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ABSTRACT

OBJECTIVES: Given the expected rise in dementia prevalence, early diagnosis is vital. As a growing body of literature has identified a potential association between vestibular function and cognition, vestibular assessment may aid in early screening. This study aims to better comprehend the proposed association between vestibular function and Alzheimer's disease (AD) by comparing vestibular parameters (vestibular function testing and clinical balance measures) between a group with Mild Cognitive Impairment (MCI), AD, and healthy controls with age-normal cognition.

DESIGN: Cross-sectional analysis of the ***ANONYMOUS*** study, an ongoing prospective single-centre longitudinal cohort study. This study included 100 older adults (55-84 years). A total of 33 participants with MCI, 17 participants with AD, and 50 age, sex, and hearing-matched healthy controls were included.

RESULTS: Participants with AD demonstrated a delayed latency of the p13 component measured by cervical Vestibular-Evoked Myogenic Potentials (cVEMP) compared to healthy controls and participants with MCI. Other measures including n23 latency, presence of intact responses, rectified amplitude, mean rectified voltage (measured by cVEMP) and lateral vestibulo-ocular reflex gain (measured by video Head Impulse Test (vHIT)) did not differ between groups. The Timed Up-and-Go (TUG), Performance-Oriented Mobility Assessment – Balance subscale (POMA-B), and Functional Gait Assessment (FGA) differed significantly between the three groups. Here, more cognitively impaired groups were associated with worse clinical balance scores.

CONCLUSIONS: Vestibular and balance deficits were more prevalent in groups with increasing cognitive decline. Regarding vestibular function testing, p13 latency as measured by cVEMP

was delayed in participants with AD. Other cVEMP or vHIT measures did not differ between groups. All three clinical balance assessments (TUG, POMA-B, and FGA) resulted in worse scores along the AD continuum. Future research integrating vestibular parameters that add value (including otolith function testing, balance, and spatial navigation) is recommended to validate the association between vestibular function and cognition while avoiding redundant testing.

KEYWORDS

Inner ear function, Dementia, Otology

INTRODUCTION

The number of older adults, including those affected by dementia, continues to grow. Worldwide around 55 million people suffered from dementia in 2021 and by 2050 this number is expected to rise to 139 million (World Health Organization 2021). Alzheimer's disease (AD) is the leading cause of dementia and accounts for up to seventy percent of all dementia cases, according to the World Health Organization (2019) (World Health Organization 2019). Because of its daunting economic, social, and psychological burden, dementia -including AD - is considered to be a public health priority.

People with AD generally evolve from an intermediate state of cognitive decline, namely Mild Cognitive Impairment (MCI). Daily life activities are preserved in people with MCI, but disturbed in people with AD. Therefore, when including biomarkers in the diagnostic process, the terms prodromal AD or MCI due to AD and dementia due to AD should be used instead of the more general terms MCI and AD, respectively. However, for precision, both MCI and

prodromal AD will be described as “MCI” and both AD and dementia due to AD will be described as “AD”.

When diagnosing AD from a neuropsychological point of view, episodic memory loss is still the go-to strategy despite its low sensitivity and specificity (Coughlan et al. 2018). However, difficulties with spatial navigation, such as getting lost in familiar places, losing or misplacing objects, and disorientation, are often reported to be one of the first cognitive losses observed in AD (Tu et al. 2015; Yew et al. 2013). Indeed, neuropathology of AD begins in brain structures crucial for successful navigation, such as the medial temporal lobe (including the hippocampus and entorhinal cortex) and parietal structures (Coughlan et al. 2018; Ghosh et al. 2022). Therefore, including navigation and orientation in the diagnostic process may help in differentiating AD from other types of dementia (Tu et al. 2015; Yew et al. 2013). Note that orientation in familiar environments remains preserved in healthy aging, in contrast to AD (Coughlan et al. 2018; Serino et al. 2015). As such, spatial navigation might be a more sensitive and specific cognitive fingerprint in addition to recent episodic memory deficits during the neuropsychological diagnostic process of AD.

The importance of accentuating spatial navigation in AD gains awareness, but it may be of interest to expand this scope further and explore vestibular function in the broad sense in AD, because of important interactions between spatial cognition, peripheral vestibular end-organ function, and balance. A recent systematic review structured measurements of the vestibular system in patients with MCI or AD, compared with a healthy control group with age-normal cognition (Bosmans et al. 2021). A higher prevalence of vestibular loss has been observed with increasing cognitive loss along the AD continuum. This cognitive loss was mainly associated with loss of otolith function, whereas semicircular canal function remained

preserved. In particular, p13 latency and amplitude as measured by the Vestibular-Evoked Myogenic Potentials (VEMP) test were the most promising parameters (Bosmans et al. 2021). An included study by Wei et al. (2019) observed a dose-response relationship between vestibular loss and the level of cognitive impairment. A note of caution is due here since the number of available studies in the systematic review was limited (n = 7), and outcome measures and inclusion criteria were heterogeneous. As such, the authors stressed the need for further research (Bosmans et al. 2021). A recent retrospective study by Cohen et al. (2022) included measures of vestibular function in patients with MCI and AD. They described more vestibular impairments in patients with MCI and AD compared to healthy controls, particularly on Dix-Hallpike manoeuvres and cervical VEMP (cVEMP), supporting previous literature (Cohen et al. 2022). In addition to peripheral vestibular end-organ dysfunction, imbalance can also be associated with AD. People with AD carry a higher incidence of imbalance, gait abnormalities and falls, often resulting in fractures (Biju et al. 2022; Dev et al. 2021; Dyer et al. 2020). A recent study observed patients with AD to fall twice as frequently as their non-AD peers (Dev et al. 2021). Wandering, related to spatial disorientation, is a common complaint of AD patients (Alzheimer's Association 2020). Thus, the association between vestibular function in the broad sense and the AD continuum is supported by many studies, but the interactions between the different aspects of vestibular function (spatial navigation, peripheral vestibular end-organ function, and balance) within the AD continuum remain currently underexplored and unreplicated.

We hypothesize a dose-response-type relationship of vestibular function loss and clinical decreased balance performance with progression of cognitive impairment in our groups. This study aims to better comprehend the proposed association between vestibular function and AD. The main objective is to compare vestibular parameters (vestibular function testing and

clinical balance measures) between a group with MCI, AD, and healthy controls with age-normal cognition. Additionally, the suitability of vestibular and balance parameters to predict cognition was explored.

MATERIALS AND METHODS

Participants

Participants were recruited from the ***ANONYMOUS*** study. This is an ongoing prospective longitudinal cohort study evaluating the effect of hearing loss and vestibular decline on cognitive functioning in older adults ***REFERENCE TO PROTOCOL, ANONYMOUS***. The current study included cross-sectional data of the ***ANONIMIZED*** study. Participant recruitment was performed at the departments of Otorhinolaryngology and Neurology of ***ANONYMOUS HOSPITAL***. The ethical committee of the ***ANONYMOUS HOSPITAL*** (EC number B300201938949) approved this protocol. All participants gave their written informed consent per the Declaration of Helsinki before participation. The study protocol builds upon the Clinical Trials protocol with identifier ***ANONYMOUS***.

People with Cognitive Impairment

Inclusion criteria were 1) age between 55-84 years; 2) diagnosis of MCI or AD; 3) fluent in Dutch; 4) ability to obtain informed consent from the participant or a legally authorized representative. A diagnosis of MCI or AD was based on the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria (Albert et al. 2011; McKhann et al. 2011). A formal neuropsychological exam was performed at the beginning of testing to support the diagnosis of MCI and AD. This neuropsychological exam included the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) and Repeatable Battery for the Assessment of

Neuropsychological Status for Hearing Impaired Individuals (RBANS-H) (Claes et al. 2016; Randolph et al. 1998). For more information about the RBANS-H, please refer to Claes et al. (2016). Participants with an RBANS-H total score ≤ percentile 16, which means that they scored 1 SD or lower from the mean, were considered patients with MCI. A formal diagnosis of AD was made by the attending neurologist based additionally on (hetero)anamnesis (in all patients), brain MRI (in all patients), additional formal extensive neuropsychological exam (in all patients), blood analysis (in all patients), brain FDG-PET scan (in 16/17 patients), and cerebrospinal fluid AD biomarker analysis (in 7/17 patients). All exams needed to be suggestive of AD and should not be indicative of an alternative diagnosis.

Patients were excluded if MMSE score ≤ 12 to ensure reliable understanding and following of instructions (Harun et al. 2017).

Healthy Controls

For each subject with cognitive impairment, a healthy control was matched based on age, sex, and hearing function (based on pure tone audiometry averaged unaided threshold of 1 kHz, 2 kHz, and 4 kHz in the best hearing ear). In addition, to ensure preserved cognitive function, a neuropsychological test battery (RBANS-H) was performed at the beginning of testing (Claes et al. 2016). Participants with an RBANS-H total score above percentile 16 were included in the healthy control group.

Vestibular Function Testing

Testing of the Peripheral Vestibular End-organ

Cervical Vestibular Evoked Myogenic Potentials (cVEMPs)

cVEMPs measured function of the sacculus and intactness of the vestibulocollic reflex (VCR) using the Neuro-Audio device with electromyography feedback (Neurosoft, DIFRA). Participants lay in supine position and lifted and rotated their head to one side, thus tensioning the contralateral sternocleidomastoid (SCM) muscle, while short 500 Hz tone bursts were presented in the ipsilateral ear through insert-earphones at suprathreshold level (95 dB nHL). A typical cVEMP potential was biphasic and characterized by two distinctive peaks (p13, n23). The presence of an intact VCR was measured based on normative ranges as described by Li et al. (2014). Outcome measures included presence of intact responses (none, 1 ear, or both ears), and for each present response p13 latency (ms), n23 latency (ms), rectified amplitude (µV), and SCM muscle contraction level (mean rectified voltage, MRV, µV).

Video Head Impulse Test (vHIT)

The vHIT measured semicircular canal function and the accompanying vestibulo-ocular reflex (VOR) using the ICS Impulse (Otometrics, Natus, Pleasanton, California, USA). Participants focused on a fixation dot at eye level 1 meter in front of them. The researcher performed short, high-velocity head thrusts in the direction of all six (lateral, superior, and posterior; left and right ear) semicircular canals. Lateral VOR gains were measured, resulting in two values per participant (left and right lateral VOR gain).

Primary and Secondary Outcome Measures

Based on the systematic review by Bosmans et al. (2021), the latency of the p13 as measured by the cVEMP was chosen as the primary outcome measure for the peripheral vestibular end-organ function. Secondary outcome measures were cVEMP presence, n23 latency, rectified amplitude, MRV, and lateral VOR gains measured by the vHIT.

Clinical Balance Assessments

Timed Up-and-Go (TUG)

The TUG evaluated balance, walking pattern, fall risk, and mobility (Shumway-Cook et al. 2000). Participants started in a chair with their backs against the back of the chair. Then, they were instructed to rise from the chair, walk 3 meters, turn, walk back to the chair, and sit down again. They were encouraged to do this as quickly as possible but safely. This task was repeated 3 times and the mean time to complete this task was measured. In addition, individual mean completion times were categorized as “normal” or “abnormal”. This classification was based on age- and sex-specific normative scores published by Steffen et al. (2002). For our analyses, a score was abnormal when it exceeded the mean plus one SD, hence 10” for people in their sixties, 12” for men in their seventies, 11” for women in their seventies, 11” for men in their eighties, and 14” for women in their eighties.

Performance-Oriented Mobility Assessment (POMA) by Tinetti

The POMA test evaluated balance abilities in a chair and while standing (POMA-B) and dynamic balance during gait on an even walkway (POMA-G) (Köpke et al. 2006; Tinetti 1986). Higher scores indicate more independence, with a maximum score of 16 for the POMA-B. A cut-off score of ≤ 14 for the POMA-B was chosen for abnormal scores (Harada et al. 1995).

Functional Gait Assessment (FGA)

The FGA evaluated postural stability and balance during walking. Participants crossed a 6-meter long walkway with different instructions each time. Instructions included changing walking speed, walking with horizontal or vertical head turns, performing a 180° turn, walking up and down stairs, stepping over an obstacle, walking with arms folded across the chest and

184 with feet aligned heel to toe in tandem, walking with closed eyes, and walking backwards
185 (Beninato et al. 2014; Wrisley et al. 2010). A maximum score of 30 could be obtained. A cut-
186 off score of ≤ 22 for the FGA was chosen for abnormal scores, indicating an increased fall risk
187 (Beninato et al. 2014; Wrisley and Kumar 2010).

188 *Primary and Secondary Outcome Measures*

189 Because of its time efficiency, simplicity for use in clinical practice, and feasibility to conduct
190 in a small consulting room, the primary outcome measure for balance was the mean TUG
191 score. Secondary outcome measures included the POMA-B total score and FGA total score
192 and classification of individual normal and abnormal scores for the TUG, POMA-B, and FGA.
193 The POMA-G was not included in further analyses because of an expected and observed
194 ceiling effect.

195 **Demographic characteristics**

196 The MMSE is a routinely used screening device for cognitive impairment and takes 5-10
197 minutes to administer (Folstein et al. 1975). Based on the MMSE score, a more extensive
198 neuropsychological assessment can be indicated.

199 The RBANS-H is a comprehensive neuropsychological evaluation of cognitive function as well
200 as its subdomains, including immediate memory, visuospatial/constructional cognition,
201 language, attention, and delayed memory (Claes et al. 2016; Randolph et al. 1998). Because
202 of its accompanying slideshow presentation, cognitive function can be adequately evaluated
203 in individuals with hearing impairment.

204 Hearing function was evaluated using the Fletcher index high of the best hearing ear, unaided
205 (FI_{high}; average threshold of 1 kHz, 2 kHz, and 4 kHz). To resemble real-world hearing status

more closely, the best-aided speech-in-noise (SPIN) test in free field was assessed by the Leuven Intelligibility Sentences Test (van Wieringen et al. 2008). Analysis included the best-aided condition, where participants wore their hearing aid(s) if they had them.

Education level was calculated as the number of years spent in school, starting from the age of 6 years old.

Statistical Analysis

Levene's tests and data visualisation using histograms confirmed equal variances for all measures and a normal data distribution. Continuous variables and outcome measures were compared between the three groups (healthy controls, MCI, and AD) with ANOVA. Results of continuous data were further clarified using post-hoc comparisons with the Tukey-Kramer method, with *eta squared* (η^2) indicating the effect size of the full model (with ≥ .01 indicating small, ≥ .06 medium, and ≥ .14 large effect size) and *Cohen's d* (with 95% confidence interval) indicating the effect size of each pairwise comparison (with ≥ .2 indicating small, ≥ .5 medium, and ≥ .8 large effect size). The Pearson's Chi-squared statistic was used for categorical variables, with *phi* (*w*) indicating the effect size (with ≥ .1 indicating small, ≥ .3 medium, and ≥ .5 large effect size). Post-hoc comparisons were made by performing pairwise comparisons for all combinations. In addition, a multiple linear regression model using the backward elimination technique was used to explore the suitability of vestibular and balance parameters to predict cognitive status (RBANS-H percentile score) for individuals. A *p*-value of <.05 was used as the stopping rule. For all statistical analyses, the program JMP Pro 15 (Medmenham, UK) was used.

RESULTS

Study Population

Demographic characteristics of people with cognitive impairment (MCI and AD) and healthy controls matched on age, sex, and hearing level can be found in Table 1. Hearing loss is a recognized risk factor for dementia and is often associated with vestibular dysfunction (Livingston et al. 2020; Lucieer et al. 2016; Santos et al. 2015). Therefore, the matching procedure used the Fletcher index high of the best hearing ear, unaided. To resemble real-world hearing status more closely, the best-aided speech-in-noise (SPIN) test in free field was included in the analysis of participant characteristics. The three groups did not differ in hearing level. Education level was included as a demographic characteristic, resulting in a significant difference. This needs to be considered when interpreting results. For transparency reasons, cognitive measurements including the RBANS-H total percentile score and MMSE are also included. MMSE scores only serve as an exclusionary criterion. Median [range] for the RBANS-H total percentile were 62 [18, 95] for healthy controls, 9 [1, 16] for MCI, and 0.2 [0, 2] for AD ($p < .0001$). Median [range] for the MMSE were 29 [24, 30] for healthy controls, 27 [23, 30] for MCI, and 19 [14,25] for AD ($p < .0001$).

Vestibular Function Testing

An overview of the vestibular function tests, their mean scores and standard deviations per group, their p-values, effect sizes, and post-hoc comparisons can be found in Table 2. A visual overview represented by boxplots can be found in Fig. ***1***. Regarding the primary outcome measure of vestibular function testing, participants with AD demonstrated a significantly delayed latency of the p13 component measured by cVEMP in comparison with the MCI and healthy control group, who did not differ in p13 latency ($p = .001$; $\eta^2 = .13$, medium effect; difference in means healthy controls vs. AD = 1.02; 1.10 SD). Secondary outcome measures

of vestibular function testing (including n23 latency, presence of intact responses, rectified amplitude, and MRV as measured by cVEMP; and lateral VOR gain as measured by vHIT) demonstrated no significant differences between the three groups. Effect sizes for these variables ranged from trivial to small effects. In 98 out of a total of 200 ears, an intact cVEMP response was found (healthy controls: 49/100; MCI: 34/62; AD: 15/30).

Regarding clinical balance assessments, the primary outcome measure mean TUG scores demonstrated a significant difference between healthy controls and people with cognitive impairment (participants with MCI and AD combined) (p <.0001; η^2 = .26, large effect). People with cognitive impairment took longer to complete this task successfully. Post-hoc comparisons indicated that the TUG time-to-complete was able to differentiate healthy controls from the MCI group in a significant way (p = .0014; d = 0.8, large effect; difference in means healthy controls vs. AD = 4.33; 1.96 SD). A similar pattern was observed in the total score of the FGA (p = .0001; η^2 = .18, large effect). People with cognitive impairment obtained lower scores in comparison to healthy controls. Here, a differentiation between healthy controls and the MCI group was significant (p = .0049; d = 0.7, medium effect). On the other hand, the MCI and AD groups obtained equivalent scores (p = .3734; d = 0.4, small effect; difference in means healthy controls vs. AD = 5.15; 1.22 SD). Last, the POMA-B score was significantly decreased in participants with AD compared with the MCI and healthy control group (p = .0031; η^2 = .12, medium effect). Here, equivalent scores were obtained for the healthy control and MCI group (p = .4581; d = 0.3, small effect). However, the MCI and AD groups differed significantly (p = .0461; d = 0.7, medium effect; difference in means healthy controls vs. AD = 1.45; 1.28 SD).

Similar results were obtained when individually classifying each balance result as “normal” or “abnormal”. Again, the TUG demonstrated a significant difference between healthy controls and people with cognitive impairment (p <.0001; w = .42, medium effect). The POMA-B classification differentiated in a significant way between the AD group and the healthy control and MCI group combined (p = .0019; w = .31, medium effect). Finally, the FGA classification differed significantly between groups (p = .0494; w = .21, small effect). Post-hoc comparisons did not reveal significant differences between pairwise comparisons.

To explore whether vestibular and balance parameters were suitable to predict cognition in this population, a multiple linear regression model using the backward elimination technique was conducted. Input of the initial model included demographic parameters (age, sex, and years of education), hearing function (Fletcher index high of the best hearing ear), peripheral vestibular end-organ parameters (cVEMP: p13 latency, n23 latency, rectified amplitude, MRV; vHIT: lateral gain), and clinical balance (TUG, POMA-B, FGA) to predict RBANS-H total scaled score. We used the RBANS-H total scaled score instead of the percentile score as this scaled score was more accurate in describing distinctly low scores (e.g.: percentile <0.1 reflected scaled scores 47 through 54 in the current dataset). This scaled score followed the distribution of the Wechsler IQ scale (100[SD,15]) (Weiss et al. 2006). A backward elimination regression model was able to reduce to five parameters which were: TUG, sex, and cVEMP: p13 latency, n23 latency, and rectified amplitude. These five final predictors added significance to the final equation (TUG, p < .0001, η^2 = .3078; sex, p = .0291, η^2 = .0265; cVEMP p13 latency, p = .0006, η^2 = .0683; cVEMP n23 latency, p = .0047, η^2 = .0453; cVEMP rectified amplitude, p = .0364, η^2 = .0243). The final equation was statistically significant ($F(5,89) = 19.3093$, p < .0001) with an R^2 of .5203. The equation for predicting cognition via the RBANS-H total scaled score is established as follows:

297 RBANS-H total scaled score

$$= 157.37 + (\text{Sex}) \begin{pmatrix} \text{female} \rightarrow -3.31 \\ \text{male} \rightarrow +3.31 \end{pmatrix} - 3.65 * (\text{TUG mean}) - 6.24$$

$$* (\text{cVEMP p13 latency}) + 2.73 * (\text{cVEMP n23 latency}) - 12.08$$

$$* (\text{cVEMP rectified amplitude})$$

DISCUSSION

This study aimed to better comprehend the proposed association between vestibular function and AD by comparing vestibular parameters (vestibular function testing and clinical balance assessments) between a group with MCI, AD, and healthy controls with age-normal cognition. These groups were matched on age, sex, and hearing level. In general, vestibular and balance deficits were more prevalent in the groups with increasing cognitive decline. Regarding vestibular function testing, only p13 latency as measured by cVEMP demonstrated an increase in latency in participants with AD compared to the MCI and healthy control groups. Other variables of the cVEMP (measuring saccular function) or vHIT (measuring semicircular canal function) demonstrated no difference among the three groups. This implied that saccular function, rather than semicircular canal function, may underlie the association between vestibular loss and cognitive impairment. In addition, saccular function testing (in particular p13 latency as measured by cVEMP) may allow for early detection of individuals at risk for MCI and AD with a potential fall risk. These results support and extend previous literature on this topic (for a review, see Bosmans et al. (2021) and Agrawal et al. (2020)). Hence, this manuscript was able to confirm and replicate what existing literature has shown. A note of caution is due here as in the current study, intact cVEMP responses needed to have p13 and n23 latencies within the latency ranges defined by Li et al. (2014) (p13: 11.81-

15.59 ms; n23: 18.15-25.64 ms). However, multiple studies reporting cVEMP latencies applied different criteria. A recent systematic review with meta-analysis by Macambira et al. (2017) provided an overview of mean p13 and n23 latencies of studies comparing young and older adults. However, multiple mean p13 and n23 latencies in both young and older adult groups of this meta-analysis fell outside the ranges defined by Li et al. (2014), complicating comparisons across studies. This emphasizes the need for generally-accepted latency ranges and reporting of cVEMP variables to guarantee reliable interpretations and implications.

Regarding clinical balance assessment, participants with AD showed poorer performance on all three included tests (TUG, POMA-B, and FGA). The TUG and FGA were able to differentiate healthy controls from participants with cognitive impairment (MCI and AD combined). On the other hand, the POMA-B differentiated in a later stage along the AD continuum (healthy control and MCI versus AD). Caution should be exercised, however, when extrapolating the results of balance tests in order to assess vestibular function. In principle, static balance tasks are more appropriate to get an idea of vestibular function (sensory organization test) through changes in sensory test conditions (Cohen et al. 2019; Verbecque et al. 2021). Balance tasks including locomotion provide a better idea about the functional impact of a vestibular problem (Vereeck et al. 2007), but one should be aware that additional aspects such as non-vestibular sensory inputs, motor and executive functions may be involved in locomotion. This must be kept in mind, especially in a population with cognitive impairment.

Fig. ***2*** provides a schematic overview of actual clinical balance assessment data and how they change with cognitive decline. People with age-normal cognition demonstrated little deficits in any of the three clinical balance assessments. More than half of participants with AD demonstrated abnormal clinical balance function in all assessments. However, included

balance assessments converge from normal to abnormal at different rates, resulting in heterogeneous outcomes in the MCI stage. The combination of these three clinical balance assessments could give the impetus to construct a timeline and aid in pinpointing where a subject with cognitive impairment is located on the AD continuum, based on their balance function. Future research can extend this concept by integrating the vestibular-related parameters that add value and step away from redundant testing. As a recommendation, otolith function testing (including saccular and utricular function), spatial cognition, clinical balance, and subjective balance measurements (fear of falling, balance confidence, etc.) should be further investigated, whereas horizontal semicircular canal testing (by means of VOR testing) appears to be less relevant in a population with cognitive impairment. However, an important side note is that topographical memory has been related to horizontal semicircular canal functioning (Previc et al. 2014). Another important side note is that one study observed significantly reduced VOR gains in the anterior and posterior semicircular canals in patients with MMSE scores < 21 in comparison to healthy controls, while observing no significant differences in VOR gains of the horizontal semicircular canals (Yargholi et al. 2018). By plotting these parameters on a timeline covering the AD continuum, we may gain a more extensive understanding about the gradual changes of the vestibular system and its associated regions. This may increase our knowledge about the potential of vestibular rehabilitation or other vestibular interventions such as a vestibular implant to slow the progression of AD.

A first limitation of the current study is that we considered participants with an RBANS-H total score ≤ percentile 16 (hence ≤ 1 SD from the mean) as patients with MCI. According to guidelines by Albert et al. (2011), cognitive scores are typically 1 to 1.5 SD below the mean for the appropriate normative data. Our study uses the less stringent approach regarding

inclusion of participants with MCI, which has to be taken into account. Furthermore, biomarkers were not routinely tested in our MCI group, resulting in a heterogeneous group consisting of MCI due to AD as well as other causes of MCI. Another limitation of the current study is the absence of caloric irrigation, rotatory chair, and ocular VEMP (oVEMP) data to fully map peripheral vestibular end-organ function. Future research untangling vestibular function and its association with cognitive decline should include a complete and complementary battery of vestibular function tests, with special focus on cVEMP and oVEMP testing. We hypothesize that measures of horizontal semicircular canal function (vHIT, rotatory chair, and caloric irrigation) will demonstrate no change in people with advancing degrees of AD. This hypothesis is based on considerable evidence describing distinct pathways for motoneurons involved in the vestibulo-ocular reflex (VOR; associated with semicircular canal function) and saccular pathways (involved with the vestibulocollic reflex; VCR) transmitting vestibular information to higher brain areas. Here the VCR decreases simultaneously with cognitive decline, whereas the VOR gain would remain intact (Bosmans et al. 2021). However, this distinction should be nuanced as there is a large semicircular canal projection to the hippocampus in the form of head-direction cells so a higher-order semicircular canal influence should not be completely dismissed (Previc 1998, 2013). Keeping that in mind, otolith function (as measured by both oVEMP for the utriculus and cVEMP for the sacculus) may underlie the association between vestibular function and cognitive impairment and would therefore be interesting to further explore in a population with varying degrees of AD.

CONCLUSION

This cross-sectional study included participants with MCI, AD, and healthy controls and found that vestibular and balance deficits were more prevalent in groups with increasing cognitive decline. P13 latency as measured by cVEMP was delayed in participants with AD. Other cVEMP or vHIT measures did not differ between groups. All three included clinical balance assessments (TUG, POMA-B, and FGA) resulted in worse scores in participants with AD. However, included balance assessments converged from normal to abnormal at different rates, resulting in heterogeneous outcomes in the MCI stage. Future research integrating a complete assessment of otolith function testing, balance, and spatial cognition is recommended to fully comprehend the gradual changes of the vestibular system and its associated regions in advancing degrees of cognitive decline.

STATEMENTS AND DECLARATIONS

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

A separate "Acknowledgments and Author Contribution Statement" document has been uploaded.

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TABLES

Table 1. Demographic, hearing, and cognitive characteristics of people with cognitive impairment (Mild Cognitive Impairment and Alzheimer's disease) and healthy controls. p-Values in *italics* are the result of the Pearson's Chi-squared statistic, whereas all other p-values reflect results of ANOVA. Education level indicates the number of years spent in school, starting from 6 years old. SD, standard deviation; FI_{high}, Fletcher index high; dB HL, decibel hearing level; SPIN, speech-in-noise; SRT, speech reception threshold; RBANS-H, Repeatable Battery for the Assessment of Neuropsychological Status for Hearing Impaired Individuals; MMSE, Mini-Mental State Examination.

Table 2. Results of vestibular function tests in healthy controls, Mild Cognitive Impairment, and Alzheimer's disease. Degrees indicate an interpretation of effect size (° = small, °° = medium, °°° = large). The Pearson's Chi-squared statistic was used for categorical variables, with phi (w) indicating the effect size. Categorical post-hoc comparisons were made by performing pairwise comparisons for all combinations. Here, phi (w) is reported as a measure of effect size. cVEMP, cervical Vestibular-Evoked Myogenic Potentials; MRV, mean rectified voltage; vHIT, video Head Impulse Test; VOR, vestibulo-ocular reflex; TUG, Timed Up-and-Go; POMA-B, Performance-Oriented Mobility Assessment Balance subscale; FGA, Functional Gait Assessment; HC, healthy controls; MCI, Mild Cognitive Impairment; AD, Alzheimer's disease.

FIGURES

Fig. 1 Visual overview of vestibular function tests, including testing of the peripheral vestibular end-organ and clinical balance assessments. A) cVEMP: p13 and n23 latency, B) cVEMP: rectified amplitude, C) cVEMP: MRV, D) vHIT: lateral VOR gain, E) clinical balance assessments. Whiskers indicate range; boxes, IQR; bold line, median. As different parameters are expressed in various units, the appropriate unit is defined between brackets. cVEMP, cervical Vestibular-Evoked Myogenic Potentials; MRV, mean rectified voltage; vHIT, video Head Impulse Test; HC, healthy controls; MCI, Mild Cognitive Impairment; AD, Alzheimer's disease; FGA, Functional Gait Assessment; POMA-B, Performance-Oriented Mobility Assessment Balance subscale; TUG, Timed Up-and-Go.

Fig. 2 Schematic overview of changes in balance through the Alzheimer's disease continuum. Each clinical balance result was per subject classified as "normal" or "abnormal". This classification was plotted against the RBANS-H total score. Each coloured line represents the logistic fit of a clinical balance assessment by the RBANS-H total score. HC, healthy controls; MCI, Mild Cognitive Impairment; AD, Alzheimer's disease; TUG, Timed Up-and-Go; POMA-B, Performance-Oriented Mobility Assessment – Balance subscale; FGA, Functional Gait Assessment.

Figure 1

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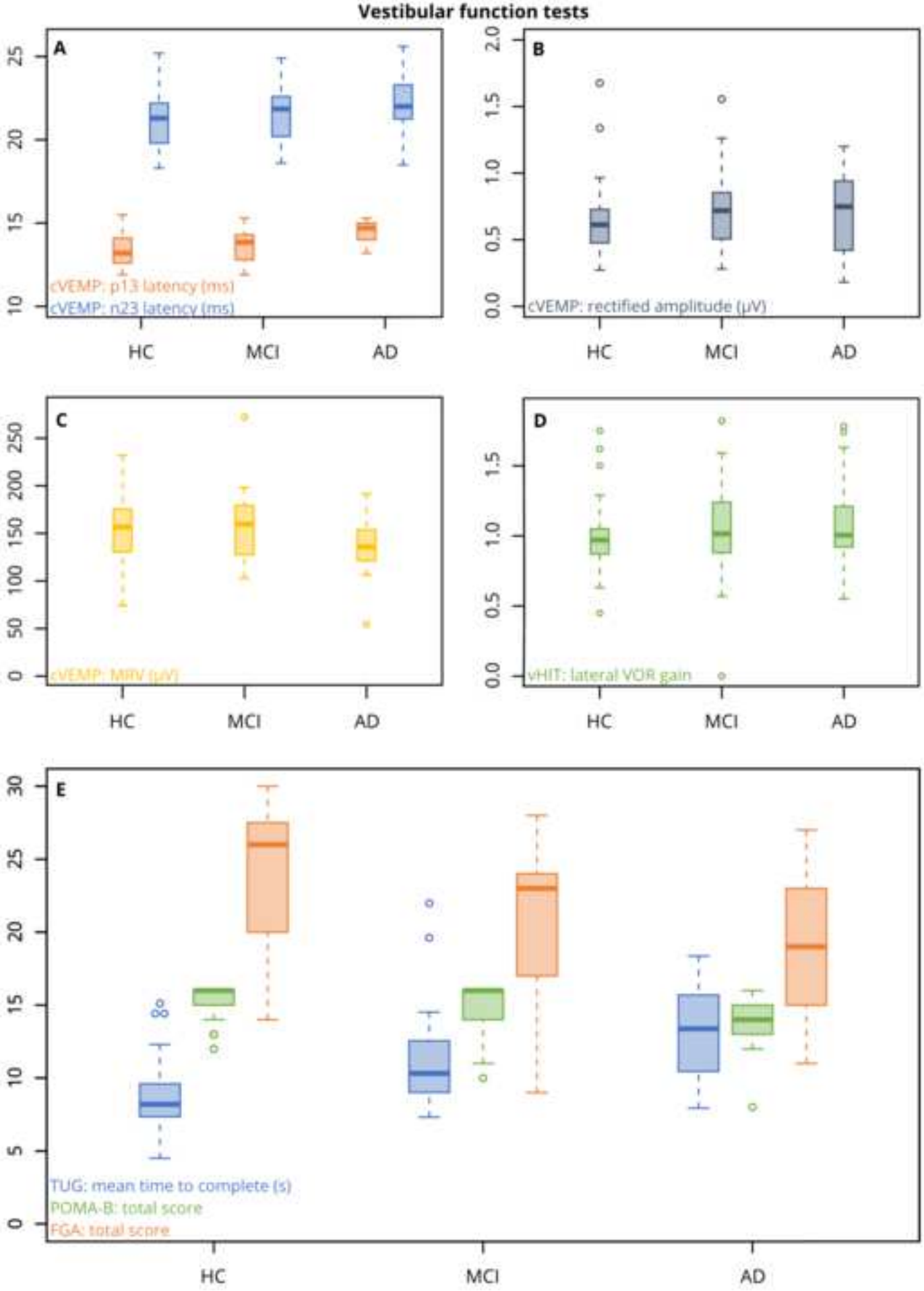

Figure 2

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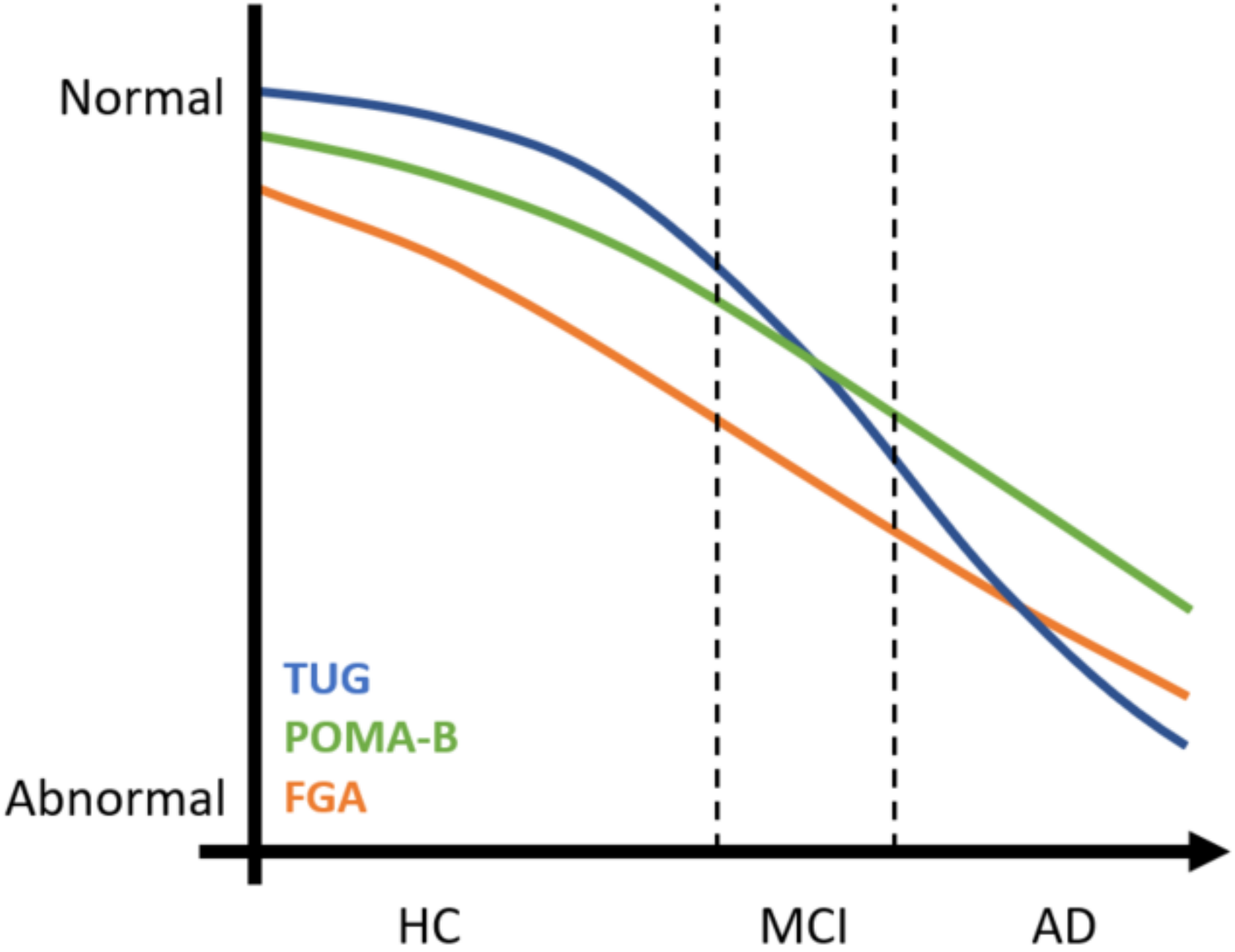

Table

Table 1. Demographic, hearing, and cognitive characteristics of people with cognitive impairment (Mild Cognitive Impairment and Alzheimer's disease) and healthy controls. p-Values in *italics* are the result of the Pearson's Chi-squared statistic, whereas all other p-values reflect results of ANOVA. Education level indicates the number of years spent in school, starting from 6 years old. SD, standard deviation; FI_{high}, Fletcher index high; dB HL, decibel hearing level; SPIN, speech-in-noise; SRT, speech reception threshold; RBANS-H, Repeatable Battery for the Assessment of Neuropsychological Status for Hearing Impaired Individuals; MMSE, Mini-Mental State Examination.

	Healthy Controls (n = 50)	Mild Cognitive Impairment (n = 33)	Alzheimer's disease (n = 17)	p-Value
Age (year: mean (SD))	74 (6.3)	74 (6.0)	76 (5.3)	.5206
Sex (n: M/F)	28/22	17/16	11/6	.6729
Education level (year: mean (SD))	13.7 (0.4)	12.4 (0.6)	11.6 (0.8)	.0319
Hearing level				
FI_{high} best ear (unaided dB HL: mean (SD))	43.0 (17.0)	43.3 (20.1)	39.4 (13.3)	.7194
SPIN (best-aided SRT: mean (SD))	-0.8 (4.0)	0.1 (3.9)	-0.2 (2.1)	.5358
Cognition				
RBANS-H total percentile (mean (SD))	59.4 (20.6)	8.5 (4.8)	0.3 (0.5)	<.0001
MMSE (mean (SD))	28.5 (1.6)	26.8 (1.9)	19.5 (3.4)	<.0001

Table 2. Results of vestibular function tests in healthy controls, Mild Cognitive Impairment, and Alzheimer's disease. Degrees indicate an interpretation of effect size (° = small, °° = medium, °°° = large). The Pearson's Chi-squared statistic was used for categorical variables, with phi (w) indicating the effect size. Categorical post-hoc comparisons were made by performing pairwise comparisons for all combinations. Here, phi (w) is reported as a measure of effect size. cVEMP, cervical Vestibular-Evoked Myogenic Potentials; MRV, mean rectified voltage; vHIT, video Head Impulse Test; VOR, vestibulo-ocular reflex; TUG, Timed Up-and-Go; POMA-B, Performance-Oriented Mobility Assessment Balance subscale; FGA, Functional Gait Assessment; HC, healthy controls; MCI, Mild Cognitive Impairment; AD, Alzheimer's disease.

	HC	MCI	AD	*p*-Value	η^2	Post-hoc comparison	Cohen's d [95% CI]
Peripheral vestibular end-organ							
cVEMP: p13 latency	13.4 (0.9)	13.7 (0.9)	14.4 (0.7)	.0010	.13°°	(HC = MCI) < AD	HC – AD: 1.1 [0.5,1.7]°°° HC – MCI: .3 [-0.2,0.7]° MCI – AD: .9 [0.2,1.5]°°
cVEMP: n23 latency	21.4 (1.7)	21.6 (1.6)	22.3 (1.9)	.1991	.03°	HC = MCI = AD	HC – AD: .5 [-0.1, 1.1]°° HC – MCI: .1 [-0.3, 0.6] MCI – AD: .4 [-0.2, 1.0]°
cVEMP: presence	0: 15 1: 21 2: 14 NA: 0	0: 9 1: 10 2: 12 NA: 2	0: 4 1: 7 2: 4 NA: 2	Chi-square (df=3): .8177	w: .09	HC = MCI = AD	HC – AD: w = .03 HC – MCI: w = .08 MCI – AD: w = .10°
cVEMP: rectified amplitude	0.6 (0.2)	0.7 (0.3)	0.7 (0.3)	.3579	.02°	HC = MCI = AD	HC – AD: .3 [-0.3, 0.8]° HC – MCI: .3 [-0.1, 0.7]° MCI – AD: .0 [-0.6, 0.7]
cVEMP: MRV	158.1 (33.9)	150.5 (37.9)	136.9 (32.9)	.0684	.05°	HC = MCI = AD	HC – AD: .6 [0.1, 1.1]°° HC – MCI: .2 [-0.2, 0.6]° MCI – AD: .4 [-0.2, 0.9]°

vHIT: Lateral VOR gain	1.0 (0.2)	1.0 (0.3)	1.1 (0.3)	.1049	.02°	HC = MCI = AD	HC – AD: .4 [-0.0,0.8]° HC – MCI: .3 [-0.1,0.6]° MCI – AD: .1 [-0.3,0.5]
Clinical balance assessments							
TUG: mean (SD)	8.8 (2.2)	11.1 (3.3)	13.1 (3.4)	<.0001	.26°°°	HC < (MCI = AD)	HC – AD: 1.5 [0.9,2.1]°°° HC – MCI: 0.8 [0.4,1.3]°°° MCI – AD: 0.7 [0.1,1.3]°°
TUG: classification	Normal: 43 Abnormal: 4 NA: 3	Normal: 19 Abnormal: 13 NA: 1	Normal: 7 Abnormal: 10	Chi-square (df=2): <.0001	w: .42°°	HC < (MCI = AD)	HC – AD: w = .50°°° HC – MCI: w = .38°° MCI – AD: w = .15°
POMA-B: total score	15.3 (1.1)	14.9 (1.6)	13.8 (1.9)	.0031	.12°°	(HC = MCI) > AD	HC – AD: 1.0 [0.4,1.6]°°° HC – MCI: .3 [-0.2,0.7]° MCI – AD: .7 [0.1,1.3]°°
POMA-B: classification	Normal: 38 Abnormal: 9 NA: 3	Normal: 24 Abnormal: 9	Normal: 6 Abnormal: 11	Chi-square (df=2): .0019	w: .31°°	(HC = MCI) > AD	HC – AD: w = .38°° HC – MCI: w = .09 MCI – AD: w = .31°°
FGA: total score	24.4 (4.2)	21.1 (4.8)	19.3 (4.9)	.0001	.18°°°	HC < (MCI = AD)	HC – AD: 1.1 [0.6,1.7]°°° HC – MCI: .7 [0.3,1.2]°° MCI – AD: .4 [-0.2,1.0]°
FGA: classification	Normal: 32 Abnormal: 15 NA: 3	Normal: 17 Abnormal: 16	Normal: 6 Abnormal: 11	Chi-square (df=2): .0494	W: .21°	HC = MCI = AD	HC – AD: w = .25° HC – MCI: w = .14° MCI – AD: w = .13°