



# Vestibular rehabilitation in older adults with and without mild cognitive impairment: Effects of virtual reality using a head-mounted display

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## ABSTRACT

**Purpose:** Due to the gap in the knowledge in the field of vestibular rehabilitation the purpose of this randomized study is to highlight the outcomes of head-mounted display (HMD) implementation in older adults and patients with mild cognitive impairment (MCI), suffering from unilateral vestibular hypofunction (UVH).

**Materials and methods:** Vestibulo-ocular reflex (VOR) gain, postural sway examination and dizziness-related and quality of life scores were collected in 12 UVH elderly and 12 UVH subjects suffering from MCI only undergoing vestibular rehabilitation and in 11 UVH elderly and 12 UVH subjects suffering from MCI undergoing a home-based HMD + vestibular rehabilitation protocol.

**Results:** Although the within-subjects analysis found in all groups a significant ( $p < 0.05$ ) improvement in posturography parameters and dizziness-related and quality of life scores and no changes in VOR gain, implementation of HMD demonstrated a significant ( $p < 0.05$ ) increase in post-treatment between-group comparisons in the same tests and VOR gain with respect to those older adults and participants with MCI only undergoing vestibular rehabilitation. Positive correlations were discovered between Mini-Mental Score Exam values and pre-/post-treatment differences in (i) power spectra values in the low-frequency interval ( $r = 0.72$ ) and in (ii) Dynamic Gait Index scores ( $r = 0.76$ ).

**Conclusions:** This study demonstrates that the implementation of a home-based virtual reality protocol may be a safe option in order to ameliorate VOR, postural control and the quality of life also in the vestibular impaired patients in whom the presence of cognitive decline could hinder the achievement of the goal of rehabilitation.

## 1. Introduction

Vestibular rehabilitation employs neuroplasticity processes (adaptation, habituation, and substitution) in order to control dizziness and to improve static and dynamic balance stability and visuo-vestibular interactions in circumstances that provoke a mismatch in sensory information processing (Bergeron, Lortie, & Guitton, 2015). In unilateral vestibular hypofunction (UVH) patients, vestibular rehabilitation may enhance static and dynamic postural control, thus reducing imbalance and comorbid depression and anxiety, while enhancing self-confidence and quality of life (Bergeron et al., 2015). However, it has previously been demonstrated that the generally poor patient compliance related to the time-consuming, repetitive, and monotonous aspects of vestibular rehabilitation may sometimes induce patients to a reduction in adherence to the protocol. On the other hand, it has been found that

older adults suffer from reduced multisensory integration (Anson et al., 2017; Deshpande et al., 2016; Harun, Oh, Bigelow, Studenski, & Agrawal, 2016; Li et al., 2015; Micarelli, Viziano, Della-Morte, Augimeri, & Alessandrini, 2018) and that an age-related detriment to visual, proprioceptive, or vestibular subsystems could affect balance due to an impaired cognitive-related sensory signal processing (Anson et al., 2017; Deshpande et al., 2016; Harun et al., 2016; Horak & Hlavacka, 2001; Micarelli, Viziano, Della-Morte et al., 2018). In this light, previous evidence has highlighted that imbalance affecting UVH patients is not only related to the peripheral vestibular illness. In fact, a dysfunction involving the neural streams from the vestibular nucleus to limbic and cortical areas entailed in both cognition and orientation may also foster this process (Smith, 2017). In turn, among these patients affected by UVH, the degree of cognitive decline was found to be related to worse vestibular rehabilitation outcomes (Micarelli, Viziano,

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Bruno et al., 2018): modifications in vestibulo-ocular reflex (VOR) gain, postural changes and quality of life seem to rely pivotally on brain regions involved in both cognitive and vestibular input processing (Kingma & van de Berg, 2016; Micarelli, Viziano, Bruno et al., 2018). These recent findings suggest that cognitive decline may act as a disrupting factor to vestibular function recovery, even during the rehabilitation process. In this scenario, efficient and cost-effective vestibular rehabilitation-based virtual reality treatments were not tested in improving vestibular rehabilitation in patients with cognitive decline. Such treatments have been proposed as a potential alternative (Bergeron et al., 2015) in enabling adaptation, habituation, and substitution exercises for more motivated vestibular rehabilitation (Micarelli, Viziano, Augimeri, Micarelli, & Alessandrini, 2017; Viziano, Micarelli, Augimeri, Micarelli, & Alessandrini, 2018; Whitney et al., 2006), in treating persistent unsteadiness in vestibular disorders (e.g. acute vestibular neuritis and Meniere's disease) (Gottshall, Sessoms, & Bartlett, 2012; Hsu et al., 2017; Sparrer, Duong Dinh, Ilgner, & Westhofen, 2013; Whitney et al., 2006; Yeh et al., 2014), in gaze stabilization exercise training in UVH patients (Chen, Hsieh, Wei, & Kao, 2012) and in desensitizing patients to diverse disorienting visual stimuli (Hsu et al., 2017). In this field, the implementation of head mounted displays (HMD) was demonstrated to improve otoneurological performances in UVH patients also undergoing vestibular rehabilitation (Gottshall et al., 2012; Viziano et al., 2018). This may be due to HMD being able to follow the user's movements and offering images at a high definition due to their nearness to the eye (Gatica-Rojas & Mendez-Rebolledo, 2014).

The aspects - related to both the impact of cognitive decline on vestibular rehabilitation and those studies demonstrating a beneficial effect of HMD training on vestibular-related performances - were found to be possibly related to adaptation phenomena and/or central programming of eye movements (Micarelli, Viziano et al., 2017; Viziano et al., 2018). Thus the aim of the present study is to discover possible improvements that can be achieved with a patient-friendly, low-cost, and domestic HMD-based virtual reality procedure (Micarelli, Viziano et al., 2017; Viziano et al., 2018) and its relationship with cognitive decline when combined with a vestibular rehabilitation protocol. This has been performed with a randomized study involving both elderly and cognitive declined patients affected by UVH, compared with age- and cognitive- matched groups of patients affected by UVH and previously undergoing only vestibular rehabilitation protocol (Micarelli, Viziano, Bruno et al., 2018).

## 2. Materials and methods

### 2.1. Subjects

UVH subjects with Mild Cognitive Impairment (MCI) enrolled in the rehabilitation protocol were extracted after their enrollment and otoneurological evaluation (Micarelli, Viziano, Della-Morte et al., 2018) in the local longitudinal cohort study of aging performed by the ITER Center for Balance and Rehabilitation Research, a regional institutional interdisciplinary disorder clinic. The inclusion criteria for MCI were operationalized as follows by an expert clinician blinded to the study (BM): (1) age  $\geq 55$  years; (2) diagnosis of MCI; (3) Mini-Mental State Exam (MMSE) score  $\geq 11$ ; (4) fluency in Italian; and (5) ability to obtain informed consent from the participant or legally authorized representatives (Micarelli, Viziano, Della-Morte et al., 2018). The National Institute on Aging/Alzheimer's Association diagnostic criteria were employed by an expert clinician for the diagnosis of MCI (Albert et al., 2011; McKhann et al., 2011). The MMSE cut-off score was selected based on selective criteria for moderate-to-severe cognitive impairment (Perneczky et al., 2006). Vestibular testing parameters regarding twenty-three age-, gender- and education-matched UVH older adults with age-appropriate cognitive function were recruited from the Tor Vergata University Hospital database (Micarelli, Viziano, Della-

Morte et al., 2018). The degree of dementia-related orientation behavior was also evaluated following the Alzheimer's Disease Assessment Scale (ADAS-cog) orientation subscale in both groups (Fioravanti et al., 1994). According to accepted criteria (Hall et al., 2016), the diagnosis of chronic UVH was reached with at least 25% reduced vestibular response to bithermal water caloric irrigation on one side when calculated using the Jongkees' formula (Alessandrini et al., 2014) at least 3 months after the beginning of symptoms. Individuals were excluded if they were unable to figure out the protocol procedures, or were not able to be enrolled in the study due to neurological, orthopaedic conditions or general physical impairment, reducing the possibility to correctly perform the protocol. The demographic information (age, sex, and education) was extracted from the patients' charts. The level of education was assessed as less than 4, 5–7, 8–13 or more than 14 years. The clinical history of the subjects enrolled in the procedures did not highlight any falls, or relevant cardiovascular, metabolic, rheumatologic, orthopedic or other neurological disorders (Harun et al., 2016). The study – accepted by the Regional Ethical Committee Review Board – was registered in the clinicaltrials.gov website with identification number NCT03553264, it adhered to the principles of the Declaration of Helsinki and all the participants provided written informed consent after receiving a detailed explanation of the study.

After a thorough clinical otoneurological examination (Micarelli, Viziano, Bruno, Micarelli, & Alessandrini, 2016) performed by an expert otoneurologist (AV) blinded to the study, all UVH subjects underwent the following, 1 week before and 1 week after the vestibular rehabilitation or the HMD + vestibular rehabilitation protocol in which they were allocated - in terms of age, sex, body mass index, pathology, and cause of vertigo - by means of a computer-generated randomization schedule:

### 2.2. Otoneurological testing

#### 2.2.1. Video head impulse testing (vHIT)

The EyeSeeCam™ System (Schneider et al., 2009) and the technique used in previous protocols were used (Blodow, Pannasch, & Walther, 2013; Micarelli et al., 2016) for the evaluation of vHIT. The vHIT outcomes were defined as abnormal if two conditions were encountered: abnormal VOR gain with regard to the normative data and the presence of refixation saccades (revealed by visual inspection, according to (Blodow et al. (2013). With the manufacturer's software (OtoAccess™), both side median values registered at 60 ms were transferred onto .xls files for analysis. In line with previous procedures (Blodow et al., 2013; Micarelli et al., 2016, Micarelli, Liguori et al., 2017), the diagnosis of UVH was established in the present cohort when the VOR gain was found below 0.83 and 0.84 for right and left side respectively. These values represent the lower cut-off score of the gain-reference range ( $\text{mean}_{\text{normal}} \pm 2(\text{standard deviations; SD})$  equal to  $0.91 \pm 2(0.04)$  and  $0.90 \pm 2(0.03)$  for right and left side respectively) of a database including 153 healthy subjects, age- and gender- matched with the current sample of patients (Blodow et al., 2013; Micarelli et al., 2016; Micarelli, Liguori et al., 2017).

#### 2.2.2. Static posturography testing (SPT)

Each subject was trained – with sham testing – to maintain an upright position with the knees slightly apart, arms crossed over the chest, and heels together but not touching, the feet forming an angle of 30° on a stiff platform for static posturography (EDM Euroclinic™) (Karlberg, Magnusson, Malmstrom, Melander, & Moritz, 1996). The recording period then started with an interval of 60 s for each test (eyes closed or open while standing on the stiff platform) and the sampling frequency in the time domain set at 25 Hz (Micarelli et al., 2016; Micarelli, Liguori et al., 2017). The center of pressure (CoP) was observed, while patients were doing the test. The posturography measures evaluated were the trace length (length), the surface of the ellipse of confidence (surface) and the fast Fourier transform (FFT) processing of swaying on both the

X (right-left) and Y (forward-backwards) planes (Micarelli et al., 2016; Micarelli, Liguori et al., 2017). Time-domain oscillations outputs (X and Y) were moved from the original producer's software into a .txt format and the FFT processing was obtained by means of a Matlab function (Micarelli, Viziano, Della-Morte et al., 2018). Spectral values (power spectra, PS) of body oscillations were estimated on an .xls file, for every frequency included in the range between 0.0122–4.9927 Hz (Micarelli et al., 2016; Micarelli, Liguori et al., 2017). Spectral analysis has been frequently implemented in the field of posturography in order to separate the numerous physiological contributions to maintaining static balance (Bizid et al., 2009; Kohen-Raz, Himmelfarb, Tzur, Kohen-Raz, & Shub, 1996). Several Authors have proposed a characterization of frequency inputs in different groups, with a lower frequency interval associated with visuovestibular inputs, a middle frequency band related to cerebellar and proprioceptive cues and higher frequency oscillations representing perturbations of central origin (Bizid et al., 2009; Karapolat et al., 2010; Kohen-Raz et al., 1996). Although some discrepancies in range distribution exist between different Authors (Bizid et al., 2009; Kohen-Raz et al., 1996), previous experiences conducted on both healthy subjects and people suffering from various balance disorders (Giacomini, Sorace, Magrini, & Alessandrini, 1998; Micarelli et al., 2016; Micarelli, Liguori et al., 2017) showed consistency in discriminating balance organization. Thus, the frequency spectrum was split into three groups: 0.0122–0.6958 Hz (low frequency interval); 0.708–0.9888 Hz (middle frequency interval); 1.001–4.9927 Hz (high frequency interval). Inside each group of intervals, the spectral intensity was assessed by adding the relative PS of the single frequency and the group mean PS ( $\pm$  SD) (Micarelli et al., 2016; Micarelli, Liguori et al., 2017).

### 2.3. Self-report (SRM) and performance measure (PM)

- (1) The Italian Dizziness Handicap Inventory (DHI) version includes 25 questions conceived to evaluate a patient's functional (DHI-F; 9 questions), emotional (DHI-E; 9 questions) and physical (DHI-P; 7 questions) limitations on a three-point scale (Nola, Mostardini, Salvi, Ercolani, & Ralli, 2010).
- (2) The Activities-specific Balance Confidence scale (ABC) was used to assess the patient's subjective level of balance confidence experienced in 16 daily living activities ranging from 0% to 100% (Alahmari et al., 2014; Herdman et al., 2015).
- (3) The Dynamic Gait Index (DGI), which scores the subject's competence to accomplish diverse gait activities (e.g. walking with head turned and avoiding obstacles) (Herdman et al., 2015; Wrisley, Walker, Echternach, & Strasnick, 2003). The scale includes eight questions, with a score ranging from 0 to 3 (Alahmari et al., 2014; Herdman et al., 2015; Wrisley et al., 2003).

Finally, only the experimental HMD + vestibular rehabilitation groups were evaluated with the Simulator Sickness Questionnaire (SSQ), which was implemented to assess the relevance of 16 different manifestations across three subscales: nausea, oculomotor stress and disorientation. For each item, a 0 was recorded if none of these symptoms were present and a 1 was recorded if any degree of the symptom was present (mild, medium, or severe) (Nola et al., 2010). Scores for each subscale were summed and calculated by the patient or his/her relatives every day after the self-assessed HMD procedure, and the research team calculated a weekly mean.

### 2.4. Rehabilitation protocol

#### 2.4.1. Vestibular rehabilitation

In the light of the history, physical examination, and diagnostic tests for each patient, an exercise program was developed by a rehabilitation physician and administered to the patient after discussing it with the physiotherapist blinded to the study (IA). The treatment program given

to both groups of UVH patients consisted of training and exercises. Functions of the postural system, reasons for imbalance, and the purposes and contraindications for following the rehabilitation protocol were elucidated during the training. Patients were as engaged in conforming to the rehabilitation plan as their symptoms and skills allowed. Following previous protocols (Giray et al., 2009; Herdman et al., 2015), the home exercise schedule consisted of a patient-tailored association of adaptation (without and with the target moving on pitch and yaw planes for 1 min each three times per day), substitution, habituation, and balance and gait exercises. All the chronic UVH patients included in both vestibular rehabilitation and HMD groups were followed in the clinic twice a week for 4 weeks for 30–45 min and evaluated for adherence. Between supervised sessions, patients did a twice-daily home exercise plan for a total of 30–40 min/day (Micarelli, Viziano et al., 2017; Viziano et al., 2018).

#### 2.4.2. Description of apparatus and HMD-based vestibular rehabilitation session

According to previous experiences (Micarelli, Viziano et al., 2017; Viziano et al., 2018), the Track Speed Racing 3D game was run on the 5.2" display of a Windows Phone (Lumia 930, Windows 10 Mobile, Microsoft Corporation, Redmond, Washington, USA) after it was placed in the HMD 'Revelation' 3D VR Headset (length  $\times$  width  $\times$  depth = 140  $\times$  105  $\times$  64 mm, weight = 165 g, Chinavasion, Shenzhen, China). The headset was adjusted every day in terms of head band length, interpupillary distance, and focal depth of spherical resin lens by the patients themselves. The patients were specifically trained in the clinic at the beginning of the protocol by an otoneurologist with expertise in HMD implementation and blinded to the protocol (AM), and during the 4-week period of vestibular rehabilitation, each HMD group patient – with their relatives present, when necessary, for home supervision – was accurately instructed to perform the game protocol uninterruptedly for 20 min/day, while sitting on a chair or sofa and he was adequately motivated to reach the total amount of time to spend in both vestibular and head-mounted device-based rehabilitation protocol. As previously described (Micarelli, Viziano et al., 2017; Viziano et al., 2018), the Track Speed Racing 3D game consisted of a point-of-view never-ending race in which the car is steered from the cockpit by tilting the head to the left and to the right (Fig. 1). Compliance (including discomfort perception by means of the SSQ), supervision of correct adjustment, and performances of the patients were strictly evaluated twice a week by the trainers in the clinic (AM and MA).

#### 2.5. Data handling and statistical analysis

The Chi-square test was implemented to define associations between category factors and groups. Mean and standard deviations (SDs) of otoneurological, SRM/PM scores and neuropsychological measurements were assessed in all groups. In order to define that data were of Gaussian distribution, D'Agostino K-squared normality and Levene's homoscedasticity test were performed (where the null hypothesis is that the data are normally and homogeneously distributed). A mixed analysis of variance (ANOVA) was performed with group as between factor and pre- and post-treatment otoneurological and SRM/PM variables – including SSQ – as within-subject factors. Gender, age, neuropsychological measures, MCI disease duration (DD, in months), elapsing time (ET, in years) between UVH and MCI diagnosis were used—where possible—as categorical and continuous predictors. The significant cut-off level ( $\alpha$ ) was set at a p value of 0.05. Bonferroni correction for multiple comparisons was applied to test the significant main effects *post hoc*. Then, according to previous protocols (Alessandrini et al., 2018; Micarelli, Viziano, Bruno et al., 2018), given the exploratory nature of the study and the homoscedasticity of pre-treatment vestibular impairment between the two groups of patients, a two-tailed Spearman's rank correlation was applied between pre-/post-treatment differences ( $\Delta$ ) in otoneurological scores, SRM/PM scores and



Fig. 1. A participant wearing the head-mounted display and first point of view of gaming task in upright position (A and B, respectively) and in rightward head-tilted position (C and D, respectively).

neuropsychological measures, considering UVH patients values as ‘a continuum’. Thus, considering the sample size of this group and the two-tailed nature of the test, a significant cut-off level ( $\alpha$ ) was set at a  $p$  value of 0.05 (STATISTICA 7 package for Windows).

### 3. Results

#### 3.1. Subjects

After the randomization procedure 12 UVH elderly and 12 UVH participants with MCI underwent vestibular rehabilitation and 11 UVH elderly and 12 UVH participants with MCI subjects underwent the HMD + vestibular rehabilitation protocol. No patient from either group left the vestibular rehabilitation protocol before the end of the program (Fig. 2, Table 1).

#### 3.2. Otoneurological testing

Post-hoc comparisons found a significant post-treatment improvement in surface and length in both eyes open and closed condition in all study groups, a significant post-treatment reduction of PS values in the low-frequency interval, in both eyes closed and eyes open condition, on X and Y planes in all four groups and no significant VOR gain changes when comparing pre- and post-treatment values (Table 2 and 3).

The between-group analysis highlighted that VOR gain significantly increases in HMD + vestibular rehabilitation older adults when compared with vestibular rehabilitation older adults ( $p = 0.0080$ ), vestibular rehabilitation subjects with MCI ( $p = 0.0074$ ) and HMD + vestibular rehabilitation participants with MCI ( $p = 0.0081$ ). This parameter also significantly increases in HMD + vestibular rehabilitation participants with MCI with respect to vestibular rehabilitation subjects suffering from MCI ( $p = 0.0080$ ) and in older adults when compared to participants affected by MCI, both undergoing vestibular rehabilitation alone ( $p = 0.0082$ ) (Table 4, Fig. 3A). No differences were found when comparing HMD + vestibular rehabilitation participants with MCI and vestibular rehabilitation older adults.

Between-group effect in main post-treatment otoneurological, self-reported and performance measures differences in unilateral vestibular hypofunction (UVH) Older Adults and participants with Mild Cognitive Impairment undergoing vestibular rehabilitation (VR) or head-mounted displays + VR protocol. PS, power spectra; LF, low frequency interval; EO, eyes open; EC, eyes closed; X, X plane; Y, Y plane; VOR, vestibular-ocular reflex; DHI, Dizziness Handicap Inventory; DGI, Dynamic Gait Index; ABC, Activities-specific Balance Confidence scale. Exact  $p$ -values are given in the text.

The same analysis found that HMD + vestibular rehabilitation older adults significantly improved in post-treatment surface and length results in eyes closed condition compared with vestibular rehabilitation older adults ( $p = 0.0075$  and  $p = 0.0071$ , respectively) and subjects with MCI ( $p = 0.0069$  and  $p = 0.0066$ , respectively) as well as compared to HMD + vestibular rehabilitation participants with MCI ( $p = 0.0074$  and  $p = 0.0078$ , respectively) (Table 4). On the other hand, HMD + vestibular rehabilitation participants with MCI significantly improved in post-treatment surface and length in eyes closed condition with respect to vestibular rehabilitation subjects suffering from MCI ( $p = 0.0073$  and  $p = 0.0076$ , respectively). No differences were found when comparing the post-treatment surface and length measure between HMD + vestibular rehabilitation participants with MCI and vestibular rehabilitation older adults (Table 4).

Finally, a significant reduction in post-treatment PS values in this interval in both eyes closed and eyes open condition on X and Y planes was found in HMD + vestibular rehabilitation elderly compared to vestibular rehabilitation elderly ( $p = 0.0072$ ,  $p = 0.0077$ ,  $p = 0.0071$  and  $p = 0.008$ , respectively) and subjects with MCI ( $p = 0.0067$ ,  $p = 0.0065$ ,  $p = 0.0061$  and  $p = 0.0060$ , respectively) and to HMD + vestibular rehabilitation participants with MCI ( $p = 0.0069$ ,  $p = 0.0072$ ,  $p = 0.0067$  and  $p = 0.0066$ , respectively) (Table 4, Fig. 3B). The latter group and vestibular rehabilitation elderly patients demonstrated significant lower post-treatment PS values in all conditions when compared to vestibular rehabilitation patients suffering from MCI ( $p = 0.0069$ ,  $p = 0.0072$ ,  $p = 0.0079$  and  $p = 0.0078$ , respectively and  $p = 0.0066$ ,  $p = 0.0068$ ,  $p = 0.0072$ ,  $p = 0.0076$ ,

### Flow-diagram of participants in the study

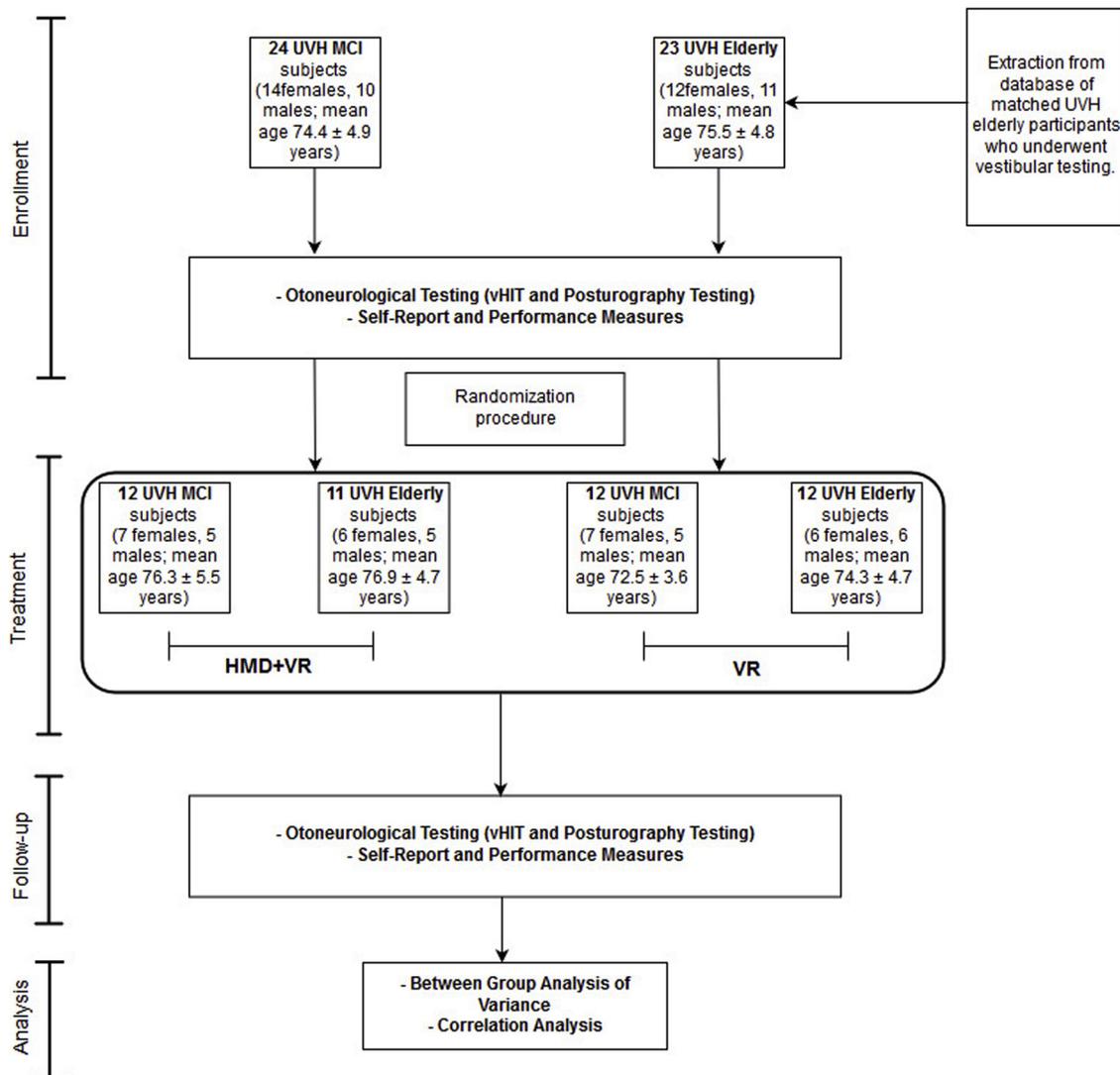


Fig. 2. Flow-diagram of participants in the study, randomization procedure and main outcomes. UVH indicates unilateral vestibular hypofunction; MCI, mild cognitive impairment; vHIT, video-head impulse test; HMD, Head Mounted Displays; VR, vestibular rehabilitation.

respectively) (Table 4, Fig. 3B).

### 3.3. Self-report (SRM) and performance measure (PM)

Although both interventions were found to lead to significant changes in physical, emotional, functional and total DHI values, as well as in DGI and ABC scores in all groups of patients (Table 3), HMD + vestibular rehabilitation older adults were found to have significant changes in post-treatment total DHI, DGI and ABC compared to vestibular rehabilitation older adults ( $p = 0.0077$ ,  $p = 0.008$ ,  $p = 0.0082$ , respectively) and subjects with MCI ( $p = 0.0068$ ,  $p = 0.0073$ ,  $p = 0.0076$ , respectively) as well as in DGI and ABC with regard to HMD + vestibular rehabilitation participants with MCI ( $p = 0.0075$  and  $p = 0.0081$ , respectively) (Table 4). Furthermore, the latter group was found to have a significant reduction in post-treatment total DHI when compared to vestibular rehabilitation older adults ( $p = 0.0078$ ) and significantly lower and higher values in total DHI and in DGI compared to vestibular rehabilitation patients suffering from MCI ( $p = 0.0074$  and  $p = 0.0082$ , respectively) (Table 4).

When evaluating UVH subjects' measures as 'a continuum',

significant ( $p < 0.05$ ) positive correlations were demonstrated between MMSE score and (i)  $\Delta$  PS values during closed eyes condition on Y plane in the low-frequency interval ( $r = 0.72$ , Fig. 4A) and (ii)  $\Delta$  DGI scores ( $r = 0.76$ , Fig. 4B).

In both HMD groups the within-subject analysis of SSQ scores demonstrated a significant reduction in symptoms related to nausea, oculomotor stress, and disorientation when comparing first versus second, first versus third and first versus fourth weeks' scores (Table 2).

## 4. Discussion

The first interesting finding in the present study is the significant improvement in otoneurological outcome measures in the UVH older adults patients with or without MCI in whom the vestibular rehabilitation protocol was implemented with the HMD procedure (Table 1 and 2). As previously highlighted in the literature, a pivotal intervention for patients with vestibular illnesses consists in performing exercises that encompass somatosensory-vestibular and/or visual-vestibular conflict (Herdman, 1989; Herdman, Schubert, & Tusa, 2001; Sienko, Whitney, Carender, & Wall, 2017). Considering the latter

**Table 1**  
Clinical and socio-demographic description of participants with unilateral vestibular hypofunction (UVH).

	VR Older Adults (n = 12)	VR MCI (n = 12)	HMD + VR Older Adults (n = 11)	HMD + VR MCI (n = 12)
Age (years)	74.3 ± 4.7	72.5 ± 3.6	76.9 ± 4.7	76.3 ± 5.5
Male	6	5	5	5
Female	6	7	6	7
Lesioned side	R = 7 L = 5	R = 6 L = 6	R = 5 L = 6	R = 7 L = 5
Pre-treatment VOR gain of affected side	0.63 ± 0.03	0.62 ± 0.03	0.63 ± 0.05	0.65 ± 0.03
Post-treatment VOR gain of affected side	0.71 ± 0.03	0.67 ± 0.02	0.74 ± 0.05	0.72 ± 0.03
ET (years)	16.5 ± 5.7	17.4 ± 4.9	17.2 ± 6	18.8 ± 7.5
DD (months)	–	23.5 ± 5	–	22.1 ± 6.1
MMSE	28.1 ± 1.2	25.5 ± 1.4	28 ± 1.4	25.7 ± 1.3
ADAS-cog (orientation subscale)	7.2 ± 0.7	5 ± 0.9	7.1 ± 0.6	5.1 ± 1
Level of education				
< 4 years	2	2	2	2
5–7 years	5	6	4	2
8–13 years	3	2	3	5
> 14 years	2	2	2	3
UVH etiology				
Neuritis	7	8	7	7
AN	2	1	2	1
Previous petrous	1	2	1	3
Previous cochlear	1	1	–	–
Ramsay-Hunt	1	–	–	1

Clinical and socio-demographic aspects of UVH older adults and participants with mild cognitive impairment (MCI) undergoing vestibular rehabilitation (VR) or head-mounted displays (HMD) + VR protocol. Time from diagnosis of MCI (disease duration), DD; time from diagnosis of UVH (elapsing time), ET; Right, R; Left, L; Mini-Mental State Exam, MMSE; Alzheimer’s Disease Assessment Scale orientation-related subscale; ADAS-cog; acoustic neuroma, AN; petrous surgery, petrous; cochlear surgery, cochlear. Where required, mean ± standard deviations are given.

condition and following previous experiences in the field of virtual reality (Alahmari et al., 2014; Bergeron et al., 2015; Micarelli, Viziano et al., 2017; Viziano et al., 2018; Whitney et al., 2006; Yeh et al., 2014), visual information in the present study was modified by inducing patients to do exercises in visually enriched environments (Alahmari et al., 2014; Herdman, 1989; Herdman et al., 2001; Micarelli, Viziano et al., 2017; Pavlou et al., 2012; Viziano et al., 2018) and increasing the

complexity of the protocol by including vestibular stimulation, such as eliciting head movements (Alahmari et al., 2014). As a consequence, the addition of this well-established, home-based virtual reality protocol for vestibular rehabilitation resulted – together with a progressive habituation to virtual reality stimuli (Table 3) – in a significant increase in VOR gain compared to those undergoing vestibular rehabilitation alone, both for older adults and patients with MCI (Fig. 3A, Table 4).

**Table 2**  
Pre- post-treatment within-subjects effect of main otoneurological measures in UVH Older Adults and patients with Mild Cognitive Impairment undergoing vestibular rehabilitation or HMD + vestibular rehabilitation protocol.

	VR Older Adults				VR MCI				HMD + VR Older Adults				HMD + VR MCI			
	Pre-treatment		Post-treatment		Pre-treatment		Post-treatment		Pre-treatment		Post-treatment		Pre-treatment		Post-treatment	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PS LF EC X	8.75	1.9	6.38	1.51	10.19	0.83	8.98	0.7	8.32	1.94	5.12	1.29	10.83	1.06	8.65	1.2
PS LF EC Y	8.15	2	5.62	1.69	10.21	0.89	8.86	1.02	8.63	1.51	5.03	0.71	10.75	1.33	8.52	1.47
PS LF EO X	5.94	0.61	4.41	0.58	6.87	0.86	5.73	0.81	6	0.57	3.1	0.5	6.91	0.86	4.88	0.68
PS LF EO Y	5.13	0.53	3.79	0.54	5.7	0.55	4.62	0.5	5.03	0.47	2.82	0.32	5.77	0.57	4.17	0.43
PS MF EC X	0.57	0.03	0.64	0.05	0.62	0.02	0.64	0.02	0.57	0.04	0.64	0.02	0.61	0.01	0.64	0.01
PS MF EC Y	0.5	0.02	0.55	0.02	0.54	0.01	0.56	0.01	0.51	0.02	0.55	0.01	0.55	0.01	0.57	0
PS MF EO X	0.31	0.02	0.38	0.02	0.33	0.01	0.37	0.01	0.31	0.02	0.39	0.02	0.33	0.02	0.36	0.01
PS MF EO Y	0.22	0.01	0.28	0.02	0.23	0.01	0.27	0.01	0.22	0.01	0.29	0.01	0.24	0.01	0.26	0.01
PS HF EC X	1.18	0.12	1.13	0.13	1.14	0.09	1.09	0.08	1.07	0.1	1.14	0.11	1.22	0.04	1.1	0.06
PS HF EC Y	1.07	0.12	1	0.08	1.14	0.08	1.08	0.08	1.06	0.12	0.99	0.1	1.1	0.06	1.06	0.06
PS HF EO X	1.07	0.12	0.98	0.11	1.08	0.06	1.03	0.06	1.02	0.21	0.97	0.19	1.12	0.03	1.05	0.04
PS HF EO Y	0.91	0.14	0.84	0.13	0.99	0.06	0.95	0.06	0.92	0.16	0.83	0.15	0.95	0.02	0.91	0.03
Surface EO	721.36	188.75	499.72	210.67	918.81	2062.83	703.12	1855.42	773.4	272.5	481.86	236.61	865.59	165.8	591.06	173.26
Surface EC	1742.83	323.98	1154.44	214.79	183.81	287.87	133.83	280.88	1645.06	563.39	831.94	357.51	2121.06	346.42	1537.84	327.36
Length EO	654.89	109.42	407.92	99.55	768.47	1100.35	633.98	968.85	633.49	120.01	338.51	93.19	743.58	125.18	550.21	101.68
Length EC	942.01	190.5	642.31	180.9	105	126.58	110.16	108.4	996.85	173.22	471.91	113.8	1165.9	125.65	807.33	192.89
VOR gain of the affected side	0.63	0.03	0.71	0.03	0.62	0.03	0.67	0.02	0.63	0.05	0.74	0.05	0.65	0.03	0.72	0.03

Significant changes in main otoneurological measures before and after vestibular rehabilitation (VR) or head-mounted displays (HMD) + VR protocol in unilateral vestibular hypofunction (UVH) Older Adults and patients with Mild Cognitive Impairment (MCI). PS, power spectra; LF, low frequency interval; MF, middle frequency interval; HF, high frequency interval; EO, eyes open; EC, eyes closed; X, X plane; Y, Y plane; VOR, vestibulo-ocular reflex; DHI, Dizziness Handicap Inventory; P, Physical; E, Emotional; F, Functional; DGI, Dynamic Gait Index; ABC, Activities-specific Balance Confidence scale; SSQ, Simulator Sickness Questionnaire; N, Nausea; O, Oculomotor Stress; D, Disorientation; SD, standard deviation. In bold significant within-subjects changes.

**Table 3**

Pre- post-treatment significant within-subjects effect of main self-reported and performance measures in UVH Older Adults and patients with Mild Cognitive Impairment undergoing vestibular rehabilitation or HMD + vestibular rehabilitation protocol.

	VR Older Adults				VR MCI				HMD + VR Older Adults				HMD + VR MCI			
	Pre-treatment		Post-treatment		Pre-treatment		Post-treatment		Pre-treatment		Post-treatment		Pre-treatment		Post-treatment	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
DHI-P	17.83	4.13	9.66	2.05	25	2.33	18.83	2.32	18.54	4.56	7.81	3.73	24.5	4.52	13.33	4.03
DHI-E	22.66	3.22	12.83	2.16	25.33	3.22	18.83	2.75	22.72	3.92	12	3.79	26.83	3.76	16.16	3.95
DHI-F	20.66	5.41	11	3.35	20.5	4.44	13.66	3.49	22.72	2.86	10.9	2.58	23.33	4.92	12.5	4.27
Total DHI	61.16	7.25	33.5	4.98	70.83	4.7	51.33	4.2	64	5.05	30.72	5.67	74.66	4.11	42	6.09
DGI	12.5	1.62	19	1.47	10.5	1.97	14.41	2.02	11.36	1.68	20	1.84	10	2.04	15.08	2.6
ABC	64.91	5.94	72.41	6.15	56.66	5.83	62.58	5.35	62.54	4.8	71.36	4.24	57.41	5.64	64	5.73

SSQ

	1st week		2nd week		3rd week		4th week		Significance		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	1st vs 2nd	1st vs 3rd	1st vs 4th
HMD + VR Older adults											
N	2.9	0.7	2.27	0.46	1.81	0.6	1.36	0.5	p < 0.05	p < 0.05	p < 0.05
O	4	0.63	3.36	0.5	2.72	0.64	2.09	0.53	p < 0.05	p < 0.05	p < 0.05
D	4	0.77	3.36	0.5	2.72	0.64	1.9	0.7	p < 0.05	p < 0.05	p < 0.05
HMD + VR MCI											
N	2.81	0.6	2.27	0.46	1.81	0.6	1.45	0.52	p < 0.05	p < 0.05	p < 0.05
O	4.18	0.75	3.36	0.67	2.72	0.46	2	0.44	p < 0.05	p < 0.05	p < 0.05
D	3.9	0.53	3.36	0.67	2.63	0.5	1.9	0.53	p < 0.05	p < 0.05	p < 0.05

Significant changes in main self-reported and performance measures before and after vestibular rehabilitation (VR) or head-mounted displays (HMD) + VR protocol in unilateral vestibular hypofunction (UVH) Older Adults and patients with Mild Cognitive Impairment (MCI). DHI, Dizziness Handicap Inventory; P, Physical; E, Emotional; F, Functional; DGI, Dynamic Gait Index; ABC, Activities-specific Balance Confidence scale; SSQ, Simulator Sickness Questionnaire; N, Nausea; O, Oculomotor Stress; D, Disorientation; SD, standard deviation.

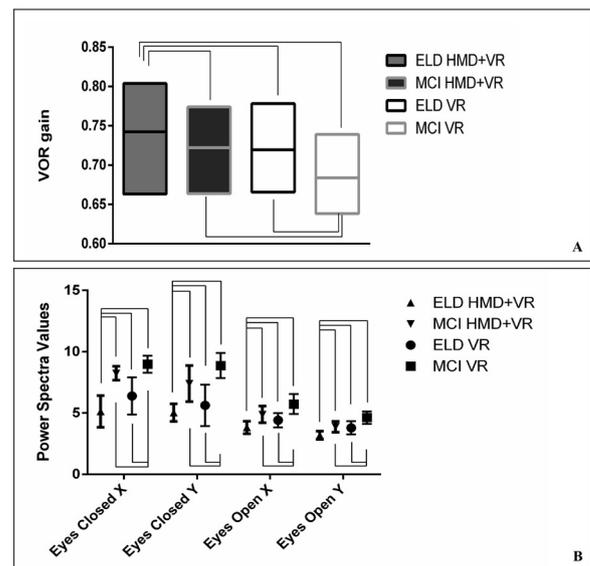
**Table 4**

Between-group effect of main post-treatment values in UVH Older Adults and participants with Mild Cognitive Impairment undergoing the vestibular rehabilitation or the HMD + vestibular rehabilitation protocol.

	Significance
PS LF EC X	F(3, 43) = 29.859, p < 0.001
PS LF EC Y	F(3, 43) = 21.141, p < 0.001
PS LF EO X	F(3, 43) = 17.375, p < 0.001
PS LF EO Y	F(3, 43) = 18.708, p < 0.001
Surface EC	F(3, 43) = 25.843, p < 0.001
Length EC	F(3, 43) = 22.045, p < 0.001
VOR gain of lesioned side	F(3, 43) = 9.603, p = 0.0072
Total DHI	F(3, 43) = 31.787, p < 0.001
DGI	F(3, 43) = 21.841, p < 0.001
ABC	F(3, 43) = 11.025, p < 0.001

This finding might extend previous studies (Micarelli, Liguori et al., 2017; Viziano et al., 2018) demonstrating that the implementation of home-based virtual reality protocol is useful in reinforcing the vestibular rehabilitation-related effects on VOR gain and for the first time could indicate further chances for vestibular rehabilitation in patients in whom cognitive decline has been addressed as an aspect that probably impacts the results of vestibular rehabilitation (Micarelli, Viziano, Bruno et al., 2018). On the other side, the absence of a significant within-subject effect of VOR gain increase might possibly indicate – according to the literature (McGarvie et al., 2015) – that vestibular responsiveness could possibly decrease throughout the increase of age-related cognitive decline. This behaviour appears indirectly more evident when comparing the present findings with those in which VOR gain had a more pronounced within-subject effect in younger patients undergoing similar rehabilitation protocols (with or without implementation of virtual reality) (Micarelli, Viziano et al., 2017; Viziano et al., 2018). Thus – beyond the significance of the VOR gain improvement (and its related consequences in terms of quality of life and balance) exhibited by older patients in the present study – such

Between-group effect of post-treatment VOR gain and low frequency domain power spectra values in UVH older adults and participants with MCI

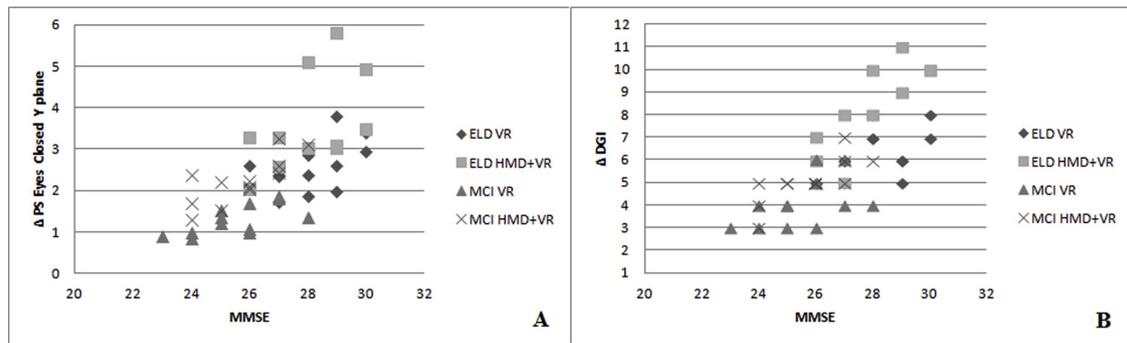


**Fig. 3.** Mean and standard deviations of significant post-treatment vestibulo-ocular reflex (VOR) gain (A) and power spectra on X and Y planes (B) when comparing older adults (ELD) and participants with mild cognitive impairment (MCI) affected by unilateral vestibular hypofunction (UVH) undergoing vestibular rehabilitation (VR) or head-mounted displays (HMD) + VR protocol. Brackets indicate significant comparisons. Exact p-values are given in the text.

differences may speculatively suggest that the vestibular system could suffer from a less susceptibility to rehabilitation, possibly related to its progressive weakness in physiological activity throughout the increase of age (Harun et al., 2016; McGarvie et al., 2015).

Extending these theories, although the route through which the

## Correlations between pre- and post-treatment otoneurological/performance measures differences and MMSE



**Fig. 4.** Single-case plotted scatterplots of correlations between (A) low-frequency power spectra (PS) pre-/post-treatment differences ( $\Delta$ ) values during EC on Y plane and Mini-Mental State Exam (MMSE) scores and (B) between Dynamic Gait Index  $\Delta$  values and MMSE scores in unilateral vestibular hypofunction older adults (ELD) and participants with mild cognitive impairment (MCI) enrolled in vestibular rehabilitation (VR) or head-mounted displays (HMD) + VR protocol.

neural pathways may counterbalance the impairments in the sensory integration of vestibular, visual, and somatosensory inflows (Hall et al., 2016; Herdman et al., 2001; Micarelli, Viziano et al., 2017) is not fully understood, the main rehabilitative rules (including adaptation, behavioral substitution and habituation (Hondebrink, Mert, van der Lint, de Ru, & van der Wurff, 2017)) are hypothesized also to rely on the relationship between the vestibular system and cognitive areas (Klatt, Ries, Dunlap, Whitney, & Agrawal, 2019). For instance, some evidences demonstrated that projections starting from the vestibular system — in part engaged in vestibular rehabilitation neural maps — might interact at multiple levels during the processing inflow (Harun, Semenov, & Agrawal, 2015). This is particularly interesting especially when taking into account that the temporal lobe and hippocampus are thought to be engaged in memory and spatial orientation (Brandt & Dieterich, 1999; Brandt et al., 2005; Harun et al., 2016) and that ascending and descending neural pathways may connect the two systems involved in cognitive domain and balance control, respectively (Furman, Redfern, Fuhrman, & Jennings, 2012), in human and animal models (Besnard et al., 2012; Furman, Muller, Redfern, & Jennings, 2003, 2012; Harun et al., 2016; Russell, Horii, Smith, Darlington, & Bilkey, 2006; Seemungal et al., 2013). In line with these notions and previous similar protocols (Micarelli, Viziano et al., 2017; Viziano et al., 2018), the premises for which implementation of HMD may have maximized the vestibular-related parameters in both groups of patients, could be possibly related to the peculiarity of the present virtual reality protocol. As previously highlighted (Micarelli, Viziano et al., 2017), the protocol has been found to enhance the pre-programmed eye movements that tend to occur more frequently during active and predictable head movements (Herdman, Schubert, Das, & Tusa, 2003). In fact, the present HMD gaming task procedure was hypothesized to increase the frequency of the visuo-vestibular conflicting movements, such as centrally programmed eye movements, with the request for improved smooth pursuit or use of saccades (Szturm, Reimer, & Hochman, 2015), head movement activities coupled with the altered visual scene motion emulating eye-head exercises (Viirre & Sitarz, 2002) and exposure to background motion during gameplay (Chang & Hain, 2008). These sensory-motor challenges may be supposed as factors involved in also stimulating the widespread projections to cortical centers involved in both memory and spatial orientation (Besnard et al., 2012; Bigelow & Agrawal, 2015; Brandt et al., 2005; Harun et al., 2016; Russell et al., 2006; Stackman & Herbert, 2002).

Secondly, although an overall improvement of posturography parameters was present in all groups after HMD + vestibular rehabilitation and/or vestibular rehabilitation treatment alone (Table 2), VOR findings have been further corroborated by the significant reduction found in surface and length values and in PS values in low-frequency intervals in many conditions – including those recorded in

challenging situations (e.g. eyes closed) – in both older adults and participants with MCI undergoing HMD + vestibular rehabilitation protocol when compared to patients with greater cognitive decline and/or vestibular rehabilitation alone groups (Fig. 3B, Table 4).

These findings are in line with those differences in posturography parameters - such as sway path (length) and area (surface) – that have been demonstrated between healthy people, patients with vestibular disorders (Giacomini et al., 1998; Micarelli et al., 2016; Teggi et al., 2009) and subjects suffering from cognitive decline (Leandri et al., 2009; Micarelli, Viziano, Della-Morte et al., 2018) and have also been reliably associated with improvements after balance treatment (Jauregui-Renaud, Cruz-Gomez, & Villanueva-Padron, 2013; Uehara et al., 2011). With regards to spectral analysis, although previous experiences have shown good consistency with other posturographic parameters (Alessandrini, Lanciani, Bruno, Napolitano, & Di Girolamo, 2006; Bizid et al., 2009; Giacomini et al., 1998; Kohen-Raz et al., 1996), and modifications in low-frequency signal are thought to be especially influenced by vestibular inputs (Alessandrini et al., 2014; Bizid et al., 2009; Karapolat et al., 2010; Karlberg et al., 1996; Kohen-Raz et al., 1996; Uehara et al., 2011) and degree of cognitive decline (Micarelli, Viziano, Bruno et al., 2018; Micarelli, Viziano, Della-Morte et al., 2018), some limitations must be taken into account; for example, most of the spectral power in postural swinging lies within the low-frequency interval also in healthy subjects (Lacour, Bernard-Demanze, & Dumitrescu, 2008; Yamamoto et al., 2015), while cut-off points between different frequency ranges are debated among different research groups (Bizid et al., 2009; Golomer, Dupui, & Bessou, 1994; Kohen-Raz et al., 1996). Moreover, inherent limitations of FFT analysis, such as limited test duration and sampling frequency, must be considered (Lacour et al., 2008). Taken together, we may interpret posturography results as indicating a more lenient recovery in those patients undergoing only vestibular rehabilitation treatment and/or affected by cognitive decline (Micarelli, Viziano, Bruno et al., 2018), thus suggesting possible reinforcing strategies based on HMD in these subjects.

Moreover, previous theories postulated that i) vestibular rehabilitation is not exclusively related to VOR improvement but also to vestibulo-spinal streams – associated with a longer loop in relation with visuo-vestibular regulation (lower frequencies) - that are pivotally involved in the control of balance (Paillard, Costes-Salon, Lafont, & Dupui, 2002; Charpiot, Tringali, Ionescu, Vital-Durand, & Ferber-Viart, 2010; Dichgans & Brandt, 1978; Viziano et al., 2018), and ii) vestibular-hippocampal connections underpinning the relationship between vestibular impairment and cognitive decline (Harun et al., 2016; Micarelli, Viziano, Della-Morte et al., 2018) as the path of connections between the latter and increased values in body sway (Leandri et al., 2009; Micarelli, Viziano, Della-Morte et al., 2018). Considering these aspects, the significant between-group effect found in the low frequency

domain (Fig. 3B, Table 4) and in the classical posturography parameters (Table 4) could further highlight the prospective HMD-related maximizing processes of vestibular inflows enhancing the vestibular source of spatial information and consequent body sway control in vestibular rehabilitation protocols (Harun et al., 2016; Schlindwein et al., 2008) involving UVH elderly patients with or without cognitive decline.

These findings are further corroborated by the significant improvement in many tests that examine the quality of life (Table 3) and by the significant positive correlations demonstrated—when combining all UVH cases—between both  $\Delta$  PS values within the low-frequency interval on Y plane in eyes closed condition (Fig. 4A) and  $\Delta$  DGI scores (Fig. 4B) and the level cognitive decline when evaluated by MMSE. In fact, the gradual decrease in these measurements along with the cognitive decline and the implementation of HMD may broaden previous protocols demonstrating respectively i) the connection existing between the cognitive decay and executive processes as actively engaged in driving postural control (Bigelow & Agrawal, 2015; Micarelli, Viziano, Bruno et al., 2018; Micarelli, Viziano, Della-Morte et al., 2018) and ii) those central rearrangement – further fostered by virtual reality implementation - possibly counterbalancing the postural decay related to cognitive decline, previously established in the literature (Leandri et al., 2009; Micarelli, Viziano, Bruno et al., 2018; Micarelli, Viziano, Della-Morte et al., 2018).

In conclusion, the present study advocates, for the first time, the implementation of a home-based virtual reality protocol as a low-cost, user-friendly and safe option in order to ameliorate VOR, postural control and quality of life also in the vestibular impaired patients in whom the presence of cognitive decline could hinder the achievement of the rehabilitation goal.

## 5. Limitations of the study

This study suffers from some limitations that have to be adequately elucidated in order to provide a thorough comprehension of the study. First of all, some factors (adherence to the study, selection of unilateral vestibular deficits, etc.) reduced the possibility to enroll a larger sample size of patients in which UVH and cognitive decline occurred. Secondly, no specific test was administered apart from weekly monitoring of the compliance and SSQ of both groups of patients. Then, the ethical choice to treat all patients with the state-of-the-art rehabilitative intervention (Mitsutake, Sakamoto, Ueta, Oka, & Horikawa, 2017; Viziano et al., 2018) led to a different amount of time spent in rehabilitation in the two groups of patients, which probably had an effect on the final outcomes and which was driven by ethical reasons in administering the conventional rehabilitation protocol to all the patients. Thus, the results in the head-mounted device group may have been biased by patients receiving additional treatment, with considerable extra time spent on rehabilitation procedures. Motivation and other psychological factors must be accounted for when interpreting the results, especially with respect to self-report measures. These aspects, together with the absence of the implementation of an exact test of goodness-of-fit, has to be borne in mind when considering the results.

## Authors' contributions

Conceptualization, MA, AM and AV; Methodology, AM, AV and MA; Software, AM and MA; Validation, MA, AM and IA; Investigation, AM, AV, MA, BM, IA; Resources, MA, AM and BM; Data Curation, AM, MA, and AV; Writing - Original Draft Preparation, AM, MA, AV, BM, IA; Writing - Review & Editing, AM, MA, BM; Visualization, AM, MA, AV, IA; Supervision, MA, AM; Project Administration, MA and AM.

## Declaration of interest

All authors of the Manuscript “Vestibular Rehabilitation in older adults with and without mild cognitive impairment: effects of virtual

reality using a head-mounted display” certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

## References

- Alahmari, K. A., Sparto, P. J., Marchetti, G. F., Redfern, M. S., Furman, J. M., & Whitney, S. L. (2014). Comparison of virtual reality based therapy with customized vestibular physical therapy for the treatment of vestibular disorders. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 22, 389–399. <https://doi.org/10.1109/tmsre.2013.2294904>.
- Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). 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. *Alzheimer's & Dementia*, 7, 270–279. <https://doi.org/10.1016/j.jalz.2011.03.008>.
- Alessandrini, M., Lanciani, R., Bruno, E., Napolitano, B., & Di Girolamo, S. (2006). Posturography frequency analysis of sound-evoked body sway in normal subjects. *European Archives of Otorhinolaryngology*, 263, 248–252. <https://doi.org/10.1007/s00405-005-0965-7>.
- Alessandrini, M., Micarelli, A., Chiaravalloti, A., Candidi, M., Bruno, E., Di Pietro, B., et al. (2014). Cerebellar metabolic involvement and its correlations with clinical parameters in vestibular neuritis. *Journal of Neurology*, 261, 1976–1985. <https://doi.org/10.1007/s00415-014-7449-x>.
- Alessandrini, M., Liguori, C., Viziano, A., Izzi, F., Capoccia, D., Lanzillotta, A., et al. (2018). Postural and vestibular changes related to CPAP treatment in moderate-to-severe OSA patients: A 12-month longitudinal study. *Sleep & Breathing*. <https://doi.org/10.1007/s11325-018-1754-z>.
- Anson, E., Bigelow, R. T., Swenor, B., Deshpande, N., Studenski, S., Jeka, J. J., et al. (2017). Loss of peripheral sensory function explains much of the increase in postural sway in healthy older adults. *Frontiers in Aging Neuroscience*, 9, 202. <https://doi.org/10.3389/fnagi.2017.00202>.
- Bergeron, M., Lortie, C. L., & Guitton, M. J. (2015). Use of virtual reality tools for vestibular disorders rehabilitation: A comprehensive analysis. *Advances in Medicine*, 2015, 916735. <https://doi.org/10.1155/2015/916735>.
- Besnard, S., Machado, M. L., Vignaux, G., Boulouard, M., Coquerel, A., Bouet, V., et al. (2012). Influence of vestibular input on spatial and nonspatial memory and on hippocampal NMDA receptors. *Hippocampus*, 22, 814–826. <https://doi.org/10.1002/hipo.20942>.
- Bigelow, R. T., & Agrawal, Y. (2015). Vestibular involvement in cognition: Visuospatial ability, attention, executive function, and memory. *Journal of Vestibular Research*, 25, 73–89. <https://doi.org/10.3233/ves-150544>.
- Bizid, R., Jully, J. L., Gonzalez, G., Francois, Y., Dupui, P., & Paillard, T. (2009). Effects of fatigue induced by neuromuscular electrical stimulation on postural control. *Journal of Science and Medicine in Sport*, 12, 60–66. <https://doi.org/10.1016/j.jsams.2007.10.006>.
- Blodow, A., Pannasch, S., & Walther, L. E. (2013). Detection of isolated covert saccades with the video head impulse test in peripheral vestibular disorders. *Auris Nasus Larynx*, 40, 348–351. <https://doi.org/10.1016/j.anl.2012.11.002>.
- Brandt, T., & Dieterich, M. (1999). The vestibular cortex. Its locations, functions, and disorders. *Annals of the New York Academy of Sciences*, 871, 293–312.
- Brandt, T., Schautzer, F., Hamilton, D. A., Bruning, R., Markowitsch, H. J., Kalla, R., et al. (2005). Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans. *Brain*, 128, 2732–2741. <https://doi.org/10.1093/brain/awh617>.
- Chang, C. P., & Hain, T. C. (2008). A theory for treating dizziness due to optical flow (visual vertigo). *Cyberpsychology & Behavior*, 11, 495–498. <https://doi.org/10.1089/cpb.2007.0075>.
- Charpiot, A., Tringali, S., Ionescu, E., Vital-Durand, F., & Ferber-Viart, C. (2010). Vestibulo-ocular reflex and balance maturation in healthy children aged from six to twelve years. *Audiology & Neurootology*, 15, 203–210. <https://doi.org/10.1159/000255338>.
- Chen, P. Y., Hsieh, W. L., Wei, S. H., & Kao, C. L. (2012). Interactive wimote gaze stabilization exercise training system for patients with vestibular hypofunction. *Journal of Neuroengineering and Rehabilitation*, 9, 77. <https://doi.org/10.1186/1743-0003-9-77>.
- Deshpande, N., Simonsick, E., Metter, E. J., Ko, S., Ferrucci, L., & Studenski, S. (2016). Ankle proprioceptive acuity is associated with objective as well as self-report measures of balance, mobility, and physical function. *Age (Dordrecht, Netherlands)*, 38, 53. <https://doi.org/10.1007/s11357-016-9918-x>.
- Dichgans, J., & Brandt, T. (1978). Visual-vestibular interaction: Effects on self-motion perception and postural control. In R. Held, H. W. Leibowitz, & H.-L. Teuber (Eds.). *Perception* (pp. 755–804). Berlin, Heidelberg: Springer. [https://doi.org/10.1007/978-3-642-46354-9\\_25pp](https://doi.org/10.1007/978-3-642-46354-9_25pp).
- Fioravanti, M., Nacca, D., Buckley, A. E., Ferrario, E., Varetto, O., Moggi, P., et al. (1994). The Italian version of the Alzheimer's Disease Assessment Scale (ADAS): Psychometric and normative characteristics from a normal aged population. *Archives of Gerontology and Geriatrics*, 19, 21–30.

- Furman, J. M., Muller, M. L., Redfern, M. S., & Jennings, J. R. (2003). Visual-vestibular stimulation interferes with information processing in young and older humans. *Experimental Brain Research*, 152, 383–392. <https://doi.org/10.1007/s00221-003-1560-z>.
- Furman, J. M., Redfern, M. S., Fuhrman, S. I., & Jennings, J. R. (2012). Visual-vestibular stimulation influences spatial and non-spatial cognitive processing. *Journal of Vestibular Research*, 22, 253–259. <https://doi.org/10.3233/ves-2012-00460>.
- Gatica-Rojas, V., & Mendez-Rebolledo, G. (2014). Virtual reality interface devices in the reorganization of neural networks in the brain of patients with neurological diseases. *Neural Regeneration Research*, 9, 888–896. <https://doi.org/10.4103/1673-5374.131612>.
- Giacomini, P., Sorace, F., Magrini, A., & Alessandrini, M. (1998). Alterations in postural control: The use of spectral analysis in stability measurement. *Acta Otorhinolaryngologica Italica*, 18, 83–87.
- Giray, M., Kirazli, Y., Karapolat, H., Celebisoy, N., Bilgen, C., & Kirazli, T. (2009). Short-term effects of vestibular rehabilitation in patients with chronic unilateral vestibular dysfunction: A randomized controlled study. *Archives of Physical Medicine and Rehabilitation*, 90, 1325–1331. <https://doi.org/10.1016/j.apmr.2009.01.032>.
- Golomer, E., Dupui, P., & Bessou, P. (1994). Spectral frequency analysis of dynamic balance in healthy and injured athletes. *Archives of International Physiology Biochemistry and Biophysics*, 102, 225–229.
- Gottshall, K. R., Sessoms, P. H., & Bartlett, J. L. (2012). Vestibular physical therapy intervention: Utilizing a computer assisted rehabilitation environment in lieu of traditional physical therapy. *Conference of the IEEE Engineering in Medicine and Biology Society*, 2012, 6141–6144. <https://doi.org/10.1109/embc.2012.6347395>.
- Hall, C. D., Herdman, S. J., Whitney, S. L., Cass, S. P., Clendaniel, R. A., Fife, T. D., et al. (2016). Vestibular rehabilitation for peripheral vestibular hypofunction: An evidence-based clinical practice guideline: FROM THE AMERICAN PHYSICAL THERAPY ASSOCIATION NEUROLOGY SECTION. *Journal of Neurologic Physical Therapy: JNPT*, 40, 124–155. <https://doi.org/10.1097/npt.0000000000000120>.
- Harun, A., Semenov, Y. R., & Agrawal, Y. (2015). Vestibular function and activities of daily living: Analysis of the 1999 to 2004 national health and nutrition examination surveys. *Gerontology & Geriatric Medicine*, 1. <https://doi.org/10.1177/2333721415607124>.
- Harun, A., Oh, E. S., Bigelow, R. T., Studenski, S., & Agrawal, Y. (2016). Vestibular impairment in dementia. *Otology & Neurotology*, 37, 1137–1142. <https://doi.org/10.1097/mao.0000000000001157>.
- Herdman, S. J. (1989). Exercise strategies for vestibular disorders. *Ear, Nose, & Throat Journal*, 68, 961–964.
- Herdman, S. J., Schubert, M. C., & Tusa, R. J. (2001). Strategies for balance rehabilitation: Fall risk and treatment. *Annals of the New York Academy of Sciences*, 942, 394–412.
- Herdman, S. J., Schubert, M. C., Das, V. E., & Tusa, R. J. (2003). Recovery of dynamic visual acuity in unilateral vestibular hypofunction. *Archives of Otolaryngology-Head & Neck Surgery*, 129, 819–824. <https://doi.org/10.1001/archotol.129.8.819>.
- Herdman, S. J., Hall, C. D., Maloney, B., Knight, S., Ebert, M., & Lowe, J. (2015). Variables associated with outcome in patients with bilateral vestibular hypofunction: Preliminary study. *Journal of Vestibular Research*, 25, 185–194. <https://doi.org/10.3233/ves-150556>.
- Hondebrink, M. S., Mert, A., van der Lint, R., de Ru, J. A., & van der Wurff, P. (2017). Motion-based equilibrium reprocessing therapy a novel treatment method for chronic peripheral vestibulopathies: A pilot study. *Medicine (Baltimore)*, 96, e7128. <https://doi.org/10.1097/md.00000000000007128>.
- Horak, F. B., & Hlavacka, F. (2001). Somatosensory loss increases vestibulospinal sensitivity. *Journal of Neurophysiology*, 86, 575–585. <https://doi.org/10.1152/jn.2001.86.2.575>.
- Hsu, S. Y., Fang, T. Y., Yeh, S. C., Su, M. C., Wang, P. C., & Wang, V. Y. (2017). Three-dimensional, virtual reality vestibular rehabilitation for chronic imbalance problem caused by Meniere's disease: A pilot study. *Disability and Rehabilitation*, 39, 1601–1606. <https://doi.org/10.1080/09638288.2016.1203027>.
- Jauregui-Renaud, K., Cruz-Gomez, N. S., & Villanueva-Padron, L. A. (2013). Repeatability of static posturography on the follow-up of vestibular rehabilitation. *Archives of Medical Research*, 44, 151–158. <https://doi.org/10.1016/j.arcmed.2012.12.008>.
- Karapolat, H., Celebisoy, N., Kirazli, Y., Bilgen, C., Eyigor, S., Gode, S., et al. (2010). Does betahistine treatment have additional benefits to vestibular rehabilitation? *European Archives of Oto-Rhino-Laryngology*, 267, 1207–1212. <https://doi.org/10.1007/s00405-010-1216-0>.
- Karlberg, M., Magnusson, M., Malmstrom, E. M., Melander, A., & Moritz, U. (1996). Postural and symptomatic improvement after physiotherapy in patients with dizziness of suspected cervical origin. *Archives of Physical Medicine and Rehabilitation*, 77, 874–882.
- Kingma, H., & van de Berg, R. (2016). Anatomy, physiology, and physics of the peripheral vestibular system. *Handbook of Clinical Neurology*, 137, 1–16. <https://doi.org/10.1016/b978-0-444-63437-5.00001-7>.
- Klatt, B. N., Ries, J. D., Dunlap, P. M., Whitney, S. L., & Agrawal, Y. (2019). Vestibular physical therapy in individuals with cognitive impairment: A theoretical framework. *Journal of Neurologic Physical Therapy: JNPT*, 43(Suppl. 2), S14–s19. <https://doi.org/10.1097/npt.0000000000000266> Supplement, Special Supplement: International Conference on Vestibular Rehabilitation.
- Kohen-Raz, R., Himmelfarb, M., Tzur, S., Kohen-Raz, A., & Shub, Y. (1996). An initial evaluation of work fatigue and circadian changes as assessed by multiplate posturography. *Perceptual and Motor Skills*, 82, 547–557. <https://doi.org/10.2466/pms.1996.82.2.547>.
- Lacour, M., Bernard-Demanze, L., & Dumitrescu, M. (2008). Posture control, aging, and attention resources: Models and posture-analysis methods. *Clinical Neurophysiology*, 38, 411–421. <https://doi.org/10.1016/j.neucli.2008.09.005>.
- Leandri, M., Cammisuli, S., Cammarata, S., Baratto, L., Campbell, J., Simonini, M., et al. (2009). Balance features in Alzheimer's disease and amnesic mild cognitive impairment. *Journal of Alzheimer's Disease*, 16, 113–120. <https://doi.org/10.3233/jad-2009-0928>.
- Li, C., Layman, A. J., Geary, R., Anson, E., Carey, J. P., Ferrucci, L., et al. (2015). Epidemiology of vestibulo-ocular reflex function: Data from the Baltimore Longitudinal Study of Aging. *Otology & Neurotology*, 36, 267–272. <https://doi.org/10.1097/mao.0000000000000610>.
- McGarvie, L. A., MacDougall, H. G., Halmagyi, G. M., Burgess, A. M., Weber, K. P., & Curthoys, I. S. (2015). The video head impulse test (vHIT) of semicircular canal function-age-dependent normative values of VOR gain in healthy subjects. *Frontiers in Neurology*, 6, 154. <https://doi.org/10.3389/fneur.2015.00154>.
- McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., et al. (2011). 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. *Alzheimer's & Dementia*, 7, 263–269. <https://doi.org/10.1016/j.jalz.2011.03.005>.
- Micarelli, A., Viziano, A., Bruno, E., Micarelli, E., & Alessandrini, M. (2016). Vestibular impairment in multiple chemical sensitivity: Component analysis findings. *Journal of Vestibular Research*, 26, 459–468. <https://doi.org/10.3233/ves-160594>.
- Micarelli, A., Liguori, C., Viziano, A., Izzi, F., Placidi, F., & Alessandrini, M. (2017). Integrating postural and vestibular dimensions to depict impairment in moderate-to-severe obstructive sleep apnea syndrome patients. *Journal of Sleep Research*, 26, 487–494. <https://doi.org/10.1111/jsr.12516>.
- Micarelli, A., Viziano, A., Augimeri, I., Micarelli, D., & Alessandrini, M. (2017). Three-dimensional head-mounted gaming task procedure maximizes effects of vestibular rehabilitation in unilateral vestibular hypofunction: A randomized controlled pilot trial. *International Journal of Rehabilitation Research*, 40, 325–332. <https://doi.org/10.1097/mrr.0000000000000244>.
- Micarelli, A., Viziano, A., Bruno, E., Micarelli, E., Augimeri, I., & Alessandrini, M. (2018). Gradient impact of cognitive decline in unilateral vestibular hypofunction after rehabilitation: Preliminary findings. *European Archives of Oto-Rhino-Laryngology*, 275, 2457–2465. <https://doi.org/10.1007/s00405-018-5109-y>.
- Micarelli, A., Viziano, A., Della-Morte, D., Augimeri, I., & Alessandrini, M. (2018). Degree of functional impairment associated with vestibular hypofunction among older adults with cognitive decline. *Otology & Neurotology*, 39, e392–e400. <https://doi.org/10.1097/mao.0000000000001746>.
- Mitsutake, T., Sakamoto, M., Ueta, K., Oka, S., & Horikawa, E. (2017). Effects of vestibular rehabilitation on gait performance in poststroke patients: A pilot randomized controlled trial. *International Journal of Rehabilitation Research*, 40, 240–245. <https://doi.org/10.1097/mrr.0000000000000234>.
- Nola, G., Mostardini, C., Salvi, C., Ercolani, A. P., & Ralli, G. (2010). Validity of Italian adaptation of the Dizziness Handicap Inventory (DHI) and evaluation of the quality of life in patients with acute dizziness. *Acta Otorhinolaryngologica Italica*, 30, 190.
- Paillard, T., Costes-Salon, C., Lafont, C., & Dupui, P. (2002). Are there differences in postural regulation according to the level of competition in judoists? *British Journal of Sports Medicine*, 36, 304–305.
- Pavlou, M., Kanegaonkar, R. G., Swapp, D., Bamiou, D. E., Slater, M., & Luxon, L. M. (2012). The effect of virtual reality on visual vertigo symptoms in patients with peripheral vestibular dysfunction: A pilot study. *Journal of Vestibular Research*, 22, 273–281. <https://doi.org/10.3233/ves-120462>.
- Pernecky, R., Wagenpfeil, S., Komossa, K., Grimmer, T., Diehl, J., & Kurz, A. (2006). Mapping scores onto stages: Mini-mental state examination and clinical dementia rating. *The American Journal of Geriatric Psychiatry*, 14, 139–144. <https://doi.org/10.1097/01.JGP.0000192478.82189.a8>.
- Russell, N. A., Horii, A., Smith, P. F., Darlington, C. L., & Bilkey, D. K. (2006). Lesions of the vestibular system disrupt hippocampal theta rhythm in the rat. *Journal of Neurophysiology*, 96, 4–14. <https://doi.org/10.1152/jn.00953.2005>.
- Schindwein, P., Mueller, M., Bauermann, T., Brandt, T., Stoeter, P., & Dieterich, M. (2008). Cortical representation of saccular vestibular stimulation: VEMPs in fMRI. *Neuroimage*, 39, 19–31. <https://doi.org/10.1016/j.neuroimage.2007.08.016>.
- Schneider, E., Villgratner, T., Vockeroth, J., Bartl, K., Kohlbecher, S., Bardins, S., et al. (2009). EyeSeeCam: An eye movement-driven head camera for the examination of natural visual exploration. *Annals of the New York Academy of Sciences*, 1164, 461–467. <https://doi.org/10.1111/j.1749-6632.2009.03858.x>.
- Seemungal, B. M., Guzman-Lopez, J., Arshad, Q., Schultz, S. R., Walsh, V., & Yousif, N. (2013). Vestibular activation differentially modulates human early visual cortex and V5/MT excitability and response entropy. *Cerebral Cortex*, 23, 12–19. <https://doi.org/10.1093/cercor/bhr366>.
- Sienko, K. H., Whitney, S. L., Carender, W. J., & Wall, C. (2017). The role of sensory augmentation for people with vestibular deficits: Real-time balance aid and/or rehabilitation device? *Journal of Vestibular Research*, 27, 63–76. <https://doi.org/10.3233/ves-170606>.
- Smith, P. F. (2017). The vestibular system and cognition. *Current Opinion in Neurology*, 30, 84–89. <https://doi.org/10.1097/wco.0000000000000403>.
- Sparrer, I., Duong Dinh, T. A., Ilgner, J., & Westhofen, M. (2013). Vestibular rehabilitation using the Nintendo(R) Wii Balance Board—A user-friendly alternative for central nervous compensation. *Acta Otolaryngologica*, 133, 239–245. <https://doi.org/10.3109/00016489.2012.732707>.
- Stackman, R. W., & Herbert, A. M. (2002). Rats with lesions of the vestibular system require a visual landmark for spatial navigation. *Behavioural Brain Research*, 128, 27–40.
- Szturm, T., Reimer, K. M., & Hochman, J. (2015). Home-based computer gaming in vestibular rehabilitation of gaze and balance impairment. *Games for Health Journal*, 4, 211–220. <https://doi.org/10.1089/g4h.2014.0093>.
- Teggi, R., Colombo, B., Bernasconi, L., Bellini, C., Comi, G., & Bussi, M. (2009). Migrainous vertigo: Results of caloric testing and stabilometric findings. *Headache*,

- 49, 435–444. <https://doi.org/10.1111/j.1526-4610.2009.01338.x>.
- Uehara, N., Tanimoto, H., Nishikawa, T., Doi, K., Katsunuma, S., Kimura, H., et al. (2011). Vestibular dysfunction and compensation after removal of acoustic neuroma. *Journal of Vestibular Research*, 21, 289–295. <https://doi.org/10.3233/ves-2011-0429>.
- Viire, E., & Sitarz, R. (2002). Vestibular rehabilitation using visual displays: Preliminary study. *Laryngoscope*, 112, 500–503. <https://doi.org/10.1097/00005537-200203000-00017>.
- Viziano, A., Micarelli, A., Augimeri, I., Micarelli, D., & Alessandrini, M. (2018). Long-term effects of vestibular rehabilitation and head-mounted gaming task procedure in unilateral vestibular hypofunction: A 12-month follow-up of a randomized controlled trial. *Clinical Rehabilitation*, 33(1), 24–33. <https://doi.org/10.1177/0269215518788598>.
- Whitney, S. L., Sparto, P. J., Hodges, L. F., Babu, S. V., Furman, J. M., & Redfern, M. S. (2006). Responses to a virtual reality grocery store in persons with and without vestibular dysfunction. *Cyberpsychology & Behavior*, 9, 152–156. <https://doi.org/10.1089/cpb.2006.9.152>.
- Wrisley, D. M., Walker, M. L., Echternach, J. L., & Strasnick, B. (2003). Reliability of the dynamic gait index in people with vestibular disorders. *Archives of Physical Medicine and Rehabilitation*, 84, 1528–1533.
- Yamamoto, T., Smith, C. E., Suzuki, Y., Kiyono, K., Tanahashi, T., Sakoda, S., et al. (2015). Universal and individual characteristics of postural sway during quiet standing in healthy young adults. *Physiological Reports*, 3. <https://doi.org/10.14814/phy2.12329>.
- Yeh, S. C., Chen, S., Wang, P. C., Su, M. C., Chang, C. H., & Tsai, P. Y. (2014). Interactive 3-dimensional virtual reality rehabilitation for patients with chronic imbalance and vestibular dysfunction. *Technology and Health Care*, 22, 915–921. <https://doi.org/10.3233/thc-140855>.