HHS Public Access

Author manuscript

Otol Neurotol. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Otol Neurotol. 2016 September ; 37(8): 1137–1142. doi:10.1097/MAO.0000000000001157.

Vestibular Impairment in Dementia

Aisha Harun, MD[1], **Esther S. Oh, MD, PhD**[2,3,4], **Robin T. Bigelow, BS**[1], **Stephanie Studenski, MD, MPH**[5], and **Yuri Agrawal, MD, MPH**[1]

[1]Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD

[2]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

[3]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

[4]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD

[5]Longitudinal Studies Section, Translational Gerontology Branch, National Institute of Aging, National Institutes of Health, Baltimore, MD

Abstract

Objective—Recent studies suggest an association between vestibular and cognitive function. The goal of the study was to investigate whether vestibular function was impaired in individuals with mild cognitive impairment (MCI) and Alzheimer's disease (AD) compared to cognitively normal individuals.

Study Design—Cross-sectional study.

Setting—Outpatient memory clinic and longitudinal observational study unit.

Patients—Older individuals ≥ 55 years with MCI or AD. Age, gender and education-matched normal controls were drawn from the Baltimore Longitudinal Study of Aging (BLSA).

Intervention—Saccular and utricular function was assessed with cervical and ocular vestibular-evoked myogenic potentials (c- and oVEMPs) respectively, and horizontal semicircular canal function was assessed with video head impulse testing.

Main Outcome Measures—Presence or absence of VEMP responses, VEMP amplitude and vestibular ocular reflex (VOR) gain were measured.

Results—Forty-seven individuals with cognitive impairment (MCI N=15 and AD N=32) underwent testing and were matched with 94 controls. In adjusted analyses, bilaterally absent cVEMPs were associated with an over three-fold odds of AD (OR 3.42, 95% CI 1.33–8.91, p=0.011). One microvolt increases in both cVEMP and oVEMP amplitudes were associated with decreased odds of AD (OR 0.28, 95% CI 0.09–0.93, p=0.038 and OR 0.92, 95% CI 0.85–0.99, p=0.036, respectively). There was no significant difference in VOR gain between the groups.

Corresponding Author and Reprint Requests: Aisha Harun, MD, 601 N. Caroline St Suite 6210, Department of Otolaryngology-Head and Neck Surgery, Baltimore, MD 21287, Phone: 410-955-7876, Fax 410-955-0035, aisha@jhmi.edu.

There are no conflicts of interest to report

Conclusions—These findings confirm and extend emerging evidence of an association between vestibular dysfunction and cognitive impairment. Further investigation is needed to determine the causal direction for the link between peripheral vestibular loss and cognitive impairment.

The burden of Alzheimer's disease (AD) and other dementias continues to grow, with an estimated 5.1 million cases in the U.S. in 2015.[1] A growing body of literature suggests that vestibular loss is associated with cognitive impairment in both human and animal studies.[2–20] Individuals with vestibular loss were found to have reduced visuospatial skills such as spatial memory and spatial navigation,[6, 17–19] and were also observed to have volume loss in regions of the brain associated with these skills, specifically the hippocampus.[6] Interestingly, visuospatial impairments are among the most frequent cognitive deficits in individuals with dementia.[21, 22] Wandering, for instance, is a frequent symptom of patients with AD.[23]

Cognitive impairment is a highly morbid condition whose prevalence increases significantly with age.[1] Individuals with mild cognitive impairment (MCI) have difficulties with objective cognitive tasks, but their day-to-day functioning is preserved.[24] Some individuals with MCI may progress clinically to dementia, which is characterized by a decline in their daily functioning not explained by other illnesses.[21] Dementia may have several underlying etiologies, including vascular disease and Alzheimer's disease, which is defined as a progressive cognitive decline due to cerebral degeneration.[21] Vestibular dysfunction in the dementia population, therefore, may compound the difficulties in caring for these individuals. For instance, vestibular impairment is known to lead to dizziness and imbalance owing to gaze and postural instability,[25] and has been associated with an increased risk of falls.[26–28] Individuals with vestibular dysfunction have also been found to have difficulty in carrying out Activities of Daily Living.[29]

There are few studies, however, that have examined the prevalence of vestibular dysfunction in cognitively impaired individuals.[5, 7] One study found that individuals with AD had impaired caloric responses relative to younger, but not age-matched controls.[7] Patients with AD were also observed to have poorer postural control – a proxy measure of vestibular function and other sensory and motor inputs– compared to normal older individuals.[30] Another study found that individuals with different degrees of cognitive impairment had abnormal sacculocollic reflexes.[5] These studies suggest an association between vestibular loss and cognitive decline in human subjects. However, the extent to which vestibular dysfunction varies among specific cognitive impairment subgroups (e.g. AD and MCI) and with age-matched controls is unknown.

The goal of this study, therefore, was to comprehensively assess vestibular physiologic function in a well-characterized cohort of patients with MCI and AD. We hypothesized that patients with cognitive impairment will have poorer vestibular function relative to age-matched controls and that individuals with more advanced cognitive impairment (i.e. AD) will have a greater degree of vestibular impairment. Further evidence of vestibular loss among patients with dementia would support the growing evidence of a link between peripheral vestibular loss and cognitive decline.

METHODS

Study Participants

Participants were recruited from the Johns Hopkins Memory and Alzheimer's Treatment Center (JHMATC), an interdisciplinary memory disorder clinic, and the Johns Hopkins Alzheimer's Disease Research Center (JHADRC). The study was comprised of 47 subjects who participated in the study from December 2014 until February 2016: 15 with MCI and 32 with AD (Table 1).

The inclusion criteria for the cases were as follows: 1) Age ≥ 55 years; 2) Diagnosis of MCI or AD; 3) Mini-Mental State Exam (MMSE) score ≥11; 4) Fluency in English; and 5) Ability to obtain informed consent from the participant or legally authorized representative. The National Institute on Aging/Alzheimer's Association (NIA/AA) diagnostic criteria were used for the diagnosis of MCI and AD.[21, 31] The MMSE cutoff was chosen as it has been shown to correspond to the cutoff for moderate-to-severe cognitive impairment.[32] Patients with a Mini-Mental State Exam (MMSE) score ≥11 were screened by a Memory Center Physician who determined that the patient was able to follow exam procedures. Individuals were excluded if they had a previous history of vestibular disease, were unable to understand exam procedures, or were unable to participate in study procedures because of physical conditions, such as blindness, poor neck range of motion, or cervical spine instability. Demographic information (age, gender, and education) was extracted from the patients' chart. Gender was classified as male or female. Education was classified as less than college, college, or greater than college. The study was approved by the Johns Hopkins Institutional Review Board, and all participants gave informed consent.

Age, gender, and education-matched control data came from the Baltimore Longitudinal Study of Aging (BLSA). The BLSA is a prospective cohort study of participant volunteers aged 21 to 103 in the National Institute on Aging Clinical Research Unit at Harbor Hospital in Baltimore, Maryland. This study evaluated a cross-sectional sample of BLSA participants who underwent vestibular testing. All participants provided written informed consent, and the hospital institutional review board approved the BLSA study protocol. BLSA participants with vestibular testing data were matched two-to-one by age (within 5 years), gender, and education with participants from the cognitive impairment study group.

Vestibular Function Tests

Vestibular-evoked myogenic potentials—For vestibular-evoked myogenic potential recording, a commercial electromyographic system (software version 14.1; Carefusion Synergy, Dublin, OH, USA) was used. Electromyogram signals were recorded with disposable, self-adhesive, pre-gelled Ag/AgCl electrodes with 40-inch safety lead wires from GN Otometrics (Schaumburg, IL, USA). Electromyogram signals were amplified and band-pass filtered, 20–2000 Hz for the cervical vestibular-evoked myogenic potentials (cVEMPs) and 3–500 Hz for the ocular vestibular-evoked myogenic potentials (oVEMPs).

Sound-evoked cVEMP testing methods of measuring saccular function have been published in detail previously and are discussed briefly here.[33, 34] Participants sat on a chair inclined at 30 degrees from the horizontal. Trained examiners placed recording electromyographic

(EMG) electrodes on the sternocleidomastoid (SCM) muscles and at the sternoclavicular junction bilaterally, and a ground electrode was placed on the manubrium sterni. Sound stimuli consisted of 500 Hz, 125 dB sound pressure level tone bursts delivered monaurally through headphones (VIASYS Healthcare, Madison, WI, USA). Amplitudes of cVEMP response were recorded and normalized for the background EMG activity recorded in the 10 milliseconds before the stimulus onset. An absent response was determined if the characteristic waveform did not occur per published guidelines.[35] For those who had a response, the cVEMP amplitude of the better ear was used for the analysis. One individual from the dementia case group (MMSE of 12) had missing cVEMP data because he was unable to follow testing procedures after several attempts were made.

Vibration-evoked oVEMPs assess utricular function and testing methods have also been published previously and are discussed briefly here.[33, 34] Participants sat on a chair inclined at 30 degrees from the horizontal. A non-inverting electrode was placed on the cheek directly beneath the pupil approximately 3 mm below the eye. A second inverting electrode was placed 2 cm below the non-inverting electrode, and a ground electrode was placed on the manubrium sterni. Before stimulation, participants were instructed to perform 20-degree vertical saccades to ensure that symmetrical signals were recorded from both eyes. If signals showed >25% asymmetry, the electrodes were removed and new ones applied. Participants were instructed to maintain a 20-degree upgaze during oVEMP stimulation and recording. Head taps were delivered using a reflex hammer (Aesculap model ACO12C) in the mid-line at the hairline, 30% of the distance between the inion and nasion. An absent response was determined if the characteristic waveform did not occur per published guidelines.[35] In these cases, the assessment was repeated to confirm an absent response. For those who had a response, the oVEMP amplitude of the better ear was used for the analysis. Two individuals from the AD case group (MMSE of 12 and 12) had missing oVEMP data because they were unable to follow the testing instructions after several trials were attempted.

Video Head Impulse Testing (vHIT)—The horizontal vestibular ocular reflex (VOR) was assessed using the video head impulse test (vHIT).[36, 37] The vHIT was performed in the plane of the right and left horizontal semicircular canals using the EyeSeeCam system (Interacoustics, Eden Prairie, MN, USA), which has been shown to accurately assess the VOR.[37, 38] The EyeSeeCam consists of a high-speed digital camera that tracks the pupil and an inertial measurement device that quantifies head movements, both of which are mounted on a lightweight glasses frame. The patient's head was pitched down 30 degrees to place the horizontal canals in the plane of stimulation, and subjects were asked to fix their gaze on a wall target about 1.5 meters away. The head was moved a small amplitude (approximately 5–15 degrees) with high velocity (typically 150–250 degrees per second) horizontally toward the right and left side at least 10 times in both directions. The direction of the head movement was randomized to be unpredictable. The EyeSeeCam system measured eye velocity and head velocity, and a corresponding VOR gain was calculated by dividing the eye velocity by the head velocity. A normal, compensatory VOR gain should equal 1.0. VOR gains less than 0.8,[39] along with compensatory refixation saccades, suggested a loss of peripheral vestibular function.[40] Six individuals from the dementia case group had missing

VOR data (two individuals were unable to follow testing instructions, MMSE of 12 and 12, and the equipment was unavailable for testing for the remaining four individuals).

Statistical Analysis

Our objective was to obtain a sample size that would give us adequate power to detect a clinically significant difference between cases and age-matched control values with respect to cervical and ocular VEMP testing and VOR gain scores. For each of these three tests, a separate sample size calculation was performed assuming an alpha level of 0.05, a power of 0.8, and a control to case ratio of two-to-one. For cVEMP testing, a 0.5 μV change in response amplitude was chosen as a clinically significant difference, and the standard deviation of cVEMP amplitudes was also around 0.5 μV.[41] For oVEMP testing, a 3μV change in amplitude was selected as a clinically significant difference, and the standard deviation of the oVEMP amplitude was around 3 μV.[42] The calculated minimal sample size of the cases for the cVEMP and oVEMP analyses was 12 individuals. For vHIT testing, a 0.05 difference in VOR gain (standard deviation around 0.1) was chosen as clinically significant.[39] The calculated sample size for the VOR gain analyses was 48 individuals.

The main outcome of interest was diagnosis (cases versus controls). The cases were subdivided into mild cognitive impairment (MCI) and Alzheimer's disease (AD). The main variables of interest were VEMP amplitude, bilaterally absent VEMPs, and VOR gain. Data were initially analyzed using bivariate analyses to compare the variables of interest between each group (MCI and AD) and their matched controls; t-tests were used for continuous data and χ^2 tests for categorical variables. Logistic regression analyses adjusted for age, gender, and education were used to analyze the association between vestibular function (bilateral absent cVEMPs, bilateral absent oVEMPs, best cVEMP amplitude, best oVEMP amplitude, or VOR gain) and each of the control and cognitive impairment groups (MCI and AD). All statistical analyses were conducted with Stata version 13 (College Station, TX).

RESULTS

The study population included a total of 47 cases and 94 controls (Table 1). Of the 47 cases, 15 (31.9%) were diagnosed with MCI and 32 (68.1%) with AD. The mean age of the study population was 75.1 years (SD 7.7, range 60–98 years). Seventy percent of the population was female and 47.5% was college educated. The controls had a higher mean MMSE compared to the cases (28.6 versus 25.7 in the MCI group and 19.7 in the AD group). There was no significant difference between the cases and controls in terms of age, gender, or education.

Prevalence of vestibular dysfunction across cognitive impairment categories

In bivariate analyses, individuals with AD had a greater prevalence of bilateral absent cVEMPs compared to their age, gender, and education-matched controls (50.0% versus 25.0%, p=0.010, Table 2). The AD group had a lower mean cVEMP amplitude compared with their matched controls (0.8 μV versus 1.3 μV, p=0.039). Similarly, the AD group had a lower mean oVEMP amplitude (9.4 μV versus 13.7 μV, p=0.036). There was no significant

difference between the MCI group and their matched controls in the prevalence of vestibular dysfunction.

Multivariate associations between cognitive impairment and vestibular loss

We evaluated the association between vestibular loss and cognitive impairment category using logistic regression models adjusted for age, gender and educational level (Table 3). Individuals with bilaterally absent cVEMPs had an over three-fold increased odds of AD (OR 3.42, 95% CI 1.32–8.91, p=0.011). In addition, one-microvolt increases in cVEMP amplitude were associated with decreased odds of AD (OR 0.28, 95% CI 0.09–0.93, p=0.038). Similarly, higher oVEMP amplitude was also significantly associated with decreased odds of AD (OR 0.92, 95% CI 0.85–0.99, p=0.036). Vestibular loss was not associated with an increased odds of mild cognitive impairment. Additionally, VOR gain did not significantly differ by cognitive impairment category, including AD.

DISCUSSION

We hypothesized that patients with cognitive impairment will have poorer vestibular function relative to age-matched controls. We observed in this study a significantly higher prevalence of vestibular loss among individuals with dementia relative to age-matched controls. Specifically, we found that patients with dementia had greater impairments of saccular and utricular function but not of semicircular canal function relative to controls. Moreover, we observed that individuals with Alzheimer's disease, but not mild cognitive impairment, were more likely to have vestibular loss relative to age-matched controls.

These data corroborate an emerging literature establishing a link between vestibular and cognitive function. The peripheral vestibular system makes widespread projections to cortical centers involved in memory and spatial orientation, notably the hippocampus.[2, 3, 6, 10, 12–15, 19, 43–46] These projections may represent the neural basis for the association between vestibular and cognitive function. Stimulation of the vestibular system in animal models has been shown to produce increased firing of hippocampal neurons.[43, 44] Furthermore, vestibular-lesioned animals have been found to have disruption of their hippocampal theta rhythm (which is thought to encode spatial information) compared to controls,[10] as well as behavioral deficits when performing spatial navigation tasks.[2, 12] These deficits have also been observed in humans. For instance, one landmark study observed that individuals with bilateral vestibular loss had deficits in spatial memory and navigation, and had concomitant selective hippocampal atrophy on neuro-imaging.[6] Hippocampal atrophy is a pathologic hallmark of Alzheimer's disease,[47] and the well-established vestibular-hippocampal connections may underlie the association between vestibular loss and dementia.

Our study builds on several prior studies that also noted vestibular impairment among individuals with dementia.[5, 7] Nakamagoe et al.[7] previously reported impaired caloric responses in 12 AD patients compared with younger controls, although there was no difference relative to age-matched controls. Further, in a study of postural sway among individuals with cognitive impairment, Leandri et al.[30] observed progressively increased anterior-posterior sway in control, MCI and AD patients. Birdane et al.[5] observed that

individuals with any cognitive impairment (both AD and MCI) had lower mean cVEMP amplitudes compared to age-matched controls. We evaluated the function of both otolith and semicircular canal end-organs. We found that individuals with dementia had poorer function of both the saccular and utricular otolith organs relative to controls, with relative preservation of horizontal canal function. Moreover, we stratified patients by MCI versus AD compared to age-matched controls, and we observed significantly poorer vestibular function among AD patients specifically. We did not observe significant vestibular impairment among individuals with MCI. Our study extends prior work by showing that loss of function of both otolith organs was more prevalent in individuals with AD relative to age-matched controls.

In the current study, there was no association between VOR and cognitive function. Vestibular nucleus neurons involved in the VOR have been postulated to be distinct from other vestibular neurons as they do not ascend to the thalamus and project cortically.[48] Conversely, saccular stimulation leads to widespread cortical activation, including the posterior insular cortex, the inferior parietal cortex, the intraparietal sulcus, and temporo-parietal junction,[49, 50] all of which are involved in cognitive processing. We hypothesize that disruption in the peripheral vestibular projections to the cortex, therefore, may underlie the association between cognition and otolith function (but not semicircular canal function as measured by the VOR) that was observed in the current study. It should be noted that the otolith-cervical and otolith-ocular projections that underlie the VEMP responses are distinct from the otolith-cortical projections that may account for the association between otolith and cognitive function.

We note several limitations of the current study. First, this is a cross-sectional study of patients and healthy controls seen at a tertiary care referral clinic and longitudinal observation study respectively, and therefore the findings may not be representative of the broader population of individuals with cognitive impairment and dementia. Additionally, based on our sample size calculations, additional patients may have been needed to detect a clinically significant difference in VOR gain between the controls and cases for both the AD and MCI subgroups. We did not group the AD and MCI individuals together, which would have limited the interpretability of our results. A larger sample size may be needed to adequately determine any differences in VOR gain in the future. In addition, given that we excluded patients with severe dementia who may have been unable to complete the vestibular testing procedures, our findings may only be applicable to patients with mild-to-moderate cognitive impairment. It is also possible that the results of poor vestibular testing among individuals with dementia were due to their inability to perform the test procedures. However, all individuals who were tested were able to successfully follow the instructions to calibrate each individual test (i.e. follow the calibration laser point for vHIT, generate sufficient background neck contraction for cVEMP testing, and generate vertical saccades for oVEMP testing). Further, these findings cannot support causal inferences about whether vestibular loss causes cognitive impairment or the reverse. Prior studies in animals and in small clinical populations suggest that peripheral vestibular loss results in cognitive deficits (particularly with respect to spatial cognition), and we hypothesize that vestibular loss may contribute to cognitive decline in individuals with dementia. However, it is possible that dementia-related neurodegeneration may lead to vestibular dysfunction through impaired

afferent signaling and processing. Indeed, in this study we did not observe consistent dose-response relationships whereby the degree of vestibular impairment increased with worsening cognitive status (MCI versus AD), which would support that vestibular loss causes cognitive decline. Further longitudinal studies will be needed to further evaluate this question of causal direction.

In summary, our work confirms and extends emerging evidence of an association between vestibular loss and cognitive decline. Further investigation is needed to determine the causal direction for the link between peripheral vestibular loss and cognitive impairment. Identification of a possible modifiable risk factor such as vestibular loss for cognitive impairment could lead to interventions to help slow the progression of dementia and reduce the risks of postural instability and falls in this already vulnerable population.

Acknowledgments

Funding for work: Aisha Harun was funded by a NIH T32 Award (5T32DC000027-25) and a AAO-HNSF Core Grant (349386). Robin Bigelow was funded by a T32 Award (NIH/NIDCD 5T32DC000030-1). Yuri Agrawal was funded by a NIH K23 Award (5K23DC013056-02). Esther Oh was funded by a NIA/NIH K23 Award **(**1K23AG043504-01), the Roberts Gift Fund and the Ossoff Family Fund. The Alzheimer's disease Research Council is supported by an NIA award (3P50AG005146-32S1). The Baltimore Longitudinal Study of Aging is supported by an NIA award (1ZIAAG000015-57).

References

1. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology. 2013; 80:1778–1783. [PubMed: 23390181]
2. Besnard S, Machado ML, Vignaux G, et al. Influence of vestibular input on spatial and nonspatial memory and on hippocampal NMDA receptors. Hippocampus. 2012; 22:814–826. [PubMed: 21538662]
3. Bigelow RT, Agrawal Y. Vestibular involvement in cognition: Visuospatial ability, attention, executive function, and memory. Journal of Vestibular Research. 2015; 25:73–89. [PubMed: 26410672]
4. Bigelow RT, Semenov YR, Trevino C, et al. Association Between Visuospatial Ability and Vestibular Function in the Baltimore Longitudinal Study of Aging. J Am Geriatr Soc. 2015; 63:1837–1844. [PubMed: 26311169]
5. Birdane L, Incesulu A, Gurbuz MK, Ozbabalik D. Sacculocolic reflex in patients with dementia: Is it possible to use it for early diagnosis? Neurological Sciences. 2012; 33:17–21. [PubMed: 21559855]
6. Brandt T, Schautzer F, Hamilton Da, et al. Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans. Brain. 2005; 128:2732–2741. [PubMed: 16141283]
7. Nakamagoe K, Fujimiya S, Koganezawa T, et al. Vestibular Function Impairment in Alzheimer's Disease. Journal of Alzheimer's Disease. 2015; 47:185–196.
8. Palla A, Lenggenhager B. Ways to investigate vestibular contributions to cognitive processes. Front Integr Neurosci. 2014; 8:40. [PubMed: 24860448]
9. Previc FH. Vestibular loss as a contributor to Alzheimer's disease. Med Hypotheses. 2013; 80:360–367. [PubMed: 23375669]
10. Russell, Na, Horii, A., Smith, PF., Darlington, CL., Bilkey, DK. Lesions of the vestibular system disrupt hippocampal theta rhythm in the rat. Journal of neurophysiology. 2006; 96:4–14. [PubMed: 16772515]
11. 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. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2016; 71:243–250.

12. Stackman RW, Herbert AM. Rats with lesions of the vestibular system require a visual landmark for spatial navigation. Behav Brain Res. 2002; 128:27–40. [PubMed: 11755687]
13. Yoder RM, Taube JS. The vestibular contribution to the head direction signal and navigation. Front Integr Neurosci. 2014; 8:32. [PubMed: 24795578]
14. Mast FW, Preuss N, Hartmann M, Grabherr L. Spatial cognition, body representation and affective processes: the role of vestibular information beyond ocular reflexes and control of posture. Front Integr Neurosci. 2014; 8:44. [PubMed: 24904327]
15. Smith PF, Darlington CL, Zheng Y. Move it or lose it - Is stimulation of the vestibular system necessary for normal spatial memory? Hippocampus. 2010; 20:36–43. [PubMed: 19405142]
16. Besnard S, Lopez C, Brandt T, Denise P, Smith PF. Editorial: The Vestibular System in Cognitive and Memory Processes in Mammalians. Front Integr Neurosci. 2015; 9:55. [PubMed: 26617498]
17. Schautzer F, Hamilton D, Kalla R, Strupp M, Brandt T. Spatial memory deficits in patients with chronic bilateral vestibular failure. Ann N Y Acad Sci. 2003; 1004:316–324. [PubMed: 14662471]
18. Guidetti G, Monzani D, Trebbi M, Rovatti V. Impaired navigation skills in patients with psychological distress and chronic peripheral vestibular hypofunction without vertigo. Acta Otorhinolaryngol Ital. 2008; 28:21–25. [PubMed: 18533551]
19. Peruch P, Lopez C, Redon-Zouiteni C, et al. Vestibular information is necessary for maintaining metric properties of representational space: evidence from mental imagery. Neuropsychologia. 2011; 49:3136–3144. [PubMed: 21820000]
20. Lakshminarayanan V, Friedland RP, Muller EC, Koss E, Stark L. The vestibular ocular reflex in Alzheimer's disease. Neuro-ophthalmology. 1986; 6:205–208.
21. McKhann G, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging- Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dementia. 2011; 7:263–269.
22. Johnson DK, Storandt M, Morris JC, Galvin JE. Longitudinal study of the transition from healthy aging to Alzheimer disease. Archives of neurology. 2009; 66:1254–1259. [PubMed: 19822781]
23. 2012 Alzheimer's disease facts and figures. Alzheimers Dement. 2012; 8:131–168. [PubMed: 22404854]
24. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004; 256:240–246. [PubMed: 15324367]
25. Whitney SL, Marchetti GF, Pritcher M, Furman JM. Gaze stabilization and gait performance in vestibular dysfunction. Gait Posture. 2009; 29:194–198. [PubMed: 18815040]
26. Whitney SL, Hudak MT, Marchetti GF. The dynamic gait index relates to self-reported fall history in individuals with vestibular dysfunction. J Vestib Res. 2000; 10:99–105. [PubMed: 10939685]
27. Herdman SJ, Blatt P, Schubert MC, Tusa RJ. Falls in patients with vestibular deficits. Am J Otol. 2000; 21:847–851. [PubMed: 11078074]
28. 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; 169:938–944. [PubMed: 19468085]
29. Harun A, Semenov YR, Agrawal Y. Vestibular Function and Activities of Daily Living: Analysis of the 1999 to 2004 National Health and Nutrition Examination Surveys. Gerontol Geriatr Med. 2015; 1
30. Leandri M, Cammisuli S, Cammarata S, et al. Balance features in Alzheimer's disease and amnestic mild cognitive impairment. Journal of Alzheimer's Disease. 2009; 16:113–120.
31. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7:270–279. [PubMed: 21514249]
32. Perneczky R, Wagenpfeil S, Komossa K, Grimmer T, Diehl J, Kurz A. Mapping scores onto stages: mini-mental state examination and clinical dementia rating. The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry. 2006; 14:139–144. [PubMed: 16473978]

33. Li C, Zuniga MG, Nguyen KD, Carey JP, Agrawal Y. How to interpret latencies of cervical and ocular vestibular-evoked myogenic potentials: Our experience in fifty-three participants. Clinical otolaryngology: official journal of ENT-UK; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 2014; 39:297–301.
34. 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. [PubMed: 20517167]
35. 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; 126:2207–2215. [PubMed: 25703943]
36. 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; 34:1729–1735. [PubMed: 23928523]
37. Agrawal Y, Schubert MC, Migliaccio Aa, et al. Evaluation of Quantitative Head Impulse Testing Using Search Coils Versus Video-oculography in Older Individuals. Otol Neurotol. 2014; 35:283–288. [PubMed: 24080977]
38. Schneider E, Villgrattner T, Vockeroth J, et al. Eyeseecam: An eye movement-driven head camera for the examination of natural visual exploration. Ann N Y Acad Sci. 2009; 1164:461–467. [PubMed: 19645949]
39. Li C, Layman AJ, Geary R, et al. Epidemiology of vestibulo-ocular reflex function: data from the Baltimore Longitudinal Study of Aging. Otol Neurotol. 2015; 36:267–272. [PubMed: 25275869]
40. Weber KP, MacDougall HG, Halmagyi GM, Curthoys IS. Impulsive testing of semicircular-canal function using video-oculography. Ann N Y Acad Sci. 2009; 1164:486–491. [PubMed: 19645955]
41. Welgampola MS, Colebatch JG. Vestibulocollic reflexes: normal values and the effect of age. Clin Neurophysiol. 2001; 112:1971–1979. [PubMed: 11682335]
42. Welgampola MS, Migliaccio AA, Myrie OA, Minor LB, Carey JP. The human sound-evoked vestibulo-ocular reflex and its electromyographic correlate. Clin Neurophysiol. 2009; 120:158–166. [PubMed: 19070541]
43. Cuthbert PC, Gilchrist DP, Hicks SL, MacDougall HG, Curthoys IS. Electrophysiological evidence for vestibular activation of the guinea pig hippocampus. Neuroreport. 2000; 11:1443–1447. [PubMed: 10841354]
44. Horii A, Russell NA, Smith PF, Darlington CL, Bilkey DK. Vestibular influences on CA1 neurons in the rat hippocampus: an electrophysiological study in vivo. Exp Brain Res. 2004; 155:245–250. [PubMed: 14666395]
45. Brandt T, Dieterich M. The vestibular cortex: Its locations, functions, and disorders. Ann N Y Acad Sci. 1999:293–312.
46. Grabherr L, Mast FW. Effects of microgravity on cognition: The case of mental imagery. Journal of Vestibular Research: Equilibrium and Orientation. 2010; 20:53–60. [PubMed: 20555167]
47. Jack CR Jr, Shiung MM, Weigand SD, et al. Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnestic MCI. Neurology. 2005; 65:1227–1231. [PubMed: 16247049]
48. Smith PF. Vestibular dysfunction and Alzheimer's disease. Med Hypotheses. 2013; 81:1169–1170. [PubMed: 24436971]
49. Miyamoto T, Fukushima K, Takada T, de Waele C, Vidal PP. Saccular stimulation of the human cortex: a functional magnetic resonance imaging study. Neurosci Lett. 2007; 423:68–72. [PubMed: 17662530]
50. Schlindwein P, Mueller M, Bauermann T, Brandt T, Stoeter P, Dieterich M. Cortical representation of saccular vestibular stimulation: VEMPs in fMRI. Neuroimage. 2008; 39:19–31. [PubMed: 17919936]

Table 1

Characteristics of the study population

	Total n=141 (n/%)	Group			
		MCI n=15 (n/%)	AD n=32 (n/%)	Controls n=94 (n/%)	p-value
Mean age in years (SD)	75.1 (7.7)	74.3 (7.8)	75.7 (6.9)	75.0 (8.0)	0.850
Gender					
Male	42 (29.8%)	6 (40.0%)	8 (25.0%)	28 (29.8%)	0.577
Female	99 (70.2%)	9 (60.0%)	24 (75.0%)	66 (70.2%)	
Education					
Less than college	50 (35.5%)	4 (26.7%)	13 (40.6%)	33 (35.1%)	0.926
College	67 (47.5%)	8 (53.3%)	14 (43.8%)	45 (47.9%)	
Greater than college	24 (17.0%)	3 (20.0%)	5 (15.6%)	16 (17.0%)	
MMSE (SD)	26.2 (4.5)	25.7 (2.1)	19.7 (4.7)	28.6 (1.4)	<**0.0001**

MMSE: mini-mental state exam. MCI: mild cognitive impairment. AD: Alzheimer's disease.

Table 2

Mean vestibular function among controls and cognitive impairment categories

	MCI			AD		
	Cases (n=15)	**Controls (n=30)**	**p-value**	**Cases (n=32)**	**Controls (n=64)**	**p-value**
Bilateral absent cVEMPs						
Yes	4 (26.7%)	7 (23.3%)	0.806	**16 (50.0%)**	**16 (25.0%)**	**0.010**
No	11 (73.3%)	23 (76.7%)		**15 (50.0%)**	**48 (75.0%)**	
cVEMP amplitude in μV (SD)	1.7 (1.4)	1.2 (0.6)	0.175	**0.8 (0.5)**	**1.3 (0.8)**	**0.039**
Bilateral absent oVEMPs						
Yes	4 (26.7%)	6 (20.0%)	0.612	4 (13.3%)	8 (12.5%)	0.910
No	11 (73.3%)	24 (80.0%)		26 (86.7%)	56 (87.5%)	
oVEMP amplitude in μV (SD)	13.8 (5.2)	15.2 (7.3)	0.554	**9.4 (5.6)**	**13.7 (9.3)**	**0.036**
Mean VOR gain (SD)	1.0 (0.1)	1.0 (0.2)	0.621	1.0 (0.1)	1.0 (0.2)	0.820

cVEMPs: cervical vestibular-evoked myogenic potentials. oVEMPs: ocular vestibular-evoked myogenic potentials. VOR: vestibular ocular reflex. μV: microvolts. MCI: mild cognitive impairment. AD: Alzheimer's disease.

Table 3

Logistic regression models for the odds of cognitive impairment associated with vestibular loss*

	Cognitive Impairment					
	MCI			AD		
	OR	95% CI	p-value	OR	95% CI	p-value
Bilateral absent cVEMPs	1.20	0.28–5.03	0.807	**3.42**	**1.32–8.91**	**0.011**
cVEMP amplitude in μV	1.97	0.80–4.87	0.142	**0.28**	**0.09–0.93**	**0.038**
Bilateral absent oVEMPs	1.59	0.31–8.17	0.581	1.07	0.30–3.94	0.921
oVEMP amplitude in μV	0.97	0.85–1.09	0.581	**0.92**	**0.85–0.99**	**0.036**
Mean VOR gain	0.33	0.01–38.47	0.649	0.60	0.03–13.58	0.750

*Adjusted for age, gender, and education. Reference category is the age, gender, and education-matched reference group.

MCI: mild cognitive impairment. AD: Alzheimer's disease. cVEMPs: cervical vestibular-evoked myogenic potentials. oVEMPs: ocular vestibular-evoked myogenic potentials. VOR: vestibular ocular reflex. μV: microvolts.