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# Vertigo/Vestibular disorders and cognitive impairment in the elderly

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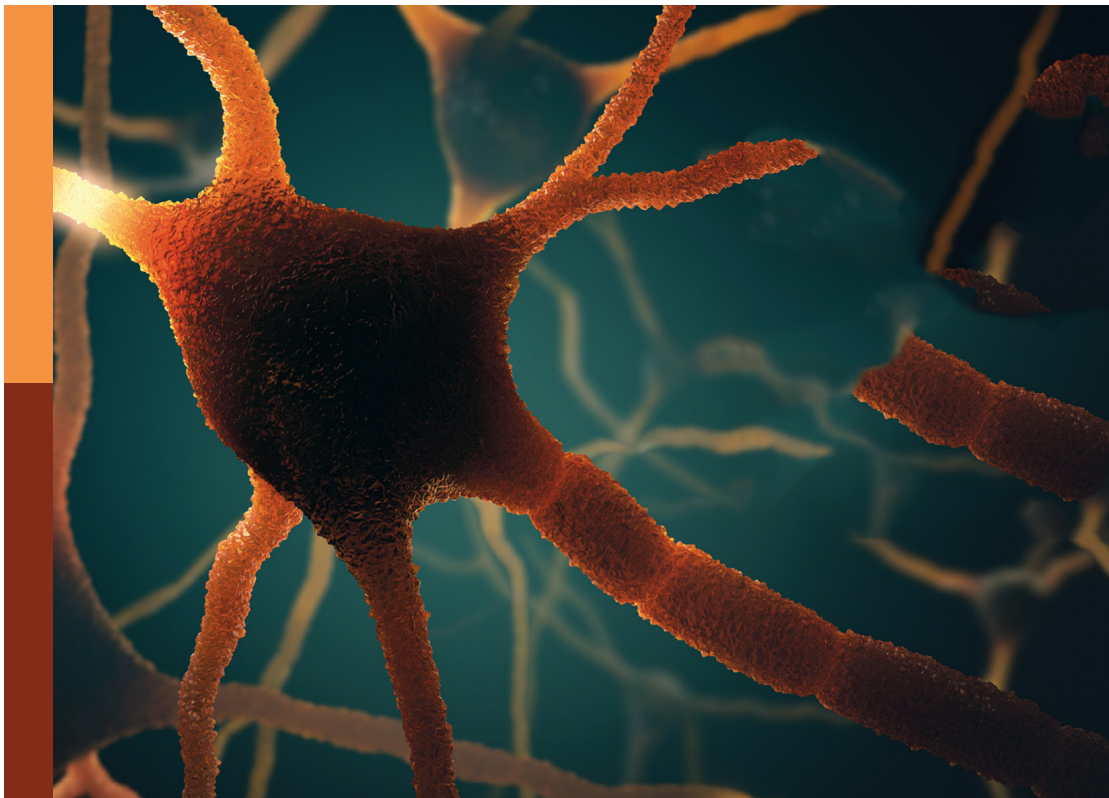

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# Vertigo/Vestibular disorders and cognitive impairment in the elderly

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# Early detection and monitoring of hearing loss in vestibular migraine: Extended high-frequency hearing

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**Background:** Vestibular migraine (VM) presents mainly with recurrent vestibular symptoms and migraine. A great number of patients with VM have cochlea symptoms such as tinnitus, hearing loss.

**Methods:** A cross-sectional study was conducted on patients with definite VM (dVM) and probable VM (pVM) who met the diagnostic criteria. Auditory-vestibular tests and psychological assessments were performed. Logistic regression was used to evaluate the predictive effect of EHF pure tone audiometry (PTA) for standard frequency (SF) hearing loss.

**Results:** Fifteen patients with pVM and 22 patients with dVM were recruited. Overall, the two most vertigo types were vestibulo-visual symptoms (83.78%) and internal vertigo (54.05%). A vertigo attack persisted for <5 min in approximately 57% of patients, compared with 5 min to 72 h in 43%, and lasted longer than 72 h in 8%. Approximately 87% of patients had psychological disorders. Most patients with VM (92%) suffered from some degree of EHF hearing impairment, and 68% had SF hearing loss, which is substantially higher than their complaints (43%). Moreover, the mean EHF hearing threshold cutoff value (57 dB HL) worked well in predicting SF hearing loss (area under curve, AUC, 0.827), outperforming distortion product optoacoustic emission (AUC, 0.748).

**Conclusion:** VM has a wide range of clinical manifestations. Hearing loss had a considerably higher rate compared to actual complaints. Moreover, patients with VM tended to have bilateral EHF and high-frequency hearing loss. The effectiveness of the mean EHF hearing threshold cutoff value in predicting hearing loss supported its use in the early detection of hearing loss and monitoring disease progression.

KEYWORDS

**vertigo, vestibular migraine, hearing loss, extended high frequency, pure tone audiometry, prediction**

# Introduction

Vestibular migraine (VM) presents with a recurrence of vestibular symptoms, a history of migraine, and a temporal association between vestibular spells and migraine symptoms (Lempert et al., 2012). Its lifetime prevalence in the general population is roughly 1%, accounting for approximately 12.3% of the cases in vertigo centers (Neuhauser et al., 2006; Strupp et al., 2020). VM can develop at any age (average age 40.9 years), while it tends to afflict those with a history of migraine (Neuhauser et al., 2006) and women who are below 40 years of age, those who have anxiety or depression, and those who have previously developed sustained head trauma (Formeister et al., 2018). Patients with VM usually have central and/or peripheral vestibular and auditory dysfunction (Radtke et al., 2012).

Nevertheless, the audiological symptoms of VM are still poorly understood. Neuhauser et al. (2006) reported that 36% of patients with VM had cochlear symptoms, including tinnitus (15%), hearing loss (9%), and aural fullness (15%), during vertigo episodes. Moreover, Radtke et al. (2012) found that the presence of cochlear symptoms increased from an initial 26 to 77% after a 9-year follow-up.

Notably, hearing loss is the third leading cause of years lived with disability worldwide and affects 36.3 million people (Vos et al., 2017). Migraine is one of the leading causes of sudden sensorineural hearing loss (SSNHL), particularly in people over the age of 40 (Viirre and Baloh, 1996; Mohammadi et al., 2020). VM is associated with both peripheral and central auditory dysfunction (Xue et al., 2020). However, researchers disagreed on the features of hearing loss in VM. During attacks, 26.2 and 15.4% of patients with VM and pVM experienced hearing loss (Lopez-Escamez et al., 2014). Zhang et al. (2016) reported that only 3% of patients with VM in Chinese subjects experienced hearing loss during vertigo attacks. Radtke et al. (2012) found that patients with VM were more likely to have bilateral high-frequency hearing loss than low-frequency hearing loss. Xue et al. (2020) reported that patients with both migraine and VM were at a higher risk for low-frequency sensorineural hearing loss (SNHL). Furthermore, current treatments for VM mainly included acute pharmacologic treatment for attacks, preventive pharmacologic therapy for migraine, and vestibular rehabilitation with little attention to addressing hearing loss.

To the best of our knowledge, extended high-frequency (EHF; 8–20 kHz) hearing plays an obscure but important role in our work and daily lives, including enhancing speech perception in noise (Zadeh et al., 2019) and cognitive ability, particularly global executive function (Brännström et al., 2018). Moreover, EHF pure-tone audiometry (PTA) can be used for the early detection of hearing loss caused by ototoxic drugs (Sakamoto et al., 2000; Al-Malky et al., 2015), noise (Le Prell et al., 2013), and autoimmune diseases (Öztürk et al., 2004; González et al., 2017). Nevertheless, few studies investigated EHF (8–20 kHz) audiometry in patients with VM.

Therefore, the aim of the present study was to (1) explore the audiological features of patients with VM between standard frequencies (SFs) and EHFs, (2) determine the use of EHF audiometry as a tool for the early detection of hearing loss in patients with VM, and (3) offer a rationale for the integration of a specific audiological assessment in the differential diagnosis and treatment of VM.

# Methods

A prospective cross-sectional study was conducted in the Department of Otorhinolaryngology of a tertiary hospital. The study was approved by the Ethics Committee of Wuhan Union Hospital under code number 20210873. A detailed medical history was taken, auditory-vestibular tests and psychological assessments on the participants were performed, and these data were analyzed in detail.

## Inclusion criteria

Patients who had a definite VM (dVM) and probable VM (pVM) and attended the otolaryngology outpatient service of a tertiary medical institute between October 2021 and February 2022 were sequentially included. The diagnosis of VM was established on basis of the criteria formulated by Barany society in 2012 (Lempert et al., 2012). Existing migraine or a previous history of migraine with or without aura was assessed based on the International Classification of Headache Disorders (Olesen, 2018).

## Exclusion criteria

All patients underwent auditory, vestibular, and neurological examinations or tests, such as otoscopy, an acoustic impedance test, PTA, a glycerin test, electrocochleography, and magnetic resonance imaging (MRI). The study excluded patients who had any external or middle ear diseases, had received ear surgery, had Meniere's disease (MD), had an acoustic neuroma, had chronic exposure to noise, had hereditary deafness, had an inner ear deformity, and took ototoxic drugs (Supplementary Figure S1).

## Clinical evaluation

A predetermined set of variables was extracted from medical records, supplemented by follow-up telephone calls when necessary, and then entered into a database. Clinical variables

included gender, age, vertigo attacks, hearing loss, headache or migraine features, and other accompanying symptoms (e.g., aural fullness, tinnitus, nausea, and vomiting), motion sickness, sleep disorders, allergies, autoimmune diseases, cardiovascular risk factors, anxiety, depression, and a family history of vertigo or migraine.

## Pure-tone audiometry

Pure-tone air conduction audiometry was performed separately in each ear for SFs (0.125, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 kHz) and EHFs (10, 12.5, 16, and 20 kHz) using an Astera audiometer (Otometrics A/S, Taastrup, Denmark). As ISO 389-5 2006 did not provide an equivalent reference threshold for a frequency of 20 kHz, it was excluded from the analysis. The underdetected frequency threshold was measured at 120 dB HL. The frequency could be divided into low frequency (0.125–0.5 kHz), middle frequency (1–2 kHz), high frequency (4–8 kHz), and EHF (10–16 kHz). If no response was obtained at one frequency, it was recorded as 120 dB HL. The result was taken as EHF hearing loss when the hearing threshold was greater than 20 dB HL at one or more frequencies ranging from 10 to 16 kHz in one or both ears.

A chart was prepared by comparing the results of a previous study on ETF PTA in healthy people (Wang et al., 2021). Statistical analysis (chi-squared test for independent samples) was performed to analyze the normalized percentage at 8–16 kHz. For comparison purposes, this study did not take into account the publication year or the measurement method.

## Otoacoustic emission testing

Distortion product optoacoustic emission (DPOAE) was recorded by using a cochlear emission analyzer (Otometrics A/S, Taastrup, Denmark). The frequency ratio was set to 1.22 (L1 = 70 dB SPL, L2 = 60 dB SPL). DPOAE data were recorded for different frequency regions at 0.75, 1, 2, 3, 4, 6, and 8 kHz. For all frequencies, DPOAE measurements were considered detectable when the signal-to-noise ratio was greater than 6 dB. Abnormality was defined as a decreased or undetectable reactive amplitude at one or more frequencies.

## Vestibular autorotation test

The vestibular autorotation test (VAT) was performed using a VAT device (NeuroCom International, Inc., Clackamas, OR, USA). VAT was considered abnormal when the gain, phase, or asymmetry decreased or increased.

## Psychological evaluation

All patients were psychometrically assessed to confirm the presence of anxiety, depression, and somatic symptoms.

Generalized anxiety disorder (GAD) assessment (Spitzer et al., 2006): GAD-7 consisted of seven items. Scores of 5, 10, and 15 were taken as the cutoff points for mild, moderate, and severe anxiety, respectively.

Patient health questionnaire 9 (PHQ-9) (Kroenke et al., 2001): It was used to make a preliminary diagnosis of depression. Depression severity was rated on a scale of 0–27, with points 0–4 being no depression, 5–9 being mild, 10–14 being moderate, 15–19 being moderately severe, and 20–27 being severe depression.

Somatic symptom self-rating scale (SSS) (Jiang et al., 2019): It consisted of 20 items, covering physical disorders, anxiety disorders, depression disorders, and anxiety and depression disorders. The SSS-CN scores 20–29, 30–39, 40–59, and ≥60 corresponded to normal, mild, moderate, and severe somatic symptom disorder (SSD), respectively.

## Statistical analysis

Data were entered into the EpiDate 3.1 database and then analyzed with GraphPad Prism 9. First, the distribution state of continuous variables was determined as normal or skewed. For non-normally distributed continuous variables, data distribution was described using the median and interquartile range, and difference analysis was done using the nonparametric Mann–Whitney U test; for normally distributed variables, dispersion and central tendency were represented respectively by using the mean and standard deviation (SD), and difference analysis was done using two independent sample *t*-tests. The chi-squared test was used to observe differences between dichotomous variables.

To analyze the predictive factors for hearing loss (outcome, SF hearing loss = 1, normal SF hearing = 0), the mean EHF hearing threshold and DPOAE results (abnormal = 1 and normal SF hearing = 0) were used to perform logistic regression analysis. AUC was used to evaluate the predictive power.

# Results

## Clinical manifestations

A total of 37 adult patients with VM/pVM (aged 19–68 years, with a mean age of 47.1 years, including 27 women and eight men) were enrolled in this study. Fifteen patients with pVM having a mean age of 45.13 and 22 patients with VM having a mean age of 46.68 years were recruited. The female-to-male ratio was higher in patients with VM (1.5) than in patients with pVM (6.3), but the difference between the two was

TABLE 1 Clinical characteristics of patients with probable vestibular migraine (pVM) and vestibular migraine (VM).

| | pVM ($n = 15$) | VM ($n = 22$) | All ($n = 37$) |
|---|---|---|---|
| Female-to-male ratio | 1.5 | 6.3 | 3.1 |
| Mean age (SD) (years) | 45.13 (13.38) | 46.68 (14.31) | 46.05 (13.97) |
| Disease duration, m (Q1, Q3), (month) | 8 (1, 33) | 28.5 (4.5, 72) | 16 (2.75, 60) |
| Frequency of vertigo spell, m (Q1, Q3), (/6 months) | 2 (1, 4.5d) | 2.5 (1, 5.75) | 2 (1, 5) |
| Days affected, m (Q1, Q3), (/month) | 2 (0.4, 27.5) | 4 (2, 10) | 4 (1.8, 10) |
| Vertigo type[a] | | | |
| Internal vertigo | 60% ($n = 9$) | 47.83% ($n = 11$) | 54.05% ($n = 20$) |
| Dizziness | 60% ($n = 9$) | 31.82% ($n = 7$) | 43.24% ($n = 16$) |
| Vestibulo-visual symptoms | 80% ($n = 12$) | 86.36% ($n = 19$) | 83.78% ($n = 31$) |
| Posture symptoms | 6.67% ($n = 1$) | 13.64% ($n = 3$) | 10.81% ($n = 4$) |
| Duration of vertigo attacks[a] | | | |
| <5 min | 53.33% ($n = 8$) | 59.09% ($n = 13$) | 56.76% ($n = 21$) |
| 5 min−72 h | 60% ($n = 9$) | 31.82% ($n = 7$) | 43.24% ($n = 16$) |
| >72 h | 0 ($n = 0$) | 13.64% ($n = 3$) | 8.11% ($n = 3$) |
| Migraine diagnosis | 26.67% ($n = 4$) | 100% ($n = 22$) | 72.97% ($n = 27$) |
| Phonophobia* | 20% ($n = 3$) | 54.% ($n = 12$) | 40.54% ($n = 15$) |
| Nausea and/or vomiting | 26.67 ($n = 4$) | 54.55% ($n = 12$) | 43.24% ($n = 16$) |
| Photophobia* | 20% ($n = 3$) | 54% ($n = 12$) | 37.84 ($n = 14$) |
| Tinnitus[b] | 53.33% ($n = 8$) | 54.55% ($n = 12$) | 54.05% ($n = 20$) |
| Hearing loss complaint[b] | 40% ($n = 6$) | 45.45% ($n = 10$) | ai% ($n = 16$) |
| Autoimmune diseases | 13.33% ($n = 2$) | 18.18% ($n = 4$) | 16.22% ($n = 6$) |
| Cardiovascular risk factors | 46.67% ($n = 7$) | 50% ($n = 11$) | 48.65% ($n = 18$) |
| Motion sickness[b*] | 40% ($n = 6$) | 81.82% ($n = 18$) | 64.86% ($n = 24$) |
| Family history of vertigo/migraine | 46.67% ($n = 7$) | 40.91% ($n = 9$) | 43.24% ($n = 16$) |
| Psychological disorder[b] | 33.33% ($n = 5$) | 36.36% ($n = 8$) | 35.14% ($n = 13$) |
| Sleep disorder[b] | 66.67% ($n = 10$) | 77.27% ($n = 17$) | 72.97% ($n = 27$) |

[a]More than one result. [b]In the interval episode. SD, standard deviation; m, median; Q1, quartile 1; Q3, quartile 3. *$p < 0.05$, indicating that a statistically significant difference was found between patients with VM and pVM.

not significant. There were no statistically significant differences in vertigo features between patients with VM and their pVM counterparts. For the total cohort, the median disease duration was 16 months, the median vertigo spell lasted for 2 days, and the affected median duration was 4 days per month in the past 6 months. Vertigo types in patients with both VM and pVM varied. Overall, the most common types were vestibulo-visual symptoms (83.78%) and internal vertigo (54.05%), followed by dizziness (43.24%), and the rarest was a posture symptom (10.81%). We found that, in 56.76% of patients, the vertigo attack persisted no longer than 5 min, compared with 5 min to 72 h in 43.24% of the subjects. In three patients with VM, the vertigo episode lingered for more than 72 h.

It was found that 26.67% of patients with pVM had migraine currently or earlier with or without aura, with the rate being 100% in patients with VM. Migraine features, such as, phonophobia and photophobia, were more frequent in the VM group than in the pVM group.

The cochlear symptom in the interval episode were common in patients with VM and pVM. A total of 16 participants (43.24%) complained of hearing loss in one or both ears, and 20 patients (54.05%) had unilateral or bilateral tinnitus.

TABLE 2 The threshold of both ears in patients with pVM and VM at standard frequency (SF) and extended high frequency (EHF).

| Frequency (kHz) | pVM ($n = 15$), mean (SD) (dB HL) | VM ($n = 22$), mean (SD) (dB HL) | All ($n = 37$), mean (SD) (dB HL) |
|---|---|---|---|
| 0.125 | 17.83 (5.68) | 16.19 (5.10) | 16.77 (5.47) |
| 0.25 | 16.73 (5.68) | 14.24 (6.67) | 15.14 (7.52) |
| 0.5 | 15.96 (8.31) | 14.22 (7.99) | 15.06 (7.72) |
| 1 | 20.00 (6.80) | 16.52 (9.83) | 17.97 (9.45) |
| 2 | 22.12 (7.84) | 19.46 (13.11) | 20.65 (12.42) |
| 4 | 25.38 (10.30) | 21.96 (17.37) | 23.41 (17.39) |
| 8 | 32.31 (16.52) | 26.85 (23.85) | 28.91 (26.59) |
| 10 | 41.04 (29.98) | 35.76 (31.78) | 38.21 (33.71) |
| 12.5 | 58.33 (41.07) | 48.70 (36.20) | 52.24 (37.46) |
| 16 | 108.8 (29.80) | 105.87 (36.88) | 107.54 (34.22) |

VM, vestibular migraine; pVM, probable vestibular migraine.

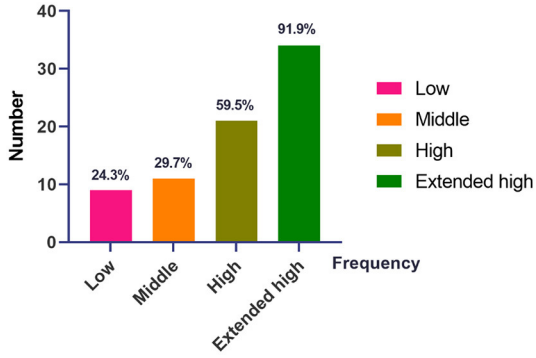


FIGURE 1
The distribution of hearing loss at different frequencies in patients with pVM/VM. VM, vestibular migraine; pVM, probable vestibular migraine. Low, low frequency, 0.125–0.5 kHz. Middle, middle frequency, 1.0–2.0 kHz. High, high frequency, 4.0–8.0 kHz. Extended high, extended high frequency (EHF), 10.0–16.0 kHz.

TABLE 3 A comparison of normalized percentage at 8–16 kHz from the current study with that of a previous study.

| | | Frequency (kHz) | | | |
|---|---|---|---|---|---|
| Age group (years) | | 8 | 10 | 12.5 | 16 |
| 21–30 | Present study ($n = 4$) | 100 | 100 | 100 | 75 |
| | Wang et al. (2021) ($n = 46$) | 100 | 100 | 100 | 100 |
| 31–40 | Present study ($n = 9$) | 100 | 100 | 100 | 33.3 |
| | Wang et al. (2021) ($n = 50$) | 100 | 100 | 100 | 64 |
| 41–50 | Present study ($n = 9$) | 100 | 75** | 75 | 0* |
| | Wang et al. (2021) ($n = 88$) | 100 | 100 | 93.2 | 38.6 |
| 51–60 | Present study ($n = 11$) | 90.9* | 90.9* | 72.7 | 0* |
| | Wang et al. (2021) ($n = 78$) | 100 | 100 | 82.1 | 30.8 |
| 61–70 | Present study ($n = 4$) | 75 | 50* | 25 | 0 |
| | Wang et al. (2021) ($n = 62$) | 100 | 97.4 | 74.2 | 16.1 |

*$p < 0.05$, **$p < 0.01$; ***$p < 0.001$.

The prevalence of motion sickness, phonophobia, and photophobia was higher in patients with VM than in patients with pVM. The rates of nausea and vomiting, family history, psychological disorder, autoimmune diseases, cardiovascular risk factors, and sleep disorder were frequent in both the pVM and VM groups, and no statistically significant differences in these accompanying disorders or conditions were observed (Table 1).

## Pure-tone audiometry

A difference in SF and EHF threshold of both ears in patients with pVM and VM was not significant (Table 2).

Hearing loss at standard frequency (>20 dB HL; 0.125–8 kHz) was found to be common in patients with pVM/dVM. Approximately 67.57% of patients ($n = 25$) had hearing loss, which was much more than their complaint/counterpart (43.24%). In 60% of patients with pVM ($n = 9$) and 72.73% of patients with VM ($n = 16$), the threshold was unilaterally or bilaterally elevated across SFs. The rate of bilateral hearing loss at SF (68%, $n = 17$) was higher than that of unilateral hearing loss as SF ($n = 8$, 32%).

A total of 34 participants (91.89%) suffered from some degree of EHF hearing loss (>20 dB HL, 10–16 kHz), as defined by the International Organization for Standardization. Of them, 94.12% ($n = 32$) had bilateral EHF hearing loss. Patients mainly developed total hearing loss (107.54 ± 34.22) at 16 kHz and moderate to severe hearing loss at 10 and 12.5 kHz (38.21 ± 33.71 and 52.24 ± 37.46).

When analyzing thresholds at all frequencies (0.125–20 kHz) by gender, statistically significant differences were found only at 12.5 kHz but not at other frequencies (Supplementary Table S1).

A large number of patients with pVM/dVM had high-frequency (59.5%) and EHF (91.9%) hearing loss as compared to low- (24.3%) and middle-frequency (24.3%) hearing loss (Figure 1).

In comparison to the study by Wang et al. (2021), no difference was found between patients who had pVM/dVM and those between the ages of 20–40, but only a significant difference was found between patients with pVM/dVM over 40 years and healthy people (Table 3 and Supplementary Tables S2, S3).

In terms of SF hearing loss, subjects in our cohort could be further divided into two subgroups, patients with VM who

had normal SF hearing and those who had SF hearing loss. In addition, we then selected the ear with the more severe hearing loss to represent the patient's hearing condition. We found that the subgroup with SF hearing loss had poor SF hearing as well as EHF hearing (Figure 2). Moreover, there was a more remarkable difference with the frequency increasing from low to extended high levels (Table 4).

In terms of the presence or absence of tinnitus, patients could be classified into VM with tinnitus and VM without tinnitus. The group of VM with tinnitus consisted of 20 patients (54.1%), and the group of VM without tinnitus consisted of 17 patients (45.9%). VM with tinnitus had a slightly higher SF and EHF threshold than VM without tinnitus, but the difference between the two was not significant (Supplementary Table S4). Patients with VM who had tinnitus and those who had no tinnitus had hearing loss principally at 2–16 kHz.

## Distortion product optoacoustic emission

Seven patients with pVM and 15 patients with VM both had abnormal DPOAE in one or both ears (Supplementary Table 5S). In contrast to the result of SF and EHF PTA, the DPOAE abnormal rate from low frequency to EHF remained the same, while during impairment it progressed severely with the frequency increasing from the lower to higher level.

## Vestibular autorotation test

Twenty-seven patients had VM and seven patients had an abnormal VAT. In patients with abnormal VAT ($n = 27$), approximately 66.7% ($n = 18$) had central vestibular disorder, 11.1% ($n = 3$) had peripheral vestibular dysfunction, and 10.8% ($n = 4$) had vestibular impairment of unknown origin.

## Psychological assessment

Approximately 86.5% ($n = 32$) of patients were found to have much more psychological disorder than their complaint (35.14%). In our cohort, 37.8% ($n = 14$) were suffering from depression, 32.4% ($n = 12$) from anxiety, and 70.3% ($n = 26$) from somatic symptoms. The psychological disorders were mostly mild to moderate in nature (Supplementary Table S6).

## Magnetic resonance imaging

Magnetic resonance imaging revealed no characteristic findings in patients with VM. Some non-specific findings were inclusive of a close correlation between the facial auditory nerve and peripheral small blood vessels and lacunar cerebral infarction.

## The mean EHF threshold, the more powerful predictive diagnostic factor for SF hearing loss

For those patients for whom the EHF threshold was evaluated, 81.48% of them had an elevated threshold at SF. In patients with pVM/dVM and unilateral SF hearing loss, there was a constant increase in EHF threshold.

Both mean EHF and DPOAE hearing thresholds were risk factors for SF hearing loss. Their effect on the probability of hearing loss occurring is shown in the following formulas: $P = -4.182 + 0.07325X_{EHF}$, $P = -1.946 + 3.290X_{DPOAE}$.

Then, the receiver operating characteristic (ROC) curve analysis revealed that another cutoff value of >57.09 dB HL of the mean EHF hearing threshold had maximal sensitivity and specificity for predicting poor hearing [ROC curve area, 0.827 (95% confidence interval (CI), 0.688–0.968); $p = 0.0015$] (Figure 3A). Moreover, the predictive power for SF hearing loss of the mean EHF hearing threshold was greater than that for DPOAE [ROC curve area, 0.748, (95%CI, 0.5638–0.9330); $p = 0.0137$] (Figure 3B).

## Clinical features according to the mean EHF hearing threshold

In terms of EHF mean hearing threshold, our patients were classified into two groups: patients with low mean EHF hearing threshold (LEHF) and those with high mean EHF hearing threshold (HEHF). Statistically significant differences were found in several clinical features between the two groups (Table 5). Patients with HEHF were older, and most of them had more severe SF hearing loss than their LEHF counterparts. Moreover, the HEHF group had a greater number of patients with pVM.

# Discussion

First, this study showed that VM had a wide variety of clinical manifestations, and some of its clinical features were inconsistent with previously reported characteristics. Secondly, we found that auditory system dysfunction, especially hearing loss, was common but less explicable in pVM/dVM. In patients with dVM/pVM, hearing loss was characterized by bilateral involvement and greater severity, particularly at EHF and high frequency, followed by middle and low frequencies. Moreover, we identified the mean EHF threshold as a better

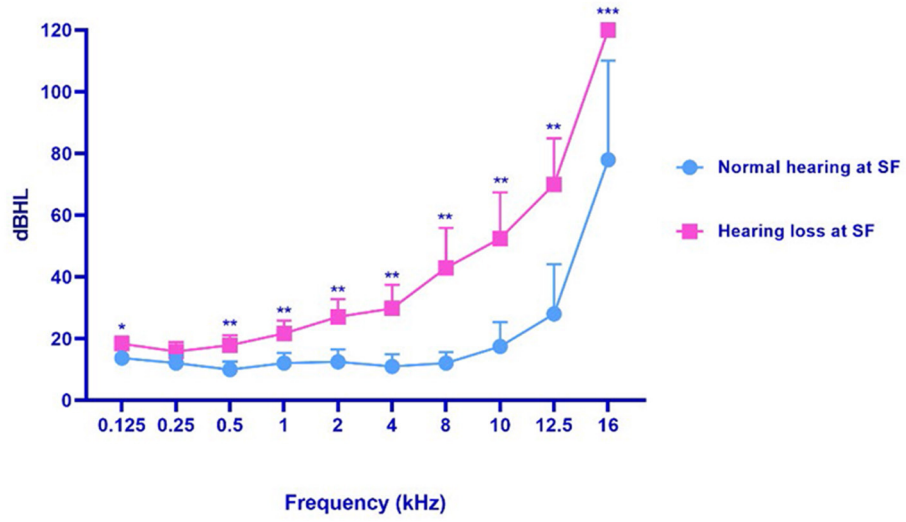


FIGURE 2
The hearing threshold of patients with SF normal hearing and patients with SF hearing loss. VM, vestibular migraine, including definite and probable vestibular migraine. SF, standard frequency (0.125–8 kHz). *$p < 0.05$, **$p < 0.01$; ***$p < 0.001$.

**TABLE 4** The frequency characteristics of hearing threshold in patients with VM with SF normal hearing and patients with SF hearing loss.

| Frequency | Group with SF hearing loss | Group with SF normal hearing | *p* |
|---|---|---|---|
| Low, mean (SD) | 17.38 (6.55) | 11.94 (3.11) | 0.012096 |
| Middle, mean (SD) | 24.38 (11.51) | 12.29 (5.35) | 0.001945 |
| High, mean (SD) | 36.35 (23.72) | 11.67 (4.12) | 0.001403 |
| Extended high, mean (SD) | 80.83 (22.92) | 41.25 (27.24) | 0.000126 |

VM, vestibular migraine; including definite and PVM. SF, standard frequency (0.125–8 kHz). Low frequency, 0.125–0.5 kHz. Middle frequency, 1.0–2.0 kHz. High frequency, 4.0–8.0 kHz. EHF, 10.0–16.0 kHz. SD, standard deviation.

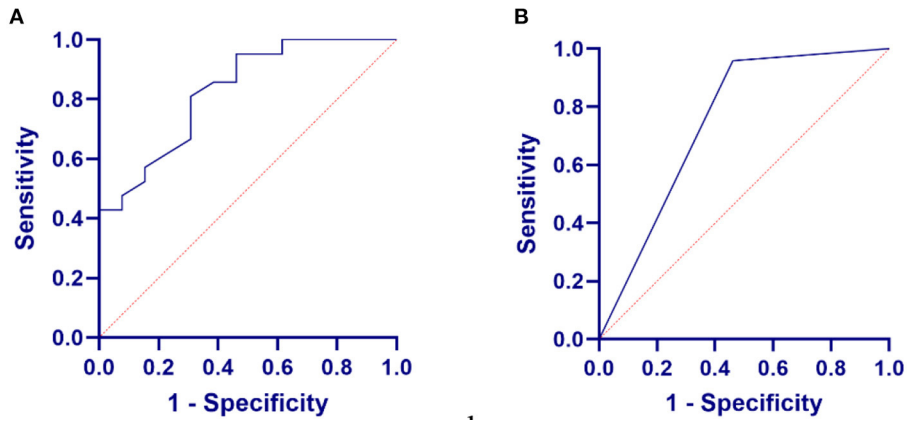


FIGURE 3
Relationship between EHF pure-tone test or distortion product optoacoustic emission (DPOAE) in VM and SF hearing loss. **(A)** The relationship between the mean EHF hearing threshold in VM and SF hearing loss. **(B)** The relationship between the DPOAE in VM and SF hearing loss.

predictor for poor SF hearing. Patients with VM could be classified into two groups, namely the LEHF and HEHF groups, in terms of the cutoff value of 57 dB HL of the mean EHF threshold.

TABLE 5 Clinical characteristics of patients with low mean EHF hearing threshold (LEHF) and those with high mean EHF hearing threshold (HEHF).

| | Patients with LEHF ($n = 10$) | Patients with HEHF ($n = 27$) |
|---|---|---|
| Female-to-male ratio | 9 | 2.375 |
| Mean age (SD) (years)* | 34.2 (10.51) | 50.44 (12.45) |
| Disease duration, m (Q1, Q3), (month) | 31.25 (0.53, 84) | 16 (4, 48) |
| Frequency of vertigo spell, m (Q1, Q3), (/6 months) | 1.5 (1, 5.25) | 2 (1, 5.25) |
| Days affected, m (Q1, Q3), (/month) | 6.5 (2, 13.75) | 3 (1, 10) |
| **Vertigo type**[a] | | |
| Internal vertigo | 50% ($n = 5$) | 59.09% ($n = 15$) |
| Dizziness | 30% ($n = 3$) | 48.15% ($n = 13$) |
| Vestibulo-visual symptoms | 70% ($n = 7$) | 88.89% ($n = 24$) |
| Posture symptoms | 10% ($n = 1$) | 11.11% ($n = 3$) |
| **Duration of vertigo attacks**[a] | | |
| <5 min | 70% ($n = 7$) | 59.09% ($n = 15$) |
| 5 min–72 h | 30% ($n = 3$) | 48.15% ($n = 13$) |
| >72 h | 0 ($n = 0$) | 11.11% ($n = 3$) |
| VM* | 90% ($n = 9$) | 48.15% ($n = 13$) |
| pVM* | 10% ($n = 1$) | 51.85% ($n = 14$) |
| Phonophobia | 40% ($n = 5$) | 37.04% ($n = 10$) |
| Nausea and/or vomiting | 30% ($n = 3$) | 48.15% ($n = 13$) |
| Photophobia | 40% ($n = 4$) | 37.03% ($n = 10$) |
| Tinnitus[b] | 60% ($n = 6$) | 51.85% ($n = 14$) |
| Hearing loss complaint[b] | 20% ($n = 2$) | 51.85% ($n = 14$) |
| Autoimmune disease | 10% ($n = 1$) | 18.52% ($n = 5$) |
| Cardiovascular risk factors | 30% ($n = 3$) | 55.56% ($n = 15$) |
| Motion sickness[b] | 90% ($n = 9$) | 55.56% ($n = 15$) |
| Family history of vertigo/migraine | 30% ($n = 3$) | 48.15% ($n = 13$) |
| Psychological disorder[b] | 60% ($n = 6$) | 81.48% ($n = 22$) |
| Sleep disorder[b] | 70% ($n = 7$) | 74.07% ($n = 20$) |
| Abnormal PTA at SF* | 30% ($n = 3$) | 81.48% ($n = 22$) |
| Abnormal VAT | 60% ($n = 6$) | 77.78% ($n = 21$) |
| Abnormal DPOAE | 50% ($n = 5$) | 55.56% ($n = 17$) |

[a]More than one result. [b]In the interval episode. *$p < 0.05$, indicating a statistically significant difference between patients with VM and pVM.

Vestibular migraine had clinical manifestations, which varied substantially. Women and people at the age of 40 were preponderant, which coincided with previous findings (Formeister et al., 2018). VM had a robust trend toward familial clustering (Requena and Espinosa-sanchez, 2014). A family history of migraine and/or vertigo was common in patients with VM (43.24%) but less common than previously reported (Teggi et al., 2018). Teggi et al. (2018) found that approximately 70.2% of patients with VM had a positive family history of migraine and 66.3% had a family history of vertigo. This difference might be attributed to the relatively small sample size of our cohort and racial differences.

Similar to other studies, our study also found that the features of migraine and vertigo showed great variations in terms of type, duration, attack frequency, and the mean number of days affected per month (Radtke et al., 2012; Dieterich et al., 2016; Teggi et al., 2018). The type and duration of vertigo differed considerably across numerous studies. Patients with dVM and pVM presented similarly in our cohort. As a result, dizziness and vestibulo-visual symptoms (83.78%) and internal

vertigo (54.05%) were the major manifestations, followed by dizziness (43.24%) and posture symptoms (10%). Meanwhile, Teggi et al. (2018) reported that internal vertigo (73%) and postural symptoms (61.5%) were the most common symptoms in dVM, followed by spontaneous dizziness (47.2%) and external vertigo (25%). However, according to one study, unsteadiness (91%), balance problems (82%), and vertigo (57%) were the most common symptoms (Cohen et al., 2011). To date, what are the major and characteristic presentations of vertigo in VM remain a head-scratching issue among otorhinolaryngologists. Consistent with previously published data, our study found that the duration of vertigo attacks was highly variable, but the vertigo episode lasted for less than 5 min in 56.76% of patients with VM, as opposed to the much lower rate of 21% reported by other researchers (Teggi et al., 2018). According to the diagnostic criteria for the VM state, 30% of patients with VM experienced attacks that lasted only minutes and 10% experienced attacks that lasted only seconds (Lempert et al., 2012), with the rates being much lower than our findings. We speculated that patients with VM who visited the department of otolaryngology might present vestibular symptoms different from those who visited the emergency room or neurology clinics, and, reportedly, many patients with VM might have experienced vertigo spells that lasted less than 5 min. Therefore, to accurately identify patients with VM, special attention should be paid to the duration of a vertigo attack in patients with VM.

Regarding the comorbidities of VM, sleep disorders, anxiety, depression, and somatic conditions, cardiovascular risk factors, and autoimmune diseases were reportedly common, on par with migraine (Macgregor et al., 2011). Some researchers even proposed that migraine-anxiety-related dizziness was a symptom complex of balance disorder, migraine, and anxiety (Furman, 2005). Comorbidities of VM warrant further research and are important to VM therapy.

Migraine raises serious concerns because it is an important risk factor for sudden hearing loss (Viirre and Baloh, 1996; Dash et al., 2008; Hwang et al., 2018), and auditory system dysfunction was found to be more common in pVM/dVM than what was was previously thought. This study found accompanying cochlear symptoms in the interval episode, which was in line with prior studies (Radtke et al., 2012; Lopez-Escamez et al., 2014; Teggi et al., 2018; Benjamin et al., 2022). Notably, 74.3% of patients with VM had abnormal SF PTA, which was higher than the rates reported in other studies (Dash et al., 2008; Radtke et al., 2012). The rate of bilateral involvement was higher in our cohort than that in other studies. This phenomenon indicated that a large number of patients with VM suffered from hearing loss, which is contrary to what was previously considered. Similar to earlier findings, our subjects reported tinnitus and hearing loss rates of 42.8 and 45.7%, respectively (Radtke et al., 2012).

Hearing loss in patients with VM is frequency-specific but remains controversial. In some studies, patients with VM developed mild and reversible low-frequency hearing loss (Hwang et al., 2018; Xue et al., 2020). Xue et al. (2020) found that low-frequency hearing was more likely to be involved in VM and proposed that a history of migraine might be the cause of sudden low-frequency hearing loss. Nonetheless, our study found that SF, middle-frequency, and high-frequency (2–8 kHz) hearing loss were the most common and aggravated, and low-frequency hearing loss was much less common and much milder. Radtke et al. (2012) and Lai et al. (2019) also reported that patients with VM developed high-frequency hearing loss. Our findings can help in differentiating VM from other vestibular disorders, such as MD. Patients with MD have low-frequency hearing loss, and hearing loss can progress from low- to middle-to-high frequency hearing loss, ultimately deteriorating into pantonal hearing loss (Lopez-Escamez et al., 2015). However, patients with VM tend to have bilateral EHF and high-frequency hearing loss, followed by middle- and low-frequency hearing loss. Our findings support the notion that hearing loss in VM tends to be at high frequency, which contributes to disease differentiation.

Moreover, this was the first study to comprehensively test the EHF hearing threshold in patients with VM. We found that 91.89% of patients had an elevated threshold at one or more frequencies, especially at 16 kHz and subsequently at 12.5 kHz. An examination of the function of outer hair cells revealed that EHF had a higher rate of abnormality than PTA (74.3%) and DPOAE (62.9%),. This discrepancy could be explained by central and peripheral auditory system damage in VM: (1) reversible vasospasm of the internal auditory artery or its branches (Viirre and Baloh, 1996; Baloh, 1997; Lai et al., 2019); (2) some inflammation and vasoactive neuropeptides (e.g., substance P, 5-HT, and GCRP) affect the activity of sensory fibers innervating the inner ear and central auditory system (Cabanillas and Luebke, 2002; Vass et al., 2004; Koo and Balaban, 2006); (3) VM responds to abnormal brain sensitization, which results in a disordered multimodal sensory integration and processing involving the pain matrix, vestibular pathways, auditory pathways, etc. (Shin et al., 2014; Espinosa-Sanchez and Lopez-Escamez, 2015); (4) several genetic variants of ionic channels and receptors have been identified to be associated with migraine, both in the brain and inner ear, such as CACNA1A (Wiest et al., 2001), and neuronal voltage-gated calcium channels (Cav2.1) (Moskowitz et al., 2004). Furthermore, the different cochlea parts were vulnerable in different ways. Wu et al. (2018) reported that the gene Calca/Cgrpα was highly expressed in type II afferent neurons as compared to type I ones after hearing the onset. Furthermore, Calca/Cgrpα drives reporters preferentially in "higher frequency" type II SGNs near the cochlear base. CGRP is a neurotransmitter that plays an important role in the development of migraine. Ying et al. found an innate apical-to-basal gradient of decreasing SOD2 expression in mammals in the absence of an ototoxic challenge. It might suggest a selection bias in the evolutionary process of cochlear design that favored higher SOD2 expression in the apex,

corresponding to higher ROS load in the apical cochlear turn but lower response capacity at the cochlear base, contributing to cumulative susceptibility to high-frequency hearing loss. Therefore, cochlear basal turns, such as high-frequency and EHF hearing, were more vulnerable than low-frequency hearing. Ying and Balaban (2009) found an innate apical-to-basal gradient of decreasing SOD2 expression in mammals in the absence of ototoxic challenge. It might suggest a selection bias in the evolutionary process of a cochlear design that favored higher SOD2 expression in the apex, corresponding to higher ROS load in the apical cochlear turn, but lower response capacity at the cochlear base, contributing to cumulative susceptibility to high-frequency hearing loss. Therefore, cochlear basal turns, such as high-frequency and EHF hearing, had more vulnerability than low-frequency hearing. The combination of vasodilatory and contractile activity, neuroinflammation, and neuroexcitatory plasticity during the recurrence of a VM attack led to such a vulnerability.

We further explored the risk factors for hearing loss in VM. Our results indicated that the mean EMF hearing threshold could be used to predict SF hearing loss. Moreover, the cutoff value of 57 dB HL (the mean EHF hearing threshold) outperformed DPOAE in predicting poor SF hearing. Therefore, EHF PTA might detect potential hearing damage in VM to allow for early intervention. Our study also showed that EHF PTA could be used to monitor disease progression and evaluate treatment efficacy. Hearing function was related to life quality, drop risk, and cognitive ability (Wang et al., 2022); therefore, those with an elevated EHF hearing threshold, especially those with HEHF, should receive multimodal migraine prophylaxis therapy and hearing protection to evaluate the quality of life, such as prophylactic migraine drugs, and noise avoidance.

To date, few studies focused on the differences in clinical features between patients with VM and hearing loss and those without. In this study, we found that patients with HEHF were older, but the disease duration was not different between the two groups. The EHF hearing threshold would be physically evaluated with age. The presence of VM might accelerate the progression of age-related hearing loss. In addition, when compared to patients with dVM, those with pVM were more likely to have HEHF. This might be attributed to the fact that the pVM organs involved were less vestibule-specific.

There are several limitations to this study. Achieving homogeneity was a challenge, as both dVM and pVM were included. Above all, the evaluation of familial cases of vertigo (and their diagnoses) and the clinical history of migraine precursors might present some uncertainties, as these data were only collected during a structured interview of the patient. Finally, our sample size was not sufficient, and there was no control group to allow for a more in-depth analysis and the identification of additional risk factors for hearing loss.

## Conclusion

Vestibular migraine has a wide range of clinical manifestations, including core symptoms (vestibular symptoms and migraine features), accompanying symptoms (auditory symptoms), and comorbidities (cardiovascular risk factors, sleep disorders, and psychological disorders). Auditory symptoms, especially hearing loss, were more common than previously thought. The majority of the patients with VM (74.3%) had SF hearing loss (0.125–8.0 kHz) and 97.1% had EHF hearing loss (8.0–20 kHz). Patients with VM tend to have bilateral EHF and high-frequency hearing loss (4.0–8 kHz). Moreover, EHF PTA may be used to predict hearing loss, monitor disease progression, and evaluate treatment efficacy. Patients with a high mean EHF hearing threshold (>57 dB HL) may benefit from positive multimodal migraine prophylaxis therapy and should put on hearing protection.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Wuhan Union Hospital. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

SZ, ZG, and WK designed the research and directed its implication. ZG drafted and modified the manuscript. ZG, ET, JW, and JC contributed to the medical record collection. All authors have read and agreed to the published version of the manuscript.

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## Conflict of interest

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

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.1090322/full#supplementary-material

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# Examination of brain area volumes based on voxel-based morphometry and multidomain cognitive impairment in asymptomatic unilateral carotid artery stenosis

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**Objective:** Recent evidence has demonstrated that unilateral carotid artery stenosis (CAS) can contribute to the development of cognitive impairment. However, the features of cognitive dysfunction induced by unilateral CAS remain unclear.

**Methods:** Sixty asymptomatic patients with unilateral CAS were divided into mild, moderate and severe stenosis groups. These patients and 20 healthy controls provided clinical data and serum, which was used to assess the levels of certain vascular risk factors. Then, they participated in a battery of neuropsychological tests. Additionally, all participants underwent a 3.0T magnetic resonance imaging (MRI) scan of the brain. Chi-square tests and one-way ANOVA were used to determine significant differences in the risk factors and cognitive test scores between groups. Multiple logistic regression analysis and the receiver operating characteristic (ROC) curve analysis were performed to identify the independent risk factors for cognitive impairment in patients with CAS. Finally, fluid attenuated inversion recovery (FLAIR) T1-weighted MRI images were processed by voxel-based morphometry (VBM) analysis using the Statistical Parametric Mapping (SPM) 8 software.

**Results:** Compared with healthy controls, the scores of the Mini-Mental State Examination, Digital Span Test backward, and Rapid Verbal Retrieve were significantly reduced in patients with left CAS. The scores in all cognitive scales were significantly lower in patients with right CAS than in controls. Logistic regression analysis demonstrated that the degree of carotid stenosis was an independent risk factor for cognitive impairment in asymptomatic patients with unilateral CAS. Furthermore, VBM analysis showed that, compared with those in healthy controls, gray matter and white matter volumes in specific brain areas were markedly decreased in patients with severe unilateral CAS. However, in patients with moderate right CAS, there was a significant decline in the volume of gray matter in the left parahippocampal gyrus and supplementary motor area. Additionally, the volume of white matter in the left insula was obviously lower in patients with moderate right CAS than in healthy controls.

**Conclusion:** Unilateral asymptomatic CAS, especially on the right side, contributed to cognitive impairment, including memory, language, attention, executive

function and visuospatial function. In addition, based on VBM analysis, both gray matter atrophy and white matter lesions were found in patients with unilateral asymptomatic CAS.

KEYWORDS

carotid artery stenosis, cognitive impairment, gray matter, white matter, voxel-based morphometry analysis

# Introduction

Cognitive impairment affects the patients' well-being and their ability to live independent and productive lives (Chaytor and Schmitter-Edgecombe, 2003). It also places large demands on societal, hospital, and financial resources (Rockwood et al., 2002). Although, the prevalence of vascular cognitive impairment induced by ischemic or hemorrhagic stroke or transient ischemic attack increases gradually with age, increasing evidence suggests that cognitive impairment also occurs in patients with asymptomatic carotid artery stenosis (CAS) (Xiang et al., 2013; Lal et al., 2017; Pillai, 2022). Atherosclerosis is a direct consequence of multiple vascular risk factors and can lead to increased intima-media thickness (IMT), plaque formation, and subsequent carotid artery stenosis or occlusion (Xiang et al., 2013). An increasing number of studies have demonstrated that CAS induced by atherosclerosis might be a potential risk factor for cognitive impairment in elderly people. Recent data has further indicated that patients with unilateral CAS might present with specific cognitive impairment relevant to the ipsilateral hemispheric functions (Huang et al., 2014). Moreover, high-grade stenosis of the unilateral carotid artery might contribute to multidomain cognitive impairment (Yue et al., 2016; He et al., 2021). However, there is limited knowledge on the characteristics and differences in cognitive impairment caused by unilateral CAS. Furthermore, the underlying mechanism of cognitive dysfunction induced by CAS remains unclear.

In the present study, we enrolled asymptomatic patients with three different levels of unilateral CAS as well as age-, sex-, and education level-matched healthy controls. A comprehensive battery of standardized neuropsychological tests was performed to analyze the cognitive impairment of the four groups. Additionally, we compared clinical vascular risk factors between the patients with unilateral CAS and healthy controls and determined independent risk factors for cognitive impairment. Finally, fluid-attenuated inversion recovery (FLAIR) T1-weighted magnetic resonance imaging (MRI) images were acquired, and voxel-based morphometry (VBM) analysis (Takeuchi and Kawashima, 2017) using statistical parametric mapping (SPM) was performed to explore the abnormal gray and white matter volumes in asymptomatic patients with unilateral CAS.

# Materials and methods

## Subjects

Patients with different levels of unilateral carotid artery stenosis (n = 60) and healthy controls (n = 20) were recruited to participate in this study between June 2017 and January 2021 in the Department of Neurology in Xinqiao Hospital, Army Military Medical University. All patients underwent head and neck computed tomography angiography (CTA) to identify the degree of their carotid artery stenosis. The enrolled patients with carotid artery stenosis were divided into three groups by 2 neurologists and 1 radiologist: mild, moderate and severe. The degree of CAS was also classified according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) standard into categories of no stenosis, mild stenosis (0–29%), moderate stenosis (30–69%), severe stenosis (70–89%), subtotal occlusion and occlusion. It should be noted that patients with previous stroke history or transient ischemic attack in either hemisphere or other diseases or medical events, such as intracranial tumors, central nervous system demyelinating diseases, severe brain trauma, history of neurological surgery, infection, or carbon monoxide poisoning, were excluded from the study. We also excluded patients with severe hearing and visual impairment, precluding a reliable assessment of cognitive function, or with severe psychotic disorders. Finally, patients with carotid revascularization on either side, contralateral arterial occlusion, known vertebral basilar or intracranial stenosis or occlusion, intracranial arteriovenous malformation, or documented dementia were excluded. Patients with carotid artery stenosis did not have ischemic or hemorrhagic lesions in the brain, and healthy controls had no stenosis in the bilateral carotid artery detected by head and neck CTA. This study was approved by the medical ethics committee of Xinqiao Hospital, Army Military Medical University, Chongqing, China. Full written informed consent for participation was obtained from each subject.

During admission, all participants provided demographic data and medical history. Age, sex, education, high blood pressure (HBP) and diabetes mellitus (DM) history, current smoking (CS) and current alcohol use (CAU) were obtained from the patient-administered questionnaire. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and uric acid (UA) were also measured.

## Neuropsychological evaluation

The battery of neuropsychological tests assessing a range of cognitive domains comprised the Chinese version of the Mini-Mental State Examination (MMSE), Trail-Making Test (TMT), Digital Span Test (DST), Rapid Verbal Retrieve (RVR), and Clock Drawing Test (CDT). All participants were administered the full cognitive battery. Testing was conducted in a quiet room and administered by a master's-level neuropsychology technician blinded to study participant status (stenosis vs. control) under the supervision of a senior neuropsychologist. The order of administration was consistent across participants. The total testing time varied modestly among

participants, ranging from 70 to 90 min, because of interindividual variability in completion time for tests without specific time limits. The tests were scored by a single neuropsychologist. Because mood could also influence results, the Hamilton Depression Scale (HAMD) was administered concurrently.

Overall cognitive functions were detected in the MMSE. The MMSE was developed from different neuropsychological batteries and includes five sections worth a total of 30 points: orientation (10 points); registration (3 points); attention and calculation (5 points); recall (3 points); and language (9 points). A score of less than 24 points indicated cognition impairment. The TMT score reflected the information processing speed of the participants. In the TMT, patients were required to quickly draw lines to connect consecutively numbered circles in ascending order. The maximum test duration was set at 300 s, and the number of errors, as well as the time taken to complete the test (measured in seconds), were recorded. Any patient who stopped midway was asked to continue the test for the remainder of the test duration. If not completed within the time limit, an error was recorded. The DST score reflected the concentration, instantaneous memory, and resistance to information interference of the participants. These included forward and backward count tests, where an evaluator read a series of numbers aloud to the patients. Patients were then required to repeat these numbers in the same order that they heard or in the reverse order. One point was awarded for each test passed, and zero points were awarded for a failed test. The highest scores in the forward count test and backward count test were 16 and 14 points, respectively. Therefore, the highest total score was 30 points. The RVR score reflected the language and executive function of the participants. During the RVR, the patients were required to say as many animal names (such as cattle, horses, and sheep) as possible within 1 min and were scored based on the number of correct animal names. The patients were then asked to complete two more sections, listing the names of fruits and vegetables within 1 min each. The sum of the three scores was the total score of this test. The executive and visuospatial functions were examined in the CDT. The CDT required the patients to draw a clock dial on white paper independently, place the 12 numbers in the correct positions, and mark the position of the specified time with a watch needle. The most common and simple scoring method of CDT was the quartering method: (1) draw a closed circle, 1 point; (2) put the numbers in the correct positions, 1 point; (3) the dial includes all 12 correct figures, 1 point; and (4) place the pointer in the correct position.

## Magnetic resonance imaging protocols

MRI scanning of the brain was performed using a 3.0 Tesla scanner (General Electric, Milwaukee, WI, United States) with a 12-channel head coil. Fast spin-echo (FSE) T2-weighted images and FLAIR T1-weighted images were acquired with TE/TR = 112.2/3160 ms and TE/IT/TR = 27.072/860/1696.68 ms. All MRI images were acquired with a voxel size of 0.4688 × 0.4688 × 5 mm (Lal et al., 2017), 20 sagittal slices and an in-plane resolution of 512 × 512.

## Data analysis

All statistical analyses of demographic and clinical variables were performed using SPSS version 20.0 (IBM SPSS, Chicago, IL, United States), and a value of $p < 0.05$ was considered statistically significant. Continuous variables are presented as their means ± standard deviations. Categorical variables are presented as percentages. Chi-square tests and one-way ANOVA were used to determine significant differences in the frequencies of categories and differences in continuous variables between the groups, respectively. The Pearson correlation coefficient was used to evaluate the correlation between vascular risk factors and declined cognitive functions. Multiple logistic regression analysis and receiver operating characteristic (ROC) curve analysis were performed to identify the independent risk factors for cognitive impairment in patients with carotid artery stenosis, with the degree of stenosis as a categorical variable.

The MRI data were processed using Statistical Parametric Mapping (SPM) 8 software (Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, United Kingdom) with VBM implemented in the VBM 8 toolbox[1] with default parameters (Duan et al., 2016). Images were bias-corrected, tissue classified, and registered using linear (12-parameter affine) and nonlinear transformations (warping) within a unified model. Subsequently, VBM analysis was performed on the normalized gray matter and white matter segments, which were multiplied by the nonlinear components derived from the normalization matrix to preserve actual gray matter and white matter values locally (modulated GM and WM volumes). Importantly, the segments were not multiplied by the linear components of the registration to account for individual differences in brain orientation, alignment, and size globally. Finally, the images were smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM). Voxelwise differences in gray matter and white matter between each group were examined using independent-sample *t-test*s. To avoid possible edge effects between different tissue types, we excluded all voxels with gray matter and white matter values of less than 0.09 (absolute threshold masking). We also applied a threshold of $p < 0.05$ with 10-voxel clustering criteria.

# Results

## Clinical characteristics and cognitive assessments

Table 1 shows a comparison of clinical data between the patients with left carotid artery stenosis and healthy controls. There was a significant difference in smoking status, alcohol consumption and high blood pressure among the groups with different levels of carotid artery stenosis and the healthy control group ($p < 0.05$). Additionally, marked differences in the levels of TC and HCY are also shown in Table 1. As shown in Table 1, there were significant differences in the MMSE, DST (backward) and RVR scores of patients and healthy controls ($p<0.05$). Obvious differences were not present in the scores of the HAMD, TMT, DST (forward) and CDT. These data indicated that instantaneous memory and language function significantly declined in asymptomatic patients with left CAS.

1 http://dbm.neuro.uni-jena.de/vbm.html

TABLE 1 Differences of clinical risk factors and neuropsychological examinations of patients with left carotid artery stenosis.

| Characteristic | Patients with left carotid artery stenosis | | | Healthy control | $\chi^2/F^1$ | *p*-value |
|---|---|---|---|---|---|---|
| | Mild group | Moderate group | Severe group | | | |
| *n* | 20 | 20 | 20 | 20 | | |
| Sex (*n*%, male) | 9 (45) | 14 (70) | 15 (75) | 12(60) | 4.45[1] | 0.108 |
| Age (years) | 65.06 ± 7.83 | 67.81 ± 6.40 | 62.35 ± 7.7 | 62.26 ± 8.14 | 2.09[2] | 0.110 |
| Education (years) | 8.6 ± 1.83 | 9.2 ± 0.23 | 8.8 ± 0.85 | 8.5 ± 0.53 | 3.74[2] | 0.637 |
| CS (*n*, %) | 4 (20) | 10 (50) | 12 (60.0) | 5 (25) | 7.06[1] | 0.029* |
| CAU (*n*, %) | 2 (10) | 8 (40) | 9 (45) | 3 (15.0) | 6.62[1] | 0.036* |
| HBP (*n*, %) | 6 (30) | 15 (75) | 7 (35) | 8 (40.0) | 9.78[1] | 0.008* |
| DM (*n*, %) | 5 (25) | 7 (35) | 4 (20) | 4 (20.0) | 1.19[1] | 0.5501 |
| TC | 4.67 ± 0.68 | 4.106 ± 0.86 | 3.57 ± 0.99 | 4.39 ± 0.96 | 5.43[2] | 0.002* |
| TG | 1.80 ± 1.82 | 1.58 ± 0.72 | 1.29 ± 0.57 | 1.45 ± 0.68 | 0.77[2] | 0.516 |
| HDL-C | 1.23 ± 0.34 | 1.0275 ± 0.25 | 1.0155 ± 0.252 | 1.20 ± 0.31 | 2.71[2] | 0.0512 |
| LDL-C | 2.60 ± 0.68 | 2.7300 ± 1.48 | 1.9605 ± 0.61 | 2.38 ± 0.72 | 2.50[2] | 0.067 |
| HCY | 11.13 ± 2.74 | 16.87 ± 10.51 | 12.54 ± 3.23 | 12.59 ± 5.07 | 2.82[2] | 0.045* |
| UA | 327.07 ± 84.04 | 368.163 ± 79.51 | 296.495 ± 80.24 | 318.85 ± 59.87 | 2.69[2] | 0.053 |
| HAMD | 18.53 ± 7.31 | 15.13 ± 9.60 | 15.55 ± 7.58 | 11.37 ± 7.68 | 2.42[2] | 0.074 |
| MMSE | 24.94 ± 2.28 | 24.81 ± 2.17 | 23.25 ± 3.04 | 28.26 ± 1.046 | 16.6[2] | 0.003* |
| TMT | 24.06 ± 1.35 | 23.50 ± 4.49 | 22.75 ± 2.31 | 24.74 ± 0.93 | 2.08[2] | 0.111 |
| DST (forward) | 5.76 ± 0.66 | 5.63 ± 0.72 | 5.65 ± 01.14 | 6.05 ± 0.41 | 1.15[2] | 0.337 |
| DST (backword) | 4.53 ± 0.72 | 4.75 ± 0.56 | 3.95 ± 0.76 | 5.32 ± 0.67 | 13.05[2] | 0.000* |
| RVR | 26.71 ± 0.99 | 22.00 ± 1.75 | 22.30 ± 2.578 | 26.00 ± 1.94 | 28.17[2] | 0.000* |
| CDT | 3.06 ± 0.243 | 3.00 ± 0.52 | 3.15 ± 0.67 | 3.42 ± 0.51 | 2.35[2] | 0.080 |

Continuous variables were presented as the means ± standard deviation. Categorical variables were presented as percentage. Chi-square test and one-way ANOVA were used to determine significant differences of the frequencies of categories and differences in continuous variables, respectively, between the groups. CS, current smoking; CAU, current alcohol use, HBP, high blood pressure; DM, diabetes mellitus; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HCY, homocysteine; UA, uric acid; HAMD, Hamilton Depression Scale; MMSE, Mini-Mental State Examination; TMT, Trail-Making Test; DST, Digital Span Test; RVR, Rapid Verbal Retrieve; CDT, Clock Drawing Test. [1,2,*]: Chi-square test, one-way ANOVA, and $p < 0.05$, respectively.

The clinical characteristics of the asymptomatic patients with right carotid artery stenosis and healthy controls are shown in Table 2. There was no significant difference in age, sex and education nor in vascular risk factors examined in the study. However, Table 2 demonstrates that the scores of all the cognitive tests, including MMSE, TMT, DST, and CDT ($p < 0.05$), in patients with right CAS showed statistically significant differences when compared with healthy controls. These results revealed that many more special cognitive domains were impaired in asymptomatic patients with right CAS, including memory, language, attention, executive function and visuospatial function, than in those with left CAS.

## Pearson correlation analysis between vascular risk factors and impaired cognitive function

The correlative analysis between vascular risk factors and decreased cognitive function in asymptomatic patients with left CAS evaluated by the Pearson correlation coefficient is presented in Table 3. For these patients, there was a negative correlation between the degree of carotid stenosis and MMSE ($r = -0.591$, $p = 0.000$), DST (backward) ($r = -0.544$, $p = 0.000$), and RVR ($r = -0.627$, $p = 0.000$). In addition, there was a negative correlation between patient age and the MMSE ($r = -0.240$, $p = 0.003$) and RVR ($r = -0.293$, $p = 0.008$) scores. The MMSE scores were positively correlated with HDL-C ($r = 0.244$, $p = 0.030$) and negatively correlated with HAMD ($r = -0.316$, $p = 0.004$). The DST (backward) scores were negatively correlated with both TG ($r = -0.248$, $p = 0.027$) and HAMD ($r = -0.496$, $p = 0.000$). RVR scores were positively correlated with TC ($r = 0.229$, $p = 0.041$) and HDL-C ($r = 0.300$, $p = 0.007$) and negatively correlated with HCY ($r = -0.301$, $p = 0.009$).

Similarly, Table 4 shows the correlative analysis between vascular risk factors and decreased cognitive function in asymptomatic patients with right CAS evaluated by the Pearson correlation coefficient. As shown in Table 4, there was a negative correlation between patient age and all the cognitive scales. There was a negative correlation between the degree of carotid stenosis and MMSE ($r = -0.675$, $p = 0.000$), TMT ($r = -0.520$, $p = 0.000$), DST (forward) ($r = -0.657$, $p = 0.000$), DST (backward) ($r = -0.641$, $p = 0.000$), RVR ($r = -0.730$, $p = 0.000$) and CDT ($r = -0.377$, $p = 0.001$) for patients with right CAS. At the same time, there was a positive correlation with TC ($r = 0.228$, $p = 0.042$) and HDL-C ($r = 0.224$, $p = 0.047$) in the MMSE results.

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TABLE 2 Differences of clinical risk factors and neuropsychological examinations of patients with right carotid artery stenosis.

| Characteristic | Patients with right carotid artery stenosis | | | Healthy control | $\chi^2$/F | *p*-value |
|---|---|---|---|---|---|---|
| | Mild group | Moderate group | Severe group | | | |
| *n* | 20 | 20 | 20 | 20 | | |
| Sex (*n*%, male) | 11 (55) | 16 (80.0) | 16 (80.0) | 12 (60.0) | 4.829[1] | 0.185 |
| Age (years) | 59.80 ± 9.17 | 62.00 ± 9.60 | 62.20 ± 8.59 | 62.25 ± 7.93 | 0.356[2] | 0.785 |
| Education (years) | 9.1 ± 0.92 | 8.5 ± 0.68 | 8.6 ± 0.93 | 8.5 ± 0.53 | 7.365[2] | 0.683 |
| CS (*n*, %) | 6 (30) | 12 (60) | 11 (55) | 5 (25) | 7.570[1] | 0.056 |
| CAU (*n*, %) | 6 (30) | 9 (45) | 7 (35) | 3 (15) | 4.363[1] | 0.225 |
| HBP (*n*, %) | 15 (75) | 13 (65) | 9 (45) | 8 (40) | 6.654[1] | 0.084 |
| DM (*n*, %) | 3 (15) | 7 (35) | 6 (30) | 4 (20) | 2.667[1] | 0.446 |
| TC | 4.19 ± 1.14 | 4.25 ± 1.47 | 3.84 ± 1.32 | 4.48 ± 1.01 | 0.905[2] | 0.443 |
| TG | 1.35 ± 0.52 | 1.67 ± 1.06 | 1.95 ± 1.46 | 1.47 ± 0.67 | 1.428[2] | 0.241 |
| HDL-C | 1.15 ± 0.35 | 1.04 ± 0.26 | 0.98 ± 0.23 | 1.20 ± 0.31 | 2.299[2] | 0.084 |
| LDL-C | 2.55 ± 0.87 | 2.38 ± 1.10 | 1.95 ± 0.84 | 2.38 ± 0.72 | 1.643[2] | 0.187 |
| HCY | 11.82 ± 4.76 | 12.53 ± 3.26 | 13.32 ± 6.86 | 12.31 ± 5.10 | 0.283[2] | 0.838 |
| UA | 340.59 ± 76.92 | 347.83 ± 61.37 | 326.63 ± 81.89 | 318.74 ± 58.27 | 0.702[2] | 0.554 |
| HAMD | 20.65 ± 8.98 | 19.50 ± 9.32 | 14.95 ± 8.76 | 11.75 ± 7.66 | 4.493[2] | 0.006* |
| MMSE | 26.05 ± 1.67 | 22.05 ± 5.65 | 22.70 ± 3.20 | 28.20 ± 1.06 | 14.520[2] | 0.000* |
| TMT | 24.50 ± 1.24 | 22.25 ± 2.221 | 22.65 ± 2.43 | 24.75 ± 0.91 | 9.772[2] | 0.000* |
| DST (forward) | 6.00 ± 0.65 | 5.45 ± 0.83 | 4.40 ± 0.75 | 6.05 ± 0.39 | 25.735[2] | 0.000* |
| DST (backward) | 5.25 ± 0.85 | 4.05 ± 0.83 | 3.90 ± 0.55 | 5.30 ± 0.66 | 21.194[2] | 0.000* |
| RVR | 25.30 ± 2.13 | 21.30 ± 2.18 | 20.70 ± 2.13 | 25.95 ± 1.91 | 33.287[2] | 0.000* |
| CDT | 3.20 ± 0.41 | 3.05 ± 0.67 | 2.80 ± 0.52 | 3.40 ± 0.50 | 4.389[2] | 0.007* |

Continuous variables were presented as the means ± standard deviation. Categorical variables were presented as percentage. Chi-square test and one-way ANOVA were used to determine significant differences of the frequencies of categories and differences in continuous variables, respectively, between the groups. CS, current smoking; CAU, current alcohol use, HBP, high blood pressure; DM, diabetes mellitus; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HCY, homocysteine; UA, uric acid; HAMD, Hamilton Depression Scale; MMSE, Mini-Mental State Examination; TMT, Trail-Making Test; DST, Digital Span Test; RVR, Rapid Verbal Retrieve; CDT, Clock Drawing Test. [1,2,*]: Chi-square test, one-way ANOVA and $p < 0.05$, respectively.

TABLE 3 Pearson correlation analysis between vascular risk factors and impaired cognitive function in asymptomatic patients with left carotid artery stenosis.

| Risk factors | *n* | MMSE | | DST (backward) | | RVR | |
|---|---|---|---|---|---|---|---|
| | | *r* | *p* (two-tailed) | *r* | *p* (two-tailed) | *r* | *p* (two-tailed) |
| Age | 80 | −0.240 | 0.003* | −0.065 | 0.569 | −0.293 | 0.008* |
| Sex | 80 | −0.122 | 0.282 | 0.081 | 0.473 | −0.234 | 0.037* |
| Degree of stenosis | 80 | −0.591 | 0.000* | −0.544 | 0.000* | −0.627 | 0.000* |
| CS | 80 | −0.171 | 0.129 | −0.099 | 0.382 | −0.298 | 0.007* |
| CAU | 80 | −0.143 | 0.207 | −0.132 | 0.243 | −0.373 | 0.001* |
| HBP | 80 | 0.041 | 0.721 | 0.056 | 0.623 | −0.071 | 0.529 |
| DM | 80 | 0.064 | 0.570 | 0.078 | 0.491 | −0.020 | 0.857 |
| TC | 80 | 0.114 | 0.312 | −0.022 | 0.848 | 0.229 | 0.041* |
| TG | 80 | −0.107 | 0.347 | −0.248 | 0.027* | −0.065 | 0.567 |
| HDL-C | 80 | 0.244 | 0.030* | 0.091 | 0.424 | 0.300 | 0.007* |
| LDL-C | 80 | −0.027 | 0.816 | 0.087 | 0.445 | 0.044 | 0.697 |
| HCY | 80 | −0.132 | 0.259 | −0.001 | 0.994 | −0.301 | 0.009* |
| UA | 80 | −0.089 | 0.433 | 0.061 | 0.592 | −0.021 | 0.852 |

CS, current smoking; CAU, current alcohol use, HBP, high blood pressure; DM, diabetes mellitus; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HCY, homocysteine; UA, uric acid. *r*: Pearson correlation coefficients. *$p < 0.05$. *p*-values were obtained using the two-tailed Pearson correlation analysis.

TABLE 4 Pearson correlation analysis between vascular risk factors and impaired cognitive function in asymptomatic patients with right carotid artery stenosis.

| Risk factors | *n* | MMSE | | TMT | | DST (forward) | | DST (backward) | | RVR | | CDT | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *r* | *p* (two-tailed) | *r* | *p* (two-tailed) | *r* | *p* (two-tailed) | *r* | *p* (two-tailed) | *r* | *p* (two-tailed) | *r* | *p* (two-tailed) |
| Age | 80 | −0.315 | 0.004* | −0.360 | 0.001* | −0.332 | 0.003* | −0.284 | 0.011* | −0.372 | 0.001* | −0.308 | 0.005* |
| Sex | 80 | −0.188 | 0.095 | −0.154 | 0.174 | −0.322 | 0.004* | −0.126 | 0.265 | −0.338 | 0.002* | −0.197 | 0.080 |
| Degree of stenosis | 80 | −0.675 | 0.000* | −0.520 | 0.000* | −0.657 | 0.000* | −0.641 | 0.000* | −0.730 | 0.000* | −0.377 | 0.001* |
| CS | 80 | −0.215 | 0.055 | −0.218 | 0.052 | −0.284 | 0.011* | −0.188 | 0.094 | −0.264 | 0.018* | −0.119 | 0.294 |
| CAU | 80 | −0.145 | 0.200 | −0.101 | 0.374 | −0.153 | 0.175 | −0.103 | 0.364 | −0.135 | 0.234 | 0.004 | 0.971 |
| HBP | 80 | −0.051 | 0.653 | −0.037 | 0.742 | 0.069 | 0.540 | 0.052 | 0.648 | 0.020 | 0.862 | −0.056 | 0.624 |
| DM | 80 | −0.145 | 0.198 | −0.169 | 0.135 | −0.139 | 0.218 | −0.219 | 0.051 | −0.170 | 0.132 | −0.061 | 0.588 |
| TC | 80 | 0.228 | 0.042* | 0.108 | 0.341 | −0.031 | 0.783 | 0.118 | 0.298 | 0.029 | 0.800 | −0.094 | 0.406 |
| TG | 80 | 0.030 | 0.790 | 0.055 | 0.625 | −0.106 | 0.348 | −0.040 | 0.725 | −0.092 | 0.416 | −0.094 | 0.407 |
| HDL-C | 80 | 0.224 | 0.047* | 0.086 | 0.450 | 0.198 | 0.080 | 0.178 | 0.116 | 0.171 | 0.131 | 0.067 | 0.560 |
| LDL-C | 80 | 0.171 | 0.131 | 0.138 | 0.225 | 0.017 | 0.880 | 0.154 | 0.175 | 0.080 | 0.481 | −0.116 | 0.309 |
| HCY | 80 | −0.085 | 0.462 | −0.212 | 0.062 | −0.079 | 0.490 | −0.180 | 0.114 | −0.062 | 0.591 | −0.081 | 0.480 |
| UA | 80 | −0.146 | 0.196 | 0.100 | 0.377 | −0.035 | 0.758 | 0.106 | 0.349 | −0.011 | 0.923 | 0.073 | 0.522 |

CS, current smoking; CAU, current alcohol use, HBP, high blood pressure; DM, diabetes mellitus; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HCY, homocysteine; UA, uric acid. *r*: Pearson correlation coefficients. *$p < 0.05$. *p*-values were obtained using the two-tailed Pearson correlation analysis.

TABLE 5 Multiple logistic regression analysis for risk factors of cognitive impairment in patients with left carotid artery stenosis.

| Risk factors | *B* coefficient | Std. error | *p* | OR | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Upper | Lower |
| MMSE | | | | | | |
| Age | −0.095 | 0.040 | 0.018* | 0.910 | 0.841 | 0.984 |
| Degree of stenosis | −1.289 | 0.335 | 0.000* | 0.275 | 0.143 | 0.531 |
| HDL-C | 0.323 | 1.076 | 0.764 | 1.382 | 0.168 | 11.382 |
| DST (backward) | | | | | | |
| Degree of stenosis | −1.036 | 0.283 | 0.000* | 0.355 | 0.204 | 0.618 |
| TG | −0.294 | 0.279 | 0.293 | 0.746 | 0.431 | 1.289 |
| RVR | | | | | | |
| Age | −0.127 | 0.054 | 0.019* | 0.881 | 0.792 | 0.979 |
| Sex | 1.744 | 1.084 | 0.108 | 5.720 | 0.683 | 47.910 |
| Degree of stenosis | −1.915 | 0.478 | 0.000* | 0.147 | 0.058 | 0.376 |
| CS | −0.736 | 1.168 | 0.528 | 0.479 | 0.049 | 4.724 |
| CAU | −0.196 | 1.214 | 0.872 | 0.822 | 0.076 | 8.880 |
| TC | 0.089 | 0.507 | 0.860 | 1.093 | 0.405 | 2.950 |
| HDL-C | 0.219 | 1.545 | 0.887 | 1.244 | 0.060 | 25.731 |
| HCY | −0.218 | 0.135 | 0.106 | 0.804 | 0.617 | 1.047 |

CS, current smoking; CAU, current alcohol use, TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; HCY, homocysteine. OR, Odds ratio. *$p < 0.05$.

## Multiple logistic regression analysis for risk factors of cognitive impairment

Multiple logistic regression analyses of age, sex, degree of stenosis, CS, CAU, TC, TG, HDL-C, LDL-C, and HCY were performed to identify risk factors for cognitive impairment (Tables 5, 6). In patients with left CAS, the degree of stenosis was a risk factor for low MMSE (OR = 0.275, 95% CI 0.143–0.531), DST (backward) (OR = 0.355, 95% CI 0.204–0.618) and RVR (OR = 0.147, 95% CI 0.058–0.376) scores. Patient age was a risk factor for low MMSE (OR = 0.910, 95% CI

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TABLE 6 Multiple logistic regression analysis for risk factors of cognitive impairment in patients with right carotid artery stenosis.

| Risk factors | *B* coefficient | Std. error | *p* | OR | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Upper | Lower |
| MMSE | | | | | | |
| Age | −0.051 | 0.036 | 0.153 | 0.950 | 0.885 | 1.019 |
| Degree of stenosis | −1.390 | 0.345 | 0.000* | 0.249 | 0.127 | 0.490 |
| TC | 0.199 | 0.258 | 0.441 | 1.220 | 0.735 | 2.024 |
| HDL-C | −0.196 | 1.131 | 0.863 | 0.822 | 0.090 | 7.546 |
| TMT | | | | | | |
| Age | −0.116 | 0.039 | 0.003* | 0.890 | 0.825 | 0.960 |
| Degree of stenosis | −1.400 | 0.335 | 0.000* | 0.247 | 0.128 | 0.475 |
| DST (forward) | | | | | | |
| Age | −0.093 | 0.039 | 0.017* | 0.912 | 0.845 | 0.984 |
| Sex | −1.704 | 0.987 | 0.084 | 0.182 | 0.026 | 1.259 |
| Degree of stenosis | −1.878 | 0.416 | 0.000* | 0.153 | 0.068 | 0.345 |
| CS | 0.408 | 0.825 | 0.621 | 1.504 | 0.298 | 7.583 |
| DST (backward) | | | | | | |
| Age | −0.115 | 0.042 | 0.007* | 0.892 | 0.821 | 0.969 |
| Degree of stenosis | −2.103 | 0.469 | 0.000* | 0.122 | 0.049 | 0.306 |
| RVR | | | | | | |
| Age | −0.203 | 0.056 | 0.000* | 0.816 | 0.731 | 0.912 |
| Sex | −1.175 | 1.115 | 0.292 | 0.309 | 0.035 | 2.746 |
| Degree of stenosis | −2.687 | 0.616 | 0.000* | 0.068 | 0.020 | 0.228 |
| CS | 0.596 | 1.060 | 0.574 | 1.815 | 0.227 | 14.482 |
| CDT | | | | | | |
| Age | −0.099 | 0.039 | 0.010* | 0.906 | 0.840 | 0.977 |
| Degree of stenosis | −0.691 | 0.291 | 0.018* | 0.501 | 0.283 | 0.886 |

CS, current smoking; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol. OR, odds ratio. *$p < 0.05$.

0.841–0.984) and RVR (OR = 0.881, 95% CI 0.792–0.979) scores (Table 5). Moreover, the degree of stenosis (OR = 0.147, 95% CI 0.058–0.376) was a risk factor for low DST (backward) scores in patients with left CAS (Table 5). As shown in Table 6, patient age was a risk factor for all cognitive scales except MMSE. The degree of stenosis was a risk factor for low TMT (OR = 0.247, 95% CI 0.128–0.475), DST (forward) (OR = 0.153, 95% CI 0.068–0.345), DST (backward) (OR = 0.122, 95% CI 0.049–0.306), RVR (OR = 0.068, 95% CI 0.020–0.228) and CDT (OR = 0.501, 95% CI 0.283–0.886) scores in patients with right CAS. Additionally, the degree of stenosis was also a risk factor for MMSE (OR = 0.249, 95% CI 0.127–0.490) in patients with right CAS (Table 6).

## Receiver operating characteristic curve for independent risk factors of cognitive impairment

Table 7 presents the independent risk factors for cognitive impairment in asymptomatic patients with unilateral CAS that were evaluated by ROC curve analysis. In the patients with left CAS, degree of stenosis was an independent risk factor for low MMSE (AUC = 0.194, $p = 0.000$), DST (backward) (AUC = 0.056, $p = 0.000$) and RVR (AUC = 0.129, $p = 0.000$) scores. Patient age was an independent risk factor for low MMSE scores (AUC = 0.355, $p = 0.025$). In the patients with right CAS, degree of stenosis was an independent risk factor for low MMSE (AUC = 0.172, $p = 0.000$), TMT (AUC = 0.190, $p = 0.000$), DST (forward) (AUC = 0.129, $p = 0.000$), DST (backward) (AUC = 0.134, $p = 0.000$), RVR (AUC = 0.112, $p = 0.039$) and CDT (AUC = 0.321, $p = 0.021$) scores. Patient age was an independent risk factor for all cognitive scale scores except the MMSE score (Table 7). Thus, these data revealed that the degree of stenosis was an independent risk factor for impaired cognition in asymptomatic patients with CAS.

## Voxel-based morphometry analysis of brain area volumes

Figure 1 showed the VBM results for gray matter atrophy and white matter lesions in asymptomatic patients with right severe carotid artery stenosis compared with those in healthy controls. The red or yellow spots in Figure 1 indicated the brain regions with abnormal volumes in patients with right severe carotid artery stenosis.

TABLE 7 The receiver operating characteristic curve performed for independent risk factors of cognitive impairment in patients with carotid artery stenosis.

| Risk factors | AUC | Std. error | *p* | 95% CI | |
|---|---|---|---|---|---|
| | | | | Upper | Lower |
| Patients with left carotid artery stenosis | | | | | |
| MMSE | | | | | |
| Age | 0.355 | 0.063 | 0.025* | 0.478 | 0.232 |
| Degree of stenosis | 0.194 | 0.049 | 0.000* | 0.289 | 0.098 |
| DST (backward) | | | | | |
| Degree of stenosis | 0.244 | 0.056 | 0.000* | 0.353 | 0.134 |
| TG | 0.523 | 0.070 | 0.735 | 0.660 | 0.386 |
| RVR | | | | | |
| Age | 0.386 | 0.063 | 0.079 | 0.510 | 0.261 |
| Degree of stenosis | 0.129 | 0.046 | 0.000* | 0.220 | 0.038 |
| Patients with right carotid artery stenosis | | | | | |
| MMSE | | | | | |
| Degree of stenosis | 0.172 | 0.045 | 0.000* | 0.261 | 0.084 |
| TMT | | | | | |
| Age | 0.300 | 0.060 | 0.003* | 0.420 | 0.180 |
| Degree of stenosis | 0.190 | 0.050 | 0.000* | 0.290 | 0.100 |
| DST (forward) | | | | | |
| Age | 0.347 | 0.062 | 0.020* | 0.469 | 0.225 |
| Degree of stenosis | 0.129 | 0.040 | 0.000* | 0.208 | 0.050 |
| DST (backward) | | | | | |
| Age | 0.351 | 0.062 | 0.023* | 0.473 | 0.230 |
| Degree of stenosis | 0.134 | 0.043 | 0.000* | 0.217 | 0.050 |
| RVR | | | | | |
| Age | 0.266 | 0.057 | 0.000* | 0.378 | 0.154 |
| Degree of stenosis | 0.112 | 0.039 | 0.000* | 0.187 | 0.036 |
| CDT | | | | | |
| Age | 0.299 | 0.071 | 0.010* | 0.439 | 0.159 |
| Degree of stenosis | 0.321 | 0.068 | 0.021* | 0.455 | 0.187 |

TG, triglyceride. AUC: area under curve. *$p < 0.05$.

The gray and white matter volumes based on VBM analysis were compared between the patients with unilateral CAS and healthy controls by independent-sample *t-tests*. Table 8 shows that the gray matter volumes of three areas, left parietal lobe precuneus ($T = 2.08$, $p < 0.05$), right anterior cingulate ($T = 2.82$, $p < 0.05$), and right cingulate gyrus ($T = 4.78$, $p < 0.05$), obviously declined in the patients with left severe CAS when compared with healthy controls. Significantly decreased gray matter volumes were detected not only in the right parahippocampal gyrus ($T = 1.93$, $p < 0.05$) but also in the left supplementary motor area ($T = 3.32$, $p < 0.05$) in patients with right moderate CAS compared with healthy controls. Finally, there was a significant decrease in gray matter volume in the right occipital lobe precuneus ($T = 2.06$, $p < 0.05$) and right occipital lobe cuneus ($T = 2.98$, $p < 0.05$) in patients with right severe CAS compared with healthy controls. As shown in Table 9, significantly decreased white matter volume was detected in the left subgyral region in the patients with left severe CAS compared with healthy controls ($T = 3.85$, $p < 0.05$). There was a significant decline in left insula white matter volume in the patients with right moderate CAS compared with healthy controls ($T = 3.63$, $p < 0.05$). Additionally, white matter volume in the right subgyral region in the patients with right severe CAS was significantly decreased compared with that in the healthy controls ($T = 5.47$, $p < 0.05$).

## Discussion

Carotid artery atherosclerotic stenosis increases the risk of ischemic stroke, and the estimated rate of ipsilateral carotid-related acute ischemic stroke is 4.7% over 5 years (Balestrini et al., 2013; Chang et al., 2022). Increasing evidence has demonstrated that cognitive impairment is also associated with asymptomatic bilateral and unilateral CAS (Cheng et al., 2012; Xiang et al., 2013; Zavoreo et al., 2013; Buratti et al., 2014). Consistent with previous studies, our results revealed that unilateral CAS can contribute to cognitive decline. More importantly, many more cognitive domains were impaired in the patients with right CAS than in those with left CAS. Cognitive impairments found in asymptomatic patients with right CAS included those in the memory, language, attention, executive and visuospatial functions. These cognitive functions are also impaired as a result of vascular cognitive impairment (Bogolepova, 2022; Boomsma et al., 2022). Thus, our results indicated that CAS, especially right CAS, might play an important role in the development of vascular cognitive impairment. Additionally, multiple logistic regression analysis and the ROC curve analysis were used to confirm whether CAS is an important contributor to cognitive decline. The results of statistical analysis revealed that the degree of carotid stenosis was an independent risk factor for cognitive impairment. Our results suggest that, for the asymptomatic patients with CAS, revascularization could not only relieve stenosis of the carotid artery, but also, to a certain extent, improve the cognitive impairment. This finding was in line with those of several recent studies (Gupta et al., 2020; Turowicz et al., 2021).

The underlying mechanism of the cognitive impairment induced by unilateral CAS remains unclear. Previous studies have speculated on the involvement of cerebral hypoperfusion caused by hemodynamic disorders (Kaczmarz et al., 2021) and the uncoupling of cerebral hemodynamic and metabolic states (Gottler et al., 2019). Recently, thinning of the cortex was considered a potential biomarker, as it was previously shown to be associated with cognitive impairment in aging, neurodegenerative disease, and small vascular disease (Pettigrew et al., 2016; Weston et al., 2016). Increasing evidence has shown that gray matter atrophy is correlated with cognitive decline measured in asymptomatic patients with CAS (Benli et al., 2021; Gao et al., 2021; Wang et al., 2021). In contrast, a significant reduction in cortical

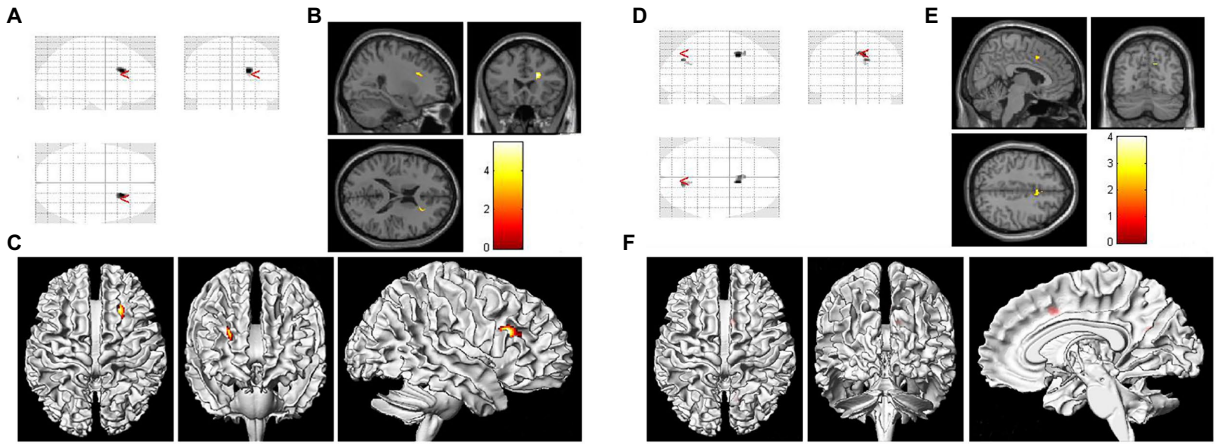


FIGURE 1
Voxel-based morphometry (VBM) results of gray matter atrophy and white matter lesions in asymptomatic patients with right severe carotid artery stenosis compared with healthy controls. **(A,D)** Statistical parametric mapping (SPM) results in various brain regions. **(B)** Significantly decreased white matter volume was found in the right subgyral region ($p<0.05$). **(E)** Gray matter atrophy was found in the right occipital lobe precuneus and right occipital lobe cuneus ($p<0.05$). **(C,F)** Three-dimensional images of the asymptomatic patient with right severe carotid artery stenosis.

**TABLE 8** Voxel-based morphometry (VBM) analysis of the declined gray matter volume in patients with carotid artery stenosis compared with healthy controls.

| Groups | Gray matter | | | | |
|---|---|---|---|---|---|
| | Brain area | *T* value | MNI coordinate | | |
| | | | *x* | *y* | *z* |
| Group with left severe carotid stenosis *vs.* healthy controls | Left parietal lobe// Precuneus | 2.08 | −9.0 | −70.5 | 24.0 |
| | Right limbic lobe// Anterior cingulate | 2.82 | 9.0 | 22.5 | 27.0 |
| | Right frontal lobe// Cingulate gyrus | 4.78 | 6.0 | 10.5 | 40.5 |
| Group with right moderate carotid stenosis *vs.* healthy controls | Left limbic lobe// Parahippocampal gyrus | 1.93 | −27.0 | −18.0 | −16.5 |
| | Supp_Motor_Area_L | 3.32 | −0.0 | 19.5 | 45.0 |
| Group with right severe carotid stenosis *vs.* healthy controls | Right occipital lobe// Precuneus | 2.06 | 10.5 | −61.5 | 27.0 |
| | Right occipital lobe// Cuneus | 2.98 | 12.0 | −70.5 | 31.5 |

thickness was not found in brain regions ipsilateral to the carotid stenosis (Nickel et al., 2019). Whether gray matter atrophy plays an important role in cognitive decline in patients with CAS is currently still under debate. In the present study, the T1-weighted MRI images of the recruited patients were acquired and processed by VBM analysis using the VBM 8 toolbox for SPM 8 software in MATLAB 2012a. In line with a previous study (Wang et al., 2021), loss of gray matter volume in patients was not only limited to the hemisphere ipsilateral to the stenosis but also observed in the contralateral hemisphere. We found that compared with healthy controls, gray matter volumes in patients with left severe CAS were significantly lower, and gray matter atrophy was widely distributed in the left precuneus, right anterior cingulate, and right cingulate gyrus. Furthermore, the gray matter volumes in patients with both moderate and severe right CAS were significantly decreased compared with those in healthy controls, and gray matter atrophy was detected in the left parahippocampal gyrus, right precuneus and right cuneus. Our findings indicated that gray matter atrophy was particularly vulnerable to stenosis of the right carotid artery.

In addition, we analyzed and compared the white matter volume between patients with CAS and healthy controls. Our results showed that white matter volume significantly decreased in asymptomatic patients with CAS compared with healthy controls. Consistent with the results of gray matter volume analysis, markedly decreased white matter volume was found in patients not only with left CAS but also with right CAS. Moreover, white matter volume in the left insula and right subgyral regions was significantly reduced in patients with moderate and severe right CAS compared with healthy controls. Chronic cerebral hypoperfusion due to carotid stenosis or occlusion has been shown to cause white matter injuries in animal experiments (Washida et al., 2019). Recently, increasing evidence shows that white matter hyperintensities are also present in patients with CAS (Ye et al., 2018; Benli et al., 2021; Gao et al., 2021). Cerebral hypoperfusion might be an important contributor to white matter hyperintensities induced by carotid stenosis, and the completeness of collateral circulation could protect these patients against white matter hyperintensities (Ye et al., 2019). It has also been reported that the development of cognitive dysfunction might be associated with the destructive effect of white matter hyperintensities on brain functional connectivity in patients with CAS (Porcu et al., 2020a,b).

Finally, our findings also revealed that there was a positive correlation between the level of TC and the scores of the MMSE and RVR tests. High levels of serum cholesterol could alleviate the cognitive dysfunction, especially language and executive function. Previous studies have shown that a high level of serum cholesterol is positively correlated with an increased risk of dementia (Loera-Valencia et al., 2019), and some studies have reported a decreased

TABLE 9 Voxel-based morphometry analysis of the declined white matter volume in patients with carotid artery stenosis compared with healthy controls.

| Groups | White matter | | | | |
|---|---|---|---|---|---|
| | Brain area | *T* value | MNI coordinate | | |
| | | | *x* | *y* | *z* |
| Group with left severe carotid stenosis *vs.* healthy controls | Left temporal lobe/Sub-Gyral | 3.85 | 13.5 | −67.5 | −39.0 |
| Group with right moderate carotid stenosis *vs.* healthy controls | Left sub-lobar/Insula | 3.63 | −34.5 | −9.0 | 22.5 |
| | | | | | |
| Group with right severe carotid stenosis *vs.* healthy controls | Right frontal lobe/Sub-gyral | 5.47 | 22.5 | 22.5 | 22.5 |

prevalence of Alzheimer's dementia in patients taking cholesterol-lowering drugs (Barone et al., 2014). In contrast, a meta-analysis showed that there was no clear consistent relationship between cholesterol and cognitive decline (Peters et al., 2021). Furthermore, some studies have demonstrated that a higher concentration of TC might be a protective factor for cognitive performance (Lv et al., 2016; Pang et al., 2022). Therefore, further experiments are needed to identify the correlation between serum TC and cognitive impairment.

## Limitation

Our study had a relatively small sample size and was a cross-sectional experiment based in a hospital. A specifically designed, randomized, controlled prospective population-based study is warranted in the future. Additionally, although we found abnormal brain regions in patients with CAS based on VBM analysis, we did not confirm the correlation between abnormal brain areas and impaired cognitive function. Finally, we did not explore the formation mechanism of abnormal brain areas caused by unilateral CAS.

## Conclusion

The current study provided insights into the association between cognitive impairment and carotid artery stenosis. Unilateral asymptomatic carotid artery stenosis, especially of the right carotid artery, was significantly related to cognitive impairment, including memory, language, attention, executive function and visuospatial function. More importantly, both gray matter and white matter volumes detected by VBM analysis significantly declined in patients with unilateral asymptomatic carotid artery stenosis. The degree of carotid stenosis was an independent risk factor for cognitive impairment. Revascularization might prevent cognitive dysfunction in patients. In addition, there was a positive correlation with TC and special cognitive domains. The lower the cholesterol level is, the more severe the cognitive impairment.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Author contributions

DD: conception and design, final approval of the version to be published. WD: participation in the whole work, drafting of the manuscript, and data analysis. CC and TS: MRI data acquisition and assessment. LL: demographic and cardiovascular risk factor data collection. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

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# Research progress on vestibular dysfunction and visual–spatial cognition in patients with Alzheimer's disease

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Alzheimer's disease (AD) or vestibular dysfunction may impair visual–spatial cognitive function. Recent studies have shown that vestibular dysfunction is increasingly common in patients with AD, and patients with AD with vestibular impairment show more visual–spatial cognitive impairment. By exploring the relationship and interaction mechanism among the vestibular system, visual–spatial cognitive ability, and AD, this study aims to provide new insights for the screening, diagnosis, and rehabilitation intervention of patients with AD. In contrast, routine vestibular function tests are particularly important for understanding the vestibular function of patients with AD. The efficacy of vestibular function test as a tool for the early screening of patients with AD must also be further studied. Through the visual–spatial cognitive ability test, the "spatial impairment" subtype of patients with AD, which may be significant in caring for patients with AD to prevent loss and falls, can also be determined. Additionally, the visual–spatial cognitive ability test has great benefits in preventing and alleviating cognitive decline of patients with AD.

KEYWORDS

**Alzheimer's disease, cognition, rehabilitation, vestibular dysfunction, visual–spatial cognition**

## Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease with a hidden onset. In 2018, the Alzheimer's Disease International estimated that the global prevalence of dementia was approximately 50 million, which is expected to triple by 2050. Two-thirds of these individuals live in low-and middle-income countries (Scheltens et al., 2021), which has a huge impact on public health (2021 Alzheimer's Disease Facts and Figures, 2021). Cognitive disorders, including memory disorders, impairment of visual–spatial skills, and executive dysfunction, often present as a clinical manifestation of AD. Moreover, the etiology of AD remains unclear (van der Flier et al., 2011).

The vestibular system plays an important role in body balance and maintaining the stability of movement. In addition to providing input information for brainstem reflexes, the vestibular system also sends projection signals to the subcortical and cortical structures, in which

information about the head direction and movement is used in advanced cognitive processes, such as spatial memory and navigation (Bigelow and Agrawal, 2015; Smith, 2017). Loss or disorder of the vestibular sensory function is one of the reasons for visual–spatial cognitive impairment. Increasing evidence shows that a decline in vestibular function is related to poor spatial cognitive ability in healthy older adults (Bigelow et al., 2015). Zhang et al. (2022) found that (i) visuospatial ability may decline with age, (ii) older adults have weaker visuospatial cognition than younger adults, and (iii) older patients with vestibular dysfunction have worse visuospatial cognition than normal older adults.

Patients with AD differ, on average, from each other on a number of clinical, neuropsychological, neuroimaging, and neuropathological variables. Some patients with AD tend to have worse ideomotor praxis and visual–spatial skills (Palasí et al., 2015; Joubert et al., 2016). The degree of vestibular damage in patients with AD is higher than that in healthy older adults of the same age (Previc, 2013). Therefore, there is a certain relationship between vestibular dysfunction and AD. This article discusses the relationship and interaction mechanism between the vestibular system, visual–spatial cognitive ability, and AD to provide information for the screening, diagnosis, and rehabilitation intervention in patients with AD.

## Vestibular dysfunction in patients with AD

Vestibular dysfunction is becoming increasingly common in patients with AD, with a study showing an 85.19% probability of cervical vestibular evoked myogenic potential (cVEMP) failing to elicit a distinct waveform bilaterally at a tone burst of 500 Hz and 125 dB SPL in patients with AD (Wei et al., 2018). Wei et al. (2019) evaluated the vestibular physiological function of 51 patients with AD and 295 normal controls using cVEMP, ocular vestibular evoked myogenic potentials, and video head impulse test (v-HIT). It was found that, compared with the normal control group, the probability of vestibular function impairment increased by at least three to four times in patients with AD. Thus, there is increased attention to whether vestibular function tests can be used as a means of early dementia screening. Bosmans et al. (2021) reviewed seven articles and analyzed the vestibular function test results of 150 patients with AD and 481 older adults with normal cognition as controls. The vestibular tests included the v-HIT, caloric test, and cVEMP. The results showed that the latency of P13 in patients with AD was significantly longer than that in the normal control group, and the amplitude of cVEMP was significantly lower than that in the normal control group. This study suggests that cVEMP may be used as a screening tool to distinguish patients with AD from older adults with normal cognitive function. However, more clinical trials are needed to verify the sensitivity of v-HIT in screening patients with AD.

The mechanism underlying the higher incidence of vestibular dysfunction in AD patients is unclear. The degeneration of the cholinergic system in the posterior parietotemporal region, medial temporal region, and posterior cingulate region can occur at an early stage of AD disease progression. The progression of AD disease also affects the function of the hippocampus, temporoparietal junction, insular cortex, and dorsal thalamus, which are related to the input of vestibular information (Previc, 2013; Agrawal et al., 2020). Amyloid-β (Aβ) protein, a macromolecular substance derived from the fat membrane of nerve cells, is the main pathological deposit in patients with AD. Accumulation of Aβ in the central vestibular pathway may damage the physiological function of the vestibule (Kamil et al., 2018). Other risk factors of AD, such as age, cardiovascular disease, diabetes, and traumatic brain injury, may also be related to vestibular dysfunction (Oron et al., 2017; Chen et al., 2021).

## Visual–spatial cognitive impairment in patients with AD

In addition to prominent memory problems, Alzheimer's disease is characterized by visual–spatial perception dysfunction (Mendez et al., 1990; Rizzo et al., 2000). Visual–spatial cognitive ability includes spatial memory, spatial navigation, and mental rotation. Spatial memory refers to the process by which the human body uses visual information or other sensory information, such as vestibular, auditory, and proprioceptive, to sort out, encode, process, and store surrounding environmental information. Successful spatial navigation depends on good spatial memory in the early stage (Iachini et al., 2021). Spatial navigation is the ability of an individual to identify the current location and environment and navigate to the next destination. Spatial navigation is a basic behavioral ability of human beings, which integrates various cognitive abilities, such as memory, execution, and perception, and helps them choose and apply the corresponding navigation strategies. Navigation strategies include two types: allocentric strategy and egocentric strategy. The allocentric strategy relies on landmarks and signs for spatial positioning and navigation; the egocentric strategy mainly depends on the main body orientation and geographical spatial clues (such as the orientation of the sun or moon) (Stewart et al., 2022). In the real-world, these two strategies can be used separately or jointly. Mental rotation refers to the rotation and direction change of different dimensions in the brain according to the representation of objects or graphics (Stewart et al., 2022). Currently, the evaluation scales and means used to evaluate visual–spatial cognitive ability in clinics mainly include the card rotations test, Benton visual retention test, money road map test (MRMT), Corsi block tapping task, and virtual Morris water task (MWT).

AD is characterized by the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles. Neuroinflammation and synaptic and neurotransmitter loss also participate in the pathogenesis of AD. Clinically, patients' memory loss and related cognitive dysfunction are the main characteristics of AD. According to the age of onset, AD can be further divided into two subtypes: early onset and late onset (Mendez, 2017; Di Resta and Ferrari, 2019; Ayodele et al., 2021). High permeability mutations in β-amyloid precursor protein, recombinant presenilin 1, and recombinant presenilin 2 lead to autosomal dominant early onset (Sun et al., 2017). Many patients with early-onset AD have a gradual decline in visuospatial skills, known as posterior cortical atrophy or "Benson's disease." In 1988, Benson et al. (1988) described 83 patients with this syndrome with complex visual symptoms, including dyslexia, perceptual visual agnosia, Bahrain syndrome (simultaneous agnosia, visual ataxia, optokinetic eye muscle apraxia), visual–spatial positioning difficulties, Gerstmann syndrome, and possible left visual field defect and visual structure test disproportional damage (Mendez, 2017). Several patients with AD have an obvious decline in visuospatial skills.

The plaques and tangles of abnormal AD proteins spread to the different regions of the brain, destroy brain function, and cause multi-dimensional cognitive impairment, including visual–spatial cognition. Reliable prediction indicators of amyloidosis *in vivo* have been reported in the literature (Dubois et al., 2014). However, they are often limited to the research environment due to cost, availability, or patient safety. Before the development of amyloid biomarkers, the clinical diagnostic criteria for diagnosing AD mainly depended on neuropsychological tests (Blessed et al., 1968; Chapman et al., 2011; Burrell and Hodges, 2015). In routine clinical practice, some cognitive function test scales, such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment, are used to assess the overall cognitive ability of patients with AD.

However, in some current studies, the accuracy of the visuospatial cognitive correlation test in screening patients with AD may be better than that of conventional global cognitive tests. Plácido et al. (2021) recruited 72 older people aged 60 years and above (39 healthy people and 43 with AD) to assess their spatial navigation ability using the floor maze test (FMT) and assessed their overall cognitive ability using the MMSE. The results showed that, compared with the MMSE test, FMT had better sensitivity in distinguishing patients with AD from healthy peers, indicating that the decline in visual–spatial cognitive ability could be independent of the decline in general cognitive ability. In addition, visual–spatial cognitive impairment may be an important cognitive marker for recognizing patients with early AD (Lester et al., 2017). Parizkova et al. (2018) studied the preferences of patients with AD regarding navigation strategies. With an increase in AD severity, the patient's preference for self-centered strategies was higher than that for object-centered navigation strategies. Atrophy of the hippocampus and basal forebrain in patients with AD may lead to the reduction of object-centered navigation strategies, some of which are replaced by self-centered navigation strategies. This obstacle can be detected using a simple visual–spatial cognition questionnaire (Cerman et al., 2018). Salimi et al. (2019) used Addenbrooke's Cognitive Examination-Revised (before 2014) and Addenbrooke's Cognitive Examination-III (after 2014) for cognitive screening, and found that the visual–spatial ability of patients with AD was impaired in all tests. The visual space defect of patients with AD is manifested as the impaired performance in the Addenbrooke's Cognitive Examination visual space subscale, Rey-Osterrieth complex figure copy, and visual object and space perception battery point count and position discrimination subtasks. It supports the view that visuospatial dysfunction is a prominent early feature of clinically possible AD.

Vogel et al. (2021) used positron emission tomography imaging technology to monitor the accumulation of tau protein in the brains of 1,612 patients. They delineated four different subtypes of AD pathology: (1) subtype 1, wherein tau protein is mainly deposited in the temporal cortex, affecting memory, accounting for 33%; (2) subtype 2, wherein tau protein is mainly deposited in the occipital cortex, affecting visual–spatial processing, accounting for 30%; (3) subtype 3, wherein tau protein spreads asymmetrically in the left brain, affecting language ability, accounting for 19%; and (4) subtype 4, wherein tau protein deposits and spreads in other parts of the cerebral cortex, affecting executive function, accounting for 18%. This explains why different patients with AD may have different symptoms. Wei et al. (2018) recruited 28 patients with AD and measured their cVEMP. The MRMT and trail-making test B were used to assess visual–spatial cognitive ability. According to the MRMT test results, patients with AD were divided into "space normal" and "space impaired" groups. The results showed that the rate of cVEMP unreduced in the "space impaired" AD group was significantly higher than that in the "space normal" AD group. This also indirectly indicates that there may be a specific "space impaired" subtype in patients with AD.

## Relationship among AD, vestibular system, and visual–spatial cognition

Visual–spatial cognition involves the fusion and coding of multiple sensory organs, of which visual nerve conduction and coding are the main ones. Nerve conduction mainly includes the dorsal and ventral pathways, which cooperate to complete the perception and control of the spatial environment (Zou, 2014). The dorsal pathway originates from the primary visual cortex V1 of the occipital lobe and reaches the parietal lobe and other related brain regions through MT, which is responsible for processing the visual and perceptual information related to movement. The ventral pathway also comes from the primary visual cortex V1 of the occipital lobe and reaches the lower temporal lobe and other related brain regions through V4, which is responsible for processing color, shape, and other related information (Bao et al., 2017). Visual–spatial information is transmitted layer-by-layer through the visual transmission pathway, and the information extracted from the changing visual images by the relevant functional brain regions also changes from simple to abstract and complex. In addition to the advanced visual conduction pathway, the vestibular thalamic cortical pathway affects the processing of spatial cognition and spatial recognition and navigation through vestibular information (Hitier et al., 2014). When these neural conduction networks and the cortex related to spatial processing are abnormal, the visual–spatial cognitive ability will have corresponding obstacles.

Vestibular information provides basic clues regarding spatial orientation, such as eye movement control, posture control, balance, and orientation. In addition to traditional low-level reflex motor circuits, the vestibular system is associated with higher levels of cognitive function. There are four main reflex pathways from the vestibule to the cortex, including the vestibulo-cerebello-cortical pathway, vestibulo-thalamo-cortical pathway, head direction pathway, and theta pathway (Hitier et al., 2014). Vestibular information can be transmitted to the parietal lobe through the thalamus and further to the entorhinal cortex or hippocampus to complete the recognition of environmental spatial information. Loss of vestibular information input may damage these cognitive and emotional circuits. Brandt et al. (2005) performed magnetic resonance imaging on 10 patients with a chronic bilateral vestibular disorder, and the results showed that the hippocampus of patients with chronic bilateral vestibular disorder showed significant atrophy compared with the normal control group. Hippocampal atrophy may reflect a neuroanatomical correlation between poor spatial cognitive ability and vestibular dysfunction.

The amyloid cascade hypothesis and tau protein pathogenesis theory are the two main pathogeneses of AD (Sun et al., 2017; Khan et al., 2020). The amyloid cascade hypothesis refers to Aβ, wherein the abnormal metabolism of tau leads to an increase in its production, which leads to changes in tau protein hyperphosphorylation, neuronal

damage, and oxidative stress, ultimately leading to the impairment of cognitive function. The pathogenesis of the tau protein is related to intracellular neurofibrillary tangles that form as tau accumulates, which directly damages neurons. The first area affected by AD is the hippocampus, which is primarily responsible for general memory and spatial storage. With the development of the disease, abnormal proteins are deposited and tangled in the occipital visual cortex and related high-level visual–spatial processing pathways, which further aggravates spatial cognitive impairment.

Both the visual–spatial cognitive impairment caused by vestibular dysfunction and visual–spatial cognitive impairment caused by AD seem correlated with the hippocampus. Atrophy of the hippocampus may affect the ventral cortical conduction pathway of visual processing and the corresponding vestibular thalamic cortical pathway. With the aggravation of AD, abnormal proteins may further deposit and tangle in the different cortical and brain regions, causing ventral and dorsal visual–spatial conduction pathways, as well as more abnormalities in the cortical regions related to spatial processing. Therefore, compared with the visual–spatial cognitive impairment caused by vestibular dysfunction, the mechanism of visual–spatial cognitive impairment caused by AD may be more complex. Some patients with AD have a worse visuospatial cognitive ability due to vestibular dysfunction. Wei et al. (2017) recruited 39 patients with AD and measured their cVEMP to evaluate balloon function. A visual–spatial questionnaire survey was conducted among all patients to assess whether they had obstacles in space driving and other aspects. The results showed that, compared with patients with AD with normal balloon function, patients with AD with bilateral balloon damage were 12 times more likely to have difficulty driving.

## Improvement of cognitive ability of patients with AD through vestibular rehabilitation

Falls are the main medical and health problem faced by patients with AD and their caregivers. Vestibular dysfunction is a known risk factor for falls. The prevalence of vestibular dysfunction in patients with AD is higher than that in the age-matched control group (Wei et al., 2017). Thus, vestibular physiotherapy (VPT) improves the balance of patients with vestibular dysfunction and normal cognitive function and reduces the risk of falls. Guidetti et al. (2020) evaluated 263 patients with chronic bilateral and unilateral vestibular dysfunction and 430 healthy individuals using the Corsi building block test. The results showed that the correct rate of the Cauchy building block test in patients with vestibular dysfunction was significantly lower than that in healthy controls. However, 5 days after the vestibular rehabilitation training, the same group of patients was tested for the Cauchy bricks test. The repetition accuracy rate of patients was improved compared to that before rehabilitation training, and their memory ability was improved to some extent. However, the effectiveness of VPT in improving the balance and falls of patients with AD with vestibular dysfunction requires further study. Some scholars have suggested that the theoretical framework of VPT rehabilitation and motor learning should be appropriately improved in patients with cognitive impairment (Klatt et al., 2019).

Vestibular nerve stimulation can promote the prevention and recovery of many diseases, such as dementia, stress-related mental disorders, and neurodegenerative diseases (Jagadeesan et al., 2021). According to different stimulation types, vestibular nerve stimulation can be divided into types such as vestibular electrical stimulation (GVS), vestibular thermal stimulation, and vestibular rotation stimulation. GVS can transmit vestibular information to the hippocampus through the basal ganglia pathway and participate in the regulation of spatial learning and memory. Nguyen et al. (2021) conducted GVS treatment in mice with unilateral labyrinthectomy and found that it improved their spatial memory and navigation ability. Adel Ghahraman et al. (2016) injected streptozotocin into the brains of rats to build a cognitive impairment model. The rats were divided into three groups and received GVS with low amplitude noise one or five times, each time lasting for 30 min, or did not receive GVS at all. MWT was conducted in each group to evaluate spatial memory and spatial navigation ability. The results showed that rats that received GVS treatment five times had better performance in MWT tasks, and memory impairment was significantly improved. This effect may be partly attributed to the frequent activation of vestibular neurons and their associated hippocampi by GVS.

AD is a long-term disease that may take several years or decades from neuropathological injury to complete loss of self-care ability. At different stages of disease progression, corresponding rehabilitation and nursing measures must be formulated and implemented according to the current concerns, and comprehensive prevention and treatment must be performed (Yang and Jia, 2021). The comprehensive and systematic cognitive assessment of patients is conducive to the formulation of appropriate rehabilitation intervention programs; however, the assessment of cognitive impairment for clinical diagnosis mainly focuses on the cognitive impairment mode of AD, while the rehabilitation assessment of AD requires a comprehensive assessment of various functional disorders that may exist in patients, such as daily behavior activity ability, hearing, and vestibular function, which are not limited to cognitive function (Chinese Expert Consensus on Rehabilitation Management of Alzheimer's Disease 2019, 2020).

## Outlook

AD and other forms of dementia are major and increasingly serious global health challenges. Currently, 40–50 million people worldwide suffer from dementia (Prince et al., 2013; Wu et al., 2017), which places a heavy burden on society (GBD, 2019). Care and support for patients with dementia has a wide impact on families, medical care systems, and society (Etters et al., 2008). There are currently no strategies to cure AD or change its course. However, early screening and diagnosis are conducive to appropriate treatment measures for patients with AD. In addition to aging, many risk factors, such as microvascular disease and hearing loss, are associated with cognitive decline (Livingston et al., 2020). With the incidence rate of cognitive impairment-related diseases, such as AD, increasing gradually, the intervention and control of various risk factors become particularly important. Vestibular injury is particularly common in patients with AD, especially in those with visual–spatial cognitive impairment. Therefore, routine vestibular function tests are particularly important for understanding the vestibular function of patients with AD. The efficacy of the vestibular function test as a tool for the early screening of patients with AD must also be further

studied. Through the visual–spatial cognitive ability test, the "spatial impairment" subtype of patients with AD, which may be significant in caring for patients with AD to prevent loss and falls, can also be determined and has great benefits in preventing and alleviating the cognitive decline of patients with AD.

## Author contributions

YH and XZ: ideas, preparation, specifically writing the initial draft. JX: formulation or evolution of overarching research goals and aims. YL and EY: ensure that the descriptions are accurate and agreed upon by all authors. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

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# Relationship between cognitive dysfunction and the promoter methylation of PER1 and CRY1 in patients with cerebral small vessel disease

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**Background and purpose:** The prevalence of cerebral small vessel disease (CSVD) is increasing due to the accelerating global aging process, resulting in a substantial burden on all countries, as cognitive dysfunction associated with CSVD is also on the rise. Clock genes have a significant impact on cognitive decline and dementia. Furthermore, the pattern of DNA methylation in clock genes is strongly associated with cognitive impairment. Thus, the aim of this study was to explore the connection between DNA promoter methylation of PER1 and CRY1 and cognitive dysfunction in patients with CSVD.

**Methods:** We recruited patients with CSVD admitted to the Geriatrics Department of the Lianyungang Second People's Hospital between March 2021 and June 2022. Based on their Mini-Mental State Examination score, patients were categorized into two groups: 65 cases with cognitive dysfunction and 36 cases with normal cognitive function. Clinical data, 24-h ambulatory blood pressure monitoring parameters, and CSVD total load scores were collected. Moreover, we employed methylation-specific PCR to analyze the peripheral blood promoter methylation levels of clock genes PER1 and CRY1 in all CSVD patients who were enrolled. Finally, we used binary logistic regression models to assess the association between the promoter methylation of clock genes (PER1 and CRY1) and cognitive dysfunction in patients with CSVD.

**Results:** (1) A total of 101 individuals with CSVD were included in this study. There were no statistical differences between the two groups in baseline clinical data except MMSE and AD8 scores. (2) After B/H correction, the promoter methylation rate of PER1 was higher in the cognitive dysfunction group than that in the normal group, and the difference was statistically significant (adjusted $p$ <0.001). (3) There was no significant correlation between the promoter methylation rates of PER1 and CRY1 in peripheral blood and circadian rhythm of blood pressure ($p$>0.05). (4) Binary logistic regression models showed that the influence of promoter methylation of PER1 and CRY1 on cognitive dysfunction were statistically significant in Model 1 ($p$ <0.001; $p$ =0.025), and it still existed after adjusting for confounding factors in Model 2. Patients with the promoter methylation of PER1 gene (*OR* =16.565, 95%*CI*, 4.057–67.628; $p$ <0.001) and the promoter methylation of CRY1 gene (*OR* =6.017, 95%*CI*, 1.290–28.069; $p$ =0.022) were at greater risk

of cognitive dysfunction compared with those with unmethylated promoters of corresponding genes in Model 2.

**Conclusion:** The promoter methylation rate of PER1 gene was higher in the cognitive dysfunction group among CSVD patients. And the hypermethylation of the promoters of clock genes PER1 and CRY1 may be involved in affecting cognitive dysfunction in patients with CSVD.

KEYWORDS

**clock genes, PER1, CRY1, methylation, cognitive dysfunction, cerebral small vessel disease, aging**

## Introduction

Cerebral small vessel disease (CSVD) is a heterogeneous disease caused by both genetic and vascular risk factors. It involves structural and functional abnormalities in small cerebral vessels and can cause variety of neuroimaging changes and neurological symptoms, including cognitive decline (Wardlaw et al., 2019; Zanon Zotin et al., 2021). Despite the lack of clear pathophysiological mechanisms, most patients with CSVD have similar brain parenchymal lesions, so the current clinical diagnosis of CSVD mainly relies on the indirect signs shown on the patients' head MRI. Neuroimaging features of CSVD have been summarized as follows (Hu et al., 2021): white matter hyperintensity (WMH) of presumed vascular origin, lacunar infarction (LI), cerebral microbleed (CMB), perivascular space (PVS), recent small subcortical infarct (RSSI), and brain atrophy. Staals et al. (2014) constructed a CSVD total load model incorporating WMH, PVS, CMB, and LI to assess brain damage, which also improved the clinical diagnostic efficacy of CSVD. Given that CSVD is closely linked to aging, its prevalence is increasing in line with the global aging process (Li et al., 2020). CSVD has been identified as a key contributor to dementia by the National Institutes of Health (Gurol et al., 2020), implying that it is an important cause of cognitive dysfunction. Dementia has long posed a social and economic burden to countries around the world. China accounts for about 25% of the global dementia population (Jia et al., 2020). The status of the country with the largest number of dementia patients in the world brings great challenges to Chinese clinicians and family members. Therefore, there is an urgent need for preventing dementia and detecting cognitive dysfunction early.

24-h ambulatory blood pressure monitoring (ABPM) has been widely used in clinical practice and scientific research due to its ability to reflect blood pressure variation and circadian rhythm. As this application deepens, the relationship between blood pressure and cognitive function has gradually become a hot spot in the current research field. By monitoring ABPM in CSVD patients, Shim and Shin (2022) found that higher systolic blood pressure was linked to cognitive dysfunction and the severity of WMH in the elderly. In the same year, Tanaka and Hattori (2022) spotted that abnormal circadian rhythm of blood pressure could be related to cognitive impairment and poor outcomes in α-synucleinopathies. In addition, we also observed in our recent study that the disturbance of circadian rhythm of blood pressure might affect the cognitive function of CSVD patients, especially in non-dipper and reverse-dipper types (Xu et al., 2023).

Circadian rhythm of blood pressure, an essential aspect of circadian rhythms, is likewise regulated by the circadian clock. On a molecular level, this clock involves a complex set of autoregulatory transcription-translation feedback loops. And circadian rhythm mainly relies on the expression and function of clock genes and their encoded proteins involved in the feedback loops (Morris et al., 2016; Ramos-Lopez et al., 2018). The primary feedback loop consists of core clock components such as brain and muscle ARNT-like 1 (BMAL1, also known as MOP3, encoded by ARNTL), circadian locomotor output cycles kaput (CLOCK, encoded by CLOCK), period (PER, encoded by PER1, PER2, PER3), and cryptochrome (CRY, encoded by CRY1, CRY2; Kim and Lazar, 2020). The main circadian changes observed in aging include the decrease in amplitude and the advance of daily rhythm phase (de Souza Teixeira et al., 2020). Several aging-related degenerative diseases have been found to be related to circadian rhythms, and alterations in the expression and function of clock genes could also affect these diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and osteoarthritis (Zhu et al., 2022). Moreover, circadian rhythms have a profound impact on cognitive function. In fact, studies have found that circadian rhythm disturbances could lead to cognitive decline and even dementia (Kyriacou and Hastings, 2010; Chellappa et al., 2018, 2019; Maiese, 2021). Similarly, clock genes also play a crucial role in cognitive loss and dementia (Maiese, 2019). Several animal studies have demonstrated that clock gene pathways appear to be altered in dementia (Bellanti et al., 2017; Petrasek et al., 2018). For instance, Bacalini et al. (2022) observed that the rs3027178 polymorphism in the PER1 gene was significantly associated with AD, and the rs3027178 exhibited similar genotypic frequencies in AD patients and the elderly. Oyegbami et al. (2017) found that the expression of clock genes PER1, PER2, CRY1, and CRY2 in the medullary/pons of control mice increased at night compared to the day, while the influence of CRY1 and CRY2 expression were weakened in the AD-related transgenic mouse model (APPswe/PS1dE9). Furthermore, circadian rhythms of blood pressure and elevated blood pressure, as vital components of circadian rhythms, have also been found to be related to clock genes. Solocinski et al. (2017), in their knockout experiments on mice, found that blood pressure in wild-type mice was not affected by a high salt diet plus mineralocorticoid, whereas PER1 knockout mice exposed to this influence exhibited significantly increased mean arterial pressure and resulted in a non-dipper phenotype, suggesting that PER1 gene plays a critical role in regulating blood pressure. Kovanen et al. (2015) also supported the association of CRY1 with arterial hypertension and elevated blood pressure.

Researchers in the biomedical field have found that genetic analysis can help clarify the relationship between epigenetics, the

circadian clock, and cognition. Methylation of the CpG island region of DNA promoter is one of the major regulatory mechanisms of gene transcription. Several studies have found that DNA methylation of clock genes is closely associated with cognitive impairment (Cronin et al., 2017; Kim et al., 2022). But until now, we have not found any studies focusing on the relationship between DNA methylation of clock genes and cognitive dysfunction in CSVD patients. In light of the above background, the aim of this study was to investigate the association of DNA promoter region methylation levels of PER1 and CRY1 with cognitive dysfunction in CSVD patients.

# Materials and methods

## Study population

From March 2021 to June 2022, there were 217 individuals admitted to the Geriatrics Department of the Lianyungang Second People's Hospital. Patients over 18 years old diagnosed with CSVD according to the Chinese consensus on diagnosis and therapy of cerebral small vessel disease 2021 (Hu et al., 2021) were included in this study. The subjects meeting the following conditions were excluded: (1) combined with obvious anxiety, depression or AD affecting cognitive function; (2) combined with cerebral infarction caused by macrovascular disease, vascular malformation, cardiogenic embolism, and other factors; (3) WMH caused by other diseases such as multiple sclerosis, metabolic, or toxic encephalopathy; (4) unable to cooperate with the head MRI examination; (5) unable to complete the Mini-Mental State Examination (MMSE) due to deafness, aphasia, agnosia, and other reasons; (6) suffering from severe insomnia; and (7) missing or incomplete clinical data. After exclusion, 101 patients with CSVD were enrolled in the study. Due to the epidemic prevention and control phase in China during the recruitment period, all patients were not infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when enrolled, and 37.6% of them had received at least one dose of vaccine. Among them, 65 patients with cognitive impairment were classified as the "cognitive dysfunction group" by MMSE score, and the remaining 36 patients were classified as the "normal group," as shown in Figure 1. This study was approved by the Ethics Committee of Lianyungang Second People's Hospital and registered in the Chinese Clinical Trial Registry (ChiCTR2000041152). Written informed consent was obtained from all participants.

## Cognitive function assessment

Mini-Mental State Examination was used to evaluate the cognitive function of enrolled patients, including five main components: orientation (0–10 points), memory (0–3 points), attention and numeracy (0–5 points), recall ability (0–3 points), and language ability (0–9 points). The total score was 30 points. The higher the score was, the better the cognitive function was. The normal threshold of MMSE score was defined as (Wang and Zhang, 1989): illiterate (uneducated) >17 points, primary school (years of education ≤6) >20 points, junior high school or above (years of education >6) >24 points. According to the MMSE score, the patients were divided into cognitive dysfunction group (< normal threshold) and normal group (> normal threshold).

## Extraction of DNA

A volume of 5 mL venous blood was collected from subjects at about 9 am after fasting for 12 h and placed into EDTA anticoagulation tubes, and then being mixed for 10–20 min and stored at −80°C. The Genomic DNA was extracted in strict accordance with the instructions of TIANamp Genomic DNA Kit (Servicebio, China). Then, about 1 μg of each genomic DNA sample was removed and modified according to the requirements of the modification kit Zymo DNA Methylation Kit (ZYMO, United States).

## The design of primers

Next, we analyzed the promoter sequences of clock genes PER1 and CRY1 at Methprimer online[1] and designed methylation-specific PCR (MSP) primers for two clock genes. The designed primer sequences were shown in Table 1.

## Methylation-specific PCR

In the 50 μL MSP reaction system, the disulfite modified genomic DNA template was 1.5 μL, the 2 × Taq PCR Master Mix was 25 μL, the upstream primer was 0.8 μL, the downstream primer was 0.8 μL, and ultra-pure water was added to make up the remaining volume. The mixture was then placed on a PCR instrument (Catalog: ETC811, EASTWIN, China) for amplification. The specific reaction conditions were as follows: pre-denaturation at 95°C for 5 min, denaturation at 95°C for 30 s, annealing at 55°C for 30 s, extension at 72°C for 30 s, amplification for 40 cycles, and then extension at 72°C for 5 min, and finally cooling at 16°C for 2 min.

Upon completion of the PCR amplification, the amplified products were subjected to 2.0% agarose gel electrophoresis, and the images were recorded by the gel image analysis system. The presence of partial methylation in the DNA promoter region was represented by "M" and the absence of methylation was represented by "U", as shown in Figure 2.

## Ambulatory blood pressure monitoring

All patients were required to have a successful 24-h ABPM (MedLifeKC-2820, China) within 48 h after diagnosed with CSVD, measured by a trained nurse. In the equipment used, blood pressure was measured every 30 min during the day (7:00–21:00) and every 60 min during the night (21:00–7:00). Each monitoring lasted for more than 25 h to ensure complete recording for 24 h, and eligibility was defined as valid data >80% for 24 h. Patients were asked to get enough rest or sleep at night and maintain normal activities during the day. Daily activities, sleep and wake times needed to be recorded in a diary. After wearing the device for at least 24 h, the device was removed and its data downloaded for analysis. Then relevant blood pressure parameters were collected, such as 24-h mean systolic blood pressure, 24-h mean diastolic blood pressure, 24-h mean standard

1 http://www.urogene.org/cgi-bin/methprimer/methprimer.cgi

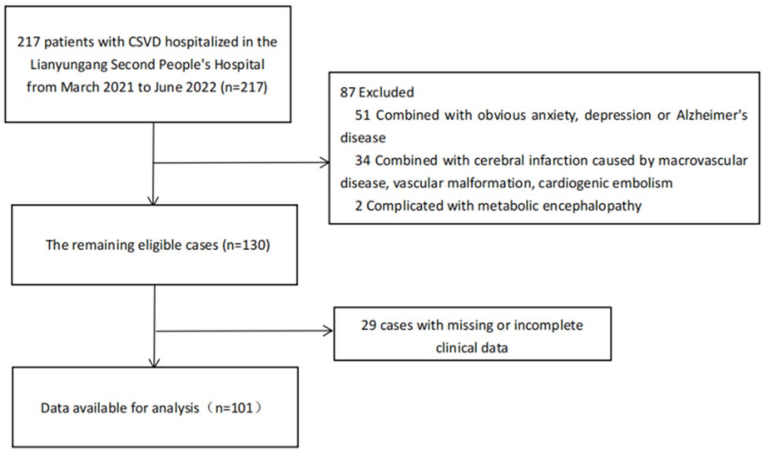


FIGURE 1
Flow diagram of included and excluded patients. CSVD, cerebral small vessel disease.

TABLE 1 The primers used for methylation analysis in the promoter of clock genes PER1 and CRY1.

| Gene name | Primer | Sequence (5′–3′) | Amplicon/bp |
|---|---|---|---|
| PER1 | Mf | GAGATTTTTAGTTAATCGGGGGC | 228 |
| | Mr | CAACGATCCGACTCAAAAACG | |
| | Uf | GAAGAGATTTTTAGTTAATTGGGGGT | 236 |
| | Ur | AATAACAACAATCCAACTCAAAAACA | |
| CRY1 | Mf | ACGTGAGGTGTCGGTGGTTAC | 220 |
| | Mr | AAATAAACCCCTATCGACGACG | |
| | Uf | GAAATGTGAGGTGTTGGTGGTTAT | 226 |
| | Ur | ATCAACAACACTATCTCTCAACCCA | |

deviation of systolic blood pressure, 24-h mean standard deviation of diastolic blood pressure, daytime mean systolic blood pressure (dmSBP), daytime mean diastolic blood pressure (dmDBP), nighttime mean systolic blood pressure (nmSBP), and nighttime mean diastolic blood pressure (nmDBP). And then we calculated the ratios of night systolic and diastolic blood pressure reduction separately: the ratio of night systolic blood pressure reduction = (dmSBP-nmSBP)÷dmSBP × 100%, the ratio of night diastolic blood pressure reduction = (dmDBP-nmDBP) ÷ dmDBP × 100%. We defined the ratio of night systolic blood pressure reduction as the ratio of night blood pressure reduction (ΔMBP) when the circadian rhythms of blood pressure shown by the ratio of night systolic and diastolic blood pressure reduction were inconsistent. Next, the circadian rhythms of blood pressure were classified according to ΔMBP: extreme-dippers (≥ 20%); dippers (10–20%); non-dippers (0–10%); and risers (< 0%; Kario et al., 2019). The classification of circadian rhythms of blood pressure was counted as an unordered categorical variable.

## CSVD total load score evaluation

The head MRI data of all subjects were acquired using a MAGNETOM Spectra 3.0 T magnetic resonance scanner with 16-channel coils. The sequences included: T1-weighted sequences (T1WI): TR 1,750 ms, TE 21.8 ms; T2-weighted image (T2WI): TR 3,598 ms, TE 107.3 ms; fluid-attenuated inversion recovery (FLAIR): TR 8,400 ms, TE 87 ms; diffusion weighted imaging (DWI): TR 6,000 ms, TE 73.5 ms; and susceptibility-weighted imaging (SWI): TR 37.5 ms, TE 22.9 ms, FOV 240 mm × 240 mm, and matrix 416 × 320. The CSVD total load score in this study included the four most classic imaging manifestations of WMH, LI, CMB, and PVS, with a total score of 0–4. It could reflect the severity of CSVD and was used as an ordered categorical variable in this study. A score of 0–1 was defined as mild, 2 as moderate, and 3–4 as severe (Xu et al., 2021). The evaluation was conducted independently by an experienced neurologist who had no other clinical information about the subjects.

## Statistical analysis

Statistical analyzes were performed using the SPSS software (IBM SPSS Statistics for Windows, version 26.0; IBM Corp., Armonk, NY, United States) and graphics were drawn by GraphPad Software (GraphPad Prism for Windows, version 9.0.0; San Diego, CA, United States). Kolmogorov–Smirnov test was used to evaluate the normality of numerical variables. Continuous variables of normal distribution were analyzed by independent sample T-test and expressed as mean ± SD. Continuous variables of skewed distribution were analyzed by Mann–Whitney U test and described

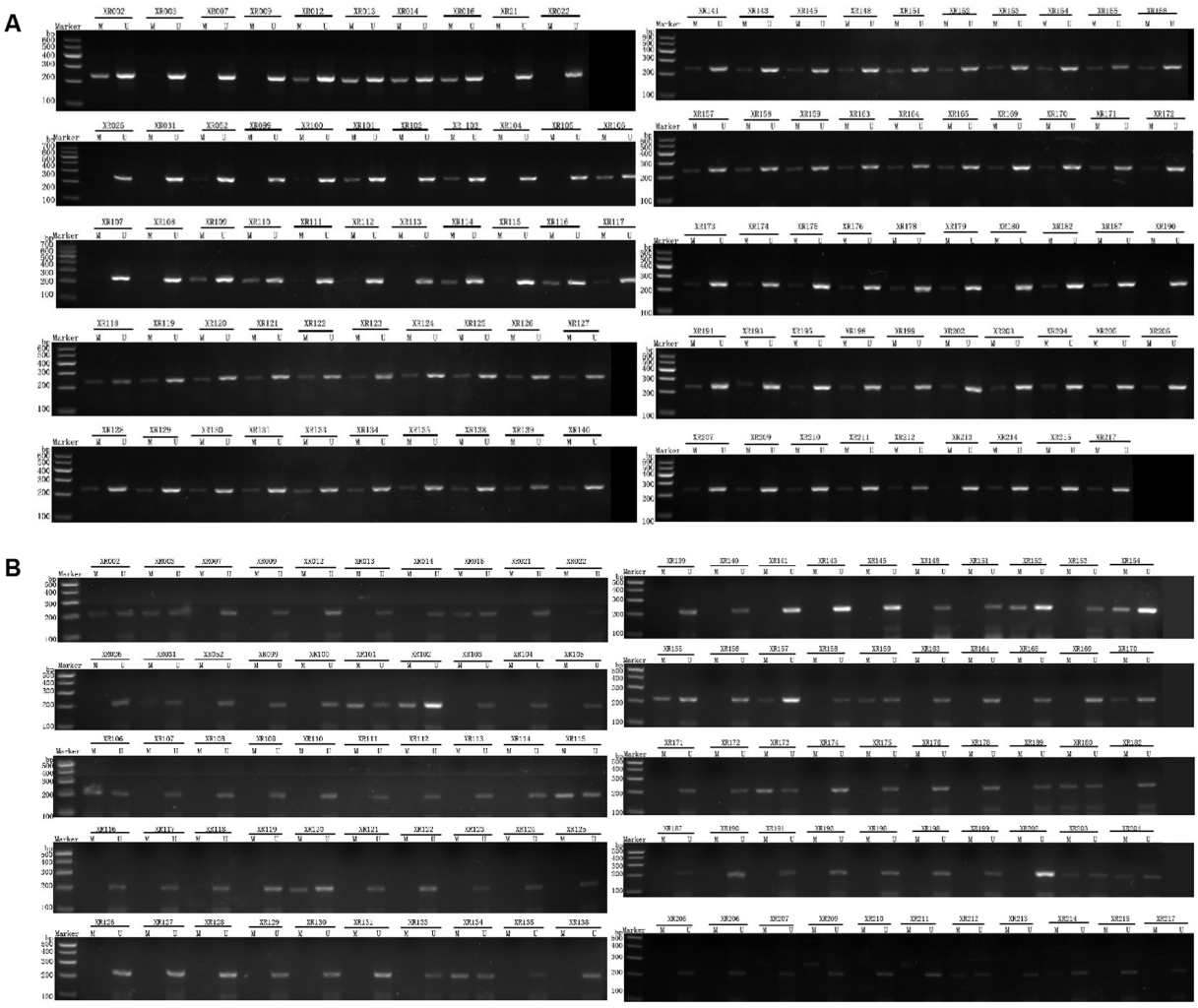

FIGURE 2
Electrophoretic diagram of test samples. **(A)** PER1; **(B)** CRY1. After PCR amplification, the amplified products were subjected to 2.0% agarose gel electrophoresis, and the images were recorded by the gel image analysis system. The presence of partial methylation in the DNA promoter region was represented by "M", while the absence of methylation was represented by "U".

by median and quartile range (IQR). And categorical variables were compared using the Chi-square test or Fisher's exact test. We also used binary logistic regression models to assess the association between the promoter methylation of clock genes (PER1 and CRY1) and cognitive dysfunction in patients with CSVD. Due to the number of statistical analyzes we did, bilateral $p$ values were adjusted according to the method of Benjamini-Hochberg (B/H) to control the false discovery rate (FDR). If the corresponding B/H-adjusted $p$ value was lower than 0.05, the difference was considered to be statistically significant.

# Results

## Clinical characteristics of the participants

From May 2021 to June 2022, a total of 101 patients (55.4% male, average age 70 years) were included in the study. The clinical parameters of the subjects were shown in Table 2. It was observed that after B/H correction, there were no statistical differences between the two groups in baseline clinical data except MMSE and AD8 scores.

## Comparison of the promoter methylation of clock genes

After B/H correction, the promoter methylation rate of the PER1 gene was higher in the cognitive dysfunction group than that in the normal group, and the difference was statistically significant (adjusted $p < 0.001$). However, there was no difference in the promoter methylation rate of the CRY1 gene between the two groups (adjusted $p = 0.243$), as shown in Table 3 and Figure 3. In terms of the amount of methylation, 59 cases (90.8%) were partially methylated in PER1 and 18 cases (27.7%) were partially methylated in CRY1 in 65 cases of cognitive dysfunction. While in the normal group, 20 cases (55.6%) had partial methylation of PER1 and three cases (8.3%) had partial methylation of CRY1.

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TABLE 2 Baseline characteristics of the participants.

| | Overall (*N*=101) | Cognitive dysfunction group (*N*=65) | Normal group (*N*=36) | Unadjusted *p* value | B/H-adjusted *p* value |
|---|---|---|---|---|---|
| **Clinical parameters** | | | | | |
| Age, Mean (SD)—year | 70.01 ± 13.01 | 72.46 ± 12.75 | 65.58 ± 12.47 | 0.010 | 0.109 |
| Gender—no. (%) | | | | 0.394 | 0.674 |
| Male | 56 (55.4%) | 34 (52.3%) | 22 (61.1%) | | |
| Female | 45 (44.6%) | 31 (47.7%) | 14 (38.9%) | | |
| Educational level—no. (%) | | | | 0.029 | 0.220 |
| Illiteracy | 15 (14.9%) | 12 (18.5%) | 3 (8.3%) | | |
| Primary school education | 23 (22.8%) | 14 (21.5%) | 9 (25.0%) | | |
| Junior high school education | 33 (32.7%) | 26 (40.0%) | 7 (19.4%) | | |
| High School education | 22 (21.8%) | 10 (15.4%) | 12 (33.3%) | | |
| Undergraduate college | 8 (7.9%) | 3 (4.6%) | 5 (13.9%) | | |
| AD8 score, Median (IQR) | 2.00 (1.00, 4.00) | 4.00 (2.00, 5.00) | 1.00 (0.00, 1.75) | <0.001 | <0.001 |
| MMSE score, Median (IQR) | 20.00 (11.00, 26.5.00) | 12.00 (7.50, 19.00) | 28.00 (26.00, 28.75) | <0.001 | <0.001 |
| BMI, Mean (SD)—kg/m$^2$ | 25.63 ± 3.53 | 25.71 ± 3.54 | 25.50 ± 3.56 | 0.782 | 0.922 |
| SBP, Mean (SD)—mmHg | 144.95 ± 20.96 | 146.11 ± 21.96 | 142.86 ± 19.15 | 0.459 | 0.737 |
| DBP, Mean (SD)—mmHg | 85.14 ± 16.22 | 85.97 ± 16.91 | 83.64 ± 15.00 | 0.492 | 0.745 |
| Glucose, Mean (SD)—mmol/L | 8.25 ± 3.51 | 7.99 ± 3.65 | 8.15 ± 3.26 | 0.837 | 0.944 |
| **Medical history** | | | | | |
| Hypertension—no. (%) | 72 (71.3%) | 51 (78.5%) | 21 (58.3%) | 0.032 | 0.212 |
| Diabetes mellitus—no. (%) | 37 (36.6%) | 28 (43.1%) | 9 (25.0%) | 0.071 | 0.251 |
| TIA or stroke—no. (%) | 41 (40.6%) | 30 (46.2%) | 11 (30.6%) | 0.126 | 0.334 |
| Cardiac disease—no. (%) | 37 (36.6%) | 23 (35.4%) | 14 (38.9%) | 0.726 | 0.916 |
| Smoking—no. (%) | 15 (14.9%) | 9 (13.8%) | 6 (16.7%) | 0.703 | 0.909 |
| Drinking—no. (%) | 18 (17.8%) | 11 (16.9%) | 7 (19.4%) | 0.751 | 0.905 |
| Antiplatelet drugs—no. (%) | 50 (49.5%) | 33 (50.8%) | 17 (47.2%) | 0.733 | 0.903 |
| Antihypertensive drugs—no. (%) | 58 (57.4%) | 39 (60.0%) | 19 (52.8%) | 0.482 | 0.751 |
| Hypoglycemic drugs—no. (%) | 26 (25.7%) | 14 (21.5%) | 12 (33.3%) | 0.194 | 0.467 |
| Antihyperlipidemics—no. (%) | 54 (53.5%) | 35 (53.8%) | 19 (52.8%) | 0.918 | 0.973 |
| **Laboratory indicators** | | | | | |
| WBC, Mean (SD)—10^9/L | 6.60 ± 1.99 | 6.77 ± 2.08 | 6.29 ± 1.78 | 0.258 | 0.526 |
| RBC, Mean (SD)—10^12/L | 4.44 ± 0.52 | 4.41 ± 0.55 | 4.49 ± 0.48 | 0.512 | 0.754 |
| HGB, Mean (SD)—g/L | 136.57 ± 17.20 | 134.58 ± 17.67 | 140.35 ± 15.82 | 0.113 | 0.334 |
| PLT, Mean (SD)—10^9/L | 216.60 ± 77.47 | 226.45 ± 87.47 | 197.76 ± 49.28 | 0.080 | 0.266 |
| NEUT, Median (IQR)—10^9/L | 3.97 (3.01, 5.17) | 4.00 (3.02, 5.06) | 3.34 (2.75, 4.25) | 0.082 | 0.256 |
| LY, Median (IQR)—10^9/L | 1.75 (1.25, 2.18) | 1.76 (1.23, 2.31) | 1.72 (1.13, 2.22) | 0.883 | 0.955 |
| ALT, Median (IQR)—U/L | 24.00 (19.00, 35.00) | 20.00 (14.00, 34.00) | 27.00 (23.50, 38.50) | 0.026 | 0.230 |
| AST, Median (IQR)—U/L | 26.00 (22.00, 31.00) | 25.00 (22.00, 31.00) | 26.00 (22.00, 30.00) | 0.950 | 0.968 |
| BUN, Median (IQR)—mmol/L | 6.40 (5.20, 8.70) | 6.00 (4.75, 8.70) | 6.20 (5.40, 7.15) | 0.211 | 0.486 |
| Cr, Median (IQR)—μmol/L | 67.00 (55.00, 87.00) | 63.00 (53.50, 92.00) | 67.00 (54.50, 83.00) | 0.241 | 0.532 |
| UA, Median (IQR)—μmol/L | 312 (258.00, 388.00) | 296.00 (248.50, 367.00) | 312.00 (261.50, 404.50) | 0.979 | 0.979 |
| ALB, Median (IQR)—g/L | 43.00 (38.50, 43.00) | 41.00 (37.90, 44.45) | 43.30 (39.70, 44.65) | 0.044 | 0.212 |
| TC, Mean (SD)—mmol/L | 4.59 ± 1.31 | 4.69 ± 1.38 | 4.40 ± 1.19 | 0.291 | 0.551 |

*(Continued)*

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TABLE 2 (Continued)

| | Overall (*N*=101) | Cognitive dysfunction group (*N*=65) | Normal group (*N*=36) | Unadjusted *p* value | B/H-adjusted *p* value |
|---|---|---|---|---|---|
| LDL-C, Mean (SD)—mmol/L | 2.87 ± 0.97 | 2.92 ± 1.00 | 2.79 ± 0.92 | 0.538 | 0.771 |
| HDL-C, Mean (SD)—mmol/L | 1.18 ± 0.29 | 1.19 ± 0.31 | 1.17 ± 0.25 | 0.683 | 0.906 |
| TG, Median (IQR)—mmol/L | 1.70 (1.19, 2.57) | 1.52 (1.06, 2.29) | 1.79 (1.30, 2.51) | 0.298 | 0.545 |
| Lp(a), Median (IQR)—mg/L | 131.00 (63.50, 242.75) | 185.00 (72.50, 324.50) | 125.00 (50.00, 159.50) | 0.118 | 0.328 |
| FT4, Mean (SD)—pmol/L | 12.24 ± 2.55 | 12.40 ± 2.56 | 11.93 ± 2.55 | 0.440 | 0.729 |
| FT3, Mean (SD)—pmol/L | 5.12 ± 0.87 | 5.09 ± 0.96 | 5.20 ± 0.66 | 0.590 | 0.802 |
| TSH, Median (IQR)—uIU/mL | 1.86 (1.28, 2.55) | 1.61 (1.28, 2.21) | 1.93 (1.05, 2.60) | 0.939 | 0.976 |
| D2-dimer, Median (IQR)—ng/ml | 120.00 (70.50, 212.00) | 131.50 (81.75, 262.75) | 88.00 (59.00, 180.50) | 0.047 | 0.193 |
| INR, Mean (SD) | 0.99 ± 0.10 | 0.98 ± 0.09 | 1.02 ± 0.11 | 0.042 | 0.224 |
| PT, Mean (SD)—s | 11.76 ± 1.22 | 11.59 ± 1.11 | 12.08 ± 1.37 | 0.059 | 0.222 |
| FIB, Mean (SD)—g/L | 4.10 ± 0.56 | 4.15 ± 0.59 | 4.02 ± 0.50 | 0.276 | |
| CRP, Median (IQR)—mg/L | 1.07 (0.40, 2.51) | 1.70 (0.40, 5.75) | 0.83 (0.41, 1.61) | 0.187 | 0.472 |
| Carotid artery ultrasonography | | | | | |
| CIMT, Mean (SD)—mm | 0.83 ± 0.17 | 0.86 ± 0.18 | 0.78 ± 0.15 | 0.559 | 0.779 |
| Carotid plaques | | | | 0.008 | 0.106 |
| No—no. (%) | 37 (36.6%) | 24 (36.9%) | 13 (36.1%) | | |
| Stable plaque—no. (%) | 44 (43.6%) | 23 (35.4%) | 21 (58.3%) | | |
| Unstable plaque—no. (%) | 20 (19.8%) | 18 (27.7%) | 2 (5.6%) | | |

SD, standard deviation; IQR, interquartile range; AD8, the Ascertain Dementia 8-item Questionnaire; MMSE, the Mini-Mental State Examination; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, the white blood cell count; RBC, red blood cell count; HGB, hemoglobin; PLT, platelet count; NEUT, neutrophil count; LY, lymphocyte count; ALT, alanine aminotransferase; AST, aspartate transaminase; BUN, urea nitrogen; Cr, creatinine; UA, uric acid; ALB, albumin; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, total glyceride; Lp(a), Lipoprotein a; FT4, free thyroxine; FT3, free tri-iodothyronine; TSH, thyroid stimulation hormone; INR, international normalized ratio; PT, prothrombin time; FIB, fibrinogen; CRP, C-reactive protein; CIMT, carotid intima-media thickness; and B/H, Benjamini-Hochberg.

TABLE 3 The amount and frequency of promoter methylation of clock genes in the two groups.

| Gene name | U/PM | Overall (*N*=101) | Cognitive dysfunction group (*N*=65) | Normal group (*N*=36) | $X^2$ | Unadjusted *p* value | B/H-adjusted *p* value |
|---|---|---|---|---|---|---|---|
| PER1 | PM | 79 (78.2%) | 59 (90.8%) | 20 (55.6%) | 16.862 | <0.001 | <0.001 |
| | U | 22 (21.8%) | 6 (9.2%) | 16 (44.4%) | | | |
| CRY1 | PM | 21 (20.8%) | 18 (27.7%) | 3 (8.3%) | 4.162 | 0.041 | 0.243 |
| | U | 80 (79.2%) | 47 (72.3%) | 33 (91.7%) | | | |

U, unmethylated; PM, partially-methylated; and B/H, Benjamini-Hochberg.

## Comparison of ABPM parameters

There were no statistically significant differences in ABPM parameters such as 24-h mean systolic blood pressure, 24-h mean diastolic blood pressure, 24-h mean standard deviation of systolic blood pressure, 24-h mean standard deviation of diastolic blood pressure, dmSBP, dmDBP, nmSBP, and nmDBP, and the classification of circadian rhythms of blood pressure between the two groups ($p > 0.05$), as shown in Table 4. In addition, no significant correlation was found between the promoter methylation rates of PER1 and CRY1 and the classification of circadian rhythms of blood pressure, as shown in Table 5.

## Comparison of CSVD total load scores

On the basis of the MRI data, we observed 40.6% cases with moderate–severe WMHs, 12.9% with enlarged perivascular spaces 2–4 Level, 13.9% with CMB, and 96.0% with LI. In these four separate imaging findings, there was no statistically significant difference between the two groups. Although it could be seen from Table 6 that, after combining these four imaging findings, more people in the cognitive dysfunction group were classified as severe compared with the normal group ($p = 0.046$). Unfortunately, after B/H correction, there was no statistically significant difference between the two groups (adjusted $p = 0.203$).

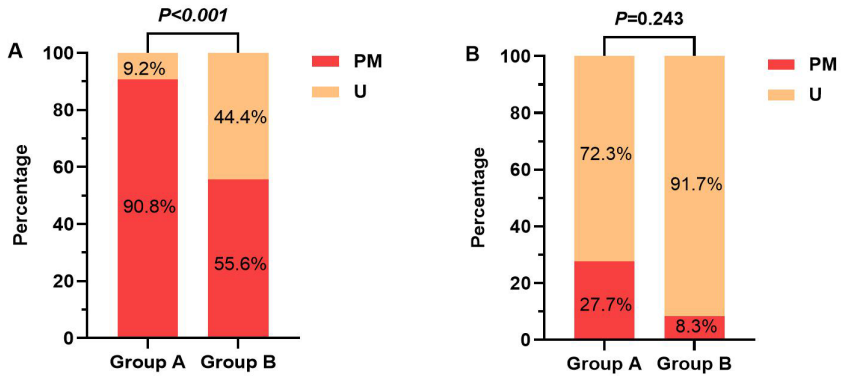


FIGURE 3
**(A)** The promoter methylation rates of PER1 gene between the two groups; **(B)** The promoter methylation rates of CRY1 gene between the two groups. Group A, Cognitive dysfunction group; Group B, Normal group; U, unmethylated; and PM, partially-methylated.

TABLE 4 Comparison of ambulatory blood pressure parameters between the two groups.

| Parameters | Overall (*n*=71) | Cognitive dysfunction group (*n*=46) | Normal group (*n*=25) | $t/X^2$ | *p* value |
|---|---|---|---|---|---|
| 24hmSBP, Mean (SD)—mmHg | 140.44 ± 17.74 | 140.57 ± 19.09 | 140.19 ± 15.24 | −0.104 | 0.917 |
| 24hmDBP, Mean (SD)—mmHg | 78.88 ± 10.32 | 77.80 ± 10.76 | 80.82 ± 9.29 | 1.418 | 0.159 |
| 24hSBP-SD, Mean (SD)—mmHg | 16.79 ± 4.05 | 16.94 ± 4.43 | 16.54 ± 3.30 | −0.473 | 0.637 |
| 24hDBP-SD, Mean (SD)—mmHg | 12.33 ± 2.82 | 12.06 ± 2.96 | 12.81 ± 2.50 | 1.281 | 0.203 |
| dmSBP, Mean (SD)—mmHg | 140.82 ± 18.47 | 140.83 ± 20.11 | 140.81 ± 15.32 | −0.006 | 0.995 |
| dmDBP, Mean (SD)—mmHg | 79.55 ± 10.78 | 78.22 ± 11.23 | 81.95 ± 9.59 | 1.679 | 0.096 |
| nmSBP, Mean (SD)—mmHg | 138.36 ± 18.85 | 138.69 ± 19.52 | 137.78 ± 17.82 | −0.231 | 0.818 |
| nmDBP, Mean (SD)—mmHg | 77.39 ± 10.40 | 76.76 ± 10.33 | 78.54 ± 10.58 | 0.822 | 0.413 |
| Circadian rhythm of blood pressure—no. (%) | | | | 2.204 | 0.564 |
| Dippers | 13 (18.3%) | 7 (15.2%) | 6 (24.0%) | 0.835 | 0.361 |
| Extreme-dippers | 1 (1.4%) | 1 (2.2%) | 0 (0.0%) | 0.876 | 0.999 |
| Non-dippers | 28 (39.4%) | 17 (37.0%) | 11 (44.0%) | 0.336 | 0.562 |
| Reverse-dippers | 29 (40.8%) | 21 (45.7%) | 8 (32.0%) | 1.249 | 0.264 |

SD, standard deviation; 24hmSBP, 24-h mean systolic blood pressure; 24hmDBP, 24-h mean diastolic blood pressure; 24hSBP-SD, 24-h mean standard deviation of systolic blood pressure; 24hDBP-SD, 24-h mean standard deviation of diastolic blood pressure; dmSBP, daytime mean systolic blood pressure; dmDBP, daytime mean diastolic blood pressure; nmSBP, nighttime mean systolic blood pressure; and nmDBP, nighttime mean diastolic blood pressure.

## Binary logistic regression analysis

We then used binary logistic regression models to investigate the relationship between the promoter methylation rates of clock genes and cognitive dysfunction in CSVD patients. The univariate analysis showed that the influence of promoter methylation of PER1 and CRY1 on cognitive dysfunction were all statistically significant in Model 1 ($p < 0.001$; $p = 0.025$), which still existed after we adjusted for confounding factors in Model 2. It was observed from Model 2 that patients with the promoter methylation of PER1 gene ($OR = 16.565$, 95%$CI$, 4.057–67.628; $p < 0.001$) and the promoter methylation of CRY1 gene ($OR = 6.017$, 95%$CI$, 1.290–28.069; $p = 0.022$) were at greater risk of cognitive dysfunction compared with those with unmethylated promoters of corresponding genes, as shown in Table 7.

# Discussion

In the present study, we demonstrated that, in patients with CSVD, the methylation level in the promoter regions of the PER1 gene was higher than that in the normal group ($p < 0.001$). To the best of

TABLE 5 Relationship between the promoter methylation of clock genes and circadian rhythm of blood pressure.

| Circadian rhythm of blood pressure—no. (%) | Overall (*N*=71) | Methylation of PER1 | | $X^2$ | *p* value | Methylation of CRY1 | | $X^2$ | *p* value |
|---|---|---|---|---|---|---|---|---|---|
| | | PM (*N*=58) | U (*N*=13) | | | PM (*N*=14) | U (*N*=57) | | |
| Dippers | 13 (18.3%) | 10 (17.2%) | 3 (23.1%) | 0.898 | 0.877 | 2 (14.3%) | 11 (19.3%) | 0.709 | 0.999 |
| Extreme-dippers | 1 (1.4%) | 1 (1.7%) | 0 (0.0%) | | | 0 (0.0%) | 1 (1.8%) | | |
| Non-dippers | 28 (39.4%) | 23 (39.7%) | 5 (38.5%) | | | 6 (42.9%) | 22 (38.6%) | | |
| Reverse-dippers | 29 (40.8%) | 24 (41.4%) | 5 (38.5%) | | | 6 (42.9%) | 23 (40.4%) | | |

U, unmethylated; PM, partially-methylated.

TABLE 6 Comparison of CSVD total load scores between the two groups.

| Imaging findings on MRI—no. (%) | Overall (*N*=101) | Cognitive dysfunction group (*N*=65) | Normal group (*N*=36) | $X^2$ | Unadjusted *p* value | B/H-adjusted *p* value |
|---|---|---|---|---|---|---|
| Moderate–severe WMH | 41 (40.6%) | 26 (40.0%) | 15 (41.7%) | 0.027 | 0.870 | 0.961 |
| EPVS 2–4 Level | 13 (12.9%) | 8 (2.3%) | 5 (13.9%) | 0.052 | 0.820 | 0.945 |
| CMB | 14 (13.9%) | 11 (16.9%) | 3 (8.3%) | 0.803 | 0.370 | 0.654 |
| LI | 97 (96.0%) | 64 (98.5%) | 33 (91.7%) | 1.310 | 0.252 | 0.534 |
| Total CSVD burden | | | | 6.150 | 0.046 | 0.203 |
| Mild | 53 (52.5%) | 35 (53.8%) | 18 (50.0%) | | | |
| Moderate | 33 (32.7%) | 17 (26.2%) | 16 (44.4%) | | | |
| Severe | 15 (14.9%) | 13 (20.0%) | 2 (5.6%) | | | |

WMH, white matter hyperintensities; EPVS, enlarged perivascular spaces; CMB, cerebral microbleeds; LI, lacunar infarcts; and B/H, Benjamini-Hochberg.

our knowledge, this is the first study to investigate the relationship between the promoter methylation of peripheral blood clock genes PER1 and CRY1 and cognitive dysfunction in patients with CSVD patients.

Circadian rhythm disturbances, such as sleep disorders, are very common in aging and are present in many neurodegenerative diseases (Kondratova and Kondratov, 2012). As mentioned in the introduction, the circadian clock regulates circadian rhythms of the organism. Therefore, at the level of molecular structure of the circadian clock, the mechanism of circadian rhythm disturbances might be as follows (Wu and Swaab, 2007): (1) A decreased input to the suprachiasmatic nucleus (SCN); (2) Alterations in the SCN; (3) Changes in the pineal gland, melatonin, and its receptors. Among them, clock genes PER and CRY aroused our interest as the important part of the core clock components with their crucial roles in both the SCN and peripheral clock.

Previous studies believed that the influence of circadian rhythm on long-term memory originated from the disorder within the SCN, which then drove alterations in peripheral structures involved in memory formation. However, Kwapis et al. (2018) found that reducing PER1 expression directly in the dorsal hippocampus could impair long-term memory in young mice whereas local overexpression of PER1 in the dorsal hippocampus could improve memory in aging mice. Their conclusions challenged conventional assumptions and demonstrated that PER1 plays a key role within local memory structures that alters memory formation, independent of its function in the SCN. In the same year, Brzezinski et al. (2018) found that CRY1, CRY2, PER1, and PER2 and other clock genes were all expressed in cultured human luteinized granulosa cells, and the expression in aged female cells generally showed a downward trend, including PER1. In addition, since the potential link between circadian rhythm disturbances and the development of AD has not been clearly established, Niu et al. (2022) attempted to establish the link through chronic sleep deprivation (CSD) in a recent study. Their results showed that CSD impaired learning and memory in AD mice and further accelerated AD progression. Also, CSD induced abnormal expressions of CRY1, CLOCK, and BMAL1 in the circadian rhythm-related nucleus of experimental mice, which were more significant in AD mice. In conclusion, these previous studies were sufficient to convince us that clock genes PER1 and CRY1 were associated with aging and cognitive dysfunction, which is also the reason why we chose these two genes. Our findings suggested that the methylation of these two genes in the promoter region of peripheral blood might be useful markers for cognitive dysfunction in CSVD patients.

In recent years, there has been increasing interest in the relationship between epigenetics and cognitive function. DNA methylation is one of the most characteristic epigenetic modifications, which can affect the activity of a DNA segment without changing the sequence (Prado et al., 2021), so it has long been favored by researchers. Previous studies have shown that epigenetics, especially DNA methylation, plays a very important role in aging (Unnikrishnan et al., 2019). A study that investigated methylation changes in 217 non-pathologic human tissue samples showed that methylation changes were significantly correlated with aging and various environmental exposures such as smoking (Christensen et al., 2009).

TABLE 7 Association between the promoter methylation of clock genes and cognitive dysfunction.

| | | *B* | SE | Wald$X^2$ | *p* value | *OR* | 95% *CI* |
|---|---|---|---|---|---|---|---|
| Model 1 | Constant | −1.352 | 0.583 | 6.316 | 0.012 | | |
| | PER1 PM | 2.191 | 0.583 | 14.107 | <0.001 | 8.945 | 2.851–28.063 |
| | CRY1 PM | 1.653 | 0.739 | 5.005 | 0.025 | 5.221 | 1.227–22.211 |
| Model 2 | Constant | −6.021 | 1.818 | 10.972 | 0.001 | | |
| | PER1 PM | 2.807 | 0.718 | 15.298 | <0.001 | 16.565 | 4.057–67.628 |
| | CRY1 PM | 1.795 | 0.786 | 5.216 | 0.022 | 6.017 | 1.290–28.069 |

B, regression coefficient; SE, standard error; WaldX2, chi-square value; OR, odds ratio; CI, confidence interval; and PM, partially-methylated.
Model 1: unadjusted.
Model 2: adjusted for age, history of hypertension, history of diabetes mellitus, and the CSVD total load score.

One of the primary end-points related to aging is the loss of neuronal function, which further leads to impaired memory and cognitive function (Yang et al., 2019). In fact, altered DNA methylation has been observed to be associated with age-related memory loss in animal studies (Ianov et al., 2017). As the most famous age-related diseases, previous studies have also attempted to investigate the underlying mechanisms of abnormal expression of clock genes in diseases such as PD and AD from the perspective of DNA methylation. Lin et al. (2012) detected the methylation levels of the promoters of seven major human clock genes in order to investigate the underlying mechanisms of the altered expression of clock genes in leukocytes from PD patients, and then found that methylation could only be detected in the CRY1 and NPAS2 promoters and the methylation frequency of NPAS2 promoter was significantly reduced in PD patients. Di Francesco et al. (2015) found an increase in global DNA methylation in late-onset AD peripheral blood mononuclear cells compared to healthy controls, and associated with worse cognitive performances. Besides, many studies have found that the promoter methylation of clock genes could also be detected in dementia. Liu et al. (2008) included 80 dementia patients and 80 age- and gender-matched controls to assess the promoter methylation status of nine clock genes in dementia, and observed that only the PER1 and CRY1 promoter CpG islands were methylated in dementia patients (7/80), while none of the other clock genes involved were methylated. Based on this, we initially proposed the hypothesis that the cognitive dysfunction group of CSVD patients would have higher promoter methylation rates of PER1 and CRY1, further suggesting lower gene expression. In fact, our results appeared to be consistent with Liu et al. (2008), but the promoter methylation rates of the two genes in our results were much higher. Given that DNA methylation has been reported to change with aging in previous studies, we suspected that this might be related to the older age of the patients we enrolled (with the average age of 70). At the same time, this study was conducted on patients with CSVD, which is known as one of age-related diseases, so we guessed that our results were relatively reasonable. Our results showed that there was no significant difference in the promoter methylation rate of CRY1 between the two groups after B/H correction. However, referring to the positive results of previous studies, we still included them in the subsequent binary logistic regression analysis. Through analysis, we also found that hypermethylation of the promoters of clock genes PER1 and CRY1 may be involved in affecting cognitive dysfunction in patients with CSVD.

It is worth noting that, to obtain test samples easily, we measured DNA methylation in peripheral blood cells rather than in other metabolically active tissues such as muscle, liver, or adipocytes. Many previous studies have been conducted on peripheral blood cells related to clock genes, and the methylation characteristics in blood cells have been consistently reflected in other tissues (Crujeiras et al., 2017; Ramos-Lopez et al., 2018).

This study had some limitations. First, the overnight polysomnography and the Pittsburgh Sleep Quality Index (PSQI) were not administered to assess patients' sleep quality and duration of the night in detail, which may affect DNA methylation. Second, we only measured the methylation level of clock genes at one point in time. Third, as a single-center study with a small sample size, there was a certain selection bias. In addition, as it was a cross-sectional study, we could not explain the causal relationship and specific mechanism between the promoter methylation of PER1, CRY1 and cognitive impairment in CSVD patients.

## Conclusion

The promoter methylation rate of PER1 gene was higher in the cognitive dysfunction group among CSVD patients. And the hypermethylation of the promoters of clock genes PER1 and CRY1 may be involved in affecting cognitive dysfunction in patients with CSVD.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Lianyungang Second People's Hospital. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

YX and XS conceived and designed the research. YX and YW analyzed the data and drafted the manuscript. YX, YJ, ML, WZ, ZG, and ZS collected the data and performed the research. ZS and XS

reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



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# The effect of vascular risk factors on the efficacy of endolymphatic sac decompression surgery for Meniere's disease: a retrospective cohort study

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**Objectives:** This study aimed to investigate the effect of vascular risk factors on the outcomes of endolymphatic sac decompression (ESD) surgery in patients with Meniere's disease.

**Methods:** The study included 56 patients with Meniere's disease, who had undergone unilateral ESD surgery. The patients' vascular risk factors were assessed based on the preoperative 10-year atherosclerotic cardiovascular diseases risk classification. Those with no or low risk were defined as the low-risk group, while those with medium, high, or very high risk were defined as the high-risk group. The correlation between the vascular risk factors and ESD efficacy was evaluated by the comparison of vertigo control grade between the two groups. The functional disability score was also assessed to investigate whether ESD improved the quality of life in Meniere's disease patients with vascular risk factors.

**Results:** After ESD, 78.95 and 81.08% of patients from the low-risk and high-risk groups, respectively, demonstrated at least grade B vertigo control; no statistically significant difference was observed ($p$=0.96). The postoperative functional disability scores in both groups were significantly lower compared with those before surgery ($p$<0.01), with a median decrease of two (1, 2) points in both groups. No statistically significant difference between the two groups was observed ($p$=0.65).

**Conclusion:** Vascular risk factors have little effect on the efficacy of ESD in patients with Meniere's disease. Patients with one or more vascular risk factors can still experience a not poor vertigo control and improved quality of life after ESD.

KEYWORDS

**Meniere's disease, endolymphatic sac decompression, vascular risk factor, vertigo, quality of life**

# 1. Introduction

Meniere's disease (MD) is an inner ear disease characterized by paroxysmal vertigo, fluctuating hearing loss, tinnitus, and ear fullness (1). The etiology of MD is unknown, and the main pathological feature is membranous labyrinthine hydrops which increased pressure in the inner ear, bringing vertigo attack, Reissner membrane displacement, and hair cell damage (2). Vertigo control is the main demand of most MD patients while protection of hearing and vestibular function is also expected. For patients with frequent vertigo attacks and ineffective non-surgical treatment for 6 months, surgical treatment can be performed (3).

The surgical methods could be divided into two types according to whether the vestibular function was preserved. Vestibular function destructive surgeries such as semicircular canal occlusion control vertigo by damaging the vestibular sensory organ, while vestibular function protection surgeries such as endolymphatic sac decompression (ESD) do it by reducing the inner pressure. With the latter surgery, the audio-vestibular function is preserved to the maximum extent and the time and money spent on vestibular rehabilitation required due to surgical injury will be avoided. However, the application of ESD is limited by its uncertain curative effect (4). Most of the studies reported a vertigo control rate of approximately 80% (5), and some reported only 66% (6) or even lower (7), suggesting poor surgical efficacy in some patients. Previous studies have shown that patients with negative results on glycerol testing or cochlear electrograms (8) and those with non-ascending audiograms (9) or stage IV hearing (average hearing threshold >70 dB) (3, 10) demonstrate low vertigo control rates after surgery. The characteristics of the population for which this surgery is applicable are still being explored.

Meniere's disease frequently occurs at the age of 40–60 years (2). Compared with young healthy adults, a larger proportion of patients with MD have one or more vascular risk factors such as hyperlipidemia, hypertension, diabetes, and smoking history (11, 12). Vascular risk factors play an important role in the development of MD. A reduction in the blood supply of the inner ear or blockage of the venous return owing to microvascular injury, oxidative stress, atherosclerotic plaque formation, and micro thrombosis affects the balance in the production and absorption of endolymphatic fluid, thereby increasing the risk of endolymphatic hydrops (13–15). Previous studies have found that patients with vascular risk factors experience vertigo attacks more frequently (16) and demonstrate a poor response to routine treatment of medication (17–19). However, whether patients with vascular risk factors demonstrate poor control after ESD remains unclear. One of the difficulties of conducting research in this area may be the lack of indicators for an overall assessment of vascular risk factors.

Numerous vascular risk factors including hyperlipidemia, hypertension, diabetes, a smoking history, and other factors increase the risk of ischemic cardiovascular disease (20); it is, therefore, inappropriate to consider only a single factor. Fortunately, the 10-year atherosclerotic cardiovascular disease (ASCVD) risk classification was recently developed to provide an overall assessment of vascular risk factors. It is recommended by the Chinese Guidelines for the Prevention of Cardiovascular Diseases (2017) (20). It has been established based on results from long-term cohort studies on cardiovascular disease incidence risk in China; it is, therefore, applicable to the Chinese population and has been widely used in clinical practice. By using it for the overall evaluation of patients and comparing the differences in surgical efficacy among patients with different ASCVD risks, the effect of vascular risk factors on the efficacy of ESD could be figured out.

For MD patients, unpredictable and disabling vertigo episodes can disrupt normal work and life, bringing great pain (21). Therefore, this study aimed to provide a reference for the ESD selection of patients with vascular risk factors in the hope of achieving a balance between function preservation and vertigo control. Individualized treatment plans could be created by the evaluation of preoperative data, and unnecessary destructive surgeries chosen due to fear of failed vertigo control could be avoided.

# 2. Materials and methods

## 2.1. Patients

This study is a retrospective cohort study. The patients who underwent unilateral ESD at the Vertigo Clinic/Research Center of Air Force Medical Center from 2013 to 2020 were included as research subjects.

As shown in Figure 1, patients conforming to the definite MD diagnosis criteria of the Clinical Practice Guideline: Meniere's Disease (2020) (4) and with an age at operation exceeding 18 years were included in this study. Patients with bilateral MD, those with comorbid vestibular migraine diagnosed before the operation or during follow-up (22), those who had undergone other surgeries for MD (except intratympanic injection) or ESD more than once, and those who underwent follow-up for less than 2 years or failed to attend follow-up were excluded.

## 2.2. Methods

### 2.2.1. Surgical procedure and postoperative medications of ESD

ESD was performed based on the method reported by Shambaugh (23) in 1975. A C-shaped incision was placed behind the patient's ear. The area of the mastoid process extending from the temporal line to the mastoid tip was then ground under the microscope. The mastoid cells were fully cleared, and the mastoid process contoured; this exposed the lateral and posterior semicircular canals and the sigmoid sinus. The endolymphatic sac was found anterior to the sigmoid sinus and between the posterior semicircular canal and the line extending from the lateral semicircular canal. An area of bone measuring $1 \times 1\,cm^2$ was then removed to fully expose the endolymphatic sac.

Data pertaining to medications used within 14 days after ESD (including betahistine, diuretics, and hormones) were obtained.

### 2.2.2. The evaluation of ASCVD risk in 10years

The patients' ASCVD risk in 10 years was evaluated based on their smoking history, blood lipid test results, sex, age, and previous history of hypertension and diabetes (20) (Table 1). The patients with no and low risk were classified as one cohort (low-risk group), while those having medium, high, and very high risk were classified as another cohort (high-risk group). The effect of ESD was compared between the low-and high-risk groups.

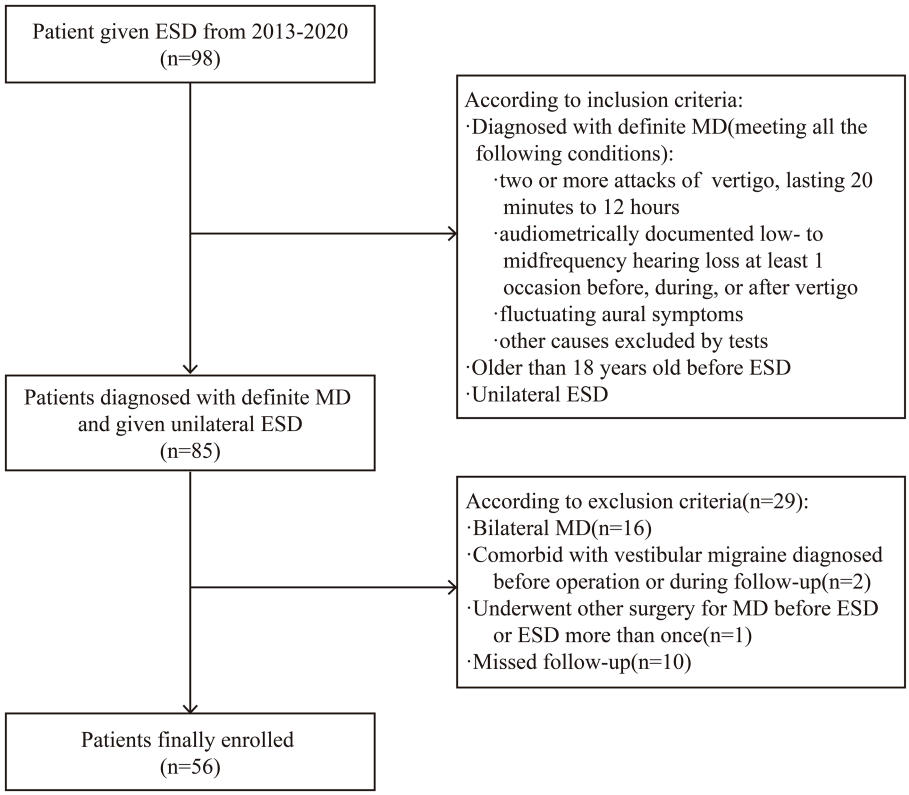


FIGURE 1
Flowchart of patient inclusion and exclusion. ESD, endolymphatic sac decompression. MD, Meniere's disease.

TABLE 1 Atherosclerotic cardiovascular diseases (ASCVD) risk in a 10-year classification.

| The number of risk factors | | Serum cholesterol (mmol/L) | | |
|---|---|---|---|---|
| | | 3.1≤TC <4.1 or 1.8≤LDL-C<2.6 | 4.1≤TC <5.2 or 2.6≤LDL-C<3.4 | 5.2≤TC <7.2 or 3.4≤LDL-C<4.9 |
| No hypertension | 0 ~ 1 | Low risk (<5%) | Low risk (<5%) | Low risk (<5%) |
| | 2 | Low risk (<5%) | Low risk (<5%) | Medium risk (5% ~ 9%) |
| | 3 | Low risk (<5%) | Medium risk (5% ~ 9%) | Medium risk (5% ~ 9%) |
| Hypertension | 0 | Low risk (<5%) | Low risk (<5%) | Low risk (<5%) |
| | 1 | Low risk (<5%) | Medium risk (5% ~ 9%) | Medium risk (5% ~ 9%) |
| | 2 | Medium risk (5% ~ 9%) | High risk (5% ~ 9%) | High risk (5% ~ 9%) |
| | 3 | High risk (5% ~ 9%) | High risk (5% ~ 9%) | High risk (5% ~ 9%) |

TC, total cholesterol. LDL-C, low-density lipoprotein cholesterol. HDL-C, high-density lipoprotein cholesterol. Risk factors include smoking, low HDL-C, age ≥ 45 (men), and age ≥ 55 (women). Patients with a history of ASCVD were directly classified as very high risk. Patients with any of the following were directly classified as high risk: history of diabetes and age ≥ 40, LDL-C ≥ 4.9 mmol/L or TC ≥ 7.2 mmol/L, systolic pressure ≥ 180 mmHg or diastolic pressure ≥ 110 mmHg, and smoking more than 30 cigarettes a day.

### 2.2.3. The evaluation of audiometric examination

Pure tone audiometry was performed on all the patients enrolled and the worst result during 6 months before ESD was used to evaluate their hearing. The preoperative hearing threshold was defined as a pure tone average (PTA) of 0.5, 1, and 2 kHz, and the hearing stage was classed based on it (3). Audiograms were divided into ascending and non-ascending types (24). The glycerol test was performed according to our previous research (25).

### 2.2.4. Subtype classification of MD

The patients with non-classical MD were classified (26) as having MD with migraine (22), autoimmune MD, or familial MD based on their medical and family history. The remainder were classified as having classical MD.

## 2.3. The evaluation of the ESD effect

### 2.3.1. Vertigo control

Vertigo control was evaluated by comparing the frequency of episodes experienced before and after surgery (27, 28). The value was calculated as follows:

Numerical value = (X/Y) × 100 (rounded to the nearest whole number), where X was the average number of definitive spells per month during 18–24 months after therapy, and Y was the average

number of definitive spells per month during 0–6 months before therapy. The vertigo control class was divided into six levels based on numerical value (Supplementary Table S1), and the basic control rate of vertigo was defined as the proportion of patients with grade A and B vertigo control (numerical value ≤ 40).

### 2.3.2. Dysfunction

The dysfunction score levels (one to six points) using the functional level scale (Supplementary Table S2) and the differences between preoperative and postoperative dysfunction were evaluated based on the functional level scale (27, 28).

## 2.4. Statistical methods

The SPSS 26.0 software package was used for statistical analysis. The *t*-test was used to compare two groups of normal data, and a non-parametric test was used to compare two groups of non-normal or grade data. The chi-square test was used to compare rates between the two groups; $p < 0.05$ was considered statistically significant.

# 3. Results

## 3.1. Basic patient characteristics

A total of 56 patients including 26 (46.43%) men and 30 (53.57%) women fulfilled the inclusion and exclusion criteria (Figure 1). The age at operation was 23–68 (average age: 50.32 ± 11.13) years and the duration of follow-up extended between 2 and 9 years, with a median duration of 6.73 (5.57 and 7.79) years. Complete preoperative and postoperative dysfunction score data were available for 43 patients. The low-and high-risk groups demonstrated statistically significant differences in terms of sex, age at operation, and course of disease ($P < 0.05$; Table 2). These variables were included during multivariate

TABLE 2 Comparison of baseline data between the low-and high-risk groups.

| | Low-risk group (*N*=37) | High-risk group (*N*=19) | *P* |
|---|---|---|---|
| Sex (*N* [%]) | | | 0.008 |
| Women | 25 (67.6%) | 5 (26.3%) | |
| Men | 12 (32.4%) | 14 (73.7%) | |
| Age/Yr (Mean ± SD) | 47.59 ± 11.06 | 55.63 ± 9.44 | 0.009 |
| Course/Yr (Median [P25, P75]) | 2.00 (1.00,4.00) | 4.00 (2.50,6.50) | 0.024 |
| Follow-up/Yr (Median [P25, P75]) | 6.55 (5.47,7.48) | 6.94 (5.80,8.30) | 0.416 |
| Subtype of MD (*N* [%]) | | | 1.000 |
| Classical MD | 30 (81.1%) | 16 (84.2%) | |
| Non-classical MD | 7 (18.9%) | 3 (15.8%) | |
| Glycerol test (*N* [%]) | | | |
| Positive | 14 (37.8%) | 9 (47.4%) | 0.689 |
| Negative | 23 (62.2%) | 10 (52.6%) | |
| PTA (Mean ± SD) | 50.32 ± 17.62 | 54.68 ± 14.82 | 0.360 |
| Hearing stage (*N* [%]) | | | 0.378 |
| I | 4 (10.8%) | 1 (5.3%) | |
| II | 7 (18.9%) | 1 (5.3%) | |
| III | 23 (62.2%) | 16 (84.2%) | |
| IV | 3 (8.1%) | 1 (5.3%) | |
| Type of audiogram (*N* [%]) | | | 0.794 |
| Ascending | 9 (24.3%) | 6 (31.6%) | |
| Non-ascending | 28 (75.7%) | 13 (68.4%) | |
| Frequency (Median [P25, P75]) | 6.00 (2.00,12.00) | 4.00 (1.50,10.50) | 0.855 |
| Dysfunction score (*N* [%]) | 28 | 15 | 0.923 |
| 2 | 9 (32.1%) | 4 (26.7%) | |
| 3 | 14 (50%) | 8 (53.3%) | |
| 4 | 3 (10.7%) | 2 (13.3%) | |
| 5 | 1 (3.6%) | 1 (6.7%) | |
| 6 | 1 (3.6%) | 0 (0%) | |
| Medication (*N* [%]) | 29 (85.29%) | 17 (94.44%) | 0.599 |
| Betahistine | 23 (67.65%) | 17 (94.44%) | 0.066 |
| Diuretic | 11 (32.35%) | 6 (33.33%) | 0.943 |
| Hormone | 11 (32.35%) | 5 (27.78%) | 0.734 |

N, number. Yr, year. SD, standard deviation. Age, age at operation. Course, Course of Meniere's disease. MD, Meniere's disease. PTA, pure tone average of 0.5, 1, and 2 kHz. Frequency: the number of monthly vertigo attacks during the 6 months before the operation. Medication: the use of betahistine, diuretic, or hormone after the operation.

analysis to exclude their influence on the results. There was no statistical difference between the two groups in terms of glycerol test positivity rates, the subtype of MD, preoperative hearing threshold, hearing stage, type of audiogram, preoperative frequency of vertigo, preoperative dysfunction score, and medications used after ESD ($p > 0.05$).

## 3.2. Comparison of the effect of ESD between low-and high-risk groups

The basic control rates of vertigo in the low-and high-risk groups were 78.95 and 81.08%, respectively (Table 3); no statistical differences were observed between the vertigo control classes of the two groups ($Z = -0.07$, $p = 0.96$). The risk of failing to achieve basic control of vertigo did not significantly increase in the high-risk group (relative risk = 0.90, 95% confidence interval: 0.30–2.69, $p = 1.00$).

Compared with the scores before surgery, the postoperative dysfunction scores decreased significantly among patients from both groups (low-risk group: $Z = -4.51$, $p < 0.01$; high-risk group: $Z = -3.11$, $p < 0.01$); both groups demonstrated a median decrease of two (1, 2) points and the difference was not statistically significant ($Z = -0.46$, $p = 0.65$).

## 3.3. Multivariate binary logistic regression analysis

Considering the failure of basic vertigo control as a positive event, the multivariate binary logistic regression equation was constructed using the following variables: risk of ASCVD in 10 years, sex, age at operation, and course of the disease. The Hosmer-Lemeshow test showed a good model fit ($p = 0.51$). After adjusting for sex, age at operation, and course of the disease, the results showed that inclusion in the high-risk group had no statistically significant impact on the failure of basic vertigo control ($p = 0.13$; Table 4).

TABLE 3 Comparison of postoperative vertigo control classes between low-and high-risk groups.

| Vertigo control class | Low-risk group (*N* [%]) (*N*=37) | High-risk group (*N* [%]) (*N*=19) |
|---|---|---|
| A | 22 (59.5%) | 12 (63.2%) |
| B | 8 (21.6%) | 3 (15.8%) |
| C | 1 (2.7%) | 0 (0.0%) |
| D | 1 (2.7%) | 0 (0.0%) |
| E | 0 (0.0%) | 0 (0.0%) |
| F | 5 (13.5%) | 4 (21.1%) |

N, number of patients.

# 4. Discussion

In this retrospective cohort study, the results of statistical analyses showed that the basic vertigo control rate was nearly 80% in both low-and high-risk groups. There was no statistical difference between the two groups regardless of whether variables such as sex, age at operation, and course of disease were controlled. In addition, the postoperative dysfunction score decreased significantly in both groups. This suggested that the existence of vascular risk factors did not worsen surgical efficacy in these patients. The patients experienced good vertigo control and the disease-related dysfunction had been resolved.

Since the introduction of ESD in 1927, surgical outcomes have varied across different studies (5–7). As this may be attributed to differences in the included patient groups, it is essential to identify the clinical characteristics of patients who are appropriate candidates for this operation; this may help predict the surgical benefit and reduce unnecessary surgical intervention (29). The age associated with a high incidence of MD partly overlaps with that associated with a high incidence of vascular risk factors (such as hypertension, hyperlipidemia, and diabetes). In this context, patients with vascular risk factors have more severe symptoms and a poorer prognosis. As vascular risk factors may affect surgical efficacy, this study compared the surgical efficacy between low-and high-risk patients and found vascular risk factors to have no significant effect.

This finding, which was inconsistent with our expectations, demonstrated the complexity of the mechanisms involved in the etiopathogenesis of MD. Findings from existing studies suggest that patients with a greater number of vascular risk factors obtain less benefit from routine treatment; however, the patients in this study experienced good outcomes after ESD. This may be attributed to the fact that the operation alleviates the rapid expansion of membranous labyrinthine hydrops rather than cures it. Notably, the membranous labyrinthine hydrops caused by vascular risk factors or other causes persists after surgery (30). The operation just prevents further aggravation of the condition owing to arteriovenous mixing, which may result from endolymphatic sac vessel reflux to the inner ear due to excessive pressure (31). Current research suggests that vertigo attacks

TABLE 4 Multivariate binary logistic regression model for basic vertigo control.

| Variables | | *b* | SE of *b* | $X^2$ | *P* | OR (95%CI) |
|---|---|---|---|---|---|---|
| Sex | | | | | | |
| | Women | | | | | |
| | Men | 1.66 | 0.97 | 2.93 | 0.09 | 5.27 (0.79, 35.33) |
| Age at operation/Yr | | 0.10 | 0.05 | 5.26 | 0.02 | 1.11 (1.02, 1.21) |
| The course of disease/Yr | | 0.05 | 0.04 | 1.61 | 0.20 | 1.05 (0.97, 1.14) |
| Risk of ASCVD in 10 years | | | | | | |
| | Low risk | | | | | |
| | High risk | −1.62 | 1.08 | 2.24 | 0.13 | 0.20 (0.02, 1.65) |

SE, standard error. OR, odds ratio. CI, confidence interval.

are related to the rupture of the membranous labyrinth which is caused by an acute increase in endolymph rather than hydrops itself (32), which happened in 12.5–30.0% of healthy individuals (33). The operation provides space for the expansion of the endolymph sac; this in turn prevents any serious organ damage caused by rapid hydrops and thereby achieves the goal of reducing vertigo attacks. Patients with one or more vascular risk factors may therefore still obtain good control of vertigo despite the existence of membranous labyrinthine hydrops.

The greatest strength of our study is the control of confounding bias. As numerous factors may influence the efficacy of ESD, it is difficult to identify the actual impact of vascular risk factors. Therefore, the baseline data from the low-and high-risk groups were compared to control interference from heterogeneity in demographic characteristics (sex, age, and time of follow-up), etiology (a subtype of MD), state of hydrops (results of the glycerol test), progress and severity of MD (course of disease, hearing stage, type of audiogram, preoperative hearing threshold, preoperative frequency of vertigo, and preoperative dysfunction score), and medications used after ESD. For variables that demonstrated an imbalance in distribution between the groups (such as sex, age, and course of the disease), multifactorial analysis was performed to control their influence. Compared with single factor analysis, which does not consider the impact of other factors on ESD, our analysis fully considered various factors that affect postoperative vertigo control (8–10, 34) and identified the exclusive impact of vascular risk factors with considerable reliability.

Our study had certain limitations. First, the sample size was relatively small; the findings, therefore, need to be validated in large-scale and multi-center studies. Second, the impact of vasopressin on the ESD effect was not controlled because of the lack of prospective design. Vasopressin was proved to correlate with MD attack by overexpressing vasopressin type-2 receptor and subsequently activating aquaporin-2 (35, 36), which may interfere with the evaluation of ESD efficacy. Third, on ASCVD risk stratification, only one patient in this study demonstrated no risk in 10 years; the sample size for comparison and analysis of surgical effects in patients with/without vascular risk factors was therefore limited. Fourth, the control of vascular risk factors during follow-up was not assessed in this study, which limited further demonstration of the vascular risk factors' impact on ESD efficacy. A prospective study is needed to confirm if the changes in vascular risk factors can lead to changes in ESD efficacy. Last but not least, ASCVD risk in 10 years may not be an optimal indicator for a comprehensive evaluation of vascular risk factors. It focuses on the occurrence of ASCVD, in which the vascular lesions are more severe than those of MD. Further research will therefore be performed using more appropriate indicators.

Finally, it is worth noting that maintaining a healthy lifestyle and control of vascular risk factors are still necessary for MD patients because of the high disability rate and mortality of cerebral or myocardial infarction even though the finding above suggests that ESD efficacy is not much affected by vascular risk factors.

## 5. Conclusion

In conclusion, ESD may effectively reduce vertigo attacks and dysfunction in patients with MD, and its efficacy is not reduced by an increase in vascular risk factors. The findings from this study may increase confidence regarding the use of ESD in patients with MD, thereby preventing unnecessary destructive surgeries.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Air Force Medical Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## Author contributions

ZJ and CW designed the research. FG, YG, and YL prepared the material, collected the data, and analyzed the data. YL prepared the figures. XX and YL wrote the first draft of the manuscript. All authors contributed to the study's conception and design, commented on previous versions of the manuscript, and read and approved the final manuscript.

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## Conflict of interest

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

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1194456/full#supplementary-material

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# The reliability of a subtype-determining questionnaire in efficient benign paroxysmal positional vertigo diagnosis in geriatrics

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**Introduction:** Benign paroxysmal positional vertigo (BPPV), the most common cause of dizziness, especially for older adults, exposes patients to the lethal risk of falling. However, the diagnosis of BPPV in this population can be more elusive as they present few characteristic symptoms. Therefore, we explored the application of a subtype-determining questionnaire in BPPV diagnosis among the geriatric population.

**Methods:** Patients were assigned to the aware and unaware groups. In the aware group, the technician would directly test the suspected canal indicated by the questionnaire, whereas, in the unaware group, the technician performed the regular positional test. The diagnostic parameters of the questionnaire were examined.

**Results:** The accuracy, sensitivity, and specificity of questions 1–3 for diagnosing BPPV were 75.8, 77.6, and 74.7%, respectively. Question 4 demonstrated an accuracy of 75.6% in ascertaining the BPPV subtype, question 5 showed an accuracy of 75.6% in determining the affected side, and question 6 yielded an accuracy of 87.5% in distinguishing canalithiasis or cupulolithiasis. Examination time was shorter in the aware group than that in the unaware group ($P < 0.05$). No difference was found between the two groups for treatment time ($P = 0.153$).

**Conclusion:** This subtype-determining questionnaire is practical in daily use and capable of providing instructive information for an efficient diagnosis in geriatric patients with BPPV.

KEYWORDS

**benign paroxysmal positional vertigo (BPPV), questionnaire, diagnosis, geriatrics, treatment**

## 1. Introduction

Benign paroxysmal positional vertigo (BPPV) is the most frequent vestibular disease that exhibits a cumulative lifetime incidence of 10% (von Brevern et al., 2015). The 1-year prevalence of BPPV increases with age (von Brevern et al., 2007), accounting for approximately 30% of older adult patients with vertigo (Balatsouras et al., 2018). BPPV adversely affects the quality of life and interrupts daily activities (Parham and Kuchel, 2016).

Moreover, for older patients, it increases the risk of falls which can be lethal to this population (Ganança et al., 2010). It is reported that approximately 8% of general patients with BPPV have received proper treatment (von Brevern et al., 2007). Diagnosis can become even more elusive for older adults who present few characteristic symptoms and a more protracted course (Parham and Kuchel, 2016). Therefore, a swift and accurate diagnosis could be significant for these patients. Besides the widely recognized diagnostic measures such as Dix–Hallpike and supine roll tests, some scholars invented questionnaires based on the nature of the key elements of BPPV and explored the validity of this new tool (Friedland et al., 2016; Lindell et al., 2018; van Dam et al., 2020). The emergence of questionnaires has provided new ideas for BPPV diagnosis in addition to the traditional methods with their feasible prediction power (Higashi-Shingai et al., 2011). Questionnaires also bear advantages with regard to patients with limited spinal motion, atypical nystagmus, post-surgery status, subjective BPPV, or recurrence (Higashi-Shingai et al., 2011; Kim et al., 2020). Based on Kim et al.'s (2020) study, our previous study demonstrated that applying an innovative subtype-determining questionnaire is practical and beneficial when encountering dizzy patients (Wan et al., 2023). However, after an extensive literature review, only one study that specifically addressed the usage of diagnostic BPPV questionnaires among the geriatric population was found (Lapenna et al., 2016). The main purpose of this study was to reduce the risk of missed diagnosis of BPPV rather than attempting to elicit precise information about each BPPV precipitation. Therefore, this study aimed to explore the significance of the subtype-determining questionnaire in guiding the diagnostic and treatment procedure in older adults with BPPV.

## 2. Materials and methods

This prospective single-blinded study was conducted at Peking University International Hospital from September 2022 to March 2023. After ruling out three patients diagnosed with multi-canal BPPV, the remaining 153 patients aged ≥65 years with vertigo as their chief complaint were recruited. Patients with the following conditions were excluded from our study: intracranial pathologies, severe cardiovascular disease, severe spinal lesions, post-surgery status, major head/ear trauma, severe obesity, cognitive/communicative impairment, inability to endure the procedure, and spontaneous nystagmus.

The questionnaire used in our study was originally introduced by Kim et al. (2020) and was slightly modified by the authors (Wan et al., 2023). The questionnaire not only screens BPPV but also predicts the affected canal. The validity of its usage among general Chinese patients has been demonstrated in our previous study (Wan et al., 2023). The first three questions screen patients with BPPV, and the following ones aim to determine the subtype.

Participants were divided into unaware and aware groups on a random basis, in which the technician was blinded or informed about the questionnaire results, respectively. In the unaware group, the technician performed the supine roll test; if negative, Dix–Hallpike test was carried out. Initially, the technician would pick up either side, depending alternatively on the order of patients' presence. The consideration and validity of adopting this order were elaborated on in our previous study (Wan et al., 2023). In the aware group, the technician knew the result of the questionnaire and would test the suspected canal straightforwardly. If BPPV was denied by the first three questions, the technician performed the positional test based on the aforementioned order.

Diagnosis of BPPV was established based on typical nystagmus elicited by the positional test. Patients were treated using Epley, Lempert/Gufoni, and Yacovino maneuvers according to their respective subtypes. Time spent on diagnosis and treatment was recorded.

### 2.1. Statistical analysis

We calculated the accuracy, sensitivity, specificity, positive/negative predictive value, and positive/negative likelihood ratio. Mann–Whitney U test was used for continuous variables, whereas the chi-square or Fisher exact test was used for nominal variables. A $P$-value $< 0.05$ was considered statistically significant. Statistical analyses were performed using R version 4.2.0[1].

## 3. Results

A total of 153 older adult patients were included in this study. No significant difference was found between the aware and unaware groups in terms of age, course, sex, and proportion of true BPPV. In the aware group, the examination time was shorter than that in the unaware group, with statistical significance ($P = 0.001$). In patients verified as BPPV using the positional test, examination time remained shorter in the aware group ($P = 0.000$); however, the same conclusion could not be established for the treatment time ($P = 0.153$) (**Table 1**).

We also analyzed the similarities and discrepancies between the groups regarding whether the accurate prediction was achieved using the questionnaire (identical results in both sides and subtypes using the positional test) (**Table 3**). No statistical difference was found in age, sex, course, if informed or not, sidedness, subtype, and treatment time; however, the accurately diagnosed group showed shorter examination ($P = 0.046$) and treatment time ($P = 0.035$) than that in the inaccurate group (**Table 2**).

### 3.1. BPPV screening: Questions 1–3

As shown in **Figure 1**, among the 156 patients initially recruited who agreed to participate in this study, three were diagnosed with multi-canal BPPV and thus were excluded from further study. Of the 153 patients enrolled, 69 and 84 were assumed as with and without BPPV using the questionnaire, and the judgments were similar to the positional test results in 45 out of 69 patients and 71 out of 84 patients, respectively. Therefore, questions 1–3 could correctly decide whether a patient has BPPV in 116 out of

1 R-project.org/

TABLE 1 Questionnaire used in our study.

| Questionnaire for BPPV diagnosis by Kim et al. (2020) and slightly modified by us |
|---|
| **Question 1** Do you have spinning or a whirling sensation of the surroundings or yourself? |
| **Question 2** Do you feel dizzy mostly when your head is moved? |
| **Question 3** Does the dizziness last <3 min? |
| **Question 4** Which positional change makes you feel more dizzy?<br>Lying down or getting out of bed?<br>Turning your head (or body) **while lying flat or on the pillow?** |
| **Question 5** Which makes you more dizzy?<br>Turning your head to the right?<br>Turning your head to the left? |
| **Question 6** How long does the dizziness induced by head turning last?<br><1 min<br>>1 min |

BPPV, Benign Paroxysmal Positional Vertigo. Bold letter is the modified parts according to Chinese language habits, it was "while lying down" originally in Dr. Kim's questionnaire.

153 patients, with an accuracy of 75.8%. Other parameters, such as sensitivity, specificity, positive/negative predictive value, and positive/negative likelihood ratio were calculated using data shown in **Figure 1** and demonstrated in **Table 3**.

## 3.2. Locating the culprit canal: Questions 4–6

Question 4 was designed to distinguish vertical canal from horizontal canal BPPV. Of the 33 patients verified having posterior/anterior canal BPPV using the positional test, 25 (75.8%) answered that they felt dizzier when lying down or getting out of bed (including three patients who answered the question as undetermined category, not shown in **Figure 1**, but was checked out from our data). Of the 12 patients confirmed having horizontal canal BPPV using the positional test (eight geotropic and four apogeotropic types), six (75.0%, including one patient with geotropic-type BPPV in the undetermined category, not shown in **Figure 1**, but was checked out from our data) out of eight patients with geotropic type and three (75.0%) out of four with apogeotropic type BPPV thought they felt dizzier when turning their body or head while lying flat or on the pillow. Hence the diagnostic accuracy of question 4 was 75.6% (34 of 45).

Question 5 was intended to determine the inflicted side of BPPV. Twenty-five out of 33 (75.8%) patients with posterior/anterior, seven out of eight (87.5%) patients with geotropic type, and two out of four (50.0%) with apogeotropic type BPPV chose the side consistent using the positional test. Therefore, the diagnostic accuracy of question 5 was 75.6% (34/45).

Question 6 was intended for patients who answered that they felt dizzier when turning their head or body while lying flat or on the pillow to determine the canalithiasis and cupulolithiasis. It had correctly predicted the subtype in 100% (5/5) of the patients with geotropic type and 66.7% (2/3) of those with apogeotropic type BPPV, yielding a diagnostic accuracy of 87.5% (7/8).

Among the 14 patients screened for BPPV but failed to give an assertive answer to either questions 4 and/or 5, nine (64.3%) were proved to not have BPPV.

# 4. Discussion

Benign paroxysmal positional vertigo is the most common diagnosis in dizzy patients, particularly older adults. Its 1-year prevalence increases sharply with age and can be seven times higher in the older population than in the younger population (Neuhauser et al., 2005). The prevalence of unrecognized geriatric BPPV is also high. In addition to the catastrophic consequence of falls rendered by BPPV, adverse psychological conditions, such as depression, disrupted daily activities, and avoidance of leaving the house can also be caused by this incapacitating disease (Parham and Kuchel, 2016). Older patients with BPPV report less rotatory dizziness, more unsteadiness, present with a more protracted course (Piker and Jacobson, 2014; Parham and Kuchel, 2016), and are often accompanied by various comorbidities. All these factors make BPPV diagnosis in this population more challenging. Currently, besides the classic positional test, scholars attempted to identify this disease by extracting the most representative elements about the nature of this disorder and integrating them into questionnaires to facilitate diagnosis (Higashi-Shingai et al., 2011; Friedland et al., 2016; Lindell et al., 2018; van Dam et al., 2020). Given the fact that presentation of BPPV is usually atypical among the geriatrics who report more unsteadiness and imbalance instead of the rotatory sensation because of their aging vestibular system, it just made us wonder if the subtype-determining questionnaire, the development of which was based upon the typical presentation of BPPV, still works as efficiently as it does among younger patients. Although few studies could be found on the application of a subtype-targeting BPPV diagnostic questionnaire in the geriatric population, we believe this field is worth looking into because of the potentiality of a reliable subtype-determining questionnaire in the swift identification of BPPV, making an efficient diagnosis, providing instructive information for otologist, and even guiding the patients' home-based canalith repositioning procedure when medical service is inaccessible.

As shown in **Table 4**, the combined force of the questionnaire in diagnosing BPPV exhibited 75.8% accuracy, 77.6% sensitivity, and 74.7% specificity. Therefore, it is worthy of attention when compared with the data in our previous study of the general population (Wan et al., 2023), which showed an overall sensitivity of 90.9% and negative predictive value (NPV) of 93.9% for questions 1–3; these two parameters were significantly low in the geriatric population study ($P$ = 0.008 for sensitivity; $P$ = 0.008 for NPV). We believe this weakening in sensitivity and NPV power is well explainable and in concordance with the fact that older people tend to feel more unsteadiness or imbalance rather than rotatory vertigo, which phenomenon is essentially multisensory dizziness owing to the deterioration in the vestibular, proprioceptive, and central integration ability in the aging process (Balatsouras et al., 2018). The gradual vestibular loss enables older adults to process such change more properly and perceive more instability and movement intolerance, rather than the intense rotatory vertigo experienced by younger patients with BPPV (Fernández et al., 2015). Consequently, older patients without rotatory dizziness would be disapproved of having BPPV using the questionnaire, while typical nystagmus can still be evoked using a positional test that warrants a BPPV diagnosis. This may account for the relatively lower specificity and NPV of this questionnaire in the geriatric

population. A similar result was presented by Lapenna et al. (2016) in their study of the anamnestic BPPV questionnaire in older adults. Nevertheless, with a 75.8% accuracy, 77.6% sensitivity, and 74.7% specificity of questions 1 to 3, we still consider this diagnostic property acceptable and applicable in daily practice.

The logic behind the designing of questions 4, 5, and 6 was elucidated in Kim's work (Kim et al., 2020) and is easily understandable. Questions 4, 5, and 6 aimed at pinpointing the affected canal; therefore, only accuracy was calculable, which were 75.6, 75.6, and 87.5%, respectively. Surprisingly, the diagnostic accuracy of these three questions was similar to those in the general population, with 80.7% accuracy, 78.7% sensitivity, and 87.2% specificity (Wan et al., 2023). Originally, we expected less competent predictive ability of these parameters because hair cell and neuronal loss, a functional decline of the vestibular nerve, and reduced blood flow to the inner ear all contributed to an aging vestibular system (Zalewski, 2015; Ji and Zhai, 2018; Abdul Razzak et al., 2020). These degenerative changes happen in the forms of decreased cervical/ocular vestibular-evoked myogenic potentials amplitudes and abnormal head impulse (HIT) and modified Romberg tests (Davalos-Bichara and Agrawal, 2014; Fernández et al., 2015). This led us to assume a weaker power of questions 4 to 6. Nevertheless, the comparative diagnostic property of these three questions compelled us to look for an explanation. It is much easier to say it is due to the inclusion of older adults in the general population (different patient entity from this study); however, with only 21.1% (108/512) of patients aged ≥65 years in our last study (Wan et al., 2023), we believe this result deserves a deeper investigation.

The enhanced multisensory integration in the elderly seems to be a good candidate for an explanation, with the potential mechanism such as increased time window of integration; deficits in top-down attention control enable more distraction by stimuli through sensory modalities, inverse effectiveness, and elevated background sensory processing baseline (McGovern et al., 2014; Abdul Razzak et al., 2020). Similarly, Anson et al. (2016) found that older adults exhibited significantly larger compensatory saccades relative to the young in the HIT test, which was used to evaluate the function of the three semicircular canals. The intricacy of the vestibular system was recognized by virtue of its complex anatomy and sophisticated multi-integrational role in postural stability (Zalewski, 2015; Ji and Zhai, 2018). In fact, tests sometimes do fall short in detecting vestibular deterioration in aging on account of central compensatory mechanisms (Zalewski, 2015). In such context, it seems convincing that, as strong a stimulus as the otolith fell and moved in the semicircular canal, it was capable of irritating the vestibular system, which was, despite age-related degeneration, still functioning enough to perceive the stimulus

TABLE 2 Comparison between the aware group and the unaware group in the elderly.

| | Aware (*n* = 79) | Unaware (*n* = 74) | *P*-value | Estimated difference (95% CI) | Total |
|---|---|---|---|---|---|
| In general | | | | | |
| Age, Median (Q1, Q3) | 69.00 (67.00, 76.00) | 71.00 (67.00, 75.00) | 0.417 | | 71.00 (67.00, 76.00) |
| Course, Median (Q1, Q3) (d) | 7.00 (3.00, 28.00) | 7.00 (2.00, 20.50) | 0.830 | | 7.00 (3.00, 24.50) |
| Gender n (%) | | | | | |
| Male | 28 (35.40) | 20 (27.00) | 0.262 | | 48 (31.4) |
| Female | 51 (64.60) | 54 (73.00) | | | 105 (68.6) |
| BPPV | | | | | |
| Yes | 34 (43.0) | 24 (32.4) | 0.177 | | 58 (37.9) |
| No | 45 (57.0) | 50 (67.6) | | | 95 (62.1) |
| Examination time, Median (Q1, Q3) (s) | 75.00 (42.00, 109.00) | 97.00 (85.25, 107.25) | 0.001 | −23.00 (−36.00 to −10.00) | |
| In verified BPPV patients | | | | | |
| Side | | | | | |
| Left | 15 (60.0) | 19 (57.6) | 0.853 | | 34 (58.6) |
| Right | 10 (40.0) | 14 (42.4) | | | 24 (41.4) |
| Subtype | | | | | |
| Posterior/ anterior | 23 (60.5) | 11 (55.0) | 0.685 | | 34 (58.6) |
| Horizontal | 15 (39.5) | 9 (45.0) | | | 24 (41.4) |
| Examination time, Median (Q1, Q3) (s) | 42.00 (24.00, 83.25) | 100.00 (87.75, 106.50) | 0.000 | −55.00 (−66.00 to −40.00) | |
| Treatment time, Median (Q1, Q3) (s) | 141.50 (105.50, 206.50) | 167.00 (128.25, 224.25) | 0.153 | | |

by the provocative position in the right sense, credited to central compensatory mechanisms. We consider this might be accountable for a similarly good quality of diagnostic accuracy of questions 4 to 6 in comparison with the general population.

We noticed in Figure 1 that there were 36 patients judged by the questionnaire as having posterior/anterior canal BPPV, and only four showed negative results after the positional test; while this proportion is 10/30 in the questionnaire judged canalithiasis, a statistical difference existed ($P$ = 0.028). This is in accordance with studies that spontaneous resolution is more frequent in the horizontal canal because the horizontal canal otolith has the predisposition to flow back into the utricle spontaneously by

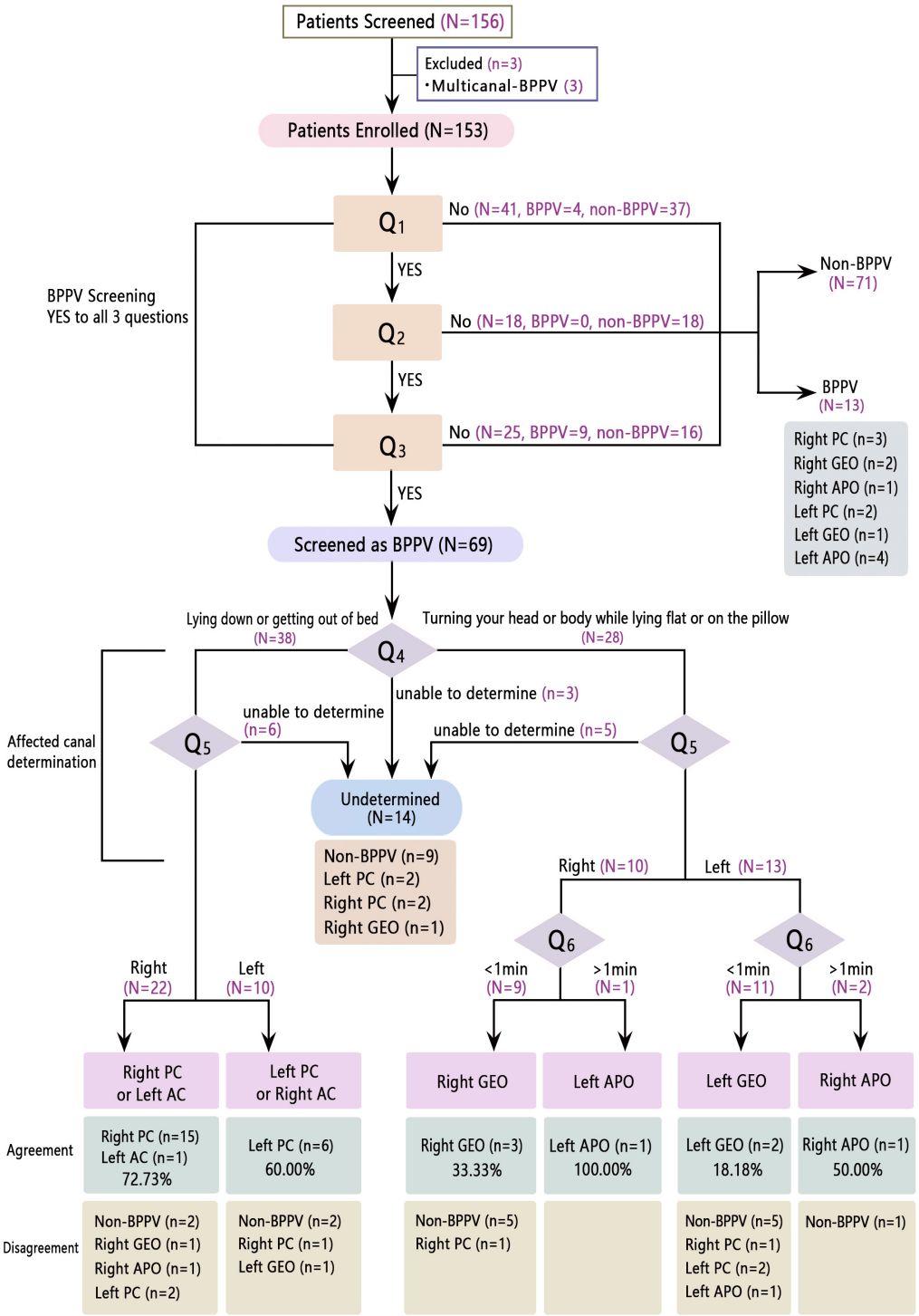


FIGURE 1
Flowchart of the algorithms and results of this subtype-determining questionnaire in geriatrics. PC, posterior canal; AC, anterior canal; GEO, geotropic; APO, apogeotropic.

random head movement given the 30° tilt (Moon et al., 2006; Sekine et al., 2006; Pollak et al., 2018). Nonetheless, a multicentered descriptive study conducted in Spain didn't find any difference of spontaneous resolve rate between different canal types (de Sande et al., 2019).

Examination time in the aware group was significantly shorter than that in the unaware group ($P$ = 0.000), both in the general participants and those with verified BPPV. This finding forcefully endorses the value of this subtype-determining questionnaire in identifying the culprit canal and its practical value in aiding in the diagnostic process. An efficient diagnosis spares older adults unpleasant experiences of undergoing the positional test. Treatment time did not differ between the aware and unaware groups ($P$ = 0.153), which is comprehensible due to the same repositioning maneuver adopted for each BPPV subtype.

Both examination and treatment time in the accurately diagnosed group was shorter than that in the inaccurately diagnosed group ($P$ = 0.046), which is an interesting result that we propose the "optimal BPPV" theory for an explanation. Gradual aggregation of micro-otoconia over a long time period was advocated as a pathological change underlying BPPV precipitation (Ichijo, 2017). In addition, the movement of free otoconia in the semicircular canal may be affected by the composition of fibrils and matrix within it, a higher proportion of which would cause

TABLE 3 Comparison between the accurately diagnosed with the inaccurately diagnosed groups in confirmed BPPV patients.

| | Accurate ($n$ = 29) | Inaccurate ($n$ = 29) | $P$-value | Estimated difference (95% CI) |
|---|---|---|---|---|
| Age | 68.00 (67.00, 74.00) | 71.00 (67.00, 76.00) | 0.924 | |
| Gender | | | | |
| Male | 8 (27.6) | 9 (31.0) | 0.773 | |
| Female | 21 (72.4) | 20 (69.0) | | |
| Course (d) | 7.00 (2.00, 13.00) | 4.00 (2.00, 10.00) | 0.583 | |
| Aware or not | | | | |
| Yes | 17 (58.6) | 17 (58.6) | 1.000 | |
| No | 12 (41.4) | 12 (41.4) | | |
| Side | | | | |
| Left | 10 (34.5) | 15 (51.7) | 0.185 | |
| Right | 19 (65.5) | 14 (48.3) | | |
| subtype | | | | |
| Posterior/ anterior | 22 (75.9) | 16 (55.2) | 0.097 | |
| Horizontal | 7 (24.1) | 13 (44.8) | | |
| Examination time, Median (Q1, Q3) (s) | 56.00 (29.00, 95.00) | 94.00 (42.50, 107.50) | 0.046 | −17.00 (−44.00 to 0.00) |
| Treatment time, Median (Q1, Q3) (s) | 132.00 (105.00, 187.00) | 174.00 (127.00, 271.00) | 0.035 | −35.00 (−66.00 to −4.00) |

TABLE 4 Diagnostic property of the questionnaire in the elderly.

| | Accuracy (95% CI),% | Sensitivity (95% CI),% | Specificity (95% CI),% | Positive predictive value, (95% CI),% | Negative predictive value, (95% CI),% | Positive likelihood ratio, (95% CI), | Negative likelihood ratio, (95% CI), |
|---|---|---|---|---|---|---|---|
| Q1 | 59.5 (51.3, 67.3) | 93.1 (83.3, 98.1) | 38.9 (29.1, 49.5) | 48.2 (38.7, 57.9) | 90.2 (76.9, 97.3) | 1.53 (1.28, 1.82) | 0.18 (0.07, 0.47) |
| Q1 + Q2 | 71.2 (63.4, 78.3) | 93.1 (83.3, 98.1) | 57.9 (47.3, 68.0) | 57.4 (46.8, 67.6) | 93.2 (83.5, 98.1) | 2.21 (1.73, 2.83) | 0.12 (0.05, 0.31) |
| Q1 + Q2 + Q3 | 75.8 (68.2, 82.4) | 77.6 (64.7, 87.5) | 74.7 (64.8, 83.1) | 65.2 (52.8, 76.3) | 84.5 (75.0, 91.5) | 3.07 (2.12, 4.46) | 0.30 (0.18, 0.49) |
| Q4 | 75.6 (60.5, 87.1) | | | | | | |
| Q5 | 75.6 (60.5, 87.1) | | | | | | |
| Q6 | 87.5 (47.3, 99.7) | | | | | | |

more impediments to its movement (Bojrab and Schutt, 2018). Therefore, it is plausible to deduce that during the accumulative process of the otolith, there is a certain "optimal" section when the otolith is around the right size and composition, which enables an unhindered movement within the semicircular canal. We believe such otolith movement gives the patient a more unambiguous perception of the most evocative head position instead of an inexplicit feeling when the otolith is either too small to trigger a clear sense or subjective BPPV (Jung and Kim, 2016) or too large and sticky to move in a common manner. Treatment time was also shorter in the accurately diagnosed group than that in the inaccurately diagnosed group.

The same phenomenon was observed in Kim's and the present study of the general population (Kim et al., 2020; Wan et al., 2023), which we think were no coincidental findings. A higher proportion of fibrils and matrix contributes to increasing repositioning difficulties (Bojrab and Schutt, 2018), and refractory BPPV might happen if there are multiple deposit sites, which would not only muddle a clear perception of BPPV burst but also complicate treatment as they would block the returning pathway of otoconia (Ichijo, 2017). Therefore, conditions interfering with diagnosis might also make treatment more challenging. Therefore, these considerations might give us some hint in understanding the reduced treatment time for the accurately diagnosed group.

## 5. Conclusion

Though slightly less sensitive, the subtype-determining questionnaire still bears a competent screening power in identifying patients with BPPV in the geriatric population. It is also capable of eliciting valuable referable information to facilitate an efficient diagnosis.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Peking University International Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## Author contributions

YW designed the study, collected clinical data, and wrote the manuscript. YL performed the positional tests and treatment of the patients. JS supervised and guided the study. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

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# The effect of accompanying anxiety and depression on patients with different vestibular syndromes

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**Objective:** This study aims to investigate the situation of vertigo disorder combined with anxiety and depression in patients with different types of vestibular syndrome.

**Methods:** A total of 330 patients with vertigo in otolaryngology outpatient department were selected, and clinical information such as age, gender, and scores of Dizziness handicap inventory (DHI), Generalized anxiety disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9) were collected. Analyzed the differences among acute vestibular syndrome (AVS), episodic vestibular syndrome (EVS) and chronic vestibular syndrome (CVS) in terms of age, gender, comorbid anxiety and depression, and the multivariate ordered logistic regression analysis was used to evaluate the relationship between the above factors and the degree of vertigo disorder.

**Results:** The three types of vestibular syndrome had no significant difference in age composition, sex composition, anxiety and depression. There was no significant difference in the probability of anxiety and depression among vertigo patients of different ages and genders. The total score of vertigo disorder and each sub-item score were higher in patients with anxiety and depression. Patients with anxiety mainly manifested in EVS and CVS, while patients with depression mainly manifested in EVS and AVS. The probability of increased vertigo in anxious patients was 4.65 times that of non-anxious patients, and the probability of increased vertigo in depressed patients was 3.49 times that of non-depressed patients. Age and gender had no statistically significant effect on the degree of vertigo. In patients with EVS, anxiety and depression had a significant effect on the degree of vertigo; in patients with CVS, anxiety had a significant effect on the degree of vertigo, but depression had no significant effect.

**Conclusion:** Age and gender do not significantly affect the degree of vertigo disorder and mental state in various vestibular syndromes. Instead, anxiety and depression are the risk factors for aggravating the degree of vertigo disorder, and manifest differently in each type of vestibular syndrome. Therefore, it is necessary to use a quick scale tool to conduct a standardized screening of the psychological status of patients with vertigo.

KEYWORDS

**vertigo, vestibular syndrome, anxiety, depression, dizziness handicap inventory**

## 1. Introduction

Vertigo, a common clinical symptom, is the most prominent manifestation of vestibular disorders. Dysfunction of the vestibular system can lead to a variety of symptoms, from vertigo, vision and balance problems, to mood, memory, and self-perception problems. Large population-based studies have shown that dizziness and vertigo affect approximately 15% to over 20% of adults annually. Vestibular vertigo accounts for approximately 1/4 of dizziness complaints and can cause unilateral or bilateral deterioration and loss of vestibular function, which can significantly impact work and living activities (Quimby et al., 2018). The prevalence of vertigo increases with age and is approximately 2–3 times higher in women than in men. An epidemiological study in the United States showed that the number of patients with dizziness and balance disorders as the chief complaint was about 33 million, for an annual prevalence of 14.8% (Kerber et al., 2017).

The 2015 International Classification of Vestibular Disorders (ICVD) divides vestibular disorders into acute vestibular syndrome (AVS), episodic vestibular syndrome (EVS), and chronic vestibular syndrome (CVS) (Bisdorff et al., 2015). The generally accepted definition of AVS is sudden-onset, continuous vertigo lasting over 24 h and accompanied by nausea/vomiting, exercise intolerance, and gait instability; acute unilateral peripheral vestibular lesions are considered the most common cause, including diseases such as acute unilateral vestibulopathy (AUVP)/vestibular neuritis (VN) and sudden deafness with vertigo. EVS refers to recurrent vestibular disorders that are symptomatic during episodes with remission between episodes, and usually includes some transient vestibular system dysfunction (e.g., nystagmus, drop attacks). Signs and symptoms suggestive of cochlear or central nervous system dysfunction may also be present, including diseases such as benign paroxysmal positional vertigo (BPPV), Menière's disease (MD), vestibular migraine (VM), transient ischemic attack (TIA), vestibular paroxysmia (VP). CVS is a group of clinical syndromes characterized by chronic dizziness, vertigo, or instability. It lasts from several months to several years, usually with persistent vestibular system dysfunction (visual oscillations, nystagmus, gait instability), including diseases such as bilateral vestibulopathy (BVP) and persistent postural perceptual dizziness (PPPD). The symptoms of CVS can be a gradual progression of deterioration, or they can manifest as persistent symptoms of stable but incomplete recovery from AVS or EVS (Trinidade et al., 2023).

About 20–50% of patients with vertigo and balance disorders have concomitant psychiatric disorders (McKenna et al., 1991; Best et al., 2009; Al-Rawashdeh et al., 2019). Due to the long disease duration, many vertigo patients suffer from anxiety, and concomitant psychiatric disorders such as anxiety and depression have become commonplace among vertigo patients. The prevalence of anxiety and depression among patients with symptoms of vertigo has been reported to be 18 and 11%, respectively (Kim et al., 2016). Ketola et al. (2007) found that 20% of a random sample of 100 vertigo patients reported symptoms of depression. Eckhardt-Henn et al. (2003) conducted neuro-otological examination, vestibular tests, and psychiatric examination and administered evaluations and questionnaires to 129 patients with vertigo accompanied by psychiatric disorders and found a higher prevalence of anxiety (41%) than depression (15%). An analysis of 621 patients in a vertigo clinic by van Leeuwen et al. (2017) found that the most common secondary diagnosis in patients with vertigo was anxiety (~50.1%), which was found primarily in conjunction with peripheral vestibular disorders such as BPPV, vestibular neuritis, and Ménière disease. Grunfeld et al. (2003) found a higher incidence of depression and anxiety among vertigo patients than in normal individuals using the HADS instrument. A cross-sectional study of vertigo patients by Roh et al. (2017) concluded that the emotional state of vertigo patients may be associated with the persistence of vertigo symptoms and that vertigo-induced psychiatric distress may contribute to a prolonged duration of disease; they recommend timely screening for psychiatric disorders.

Brandt and Dieterich (2020) suggested that damage to the vestibular system is a central factor in the development of mood disorders such as anxiety and depression, and that vestibular hyperfunction (acute excitation or acute vestibular tone imbalance) or hypofunction (chronic vestibular loss) under certain conditions can lead to the development of mood disorders. Furman et al. (2005) and Goddard et al. (2008) found that the onset and interaction between vestibular disorders and psychiatric disorders is associated with overlapping central nervous system transmission of the vestibular and mood information pathways. The vestibular nucleus, which controls vertigo, has many nerve fiber projections with mood-related nuclei such as the parabrachial nuclei, the locus coeruleus, and the dorsal raphe nuclei, and also interacts with the frontal lobe, hippocampus, and dentate gyrus. This affects the release of catecholamines (dopamine, norepinephrine), 5-HT, and other neurotransmitters, causing dysfunction in these mood-related regions and affecting the development of anxiety and depression (Furman et al., 2005; Goddard et al., 2008; Bednarczuk et al., 2018; Hilber, 2022).

By far the most common psychiatric comorbidity in vertigo patients is anxiety and/or depression, which is primarily associated with gender, age, duration of vertigo, frequency of vertigo episodes, and degree of severity of vertigo. The psychiatric state of the patient plays an important role in the prognosis of vertigo disease (Tschan et al., 2011) but is often neglected by clinicians, which affects the efficacy of vertigo treatment. Both psychological and physical factors must be considered in the clinical treatment of vertigo, and the psychological status of patients warrants increased attention. In addition, intervention with anxiolytic and antidepressant medications and psychotherapy should be considered when determining the best treatment plan. In the present study, we analyzed the general condition and etiology of each type of vestibular syndrome among vertigo outpatients, and also conducted an assessment of anxiety and depression in the patients with the aim of enabling physicians to improve outcomes through more comprehensive communication, psychological guidance, and medication for vertigo patients. The present study analyzed the relationship between vestibular syndrome and anxiety and

depression in different genders, age groups, and types of vestibular syndrome.

## 2. Materials and methods

### 2.1. Source of cases

A cross-sectional study design was adopted. The study was approved by the Ethics Committee. The study population consisted of 386 patients with vertigo who visited the otolaryngology department of the first hospital of China medical university between March 2022 and October 2022. A total of 330 cases were collected after applying the inclusion and exclusion criteria.

### 2.2. Inclusion criteria

Chief complaint of vertigo or dizziness, meets the diagnostic criteria for each disorder, and relatively complete medical records.

### 2.3. Exclusion criteria

Patients with major psychiatric disorders or cognitive dysfunction and patients with vertigo clearly caused by other

TABLE 1 Clinical data of participants with vestibular disorder.

| Characteristic | Full sample ($n$ = 330) | AVS ($n$ = 42) | EVS ($n$ = 236) | CVS ($n$ = 52) |
|---|---|---|---|---|
| **Age** | | | | |
| Average age[b] | 53.18 ± 14.40 | 53.71 ± 15.18 | 52.26 ± 14.95 | 56.94 ± 9.87 |
| <60[a] | 205 (62.12) | 24 (57.14) | 151 (63.98) | 30 (57.69) |
| ≥60[a] | 125 (37.88) | 18 (42.86) | 85 (36.02) | 22 (42.31) |
| **Gender[a]** | | | | |
| Male | 94 (28.48) | 11 (26.19) | 68 (28.81) | 15 (28.85) |
| Female | 236 (71.52) | 31 (73.81) | 168 (71.19) | 37 (71.15) |
| **Complications[a]** | | | | |
| Deafness | 58 (17.58) | 8 (19.05) | 40 (16.95) | 10 (19.23) |
| Tinnitus | 125 (37.88) | 16 (38.10) | 88 (37.29) | 21 (40.38) |
| Headache | 102 (30.91) | 13 (30.95) | 65 (27.54) | 24 (46.15) |
| **Past history[a]** | | | | |
| Cardiovascular and cerebrovascular diseases | 123 (37.27) | 13 (30.95) | 85 (36.02) | 25 (48.08) |
| Diabetes | 29 (8.79) | 8 (19.05) | 19 (8.05) | 2 (3.85) |
| Neurological disorders | 19 (5.76) | 3 (7.14) | 12 (5.08) | 4 (7.69) |
| Sleep disturbances | 33 (10.00) | 6 (14.29) | 18 (7.63) | 9 (17.31) |
| **GAD-7 (anxiety)[a]*** | | | | |
| Total < 10 | 273 (87.50) | 36 (92.31) | 194 (87.39) | 43 (84.31) |
| Total ≥ 10 | 39 (12.50) | 3 (7.69) | 28 (12.61) | 8 (15.69) |
| **PHQ-9 (depression)[a]*** | | | | |
| Total < 10 | 271 (88.27) | 35 (89.74) | 194 (88.18) | 42 (87.50) |
| Total ≥ 10 | 36 (11.73) | 4 (10.26) | 26 (11.82) | 6 (12.50) |
| **Vertigo disorder (DHI)** | | | | |
| Total[b] | 43.36 ± 24.69 | 41.52 ± 26.28 | 41.74 ± 24.09 | 52.33 ± 24.11 |
| Physical[b] | 13.65 ± 7.42 | 13.19 ± 9.70 | 13.22 ± 6.84 | 16.00 ± 7.56 |
| Emotional[b] | 11.68 ± 9.71 | 10.00 ± 8.33 | 11.37 ± 9.71 | 14.46 ± 10.38 |
| Functional[b] | 18.60 ± 11.46 | 18.29 ± 11.43 | 17.73 ± 11.54 | 22.81 ± 10.34 |
| Mild[a] | 116 (35.15) | 19 (45.24) | 83 (35.17) | 14 (26.92) |
| Moderate[a] | 130 (39.39) | 13 (30.95) | 101 (42.80) | 16 (30.77) |
| Severe[a] | 84 (25.45) | 10 (23.81) | 52 (22.03) | 22 (42.31) |

[a] $n$ (%).
[b] Mean ± SD.
*The full sample $n$ = 330, where the GAD-7 score has 18 missing values and the PHQ-9 score has 23 missing values.

disorders, such as cranial lesions, middle ear lesions, inner ear malformations, internal auditory tract lesions, drug effects, and other medical disorders.

## 2.4. Diagnostic standards for classification of vertigo

(1) Vestibular syndrome was classified into three categories in accordance with the 2015 ICVD (Bisdorff et al., 2015): AVS, EVS, and CVS.
(2) Benign paroxysmal positional vertigo was diagnosed in accordance with the 2015 diagnostic criteria for BPPV formulated by the Bárány Society (von Brevern et al., 2015).
(3) Vestibular migraine was diagnosed in accordance with the 2022 diagnostic criteria for VM formulated by the Bárány Society and the International Headache Society (Lempert et al., 2022).
(4) Menière's disease was diagnosed in accordance with the 2015 diagnostic criteria for MD formulated by the Bárány Society, the Japan Society for Equilibrium Research, the European Academy of Otology and Neurotology, the Equilibrium Committee of the American Academy of Otolaryngology-Head and Neck Surgery, and the Korean Balance Society (Ihler et al., 2022).
(5) Acute unilateral vestibulopathy/vestibular neuritis were diagnosed in accordance with the 2022 diagnostic criteria for AUVP/VN formulated by the Bárány Society (Strupp et al., 2022).
(6) Persistent postural perceptual dizziness was diagnosed in accordance with the 2017 consensus document of the committee for the Bárány Society (Staab et al., 2017).
(7) Sudden hearing loss with vertigo was diagnosed in accordance with the 2019 American Academy of Otolaryngology-Head and Neck Surgery Clinical Practice Guideline for Sudden Hearing Loss (Chandrasekhar et al., 2019).
(8) Unilateral vestibular hypofunction (UVH) was diagnosed in accordance with the 2022 Vestibular Rehabilitation for Peripheral Vestibular Hypofunction: An Updated Clinical Practice Guideline From the Academy of Neurologic Physical Therapy of the American Physical Therapy Association (Hall et al., 2022).
(9) Bilateral vestibulopathy was diagnosed in accordance with the 2017 diagnostic criteria for BVP developed by the Classification Committee of the Bárány Society (Strupp et al., 2017).
(10) Unspecified diagnosis: failure to meet the diagnostic criteria due to lack of clinical evidence, including history of suspected VP, posterior circulation ischemic stroke, and TIA.

## 2.5. Evaluation of vertigo disorder

The DHI is a widely used self-report questionnaire for patients with dizziness or vertigo that has been translated into 14 languages and is widely validated (Mutlu and Serbetcioglu, 2013). The DHI consists of 25 items and 4 measurements: the total score and 3 sub-scores (emotional subdomain, DHI-E; functional subdomain, DHI-F; physical subdomain, DHI-P). The total DHI score ranges between 0 and 100 and is used to holistically assess the subjective severity of vertigo symptoms (mild, 0–30; moderate, 31–60; severe, >60).

## 2.6. Psychological evaluation

The GAD-7 is a simple and effective assessment tool for identifying generalized anxiety disorder and has good sensitivity and specificity for screening anxiety (89% sensitivity, 82% specificity) when the GAD-7 score is ≥10 (Spitzer et al., 2006). Therefore, a GAD-7 score ≥10 was defined as anxiety in this study.

TABLE 2 Age, gender and manifestations of anxiety and depression in patients with different syndromes.

| Characteristic | AVS ($n$ = 42) | EVS ($n$ = 236) | CVS ($n$ = 52) | $\chi^2$ | $P$ |
|---|---|---|---|---|---|
| Age | | | | 1.224 | 0.542 |
| <60 ($n$ = 205) | 24 (57.14) | 151 (63.98) | 30 (57.69) | | |
| ≥60 ($n$ = 125) | 18 (42.86) | 85 (36.02) | 22 (42.31) | | |
| Gender | | | | 0.124 | 0.940 |
| Male ($n$ = 94) | 11 (26.19) | 68 (28.81) | 15 (28.85) | | |
| Female ($n$ = 236) | 31 (73.81) | 168 (71.19) | 37 (71.15) | | |
| GAD-7* | | | | 1.228 | 0.585 |
| Total < 10 ($n$ = 273) | 36 (92.31) | 194 (87.39) | 43 (84.31) | | |
| Total ≥ 10 ($n$ = 39) | 3 (7.69) | 28 (12.61) | 8 (15.69) | | |
| PHQ-9* | | | | 0.130 | 0.961 |
| Total < 10 ($n$ = 271) | 35 (89.74) | 194 (88.18) | 42 (87.50) | | |
| Total ≥ 10 ($n$ = 36) | 4 (10.26) | 26 (11.82) | 6 (12.50) | | |

*In the GAD-7 score, there were 18 missing values in the full sample, 3 missing values in AVS, 14 missing values in EVS, 1 missing value in CVS. In the PHQ-9 score, there were 23 missing values in the full sample, 3 missing values in AVS, 16 missing values in EVS, 4 missing values in CVS.

GAD-7 scores can be divided into three ranges: 5–9, 10–14, and 15–21, representing mild, moderate, and severe anxiety disorder, respectively.

The PHQ-9 is an important tool for assessing depression and its severity and is widely used for the screening of psychiatric disorders. A score of 10 or more exhibits good sensitivity and specificity (88% sensitivity, 85% specificity) (Levis et al., 2019, 2020). Therefore, a PHQ-9 score ≥10 was defined as depression in this study. PHQ-9 scores can be divided into four ranges: 5–9, 10–14, 15–19, and 20–27, representing mild, moderate, moderate-severe, and major depression, respectively.

## 2.7. Case data collection and processing

Collected information on the patient's general condition, type of vertigo symptoms, duration, precipitating factors, past medical history, concomitant symptoms, ancillary examinations, and disease diagnosis.

Under the guidance of specialists, patients completed the DHI questionnaire, the GAD-7 anxiety screening scale, and the PHQ-9 depression screening scale.

Two independent researchers reviewed and validated the completed questionnaires and entered the collected and organized data into the Epidate 3.1 database.

## 2.8. Data analysis

Data were imported into SPSS 22.0 statistical software for analysis. Descriptive statistic included mean and standard deviation (SD), and proportion. The *t*-test were used for analyzing measurement data, and the chi-square test and fisher's exact test were used for analyzing count data. The relationships between influencing factors were analyzed using multivariate ordered logistic regression analysis. Differences with $p < 0.05$ were considered statistically significant.

# 3. Results

The baseline characteristics of the vertigo patients are shown in **Table 1**.

The mean age of the 330 vertigo patients was 53.18 years (SD: 14.40 years), and 37.88% were aged ≥60 years. The male-to-female ratio of the patients was 1:2.51. Of these patients, 12.50% were anxious and 11.73% were depressed. With respect to syndrome typing, AVS accounted for 12.72%, EVS accounted for 71.52%, and CVS accounted for 15.76%. The mean DHI score was 43.36 (SD: 24.69), with 35.15% of mild disorder, 39.39% of moderate disorder, and 25.45% of severe disorder.

There was no significant differences in age structure, gender ratio, comorbid anxiety, or comorbid depression among patients with AVS, EVS, and CVS (**Table 2**).

The probability of presenting with anxiety and depression did not differ significantly among vertigo patients of different ages and genders (**Tables 3**, **4**).

TABLE 3 Combined anxiety in patients with vertigo of different ages and genders.

| | Full sample ($n$ = 312) | | $P$ | AVS ($n$ = 39) | | $P$ | EVS ($n$ = 222) | | $P$ | CVS ($n$ = 51) | | $P$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | GAD7 < 10 | ≥10 | | GAD7 < 10 | ≥10 | | GAD7 < 10 | ≥10 | | GAD7 < 10 | ≥10 | |
| Age | | | 0.894 | | | 1.000 | | | 0.945 | | | 1.000 |
| <60 | 172 (63.00) | 25 (64.10) | | 22 (61.11) | 2 (66.67) | | 126 (64.95) | 18 (64.29) | | 24 (55.81) | 5 (62.50) | |
| ≥60 | 101 (37.00) | 14 (35.90) | | 14 (38.89) | 1 (33.33) | | 68 (35.05) | 10 (35.71) | | 19 (44.19) | 3 (37.50) | |
| Gender | | | 0.704 | | | 0.127 | | | 0.930 | | | 1.000 |
| Male | 76 (27.84) | 12 (30.77) | | 7 (19.44) | 2 (66.67) | | 57 (29.38) | 8 (28.57) | | 12 (27.91) | 2 (25.00) | |
| Female | 197 (72.16) | 27 (69.23) | | 29 (80.56) | 1 (33.33) | | 137 (70.62) | 20 (71.43) | | 31 (72.09) | 6 (75.00) | |

Chi-square test was used to analysis for full sample and EVS, and Fisher's exact test was used to analysis for AVS and CVS.

TABLE 4 Combined depression in patients with vertigo of different ages and genders.

| | Full sample ($n$ = 307) | | $P$ | AVS ($n$ = 39) | | $P$ | EVS ($n$ = 220) | | $P$ | CVS ($n$ = 48) | | $P$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PHQ9 < 10 | ≥10 | | PHQ9 < 10 | ≥10 | | PHQ9 < 10 | ≥10 | | PHQ9 < 10 | ≥10 | |
| Age | | | 0.645 | | | 1.000 | | | 0.630 | | | 1.000 |
| <60 | 170 (62.73) | 24 (66.67) | | 21 (60.00) | 3 (75.00) | | 125 (64.43) | 18 (69.23) | | 24 (57.14) | 3 (50.00) | |
| ≥60 | 101 (37.27) | 12 (33.33) | | 14 (40.00) | 1 (25.00) | | 69 (35.57) | 8 (30.77) | | 18 (42.86) | 3 (50.00) | |
| Gender | | | 0.718 | | | 1.000 | | | 0.798 | | | 1.000 |
| Male | 75 (27.68) | 11 (30.56) | | 8 (22.86) | 1 (25.00) | | 55 (28.35) | 8 (30.77) | | 12 (28.57) | 2 (33.33) | |
| Female | 196 (72.32) | 25 (69.44) | | 27 (77.14) | 3 (75.00) | | 139 (71.65) | 18 (69.23) | | 30 (71.43) | 4 (66.67) | |

Chi-square test was used to analysis for full sample and EVS, and Fisher's exact test was used to analysis for AVS and CVS.

TABLE 5 Differences of anxiety in various forms of vertigo disorder.

| | Full sample ($n$ = 312) | | $P$ | AVS ($n$ = 39) | | $P$ | EVS ($n$ = 222) | | $P$ | CVS ($n$ = 51) | | $P$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | GAD7 < 10 | ≥10 | | GAD7 < 10 | ≥10 | | GAD7 < 10 | ≥10 | | GAD7 < 10 | ≥10 | |
| DHI Total | 40.99 ± 24.27 | 61.42 ± 22.75 | <**0.001** | 41.67 ± 26.84 | 56.67 ± 33.01 | 0.365 | 39.13 ± 23.57 | 59.11 ± 22.80 | <**0.001** | 48.93 ± 24.10 | 71.00 ± 18.94 | **0.018** |
| Physical | 13.37 ± 7.48 | 16.36 ± 7.33 | **0.020** | 13.83 ± 10.09 | 10.00 ± 9.17 | 0.529 | 12.85 ± 6.77 | 16.07 ± 7.35 | **0.021** | 15.35 ± 7.84 | 19.75 ± 5.29 | 0.135 |
| Emotional | 10.51 ± 9.25 | 20.36 ± 9.41 | <**0.001** | 9.67 ± 7.89 | 18.67 ± 12.22 | 0.075 | 10.05 ± 9.29 | 20.00 ± 9.11 | <**0.001** | 13.26 ± 9.82 | 22.25 ± 10.61 | **0.023** |
| Functional | 17.55 ± 11.37 | 26.15 ± 10.14 | <**0.001** | 18.17 ± 11.55 | 26.67 ± 12.86 | 0.231 | 16.55 ± 11.35 | 25.29 ± 10.92 | <**0.001** | 21.53 ± 10.66 | 29.00 ± 6.23 | 0.062 |

The bold values indicate mean $p < 0.05$, these values were considered statistically significant.



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TABLE 6 Differences of depression in various forms of vertigo disorder.

| | Full sample ($n$ = 307) | | $P$ | AVS ($n$ = 39) | | $P$ | EVS ($n$ = 220) | | $P$ | CVS ($n$ = 48) | | $P$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PHQ9 < 10 | ≥10 | | PHQ9 < 10 | ≥10 | | PHQ9 < 10 | ≥10 | | PHQ9 < 10 | ≥10 | |
| DHI Total | 41.28 ± 24.62 | 58.72 ± 23.69 | **<0.001** | 38.86 ± 25.59 | 77.50 ± 11.36 | **0.005** | 39.60 ± 24.09 | 53.00 ± 23.67 | **0.008** | 51.20 ± 24.50 | 71.00 ± 20.39 | 0.066 |
| Physical | 13.32 ± 7.57 | 17.00 ± 6.30 | **0.006** | 12.80 ± 10.07 | 20.00 ± 6.73 | 0.174 | 12.79 ± 6.89 | 15.92 ± 6.49 | **0.030** | 16.19 ± 7.74 | 19.67 ± 4.27 | 0.290 |
| Emotional | 10.92 ± 9.67 | 17.00 ± 9.90 | **<0.001** | 8.91 ± 7.25 | 23.00 ± 8.25 | **<0.001** | 10.64 ± 9.86 | 14.85 ± 9.25 | **0.041** | 13.90 ± 10.10 | 22.33 ± 11.41 | 0.066 |
| Functional | 17.81 ± 11.52 | 24.61 ± 10.46 | **<0.001** | 17.14 ± 11.15 | 33.50 ± 1.92 | **0.006** | 16.96 ± 11.61 | 22.23 ± 10.90 | **0.030** | 22.29 ± 10.54 | 29.00 ± 7.35 | 0.140 |

The bold values indicate mean $p < 0.05$, these values were considered statistically significant.

When patients with various forms of vertigo were analyzed, a significant difference in the total DHI score among all patients was found between those with and without anxiety ($P < 0.001$), and there were differences in physical symptoms ($P = 0.020$), emotional state ($P < 0.001$), and social functioning ($P < 0.001$). In EVS, there was a significant difference in total DHI score between those with and without anxiety ($P < 0.001$), and there were differences in physical symptoms ($P = 0.021$), emotional state ($P < 0.001$), and social functioning ($P < 0.001$). In CVS, there was a significant difference in total DHI score between those with and without anxiety ($P = 0.018$), which was primarily manifested in a difference in emotional state ($P = 0.023$) (Table 5).

When patients with various forms of vertigo were analyzed, a significant difference in the total DHI score among all patients was found between those with and without depression ($P < 0.001$), and there were differences in physical symptoms ($P = 0.006$), emotional state ($P < 0.001$), and social functioning ($P < 0.001$). In EVS, there was a significant difference in total DHI score between those with and without depression ($P = 0.008$), and there were differences in physical symptoms ($P = 0.030$), emotional state ($P = 0.041$), and social functioning ($P = 0.030$). In AVS, there was a significant difference in total DHI score between those with and without depression ($P = 0.005$), which was primarily manifested in difference in emotional state ($P < 0.001$) and social functioning ($P = 0.006$) (Table 6).

The relationship between each influencing factor and the severity of vertigo was determined using multivariate ordered logistic regression analysis (DHI "mild/moderate/severe" severity was the ordered classification outcome, model fit $p < 0.001$ indicated effective establishment of the regression equation, test of parallel lines $p = 0.776 > 0.05$ indicated equivalence to mild/moderate/severe). Age ≥60 or <60 years and gender had no statistically significant effects on the severity of vertigo.

Among all patients, patients with anxiety were 4.65 times more likely to have severe vertigo than patients without anxiety, and patients with depression were 3.49 times more likely to have severe vertigo than patients without depression.

Among AVS patients, anxiety and depression had no statistically significant effect on the severity of vertigo. Among EVS patients, patients with anxiety were 4.42 times more likely to have severe vertigo than patients without anxiety, and patients with depression were 3.58 times more likely to have severe vertigo than patients without depression. Among CVS patients, patients with anxiety were 5.83 times more likely to have severe vertigo than patients without anxiety, and depression had no statistically significant effect on the severity of vertigo (Table 7 and Figure 1).

## 4. Discussion

In recent years, comorbid psychological and physical symptoms in vertigo patients has gained interest among clinicians. The coexistence of vestibular and psychiatric disorders has been repeatedly described in the literature (Best et al., 2009; Lahmann et al., 2015; Limburg et al., 2018; Bronstein and Dieterich, 2019; Toupet et al., 2019; Özdilek et al., 2019; Kısabay Ak et al., 2022), with anxiety and depression cited as the primary factors. Many

TABLE 7 Influence of various factors on vertigo degree in patients with different vestibular syndromes.

| | Full sample ($n$ = 330) | | AVS ($n$ = 42) | | EVS ($n$ = 236) | | CVS ($n$ = 52) | |
|---|---|---|---|---|---|---|---|---|
| | *OR* | *P* | *OR* | *P* | *OR* | *P* | *OR* | *P* |
| Age | 0.999 (0.66, 1.51) | 0.996 | 0.63 (0.20, 1.997) | 0.435 | 1.05 (0.64, 1.72) | 0.851 | 1.13 (0.41, 3.14) | 0.809 |
| Gender | 1.14 (0.73, 1.78) | 0.560 | 1.63 (0.44, 6.07) | 0.463 | 1.29 (0.76, 2.18) | 0.346 | 0.60 (0.19, 1.85) | 0.373 |
| GAD-7 | **4.65 (2.40, 9.03)** | **<0.001** | 4.45 (0.44, 45.19) | 0.206 | **4.42 (2.04, 9.58)** | **<0.001** | **5.83 (1.03, 33.04)** | **0.047** |
| PHQ-9 | **3.49 (1.79, 6.82)** | **<0.001** | –[#] | –[#] | **3.58 (1.19, 5.57)** | **0.016** | 3.32 (0.54, 20.53) | 0.198 |

[#]The value is abnormality. The bold values indicate mean $p < 0.05$, these values were considered statistically significant.

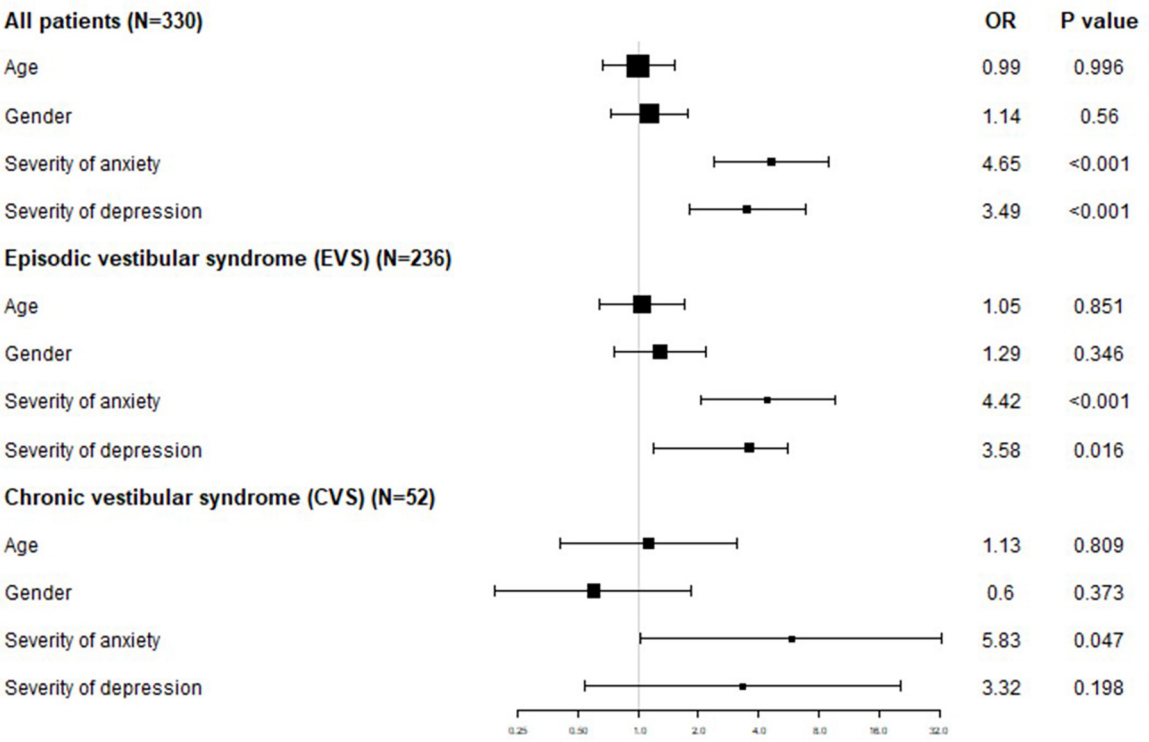


FIGURE 1
Influence of age, gender, anxiety, and depression on vertigo degree.

studies have reported a significantly higher prevalence of comorbid peripheral vertigo and anxiety and depression than in the general population (Brandt and Dieterich, 2020). Kim et al. (2016) found a higher prevalence of psychiatric disorders such as depression and generalized anxiety in patients with BPPV compared to the general population (Kozak et al., 2018). A prospective study by Özdilek et al. (2019) showed that Beck Anxiety Inventory (BAI) scores were higher in patients with BPPV than in control individuals, indicating higher levels of anxiety in patients with BPPV. Psychological symptoms such as anxiety and depression are common in patients with vertigo regardless of its primary cause (Ketola et al., 2015; Zhai et al., 2016; Limburg et al., 2018; Balci and Akdal, 2020; Kısabay Ak et al., 2022). Our study suggests that the association between vertigo and anxiety and depression is very strong. In our sample, 12.50% of vertigo patients had comorbid anxiety and 11.73% of vertigo patients had comorbid depression.

The potential mechanisms underlying the connection between vertigo and psychiatric disorders remain unclear. Neural circuits associated with the vestibular nervous system and psychiatric disorders such as anxiety and depression have been found to be interrelated (Bednarczuk et al., 2018; Bronstein and Dieterich, 2019; Decker et al., 2019; Toupet et al., 2019; Brandt and Dieterich, 2020), and there is growing evidence to support that psychological factors influence vertigo episodes and response to treatment in a complex manner (Bigelow et al., 2016; Wei et al., 2018; Brandt and Dieterich, 2020; Ogihara et al., 2022). Two large-scale, population-based retrospective studies have confirmed that patients with anxiety and depression have a higher risk of developing BPPV than healthy individuals, with hazard ratios of 2.52 and 1.79, respectively (Chen et al., 2016; Hsu et al., 2019). Bronstein and Dieterich (2019) found that the long-term prognostic outcome of vestibular neuritis is largely dependent on psychophysiological and psychological factors. Ogihara et al. (2022) suggest that psychological factors may influence the rehabilitation of vestibular balance disorders, leading to long-term vertigo or dizziness. Anxiety and depression can significantly reduce the efficacy of the initial canalith repositioning

treatment in patients with BPPV and lead to a pronounced risk of relapse within 6 months after treatment (Wei et al., 2018). Kısabay Ak et al. (2022) investigated risk factors for reduced treatment response in patients with comorbid anxiety and depressive VM, and found that VM patients who do not respond to prophylactic medication should be examined for the presence of comorbid psychiatric disorders and additional treatment strategies should be implemented. Monzani et al. (2006) found that BPPV patients had significantly higher rates of negative life events, objective negative affect and poor control, anxiety, depression, somatization levels, and obsessive-compulsive attitudes than controls in the year prior to the vertigo episode, suggesting that emotional stress may be a trigger for vestibular dysfunction. A prospective study found that the probability of RD increased with increasing DHI-E scores and that mood disorders may be an important risk factor for RD (Martellucci et al., 2016). The consensus diagnostic criteria for PPPD formulated by the Bárány Society state that anxiety and depression are risk factors for PPPD (Staab et al., 2017). In this study, we found that patients with comorbid anxiety or depression exhibited more severe vertigo and impacts on somatic symptoms, emotional state, and social function than patients without anxiety and/or depression. Multivariate ordered logistic regression analysis showed that comorbid anxiety or depression was an important risk factor that could significantly exacerbate vertigo. When different types of vestibular syndrome were analyzed separately, the association between EVS and anxiety or depression was most pronounced, with EVS exacerbated by either anxiety or depression. In patients with CVS, anxiety also significantly exacerbated vertigo, consistent with the results of many studies (Morimoto et al., 2019; Toupet et al., 2019). Depression had no significant effect on the degree of vertigo in patients with AVS and CVS in the present study, although of course the effect of anxiety and depression on the severity of these two types of vertigo may not be reflected due to the small number of cases of AVS and CVS patients in the study.

Age is one of the principal risk factors for development of both vestibular syndrome and psychological disorders (Maarsingh et al., 2010). However, there was no significant difference in comorbid anxiety or depression between patients with vertigo of different ages (60 years and older compared with those under 60 years) in the present study. Dietzek et al. (2018) analyzed 650 patients with chronic vertigo who underwent multimodal vestibular rehabilitation and found that anxiety-related scores were lower in older patients over 65 years of age compared to young and middle-aged adults, and concluded that older adults are affected primarily by physical deficits and anxiety and other psychological factors are less influential. It was previously reported that female patients with vertigo are more likely to experience anxiety and depression than male patients, and that the degree of anxiety and depression in female patients is higher than in male patients. This may be associated with differences in brain structure and function between males and females (Asher and Aderka, 2018; Lindell et al., 2022). In the present study, the probability of anxiety and depression did not differ by gender among vertigo patients. This differs from previous studies and may be related to the small sample size of the present study; future studies will focus on large, multi-center samples of vertigo patients.

## 5. Limitation

This study compared the psychological factors of AVS, EVS, and CVS in patients with vestibular syndrome. In the same type of vertigo syndrome, the psychological manifestations of each classified diagnosis disease may differ, especially in EVS. In this study, the statistical analysis among classified diseases was limited due to the small number of cases in a few classified diseases. Also, the psychological status of different diagnosed diseases in the same syndrome was not studied extensively. In future studies, we will conduct more in-depth research and improve on this.

## 6. Conclusion

In this study, age and gender were not major contributors to a more severe course of vestibular syndromes. Instead, anxiety and depression were found to play a more prominent role. However, the comorbidity of anxiety and depression in patients with vertigo is often overlooked in clinical practice, which exacerbates subjective disability and diminishes patients' quality of life. This highlights a crucial insight into managing vertigo: conducting a standardized psychological screening at the outset of treatment can effectively identify patients with comorbid anxiety/depression or other psychological factors, enabling the targeted implementation of psychological interventions. In this regard, scales such as GAD-7/PHQ-9 are valuable tools for rapidly screening patients with vertigo. Also, it is necessary to develop and implement a new screening tool that can assess more accurately the psychological distress experienced by patients with vertigo.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by the Medical Research Ethics Committee of the First Affiliated Hospital of China Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## Author contributions

SF designed the research. SF and JZ drafted the manuscript. JZ modified the manuscript. Both authors have read and approved to the final version of the manuscript.

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## Conflict of interest

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

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1208392/full#supplementary-material

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# Increased roll tilt thresholds are associated with subclinical postural instability in asymptomatic adults aged 21 to 84 years

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**Background:** Balance assessments that intentionally alter the reliability of visual and proprioceptive feedback (e.g., standing on foam with eyes closed) have become a standard approach for identifying vestibular mediated balance dysfunction in older adults. However, such assessments cannot discern which specific element of the vestibular system (e.g., semicircular canal, otolith, or combined canal-otolith) underlies the observed age-related changes in balance performance. The present study was designed to determine the associations between specific sources of vestibular noise and quantitative measures of quiet stance postural control measured during standard "vestibular" balance conditions.

**Methods:** A group of 52 asymptomatic adults (53.21 ± 19.7, 21 to 84 years) without a history of vestibular or neurologic disorders volunteered for this study. We measured a battery of five vestibular perceptual thresholds that assay vestibular noise with predominant contributions from the vertical canals, lateral canals, utricles, saccules, and the centrally integrated canal-otolith signal. In addition, participants completed two standard balance assessments that were each designed to prioritize the use of vestibular cues for quiet stance postural control—eyes closed on foam (Condition 4 of the Modified Romberg Balance Test) and eyes closed, on a sway referenced support surface (Condition 5 of the Sensory Organization Test).

**Results:** In age adjusted models, we found strong positive associations between roll tilt vestibular thresholds, a measure of noise in the centrally integrated canal-otolith signal, and the root mean square distance (RMSD) of the anteroposterior and mediolateral center of pressure (CoP) captured during eyes closed stance on a sway referenced support surface. The strength of the association between roll tilt thresholds and the RMSD of the CoP was between 3-times and 30-times larger than the association between postural sway and each of the other vestibular thresholds measured.

**Conclusion:** We posit that noise in the centrally estimated canal-otolith "tilt" signal may be the primary driver of the subclinical postural instability

experienced by older adults during the "vestibular" conditions of balance assessments. Additional testing in adults with clinical balance impairment are needed to identify if roll tilt thresholds may also serve as a surrogate metric by which to detect vestibular mediated balance dysfunction and/or fall risk.

KEYWORDS

vestibular, Aging, balance, postural control, vestibular threshold, perception

# Introduction

When standing on a solid surface in a well-lit room, sensory feedback from the visual system, lower extremities, and vestibular system each provide information used to minimize postural sway (Forbes et al., 2018). Distal proprioceptive cues from the lower extremities provide feedback about body sway relative to a reference frame defined by the surface upon which a person is standing, whereas visual cues are referenced to the visual environment. The vestibular system instead senses changes in head motion relative to a constant reference frame defined by gravity (Goldberg et al., 2012; Wolfe et al., 2021). As a result, balance tests can measure postural control under the presumed reliance upon the unperturbed vestibular inputs by modifying the testing environment to manipulate the veracity of visual (e.g., blindfold or moving visual scene) and support surface (e.g., standing on foam) cues. The observations of marked instability in patients with known vestibular lesions (Fetter et al., 1991) have made such assessment techniques a standard approach for identifying balance dysfunction mediated by impaired vestibular sensation (Nashner et al., 1982; Nashner and Peters, 1990; Horak, 2009; Wagner et al., 2021a), including in older adults.

In a large nationally representative sample of adults above 40 years of age, Agrawal and colleagues showed that the inability to stand on a foam pad (altering the reliability of proprioceptive cues) with eyes closed (removing visual cues) was associated with a significant increase in the likelihood of reporting a difficulty with falls (Agrawal et al., 2009). While these data strongly point to the vestibular system as being at least one of the primary contributors to age-related imbalance, balance assessments cannot isolate the influences of individual vestibular modalities on postural control. The vestibular system as a whole is often inextricably linked to balance, however, the peripheral vestibular system encapsulates ten individual sensors (three semicircular canals and two otolith organs in each ear) that collectively allow us to sense and respond to tilts, translations, and rotations of the head in the three-dimensions of space (Wolfe et al., 2021). Due to limited specificity of "vestibular" balance tests, the specific element of the vestibular sensory apparatus that leads to the observed age-related declines in balance is largely unknown.

Past attempts to define the specific contributions of the vestibular system to age-related imbalance have used clinical vestibular assays designed to probe the integrity of specific vestibular reflex pathways. However, the interpretation of correlations between these assessments and postural control measures are limited by (1) the reliance upon sensorimotor outcomes to indirectly infer sensory function and (2) fundamental differences in the methodologies used to probe function of the otoliths (e.g., vestibular evoked myogenic potentials) compared to the semicircular canals (vestibulo-ocular reflex) (see (Wagner et al., 2021a) for a review on this topic). The present study was designed to fill this gap by using a common experimental methodology—vestibular perceptual thresholds—to determine the relative associations between each aspect of the vestibular system (e.g., semicircular canals, otoliths, and the combined canal-otolith signal) and quiet stance postural control measured during traditional "vestibular" balance conditions.

Vestibular thresholds represent a behavioral assay of sensory noise (or conversely sensory precision) and are defined as the smallest motion stimulus that a person can reliably perceive when moved in a specific motion plane (e.g., rotation, tilt, or translation) known to preferentially excite a vestibular end organ (e.g., semicircular canals or otoliths) (Merfeld, 2011; Kobel et al., 2021b). Secondary to the closed loop nature of quiet stance postural sway (Peterka, 2002; Maurer and Peterka, 2005; Cenciarini and Peterka, 2006; van der Kooij and Peterka, 2011; van Kordelaar et al., 2018), we hypothesized that individuals with increased vestibular thresholds (i.e., greater sensory noise) would show greater variability (i.e., imprecision) in postural sway.

A previously published dataset in young adults showed a specific correlation between mid-frequency (i.e., 0.5 Hz) roll tilt vestibular thresholds and quiet stance postural sway during an eyes closed, on foam balance task (Wagner et al., 2021c). Similarly, roll tilt thresholds have been shown to correlate with the likelihood of being able to complete (i.e., stand for 30 s) the same eyes closed on foam balance task in a sample of adults over the age of 40 (Bermúdez Rey et al., 2016). Given these findings, alongside the presumed necessity to precisely estimate dynamic head in space orientation during quiet stance sway, we hypothesized that 0.5 Hz roll tilt vestibular thresholds—quantifying the precision in perceptual estimates of dynamic head-in-space orientation, and reflecting noise in the centrally integrated canal-otolith signal—would display the strongest correlation with quiet stance postural sway in conditions that remove vision and provide unreliable proprioceptive cues.

# Materials and methods

## Recruitment and study procedures

A total of fifty-four participants were recruited from The Ohio State University, as well as from surrounding regions of

central Ohio. We recruited individuals within each of three age ranges: 18–39, 40–64, and 65–89 years of age. The delineation between young and middled aged adults was made based upon prior data showing an increase in vestibular thresholds beginning at age 40 (Bermúdez Rey et al., 2016). The designation of older adults as those participants ≥ 65 years of age was made based upon the definition adopted by the American Medical Association (Lundebjerg et al., 2017). Prior to enrollment, each participant completed questionnaires pertaining to their overall health and medical history. The responses provided were reviewed by a vestibular audiologist to identify the presence of any conditions that may impact balance or vestibular assessments. Participants were excluded if they reported having a neurologic disorder, vestibular disorder (excluding resolved BPPV), recent surgery, uncorrected visual impairment, diabetes, or a recent orthopedic injury (<6 months). In addition, due to mechanical constraints of the motion platform, a weight limit of 250 pounds was used for inclusion in the study. We also screened for the presence of frailty using the PRISMA-7; a score of < 3 was required for inclusion in the study (Dent et al., 2016). Given the attentional demands of perceptual threshold testing, as well as a previously identified association between cognitive impairment and balance (Semenov et al., 2016), we also screened for mild cognitive impairment (MCI) and possible undiagnosed dementia using the Self-Administered Gerocognitive Examination (SAGE) (Scharre et al., 2010). A cut off score of 16 or greater was used for inclusion in this study (Scharre et al., 2010).

Testing was broken up into 2 days (2–2.5 h each day) and each participant was compensated monetarily for their time spent in the lab. Threshold assessments and the instrumented Modified Romberg Balance Test (MRBT) were performed on the same day in a single session. We used a standard four condition MRBT protocol. The four MRBT conditions are illustrated in **Supplementary Figure 1**. To mitigate the effects of fatigue, the sensory organization test (SOT) was performed on a separate day. We used a standard six-condition SOT protocol. The six SOT conditions are also illustrated in **Supplementary Figure 1**. Additional tests of postural control were also collected during the second visit, and are reported in detail within the doctoral thesis of the lead author (Wagner, 2023). Within this published thesis, alternative analyses of the present data can also be found (Wagner, 2023). The study protocol was approved by the Ohio State University Institutional Review Board and each participant provided informed consent.

## Vestibular perceptual thresholds

Vestibular perceptual thresholds were measured using a direction recognition task, that we (Grabherr et al., 2008; Valko et al., 2012; Bermúdez Rey et al., 2016; Kobel et al., 2021a; Wagner et al., 2021c, 2022a,b), and others (MacNeilage et al., 2010; Crane, 2016; Keywan et al., 2020; Karmali et al., 2021) have used extensively to quantify vestibular precision. Motion stimuli were delivered using a MOOG (Aurora, NY) six degree of freedom (6DOF) motion platform. Participants were seated in a custom-built chair rigidly fixed to the motion platform. The head was restrained in a motorcycle helmet which was also rigidly mounted to the platform; this allowed for the motions of the head to be coupled to the platform, and for the participant to be moved en bloc (i.e., no motion at the cervical spine). All testing took place in a dark (light tight) room to remove the influence of visual motion cues. In addition, insert headphones were used to provide (1) passive sound attenuation (∼20 dB sound pressure level (SPL)) and (2) binaural white noise (at ∼60 dB SPL) during each test motion.

For each threshold assessment, the participant was asked to indicate (using buttons in either hand) the perceived direction of motion (e.g., right vs. left). Each test consisted of 100 trials of a single motion profile (e.g., roll tilt) and the stimuli were adjusted using an adaptive 4-Down, 1-Up (4D1U) staircase procedure, with the step sizes determined using PEST rules (Leek, 2001). The motion stimulus used for each test was a single cycle of sinusoidal acceleration [$a(t) = A \sin(2\pi f t)$] with the frequency of the motion being reflected by the inverse of the cycle duration (e.g., 2 Hz motion = 0.5 s per cycle). This yields a motion where the peak velocity [$v = AT/\pi$] and displacement [$d = AT^2/2\pi$] are each proportional to acceleration (A) (Grabherr et al., 2008). In the present study, five distinct vestibular thresholds were measured (**Figure 1**):

(1) 1 Hz y-translation (sliding horizontally left or right) targeting the utricles (Fernandez and Goldberg, 1976; Valko et al., 2012; Kobel et al., 2021a).
(2) 1 Hz z-translation (sliding vertically up or down) targeting the saccules (Fernandez and Goldberg, 1976; Valko et al., 2012; Kobel et al., 2021a).
(3) 2 Hz RALP (right-anterior left-posterior) tilt (tilting the head forward and to the right or backward and to the left) targeting the vertical canals (Suzuki et al., 1964; Wagner et al., 2022a).
(4) 0.5 Hz roll tilt (tilting the head left or right in the coronal plane) targeting central canal-otolith integration (Angelaki et al., 2000, 2004; Angelaki and Yakusheva, 2009; Lim et al., 2017; Wagner et al., 2022a).
(5) 2 Hz yaw rotation (rotating in the horizontal plane about an earth vertical axis) targeting the lateral canals (Grabherr et al., 2008; Valko et al., 2012; Cousins et al., 2013; Priesol et al., 2014).

For each individual condition, the binary response data and stimulus magnitudes were fit to a Gaussian cumulative distribution function and the vestibular threshold parameter was estimated from a bias reduced generalized linear model (Chaudhuri et al., 2013). In the absence of bias, the "one-sigma" threshold parameter represents the stimulus magnitude that would be expected to, on average, yield an accuracy of 84.1%. A delete one jackknife approach was used to detect and remove attentional lapses during each threshold assessment (Clark and Merfeld, 2021).

## Quiet stance balance

Center of pressure (CoP) data were collected during two standard quiet stance balance assessments, the MRBT and SOT. The two primary sway measures were collected from the two conditions that each involved standing quietly with vision removed, and with the support surface cues made to be unreliable—MRBT-4 and 2D-SOT-5. Condition 4 of the modified Romberg balance test (MRBT-4) was performed with the eyes closed and while standing atop a medium density (5 lbs./ft3) foam pad of the dimensions

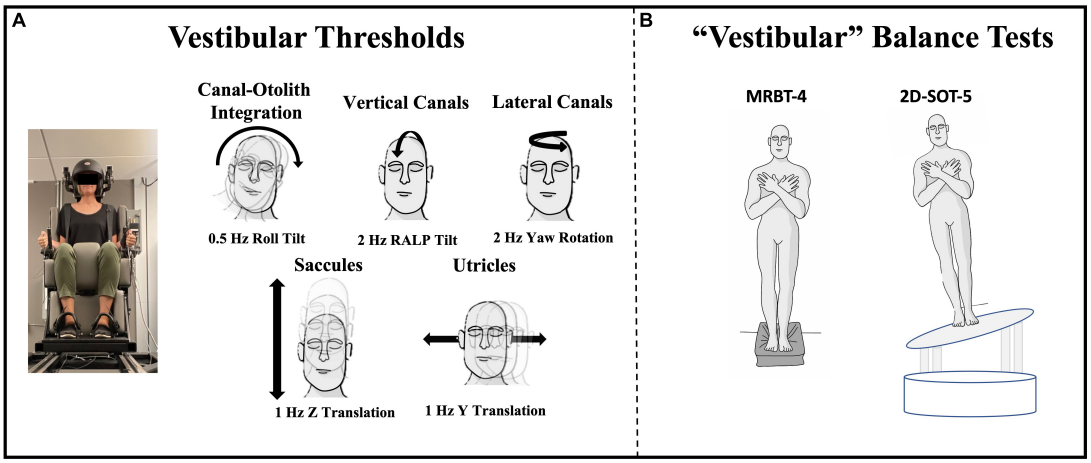


FIGURE 1
Vestibular threshold motions and the two quiet stance balance conditions focused upon herein are shown. **(A)** Each vestibular threshold was measured using a direction recognition task, with motion stimuli delivered using a MOOG 6DOF motion platform. Motion profiles of a specific trajectory and frequency were used to identify measures of noise with primary contributions from each vestibular end-organ or end-organ pair. Black arrows show the plane of motion for each threshold. **(B)** Center of pressure data were collected from force plates during condition 4 of the Modified Romberg Balance Test (MRBT-4; eyes closed, on foam) and a modified condition 5 of the Sensory Organization Test (2D-SOT-5; eyes closed, on a support surface sway referenced in both ML and AP planes) (Wagner and Merfeld, 2023).

16" × 18" × 3' (SunMate, Leicester, North Carolina). Stance was maintained for 67 s. During each trial, ambient auditory cues were mitigated using over the ear, active noise cancelling headphones (Bose Quiet Comfort II, Framingham, MA) with approximately 60 dB SPL of white noise added. Participants stood with their arms crossed at the chest and their feet positioned such that the medial borders of each foot were touching. CoP data were collected at 100 Hz from a triaxial AMTI force plate (Watertown, MA).

A modified condition 5 of the Sensory Organization Test (2D-SOT-5) was administered using a Virtualis MotionVR (Perols, Herault, France) motion platform. Participants stood with eyes closed and with the support surface sway referenced in both the mediolateral and anteroposterior directions (Wagner and Merfeld, 2023). CoP data were recorded at 90 Hz from two tri-axial force plates embedded within the platform. As in the MRBT-4, participants stood with their arms folded across the chest, with a narrow base of support, and were instructed to stand as still as possible. Active noise cancelling headphones were also worn throughout the SOT assessment. Consistent with the standard SOT procedures, three trials of 20 s each were completed, rather than a single trial of 67 s. In addition to the primary outcomes derived from performance on 2D-SOT-5 and MRBT-4, the remainder of the MRBT and SOT test conditions (**Supplementary Figures 1**, **2**) were analyzed as secondary variables.

The raw CoP data from each balance assessment were processed off-line using a custom script written in Matlab (v2020a, Natick, MA). The CoP data were low pass filtered using a 4th order zero-phase-lag digital filter (filtfilt.m; MATLAB, Natick MA) with a 25 Hz cut off. The primary outcome measure, the root mean square distance (RMSD), was calculated by taking the standard deviation of the filtered and zero-meaned CoP signal for both the medio-lateral (ML) and anterior-posterior (AP) planes. To remove transient responses, the first 7 s of the MRBT trial was removed prior to the calculation of the RMSD and for the SOT, the median of the three trials was used.

## Statistical analysis

Vestibular perceptual thresholds have previously been shown to display a log normal distribution. Consistent with several past studies (Grabherr et al., 2008; Bermúdez Rey et al., 2016; Kobel et al., 2021a; Wagner et al., 2022a), each of the vestibular thresholds showed a lognormal distribution and were transformed prior to the analysis described below. Age effects were described using linear regression models with the regression coefficients extrapolated to estimate the percent change in thresholds per decade. Based on previous studies (Bermúdez Rey et al., 2016; Karmali et al., 2017; Beylergil et al., 2019; Wagner et al., 2021c), our *a priori* hypothesis was that roll tilt thresholds would positively correlate with sway (i.e., larger roll tilt thresholds would correlate with greater sway). Nonetheless, since none of the prior studies had quantified the relative strength of the associations between different thresholds and quantitative measures of postural sway, multivariable regression models were used to determine the association between each threshold measure and the RMSD of the CoP measured during MRBT-4 and 2D-SOT-5, while controlling for the effects of age. This was repeated for the both the ML and AP RMSD values. Postural sway data were only analyzed for those participants who were able to complete the individual test conditions without a loss of balance ($N$ = 47 in MRBT-4 and $N$ = 51 in 2D-SOT-5). Additionally, in five out of the twenty older adult participants, RALP tilt thresholds could not be collected due to the psychophysical staircase exceeding the displacement limits of the motion device. Since these data were not missing at random, we did not impute values to replace the missing data points. Instead, the association with RALP tilt thresholds was restricted to univariable regression analysis. The total sample size included in each analysis can be found within each table that follows.

Univariable linear regression models were used to characterize the association between each threshold measure and the RMSD of postural sway, both with and without adjusting for the effects of age. To account for the number of comparisons (twenty in total), and to also mitigate Type II errors inherent to Bonferroni correction (Perneger, 1998), the Benjamini-Hochberg False Discovery Rate method (FDR) was used to account for multiple comparisons (Benjamini and Hochberg, 1995). This method ranks the *p*-values from smallest to largest, and then sets a critical value based upon an acceptable level of error (0.05 or 5%), the rank of a given *p*-value (m), and total number of comparisons being made (*N*) (Critical Value = 0.05 * (m/*N*)) (Benjamini and Hochberg, 1995). Each *p*-value was compared to the critical value to determine statistical significance; the reported *p*-values are corrected using the same approach [*p* x (*N*/m)]. In addition to the primary analysis, separate age-adjusted univariable regression models were run to investigate the linear association between each threshold and the secondary sway outcomes (AP and ML RMSD) captured from the remaining conditions of the MRBT and SOT.

# Results

## Sample characteristics

We measured vestibular perceptual thresholds and quiet stance balance in a sample of 52 healthy adults between the ages of 21 and 84 (Mean = 53.21, SD = 19.7) (**Table 1**). Two of the 54 enrolled participants completed half of the test battery but did not return for the second session. The final sample ($N$ = 52) included 17 young adults aged 18 to 39 ($N$ = 17, Mean = 29.65, SD = 5.42, Range = 21 to 37), 15 middle aged adults aged 40 to 64 ($N$ = 15, Mean = 52.07, SD = 6.02, Range = 44 to 64), and 20 older adults aged 65 and older ($N$ = 20, Mean = 74.1, SD = 5.78, Range = 66 to 84). One older adult reported a remote history of BPPV but denied any current symptoms of positional vertigo; otherwise, no participants reported a history of vestibular or neurological disorders. Each individual lived independently in the community and ambulated into the research lab without use of an assistive device. In addition, none of the participants were found to be at risk for frailty based upon the PRISMA-7 (< 3) (Dent et al., 2016) and 51/52 of the participants scored above the cut off for MCI on the SAGE (Scharre et al., 2010) (Mean = 21.06, SD = 1.48, Range = 16 to 22); the total SAGE score for one participant was not available.

## Effect of age on vestibular thresholds

Age showed a significant positive linear relationship with each of the vestibular thresholds surveyed in this study, except for yaw rotation. Per decade, we found a 30.30% increase in the geometric mean of Z-translation thresholds ($p < 0.0001$), a 23.60% increase in Y translation thresholds ($p < 0.0001$), a 14.8% increase in roll tilt thresholds ($p < 0.001$), and a 22.9% increase in RALP tilt thresholds ($p < 0.0001$). For yaw rotation thresholds we saw only a trend toward a significant association with age (9.39% per decade, $p = 0.09$).

## Associations between vestibular thresholds and postural sway in 2D-SOT-5

In multivariable regression models ($N$ = 51), roll tilt perceptual thresholds showed significant positive associations with the ML (β = 6.77, $p = 0.0093$) and AP (β = 7.88, $p < 0.0001$) RMSD of the CoP when controlling for age and each of the remaining vestibular thresholds (**Table 2**). Yaw rotation thresholds also showed a weak, but significant, negative association with the AP RMSD (β = -2.64, $p = 0.026$). In each model, roll tilt thresholds showed the strongest association with the RMSD of the ML and AP RMSD ($\beta_{stand}$ = 0.501 and 0.737 respectively) (**Table 2**). In the unadjusted univariable regression models (i.e., age excluded from each of these univariable models), roll tilt thresholds showed significant positive associations with the RMSD of ML (β = 6.33, $R^2 = 0.22$, $p = 0.0035$) and AP (β = 5.64, $R^2 = 0.28$, $p = 0.001$) CoP (**Figures 2**, **3**). Z-translation (β = 3.43, $R^2 = 0.16$, $p = 0.021$) thresholds also showed a significant positive association with the ML RMSD of the CoP in 2D-SOT-5. None of the remaining thresholds showed a significant association with either the ML or AP RMSD in the uncontrolled regression models (**Table 3**). After including age as a covariate in each model, only roll tilt thresholds continued to show a significant positive association with the ML (β = 5.90, $p = 0.023$) and AP RMSD (β = 6.34, $p = 0.001$) of the CoP.

## Associations between vestibular thresholds and postural sway in MRBT-4

In the multivariable analysis of the 47 adults who completed the MRBT-4 balance test, none of the individual thresholds showed a significant association with the RMSD of the ML or AP CoP (**Table 4**). Compared to the individual effects of each threshold, age showed the strongest association with ML and AP postural sway in the multivariable models ($\beta_{stand}$ = 0.407 and 0.318 respectively) (**Table 4**). In the non-age adjusted univariable linear regression models, roll tilt (β = 3.28, $R^2 = 0.16$, $p = 0.040$) and z-translation thresholds (β = 2.72, $R^2 = 0.25$, $p = 0.006$) each showed significant positive associations with the ML RMSD of the CoP in the "eyes closed, on foam" condition (**Figures 4**, **5**). For the AP RMSD no significant associations were found (**Table 5**). When age was included as a covariate, none of the five vestibular thresholds showed a significant association with either the ML or AP RMSD of the CoP ($p > 0.05$).

## Associations between vestibular thresholds and sway during alternative balance conditions

In the secondary analysis of the CoP data captured from conditions 1-3 of the MRBT (**Supplementary Figure 1**) and conditions 1-4 and 6 of the SOT (**Supplementary Figure 2**), none of the threshold measures showed significant associations with the CoP RMSD in age adjusted regression models. Consistent with the analysis of the primary outcome variables, the strongest

TABLE 1 Demographic data and descriptive statistics (Mean ± 1 SD) are shown for the primary variables of interest.

| | Young adult | Middle aged | Older adult | Total |
|---|---|---|---|---|
| *N* (Female) | 17 (9) | 15 (11) | 20 (13) | 52 (33) |
| Age | 29.65 ± 5.42 | 52.07 ± 6.02 | 74.1 ± 5.78 | 52.81 ± 20.20 |
| ML MRBT-4 RMSD (mm) | 10.74 ± 3.65 | 13.39 ± 4.13 | 15.36 ± 2.99 | 13.06 ± 4.04 |
| AP MRBT-4 RMSD (mm) | 11.14 ± 4.33 | 12.51 ± 3.54 | 14.46 ± 5.10 | 12.64 ± 4.49 |
| ML 2D-SOT-5 RMD (mm) | 23.03 ± 7.24 | 25.66 ± 3.46 | 27.18 ± 7.70 | 25.35 ± 6.68 |
| AP 2D-SOT-5 RMD (mm) | 15.54 ± 6.10 | 17.24 ± 3.31 | 17.79 ± 5.77 | 16.88 ± 5.28 |
| Roll tilt threshold (°/s) | 0.82 ± 0.27 | 1.11 ± 0.56 | 1.64 ± 0.96 | 1.22 ± 0.76 |
| RALP tilt threshold (°/s) | 0.63 ± 0.26 | 0.93 ± 0.33 | 1.91 ± 1.18* | 1.13 ± 0.88 |
| Yaw rotation threshold (°/s) | 0.67 ± 0.30 | 1.21 ± 1.16 | 1.07 ± 0.55 | 0.98 ± 0.75 |
| Z translation threshold (cm/s) | 1.59 ± 0.88 | 2.88 ± 1.48 | 6.01 ± 3.03 | 3.66 ± 2.83 |
| Y translation threshold (cm/s) | 0.66 ± 0.40 | 0.78 ± 0.28 | 2.19 ± 2.33 | 1.28 ± 1.62 |

Due to falls, data were only available for $N = 47$ subjects for MRBT-4 and $N = 51$ subjects for 2D-SOT-5. In addition, RALP tilt thresholds could not be collected in 5 older adults due to the staircase surpassing the limits of the motion device. Threshold values are shown in original units, however data were log transformed prior to performing the statistical analysis. AP, anteroposterior; ML, mediolateral; RALP, right-anterior; left-posterior; MRBT, Modified Romberg Balance Test; RMSD, root mean square distance.

TABLE 2 Results of multivariable linear regression models for test condition 2D-SOT-5 ($N = 51$).

| | β | SE | *t* | *p* | β stand |
|---|---|---|---|---|---|
| 2D-SOT-5: Mediolateral CoP RMSD | | | | | |
| **Roll tilt** | **6.77** | **2.49** | **2.72** | **0.0093** | **0.501** |
| **Yaw rotation** | **−1.50** | **1.57** | **−0.96** | **0.344** | **−0.128** |
| Y translation | −2.41 | 1.51 | −1.59 | 0.118 | −0.272 |
| Z translation | 1.07 | 1.87 | 0.57 | 0.571 | 0.123 |
| Age | 0.047 | 0.073 | 0.64 | 0.526 | 0.136 |
| 2D-SOT-5: Anteroposterior CoP RMSD | | | | | |
| **Roll tilt** | **7.88** | **1.81** | **4.35** | **<0.0001** | **0.737** |
| Yaw rotation | −2.64 | 1.14 | −2.31 | 0.026 | −0.284 |
| Y translation | −1.99 | 1.10 | −1.81 | 0.076 | −0.284 |
| Z translation | −0.20 | 1.36 | −0.15 | 0.885 | −0.029 |
| Age | 0.021 | 0.053 | 0.39 | 0.699 | 0.076 |

Standardized β values represent the amount of change in the response variable for a one standard deviation change in the predictor variable. Statistically significant ($p < 0.05$) variables are bolded. 2D-SOT-5 = A modified condition 5 of the Sensory Organization Test (eyes closed, on a support surface sway referenced in both ML and AP planes).

associations observed were between roll tilt thresholds and postural sway, and, to a lesser extent, z-translation thresholds and postural sway (**Supplementary Figure 3**).

# Discussion

In support of our primary hypothesis, we showed that 0.5 Hz roll tilt perceptual thresholds, reflecting noise in the centrally integrated canal-otolith roll tilt signal, displayed the strongest association with quiet stance postural control in the "vestibular" balance conditions that removed visual feedback and provided unreliable proprioceptive feedback (MRBT-4 and 2D-SOT-5). The specific association between roll tilt perceptual thresholds and the RMSD of the CoP signal, a measure of sway variability, suggests that imprecision (or noise) in the dynamic estimation of head in space orientation is associated with increased noise in the sensorimotor output of the postural control system. Below we discuss these findings in the context of the available literature, as well as provide a putative mechanistic explanation for the identified link between roll tilt perceptual thresholds and quiet stance postural sway.

## Comparison to past findings

Our findings are consistent with previously published data comparing perceptual thresholds to a categorical measure of "pass/fail" balance in condition 4 of the MRBT (i.e., eyes closed, on foam). Bermudez-Rey and colleagues showed that 0.2 Hz roll tilt thresholds (1) were a strong predictor of the ability to complete (i.e., stand 30 s) the "eyes closed, on foam" balance task (Bermúdez Rey et al., 2016; Karmali et al., 2017) and (2) mediated 46% of the age effect on balance (Beylergil et al., 2019). In a recent study of young adults ($N = 33$; 21 to 32 years of age), we also showed a significant positive correlation between 0.5 Hz roll tilt thresholds and the ML RMSD of the CoP captured during this same balance

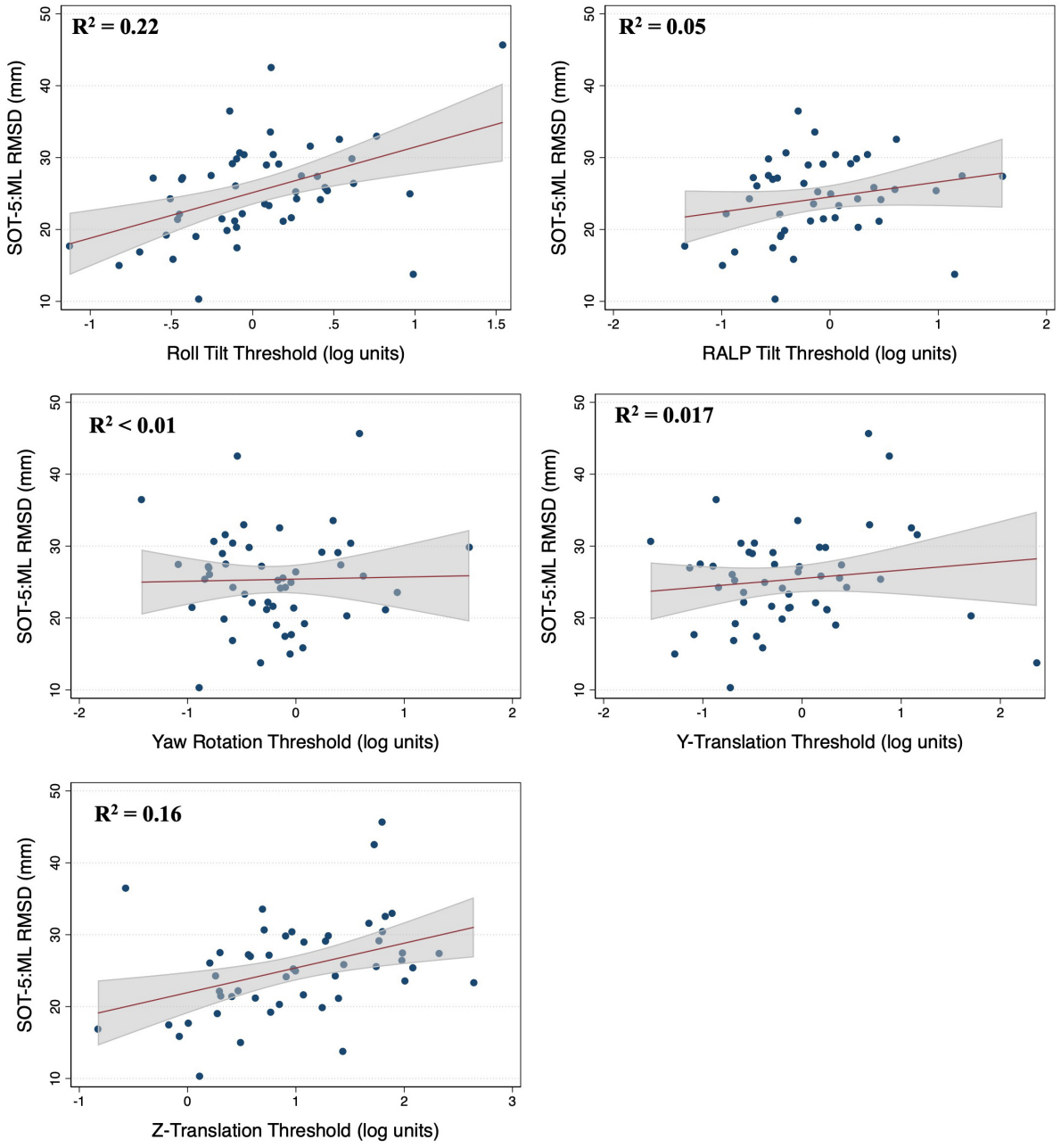


FIGURE 2
Scatter plots showing the association between each vestibular threshold and the mediolateral (ML) root mean square distance (RMSD) of the center of pressure in the "eyes closed, sway referenced support surface" condition (2D-SOT-5). A linear fit (red) and surrounding 95% confidence interval (gray) are shown. mm, millimeter.

task (Wagner et al., 2021c). However, to this point, quantitative measures of postural sway had yet to be compared to roll tilt vestibular thresholds in a sample that included adults over the age of 40. The present study fills a gap left by these earlier studies, by showing that 0.5 Hz roll tilt thresholds display a significant positive association with quantitative measures of quiet stance postural sway, as measured using two independent assessments of postural control (MRBT-4 and 2D-SOT-5), in a sample of adults with a broad age distribution (21 to 84 years of age).

Karmali et al. (2021) also recently compared y-translation, z-translation, yaw rotation, and roll tilt (1 and 0.2 Hz) thresholds to the ML and the AP RMSD of the CoP during the SOT (Karmali et al., 2021). In a secondary experiment, several 0.2 Hz tilt thresholds (roll, pitch, left-anterior right posterior (LARP) and RALP) were also compared to postural sway during each condition of the MRBT. The only significant correlation found across both arms of the study was between 1 Hz y-translation thresholds and the ML RMSD in 2D-SOT-5 (i.e., eyes closed, sway referenced support) (Karmali et al., 2021). In the present study, 1 Hz y-translation thresholds showed minimal association with postural sway in either 2D-SOT-5 or MRBT-4. Although surprising, differences in the study populations likely explains this incongruous finding. Karmali

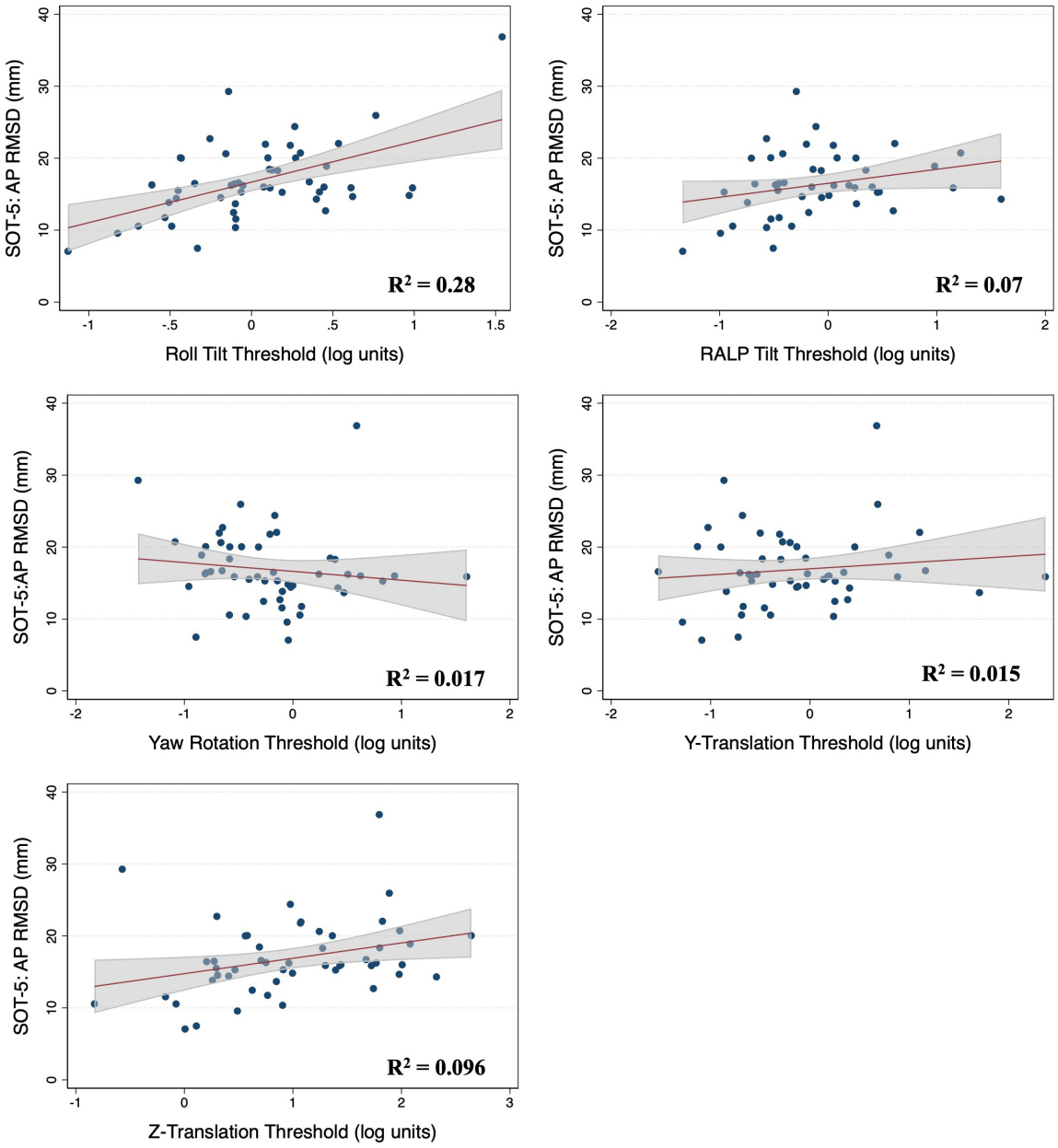


FIGURE 3
Scatter plots showing the association between each vestibular threshold and the anteroposterior (AP) root mean square distance (RMSD) of the center of pressure in the "eyes closed, sway referenced support surface" condition (2D-SOT-5). A linear fit (red) and surrounding 95% confidence interval (gray) are shown. mm, millimeter.

and colleagues analyzed a sample of twelve, young to middle aged adults (mean age of 34 ± 9, range of 21–50), whereas our dataset included fifty-two adults between the ages of 21 and 84. The effect of y-translation thresholds shown by Karmali et al. (2021) may have therefore represented a finding specific to the young adult population or may have been simply a result of sampling variability. In support of the explanation based upon sampling, we failed to show a significant correlation between y-translation thresholds and the ML RMSD in 2D-SOT-5 when our analysis was repeated using only the 17 participants under the age of 40 ($r = 0.04$, $p = 0.88$).

Karmali et al. (2021) also failed to identify a significant association between roll tilt thresholds and measures of postural sway. Yet, while similar, our two studies differed in the frequency of the roll tilt stimulus used—Karmali, et al. used a 0.2 Hz motion, compared to 0.5 Hz in the present study. Recently we showed that 0.2 Hz (in addition to 1 Hz) roll tilt thresholds did not show a significant correlation with the RMSD of the ML CoP in an identical "eyes closed, on foam" balance task in a sample of young adults (Wagner et al., 2021c). Yet, as described above, in a study that instead sampled across a wider age distribution (18 to 80 years old), Bermudez-Rey and colleagues showed that an increase in 0.2 Hz roll tilt thresholds was a strong predictor of the likelihood of completing the "eyes closed, on foam" balance task (Bermúdez Rey et al., 2016). In a recent study of 37 healthy adults,

TABLE 3 Results of individual univariable linear regression models for test condition 2D-SOT-5.

| 2D-SOT-5 | ML CoP RMSD | | | AP CoP RMSD | | | Sample size |
|---|---|---|---|---|---|---|---|
| | β | t-stat | *p*-value | β | t-stat | *p*-value | |
| **Roll tilt** | 6.33 (5.90) | 3.71 (2.89) | **0.0035 (0.023)** | 5.64 (6.34) | 4.34 (4.07) | **0.001(0.001)** | 51 |
| **RALP tilt** | 2.08 (2.42) | 1.57 (1.31) | 0.225 (0.306) | 1.94 (2.76) | 1.82 (1.87) | 0.167 (0.173) | 47 |
| **Yaw rotation** | 0.002 (−0.007) | 0.18 (−0.54) | 0.907 (0.696) | −0.014 (−0.022) | −0.93 (−1.48) | 0.509 (0.242) | 51 |
| **Y translation** | 1.16 (−0.59) | 0.92 (−0.39) | 0.48 (0.777) | 0.85 (0.089) | 0.86 (0.07) | 0.494 (0.943) | 51 |
| **Z translation** | 3.43 (3.41) | 3.00 (1.97) | **0.021** (0.154) | 2.14 (2.58) | 2.28 (1.82) | 0.09 (0.15) | 51 |

Model statistics for age-adjusted models are shown parenthetically. *P*-values were corrected using the False Discovery Rate (FDR) method. Significance was defined as a corrected *p*-value of <0.05 and is signified by the bolding of the significant *p*-values. 2D-SOT-5 = A modified condition 5 of the Sensory Organization Test (eyes closed, on a support surface sway referenced in both ML and AP planes). Sample size indicates the number of participants included in each analysis.

TABLE 4 Results of multivariable linear regression models for test condition MRBT-4 (*N* = 47).

| | β | SE | *t* | *p* | β stand |
|---|---|---|---|---|---|
| MRBT-4: Mediolateral CoP RMSD | | | | | |
| Roll tilt | 1.49 | 1.49 | 1.00 | 0.324 | 0.183 |
| Yaw rotation | −0.735 | 1.01 | −0.73 | 0.471 | −0.103 |
| Y translation | −0.640 | 0.92 | −0.69 | 0.491 | −0.118 |
| Z translation | 0.973 | 1.13 | 0.86 | 0.396 | 0.178 |
| Age | 0.086 | 0.044 | 1.97 | 0.056 | 0.407 |
| MRBT-4: Anteroposterior CoP RMSD | | | | | |
| Roll tilt | 2.01 | 1.83 | 1.10 | 0.277 | 0.222 |
| Yaw rotation | 1.054 | 1.24 | 0.85 | 0.399 | 0.133 |
| Y translation | −0.686 | 1.13 | −0.61 | 0.546 | −0.114 |
| Z translation | −0.418 | 1.39 | −0.30 | 0.765 | −0.069 |
| Age | 0.075 | 0.054 | 1.40 | 0.169 | 0.318 |

Standardized β values represent the amount of change in the response variable for a one standard deviation change in the predictor variable. Results significant at $p < 0.05$. MRBT-4 = condition 4 of the Modified Romberg Balance Test (eyes closed, on a foam surface).

Gabriel and colleagues also showed that pitch tilt perception was significantly correlated with the total CoP path length during a similar "eyes closed, on foam" quiet stance balance task, but only in the subset of adults over the age of 65 ($N = 19$) (Gabriel et al., 2022). Collectively these findings suggest that the absence of a significant correlation between 0.2 Hz roll tilt thresholds and quantitative measures of quiet stance sway (Karmali et al., 2021; Wagner et al., 2021c) likely resulted from the inclusion of only young healthy adult participants in these previous studies. Since neither Bermúdez Rey et al. (2016), nor the present study, included both 0.2 and 0.5 Hz roll tilt thresholds, we cannot fully discern which, if either, is a superior metric for quantifying the influence of noisy canal-otolith integration on age-related imbalance. However, since (a) the processing of 0.2 and 0.5 Hz roll tilt cues each requires the dynamic integration of canal and otolith signals (Lim et al., 2017; Wagner et al., 2022a), (b) each measure provides relevant cues for head in space orientation, and (c) 0.2 and 0.5 Hz roll tilt thresholds have been shown to be strongly correlated with one another (Lim et al., 2017; Wagner et al., 2021c), we expect that such differences would be small. Since multiple studies (Bermúdez Rey et al., 2016; Karmali et al., 2017; Beylergil et al., 2019; Wagner et al., 2021c) suggest that increased roll tilt thresholds show a robust association with subclinical balance dysfunction, optimizing the roll tilt test frequency may prove beneficial.

## Proposed mechanistic link between roll tilt vestibular noise and postural sway

A roll tilt of the head to the right, and a linear acceleration of the head to the left, each cause the hair cells embedded within the neuroepithelium of the utricles to deflect in an identical fashion (Baloh et al., 2011). As a result of this ambiguity in the otolith signal, during roll tilt, signals from the otolith organs alone cannot differentiate between changes in gravitoinertial force (the combined acceleration from translation and gravity) that occur secondary to (1) the head being tilted *versus* (2) the head being translated horizontally (Angelaki et al., 1999). As a result, to achieve a precise estimate of the head's orientation relative to gravity, the brain must use an internal model to combine angular velocity signals from the vertical semicircular canals with the ambiguous gravitoinertial forces encoded by the otolith organs (Angelaki et al., 1999; Lim et al., 2017; Wagner et al., 2022a). Considering the inverted pendulum dynamics of quiet stance sway, the ability to dynamically sense the orientation of the head in space holds a clear ecological advantage for the maintenance of stable quiet stance balance.

In quiet stance, corrective torques from the distal lower extremities are generated directly in response to the sense of the body's deviation away from upright (Peterka, 2002;

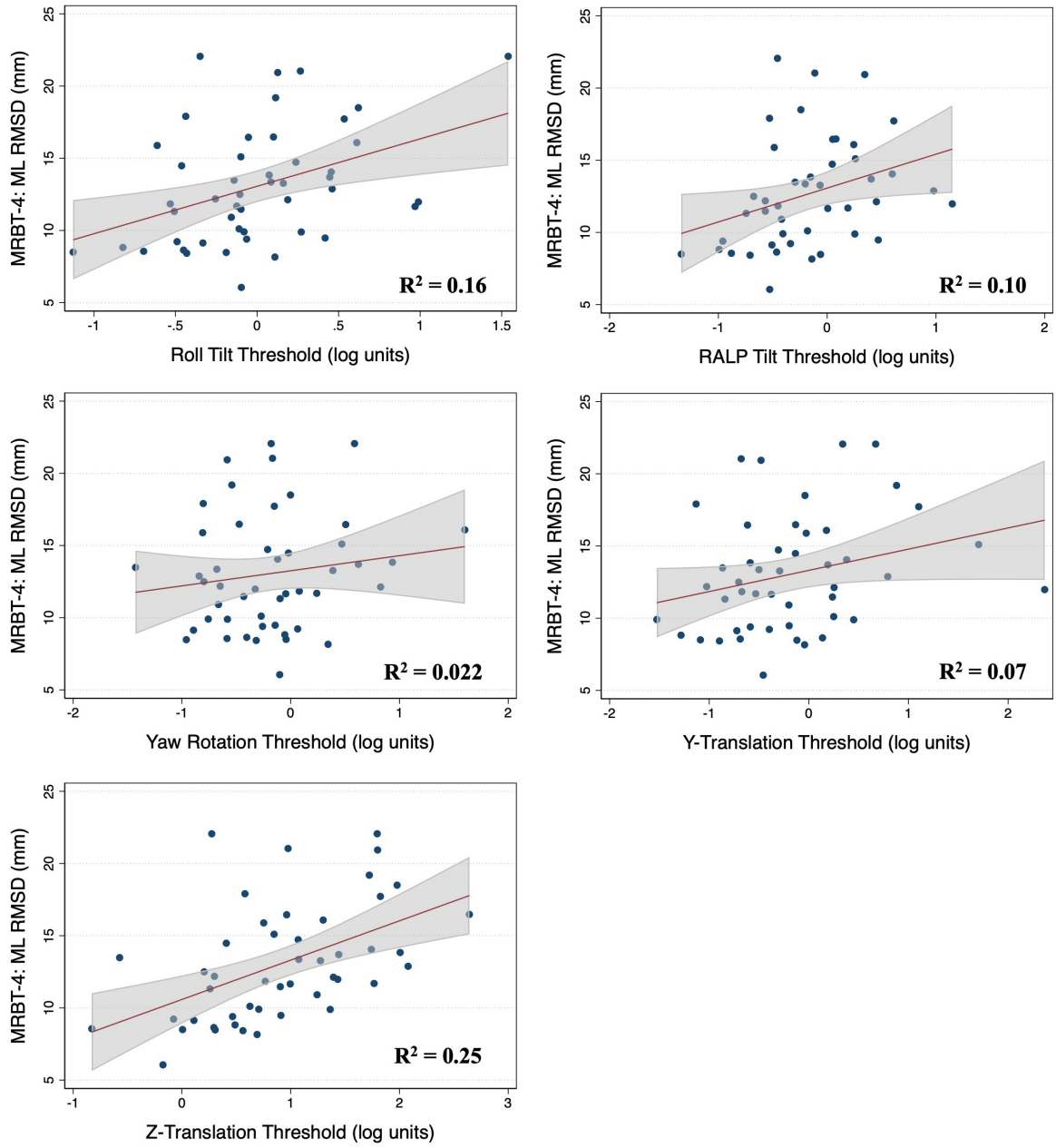


FIGURE 4
Scatter plots showing the association between each vestibular threshold and the mediolateral (ML) root mean square distance of the center of pressure in the "eyes closed, on foam" condition (MRBT-4). A linear fit (red) and surrounding 95% confidence interval (gray) are shown. mm, millimeter; RMSD, root mean square distance.

Maurer and Peterka, 2005; Cenciarini and Peterka, 2006; van der Kooij and Peterka, 2011; Assländer and Peterka, 2014; Pasma et al., 2015; Peterka et al., 2017). Secondary to the closed loop nature of the system, imprecision in dynamic estimates of head orientation (resulting from noise in the vestibular tilt signal) would therefore be expected to yield an increase in the variability and/or amplitude of postural sway (van der Kooij and Peterka, 2011; Diaz-Artiles and Karmali, 2021); furthermore, the effects should be greatest in conditions where vestibular inputs are prioritized due to the removal of visual cues and the degradation of proprioceptive cues. By using an empirical measure of noise in the centrally derived estimate of head in space orientation—0.5 Hz roll tilt thresholds—here we showed that individuals with increased vestibular noise demonstrated greater variability (i.e., greater RMSD) in CoP displacement during two balance conditions that each degrade the veracity of non-vestibular sensory feedback (i.e., 2D-SOT-5 and MRBT-4). The agreement between our empirical findings, and the anticipated effects on sway that should, according to theory, result from an increase in vestibular noise, support our suggestion that when exposed to impoverished non-vestibular sensory cues, older adults show greater postural sway primarily due to greater noise in the vestibular tilt signal.

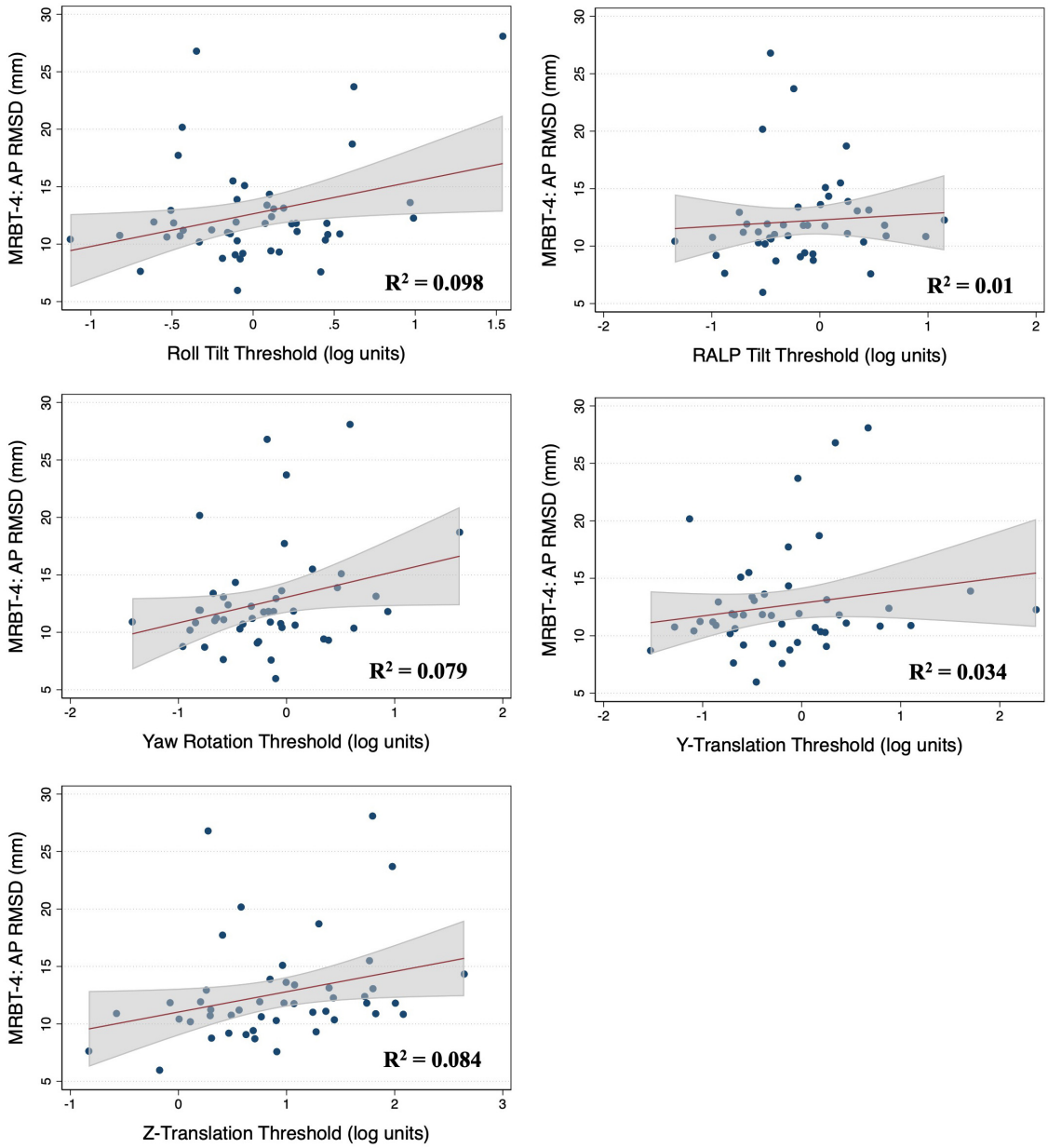


FIGURE 5
Scatter plots showing the association between each vestibular threshold and the anteroposterior (AP) root mean square distance (RMSD) of the center of pressure in the "eyes closed, on foam" condition (MRBT-4). A linear fit (red) and surrounding 95% confidence interval (gray) are shown. mm, millimeter.

TABLE 5 Results of individual linear regression models for test condition MRBT-4.

| MRBT-4 | ML CoP RMSD | | | AP CoP RMSD | | | Sample size |
|---|---|---|---|---|---|---|---|
| | β | t-stat | *p*-value | β | t-stat | *p*-value | |
| Roll tilt | 3.28 (1.59) | 2.96 (1.19) | **0.040** (0.378) | 2.84 (1.56) | 2.21 (1.08) | 0.171 (0.415) | 47 |
| RALP tilt | 2.35 (0.295) | 2.21 (0.22) | 0.128 (0.946) | 0.55 (−1.79) | 0.48 (−1.23) | 0.843 (0.360) | 47 |
| Yaw rotation | 0.021 (−0.011) | 1.00 (−0.50) | 0.325 (0.619) | 0.036 (0.020) | 1.97 (1.06) | 0.055 (0.295) | 47 |
| Y translation | 1.47 (−0.166) | 1.89 (−0.20) | 0.173 (0.845) | 1.11 (−0.219) | 1.26 (−0.21) | 0.380 (0.886) | 47 |
| Z translation | 2.72 (1.45) | 3.85 (1.49) | **0.006** (0.329) | 1.77 (0.35) | 2.03 (0.29) | 0.154 (0.949) | 47 |

Model statistics for the age-adjusted models are shown parenthetically. *P*-values were corrected using the False Discovery Rate (FDR) method. Significance was defined as a corrected *p*-value of <0.05 and is signified by the bolding of the significant *p*-values. MRBT-4 = condition 4 of the Modified Romberg Balance Test (eyes closed, on a foam surface). Sample size indicates the number of participants included in each analysis.

However, although our data are supportive of the hypothesized association between roll tilt thresholds and subclinical postural instability, due to our cross-sectional design, we cannot determine if roll tilt vestibular noise was the cause of the observed increase in RMS sway. Instead, it remains possible that postural control and vestibular precision change in parallel with age, without causal interactions. However, while acknowledging that correlation cannot prove causation, we posit that the available data points to vestibular noise being at least one of the primary contributors to subclinical postural instability (see Wagner et al., 2021b for a mini review we penned on this topic). This supposition of a causal link between vestibular noise and postural sway is based on several factors, including (1) our data showing that roll tilt thresholds displayed a significant positive association with postural sway in age adjusted models, across a broad distribution of adults ranging in age between 21 and 84 years, (2) our finding that although roll tilt thresholds showed the strongest association with postural sway, they displayed one of the weakest associations with age, and (3) previously published data showing that a paradigm designed to improve roll tilt perception was able to yield a significant reduction in sway (Wagner et al., 2022b). In addition to these empirical findings, roll tilt represents an ecologically valid signal to encode human postural sway given the inverted pendulum dynamics of the human body. For these reasons, we posit that the observed relationship between vestibular noise and postural sway is likely causal such that age-related increases in roll tilt vestibular noise contribute to subclinical postural instability in asymptomatic adults.

## Vestibular contributions to sway on a "foam" vs a "sway referenced" support surface

The results of the simple linear regression analysis showed that roll tilt thresholds explained a greater amount of the variance in postural sway in the two-dimensional "sway referenced" (2D-SOT-5), compared to the "foam standing" (MRBT-4) balance condition (ML: $R^2$ = 0.22 vs. 0.16 and AP: $R^2$ = 0.28 vs. 0.098). In the multivariable analysis of sway in the "eyes closed, on foam" condition, the effect of age was greater than that of roll tilt thresholds (**Tables 2**, **3**), and in the individual age-adjusted linear regression models, the effect of age either remained significant (ML RMSD, $p$ = 0.006), or trended toward significance (AP RMSD, $p$ = 0.083), when controlling for roll tilt thresholds (**Supplementary Table 1**). Conversely, in the multivariable analysis of 2D-SOT-5 performance, the associations between roll tilt thresholds and RMS sway were stronger than the effects of age (as quantified by the standardized β, **Table 2**) and in the age-adjusted individual regression models, age did not show a significant effect on the ML ($p$ = 0.693) or AP RMSD (0.374) when controlling for 0.5 Hz roll tilt thresholds (**Supplementary Table 1**).

These data suggest that the variation in postural sway in the "eyes closed, on foam" condition may primarily be explained by the variance in alternative age-related sensorimotor factors (e.g., tactile sensation, strength) (Ko et al., 2015; Deshpande et al., 2016), whereas postural sway in the "eyes closed, sway referenced support" condition appears instead to be more strongly influenced by roll tilt vestibular noise. This is further supported by an increase in the coefficients of determination in the linear regression models relating age to postural sway in MRBT-4 (AP: $R^2$ = 0.14, ML: $R^2$ = 0.27), compared to the 2D-SOT-5 (AP: $R^2$ = 0.037, ML: $R^2$ = 0.087). Future studies should test this supposition by comparing the postural responses during each of these assessments in a sample of adults with known vestibular lesions.

## Clinical relevance and applications

As measures of postural control have been shown to be insensitive to vestibular lesions (Nashner and Peters, 1990; Voorhees, 1990; Di Fabio, 1995), increased sway in the "vestibular" condition of a balance assessment cannot be reliably used as a marker of vestibular pathology in older adults (Evans and Krebs, 1999; Jacobson et al., 2011). Based upon the present data, we suggest that a concordant finding of both imbalance (e.g., increased sway in MRBT-4 or 2D-SOT-5), alongside an elevation in 0.5 Hz roll tilt thresholds, may serve as potential evidence of a vestibular mediated balance syndrome. However, the ability to generalize these findings to symptomatic older adults with clinical balance impairment and a falls history is limited by the healthy nature of our sample. In addition, our data also point to roll tilt precision as a potential target for future interventions that aim to improve postural control in older adults (Wagner et al., 2022b).

## Limitations

Increased sway variability, as reflected by the CoP RMSD, does not definitively connote worse postural control. Others have posited that changes in quiet stance balance may reflect greater exploratory behavior, rather than an unstable postural control system (Carpenter et al., 2010). Thus, the relationships between perceptual thresholds and either the velocity of sway or the frequency of sway may differ from those shown here for the RMSD. Future investigations may benefit from the inclusion of such measures, as well as alternative non-linear computational approaches (e.g., sample entropy) to further characterize the associations between vestibular noise and quiet stance balance. Additionally, although alternative "non-vestibular" influences (e.g., attention, tactile cues, etc.) are unavoidable during the assessment of vestibular thresholds, such factors similarly influence each of the thresholds measured, and thus do not prevent the use of vestibular perceptual thresholds to infer the relative contributions of each vestibular modality to age-related changes in quiet stance postural control. At the stimulus frequencies tested here (0.5 to 2 Hz) vestibular perceptual thresholds were also previously found to be 2.03-56.78 times higher in patients with absent bilateral vestibular function (due to bilateral labyrinthectomy), further supporting the predominant use of vestibular cues when perceiving passive whole body self-motion cues in the dark (Valko et al., 2012).

## Conclusion

Our data show a link between vestibular noise, specifically associated with the processing of roll tilt self-motion cues, and the

variability of postural sway during quiet stance. These data support that noise in the centrally integrated canal-otolith signal, relative to the canal or otolith signals in isolation, may be the primary vestibular contributor to quiet stance postural sway in conditions of unreliable visual and proprioceptive cues. Consistent with our primary hypothesis, this suggests that imprecision in the dynamic estimation of head in space orientation, as represented by increased 0.5 Hz roll tilt perceptual thresholds, may contribute to subclinical postural instability observed in asymptomatic older adults.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by The Ohio State University Biomedical Sciences Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

AW, MK, and DM conceptualized the experiments. AW and MK collected and processed the behavioral data. AW performed the statistical analyses, interpreted the results of the analyses, and wrote the initial draft of the manuscript. DM and MK each contributed to, and approved of, the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1207711/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Alternative conditions of the Modified Romberg Balance Test (MRBT) are shown. MRBT-1 involved standing on a firm surface with eyes open, MRBT-2 involved standing on a firm surface with eyes closed. MRBT-3 and MRBT-4 were performed on a compliant medium density foam pad with eyes open in MRBT-3 and closed in MRBT-4. Each condition lasted 67 s and noise cancelling headphones were worn throughout. Center of pressure data were collected at 100 Hz from a tri-axial force plate.

SUPPLEMENTARY FIGURE 2
Alternative conditions of the Sensory Organization Test (SOT) are shown. In SOT-1, SOT-2, and SOT-3 the platform was stationary whereas during 2D-SOT-4, 2D-SOT-5 (**Figure 1**), and 2D-SOT-6, the platform tilted in the sway referenced conditions in two dimensions (anteroposterior and mediolateral) in response to an estimate of the displacement of the center of gravity. In SOT-1 and SOT-3 the eyes were open, and the participant viewed a veridical visual scene, in SOT-2 and 2D-SOT-5 the eyes were closed, and in SOT-3 and 2D-SOT-6 the VR goggles provided a sway referenced visual scene. The black masks in SOT-3 and 2D-SOT-6 denote the use of VR to provide a sway referenced visual scene. While VR goggles were worn throughout, they are removed from the graphic in the remaining tasks to allow visualization of the eyes (open vs. closed).

SUPPLEMENTARY FIGURE 3
Pearson correlation coefficients are provided within each box to demonstrate the strength of association between each of the secondary conditions of the sensory organization test (SOT conditions 1-4 and 6) and Modified Romberg Balance Test (MRBT conditions 1-3) and each of the five vestibular threshold measures—0.5 Hz roll tilt, 2 Hz RALP tilt, 2 Hz yaw rotation, 1 Hz Y-Translation, and 1 Z-Translation. The strength of the correlation is graphically indicated by the color of each cell, ranging from dark red (strongest positive association) to dark blue (strongest negative association).

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# Associations between cognition, anxiety, depression, and residual dizziness in elderly people with BPPV

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**Objective:** To investigate the associations between cognition, anxiety, depression, and residual dizziness after successful repositioning maneuvers in the elderly with benign paroxysmal positional vertigo (BPPV).

**Methods:** We enrolled 40 elderly patients with BPPV in our outpatient department. We used the Dizziness Handicap Inventory (DHI), Visual Analog Scale (VAS), Patient Health Questionnaire-9 (PHQ-9), and Generalized Anxiety Disorder Questionnaire-7 (GAD-7) to assess the degree of dizziness, anxiety, and depression of participants before repositioning therapy, respectively. At the 1-week follow-up after BPPV treatment, each participant will be reassessed and divided into a group with residual dizziness (RD) and a group without residual dizziness (NRD) based on the follow-up DHI score. The Mini-Mental State Examination (MMSE) evaluated the cognitive function of the participants.

**Results:** The age, gender, duration of BPPV, and involved semicircular canals in the two groups did not show a significant difference. The RD group scored significantly higher on the DHI ($p = 0.006$), GAD-7 ($p < 0.001$), and PHQ-9 ($p = 0.002$) before the repositioning treatment than the NRD group. The two groups had no significant difference in MMSE score ($p = 0.381$). Anxiety and depression scores before repositioning treatment significantly and positively correlated with follow-up DHI scores ($r = 0.678$ and 0.522, respectively), but the MMSE score did not significantly relate to it. The univariate linear regression showed that the DHI ($p < 0.001$), GAD-7 ($p < 0.001$), and PHQ-9 ($p = 0.002$) scores before treatment could predict residual dizziness. The multivariate linear regression showed that GAD-7 before treatment was the only significant predictor of residual dizziness ($p < 0.001$).

**Conclusion:** The level of dizziness, anxiety, and depression before treatment can predict residual dizziness after successful repositioning maneuvers in the elderly with BPPV. Anxiety may be the strongest predictor of residual dizziness after successful repositioning treatment in elderly BPPV patients.

KEYWORDS

**elderly, BPPV, residual dizziness, anxiety, depression, cognition, vertigo**

# 1. Introduction

Benign paroxysmal positional vertigo (BPPV) is the most common cause of recurrent vertigo in the elderly. Nearly 40% of elderly patients seen for dizziness reported having BPPV (Ekvall Hansson et al., 2005). The 1-year prevalence of BPPV increases steeply with age, from 0.5 percent in those under 40 years old to 3.4 percent in those above 60 years old (von Brevern et al., 2007). The cumulative incidence of BPPV reaches almost 10% by age 80 (von Brevern et al., 2007). The typical clinical manifestations of BPPV are recurrent short-duration vertigo and positional nystagmus provoked by changes in the head position relative to gravity (Bhattacharyya et al., 2017). Treatment of geriatric BPPV patients included canalith repositioning procedures (CRPs), the same as CRPs for younger patients.

Some patients reported residual symptoms, such as lightheadedness, dizziness, unsteadiness, and disequilibrium, called residual dizziness, after successful CRPs. The reported prevalence of residual dizziness varied from 31 to 61% (Seok et al., 2008; Teggi et al., 2011, 2013). Patients older than 65 years reported more commonly experienced residual dizziness after BPPV was resolved, with percentages from 34.8 to 36.6% and a mean duration of 13.4 ± 7.5 days (Teggi et al., 2011; Vaduva et al., 2018). Vertigo and residual dizziness put elderly BPPV patients at higher risk for falls and fractures when compared with their healthy peers (Balatsouras et al., 2018). Disabilities caused by vertigo and residual dizziness, and fears of falls make old patients physically inactive and reduce daily activities. Eventually, the health-related quality of life of elderly BPPV patients is impaired (Lopez-Escamez et al., 2005). The age of BPPV onset, duration of vertigo, and times of CRP performed were related to residual dizziness (Vaduva et al., 2018). However, the underlying mechanism of residual dizziness after the resolution of vertigo has not yet been fully understood.

Increasingly, studies reported the potential links between psychological impairment, vertigo, and residual dizziness in BPPV patients. A study showed that nearly half of BPPV patients with a history of psychiatric disorder described residual dizziness (Vaduva et al., 2018). The risk of residual dizziness symptoms was related to self-perceived anxiety and depression in elderly BPPV patients as well (Oghalai et al., 2000; Teggi et al., 2011). Indeed patients with high anxiety showed more enduring dizziness after vertigo and nystagmus had resolved (Bayat et al., 2020). The coexistence of vestibular symptoms, anxiety, and depression might suggest a possible somatopsychic component to residual dizziness in BPPV patients.

In addition, it has been reported that vestibular disorders are associated with cognitive dysfunction (Rizk et al., 2020). Literature showed that individuals with vestibular vertigo had an eightfold increase in the difficulty of concentration or memory (Bigelow et al., 2016). Individuals with vestibular disorders also had more difficulties participating in cognition-relied daily activities than mobility-relied activities (Harun et al., 2015). However, the studies on cognition impairment in the elderly BPPV population and relations with residual dizziness are limited by far.

The study aimed to investigate the associations between cognition function, psychiatric conditions of anxiety and depression, and residual dizziness after successful CRPs in elderly BPPV patients. We used a set of scales to assess the psychiatric conditions of anxiety and depression, perceived degree of vertigo and dizziness, residual dizziness, and cognition function. We compared these variables between patients who exhibited residual dizziness and patients without residual symptoms. We hypothesized that anxiety and depression were associated with residual dizziness after successful CRPs, which could negatively impact cognitive function among the elderly population diagnosed with BPPV. This research will contribute to understanding residual dizziness's mechanism after successful CRPs and the potential relationships between vestibular conditions and cognition function among the elderly.

# 2. Materials and methods

## 2.1. Subjects

We recruited 68 elderly subjects (older than 65 years) who presented to our vertigo center between September 2022 and March 2023. We used the diagnostic criteria of clinical practice guideline of BPPV released by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) in 2017 (Bhattacharyya et al., 2017). In all patients, positional vertigo and typical nystagmus (latency, duration, and direction) were triggered through Dix-Hallpike tests and/or Supine Roll Tests. To exclude the central pathologies that cause positional nystagmus, all patients received neurotologic examinations, including spontaneous and gaze-evoked nystagmus, smooth pursuit and ocular saccades, optokinetic nystagmus, and balance assessment. Patients with pathological signs in these tests underwent MRIs. The exclusion criteria were: (1) patients with central nervous system pathologies that caused positional vertigo and nystagmus; (2) patients with other dizziness conditions that cause secondary BPPV, such as Ménière's disease (MD), vestibular migraines (VM), or vestibular neuritis (VN); (3) Patients had unresolved vertigo and nystagmus after three times repositioning maneuvers at the first visit and the next day. (4) Illiterate patients who were unable to complete the assessments. (5) patients with a history of psychiatric disorders. Eventually, we enrolled 40 patients for analyses; 28 patients were excluded for the absence of the follow-up ($n$ = 18) and for not completing all questionnaires ($n$ = 10). The sample size meets the minimum requirements of statistical analyses according to the power calculation.

## 2.2. Questionnaires

This study utilized a set of scales to collect relevant data. The Dizziness Handicap Inventory (DHI) and Visual Analog Scale (VAS) were used to assess the degree of dizziness. The DHI comprises 25 items grouped into three dimensions: physical, functional, and emotional (Jacobson and Newman, 1990). The VAS was designed to reflect the perceived vertigo and dizziness in this study. VAS is on a scale of 0–10, with 0 indicating no vertigo and 10 indicating extreme vertigo.

The 7-item Generalized Anxiety Disorder Scale (GAD-7) evaluated the anxiety state. The total score on the GAD-7 is 21, with higher scores representing higher anxiety levels. Scores of 5, 10, and 15 represented cut-off points for mild, moderate, and severe levels

of anxiety, respectively (Spitzer et al., 2006). The 9-item Patient Health Questionnaire (PHQ-9) screened the depressive symptom of patients. PHQ-9 scores range from 0 to 27. For the PHQ-9, 5, 10, 15, and 20 cut-off points were interpreted as mild, moderate, moderately severe, and severe depression symptoms, respectively (Bianchi et al., 2022). In this study, the GAD-7 and PHQ-9 were only used to evaluate the anxiety and depressive symptoms of participants. It's essential to mention that none of the patients were diagnosed by psychiatrists.

The Chinese version of the Mini-Mental State Examination (MMSE) was employed to assess the cognition function of subjects. The MMSE includes the orientation, memory, recall, calculation, and language subcomponents, scoring 30 (Pinto et al., 2019). The MMSE is widely used in cognition assessment and was proven to be sensitive to detecting mild cognition impairment. The lower the score, the more severe the impairment in cognitive function.

## 2.3. Study design

We performed Dix-Hallpike tests and Supine Roll Tests on all patients to diagnose BPPV and determine which semicircular canal (SCC) was affected. In the Dix-Hallpike maneuvers, positional vertigo and up-beating nystagmus with torsional component illustrated posterior semicircular canal BPPV (PSC-BPPV). In the Supine Roll Tests, the presence of geotropic or ageotropic horizontal nystagmus accompanied by positional vertigo indicated horizontal semicircular canal BPPV (HSC-BPPV). Nystagmus was recorded without visual fixation using a wired infrared video-Frenzel goggle connected to G-force$^{TM}$ otolith diagnosis and CRP therapy instrument. Two experienced otolaryngologists made the diagnosis of BPPV. Once the diagnosis was confirmed, we used a set of scales to assess the patients' dizziness handicap, anxiety, depression, and cognition function before applying CRPs.

We chose the CRPs based on the involved SCC and strongly recommended in the clinical practice guideline by AAO_HNS in 2017. Patients with PSC-BPPV were treated with the Epley maneuver. The Epley maneuver utilizes gravity to transport the free-floating otoliths in the posterior SCC back to the vestibule (Bhattacharyya et al., 2017). Patients with geotropic or ageotropic type of HSC-BPPV were treated with the Barbecue maneuver or Gufoni maneuver, respectively. The Barbecue maneuver was designed to move free-floating otoliths in horizontal SCC and treat the geotropic type of HSC-BPPV. In contrast, the Gufoni maneuver aims to detach otoliths from the cupula and treat the ageotropic type of HSC-BPPV (Bhattacharyya et al., 2017). Two physiotherapists applied the CRPs. The CRPs were performed up to a maximum of three times in a single session.

Two doctors applied positional tests for patients after the CRPs. The complete remission of subjective vertigo and objective positional nystagmus was the criteria for successful CRPs treatment. Patients attended a 1-week follow-up after the resolution and received evaluations of residual dizziness, anxiety, and depression. The cognition function of patients was only evaluated at the first presentation due to the stability of cognition within 1 week (Fu et al., 2021; Lee et al., 2022). The patients were divided into the no residual dizziness (NRD) group and the residual dizziness (RD) group based on the follow-up DHI scores. A flow chart showing the study design is shown in **Figure 1**. The studies involving human participants were reviewed and approved by the Ethics Committee of Xinhua Hospital Affiliated with Shanghai Jiao Tong University School of Medicine (Approval No. XHEC-D-2017-046). All patients were informed in detail about the purpose and method of the study, and written informed consent was obtained from all patients.

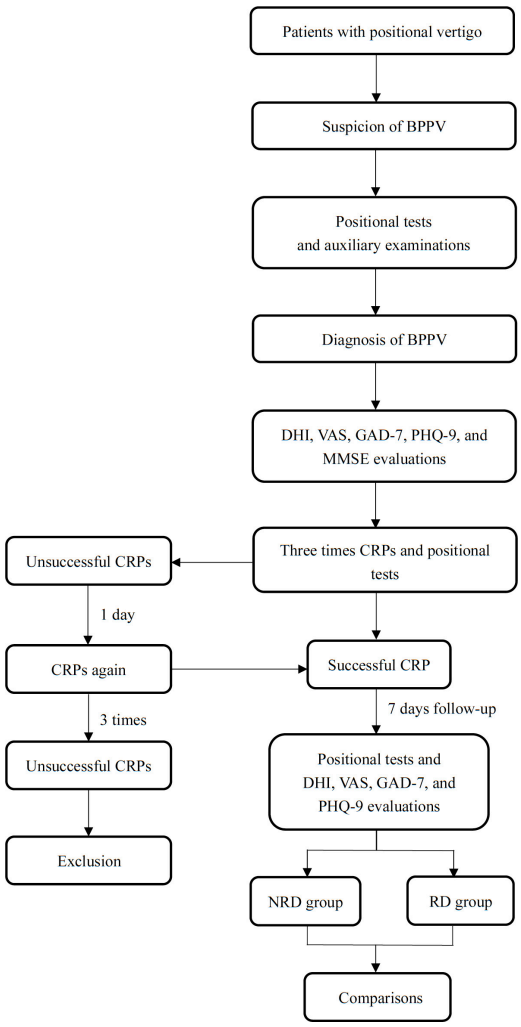


FIGURE 1
A flow chart describing the research design. BPPV, benign paroxysmal positional vertigo; DHI, dizziness handicap inventory; VAS, visual analog scale; GAD-7 indicates generalized anxiety disorder 7-item scale; PHQ-9, patient health 9-item questionnaire; CRP, canalith repositioning procedure.

## 2.4. Statistical analysis

We used a Chi-square test to study the demographics in the two groups of BPPV patients. The normality of DHI, VAS, MMSE, GAD-7, and PHQ-9 scores of the two groups was analyzed by the Shapiro-Wilk test. The study measures were normally distributed except for the GAD-7 and PHQ-9 scores of the NRD group at pre- and post-treatment assessment and VAS ratings of two groups at post-treatment assessment. An unpaired t-test

was applied to analyze the differences in cognition function and DHI scores between the NRD and RD groups. All data meet the homogeneity of variance. We performed the non-parametric Mann-Whitney *U*-test to study the differences in anxiety and depression symptoms between the NRD and RD groups. Pearson's correlation test was applied for the correlation between variables. Significance was determined at $p < 0.05$, and all statistical analyses were performed by SPSS 23 (SPSS Inc, Chicago, IL, USA). The power calculation was conducted by G*Power 3.1 (Heinrich-Heine-Universität Düsseldorf). The power was above 90% in correlation, *t*-tests, and linear regression tests.

# 3. Results

## 3.1. Demographics

Forty patients met all criteria in all recruited subjects. The average age of the cohort was 69.60 ± 4.06 years. Of the 40 patients, 28 were female (the gender ratio was 2.33:1), consistent with the prevalence characteristics of BPPV (Neuhauser and Lempert, 2009). The average duration of symptoms for the entire cohort at the time of presentation was 16.94 days, and the median (P25, P75) was 7.5 (5, 23) days. The average years of education for all included patients was 8.91 ± 1.96 years.

The 40 patients were divided into two groups with 20 cases in each group based on the follow-up DHI scores, namely the NRD group (DHI < 16) and RD group (DHI ≥ 16). Table 1 shows the demographics and results of Chi-square tests in the two groups.

TABLE 1 Overall description of the demographics of the two groups.

| | NRD | RD | *p*-value |
|---|---|---|---|
| Gender (women: men) | 14:6 | 15:5 | 0.723 |
| Age, mean (SD) | 69.47 (3.62) | 69.73 (4.57) | 0.860 |
| Duration of symptoms (days) | | | |
| Mean (SD) | 15.81 (21.46) | 18.06 (19.76) | 0.760 |
| Median | 8 | 7 | |
| Education (years) | 9.06 (2.21) | 8.75 (1.73) | 0.659 |
| Semicircular canal, *n* (%) | | | |
| Posterior | 19 (95%) | 17 (85%) | 0.292 |
| Horizontal | 1 (5%) | 3 (15%) | |
| Right | 15 (75%) | 11 (55%) | 0.185 |
| Left | 5 (15%) | 9 (45%) | |
| Type of BPPV, *n* | | | |
| Canalolithiasis | 20 | 18 | 0.147 |
| Cupulolithiasis | 0 | 2 | |
| Recurrence | 2 (10%) | 3 (15%) | 0.633 |

## 3.2. Dizziness handicap inventory

In the pre-treatment assessment, the NRD group had a DHI mean total score of 33.38 ± 21.09, which were significantly different from the mean total score in the RD group of 55.5 ± 20.82 ($t = -2.987$, $p = 0.006$, effect size = 1.055). Figure 1 compares three DHI subscales between the groups in two assessments. Broken down by subscale, there were statistically significant differences between NRD and RD groups in DHI-P ($t = -2.297$, $p = 0.029$), DHI-F ($t = -2.547$, $p = 0.016$), and DHI-E ($t = -2.809$, $p = 0.009$) scores. The RD group had a mean DHI-E score of 16.63 ± 9.40, more than twice the DHI-E score of 7.88 ± 8.18 in the NRD group.

At follow-up, the total score of the RD group decreased to 30.38 ± 11.87, which was significantly higher than the total score of the NRD group at 5.25 ± 4.37 ($t = -7.944$, $p < 0.001$, effect size = 2.809). This difference in DHI scores between the two groups was the principle of grouping. As is shown in Figure 2, the RD group had a significantly higher score than the NRD group in DHI-P ($t = -6.880$, $p < 0.001$), DHI-F ($t = -7.147$, $p < 0.001$), and DHI-E ($t = -4.434$, $p < 0.001$).

## 3.3. Visual analog scale

Figure 2 compares the VAS rating of the two groups at the first visit and follow-up. VAS ratings for vertigo of the two groups (NRD 6.13 ± 2.19, RD 6.75 ± 1.77) did not significantly differ ($t = -0.889$, $p = 0.381$) at the first presentation. The VAS ratings of the two groups were non-normally distributed, with the median (P25, P75) of the NRD group being 1 (0, 2) and that of the RD group being 2 (2, 3) at the follow-up. The Mann-Whitney *U*-test showed that the RD group had a significantly higher VAS rating than the NRD group ($Z = -3.671$, $p < 0.001$, effect size = 1.451) at follow-up.

## 3.4. Mini-mental state examination

The mean MMSE total score for the NRD group was 24.88 ± 3.28 and for the RD group was 25.69 ± 2.70 out of a possible 30 points. The unpaired *t*-test showed no significant difference in MMSE total score between the two groups ($t = -0.764$, $p = 0.451$, effect size = 0.270). Figure 3 shows the comparisons in the five subcomponents of the cognition function defined by MMSE. There was also no statistically significant difference between the two groups on each subcomponent.

## 3.5. Generalized anxiety disorder 7-item scale

Figure 4 shows the comparisons of GAD-7 and PHQ-9 between groups in two assessments. In the pre-treatment assessment, the median (P25, P75) GAD-7 score for the NRD group was 0 (0, 2) and 8.5 (3.5, 11) for the RD group. The Mann-Whitney *U*-test showed that the GAD-7 score of the NRD group was significantly lower than that of the RD group at ($Z = -4.229$, $p < 0.001$, effect size = 2.027). At follow-up evaluation, The NRD group had a median (P25, P75) GAD-7 score of 0 (0, 0), which was significantly lower than the GAD-7 score of 1 (0, 3) in the RD group as well ($Z = -3.955$, $p < 0.001$, effect size = 1.556).

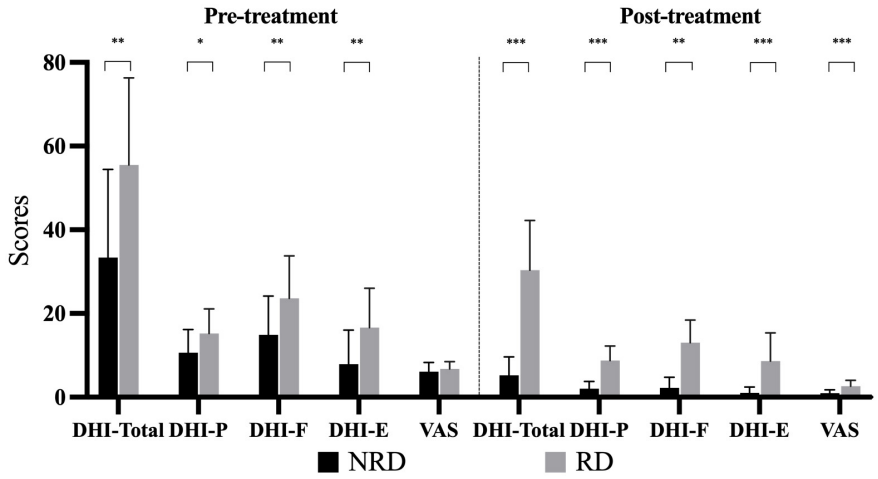


FIGURE 2
Bar chart depicting the DHI subscales and VAS scores of two groups at pre- and post-treatments. *$p$-value < 0.05; **$p$-value < 0.01; ***$p$-value < 0.001. DHI-P indicates physical subscale; DHI-F, functional subscale; DHI-E, emotional subscale; VAS, visual analog scale; RD, residual dizziness; NRD, no residual dizziness.

## 3.6. Patient health 9-item questionnaire

At the first presentation, the NRD group had a median (P25, P75) PHQ-9 score of 1 (0, 4.5) and the RD group had a median (P25, P75) PHQ-9 score of 5 (3.25, 8). The Mann-Whitney $U$-test showed that the PHQ-9 score of the NRD group was significantly lower than that of the RD group ($Z = -3.101$, $p = 0.002$, effect size = 1.200). At the follow-up assessment, PHQ-9 scores significantly differed between the two groups ($Z = -3.285$, $p = 0.002$, effect size = 1.410). The RD group scored 3.5 (1.25, 6), and the NRD group scored 0.5 (0, 1), see Figure 4.

## 3.7. Correlations

We performed Person's correlation method to analyze the relationship between residual dizziness surveys and cognition, anxiety, and depression scores at the first presentation in all patients. Table 2 shows all correlations. The results showed that the pre-treatment anxiety and depression scores moderately correlated with the follow-up VAS rating (coefficients were 0.381, $p = 0.032$, and 0.497, $p = 0.004$) and highly correlated to the follow-up DHI-P, DHI-F, DHI-E, and total scores. While age, duration of symptom, and MMSE subcomponents did not correlate with the other variables.

## 3.8. Regression models for predictors of residual dizziness

We applied univariate regression to find predictors of residual dizziness. The follow-up DHI score was used as the dependent variable. The duration of BPPV, the DHI score, the GAD-7 score, and the PHQ-9 score before treatment was chosen as independent

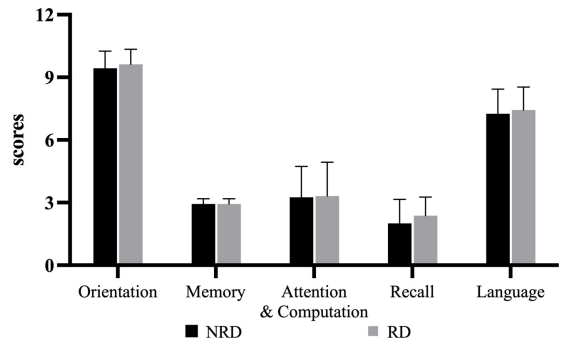


FIGURE 3
Five categories of MMSE for two groups. RD, residual dizziness; NRD, no residual dizziness.

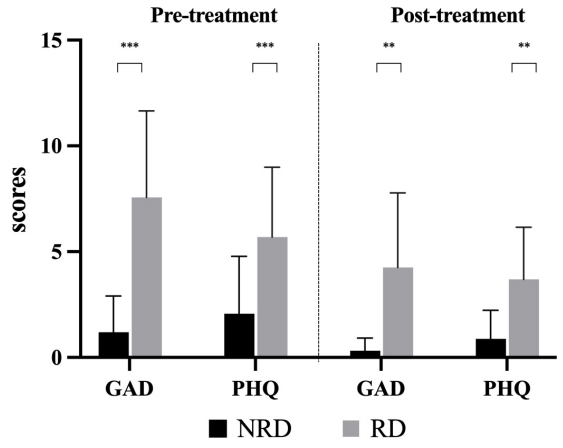


FIGURE 4
Comparison of the degree of anxiety and depression in two groups at pre- and post-treatment assessments. **$p$-value < 0.01; ***$p$-value < 0.001. RD, residual dizziness; NRD, no residual dizziness.

TABLE 2 Correlations between surveys in all patients.

| | VAS-post | DHI-P post | DHI-F post | DHI-E post | DHI total score |
|---|---|---|---|---|---|
| Age | 0.069 | 0.235 | 0.273 | 0.295 | 0.305 |
| Duration of symptom | −0.17 | 0.081 | −0.041 | −0.098 | −0.034 |
| MMSE | | | | | |
| Orientation | 0.317 | −0.033 | 0.002 | −0.343 | −0.144 |
| Memory | −0.04 | 0.022 | −0.052 | −0.051 | −0.037 |
| Attention and computation | 0.147 | −0.194 | −0.125 | −0.196 | −0.188 |
| Recall | 0.051 | 0.127 | −0.017 | −0.076 | −0.002 |
| Language | 0.028 | −0.112 | 0.034 | −0.107 | −0.059 |
| Total score | 0.181 | −0.104 | −0.061 | −0.258 | −0.159 |
| GAD-7 | 0.381* | 0.634*** | 0.587*** | 0.599*** | 0.678*** |
| PHQ-9 | 0.497** | 0.596*** | 0.462** | 0.373* | 0.522** |

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
MMSE, mini-mental state examination; GAD-7, generalized anxiety disorder 7-item scale; PHQ-9, patient health 9-item questionnaire; DHI, dizziness handicap inventory; DHI-P, physical subscale; DHI-F, functional subscale; DHI-E, emotional subscale; VAS-post, visual analog scale at follow-up.

TABLE 3 Linear regression models of DHI score for all patients.

| | Unstandardized coefficient | *SE* | *p* | $R^2$ | Model *p* |
|---|---|---|---|---|---|
| Duration | −0.026 | 0.139 | 0.852 | 0.001 | 0.835 |
| DHI-pre | 0.390*** | −0.097 | <0.001 | 0.349 | <0.001 |
| GAD-7 | 2.346*** | 0.465 | <0.001 | 0.459 | <0.001 |
| PHQ-9 | 2.312** | 0.690 | 0.002 | 0.272 | 0.002 |
| Multivariate regression | | | | 0.511 | 0.000 |
| DHI-pre | 0.186 | 0.111 | 0.106 | | |
| GAD-7 | 1.692* | 0.709 | 0.024 | | |
| PHQ-9 | 0.116 | 0.847 | 0.892 | | |

*$p < 0.05$; **$p < 0.001$; ***$p < 0.001$.
DHI-pre, dizziness handicap inventory at pre-treatment; GAD-7, generalized anxiety disorder 7-item scale; PHQ-9, patient health 9-item questionnaire.

variables based on the potential effects on residual dizziness. Table 3 presents the results of the univariate regression. The DHI score, GAD-7 score, and PHQ-9 score before CRPs treatments were significant predictors. We also performed multivariate regression to compare these significant predictors' effect sizes and relationships. There was no multicollinearity among the independent variables. As presented in Table 3, GAD-7 was the only significant predictor in the model. The $R^2$ of the model was 0.511, which means that these independent variables account for 51.1% of the variability in DHI score at follow-up.

# 4. Discussion

Our study investigated the potential factors related to residual dizziness after successful CRPs in elderly BPPV patients. Our study found that the age, gender, involved canal, and duration of vertigo did not correlate with the residual dizziness handicaps after successful repositioning maneuvers. These results support previous findings that gender and involved canal were not linked to residual dizziness but disagree with the reported correlation between age and residual dizziness (Vaduva et al., 2018). The variations in population demographics could explain the inconsistency. The prior study included participants of all ages, with half of the participants above 65 years old, and found that patients older than 65 presented a higher percentage of residual dizziness. We only enrolled patients older than 65 years (mean 69.56 ± 3.93 years), and the percentage of residual symptoms in this study was similar to this of participants above 65 years old in the previous study. We thought that the discrepancy in the age span of participants led to different conclusions. The association between the duration of BPPV and residual dizziness was still in dispute. Many researchers had reported that a longer duration of vertigo before diagnosis was linked to the presence of residual dizziness and unsteadiness after the resolution of BPPV (Stambolieva and Angov, 2006; Teggi et al., 2011; Faralli et al., 2016). However, some researchers reported that the duration of BPPV may not be a risk factor for residual symptoms (Kim and Lee, 2014; Giommetti et al., 2017). The age range and sample size of previous studies were different. The different inclusion criteria and relatively small sample size may explain the discrepancy. Our findings corroborate that the duration of BPPV was not related to the presence of residual dizziness in the elderly.

## 4.1. Assessment of dizziness

Our study found that at the time of diagnosis, the DHI subscales scores of the RD group were significantly higher than those of the NRD group, and linear regression analysis demonstrated that the DHI total score before CRPs was a predictor for residual dizziness. Our results accord with previous studies reporting that high DHI subscale scores and total scores at the first presentation are sensitive factors related to the incidence of residual dizziness (Ke et al., 2022; Fu et al., 2023). Our study further confirmed that DHI could be a helpful inventory before treatment to estimate the risk of residual dizziness after successful CRPs and quantify the dizziness handicaps on the quality of life in patients over 65 years old. In this study, we employed VAS to assess the subjective perception of vertigo and dizziness. The VAS rating showed a significant difference among the two groups at follow-up, supporting the opinion that VAS could be a sensitive tool to assess residual dizziness in BPPV patients (Fu et al., 2023). Recently, VAS is getting popular in the realm of vestibular symptoms. Our study shows the advantages of VAS for elderly BPPV patients in terms of being easy to use and overcoming cultural and cognitive barriers.

## 4.2. Cognitive dysfunction and residual dizziness

Previous studies found that patients with bilateral vestibular dysfunction had deficits in visuospatial tasks, navigation, attention,

and memory (Brandt et al., 2017), especially in elderly subjects (Caixeta et al., 2012). Even patients with unilateral vestibular impaired performed worse in cognitive domains of visuospatial and navigational tasks (Guidetti et al., 2008; Popp et al., 2017). However, we found that all five categories and the total score of MMSE did not correlate with the follow-up DHI and VAS scores, and the NRD and RD groups presented no differences in the performance of MMSE tasks. Possible reasons for these results are: First, the disease characteristics of BPPV are temporary and self-limited, which may not lead to permanent cognitive impairment. The duration of BPPV of subjects in our study was relatively short. The average duration of all patients was 16.94 ± 20.33 days, with 21 patients (52.5%) diagnosed within 7 days. A study demonstrated that the duration of vestibular symptoms and certain etiologies are more curial in cognitive dysfunction (Rizk et al., 2020). Our results were consistent with previous studies reporting that compared with other chronic vestibular disorders such as MD, VM, and persistent postural-perceptual dizziness (PPPD), BPPV patients did not present vestibular-related cognition disabilities (Liu et al., 2019; Rizk et al., 2020). Second, the MMSE may not thoroughly reflect the cognitive impairment related to vertigo and dizziness in elderly BPPV patients. The cognitive function most closely associated with vestibular disorders is the visuospatial ability, which includes spatial memory, navigation, mental rotation, and mental representation of 3-D space (Bigelow and Agrawal, 2015). In addition, visuospatial functions share the same cortical networks with the vestibular system (Hitier et al., 2014; Previc et al., 2014), and researchers hypothesized that this is one of the underlying mechanisms of vestibular-related cognition dysfunction. However, only one item, namely copying intersecting pentagons, is concerned with visuospatial ability in MMSE, which may not allow for a comprehensive examination of cognition in old patients with BPPV.

## 4.3. Psychiatric disorder and residual dizziness

The most noticeable finding of our study is the relationship between psychiatric symptoms and residual dizziness in old patients with BPPV. We found that the degree of anxiety and depression before treatment was positively correlated with residual dizziness, which accords with previous studies reporting the correlation between the psychological condition and residual dizziness in BPPV patients (Teggi et al., 2011). In addition, the findings that anxiety and depression are significant predictors for residual dizziness and that anxiety is the strongest predictor further demonstrate that anxiety and depression disorder influence the presence of residual dizziness after successful CRPs.

The close association between dizziness or vertigo and psychosomatic disorders such as depression, generalized anxiety disorder, somatization disorders, and panic disorder was well-established (Balaban and Jacob, 2001; Eckhardt-Henn et al., 2008). There is research reported that nearly half of BPPV patients with a psychiatric history presented residual dizziness after repositioning maneuvers (Vaduva et al., 2018), and the incidence of psychiatric disorder raised 5–15 times in patients with vestibular disorders (Pollak et al., 2003). The coexistence of vestibular and psychiatric disorders may imply a potential overlapped neural circuit. This concept was further supported by anatomical and functional links between the vestibular system and structures involved in the pathogenesis of panic disorder or the regulation of fear responses, such as the brainstem blue spot and the nucleus accumbens (Nishiike et al., 2001; Staab et al., 2002; Best et al., 2009). Anxiety and depression have been shown to play an important role in dizziness as a somatic form of the disorder and can be caused by a few stressful events (Wei et al., 2018). Violent episodes of episodic vertigo in patients with BPPV are one such stressful event (Martellucci et al., 2016). When an episode of BPPV is followed by abnormal stimulation of the vestibular system, it can lead to changes in mood, such as tension and anxiety. It has been shown that anxiety-related arousal and hyperventilation increase the effects on various vestibular laboratory parameters, which in turn leads to vestibular dysfunction (Nishiike et al., 2001), causing RD in some patients after CRPs (Ke et al., 2022). This vicious cycle could eventually impair the quality of patients' life.

We found that the degree of anxiety and depression of the RD group was significantly higher than the NRD group at the first visit. This may be due to acute vertigo episodes triggered or exacerbated the anxiety and depression in elderly BPPV Patients. Kalderon et al. (2022) also proved that the anxiety of patients with BPPV is not a personality trait (trait anxiety) but a temporary state (state anxiety) that is provoked by acute vertigo episodes. Additionally, Jung et al. (2012) reported that a low dose of anxiolytics (etizolam) could alleviate the residual dizziness in BPPV patients, especially for functional and emotional dizziness handicaps. Even if there is no rigorous scientific evidence to generalize this medication in clinical practice, the positive effect may somewhat explain the role of psychiatric disorders in residual dizziness.

In conclusion, anxiety and depression contribute to the residual dizziness of elderly BPPV patients. It is important to incorporate psychological counseling and ongoing monitoring to manage residual dizziness in this patient population.

## 4.4. Limitations and future directions

While our study did yield valuable results, there are still limitations that need to be acknowledged. First, the evaluation tool for cognition dysfunction in elderly BPPV patients we used is not designed to assess the vestibular-related cognition impairment, which could not thoroughly reflect the visuospatial abilities of subjects. According to reports, the Neuropsychological Vertigo Inventory (NVI) can measure cognitive dysfunction in patients experiencing dizziness. Additionally, the objective P300 Event-Related Potential (ERP) can evaluate cognitive impairment that may not be reflected in subjective assessments (Liu et al., 2019; Toyoshima et al., 2020). Therefore, in future studies, we can use the NVI in combination with objective P300 ERP to target vestibular-related cognition impairment in elderly patients with BPPV. Second, the residual dizziness experienced by the elderly participants in this study had a relatively short duration. As a result, it may be unlikely to impact their cognitive function negatively. The future direction is to extend the follow-up period to 3 months and assess the cognition function each month to investigate the effect

of residual dizziness on cognition comprehensively. Furthermore, we did not investigate the association between a history of BPPV and residual dizziness due to the relatively small sample size. Future research will expand the sample size and divide the participants according to the history of BPPV to investigate this potential relationship.

## 5. Conclusion

In elderly patients with BPPV, there is a positive correlation between the degree of residual dizziness and the scores of DHI, GAD-7, and PHQ-9 at the first presentation. Vertigo and residual dizziness do not correlate cognition dysfunction in this study. The DHI, GAD-7, and PHQ-9 scores at the first presentation can predict residual dizziness. Among these factors, GAD-7 is the strongest predictor for elderly BPPV patients. The results of this study suggest that it is important to provide psychological support for elderly BPPV patients in managing residual dizziness. Doctors can clarify the mechanisms of RD after successful CRPs to alleviate anxiety and depression among elderly patients. Collaborating with psychiatrists on medication may also contribute to managing residual symptoms after CRPs in elderly BPPV patients.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Xinhua Hospital Affiliated with Shanghai Jiao Tong University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

JS responsible for CRPs application, data collection, and manuscript composition. XM and YY collected the clinical data. KH helped with CRPs practice. WW, JLS, and LW contributed to the data analysis. XC contributed to statistical consultation. JY, YLJ, and JYC responsible for the research design and manuscript revision. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



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# Optimizing vestibular neuritis management with modular strategies

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**Objective:** This study proposes a "modular management" approach for vestibular neuritis (VN) to reduce chronicization and improve patient prognosis. The approach involves multi-factor grading and hierarchical intervention and was found to be more effective than traditional treatment strategies.

**Methods:** This retrospective analysis compared two groups of VN patients from two medical institutions. The intervention group of 52 patients received "modular management," while the control group of 51 patients did not receive this kind of management. Analyzed the early treatment strategies, 6-month prognosis, and other indicators of the two groups of patients, compared and analyzed their overall prognosis, and identified the risk factors affecting the chronicization.

**Results:** The modular management group had lower dizziness severity, better balance, lower anxiety, and higher video head impulse testing (v-HIT) gain after 6months of onset. Analysis of factors related to persistent postural-perceptual dizziness (PPPD) in patients with VN showed positive correlations between the time from onset to diagnosis and PPPD, and Vertigo Symptom Scale (VSS), Dizziness Handicap Inventory (DHI), anxiety, and depression. Normalized vestibular rehabilitation was negatively correlated with PPPD, while gender, age, and early steroid use had no significant correlation. The multi-factor logistic regression model correctly classified 93.20% of the study subjects with a sensitivity of 87.50% and specificity of 94.90%.

**Conclusion:** The proposed "modular management" scheme for VN is a comprehensive and dynamic approach that includes health education, assessment, rehabilitation, therapy, evaluation, and prevention. It can significantly improve patient prognosis and reduce chronicization by shifting from simple acute treatment to continuous management.

KEYWORDS

**vestibular neuritis, modular management, risk factor, intervention, prognosis**

## 1. Introduction

Vestibular neuritis (VN) refers to an acute impairment of unilateral peripheral vestibular function, which is clinically characterized by acute and persistent vertigo (1), accompanied by nausea, vomiting, unsteadiness, and a tendency to fall toward the affected side. It is a common acute vertigo syndrome in clinical practice (2) VN has a certain degree

of spontaneous recovery, and in clinical practice, the prognosis of most VN patients is good with low recurrence rates. However, some patients may develop chronic symptoms. Previous studies on VN patients have found that 25–50% of patients develop persistent postural-perceptual dizziness (PPPD) during 3–12 months of follow-up (3, 4), around 15–30% of VN patients still experience persistent dizziness and oscillopsia 1 year after the onset of the disease (5). Once VN evolves into PPPD, patients will suffer from chronic and persistent dizziness/unsteadiness that is exacerbated by an upright posture, movement, or visual stimuli (6, 7). The development of secondary functional disorders, such as gait changes, anxiety, avoidance behavior, increased heart rate, and sweating, is also observed in patients with PPPD (8, 9). Chronic symptoms of PPPD can lead to significant decline in social functioning and some patients may become housebound and lose the ability to engage in daily activities and work. Therefore, effective prevention of VN chronicization is crucial for long-term prognosis and the patient's ability to return to normal social life.

Research on risk factors related to the chronicization of VN has not yielded a consistent conclusion. Kim et al. (10) suggested that the gain of semicircular canal in video head impulse testing (v-HIT) is the best predictor of patient symptom recovery, and a decrease in canal gain (<0.5) often indicates a prolonged disease course. Patients with covert saccades showed relatively better recovery of dynamic visual acuity, gait, and balance compared to those with overt saccades (11). However, a study by Patel et al. (12) suggested that there is no correlation between the chronicity of VN in patients and the results of bithermal caloric testing or v-HIT. Furthermore, previous studies have suggested that the chronicity of VN is associated with factors, such as patient anxiety status, personality traits, and visual dependence (13–19). Therefore, it is currently believed that the prognosis of VN patients may be related to multiple factors, and the weight of each factor may vary among individual patients. However, previous studies have mainly focused on analyzing the correlation between clinical characteristics during the acute and/or recovery periods and prognosis, but rarely addressed how to develop reasonable treatment plans to improve patient prognosis. So far, there is a lack of clear guidance on when and how to intervene, as well as how to evaluate the effectiveness of interventions for chronic risk factors such as residual vestibular dysfunction, anxiety and depression, and visual dependence. Clinical physicians often rely on personal experience when diagnosing and treating patients with VN. In our past clinical work, we have found that some doctors tend to prioritize medication over explaining the disease, and focus more on conducting tests rather than providing rehabilitation guidance. These practices leading to the chronicization of VN. Therefore, we believe that differences in clinical concepts may be an important factor contributing to differences in the prognosis of VN. Therefore, standardizing clinical diagnosis and treatment plans can help reduce the proportion of patients who develop chronic conditions, save medical expenses, and promote overall recovery.

This study proposes a modular management approach for VN, which shifts from simple acute-phase diagnosis and treatment to continuous, comprehensive, and dynamic management that includes disease knowledge dissemination, vestibular function assessment, vestibular rehabilitation (VR), cognitive behavioral therapy (CBT), prognosis evaluation, and prevention of chronicization. This study aims to investigate whether the "modular management" approach can improve the prognosis, reduce chronicization, and promote rapid recovery of social function in VN patients.

# 2. Materials and methods

## 2.1. Modular management for VN

### 2.1.1. Modular management for VN (acute phase)

#### 2.1.1.1. Applicable patients

Patients with acute onset vertigo within 14 days, or with spontaneous nystagmus (SN) to the healthy side on bedside examination.

#### 2.1.1.2. Bedside assessment

Perform a comprehensive physical examination of neurology and otology to differentiate and establish a definitive diagnosis. The evaluation should include the following components: ① Spontaneous nystagmus (SN), gaze-evoked nystagmus, and fixation suppression (horizontal head shaking or hyperventilation can be used based on patient tolerance); ② Bedside horizontal head impulse test and ocular tilt reaction (OTR); ③ Romberg test, tandem gait test, and finger-to-nose test; and ④ Tuning fork hearing test and otoscopy.

#### 2.1.1.3. Auxiliary examination

1. The type and timing of vestibular function tests should be based on the patient's tolerance. When a patient is in generally well health to tolerate vestibular function tests, these tests should be conducted as early as possible. Such tests are beneficial for accurate diagnosis, individualized vestibular rehabilitation (VR) program development, and prognosis evaluation.

The required tests include: ① Video nystagmography and caloric testing; ② Video head impulse test (v-HIT).

Optional tests include: ① Vestibular-evoked myogenic potential testing (VEMP); ② Fundus photography and ocular tilt reaction testing; and ③ Mid-frequency rotation.

2. Complete cranial MRI and pure tone audiometry (PTA) testing to rule out central structural lesions or otologic disorders. If necessary, other imaging tests such as CT plain or enhanced of the inner ear.

#### 2.1.1.4. Treatment of acute phase patients

1. Symptomatic support: In the initial 48 h of VN onset, patients may experience severe dizziness, nausea, and vomiting. Symptomatic relief with vestibular suppressants is important to prevent complications, but prolonged use can hinder central compensation (20).
2. Glucocorticoid: For patients without contraindications to steroid use, short-term low-dose corticosteroid therapy can be given during the acute phase. The specific regimen is as

follows: prednisone 1 mg/kg/day for 5 consecutive days, followed by tapering to 0.5 mg/kg/day for 3 consecutive days.

3. VRT: To facilitate clinical practice, we have divided the rehabilitation program for the acute phase of VN into two stages based on the characteristics of the disease course. Details below.

#### 2.1.1.4.1. Stage A

a. Seated oculomotor training (for patients whose static compensation has not been fully completed and who still have SN). ① The exercise involves fixing gaze on a visual target (in the forward and lateral directions) and maintaining eye position, followed by closing the eyes for 2–3 s and reopening them to continue gazing at the same target; ② Visual tracking exercises; and ③ Eye scanning exercises.
b. Postural exercises (for patients whose static compensation has been mostly completed and whose SN has disappeared or significantly weakened). ① Standing eyes-open and eyes-closed training; ② Weight shift training; ③ Gait training; ④ Single-leg standing training; and ⑤ Tandem standing training.

#### 2.1.1.4.2. Stage B

(For patients who have completed the acute phase training program) ① Standing, walking, and turning without visual cues or with altered proprioceptive feedback (such as foam pads or moving platforms) present; ② Gaze stability training (VOR × 1, VOR × 2) (21); ③ The vestibular substitution gaze stabilization training typically involves a duration of 12 min per session during the acute phase, with a minimum of three sessions per day. The final rehabilitation plan should be developed collaboratively by a vestibular specialist and rehabilitation therapist, with dynamic adjustments based on the individual needs of the patient.

4. Patients' education: Dizziness specialists should educate patients and their families about the illness characteristics and prognosis from consultation to complete recovery. The communication should focus on the underlying reasons for dizziness, recovery principles, and benign prognosis. Various forms of communication, such as verbal, written, video, group counseling, and individual Q&A sessions, can be used.
5. Promote VC drug: Recommend using drugs that promote vestibular compensation (VC), such as EGb761, an extract of Ginkgo biloba (80 mg orally three times a day for 3 months) and betahistine dihydrochloride (22) (12 mg orally three times a day for 3 months).

## 2.2. Modular management for VN (recovery phase)

### 2.2.1. Applicable patients

Acute dizziness with an onset between 14 days and 3 months ago, and no SN detected by bedside examination.

### 2.2.2. Bedside assessment

The same as acute phase.

### 2.2.3. Auxiliary examination

① The same as acute phase; ② For patients without a clear history of AVS, further investigations should be conducted to exclude EVS or CVS.

### 2.2.4. Treatment of recovery phase patients

During recovery, if patients lack proper diagnosis and treatment in the acute phase, they may restrict movements to alleviate discomfort. However, this can hinder muscle function and limit social activity. Educating and encouraging patients to increase movement and exposure is vital for recovery. To develop a personalized VR plan, consider the patient's complaints, clinical manifestations, and vestibular function tests. Adjust training intensity gradually, supervise therapy or offer home options, start with simple exercises, and modify the plan regularly. Early VR exercise initiation promotes faster and more complete vestibular function recovery (23, 24) (Figure 1).

1. This rehabilitation program is for the pre-recovery phase of vestibular disorders for patients who can complete acute phase training. ① Cross-coupled tracking: Hold a playing card in each hand and cross-move them while keeping the eyes fixed on one of the cards throughout the exercise; ② Postural control training; ③ Stair climbing exercise; ④ Walking while performing left–right gaze shifts, walking while performing up-down gaze shifts, and multitasking while walking; ⑤ Anti-saccade training, memory-based vestibulo-ocular reflex (VOR) training, memory-based saccade training; ⑥ Turning exercise; ⑦ Obstacle avoidance training; ⑧ Complex background gaze training; and ⑨ Endurance training.
2. Promote VC drug: The same as acute phase.
3. Thoroughly evaluate anxiety and depression levels in patients. Use cognitive behavioral therapy (CBT) for mild cases and anti-anxiety/antidepressant treatments for moderate to severe cases to increase compliance with rehabilitation. The 14-item Hospital Anxiety and Depression Scale (HADS), Vertigo Symptom Scale (VSS), and Dizziness Handicap Inventory (DHI) are helpful tools for clinicians to objectively assess the physical and mental conditions of patients.

### 2.2.5. Patients and inclusion/exclusion criteria

Inclusion criteria for the modular management group were: ① patients with VN treated in vertigo specialty clinics at Shanghai Changzheng Hospital and Wuhan Union Hospital between January 2019 and June 2021. The diagnosis of acute VN was based on a history of sudden onset of vertigo, without auditory or neurological symptoms. The clinical findings comprised of spontaneous contralesional horizontal-torsional nystagmus that did not change direction with gaze and increased without visual fixation and an ipsilesional pathologic head impulse test (25), it also complies with the diagnostic criteria for Acute Unilateral Vestibulopathy (AUVP) (26). ② We included patients who met the criteria for the "modular management program for vestibular neuritis" and had complete clinical case data. All patients were followed up for at least 6 months after their visit (follow-up methods included in-person visits and telephone follow-up).

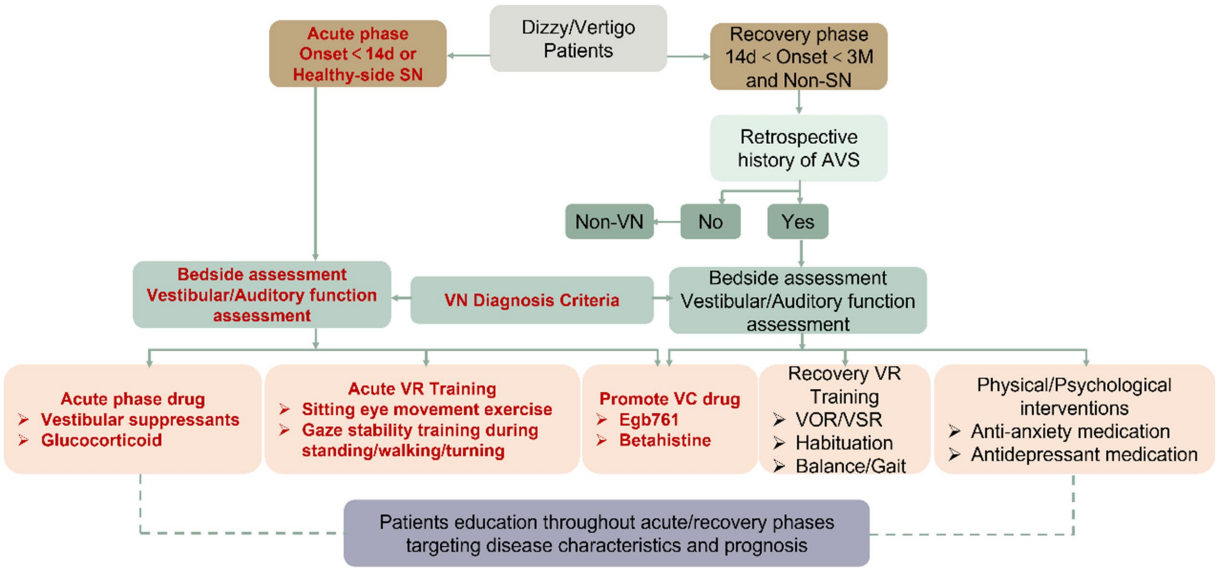


FIGURE 1
Modular management flowchart for VN. The flowchart presented in this paper represents a logical sequence of modules that can be used to manage vestibular neuritis effectively. The design incorporates key components such as vestibular rehabilitation, pharmacological interventions, lifestyle modifications, and psychological support. Each module is tailored to address specific needs and challenges encountered during different stages of the condition. VN, Vestibular neuritis; SN, Spontaneous nystagmus; VR, Vestibular rehabilitation; AVS, Acute vestibular syndrome; and VC, Vestibular compensation.

The control group comprised patients diagnosed with VN at Shanghai Changzheng Hospital and Wuhan Union Hospital or in a vertigo specialty clinic within 1–6 months after onset, excluding those in the modular management program. Telephone interviews were conducted for follow-up assessments.

This study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (NO. 20210873). All procedures performed in the studies involving human participants were in strict accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## 2.3. Methods

### 2.3.1. Rating scale

1. The 14-item Hospital Anxiety and Depression Scale (HADS) (27) has four response categories (0–3). Total score ranges from 0 to 42 points. A score of 19 points or more indicates a case of anxiety or depression, whereas 15 points indicate a possible case.
2. Vertigo Symptom Scale (VSS) (28). The scale has five response categories (0–4). Total scale scores range between 0 and 60 points, the scale has five response categories (0–4). Total scale scores range between 0 and 60 points， severe dizziness ≥ 12 points, clinically significant change ≥ 3 points.
3. Dizziness Handicap Inventory (DHI) (29) which has three response categories (0, 2, and 4). Total scores range from 0 to 100 points, interpreted as mild 0–30; moderate 31–60; and severe 61–100.

### 2.3.2. Vestibular function test

Patients in the modular management group have vestibular function tests 1 week after diagnosis and at 6 months after onset. Non-modular group (control group) patients have tests at 6 months after onset upon study entry. Tests are performed by technicians with at least 3 years of experience.

#### 2.3.2.1. Caloric test

Subject lies flat with head elevated by a 30° pillow. Eye movement recording system measures SPV, CP, and DP. Air irrigation at 24 and 50°C with 5 L/min for 60 s (30).

#### 2.3.2.2. V-HIT

Video head impulse testing conducted using videonystagmography system with subjects positioned 1.2 m from eye-level target. Goggles secured with elastic band. Multiple rotations performed on each side (31).

### 2.3.3. Diagnostic criteria of PPPD

Diagnostic criteria for PPPD: (1) Persistent dizziness/unsteadiness lasting ≥3 months. (2) Symptoms during upright position or triggering situations. (3) Not explained by other conditions. (4) Not accounted for by psychiatric disorders. (5) Causes distress/impairment. Diagnosis requires all criteria and excludes other conditions (3, 8).

## 2.4. Statistical analysis

In SPSS 23.0 software, normality and homogeneity of variance were tested before comparing continuous data. Normally distributed data were expressed as $\bar{x} \pm s$ and compared using a *t*-test if meeting

the assumptions; otherwise, the Mann–Whitney U test was used. Categorical data were presented as *n* and %, and compared using $\chi^2$ test or Fisher's test. Kendall's tau-b correlation and multivariate logistic regression analysis were performed to establish a regression model and evaluate multicollinearity. The ROC curve was used to analyze the predictive value of each indicator for PPPD development. The significance level was set at 0.05.

# 3. Results

In the modular management group, 57 patients were followed up, but two patients were uncooperative during examinations, one patient was intolerant to treatment, and two patients were lost to follow-up. Therefore, 52 patients were included in the study. In the control group, 56 patients were followed up, but four were uncooperative during examinations and one was lost to follow-up, resulting in 51 patients being included in the study. Overall, 103 patients were included in the study (Figure 2). Average age: 54.22 ± 12.899 years (15–82 years). Onset to diagnosis time: 16 (14–28) days. Onset to remission time: 6 (4–7) days. Male cases: 51, Female cases: 52, Male-to-female ratio: 1:1.020.

## 3.1. Baseline comparison between modular management and control groups

Baseline comparison showed no significant differences ($p > 0.05$) between the two groups in age, gender, time of visit, and various scale parameters during the early stage of the disease (Table 1).

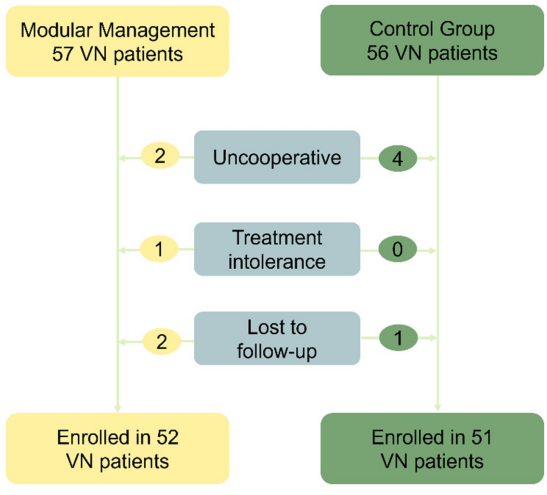


FIGURE 2
Flowchart for the screening process. The study included a total of 103 patients, with 57 patients in the modular management group. However, two patients were uncooperative during examinations, one patient was intolerant to treatment, and two patients were lost to follow-up. As a result, 52 patients were ultimately included. In the control group, 56 patients were followed up, but four were uncooperative during examinations and one was lost to follow-up, leading to 51 patients being included. VN, Vestibular neuritis.

## 3.2. Comparison of treatment and 6-month prognosis between modular management and control groups

We found that patients treated with modular management therapy were more likely to receive early corticosteroid treatment and had higher compliance with rehabilitation treatment. During the 6-month follow-up period, 10.68% of patients experienced recurrent dizziness, with most of them having a history of dizziness before VN onset. The incidence of PPPD differed significantly between the modular and non-modular management groups ($p < 0.000$). At 6 months after disease onset, all enrolled patients underwent reassessment of vestibular function, with the following parameters recorded: canal paresis (CP) values (normal range < 30%) and affected-side horizontal video head impulse test (vHIT) gains (normal range 0.8–1.2). In the modular management group, the parameters for the two groups at 6 months were as follows: 32 patients (61.538%) achieved normalization of CP values, 34 patients (65.385%) achieved normalization of vHIT gains, and 23 patients (44.231%) achieved normalization of both parameters. In contrast, in the non-modular management group, the respective numbers were 25 patients (49.020%), eight patients (15.686%), and four patients (7.843%). At 6 months after onset, the modular management group had better recovery of vHIT gain and lighter symptoms of dizziness, balance disorders, and anxiety than the non-modular group (Table 2).

## 3.3. Comparison of vestibular function and scale between two time points in modular management group

The vestibular function and various clinical parameters, including dizziness symptoms, social function, balance disorders, and anxiety, showed significant improvement in the modular management group compared to the non-modular group at both the early stages of the disease and 6 months after onset ($p < 0.05$; Table 3).

## 3.4. Analysis of factors related to secondary PPPD in VN patients

A correlation analysis was conducted to explore the factors related to the development of PPPD in patients with VN. Results showed that patients with longer time from onset to diagnosis, higher VSS and DHI scores at 6 months after onset, and more severe anxiety and depression were more likely to develop PPPD. Patients who received standardized vestibular rehabilitation therapy had a significantly lower likelihood of developing PPPD ($p < 0.05$). There was no significant correlation between gender, age, or early use of steroids and the development of PPPD (Table 4).

We established a model using multiple logistic regression to identify independent factors associated with the development of PPPD in patients with VN. The model had statistical significance ($p = 0.000$) and accurately classified 93.200% of patients with a sensitivity of 87.50% and a specificity of 94.900%. There was no multicollinearity among the six predictor variables included in the model. The DHI score, anxiety level, and whether standard VRT was performed at 6 months after onset were identified as independent

TABLE 1 Baseline comparison between modular management and control groups.

| Parameter | Control group | Modular management | Statistical value | *p* value |
|---|---|---|---|---|
| | *n* = 51 | *n* = 52 | | |
| Age (year) | 53.59 ± 11.979 | 54.85 ± 13.831 | $F = 0.243$ | 0.623 |
| Gender (*n*, %) | | | $\chi^2 = 0.244$; $p = 0.622$ | |
| Male | 24 (47.060) | 27 (51.920) | | |
| Female | 27 (52.940) | 25 (48.080) | | |
| Onset-to-diagnosis (d) | 15.000 | 16.670 | $U = 1098.000$ | 0.131 |
| Onset-to-relief (d) | 5.670 | 6.320 | $U = 1177.000$ | 0.321 |
| VSS (score), *M* | 55.000 | 58.330 | $U = 1258.000$ | 0.654 |
| DHI (score), *M* | 54.200 | 54.600 | $U = 1246.000$ | 0.597 |
| ABC (%), *M* | 50.863 | 50.450 | $U = 1259.500$ | 0.660 |
| HADS-A (score), *M* | 4.000 | 4.820 | $U = 1300.000$ | 0.863 |
| HADS-D (score), *M* | 1.590 | 1.610 | $U = 1304.500$ | 0.884 |

VSS: Vertigo symptom scale; DHI, Dizziness handicap inventory; ABC, Activities-specific balance confidence scale; HADS, The 14-item hospital anxiety and depression scale. $^*p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

TABLE 2 Comparison of treatment and prognosis between modular management and control groups.

| Parameter | Control group (*n* = 51) | Modular management (*n* = 52) | Statistical value | *p* value |
|---|---|---|---|---|
| Low-dose steroid in acute phase (*n*, %) | 6 (11.765) | 35 (67.308) | $\chi^2 = 33.151$ | 0.000*** |
| Standardized VRT (*n*, %) | 7 (13.725) | 52 (100.000) | $\chi^2 = 78.320$ | 0.000*** |
| Incidence rate of PPPD (*n*, %) | 20 (39.216) | 4 (7.692) | $\chi^2 = 14.317$ | 0.000*** |
| CP value (%), *M* | 31.000 | 25.860 | $U = 1137.500$ | 0.213 |
| vHIT gain, *M* | 0.660 | 0.824 | $U = 497.000$ | 0.000*** |
| VSS (score), *M* | 7.000 | 3.400 | $U = 1023.000$ | 0.045* |
| DHI (score), *M* | 2.210 | 1.890 | $U = 1251.500$ | 0.610 |
| ABC (%), *M* | 88.920 | 95.000 | $U = 796.000$ | 0.000*** |
| HADS-A (score), *M* | 3.900 | 2.380 | $U = 916.000$ | 0.006** |
| HADS-D (score), *M* | 1.000 | 0.910 | $U = 1249.500$ | 0.599 |

VRT, Vestibular rehabilitation therapy; CP, canal paresis; PPPD: Persistent postural-perceptual dizziness; v-HIT, video-Head impulse test; VSS, Vertigo symptom scale; DHI, Dizziness handicap inventory; ABC, Activities-specific balance confidence scale; and HADS, The 14-item hospital anxiety and depression scale. $^*p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

factors influencing the development of PPPD in patients with VN (Table 5).

We plotted ROC curves to predict PPPD in patients using different indicators. The results showed that anxiety level at 6 months after onset had the highest area under the curve (AUC = 0.940, 95% CI 0.881–0.999, $p < 0.000$, sensitivity 83.330%, specificity 94.940%), followed by DHI score at 6 months (AUC = 0.860, 95% CI 0.766–0.953, $p < 0.000$, sensitivity 87.500%, specificity 78.480%) and whether the patient received standardized vestibular rehabilitation therapy (AUC = 0.765, 95% CI 0.659–0.871, $p < 0.000$, sensitivity 83.330%, and specificity 69.620%). The ROC curves are shown in Figure 3.

# 4. Discussion

Our study found that the incidence of PPPD in the modular management group was significantly lower than that in the non-modular management group. Therefore, standardized "modular management" for VN patients will help improve prognosis, reduce the incidence of secondary PPPD, and minimize disease chronicity, thus promoting comprehensive and rapid recovery of social function in patients.

## 4.1. Health education and popularization

To further investigate the reasons for the reduction of chronicity by modular management, we analyzed the relevant clinical data of VN patients and found that initial misdiagnosis was an important risk factor for disease chronicity, but there was no clear correlation between the use of steroid therapy in the acute phase and the development of PPPD. Therefore, we believe that the difference in prognosis is not due to differences in acute drug treatment, but rather whether patients receive a clear diagnosis and disease-related education during the acute phase. Patients with an unclear diagnosis are more likely to develop anxiety, depression, and fear, leading to self-imposed physical restrictions such as reducing neck movement,

TABLE 3 Comparison of vestibular function and scale between two time points in modular management group.

| Parameter | First onset | 6 months post-onset | *U*-value | *p* value |
|---|---|---|---|---|
| CP value (%), *M* | 50.830 | 25.860 | 409.000 | 0.000*** |
| vHIT gain, *M* | 0.552 | 0.824 | 197.500 | 0.000*** |
| VSS, *M* | 58.330 | 3.400 | 19.000 | 0.000*** |
| DHI, *M* | 54.600 | 1.890 | 0.000 | 0.000*** |
| ABC (%), *M* | 50.450 | 95.00 | 22.000 | 0.000*** |
| HADS-A, *M* | 4.820 | 2.380 | 793.000 | 0.000*** |
| HADS-D, *M* | 1.610 | 0.910 | 998.500 | 0.018* |

CP, Canal paresis; vHIT, Video-head impulse test; VSS, Vertigo symptom scale; DHI, Dizziness handicap inventory; ABC, Activities-specific balance confidence scale; and HADS, The 14-item hospital anxiety and depression scale. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 4 Univariate analysis of VN chronicization factors.

| Parameter | Kendall's tau-b Correlation coeff | *p* value |
|---|---|---|
| Gender | −0.143 | 0.148 |
| Age | −0.022 | 0.785 |
| Onset-to-diagnosis | 0.285 | 0.001** |
| Onset-to-relief | 0.016 | 0.847 |
| Initial assessment post-onset | | |
| CP value | −0.090 | 0.439 |
| vHIT value | 0.150 | 0.197 |
| VSS | 0.073 | 0.376 |
| DHI | 0.046 | 0.582 |
| ABC | 0.017 | 0.842 |
| HADS-A | 0.096 | 0.255 |
| HADS-D | 0.159 | 0.071 |
| Assessment 6 months post-onset | | |
| CP value | 0.135 | 0.100 |
| vHIT value | −0.142 | 0.086 |
| VSS | 0.165 | 0.049* |
| DHI | 0.495 | 0.000*** |
| ABC | −0.147 | 0.077 |
| HADS-A | 0.558 | 0.000*** |
| HADS-D | 0.381 | 0.000*** |
| Steroids early? | −0.167 | 0.092 |
| Standard VR? | −0.453 | 0.000*** |

CP, Canal paresis; vHIT, Video-Head impulse test; VSS, Vertigo symptom scale; DHI, Dizziness handicap inventory; ABC, Activities-specific balance confidence scale; HADS, The 14-item hospital anxiety and depression scale; VR, Vestibular rehabilitation. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

slowing walking speed, shortening step length, and reducing joint movement during walking. These physical restrictions further lead to abnormal skeletal muscle function, ultimately limiting patients' social activity ability at both physiological and psychological levels.

Patients in the modular management group received a clear diagnosis and disease education from specialist doctors at the earliest time, which can greatly relieve patient anxiety, enhance patient confidence in disease recovery, and take active coping measures, thereby reducing the occurrence of chronicization. Therefore, in clinical practice, active health education for vestibular neuritis patients, encouraging patients to actively remove restrictions, increasing active exercise and life scenario exposure, will help with patient recovery.

## 4.2. Whole-course VR therapy

McDonnell et al. (32) conducted a review of 39 trials involving over 2,400 patients with unilateral vestibular dysfunction, the authors concluded that there is moderate to strong evidence supporting the use of vestibular rehabilitation therapy (VRT) as a safe and effective treatment for unilateral peripheral vestibular dysfunction. Our study also confirmed the effectiveness of VR treatment, and the low utilization rate of standardized VRT was found to be associated with the occurrence of PPPD, indicating that standardized VRT may help prevent the chronicization of VN. The mechanism may be that early VRT can prevent the formation of poor posture, while head-eye coordinated movements can promote central compensation. In the recovery phase, VRT focuses on improving postural stability and reducing visual dependence, as the development of visual dependence is a major risk factor for chronicity in vestibular disorders (33) and a core symptom of PPPD (8). Physical therapy interventions have been demonstrated to decrease dizziness induced by visual stimuli (34).

## 4.3. Assessment of anxiety and depression

Additionally, our study found a significant correlation between patients' poor prognosis and their anxiety and depression scores. Beck (35) and Bandura (36) point out the importance of the expected consequences of the event. They suggest that anxious individuals react more strongly to threatening stimuli and search more intensely for safety signals. This increases self-observation, which, in turn, tends to trigger negative emotions (37). Herdman et al. (38) found that approximately 75–88% of patients with unilateral vestibular dysfunction can benefit from VRT, but not all patients do, and anxiety and depression are the primary factors affecting rehabilitation outcomes. Cousins et al. (39) found that overactive autonomic nervous system and psychological factors are closely related to the development of visual dependence after unilateral vestibular damage. Compensation for unilateral vestibular loss depends on the reweighting of multisensory (visual-vestibular) cues, and the neural networks that process visual, vestibular, and emotional states are extensively linked and cross-connected. Thus, vestibular compensation and psychological states interact with each other, as supported by functional magnetic resonance imaging data, although the directionality of this association remains unclear (40). Therefore, we can infer that emotional disorders may interfere with VN recovery in various ways. Early identification and intervention to reduce anxiety and autonomic nervous system activation may have significant value in improving long-term prognosis. Comprehensive treatment plans, including patient education, CBT, and anti-anxiety/depression

TABLE 5 Multivariate logistic regression analysis of chronicization factors in VN.

| Parameter | β | SE | OR | 95% CI | *p* value |
|---|---|---|---|---|---|
| Onset-to-diagnosis (d) | 0.024 | 0.018 | 1.024 | 0.998–1.062 | 0.195 |
| Onset 6 months VSS | 0.065 | 0.061 | 1.068 | 0.948–1.203 | 0.282 |
| Onset 6 months DHI | 0.387 | 0.186 | 1.473 | 1.023–2.120 | 0.037* |
| Onset 6 months HADS-A | 0.716 | 0.262 | 2.047 | 1.226–3.419 | 0.006** |
| Onset 6 months HADS-D | 0.330 | 0.246 | 1.391 | 0.859–2.254 | 0.180 |
| Standard VR? | 2.996 | 1.486 | 19.998 | 1.086–368.211 | 0.044* |
| Constant | −10.261 | 2.959 | 0.000 | / | 0.001** |

VN, Vestibular neuritis; VSS, Vertigo symptom scale; DHI, Dizziness handicap inventory; HADS: The 14-item hospital anxiety and depression scale; VR, Vestibular rehabilitation; SE, Standard error; and OR, Odds ratio. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

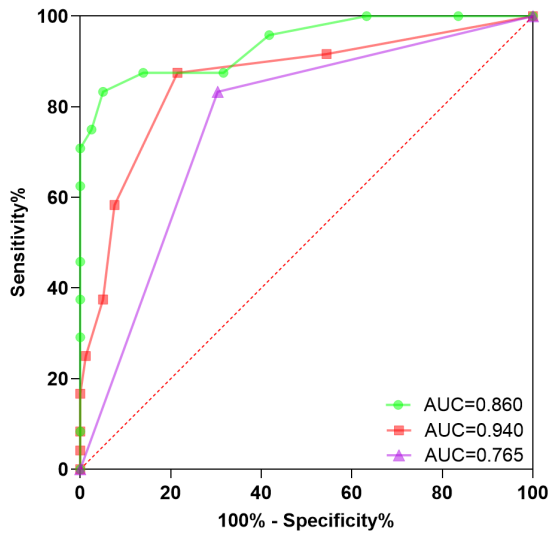


FIGURE 3
ROC curve for secondary PPPD prediction. This study conducted a rigorous evaluation of the predictive accuracy of a Receiver Operating Characteristic (ROC) curve in determining secondary PPPD. The findings provide valuable insights into the diagnostic potential of the ROC curve for identifying secondary PPPD in clinical settings, contributing to improved patient management. ROC, Receiver operating characteristic; PPPD, Persistent postural-perceptual dizziness; Green, DHI score at 6 months after onset; Red, Anxiety level at 6 months after onset; and Purple, Normalization of vestibular rehabilitation treatment.

medication, may be beneficial for patients with moderate to severe anxiety or anxiety traits, potentially reducing the risk of chronicity.

## 5. Conclusion

We have found that some VN patients may experience recurrent episodes of vertigo during their recovery period, and even fully compensated patients may experience fluctuating vestibular symptoms and balance impairments. We need to carefully differentiate the different phenotypic combinations during different stages of the disease, explore the triggering factors and background diseases. The prognosis of VN may be related to multiple factors, and the weight of each factor may vary individually among patients. Early and accurate prediction of prognosis may facilitate personalized intervention for high-risk patients, preventing chronic disease and avoiding over-treatment.

However, our study has limitations such as small sample size, incomplete data on patients in the non-modular treatment group, and retrospective design. Future work will focus on finding sensitive and specific clinical indicators in the early stage of the disease, designing a clinical prediction model, and providing help for personalized treatment of early-stage disease.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

## Ethics statement

This study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China (NO. 20210873). All procedures performed in the studies involving human participants were in strict accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Author contributions

SZ and JZ designed the research and directed its implication. FL, JX, and DL prepared and analyzed the data and reviewed drafts of the manuscript. JW, LL, RG, and XZ contributed to the manuscript's modifications. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



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# Visuospatial cognition in acute unilateral peripheral vestibulopathy

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**Background:** This study aims to investigate the presence of spatial cognitive impairments in patients with acute unilateral peripheral vestibulopathy (vestibular neuritis, AUPV) during both the acute phase and the recovery phase.

**Methods:** A total of 72 AUPV patients (37 with right-sided AUPV and 35 with left-sided AUPV; aged 34–80 years, median 60.5; 39 males, 54.2%) and 35 healthy controls (HCs; aged 43–75 years, median 59; 20 males, 57.1%) participated in the study. Patients underwent comprehensive neurotological assessments, including video-oculography, video head impulse and caloric tests, ocular and cervical vestibular-evoked myogenic potentials, and pure-tone audiometry. Additionally, the Visual Object and Space Perception (VOSP) battery was used to evaluate visuospatial perception, while the Block design test and Corsi block-tapping test assessed visuospatial memory within the first 2 days (acute phase) and 4 weeks after symptom onset (recovery phase).

**Results:** Although AUPV patients were able to successfully perform visuospatial perception tasks within normal parameters, they demonstrated statistically worse performance on the visuospatial memory tests compared to HCs during the acute phase. When comparing right versus left AUPV groups, significant decreased scores in visuospatial perception and memory were observed in the right AUPV group relative to the left AUPV group. In the recovery phase, patients showed substantial improvements even in these previously diminished visuospatial cognitive performances.

**Conclusion:** AUPV patients showed different spatial cognition responses, like spatial memory, depending on the affected ear, improving with vestibular compensation over time. We advocate both objective and subjective visuospatial assessments and the development of tests to detect potential cognitive deficits after unilateral vestibular impairments.

KEYWORDS

**acute unilateral peripheral vestibulopathy, vestibular neuritis, vestibular compensation, visuospatial cognition, higher vestibular cognition, vestibular dominance**

# Introduction

The spatial cognitive process is the result of complex multisensory signal interactions as well as various delicate synaptic integrative mechanisms involved in cognitive mapping (1, 2). The contribution of vestibular inputs to spatial cognition has been demonstrated in several neurophysiological, neuroimaging, and neuropathological studies (3). The vestibular system participates in dynamic mechanisms of spatial cognition, such as path integration, and landmark-or geometry-based strategies (1, 4), and contributes to update the navigator's current position in relation to a reference point, space knowledge of the navigable space geometry, recognition of familiar view-dependent scenes, differentiation of self-or object-motion, and optimization of distance estimation (4). Peripheral vestibular signals in convergence with other sensory inputs establish multisensory pathways for enhanced perception and effective navigation (5, 6). Vestibular signals project into many subcortical and cortical structures responsible for spatial cognition, including the thalamocortical and cerebellocortical pathways linking the head direction cells (7).

The causal association between vestibular impairments and visuospatial cognitive deficits was demonstrated in bilateral vestibulopathy (BVP), which provided a comprehensive description of severe and prolonged dysfunction of spatial cognition with hippocampal atrophy (8). Acute unilateral peripheral vestibulopathy (AUPV, most commonly vestibular neuritis) refers to a sudden loss of ipsilateral peripheral vestibular function without hearing impairment or brainstem signs (9). It is characterized by acute, prolonged spontaneous vertigo, nausea/vomiting, and unsteadiness of stance and gait. The symptoms subside within a few weeks (9). Neurotological examinations reveal spontaneous horizontal-torsional nystagmus beating away from the lesion side, an abnormal head impulse test for the involved semicircular canals, and ipsilesional caloric paresis. The vestibular compensation following AUPV was elucidated by virtue of advances in neuroimaging, such as positron emission tomography (PET) (10) and voxel-based morphometry (VBM) on MRI (11). To date, convincing evidence for visuospatial cognitive deficits is lacking in AUPV. Only a few animal studies on AUPV reported spatial cognitive impairments, particularly transient memory deficits within 2 weeks after labyrinthectomy (12), with lesions on the vestibular dominant side suspected of causing more severe cognitive deficits (13). Similarly, several studies showed spatial cognitive deficits (14) and hippocampal atrophy in patients with unilateral vestibulopathy (15). However, other studies failed to confirm these findings (16). The extent of unilateral or bilateral vestibular damage may explain these controversial results because patients often present with incomplete vestibular damage. In several neuroimaging studies, brain metabolism differed between patients with left-and right-sided AUPV, which may explain why the lesions on the dominant side of vestibular lateralization cause more severe spatial cognitive deficits (17). These findings raise questions about the hypothesis that AUPV is associated with spatial cognitive dysfunction, both during the acute stage and after symptoms have resolved in the recovery phase.

Here, we conducted a detailed study of spatial cognition in AUPV patients by using variable visuospatial-perception and-memory tasks. The main purpose of current study was to evaluate the spatial cognitive deficits, visuospatial perception and memory, in patients with AUPV during the initial and recovery phases of vestibular dysfunction. We hypothesized that patients with AUPV would present spatial cognitive deficits during the acute phase, especially when the right side, the dominant vestibular side in right-handers, is affected.

# Methods

## Participants

The study included 72 AUPV patients (37 right and 35 left AUPV; age range 34 to 80 years, median 60.5; 39 men, 54.2%) and 35 healthy controls (HCs; age range 43 to 75 years, median 59; 20 men, 57.1%) in Jeonbuk National University Hospital from March 2021 to August 2022 (Table 1). Patients who had moderate to severe visual impairment (with a best-corrected visual acuity less than 6/18 in the better eye) (18) or hearing impairment (with a threshold of pure tone audiometry over 30 dB), clinical signs of central involvement (such as gaze-evoked nystagmus, skew deviation, associated neurological deficits), abnormal MRI findings with diffusion-weighted sequence, or were on centrally active medications or vestibular sedatives were excluded. For all participants, the Mini-Mental State Examination (MMSE) was used to assess global mental status (19), and the Edinburgh Handedness Inventory, a 10-item inventory, to assess handedness (Table 1). During the acute phase, the visual analog scale (VAS) for dizziness (D-VAS) was used to gage the subjective feeling of dizziness in AUVP patients. Patients were asked about their personal experience of dizziness, which they reported using the D-VAS. The scale ranged from 0 (indicating no sensation) to 100 (representing a disabling and continuous sensation). The Visual Object and Space Perception (VOSP) battery was used to assess visuospatial perception, and the Block design test (BDT) and Corsi block-tapping test (CBTT) were performed to assess visuospatial memory (Table 2).

All participants provided informed consent and received monetary compensation for participation. The Institutional Review Board at Jeonbuk National University Hospital (no. 2020-10-134-006) reviewed and approved the experiments.

## Vestibular function tests

All patients underwent neurotological investigations using video-oculography, the video head impulse test (vHIT) and caloric test, ocular and cervical vestibular-evoked myogenic potentials (VEMPs), and pure-tone audiometry within the first 2 days (acute phase) and 4 weeks after symptom onset (recovery phase). vHIT was performed more than 20 times (head rotation 15–20°, duration 150–200 ms, peak velocity > 150°/s) on both sides of each plane and was analyzed using oculography (SLMED, Seoul, Korea) (20). The caloric irrigation test was performed with the patient in the supine position and $30^0$ head elevation using closed-loop water irrigators at 30°C and 44°C (irrigation time 30 s, intervals 5 min) and was characterized by induced nystagmus (SLMED, Seoul, Korea) (21), especially the slow-phase velocity to estimate unilateral weakness using Jongkees formula (22). For cervical VEMPs (23), active electrodes were placed over the middle or upper portion of the sternocleidomastoid muscle; for ocular VEMPs (24), electrodes

TABLE 1 Comparison of demographic features and vestibular function tests in AUPV (vestibular neuritis, VN) patients ($n = 72$) and healthy controls ($n = 35$).

| | VN ($n = 72$) | R.VN ($n = 37$) | L.VN ($n = 35$) | HC ($n = 35$) | Value of $p$ (VN-HC) | Value of $p$ (R.VN-HC) | Value of $p$ (L.VN-HC) | Value of $p$ (R.VN-L.VN) |
|---|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | | |
| Sex, male, $n$ (%) | 39 (54.17) | 20 (54.05) | 19 (54.29) | 20 (57.1) | 0.758 | 0.777 | 0.793 | 0.984 |
| Age, years, median (95% CI) | 60.5 (59–63) | 62 (58–65) | 60 (58–63) | 59 (53–65) | 0.421 | 0.252 | 0.78 | 0.379 |
| Education, years, median (95% CI) | 12 (12–16) | 12 (12–16) | 12 (12–16) | 16 (11–16) | 0.474 | 0.503 | 0.539 | 0.9 |
| MMSE (30 points), median (95% CI) | 28 (28–29) | 28 (28–29) | 29 (28–30) | 28 (28–30) | 0.581 | 0.417 | 0.87 | 0.455 |
| Right handedness, $n$ (%) | 72 (100) | 37 (100) | 35 (100) | 35 (100) | | | | |
| D-VAS | 39.95 ± 1.75 | 41.01 ± 1.07 | 37.24 ± 1.90 | - | | | | 0.591 |
| Audio-Vestibular function tests | | | | | | | | |
| Acute phase (within 2 days of onset) | | | | | | | | |
| Spontaneous nystagmus, mean (°/sec) | 13.7 ± 14.5 | 14.2 ± 11.3 | 12.9 ± 14.1 | - | - | | | 0.061 |
| vHIT hVOR mean gain | | | | | | | | |
| Ipsilesional, median (95% CI) | 0.69 (0.61–0.76) | 0.64 (0.53–0.83) | 0.72 (0.62–0.76) | - | - | | | 0.968 |
| Contralesional, median (95% CI) | 0.96 (0.94–0.99) | 0.94 (0.91–0.98) | 0.97 (0.96–1.01) | - | - | | | 0.178 |
| Presence of corrective saccades, $n$ (%) | 58 (80.56) | 28 (75.68) | 30 (85.71) | - | - | | | 0.285 |
| Caloric paresis, %, median (95% CI) | 66.96 (45.7–98) | 68.8 (36.4–110) | 66.96 (36.4–111) | - | - | | | 0.782 |
| Caloric paresis ≥35%, $n$ (%) | 48 (66.67) | 25 (67.57) | 23 (65.71) | - | - | | | 0.933 |
| Cervical and ocular VEMP | | | | | | | | |
| cVEMP p13 mean latency | | | | | | | | |
| Ipsilateral, ms, median (95% CI) | 13.9 (13.6–14.6) | 13.9 (13.6–14.4) | 14.2 (13.5–15.3) | - | - | | | 0.515 |
| Contralateral, ms, median (95% CI) | 13.9 (13.5–14.2) | 13.6 (13.2–14.2) | 14.1 (13.2–14.6) | - | - | | | 0.48 |
| cVEMP amplitude AR, %, median (95% CI) | 21 (13–26) | 16 (12–25) | 25 (15–31) | - | - | | | 0.28 |
| cVEMP amplitude AR ≥ 40%, $n$ (%) | 11 (15.28) | 4 (10.81) | 7 (20) | - | - | | | 0.116 |
| oVEMP n10 mean latency | | | | | | | | |
| Ipsilateral, ms, median (95% CI) | 11 (10.8–11.8) | 11 (10.7–11.8) | 11.3 (10.8–12.8) | - | - | | | 0.118 |
| Contralateral, ms, median (95% CI) | 10.7 (10.4–10.8) | 10.7 (10.3–10.8) | 10.55 (10.2–11) | - | - | | | 0.624 |
| oVEMP amplitude AR, %, median (95% CI) | 26 (17–36) | 21.5 (14–45) | 27 (14–44) | - | - | | | 0.925 |
| oVEMP amplitude AR ≥ 40%, $n$ (%) | 20 (27.78) | 11 (29.73) | 9 (25.71) | - | - | | | 0.855 |
| PTA, dB, median (95% CI) | 19.5 (15–24) | 20.5 (16–24.5) | 15.8 (12.5–24.5) | - | - | | | 0.396 |
| Recovery phase (follow-up 4 weeks after onset) | | | | | | | | |
| vHIT hVOR mean gain | | | | | - | | | |
| Ipsilesional, median (95% CI) | 0.82 (0.57–1.02) | 0.85 (0.57–1.03) | 0.76 (0.53–1.06) | - | - | | | 0.48 |
| Contralesional, median (95% CI) | 0.97 (0.93–1.03) | 0.96 (0.91–1.01) | 0.99 (0.91–1.07) | - | - | | | 0.41 |
| Presence of corrective saccades, $n$ (%) | 22 (30.56%) | 9 (24.3%) | 13 (37.1%) | | | | | 0.307 |

Values are presented as median (95% CI). Statistical significance was calculated using the Mann–Whitney U test. D-VAS, the visual analog scale (VAS) for dizziness; vHIT-ipsi, video head impulse test-ipsilesional; UW, unilateral weakness; VEMP, vestibular evoked myogenic potential; AR, asymmetry ratio; MMSE, mini–mental state examination; PTA, pure tone audiometry; dB, decibel; ms, millisecond.

were placed on the infraorbital margin 1 cm below the center of the contralateral lower eyelid. The VEMP results can be easily interpreted based on the asymmetry ratio (AR) of the amplitude, computed as the difference in amplitudes between the ears divided by the sum of the amplitudes in both ears (25).

## Visuospatial perception testing (VOSP battery)

The Visual Object and Space Perception (VOSP) battery is a neuropsychological assessment tool used to evaluate visual perception

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TABLE 2 Assessment of visuospatial cognitive abilities in AUPV (vestibular neuritis, VN) patients during acute and recovery phases.

| | VN ($n$ = 72) | R.VN ($n$ = 37) | L.VN ($n$ = 35) | HC ($n$ = 35) | Value of $p$ between group[K] | Value of $p^M$ (VN-HC) | Value of $p^M$ (R.VN-HC) | Value of $p^M$ (L.VN-HC) | Value of $p^M$ (R.VN-L.VN) |
|---|---|---|---|---|---|---|---|---|---|
| Acute phase (within 2 days of onset) | | | | | | | | | |
| Visuospatial perception tests | | | | | | | | | |
| Position discrimination (20 points) | 18 (18–19) | 18 (17–19) | 19 (18–20) | 20 (19–20) | **0.003** | **0.006** | **0.001** | 0.083 | 0.042 |
| Number location (10 points) | 9 (8–9) | 8 (8–9) | 9 (9–10) | 10 (9–10) | **<0.001** | **<0.001** | **<0.001** | 0.023 | **0.006** |
| Cube analysis (10 points) | 9 (8–9) | 8 (8–9) | 10 (9–10) | 9 (9–10) | **<0.001** | 0.048 | **<0.001** | 0.834 | **<0.001** |
| Visuospatial memory tests | | | | | | | | | |
| BDT (48 points) | 32 (32–32) | 30 (28–32) | 32 (32–36) | 37 (32–40) | **<0.001** | **0.002** | **<0.001** | 0.095 | **0.003** |
| BDT Plus (66 points) | 34 (32–35) | 33 (29–34) | 35 (34–41) | 43 (38–48) | **<0.001** | **0.001** | **<0.001** | 0.041 | 0.019 |
| CBTT-block span | 5 (5–6) | 5 (5–6) | 6 (5–6) | 7.5 (7–8) | **<0.001** | **<0.001** | **<0.001** | **<0.001** | 0.098 |
| CBTT-total score | 25 (23–28) | 24 (21–28) | 27 (22–33) | 40.5 (34–44) | **<0.001** | **<0.001** | **<0.001** | **<0.001** | 0.047 |
| Recovery phase (follow-up 4 weeks after onset) | | | | | | | | | |
| Visuospatial perception tests | | | | | | | | | |
| Position discrimination (20 points) | 19 (19–20) | 19 (19–20) | 20 (19–20) | 20 (19–20) | 0.488 | 0.708 | 0.402 | 0.868 | 0.259 |
| Number location (10 points) | 9 (9–10) | 9 (9–10) | 10 (9–10) | 10 (9–10) | 0.138 | 0.353 | 0.091 | 0.983 | 0.094 |
| Cube analysis (10 points) | 9 (9–10) | 9 (9–10) | 9 (9–10) | 9 (9–10) | 0.289 | 0.362 | 0.17 | 0.793 | 0.205 |
| Visuospatial memory tests | | | | | | | | | |
| BDT (48 points) | 32 (32–36) | 32 (32–38) | 32 (32–38) | 37 (32–40) | 0.155 | 0.065 | 0.075 | 0.131 | 0.528 |
| BDT Plus (66 points) | 38 (35–40) | 36 (34–41) | 38 (35–47) | 43 (38–48) | 0.097 | 0.067 | 0.037 | 0.231 | 0.236 |
| CBTT-block span | 7 (6–7) | 7 (6–7) | 7 (6–8) | 7 (7–8) | 0.187 | 0.099 | 0.062 | 0.272 | 0.446 |
| CBTT-total score | 35.5 (31–38) | 35 (29–36) | 37 (31–43) | 40.5 (34–44) | **0.037** | 0.051 | **0.012** | 0.308 | 0.1 |

Values are presented as median (95% CI). Statistical significance was calculated using the [K]Kruskal-Wallis test (between group comparison) and the [M]Mann–Whitney U test (pairwise comparisons) with a Bonferroni-adjusted significance level of 0.017 (0.05/3). Bold indicates a statistically significant difference. In the BDT, scores are added based on whether the block design for each question is correct regardless of time, and the BDT Plus is a summation assigning additional points for faster answers. CBTT-block span is the length of the last correctly repeated sequence. CBTT-total score is the product of the CBTT-block span and the number of correctly repeated sequences until the test is discontinued (i.e., the number of correct trials). This latter score takes into account the performance on both trials of an equal length and is more reliable than the CBTT-block span alone.

and spatial processing abilities. It includes subtests for Object Perception and Space Perceptions, which are designed to elicit straightforward responses from participants and minimize the influence of other cognitive abilities (26, 27). In this study, we first conducted a preliminary visual sensory efficiency test (Shape detection screening test), and then administered the Space Perceptions subtests, including Position discrimination, Number location, and Cube analysis.

*The shape detection screening test* was conducted to ensure that participants had adequate visual capacity to complete the other subtests. Visual acuity of the participants was assessed using 20 stimulus cards, half of which contained a degraded 'X' symbol (degraded by 30%), and participants were required to identify the presence or absence of the 'X' (28). Participants with scores of 15 or below were excluded from further participation in the VOSP test battery, as research has shown that low visual acuity can significantly affect performance on the VOSP tasks (28).

*The position discrimination test* includes 20 boards, each featuring a square with a black dot (5 mm) positioned exactly at the center, and another square with a slightly off-center black dot that is horizontally adjacent. The score is determined by counting the number of correct responses in identifying the square with the black dot at the exact center, with a maximum possible score of 20 (20). The cutoff value for failure is 18/20 (28).

*The number location test* comprises of 10 boards, each containing two squares with a small gap between them. The top square displays

randomly arranged numbers (1–9), while the bottom square has a single black dot that corresponds to the position of one of the numbers. The score is based on the number of correct responses identifying the number that matches the dot's position, with a maximum score of 10 (20). The cutoff value for failure is 7/10 (28).

*The cube analysis test* is a three-dimensional (3D) analysis presented on a two-dimensional (2D) plane consisting of 10 boards with 3D-arranged cubes. The score is determined based on the number of correct responses accurately identifying the number of cubes were on each board, including the hidden cube (maximum score: 10) (20). The cutoff value for failure is 6/10 (28).

## Visuospatial memory testing

### Block design test

Participants were given nine individual blocks with two sides of solid white, two sides of solid red, and two sides of half red/half white (crossed diagonally) and were asked to assemble the blocks to exactly reconstruct the 2D pattern shown (29). Gradually more complex patterns are presented and reproduction times are measured. Each trial is timed and bonus points are given for faster completion. BDT scores range from 0 to 48, with bonus points up to 66 (BDT Plus). BDT is considered to reflect spatiotemporal structural capabilities and is a reasonably good predictor for routine spatial measurements (30). A higher score reflects better visuospatial functioning.

### Corsi block-tapping test

The examiner tapped cubes starting with a sequence of two blocks in front of the participant. Two trials were performed per block sequence length. The participant had to tap the cube sequence in the same order immediately after the examiner had finished. The number of cubes tapped ranged from 2 to 9. The subject had two chances to tap the cubes in the correct order; the subject only proceeded to the next step if he or she provided the correct answer (20). For each patient, the two metrics block span and total score were measured. The CBTT-block span is equal to the length of the last correctly repeated sequence. The CBTT-total score is the product of the block span and the number of correctly repeated sequences during the test. Considering the performance on both trials of equal length, the CBTT-total score is more accurate (31). The CBTT is a simple and effective method to assess visuospatial working memory and spatial attention.

## Statistical analysis

All data were analyzed using SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Nonparametric variables are displayed as median values accompanied by a 95% confidence interval (CI), whereas parametric variables are shown as the mean ± standard deviation (SD). Frequencies are represented by counts and their respective percentages. To assess statistical significance, the Kruskal-Wallis test was utilized for comparisons between groups, while the Mann–Whitney U test was employed for pairwise comparisons. For each subgroup, comparisons between acute and recovery phases were assessed using the Wilcoxon Signed Rank test. A value of $p$ less than 0.05 and a Bonferroni-adjusted significance level of 0.017 (0.05/3) was considered statistically significant for pairwise comparisons within the three groups.

# Results

## Demographics and clinical data

The demographic and clinical characteristics of the patients are summarized in Table 1. The patients had a median education of 12 years (95% CI: 12–16) and maintained an overall cognitive function, as indicated by a median MMSE score of 28 (95%CI: 28–29). No significant differences were observed in baseline education levels and general cognitive abilities (MMSE) between AUPV patients and HCs, as assessed by the Mann–Whitney U test. Furthermore, the shape detection screening test confirmed that patients had sufficient visual capacity to undertake the other subtests and demonstrated no significant variations between AUPV patients and the HC group in the current study. All participants in the study were identified as right-handed. AUPV patients were categorized according to the affected ear into either right ($n = 37$) or left ($n = 35$) subgroups. Importantly, there were no notable demographic differences between these subgroups. During the acute phase, both groups exhibited comparable levels in general cognition, sex distribution, education, and visual capability. Moreover, the D-VAS scores, which evaluate the subjective feeling of dizziness in AUPV patients, did not show any significant difference between the right VN and left VN groups. This is another factor to consider that during the acute phase of AUPV, patients' sensations of dizziness might have influenced their performance on visuospatial attention and memory tasks.

The patients with AUPV (vestibular neuritis) mostly presented with acute or subacute spontaneous vertigo with nausea, vomiting, and unsteadiness. Vertigo was usually described as rotational and markedly increased with head position changes. On first examination, spontaneous nystagmus was directed to the contralesional side with a mean slow phase velocity of 13.7°/s (± 14.5) in the patient group, which was similar between the right and left AUPV subgroups (14.2 ± 11.3°/s vs. 12.9 ± 14.1°/s, $p = 0.061$). Almost all patients showed pathological findings on bedside HIT, and the median caloric weakness value was 66.96% (95%CI: 45.7–98%) in the patient group. The vHIT gain was decreased with a mean value of 0.69 (95%CI: 0.61–0.76) for the ipsilesional side and within normal range with a mean of 0.96 (95%CI: 0.94–0.99) for the contralesional side; corrective saccades were mostly observed on the ipsilesional side. In the AUPV group, the average pure tone audiometry value was 19.5 dB (95% CI: 15–24), which demonstrates normal hearing capabilities. The AR of cervical VEMP amplitudes was 21% (median, 95%CI: 13–26%), with abnormal AR (>40%) in 15.28% (11/72). The AR of ocular VEMP amplitudes was 26% (median, 95%CI: 17–36%), with abnormal AR found in 27.78% (20/72). Significant differences were not observed in the vestibular function tests between the right and left AUPV subgroups (Table 1).

## Visuospatial cognition during the acute phase of AUPV

During the acute phase, the AUPV group displayed impairments in visuospatial perception and memory tests compared to the HCs, as shown in Table 2. In the visuospatial perception test, the AUPV patients scored significantly lower in Position discrimination (18 vs. 20, $p = 0.006$, the Mann–Whitney U test), Number location (9 vs. 10,

$p < 0.001$), and Cube analysis (9 vs. 10, $p = 0.048$) compared to HCs. However, despite these lower scores, all values surpassed the cutoff values for failure, which are 18, 7, and 6, respectively. In the visuospatial memory test, the AUPV patients demonstrated significantly lower scores in the Block design tests (BDT, 32 vs. 37, $p = 0.002$; BDT Plus, 34 vs. 43, $p = 0.001$) and CBTT tests (block span, 5 vs. 7.5, $p < 0.001$; total score, 25 vs. 40.5, $p < 0.001$) compared to HCs, as assessed by the Mann–Whitney U test (Figure 1).

In a subgroup analysis comparing right and left AUPV patients, the right AUPV group scored significantly lower in visuospatial perception (Position discrimination, 18 vs. 19, $p = 0.042$; Number location, 8 vs. 9, $p = 0.006$; Cube analysis, 8 vs. 10, $p < 0.001$) and visuospatial memory tests (BDT, 30 vs. 32, $p = 0.003$; BDT Plus, 33 vs. 35, $p = 0.019$; CBTT-total score, 24 vs. 27, $p = 0.047$) according to the Mann–Whitney U test (Table 2). Compared to the HC group, the right AUPV group had also significantly lower scores in both visuospatial perception (Position discrimination, 18 vs. 20, $p = 0.001$; Number location, 8 vs. 10, $p < 0.001$; Cube analysis, 8 vs. 9, $p < 0.001$) and memory (BDT, 30 vs. 37, $p < 0.001$; BDT Plus, 33 vs. 43, $p < 0.001$; CBTT-block span, 5 vs. 7.5, $p < 0.001$; CBTT-total score, 24 vs. 40.5, $p < 0.001$) as evaluated by the Mann–Whitney U test. The left AUPV subgroup exhibited a lesser degree of impairment, with significantly lower scores in the Number location test (9 vs. 10, $p = 0.023$), BDT Plus (35 vs. 43, $p < 0.001$), and CBTT (block span, 5 vs. 7.5, $p < 0.001$; total score, 24 vs. 40.5, $p < 0.001$) relative to the HCs, as assessed by the Mann–Whitney U test (Figure 1).

Correlation analysis between the vestibular function tests of ipsilesional vHIT gain and caloric weakness, asymmetry ratio of cervical and ocular VEMP, and the visuospatial cognition tests did not show significant relationships (Table 3, Spearman's correlation).

## Visuospatial cognition during the recovery phase of AUPV

Most AUPV patients experienced significant improvement in severe vertigo and static vestibular imbalance within a few days, which continued to resolve over the subsequent weeks. Four weeks after the onset of symptoms, all patients showed recovery from initial symptoms such as vertigo, imbalance, spontaneous nystagmus, and abnormal vestibulo-ocular reflex (VOR) gain (Table 1). Alongside the vestibular compensation process, visuospatial cognitive deficits also improved, resulting in AUPV patients' scores being comparable to those of the HCs (Tables 2, 4; Figure 1). However, subgroup analysis indicated that the right AUPV group still had significantly lower scores in the visuospatial memory tests with BDT Plus (36 vs. 43, $p = 0.039$) and CBTT-total score (35 vs. 40.5, $p = 0.019$) compared to the HC group, as assessed by the Mann–Whitney U test (Tables 2, 4; Figure 1).

# Discussion

Although AUPV patients were able to successfully perform visuospatial perception tasks within normal parameters, the current findings revealed a decline in visuospatial perception and memory

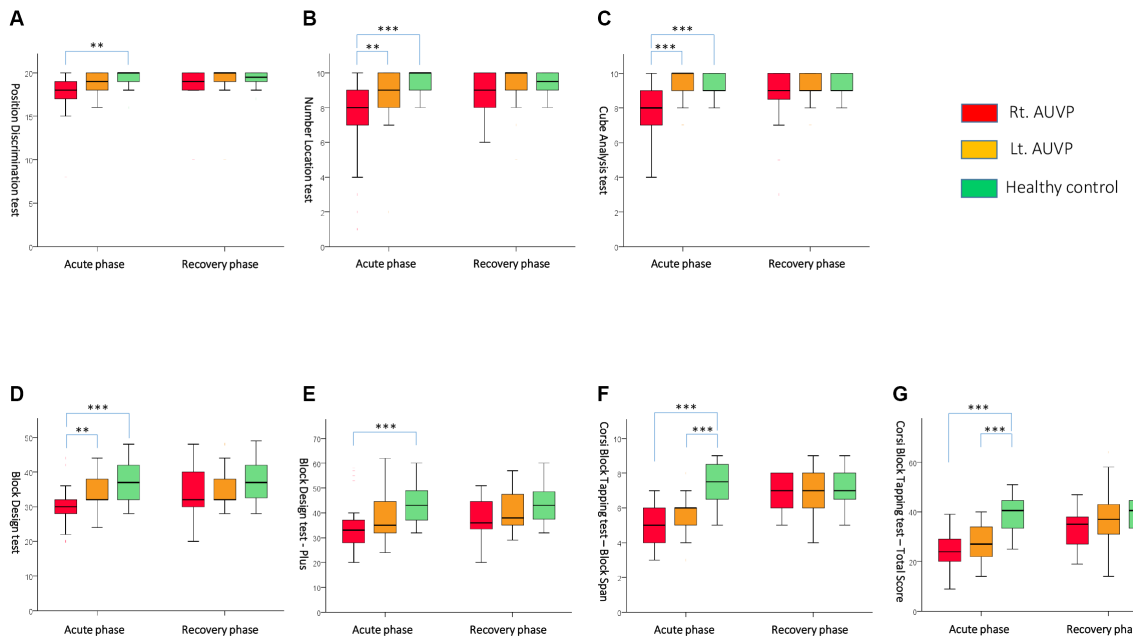


FIGURE 1
Comparisons of visuospatial cognitive performances between subgroups during the acute and recovery phases with **(A)** Position Discrimination test, **(B)** Number Location test, **(C)** Cube Analysis test, **(D)** Block Design test, **(E)** Block Design test-Plus, **(F)** Corsi Block Tapping test-Block Span, and **(G)** Corsi Block Tapping test-Total Score. Rt. AUVP, right-sided acute unilateral vestibulopathy; Lt. AUVP, left-sided acute unilateral vestibulopathy. **Indicates $p < 0.01$; ***indicates $p < 0.001$. Statistical significance was calculated using the Mann–Whitney U test with a Bonferroni-adjusted significance level of 0.017 (0.05/3).

TABLE 3 Spearman's correlation analysis of vestibular function tests and visuospatial cognition parameters.

| | vHIT-ipsi HC-gain | | Caloric UW | | Cervical VEMP AR | | Ocular VEMP AR | | PTA | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| Position discrimination | −0.089 | 0.459 | −0.071 | 0.568 | −0.195 | 0.113 | 0.24 | 0.069 | −0.045 | 0.714 |
| Number location | −0.035 | 0.771 | −0.135 | 0.276 | −0.076 | 0.543 | −0.001 | 0.996 | −0.116 | 0.344 |
| Cube analysis | 0.117 | 0.332 | −0.06 | 0.628 | 0.205 | 0.096 | 0.083 | 0.534 | −0.181 | 0.137 |
| BDT | 0.086 | 0.478 | −0.142 | 0.251 | −0.039 | 0.755 | −0.045 | 0.735 | −0.17 | 0.162 |
| BDT Plus | −0.047 | 0.7 | −0.116 | 0.35 | −0.056 | 0.655 | −0.051 | 0.703 | −0.239 | 0.058 |
| CBTT-block span | −0.037 | 0.768 | 0.047 | 0.716 | −0.019 | 0.88 | −0.033 | 0.81 | −0.175 | 0.168 |
| CBTT-total score | −0.111 | 0.374 | 0.025 | 0.845 | −0.085 | 0.507 | −0.1 | 0.472 | −0.186 | 0.14 |

vHIT-ipsi, video head impulse test-ipsilesional; HC, horizontal semicircular canal; UW, unilateral weakness; VEMP, vestibular evoked myogenic potential; AR, asymmetry ratio; PTA, pure tone audiometry. The correlations between vestibular function tests and visuospatial cognition parameters were assessed using Spearman's nonparametric bivariate correlation.

compared to HCs in the acute phase. These visuospatial cognitive impairments were more pronounced in the acute stage and gradually improved over the course of 4 weeks. These findings align with previous research that also identified visuospatial cognitive deficits in AUPV patients (32). One possible explanation for these impairments might be abnormalities in the vestibular reflex, such as oscillopsia/nystagmus-induced blurred vision or VOR deficits, or from imbalances in stance and gait due to VSR deficits (33). However, this explanation would predict similar spatial cognitive deficits in both left and right AUPV during acute and recovery phases, which was not supported by the current findings. Nonetheless, during the acute phase, there was no significant difference in the D-VAS scores, a measure used to gage the subjective feeling of dizziness in AUPV patients, between those with right VN and those with left VN. Given that there were no marked differences in general cognition, gender distribution, education level, vestibular imbalance, and subjective feelings of dizziness between the right and left VN groups, a more plausible hypothesis might be that spatial cognitive discrepancies during the early stages of AUPV arise from disrupted vestibular information to the hippocampal formation that negatively impacts the multisensory integration of cognitive mapping.

The results revealed a significant difference in performance between right and left AUPV subgroups compared to each other and the HC group. Specifically, more severe and lasting deficits in visuospatial perception and memory were observed in the right AUPV subgroup (vestibular dominant side) than in the left AUPV subgroup (vestibular non-dominant side) of the right-handed patients. A plausible explanation for these differing impairments could be the initial disruption or absence of peripheral input into the bilateral vestibular cortical network, which features predominantly ipsilateral right-sided pathways from the vestibular nuclei to the parietoinsular core region and a right hemispheric vestibular dominance in right-handers (34, 35). This is consistent with a three-month follow-up study in UVD rats, which demonstrated spatial memory deficits in darkness, suggesting spatial navigation impairments independent of oscillopsia (36). Similarly, previous studies, especially differences according to the gender or lesion side, revealed that spatial cognitive performance appeared substantially poorer in female patients (37), and deficits in spatial memory and navigation were found in right but not in left vestibular loss (37). Regarding vestibular lateralization (38), the unilateral lesions on the vestibular dominant side appeared to show more severe deficits than those on the non-dominant side (38). Neuroimaging data also indicated that brain activity in the acute phase of right-and left-sided AUPV exhibited different compensatory patterns, with more pronounced negative metabolic brain activities with right-sided lesions in right-handed patients (39).

Given the complexity of visuospatial memory tests in contrast to visuospatial perception tasks, the more sophisticated the task, the greater the chance of identifying visuospatial deficiencies. From this point of view AUPV tends to cause more recognizable deficits in visuospatial memory, which involves intricate vestibular processes (40), compared to visuospatial perception which is predominantly influenced by visual information (41). This is in alignment with numerous earlier studies that have focused on identifying and defining the impact of vestibular impairment on visuospatial memory (42). Consequently, there is a need to develop clinical visuospatial behavioral tests that can more sensitively identify these minor alterations across different patient groups.

Vestibular information must ascend to the hippocampus to be integrated with visual and other sensory data pertinent to spatial memory (43, 44). This information has been demonstrated to reach the hippocampal formation, a complex brain structure involved in spatial cognition, through various pathways such as thalamocortical, theta-generating, cerebellocortical, and head direction pathways (7, 45). Furthermore, place cells in the hippocampus, which react to specific locations in the environment, are influenced by vestibular stimulation (33). The vestibular system plays a role in the dynamic processes of spatial cognition, including path integration, landmark-based strategies, and geometry-based strategies (1, 4). As for brain morphological changes related to spatial cognition, there is no definitive neuroimaging evidence of hippocampal atrophy in UVD patients (37). Some studies have reported atrophy in the ipsilateral supramarginal nucleus, postcentral and superior temporal gyrus, MT/V5 area, contralateral thalamus, and mesencephalon tegmentum (11, 46). Other studies of patients who recovered from AUPV showed a significant decrease in the volume of left posterior hippocampus (11). The authors speculated that the relative atrophy was the result of interaction between the diminished vestibular input and the insufficient central compensation to ameliorate all features of unilateral peripheral vestibular loss (11).

Despite the vestibular system's role in integrating multisensory signals of various ipsilateral and contralateral brain regions, both this study and past animal behavioral studies (12),

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TABLE 4 A paired test illustrating the time-dependent alterations in visuospatial cognitive parameters.

| | VN ($n = 72$) | | | R.VN ($n = 37$) | | | L.VN ($n = 35$) | | | HC ($n = 35$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Acute phase | Recovery phase | Value of $p$ | Acute phase | Recovery phase | Value of $p$ | Acute phase | Recovery phase | Value of $p$ | Acute phase | Recovery phase | Value of $p$ |
| Visuospatial perception tests | | | | | | | | | | | | |
| Position discrimination | 18 (18–19) | 19 (19–20) | **<0.001** | 18 (17–19) | 19 (19–20) | **<0.001** | 19 (18–20) | 20 (19–20) | 0.055 | 20 (19–20) | 19.5 (19–20) | 0.564 |
| Number location | 9 (8–9) | 9 (9–10) | **<0.001** | 8 (8–9) | 9 (9–10) | **0.001** | 9 (9–10) | 10 (9–10) | 0.149 | 10 (9–10) | 9.5 (9–10) | 1 |
| Cube analysis | 9 (8–9) | 9 (9–10) | **0.001** | 8 (8–9) | 9 (9–10) | **<0.001** | 10 (9–10) | 9 (9–10) | 0.484 | 9 (9–10) | 9 (9–10) | 0.157 |
| Visuospatial memory tests | | | | | | | | | | | | |
| BDT | 32 (32–32) | 32 (32–36) | **<0.001** | 30 (28–32) | 32 (32–38) | **0.001** | 32 (32–36) | 32 (32–38) | 0.089 | 37 (32–40) | 37 (33–40) | 0.083 |
| BDT Plus | 34 (32–35) | 38 (35–40) | **<0.001** | 33 (29–34) | 36 (34–41) | **<0.001** | 35 (34–41) | 38 (35–47) | 0.109 | 43 (38–48) | 43 (38–48) | 0.854 |
| CBTT-block span | 5 (5–6) | 7 (6–7) | **<0.001** | 5 (5–6) | 7 (6–7) | **<0.001** | 6 (5–6) | 7 (6–8) | **<0.001** | 7.5 (7–8) | 7 (7–8) | 0.234 |
| CBTT-total score | 25 (23–28) | 35.5 (31–38) | **<0.001** | 24 (21–28) | 35 (29–36) | **<0.001** | 27 (22–33) | 37 (31–43) | **0.001** | 40.5 (34–44) | 40.5 (34–44) | 0.276 |

Values are presented as median (95% CI). Statistical significance was calculated using the Wilcoxon Signed Rank test. Bold $p$-values indicate significant differences.

have indicated that a loss of half of the vestibular afferents causes spatial memory and navigation dysfunction during the acute phase of vestibular damage. The swift recovery of spatial cognitive performance in AUPV patients is due to vestibular compensation and adaptation, which restore the reduced activity in the ipsilateral vestibular nuclei and rebalance activity between both sides. Recent studies that focused on visualizing the relative changes in glucose metabolism (rCGM) found significant asymmetries in the vestibular nuclei complexes and related structures of the vestibulo-cerebellum, thalamus, vestibular cortex, hippocampus, and amygdala during the acute stage of UVD (10). This was followed by a rebalance of rCGM within these structures. Additional research has identified abnormalities in cortical and subcortical activations following AUPV. For instance, in a functional MRI study, significant decreases were observed in resting-state activities of the medial aspect of the superior parietal lobule, posterior cingulate cortex, middle frontal gyrus, middle temporal gyrus, parahippocampal gyrus, anterior cingulate cortex, insular cortex, caudate nucleus, thalamus, and midbrain (47). Thus, central compensation of unilateral peripheral vestibular loss involves numerous structures of the bilateral central vestibular network from the vestibular nuclei complexes to vestibular cortex and hippocampus to improve the different vestibular assignments from vestibulo-ocular reflexes at brain stem level to cognitive tasks like spatial orientation and navigation at subcortical/cortical level.

A limitation of this study is the lower sensitivity of the clinical behavioral tests employed, and the absence of functional imaging-based evidence to support the observed cognitive performance findings. Although we observed no marked differences in general cognition or subjective dizziness, the results do not negate potential general cognitive abilities or attentional deficits. Given the limited sensitivity of the MMSE, our chosen cognitive test, interpretations should be approached with caution. Further research using more sensitive cognitive assessments is warranted. Additionally, the study exclusively involved right-handed patients, indicating a need for further research with left-handed AUPV patients for a comprehensive understanding.

In conclusion, for the first time, we assessed visuospatial perception and memory cognition in AUPV patients during the acute phase and early compensation stages. Specifically, AUPV patients demonstrated varying sensitivities in spatial cognition areas, such as spatial memory, based on the affected ear side, with improvements observed as vestibular compensation progressed in the subsequent weeks. We suggest examining both objective and subjective visuospatial cognitive measures and the development of cognitive behavioral tests capable of discerning and identifying potential visuospatial cognitive deficits that may arise following acute or chronic unilateral vestibular impairments.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by the Institutional Review Board at Jeonbuk National University Hospital (no. 2020-10-134-006) reviewed and approved the experiments. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

S-YO and MD: study conception and design. S-YO and J-JK: data collection. S-YO and TTN: analysis, interpretation of results, and draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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## Conflict of interest

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

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# Investigation of hearing loss in elderly vertigo and dizziness patients in the past 10 years

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**Background:** Vertigo and hearing loss are both prevalent in the elderly. This study retrospectively analyzed hearing test results from elderly patients experiencing vertigo and dizziness at ENT outpatient over a 10-year period, in order to study the patterns of hearing loss in this patient population.

**Methods:** Nine thousand three hundred eighty four patients over 50 years old underwent retrospective collection and screening of outpatient diagnosis, pure tone audiometry, acoustic immittance measurement (tympanogram) and auditory brainstem response (ABR) test. The patient's audiograms are divided into 7 subtypes according to a set of fixed criteria. Meanwhile, K-Means clustering analysis method was used to classify the audiogram.

**Results:** The Jerger classification of tympanogram in elderly patients with vertigo and dizziness showed the majority falling under type A. The leading audiogram shapes were flat (27.81% in right ear and 26.89% in left ear), high-frequency gently sloping (25.97% in right ear and 27.34% in left ear), and high-frequency steeply sloping (21.60% in right ear and 22.53% in left ear). Meniere's disease (MD; 30.87%), benign recurrent vertigo (BRV; 19.07%), and benign paroxysmal positional vertigo (BPPV; 15.66%) were the most common etiologies in elderly vestibular diseases. We observed statistically significant differences in hearing thresholds among these vestibular diseases ($P < 0.001$). K-Means clustering analysis suggested that the optimal number of clusters was three, with sample sizes for the three clusters being 2,747, 2,413, and 4,139, respectively. The ANOVA statistical results of each characteristic value showed $P < 0.001$.

**Conclusion:** The elderly patients often have mild to moderate hearing loss as a concomitant symptom with vertigo. Female patients have better hearing thresholds than males. The dominant audiometric shapes in this patient population were flat, high-frequency gently sloping, and high-frequency steeply sloping according to a set of fixed criteria. This study highlights the need for tailored strategies in managing hearing loss in elderly patients with vertigo and dizziness.

KEYWORDS

**hearing loss, vertigo, elderly, dizziness, pure tone audiometry, acoustic immittance measurement, auditory brainstem response (ABR)**

# 1. Introduction

Previous studies indicate that vertigo is prevalent in the elderly population, with estimates of incidence ranging from 20 to 58% (Lasisi and Gureje, 2014; Lindell et al., 2021; Fancello et al., 2023). The pathogenesis of vertigo is multifactorial and primarily characterized by illusions of rotational motion, often accompanied by symptoms such as nystagmus, postural imbalance, falls, and neurovegetative effects (Roque Reis et al., 2016; Du et al., 2022). These symptoms limit daily activities, significantly impacting the physical and mental health and overall quality of life of affected individuals.

The inner ear, with its complex metabolic mechanisms, can be adversely affected by alterations in blood concentrations of glucose and insulin, potentially leading to hearing loss and vestibular disorders (Albernaz, 2016). Approximately 20% of patients with dizziness also experience hearing loss (Sunitha et al., 2019). These patients often show severe cochlear damage and may have extensive or deep ischemia in the inner ear (Kuhn et al., 2011). Notably, the incidence of vertigo can reach 20–60% among individuals with sensorineural hearing loss (Rambold et al., 2005). The co-occurrence of sudden hearing loss (SHL) and vertigo, especially when occurring in close temporal proximity, has been associated with a higher risk of subsequent stroke compared to SHL or vertigo alone (Chang et al., 2018). This indicates that SHL in vertigo patients should not be viewed as merely a benign peripheral vestibular sign.

Given the potential severe consequences of concomitant hearing loss in elderly patients with vertigo and dizziness, this condition merits increased clinical attention. Accordingly, this study retrospectively analyzes hearing examination reports of elderly patients experiencing dizziness from outpatient hearing centers over a 10-year period. Our aim is to characterize the types of hearing loss in this specific population.

# 2. Materials and methods

## 2.1. Participants

This study involved retrospective collection and examination of outpatient diagnosis reports, pure tone audiometry, acoustic immittance measurement and auditory brainstem response (ABR) tests from January 2010 to December 2021. Participants were patients over 50 years old with vertigo and dizziness, visiting the General Hospital of the People's Liberation Army in the Chinese People's Republic. A total of 9,384 patients (3,582 males and 5,802 females, aged 50–96 years, average age 66.24 ± 7.04 years) with hearing loss were included. The study was approved by the PLA General Hospital's Ethics Committee (No. S2022-673-01), and all procedures complied with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## 2.2. Hearing evaluation methods

### 2.2.1. Pure tone audiometry

Post-routine otolaryngology examinations and history collection, the Astera pure tone audiometry (Natus, US) was used to obtain the hearing threshold. The EAR-3A insert phones were applied (American Speech-Language-Hearing Association, 2005), and frequencies from 250 Hz to 8 kHz were tested using the ascending method (ISO 8253-1: 2010).

### 2.2.2. Tympanogram

The middle ear's tympanograms were obtained using TympStar clinical tympanometer (Grason-Stadler, US) and Titan tympanometer (Interacoustics, Denmark), with a probe tone of 226 Hz. Tympanograms were classified into five types (A, AD, AS, B, and C) according to the Liden-Jerger classification criteria.

### 2.2.3. Auditory electrophysiology tests

ABR tests were conducted using the Eclipse EP25 platform (Interacoustics, Denmark) with insert earphones (3A, Etymotic Research, US). Alternating short-duration clicks with a repetition rate of 19.3 Hz were used as stimuli. Parameters for the test are detailed.

## 2.3. Pure-tone audiogram typing

To facilitate the diagnostic classification of hearing loss in elderly patients, we adopted a typing criterion for pure-tone audiograms based on clinical observations and a review of existing literature (see Figure 1) (Demeester et al., 2009; Lee et al., 2020). We defined 250 and 500 Hz as "low frequency (LF)," 1 and 2 kHz as "middle frequency (MF)," and 4 and 8 kHz as "high frequency (HF)."

## 2.4. Inclusion and exclusion criteria

### 2.4.1. Inclusion criteria

(1) Age ≥ 50 years;

(2) Diagnosed by a careful interview and vestibular function results by an otologist, and another specialist reviewed the clinical notes to confirm the diagnosis. All diagnoses could be divided into benign recurrent vertigo (BRV) (van Leeuwen et al., 2022), MD (Monsell et al., 1995), vestibular neuropathy (VN, the diagnosis was based on the history of acute sustained vertigo or imbalance, positive spontaneous nystagmus or unilateral weakness >25% in vHIT or unilateral VOR gain loss combined with obvious catch-up saccades in vHIT and no additional central lesion signs) (Haeussler et al., 2022), BPPV (Kim et al., 2021), functional and psychiatric vertigo (PV) (Traschütz et al., 2021), vestibular migraine (VM) (García et al., 2021), bilateral vestibular hypofunction (BVH) (Lucieer et al., 2016), delayed endolymphatic hydrops (DEH) (Reynard et al., 2018), others [including vestibular paroxysmia (VP), acoustic neurinoma (AN, radiologically diagnosed and went through vHIT before surgery), traumatic vertigo (TV, diagnosed by imaging), Ramsay Hunt Syndrome (RHS, diagnosed with an ipsilateral herpetic eruption on the auricle and external ear canal, facial palsy, and vertigo) and vascular vertigo, cervicogenic vertigo, tinnitus with vertigo, and

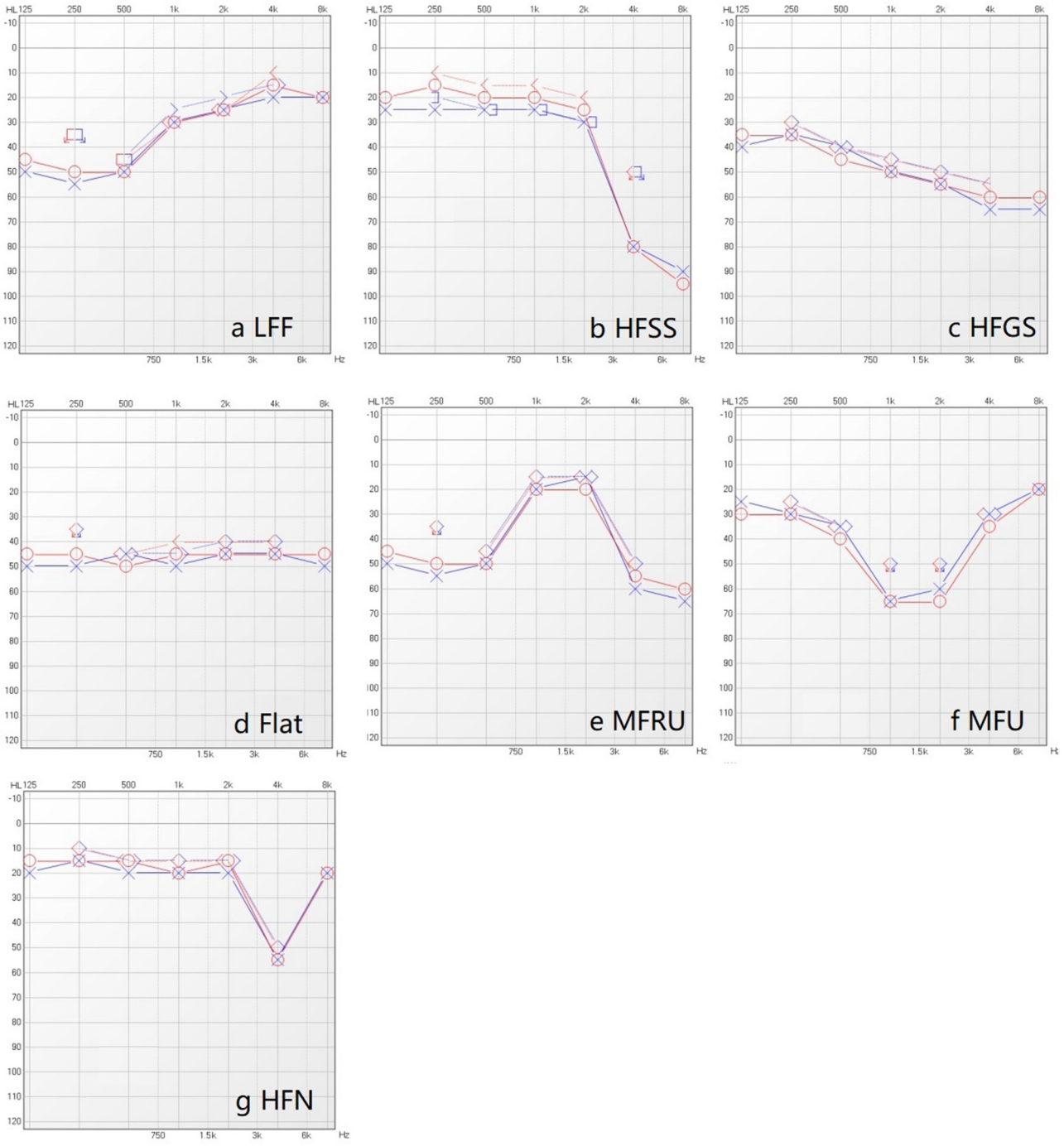


FIGURE 1
Seven typing of pure-tone audiogram. **(a)** Low frequency falling (LFF): The difference between the poor low frequency threshold (i.e., the larger listening threshold in 250 Hz and 500 Hz) and the good high frequency threshold (i.e., the smaller listening threshold in 4 kHz and 8 kHz) is greater than 15 dB, and the former is greater than the latter. **(b)** High frequency steeply sloping (HFSS): The difference between the mean value of 500 Hz and 1 kHz air conduction hearing thresholds and the average values of high frequency (4 kHz and 8 kHz) air conduction hearing thresholds is greater than 30 dB, and the former was smaller than the latter. **(c)** High frequency gently sloping (HFGS): The difference between the average values of air conduction threshold (500 Hz and 1 kHz) and the average value of high frequency air conduction thresholds (4 kHz and 8 kHz) is greater than 15 dB, meanwhile less than or equal to 29 dB, and the former is less than the latter. **(d)** Flat: The difference between the average values of the three air conduction hearing thresholds(low-frequency, medium-frequency, high-frequency) is less than 15 dB. **(e)** Mid frequency Reverse U-shape (MFRU): The difference between the medium frequency optimal threshold (i.e., the smaller threshold in 1 kHz and 2 kHz), the low frequency optimal threshold (i.e., the smaller threshold in 250 Hz and 500 Hz) and the high frequency optimal threshold (i.e., the smaller threshold in 4 kHz and 8 kHz) is more than 15 dB, and the medium frequency is better than (the threshold is less than) the low frequency and high frequency. **(f)** Mid frequency U-shape (MFU): The difference between the worst listening threshold of medium frequency (the larger threshold of 1 kHz and 2 kHz), the poor listening threshold of low frequency (the larger threshold of 250 Hz and 500 Hz) and the poor threshold of high frequency (the larger listening threshold of 4 kHz and 8 kHz) is more than 15 dB, and the medium frequency less than (the threshold is greater than) low frequency and high frequency. **(g)** High frequency notching (HFN): The threshold of 4 kHz is the worst, and the difference between 4kHz and other frequency thresholds is greater than 15 dB.

complication with MD and VM, complication with MD and BPPV].

(3) The complete binaural (L, R) air conduction (125, 250, 500, 1,000, 2,000, 4,000, 8,000 Hz) and bone conduction (250, 500 Hz, 1, 2, 4 kHz) based on the data of pure-tone threshold;
(4) The results of acoustic immittance test and auditory brainstem response (ABR) test.

### 2.4.2. Exclusion criteria

Participants were excluded from the study if they:

(1) Had incomplete data from the pure tone audiometry (either not done or if the air bone conduction threshold data was incomplete).
(2) Had missing age, gender, or diagnostic information.

## 2.5. Statistical analysis

In this study, the descriptive analysis was mainly used. The counting data was expressed as frequency (percentage). Comparison of pure tone hearing threshold and acoustic immittance measurement applied one-way ANOVA (When $P < 0.05$, there is a statistical difference). Least-significant difference (LSD) was used for *Post-hoc* Multiple Comparisons.

K-Means clustering was used for the secondary classification of audiograms. We extracted the features of the left and right audiogram curves, including maximum, minimum, mean, variance, slope of each inflection point, and curve distance as the feature values. These variables were standardized to ensure comparability, and the resulting dataset was used as the input for the subsequent K-means clustering. The optimal number of clusters was determined by fitting the K-means unsupervised machine learning algorithm to 3–6 clusters, respectively.

TABLE 1 Basic information for patients with vertigo and dizziness.

| Variable | | Number | Percentage |
|---|---|---|---|
| Age (years) | 50∼59 | 1,108 | 11.81 |
| | 60∼69 | 5,726 | 61.02 |
| | 70∼79 | 2,072 | 22.08 |
| | 80∼89 | 464 | 4.94 |
| | 90∼99 | 14 | 0.15 |
| Gender | Male | 3,582 | 38.17 |
| | Female | 5,802 | 61.83 |
| 1997 Classification of hearing loss | 0 | 4,166 | 44.39 |
| | 1 | 3,155 | 33.62 |
| | 2 | 1,580 | 16.84 |
| | 3 | 409 | 4.36 |
| | 4 | 74 | 0.79 |
| 2021WHO classification for hearing loss | Normal | 1,701 | 18.13 |
| | Mild | 4,188 | 44.63 |
| | Moderate | 1,960 | 20.89 |
| | Moderate to severe | 777 | 8.28 |
| | Severe | 271 | 2.89 |
| | Profond | 62 | 0.66 |
| | Total deafness | 20 | 0.21 |
| | Single sided deafness | 405 | 4.32 |

# 3. Results

## 3.1. Data overview

As depicted in Table 1, the largest group of patients with vertigo and dizziness was aged between 60 and 69 years old, with a total of 5,726 cases, which accounted for 61.02% of all admissions. There was a higher prevalence of female patients (61.83%) than male patients (38.17%). Male patients generally had a worse hearing threshold than females, with a difference of 10 dB HL observable at 4 k and 8 kHz (see Figure 2A). In the 2021 WHO's hearing classification, the largest category of hearing loss patients, comprising 44.63% ($n = 4,188$), was classified as "mild."

## 3.2. Jerger classification of the tympanic diagram

Figure 2B shows the Jerger classification of tympanograms in patients with vertigo and dizziness (additional details can be found in Supplementary Table 2). There was a near equal distribution between left and right ears, with type A being the most common Jerger classification of tympanogram.

## 3.3. ABR results

Each wave latency and inter-wave period fell within the normal range, as shown in Table 2.

## 3.4. Classification of audiogram shapes in elderly patients with vertigo and dizziness

Table 3 outlines the pure-tone audiogram typing and the corresponding proportions of patients with vertigo and dizziness. Similar patterns were observed in both left and right ears. Predominant audiometric shapes included flat (27.81% in the right ear, 26.89% in the left), high-frequency gently sloping (HFGS) (25.97% in the right ear, 27.34% in the left), and high-frequency steeply sloping (HFSS) (21.60% in the right ear, 22.53% in the left) (see Figure 3).

However, Figure 3 also reveals a significant number of patients categorized as "No typing" (18.3% in the left ear, 19.25% in the

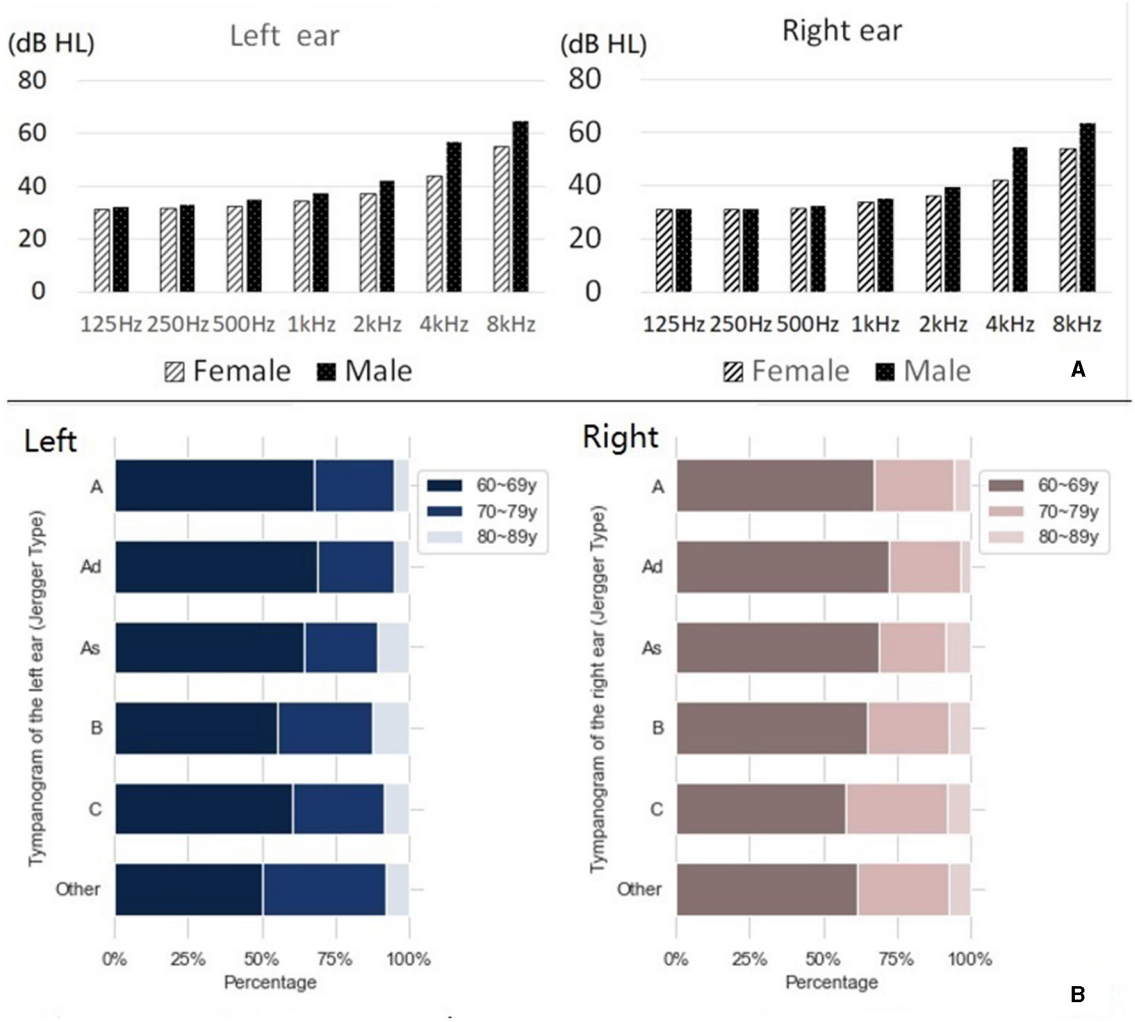


FIGURE 2
Hearing results of elderly patients with vertigo and dizziness. **(A)** Hearing thresholds for males and females at each frequency. **(B)** Jerger classification of tympanic diagram.

right) based on existing criteria, suggesting that current hearing classification standards may not be entirely suitable for elderly vertigo and dizziness patients with hearing loss.

Upon reclassification of the pure tone results ($n$ = 9,299), K-Means clustering analysis suggested that the optimal number of clusters was three (Table 4). The ANOVA statistical results of each characteristic value showed $P$ = 0.000, with sample sizes for the three clusters being 2,747, 2,413, and 4,139, respectively.

## 3.5. Auditory examination results of patients with definite diagnosis

Among the 907 elderly patients with definitively diagnosed vestibular syndrome in this study, the three most prevalent were Ménière's disease (MD, 30.87%), benign recurrent vertigo (BRV, 19.07%), and benign paroxysmal positional vertigo (BBPV, 15.66%). The distribution of these diseases is presented in Figure 4A.

Auditory examination results from the eight main types of vestibular syndrome (each comprising more than 2.00% of the total) were analyzed, with the corresponding auditory thresholds depicted in Figure 4B. The hearing thresholds in low, medium, and high frequencies for the left and right ears are presented in Table 5. Statistical analysis revealed significant differences in hearing thresholds among the various vestibular diseases ($P$ < 0.001). Detailed results from multiple comparisons of hearing thresholds for different diseases are provided in Table 6.

# 4. Discussion

From the overall result of elderly patients with vertigo and dizziness, 83.10% of them were aged from 60 to 79. Among them, the grading of hearing loss was mainly in level 1 (44.63%) and 2(20.89%), indicating that elderly patients with vertigo and dizziness generally have mild to moderate hearing loss in this age range. Previous studies abroad have shown that caloric test

TABLE 2 ABR test results of patients with vertigo and dizziness.

| Test ear | ABR wave | Statistical description | 60∼69 (y) | 70∼79 (y) | 80∼89 (y) |
|---|---|---|---|---|---|
| Left | I | Observed cases (unobserved cases) | 162 (46) | 51 (19) | 4 (6) |
| | | Mean ± SD | 1.59 ± 0.20 | 1.57 ± 0.18 | 1.57 ± 0.21 |
| | | Median | 1.57 (1.48∼1.70) | 1.52 (1.45∼1.70) | 1.61 (1.43∼1.70) |
| Left | III | Observed cases (unobserved cases) | 153 (55) | 53 (17) | 4 (6) |
| | | Mean ± SD | 3.86 ± 0.27 | 3.86 ± 0.26 | 3.91 ± 0.21 |
| | | Median | 3.85 (3.70∼4.00) | 3.88 (3.70∼4.03) | 3.94 (3.77∼4.06) |
| Left | V | Observed cases (unobserved cases) | 194 (14) | 70 (0) | 8 (2) |
| | | Mean ± SD | 5.83 ± 0.38 | 5.84 ± 0.32 | 5.95 ± 0.32 |
| | | Median | 5.73 (5.60∼5.95) | 5.85 (5.60∼6.03) | 5.85 (5.71∼6.27) |
| Left | I-III | Observed cases (unobserved cases) | 139 (69) | 46 (24) | 3 (7) |
| | | Mean ± SD | 2.27 ± 0.21 | 2.25 ± 0.17 | 2.46 ± 0.34 |
| | | Median | 2.27 (2.15∼2.35) | 2.21 (2.13∼2.33) | 2.32 (2.21∼2.85) |
| Left | III-V | Observed cases (unobserved cases) | 153 (55) | 53 (17) | 4 (6) |
| | | Mean ± SD | 1.90 ± 0.16 | 1.92 ± 0.18 | 1.89 ± 0.12 |
| | | median | 1.92 (1.80∼2.00) | 1.90 (1.82∼2.00) | 1.91 (1.81∼1.97) |
| Left | I-V | Observed cases (unobserved cases) | 162 (46) | 51 (19) | 4 (6) |
| | | Mean ± SD | 4.16 ± 0.21 | 4.18 ± 0.22 | 4.28 ± 0.41 |
| | | Median | 4.14 (4.03∼4.27) | 4.15 (4.04∼4.32) | 4.16 (4.01∼4.55) |
| Right | I | Observed cases (unobserved cases) | 172 (36) | 55 (15) | 5 (5) |
| | | Mean ± SD | 1.59 ± 0.19 | 1.57 ± 0.16 | 1.70 ± 0.08 |
| | | Median | 1.57 (1.48∼1.69) | 1.55 (1.48∼1.68) | 1.68 (1.63∼1.73) |
| Right | III | Observed cases (unobserved cases) | 165 (43) | 54 (16) | 6 (4) |
| | | Mean ± SD | 3.82 ± 0.22 | 3.85 ± 0.21 | 4.02 ± 0.27 |
| | | Median | 3.81 (3.65∼3.98) | 3.85 (3.70∼4.00) | 3.91 (3.85∼4.08) |
| Right | V | Observed cases (unobserved cases) | 199 (9) | 66 (4) | 9 (1) |
| | | Mean ± SD | 5.80 ± 0.36 | 5.78 ± 0.27 | 5.95 ± 0.34 |
| | | Median | 5.75 (5.58∼5.95) | 5.75 (5.63∼5.92) | 5.95 (5.70∼6.22) |
| Right | I-III | Observed cases (unobserved cases) | 149 (59) | 47 (23) | 4 (6) |
| | | Mean ± SD | 2.23 ± 0.18 | 2.25 ± 0.14 | 2.21 ± 0.11 |
| | | Median | 2.23 (2.12∼2.35) | 2.23 (2.15∼2.32) | 2.20 (2.13∼2.30) |
| Right | III-V | Observed cases (unobserved cases) | 165 (43) | 54 (16) | 6 (4) |
| | | Mean ± SD | 1.91 ± 0.15 | 1.92 ± 0.17 | 1.93 ± 0.24 |
| | | Median | 1.90 (1.82∼2.00) | 1.90 (1.83∼2.00) | 1.86 (1.80∼2.12) |
| Right | I-V | Observed cases (unobserved cases) | 172 (36) | 55 (15) | 5 (5) |
| | | Mean ± SD | 4.15 ± 0.20 | 4.17 ± 0.21 | 4.10 ± 0.25 |
| | | Median | 4.13 (4.02∼4.26) | 4.15 (4.05∼4.32) | 4.15 (3.90∼4.27) |

responses depend on several factors that could be affected by age, such as ear canal volume, temporal bone thickness, and blood supply to the temporal bone (Enrietto et al., 1999). Several studies have found that caloric responses tend to increase in middle age with a peak between 50 and 70 years, and then decline modestly thereafter (Fernández et al., 2015). In clinical diagnosis, it's difficult to obtain a complete, meaningful, and treatment-oriented diagnosis in elderly dizzy patients. More than half of elderly patients with balance disorders are vague, inconsistent, or contradictory in describing their symptoms (Newman-Toker et al., 2007). Besides, there is not a single symptom that can predict with specificity the underlying causes of dizziness, and most of the time, elderly

TABLE 3 Audiogram classification of patients with vertigo and dizziness.

| Audiogram classification | 2010 (%) | 2011 (%) | 2012 (%) | 2013 (%) | 2014 (%) | 2015 (%) | 2016 (%) | 2017 (%) | 2018 (%) | 2019 (%) | 2020 (%) | 2021 (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Flat (R) | 11 (26.19) | 8 (32.00) | 28 (20.14) | 172 (26.88) | 113 (25.11) | 274 (27.45) | 281 (25.57) | 382 (27.21) | 332 (25.62) | 162 (29.24) | 362 (34.77) | 559 (32.96) |
| Flat (L) | 11 (26.19) | 5 (20.00) | 29 (20.86) | 153 (23.91) | 109 (24.22) | 250 (25.05) | 260 (23.66) | 367 (26.14) | 345 (26.62) | 160 (28.88) | 353 (33.91) | 545 (32.13) |
| HFGS (R) | 7 (16.67) | 7 (28.00) | 42 (30.22) | 164 (25.63) | 118 (26.22) | 295 (29.56) | 324 (29.48) | 352 (25.07) | 369 (28.47) | 146 (26.35) | 244 (23.44) | 438 (25.83) |
| HFGS (L) | 12 (28.57) | 8 (32.00) | 41 (29.50) | 183 (28.59) | 138 (30.67) | 290 (29.06) | 343 (31.21) | 390 (27.78) | 388 (29.94) | 136 (24.55) | 264 (25.36) | 437 (25.77) |
| HFSS (R) | 11 (26.19) | 5 (20.00) | 35 (25.18) | 166 (25.94) | 108 (24.00) | 225 (22.55) | 250 (22.75) | 332 (23.65) | 278 (21.45) | 125 (22.56) | 194 (18.64) | 355 (20.93) |
| HFSS (L) | 14 (33.33) | 7 (28.00) | 37 (26.62) | 174 (27.19) | 98 (21.78) | 233 (23.35) | 275 (25.02) | 356 (25.36) | 293 (22.61) | 136 (24.55) | 199 (19.12) | 345 (20.34) |
| LFF (R) | 2 (4.76) | 0 (0.00) | 7 (5.04) | 19 (2.97) | 16 (3.56) | 25 (2.51) | 37 (3.37) | 53 (3.77) | 72 (5.56) | 15 (2.71) | 50 (4.80) | 79 (4.66) |
| LFF (L) | 0 (0.00) | 1 (4.00) | 7 (5.04) | 13 (2.03) | 10 (2.22) | 27 (2.71) | 27 (2.46) | 50 (3.56) | 73 (5.63) | 19 (3.43) | 51 (4.90) | 86 (5.07) |
| MFU (R) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (0.08) | 0 (0.00) | 1 (0.10) | 0 (0.00) |
| MFU (L) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (0.10) | 0 (0.00) |
| MFRU (R) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 3 (0.67) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (0.08) | 0 (0.00) | 0 (0.00) | 2 (0.12) |
| MFRU (L) | 0 (0.00) | 0 (0.00) | 1 (0.72) | 2 (0.31) | 1 (0.22) | 0 (0.00) | 0 (0.00) | 1 (0.07) | 0 (0.00) | 0 (0.00) | 1 (0.10) | 1 (0.06) |
| HFN (R) | 0 (0.00) | 0 (0.00) | 1 (0.72) | 8 (1.25) | 5 (1.11) | 15 (1.50) | 16 (1.46) | 23 (1.64) | 15 (1.16) | 4 (0.72) | 17 (1.63) | 31 (1.83) |
| HFN (L) | 0 (0.00) | 1 (4.00) | 1 (0.72) | 6 (0.94) | 3 (0.67) | 11 (1.10) | 9 (0.82) | 10 (0.71) | 13 (1.00) | 6 (1.08) | 14 (1.34) | 30 (1.77) |
| No typing (R) | 12 (28.57) | 5 (20.00) | 29 (20.86) | 128 (20.00) | 101 (22.44) | 190 (19.04) | 217 (19.75) | 299 (21.30) | 267 (20.60) | 111 (20.04) | 208 (19.98) | 291 (17.16) |
| No typing (L) | 6 (14.29) | 4 (16.00) | 27 (19.42) | 121 (18.91) | 96 (21.33) | 206 (20.64) | 206 (18.74) | 258 (18.38) | 227 (17.52) | 108 (19.49) | 188 (18.06) | 313 (18.46) |

HFGS, High frequency gently sloping; HFSS, High frequency steeply sloping; LFF, Low frequency falling; MFU, Mid frequency U-shape; MFRU, Mid frequency Reverse U-shape; HFN, High frequency notching.

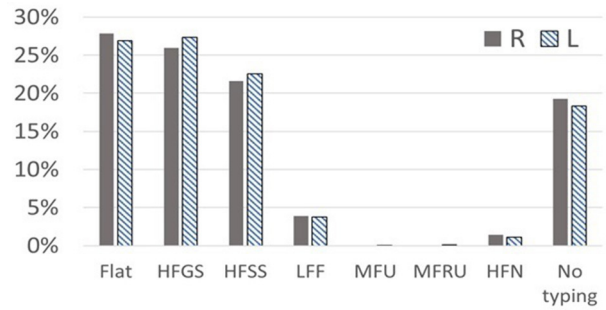


FIGURE 3
The classification of audiogram shapes in elderly patients with vertigo syndrome. Typing of pure-tone audiogram: Flat, HFGS (high frequency gently sloping), HFSS (high frequency steeply sloping), LFF (low frequency falling), MFU (mid frequency U-shape), MFRU (mid frequency Reverse U-shape), and HFN (high frequency notching).

TABLE 4 K-Means clustering analysis results.

| Cluster | Sample sizes | | | | | |
|---|---|---|---|---|---|---|
| 3 | 1 | 2 | 3 | | | |
| | 2,747 | 2,413 | 4,139 | | | |
| 4 | 1 | 2 | 3 | 4 | | |
| | 4,147 | 1 | 2,745 | 2,406 | | |
| 5 | 1 | 2 | 3 | 4 | 5 | |
| | 2,618 | 1,160 | 1,633 | 3,887 | 1 | |
| 6 | 1 | 2 | 3 | 4 | 5 | 6 |
| | 1,505 | 1 | 2,171 | 3,030 | 1,107 | 1,485 |

patients have more than one cause of dizziness (Fernández et al., 2015). In this study, the incidence of dizziness in females is higher than that in males, but the hearing threshold of females is better.

In this study, the tympanogram of elderly vertigo patients was mainly classified as type A. The wave latency and inter wave period of ABR were within normal range. Analyzing the cause of deafness may be related to blood supply disorders in the inner ear. According to the theory of internal ear blood supply disorder, the labyrinthine artery is the main artery of internal ear blood supply. When the labyrinthine artery has thrombosis, embolism or vasospasm, it will cause labyrinthine artery blood supply disorder, leading to sudden deafness; At the same time, since the labyrinthine artery enters the inner ear and is divided into the common cochlear artery and the vestibular artery, when the blood supply of the labyrinthine artery is impaired, the vestibular function of the patient will also be affected, and vertigo symptoms will appear (Prince and Stucken, 2021). The appearance of vestibular symptoms such as dizziness indicates the severity of the disease and the breadth of the lesion. In previous studies, the wave latency and inter wave period of ABR in elderly patients should be prolonged (Gupta et al., 2014). This phenomenon did not occur in this study, which may be related to the low patient sample size in the age group over 80 years old. For elderly people, it is also necessary to give a special normal reference value for the judgment of each wave latency and wave interval.

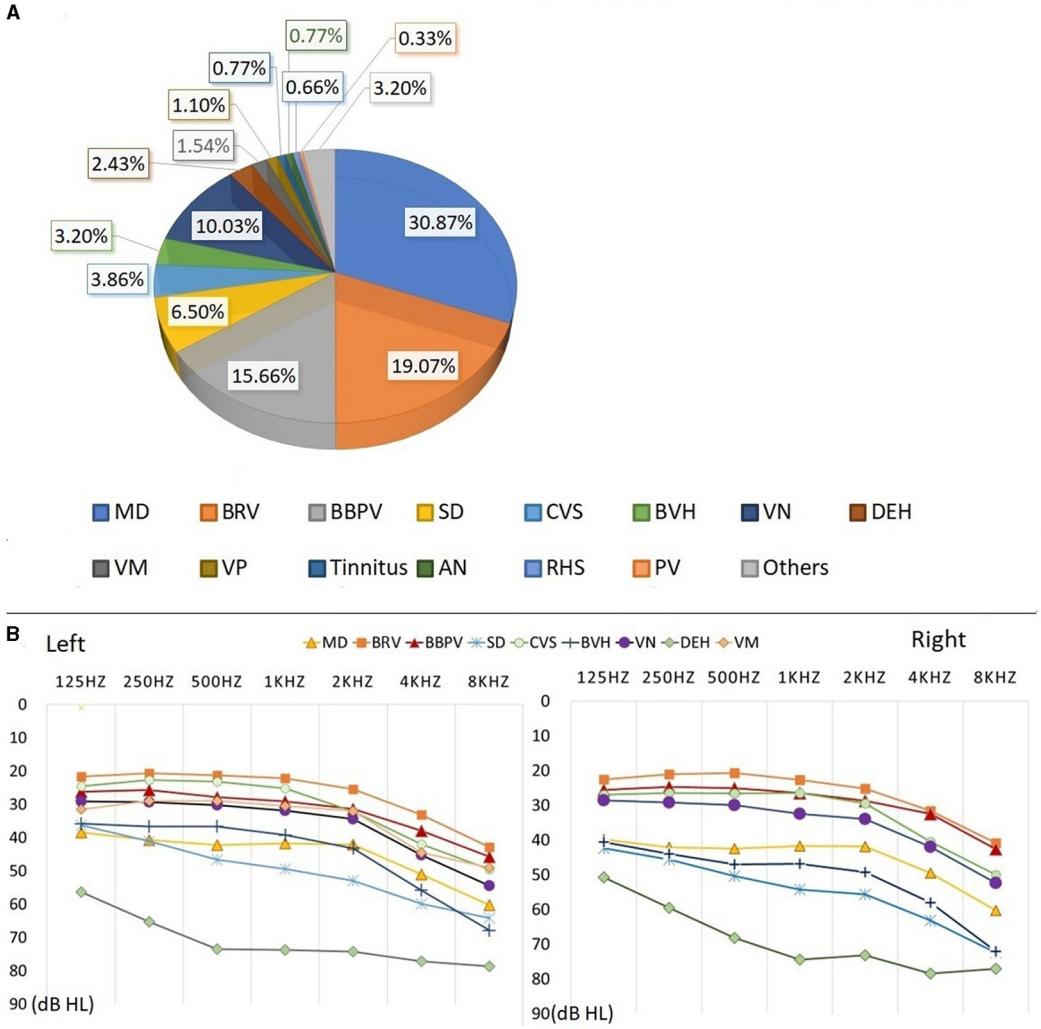


FIGURE 4
Auditory examination results of patients with definite diagnosis. The percentage of different vestibular syndrome is shown in this figure [Diagnosis types of vestibular syndrome: Meniere disease (MD), Benign recurrent vertigo (BRV), Benign paroxysmal positional vertigo (BPPV), Sudden deafness (SD), Chronic vestibular syndrome (CVS), Bilateral vestibular hypofunction (BVH), Vestibular neuropathy (VN), Delayed endolymphatic hydrops (DEH) Vestibular migraine (VM), Vestibular paroxysmia (VP), Tinnitus, Acoustic neurinoma (AN), Ramsay Hunt Syndrome (RHS), Psychiatric vertigo (PV)]. Eight diseases (MD, BRV, BBPV, VN, SD, CVS, BVH, and DEH) with a higher proportion are analyzed. The percentage of remaining diseases(VM, VP, Tinnitus, AN, RHS, PV and other diseases) is less than 2.00%. **(A)** Hearing thresholds of MD, BRV, BBPV, VN, SD, CVS, BVH, and DEH are shown in this figure. **(B)** The patient's hearing threshold gradually increases from 125 to 8,000 Hz. The hearing threshold of 8000 Hz can be 17.03–32.00dB HL higher than that of 125 Hz. The average hearing thresholds (500, 1,000, 2,000, 4,000 Hz) for eight types of vestibular diseases were calculated, and the results show that he hearing threshold of DEH is higher than other vestibular diseases, at around 75 dB HL. The average hearing threshold of other seven vestibular diseases is between 25.04 and 55.86 dB HL.

**TABLE 5** Mean and standard deviation of low, medium and high frequency hearing threshold for different vestibular diseases in the left and right ears.

| Type | LLF | LMF | LHF | RLF | RMF | RHF |
|---|---|---|---|---|---|---|
| MD | 39.56 ± 21.97 | 42.00 ± 23.76 | 55.61 ± 23.51 | 40.99 ± 21.68 | 42.00 ± 23.98 | 54.94 ± 24.44 |
| BRV | 21.10 ± 10.99 | 22.95 ± 12.52 | 38.02 ± 22.07 | 21.76 ± 10.29 | 22.85 ± 11.42 | 36.22 ± 21.04 |
| BPPV | 25.93 ± 19.80 | 29.41 ± 23.96 | 41.81 ± 24.73 | 25.16 ± 16.21 | 26.76 ± 19.50 | 37.54 ± 22.98 |
| VN | 29.22 ± 18.53 | 32.12 ± 21.40 | 49.78 ± 24.95 | 28.84 ± 19.43 | 32.13 ± 25.75 | 47.16 ± 26.70 |
| SD | 38.70 ± 27.32 | 49.66 ± 34.68 | 61.99 ± 32.62 | 43.94 ± 28.70 | 53.43 ± 34.45 | 67.78 ± 35.74 |
| CVS | 23.53 ± 16.17 | 26.77 ± 15.81 | 45.67 ± 23.85 | 26.64 ± 18.19 | 27.47 ± 17.80 | 45.24 ± 25.51 |
| BVH | 36.20 ± 17.40 | 39.67 ± 21.05 | 61.80 ± 24.75 | 42.30 ± 21.11 | 47.67 ± 27.03 | 65.00 ± 27.59 |
| DEH | 60.79 ± 27.78 | 73.77 ± 37.70 | 77.89 ± 35.38 | 33.55 ± 22.50 | 41.05 ± 35.26 | 53.16 ± 33.66 |
| F | 21.509 | 22.468 | 14.972 | 20.674 | 18.868 | 16.792 |
| *P* | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

TABLE 6 Multiple comparison results of different vestibular diseases in the left and right ears.

| LLF | MD | BRV | BPPV | VN | SD | CVS | BVH | DEH |
|---|---|---|---|---|---|---|---|---|
| MD | | 0.000 | 0.000 | 0.000 | 0.771 | 0.000 | 0.415 | 0.000 |
| BRV | 0.000 | | 0.049 | 0.003 | 0.000 | 0.539 | 0.000 | 0.000 |
| BPPV | 0.000 | 0.049 | | 0.256 | 0.000 | 0.560 | 0.019 | 0.000 |
| VN | 0.000 | 0.003 | 0.256 | | 0.006 | 0.183 | 0.599 | 0.000 |
| SD | 0.771 | 0.000 | 0.000 | 0.006 | | 0.001 | 0.599 | 0.000 |
| CVS | 0.000 | 0.539 | 0.560 | 0.001 | 0.001 | | 0.019 | 0.000 |
| BVH | 0.415 | 0.000 | 0.019 | 0.599 | 0.599 | 0.019 | | 0.000 |
| DEH | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | |
| LMF | MD | BRV | BPPV | VN | SD | CVS | BVH | DEH |
| MD | | 0.000 | 0.000 | 0.001 | 0.025 | 0.001 | 0.625 | 0.000 |
| BRV | 0.000 | | 0.023 | 0.003 | 0.000 | 0.407 | 0.001 | 0.000 |
| BPPV | 0.000 | 0.023 | | 0.417 | 0.000 | 0.579 | 0.042 | 0.000 |
| VN | 0.001 | 0.003 | 0.417 | | 0.000 | 0.278 | 0.149 | 0.000 |
| SD | 0.025 | 0.000 | 0.000 | 0.000 | | 0.000 | 0.070 | 0.000 |
| CVS | 0.001 | 0.407 | 0.579 | 0.278 | 0.000 | | 0.038 | 0.000 |
| BVH | 0.625 | 0.001 | 0.042 | 0.149 | 0.070 | 0.038 | | 0.000 |
| DEH | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | |
| LHF | MD | BRV | BPPV | VN | SD | CVS | BVH | DEH |
| MD | | 0.000 | 0.000 | 0.067 | 0.086 | 0.041 | 0.234 | 0.000 |
| BRV | 0.000 | | 0.219 | 0.001 | 0.000 | 0.127 | 0.000 | 0.000 |
| BPPV | 0.000 | 0.219 | | 0.029 | 0.000 | 0.456 | 0.000 | 0.000 |
| VN | 0.067 | 0.001 | 0.029 | | 0.005 | 0.444 | 0.034 | 0.000 |
| SD | 0.086 | 0.000 | 0.000 | 0.005 | | 0.004 | 0.975 | 0.016 |
| CVS | 0.041 | 0.127 | 0.456 | 0.444 | 0.004 | | 0.017 | 0.000 |
| BVH | 0.234 | 0.000 | 0.000 | 0.034 | 0.975 | 0.017 | | 0.033 |
| DEH | 0.000 | 0.000 | 0.000 | 0.000 | 0.016 | 0.000 | 0.033 | |
| RLF | MD | BRV | BPPV | VN | SD | CVS | BVH | DEH |
| MD | | 0.000 | 0.000 | 0.000 | 0.307 | 0.000 | 0.745 | 0.105 |
| BRV | 0.000 | | 0.157 | 0.008 | 0.000 | 0.211 | 0.000 | 0.012 |
| BPPV | 0.000 | 0.157 | | 0.193 | 0.000 | 0.713 | 0.000 | 0.080 |
| VN | 0.000 | 0.008 | 0.193 | | 0.000 | 0.597 | 0.002 | 0.338 |
| SD | 0.307 | 0.000 | 0.000 | 0.000 | | 0.000 | 0.726 | 0.043 |
| CVS | 0.000 | 0.211 | 0.713 | 0.597 | 0.000 | | 0.003 | 0.224 |
| BVH | 0.745 | 0.000 | 0.000 | 0.002 | 0.726 | 0.003 | | 0.136 |
| DEH | 0.105 | 0.012 | 0.080 | 0.338 | 0.043 | 0.224 | 0.136 | |
| RMF | MD | BRV | BPPV | VN | SD | CVS | BVH | DEH |
| MD | | 0.000 | 0.000 | 0.001 | 0.025 | 0.001 | 0.625 | 0.000 |
| BRV | 0.000 | | 0.023 | 0.003 | 0.000 | 0.407 | 0.001 | 0.000 |
| BPPV | 0.000 | 0.023 | | 0.417 | 0.000 | 0.579 | 0.042 | 0.000 |
| VN | 0.001 | 0.003 | 0.417 | | 0.000 | 0.278 | 0.149 | 0.000 |
| SD | 0.025 | 0.000 | 0.000 | 0.000 | | 0.000 | 0.070 | 0.000 |
| CVS | 0.001 | 0.407 | 0.579 | 0.278 | 0.000 | | 0.038 | 0.000 |
| BVH | 0.625 | 0.001 | 0.042 | 0.149 | 0.070 | 0.038 | | 0.000 |
| DEH | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | |
| RHF | MD | BRV | BPPV | VN | SD | CVS | BVH | DEH |
| MD | | 0.000 | 0.000 | 0.017 | 0.001 | 0.050 | 0.058 | 0.766 |
| BRV | 0.000 | | 0.675 | 0.002 | 0.000 | 0.078 | 0.000 | 0.006 |
| BPPV | 0.000 | 0.675 | | 0.010 | 0.000 | 0.144 | 0.000 | 0.013 |
| VN | 0.017 | 0.002 | 0.010 | | 0.000 | 0.726 | 0.002 | 0.352 |
| SD | 0.001 | 0.000 | 0.000 | 0.000 | | 0.000 | 0.649 | 0.030 |
| CVS | 0.050 | 0.078 | 0.144 | 0.726 | 0.000 | | 0.004 | 0.288 |
| BVH | 0.058 | 0.000 | 0.000 | 0.002 | 0.649 | 0.004 | | 0.124 |
| DEH | 0.766 | 0.006 | 0.013 | 0.352 | 0.030 | 0.288 | 0.124 | |

*(Continued)*

TABLE 6 (Continued)

In this study, the main audiometric shapes of elderly patients with dizziness were flat, high-frequency gently sloping (HFGS) and high-frequency steeply sloping (HFSS). Due to the large oxygen consumption of the cochlea bottom, the metabolic rate is high. Compared with the cochlea top, the blood supply of the cochlea bottom is poor, and its auditory hair cell is more vulnerable to damage. The cause of deafness in patients with dizziness involves a wide range of surrounding organs, affecting the vestibular area. Moreover, as a result of the bottom of the cochlea near the vestibule, patients with dizziness may have relatively severe cochlear damage, and their inner ear may have a larger or deeper degree of ischemia (Yu and Li, 2018). From Figure 3, it can be seen that a large number of deaf patients are classified as having "No typing" (18.3% in the left ear, and 19.25% in the right ear) based on the current criteria. Presbycusis patients with vertigo and dizziness are often associated with complicated basic diseases such as diabetes, hypertension and coronary heart disease, and the degree of hearing loss is high and cause the diversity of hearing changes in elderly deaf patients. This indicated the possibility of inappropriate classification methods for elderly patients with hearing loss according to the fixed criteria for audiometric classification. Further detailed research is needed to analyze the hearing status of aged patients with different diseases.

## 5. Conclusion

Our study revealed that elderly patients with vertigo and dizziness primarily experienced mild to moderate hearing loss. Interestingly, we found that the hearing threshold of female patients was generally better than that of their male counterparts. We also discovered that the most common audiometric shapes in these patients were flat, high-frequency gently sloping (HFGS), and high-frequency steeply sloping (HFSS). Importantly, we identified significant differences in hearing thresholds across various vestibular diseases.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by PLA General Hospital's Ethics Committee (No. S2022-673-01). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

QW performed the methodology and writing—original draft. AC performed the data curation. MH performed the formal analysis. XL performed the writing—review and editing. YD performed the visualization. ZW performed the supervision. FJ performed the conceptualization, project administration, and funding acquisition. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1225786/full#supplementary-material

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# Parvalbumin-positive neurons in the medial vestibular nucleus contribute to vestibular compensation through commissural inhibition

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**Background:** The commissural inhibitory system between the bilateral medial vestibular nucleus (MVN) plays a key role in vestibular compensation. Calcium-binding protein parvalbumin (PV) is expressed in MVN GABAergic neurons. Whether these neurons are involved in vestibular compensation is still unknown.

**Methods:** After unilateral labyrinthectomy (UL), we measured the activity of MVN PV neurons by *in vivo* calcium imaging, and observed the projection of MVN PV neurons by retrograde neural tracing. After regulating PV neurons' activity by chemogenetic technique, the effects on vestibular compensation were evaluated by behavior analysis.

**Results:** We found PV expression and the activity of PV neurons in contralateral but not ipsilateral MVN increased 6 h following UL. ErbB4 is required to maintain GABA release for PV neurons, conditional knockout ErbB4 from PV neurons promoted vestibular compensation. Further investigation showed that vestibular compensation could be promoted by chemogenetic inhibition of contralateral MVN or activation of ipsilateral MVN PV neurons. Additional neural tracing study revealed that considerable MVN PV neurons were projecting to the opposite side of MVN, and that activating the ipsilateral MVN PV neurons projecting to contralateral MVN can promote vestibular compensation.

**Conclusion:** Contralateral MVN PV neuron activation after UL is detrimental to vestibular compensation, and rebalancing bilateral MVN PV neuron activity can promote vestibular compensation, via commissural inhibition from the ipsilateral MVN PV neurons. Our findings provide a new understanding of vestibular compensation at the neural circuitry level and a novel potential therapeutic target for vestibular disorders.

KEYWORDS

**vestibular compensation, unilateral labyrinthectomy, commissural inhibitory system, medial vestibular nucleus, parvalbumin**

# 1. Introduction

Vestibular disorder is a common clinical symptom characterized by postural imbalance, gaze instability, and vertigo, affecting over 20% individuals yearly, strongly limiting daily activities and the quality of life, and leading to falls or other accidents (Casani et al., 2021). However, some balance system disturbances, including unilateral vestibular hypofunction or loss, can partially ameliorate over time in a process known as "vestibular compensation" (Smith and Curthoys, 1989; Hatat et al., 2022). Investigating the mechanism will facilitate the search for new treatment options for treating vestibular disorders and the comprehension of central nervous system (CNS) plasticity during behavioral recovery (Dieringer, 1995).

The medial vestibular nuclei (MVN) are the primary central target of inner ear afferents, essential in maintaining equilibrium, posture, and head position (Dieringer, 1995; Ris and Godaux, 1998; Barmack, 2003). The activity asymmetry between bilateral MVN underlies the postural and oculomotor deficits induced by unilateral labyrinthectomy (UL) (Fisch, 1973), which is assumed due to the imbalance of the reciprocal commissural inhibitory system of bilateral MVN, and the reduction of the afferent input from the lesioned vestibular (Bergquist et al., 2008; Gaal et al., 2015; Magyar et al., 2022). However, no direct evidence supports the efficacy of commissural system rebalancing in vestibular compensation, and the cellular and neural circuitry mechanism is largely unknown (Paterson et al., 2004; Olabi et al., 2009).

GABAergic neurons in MVN can be classified into subtypes according to the expressed markers (Dutia et al., 1992; Hong et al., 2008; Zeeh et al., 2013). Parvalbumin (PV) is a $Ca^{2+}$ binding protein, and PV-positive neurons are a crucial subtype of GABAergic neurons, characterized by their fast-spiking property and their projecting to the soma or axon initial segments to other neurons (Heizmann, 1993; Arif, 2009; Permyakov and Uversky, 2022). ErbB4 is a tyrosine kinase receptor of neuregulin 1, a neurotrophic growth factor, the majority of PV neurons co-localize with ErbB4 in many brain regions (Bean et al., 2014), and ErbB4 is required to maintain PV neurons' normal function (Lu et al., 2014). It has been reported that PV expression exhibits asymmetric changes during vestibular compensation (Hong et al., 2008); nevertheless, it is unclear whether MVN PV neurons are involved in vestibular compensation. In the present study, we observed the MVN PV neurons project to the other side of MVN, and this projection mediates vestibular compensation via commissural inhibition.

# 2. Materials and methods

## 2.1. Animals

One hundred forty-five male C57BL/6J mice were purchased from Charles River, China. PV-Cre and loxP-flanked ErbB4 (Floxed-ErbB4) mice have been described previously (Wen et al., 2010; Yi et al., 2020) and backcrossed with C57BL/6J for over 10 generations.

PV-Cre mice were crossed with floxed-ErbB4 mice to generate PV-Cre; floxed-ErbB4$^{+/+}$ (ErbB4 KO) mice, in which ErbB4 was ablated in PV neurons (Yi et al., 2020). Forty-eight PV-Cre or ErbB4 KO mice were used for behavior analysis, most of which (~70%) were male.

Less than 5 mice were housed per cage at 22°C–24°C and 55%–80% humidity, on a 12:12 h light/dark cycle, with water and food available. The Animal Care and Use Committee of Huazhong University of Science and Technology approved all experiments.

## 2.2. Unilateral labyrinthectomy

UL has been previously described (Campos-Torres et al., 2005; Chen et al., 2019; Simon et al., 2020; Magyar et al., 2022) in detail. Briefly, after adult male mice (8–10 weeks) were anesthetized with sodium pentobarbital (50 mg/kg, i.p.), an incision was made behind the ear, and the tympanic membrane, malleus, incus, and stapes were surgically removed. A crooked syringe needle tip was inserted into the oval window for mechanical damage and then rinsed with 100% ethanol for chemical demolition of the vestibule. The space created by labyrinthectomy was filled with a hemostatic sponge. For the sham group, the tympanic membrane, malleus, incus, and stapes were removed without damaging the vestibule.

## 2.3. Behavioral analysis

Only the adult male mice (8–10 weeks) were used in behavioral tests. C57BL/6J mice were acclimatized for 7 days after purchase. All mice were handled in the testing room for at least 30 min per day for 3 days before taking behavioral measurements. Tests of static compensation include scoring for posture asymmetry, spontaneous nystagmus, and head tilt. One day prior to UL and one to 5 days following UL, the tests were performed at the same time of day. Blinded assessors scored the static symptoms.

## 2.4. Posture asymmetry

Posture deficits were scored as previously described (Chen et al., 2019): 10 points for spontaneous barrel rolling; 9 points for barrel rolling elicited by a light touch or puff of air; 8 points for the recumbent position on the deafferented side without leg support; 7-6 points for some ipsilateral leg support; 5 points for moving with bilateral leg support; 4-3 points for occasional postural asymmetry; 2-1 points for barely perceptible postural asymmetry.

## 2.5. Spontaneous nystagmus

Electronystagmography was recorded by inserting electrodes into the nasal and lateral orbital margins of the two eyes. The frequency of the fast-phase pullback of the cornea-retinal potential was used to evaluate spontaneous nystagmus (Pietkiewicz et al., 2012).

## 2.6. Head tilt

Head tilt was measured based on the angle between the line from the center of the sacrum to the center of the first thoracic vertebra and the line from the tip of the nose to the center of the parietal.

## 2.7. Western blot

The medial vestibular nuclei were isolated from both sides after the mice were anesthetized. Tissues were homogenized in ice-cold RIPA buffer (Beyotime Biotechnology) supplemented with proteinase inhibitors and subjected to centrifugation at 12,000 rpm for 15 min at 4°C to collect the supernatant. SDS-PAGE separated proteins were transferred to PVDF membranes. After being blocked with tris-buffered saline (TBS) containing 0.1% Tween-20, and 5% nonfat powdered milk for 1 h at room temperature, PVDF membranes were incubated with primary antibodies overnight at 4°C with antibody dilution buffer (Elabscience, Cat. No. E-IR-R125). After washing, the PVDF membrane was incubated with horseradish peroxidase (HRP)-labeled secondary antibodies (AS014, ABclonal, 1:10000) in TBS and 0.1% Tween-20 for 1 h at room temperature. Signal revelation was performed using an enhanced chemiluminescence substrate (RM00021, ABclonal) detection system. Band intensities were scanned using MicroChemi 4.2 (DNR Bio-imaging Systems, Israel), and quantified using ImageJ (National Institutes of Health, United States). Primary antibodies used were: rabbit anti-α-tubulin (AC003, ABclonal, 1:4000), rabbit anti-parvalbumin (A2791, ABclonal, 1:800), and rabbit anti-ErbB4 (A10853, ABclonal, 1:800), and rabbit anti-GABA (A2052, Sigma, 1:50).

## 2.8. Immunofluorescence

Mice were anesthesia with sodium pentobarbital (50 mg/kg, i.p.) and perfused transcardially with 0.1 mol/L phosphate-buffered saline (PBS) and 4% paraformaldehyde (PFA) in PBS. After post-fixed at 4°C overnight with PFA and gradient dehydration with 15% and 30% sucrose solution, brains were frozen in OCT medium (Tissue-Tek, Sakura, Japan), and sliced at 35 μm using a Leica cryostat (Thermo Scientific, HM550). After washing with PBS five times, slices were mounted to a slide with anti-florescence decay sealant containing DAPI (Solarbio, China). Fluorescent signals were imaged with Olympus Fluoview FV1000. Five films were analyzed per mouse, and each group contained 3 mice.

## 2.9. Stereotaxic viral injection

Adult mice were anesthesia with sodium pentobarbital (50 mg/kg, i.p.) and head-fixed in a stereotaxic device (RWD life science; 68025). Viruses were injected into the unilateral medial vestibular nucleus coordinates relative to bregma: anteroposterior, −6.05 mm; mediolateral, ±0.75 mm; dorsoventral, −4.3 mm using a glass pipette (Cetin et al., 2006) (300 nL per mouse, 50 nL/min). After injection, the glass pipette was left in place for 15 min and removed slowly. The skin was sutured and sterilized with iodophors. The titers of AAV-EF1α-DIO-GCaMP6m-WPRE-hGH-polyA (Brain VTA, PT-0283), AAV-EF1α-DIO-hM3Dq-EGFP-WPRE (Obio Technology, Shanghai, H15959), AAV-EF1α-hM4Di-EGFP-WPRE (Obio Technology, Shanghai, H15963), AAV-retro-hSyn-DIO-hM3Dq-EGFP (GeneChem technologies, AAV0071), AAV-retro-CMV-DIO-EGFP (ViGene Biosciences, AV200001) were $10^{12}$ genome copies per mL. Mice were injected with clozapine-N-oxide [CNO, dissolved in saline 3 mg/kg, i.p.; 10 μM, 1 μL per mouse, guide cannula, (coordinates relative to bregma: anteroposterior, −6.05 mm; mediolateral, ±0.75 mm; dorsoventral, −4.3 mm)] or vehicle to active hM3Dq or hM4Di, guide cannula was implanted 100 μm above the MVN (coordinates relative to bregma: anteroposterior, −6.05 mm; mediolateral, 0.75 mm; dorsoventral, −4.2 mm), 30 min before the behavioral tests.

## 2.10. *In vivo* calcium imaging

The procedures have been described previously (Chen et al., 2021). To record contralateral MVN PV neuron's activity after UL, PV-Cre mice were injected with viruses (AAV-EF1α-DIO-GCaMP6m-WPRE-hGH-polyA) in contralateral MVN. Three weeks later, a gradient-index (GRIN) lens (0.5 mm in diameter and 5.7 mm in length, Fsphotonics Technology, Shanghai, China) was placed above MVN with 100 μm. The GRIN lens was fixed on the skull with dental cement. After a day of recovery, mice underwent UL and recorded 0 h, 1 h, 3 h, 6 h in contralateral MVN. During recording, the distance of the microscope to the GRIN lens was adjusted by a micro-manipulator until the field of view was in focus. Images were collected at 30 frames per second using the MiniScope V2.0 software.

Images were processed using MATLAB R2020b (Mathworks, Natick, MA) with customized code (https://github.com/thinkertech333/analysisforminiscope, Thinkertech, Nanjing, China), and Cellsort 4.0 software. After motion correction (set to 10) and denoising (set to 100), the region of interest was manually selected according to the fluorescence intensity. The $Ca^{2+}$ signals in the 0 h were considered a baseline and the average $Ca^{2+}$ signal in this period was used as a reference ($F_0$) to normalize the fluorescence signal ($\Delta F/F$). The formula is as the following:

$$\Delta F/F = \frac{F_{\text{signal}} - F_0}{F_0}$$

$F_{\text{signal}}$ is the real-time $Ca^{2+}$ signal intensity of the PV neurons of interest, and $F_0$ is the average $Ca^{2+}$ signal intensity in the baseline period.

## 2.11. Statistical analysis

Data were analyzed by paired or unpaired *t*-tests, one-way ANOVA followed by Tukey's test, or two-way ANOVA followed by the Bonferroni test, using GraphPad Prism 8.00 (GraphPad Software) software. Data are expressed as the mean ± SEM, and statistical significance was considered when $p < 0.05$.

# 3. Results

## 3.1. The activity of PV neurons is selectively elevated in the contralateral MVN after UL

To investigate the role of PV in bilateral MVN after UL, we first evaluated the expression of PV protein by western blotting. Compared to the sham group, PV expression was increased in the contralateral rather than ipsilateral MVN at 6 h after UL, (Figures 1A,B), one-way

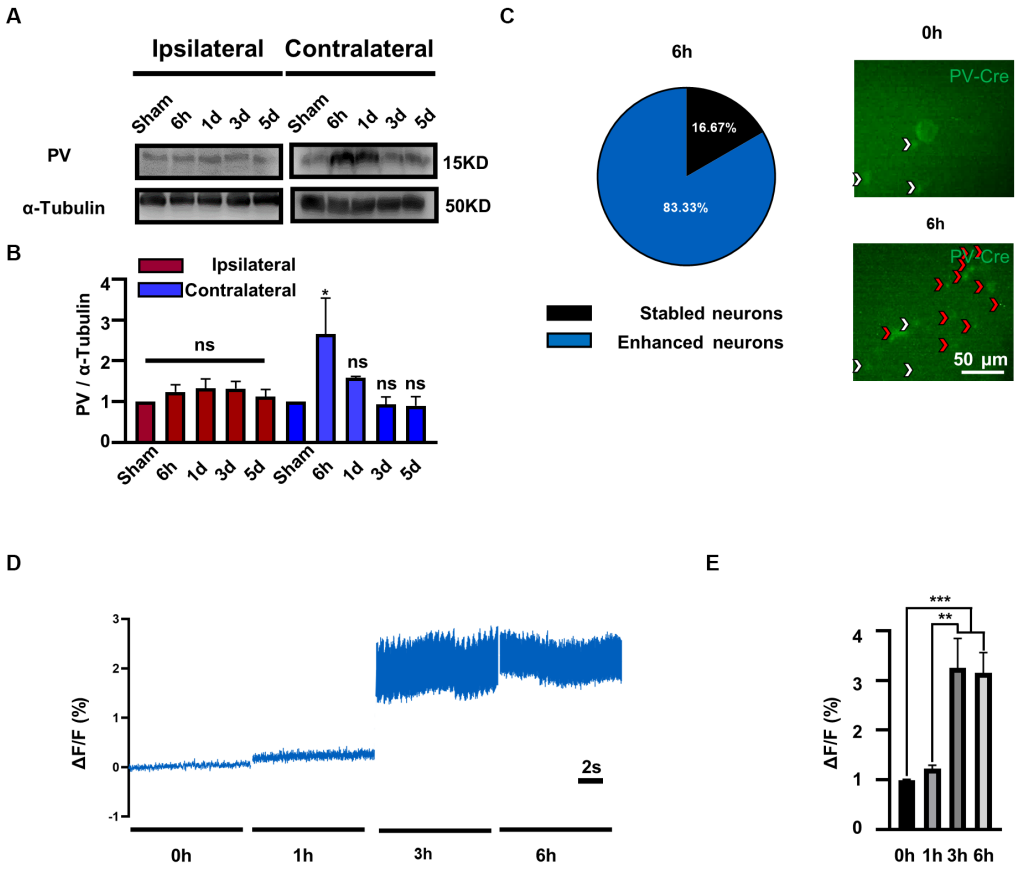


FIGURE 1
PV expression and PV neurons activity is selectively increased in contralateral MVN after UL. **(A)** Representative western blotting images of PV in the bilateral MVNs after UL. α-tubulin was used as the loading control. **(B)** Quantitative analysis of PV in the bilateral MVNs in **(A)**. $n = 3$ per group. One-way ANOVA, $F$ (4, 15) = 3.231, $p = 0.0423$; Dunnett's *post hoc* test: Sham vs. 6 h, $p = 0.0427$. *$p < 0.05$, ns, no significant difference. **(C)** Most PV neurons in the contralateral MVN activated 6 h after UL (83.3%). Representative *in vivo* calcium imaging photomicrographs of PV neurons in contralateral MVN 0 h and 6 h shown on the right, white arrows indicate stable neurons and red arrows indicate activity enhanced neurons. **(D,E)** PV neurons activity in the contralateral MVN increased after UL, revealed by *in vivo* calcium imaging. **(D)** Representative traces of $Ca^{2+}$ signals from PV neurons in contralateral MVN after UL 0 h to 6 h. **(E)** Quantification of $\Delta F/F$ in **(D)**. $n = 20$ neurons from 3 mice. One-way ANOVA, $F$ (3, 76) = 11.05, $p < 0.0001$; Tukey's *post hoc* test, 0 h vs. 3 h, $p = 0.0002$; 0 h vs. 6 h, $p = 0.0004$; 1 h vs. 3 h, $p = 0.0011$; 1 h vs. 6 h, $p = 0.0021$. **$p < 0.01$ and ***$p < 0.001$.

ANOVA, [$F$ (4, 15) = 3.231, $p = 0.0423$], returning to baseline at 1 day after UL.

To further validate whether enhanced protein expression is associated with PV neurons activity, we observed the calcium signals of contralateral MVN PV neurons. Interestingly, we discovered that the majority of PV neurons (83.3%) (Figure 1C) displayed enhanced activity in 3–6 h after UL [Figures 1D,E, One-way ANOVA, $F$ (3, 76) = 11.05, $p < 0.0001$]. In comparison, the other (16.7%) maintained a stable activity throughout the procedure (data not shown). Together, these results suggest that the expression of PV protein may be selectively increased in the contralateral MVN and accompanied by increased PV neuron activity.

## 3.2. ErbB4 KO can promote vestibular compensation

To investigate whether ErbB4 is involved in vestibular compensation, we first detected the alterations in ErbB4 protein expression in MVN following UL. Compared with the control group, the expression of ErbB4 protein significantly increased in the contralateral MVN at 3–24 h after UL, while there was no significant change in the ipsilateral MVN [Figures 2A–D, one-way ANOVA, $F$ (7, 21) = 8.604, $p < 0.0001$ for contralateral]. We next examined the mice that specifically knock out ErbB4 in PV neurons (PV-Cre; ErbB4-floxed$^{+/+}$, ErbB4 KO) (Figures 2E,F), thereby attenuating the activation of PV neurons in both sides of MVN after UL. ErbB4 KO mice exhibited faster vestibular compensation, [Figures 2G–I, postural asymmetry, $F$ (1, 6) = 6.919, $p = 0.039$; spontaneous nystagmus, $F$ (1, 6) = 39.94, $p = 0.0007$; head tilt, $F$ (1, 6) = 21.2, $p = 0.0037$], suggesting ErbB4 in MVN PV neurons is detrimental to the vestibular compensation.

## 3.3. Inhibition of PV neurons activity in contralateral MVN can promote vestibular compensation

To confirm whether the hyperactivation of PV neurons in contralateral MVN is detrimental to the vestibular compensation, we employed a chemogenetic technique to specifically inhibit the

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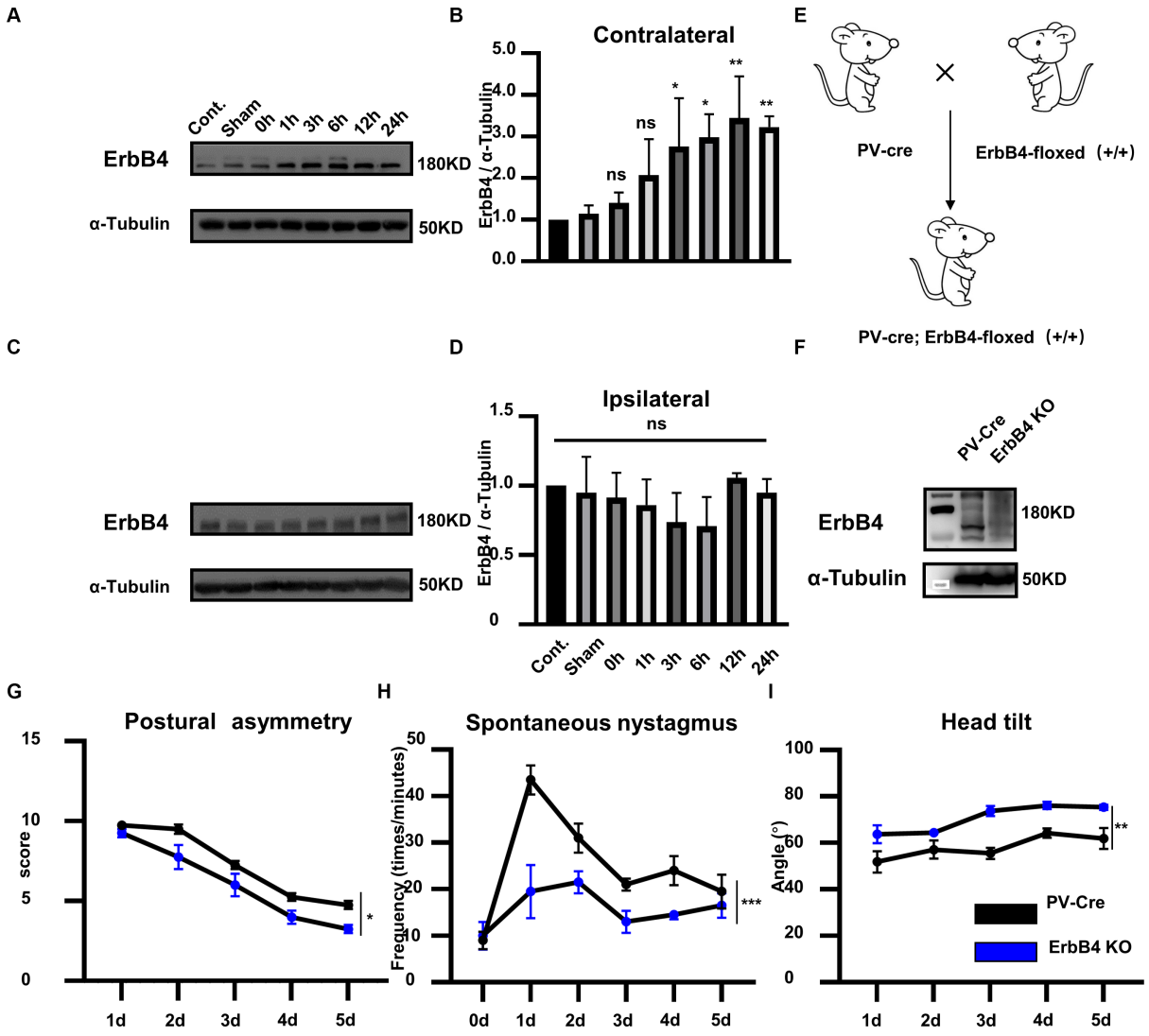


FIGURE 2
ErbB4 in MVN PV neurons is detrimental to the vestibular compensation. **(A–C)** Western blot for ErbB4 in the bilateral MVNs after UL 0 h, 1 h, 3 h, 6 h,12 h, 24 h, 3 days, and control, sham. α-tubulin served as a loading control. **(B)** Quantitative analysis of the expression of ErbB4 in contralateral MVN in **(A)**. Data are expressed as mean ± SEM, and there are 3 to 5 mice in each group. One-way ANOVA, $F$ (7, 21) = 8.604, $p < 0.0001$; Tukey's *post hoc* test: cont. vs. 1 h, $p = 0.487$; cont. vs. 3 h, $p = 0.0486$; cont. vs. 6 h, $p = 0.0115$; cont. vs. 12 h, $p = 0.0013$; cont. vs. 24 h, $p = 0.007$. One-way ANOVA, $^{*}p < 0.05$ and $^{**}p < 0.01$, ns, no significant difference. **(D)** Quantitative analysis of the expression of ErbB4 in ipsilateral MVN in **(C)**. Data are expressed as mean ± SEM, and there are three mice in each group. One-way ANOVA, Bonferroni's *post hoc* test, ns, no significant. **(E)** Schematic illustrator of PV-Cre; ErbB4-floxed$^{+/+}$ (ErbB4 KO). **(F)** Western blot for ErbB4 in the MVN in ErbB4 KO compared with PV-Cre mice. α-tubulin served as a loading control. **(G–I)** The behavior detection after UL in ErbB4 KO mice. **(G)** Postural asymmetry, $F$ (1, 6) = 6.919, $p = 0.039$; **(H)** spontaneous nystagmus, $F$ (1, 6) = 39.94, $p = 0.0007$; **(I)** head tilt, $F$ (1, 6) = 21.2, $p = 0.0037$. $n = 4$ mice in PV-Cre and WT group, respectively. Two-way ANOVA, Bonferroni's *post hoc* test. $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

activity of PV neurons in the contralateral MVN after UL. PV-Cre mice were injected with AAV-EF1α-hM4Di-EGFP-WPRE virus in the contralateral MVN (Figures 3A–E), and wild-type mice were used as control. Twenty days later, these mice were subjected to UL followed by CNO i.p. injection for five days (once the mice had undergone UL, CNO was given immediately). Behavior tests were performed 30 min after CNO administration. For the control mice, vestibular symptoms were gradually alleviated, including postural asymmetry, spontaneous nystagmus, and head tilt; interestingly, in PV-Cre mice, all these behavior symptoms were alleviated faster than wild-type mice [Figures 3F–H, postural asymmetry, $F$ (1, 6) = 13.97, $p = 0.0096$; spontaneous nystagmus, $F$ (1, 6) = 11.18, $p = 0.0156$; head tilt, $F$ (1, 6) = 20.93, $p = 0.0038$], suggesting inhibition of contralateral MVN PV neurons effectively accelerated vestibular compensation.

## 3.4. Activation of PV neurons activity in ipsilateral MVN can promote vestibular compensation

Previously we have demonstrated that reducing the activity of PV neurons in the contralateral MVN is beneficial to vestibular

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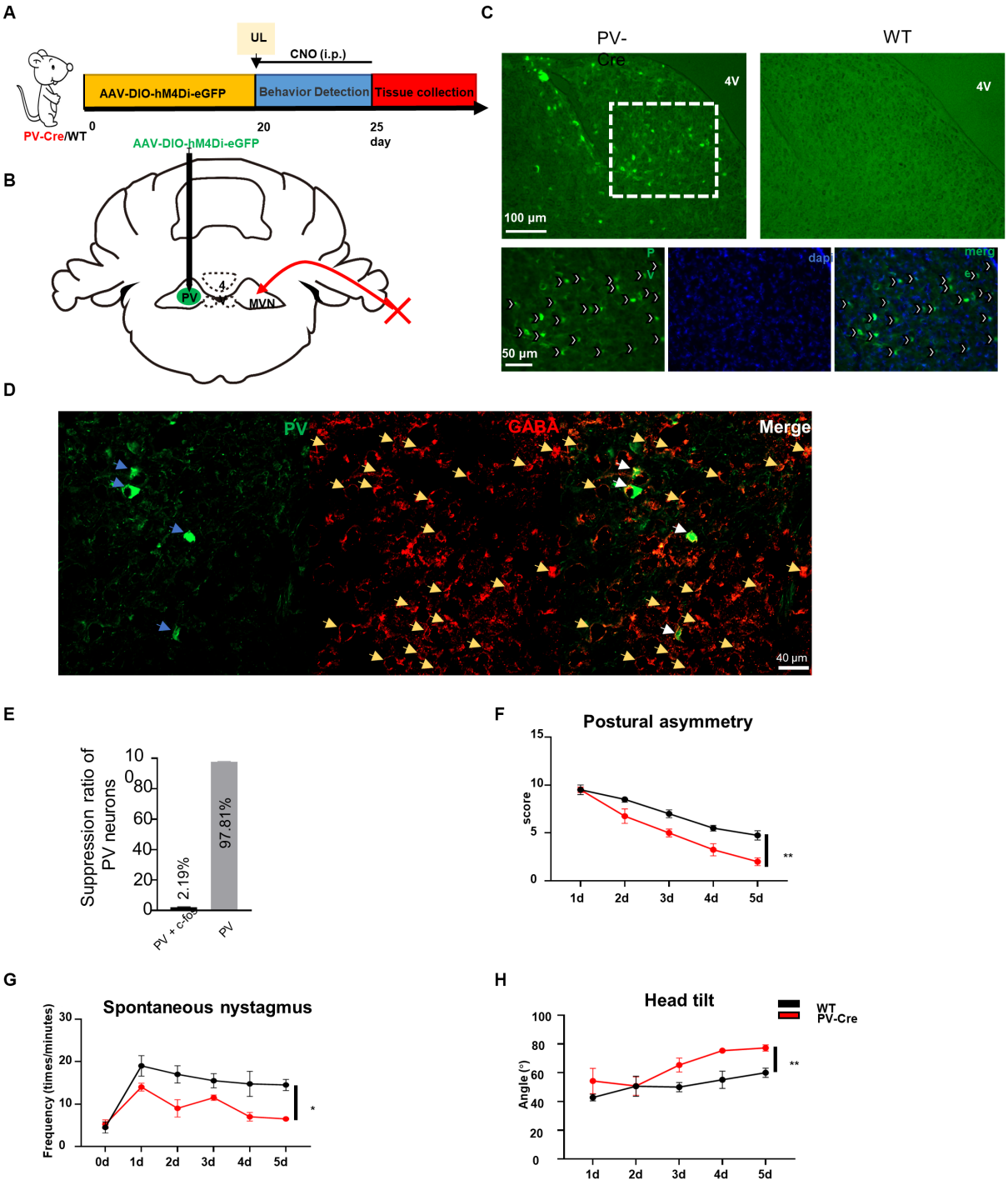


FIGURE 3
Inhibition of contralateral MVN PV neurons promotes vestibular compensation. **(A)** Schematic experimental design. Twenty days after AAV-hSyn-DIO-hM4Di-eGFP stereotaxic injection into contralateral MVN of PV-Cre mice, UL was conducted followed by CNO i.p. injection twice every day. Vestibular dysfunction was evaluated within 1–2 h after injecting of CNO every day. **(B)** Schematic illustration of AAV injection in contralateral MVN of PV-Cre mice. **(C)** Representative photomicrographs showing PV neurons in contralateral MVN after injecting the virus. Images at the bottom are magnified images of the boxed regions in the upper image. Arrows (in white) indicate PV neurons. Scale bar, top, 100 μm; bottom, 50 μm. **(D)** Representative image of co-staining of PV and GABAergic neurons. **(E)** The percentage of PV neuron inhibition after CNO injection. **(F–H)** Inhibiting the contralateral MVN PV neurons promotes vestibular compensation. **(F)** Postural asymmetry, $F$ (1, 6) = 13.97, $p$ = 0.0096; **(G)** spontaneous nystagmus, $F$ (1, 6) = 11.18, $p$ = 0.0156; **(H)** head tilt, $F$ (1, 6) = 20.93, $p$ = 0.0038. $n$ = 4 mice in PV-Cre and WT group, respectively. Two-way ANOVA, Bonferroni's *post hoc* test. *$p < 0.05$ and **$p < 0.01$.

compensation, it needs to be further investigated whether vestibular compensation could also be promoted by enhancing the activity of ipsilateral MVN PV neurons to achieve a new balance between bilateral MVN PV neurons. By injecting AAV-EF1α-DIO-hM3Dq-EGFP-WPRE virus into the ipsilateral MVN of PV-Cre mice, and intraperitoneal injecting CNO (Figures 4A–D), we found that for the wild-type control mice, spontaneous vestibular compensation could be observed 1–5 days after UL, however, activation of PV neurons in the ipsilateral MVN could

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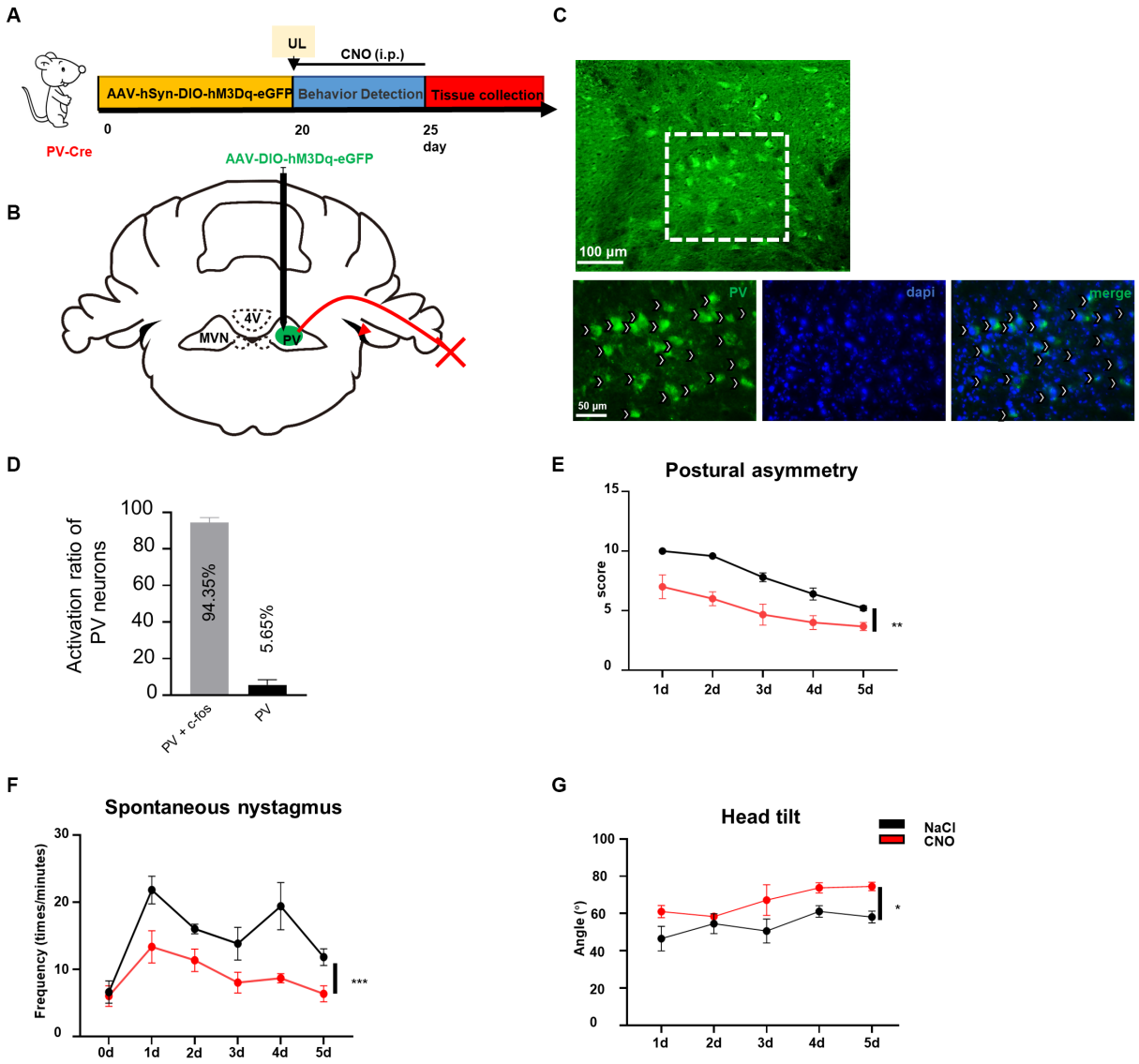


FIGURE 4
Activation of ipsilateral vestibular PV neurons can improve vestibular compensation. **(A)** Schematic experimental design for PV-Cre. **(B)** Schematic illustration of AAV-hSyn-DIO-hM3Dq-eGFP injection in ipsilateral MVN of PV-Cre mice. **(C)** Representative photomicrographs showing PV neurons in ipsilateral MVN after injecting the virus. Arrows (in white) indicate PV neurons. Scale bar, top, 100 μm; bottom, 50 μm. **(D)** The percentage of PV neuron activation after CNO injection. **(E–G)** The behavior detection after UL by activating the ipsilateral MVN PV neurons. **(D)** Postural asymmetry, $F$ (1, 6) = 26.05, $p$ = 0.0022; **(E)** spontaneous nystagmus, $F$ (1, 6) = 35.75, $p$ = 0.001; **(F)** head tilt, $F$ (1, 6) = 11.08, $p$ = 0.0158. $n$ = 4 mice in PV-Cre and WT group, respectively. Two-way ANOVA, Bonferroni's *post hoc* test. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

also further promote vestibular compensation [Figures 4E,G, postural asymmetry, $F$ (1, 6) = 26.05, $p$ = 0.0022; spontaneous nystagmus, $F$ (1, 6) = 35.75, $p$ = 0.001; head tilt, $F$ (1, 6) = 11.08, $p$ = 0.0158]. Together, these results suggest that a new balance of activity in bilateral MVN PV neurons contributes to the amelioration of static deficits after UL.

## 3.5. PV neurons project to the contralateral MVN

Vestibular commissures connections are essential in vestibular compensation and are mediated predominantly by inhibitory GABAergic neurons (Gliddon et al., 2005; Malinvaud et al., 2010). To verify whether PV neurons project from one side of MVN to the other, we injected AAV-retro-CMV-DIO-EGFP virus into one side of MVN (Figure 5A). Twenty-eight days later, we found PV neuron projections from the other side of MVN (Figure 5B). Next, we counted the number of PV neurons in bilateral MVN, the injection side accounted for 70.4% of the total, while the contralateral accounted for 29.6% (Figure 5C), suggesting considerable PV neurons in MVN projecting to the opposite side MVN, though we could not exclude the possibility of PV neurons may also innervate other neurons in the same side of MVN. These results suggest PV neurons may influence vestibular compensation through commissural inhibition (Figure 5D).

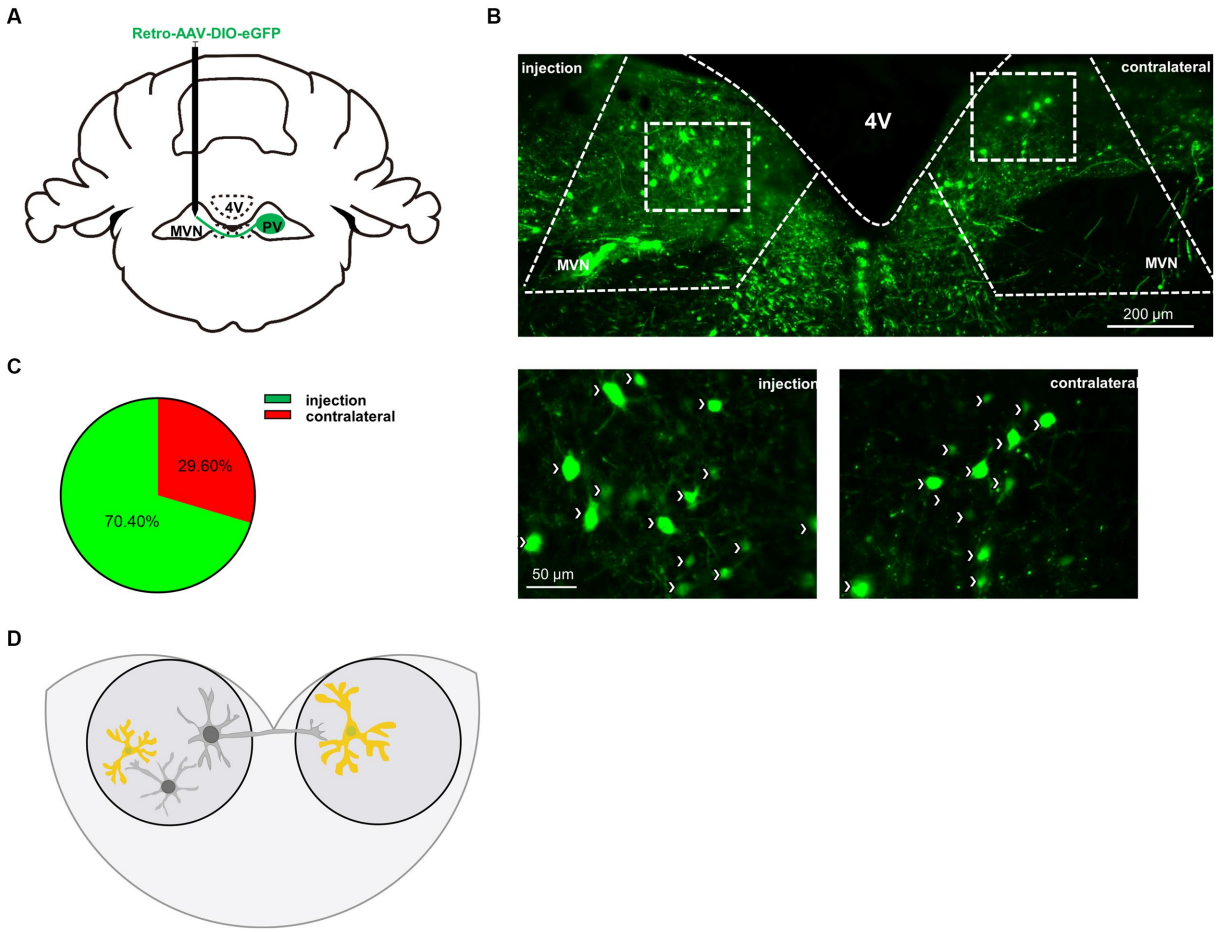


FIGURE 5
PV neurons project to the contralateral MVN. **(A)** Schematic illustration of AAV-retro-CMV-DIO-EGFP injection in unilateral MVN of PV-Cre mice to trace the soma in contralateral MVN. **(B)** Representative photomicrographs showing EGFP-expression PV neurons in bilateral MVNs after virus injection. Arrows (in white) indicate PV neurons. Scale bar, top, 200 μm; bottom, 50 μm. **(C)** Quantification the distribution of bilateral MVNs PV neurons, $n = 3$ mice. **(D)** Schematic illustration of PV neurons in MVN.

### 3.6. Activation of PV neurons from ipsilateral to contralateral MVN promotes vestibular compensation

The vestibular commissural inhibitory system is essential for vestibular compensation (Bergquist et al., 2008; Malinvaud et al., 2010). Modulation of the vestibular commissures inhibitory system facilitates vestibular compensation by enhancing ipsilateral to contralateral GABAergic neuron projections (Chen et al., 2019); however, the cell type of these neurons are unknown. We wondered whether ipsilateral MVN PV neurons could contribute to vestibular compensation through this way. The AAV-retro-hSyn-DIO-hM3Dq-EGFP virus was injected into the contralateral MVN, then a guide cannula was implanted into the ipsilateral MVN on day 10. This allowed for the local injection of CNO into one side of MVN and selective activation of only PV neurons that were projecting from ipsilateral to contralateral MVN (Figures 6A–C). Behavioral analysis revealed that activation of these PV neurons promoted vestibular compensation [Figures 6D–F, postural asymmetry, $F\ (1,\ 6) = 53.8$, $p = 0.0003$; spontaneous nystagmus, $F\ (1, 6) = 17.5$, $p = 0.0058$; head tilt, $F\ (1, 6) = 10.7$, $p = 0.017$]. These results indicate that PV neurons in the ipsilateral MVN regulate the activity of neurons in the contralateral MVN through commissural inhibition between both sides of MVN, and activation of these PV neurons can facilitate vestibular compensation, which may be brought about by the restoration of activity balance in both sides of MVN (Figure 7).

## 4. Discussion

Here, we found that MVN PV-positive GABAergic neurons contribute to vestibular compensation via commissural inhibition. First, we observed that the expression of PV in contralateral but not ipsilateral MVN was up-regulated, and contralateral MVN PV neurons displayed higher activity at 6 h after UL. Second, compromising PV neurons' function by conditional knockout ErbB4 in PV neurons facilitates vestibular compensation, suggesting contralateral MVN PV neurons' detrimental role in vestibular compensation. Third, promoting vestibular compensation by chemogenetic inhibition of contralateral or activation of ipsilateral MVN PV neurons raises the importance of activity rebalancing in bilateral MVN PV neurons. Fourth, we found that PV neurons project

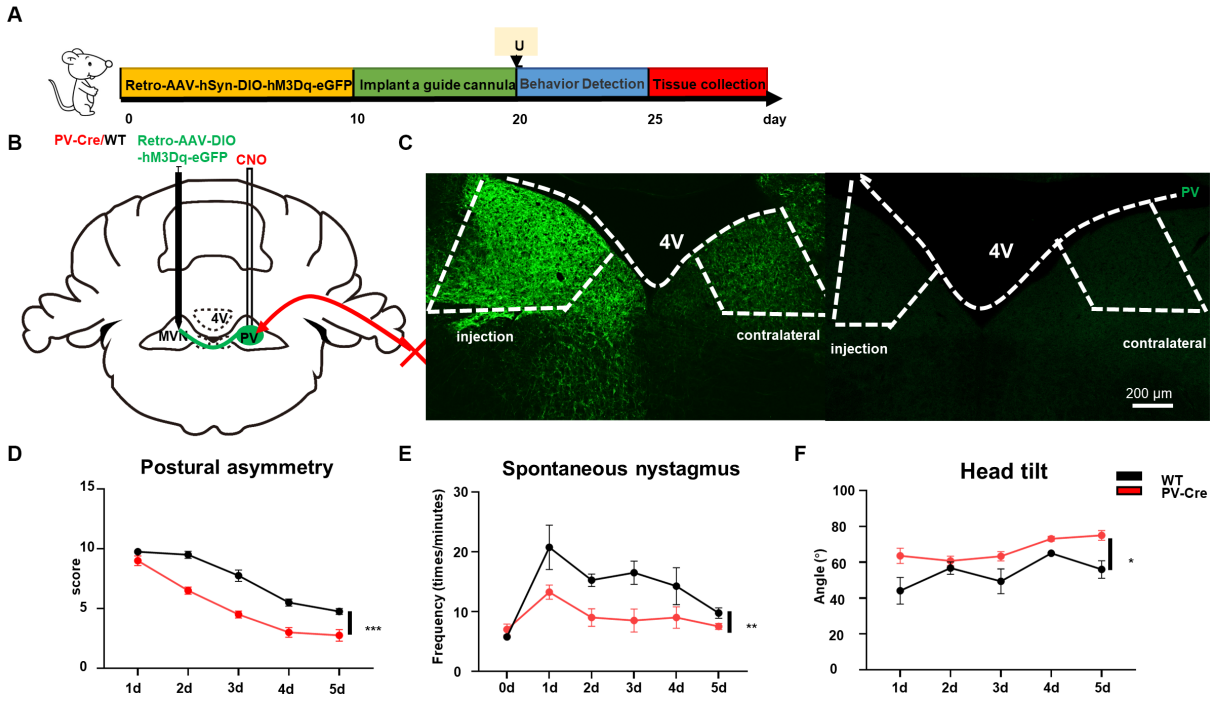


FIGURE 6
Activation of commissural PV neurons can change vestibular compensation. **(A)** Schematic experimental design for PV-Cre and littermates. Illustration of retro-AAV-hSyn-DIO-hM3Dq-eGFP injection in contralateral MVN of PV-Cre mice. **(B)** Schematic illustration of retro-AAV-hSyn-DIO-hM3Dq-eGFP injection in contralateral MVN of PV-Cre mice. **(C)** Representative photomicrographs showing PV-positive neurons in bilateral MVNs after injecting the virus. Scale bar, 200 μm. Schematic illustration of retro-AAV-hSyn-DIO-hM3Dq-eGFP injection in contralateral MVN of PV-Cre mice. **(D–F)** The behavior detection after UL by activating the commissural PV neurons. **(D)** Postural asymmetry, $F$ (1, 6) = 53.8, $p$ = 0.0003; **(E)** spontaneous nystagmus, $F$ (1, 6) = 17.5, $p$ = 0.0058; **(F)** head tilt, $F$ (1, 6) = 10.7, $p$ = 0.017. $n$ = 4 mice in PV-Cre and WT group, respectively. Two-way ANOVA, Bonferroni's *post hoc* test. *$p$ < 0.05, **$p$ < 0.01, and ***$p$ < 0.001.

to the other MVN by circuit tracing, and activation of ipsilateral MVN PV neurons projecting to the other side MVN could also promote vestibular compensation, suggesting PV neurons may be involved in vestibular compensation through the commissural inhibitory system.

PV is widely distributed in the peripheral and central nervous system (MacManus et al., 1982; Heizmann, 1984; Hontanilla et al., 1998; Permyakov and Uversky, 2022), acting as a calcium buffer in the cytosol (Heizmann, 1993). PV expression positively correlates with PV neuron activities, suggesting the importance of PV in buffering the cytosol calcium (Heizmann, 1984; Vreugdenhil et al., 2003). Due to their fast spiking property and their targeting to the soma and axon initial segments of glutamate neurons, PV neurons are the main cell type controlling the local neuron population firing rates, through their GABA release (Schwaller, 2010; Olinger et al., 2012). Consistent with the literature, we observed asymmetric PV expression after UL, and the firing frequency of contralateral PV neurons was increased, suggesting the involvement of PV neurons in vestibular compensation (Hong et al., 2008). It is important to note that the activity of contralateral MVN PV neurons was increased 1 h after UL, observed by *in vivo* calcium imaging. Further investigation of the pathophysiological procedure during the first hour after UL will be crucial for understanding postlesion plasticity in the adult CNS (Lacour et al., 2016). *In vivo* calcium imaging results also show that the activity of contralateral MVN PV neurons is greatly increased during 3 h and 6 h after UL, consistent with the PV overexpression, suggesting the importance of contralateral PV neurons during the first several hours. Though the PV expression of contralateral MVN resumed to normal 1 day after UL, we cannot exclude the possibility that the contralateral MVN PV neurons are still involved in the postlesion plasticity.

For the *in vivo* calcium imaging experiment, we did not observe the size difference between the active and dormant PV neurons, due to technological limitations that we cannot label the dormant PV neurons *in vivo*. According to the literature, it has been reported that the long-range projecting PV neurons exhibit morphology and intrinsic electrophysiological properties similar to local PV neurons (Lee et al., 2014; Bertero et al., 2020); however, in the auditory cortex, long-range projecting PV neurons exhibit a higher expression of a subtype of voltage-sensitive potassium channel (i.e., Kv1.1) than local PV neurons and thus were less excitable (Zurita et al., 2018). We speculate that the dormant PV neurons in the calcium imaging experiment might be more long-range projecting PV neurons, and on the contrary, the active PV neurons might be more local. However, in the last experiment (Figure 6), we specifically activate the long-projecting PV+ neurons from ipsilateral to contralateral MVN, which promotes the vestibular compensation, suggesting the possibility that at least some of the activated PV neurons in the calcium imaging experiment should be long-range projecting PV neurons.

To further investigate PV neurons' hyperactivation in contralateral MVN, ErbB4 was specifically knocked out from PV neurons. ErbB4 is the receptor of neurotrophic factor neuregulin 1, which is required to maintain PV GABA release (Sweeney et al., 2000; Buonanno, 2010;

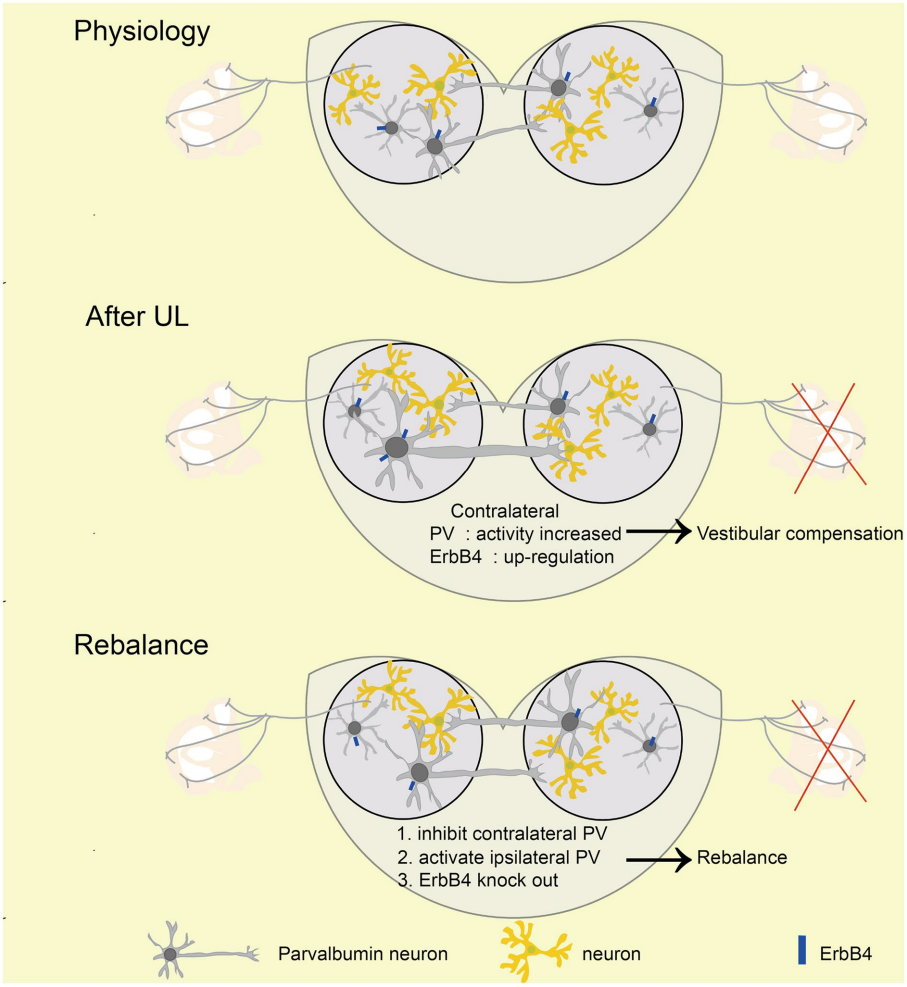


FIGURE 7
Mechanism of rebalancing MVN PV neurons' activity promotes vestibular compensation via commissural inhibition Schematic diagrams showing the role of PV neurons in vestibular compensation. In the physiology state, the activity of bilateral MVN neurons is balanced. After UL, loss of afferent from peripheral leads to neuronal silencing in the ipsilateral MVN, which is major caused by sustained and enhanced input from contralateral MVN inhibitory neurons. Activation of ipsilateral or inhibition of contralateral PV neurons, as well as knockout of ErbB4 of PV, could promote the rebalance of the activity of bilateral MVN neurons.

Lu et al., 2014). Interestingly, vestibular compensation is promoted, compared to PV-Cre mice as control. More importantly, we observed the expression of ErbB4 was increased 3 h after UL, and maintained overexpression for more than 24 h. Considering that ErbB4 is expressed in GABAergic neurons, and mainly in the PV-positive subtype (Fazzari et al., 2010; Bernard et al., 2022), ErbB4 in MVN PV neurons might play a certain detrimental role in vestibular compensation more than 1 day.

To further confirm the causal relationship of contralateral MVN PV neurons in compromising vestibular compensation, these neurons were chemogenetically inhibited after UL once a day for 5 days by CNO administration. The first CNO administration was given immediately after UL, however, the behavior phenotypes induced by UL were not alleviated on day one, suggesting contralateral MVN PV neurons might be involved in vestibular compensation 1 day after UL, which was consistent with ErbB4 overexpression in MVN. Because PV neurons are critical for neural population activity (Hu et al., 2014; Contractor et al., 2021), and the behavior phenotypes induced by UL are related to the unbalance of bilateral MVN activities (Olabi et al., 2009), we expected improving vestibular compensation by activating the ipsilateral MVN PV neurons. Once a day chemogenetic activation of ipsilateral MVN PV neurons after UL for 5 days can also improve vestibular compensation, suggesting the balance of MVN PV neurons activity is crucial for maintaining the vestibular normal function.

PV neurons in the cortex and hippocampus are mainly locally projected GABAergic neurons (Szabo et al., 2022; Zhang et al., 2022). However, long-range GABAergic projections exist from PV neurons in the cortex to subcortical regions of the brain. In the hippocampus, CA3 and CA1 receive PV neuron projections from the entorhinal cortex (Melzer et al., 2012; Basu et al., 2016; Melzer et al., 2017) and medial septum (Freund and Antal, 1988); and in the amygdala, many of the intercalated cells are PV, projecting to the perirhinal, entorhinal, and piriform cortex (Bienvenu et al., 2015). PV neurons in sensory-motor cortical regions project to the striatum, including the somatosensory cortex (Jinno and Kosaka, 2004), auditory cortex (Rock et al., 2016; Bertero et al., 2020), and primary motor cortex (M1) (Melzer et al., 2017). PV neurons in the associative cortex, and the medial prefrontal cortex also project to the striatum, especially the

nucleus accumbens (Lee et al., 2014). PV neurons are also involved in cortico-cortical long-range GABAergic projections. Interestingly, according to the present literature, all these PV neurons' cortico-cortical long-range projections target their contralateral counterparts, including PV neurons in the auditory cortex, visual cortex, and motor cortex (Rock et al., 2018; Zurita et al., 2018). Except for PV neurons, only vasoactive intestinal peptide (VIP)-positive GABAergic neurons in the cortex project to the other side of the counterpart (Bertero et al., 2021) whether PV neurons in MVN can project to the opposite side MVN needs investigation. Retro-AAV virus can infect neurons through the terminal and cell body, and only PV-positive neurons can express eGFP due to the Double-Floxed Inverted Open reading frame in the virus (Tervo et al., 2016). Interestingly, besides the virus injection side, a certain number of eGFP-positive neurons can also be observed on the opposite side of MVN, suggesting MVN PV neurons are an important component in the commissural inhibitory system of MVN. Further investigation illustrated that specifically activation of the commissural MVN PV neurons from the ipsilateral to the contralateral side could also promote vestibular compensation, suggesting besides the local projection, MVN PV neurons are also involved in vestibular compensation through commissural inhibition (Olabi et al., 2009).

MVN has been divided into parvocellular and magnocellular subdivisions (Sekirnjak and du Lac, 2006; Bagnall et al., 2007; Kodama et al., 2012). Here in Figure 3, we observed PV neurons were almost exclusively in the parvocellular division, and importantly, in Figure 5, the MVN PV neurons projecting to the contralateral MVN were also mainly in the parvocellular division, which is consistent with previous findings that GABAergic neurons are mainly located in the parvocellular division (Buttner-Ennever, 1992), and these GABAergic neurons mediate commissural projection (Delfini et al., 2000).

## 5. Conclusion

In conclusion, this study revealed that the balance of MVN PV neurons' activity via commissural inhibition is essential for vestibular compensation, offering a unique potential therapeutic target for vestibular disorders as well as a new understanding of vestibular compensation at the neuronal circuitry level.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

## Ethics statement

The animal study was approved by Committee of Huazhong University of Science and Technology. The study was conducted in accordance with the local legislation and institutional requirements.

## Author contributions

YZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. GC: Conceptualization, Formal analysis, Software, Writing – review & editing. YaL: Funding acquisition, Writing – review & editing. XL: Writing – review & editing, Formal analysis, Software. HZ: Formal analysis, Software, Writing – review & editing. YiL: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing. BL: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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## Conflict of interest

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

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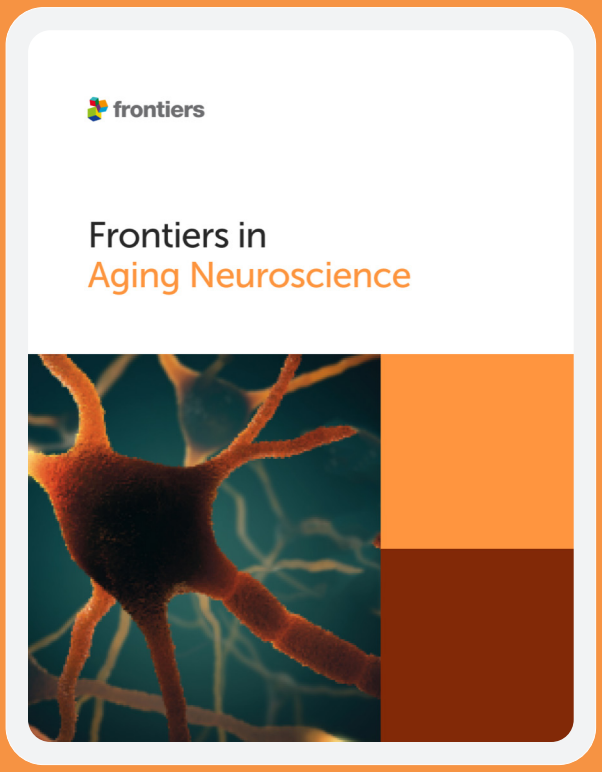


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