviation. Moreover, the greatest impairment in TCT performance occurred in individuals with both abnormal cVEMP and VOR gain. Altogether, these findings support several inferences. First, the data corroborate the importance of vestibular information for path integration. Second, vestibular deficits that accrue as a result of aging contribute to navigational impairment, as evidenced by the substantial impairment present in the older clinic patients with vestibular physiologic loss. Third, other factors beyond clinical vestibular loss also appear to contribute to impaired egocentric navigation, as demonstrated by the healthy older controls with relative preservation of vestibular physiologic function but with greater navigational impairments compared to young controls. These factors may include subclinical vestibular

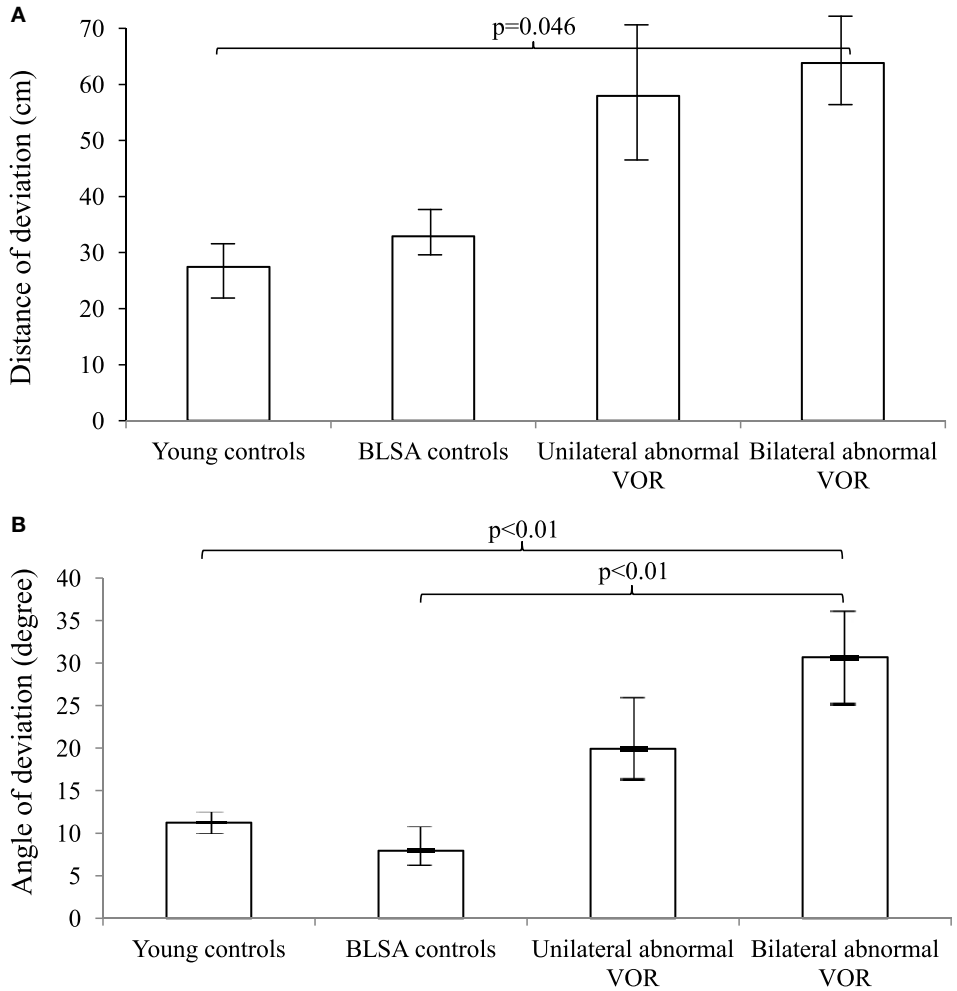


FIGURE 2 | **Distance (A) and angles (B) of deviation by vestibulo-ocular reflex (VOR) gain**. We included 9 young controls, 15 Baltimore Longitudinal Study of Aging (BLSA) controls, and 19 Neuro-Otology Clinic patients (13 unilateral abnormal and 6 bilaterally abnormal VOR gain). An analysis of variance (ANOVA) demonstrated differences in the distance and angles across VOR categories ($p = 0.03$ for the distance and $p < 0.01$ for the angle). A pairwise *post hoc* analysis revealed differences that were indicated by the brackets. Error bars indicate the SEM.

loss, proprioceptive impairment, and decline in the sensitivity to motor efference information.

Our study confirms and extends prior reports of impaired egocentric spatial navigation in labyrinthine-defective patients. A previous study by Glasauer et al. using a similar triangle completion paradigm in 5 patients with vestibular loss due to acoustic neuroma resection or bilateral vestibular ototoxicity found that the patients made significantly greater rotation angle errors though not distance errors compared to both young and age-matched controls (5). Interestingly, the investigators had previously observed that patients with bilateral labyrinthine deficiency did not make navigation errors on a task that involved walking toward a memorized target along a simple linear trajectory (20). Glasauer and colleagues proposed that vestibular information is particularly critical to navigating across more complex trajectories involving rotations and the need for angular velocity estimation. In another study, Adamo et al. investigated age-related differences in TCT performance among healthy individuals and reported that older compared to younger individuals showed greater errors in angle rotation estimations (19). Our study extends these two prior reports in finding that both vestibular loss and age are independent contributors to spatial navigation ability.

The hippocampus and entorhinal cortex are thought to be sites where a cognitive map of space is maintained by special populations of place cells and grid cells, respectively (21). Studies suggest that the vestibular system provides critical inputs to the generation of the cognitive map. In animal models, peripheral vestibular stimulation has been shown to result in increased firing of hippocampal cholinergic neurons (22). Selective lesion of the peripheral vestibular system in rats has also been shown to lead to a loss of specificity of hippocampal place cell firing (23). Moreover, so-called "head direction cells" present in the subiculum, thalamus, and other regions fire when an animal faces a particular direction, and are known to be dependent on vestibular input (24). Most importantly for the present purposes is the observation that the head direction system codes for heading accuracy (and error)

TABLE 2 | Multivariate linear regression models of the association between vestibular function and triangle completion task performance in all participants.[a]

	Distance of deviation (cm)		Angle of deviation (°)	
	Unadjusted β (95% CI)	Adjusted β (95% CI)	Unadjusted β (95% CI)	Adjusted β (95% CI)
cVEMP response				
Abnormal cVEMP response	**31.3 (15.2, 47.4)**	**18.2 (1.2, 35.1)**	**11.7 (6.1, 17.3)**	**9.2 (3.0, 15.5)**
cVEMP amplitude of the better ear (μV)	−5.4 (−13.9, 3.1)	−9.6 (−20.4, 1.2)	−0.5 (−3.1, 2.1)	−2.1 (−5.3, 1.1)
VOR gain				
Abnormal VOR gain	27.4 (−0.5, 55.1)	**26.0 (0.2, 51.8)**	**11.2 (1.2, 21.2)**	**10.8 (0.9, 20.7)**
VOR gain of the better-hearing ear	−14.7 (−69.6, 40.1)	−38.3 (−92.6, 16.0)	−11.0 (−36.8, 14.8)	−15.4 (−42.8, 12.1)
cVEMP and VOR function				
Concurrent cVEMP and VOR abnormality	**33.5 (17.4, 49.7)**	**25.3 (6.2, 44.4)**	**16.3 (9.4, 23.1)**	**18.1 (10.1, 26.2)**

[a]Models were adjusted for demographic covariates (age, sex, race/ethnicity). An abnormal cVEMP response includes unilaterally or bilaterally absent cVEMP. Likewise, an abnormal VOR gain includes unilaterally or bilaterally abnormal VOR gain value (<0.8 or >1). Statistically significant regression models are bolded.

cVEMP, cervical vestibular-evoked myogenic potential; VOR, vestibulo-ocular reflex; 95% CI, 95% confidence interval.

in a non-visual path integration task (25). In humans, a study of 10 patients who underwent bilateral vestibular deafferentation found that the patients exhibited impaired spatial navigation skills and reduced hippocampal volumes relative to age-matched controls (26). In the current study, we sought to further evaluate whether age-related vestibular loss influences performance of a dynamic spatial navigation task. This task may be a better proxy for real-world navigational tasks, such as driving, wayfinding, and route-learning which are known to deteriorate with age (27). Our data suggest that vestibular loss associated with aging may contribute to these navigational impairments in older adults. Combined with the results from studies in non-human species, the loss or reduction in vestibular input could affect both the place and head direction systems and impair path integration and navigation performance in older adults.

In a recent work on a cohort of healthy older adults, we observed that poorer vestibular function was associated with reduced spatial cognitive skills (8, 27, 28). These studies involved pencil and paper-based neurocognitive tests of spatial cognitive skills, such as mental rotation and visual image retention. These tests were administered with the subject seated and did not involve real-time vestibular stimulation. We observed that both semicircular canal and otolith deficits are associated with spatial navigation impairment and that individuals with both semicircular canal and otolith deficits had the poorest performance on the TCT. These findings suggest that both vestibular end-organs contribute independently to spatial navigation ability. The semicircular canals detect angular rotations of the head, and not surprisingly, semicircular canal function was significantly associated with the angle and distance of deviation. The otolith organs sense linear head translations and the orientation of the head with respect to gravity. In prior work in healthy older adults, we observed that otolith (specifically saccular) function was significantly associated with spatial memory and mental orientation performance (8). While the canals may be important for sensing and computing angular movements, the otoliths may provide a constant input to the brain about head orientation which is used to generate a cognitive map of the external environment.

We note that several participants in the BLSA control group had cVEMP and/or VOR gain abnormalities. These older subjects from the Baltimore Longitudinal Study of Aging are healthy individuals with no complaints of vertigo or imbalance. It is interesting that 2 (13.3%) BLSA controls had abnormal cVEMP, while 8 (53.3%) individuals had VOR gain abnormality. In a previous study, we observed that more than 50% of BLSA participants >60 who underwent vHIT had compensatory saccades, which were indicative of poor VOR function (29). Moreover, we observed in the same study that the prevalence of compensatory saccades was linked to VOR gain. In the present study involving more than 50% of BLSA controls with abnormal VOR gain, these findings may represent a subclinical decline of vestibular function in older adults. Future studies are needed to understand the significance of abnormal vestibular findings in older adults with no subjective vertigo or balance complaints.

We note the following limitations of our study. The study was cross-sectional; therefore, causal inferences about the relationship between vestibular function and TCT performance cannot be made. Additionally, our older clinic patients with vestibular physiologic loss were assumed to have this loss attributable to age, given that they did not have any other specific vestibular disorders. However, given that age-related vestibular loss is a diagnosis of exclusion, this cannot be definitively confirmed. We have currently added the TCT to the BLSA test battery and will be able to test a substantially larger sample of older adults with greater variation in vestibular function from which we will be able to more clearly evaluate the relationship between age-related vestibular loss and spatial navigation. Secondly, horizontal VOR gain and cVEMP response were used to assess horizontal semicircular canal and saccular function, respectively. Functions of the remaining anterior and posterior semicircular canals (evaluated by vertical vHIT) and utricle (evaluated by ocular VEMP testing) would be informative. These tests were not performed given the time and participant burden constraints with healthy subjects in the Baltimore Longitudinal Study of Aging (30).

Furthermore, we observed several cases of VOR gain >1.0 in both BLSA controls and clinic patients. In our previous study of BLSA participants, we also observed similar rates of super-unity gains among the BLSA participants and found that super-unity gains were significantly associated with the presence of "back-up" compensatory saccades (i.e., in the anti-compensatory direction).

These data suggest that the super-unity gains may not simply be artifactual from goggle slippage. Nevertheless, we recognize several mechanisms by which super-unity VOR gains may be observed, including cerebellar disinhibition, use of magnifying spectacles for the correction of presbyopia, as well as artifact from goggle slippage (29). In our testing, we tried to apply the goggles as tightly as we thought possible around the participants' head while maintaining their comfort. Nevertheless, slippage may have occurred. Finally, spatial navigation relies on multiple sensory inputs as well as judgment of motor output. We attempted to independently assess vestibular input to navigation by eliminating visual and hearing cues during the TCT. In the present study, we did not include patients with inability to walk unassisted. A recent study showed that beyond the common influence of age, sensorimotor declines appeared to occur independently (31). As such, we expected that including age in the regression models should account for much of the other potential deficits that may occur in participants. However, we acknowledged that we could not exclude proprioceptive or motor efference input during the TCT, and thus cannot definitively rule out their contribution to performance of the TCT. We selected the TCT protocol described because it is easily administered in the clinical setting and a reasonable first step for testing our hypothesis about the influence of age-related vestibular loss on spatial navigation. Further work is in progress in our group using other tests, including chair rotation tests, which evaluate spatial cognition in a condition involving active vestibular stimulation but while also eliminating proprioceptive and motor efference inputs.

In summary, we observed that vestibular loss associated with age contributed to impaired spatial navigation, as measured by angle and distance of deviation on the TCT. Both semicircular canal and otolith function were significantly associated with TCT performance, and abnormality in both semicircular canal and otolith function was associated with poorest performance. Vestibular loss in aging adults may contribute to the difficulties older adults experience with real-life navigation tasks, including driving, wayfinding, and route-learning, which substantially limit their autonomy and quality of life (32, 33).

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Johns Hopkins Hospital Institutional Review Board and the Institutional Review Board of the National Institute of Environmental Health Sciences in Research Triangle Park with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Johns Hopkins Hospital Institutional Review Board and the Institutional Review Board of the National Institute of Environmental Health Sciences.

AUTHOR CONTRIBUTIONS

YX: substantial contribution to the conception and design of the work; acquisition, analysis, and interpretation of the data; drafting the manuscript and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for the work. RB and YA: substantial contribution to the conception and design of the work; acquisition, analysis, and interpretation of the data; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for the work. SF: acquisition, analysis, and interpretation of the data; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for the work. SS and SM: substantial contribution to the conception and design of the work; analysis and interpretation of the data; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for the work.

ACKNOWLEDGMENTS

YA received funding support from the National Institute of Health, grant # National Institute on Deafness and Other Communication Disorders (NIDCD) K23-DC013056.

REFERENCES

1. Marquardt G. Wayfinding for people with dementia: a review of the role of architectural design. *HERD* (2011) 4(2):75–90.
2. Allen GL, Kirasic KC, Rashotte MA, Haun DBM. Aging and path integration skill: kinesthetic and vestibular contributions to wayfinding. *Percept Psychophys* (2004) 66(1):170–9. doi:10.3758/BF03194870
3. Cooney R, Arbuckle T. Age, context, and spatial memory: a neuropsychological approach. *Aging Neuropsychol Cogn* (1997) 4(4):249–65. doi:10.1080/13825589708256650
4. Borel L, Harlay F, Lopez C, Magnan J, Chays A, Lacour M. Walking performance of vestibular-defective patients before and after unilateral vestibular neurotomy. *Behav Brain Res* (2004) 150(1–2):191–200. doi:10.1016/S0166-4328(03)00257-2
5. Glasauer S, Amorim M-A, Viaud-Delmon I, Berthoz A. Differential effects of labyrinthine dysfunction on distance and direction during blindfolded walking of a triangular path. *Exp Brain Res* (2002) 145(4):489–97. doi:10.1007/s00221-002-1146-1
6. 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
7. Li C, Layman AJ, Carey JP, Agrawal Y. Epidemiology of vestibular evoked myogenic potentials: data from the Baltimore Longitudinal Study of Aging. *Clin Neurophysiol* (2015) 126(11):2207–15. doi:10.1016/j.clinph.2015.01.008
8. Bigelow RT, Semenov YR, Trevino C, Ferrucci L, Resnick SM, Simonsick EM, et al. Association between visuospatial ability and vestibular function in the Baltimore Longitudinal Study of Aging. *J Am Geriatr Soc* (2015) 63(9):1837–44. doi:10.1111/jgs.13609
9. Loomis JM, Klatzky RL, Golledge RG, Cicinelli JG, Pellegrino JW, Fry PA. Nonvisual navigation by blind and sighted: assessment of path integration ability. *J Exp Psychol Gen* (1993) 122(1):73–91. doi:10.1037/0096-3445.122.1.73
10. Marlinsky VV. Vestibular and vestibulo-proprioceptive perception of motion in the horizontal plane in blindfolded man – III. Route inference. *Neuroscience* (1999) 90(2):403–11. doi:10.1016/S0306-4522(98)00448-5
11. Ciorba A, Hatzopoulos S, Bianchini C, Aimoni C, Skarzynski H, Skarzynski P. Genetics of presbycusis and presbystasis. *Int J Immunopathol Pharmacol* (2015) 28(1):29–35. doi:10.1177/0394632015570819
12. Zalewski CK. Aging of the human vestibular system. *Semin Hear* (2015) 36(3):175–96. doi:10.1055/s-0035-1555120

13. Walther LE, Westhofen M. Presbyvertigo-aging of otoconia and vestibular sensory cells. *J Vestib Res* (2007) 17(2–3):89–92.
14. Colebatch JG, Halmagyi GM, Skuse NF. Myogenic potentials generated by a click-evoked vestibulocollic reflex. *J Neurol Neurosurg Psychiatry* (1994) 57(2):190–7. doi:10.1136/jnnp.57.2.190
15. Bartl K, Lehnen N, Kohlbecher S, Schneider E. Head impulse testing using video-oculography. *Ann N Y Acad Sci* (2009) 1164:331–3. doi:10.1111/j.1749-6632.2009.03850.x
16. MacDougall HG, Weber KP, McGarvie LA, Halmagyi GM, Curthoys IS. The video head impulse test: diagnostic accuracy in peripheral vestibulopathy. *Neurology* (2009) 73(14):1134–41. doi:10.1212/WNL.0b013e3181bacf85
17. Mantokoudis G, Saber Tehrani AS, Kattah JC, Eibenberger K, Guede CI, Zee DS, et al. Quantifying the vestibulo-ocular reflex with video-oculography: nature and frequency of artifacts. *Audiol Neurootol* (2015) 20(1):39–50. doi:10.1159/000362780
18. Macdougall HG, McGarvie LA, Halmagyi GM, Curthoys IS, Weber KP. The video Head Impulse Test (vHIT) detects vertical semicircular canal dysfunction. *PLoS One* (2013) 8(4):e61488. doi:10.1371/journal.pone.0061488
19. Adamo DE, Briceño EM, Sindone JA, Alexander NB, Moffat SD. Age differences in virtual environment and real world path integration. *Front Aging Neurosci* (2012) 4:26. doi:10.3389/fnagi.2012.00026
20. Glasauer S, Amorim MA, Vitte E, Berthoz A. Goal-directed linear locomotion in normal and labyrinthine-defective subjects. *Exp Brain Res* (1994) 98(2):323–35. doi:10.1007/BF00228420
21. O'Keefe J, Nadel L. *Hippocampus as a Cognitive Map* (Vol. 1). London: Oxford University Press (1987).
22. 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(2):605–11.
23. Stackman RW, Clark AS, Taube JS. Hippocampal spatial representations require vestibular input. *Hippocampus* (2002) 12(3):291–303. doi:10.1002/hipo.1112
24. Yoder RM, Taube JS. The vestibular contribution to the head direction signal and navigation. *Front Integr Neurosci* (2014) 8:32. doi:10.3389/fnint.2014.00032
25. Valerio S, Taube JS. Path integration: how the head direction signal maintains and corrects spatial orientation. *Nat Neurosci* (2012) 15(10):1445–53. doi:10.1038/nn.3215
26. 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(Pt 11):2732–41. doi:10.1093/brain/awh617
27. Bigelow RT, Semenov YR, du Lac S, Hoffman HJ, Agrawal Y. Vestibular vertigo and comorbid cognitive and psychiatric impairment: the 2008 National Health Interview Survey. *J Neurol Neurosurg Psychiatry* (2016) 87(4):367–72. doi:10.1136/jnnp-2015-310319
28. Semenov YR, Bigelow RT, Xue Q-L, du Lac S, Agrawal Y. Association between vestibular and cognitive function in U.S. adults: data from the National Health and Nutrition Examination Survey. *J Gerontol A Biol Sci Med Sci* (2016) 71(2):243–50. doi:10.1093/gerona/glv069
29. Anson ER, Bigelow RT, Carey JP, Xue QL, Studenski S, Schubert MC, et al. VOR gain is related to compensatory saccades in healthy older adults. *Front Aging Neurosci* (2016) 8:150. doi:10.3389/fnagi.2016.00150
30. Alhabib SF, Saliba I. Video head impulse test: a review of the literature. *Eur Arch Otorhinolaryngol* (2017) 274(3):1215–22. doi:10.1007/s00405-016-4157-4
31. Gadkaree SK, Sun DQ, Li C, Lin FR, Ferrucci L, Simonsick EM, et al. Does sensory function decline independently or concomitantly with age? Data from the Baltimore Longitudinal Study of Aging. *J Aging Res* (2016) 2016:1–8. doi:10.1155/2016/1865038
32. Techentin C, Voyer D, Voyer SD. Spatial abilities and aging: a meta-analysis. *Exp Aging Res* (2014) 40(4):395–425. doi:10.1080/0361073X.2014.926773
33. Gazova I, Vlcek K, Laczó J, Nedelska Z, Hyncicova E, Mokrisova I, et al. Spatial navigation – a unique window into physiological and pathological aging. *Front Aging Neurosci* (2012) 4:16. doi:10.3389/fnagi.2012.00016

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.

frontiers in Neurology

MINI REVIEW
published: 19 December 2016
doi: 10.3389/fneur.2016.00231

Age-Related Vestibular Loss: Current Understanding and Future Research Directions

*Dominic Allen, Luis Ribeiro, Qadeer Arshad and Barry M. Seemungal**

Division of Brain Sciences, Imperial College London, London, UK

The vestibular system sub-serves a number of reflex and perceptual functions, comprising the peripheral apparatus, the vestibular nerve, the brainstem and cerebellar processing circuits, the thalamic relays, and the vestibular cerebral cortical network. This system provides signals of self-motion, important for gaze and postural control, and signals of traveled distance, for spatial orientation, especially in the dark. Current evidence suggests that certain aspects of this multi-faceted system may deteriorate with age and sometimes with severe consequences, such as falls. Often the deterioration in vestibular functioning relates to how the signal is processed by brain circuits rather than an impairment in the sensory transduction process. We review current data concerning age-related changes in the vestibular system, and how this may be important for clinicians dealing with balance disorders.

Keywords: vestibular system, aging, vestibular perception, vestibular apparatus, vestibular reflexes

OPEN ACCESS

Edited by:
Yuri Agrawal,
Johns Hopkins University, USA

Reviewed by:
Michael Schubert,
Johns Hopkins University, USA
Olympia Kremmyda,
University Hospital of Munich, Germany

****Correspondence:***
Barry M. Seemungal
b.seemungal@imperial.ac.uk

Specialty section:
This article was submitted to Neuro-otology, a section of the journal Frontiers in Neurology

Received: *03 December 2015*
Accepted: *02 December 2016*
Published: *19 December 2016*

Citation:
Allen D, Ribeiro L, Arshad Q and Seemungal BM (2016) Age-Related Vestibular Loss: Current Understanding and Future Research Directions. Front. Neurol. 7:231. doi: 10.3389/fneur.2016.00231

INTRODUCTION

Age-related vestibular dysfunction and associated imbalance has a major impact on morbidity, mortality, and health-care resources. According to the National Institute of Deafness and Other Communication Disorders of the NIH, falls account for over 50% of all accidental deaths in the elderly (1), and a recent analysis calculated the medical costs associated with fatal and non-fatal falls in the USA to be over $19 billion annually (2).

The overall prevalence of vestibular dysfunction in adults aged over 40 in the USA is 35.4%, corresponding to 69 million individuals (3). Patients with vestibular dysfunction are at significantly greater risk of falls (odds ratio 12.3 for patients with concurrent dizziness). Although this is also associated with an increased risk of patient-reported dizziness, as many as 32% of individuals aged over 40 without any symptoms of dizziness have evidence of vestibular dysfunction. These patients, though asymptomatic, also have an increased risk of falls (odds ratio 6.3) (3). A case–control study in the UK, in a sample of 56 adults, found that the prevalence of vestibular impairment in older adults who fall was 80%, compared with 19% in age-matched non-fallers (4). Other prospective studies in general practice and neurology clinics have reported that in patients aged over 50 with dizziness, the prevalence of vestibular causes ranges from 18 to 56% (5, 6). Risk factors for decline in vestibular function include smoking, hypertension, and diabetes but even when these are controlled for the effect of age is far more pronounced (3).

Progressive disequilibrium of aging is a complex, multifactorial condition leading to instability and increased risk of falls (7, 8), with vestibular dysfunction, albeit in combination with other factors (e.g., musculoskeletal and visual impairment), being a key contributor to imbalance (9, 10). One factor in balance dysfunction may be changes in the robustness of peripheral vestibular signaling in

the elderly (11). Another factor may be changes in how sensory information is processed by central circuits, as exemplified by a study which found that compared with younger subjects, the elderly favor the use of proprioceptive rather than visual and vestibular cues for postural motor control (12). Overall, there is an age-related decline of peripheral vestibular sensing and the central combination of different sensory signals for balance. Herewith, we review the literature regarding these two aspects.

THE PERIPHERAL VESTIBULAR SYSTEM

Neuronal and hair cell loss are the two biggest effects that aging has on the peripheral vestibular system; affecting both the otolith organs and the semicircular canals. Multiple studies have shown that aging reduces the number of sensory hair cells in the vestibular end organs (13–16). More recently, one group has studied human temporal bone sections from 67 subjects aged from birth to 100 years of age and found that there was a significant age-related decline in the number of hair cells and a decline in individual hair cell subtypes (1, 17).

Several studies have shown degeneration of the vestibular ganglion (Scarpa's ganglion) and nerve (15, 18–20). The vestibular nerve has two divisions, receiving conveying afferents from both the semicircular canals and the otolith organs *via* the superior and inferior vestibular nerves, respectively (15, 21). Ganglion cell counts from 106 temporal bones from 75 individuals showed age-related reduction in ganglion cell counts with a greater decline in the superior division compared with the inferior division.

Otolith Organs

The signal from the otolith organs (comprising the utricle and saccule) transduces linear acceleration (and detect tilt), and with respect to these organs, with age, they are not only affected by degeneration of the ganglion cells but also by hair cell loss, in addition to specific degenerative effects within the otolith organ ultrastructure. The use of vestibular evoked myogenic potentials (VEMPs) has been used in multiple studies to assess the effect of aging upon otolith function. VEMPs are short-latency myogenic potentials that are elicited from specific muscles, in response to vestibular stimulation (*via* sound). The muscle measured is the sternocleidomastoid ("cervical" VEMP—cVEMP), hence assessing saccular and inferior vestibular nerve function as well as the inferior oblique muscle of the eye ("ocular" VEMP—oVEMP), which measures utricular and superior vestibular nerve function (22–24). Reduction in the amplitude of VEMPs is indicative of reduced otolith organ function, while increased VEMP latency may relate to slowed brainstem signal processing (25, 26).

Brantberg et al. found an age-related decrease in cVEMP amplitude and increase in cVEMP latency in a study of 1,000 patients ranging from 7 to 91 years old with no known vestibular disorders (25). These findings have been corroborated by Agrawal et al. who found reduced cVEMP as well as oVEMP amplitude in a group of 50 patients above 70 years of age compared to younger individuals (27). Other studies measuring oVEMP have reported similar findings including an age-related increase in oVEMP latencies (28, 29). Further, a more recent study by Li et al. in 257 subjects demonstrated that with aging, there was a reduction in oVEMP amplitude by 2.9 μV per decade of life and an increase in latency of 0.12 ms per decade of life. With respect to cVEMP, they found that the amplitude decreased by 0.14 μV per decade but found no significant difference in latency between the age groups (30).

The otoconia contained in the utricle and saccule have also been shown to undergo morphological changes and degeneration during a human's lifespan as observed in postmortem analyses (31). Aging has been associated with reduction in otoconia mass as well as fracture and fragment formation in both animals and humans (31–35). While it is easy to assume that reduction in otoconia would result in the reduction of organ function, otoconia degeneration has been shown to affect the utricle more than the saccule (31, 36), which would not explain the findings in the Agrawal et al. study (27). In contrast, it has been previously reported that, while hair loss occurs in all the peripheral vestibular organs with increasing age, the utricle is relatively spared (17). Currently, the implications of otoconia degeneration of otolith organ function are unknown, but it is suspected that these changes in otoconia are involved in the development of peripheral vestibular disorders, such as benign paroxysmal positional vertigo (BPPV) (37).

Benign paroxysmal positional vertigo is one of the most common causes of vertigo, especially in the elderly as there is an increase in the incidence with age, peaking at 60 (38–40). It is a disorder characterized by vertigo upon certain positional head movements. BPPV is caused by the presence of otoconia debris, which moves in the endolymph or cupula of the semicircular canals (41, 42). It is thought that the otoconia are dislodged from the utricular macula, which is precipitated by the morphological changes that can happen to the otoconia during aging (37). While BPPV can be effectively treated with repositioning maneuvers (43), a large observational study of 1,092 BPPV sufferers has recently shown that comorbidities, such as hypertension, osteoporosis, and diabetes, may be correlated with the risk of recurrence of BPPV in the elderly (44).

Semicircular Canals

The semicircular canals transduce head angular acceleration *via* the anterior, posterior, and horizontal semicircular canals. Decline in the semicircular canals forms a significant component of the overall age-related decline in the vestibular system. A study of 67 human temporal bones from birth to age 100 found that Type I hair cells in the cristae are lost at a significantly greater rate than in the macula (1), further reflected by a cross-sectional study, which found the decline in semicircular canal function to be greater than the decline in otolith function (27). This age-related decline stands in contrast to what happens in peripheral vestibular dysfunction, such as Meniere's disease, in which there is selective loss of Type II hair cells (45). Decline in the semicircular canals can be evaluated through the angular vestibule–ocular reflex (VOR), for example, using caloric testing; although this technique only tests the horizontal semicircular canals. Up to a few years ago, the only way to assess the VOR was with rotating chairs or by caloric ear stimulation. Recently, advances in understanding of vestibulo–ocular physiology, largely by Curthoys and Halmagyi in Sydney, have led to the development of, first, a bed-side clinical

head thrust or impulse test (HIT) and, subsequently, video-image-based versions of the test that are now available commercially for clinical use (vHIT or videoHIT), which allow not only for the assessment of the horizontal but also the anterior and posterior semicircular canals (46).

Numerous studies have investigated age-related decline in the semicircular canal function. Baloh et al. followed 7 patients with severe bilateral vestibulopathy and 51 normal controls over a 5-year period; in the normal subjects, there was a significant decrease in gain and time constant and increase in phase lead of the VOR over this period. Notably, this decline was not associated with any symptoms or signs of disequilibrium (47). By contrast, the patients, whose VOR responses were depressed at the start of testing, did not show any significant decline (48). Carol et al. analyzed 109 subjects using data from the Baltimore Longitudinal Study of Aging and found that VOR gain remained stable from ages 26 to 79, after which it significantly declined at a rate of 0.012/year; the prevalence of VOR gain less than 0.8 was 13% in individuals aged ≥80 compared with 2.8% in those aged under 80 (48).

Agrawal et al. carried out head thrust dynamic visual acuity testing on 50 individuals aged ≥70, finding a significant decline in dynamic visual acuity during tests of all three semicircular canals. Decline in each semicircular canal was strongly correlated with decline in the other two; interestingly, decline in the horizontal and superior semicircular canals was well correlated with decline in utricular but not in saccular function. Decline in posterior semicircular canal function, however, showed no clear trend compared with function of the otolith organs. It was also found that the prevalence of vestibular dysfunction was significantly higher for the semicircular canals (82–94%) compared with the saccule (54–62%) and the utricle (18–24%) (27).

From reviewing the above studies, it can be observed that decline in the function of the semicircular canals plays a significant component of age-related decline in the vestibular system, with a significantly higher prevalence and severity than otolith associated age-related decline. Given the function of the semicircular canals is to measure angular acceleration, it could be postulated that decline in these structures may be more associated with patient-reported dizziness—the presence of which represents a significant increase in the risk of falls in patients with vestibular dysfunction (3).

THE CENTRAL VESTIBULAR SYSTEM

The Brainstem and Cerebellum

The main component of the brainstem vestibular system is the vestibular nuclear complex straddling the pontomedullary junction. This complex of nuclei receives primary vestibular afferents conveyed by the vestibular nerve and also connects to various structures, including the cerebellum (49). The main vestibular nuclei comprise the descending or inferior (DVN), lateral (LVN), superior (SVN), and medial (MVN) vestibular nuclei (49). Lopez et al., in a study of 15 vestibular nuclei from people aged 40–93, found a neuronal loss of 3% per decade in the vestibular nuclear complex (50, 51). They also found that neuronal loss was higher in the SVN and least in the MVN. This is in contrast to a more recent study of eight brainstems, which showed neuronal loss in the DVN, MVN, and LVN, but sparing of the SVN. This study also found that aging had no effect on the volume or length of the vestibular nuclei (49). However, both studies have found an increase in giant neurons in the elderly, related to lipofuscin deposits within the cells (49, 50). Similar studies have been done in animals, with one study showing an age-related decline in the number of neurons of the mouse vestibular nuclei (52). Conversely, a study in male golden hamsters found conflicting results (53).

The cerebellum plays a critical role in the function of the vestibular system and is known to receive efferent inputs from the vestibular nuclei (54, 55). In aging, cerebellar volume and Purkinje cell density in the cerebellar vermis and white matter in the floccular nodular lobe have been shown to decrease (56–58). There is also a vast network in the cerebral cortex that activates with vestibular stimulation (59–61). Cyran et al. have recently used functional magnetic resonance imaging on 45 subjects aged 20–70 to determine age-related effects on functional connectivity of this vestibular cortical network (62). Using galvanic vestibular stimulation (GVS), which bypasses the peripheral vestibular system and directly stimulates the vestibular nerve, they found a reduction in connectivity with increasing age while controlling for vascular, atrophic, or structural connectivity changes. Jahn et al. have also used GVS to study age-related vestibular function changes in 57 subjects aged 20–69 (63). Specifically, by measuring torsional nystagmus in response to GVS, they found a U-shaped distribution of central vestibular function by age. They speculate that due to a reduction in neuronal hair cells and other peripheral vestibular changes, central processing becomes hypersensitive in order to compensate for such a loss. After the sixth decade, central compensation will breakdown as well and thus lead to impaired vestibular function in the elderly.

The cerebellum is also involved in vestibular adaptation. Previous work has focused on the cerebellar role in VOR adaptation (64). However, recent work has demonstrated an additional but critical role for the cerebellum, which mediates the partitioning of vestibular signals involved in eye movement control versus those that ascend to perceptual regions mediating sensations of self-motion (i.e., vertigo) and spatial orientation (65). Curiously, relatively little work has been focused on the effect of aging upon cerebellar function (66). However, it is likely that aging in the cerebellum will impact directly upon vestibular reflex and perceptual functioning and adaptation to lesions or with training.

THE VESTIBULAR THALAMIC PROJECTIONS AND THE VESTIBULAR CORTICAL SYSTEM

Spatial orientation is a critically important function in everyday life. Up to third of newly diagnosed dementia patients complain of spatial disorientation (67), causing significant disruption of everyday life. A core brain area implicated in spatial orientation and memory is the hippocampus (67). Indeed, previous neuroimaging study has shown hippocampal atrophy with bilateral

vestibular failure (68). Animal neuronal recordings also show cells sensitive to spatial orientation status that are disrupted by vestibular loss. A key concept is the notion of converting vestibular motion signals to spatial signals. Given the above evidence, it has been argued that the hippocampus is important for this. However, some authors have found normal path integration function with hippocampal lesions in humans but not rats (69). This conundrum has recently been solved by a recent human lesion study, which shows in fact that the important region is the temporoparietal junction (70). In addition, this study also found no impact of hippocampal lesions upon angular path integration function. It follows that dementia, which is more frequent in the elderly, may affect spatial orientation by its effect on vestibular cortical regions such as the TPJ (70).

Another currently unsolved question is the cortical location mediating the sensation of vertigo. Current wisdom suggests that the posterior insular cortex is the primary vestibular cortex. However, focal stroke, including in the posterior insular, did not affect vestibular sensation of self-motion (kaski). Previous work (65, 71) suggests, however, that the vestibular sensation of self-motion may be distributed and hence not localizable. Whether such vestibular cortical networks are disrupted by aging will require further work.

CONCLUSION

As with most systems in the body, aging causes a degenerative effect within the vestibular system. Aging in the vestibular system is a multifactorial process, affecting both the peripheral organ and central circuits, from the peripheral end-organ to the brainstem to the cerebellum to the cerebral cortex. It follows that diseases that affect any one of these brain areas will disrupt one or more facets of vestibular functioning. Recent studies using VEMP and VOR testing have shown that there is a quantifiable decline in function in specific peripheral vestibular organs with age, which theoretically correlates with the histological and microscopic changes previously seen. There is also similar ongoing research using GVS to identify functional loss with age of central vestibular pathways. While the cause of dizziness in the elderly is a multisystem processes, the data suggest that aging causes a reduction in peripheral vestibular function and also the cortical efficiency with which these signals are used for balance, which together play a significant role in the increasing the risk of falls in the elderly.

AUTHOR CONTRIBUTIONS

LR and DA: initial drafting of manuscript. QA: initial drafting and final revision of manuscript. BS: general organization of manuscript. Interim and final revision of manuscript.

FUNDING

This work was supported by a Health Foundation and Academy of Medical Sciences Clinician Scientist Fellowship and the Medical Research Council (BS).

REFERENCES

1. Rauch SD, Velazquez-Villasenor L, Dimitri PS, Merchant SN. Decreasing hair cell counts in aging humans. *Ann N Y Acad Sci* (2001) 942:220–7. doi:10.1111/j.1749-6632.2001.tb03748.x
2. Stevens JA, Corso PS, Finkelstein EA, Miller TR. The costs of fatal and non-fatal falls among older adults. *Inj Prev* (2006) 12(5):290–5. doi:10.1136/ip.2005.011015
3. 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
4. Liston MB, Bamiou DE, Martin F, Hopper A, Koohi N, Luxon L, et al. Peripheral vestibular dysfunction is prevalent in older adults experiencing multiple non-syncopal falls versus age-matched non-fallers: a pilot study. *Age Ageing* (2014) 43(1):38–43. doi:10.1093/ageing/aft129
5. Davis LE. Dizziness in elderly men. *J Am Geriatr Soc* (1994) 42(11):1184–8. doi:10.1111/j.1532-5415.1994.tb06986.x
6. Lawson J, Fitzgerald J, Birchall J, Aldren CP, Kenny RA. Diagnosis of geriatric patients with severe dizziness. *J Am Geriatr Soc* (1999) 47(1):12–7. doi:10.1111/j.1532-5415.1999.tb01895.x
7. Aggarwal NT, Bennett DA, Bienias JL, Mendes de Leon CF, Morris MC, Evans DA. The prevalence of dizziness and its association with functional disability in a biracial community population. *J Gerontol A Biol Sci Med Sci* (2000) 55(5):M288–92. doi:10.1093/gerona/55.5.M288
8. Tinetti ME, Williams CS, Gill TM. Dizziness among older adults: a possible geriatric syndrome. *Ann Intern Med* (2000) 132(5):337–44. doi:10.7326/0003-4819-132-5-200003070-00026
9. Iwasaki S, Yamasoba T. Dizziness and imbalance in the elderly: age-related decline in the vestibular system. *Aging Dis* (2015) 6(1):38–47. doi:10.14336/AD.2014.0128
10. Baloh RW, Ying SH, Jacobson KM. A longitudinal study of gait and balance dysfunction in normal older people. *Arch Neurol* (2003) 60(6):835–9. doi:10.1001/archneur.60.6.835
11. Fife TD, Baloh RW. Disequilibrium of unknown cause in older people. *Ann Neurol* (1993) 34(5):694–702. doi:10.1002/ana.410340512
12. Wiesmeier IK, Dalin D, Maurer C. Elderly use proprioception rather than visual and vestibular cues for postural motor control. *Front Aging Neurosci* (2015) 7:97. doi:10.3389/fnagi.2015.00097
13. Engstrom H, Bergstrom B, Rosenhall U. Vestibular sensory epithelia. *Arch Otolaryngol* (1974) 100(6):411–8. doi:10.1001/archotol.1974.00780040425002
14. Rosenhall U. Degenerative patterns in the aging human vestibular neuroepithelia. *Acta Otolaryngol* (1973) 76(2):208–20. doi:10.3109/00016487309121501
15. Richter E. Quantitative study of human Scarpa's ganglion and vestibular sensory epithelia. *Acta Otolaryngol* (1980) 90(3–4):199–208. doi:10.3109/00016488009131716
16. Johnsson LG. Degenerative changes and anomalies of the vestibular system in man. *Laryngoscope* (1971) 81(10):1682–94. doi:10.1288/00005537-197110000-00016
17. Merchant SN, Velazquez-Villasenor L, Tsuji K, Glynn RJ, Wall C III, Rauch SD. Temporal bone studies of the human peripheral vestibular system. Normative vestibular hair cell data. *Ann Otol Rhinol Laryngol Suppl* (2000) 181:3–13.
18. Park JJ, Tang Y, Lopez I, Ishiyama A. Age-related change in the number of neurons in the human vestibular ganglion. *J Comp Neurol* (2001) 431(4):437–43. doi:10.1002/1096-9861(20010319)431:4<437::AID-CNE1081>3.0.CO;2-P
19. Alidina A, Lyon MJ. Aging rat vestibular ganglion: I. Quantitative light microscopic evaluation. *Am J Otolaryngol* (1990) 11(3):174–81. doi:10.1016/0196-0709(90)90034-S
20. Velazquez-Villasenor L, Merchant SN, Tsuji K, Glynn RJ, Wall C III, Rauch SD. Temporal bone studies of the human peripheral vestibular system. Normative Scarpa's ganglion cell data. *Ann Otol Rhinol Laryngol Suppl* (2000) 181:14–9.

21. Sato H, Sando I, Takahashi H. Three-dimensional anatomy of human Scarpa's ganglion. *Laryngoscope* (1992) 102(9):1056–63. doi:10.1288/00005537-199209000-00018
22. Welgampola MS, Colebatch JG. Characteristics and clinical applications of vestibular-evoked myogenic potentials. *Neurology* (2005) 64(10):1682–8. doi:10.1212/01.WNL.0000161876.20552.AA
23. Chihara Y, Iwasaki S, Ushio M, Murofushi T. Vestibular-evoked extraocular potentials by air-conducted sound: another clinical test for vestibular function. *Clin Neurophysiol* (2007) 118(12):2745–51. doi:10.1016/j.clinph.2007.08.005
24. 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):281–3. doi:10.1016/j.otohns.2010.05.024
25. Brantberg K, Granath K, Schart N. Age-related changes in vestibular evoked myogenic potentials. *Audiol Neurootol* (2007) 12(4):247–53. doi:10.1159/000101332
26. Su HC, Huang TW, Young YH, Cheng PW. Aging effect on vestibular evoked myogenic potential. *Otol Neurotol* (2004) 25(6):977–80. doi:10.1097/00129492-200411000-00019
27. Agrawal Y, Zuniga MG, Davalos-Bichara M, Schubert MC, Walston JD, Hughes J, et al. Decline in semicircular canal and otolith function with age. *Otol Neurotol* (2012) 33(5):832–9. doi:10.1097/MAO.0b013e3182545061
28. Iwasaki S, Smulders YE, Burgess AM, McGarvie LA, Macdougall HG, Halmagyi GM, et al. Ocular vestibular evoked myogenic potentials to bone conducted vibration of the midline forehead at Fz in healthy subjects. *Clin Neurophysiol* (2008) 119(9):2135–47. doi:10.1016/j.clinph.2008.05.028
29. Tseng CL, Chou CH, Young YH. Aging effect on the ocular vestibular-evoked myogenic potentials. *Otol Neurotol* (2010) 31(6):959–63. doi:10.1097/MAO.0b013e3181e8fb1a
30. Li C, Layman AJ, Carey JP, Agrawal Y. Epidemiology of vestibular evoked myogenic potentials: data from the Baltimore longitudinal study of aging. *Clin Neurophysiol* (2015) 126(11):2207–15. doi:10.1016/j.clinph.2015.01.008
31. Johnsson LG, Hawkins JE Jr. Sensory and neural degeneration with aging, as seen in microdissections of the human inner ear. *Ann Otol Rhinol Laryngol* (1972) 81(2):179–93. doi:10.1177/000348947208100203
32. Walther LE, Westhofen M. Presbyvertigo-aging of otoconia and vestibular sensory cells. *J Vestib Res* (2007) 17(2–3):89–92.
33. Ross MD, Peacor D, Johnsson LG, Allard LF. Observations on normal and degenerating human otoconia. *Ann Otol Rhinol Laryngol* (1976) 85(3 Pt 1):310–26. doi:10.1177/000348947608500302
34. Campos A, Canizares FJ, Sanchez-Quevedo MC, Romero PJ. Otoconial degeneration in the aged utricle and saccule. *Adv Otorhinolaryngol* (1990) 45:143–53. doi:10.1159/000418950
35. Jang YS, Hwang CH, Shin JY, Bae WY, Kim LS. Age-related changes on the morphology of the otoconia. *Laryngoscope* (2006) 116(6):996–1001. doi:10.1097/01.mlg.0000217238.84401.03
36. Igarashi M, Saito R, Mizukoshi K, Alford BR. Otoconia in young and elderly persons: a temporal bone study. *Acta Otolaryngol Suppl* (1993) 504:26–9. doi:10.3109/00016489309128117
37. Walther LE, Wenzel A, Buder J, Bloching MB, Kniep R, Blodow A. Detection of human utricular otoconia degeneration in vital specimen and implications for benign paroxysmal positional vertigo. *Eur Arch Otorhinolaryngol* (2014) 271(12):3133–8. doi:10.1007/s00405-013-2784-6
38. Katsarkas A. Dizziness in aging: a retrospective study of 1194 cases. *Otolaryngol Head Neck Surg* (1994) 110(3):296–301. doi:10.1177/019459989411000306
39. Neuhauser HK. Epidemiology of vertigo. *Curr Opin Neurol* (2007) 20(1):40–6. doi:10.1097/WCO.0b013e328013f432
40. von Brevern M, Radtke A, Lezius F, Feldmann M, Ziese T, Lempert T, et al. Epidemiology of benign paroxysmal positional vertigo: a population based study. *J Neurol Neurosurg Psychiatry* (2007) 78(7):710–5. doi:10.1136/jnnp.2006.100420
41. Schuknecht HF. Cupulolithiasis. *Arch Otolaryngol* (1969) 90(6):765–78. doi:10.1001/archotol.1969.00770030767020
42. Hall SF, Ruby RR, McClure JA. The mechanics of benign paroxysmal vertigo. *J Otolaryngol* (1979) 8(2):151–8.
43. Iwasaki S, Chihara Y, Ushio M, Ochi A, Murofushi T, Yamasoba T. Effect of the canalith repositioning procedure on subjective visual horizontal in patients with posterior canal benign paroxysmal positional vertigo. *Acta Otolaryngol* (2011) 131(1):41–5. doi:10.3109/00016489.2010.514008
44. De Stefano A, Dispenza F, Suarez H, Perez-Fernandez N, Manrique-Huarte R, Ban JH, et al. A multicenter observational study on the role of comorbidities in the recurrent episodes of benign paroxysmal positional vertigo. *Auris Nasus Larynx* (2014) 41(1):31–6. doi:10.1016/j.anl.2013.07.007
45. Tsuji K, Velazquez-Villasenor L, Rauch SD, Glynn RJ, Wall C III, Merchant SN. Temporal bone studies of the human peripheral vestibular system. Meniere's disease. *Ann Otol Rhinol Laryngol Suppl* (2000) 181:26–31.
46. Schubert MC, Migliaccio AA, Della Santina CC. Dynamic visual acuity during passive head thrusts in canal planes. *J Assoc Res Otolaryngol* (2006) 7(4):329–38. doi:10.1007/s10162-006-0047-6
47. Baloh RW, Enrietto J, Jacobson KM, Lin A. Age-related changes in vestibular function: a longitudinal study. *Ann N Y Acad Sci* (2001) 942:210–9. doi:10.1111/j.1749-6632.2001.tb03747.x
48. Li C, Layman AJ, Geary R, Anson E, Carey JP, Ferrucci L, et al. Epidemiology of vestibulo-ocular reflex function: data from the Baltimore longitudinal study of aging. *Otol Neurotol* (2015) 36(2):267–72. doi:10.1097/MAO.0000000000000610
49. Alvarez JC, Diaz C, Suarez C, Fernandez JA, Gonzalez del Rey C, Navarro A, et al. Aging and the human vestibular nuclei: morphometric analysis. *Mech Ageing Dev* (2000) 114(3):149–72. doi:10.1016/S0047-6374(00)00098-1
50. Lopez I, Honrubia V, Baloh RW. Aging and the human vestibular nucleus. *J Vestib Res* (1997) 7(1):77–85. doi:10.1016/S0957-4271(96)00137-1
51. Tang Y, Lopez I, Baloh RW. Age-related change of the neuronal number in the human medial vestibular nucleus: a stereological investigation. *J Vestib Res* (2001) 11(6):357–63.
52. Sturrock RR. Age related changes in neuron number in the mouse lateral vestibular nucleus. *J Anat* (1989) 166:227–32.
53. Fernandez JA, Suarez C, Navarro A, Diaz C, Alvarez JC, Gonzalez del Rey C, et al. Aging in the vestibular nuclear complex of the male golden hamster (*Mesocricetus auratus*): anatomic and morphometric study. *Histol Histopathol* (2007) 22(8):855–68.
54. Kleine JF, Guan Y, Kipiani E, Glonti L, Hoshi M, Buttner U. Trunk position influences vestibular responses of fastigial nucleus neurons in the alert monkey. *J Neurophysiol* (2004) 91(5):2090–100. doi:10.1152/jn.00849.2003
55. Manzoni D, Andre P, Bruschini L. Coupling sensory inputs to the appropriate motor responses: new aspects of cerebellar function. *Arch Ital Biol* (2004) 142(3):199–215.
56. Torvik A, Torp S, Lindboe CF. Atrophy of the cerebellar vermis in ageing. A morphometric and histologic study. *J Neurol Sci* (1986) 76(2–3):283–94. doi:10.1016/0022-510X(86)90176-0
57. Luft AR, Skalej M, Schulz JB, Welte D, Kolb R, Burk K, et al. Patterns of age-related shrinkage in cerebellum and brainstem observed in vivo using three-dimensional MRI volumetry. *Cereb Cortex* (1999) 9(7):712–21. doi:10.1093/cercor/9.7.712
58. Andersen BB, Gundersen HJ, Pakkenberg B. Aging of the human cerebellum: a stereological study. *J Comp Neurol* (2003) 466(3):356–65. doi:10.1002/cne.10884
59. Lobel E, Kleine JF, Bihan DL, Leroy-Willig A, Berthoz A. Functional MRI of galvanic vestibular stimulation. *J Neurophysiol* (1998) 80(5):2699–709.
60. Brandt T, Dieterich M. The vestibular cortex. Its locations, functions, and disorders. *Ann N Y Acad Sci* (1999) 871:293–312. doi:10.1111/j.1749-6632.1999.tb09193.x
61. Lopez C, Blanke O, Mast FW. The human vestibular cortex revealed by coordinate-based activation likelihood estimation meta-analysis. *Neuroscience* (2012) 212:159–79. doi:10.1016/j.neuroscience.2012.03.028
62. Cyran CA, Boegle R, Stephan T, Dieterich M, Glasauer S. Age-related decline in functional connectivity of the vestibular cortical network. *Brain Struct Funct* (2016) 221(3):1443–63. doi:10.1007/s00429-014-0983-6
63. Jahn K, Naessl A, Schneider E, Strupp M, Brandt T, Dieterich M. Inverse U-shaped curve for age dependency of torsional eye movement responses to galvanic vestibular stimulation. *Brain* (2003) 126(Pt 7):1579–89. doi:10.1093/brain/awg163
64. Schubert MC, Zee DS. Saccade and vestibular ocular motor adaptation. *Restor Neurol Neurosci* (2010) 28(1):9–18. doi:10.3233/RNN-2010-0523
65. 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

66. Bernard JA, Seidler RD. Moving forward: age effects on the cerebellum underlie cognitive and motor declines. *Neurosci Biobehav Rev* (2014) 42:193–207. doi:10.1016/j.neubiorev.2014.02.011
67. Guariglia CC, Nitrini R. Topographical disorientation in Alzheimer's disease. *Arq Neuropsiquiatr* (2009) 67(4):967–72. doi:10.1590/S0004-282X2009000600001
68. Brandt T, Schautzer F, Hamilton DA, Bruning R, Markowitsch HJ, Kalla R, et al. Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans. *Brain* (2005) 128(Pt 11):2732–41. doi:10.1093/brain/awh617
69. 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
70. 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
71. Kahane P, Hoffmann D, Minotti L, Berthoz A. Reappraisal of the human vestibular cortex by cortical electrical stimulation study. *Ann Neurol* (2003) 54(5):615–24. doi:10.1002/ana.10726

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.

The reviewer MS and handling Editor declared their shared affiliation, and the handling Editor states that the process nevertheless met the standards of a fair and objective review.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read, for greatest visibility

COLLABORATIVE PEER-REVIEW
Designed to be rigorous – yet also collaborative, fair and constructive

FAST PUBLICATION
Average 85 days from submission to publication (across all journals)

COPYRIGHT TO AUTHORS
No limit to article distribution and re-use

TRANSPARENT
Editors and reviewers acknowledged by name on published articles

SUPPORT
By our Swiss-based editorial team

IMPACT METRICS
Advanced metrics track your article's impact

GLOBAL SPREAD
5'100'000+ monthly article views and downloads

LOOP RESEARCH NETWORK
Our network increases readership for your article

Frontiers
EPFL Innovation Park, Building I • 1015 Lausanne • Switzerland
Tel +41 21 510 17 00 • Fax +41 21 510 17 01 • info@frontiersin.org
www.frontiersin.org

Find us on