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Vestibular rehabilitation, neuromodulation and balance in clinical applications of neurology and otoneurology: what is the recent evidence from basic and clinical research?

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Vestibular rehabilitation, neuromodulation and balance in clinical applications of neurology and otoneurology: what is the recent evidence from basic and clinical research?

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Editorial: Vestibular rehabilitation, neuromodulation and balance in clinical applications of neurology and otoneurology: what is the recent evidence from basic and clinical research?

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KEYWORDS

vestibular rehabilitation, BPPV, nystagmus, compensation, neuro-otology, postural control

Editorial on the Research Topic
Vestibular rehabilitation, neuromodulation and balance in clinical applications of neurology and otoneurology: what is the recent evidence from basic and clinical research?

Vestibular rehabilitation has its origins in the United Kingdom in the 1940s when patients suffering symptoms of dizziness and imbalance related to either Meineire's disease or traumatic brain injury were tasked to perform a series of visual-vestibular exercises. In recent times, evidence on the clinical utility and mechanisms responsible for vestibular rehabilitation has flourished, including a growing number of investigators engaged in such research. Related topics of interest include anatomical and physiological studies as well as the relevance of the physical and functional impairments related to postural and oculomotor control. The current Research Topic, entitled "Vestibular Rehabilitation, Neuromodulation and Balance in Clinical Applications of Neurology and Otoneurology: What is the Recent Evidence from Basic and Clinical Research?" merges a broad collection of articles captured over a two-year period that represent advanced knowledge and future technologies. Challenging presentations of common clinical diagnoses are included.

Lacour et al. challenge the notion that spontaneous nystagmus is an unmodifiable measure of static compensation, suggesting instead that it can be influenced by vestibular rehabilitation. This reinforces our understanding that the mechanisms of vestibular rehabilitation do indeed engender neuroplasticity and modulation of neuronal networks. The exciting work of Kobel et al. improves computerized dynamic posturography and uses non-linear metrics to identify a pattern-specific sway that distinguishes patients with persistent postural and perceptual dizziness from healthy controls. Wagner and Merfeld further advance posturography by considering medial-lateral sway in addition to anterior-posterior sway and suggest that changes in head position and base of support offer a

more challenging task. Harrell et al. reveal that physical therapists do not universally examine for Benign Paroxysmal Positional Vertigo (BPPV) but instead tend to perform clinical testing for BPPV depending on the patient's subjective report. Ludwig and Schubert remind the reader that BPPV can present with atypical nystagmus patterns that warrant critical observation and testing relative to the head position. Meldrum et al. illustrate the novel delivery of vestibular rehabilitation using wearable sensors in persons living with multiple sclerosis to improve their frequency of head motion in addition to reducing the symptoms and impairments related to their dizziness. Xavier et al. used a retrospective design to tackle the complicated, chronic vestibular patient who has not experienced the expected compensation. Their work suggests that vestibular rehabilitation, which includes not only cognitive and emotional tasks but also cervical spine and maxillofacial methods to reduce muscle tension, can further improve rehabilitation outcomes. DiLiberto et al. remind us of the importance of assessing vestibular function in people living with diabetes and provide a rationale for conducting vestibular function tests in this population, in addition to ideas for future research and clinical care. Exciting work from Maruta et al. suggests that attenuating velocity storage by exposing patients with Mal de Debarquement to incremental, low-frequency horizontal rotation coupled with conflicting visual stimuli caused a longer duration of improvement than efforts to correct spatial disorientation without modifying velocity storage. We hope that you will enjoy this special article as much as we have enjoyed curating it.

Author contributions

MCS: Methodology, Supervision, Writing – original draft, Writing – review & editing, Visualization, Resources, Conceptualization. CB: Visualization, Writing – review & editing, Methodology, Writing – original draft, Supervision, Conceptualization, Resources.

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A modified two-dimensional sensory organization test that assesses both anteroposterior and mediolateral postural control

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Background: The Sensory Organization Test (SOT) was designed to measure changes in postural control in response to unreliable visual and/or proprioceptive feedback. However, secondary to the manipulation of sensory cues in only the sagittal plane, the SOT is capable of only describing postural control in a single direction. The present study aimed to characterize postural responses to a modified SOT designed to concurrently challenge both anteroposterior and mediolateral postural control.

Methods: Twenty-one healthy adult volunteers (30.6 $\pm$ 10.2 years) completed the standard anteroposterior one-dimensional (1D) SOT, in addition to a modified SOT with the support surface sway-referenced to both anteroposterior and mediolateral postural sway (two-dimensional, 2D). Our primary analysis concerned a comparison of mediolateral, as well as anteroposterior postural sway measured during the standard one-dimensional (i.e., pitch tilt) and the novel two-dimensional (i.e., roll and pitch tilt) sway-referenced paradigms. Here, postural sway was quantified by calculating the root mean square distance (RMSD) of the center of pressure (CoP) during each trial.

Results: Our data showed that the 2D sway-referenced conditions yielded a selective increase in mediolateral postural sway relative to the standard 1D conditions for both wide ($\eta^2 = 0.66$) and narrow ($\eta^2 = 0.78$) stance conditions, with anteroposterior postural sway being largely unaffected ($\eta^2 = 0.001$ to 0.103, respectively). The ratio between mediolateral postural sway in the sway-referenced conditions and postural sway in the corresponding stable support surface conditions was greater for the 2D (2.99 to 6.26 times greater) compared to 1D paradigms (1.25 to 1.84 times greater), consistent with a superior degradation of viable proprioceptive feedback in the 2D paradigm.

Conclusion: A modified 2D version of the SOT was shown to provide a greater challenge to mediolateral postural control relative to the standard 1D SOT protocol, putatively as a result of a superior capacity to degrade proprioceptive feedback in the mediolateral direction. Given these positive findings, future studies should investigate the clinical utility of this modified SOT as a means by which to better characterize sensory contributions to postural control in the presence of various sensorimotor pathologies, including vestibular hypofunction.

KEYWORDS

balance, postural control, sway, vestibular, sensory organization test, posturography, proprioception

Introduction

The Sensory Organization Test (SOT) was developed in the 1970's as a way to study how the interactions between vestibular, somatosensory, and visual sensory feedback influence postural control (1–3). The ability of the SOT to identify sensory contributions to balance results from the inclusion of balance tasks designed specifically to manipulate the reliability of visual feedback and/or proprioceptive feedback from the distal lower extremities. This is accomplished through the use of a technique referred to as "sway-referencing" (**Figure 1**). By moving either the support surface, or visual surround, in phase with an estimate of postural sway, sway-referencing renders the resultant feedback as unreliable. At the distal lower extremities, sway-referencing aims to maintain a near constant angle at the ankle joint and in the visual system it aims to keep a constant distance between the eyes and the visual surround. In both cases, such paradigms place the resultant visual and/or proprioceptive cues in direct conflict with any remaining unperturbed sensory information. As such, the SOT can help to determine (1) an individual's reliance upon a given sensory system (e.g., "visual dependence") and/or (2) the capacity to remain balanced when forced to primarily use an unperturbed source of sensory feedback (e.g., the vestibular system). Given the ability to parse the reliance upon different sensory modalities, the SOT has become a standard methodology for probing the impact of sensory dysfunction on postural control (4–6).

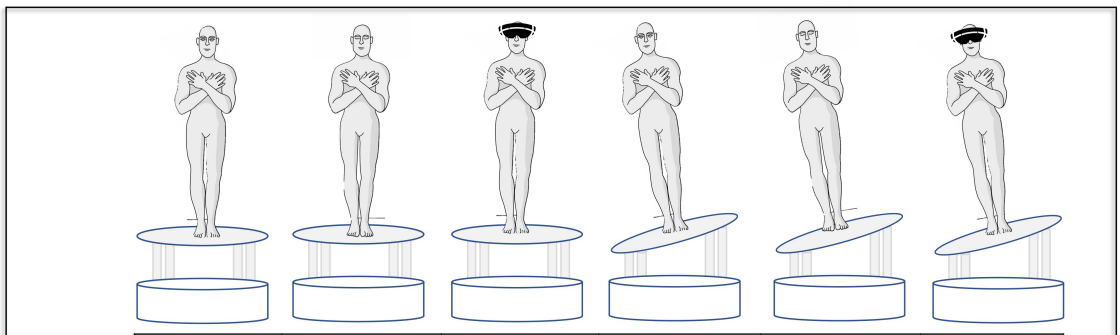
However, a principal limitation of the standard SOT is its manipulation of sensory feedback in only the anteroposterior direction, which leaves a blind spot in our understanding of mediolateral balance control. The platform and/or visual scene are sway-referenced relative only to an estimate of pitch plane postural sway, and as such, only the sensory cues relevant to the control of balance in the pitch (i.e., anteroposterior) direction are made to be unreliable. This is reflected by the standard summary output of the SOT, the Equilibrium Score, which describes the maximal displacement of the center of gravity in only the anteroposterior direction (7). This limitation bears relevance to the testing of clinical populations secondary to, (1) data showing that mediolateral or "roll plane" postural control is an important predictor of fall risk (8), and of fall related injury (9–11) and (2) the fundamental knowledge that the postural control system is inherently multidimensional, as humans must simultaneously control the orientation of their body in both the roll and pitch directions during daily life.

Therefore, the purpose of the present study was to test a modified two-dimensional (2D) SOT paradigm designed to manipulate the fidelity of proprioceptive cues in both the roll and pitch directions. In addition, we aimed to determine if the width of the base of support influenced postural sway during both the standard 1D, as well as novel 2D sway-referenced conditions. We hypothesized that the 2D sway-referenced conditions would yield an increase in ML postural sway compared to the 1D conditions, and that AP postural sway would remain unchanged.

Methods

Study design

Participants were recruited from The Ohio State University and The Ohio State University Wexner Medical Center. Exclusionary criteria included a history of vestibular disorders, alternative neurological disease or injury, uncorrected visual impairment, or recent (within 6 months) orthopedic injuries/surgeries.



	SOT-1	SOT-2	SOT-3	SOT-4	SOT-5	SOT-6
Vision	Intact	Absent	Unreliable (SR)	Intact	Absent	Unreliable (SR)
Proprioception	Intact	Intact	Intact	Unreliable (SR)	Unreliable (SR)	Unreliable (SR)
Vestibular	Intact	Intact	Intact	Intact	Intact	Intact

FIGURE 1
Each of the six conditions of the sensory organization test are shown. All conditions were completed with both a wide and narrow base of support. Per standard protocol the first three conditions (SOT-1, -2, -3) did not include sway-referencing. The final three conditions (SOT-4, -5, -6) were completed using both a one-dimensional (pitch) and a two-dimensional (pitch & roll) sway-reference paradigm. The black masks in SOT-3 and 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).

TABLE 1 Order of sensory organization test conditions.

	N = 5		N = 5		N = 6[a]		N = 5	
	Sway-ref	Width	Sway-ref	Width	Sway-ref	Width	Sway-ref	Width
Block 1	1D	Wide	2D	Wide	1D	Narrow	2D	Narrow
Block 2	2D	Wide	1D	Wide	2D	Narrow	1D	Narrow
Block 3	1D	Narrow	2D	Narrow	1D	Wide	2D	Wide
Block 4	2D	Narrow	1D	Narrow	2D	Wide	1D	Wide

Wide = stance with the heads of the fifth metatarsals 33 cm apart. Narrow = stance with the heads of the first metatarsals 1.5 cm apart, 1D = sway-referencing only in the pitch plane, 2D = sway-referencing both in the pitch and roll planes.
[a]Six subjects completed the third test order as we over-recruited to 21 to account for dropouts or data collection errors.

All individuals provided informed consent and the study was approved by the Ohio State University Institutional Review Board. Testing occurred in a single session that lasted no longer than 60 min (including rest). The order of testing was randomized and counterbalanced allowing an equal proportion of individuals to start with each combination of sway-referencing (1D vs. 2D) and stance width (wide vs. narrow) (Table 1).

Equipment and procedures

Each SOT task was performed using a Virtualis (Perrault, France) MotionVR platform that can provide simultaneous sway-referencing in both the mediolateral and anteroposterior directions. The Virtualis system consists of a motion platform, controlled via four linear actuators that yield a rotation axis 29 cm below the platform surface, synchronized with an HTC Vive Virtual Reality headset through Steam VR (v2.0) (Figure 2A). During each balance trial, two tri-axial force plates rigidly contained within the moving platform sampled center of pressure data at rate of 90 Hz. During "sway-referenced" trials, the platform was tilted in concert with an estimate of the displacement of the center of gravity, consistent with traditional SOT testing. The HTC Vive VR headset was used to provide both a stationary, as well as a sway-referenced visual scene [per eye resolution of 1,080 × 1,200 pixels and a 108-degree field of view (12)] (Figure 2C). Motion of the visual scene and platform was produced with a resolution of 0.011 s (90 Hz).

Instructions were provided before each task to inform the participant of the visual environment ("eyes open" or "eyes closed") and platform condition ("the platform will be stationary" or "the platform may move"). The participant was also instructed to minimize volitional movement and to simply remain upright and as still as possible. To avoid unintended tactile cues, a harness was not worn, but instead a ring around the platform was used to provide assistance in the event of a fall; a trained operator was also present and available immediately to assist if a loss of balance occurred. Each of the SOT tasks lasted 20 s and were repeated three times. Between tasks (i.e., after 1 min of testing), the participant was asked to step-down from the platform to rest and to allow for zeroing of the force plates.

Test conditions

Each participant completed a total of 18 unique SOT tasks, with each task consisting of three trials of 20 s each. The first three SOT conditions (each with a fixed support surface) were performed with a narrow (first metatarsals 1.5 cm apart), as well as wide stance (fifth metatarsals 33 cm apart), to allow

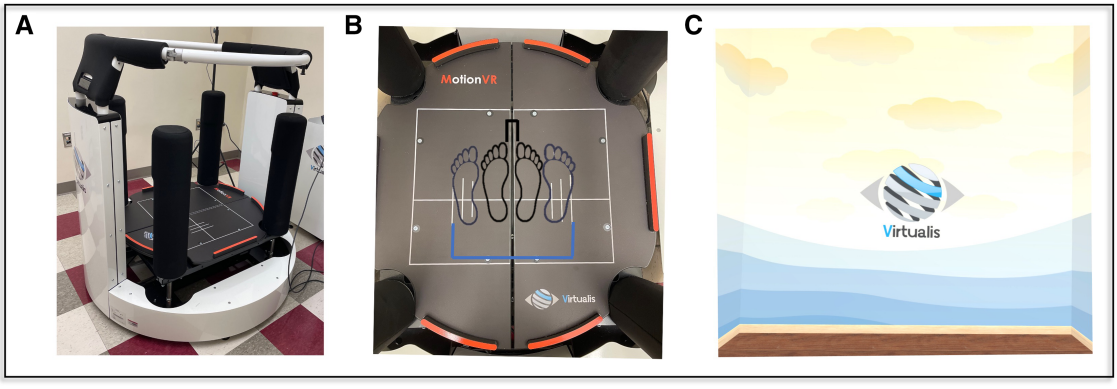


FIGURE 2
The virtualis motionVR (A) platform was used to perform the SOT test protocol. Embedded force plates (B) recorded the CoP while the participant stood with a narrow (black) and wide (blue) base of support. A virtual room (C) was used as visual feedback; in visual sway-referenced conditions the image moved in concert with the head (SOT3, SOT6), in normal vision conditions (SOT1, SOT4) the virtual room appeared to remain stationary relative to the participant's sway. For conditions without visual cues (SOT2, SOT5) the headset went black, removing all visual cues, and subjects were asked to close their eyes.

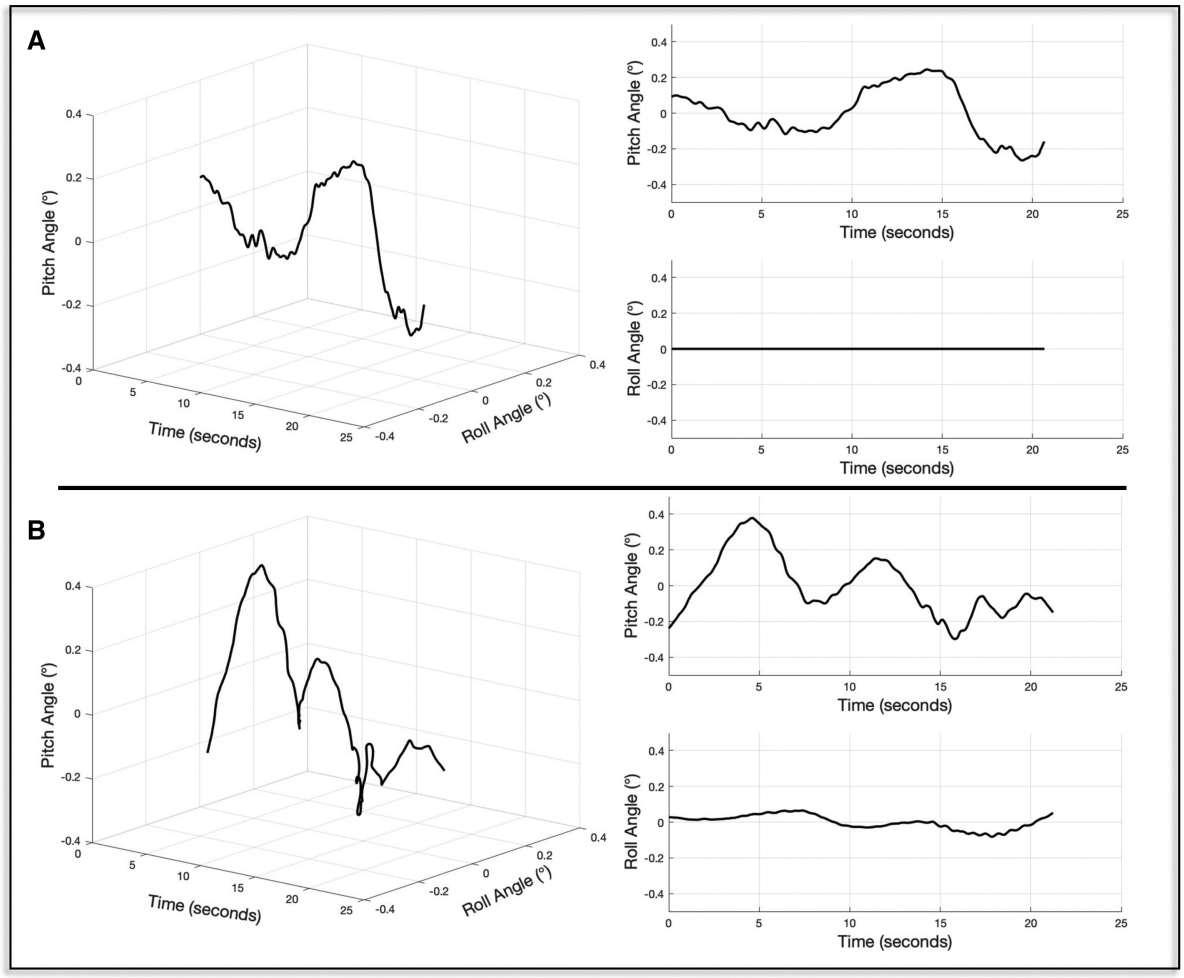


FIGURE 3
The time series of platform tilts for exemplar one- (A) and two-dimensional (B) sway-reference trials are shown. To the right, the pitch and roll components of each motion stimulus are shown.

comparisons to the sway-referenced trials (Figure 1). The latter three conditions of the SOT that include a sway-referenced support surface — SOT-4, SOT-5, and SOT-6 — were completed (a) with the platform sway-referenced in only the pitch plane [i.e., standard one-dimensional (1D) sway-referencing], or (b) with the platform sway-referenced to both pitch and roll postural sway [i.e., two-dimensional (2D) sway-referencing] (Figure 1). Each of the 1D and 2D sway-referenced conditions were also completed using both a wide and narrow base of support (Figure 2B). The base of support for the wide stance trials was consistent with the recommended stance width for individuals between 65 and 78 inches in the standard SOT assessment (13). A fixed width, rather than a width dictated by height, was used to standardize the comparison to the narrow stance trials. Prior to each condition, we confirmed the alignment of the feet using markers located on the platform and also confirmed that the malleoli were aligned with the axis of rotation in the anteroposterior direction.

Sway-referencing has been described previously at length (14), so here we provide only a terse overview to highlight the differences between the 1D and 2D conditions. In the traditional "one-dimensional" (1D) SOT, during each of the sway-referenced conditions the platform is tilted in synchrony with an estimate of the body's center of gravity in the pitch plane — i.e., forward body sway causes the front of the platform to pitch downward and backward sway causes the front of the platform to pitch upward (Figure 3A). This motion serves the primary purpose of minimizing the typical change in sagittal plane ankle motion experienced during sway with a fixed base of support. In the present study we compared this protocol to a "two-dimensional (2D)" sway-referenced condition whereby the platform instead tilted in response to estimates of sway angle in both the pitch and roll planes (Figure 3B) — e.g., diagonal sway forward and to the right yielded a simultaneous forward pitch of the platform alongside a rightward tilt in the roll plane.

Analysis of CoP data

CoP data were recorded during each trial and analyzed off-line to calculate the outcome of interest. The CoP data were first low-pass filtered using a 4th order zero-phase-lag butterworth filter

with a cutoff of 25 Hz (*filtfilt.m*; MATLAB, Natick, MA). The root mean square distance (RMSD) was then calculated by taking the standard deviation of the zero-meaned and filtered CoP signal (15–17). RMSD values were calculated separately for the ML and AP CoP. Secondary to potential learning effects or transient responses, the median values are reported from each block of three SOT trials. The standard outcome for the sensory organization test, the Equilibrium Score (7), was not calculated as such values only consider AP postural sway. In addition, the Equilibrium Score is based upon an assumed limit of stability (12.5°), which applies only to wide stance, 1D (i.e., pitch plane) sway-referenced conditions.

In addition to the raw sway responses, we also calculated normalized sway ratios by taking the median RMSD values in SOT-4, SOT-5, and SOT-6 and dividing them by the RMSD values captured in the corresponding SOT conditions that were identical, with the exception of providing a stable base of support (i.e., SOT-1, SOT-2, and SOT-3 respectively) [**Figure 1**, Equations (1)–(3)]. As the sway-referencing paradigm is intended to degrade the fidelity of proprioceptive inputs from the distal lower extremities, the normalized sway ratios were calculated as means to quantify the success of each paradigm (i.e., greater sway ratio = greater decrement in balance performance with the manipulation of proprioceptive cues via sway-referencing).

$$Norm_{SOT4} = \frac{RMSD_{SOT4}}{RMSD_{SOT1}} \quad \text{(Eq. 1)}$$

$$Norm_{SOT5} = \frac{RMSD_{SOT5}}{RMSD_{SOT2}} \quad \text{(Eq. 2)}$$

$$Norm_{SOT6} = \frac{RMSD_{SOT6}}{RMSD_{SOT3}} \quad \text{(Eq. 3)}$$

Data analysis

A 2 × 3 repeated measures analysis of variance (RM-ANOVA) model was used to determine the differences in postural sway between the 1D and 2D sway-referenced conditions for each of the three sway-referenced conditions of the SOT (SOT-4, -5, and -6). Four separate models were run to separately analyze AP, as well as ML postural sway, in both the narrow and wide stance conditions. In each model, a sway-reference (1D vs. 2D) times SOT condition (SOT-4, SOT-5, SOT-6) interaction term was also tested. After each of the four models, we performed pairwise comparisons to determine the differences in postural sway between the 1D and 2D sway-referenced conditions (3 comparisons each × 4 models = 12 comparisons total); the reported p-values were corrected using the Bonferroni method (p-value × 12). Although the CoP data were found to deviate from normality (as tested by visualization of normal probability plots and by the results of Shapiro-Wilk test), ANOVA models have been shown to be robust to such violations (18). Normalized sway ratios for the 1D and 2D trials were compared using pairwise Wilcoxon Rank-Sum tests of medians due to the rightward skew of the distributions. The six comparisons for wide stance and six comparisons for narrow stance were corrected using the Bonferroni method (p-value × 12). We also calculated intraclass correlation coefficients (ICC) and the corresponding 95% confidence intervals for each of the different sway-referenced SOT conditions. The ICC model (a) included both random and fixed effects, (b) was based upon a single measure at each of three time points (Trial 1, 2, and 3) and (c) yielded a measure of absolute agreement (including both random and systemic variance) (Stata v.17, College Station, TX). Here we defined repeatability as low (ICC < 0.5), moderate (ICC = 0.5 to 0.75), good (ICC = 0.75 to 0.9), or excellent (ICC > 0.9) (19).

Results

Differences in postural sway between the 1D and 2D sway-referenced conditions

Mediolateral sway

In the analysis of SOT trials that used a wide base of support, we identified a significant main effect of sway-reference condition (1D vs. 2D) ($\eta^2 = 0.66$, F(1,100) = 189.90, $p < 0.0001$) on the RMSD of the ML CoP. The effect of 2D vs. 1D sway-referencing was not significantly modified by SOT condition (sway-reference times SOT condition interaction; $\eta^2 = 0.017$, F(2,100) = 0.86, $p = 0.43$). Post-hoc pairwise comparisons showed that the ML RMSD was significantly increased for the 2D compared to 1D-sway-reference trials in SOT-4 [Diff = 6.6, $p < 0.0001$, 95% CI (3.98, 9.23)], SOT-5 [Diff = 6.70, $p < 0.0001$, 95% CI (4.07, 9.32)], and SOT-6 [Diff = 8.08, $p < 0.0001$, 95% CI (5.46, 10.71)] (**Figure 4A**, **Table 2**).

For narrow stance trials, the effect of 1D vs. 2D sway-referencing was also significant, and the size of the effect was larger than for the wide stance trials ($\eta^2 = 0.78$, F(1,100) = 360.24, $p < 0.0001$). We also identified a borderline significant interaction between SOT condition and sway-reference paradigm (1D vs. 2D) ($\eta^2 = 0.058$, F(2,100) = 3.06, $p = 0.051$). Post-hoc pairwise comparisons showed that the ML RMSD was significantly increased for 2D vs. 1D sway-referencing for SOT-4 [Diff = 10.86, $p < 0.0001$, 95% CI (7.42, 14.3)], SOT-5 [Diff = 12.78, $p < 0.0001$, 95% CI (9.34, 16.22)] and SOT-6 [Diff = 14.97, $p < 0.0001$, 95% CI (11.53, 18.41)] (**Figure 4B**, **Table 2**).

Anteroposterior sway

Sway-reference condition (1D vs. 2D) did not show a significant main effect on the RMSD of the AP CoP in the wide stance trials ($\eta^2 = 0.00099$, F(1,100) = 0.1, $p = 0.75$). The effect of 2D vs. 1D sway-referencing on AP postural sway was also not significantly modified by SOT condition ($\eta^2 = 0.029$, F(2, 100) = 1.50, $p = 0.23$). Pairwise comparisons showed that the RMSD of the AP CoP was not significantly different between the 1D compared to 2D sway-referenced conditions for SOT-4 [Diff = −1.16, $p > 0.99$, 95% CI (−3.28, 0.97)], SOT-5 [Diff = 0.47, $p > 0.99$,

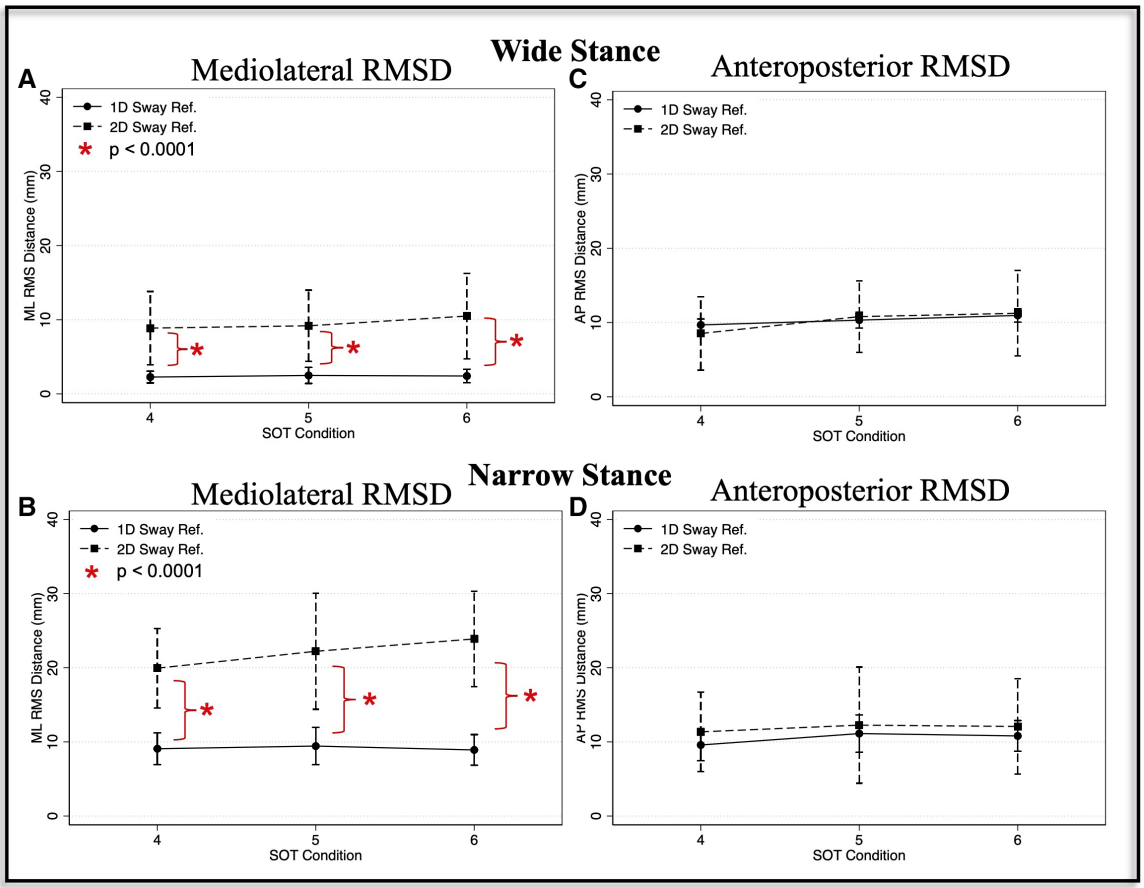


FIGURE 4
Mediolateral (A, B) and anteroposterior (C, D) root mean square distance (RMSD) values are shown for the one-dimensional (1D, circle with solid line) and two-dimensional (2D, square with broken line) sway-referenced trials, and for both wide (A, C) and narrow (B, D) stance conditions. Red asterisks indicate significant differences ($p < 0.0001$) between the 1D and 2D conditions based on pairwise comparisons.

95% CI (−1.66, 2.6)], or SOT-6 [Diff = 0.29, $p > 0.99$, 95% CI (−1.84, 2.42)] (Figure 4C, Table 2).

We did however identify a significant, albeit small ($\eta^2 = 0.103$), main effect of 2D vs. 1D sway-referencing on the RMSD of the AP CoP in the narrow stance trials [F(1,100) = 11.50, $p = 0.001$]. However, the effect of 1D vs. 2D sway-referencing was not significantly influenced by SOT condition ($\eta^2 = 0.0044$, F(2, 100) = 0.22, $p = 0.804$) and pairwise comparisons showed that the AP RMSD was not significantly different between the 1D and 2D trials for any of the individual SOT conditions [SOT-4: Diff = 1.77, $p = 0.18$, 95% CI (−0.316, 3.86); SOT-5: Diff = 1.13, $p > 0.99$, 95% CI (−0.95, 3.22); SOT-6: Diff = 1.28, $p = 0.91$, 95% CI (−0.81, 3.36)] (Figure 4D, Table 2).

Normalized sway ratios

The ratios describing the RMSD in the sway-referenced conditions relative to the RMSD in the corresponding stable support conditions — (a) SOT-4/SOT-1, (b) SOT-5/SOT-2, and (c) SOT-6/SOT-3—were also compared between trials that used a 2D compared to a 1D sway-referencing protocol. For ML postural sway, the normalized sway ratios were significantly increased for the 2D relative to the 1D sway-referenced conditions, suggesting a greater degradation of ML proprioceptive cues in the 2D condition (Figures 5A,B). In the wide stance trials, ML RMSD values in the 1D sway-referenced conditions were increased 1.59 to 1.84 times relative to sway in the stable support surface conditions (i.e., sway ratios between 1.59 and 1.84 for SOT-4, -5, and -6). By contrast, ML RMSD values in the 2D sway-referenced conditions were between 5.22 to 6.26 times higher than in the stable support surface conditions (Table 3). Similarly, in narrow stance mediolateral sway ratios for the 1D sway-referenced trials were between 1.25 to 1.36 compared to 2.99 to 3.29 for the 2D trials (Table 3). For each of these comparisons, the difference in sway ratios between 1D and 2D conditions was significant at $p < 0.001$.

Regarding AP postural sway, the normalized sway ratios did not significantly differ between any of the 1D and 2D sway-referenced trials, consistent with the 1D and 2D sway-referencing paradigms yielding similar increases in the AP RMSD relative to the stable support surface conditions (Figure 5C, Table 3). This finding was true both for wide (1D Ratios = 2.75 to 3.03, 2D ratios = 2.85 to 3.49), as well as narrow stance (1D Ratios = 2.6 to 2.77, 2D Ratios = 2.98 to 3.02) conditions (Figure 5D, Table 3).

TABLE 2 Comparison of postural sway between the one-dimensional (1D) and two-dimensional (2D) sway-referenced conditions.

1D and 2D RMSD values						
		1D sway-ref.	2D sway-ref.	*t*	*p*-value	95% CI
Wide						
AP	SOT-4	9.68 ± 4.29	8.52 ± 3.06	−1.59	>0.99	−3.28, 0.97
	SOT-5	10.33 ± 3.46	10.80 ± 4.30	0.65	>0.99	−1.66, 2.6
	SOT-6	10.96 ± 4.04	11.25 ± 4.21	0.40	>0.99	−1.84, 2.42
ML	SOT-4	2.27 ± 0.8	8.87 ± 4.94	7.37	<0.0001	3.98, 9.23
	SOT-5	2.49 ± 1.08	9.18 ± 4.81	7.48	<0.0001	4.07, 9.32
	SOT-6	2.41 ± 0.91	10.50 ± 5.76	9.02	<0.0001	5.46, 10.71
Narrow						
AP	SOT-4	9.59 ± 3.69	11.35 ± 3.99	2.49	0.18	−0.32, 3.86
	SOT-5	11.13 ± 3.75	12.26 ± 4.61	1.59	>0.99	−0.95, 3.22
	SOT-6	10.81 ± 4.08	12.08 ± 3.07	1.80	0.91	−0.8, 3.36
ML	SOT-4	9.08 ± 2.13	19.94 ± 5.35	9.25	<0.0001	7.42, 14.3
	SOT-5	9.44 ± 2.52	22.22 ± 7.83	10.88	<0.0001	9.34, 16.22
	SOT-6	8.92 ± 2.07	23.88 ± 6.44	12.74	<0.0001	11.53, 18.41

Comparisons made were the result of pairwise comparisons performed following the repeated measures ANOVA. Reported *p*-values and confidence intervals are corrected using the Bonferroni method (12 comparisons).
AP, anteroposterior; ML, mediolateral; SOT, sensory organization test.

Repeatability of the 2D SOT conditions

Table 4 shows the ICC values for SOT-4, SOT-5, and SOT-6 during both the 1D and 2D sway-referenced conditions. Overall, the 2D sway-referencing paradigm yielded moderate to good agreement between trials for the ML RMSD values captured during both the narrow and wide stance trials (Table 4, Range: $0.566 < ICC < 0.763$). With a single exception (SOT-5 in wide stance) where the 1D condition yielded an 11% higher ICC value, the ICC values were higher for the 2D compared to 1D trials. For sway measured in the AP direction, we observed a similar but slightly lower degree of reliability (Table 4, Range: $0.411 < ICC < 0.669$), with all but 2 of the conditions (SOT-4, wide and SOT-5, narrow) showing greater agreement for the 2D compared to 1D trials.

Discussion

Our primary hypothesis was that the 2D sway-referencing paradigm, owing to the manipulation of roll plane proprioceptive feedback, would yield an increase in mediolateral postural sway when compared to the standard 1D SOT protocol. Consistent with this hypothesis, our data showed that the RMSD of the ML CoP was significantly increased for the 2D sway-referenced trials in both narrow and wide stance conditions. We also showed that the 2D and 1D trials yielded similar amounts of postural sway in the AP direction, indicative of a similar level of challenge to AP postural control. In our secondary analysis, we showed that when the RMSD values for the sway-referenced conditions were compared to postural sway in the corresponding fixed support surface conditions (i.e., without sway-referencing), the 2D protocol yielded significantly greater increases in ML sway compared to the 1D protocol, consistent with a greater degradation in proprioceptive feedback in the 2D paradigm. Below we discuss the implications of these findings in the context of the available literature, as well as putative applications for using the modified 2D SOT to better characterize human postural control in both health and disease.

Influences of a 1D vs. a 2D sway-referenced surface on postural control

To our knowledge, this is the first study to characterize postural responses to a two-dimensional (i.e., in both roll and pitch planes) sway-referenced support surface. Allum and colleagues did however separately measure postural sway in response to a 1D roll, as well as a 1D pitch sway-referenced support surface. When compared to a standard "foam standing" condition, they found ML postural responses to be reduced for the 1D pitch sway-referenced condition (20). Foam standing, although methodologically distinct from a sway-referenced support surface, is conceptually similar to our 2D sway-referencing paradigm, as each degrades the efficacy of ankle proprioceptive feedback in both the AP and ML planes. Consistent with their finding, here we showed less ML postural sway in the 1D (pitch only) compared to the 2D (pitch and roll) sway-referenced conditions.

We posit that the ability for individuals to minimize mediolateral sway in a 1D sway-referenced condition likely results from the persistent availability of reliable proprioceptive cues derived from the stationary (in the roll plane) support surface. During the 1D sway-referenced condition, the platform fails to tilt in the roll plane, and thus, any off-axis mediolateral sway yields stimulation of distal receptors in the lower limbs, providing accurate information about the orientation of the body relative to support surface. Our data show that when this feedback is made to be unreliable through use of a 2D sway-referenced condition — whereby mediolateral sway is met with a corresponding roll tilt of the surface — that the control of postural sway in the roll plane is impaired, yielding an increase in the mediolateral RMSD of the CoP. This capacity for the 2D condition to further degrade proprioceptive inputs represents the primary advantage of this protocol over the 1D SOT. However, the ability of the different sway-referencing paradigms to manipulate proprioceptive cues can better be appreciated by looking at the ratio between (a) the amount of postural sway in conditions with altered proprioceptive cues (sway-referenced support) relative to (b) the amount of postural sway in conditions with intact proprioceptive cues (fixed support surface).

The SOT is designed such that the final three conditions (SOT-4, SOT-5, and SOT-6) mirror the first three conditions, with the exception that SOT-4 through -6 include a sway-referenced support surface (i.e., identical vestibular and visual cues). Thus, by calculating ratios between postural sway in SOT-4 and SOT-1, SOT-5 and SOT-2, and SOT-6 and SOT-3 we can determine to what extent the removal of viable proprioceptive inputs—by way of each of the different sway-referencing paradigms—influences postural control. As both the visual and vestibular feedback are fixed for each comparison (i.e., eyes closed, open, or with vision

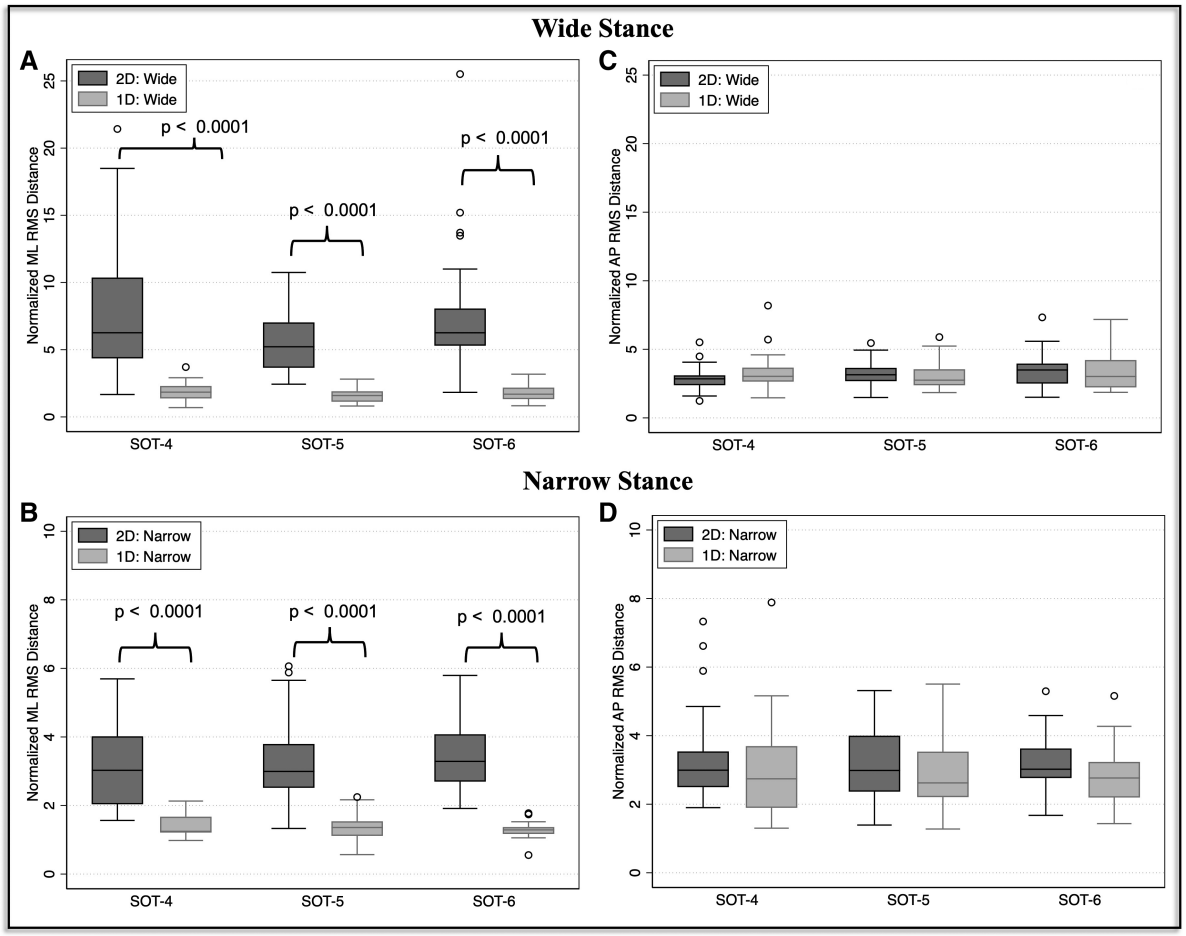


FIGURE 5
The median and interquartile range (IQR) is shown for each of the mediolateral (A, B) and anteroposterior (C, D) normalized sway ratios. Ratios were calculated by dividing the RMSD in the sway-referenced conditions by the RMSD in the corresponding condition that included a stable support surface: SOT-4/SOT-1, SOT-5/SOT-2, and SOT-6/SOT-3. In each plot, the ratios calculated from the 2D trials (dark grey) are shown against the ratios calculated from the 1D trials (light grey). *P*-values reflects the results of a Wilcoxon Rank Sum test of medians between the 1D and 2D sway-reference conditions. *P*-values are Bonferroni corrected (corrected according to 6 comparisons for wide stance and 6 comparisons for narrow stance).

sway-referenced), increases in sway relative to quiet stance can therefore be attributed to a greater deterioration of proprioceptive feedback. When analyzing mediolateral postural sway, each of the six unique ratios (i.e., SOT-4/1, SOT-5/2, SOT-6/3 for both wide and narrow stance) were significantly greater for the 2D relative 1D sway-referencing paradigm, consistent with the hypothesis that the 2D paradigm more successfully limits the use of proprioceptive cues from the support surface.

In the analysis of AP postural sway, ratios calculated from the 1D and 2D sway-referenced trials were instead similar, suggesting a similar manipulation of pitch plane support surface cues. The similarities in AP postural sway between the 1D and 2D sway-referenced conditions lends further support to our hypothesis that the 2D sway-referenced condition diminishes proprioceptive feedback in two-dimensions, rather than causing a compensatory strategy that favors body sway in the ML, as opposed to the AP, direction. The ability to more completely alter proprioceptive inputs during stance holds potential promise for the development of improved methods for evaluating patients with presumed sensorimotor impairments, including vestibular dysfunction.

Implications for testing clinical populations

The SOT has become one of the gold standard methods for characterizing the sensory contributions to balance performance. Principle amongst its clinical uses is in the evaluation of the dizzy patient (21). When considered alongside laboratory and oto-neurological findings, greater postural sway in the presence of unreliable visual and proprioceptive feedback (i.e., SOT-5) has been used to help identify a lesion to the vestibular periphery. However, in isolation, the traditional 1D SOT lacks sufficient sensitivity and specificity to serve as a suitable tool for diagnosing a peripheral vestibular lesion as the potential cause of balance dysfunction (22–24). One potential explanation for this limitation is the inability to sufficiently manipulate the veracity of extra-vestibular sensory feedback in the sway-referenced conditions, resulting in the continued reliance upon proprioceptive inputs.

Here, in a cohort of healthy adults without vestibular pathology, we showed that mediolateral postural sway was only slightly increased in the standard 1D sway-referenced conditions

TABLE 3 Median ratios between SOT-4/SOT-1, SOT-5/SOT-2 and SOT-6/SOT-3 are reported along with the IQR.

Normalized sway ratios					
		1D ratio	2D ratio	Difference	*p*-value
Wide					
AP	SOT-4	3.03 (2.64–3.66)	2.85 (2.39–3.10)	−0.43	0.51
	SOT-5	2.75 (2.38–3.54)	3.15 (2.68–3.65)	0.032	>0.99
	SOT-6	3.02 (2.23–4.22)	3.49 (2.50–3.96)	0.008	>0.99
ML	SOT-4	1.84 (1.38–2.30)	6.26 (4.36–10.36)	5.76	<0.001
	SOT-5	1.59 (1.13–1.91)	5.22 (3.66–7.03)	4.18	<0.001
	SOT-6	1.69 (1.32–2.18)	6.26 (5.30–8.06)	6.21	<0.001
Narrow					
AP	SOT-4	2.74 (1.89–3.69)	2.99 (2.5–3.54)	0.46	0.14
	SOT-5	2.60 (2.21–3.53)	2.98 (2.37–4.00)	0.20	>0.99
	SOT-6	2.77 (2.19–2.32)	3.02 (2.76–3.63)	0.41	0.55
ML	SOT-4	1.25 (1.21–1.67)	3.03 (2.04–4.02)	1.78	<0.001
	SOT-5	1.36 (1.11–1.54)	2.99 (2.52–3.79)	1.92	<0.001
	SOT-6	1.29 (1.17–1.37)	3.29 (2.70–4.08)	2.18	<0.001

The difference reflects the average difference between the 1D and 2D ratios. *P*-values reflects the results of a Wilcoxon rank sum test of medians between the 1D and 2D sway-reference conditions. *P*-values are Bonferroni corrected (corrected according to 12 comparisons).

relative to quiet stance (i.e., normalized sway ratios of 1.25 to 1.84). By comparison, in the novel 2D sway-referenced conditions, the increase in ML postural sway was striking when compared to quiet standing (i.e., normalized sway ratios of 2.99 to 6.26). We posit that the greater availability of mediolateral support surface cues in the traditional 1D SOT may potentially mask the impact of a vestibular lesion. A compensatory prioritization of proprioceptive cues in the roll plane would explain the mitigation in AP sway (i.e., as quantified by the equilibrium score) seen in a subset of patients with compensated vestibular lesions. While speculative, it is also reasonable to conjecture that the previously reported learning effect of the standard SOT could also be a manifestation of a learned behavior to rely more upon the reliable mediolateral support surface cues (25). The proposed 2D SOT should be tested in individuals with well-characterized vestibular lesions to determine if the greater ability to degrade proprioceptive cues may aide in the differentiation between vestibular mediated balance deficits and alternative causes of postural instability.

TABLE 4 Intraclass correlation coefficients (ICC) with a 95% confidence intervals are shown for each of the sway-referenced test conditions.

	Wide stance		Narrow stance	
	1D sway-referenced	2D sway-referenced	1D sway-referenced	2D sway-referenced
ML RMSD				
SOT 4	0.496 (0.233, 0.728)	0.763 (0.581, 0.887)	0.544 (0.288,0.759)	0.566 (0.314,0.773)
SOT 5	0.66 (0.436,0.830)	0.587 (0.341,0.787)	0.340 (0.072,0.617)	0.697 (0.485,0.851)
SOT 6	0.565 (0.313,0.773)	0.588 (0.341,0.787)	0.558 (0.305 to 0.769)	0.745 (0.553,0.877)
AP RMSD				
SOT 4	0.568 (0.316,0.774)	0.524 (0.265,0.747)	0.464 (0.198,0.707)	0.585 (0.338,0.785)
SOT 5	0.467 (0.201,0.709)	0.669 (0.447,0.835)	0.556 (0.302,0.767)	0.411 (0.142,0.669)
SOT 6	0.374 (0.104,0.642)	0.553 (0.299,0.765)	0.454 (0.187,0.700)	0.515 (0.255,0.741)

The ICC formula used a mixed effect model based upon a single measure and provides a measure of absolute agreement (including both random and systematic variance). Stata v.17 (College Station, TX).

Benefits of measuring sensory contributions to mediolateral postural control

In addition to minimizing the contributions of proprioceptive inputs, the 2D sway-referenced paradigm also provides an opportunity to characterize sensory contributions to ML postural control. Previous data suggests that an increase in ML, as opposed to AP, postural sway represents a strong predictor of future falls. Maki, et al. 1994 showed that the RMSD of the ML CoP measured during an eyes closed, quiet stance balance task was the single best predictor of falls in the 12-month period that followed the assessment (80% sensitivity, 46% specificity) (8). In addition, mediolateral postural control may be particularly relevant to the avoidance of serious fall related injuries, including hip fracture (9–11, 26). Greenspan showed that older adults who experienced a fall related hip fracture were more than five times as likely to have experienced a fall in the lateral direction (Odds Ratio = 5.7, 95% CI = 1.7, 18) (11). Nevitt and colleagues similarly found that falls in the lateral direction were a strong predictor of fall related hip fracture (Odds Ratio = 3.3, 95% CI = 2.0, 5.6) (27). The association between lateral instability and hip fracture appears to result from the mechanical stress caused by direct contact between the lateral hip and the ground, as Hayes and colleagues showed that falling directly on the lateral hip was associated with more than a 21-times increase in the odds of experiencing a fall-related hip fracture (Odds Ratio = 21.7, 95% CI = 8.2, 58) (26). Since 98% of hip fractures among the elderly are fall related (28), and lateral instability is predictive of hip fracture, we posit that an improved understanding of mediolateral postural control is critical to the eventual development of improved methods for preventing fall related morbidity and mortality. Whereas the traditional SOT minimizes challenge to mediolateral postural secondary to (a) the wide base of support and (b) the manipulation of only sagittal plane sensory feedback, the novel 2D SOT paradigm — in particular when paired with a narrow base of support — is well suited to aide in such efforts by helping to characterize the relative effects of sensory dysfunction on mediolateral postural control.

It is also worth mentioning that in addition to the specific assessment of ML postural control, the 2D sway-referenced protocol also measures postural responses generated simultaneously in both the AP and ML planes. As humans negotiate their environments, rarely, if ever, is balance perturbed in only a single plane of motion. Even in the atypical event of an isolated stimulus (i.e., a trolley starts suddenly from a stop), such stimuli are rarely aligned perfectly with a single plane of the human body, and therefore require a complex, multi-dimensional

motor response. Fittingly, the neuromuscular response to a balance perturbation has been shown to consistent of synergistic responses generated through a combination of muscles acting in both the sagittal and coronal planes (29, 30). As a result, assessments of mediolateral, as well as anteroposterior, postural control in the context of a 2D task may better represent the integrity of the sensorimotor system. Future studies should test this speculation by determining the capacity for a 2D, as compared to standard 1D, sway-reference paradigm to predict fall risk, and/or fall related injury.

Use of a narrow vs. wide base of support

Aside from the sway-referencing of the support surface, an alternative consideration for the challenge of mediolateral postural control is the width of the base of support. The traditional SOT manipulates stance width based upon subject height, using one of three standardized widths. For each height, the width selected yields a comfortable base of support. Here we aimed to determine how stance width influenced the relationship between 1D and 2D sway-referenced conditions. We found a stronger effect of sway-referencing (1D vs. 2D) on ML postural sway for the narrow stance ($\eta^2 = 0.78$) compared to wide ($\eta^2 = 0.66$) stance trials, consistent with a larger overall increase in ML postural sway for the 2D compared to 1D trials when in a narrow stance posture. These findings support that narrow stance may therefore be the preferred method by which to challenge ML postural control in the 2D sway-referenced condition.

Yet, we found that the normalized sway ratios (describing postural sway in SOT-4, -5, and-6 relative to the unperturbed quiet standing conditions) were greater for the wide compared to narrow stance trials. In wide stance, the use of a 2D sway-referenced surface increased postural sway by a factor of 5.22 to 6.26, whereas for narrow stance the ratios were only between 2.99 and 3.29. While both wide and narrow stance conditions showed a dramatic increase in sway relative to quiet standing, the difference between the two is worth noting. This difference is likely a result of the very small amounts of ML postural sway recorded in the wide (1.36 to 1.76 mm) compared to narrow (6.67 to 7.33 mm) quiet standing conditions, as the ML RMSD values for narrow stance in SOT-4 through SOT-6 (19.94 to 23.8 mm) were approximately double those measured in the wide stance trials (8.87 to 10.50 mm).

The choice of a narrow vs. wide base of support when implementing the 2D version of the SOT may therefore depend upon the goal of the study. If the goal is to test how postural control in the sway-referenced support surface conditions (SOT4-6) differ from the stable support surface conditions (SOT1-3), then the use of a wider base of support may be preferred. However, if the intent of the assessment is to probe 2D postural control, then narrow stance posture should be chosen due to the heightened challenge to mediolateral postural control when standing with a narrow base of support. Based upon our data, we posit that the narrow stance posture provides a suitable compromise, whereby (a) postural sway in the AP and ML directions is clearly distinct for the 2D sway-referenced tasks relative to the stable support surface conditions and (b) ML postural sway is sufficiently challenged, without compromise to the concurrent assessment of AP postural sway. Nevertheless, such claims should be tested in individuals with a broader range of functional capacities, as this may reveal unique insights, as well as provide valuable data into the feasibility of completing this narrow 2D protocol in individuals with more severe balance impairment. We do highlight that in a yet to be peer-reviewed thesis study (31), 19 out of 21 subjects over the age of 65 were able to complete all six conditions of the described 2D "narrow stance" SOT protocol.

Limitations

The study was completed in a sample of young, healthy adults, and as such the findings cannot be assumed to represent the behavior of individuals with balance dysfunction. These data instead provide the expected physiologic response to this novel test paradigm, from which future studies should compare the responses of individuals with various types of sensorimotor impairment (e.g., vestibular hypofunction, peripheral neuropathy). We also utilized a VR based SOT, which differs from the traditional SOT paradigm that utilizes a mechanical visual scene. As this test condition was used for both the 1D and 2D SOT tasks, such differences are unlikely to have influenced our results on a within subject basis. Finally, we did not include the standard output of the SOT, the Equilibrium Score, as this metric is not conducive to the novel SOT conditions used here. Specifically, no standard for "maximal" sway angle has been developed for ML postural sway or for narrow stance conditions. We did however opt to utilize a measure of sway displacement (RMSD), as this captures a similar construct as the displacement-based Equilibrium Score.

Conclusions

We showed that a two-dimensional sway-referenced SOT protocol, whereby proprioceptive cues were manipulated in both the pitch and roll planes, yielded an increase in mediolateral postural sway when compared to the standard one-dimensional SOT. In addition, our data support that a two-dimensional sway-referencing paradigm further limits the use of viable proprioceptive cues for postural control, as evidenced by a greater increase in postural sway when compared to performance on the stable support surface conditions. Future studies should investigate the clinical utility of the modified two-dimensional SOT as a means by which to characterize sensory contributions to postural control in older adults, as well as in individuals with balance dysfunction resulting from sensorimotor pathologies, including vestibular hypofunction.

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 Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AW and DM designed the experiment. AW analyzed the data and wrote the initial draft of the manuscript. AW and DM each edited the manuscript and approved its final form. 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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Vestibular rehabilitation improves spontaneous nystagmus normalization in patients with acute unilateral vestibulopathy

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Introduction: Spontaneous nystagmus (SN) can be observed after acute unilateral vestibulopathy (AUVP). The slow phase eye velocity of the SN progressively decreases in darkness as the result of rebalanced neurophysiological activity between both vestibular nuclei, a process that can take several months. Although this compensatory process can occur spontaneously, there is poor evidence that vestibular rehabilitation (VR) can facilitate the process.
Methods: We documented the natural time course of SN reduction in patients with AUVP, as well as the effects of VR by means of a unilateral rotation paradigm. In a retrospective study (Study 1: $n = 126$ AUVP patients), we compared the time course of the SN reduction in patients with VR ($n = 33$) and without VR ($n = 93$). In a prospective study (Study 2: $n = 42$ AUVP patients), we compared the effects of early VR ($n = 22$; initiated within the first two weeks of symptoms onset) or late VR ($n = 20$; initiated after the second week of symptoms onset) on the time course of the SN reduction.
Results: Study 1 showed shorter median time of SN normalization in patients with VR compared to patients without VR (14 days and 90 days, respectively). Study 2 showed that AUVP patients with early and late VR had a similar median time of SN normalization. The SN slow phase eye velocity was significantly decreased as early as the end of the first VR session in both groups, and kept decreasing at each subsequent VR session. In the early VR group, 38% of the patients had slow phase eye velocity below 2°/s after the first VR session, 100% after the fifth session. Similar findings were observed in the late VR group.
Discussion: Taken together, these results indicate that VR with a unidirectional rotation paradigm speeds up the normalization of SN. This effect seems independent of the time between symptoms onset and commencement of VR, but early intervention is recommended to speed up the SN reduction.

KEYWORDS

acute unilateral vestibulopathy, spontaneous nystagmus, vestibular rehabilitation, unidirectional rotation paradigm, early vs. late vestibular rehabilitation

Introduction

The vestibular syndrome observed in patients with an acute unilateral vestibulopathy (AUVP) comprises both static symptoms observed when patients are stationary, and dynamic symptoms when the patients' head or whole body is moved (1). Among the static symptoms is the ocular-tilt reaction, which combines oculomotor signs

(spontaneous nystagmus, skew deviation, eye cyclotorsion), postural signs (head and body tilt to the side of AUVP), and perceptual signs (vertigo, tilt of the subjective visual vertical to the side of AUVP). Static symptoms are almost fully compensated after AUVP through the process of vestibular compensation. Vestibular compensation is a spontaneous, or "naturalistic", functional recovery after damage to the peripheral vestibular system, and is among the best documented postlesional plasticity phenomena, coming to be recognized as the "neuro-otologist's best friend" (2).

Animal models of unilateral vestibular loss showed that static symptoms result from a neurophysiological imbalance between the ipsilesional and contralesional vestibular nuclei, with decreased resting activity in the neurons on the ipsilesional side and near normal resting activity on the contralesional side [unilateral labyrinthectomy in guinea pigs (3–6); unilateral vestibular neurotomy in cats (7)]. The spontaneous firing rate and sensitivity of the Type I vestibular neurons in the ipsilesional vestibular nuclei is further reduced by an increased inhibitory drive from the intact, contralesional side through commissural pathways. Compensation of these deficits in animal models is well documented and there is a general agreement that the recovery of a balanced neurophysiological activity in the vestibular nuclei is a key compensatory mechanism. The Bechterew phenomenon, that is, the mirror image of the static symptoms observed in compensated animals when the intact labyrinth is destroyed, was the first evidence of restored spontaneous activity in the deafferented vestibular nuclei (8). A combination of molecular, cellular, and sensory substitution mechanisms contributes to restore neuronal activity in the ipsilateral vestibular nuclei (9, 10).

Animal models of unilateral vestibular loss also indicate that the compensation of static symptoms has a time course similar to that of the recovery of a balanced resting discharge in the vestibular nuclei. The recovery of balanced neurophysiological activity in the vestibular nuclei after acute unilateral peripheral vestibular loss is quicker in rodents [1 week (9)] than in cats [6 weeks (10–12)]. However, time frames for AUVP patients are poorly documented. For example, head and trunk orientation as well as trunk stabilization in the roll plane are still altered three months after unilateral vestibular neurectomy (13). Other studies have noted that one year is required for the subjective visual vertical and horizontal to be fully compensated (14, 15), and for body roll-tilt perception to normalize (16). Ocular cyclotorsion is another static oculomotor sign still observed at least 3 to 6 months after unilateral vestibular neurectomy (17), suggesting that it could be a permanent otolithic problem (18). Thus, when compared to animal models, static deficits in humans are compensated within a much longer time period.

Spontaneous nystagmus (SN) in AUVP patients consists of slow horizontal and torsional eye deviations (slow phases) toward the affected side interrupted by fast eye movements (quick phases) away from the affected side. To an observer, this SN shows both eyes beating away from the affected side (18). SN is temporary and resolves or decreases on its own with time. It is reduced or suppressed by visual fixation but shows high inter-individual variability when recorded in the light. Fushiki et al. (19) showed that about 50% of the patients exhibited SN in the light on the third day after symptom onset, and 20% of the patients had SN on the eighth day. Furthermore, the recovery time of the SN increased with the prevalence of canal paresis (19). SN recorded in total darkness showed a much longer recovery time, ranging from several weeks to months after symptoms onset. For some patients, a small SN persists in darkness as a permanent legacy of their unilateral vestibular loss, suggesting an incomplete recovery of neurophysiological activity in the vestibular nuclei long after the vestibular loss (18).

Vestibular rehabilitation (VR) is recognized today as a safe and effective way to accelerate and promote functional recovery (20–25), but there is a paucity of data on how VR can impact the time course of the SN reduction [for other parameters, see (26)]. This is of high clinical relevance since faster SN reduction is expected to have positive benefits at a behavioral level [i.e., stability; see (1)] and for the patients' quality of life.

The present study aimed at determining whether VR using a unidirectional rotation protocol influences the time course of the SN reduction recorded in darkness in AUVP patients. This rehabilitation method, which consists of rotating the patient's whole body in the yaw plane towards the hypofunctioning side, was first proposed at the end of the XXth century by Alain Semont, a French physiotherapist, as a clinical tool to reduce acute vestibular asymmetries. This VR protocol is still used by French physiotherapists, but its effectiveness has never been supported by peer-reviewed publications, and has been ignored in most other countries. Only one article, published in French, reported subjective and objective improvements of posture and balance in Menière's disease patients treated with rotational exercises, albeit for reasons that remain to be clarified (27). More recently, we reported positive outcomes of the protocol on postural recovery (28, 29) and dynamic horizontal canal function (30) in AUVP patients. We postulated that unilateral rotations in darkness to the weaker side could reduce the imbalance in spontaneous activity of the bilateral vestibular nuclei by restoring the resting discharge on the weaker side using two complementary mechanisms: stimulation of remaining intact vestibular afferents on the affected side, and inhibition of the intact side that reduces the commissural inhibition exerted by the intact side on the injured side (**Figure 1**).

The impact of VR with a unidirectional rotation paradigm on the time course of the SN reduction was analyzed in patients with VR and without VR (Study 1), and in in patients who underwent VR at different stages after symptoms onset (Study 2), to determine whether there are any benefits of VR and of early intervention.

Materials and methods

Participants

Clinical examination and patient's history was done by LT (author LT) and used to diagnose AUVP. All AUVP patients exhibited the five main inclusion criteria proposed by Strupp and Magnusson (31): acute onset of spinning vertigo, horizontal rotatory SN beating to the intact side, a positive head impulse test (HIT) on the weaker side, nausea, and postural imbalance.

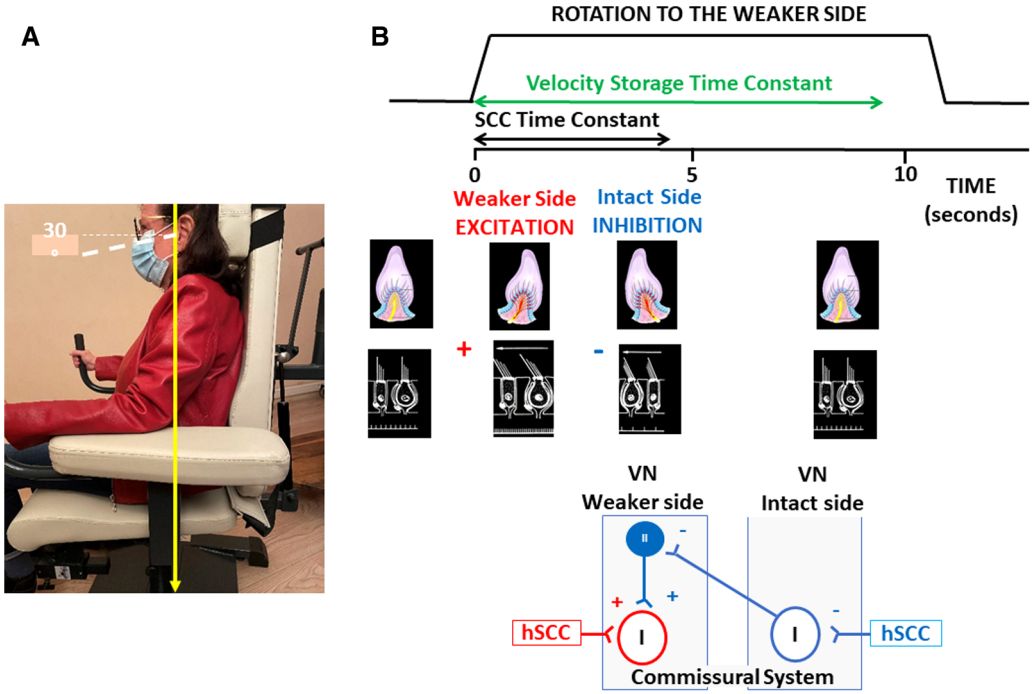

FIGURE 1
Unidirectional rotation paradigm and hypothetical mechanisms underlying its therapeutic effect. (A) Illustration of the rotating chair and position of the patient's head and body, with eyes closed. (B) From top to bottom: Schematic drawings of the velocity profile of the stimulation, the induced ampullofugal and ampullopetal flows in the ipsilateral and contralateral horizontal semicircular canals, and the hypothetical mechanisms within the vestibular nuclei. The velocity profile is for five full turns at 200°/s to the weaker side, and shows estimated values of the time constants of the cupula (in black: ~4 s) and of the velocity storage mechanisms that prolongs the patient's perception of rotation (in green: ~9 s). The displacement of the cupula is excitatory on the weaker side and inhibitory on the intact side. The hypothetical mechanisms of compensation in the vestibular nuclei are illustrated in the bottom diagrams. Unidirectional rotation to the affected side stimulates remaining intact vestibular afferents projecting to second order neurons (Type I neurons) on the weaker side, and inhibits the Type I neurons on the intact side. Type I neuronal inhibition deactivates the inhibitory drive of Type II neurons on the affected side through the commissural pathways and induces a disinhibition of the Type I neurons on the weaker side. These two mechanisms could restore the spontaneous activity of the second order vestibular neurons on the weaker side, and rebalance the resting discharge of the vestibular nuclei on both sides. hSCC, horizontal semicircular canal; VN, vestibular nuclei; I, Type I second-order vestibular neurons; II, Type II inhibitory vestibular neurons;+indicates a faciliatory effect (in red) or a disinhibitory effect (in blue);–indicates an inhibitory or a de-facilitating effects.

The pathological weaker side was determined when the angular vestibulo-ocular (aVOR) gain during passive video HIT (vHIT Ulmer, Synapsis, Marseille, France) was below 0.70 and when overt/covert saccades were observed. Horizontal aVOR gain on the intact side above 0.80 was required for patient inclusion. Positional vertigo, central vestibular pathology, ocular motor dysfunctions, and drug treatment were exclusion criteria. Vestibular deficit was documented on the basis of the HIT for the lateral, anterior and posterior canals. Caloric vestibular testing was not systematically done due to discomfort, but was always pathological on the weaker side when performed.

All patients provided written informed consent to participate and were asked to abstain from antivertigo drugs for the duration of the study.

Study 1: time course of the SN reduction with and without VR

Study 1 is a retrospective analysis that focused on the slow phase eye velocity (SPEV) of the SN measured in darkness. The compensation time course was evaluated in 92 patients who did not undergo VR with a unidirectional rotation paradigm and in 33 patients who did (see Table 1 for patients' characteristics).

The non-rehabilitated group included AUVP patients whose SPEV was measured at their initial visit, which took place 2–90 days after symptoms onset.

The rehabilitated group included patients whose initial visit took place 4–13 days after symptoms onset. Their initial visit was

TABLE 1 Characteristics of the AUVP patients in retrospective Study 1.

	Without VR	With VR
n	92	33
Sex (*n*)		
Males	44	17
Females	48	16
Age (years)		
Mean ± SD	60.5 ± 14.5	57.7 ± 12.0
Range	18–82	30–75
Side of hypofunction (*n*)		
Left ear	45	14
Right ear	47	19
Time from symptoms onset (days)		
Mean ± SD	17.3 ± 16.7	7.2 ± 2.7
Range	2–90	4–13

the day of study inclusion and the day of the first VR session. Patients received 3–9 VR sessions and the SPEV was measured at each visit. The effect of VR was assessed for each patient by comparing the SPEV of the SN recorded before and immediately after each VR session.

Study 2: time course of the SN reduction with early and late VR

Study 2 is a prospective analysis of the SPEV of the SN recorded in darkness in 42 AUVP patients who underwent VR with a unilateral rotation paradigm. VR was performed early ($n = 22$; initiated within the first two weeks) or late ($n = 20$; initiated after the second week) after symptoms onset (see Table 2 for patients' characteristics). The effect of VR was assessed for each patient by comparing the SPEV of the SN recorded before and immediately after each VR session. Study 2 included supplementary measurements of the static and dynamic subjective visual vertical (SVV) and the Dizziness Handicap Inventory (DHI) score.

Assessment of vestibular deficit

HIT was performed with passive head rotation to the healthy and weaker sides in seated patients. Head rotations were done with 10° peak amplitude, 200°/s peak velocity and ~2,000°/s^2 peak acceleration. Recording of the aVOR of the horizontal canals was done by tilting the patient's head downwards by 30° to place the lateral semicircular canals in the horizontal plane. Recordings of the aVOR of the anterior and posterior canals were done by turning the patient's head 45° to the right and to the left. HIT was performed randomly to elicit unpredictable timing and direction of head movement. Gain values of the aVOR were approximated by the Synapsis software as the ratio:

$$\text{Gain} = \frac{\text{peak eye velocity}}{\text{peak head velocity}}$$

TABLE 2 Characteristics of the AUVP patients in prospective Study 2.

	Early VR	Late VR
n	22	20
Sex (*n*)		
Males	11	11
Females	11	9
Age (years)		
Mean ± SD	62.8 ± 15.0	62.5 ± 14.5
Range	35–86	35–82
Side of hypofunction (*n*)		
Left ear	12	10
Right ear	10	10
Time from symptoms onset (days)		
Mean ± SD	6.9 ± 2.3	35.9 ± 9.5
Range	2–13	16–42

An average gain value was calculated before and after VR from 5 correctly performed tests on the intact and weaker sides. However, more than 5 trials were generally done due to blinks or imperfect target fixation.

Assessment of the spontaneous nystagmus

The SN was recorded using videonystagmography (Framiral, Grasse, France) in patients seated with their head pitched 30° downwards to a position in which the lateral semicircular canals were placed in the horizontal plane. Patients were instructed to keep their eyes open in the video headset and to look straight ahead. SN was recorded in darkness for 30 s and the mean SPEV was calculated. SN was recorded before and after each VR session (Study 1 and Study 2), and at the moment of the inclusion visit for the patients without VR (Study 1).

Vestibular rehabilitation with the unidirectional rotation paradigm

The rationale of VR with a unidirectional rotation paradigm is to reduce the vestibular asymmetry by simultaneously stimulating the weaker side and inhibiting the intact side. We postulated that unilateral rotations in darkness could reduce the imbalance in the spontaneous neuronal activity of the bilateral vestibular nuclei by restoring the spontaneous firing rate of the second-order vestibular neurons on the weaker side. Rotation to the weaker side (a) inhibits Type I neurons on the intact, contralateral side, which disinhibits the Type I neurons on the weaker side by means of the commissural pathways, and (b) stimulates remaining intact vestibular afferents contacting the Type I cells on the weaker side. Both mechanisms would act jointly to restore the spontaneous discharge in the vestibular nuclei on the affected side, and rebalance the spontaneous resting discharge on both sides. Figure 1 illustrates these hypothetical mechanisms resulting from the rotation-induced vestibular stimulation. A facilitated normalization of the SN after VR could be seen as the therapeutic effect of the unidirectional rotation paradigm. The protocol was performed in darkness to avoid possible visuo-vestibular interactions that were not investigated in the present study. Even though sensory substitution using visual cues is involved in the compensation of the static vestibular deficits, recovery of SN is not dependent on visual inputs (32). SN decreases at the same rate in animals kept in the dark immediately after unilateral labyrinthectomy as in animals kept in a lighted environment.

The physiotherapist (author AT) performed all VR sessions. The unidirectional rotation paradigm consisted of whole-body passive rotations to the patient's weaker side using a rotating chair (Framiral, Grasse, France). Patients were seated with their eyes closed and head tilted 30° downwards to place the horizontal semicircular canals close to the horizontal, and rotated during a minimum of three full 360° turns at high velocity (200°/s, 2,000°/s^2). Patients who tolerated stimulation underwent a

higher number of turns. The chair was suddenly stopped at the end of the last lap. Patients were then asked to keep their eyes closed and to indicate verbally when their sensation of rotation in the opposite direction was over (vection protocol), or to open their eyes and fixate a visual target until the illusory target motion stopped (fixation protocol). The two protocols provided comparable data used to test the habituation of the intact labyrinth after repetition of the rotations and of the training sessions (data not reported here; manuscript in preparation). This is the subject of ongoing experiments aimed to better understand the therapeutic effect of the unidirectional rotation protocol. When the post-rotatory nystagmus had disappeared, and after 1 min of rest, another series of chair rotations was performed. A minimum of three series of chair rotations were made during the same VR session and up to ten series of rotations were made if tolerated by the patient, with a total duration that did not exceed 30 min. Participants completed VR sessions until the SN recorded in darkness had a SPEV below 2°/s. VR sessions were done twice a week for four weeks after inclusion. SN with SPEV below 2°/s were considered non-pathological and used to evaluate the percentage of patients who recovered over time.

Supplementary measurements

In addition to SPEV of the SN, Study 2 analyzed perceived vestibular handicaps using the French adaptation of the Dizziness Handicap Inventory (DHI) (33) before and after VR. The total score incorporates 25 physical, functional and emotional items rated on a three-point scale, with 4, 2 and 0 corresponding to the answers "yes", "sometimes" and "no", respectively. The total DHI score ranges from 0 to 100. Patients with AUVP have generally moderate handicap with DHI scores ranging from 40 to 60 (29, 30, 34).

The perception of the static and dynamic subjective visual vertical (SVV) was also measured in Study 2 at the beginning of VR and immediately at the end of the last VR session. Patients were standing upright and faced a screen 1 m in front of them, at eye level. They wore goggles narrowing their visual field to the intended visual scene on which a red laser line was projected (Framiral, Grasse, France). The line was positioned randomly at ±15° or ±30° relative to the true gravitational vertical and patients were asked to rotate the line clockwise or counterclockwise using two handheld pushbuttons until they aligned the laser line with their perception of verticality. The static SVV was measured binocularly in darkness. Five trials were carried out for each initial positioning of the line and the mean orientation was calculated.

The dynamic SVV was measured with the same device, but with a random visual pattern made of white dots of different sizes rotating clockwise or counterclockwise at 20°/s. Patients were asked to adjust the laser line to the vertical during the visual scene rotation. In healthy participants clockwise and counterclockwise rotations result in symmetrical tilt of the SVV up to 10–15° in the direction of the visual field rotation (15) and, therefore, there is no directional preponderance. The directional preponderance of the dynamic SVV (15) in the AUVP patients was calculated as:

$$\text{Directional preponderance} = \frac{\text{ipsilateral SVV} - \text{contralateral SVV}}{\text{ipsilateral SVV} + \text{contralateral SVV}} \times 100.$$

Average values were calculated over three trials presented in a randomized order on each side.

Statistical analyses

Linear mixed-effects model

Changes in the SPEV of the SN over time was analyzed with a linear mixed-effects model using log transformed SPEV values [i.e., $\log_{10}(\text{SPEV} + 1)$]. This was to improve the normality of the SPEV distribution, to be able to perform linear regressions, and to account for repeated measures for patients tested during several VR sessions. For Study 1, we used Participants as random effects and Session (number of days after symptoms onset, coded as a covariate in the model), Rehabilitation (with VR vs. without VR), and interaction of Session × Rehabilitation as fixed effects. For Study 2, we used Participants as random effects and Session (number of days after the first VR session, coded as a covariate in the model), Timing of VR (early VR vs. late VR), and interaction of Session × Timing of VR as fixed effects. The analyses were conducted using SPSS version 28.0 (IBM). p values <0.05 were considered statistically significant.

Survival analysis

We also estimated the normalization of the SN (i.e., when SPEV was <2°/s) after symptom onset (for Study 1) or after the first VR session (for Study 2) using the Kaplan–Meier method on non-transformed SPEV values in GraphPad Prism version 9.4.1. Survival curves were plotted and a Log-rank test was calculated to compare SN normalization in AUVP patients without and with VR in Study 1, and to compare SN normalization in patients who underwent early and late VR in Study 2. p values <0.05 were considered statistically significant.

Results

Study 1: time course of the SN reduction with and without VR

Descriptive analysis of the individual curves of SN over time

Figure 2 shows the evolution of the SPEV of the SN in 33 patients who underwent VR. Despite the fact that VR commenced at various durations post AUVP (2–13 days after symptoms onset), all patients had a SN with a SPEV < 2°/s

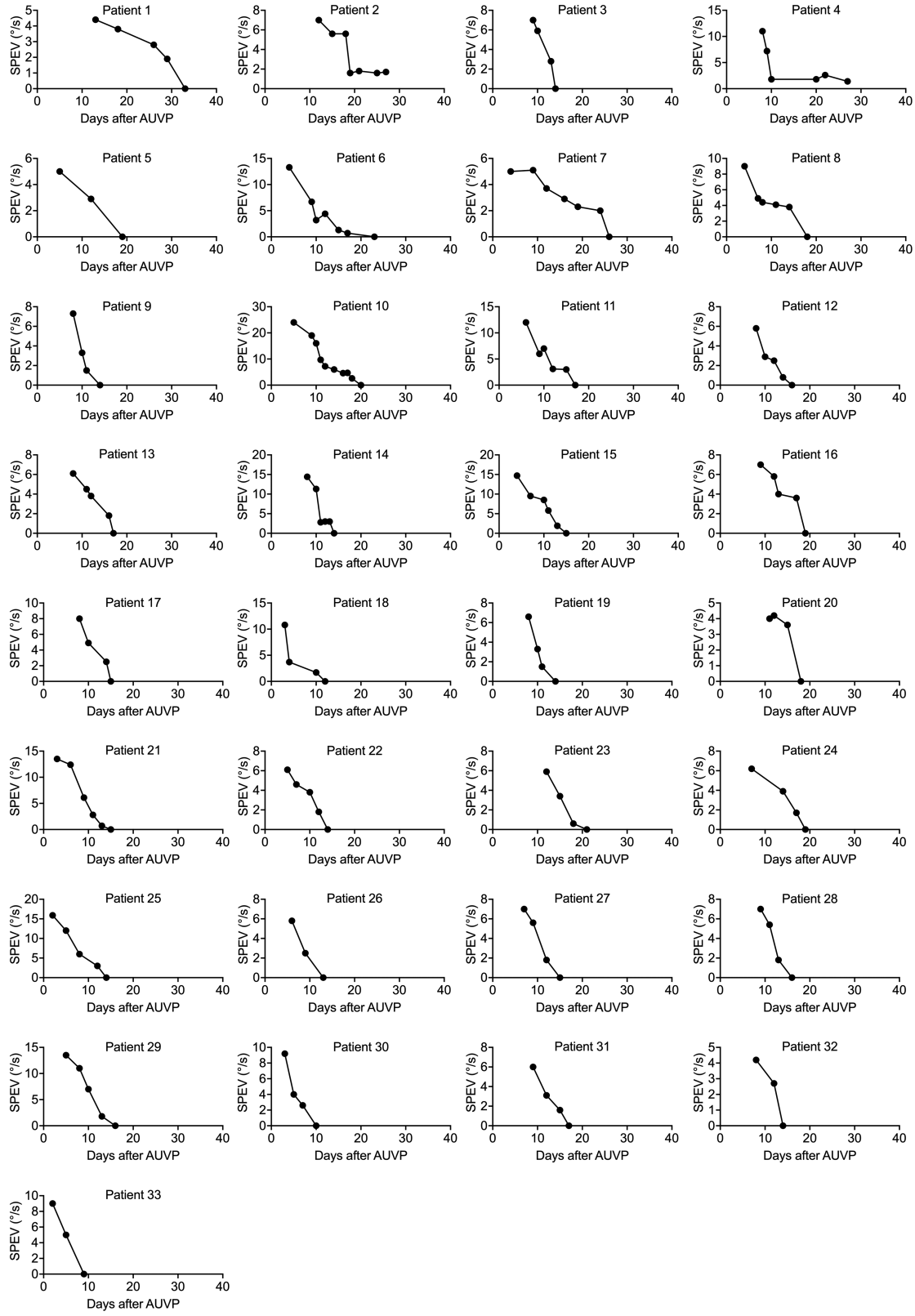

FIGURE 2
Individual curves of the SPEV of the SN over time in patients who underwent VR (study 1). SPEV of the SN as a function of days after symptoms onset for each patient who underwent VR with the unidirectional rotation paradigm. Two to nine VR sessions were completed to recover a SPEV < 2°/s. All patients recovered to non-pathological SN between 9 and 29 days after symptoms onset.

between 9 and 29 days after symptoms onset. Recovery of nystagmus with SPEV < 2°/s involved 2–9 VR sessions.

Linear mixed-effects model

A linear mixed-effects model on the log-transformed values of SPEV was used to compare the time course of SN reduction in patients with VR and without VR, accounting for multiple observations per patient for the group receiving VR. The inset in Figure 3 shows that the log-transformation allows for linear regression calculations.

Table 3 shows the parameters estimates for the fixed effects. As expected, the linear mixed-effects model indicated that the log-transformed SPEV values were significantly modulated by the time elapsed since the symptoms onset ($B = -0.009$, SE = 0.002, $p < 0.001$). There was no significant effect of VR ($B = 0.058$, SE = 0.07, $p = 0.408$), indicating no group difference in the severity of the SN at time zero. There was a significant interaction of Session × Rehabilitation ($B = -0.033$, SE = 0.005, $p < 0.001$), indicating a different evolution of SPEV over time as a function of VR. Comparison of the slope of the fit for the log-transformed SPEV values in the group with VR (−0.042) and without VR (−0.009) indicated that the recovery was 4.7 times faster in the group of patients who underwent VR.

Individual SPEV values and regression curves, showing a non-linear pattern of compensation, are displayed in Figure 3 for both groups of patients.

Survival analysis

Figure 4 shows the pattern of change in the percentage of patients from VR and non-VR groups towards non-significant SN (i.e., SPEV < 2°/s). The statistical comparison of the survival curves indicates a significant effect of group (Log-rank test: $\chi^2_{(1)} = 62.99$, $p < 0.0001$) with shorter median time for SN normalization for patients receiving VR compared to patients without. This was 14 days and 90 days, respectively. The estimated hazard ratio (logrank) was 14.6 (95% CI: 7.35–29.02), indicating that the rate of SN normalization (SPEV < 2°/s) in patients with early VR was about 15 times the rate of SN normalization in patients with a "natural" compensation of SN.

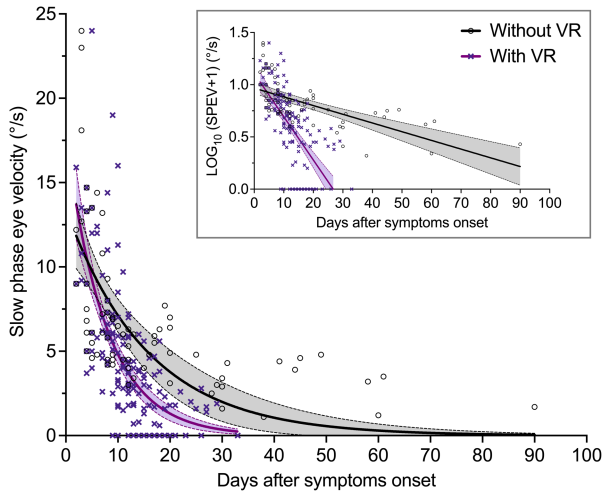

FIGURE 3
Evolution of the SPEV of the SN over time in patients with and without VR (Study 1). SPEV of the SN as a function of days after symptom onset, and one-phase decay regression curves for both groups of patients. The equation used was: $y = y_0 \times \exp(-x/\tau)$, where y is the SPEV in °/s, x is the time in day, and τ is the time constant in days (goodness of fit: $R^2 = 0.40$ for patients without VR; $R^2 = 0.47$ for patients with VR). The filled areas are the 95% confidence interval of parameters. The graph in the inset shows that log-transformation of the SPEV values allows for computation of linear regressions.

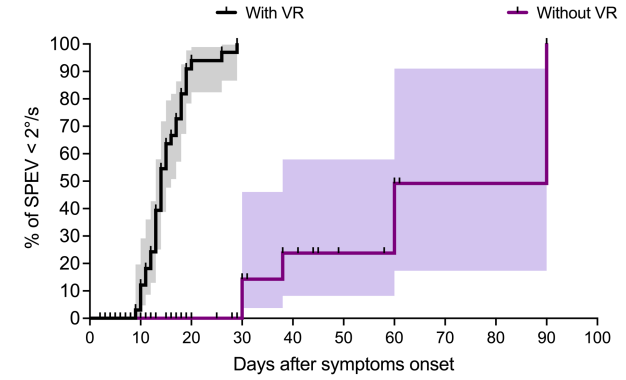

FIGURE 4
Survival analysis in patients with and without VR (Study 1). Survival analysis with the Kaplan–Meier method shows the percentage of patients with non-significant SN (i.e., SPEV < 2°/s) as a function of the time elapsed after the symptom onset. The graphs (staircase ± 95% CI) show faster recovery in the group with VR compared to the group without VR, with median for SN normalization of 14 days and 90 days for the two groups, respectively.

TABLE 3 Estimates of fixed effects for Study 1.

Parameter	*B*	SE	*df*	*t*	*p*	95% CI (lower, upper)
Intercept	0.995	0.033	213.55	30.585	<0.001	0.931, 1.059
Rehabilitation[a]	0.058	0.070	229.14	0.830	0.408	−0.080, 0.196
Session	−0.009	0.002	213.95	−5.731	<0.001	−0.012, −0.006
Rehabilitation[a] × Session	−0.033	0.005	229.95	−7.199	<0.001	−0.042, 0.024

SE, standard error; df, degrees of freedom; CI, confidence interval.
[a]Reference: group without VR.

Study 2: time course of the SN reduction with early vs. late VR

Descriptive analysis of the individual curves of SN over time

Figure 5 shows the evolution of the SPEV in 22 patients who underwent early VR (Figure 5A), and in 20 patients who underwent late VR (Figure 5B). All patients regained non pathological SN (SPEV < 2.0°/s) with similar time courses across the two groups: 3–10 VR sessions were necessary for patients with early VR, while 3–8 sessions were necessary for patients with late VR.

The SPEV was significantly reduced as early as the end of the first VR session in both groups. In patients with early VR, the SPEV decreased from 9.1 ± 4.5°/s before VR to 3.3 ± 2.2°/s after the first VR session (36% reduction). Six out of 22 patients (28%) had a SPEV below 2°/s, and two (9%) showed a reversed SN beating to the lesioned side. After the fifth VR session all patients with early VR showed a SPEV below 2°/s.

Similar changes were observed in the late VR group. The mean SPEV decreased from 4.7 ± 1.2°/s before VR to 1.1 ± 0.6°/s after VR (23% reduction), 35% had a SPEV below 2°/s, and 20% showed a reversed SN after the first VR session. All patients with late VR showed a SPEV below 2°/s after the fourth VR session.

We also note that almost all patients in both groups had a higher SPEV at the beginning of the following VR session compared to the SPEV recorded at the end of the previous VR session. However, this was lower than the SPEV measured at the beginning of the previous VR session. This typically characterises a habituation process.

Linear mixed-effects model

As participants from the early VR and late VR groups started the VR at very different times post symptoms onset, we analyzed changes in SPEV as a function of the days since the patients started the first VR session. Table 4 shows the parameters estimates for the fixed effects.

The linear mixed-effects model indicated that the log-transformed values of SPEV was significantly modulated by the time elapsed since the first VR session ($B = -0.019$, SE = 0.004, $p < 0.001$). As expected from the natural decay of the SPEV, there was a significant difference of early vs. late VR on the SPEV at time 0 ($B = 0.149$, SE = 0.048, $p = 0.003$). Lower SPEV for patients in the late VR group was likely related to the spontaneous recovery that took place between the time of the symptoms onset and the first VR session. The analysis also showed a significant interaction of Session × Timing of VR ($B = -0.012$, SE = 0.005, $p = 0.022$), indicating different patterns of SPEV change over time for both groups. Comparison of the slope of the fit for the log-transformed SPEV values in the early VR group (−0.031) and late VR group (−0.019) indicated that the recovery was 1.6 time faster in the group of patients who underwent early VR.

Individual SPEV values and regression curves are shown in Figure 6A for both groups of patients.

Survival analysis

Figure 6B shows the Kaplan–Meier graphs describing the evolution of the percentage of patients with non-significant SN (i.e., SPEV < 2°/s) after receiving early or late VR. We found that the survival curves did not differ significantly between the early VR and late VR groups (Log-rank test: $\chi^2_{(1)} = 0.31$, $p = 0.578$). The median time for SN normalization was 7 days for patients with early VR and 8 days for patients with late VR. The estimated hazard ratio (logrank) was 1.18 (95% CI: 0.63–2.20), indicating similar rate of SN normalization in patients with early and late VR.

Supplementary outcomes

The static and dynamic SVV, as well as the DHI score, have been measured before and after VR in the two groups receiving early and late VR (Table 5). The pre-post VR comparison indicates significant improvement of the static SVV in patients with early VR ($p < 0.001$) and late VR ($p < 0.02$). Before commencing VR, the static SVV deviation was significantly lower in patients in the late VR group when compared to patients in the early VR group ($p < 0.001$). This is possibly due to spontaneous recovery with time. However, both groups regained SVV in the normal range of ±2.5°, and they did not differ significantly after VR.

By contrast, the directional preponderance of the dynamic SVV did not improve significantly after VR in both groups of patients. The directional preponderance did not differ significantly between groups neither before VR nor after VR.

Finally, DHI scores were in the moderate range of handicap for both groups before VR, with significantly lower values in patients with late VR compared to patients with early VR ($p < 0.002$). After VR, the total DHI score decreased significantly in both groups of patients ($p < 0.001$), reaching values in the range of weak handicap. The DHI score did not differ significantly between two groups after VR.

Discussion

The results from Study 1 show that the SN can persist for several months without VR. Study 1 and 2 both show that VR, using a unidirectional rotation paradigm, can significantly improve the time it takes for SN to normalize. Furthermore, SN normalization (SPEV < 2°/s) after VR does not appear to be influenced by the duration since AUVP symptom onset.

Spontaneous nystagmus reduction with and without vestibular rehabilitation

The static vestibular syndrome in AUVP patients is the combination of impaired unilateral canal and otolith afferents (35–37), inducing perceptual (vertigo, verticality perception), postural (head tilt) and oculomotor (SN, ocular cyclotorsion) deficits. Animal models of unilateral vestibular loss indicate that these deficits result from the strong imbalance between the

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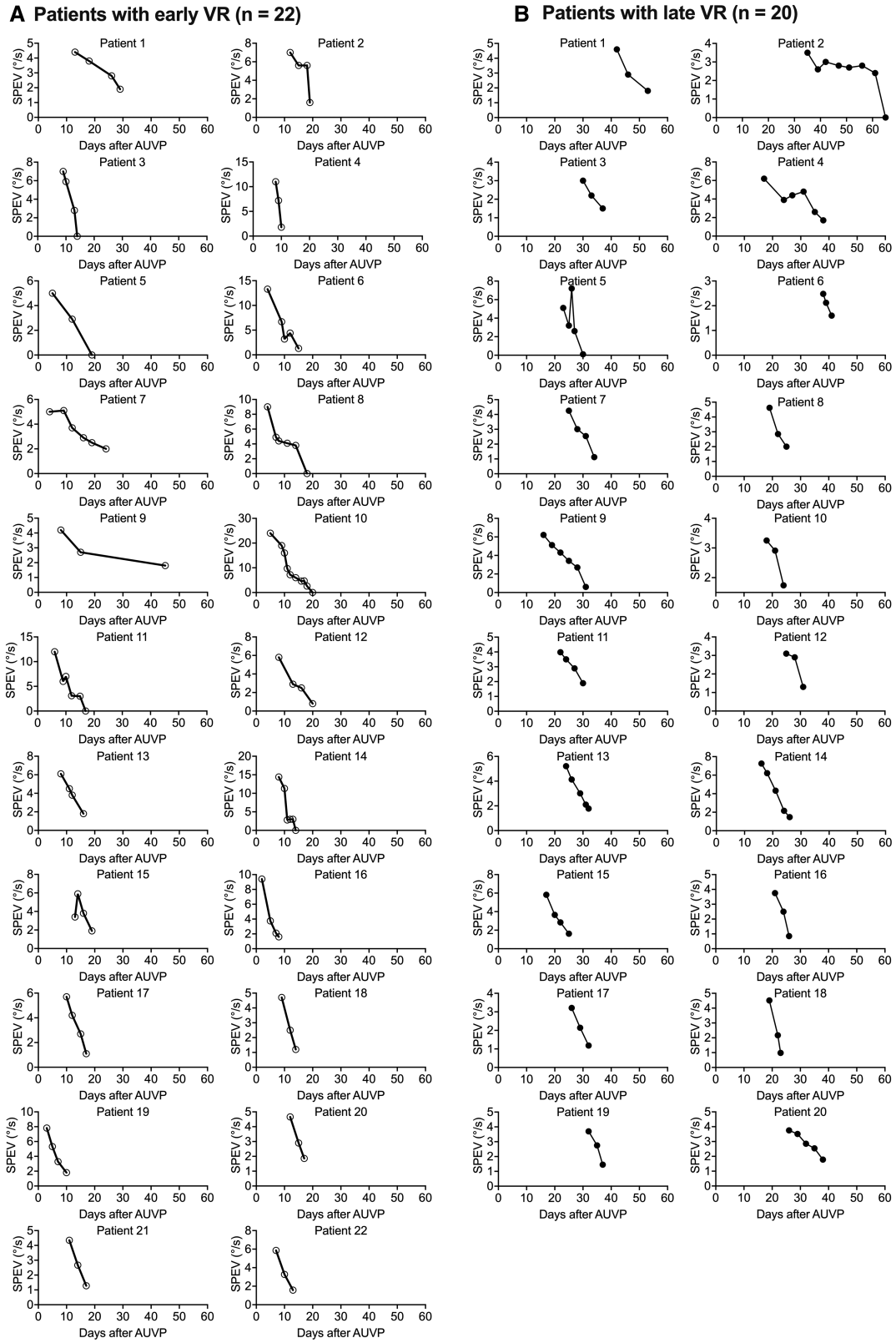

FIGURE 5
Individual curves of the SPEV of the SN over time after early and late VR (Study 2). SPEV of the SN as a function of days after symptoms onset for each of the patients who underwent and early VR (**A**) or a late VR (**B**) with the unidirectional rotation paradigm.

TABLE 4 Estimates of fixed effects for Study 2.

Parameter	*B*	SE	*df*	*t*	*p*	95% CI (lower, upper)
Intercept	0.666	0.035	80.57	19.204	<0.001	0.597, 0.735
Rehabilitation[a]	0.149	0.048	79.05	3.116	0.003	0.054, 0.244
Session	−0.019	0.004	172.47	−4.762	<0.001	−0.026, −0.011
Rehabilitation[a] × Session	−0.012	0.005	173.97	−2.304	0.022	−0.023, −0.002

SE, standard error; df, degrees of freedom; CI, confidence interval.
[a]Reference: group with late VR.

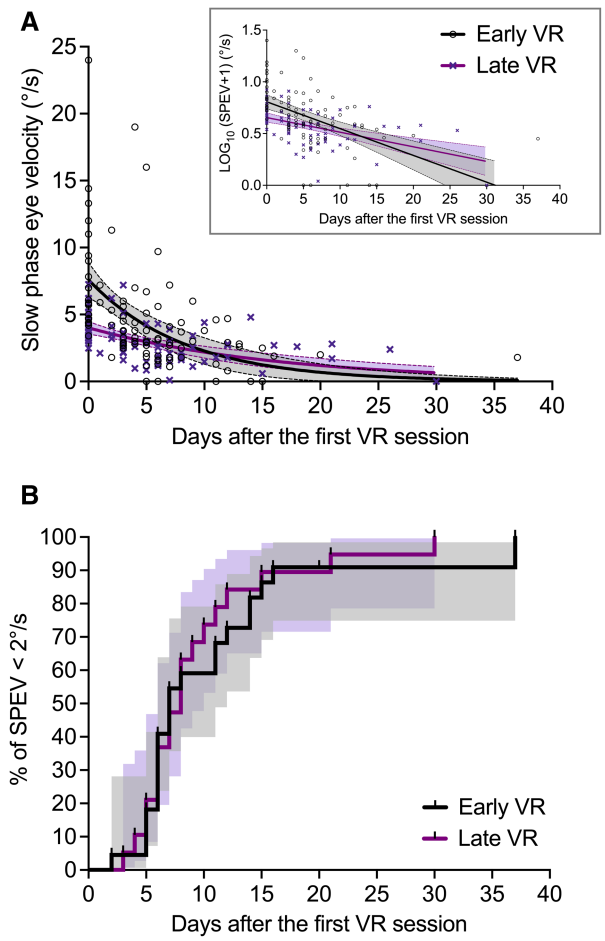

FIGURE 6
Effect of early and late VR on the evolution of the SPEV of the SN (Study 2). (**A**) SPEV of the SN as a function of the time elapsed since the first VR session (not since symptoms onset), and one-phase decay regression curves for both groups of patients (goodness of fit: $R^2 = 0.30$ for early VR; $R^2 = 0.30$ for late VR). The filled areas are the 95% confidence interval of parameters. (**B**) Kaplan–Meier graphs (staircase ± 95% CI) describing the evolution of the percentage of patients with non-significant SN (i.e., SPEV < 2°/s) in the group with early VR and late VR as a function of the time elapsed since the first VR session.

TABLE 5 Supplementary outcomes of prospective Study 2.

	Early VR		Late VR	
	Before VR	After VR	Before VR	After VR
Static SVV (°)	4.89 ± 2.84	2.10 ± 1.01	2.66 ± 1.73	1.57 ± 1.80
Dynamic SVV (%)	45.8 ± 21.7	35.5 ± 22.9	40.6 ± 23.7	30.2 ± 21.4
DHI (total score)	65.1 ± 16.6	19.1 ± 18.4	54.8 ± 20.1	23.7 ± 17.7

Mean ± SD of the static subjective visual vertical (SVV), the dynamic subjective visual vertical (percentage of directional preponderance), and the dizziness handicap inventory (DHI).

resting discharge of neurons in the ipsilesional and contralesional vestibular nuclei (3, 4). Animal models also show that the recovery of neurophysiological activity in the vestibular nuclei on the weaker side is a key mechanism to compensate the static syndrome (see Introduction). Furthermore, the timing of static symptoms recovery parallels the recovery of the resting discharge of the vestibular neurons (38). The mechanisms underlying such recovery in AUVP patients remain speculative. Sensory substitutions (2, 10, 21) and functional reorganizations (39) are very likely involved. A voxel-based morphometry study in AUVP patients showed increased gray matter volume in the vestibular nuclei and gracile nucleus on the affected side, as well as in the bilateral middle temporal/V5 area, and increased white matter volume in the pontine commissural vestibular fibers (40). The data suggests that vestibular, somatosensory, and visual inputs are involved in central compensation in AUVP patients.

SN is a static ocular motor sign largely but incompletely recovered up to 1 year after vestibular loss (18, 41). Our data confirm that SN normalization can take several months. AUVP patients without VR, that is, with spontaneous "natural" compensation, showed a non-linear pattern of compensation over time, with a significantly different time course than patients with VR. The survival analysis showed that the median time for SN normalization was significantly longer without VR (90 days without VR vs. 14 days with VR).

Taken together, our data indicate that VR with a unilateral rotation paradigm speeds up the process of SN reduction. We hypothesize that the unidirectional rotations to the weaker side decrease the spontaneous firing rate of the vestibular nuclei neurons on the intact side which, in turn, results in a disinhibition of the affected side by way of the commissural system (**Figure 1**). Electrophysiological modifications of the commissural field potentials were found after hemilabyrinthectomy in the frog, with an increased number of commissural excitatory postsynaptic potentials and a decreased number of commissural inhibitory postsynaptic potentials (42), and voxel-based morphometry showed white matter changes in the commissural pathways in AUVP patients (40). These two studies indicate a contribution of the commissural system to central vestibular compensation. Stimulation of remaining intact vestibular afferents on the weaker side is a second mechanism

that could promote the restoration of spontaneous activity on this side. Using an anti-synaptophysin antibody as a nerve terminal marker, we reported a synaptic density restoration of 60% three weeks post-lesion [(43): in cats]. Synaptic remodeling in the deafferented vestibular nuclei is likely due to the sprouting of new terminals from remaining intact afferent vestibular fibers. These would then make new synaptic contacts on the deafferented vestibular nuclei neurons. In addition, proliferation of postsynaptic membrane receptors increasing the synaptic weight of multisensory afferents to the vestibular nuclei could also contribute to compensation. Our recent investigations in AUVP patients suggest that a full recovery of dynamic canal function, that is, restoration of normal aVOR gain, could depend on the presence of remaining intact vestibular afferents on the weaker side (30). Changes in the physiological properties of the commissural system (contribution from the intact side), and activation of intact afferents (contribution from the weaker side) are two synergistic mechanisms able to restore the spontaneous firing rate on the weaker side and to rebalance the nuclear activity between the two sides. There is evidence from animal models that such mechanisms of neuroplasticity occur very early after unilateral vestibular loss in the deafferented vestibular nuclei [see (12), for review], and that they are dynamically tuned by early, postlesion stimulation and behavioral experience (Hebbian plasticity).

Although still speculative, these mechanisms could explain the reduction of the aVOR directional preponderance observed after unidirectional rotations in AUVP patients, as previously discussed (30, 34). Thus, the effects of VR with a unidirectional paradigm are in line with the effects of other similar VR paradigms, showing a decrease in the asymmetry of the aVOR gain in macaques with a unilateral labyrinthectomy (44) and a decrease in the aVOR directional preponderance in patients with chronic unilateral vestibular dysfunction (45). However, due to different parameters of rotation, the mechanisms underlying the improvement of the aVOR gain and the normalization of the SN reported here may differ in the various VR paradigms that used unidirectional rotations of the whole body. While vision contributes to the asymmetric changes in the horizontal aVOR gain [see (44)], recovery of SN seems, in part, independent of visual inputs. SN decreases at the same rate in animals kept in the dark or in a lighted environment immediately after unilateral labyrinthectomy (32). A recent meta-analysis of vestibular compensation showed that vision has a limited impact on the increase in intrinsic excitability of ipsilesional vestibular neurons and on the recovery of bilateral symmetry in the vestibular nuclei (46).

Effect of early and late vestibular rehabilitation on the reduction of spontaneous nystagmus

We have previously provided the first demonstration that early VR results in improved dynamic visual acuity and passive aVOR in AUVP patients (30, 34), confirming the concept of a postlesion critical period described in animal models (see [21]). The first few weeks after symptom onset constitutes an opportune time window during which neuroplasticity in the vestibular nuclei is tuned dynamically by sensorimotor feedback from interactions between patients and their environment.

This critical period appears restricted to the recovery of dynamic vestibular functions. Posture in non-challenging/dynamic conditions (stable support, eyes open or closed) recovered in patients who underwent early and late VR (28, 47), whereas dynamic balance (unstable support, eyes closed or with altered visual motion cues) recovered more quickly in patients with early VR (29). Several sensory signals can substitute the lost vestibular inputs to recover static vestibular functions, whereas the recovery of dynamic functions necessitates the full contribution of both labyrinths and/or requires spared vestibular functions from the affected side [see (30)].

The present data provide mixed findings about the effects of early and late VR on the SN. While the linear mixed-effects model revealed a significant interaction of Session × Timing of VR on the SPEV, the survival analysis showed similar percentage of patients with SPEV below 2.0°/s over time and similar median times for SN normalization in both groups.

In line with results from the survival analysis for the SN, the analysis of the static SVV and the DHI score showed a similar recovery timeframe in AUVP patients who underwent early or late VR. By contrast, the dynamic SVV remained uncompensated in both groups of patients. The change in ocular cyclotorsion over time follows closely that of the static SVV (18, 48), and both oculomotor and perceptual deficits recover slowly in parallel over time (49, 50). The ocular cyclotorsion has not been recorded in the present study, but previous investigations showed ocular cyclotorsion up to 3–6 months after a unilateral vestibular neurectomy (17). We also found that ocular cyclotorsion decreased in parallel with both the static SVV and the SN (51). Assuming that static SVV deviation is a static otolithic deficit caused by the neural imbalance between the vestibular nuclei (18), our data suggest that early or late VR can reduce the recovery time course of all static symptoms, including SN, ocular cyclotorsion and deviation of the SVV. By contrast, the directional preponderance of the dynamic SVV did not improve over time in patients who underwent early and late VR. This confirms that abnormal dynamic SVV is potentially a long-term impairment—even a permanent deficit—of visual-otolithic integration after unilateral vestibular loss (15).

The DHI score decreased after VR in all patients, who shifted from moderate to weak handicap. Differences in DHI score larger than 18 points represent a significant change in the patient's handicap (52). Here, we found a much larger reduction of the DHI score after early VR (47 points on average) and late VR (31 points on average). However, as the DHI score is a subjective measure that often does not correlate with objective measures of vestibular functions (53), the decrease in the DHI score reported in the present may not be solely due to the effects of VR.

Clinical considerations

The results of our studies confirm that the natural reduction of the SN in patients with AUVP is a rather slow process. In some patients, we show a 90-day process of natural normalization of SN. However, some studies have shown that compensation of static postural, oculomotor and perceptual deficits can take up to one year. Of key significance for patients, our data shows the potential for unilateral rotational VR to significantly reduce the normalization time of SN. In addition, we found clinically significant improvements in DHI. Both of these results indicate that VR could positively impact patients' quality of life, and significantly quicker than a naturalistic process. SN normalization is fairly stable once achieved, a supplementary argument in favor of VR with the rotation paradigm or other protocols aimed to reduce the vestibular asymmetries.

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 CPP Nice. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LT selected the patients; AT performed the VR; ML and CL did the statistical analysis; ML wrote the paper; ML, LT, AT, CL reviewed the final 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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Recurrence quantification analysis of postural sway in patients with persistent postural perceptual dizziness

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Background: Persistent postural perceptual dizziness (PPPD) is a common cause of chronic dizziness and imbalance. Emerging evidence suggests that changes in quantitative measures of postural control may help identify individuals with PPPD, however, traditional linear metrics of sway have yielded inconsistent results. Methodologies to examine the temporal structure of sway, including recurrent quantification analysis (RQA), have identified unique changes in dynamic structure of postural control in other patient populations. This study aimed to determine if adults with PPPD exhibit changes in the dynamic structure of sway and whether this change is modulated on the basis of available sensory cues.
Methods: Twelve adults diagnosed with PPPD and twelve age-matched controls, completed a standard battery of quiet stance balance tasks that involved the manipulation of visual and/or proprioceptive feedback. For each group, the regularity and complexity of the CoP signal was assessed using RQA and the magnitude and variability of the CoP signal was quantified using traditional linear measures.
Results: An overall effect of participant group (i.e., healthy controls vs. PPPD) was seen for non-linear measures of temporal complexity quantified using RQA. Changes in determinism (i.e., regularity) were also modulated on the basis of availability of sensory cues in patients with PPPD. No between-group difference was identified for linear measures assessing amount and variability of sway.
Conclusions: Participants with PPPD on average exhibited sway that was similar in magnitude to, but significantly more repeatable and less complex than, healthy controls. These data show that non-linear measures provide unique information regarding the effect of PPPD on postural control, and as a result, may serve as potential rehabilitation outcome measures.

KEYWORDS
persistent postural perceptual dizziness, recurrent quantification analysis, postural balance, vestibular, postural control

1. Introduction

Persistent postural perceptual dizziness (PPPD) is a chronic, functional vestibular disorder characterized by persistent non-spinning vertigo, dizziness, and imbalance exacerbated by active or passive self-motion, and exposure to complex visual stimulation (1). PPPD is one of the most common diagnoses in patients with chronic dizziness (2, 3) and onset regularly occurs following a vestibular or alternative medical event that yields

dizziness and/or imbalance (1, 4, 5). A hallmark of PPPD is perceived chronic postural instability (1) and analysis of postural control and postural sway have been suggested to potentially play a role in identifying PPPD (6). However, the mechanisms underlying PPPD are not fully known, and the potential utility of postural sway in identifying PPPD is incompletely characterized.

The diagnostic criteria for PPPD have only recently been established (1). Thus, hypotheses pertaining to the mechanisms underlying PPPD and perceived instability must also be viewed in the context of prior investigations of individuals with past diagnoses such as phobic postural vertigo (PPV) and chronic subjective dizziness (CSD). Previous investigations in patients diagnosed with PPV have revealed an increase in sway at high frequencies (7) and an increase in the velocity of sway in patients with CSD (8). Similarly, recent studies in patients with PPPD identified increased low frequency and decreased high frequency sway (9). Such findings are consistent with a stiffened strategy for postural control (i.e., co-contraction of lower limb musculature). These findings, in conjunction with the characteristic reports of perceived postural instability, support the supposition that individuals with PPPD adopt a maladaptive high-risk, stiffened postural control strategy (1, 5). While these adaptive strategies are beneficial in the acute phase of vestibular disorders, a failure to re-adapt the postural control strategy in patients with PPPD suggests that these strategies may be influenced by inadequate higher level cortical control and attentional hypervigilance (1, 10). In PPV, an attentional component to postural control is supported by past findings demonstrating reductions in amount of postural sway and reduction in postural stiffness during dual task performance (11) and increased balance performance (i.e., decreased postural sway) during more complex balance tasks (12).

In balance assessments, center of pressure (CoP) motion is commonly quantified and traditional (i.e., linear) measures of CoP have focused on quantifying the behavior of the CoP in the time domain (13–16). However, these measures fail to capture dynamic aspects of the CoP (i.e., how CoP motion changes over time) and assume stationarity of the signal. Recent evidence suggests that non-linear analytic techniques characterizing the dynamic temporal structure of postural sway may provide unique insights into functional organization of the postural control system [e.g., (14, 16, 17)]. These non-linear measures of CoP dynamics, including recurrent quantification analysis (RQA), provide an alternative to traditional posturographic assessments and have been proposed to more reliably quantify sway than traditional amplitude-based metrics (18). Additionally, several studies have identified changes in postural control strategy not captured by linear measures (14, 17, 19, 20) including individuals with imbalance from musculoskeletal pain, stroke, mild traumatic brain injury, and Parkinson's Disease (21–26). However, applications quantifying nonlinear sway metrics in PPPD patients are limited.

While there are several methods to characterize patterns of the dynamic CoP signal including RQA, detrended fluctuation analysis (DFA), sample entropy, and stabilogram diffusion analysis (SDA), methodological constraints exist in the context of non-stationary data and bounded time series of CoP trajectories when implementing non-linear techniques such as SDA (27, 28). Due to these constraints, several authors have proposed implementation of RQA for CoP time series, since this methodology has been extensively investigated by other fields (e.g., mathematics) and is linked to well defined concepts from statistical physics and nonlinear dynamics (16, 17, 25).

RQA was developed as a quantitative extension of the recurrence plot (RP), permitting a numerical, as opposed to a visual, description of the underlying dynamic behavior of a scalar times series. A full overview of RQA and RPs are outside the scope of this paper, however, several in-depth tutorials exist (14, 29–31). In brief, RPs provide a way to visualize the behavior of a higher dimensional dynamic system (32) as the RP is simply a graphical depiction of a recurrence matrix rooted in phase space reconstruction (14). Recurrence is determined by first reconstructing the original CoP signal in phase space by creating several (m) time delayed vectors of the original CoP time series. Each vector is delayed by a multiple of the time delay (τ) such that $X(i) = x(i),\ x(i+\tau),\ x(i+2\tau),\ \ldots (x(i+(m-1)\tau)]$ (33). The distances between all possible vectors in the reconstructed phase space are determined and used to generate a distance matrix. Recurrent points are considered those points in the distance matrix that fall within a specified distance (r) of one another, thus, are considered to be in the same mathematical neighborhood. The RP depicts the recurrence matrix ($R_{i,j}$) graphically in which when the m-dimensional point x (i) is in the mathematical neighborhood of $x(j)$ (i.e., is recurrent), the location (i, j) is signified by a darkened region on the RP (**Figure 1**).

RQA is a quantitative extension of the qualitative RP used to describe the predictability, complexity, and regularity of the CoP time-series signal. RQA provides a means to numerically describe the patterns visualized within the recurrence plot, focusing primarily upon the diagonal lines (**Figure 1**). Diagonal lines within the recurrence plot represent the local evolution of unique parts of the underlying trajectory. For a completely random signal, few diagonals will be present and conversely, for a predictable time series (e.g., sine wave), long diagonal structures will be observed (14, 30, 34). These diagonal structures have been shown to be related to the predictability of the signal (34, 35), and thus serve as a surrogate to quantitatively describe the underlying dynamics of the CoP signal. Usually, in a dynamic system such as postural sway, a complete analysis is only possible when all equations of motion and degrees of freedom are known (e.g., displacement, velocity, acceleration); however, often only a single variable is directly measured. RQA allows understanding of the dynamics of postural sway through examining multi-dimensional space, while only surveying a single behavioral variable (e.g., the mediolateral CoP displacement).

Several investigations have examined non-linear measures of postural sway and changes in CoP structure on the basis of postural control challenge and perturbation (14, 16, 17, 22, 24, 25). Postural sway, in general, has been seen to increase in both absolute amount and variability, as quantified by linear measures of sway, as balance condition becomes more difficult and as sensory information pertinent for balance is degraded or removed (14, 17). These increases in sway are accompanied by increased regularity of the temporal structure of the CoP as quantified by

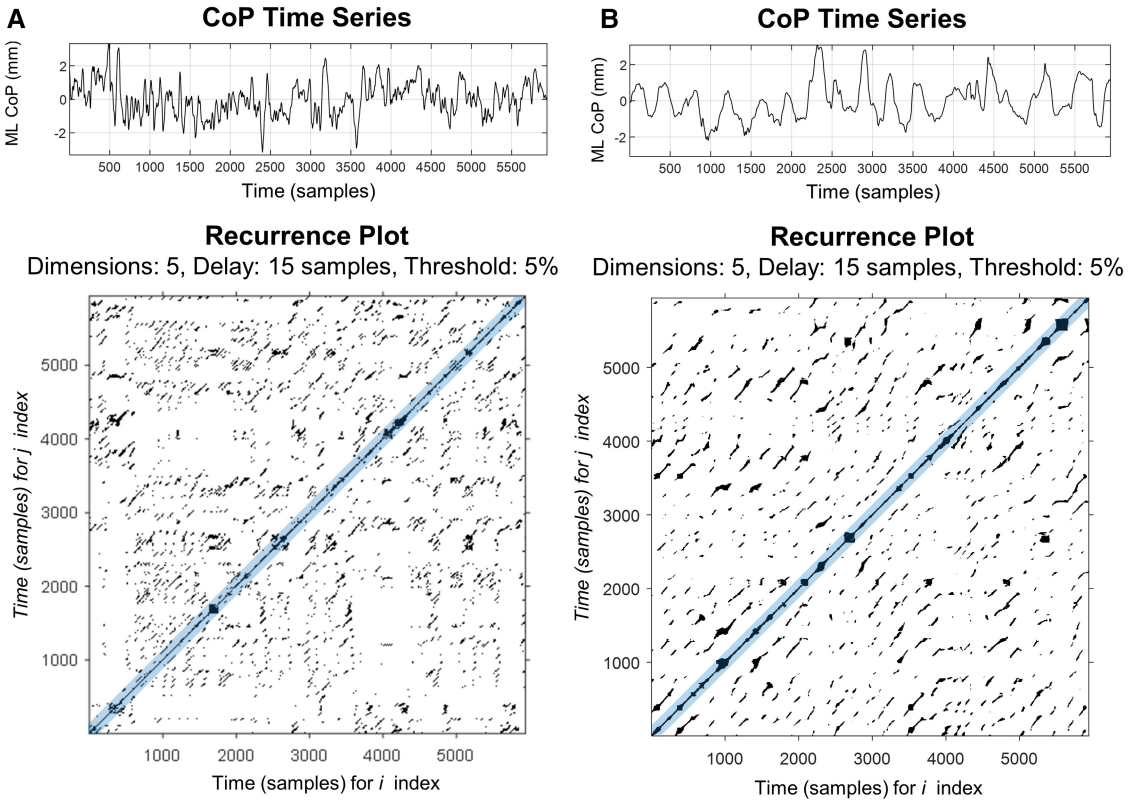

FIGURE 1
Representative recurrence plots of mediolateral CoP motion for a healthy control (A) and patients with PPPD (B) during a quiet stance on a firm surface with eyes open (condition 1). Plots were made using Marwan RQA Toolbox (v.5.24 (R34) (34). In the upper panels, the 60 s CoP time series, sampled at 100 Hz, is plotted for both participants. In the lower panels, the two-dimensional recurrence plots of the same time series are shown; these represent comparisons between two time-lagged CoP signals in multi-dimensional space. Darkened points represent points which are recurrent in time and are neighbors in the reconstructed phase space. Main diagonal (i.e., line of identify) is due to comparing each point to itself. Blue shaded region around the main diagonal represents the Theiler window, which excludes temporally close recurrence from data analysis.

RQA (14, 17). Past studies have assessed CoP behavior in patients with PPV, including DFA and SDA, and demonstrated significant changes in underlying dynamics of postural control (8, 36) suggesting higher sway regularity even during less demanding balance tasks. However, these investigations were in patients with PPV, and while PPV has been superseded by PPPD, some argue for inclusion of PPV as a distinct phobic subtype of PPPD (1). As such, whether differences in postural control dynamics exist in patients meeting current PPPD diagnostic criteria has yet to be determined.

Thus, this study aimed to explore the utility of RQA to identify changes in dynamic structure of quiet stance CoP signals in patients with PPPD. In the present study, we calculated traditional linear measures and non-linear measures of the CoP trajectory using RQA in patients with PPPD and healthy controls during standard, quiet stance balance tasks designed to manipulate the reliability and/or availability of sensory cues. We hypothesized that (1) RQA metrics would reveal changes in postural control modulated by task difficulty and attentional demands not captured by linear measures, and (2) patients with PPPD would display greater regularity (i.e., inflexibility or stiffness) of the CoP signal compared to age-matched asymptomatic controls.

2. Methods

2.1. Participants

Balance performance was assessed in 12 patients diagnosed with PPPD (11F/1M; range 19–67 years, mean = 45.11, SD = 12.86) and 12 asymptomatic healthy controls (HC; 7F/5M; range 21–69 years, mean = 46.54, SD = 12.54) without a history of dizziness or vertigo. Participants in each of the two groups were age matched within two years due to the well-known decrement in balance performance that occurs with age [e.g., (13, 37)]. Patients were recruited from the oto-neurology clinic at The Ohio State University Wexner Medical Center (OSUMC) and received a diagnosis of PPPD by an oto-neurologist using ICVD criteria (38). Precipitating events for patients with PPPD included vestibular migraine ($n = 7$), COVID-19 ($n = 1$), hospitalization for an unrelated medical illness ($n = 2$), whiplash injury ($n = 1$), and panic disorder/social stress ($n = 1$). Patients who presented with PPPD in conjunction with any disorders known to be associated with permanent peripheral vestibular loss (e.g., Meniere's Disease) were excluded. In both participant groups (i.e., HC and PPPD patients), individuals were excluded on the basis of co-existing neurological disorders (e.g., stroke, multiple sclerosis), major

chronic health conditions (e.g., cancer), and lower limb or musculoskeletal injuries that occurred within the previous 6 months.

All HC and PPPD participants completed standardized questionnaires assessing presence of psychiatric co-morbidities, dizziness symptom severity, and balance confidence outlined in **Supplementary Table S1**. All participants were screened for anxiety and depression using the Beck Anxiety Inventory [BAI; (39)] and Patient Health Questionnaire-9 [PHQ-9; (40)] but were not included/excluded on the basis of anxiety or depression. All PPPD patients reported moderate to severe anxiety on the basis of the BAI and two HC participants reported mild to moderate anxiety. Similarly, all PPPD patients reported mild to severe depression on the basis of PHQ-9 scores and one HC reported moderate depression.

Eleven patients with PPPD reported use of medications for psychiatric co-morbidities including selective serotonin reuptake inhibitors (SSRI; $n = 6$), benzodiazepine ($n = 2$), anxiolytic ($n = 2$), and atypical antipsychotic (i.e., aripiprazole; $n = 4$). Seven PPPD patients reported used of medications for migraine including anti-epileptics (i.e., topiramate; $n = 6$), beta-blockers (i.e., metoprolol; $n = 3$), or calcitonin gene-related peptide (CGRP) receptor antagonists ($n = 4$). One HC participant reported use of a SSRI, while no other HC participants reported use of medications for migraine, or psychiatric co-morbidity. Patients did not discontinue any medication prior to testing but all denied using acute medications for migraine, anxiety, or PPPD symptoms (e.g., CGRP receptor antagonists or benzodiazepines) for 2 weeks.

At the time of testing, three PPPD patients were actively enrolled in vestibular rehabilitation at OSUMC with a focus on habituation to visually provoking stimuli. All PPPD patients reported that they were still actively experiencing PPPD symptoms and indicated a moderate to severe dizziness handicap on the Dizziness Handicap Inventory (DHI) and low to moderate balance confidence on the Activities-specific Balance Confidence (ABC) Scale. No HC participants reported experiencing a significant dizziness handicap on the DHI and all reported a high balance confidence on the ABC.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Ohio State University (#2018H01279). All participants provided written informed consent prior to participation.

2.2. Balance assessment

Participants performed five balance tasks (**Table 1**) including each condition of the modified Romberg Test of Standing Balance (41) and an additional dual-task (i.e., counting backwards by threes) condition when standing on foam with the eyes closed. These conditions were selected to permit the assessment of balance performance in the presence of unreliable sensory information and in the presence of a secondary cognitive task. Each condition was performed once; however, if the participant did not complete a trial (e.g., uncrossed arms, opened eyes, took a step to regain balance, lost balance), the condition was repeated one additional time. Data from the final attempt was included in all data analyses. All HC participants were able to complete all conditions, while one participant with PPPD was unable to complete conditions 3 through 5 and an additional participant with PPPD could not complete conditions 4 and 5 (**Table 1**).

For each condition, participants were asked to stand "as still as possible" with their feet positioned in narrow stance (i.e., medial border of feet touching) and their arms folded across their chest. Data was collected for 66 s, with the first 6 s removed from analysis to allow the participant to accommodate to the task. For eyes open (EO) conditions, the participants looked at a dartboard fixed at 1.524 meters (i.e., 60 in) at eye level. In the "foam" conditions, participants stood on an Airex (Somersworth, NH, US) high-density (50 kg/m^3) closed-cell foam pad (47 cm × 39 cm × 6 cm, 0.7 kg). To mitigate any potential auditory contributions to balance performance, participants wore over the ear noise canceling headphones (Bose Quiet Comfort II) with ∼50 dB SPL of white noise presented during each balance trial.

Center of pressure (CoP) data were collected using a tri-axial force plate (AMTI, Watertown MA). CoP data were sampled at 100 Hz and prior to analysis, data were zero-meaned and low pass filtered using a 25 Hz cut off (*filtfilt*, MATLAB, Natick, MA). The primary outcome metrics were computed from CoP data collected in the mediolateral (ML) planes using custom written scripts in MATLAB (2022a). Data from the orthogonal anteroposterior (AP) plane were also captured; however, due to the exploratory nature of the study and as sway in the ML plane has been seen to correlate to falls (42, 43), we *a priori* chose to focus on metrics quantifying ML CoP. Analyses of AP sway were completed for both linear and non-linear metrics, and plane was not found to modify the effect of the fixed factors in the below-described models, and thus we report only ML metrics in the analysis in the main body. See **Supplementary Tables S2, 3** for AP linear and non-linear metrics.

2.2.1. Linear postural control measures

In each condition for each participant, path length and standard deviation (SD) of the CoP in the ML plane was

TABLE 1 Description of balance test conditions performed and sensory input available for each condition.

Condition	Vision	Surface	Sensory inputs	Participants	
				HC	PPPD
1	Eyes open	Firm	Vision, proprioception, vestibular	12	12
2	Eyes closed	Firm	Proprioception, vestibular	12	12
3	Eyes open	Foam	Vision, vestibular	12	11
4	Eyes closed	Foam	Vestibular	12	10
5	Eyes closed + dual task	Foam	Vestibular	12	10

Number of participants who were able to complete each condition and included in data analysis for each condition are presented.

examined. Path length is the total distance traveled by the CoP over the course of the trial duration and is approximated by calculating the sum of the distances between consecutive points on the CoP path. SD is the standard deviation of the zero-meaned CoP time series and has been shown to be related to vestibular function (44, 45). Path length and SD were selected as outcome metrics in order to mirror outcome metrics used in past studies that explicitly compared linear and non-linear measures (17). Also, patients with PPPD have previously been found to display increased sway area and increased sway variability (6, 9, 46).

2.2.2. Non-linear postural control measures

RQA analysis was performed using Marwan's RQA Toolbox (v.5.24 (R34) (34). Overall, analysis parameters mirrored those used by Riley and Clark (17), in order to foster comparisons (14), with the exception of modifications to the Theiler Window (as discussed below). The CoP data were first reconstructed in state space using a time delay embedding approach (33) and an iterative process was used to determine each embedding parameter [i.e., embedding dimension (m), time delay (τ), and recurrence threshold (r)]. A false nearest neighbor analysis (47) was performed on each of the CoP signals to determine the embedding dimension (m). An embedding dimension (m) of 5 was found to yield a reconstruction that maximized the available information. The average displacement method (48) yielded a time delay (τ) of 15 samples (i.e., 0.15 s). The recurrence threshold (r) was fixed at 5% and was chosen based upon a prior study of RQA and postural control which identified increased reliability with this approach (16).

In the RP, time-contiguous recurrent points forming line segments parallel to the diagonal identity line indicate repeated time series behavior. In accordance with past studies quantifying changes in regularity of the CoP modulated by changes in available sensory information (17), RQA measures included %REC (the percentage of data points identified as recurrent), %DET (the percentage of recurrent points forming line segments parallel to the diagonal identity line in the recurrence plot), and MAXL (the number of points in the longest diagonal line, excluding the main diagonal). Both %DET and %REC are positively related to the predictability or stability of the signal with higher values indicating more predictability (i.e., determinism) and less randomness in the CoP signal (30, 31, 49). MAXL is a measure of dynamical stability inversely proportional to the largest positive Lyapunov exponent (30, 31); thus, shorter MAXL values indicate less mathematically stable (i.e., more chaotic) signals and longer MAXL values indicate increased mathematical stability. While Shannon entropy of the diagonal line structure has previously been investigated, evidence suggests decreased reliability for noisy signals (50), such as that of CoP time series, thus we chose to exclude Shannon entropy from the analysis.

Use of a Theiler window has also been proposed as a best practice in RQA applications (49). The application of a Theiler window excludes points within a defined boundary surrounding the line of identity (i.e., the main diagonal) and thus eliminates any recurrence that is temporally close. In terms of CoP data, this may preferentially impact larger amplitude motion which is more common in older adults and adults with PPPD (46, 51); inclusion of these large amplitude motions would yield longer diagonal lines and higher determinism values (16, 49). Van den Hoorn et al. (16) proposed using a one second Theiler window for CoP motion, but no studies have empirically determined an appropriate length for implementation. The RQA analyses of the ML CoP in our dataset was repeated for six different Theiler Window lengths (1, 10, 25, 50, 75, and 100 samples). For all five conditions and both participant groups, similar results were seen based on Theiler window alterations. The modulation of non-linear measures on the basis of Theiler window length for Condition 1 is displayed in **Figure 2** and Conditions 2–5 can be found in **Supplementary Figure S1**. For recurrence (%REC), a large and significant increase was noted between 1 and 10 samples ($p < 0.001$); a small but significant decrease ($p < 0.05$) in %REC was noted between 10 and 25 samples, whereas increases beyond 25 did not significantly impact %REC. For determinism, a large and significant decrease was noted with changes in the Theiler Window from 1 to 10 samples ($p < 0.001$); increases beyond 10 samples did not yield a significant change in %DET. Finally, MAXL values significantly decreased as Theiler window increased up to 25 samples, however, values plateaued with additional increases in Theiler window length. As all three metrics (%REC, %DET, and MAXL) plateaued by a Theiler window of 25 samples, a value of 25 was chosen for all remaining analyses.

2.3. Statistical analysis

Linear mixed effect models (*mixed*; Stata v. 17.0, College Station, TX) were used to account for the repeated measures design. In the full model, fixed effects of group (HC, PPPD), balance testing condition, interaction of group by condition, and age were included. Separate mixed effects models were used for each linear (i.e., path length, SD) and non-linear outcome measures (i.e., %DET, %REC, MAXL) which included age, group, and balance test condition. As cognitive tasking was only performed while standing with eyes closed on foam, separate analyses for each group were completed to compare this condition to the analogous balance condition without the dual task (i.e., condition 4). Degrees of freedom in all mixed effect models were adjusted using the Kroger method to account for the small sample and unbalanced design (i.e., not all participants were able to complete all balance conditions) (52). *Post hoc* comparisons were completed using tests of simple effects (i.e., partial F-tests) to determine the effect of group for each condition of balance testing.

3. Results

3.1. Linear measures

3.1.1. Path length of the CoP

All HC participants were able to complete all balance testing conditions. However, not all participants diagnosed with PPPD

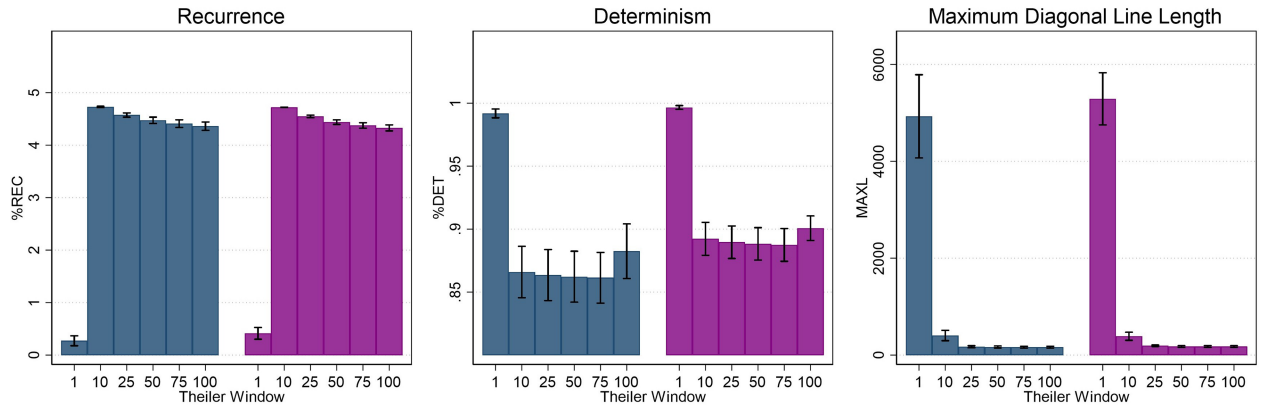

FIGURE 2
Average recurrence (%REC), determinism (%DET), and maximum diagonal line length (MAXL) as a function of theiler window length (in samples) for condition 1 (firm surface, eyes open). Error bars represent ±0.5 SD.

could complete all conditions. One participant with PPPD could not complete conditions 3–5 and an additional participant with PPPD could not complete conditions 4–5 (Table 1).

Overall, a significant effect of age was seen for path length of the ML CoP ($t = 3.46$, $p = 0.002$), while a significant effect of participant group (PPPD vs. HC) was not seen ($F(1,21.04) = 0.82$, $p = 0.376$). A significant impact of condition was seen ($F = (4,86.29) = 21.26$, $p < 0.001$) while a condition by group interaction was not (F (4,86.20) = 1.30, $p = 0.2766$).

Table 2 displays statistical results for all *post hoc* testing of linear measures (i.e., path length, standard deviation) comparing performance between groups for each balance condition. Figure 3 displays path length and standard deviation of the CoP for both participant groups. For each condition, a difference between HC and PPPD was only seen for Condition 4, while all other conditions were equivalent between groups. For both HC and PPPD, no effect of additional cognitive task was seen and both Condition 4 and Condition 5 were equivalent ($p > 0.193$).

TABLE 2 Mean and SD of both CoP path length and standard deviation in the medio-lateral (ML) plane.

	HC		PPPD		*F* ratio	*p*
	Mean	SD	Mean	SD		
ML path length						
Main effect	1,589.6	1,156.7	1,368.6	750.0	0.82	0.3767
Eyes open, firm	738.3	298.2	788.0	371.8	0.07	0.7987
Eyes flosed, firm	1,103.4	584.2	1,068.7	585.6	0.01	0.909
Eyes open, foam	1,346.7	520.7	1,236.2	634.2	0.1	0.7508
Eyes closed, foam	2,555.2	1,204.4	1,841.2	772.3	5.54	**0.0207**
Eyes closed, foam + DT	2,204.6	1,575.6	2,120.4	509.8	0.01	0.9406
ML standard deviation						
Main effect	8.164	3.763	9.501	5.305	1.49	0.2358
Eyes open, firm	5.254	1.100	8.262	5.892	3.72	0.0583
Eyes closed, firm	5.844	1.529	8.166	5.773	1.64	0.2043
Eyes open, foam	7.483	1.577	8.420	4.570	0.34	0.5625
Eyes closed, foam	11.984	3.738	10.762	4.854	0.53	0.4703
Eyes closed, foam + DT	10.256	4.429	12.685	4.655	1.62	0.2067

F ratios and *p* values for *post hoc* testing assessing differences between participant groups (i.e., healthy controls vs. adults with PPPD). Significant differences ($p < 0.05$) are in bold. Degrees of freedom were adjusted using the Kroger method to account for the small sample and unbalanced design. DT, dual task; HC, healthy control; PPPD, persistent postural-perceptual dizziness; SD, standard deviation.

3.1.2. Standard deviation of the CoP

For standard deviation of the ML CoP (SD), an overall effect of age ($t = 1.37$, $p = 0.185$) and participant group ($F(1,21.04) = 1.49$, $p = 0.236$) was not identified. There was an overall effect of condition ($F(4,85.85) = 11.83$, $p < 0.001$) but there was not a significant group by condition interaction ($F(4,85.75) = 1.70$, $p = 0.1578$). Additionally, no significant differences were noted between groups for each balance test condition (Table 2; Figure 3). No impact of dual task was seen as Condition 4 and Condition 5 were equivalent for HC ($p = 0.104$) and patients with PPPD ($p = 0.313$).

3.2. Non-linear measures

3.2.1. Recurrence

Figure 4 depicts non-linear measures for both participant groups. Table 3 contains results of statistical analyses comparing HC and individuals with PPPD for all non-linear measures (%REC, %DET, MAXL) for each test condition. %REC demonstrated a significant main effect of age ($t = 2.36$, $p = 0.029$) and condition (F (4,82.05) = 34.60, $p < 0.001$). While patients with PPPD trended to exhibit overall higher scores, this effect failed to reach statistical significance ($F(1,31.75) = 1.32$, $p = 0.109$) and there was not a group by condition interaction ($F(4,82.06) = 0.58$, $p = 0.6779$). No significant differences between groups were seen for any conditions (Table 3). No impact of dual task was seen and Condition 4 and Condition 5 were equivalent for both HC ($F(1,43.27) = 1.23$, $p = 0.203$) and PPPD ($F(1,38.18) = 1.65$, $p = 0.270$).

3.2.2. Determinism

For %DET, effects of age ($t = -2.22$, $p = 0.038$), condition ($F(4,81.19) = 14.21$, $p < 0.001$) and participant group ($F(1,31.57) = 2.50$, $p = 0.0124$) were identified. For the participant group effect,

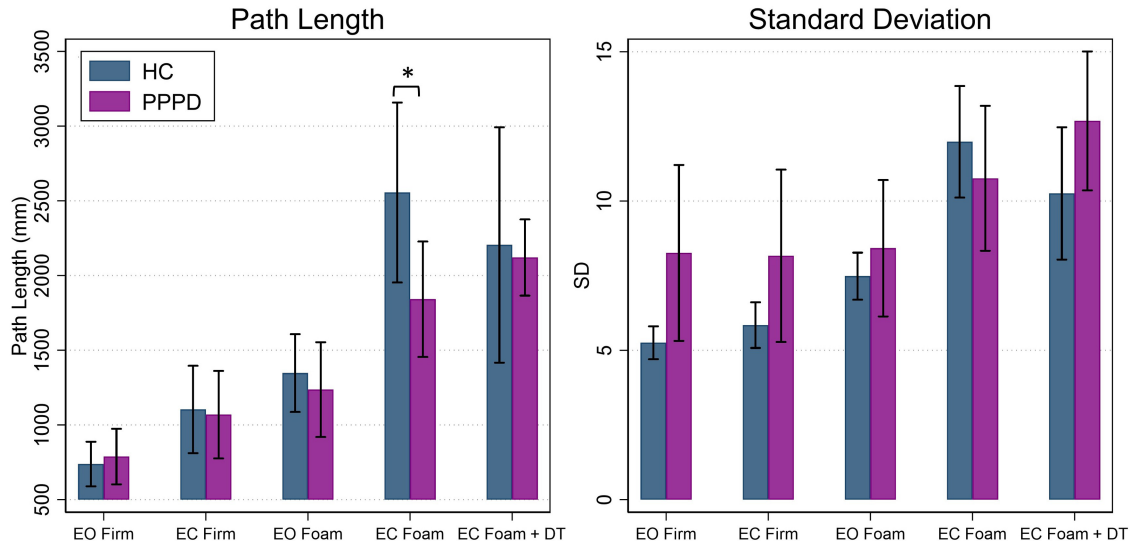

FIGURE 3
Average path length and standard deviation of the CoP in the mediolateral (ML) plane for healthy controls (navy) and patients with PPPD (purple). Significant pairwise comparisons between groups are marked (*$p < 0.05$). Error bars represent ±0.5 SD. EC, eyes closed; EO, eyes open; DT, dual task.

average %DET was higher in patients with PPPD. A group by condition interaction was not identified ($F(4,81.47) = 0.66$, $p = 0.6182$). For %DET, a significant difference between HC and PPPD was noted for firm surfaces (Condition 1 & 2) and for dual task performance (Condition 5). An impact of cognitive dual task was identified for HC as Condition 5 was significantly lower than Condition 4 ($F(1,43.05) = 8.03$, $p = 0.0059$); however, no impact was seen for PPPD as Condition 4 and Condition 5 were equivalent ($F(1,38.73) = 0.78$, $p = 0.3791$).

3.2.3. Maximum diagonal line length

MAXL revealed a significant main effect of group ($F(1,77.08) = 2.82$, $p = 0.0494$) as patients with PPPD displayed higher MAXL values. A significant main effect of age ($t = -1.96$, $p = 0.0648$) was not seen. A main effect of condition ($F(4,81.83) = 5.38$, $p < 0.001$) was identified but a condition by diagnosis interaction was not ($F(4,81.85) = 0.63$, $p = 0.641$). A significant difference between participant groups was not noted for any of the individual balance test conditions (**Table 3**). No impact of dual task was seen as Condition 4 and Condition 5 were equivalent for HC participants ($F(1,43.29) = 2.10$, $p = 0.154$) and patients with PPPD ($F(1, 35.01) = 0.84$, $p = 0.365$).

4. Discussion

During quiet stance balance, patients with PPPD and age-matched HC exhibited differences in non-linear measures of postural sway, as quantified by RQA, while linear measures that characterize the magnitude and variability of postural sway did not show systematic differences. These results suggest that patients with PPPD overall exhibit changes in the temporal structure of ML sway, which were not reflected in traditional linear quantification of the CoP signal. A significant difference between HC and PPPD participants was noted for two of the three RQA metrics examined, including %DET, and MAXL, which quantify the diagonal line structures in the recurrence plot and reflect the regularity and predictability of the CoP time series. While %REC trended to be greater in patients with PPPD, this failed to reach statistical significance ($p = 0.109$), potentially reflecting our small sample size in combination with the data variability. Our interpretation of these findings is that patients with PPPD showed a postural sway pattern that was more predictable (i.e., increased %DET and MAXL) than healthy controls. This suggests that patients with PPPD may employ maladaptive compensatory postural control strategies that yield less flexibility in their postural control system. In contrast, the healthy adult control group displayed a more flexible postural control strategy characterized by a lower %DET and shorter maximum line length.

Differences in the deterministic structure of sway between HC and PPPD was shown to be modulated on the basis of balance test condition. For balance conditions on firm surfaces (i.e., Condition 1 and 2), patients with PPPD exhibited increased %DET (i.e., increased regularity of sway) of the ML CoP time series. This suggests that for the less challenging balance tasks, patients with PPPD adopted a more rigid postural control strategy (53). While MAXL demonstrated an overall effect and was significantly higher in patients with PPPD, differences in performance modulated on the basis of task condition were not identified, in part reflecting the heterogeneity in performance. However, a somewhat similar pattern was identified for MAXL as %DET, as the largest difference between groups was seen for Condition 1, which trended to be statistically significant (0.093). Similarities in both the amount and variability of sway (i.e., linear time domain measures) between the two groups suggests that analyzing the underlying structure of sway, rather than only the amount of sway, may serve as a more sensitive technique for describing the

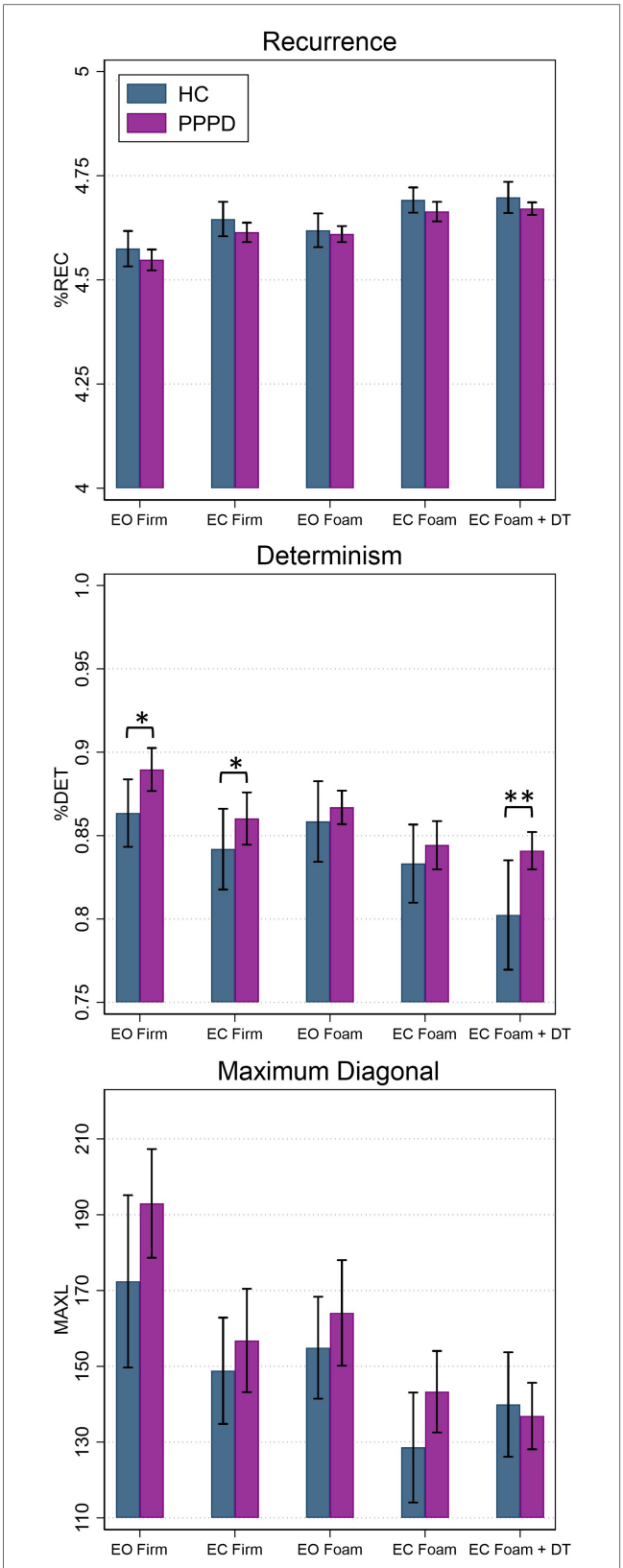

FIGURE 4
Average percent recurrence (%REC), determinism (%DET), and maximum diagonal length (MAXL) in the mediolateral (ML) plane for healthy controls (blue) and patients with PPPD (purple). Significant pairwise comparisons between groups are marked (*$p < 0.05$; **$p < 0.001$). Error bars represent ±0.5 SD. EC, eyes closed; EO, eyes open; DT, dual task.

TABLE 3 Mean and SD of percent recurrence (%REC), percent determinism (%DET), and maximum diagonal line length of the CoP in the medio-lateral (ML) plane.

	HC		PPPD		*F* ratio	*p*
	Mean	SD	Mean	SD		
ML recurrence (%REC)						
Main effect	3.883	1.623	3.797	1.680	1.32	0.109
Eyes open, firm	3.849	1.557	3.754	1.581	0.08	0.776
Eyes closed, firm	3.919	1.633	3.794	1.696	0.06	0.803
Eyes open, foam	3.874	1.596	3.798	1.671	0.01	0.939
Eyes closed, foam	3.959	1.676	3.876	1.709	0.05	0.825
Eyes closed, foam + DT	3.808	1.693	3.765	1.823	2.79	0.68
ML determinism (%DET)						
Main effect	0.8651	0.0726	0.8869	0.0580	2.50	**0.012**
Eyes open, firm	0.8865	0.0589	0.9105	0.0461	5.22	**0.025**
Eyes closed, firm	0.8669	0.0690	0.8866	0.0577	3.91	**0.050**
Eyes open, foam	0.8796	0.0648	0.8907	0.0528	1.86	0.176
Eyes closed, foam	0.8577	0.0707	0.8705	0.0621	2.6	0.111
Eyes closed, foam + DT	0.8320	0.0873	0.8704	0.0641	12.22	0.001
ML max diagonal length						
Main effect	153.16	52.17	160.41	31.48	2.82	**0.049**
Eyes open, firm	171.15	43.79	193.00	28.72	1.72	0.093
Eyes closed, firm	149.69	27.04	156.80	27.28	0.13	0.714
Eyes open, foam	178.23	87.91	164.10	27.86	0.78	0.381
Eyes closed, foam	131.70	29.97	143.30	21.51	0.48	0.492
Eyes closed, foam + DT	133.50	34.41	136.88	17.55	0.63	0.681

F ratios and *p* values for *post hoc* testing assessing differences between participant groups (i.e., healthy controls vs. adults with PPPD). Significant differences ($p < 0.05$) are in bold. Degrees of freedom were adjusted using the Kroger method to account for the small sample and unbalanced design. DT, dual task; HC, healthy control; PPPD, persistent postural-perceptual dizziness; SD, standard deviation.

changes in postural control that accompany the perceptual symptoms of PPPD. Our data provide further support that patients with PPPD display abnormal postural control strategies, and that such abnormalities are related to the nature of the sensory cues available, and potentially the underlying challenge of the balance task.

Previous applications of RQA to quiet stance balance, have shown an *increase* in the regularity of CoP sway with removal of visual cues and reliable proprioceptive cues in healthy control subjects (14, 17, 20, 22, 23); this is opposite to the behavior we observed in our healthy cohort of older adults, as we instead showed a significant *decrease* in the regularity of sway in the same "eyes closed" conditions. Several methodological differences must however be considered when comparing our data to those of the aforementioned studies. The present study used a longer recording time (60 s vs. 20–30 s), included middle aged and older adults rather than young adults, and constrained the base of support to narrow stance as opposed to a "comfortable width". Our decision to use a narrow stance posture for balance was intentional, as we intended to challenge medio-lateral postural control (54, 55) due to the relationships between ML sway and fall history (42). The increased challenge relative to comfortable stance may have resulted in the observed decrease in ML CoP regularity under more challenging eyes closed balance tasks in our sample.

Two previous studies assessed non-linear measures of postural control in phobic postural vertigo (PPV) (8, 36), but our study is the first to date to assess similar measures in adults meeting the recently defined diagnostic criteria for PPPD (1). Despite different methodologies and patient diagnoses, our results similarly suggest an overall increase in the regularity and decrease in the complexity of postural control behaviors, with the repetitive nature of CoP sway in patients with PPPD being characteristic of a more rigid and less adaptable postural control system (53).

In a sample of 12 patients with PPV, Schniepp et al. (56) identified a decrease in the ML and AP sample entropy, indicating increased regularity, and a lower scaling exponent, indicating increased strength of long-range correlations in the CoP signal, during quiet stance with the eyes open and closed, while standing on either firm or foam surfaces. With increasing demands of the balance task (i.e., eyes closed on foam), PPV patients showed normalization of entropy values, and a similar level of complexity in the CoP signal to healthy controls (36).

Similarly, in patietns with PPV, Wuehr et al. (8) identified a higher scaling exponent and higher short-term diffusion coefficients during eyes open and eyes closed stance on a firm surface, which were less prominent during the more challenging balance task (i.e., when standing eyes closed). These results are in line with the hypothesis that patients with PPV use a postural control strategy that is typically employed only for demanding balance tasks. Overall, these results are consistent with our identified increases in %DET and MAXL across condition for patients with PPPD. As well, we found a significantly higher recurrence rate for condition 1 (eyes open, firm) which normalized with increases in task difficulty, suggesting that patients with PPPD exhibit changes in the dynamic structure of postural control even for less challenging balance tasks.

In contrast to some past findings (6, 8, 9, 12, 46), we failed to identify increases in traditional, linear measures of balance performance (path length and SD) during quiet stance in patients with PPPD. This may reflect our smaller sample size ($n = 12$) or potential subgroups in patients with PPPD. Past studies that have focused upon quantifying the amount of sway, as quantified by root mean square displacement (RMSD), in PPV relative to healthy controls, have shown an overall increase in sway during assessments of balance performed with the eyes open/eyes closed on a firm surface (11) and eyes open/eyes closed in normal or tandem stance on a firm, as well as foam surface (12). However, patients with PPV or PPPD have also been found to demonstrate improved balance performance (i.e., decreases in RMS distance or decreases in degree of trunk sway) relative to healthy controls for more difficult balance tasks (12, 56). We did not explicitly compare postural sway between each participant group for each balance test condition, however, both HC and PPPD exhibited an increase in sway (i.e., greater path length) as task difficulty increased. HC participants also displayed a characteristic increase in the variability of sway (i.e., increased SD) which mirrored the increases in path length. In patients with PPPD, the SD was instead similar for Condition 1 (eyes open/firm), Condition 2 (eyes closed/firm), and Condition 3 (eyes open/foam), despite coexistent increases in the amount of sway. These data suggest that patients with PPPD may display increased variability in the CoP for both "easy", as well as "challenging" balance tasks. Increases in sway, using the sensory organization test (SOT), have previously been reported in patients with PPPD (6, 46). However, the predominant differences observed in these studies between PPPD and asymptomatic controls was found in conditions 2–6, while sway assessed with eyes open on a fixed surface was not significantly impacted in patients with PPPD (6, 46). Of note, traditional posturography manipulates availability of proprioceptive and visual cues through either sway referencing (i.e., moving the visual scene or platform in concert with an estimate of body sway) of the support surface and visual surround in the anterior-posterior (AP) plane, or through the removal of visual inputs (eyes closed stance) (58). The use of a sway referenced visual scene, as opposed to the removal of visual inputs, allows for the characterization of an individual's dependence upon visual cues, as "visually dependent" persons will continue to utilize the erroneous cues despite increases in postural sway (59, 60). As patients with PPPD have been reported to display visual dependency (61, 62), the use of unreliable visual feedback, rather than the complete removal of visual cues as was done in the present study, may have better captured the postural control strategies of patients with PPPD.

Past studies have reported changes in postural sway patterns which may vary across PPPD or CSD patients (56, 63). Potential subtypes of PPPD have been proposed on the basis of symptomology (64) with a portion of patients displaying more pronounced balance impairments. In patients with PPPD, a subset display both dizziness and impaired balance performance during standardized gait and stance tasks while others display dizziness only (56). Similarly, in patients with CSD, a subset of patients display unremarkable or narrower sway paths, which is not captured on standard scoring of the SOT, while others may display overtly abnormal postural sway patterns (63). Use of RQA or other non-linear analysis of postural sway patterns may provide insights into these potential subgroups of PPPD patients.

In healthy adults, the addition of a cognitive dual task challenge to a balance assessment has been consistently shown to impact the temporal structure of CoP, leading to a decrease in the regularity (i.e., decreased determinism and recurrence) of sway (23, 26, 65). However, these modulations were shown to be dependent on task difficulty, as in general, larger decreases were noted for the more challenging dual task conditions (23, 65). In our cohort of healthy adults, we similarly noted a decrease in MAXL and %DET in the dual task condition, without a concurrent change in the amount of sway or in the variability of sway. However, in PPPD, a significant impact of dual task was only seen for %DET and was not observed for any of the other linear or non-linear metrics. Past reports suggested that in PPV, the addition of a dual task challenge during stance on a firm surface, with either the eyes open or closed, led to improvements in RMSD and SDA metrics (i.e., short term diffusion and critical time interval) yielding a normalization of performance relative to healthy adults (11). However, similar findings were not identified in our current investigation that included a dual task challenge during the "eyes

closed, on foam" condition. In patients with PPPD, no significant differences were noted for any linear or non-linear metrics when comparing performance in the dual task condition to performance during the same task without the added cognitive load. Our methodology did however differ from the past study by Wuehr et al. (11) as we employed a cognitive dual task challenge during a condition which was more challenging and where balance performance was expected to rely more heavily upon vestibular cues (i.e., secondary to the removal of reliable visual and proprioceptive cues). A different cognitive task was also used in the previous study (i.e., naming from a category) than the current investigation (i.e., counting backwards by threes). Future investigations should further investigate the impact of a distracting cognitive task on balance performance in PPPD by administering dual task challenges in various balance conditions (e.g., eyes open, eyes closed, firm, and foam surfaces) in order to determine the potential interaction between cognitive demand and the availability of sensory information.

Although our conclusions are straight forward, our analysis and interpretation is limited by a somewhat small sample size. We included a large age range within both groups. While we age-matched between groups and adjusted for age within our statistical modeling, there may have been an impact of age that we were unable to identify. The distribution of males and females was not equal, but both the sex and age distributions of patients with PPPD included in this investigation are in line with other reports of PPPD patient demographics (4, 66, 67). However, PPPD with coexisting vestibular migraine represented a slightly higher proportion (~50%) of patients in comparison to other studies of PPPD patient population (~30%) (4). As our primary recruitment source was an oto-neurology practice, this likely reflects the differences in patient populations between this specialty clinic and other tertiary care centers. As well, the aim of this study was to investigate the utility of RQA in order to inform future efforts investigating changes in the dynamics of the temporal structure of CoP sway in patients with PPPD. We were able to use RQA to identify differences in dynamics of postural control between a group of patients with PPPD in comparison to a group of age-matched healthy controls. The differences suggest that postural sway complexity and regularity is modulated in PPPD and that patients with PPPD may exhibit maladaptive postural control behaviors even during non-challenging balance demands. These group differences were not noted for traditional linear measures, suggesting that RQA and other metrics may provide unique insights into postural control mechanisms and could potentially serve as a biomarker for diagnosis.

Future efforts should quantify if changes in postural control strategies as quantified by RQA may occur in response to therapeutical interventions (e.g., medications, vestibular rehabilitation therapy). However, three patients were currently enrolled in vestibular rehabilitation, but it is unknown whether or not other participants had completed therapy at outside practices which may have impacted balance performance. All PPPD participants still reported actively experiencing PPPD symptoms, but future studies should examine rehabilitation as a potential influence. As well, future endeavors should enroll a larger sample of participants to provide statistical power to expand the focus of the present study, including separate analyses to investigate the effect of PPPD on other dimensions of postural sway. As anxiety and neuroticism have been proposed to play an role in the progression of PPPD symptoms and the processing of visual motion stimuli (10, 68), future investigations should also assess the correlative relationship between RQA metrics and self-report measures of symptoms, including state and trait anxiety.

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 Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MK and AW conceptualized the experiment. MK collected the data. MK analyzed the data and wrote the initial draft of the manuscript. AW and DM made edits and substantive contributions to 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/fresc.2023.1142018/full#supplementary-material

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Surveying physical therapists' understanding of benign paroxysmal positional vertigo

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Introduction: Benign paroxysmal positional vertigo (BPPV) is a common condition with disabling symptoms that is diagnosed and effectively treated at the bedside. Our encounter with patients experiencing prolonged BPPV who may not have received appropriate physical therapy prompted us to explore barriers to the diagnosis and treatment for BPPV among physical therapists, which has not been extensively investigated. We hypothesize that a potential barrier may be a lack of understanding of subtle symptoms of BPPV that deviate from the classical presentation. The gold standard for diagnosing definite BPPV is subjective dizziness or vertigo with nystagmus in response to positional testing. There are variants of BPPV including subjective BPPV (subjective dizziness or vertigo without nystagmus) and vestibular agnosia (nystagmus without subjective dizziness or vertigo) that do not meet the diagnostic criteria for definite BPPV but are equally responsive to the same repositioning maneuvers. The purpose of this project was to survey physical therapists for their understanding of BPPV including subjective BPPV and vestibular agnosia.

Methods: A panel of experts created a 16-question survey, designed for physical therapists, with three categories: (1), inquiring if they treat persons with BPPV, (2) three clinical vignettes for definite BPPV, subjective BPPV, and BPPV with vestibular agnosia, and (3) demographic information. Data collection occurred at two large physical therapy meetings, one of which was a national professional meeting and the other was a professional continuing medical education course geared towards advancing vestibular rehabilitation skills.

Results: There were 426 people who completed the survey, 364 of whom treat BPPV in their practice. In the first clinical vignette created to assess the respondents' understanding of definite BPPV, 229 (62%) of respondents would always assess a patient for BPPV based on complaints of a "room spinning" vertigo from head movement. When asked if the complaint was lingering "lightheadedness or feelings of imbalance" from head movement, only 158 (43%) reported they would perform positional testing to reassess. In the BPPV variant vignettes, 187 (51%) identified the patient with subjective BPPV as having BPPV and 305 (85%) identified the patient with vestibular agnosia as having BPPV.

Discussion: The results of this survey demonstrate gaps in knowledge regarding BPPV across practice settings and experience, with opportunities to bridge these gaps to improve treatment for BPPV.

KEYWORDS

BPPV, subjective BPPV, vestibular agnosia, vestibular rehabilitation, physical therapy (Canalith-repositioning maneuver)

Introduction

Benign Paroxysmal Positional Vertigo (BPPV) has a lifetime prevalence of 2.4% and is the most common diagnosis for recurrent dizziness or vertigo (1). BPPV is a mechanical inner ear disorder caused by displaced otoconia in the semicircular canal(s) (2). Classic symptoms reported with BPPV include vertigo—a room-spinning sensation of dizziness- with a change in head position often with associated gait instability and nausea (3). Transient subjective dizziness or vertigo with nystagmus in the plane of the involved semicircular canals from positional testing are diagnostic of definite BPPV (2). If left untreated, BPPV is correlated with a decrease in activities of daily living scores, an increased rate of falling, and increased rates of depression (3–6). According to the American Academy of Otolaryngology-Head and Neck Surgery (AAHN) 2018 Clinical Practice Guidelines and recommendations by the American Academy of Neurology, positional tests are the gold standard for diagnosing BPPV, with strong recommendations for treating BPPV with canalith repositioning maneuvers (3, 7).

The criteria for definite BPPV include transient subjective positional dizziness or vertigo and positional nystagmus corresponding to the plane of the semicircular canal that is tested. There are two alternate variants of BPPV that do not meet the criteria for definite BPPV: subjective BPPV and BPPV with vestibular agnosia (8, 9). Patients with subjective BPPV report dizziness or vertigo in response to positional testing but do not have the corresponding positional nystagmus (8, 10–17). Patients with vestibular agnosia have the correct nystagmus pattern in the positional test but do not report any symptoms of dizziness (9, 18, 19).

Although other healthcare providers including neurologists, otolaryngologists, primary care physicians, and audiologists receive training in the diagnosis and management of BPPV, patients with BPPV are routinely referred for physical therapy. Diagnosing and treating BPPV is within the Physical Therapy Guide To Practice, which was compiled by the American Physical Therapy Association as a resource describing physical therapy practice and is used as the guideline for developing physical therapy curriculum (20). Diagnosing and management of BPPV is a skill all physical therapists are exposed to in their entry level education. Yet, we have encountered patients who suffered prolonged symptoms from BPPV despite physical therapy. We hypothesized that one of the potential barriers may be limited understanding of subtle manifestations of BPPV. The aim of this study was to test our hypothesis by assessing the current understanding within the physical therapy community of definite BPPV, subjective BPPV, and BPPV with vestibular agnosia. We also examined if the survey responses correlated with practice settings or clinical experience.

Methods

A panel of experts developed the survey with Qualtrics (Qualtrics, Provo, UT) to explore the familiarity of physical therapists with BPPV and its variants. The panel included four members in academic tertiary medical centers in metropolitan areas with a large referral base: two physical therapists, a vestibular neurologist, and a research assistant. The University of Pittsburgh Biomedical IRB approved the study (STUDY23020028). All respondents provided consent to complete the survey (**Appendix**).

There were three sections with a total of 16 questions. The first section asked if the physical therapist treats patients with BPPV and, if they do not, to whom they would refer the patient. The second section had three short case vignettes on definite BPPV, subjective BPPV, and BPPV with vestibular agnosia. The third section included demographic information. Questions in the second section on clinical vignettes probed how likely the therapists were to perform the correct positional testing on a 5-point Likert scale: never, sometimes, about half the time, most of the time, and always. The triggers in the vignettes involved head movement in the vertical plane to implicate the posterior semicircular canals, for which the Dix-Hallpike positional testing should be performed. For the clinical vignettes addressing the subtle presentations the respondents answered the clinical questions with what diagnosis they thought the patient presented with: Functional Dizziness (e.g., Persistent Postural Perceptual Dizziness, Mal de Debarquement Syndrome), vestibular migraine, BPPV, or unable to make a physical therapy diagnosis. If the respondent answered, "I am unable to make a physical therapy diagnosis", they then answered a series of follow-up questions including "If you are unable to make a physical therapy diagnosis, what would you do?" with answers including recommend Meclizine/Dramamine, perform repositioning exercise as dictated by the involved canal, or refer out to another provider. Any respondent who answered "refer out to another provider" then selected which specialty they would refer the patient to.

The final section of the survey included demographic information, including current practice setting and length of time working as a physical therapist. Respondents completed the survey via QR code at two large physical therapy conferences with physical therapists and physical therapy students from across the United States and from varying practice settings.

Descriptive statistics were completed on the entire sample. Sub-analyses were conducted based on years of practice as a physical therapist and practice area. *T*-tests were calculated to assess differences between physical therapists with ≤11 years of experience versus those with >11 years of experience. Kruskal-Wallis test statistics were calculated to assess for differences in response rate based on clinical practice settings. All statistical analyses were completed with SPSS (Version 27.0), with $\alpha = 0.05$ used for the level of significance.

Results

There were 426 people who completed the survey. **Table 1** demonstrates the areas of practice for those who completed the survey. The average number of years for those who do not treat people with BPPV was 7 years and those who treat people with BPPV was 11 years. For those that treat BPPV in their practice, there were 364 clinicians with a mean of 11 years of practice experience. Respondents who treat BPPV

TABLE 1 Demographics of the physical therapists and physical therapist students who completed the BPPV survey.

Physical therapists and physical therapist students who completed the survey	Frequency (percentage) 426	
Practice setting	Percentage of the sample who do not treat patients with BPPV ($n = 62$)	Percentage of the sample who treat persons with BPPV ($n = 364$)
Academic/Research	8 (13%)	10 (3%)
Acute care	5 (9%)	50 (14%)
Home health	6 (10%)	7 (2%)
Inpatient rehabilitation	4 (5%)	39 (10%)
Oncology	1 (1%)	0 (0%)
Outpatient neurologic/ vestibular	1 (1%)	152 (42%)
Outpatient orthopedics	3 (5%)	74 (21%)
Pediatrics	0 (0%)	0 (0%)
Sports	0 (0%)	3 (1%)
Skilled nursing facility	1 (1%)	1 (1%)
Women's health	0 (0%)	0 (0%)
In school	33 (53%)	24 (6%)

came from clinical practice areas including academics, acute care, home health, inpatient rehabilitation, outpatient neurological/vestibular, outpatient orthopedic, skilled nursing, sports, and students within the survey respondents. In the group of respondents who do not treat BPPV ($n = 60$), see Table 1, there was a similar range of practice settings represented and there was also one respondent who works in an oncology setting.

The first clinical vignette investigated the respondents' understanding of definite BPPV and their likelihood to perform positional testing to correctly diagnose the condition. Seen in Figure 1, 229 (62%) of respondents would always perform positional testing, with 111 (31%) who would perform positional testing most of the time. The respondents were asked if they would reassess the same patient for BPPV at a return visit if the symptoms reported included "off balance and non-spinning dizziness" in response to the same positional triggers, which would suggest subjective BPPV with residual debris (Figure 2). Only 158 (43%) of the respondents said they would always reassess the above patient for BPPV, and 100 (27%) responded that they would reassess most of the time. While there was a decrease in the number of responses who would always screen this patient for BPPV, it was not significant ($t = 2.13$, $p = 0.49$, $d = 0.15$). When the respondents' answers were analyzed broken down by years of experience, there was not a significant difference in responses between groups ($t = 1.56$, $p = 0.19$). Figure 3 shows the responses to the first clinical vignette based on practice area for those with greater than ten respondents. There was not a significant difference in responses based on clinical practice [$H(5) = 5.1$, $p = 0.2$]. The trend appeared that those in academic/research (80%) and outpatient vestibular/neurological clinics (77%) had the highest rate of always assessing for BPPV. When reassessing the same patient for BPPV, there was a reduction in the number of respondents always screening for BPPV and an increase across all practice areas of respondents never screening for BPPV (Figure 4).

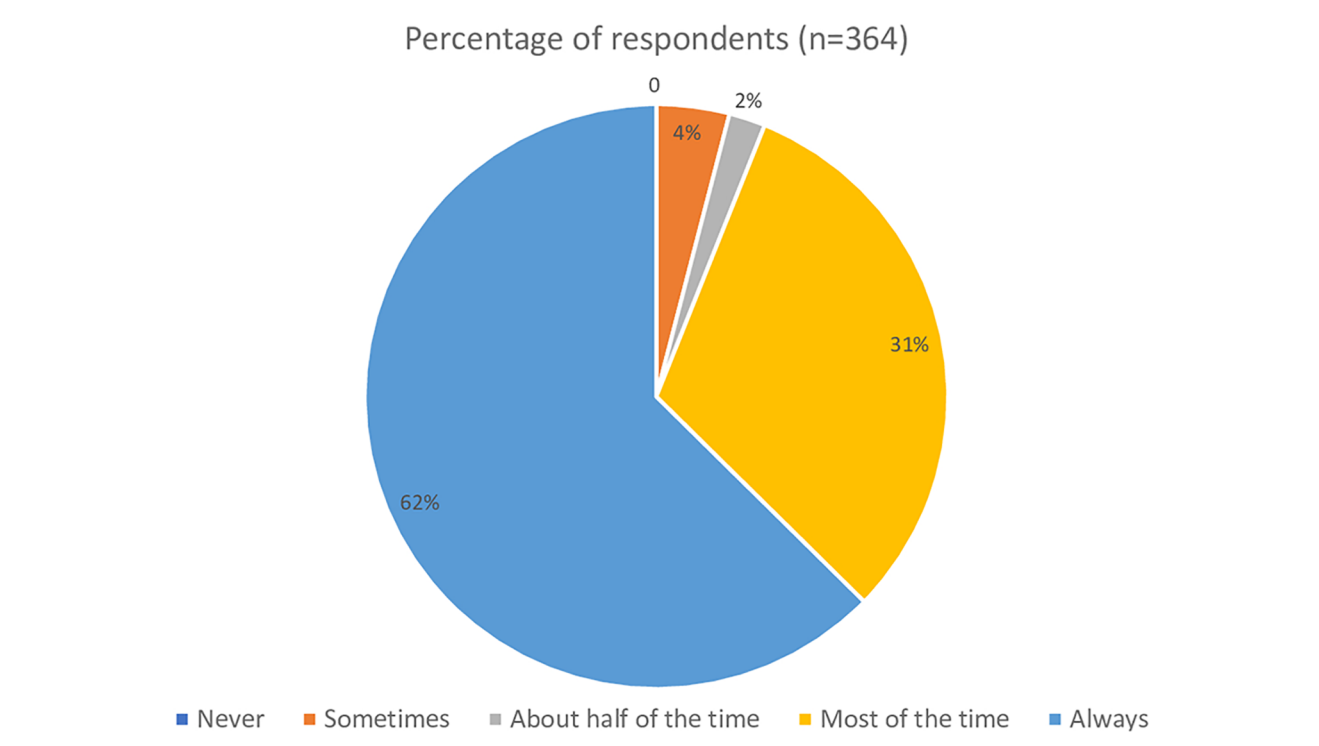

FIGURE 1
Responses from the first clinical vignette "A 65-year-old male presents to your clinic with complaints of brief spinning dizzy spells from getting in and out of bed, looking up and down, walking, and physical activities in general. Would you assess this patient using positional testing (such as the Dix-Hallpike)?".

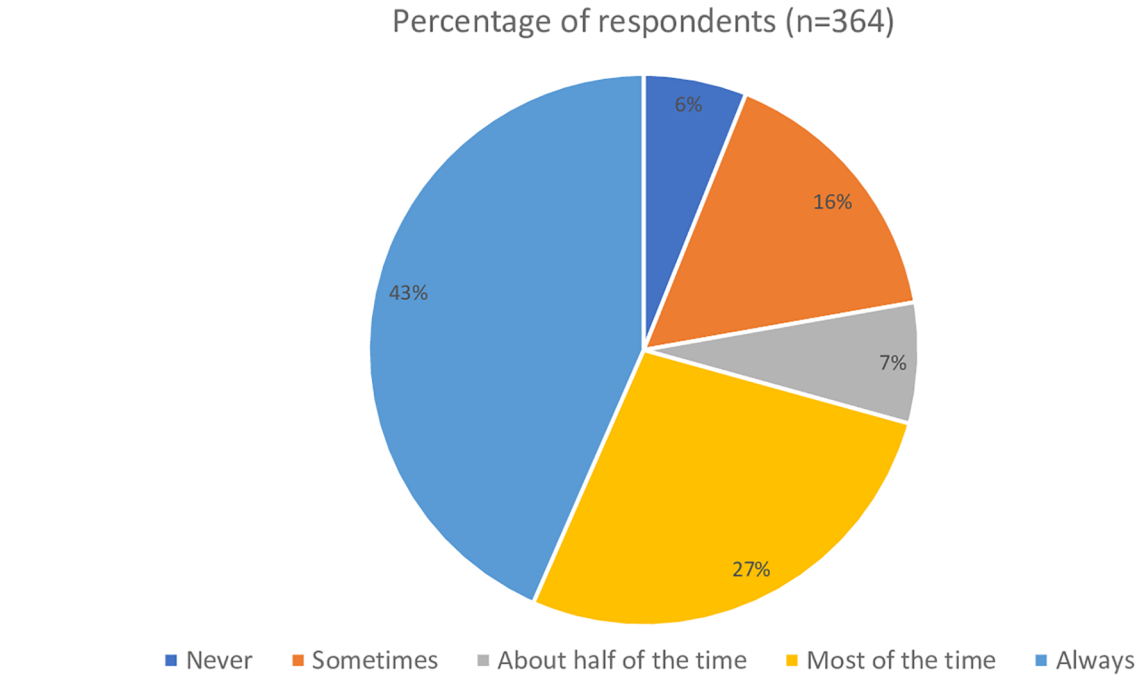

FIGURE 2
Responses from the follow up question to the first clinical vignette "When the patient returns the next visit following treatment for BPPV, he continues to complain of being off balance with slight non-spinning light-headedness in response to getting in and out of bed, looking up and down, walking, and physical activities in general. Would you reassess this patient using positional testing (such as the Dix-Hallpike)?".

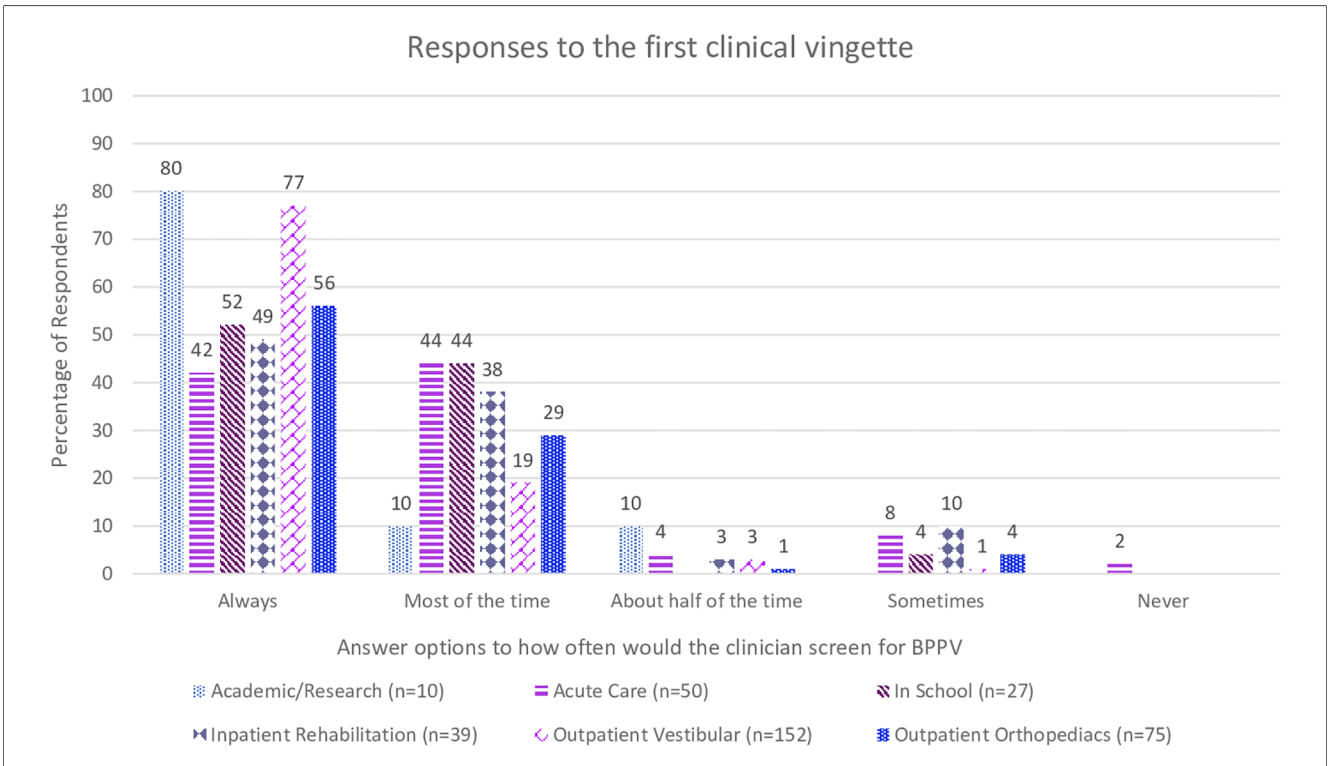

FIGURE 3
Responses from the first clinical vignette "A 65-year-old male presents to your clinic with complaints of brief spinning dizzy spells from getting in and out of bed, looking up and down, walking, and physical activities in general. Would you assess this patient using positional testing (such as the Dix-Hallpike)?" based on practice area of the respondent.

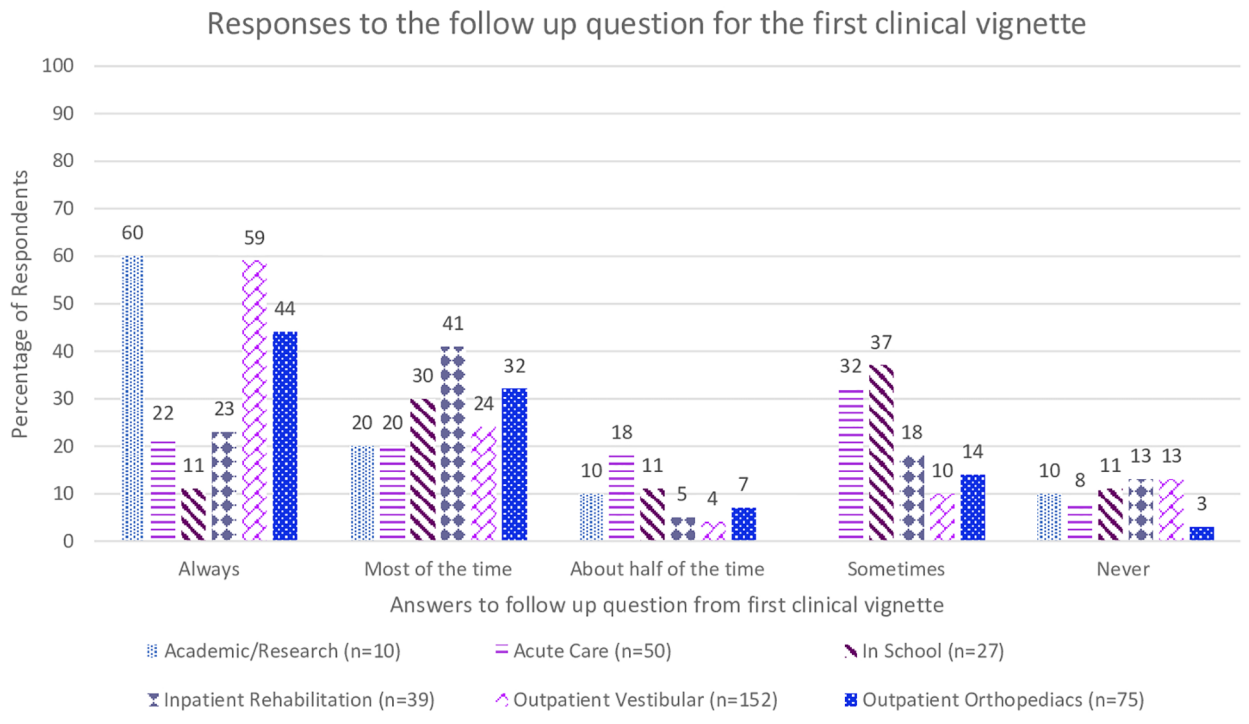

FIGURE 4
Responses from the follow up question to the first clinical vignette "When the patient returns the next visit following treatment for BPPV, he continues to complain of being off balance with slight non-spinning light-headedness in response to getting in and out of bed, looking up and down, walking, and physical activities in general. Would you reassess this patient using positional testing (such as the Dix-Hallpike)?" based on practice area of the respondent.

The second clinical vignette asked the respondents for their diagnosis of a patient with subjective dizziness without nystagmus in response to positional testing. Overall, 187 (51%) respondents selected subjective BPPV, 111 (31%) were unable to make a diagnosis, and the remainder chose vestibular migraine and functional dizziness (Figure 5). In the 111 who could not make a PT diagnosis, 87 would refer this patient to another provider. There was not a significant difference in response rates based on years of experience ($t = 1.39$, $p = 0.13$). Based on practice setting, 30% of those in an academic/research setting, 44% of acute care, 42% of those in home health, 31% of those in school, 61% of those in outpatient neurologic/vestibular, 59% of those in outpatient orthopedic, and 67% of those in sports settings diagnosed the patient with BPPV. There was not a significant difference in response rates based on clinical practice setting [$H(5) = 4.36$, $p = 0.36$]. There were 40% of those in academic/research, 36% in acute care, 42% of those in home health, 13% in school, 41% of those inpatient rehabilitation, 29% in outpatient neurologic/vestibular, and 23% of those in outpatient orthopedic settings were not able to make a physical therapy diagnosis. The providers they would refer to include Otolaryngology, Neurology, Primary Care, Vestibular Physical Therapy, and Audiology.

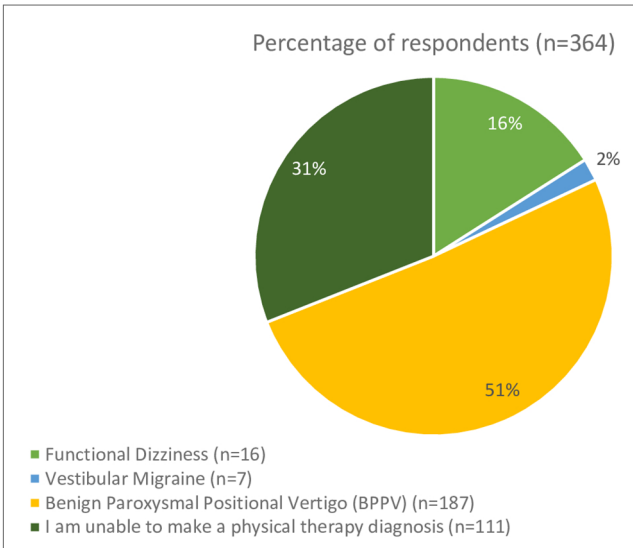

FIGURE 5
Responses from the clinical question "A patient reports spinning vertigo that lasts 10 s without nystagmus in the Dix-Hallpike position. What is your diagnosis?".

The third clinical vignette focused on BPPV with vestibular agnosia. 305 (85%) respondents correctly diagnosed this vignette as having BPPV, while 9 (2%) stated it was functional dizziness, 5 (1%) stated it was vestibular migraine, 45 (12%) could not make a PT diagnosis. Figure 6 illustrates the preferred diagnosis of the third vignette by clinical practice setting. There was not a significant difference in responses based on years of experience ($t = 0.77$, $p = 0.25$). There was not a significant difference in response rates based on clinical practice setting [$H(5) = 1.23$, $p = .87$]. Of the 45 respondents who could not make a PT diagnosis, 42 would refer them to another provider. These providers included Otolaryngology, Neurology, Primary Care, and Vestibular Physical Therapy.

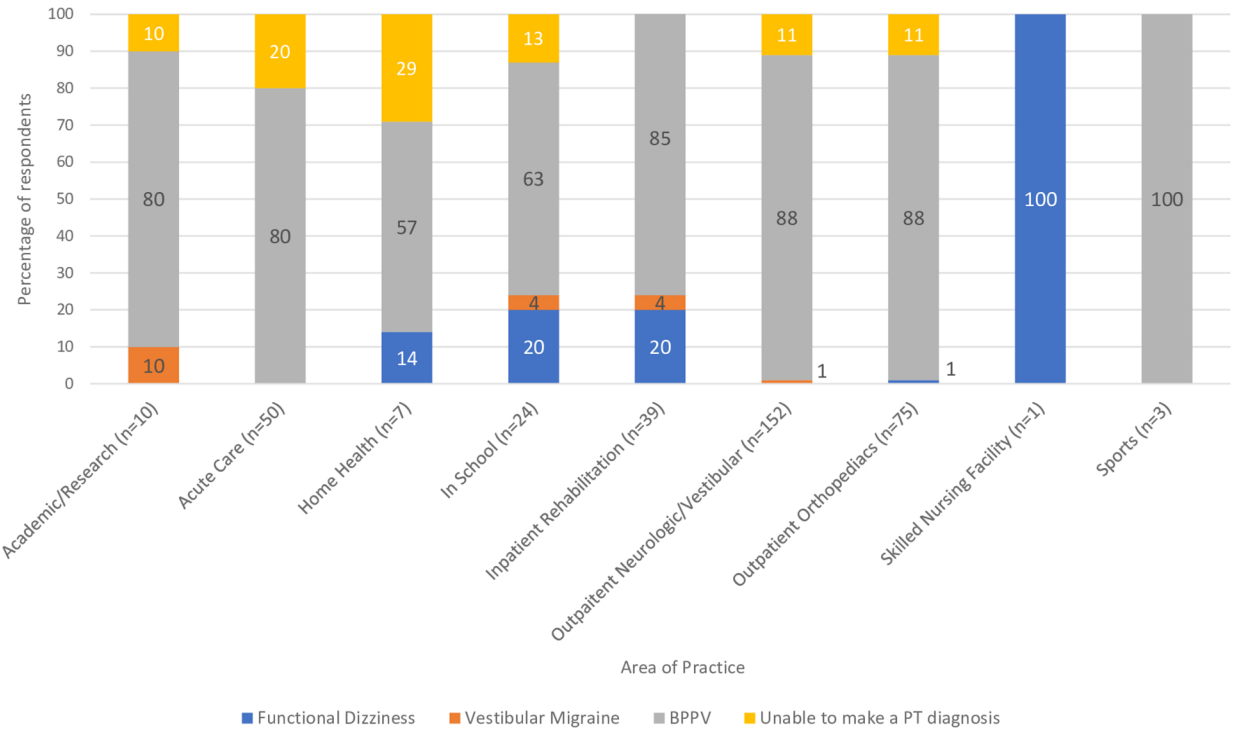

FIGURE 6
Responses from the clinical question, based on practice setting, "If you observe torsional upbeating nystagmus that fatigues in response to Dix-Hallpike head hanging, but they report no spinning. What is your diagnosis?".

Discussion

BPPV is the most common cause of recurrent dizziness and vertigo. There is often delay in the diagnosis and treatment for BPPV with documented underutilization of positional testing by physicians in primary care and emergency departments (21). Since dizzy patients are commonly referred for physical therapy, we aim to investigate the level of familiarity with BPPV among physical therapists, which has not been studied previously. We hypothesized that there may be limited familiarity with variants of BPPV with subtle manifestations. We further hypothesized that clinical experience may have a positive correlation with knowledge regarding BPPV.

The importance of a high clinical suspicion for BPPV is that positional testing specifically Dix-Hallpike positioning for posterior canal involvement would dictate treatment. Subjective BPPV and BPPV with vestibular agnosia are two variants that do not fully meet the diagnostic criteria for definite BPPV. In a cohort of 204 patients with BPPV, 64 had subjective BPPV, and there was no significant difference in treatment response between those with classic BPPV and those with subjective BPPV (8). Jung and Kim treated 134 persons with BPPV, 33 of whom had subjective BPPV (22); they found no significant difference in recovery rates between those with or without positional nystagmus (3, 22). Uz et al. found that older adults with subjective BPPV had improved quality of life after the Epley maneuver (17). If recognized and correctly diagnosed, BPPV along with its variants is effectively treated by repositioning maneuvers that physical therapists are trained to perform.

In the first part of the first clinical vignette, which presented a definite BPPV case, although 62% of respondents would always assess the patient for BPPV, there is still 38% that would not always assess a person with such classic presentation for BPPV. The second part of the first vignette is a common presentation of residual BPPV that is incompletely treated, in that the patient no longer has positional nystagmus on exam yet continues to be bothered by the same positional triggers. The correct response should be to have a high clinical suspicion for BPPV and to always perform positional testing for a treatable condition. Yet the survey showed further decrease in the number of respondents who would always assess the patient for BPPV. The change in responses is an almost 20% reduction in those who would always evaluate this patient for BPPV, while not significant this trend is still concerning as these patients will not receive appropriate treatment. Furthermore, if physical therapists could not recognize incompletely treated BPPV, it would be even less likely that they would recognize subjective BPPV, as presented in the second vignette. The AAHN Clinical Practice Guidelines recommend testing for BPPV in those who "report a history of vertigo provoked by changes in head position relative to gravity" (3). While "room spinning" dizziness is considered the hallmark symptom of posterior canal BPPV, others have reported persons with BPPV endorsing light-headedness, dizziness, sinking, floating, nausea, or feeling off balance (1, 23, 24). BPPV is a vestibular abnormality and can result in an increased risk of falling and impairments in activities of daily

living (3–5). Adults over 40 with vestibular dysfunction have a 12-fold increase in the odds of falling (25). BPPV has been correlated to falls (4, 6, 19).

The second clinical vignette sought to capture clinicians' understanding of subjective BPPV. From the current study, only 51% of respondents could identify subjective BPPV, and 31% could not make the diagnosis. The lack of nystagmus in positional testing in people with subjective BPPV likely contributes to the low diagnosis rate. It is hypothesized that subjective BPPV represents a subthreshold amount of dislodged debris that is insufficient to drive vestibular nystagmus but enough to cause subjective dizziness (2, 15, 26).

The third vignette focused on BPPV with vestibular agnosia. Vestibular agnosia was first described in 2021 by Calzolari et al. and is defined as "a loss of vertigo sensation in patients with preserved inner ear functioning" (9). This phenomenon has been primarily identified in a traumatic brain injury population but has also been reported in older adults (9, 19, 27). A person with vestibular agnosia would have positional nystagmus in the positional tests but will not report vertigo. In the current survey, the third clinical vignette sought to capture the clinician's understanding of BPPV with vestibular agnosia. Of the respondents, 85% identified the scenario as BPPV, with only 12% unable to make a diagnosis. The percentage of respondents who correctly identified this vignette as BPPV (84%) is higher than those who could identify subjective BPPV (51%). The presence of an objective sign with positional nystagmus corresponding to the stimulated semicircular canal in BPPV with vestibular agnosia likely contributes to the consideration of BPPV. A potential explanation is that subjective BPPV and BPPV with vestibular agnosia are relatively recent designations that have not been disseminated.

Several direct and indirect costs occur to the patient by not correctly identifying subjective BPPV. The US's average cost of diagnosing and treating BPPV is $2 billion annually, secondary to unnecessary imaging and referrals to specialists (3). A systematic review by Kovacs et al. found that in persons with vestibular vertigo, 61.3% of them had more than two specialist consultations before receiving a diagnosis (28). Up to 50% of persons with vertigo received a CT scan, and 18.6% received an MRI (28). The indirect costs of untreated vertigo include 63.3% of persons with vertigo losing working days related to their symptoms and 5.7% leaving the workforce because of their symptoms (29).

According to the US Bureau of Labor Statistics, there are approximately 225,350 physical therapists in the United States (30). The respondents to our survey represent a small sample of the total physical therapists in the country. Due to the continuing education nature of the meetings where the survey occurred, this may skew the sample to therapists more interested in advancing their knowledge and skill set that the true understanding of the variants of BPPV would most likely be lower than reported in this survey. We had hypothesized that those working in outpatient neurological/vestibular clinics with more years of experience would have higher rates of always screening for BPPV and recognizing the variants of BPPV. The results from our survey showed that experience did not correlate with the correct responses.

Conclusion

There is ongoing effort to improve the recognition and treatment of BPPV by front-line practitioners in primary care and emergency departments (26, 31). Our study only analyzed physical therapists' understanding of definite BPPV and the relatively recently described variants with more subtle presentation to demonstrate that there is a gap in knowledge regarding BPPV. Potential methods of improving recognition of BPPV would be increasing the training for BPPV diagnosis and management in the physical therapy curriculum and increasing access to vestibular specific continuing education courses post licensure across clinical settings and experience. We also propose greater collaboration and communication between the referring physician and physical therapist to improve the care of patients with BPPV and other vestibular disorders.

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 University of Pittsburgh Biomedical IRB. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RGH, RH, JJ, and SW all contributed to the conceptualization of the project and creation of the survey. RH and SW completed data collection. RH was responsible for data analysis and drafting the manuscript. RH, JJ, and SW all edited the manuscript. All authors contributed to the article and approved the submitted version.

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/fresc.2023.1228453/full#supplementary-material

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When, where, and why should we look for vestibular dysfunction in people with diabetes mellitus?

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The biochemistry of diabetes mellitus results in multi-system tissue compromise that reduces functional mobility and interferes with disease management. Sensory system compromise, such as peripheral neuropathy and retinopathy, are specific examples of tissue compromise detrimental to functional mobility. There is lack of clarity regarding if, when, and where parallel changes in the peripheral vestibular system, an additional essential sensory system for functional mobility, occur as a result of diabetes. Given the systemic nature of diabetes and the plasticity of the vestibular system, there is even less clarity regarding if potential vestibular system changes impact functional mobility in a meaningful fashion. This commentary will provide insight as to when we should employ diagnostic vestibular function tests in people with diabetes, where in the periphery we should look, and why testing may or may not matter. The commentary concludes with recommendations for future research and clinical care.

KEYWORDS

vestibular, diabetes mellitus, utricle, saccule, semicircular canal, balance

1 Introduction

Diabetes mellitus (DM) is a worldwide health concern. Approximately 800 billion in annual medical costs are attributed to the care of over 400 million people with DM worldwide (1). For these individuals, abnormal glycemic control propagates a cascade of biochemical processes that lead to multi-system tissue compromise. In compounding fashion, cardiovascular, renal, orthopaedic, and sensory changes combine to reduce health, quality of life, and the level of functional mobility and physical activity needed to regulate blood glucose and mitigate further tissue compromise (1–5).

Well-characterized sensory system pathology, such as peripheral neuropathy and retinopathy, are particularly prevalent and detrimental to functional mobility in people with DM (2). More specifically, the prevalence of peripheral neuropathy and/or retinopathy may be higher than 70% and is associated with reduced balance and elevated fall risk (2, 3, 6–10). With this impetus and coalescent research, indications and methods for screening peripheral neuropathy and retinopathy have been developed and translated into standard clinical practice (11). However, research exploring if the same biochemistry propagating peripheral neuropathy and retinopathy also affects the third essential sensory system for balance and mobility, the vestibular system, is much less cohesive. Lack of cohesion in the field has precluded clinical recommendations for

vestibular screening and rehabilitation approaches, and persists despite an increasingly concerted effort (Figure 1). Nevertheless, interest in this topic continues given histopathologic evidence, the importance of vestibular system signaling and rectification of altered sensory inputs (e.g., somatosensation), the responsiveness of the vestibular system to non-invasive interventions, and irrespective of inherent challenges to vestibular assessment (12–14).

Assessment of vestibular function in the context of DM is arguably more challenging than the evaluation of other sensory systems. While patients are able to readily report pain, paresthesia, and numbness or visual changes indicating peripheral neuropathy of the feet and retinopathy, the symptoms of vestibular dysfunction may not be as readily perceived. DM affects organs and tissues that depend on microvasculature blood supply and additional biochemical reactions, in a bilateral and relatively symmetrical fashion (e.g., feet, eyes, kidneys) (11, 15). This expected pattern of insult within the inner ear that depends on a similar type of local homeostasis, introduces the likelihood of vestibular signaling decline without the degree of asymmetry typically seen in symptomatic (e.g., dizzy) patients. Further, the ability of the vestibular nuclei and cerebellum to reintegrate altered vestibular signals for appropriate motor responses introduces the possibility of central compensation (16). This plasticity presents further challenges with respect to the timing of assessment, determining a meaningful degree of loss, and predicting the likelihood of functional consequences. In this way, it is quite possible that vestibular dysfunction is present, asymptomatic, and even functionally inconsequential to a varying degree in people with DM. We suggest appreciation of this level of complexity is needed to glean insight into current research examining how hyperglycemia affects vestibular function.

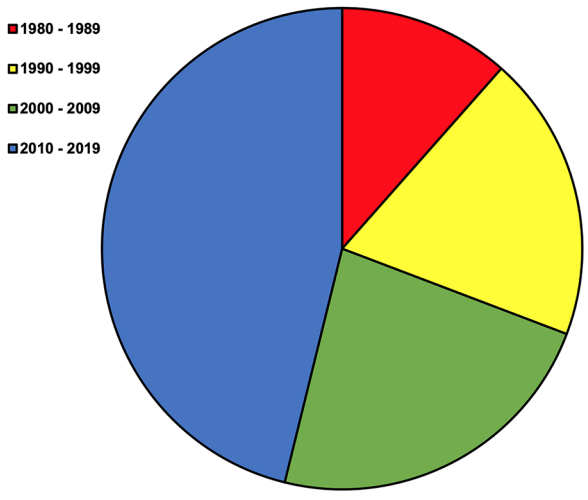

FIGURE 1
Original manuscripts by decade beginning in 1980. The term diabetes mellitus was combined with a search for vestibular OR inner ear in PubMed on July 24th 2023. This resulted in 420 articles. Review of titles, abstracts, articles, and subsequent snowball sampling was performed to identify 26 original research manuscripts written in English on peripheral vestibular diagnostic testing or structure in people or animals with DM without vestibular attributed symptoms of dizziness.

The intent of this commentary is to review the state-of-research on peripheral vestibular function in people with DM without diagnosed vestibular pathology or symptoms of dizziness. A mini-summary of the peripheral vestibular system and diagnostic tests (Tables 1, 2), and review of DM pathophysiology and histopathological studies are used to enrich our interpretation and readers' perspective on human studies. Commentary is then organized to identify the most likely indicators and location of dysfunction, and discuss why continued research is needed to substantiate the need for vestibular testing in the absence of patient symptoms.

2 Pathophysiology

Hyperglycemia defines DM. Laboratory tests are used to measure blood glucose levels and diagnose DM (e.g., HbA1c ≥ 6.5%). Type 1 and Type 2 are the most common classifications of DM in the population (20). Inability of pancreatic cells to produce insulin is the primary etiology for the typically earlier onset Type 1, or insulin dependent DM (IDDM). Inability of receptor cells to receive and utilize circulating insulin is the primary etiology of Type 2, or non-insulin dependent DM (NIDDM). Type 2 DM is most prevalent and associated with lower physical activity and higher body mass index (BMI) or weight. However, overlap between these DM classifications is recognized and ongoing research may reveal more precise classifications (20). Until then, heterogeneity of patient presentations, including the type, severity, and sequencing of cellular level tissue damage will remain a challenging reality of medical care.

Certain cells, such as endothelial cells, are ill equipped to reduce the transport of glucose across its membrane when confronted with elevated blood glucose (21). Inability to regulate the influx of glucose at the cellular level breeds excessive reactive oxygen species and leads to oxidative stress. Oxidative stress initiates a cascade of reactions via multiple pathways that result in tissue damage (21, 22). While each pathway deserves consideration, the contribution of excessive advanced glycation end products (AGEs) to cellular functions is often attributed to DM related tissue damage (retinopathy, nephropathy, peripheral neuropathy), and theorized to also cause peripheral vestibular dysfunction (13, 21, 23). Among numerous effects, intracellular, extracellular, and circulation of AGE precursors leads to observable changes in extracellular matrix, collagen and neural tissues, and small vessel characteristics which reflect microangiopathy (e.g., increased basement membrane and wall thickness). Importantly, the combination of altered tissue structure and reduced diffusion of nutrients to tissues serves to both increase and accelerate dysfunction. Animal model and post mortem human studies present the opportunity to evaluate if these mechanisms of tissue damage manifest in the peripheral vestibular system.

TABLE 1 The peripheral vestibular system.

Peripheral structure	Anatomy	Physiological functions
Otolith • Saccule • Utricle	Within a sac-like structure (otolith) are saddle shaped structures of sensory epithelium (maculae) comprised of kinocilia and stereocilia hair cells. The hair cells project into a gelatinous layer (otolithic membrane). The otolithic membrane is weighted with embedded otoconia (calcium carbonate crystals). • Saccular maculae oriented vertical • Utricular maculae oriented horizontal	Linear acceleration (e.g., head tilts and translational movements) causes movement of the weighted membrane and deflection of the hair cells generating either excitation or inhibition of the vestibular afferent. The saccule (vertical and anterior/posterior translations) and utricle (horizontal anterior/posterior and lateral) transmit signals via the inferior (from sacculus) and superior portion (from utricle) of the vestibular nerve to the vestibular nuclear complex. The vestibular nuclear complex generates a postural response (VSR) and/or eye movement (ocular tilt reaction and translational VOR).
Semicircular Canals • Anterior • Posterior • Horizontal	Endolymph-filled canals of one side are oriented orthogonally to each other. The two sides are arranged to work together as co-planar pairs (e.g., right anterior and left posterior (RALP), left anterior and right posterior (LARP), and horizontal canals). Each canal has an enlarged area called the ampulla. It contains an area of sensory epithelium consisting of hair cells (kinocilia and stereocilia) that project into the membranous diaphragm, the cupula.	Angular acceleration causes deflection of the hair cells. The orientation of the hair cells and arrangement of the co-planar canal pairs will determine if rotation in the plane of the canal will deflect the hair cells and cause excitation or inhibition of the afferent from one of the canal pairs. The inferior branch of the vestibular nerve originates from the posterior canal. The superior branch originates from the anterior and horizontal canal. Information from the vestibular nuclear complex is used to generate angular VOR and VCR.
Vestibulocochlear Nerve —CN VIII	The superior and inferior divisions of the vestibular branch of CN VIII innervates the five end-organ structures. Primary vestibular afferents form three types of endings around hair cells. Calyceal endings on Type I hair cells, bouton endings on Type II, and dimorphic endings both Type I and II hair cells.	The hair cells convert otolith and canal mechanical stimuli to neural action potentials and increase or decrease the tonic resting firing rate of CN VIII. The firing rate of the vestibular afferent may be classified based on its discharge regularity, either regular or irregular. The vestibular afferents synapse in the vestibular nuclear complex (superior, inferior, medial, and lateral nuclei) and cerebellum where the information is processed with other sensory input and a vestibular motor response is determined.

CNS, central nervous system; CN, cranial nerve; VOR, vestibulo-ocular reflex; VSR, vestibulospinal reflex; VCR, vestibulocollic reflex; SCC, semicircular canal.
The peripheral vestibular system consists of vestibular receptors and afferents. The vestibular receptors are hair cells within the otolith that detect linear acceleration and cristae ampullaris of the ampulla of each of the three semicircular canals that detect angular rotation. The afferent is the superior and inferior branch of the vestibular nerve. The primary afferents project to the central nervous system, the vestibular nuclear complex located dorsolateral to the junction of the pons, medulla, and the vestibulocerebellum. The vestibular nuclear complex processes vestibular, proprioception, and visual information. The vestibular nuclear complex projects to the three ocular motor nuclei for gaze stability (VOR), to the spinal cord for postural control such as protective extension (VSR) and head righting (VCR), and to the cortex via the thalamus for perception and spatial navigation.

TABLE 2 Peripheral vestibular system tests (17–19).

Peripheral organs	Tests
Utricle	oVEMP: An auditory stimulus is delivered, and inferior oblique muscle activity is recorded with surface EMG as the patient sits with a 30° upward gaze (typical position). An absent response, low amplitude response, or longer latency to onset of the extraocular muscle response indicates abnormality of the utricular pathway.
	SVV: In sitting, patients are asked to indicate when a slowly rotating line, projected in front of them, is in the vertical position. Error is the difference in patients' perception vs. actual vertical. Static tests with greater than 2° of error are considered abnormal. Dynamic tests that manipulate the visual system (optokinetic backgrounds) are considered abnormal when error increases from the static value. Dynamic tests while the patient turns in an offset (off axis) rotational chair, stimulates one utricle at a time, and is abnormal when error decreases from static error.
Saccule	cVEMP: A auditory stimulus is delivered, and sternocleidomastoid muscle activity is recorded with surface EMG as the patient lays supine with an active rotation and head lift of 30° (typical position). An absent or low amplitude response, or longer latency to onset of the sternocleidomastoid muscle response indicates abnormality of the saccular pathway.
Semicircular Canals	Calorics: Warm and cool water (or air) is delivered to the external auditory canal of each ear individually as the patient lays with the head elevated 30° from supine. The temperature gradient serves as a low-frequency (.003 Hz) stimulus and induces nystagmus. Oculography is used to record slow phase eye velocity. Velocity, duration of the response, symmetry, and directional preponderance are used to evaluate the activated horizontal SCC function. An asymmetry of >25% is a common metric indicative of a unilateral weakness.
	Rotational Chair: The patient undergoes passive sinusoidal harmonic acceleration at low-to-mid-range frequencies (typically 0.01–0.64 Hz) while seated in the chair. Oculography is used to record slow phase eye velocity of nystagmus. VOR gain (eye velocity/head velocity) and phase (head vs. eye position in degrees) are the main outcomes of this bilateral horizontal SCC test. Values ±2 SD of laboratory norms at a given frequency are considered abnormal.
	Active or Passive Head Thrust Tests: In sitting, head neutral, patients gaze upon a target at a set distance. A brisk (>150 °/s), low amplitude (10°), head rotation in the plane of the canal either actively induced by the patient, or passively induced by a clinician/researcher, serves to excite a SCC in the direction of the head thrust (e.g., right anterior and left posterior; right posterior and left anterior; and right and left horizontal canals). Abnormal VOR gain and/or saccadic eye movements to maintain/restabilize gaze on the target are typically used to indicate abnormal function of the stimulated SCC. Dynamic visual acuity (DVA) and video head impulse testing (vHIT) are examples of this high frequency (≈1–6 Hz) testing paradigm.

oVEMP, ocular vestibular evoked myogenic potential; EMG, electromyography; SVV, subjective visual vertigo; cVEMP, cervical vestibular evoked myogenic potential; DVA, dynamic visual acuity; vHIT, video head impulse test; SCC, semicircular canal.
Brief summaries of test procedures, outcomes, and abnormal findings are provided.

3 Histopathology studies

While early histopathological work did not detect small blood vessel changes supplying the peripheral vestibular system (24), subsequent animal model research has detected morphological alterations within the vestibule (Table 3). Across a series of light and electron microscopy case-control studies Meyers and colleagues demonstrated peripheral vestibular system changes in medically induced DM (i.e., Type 1) animal models (25–28). Characteristic signs of microangiopathy were not observed. However, the observation of DM group capillary proliferation in the otolith, in one of two studies, was theorized to be a compensatory adaptation to metabolic stress (poor oxygen diffusion). Interestingly, renal microangiopathy was observed in the group with otolith capillary proliferation; suggesting the vestibule potentially adapts differently to metabolic stress. Additional unique otolith alterations, reflecting metabolic stress and in part characteristic of AGEs, include the excessive extracellular matrix and connective tissue lipid droplets within the otolith that were correlated or trended with higher blood glucose levels. A variable degree of adaptations in myelin structure, including greater lysosomal activity with higher levels of blood glucose, were also observed in nerves supplying the otolith. Lastly, typical neuropathic changes, such as axonal dwindling and myelin sheath thinning, were observed in nerves to the horizontal semicircular canals and in relation to longer DM duration; but not in otolith nerves, along CN VIII (unpublished data), or in relation to blood glucose levels. In total, these morphological changes would be anticipated to reduce the quality and rate of end organ signals in people with DM.

More recent work further supports the likelihood of otolith dysfunction due to DM (Table 3). Perez et al. (29) demonstrated utricular pathway dysfunction in a diet induced (i.e., Type 2) DM animal model. Whether this finding was isolated to the vestibule or changes at longer durations of DM is unclear. Additionally, Kocdor et al. (30) identified loss of saccule Type I hair cells (calyceal endings) in people with Type 1 and 2 DM compared to controls, but did not find evidence of saccule microangiopathy. Combined, both studies point to a vulnerability of otolith Type I hair cells to hyperglycemia.

The above histopathologic research can frame expectations and interpretation for human subject studies evaluating peripheral vestibular function in people with DM. First, and in general, DM can create structural changes in the saccule and utricle, as well as in the nerves supplying the otolith and horizontal semicircular canals. Unique otolith capillary responses, without evidence of overt microangiopathy, as well as the collagenous/extracellular matrix and neural responses appear to be related to metabolic stress/AGEs in relation to elevated blood glucose. More characteristic signs of neuropathy may only be present in nerves supplying the semicircular canals, and in relation to longer duration DM. Further, while the anatomy (i.e., collagen type, short length of CN 8) (25) of the inner ear may underlie its unique response, at least short term, vestibular dysfunction may occur regardless of other microangiopathy signs (e.g., retinopathy, nephropathy) and potentially along with signs of AGE effects of the feet (e.g., peripheral neuropathy) (23, 31). Accordingly, key predictive factors of consideration in human studies include blood glucose level, duration of DM, and the presence of peripheral neuropathy (PN). Additionally, given the limited scope of the above research (i.e., semicircular canal not

TABLE 3 Histopathological studies.

	Sample	Main findings (DM compared to controls)
Meyers et al. (25)	• Sprague-Dawley rats • 28 DM (Streptozotocin) • 19 controls	• No basil lamina thickening of otolith • Larger CSA of utricle (18.5%) and saccule (26%) attributed to increased capillary diameter and density
Meyers et al. (26)	• Sprague-Dawley rats • 27 DM (Streptozotocin) • 14 controls	• Greater secondary lysosomes and lipid droplets in connective tissue cells, and excessive extracellular matrix, of utricle and saccule maculae • Saccule Type I hair cell degeneration in a small subset ($n = 2$) of the longer duration DM animals
Meyers (27)	• Sprague-Dawley rats • 10 DM (Streptozotocin) • 8 controls	• Saccule and utricle nerve myelin sheath changes included disrupted lamellae, lysosomal bodies, peri-axial expansion of Schwann cell bodies. • Lysosomal digestion of portions of myelinated nerve fibers in a subset • No microangiopathy signs or demyelination/axonal degeneration observed
Meyers et al. (28)	• Sprague-Dawley rats • 16 DM (Streptozotocin) • 9 controls	• Thinner myelin sheaths of hSCC nerves; thinnest with longer duration DM • Smaller nerve fibers with larger intrasheath diameters • Larger number of nerve fibers; greatest with higher blood glucose
Perez et al. (29)	• Sand rats • 7 DM (diet induced) • 7 controls	• Longer latency and lower amplitude vestibular evoked potential utricular responses from linear translations
Kocdor et al. (30)	• Post mortem humans • 39 DM (16 T1, 23 T2) • 40 age matched controls	• No difference in saccule arteriole wall thickness or Type II hair cell density • 16%–17% lower Type I hair cell density

CSA, cross sectional area; hSCC, horizontal semicircular canal; T1, Type 1 DM; T2, Type 2 DM.
Summaries of six studies examining the constitution and function of the peripheral vestibular system are presented.

assessed in diet induced DM), known age related changes and possible sex differences of the vestibular system, and relationship of obesity to elevated blood glucose, we suggest DM Type, age, sex, and BMI are also worth consideration (20, 32, 33). Lastly, the anticipated location of vestibular dysfunction includes the entirety of the vestibule, with a possibility that tests biasing Type I hair cell function (i.e., high frequency tests; Table 2) may prove more sensitive in the detection of vestibular dysfunction in people with DM.

4 Human studies

In 1961, Jorgensen and Buch provided a historical record of publications on vestibular function in people with DM (34). While details are limited, vestibular dysfunction in people with DM was detected prior to 1915. Two authors found evidence of dysfunction in a small amount of people with DM reporting dizziness, whereas an additional larger study did not detect abnormal rotatory or caloric function tests in people with DM. In the 1960′s two additional studies demonstrated horizontal semicircular canal dysfunction via caloric testing; which were often bilateral, as opposed to unilateral, in presentation. However, a third study only found caloric abnormalities in 2/69 people with DM (34). It is challenging to draw conclusions from this early time period of investigations. However, these works recognized the potential for DM to impair inner ear function and set the stage for future research as DM prevalence and life expectancy increased, and as vestibular diagnostic testing advanced.

4.1 When do we screen for peripheral vestibular dysfunction?

Patient and disease specific factors may contribute to vestibular dysfunction in people with DM. In recognition of this possibility, sample characteristics such as DM classification, participant age, and sex have been consistently reported in manuscripts examining vestibular function in people with DM without dizziness (Table 4). However, BMI and disease severity factors (e.g., HbA1c, DM duration, PN), while rooted in established DM pathophysiology, are inconsistently reported. Disease specific factors appear to be particularly important considerations given those with DM and higher HbA1c and/or longer disease duration perform worse on balance tests which exploit vestibular integration (standing on foam with eyes closed) (58). Herein we comment on each factor to provide clues as to which patients may be more likely to have peripheral vestibular dysfunction.

4.1.1 DM type

We identified 10 articles describing people with Type 1 DM and 15 including people with Type 2 DM. Type 1 DM was the focus of cohort and case control studies until 2015 (8/9 studies); after which 12/13 studies included people with Type 2 DM (Table 4). Given this chronological distribution and more recent clinical implementation of cervical and ocular vestibular evoked myogenic potential (VEMP) and multi-canal head thrust tests, the horizontal semicircular canal (SCC) was the most frequently assessed vestibular end-organ in people with Type 1 DM. In these studies, some degree of abnormal caloric responses (low frequency) were consistently reported (5/5 studies), 1/3 reported vestibulo-ocular reflex (VOR) abnormalities with higher frequency SCC tests (35, 36, 39–42, 55, 56), and 2/2 reported abnormal saccule and/or utricle function (44, 55). In contrast, the otolith received more attention than the SCCs, and SCC assessments were across a range of frequencies (low, middle, high; Table 2) (17) in people with Type 2 DM. Specifically, 10/11 studies detected some form of otolith dysfunction (43, 45–53, 57), and 4/7 studies identified SCC dysfunction (40, 48, 49, 52–54, 56). While one study did not report DM type and another did not differentiate between types (37, 38), two studies compared classes of DM; demonstrating similarity in high frequency SCC testing (passive/active head thrust, video head impulse testing: vHIT) between people with Type 1 and 2 (40, 56).

Based on the current research, it appears there is a reasonable likelihood of detecting SCC or otolith dysfunction in people with Type 1 or 2 DM. While otolith dysfunction may be more likely than SCC dysfunction in people with Type 2 DM, SCC high frequency responses appear similar between DM types. Overall, differential end-organ effects between DM classifications are not apparent.

4.1.2 Age, sex, and body mass index

Compared to sex and BMI, participant age was the most consistent reported factor in study designs (Table 4). Average DM participant age ranged from 16 to 66 years old, and often matched healthy control participant ages within studies. Consistent with younger Type 1 onset, and with the added benefit of controlling for the possible effect of age on vestibular function, studies including people with Type 1 DM were overwhelmingly younger than 50 years old. The youngest type 2 DM cohort age was 37, and most studies reported a mean group age of greater than 50; entering the age range when the VOR begins to decline regardless of DM (32). Sex was less frequently reported than age and not as frequently matched across groups. Female representation ranged from 8%–88%, but more often ranged between 30% and 60%. BMI was only reported in 6/23 reviewed studies (46, 49, 54, 56, 57). While the importance of age is implicitly recognized by authors who matched or controlled for age within designs, we are unaware of studies directly considering the possible interaction of age and DM with vestibular function. Additionally, we did not identify a study considering sex or BMI as a factor or covariate in analyses.

At present, the effect of age on study interpretation is somewhat mitigated, but it is unknown if an effect of sex or BMI underlies between study discrepancies regarding the characterization of abnormal vestibular function in people with DM.

4.1.3 Blood glucose and DM duration

Blood glucose level was consistently reported as an inclusion criterion for DM group participants and disease duration was considered by many researchers as a way to either avoid or leverage the cumulative effect of hyperglycemia (Table 4).

TABLE 4 Human subject vestibular diagnostic testing studies.

Article	Sample characteristics	Findings
1st author (year)	• *n* Group; % Female; Age; BMI • HbA1c; DM Duration; *n* PN	**Vestibular end-organ pathway:** result
Aantaa (1981) (35)	• 24 DM T1; 50%; 34 years old • NR; 12 years; 9 PN	**hSCC:** ≥6 (25% of sample) with abnormal caloric tests
Biurrun (1991) (36)	• 46 DM T1; 8%; 26 years old • 9.4%; 9 years; 16 PN • 3 HC; NR; 26 years old	**hSCC:** 22 (48% of sample) with abnormal caloric tests
Chamyal (1997) (37)	• 30 DM T1 (10) T2 (20); 88%; <50 years old • 30 HC; 50%; <50 years old	**hSCC:** Normal caloric testing
Sharma (1999) (38)	• 25 DM; 48%; ≤50 • 25 DM w/comp.; 48%; ≤50 years old • 5 HC; 48%; ≤50	**hSCC:** Normal caloric testing
Gawron (2002) (39)	• 95 DM T1; 51%; 16 years old • 44 HC; 55%; 16 years old	**hSCC:** Increase slow phase eye velocity (1.5–4 deg/s) and 11 (12% of sample) with abnormal caloric testing compared to HC (2 abnormal tests)
Nicholson (2002) (40)	• 41 DM T1 (18) T2 (23); 39%; ≈63 years old • 45 HC; 60%; 61 years old	**hSCC:** VOR phase but not gain group differences in active or passive horizontal head rotation testing.
Klagenberg (2007) (41)	• 30 DM T1; 43%; 26 years old	**hSCC:** 18 (60% of sample) with abnormal caloric tests
Rigon (2007) (42)	• 19 DM T1; 53%; ≤25 years old • 19 HC; 53%;	**hSCC:** 18 (36% of DM sample) with abnormal responses and DM group with significantly lower caloric responses than HC.
Bektas (2008) (43)	• 38 DM T2; 50%; ≈51 years old • NR; ≈7 years; 25 PN • 21 HC; 43%; 49 years old	**Saccule:** No group differences in cVEMP latencies or inter-amplitude regardless of PN status.
Kamali (2013) (44)	• 24 DM T1; 42%; ≤40 years old • NR; NR; 10 PN • 24 HC; 54%; ≤40 years old	**Saccule:** Group differences (DMPN, DM, HC) in cVEMP latencies explained by longer latencies in DMPN vs. HC. No between group inter-amplitude differences.
Konukseven (2015) (45)	• 30 DM T2; 53%; 44 years old • 9.1%; 5 years; excluded • 30 Pre-DM; 50%; 46 years old • 5.7%; NA • 31 HC; 51%; 45 years old • 5.0%; NA	**Utricle:** 10 (34% of DM sample) with abnormal oVEMP. No between group difference in inter-amplitudes, but significantly longer latencies in DM group. **Saccule:** 17 (57% of DM sample) with abnormal cVEMP. No between group difference in inter-amplitudes, but significantly longer latencies in DM group.
Razzak (2015) (46)	• 47 DM T2; 28%; 57 years old; 30 kg/m^2 • 7.1%; 10 years; excluded • 29 HC; 31%; 57 years old; 27 kg/m^2	**Utricle:** No between group difference in static SVV conditions. Both groups had greater error with dynamic condition (tilted frame). DM group had significantly greater error than HC group in dynamic condition.
Sahu (2015) (47)	• 15 DM T2; 50 years old • 15 HC; 52 years old	**Saccule:** 16/30 DM group ears (vs. 0 HC) with absent cVEMP responses. Significantly lower DM group inter-amplitudes, but no group difference in latencies.
Ward (2015) (48)	• 25 DM T2; 40%; 65 years old; 32 kg/m^2 • 8.3%; 18 years; 3.5 MNSI • 25 HC; 52%; 64 years old	**Utricle:** 46% absent or delayed n1 with oVEMP testing in DM group (vs. 12% in HC). Significantly lower n1 amplitude in DM group. **Saccule:** 32% absent cVEMP test in DM group (vs. 12% HC). Significantly lower inter-amplitude cVEMP in DM group. **SCC:** 70% of DM group had at least one abnormal canal with passive DVA (disappearing "E") test. DM group with significantly worse hSCC and aSCC DVA than HC.
Jauregui-Renaud (2017) (49)	• 101 DM T2; 73%; 60 years old; 29 kg/m^2 • 7%; ≈8 years; ≈30 PN • 51 HC; 57%; 57 years old; 28 kg/m^2	**Utricle:** Significantly worse error with static SVV in DM group, though error was <2°. Significantly more error in HC group vs. DM group in dynamic SVV during off-axis rotation. **hSCC:** No between group difference in VOR gain at.16 and 1.28 Hz rotational chair testing
Kalkan (2018) (50)	• 66 DM T2; 56%; 54 years old • NR; 7 years; 33 w/o PN • NR; 11 years; DMPN; 33 PN • 35 HC; 45%; 50 years old	**Utricle and Saccule:** Significantly lower inter-amplitude with oVEMP and cVEMP testing in DM groups vs. HC, but no difference between DM w/o PN and DMPN groups. No group differences in latencies. **SCC:** No between group difference in median VOR gain with vHIT testing
Kanumuri (2018) (51)	• 40 DM T2; 30%; <60 years old • NR; >5 years; NR • 20 HC; NR	**Saccule:** 4 (25% of asymptomatic DM subgroup) with longer cVEMP latencies
Omar (2018) (52)	• 8 DM T2; NR; 37 years old • NR; <5 years; 0 • 8 HC; NR; 35 years old	**Utricle and Saccule:** No between group differences in inter-amplitudes or latencies of cVEMP or oVEMP testing. Trend of worse DM group inter-amplitudes was noted. **SCC:** No between group difference in VOR gain with vHIT
Jauregui-Renaud (2019) (53)	• 47 DM T2; 26%; 58 years old • NR; 8 years; 13 PN • 50 HC; 50%; 56 years old	**Utricle:** No between group difference in error of static SVV testing. Significantly more error in HC group vs. DM group in dynamic SVV during off-axis rotation. **hSCC:** Significantly lower VOR gain in DM group at.16 Hz, but not 1.28 Hz, vs. HC
Li (2019) (54)	• 51 DM T2; 47%; 56 years old; 24 kg/m^2 • 8.5%; 11 years; 12 PN • 43 HC; 40%; 54 years old; 24 kg/m^2 • 5.7%; NR	**hSCC:** 29 (57% of sample) of DM group with abnormal caloric tests (vs. 27% HC)

(*Continued*)

TABLE 4 Continued

Article	Sample characteristics	Findings
Moossavi (2021) (55)	• 15 DM T1; 60%; 28 years old • 8%; 10 years; NR • 16 HC; 19%; 26 years old	**Utricle:** Significantly longer latency with oVEMP testing in DM group. No difference in oVEMP inter-amplitudes. No difference in error with static SVV, but worse error with dynamic SVV (OKN) in the DM group. **Saccule:** Significantly lower inter-amplitude with cVEMP testing in DM group. No difference in latency. **SCC:** No difference in VOR gain with vHIT

Mahalingasivam (2023) (56)	• 52 DM T1; 50%; 59 years old, 26 kg/m^2
	  • 8.2%; 28 y
	• 51 DM T2; 35%; 66 years old; 30 kg/m^2
	  • 6.6%; 11 y
	• 11 HC; 54%; 59 years old; 25 kg/m^2
		SCC: No group differences VOR gain with vHIT. No subgroup differences in VOR gain with vHIT based on autonomic, large, or small fiber PN.

Zhang (2023) (57)	• 89 DM T2; 36%; 53 years old; ≈23 kg/m^2
	  • 8.6%; 4 years; 29 w/o PN
	  • 8.7%; 5 y: 26 symptomatic PN
	  • 10.9%; 7 years; 34 asymptomatic PN
	• 42 HC; 45%; 52 years old
		Utricle and Saccule: Significantly longer oVEMP and cVEMP latencies in the DM groups with PN vs. DM w/o PN or HC groups. No group differences in inter-amplitudes and a similar rate of absent VEMP responses between DM and HC groups.

BMI, body mass index; HbA1c, hemoglobin A1c; DM, diabetes mellitus; PN, peripheral neuropathy; T1, type 1; T2, type 2; NR, not reported; hSCC, horizontal semicircular canal; HC, healthy control; w/comp, with complications (included PN, ulcer, hemiparesis); MNSI, Michigan Neuropathy Screening Instrument score; OKN, optokinetic. Sample characteristics as well as testing results organized by end-organ pathway are presented.

Focusing on the more contemporary clinical marker measuring blood glucose levels across the past three months, HbA1c, only 9/23 studies reported actual values in sample descriptions. Of the available data, all but three of the patient groups were above 8%; indicating a more severe level of disease that would be anticipated to increase the likelihood of detecting vestibular damage. To this point, 8/9 of these studies detected either otolith or SCC abnormalities in people with DM. Surprisingly, one study including people with Type 1 DM with 8.2% HbA1c, and the longest reported duration of reviewed studies (28 years), did not detect horizontal SCC dysfunction compared to people with Type 2 DM and a small subset of healthy controls (56). However, this study may not necessarily be an outlier, as a similar frequency of abnormal findings were observed in those across disease duration. Specifically, 6/7 cohorts with at least ten year and 5/7 with less than 10 year DM duration were reported to have some degree of otolith and/or SCC dysfunction. A trend toward earlier vs. later otolith or SCC onset was not evident (i.e., order effect). Studies employing correlation or factor level (i.e., high vs. lower HbA1c) analyses have attempted to address the ambiguity regarding the affect of HbA1c and DM duration. However, only 4/9 studies identified significant, small to medium effects, of these factors and VEMP latencies (2 studies) or caloric testing metrics (39, 45, 54, 57). Synthesizing this information suggests HbA1c may be a more robust predictor of vestibular dysfunction than DM duration, but inconsistency of predictions reduces confidence regarding this possibility.

Lack of consistent evidence connecting HbA1C or DM duration to vestibular function may be due to study design, the nature of DM, or their interaction. Design factors include sample heterogeneity and inadequate statistical power; the latter of which limits the ability to confidently consider multiple factors likely needed to predict tissue damage. Moreover, it is possible the timing of vestibular testing in relation to disease progression or HbA1c test influences relationships. Specifically, the degree of incremental or frequency of sporadic insults (e.g., hyperglycemic events) (39) to the inner ear and the response of the inner ear regarding vascular adaptations to metabolic stress and the possibility of spontaneous, yet incomplete, recovery are not the same across time in a person with DM or between people with DM. For example, different test results may be found in someone immediately after a series of hyperglycemic events or months of poor glucose control as compared to the same person after years of subsequent adequate glucose control. Somewhat fortunately, larger sample sizes with well-informed inclusion criteria and design (e.g., >7 years disease duration, standard time of HbA1c testing) may be the best approach to develop the profile of a patient who may need vestibular screening: mitigating the effect of more unique disease courses and allowing for the inclusion of multiple factors. To this point, in a promising study of 89 individuals with Type 2 DM, Zhang et al. (57) employed a Cox regression model that included HbA1c, additional blood markers (e.g., cholesterol), and severity of peripheral neuropathy to predict cVEMP latencies. Replication of this type of an approach may prove quite informative.

4.1.4 Peripheral neuropathy

A number of studies have considered the presence of PN of the feet as a potential clinical surrogate marker of anticipated inner ear dysfunction (Table 4). The level of consideration has ranged from intentional exclusion, to simply reporting on the proportion within the sample, to designing studies to determine the effect of PN on vestibular test outcomes. Two studies detected otolith dysfunction, but a third did not detect SCC dysfunction, in people with DM without PN in comparison to controls (45, 46, 52). Across 11 study samples, and not necessarily controlled, the proportion of people with PN has ranged from approximately 30%–70%. Of these, six studies directly considered PN in comparison or correlational analyses. While otolith function in people with DMPN was worse than controls in 3/4 studies, discrimination of DMPN and DM without PN was only detected in 1/4 studies (43, 44, 50, 57). Two studies did not detect differences in high frequency SCC function as measured by VOR gain (vHIT) between healthy controls and people with DM,

regardless of PN status (50, 56). Lastly, while Ward et al. (48) acknowledged the potential for insufficient statistical power, significant correlations between clinical scores of PN (Michigan Neuropathy Screening Instrument) and otolith and SCC function in people with DM were not observed.

Despite the consistent use of valid diagnostic tests of neuropathy (e.g., nerve conduction testing), limited presentation of data limits certainty regarding the clinical utility of considering PN related to inner ear function. However, we suggest stratifying people with DM based on severity of PN may elevate certainty. In illustration, VOR gain (vHIT) differences between people with Type 1 or 2 DMPN, verified by nerve conduction testing, and a small healthy control group, were not observed (56). Importantly, neither DMPN group registered mean vibration perception threshold test values worse than the known cut-off for loss of protective sensation, indicating the sample had a mild to moderate level of PN. In contrast, stratification of people with DM, DMPN with symptoms, and DMPN without symptoms (indicating more advanced PN), discriminated between groups and is a key predictor of cervical VEMP latencies (57). While it is possible PN affects vestibular end-organs differently, it is just as possible advanced PN (e.g., loss of protective sensation) is a surrogate clinical indicator of vestibular end-organ decline. Regardless, as it stands, otolith dysfunction can exist in the absence of PN, otolith dysfunction may be worse in people with advanced DMPN than in people with DM, and SCC dysfunction has not been detected in those with DMPN. Prudent next steps include replication of otolith assessments and a more comprehensive assessment of SCC function in people with DM and different levels of PN.

4.2 Where do we look for peripheral vestibular dysfunction?

Reviewing literature regarding the location of peripheral vestibular dysfunction in people with DM may provide clues to elevate efficiency of clinical testing. However, different study samples, designs, testing approaches, and the reality that only 4/23 studies considered each end-organ pathway within the same sample, will be reflected in our ability to make recommendations (48, 50, 52, 55). Nevertheless, studies are fairly balanced by end-organ as 10 studies assessed utricle function, 10 assessed saccule function, and 16 assessed SCC function (Table 4).

4.2.1 Utricle

Six studies employed oVEMP testing with a median DM group sample size of 27.5 and age of 48.5 years (45, 48, 50, 52, 55, 57). Tone burst VEMPs were the most commonly employed stimuli, although intensity varied across studies. Of these, all but one small case-control study ($N = 16$) (52) found abnormal utricular responses in people with DM. Significantly delayed latency, or a greater number of abnormal latencies, were the most common finding in people with DM compared to controls, and in one study comparing DMPN to DM and controls (45, 48, 55, 57). Perhaps due to differences in approaches, two studies identified low amplitude responses in people with DM vs. controls (48, 50).

Four studies conducted tests within the subjective visual vertical (SVV) paradigm with a median DM group sample size of 47 and age of 57.5 years (46, 49, 53, 55). Three studies failed to detect differences in static SVV (46, 53, 55). While the fourth and largest ($N = 152$) study found a significantly larger DM group static error, the group mean was within the typical normative range of 0–2 degrees (18, 49). In contrast, all studies identified abnormalities with dynamic SVV testing. Suggesting visual dependence, two studies identified worse responses in DM group SVV with altered visual stimuli (tilted frame, moving background) (46, 55). And in suggestion of central compensation, Jauregui-Renaud et al. (49, 53) found worse bilateral SVV responses in people with DM during unilateral centrifugation as illustrated by less deviation from static values in comparison to control participants.

Nearly all studies detected abnormal utricular function. The greater frequency of abnormal oVEMP latencies vs. amplitudes points to nerve conduction deficits as opposed to signal dampening. Somewhat conversely, SVV findings point to a greater likelihood of both visual dependence and central compensation, suggesting that dampened signals have been reintegrated. Since oVEMP and SVV testing were conducted in the same cohort only once, further work is needed to clarify utricular pathway changes (55). However, slower conduction and compensation of utricular signals seem likely in people with DM.

4.2.2 Saccule

The saccule was assessed with cVEMP testing across a median DM group sample size of 27.5 and age of 51 years. Here again tone burst VEMPs were the most commonly employed stimuli, but intensity was more consistent than in oVEMP tests across studies. Two studies did not find cVEMP abnormalities in people with DM, perhaps due to stimulus parameters or a small sample size (43, 52). However, 8/10 studies found group differences in either, but not both, amplitude or latency. Lower amplitude in people with DM vs. controls was observed in four studies, with an across study 0%–50% range of absent responses in the DM groups (47, 48, 50, 55). Significantly longer DM group latencies were observed in 3/10 studies; while another observed abnormally long latencies in 25% of their DM sample without dizziness (44, 45, 51, 57).

Based on the current research, most studies identified abnormal saccule pathway function in people with DM as measured by cVEMP testing. However, lower amplitude or longer latencies seem equally likely. Interestingly, lower amplitudes were found in cohorts with longer disease duration. Further, those with more advanced PN (and also higher blood glucose level) had longer latencies than those with less advanced PN or those with DM without PN (57). Perhaps, timing of testing with respect to otolith adaptations to metabolic stress explains between study discrepancies. Larger sample sizes may assist in clarifying expectations regarding cVEMP test results in people with DM.

4.2.3 Semicircular canals

Eight studies employed caloric testing with a median DM group sample size of 30 and age of 26 years (35–39, 41, 42, 54). Authors of 6/8 studies reported abnormal caloric responses in

people with DM, most often with a greater frequency than control subjects (35, 36, 39, 41, 42, 54). While slightly different methodology and test criteria were used, the range regarding the frequency of abnormal responses was 36%–60% in people with DM. Notably, the results of the lone study including people with Type 2 DM or older than 50 years of age were in line with the younger Type 1 cohort data of other studies (54).

Three studies employed rotational chair testing with a median DM group sample size of 64 and age of 60 years (40, 49, 53). Across two studies using rotational chair sinusoidal harmonic acceleration frequencies of 0.16 and 1.28 Hz, lower DM group VOR gain was observed in one cohort at 0.16 Hz (49, 53). In the third study, VOR gain at an unreported rotational frequency was not different between people with DM and controls; although phase differences were noted between groups of people with DM and controls (40).

Five studies used passive multi-canal high-frequency testing with a median DM group sample size of 25 and approximate age of 63 years (48, 50, 52, 55, 56). Group differences in VOR gain were not detected in the four studies employing vHIT testing between people with DM and controls. A small number of abnormal responses were noted in two studies (55, 56), while the other two studies reporting similar between-group VOR gain also reported no evidence of DM group covert or overt saccades (50, 52). However, utilizing a disappearing "E" paradigm, Ward et al. (48) demonstrated reduced dynamic visual acuity (DVA) in people with DM compared to controls. Horizontal and superior (anterior) canals were both different between groups, whereas the posterior canal was not. Combined, 70% of the DM cohort had at least one abnormal canal. Discrepancies between studies may be due to test or sampling approaches.

Overall, across low, middle, and high frequency SCC testing, people with DM had abnormal function in 9/16 studies. The most consistent case for horizontal SCC dysfunction was evident with low frequency caloric testing. Limited investigations point to the possibility of mid-range frequency horizontal SCC canal dysfunction, but the typical range of sinusoidal harmonic acceleration frequencies have yet to be employed. This is surprising since rotational chair testing is the standard for detecting bilateral vestibular loss (19); and bilateral loss is the theoretical expectation regarding the effects of chronic hyperglycemia. This limitation withstanding, behavioral VOR tests (e.g., DVA) requiring cortical/subcortical sensory integration, were convincingly abnormal in people with DM in one study (48). However, abnormalities with less complex assessments of high frequency VOR were not observed (vHIT). Together, findings suggest VOR is sufficient at frequencies needed for daily activities, but that multi-sensory integration of the VOR may be problematic. Relatedly, although clear in one study (56), greater transparency regarding how saccadic responses are defined may further understanding on if central compensation of SCC signals occurs in people with DM.

4.3 Why screen for vestibular dysfunction?

Visual, somatosensory, and vestibular systems are the primary sensory inputs for balance, and thus important factors to consider in fall prevention programs. Balance rehabilitation and fall prevention are particularly important in people with DM as falls are more frequent (25% vs. 18%) (59) and more likely to reoccur in comparison to people without DM; and falls in themselves propagate severe injury and elevate medical costs (8–10, 60–63). Moreover, the subclinical or overt compromise of visual and somatosensory systems (e.g., retinopathy, PN), along with impaired sensory integration, are well recognized major drivers of imbalance and falls in people with DM (58, 64, 65). Unfortunately, therapeutic approaches to reverse the effects of altered afferent information due to retinopathy and PN are unknown. In contrast, established exercises allow for the central reintegration of altered peripheral vestibular signals to allow for sufficient reflex responses (14). Therefore, if a connection between peripheral vestibular function and balance is identified in people with DM, vestibular exercises may prove to be a viable adjunct to current balance rehabilitation programs.

However, we are aware of only four studies including both peripheral vestibular diagnostic testing and balance assessments (40, 49, 52, 54). Nicholson et al. (40) found abnormal VOR phase during active or passive head rotations (horizontal SCC) and increased postural sway in people with DM vs. controls. In a small case-control study of a relatively young and early stage DM patient group, Omar et al. (52) observed a trend toward worse VEMP amplitudes and no group difference in VOR (vHIT) along with worse performance on clinical measures of balance (Timed up and Go test and Functional Gait Assessment). Li et al. (54) observed a greater frequency of abnormal horizontal SCC function (calorics) along with small but significant deficits in postural control in people with DM compared to controls of a similar age, sex, and BMI. In the largest case-control study, people with DM registered worse otolith (SVV) but not horizontal SCC (rotational chair) function along with worse postural control (49). However, postural control was not different between people with DM with ($n = 26$) and without ($n = 75$) a history of falling; and utricle function was not compared between these subgroups. In total, leveraging this literature to explain the possible relationship between vestibular function and balance in people with DM without dizziness is challenging due to differences in vestibular and balance metrics, and because direct analyses (e.g., correlations) were not conducted.

At present, evidence vestibular dysfunction is related to imbalance in people with DM is limited and circumstantial at best. As such, it is difficult to justify vestibular diagnostic testing in the absence of patient dizziness symptoms. While we acknowledge the potential need to consider a level of bilateral loss impacting function without symptoms of dizziness, and the likely summative effect of multi-sensory system compromise, further work is needed to clarify the potential role diagnostic vestibular testing has on the treatment of imbalance in people with DM.

5 Discussion

Our commentary has focused on which factors may increase the likelihood of vestibular dysfunction, where the dysfunction

may be located, and to what extent said dysfunction may influence functional mobility in people with DM. We provided small summaries to this effect for each section and subsection thus far. Now, briefly synthesizing information across all sections allows us to offer recommendations for future research and current clinical practice.

Although we have illustrated the likelihood of detecting abnormal peripheral vestibular function in people with DM is relatively high, study findings are somewhat incongruent with anticipated DM pathophysiology regarding a progressively worse bilateral vestibular loss. Vestibular dysfunction was detected in 18/23 studies. However, qualitative review of the available data suggests unilateral changes are at least as common as bilateral changes in people with DM. This pattern may reflect reality, patient subsets, limitations of current diagnostic tests, or some combination. Regardless, because we only reviewed studies including people with DM without dizziness (or at least minimally so), and dysfunction can include utricle, saccule, and/or SCC pathways, compensation of both asymmetric and potentially symmetric dysfunction in any end-organ pathway seems evident. Further, based on promising but inconsistent results regarding glycemic control, and minimal evidence regarding DM duration, stronger evidence is needed to conclude vestibular dysfunction progressively worsens in people with DM. As such, vestibular dysfunction is present in people with DM with minimal to no symptoms (i.e., compensated), but not necessarily bilateral or progressive in nature.

The nature of vestibular insult aside, a major impetus of delineating vestibular dysfunction in people with DM is rooted in the possibility dysfunction may reduce balance and physical activity. As discussed (4.3), the connection is essentially unknown. However, inspection of study findings can provide preliminary clues as to how a connection may be present. Specifically, utricular dysfunction was more common than saccule or SCC dysfunction, and behavioral test abnormalities (SVV, DVA) were robust in people with DM. The frequency of utricular dysfunction is concerning given the emerging role this pathway has in patient recovery following vestibular insult (66, 67). And impairments on behavioral tests point to sensory integration difficulties. Combined, these test results raise the probability that vestibular dysfunction would manifest as imbalance in people with DM. Accordingly, incorporating such a test profile into research may serve to inform the future clinical care of people with DM.

5.1 Research recommendations

Based on the state-of-research, a number of strategies are recommended to move the field forward. Large samples within a longitudinal design, or cross-sectional stratified sample designs of people with differing severity of DM, may mitigate test timing concerns and reveal the sequencing and laterality of vestibular insult. Composite metrics of DM status, such as variability of HbA1c across time or average HbA1c normalized to disease duration, as well as levels of PN or unexplored measures of AGEs (31), may prove to be an effective way to explain and predict vestibular dysfunction toward informing test indications. Further, assessment of all three end-organ pathways within the above recommended designs remains necessary until the requisite clarity is achieved to optimize clinical testing paradigms. Low to mid-range SCC and otolith pathway tests along with behavioral tests (SVV, DVA) may best position us to link dysfunction to imbalance in people with DM. To this point, conduction of multiple regression analyses are needed to evaluate if vestibular dysfunction accounts for imbalance and functional mobility. Ultimately, we suspect a multisensory assessment of somatosensation/proprioception, vision, and vestibular function will be needed to establish the unique contribution of the vestibular system to balance in people with DM.

5.2 Clinical recommendations

Despite the uncertainty regarding the contribution of vestibular dysfunction to imbalance, there are a number of reasons to consider the clinical evaluation of vestibular function in people with DM and imbalance with or without dizziness. These reasons include, (1) the high likelihood of vestibular dysfunction, (2) uncertainty regarding possible morphological adaptations to metabolic stress, (3) the degree of anticipated compensation, and (4) importance of multi-sensory integration for balance ability. Therefore, in addition to a through history to determine provoking factors/activities of imbalance, we recommend the incorporation of bedside exam tests prior to instrumented diagnostic testing. Simple oculomotor tests (i.e., pursuit, gaze, VOR cancellation, optokinetic response), DVA testing, and static and dynamic balance tests that require an integrated vestibular response are reasonable to include during patient evaluations. We expect such an approach will allow clinicians to add vestibular exercises and based movements, as indicated, to current approaches aimed at improving balance in people with DM (68, 69). Finally, in cases where individuals do not respond to this type of an approach, use of vestibular diagnostic testing may be of some benefit.

5.3 Limitations

A full review of DM pathophysiology was beyond the scope of this review. We acknowledge study findings of central vestibular dysfunction in people with DM and encourage clinicians to consider this possibility during patient care (35, 36, 39–42, 70). Some studies on peripheral vestibular function in people with DM were excluded due to the inclusion of people with unspecified vertigo or dizziness, either via discovery or as designed (71–75). Additionally, we recognize DM increases the likelihood of benign paroxysmal positional vertigo and appears to worsen the prognosis of Meniere's disease (76–78). These studies indicate not all vestibular dysfunction in people with DM is peripheral, asymptomatic, or compensated. Lastly, while study methodology and quality were considered within this review,

detailed commentary on methodology or criteria-based quality rankings were not conducted.

5.4 Conclusion

We offer mitigated conclusions regarding when, where, and why we should look for vestibular dysfunction in people with DM. It appears peripheral vestibular dysfunction is likely in people with both types of DM. It also appears greater HbA1c and severity of peripheral neuropathy increases this likelihood. Both otolith end-organs and the SCCs are candidates for dysfunction. However, it is quite uncertain if anticipated vestibular dysfunction manifests as imbalance in people with DM.

Author contributions

FD: Conceptualization, Writing – original draft. HK: Writing – review & editing. MO: Writing – review & editing. MC: Writing – review & editing. JH: Writing – review & editing. MS: Writing – review & editing.

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Conflict of interest

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Symptom reduction in mal de débarquement syndrome with attenuation of the velocity storage contribution in the central vestibular pathways

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Background: The velocity storage mechanism of the central vestibular system is closely associated with the vestibulo-ocular reflex (VOR), but also contributes to the sense of orientation in space and the perception of self-motion. We postulate that mal de débarquement syndrome (MdDS) is a consequence of inappropriate sensory adaptation of velocity storage. The premise that a maladapted velocity storage may be corrected by spatial readaptation of the VOR has recently been translated into the development of the first effective treatment for MdDS. However, this treatment's initial impact may be reversed by subsequent re-triggering events. Presently, we hypothesized that MdDS symptoms could alternatively be reduced by attenuating the velocity storage contribution in the central vestibular pathways.

Methods: Forty-three patients with MdDS (aged 47 ± 14 yo; 36 women) were randomly assigned to two treatment groups and followed for 6 months. The horizontal VOR was tested with chair rotation during laboratory visits, and the strength of velocity storage was quantified with model-based parameters—the time constant (Tc) and the gain of coupling from the vestibular primary afferent signals (g_0). To attenuate velocity storage, Group 1 underwent a progressively intensifying series of low-frequency earth-vertical oscillatory rotation coupled to conflicting visual stimuli. Group 2 underwent an established protocol combining head tilts and visual stimulation, designed to correct maladapted spatial orientation but not change the velocity storage strength. The symptom severity was self-rated on an 11-point scale and reported before and up to 6 months after the treatment.

Results: In Group 1, velocity storage was modified through reduction of g_0 ($p < 0.001$) but not Tc. The symptom rating was at least halved initially in 43% of Group 1 ($p = 0.04$), the majority of whom retained a similar level of improvement during the 6-month follow-up period. In Group 2, no systematic change was induced in the parameters of velocity storage strength, as expected. The symptom rating was at least halved initially in 80% of Group 2 ($p < 0.001$), but paralleling previous findings, symptoms often returned subsequently.

Abbreviations
g_0, velocity storage coupling gain; g_1, direct pathway gain; LOESS, locally estimated scatterplot smoothing; MdDS, mal de débarquement syndrome; OKN, optokinetic nystagmus; OKS, optokinetic stimulus; SD, standard deviation; Tc, time constant of velocity storage; VOR, vestibulo-ocular reflex.

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Conclusion: Attenuation of velocity storage shows promise as a lasting remedy for MdDS that can complement the VOR readaptation approach.

KEYWORDS

aging, central vestibular disorder, gravity, orientation vector, rocking, swaying, bobbing, non-spinning vertigo

Introduction

Mal de débarquement syndrome (MdDS) is considered a rare illness but nevertheless counted among common balance disorders (1). MdDS, which is typically triggered by prolonged exposure to passive motion during a voyage on a cruise ship or airplane, is primarily characterized by a continuous perception of oscillatory self-motion such as rocking, swaying, or bobbing, or a sensation of gravitational pull (collectively identified as non-spinning vertigo) and associated sensations of imbalance (2–4). The self-motion symptoms of MdDS are typically accompanied by somatic complaints (e.g., headaches and visually induced dizziness), reduced cognitive function (e.g., decreased attention and short-term memory), and affective problems (e.g., depression and anxiety). These symptoms can be severe enough for some patients to develop suicidal thoughts and often lead to long-term disability.

Although mal de débarquement, i.e., a transient illusion of self-motion following exposure to prolonged passive motion, has been recognized for centuries (5, 6), and its chronic manifestation, MdDS, has attracted increasing interest in the wake of a 1987 publication of a six-patient case series (2), MdDS still has not permeated the awareness of clinicians. MdDS is often misdiagnosed as a mental disorder, vestibular migraine, or peripheral vestibular dysfunction, and patients on average make 19 (but more typically 2–5) visits to healthcare professionals before their MdDS diagnosis (3, 7–9). Given these circumstances, it is presently not possible to determine the actual prevalence of the illness. However, MdDS may represent at least a small percentage of patients seen at large clinical centers specializing in balance and dizziness (10, 11) and reportedly has a strong female predominance of 80%–90% (9, 12, 13).

The number of people seeking treatment is expected to increase because general awareness of the illness is improving —according to our patients' intake forms, most patients self-diagnose for MdDS over the Internet first, and then confirm their diagnosis with specialists. Furthermore, cruises were one of the fastest-growing tourism industries before the COVID-19 pandemic, growing from 17.8 million passengers worldwide in 2009 to 29.7 million in 2019 (14). At the time of this writing, full recovery of the industry was projected in 2023 (15).

However, treatment options for MdDS are limited. In fact, until recently the illness was considered intractable, with a progressively lower likelihood of remission as time passed (3). Conventional vestibular physical therapy is generally ineffective in treating MdDS (13, 16, 17). Benzodiazepines, a class of GABA-A agonists, may provide partial symptom relief for some patients (13, 16, 18), but if effective, the site of its action is not understood, and harmful effects including dependence must be considered (19, 20). Treatment with vestibular migraine medications can improve the quality of life of patients with MdDS, but symptom improvement appears domain-specific, and a greater degree of dose management than typical may be required due to their sensitivity to medications (21, 22). Alternatively, studies have suggested that disrupting the inappropriate entrainment in a neural functional-connectivity network using non-invasive brain stimulation methods during a span of days may reduce symptoms (23–25). However, the long-term outcome of this treatment is unknown.

In contrast to these symptom-focused approaches, the recent discovery that MdDS may involve maladaptation of the velocity storage mechanism of the central vestibular system opened opportunities for positive long-term outcomes by addressing the root cause of the illness (12, 26, 27). Velocity storage is activated by head rotation, large-field visual motion, or proprioceptive cues for continuous rotation, and temporarily holds, or stores, an estimate of head rotational velocity in space (28–32). The velocity storage mechanism is thought to support spatial orientation by acting as a "neural gyroscope" (33–35). Velocity storage is closely associated with the vestibulo-ocular reflex (VOR) as it was first examined as a stored eye movement drive related to head rotation during vestibular and optokinetic nystagmus (29–31, 36), but is also thought to contribute to postural control (37, 38) and the perception of spatial orientation and self-motion (28, 30, 31, 39).

An animal-based study showed that spatial orientation properties of velocity storage could be maladapted by exposure to unnatural motion, as revealed in the consequent abnormal VOR (40). It was thus postulated that dysfunction of velocity storage, particularly in the form of misaligned spatial orientation, could cause primary symptoms and signs of MdDS. Based on this postulate, a treatment protocol was subsequently designed to correct such misalignment by stimulating readaptation of the VOR through exposure to full-field visual motion coupled with head tilts at the frequency of the phantom oscillation (26). Support for the postulate comes from the clear effect subjectively reported by the majority of over 600 patients treated with the VOR readaptation protocol in our laboratory thus far (12, 26, 27). It is unlikely that this effect was due to spontaneous recovery or a placebo response because of the chronicity of MdDS in these patients, who on average, had had the illness for two years before receiving the

readaptation treatment and approximately 5% for as long as more than a decade (up to 41 years). The protocol yielded an overall strong positive initial impact even among patients with long durations of the illness even though other treatments had been sought priorly. This method's effectiveness has been independently confirmed by others (41–44). Further support for the velocity storage involvement in MdDS comes from a sham-controlled study, which demonstrated a treatment effect when head tilts were coupled with large-field visual motion as in the original protocol but not with a non-moving but otherwise identical visual pattern (45). A recent sequel animal-based study also supports that the effect of VOR maladaptation can be systematically cumulated or reversed by the choice of the vestibular stimulus (46). Together, VOR readaptation has come to be recognized as the first effective treatment for MdDS (47).

Unfortunately, while overall significant improvement in MdDS outcomes has been attained with VOR readaptation, about 25% of patients have been found not to benefit from this method, and re-exposure to prolonged passive motion or provocative visual stimuli can reverse the initial benefit after a successful treatment (12, 26). For these patients, an alternative approach is needed, particularly in delivering a countermeasure against provocative motion and visual stimuli. Velocity storage provides a critical control point for this purpose as well given its key role in visual-vestibular integration (29–31).

Velocity storage is most conventionally characterized with its activation during the VOR in darkness. In particular, the VOR slow phase velocity profile can be modeled as the sum of the outputs of the velocity storage and non-velocity storage pathways, in which the latter directly reflects the well-characterized peripheral vestibular activity (Figure 1A) (30, 48). In response to a velocity step rotation about a spatial vertical axis, the peripheral activity suddenly rises and then decays exponentially, the time constant for which is relatively invariant across individuals and estimated to be ≈4 s (Figure 1B, Direct Pathway Signal) (48, 49). The gain of the direct pathway (g_1) corresponds to the gain of the initial rise in the slow phase velocity of the VOR nystagmus. The velocity storage component can then be profiled in terms of its rate of charge/discharge, i.e., time constant (Tc), and the strength of connection with the direct pathway, i.e., gain of coupling (g_0), estimated from the model-based fit of the VOR slow phase velocity profile (Figure 1B, Indirect Pathway Signal). The present study does not include a characterization of the three-dimensional behavior of velocity storage. Although a three-dimensional articulation of VOR parameters expanded with cross-axis coupling terms has been formulated to express the spatial orientation properties of velocity storage (34, 50, 51), pertinent parameter estimation demands three-dimensional eye movement recording with appropriate test paradigms. This limitation has made it difficult to directly demonstrate the effect of the VOR readaptation treatment in terms of a change in the spatial orientation properties of velocity storage.

Age is among the various factors for inter- as well as intra-individual variations in velocity storage characteristics—the Tc reportedly is short in infants, increases through young adulthood, and then gradually decreases with aging (52, 53). Velocity storage can be modified in an individual—repeated vestibular stimulation can shorten the duration of the VOR with a diminished contribution of velocity storage in an effect known as habituation (54, 55), interpreted as shortening of the Tc (56–58). Some reports indicate fighter jet pilots, ballet dancers, and figure skaters are habituated to vestibular stimuli, although others question such generalization (59–64). Curiously, while velocity storage, as a center of multimodal sensory integration, may be useful in some contexts (28–32), habituated individuals show no known functional impairment.

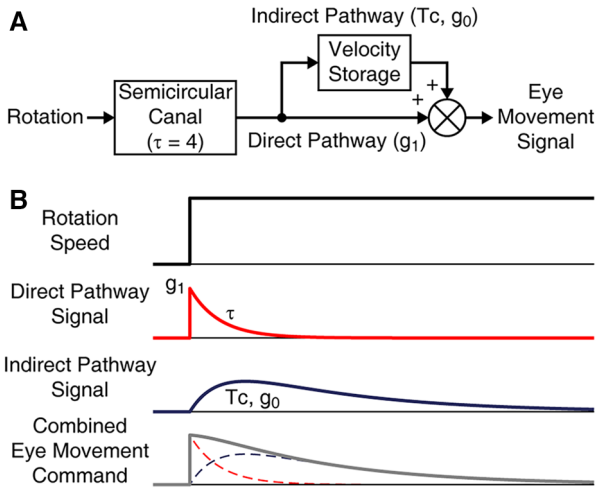

FIGURE 1
Model-based characterization of the VOR in darkness. (A) The VOR ideated as a combined output of direct and indirect pathways. The peripheral response to rotation has a time constant (τ) of 4 s. The direct pathway is in addition associated with a gain parameter g_1. The indirect pathway is associated with Tc and g_0. (B) Temporal response profiles of the model elements in reaction to a rotational velocity step stimulus.

Presently, we hypothesized that, if MdDS is caused by malfunctioning velocity storage, attenuating its contribution through reduction of Tc or g_0 will reduce the symptoms of MdDS. Velocity storage can be safely and greatly attenuated within 4–5 days using a protocol previously developed in our laboratory to reduce susceptibility to motion sickness (58). The new approach would be complementary to VOR readaptation, the latter of which aims to correct the spatial orientation properties of velocity storage rather than to change Tc or g_0. Moreover, since both animal- and human-based research suggests long-term retention of velocity storage attenuation (55, 57, 58, 65), we further hypothesized that this new utility would yield robust long-term outcomes. Thus, in this exploratory study, we set out to contrast the effects of the velocity storage attenuation and VOR readaptation regimens in the treatment of patients with MdDS and to elucidate how these approaches might be able to complement each other.

Methods

Patient selection

The study protocol was reviewed and approved by the Institutional Review Board of Icahn School of Medicine at Mount Sinai. Patient volunteers with MdDS were recruited through various sources of referral and announcements posted on the Internet, including ClinicalTrials.gov (NCT04213079). Applicants seeking treatment were screened with an intake form, and each candidate's diagnosis of MdDS with an associable motion trigger was confirmed by a board-certified physician through a telephone interview when necessary. The accuracy of the paperwork was then verified again. The eligibility criteria were similar to those in our previous studies (12, 27, 38): (1) presentation of continuous oscillatory vertigo and/or gravitational pulling, which had persisted for at least 3 weeks; (2) symptom onset within 48 h after exposure to prolonged passive motion; (3) improvement in symptoms when in a moving vehicle (e.g., a car) and a return of symptoms with the stop of the vehicle (4); (4) No history of head or neck trauma, Lyme disease, serious peripheral vestibular disease, or other major neurological disorders; (5) normal nystagmography reports; and (6) 18–78 years of age. Many had completed neurologic and otologic workups, including magnetic resonance imaging, that were unremarkable. Applicants were informed that, if selected, they would be randomly assigned to one of the two treatments. As an incentive to remain in the study, applicants were also informed that after completing a six-month post-treatment follow-up, they would have an opportunity to return to the laboratory and receive the same or alternative treatment for free of charge if the symptoms persisted or returned. Enrolled subjects were asked to stay in the New York Metropolitan area during the treatment period to minimize the risk of exposure to passive motion that might confound the effect of the treatment. None of the subjects were taking a benzodiazepine medication regularly during the study participation.

Self-reported MdDS symptom severity

The manifestation of MdDS is often only subjective, and thus, the severity of the illness cannot be judged with physical signs. As with our previous studies (12, 27), the overall severity of MdDS-related symptoms, including not only the sensation of self-motion but also somatic, cognitive, and affective problems, was subjectively reported on a single 11-point scale of 0–10, where the score 0 indicated no symptoms and 10 the most difficult of combined symptoms that the patient subject could imagine. This self-rating was used to document the presence or absence of symptoms and changes in subjective perception of their overall severity, and to assess treatment effects for a particular subject rather than to compare symptom severity between individuals. Subjects were asked to report their symptom severity before and immediately after the treatment, as well as at 2-week, and 1-, 3-, and 6-month follow-ups. This measure was the primary outcome examining the treatment regimens' efficacy for symptom reduction.

Nystagmography

Subjects were tested for their VOR while seated in a rotational chair in a closed cylindrical chamber that had an inner radius of 90 cm (Neurokinetics, Pittsburg, PA). Eye movement was recorded with videooculography at a rate of 60 frames per second (Model RK-416, ISCAN, Woburn, MA) or 240 frames per second (FN-VN-02-240B, FNND LLC, Elmwood Park, NJ) and calibrated by having the subject look at a laser-projected red dot on the wall of the darkened chamber. The VOR of one subject from Group 2 could not be tested due to claustrophobia. Eye movement of another subject from Group 2 could not be recorded due to equipment malfunction. The eye movement of an additional subject from each group could be recorded successfully only on the first day, similarly due to equipment malfunction.

To screen for a possible cerebellar abnormality, the ability to suppress the VOR with a visual cue was tested on the first day of the subject's laboratory visit. This test was conducted with sinusoidal side-to-side rotation about a spatial vertical axis at 0.1 Hz with a peak speed of 60°/s, first in complete darkness and then with a laser-projected red dot that moved with the chair, i.e., stationary relative to the subject in motion. To characterize and contrast the vestibular physiological responses to the treatment regimens, the VOR was tested with a velocity-step rotation about a vertical axis on each day of the laboratory visit before the day's treatment regimen. The VOR was characterized with daily pre-treatment assessments because expression of velocity storage depends on the levels of fatigue and alertness of the subject (66–69). The test was conducted by accelerating the chair in darkness from 0 to 60°/s within 200 ms, holding the velocity until the induced per-rotatory nystagmus dissipated, and decelerating the chair to stop within 200 ms. After the post-rotatory nystagmus dissipated, the direction of the rotation was reversed.

Data were processed using a software program developed in our laboratory (70). Saccades in eye velocity traces were identified using an order-statistic filter (71), followed by visual inspection and manual correction, and replaced with straight lines connecting the remaining segments. For the VOR suppression test, the horizontal slow phase velocity profiles were fit with sine functions to assess the percentage of response reduction. Visual suppression of the VOR by more than 85% was considered normal. For the velocity-step test, the horizontal slow phase velocity profile was fit with a double exponential curve, for which the first exponent was constrained with the initial peak velocity and a time constant of 4 s representing the semicircular canal response with g_1 denoted as the direct pathway gain, and g_0 and Tc were derived as the second component representing the velocity storage response (Figures 1, 2A,B) (48). The values of g_1, g_0 and Tc computed from two per-rotatory and two post-rotatory responses from right- and leftward rotations were then averaged to reduce statistical noise due to random performance variability. Linear regression was used to determine the trend of each VOR parameter's changes over days of treatment within individuals. The ordinate intercept and the trendline value corresponding to the last day of treatment were considered to

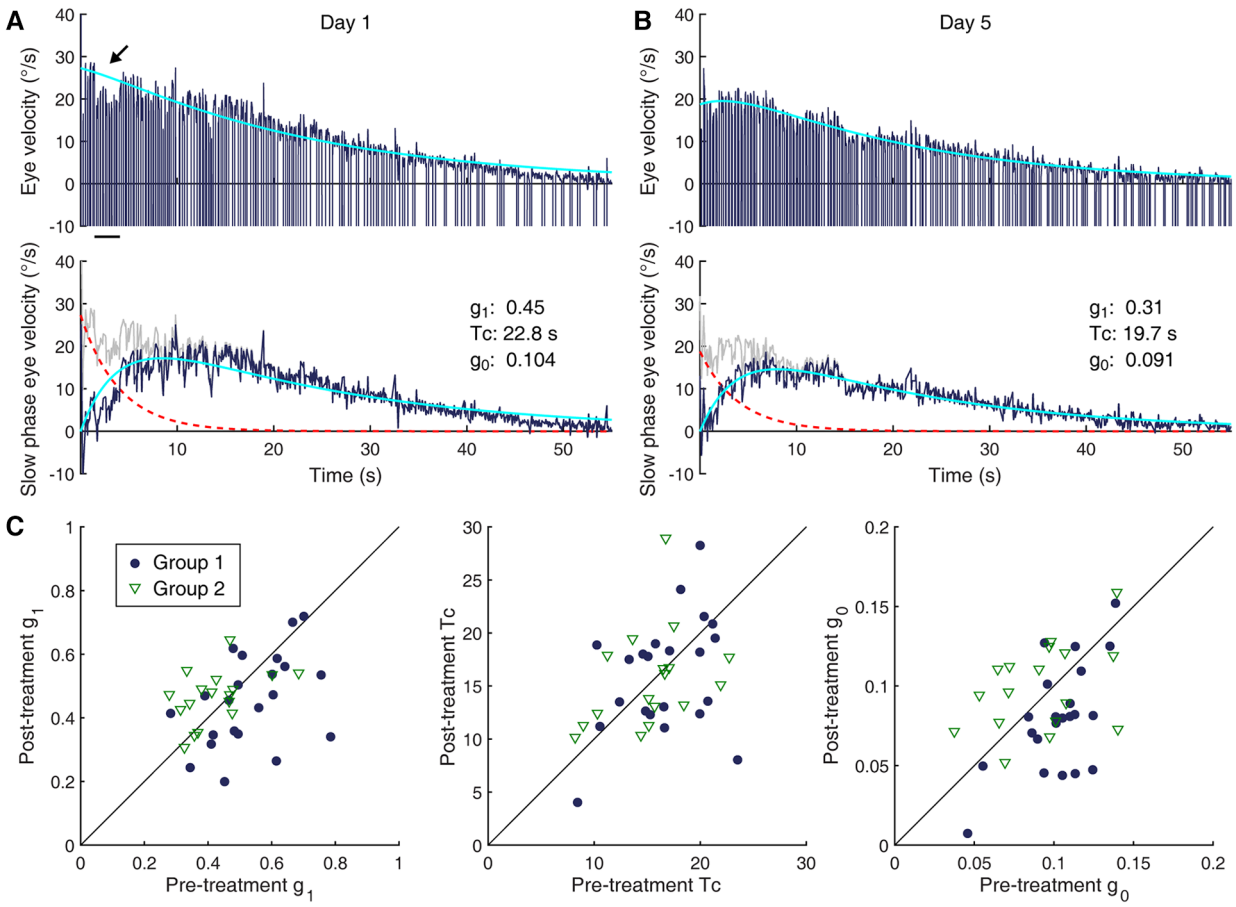

FIGURE 2
Changes in the VOR. (**A**,**B**) Characterization of VOR responses. Shown are per-rotatory eye velocity responses to a leftward 60°/s rotation by a 58-year old woman (Subject 16, Group 1) on Day 1 (**A**) and Day 5 (**B**) Top row: eye velocity profile of the nystagmus (dark blue) and a double exponential model-based fit of the slow phase modulation (cyan). Fast phase velocity profiles are truncated at −10°/s. The dip in the eye velocity profile indicated by the arrow corresponds to low-amplitude, high-frequency oscillations (shimmering nystagmus), not reflective of an actual reduction of the slow phase eye velocity. Second row: decomposition of the model elements—slow phase modulation profile (gray), direct pathway contribution (dashed red trace), velocity storage contribution (dark blue), and model fit (cyan). (**C**) Pre- and post-treatment measures of VOR parameters in individual subjects (Group 1: filled circles; Group 2: open triangles). (Left) g_1. (Center) Tc. (Right) g_0. The diagonal lines indicate lines of equality.

represent the pre- and post-treatment values, respectively. For the two subjects whose eye movement were recorded only on the first day of their laboratory visits, only the pre-treatment values represented by these data were considered.

A large data set of Tc and g_0 was available through previous clinical and research testing for velocity storage characteristics conducted in our laboratory. We reviewed 6,065 de-identified records made between 1993 and 2019. Data were selected as non-MdDS with normal vestibular function if they were part of a study with normal subjects, or taken from patients with a complaint of dizziness due to quick changes in body orientation such as standing after a long period of sitting or lying down (orthostatic intolerance) or from patients who came to the laboratory for testing after being treated for benign paroxysmal positional vertigo. We identified 911 such records (571 women; 340 men, age range: 13–95 years old). We also identified similar previous records of 28 patients diagnosed with MdDS (25 women, 3 men), not overlapping with the current cohort. Age, sex, Tc, and g_0 data were extracted from these records for analysis. The data from these historical cohorts together with those from the current MdDS cohort were used to examine potential abnormalities in Tc or g_0 in patients with MdDS.

Assessment of vestibular imbalance and posture

The internal sensation of motion or imbalance in MdDS is often not manifested as a physical sign (12). However, the Fukuda stepping test (72) and static posturography were routinely conducted to supplement the subjects' verbal description of their sensations. The results were also used to guide the stimulus parameters for the VOR readapation treatment (Group 2) as described below. The subject performed the Fukuda stepping test on the first day of the laboratory visit before the treatment. Posturography was conducted each day and

to supplement verbal feedback. Postural data were recorded using a Wii board (Nintendo Co. Ltd. Kyoto, Japan), whose output was sampled at 10 Hz and cubic-spline upsampled to 1,000 Hz (12). Posture was assessed with the feet ≈30 cm apart with the eyes open and closed, and the feet together with the eyes closed. To register the direction and frequency of the subjective sensation of self-motion, subjects were often asked to move their bodies while standing on the Wii board in a manner that exaggerated what they felt. The dominant frequencies of the postural instability in the sagittal and coronal planes were determined from the power spectra of the recorded center of pressure (73).

Group 1—treatment with velocity storage attenuation

To attenuate velocity storage, a conflict was induced between two velocity storage-mediated responses, namely optokinetic nystagmus (OKN) and the VOR during sinusoidal side-to-side rotation about a spatial vertical axis at low frequency. Following the previously described protocol that induced vestibular habituation with shortened Tc, 0.017 Hz (i.e., 60 s period) was used (58). The VOR of normal individuals at this frequency on average reportedly has a phase advance of approximately 30° and a gain of 0.68 relative to the ideal compensatory response (58). In contrast, the slow phase eye velocity of the OKN at such a low frequency has no phase advancement relative to the optokinetic stimulus (OKS) (74). A full-field horizontal OKS was generated by projecting vertical stripes against the wall of the cylindrical enclosure from a projector rotating about a vertical axis directly above the subject's chair. The width of the stripes was 8 cm for the projected light and 11 cm for the interposed shadows, respectively corresponding to 5° and 7° in visual angle. To simplify the protocol, a VOR gain of 0.68 and a phase advance of 30° relative to the ideal were assumed across all subjects, and the OKS was set 180° out of phase with the expected VOR to have OKN counteract it (58).

Since the conflict stimulus was expected to be overwhelming to subjects at high speeds, they were first trained with a peak rotation speed of 5°/s, which was gradually increased over days up to 50°/s. This speed was higher than the 20°/s benchmark used in the treatment of patients with high susceptibility to motion sickness (58). When the protocol was previously clinically applied to MdDS, patients began to show signs of symptom improvement when the peak rotation speed reached 30–40°/s; therefore, 40°/s was considered a benchmark of treatment completion in the present application, although two subjects were unable to tolerate 40°/s by the last day of the treatment. Each training session was targeted to last for 20 min, with a 10-min break provided between sessions. Two to three sessions were administered each day for a total duration of ≈300 min, typically completed in five days. To stay alert, subjects were encouraged to listen to an audio program of their choice during the session. However, a full-field OKS is so powerful that one would not need to be attentive to the moving stripes to experience vection from the visual motion. The brightness of the OKS projector was adjustable. Based on our previous experience, a brightness of 2 lux was deemed tolerable to most patients with MdDS. Thus, the projector brightness was initially set to 2 lux. One subject could not tolerate the initial setting, and the training was resumed with a peak rotation speed of 2°/s, brightness of 1 lux, and duration of 5 min. However, this subject was able to complete the treatment protocol by Day 5 with a 50°/s peak rotation speed, brightness of 2 lux, and duration of 20 min. For another subject who reported no discomfort and had no history of migraine or motion sickness, the brightness was increased to 3 lux from Day 3. In case of nausea or other elevated signs of motion sickness, the treatment was discontinued until the next day.

Group 2—treatment with VOR readaptation

To induce a change in the spatial orientation properties of velocity storage, a full-field, unidirectional horizontal OKS was generated in the cylindrical enclosure and combined with a head maneuver (12, 26). This stimulus was not presumed to change g_1, Tc, or g_0. The combination of the OKS and the head maneuver was customized for each subject based on the phantom motion sensations experienced by the subject. The stimulus was further customized to minimize side effects from overexposure to OKS, such as head pressure, brain fog, fatigue, and migraine, which were anticipated due to an elevated sensitivity to moving visual stimuli in many patients with MdDS. The initial duration of the treatment session, OKS velocity, and projector brightness were respectively set at a mild level of 1 min, 5°/s, and 2 lux based on our previous study (12). When subjects reported no discomfort with the stimulus while reporting no or negligible improvement in symptoms, the duration of the treatment session was increased up to 10 min, the OKS velocity up to 10°/s, and projector brightness up to 3 lux, as tolerated.

The OKS direction was chosen to oppose the direction indicated by the Fukuda test or that of the sensation of pull or circular body motion (12, 26). In the absence of such indications, the direction was chosen arbitrarily. The head maneuver was orthogonal to the motion sensation or the postural instability of the subject. Thus, when the motion was characterized mainly as rocking back-and-forth, the head was rolled from side to side about the naso-occipital axis. When the motion was characterized mainly as swaying from side to side, the head was pitched forward and backward about the interaural axis. The frequency of head tilts was chosen to approximate the frequency determined from the posturography measures, which typically was expected to be near 0.2 Hz (26, 75). The magnitude of head tilts was initially ≈±20° but was varied from ≈±5° to ≈±30° depending on the subject's response to the treatment. The choice of the OKS direction was tested with a 1-min administration of the stimulus combined with a head maneuver. If symptom improvement was reported, the treatment was continued at half the initial frequency of head motion for 2 min and then at a quarter of the initial frequency for 3 min. A ≈5 min break was given between trials.

After completing the sequence, subjects would often report substantial immediate improvement in their symptoms. In such

cases, we asked the subjects to go outside for 10–15 min to expose themselves to the naturally busy visual environment of New York City streets. When symptoms were re-triggered, the treatment sequence was repeated, but otherwise, no further treatment was given that day.

When worsening or no improvement of symptoms was reported with the initial choice of the OKS direction, the direction was reversed. When no improvement was reported for either direction, the treatment duration was increased to 2 min without changing the head maneuver frequency. When still no improvement was reported, the stimulus was intensified by increasing the projector brightness and/or the OKS speed, but without changing the OKS direction. The treatment, with breaks, was continued during the allocated time for the day's visit of 90 min, unless the subject reported discomfort such as head pressure and headache.

When the subject reported improvement of symptoms on the next day, the protocol used on the previous day was repeated. When the subject reported worsening or no changes in symptoms, the opposite OKS direction was applied. Additionally, we found that some subjects responded well only when the head was oscillated at a specific frequency. For these subjects, the total duration of treatment sessions at that frequency was increased.

Statistical analysis

Group characteristics were compared with a Fisher exact test (sex), a two-sample *t*-test (age and VOR parameters), or a Wilcoxon–Mann–Whitney test (MdDS duration). For each group, within-subject changes associated with the respective treatment intervention in the VOR parameters (g_1, g_0, and Tc) were tested with a paired *t*-test. The alpha level was set at 0.05. The effect size of a difference between two means or a deviation of the mean from zero in the VOR parameters was examined with a coefficient d, defined as the mean difference divided by the corrected sample standard deviation.

A trend in a scatter plot of Tc or g_0 data from the non-MdDS historical cohort in relation to age was identified with locally estimated scatterplot smoothing (LOESS) (76), and the residuals of the fit were obtained. The width of the moving window relative to the data size, or span, was chosen through iteration by visually examining the dependence of the residuals on age (77). Differences from the same fit were also obtained for the previous and current MdDS cohorts as pseudo-residuals. A between-cohort difference in the distributions of these pseudo-residuals was tested with a two-sample Kolmogorov-Smirnov test. Overall deviations of the pseudo-residuals from zero and between the cohorts were tested with one- and two-sample t-tests, respectively.

We defined a clinically significant improvement, or a success of a treatment in a subject, as the rating on the 0–10 subjective scale of symptom severity being reduced by more than one half of the pre-treatment level (12, 27). Considering the chronicity of MdDS, a symptom score reduction by half or more in an individual was deemed substantial and beyond short-term fluctuations influenced by engaged activities or hormonal changes. Thus, individual success or non-success was defined dichotomously by this criterion. A groupwise success rate was calculated as the ratio of the number of subjects with a significant improvement to the total number of subjects for the immediate post-treatment and follow-up time points. In interpreting a groupwise success rate, we compared it to the outcome of a series of two random draws from the range 0–10. The probability that a second random draw would result in less than one half of the corresponding first draw is smaller than 25%, and therefore, a groupwise probability of success above 25% should represent a strength of a treatment approach. A binomial test was used to determine if this benchmark was statistically achieved.

Interdependence between variables was tested with Spearman's rho. The strength of correlation was interpreted according to a guide suggested for behavioral sciences, such that $0 \leq |\text{rho}| < 0.2$ is interpreted as negligible, $0.2 \leq |\text{rho}| < 0.4$ as weak, $0.4 \leq |\text{rho}| < 0.6$ as moderate, $0.6 \leq |\text{rho}| < 0.8$ as strong, and $0.8 \leq |\text{rho}| \leq 1$ as very strong (78).

Results

Demographic characteristics

Patients with MdDS were recruited on a rolling basis between April, 2020 through July, 2022. There were 329 applicants, of whom 178 completed all forms with nystagmography reports and met the eligibility criteria on first screening. A total of 45 subjects were enrolled in the study in the order of confirmed eligibility and the condition of being able to be scheduled for the laboratory visits. The remaining candidates were wait-listed for another possible research opportunity if desired. Enrolled subjects were randomly assigned to Group 1 (velocity storage attenuation) or Group 2 (VOR readaptation). Two subjects from Group 2 dropped out of the study by failing to participate in the follow-up—data from the remaining 43 subjects (23 Group 1; 20 Group 2) are reported here. The majority of the subjects were women (83.7%), reflecting the female dominance of the diagnosis (9, 13). Only two subjects from Group 1 and four subjects from Group 2 were locally based, and the majority (86.1%) traveled from outside the New York Metropolitan area to undertake the experimental treatment. The subjects' age ranged from 22 to 78 years old, distributed with characteristics typical of this population (mean, 47.1; SD, 14.0) (9, 13). The durations of the subjects' MdDS episodes ranged from 1 to 90 months and their distribution approximately followed an exponential profile that was positively skewed (mean, 19.9; SD, 22.2). The two groups did not differ in the distributions of sex, age, or MdDS duration (Table 1). All subjects with eye movement recording demonstrated a normal VOR and visual suppression of the VOR.

Changes in the VOR

Example eye velocity responses to a 60°/s step rotational test, obtained from a single subject from Group 1 on the first and

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TABLE 1 Group characteristics.

	Group 1	Group 2	*p*
% women	91.3	75.0	0.22
Age in years, mean (SD)	47.4 (13.9)	46.7 (14.2)	0.87
Duration in months, mean (SD)	19.4 (21.7)	19.8 (24.0)	0.88
g_1 before, mean (SD)	0.53 (0.13)	0.42 (0.10)	**0.005**
g_1 after, mean (SD)	0.45 (0.14)	0.47 (0.08)	0.74
Tc before, mean (SD)	16.6 (3.9)	15.0 (4.0)	0.22
Tc after, mean (SD)	16.0 (5.4)	15.6 (4.5)	0.79
g_0 before, mean (SD)	0.102 (0.022)	0.093 (0.030)	0.33
g_0 after, mean (SD)	0.080 (0.033)	0.099 (0.027)	0.07

Bold typeface indicates $p < .05$.

fifth days of the laboratory visits, are illustrated in Figures 2A,B. Estimated contributions of the direct and indirect pathways of the VOR (48) are profiled in the bottom inset of each panel. The pre-treatment characterization of the VOR of all subjects with eye movement recording was such that the mean (SD) g_1, Tc, and g_0 were 0.48 (0.13), 15.9 (4.0) s, and 0.098 (0.026). The mean g_1 was statistically different between the two groups, with that of Group 1 being meaningfully larger [$|t(39)| = 2.95$, $p = 0.005$, $d = 0.93$]. As we focused on within-group changes, this unexpected imbalance in g_1 in the randomly assigned groups presumably did not create an intrinsic bias in the study. The groups did not differ significantly in the pre-treatment Tc or g_0 (Table 1), i.e., the velocity storage characteristics of the two groups were similar.

To the extent that MdDS may be caused by malfunctioning velocity storage, we sought to determine whether the pre-treatment Tc of patients with MdDS was different from those of individuals without MdDS or other vestibular dysfunction known to affect velocity storage. Since age is a known confounding variable (53), the 911 historical data points of non-MdDS laboratory visitors with presumably normal VOR were plotted against age (Figure 3A). The inter-individual variability was large relative to the 4 s time constant fixed for the semicircular canal response. To elucidate the underlying effect of age, the data were fit with LOESS with a span of 0.45. The resulting trend curve was overall convex upward and reached the maximum time constant value of 17.8 s at the age of 41 years. The SD of the residuals was 5.2 s. Given that the residuals did not differ by sex [$|t(909)| = 1.11$, $p = 0.27$] and that the number of men in the MdDS cohorts was small, comparisons were conducted with both sexes combined. The Tcs of the historical and current cohorts of patients with MdDS obtained before any treatment were then superimposed on the trend curve created for the non-MdDS laboratory visitors (Figure 3B). The inter-individual variability was also large in these cohorts. The two cohorts did differ from each other in the distributions of the pseudo-residuals relative to the trend curve [$D(28,41) = 0.334$, $p = 0.038$]. The pseudo-residual means (SD) of the historical and current patient cohorts were 1.7 (4.0) s and −1.0 (4.0) s, respectively, and their difference was also statistically significant [$|t(67)| = 2.73$, $p = 0.008$]. However, only the pseudo-residual mean of the of the historical patient cohort was significantly different from zero [$|t(27)| = 2.20$, $p = 0.036$], and the effect sizes of the deviations were both small (historical: $d = 0.42$; current: $d = 0.25$). Thus, evidence for abnormal Tcs in MdDS was deemed weak.

Similarly, we sought to determine whether the pre-treatment g_0 was different in patients with MdDS (Figures 3C,D). The LOESS trend curve obtained from the non-MdDS visitors was nearly flat from ages 13 through 70 years old, taking on values of ≈0.107, and thereafter steadily declined with a slope of ≈−0.0013 per year. The residuals statistically significantly differed by sex [$|t(909)| = 2.58$, $p = 0.01$], with the female mean (SD) 0.002 (0.033) above the trend curve and the male mean −0.004 (0.031), below the curve, but this numerically small difference was deemed not to be practically meaningful ($d = 0.18$). Therefore, as with Tc, comparisons with the MdDS cohorts were conducted with both sexes combined. The two MdDS cohorts did not differ in the means of the pseudo-residuals [$|t(67)| = 0.80$, $p = 0.42$] or their distributions [$D(28,41) = 0.21$, $p = 0.41$]. The combined pseudo-residuals in turn were not statistically different from the residuals of non-MdDS visitors [$|t(978)| = 1.48$, $p = 0.14$]. Thus, an abnormal g_0 was also not identified as a characteristic of MdDS.

With the treatment regimen, there was a statistically significant change in the g_0 of Group 1 [$|t(21)| = 3.95$, $p < 0.001$], with a mean (SD) reduction by 0.023 (0.027). The effect size of the change was large ($d = 0.84$). This change is illustrated in Figure 2C (rightmost panel) with the filled circles falling mostly below the identity line drawn diagonally. Although unintended, the change in g_1 was also statistically significant in Group 1 [$|t(21)| = 2.62$, $p = 0.016$]. The effect size of this change was medium ($d = 0.56$). On the other hand, a statistically significant change in Tc was not detected. Thus, the visual-vestibular conflict regimen applied to Group 1 modified velocity storage in patients with MdDS by reducing the coupling gain, but not the rate of charge/discharge, and additionally reduced the gain of the initial fast VOR response. The reductions in g_0 and g_1 showed only a weak, statistically non-significant correlation to each other (rho = 0.31, $p = 0.17$) while their correlation to Tc was both negligible.

As expected, no statistically significant change in any of the three VOR parameters was detected for Group 2, which in Figure 2C is illustrated as open triangles falling both above and below the identity line in each panel. Thus, the strength of the velocity storage contribution to the VOR was not systematically affected by the readaptation regimen applied to this group. There was nevertheless some fluidity in the data, and individual changes in Tc measurements showed a moderate but statistically non-significant negative correlation with those in g_0 (rho = −0.48, $p = 0.052$) and a weak, non-significant positive correlation with those in g_1 (rh0 = 0.21, $p = 0.41$). The correlation between the changes in g_1 and g_0 was negligible.

Changes in symptoms

Upon completing the treatment regimen, 19 of the 23 subjects of Group 1 rated their symptoms as having been reduced from the pre-treatment level, of whom 10 reported a reduction by more than half (Figure 4A). Thus, the immediate success rate for Group 1 was 43%, which was above a chance level ($p = 0.041$), indicating a strength of

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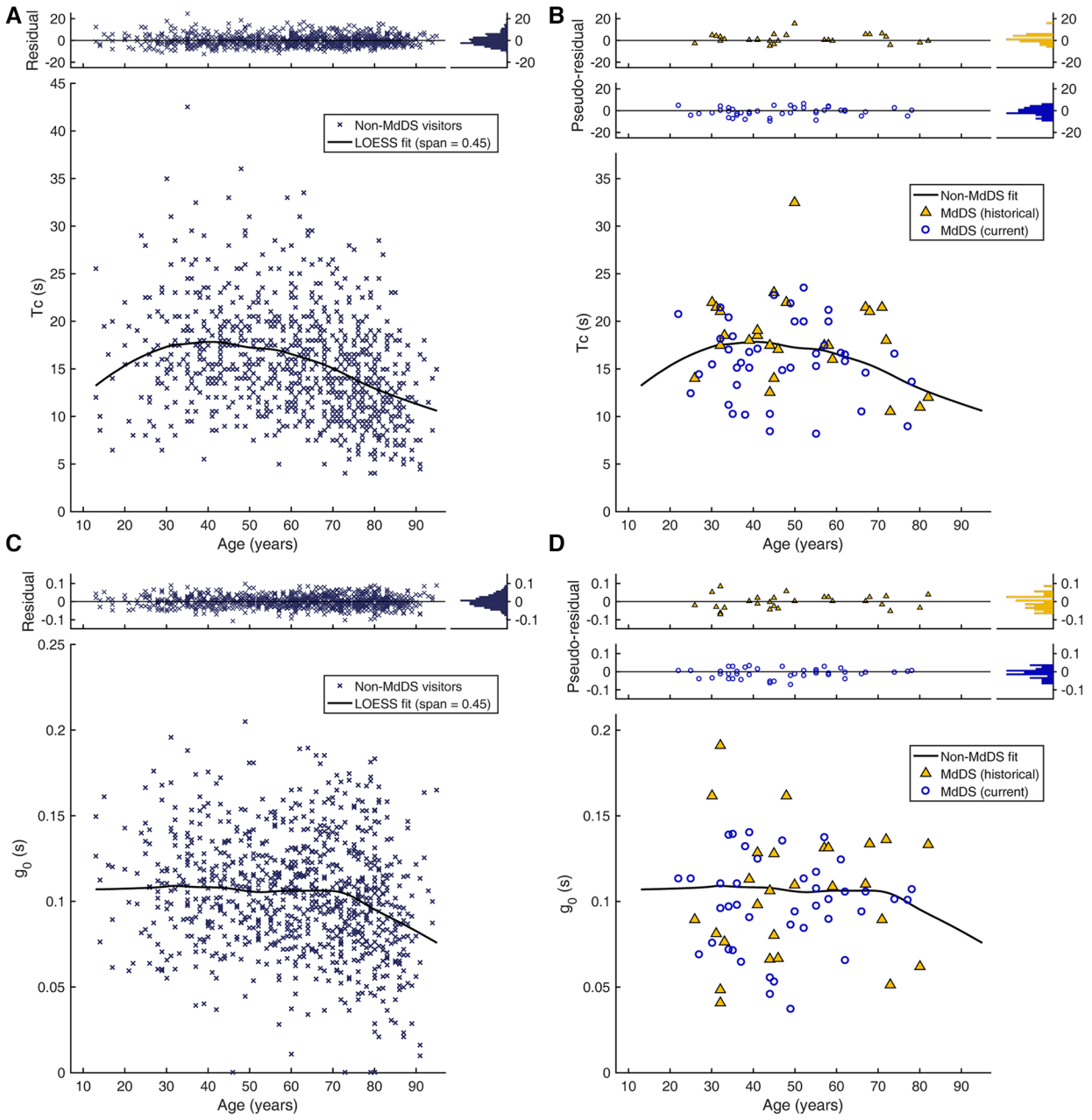

FIGURE 3
Age dependence of velocity storage parameters. (A) Tc of non-MdDS laboratory visitors (n = 911). Individual Tc values are plotted against age. The top inset shows the distributions of individual deviations from the trend curve (residuals). (B) Tc of two cohorts of patients with MdDS. The top inset shows the distributions of the two cohorts' individual deviations from the trend curve from (A) (pseudo-residuals). (C) g_0 of the non-MdDS laboratory visitors. (D) g_0 of the two patient cohorts.

the treatment. This rate is displayed as the left most filled circle marked with an asterisk in the summative figure (Figure 4C). Of the remaining four subjects, three reported no change in their symptoms, and one reported worsening of symptoms. The worsening of symptoms in this subject (Subject 15) was on account of a transient increase in visual sensitivity that occurred on the last two days of the laboratory visits as the visual-vestibular conflict used in the treatment was intensified. For Group 2, all 20 subjects rated their symptoms as having been reduced from the pre-treatment level, of whom 16 reported a reduction by more than half (Figure 4B). Thus, the immediate success rate of the readaptation protocol was 80%, indicating a great strength of this treatment ($p < 0.001$) at a rate similar to those previously reported (12, 45). This rate is displayed as the left most open triangle marked with three asterisks in Figure 4C.

Exposure to passive motion during a long travel to return home after the treatment or during any subsequent occasion was previously noted as a major trigger for symptom recurrence (12, 26). Group 2 was particularly vulnerable to this effect, as evidenced by a trend for symptoms to bounce back in individuals and a corresponding sharp decline in the groupwise

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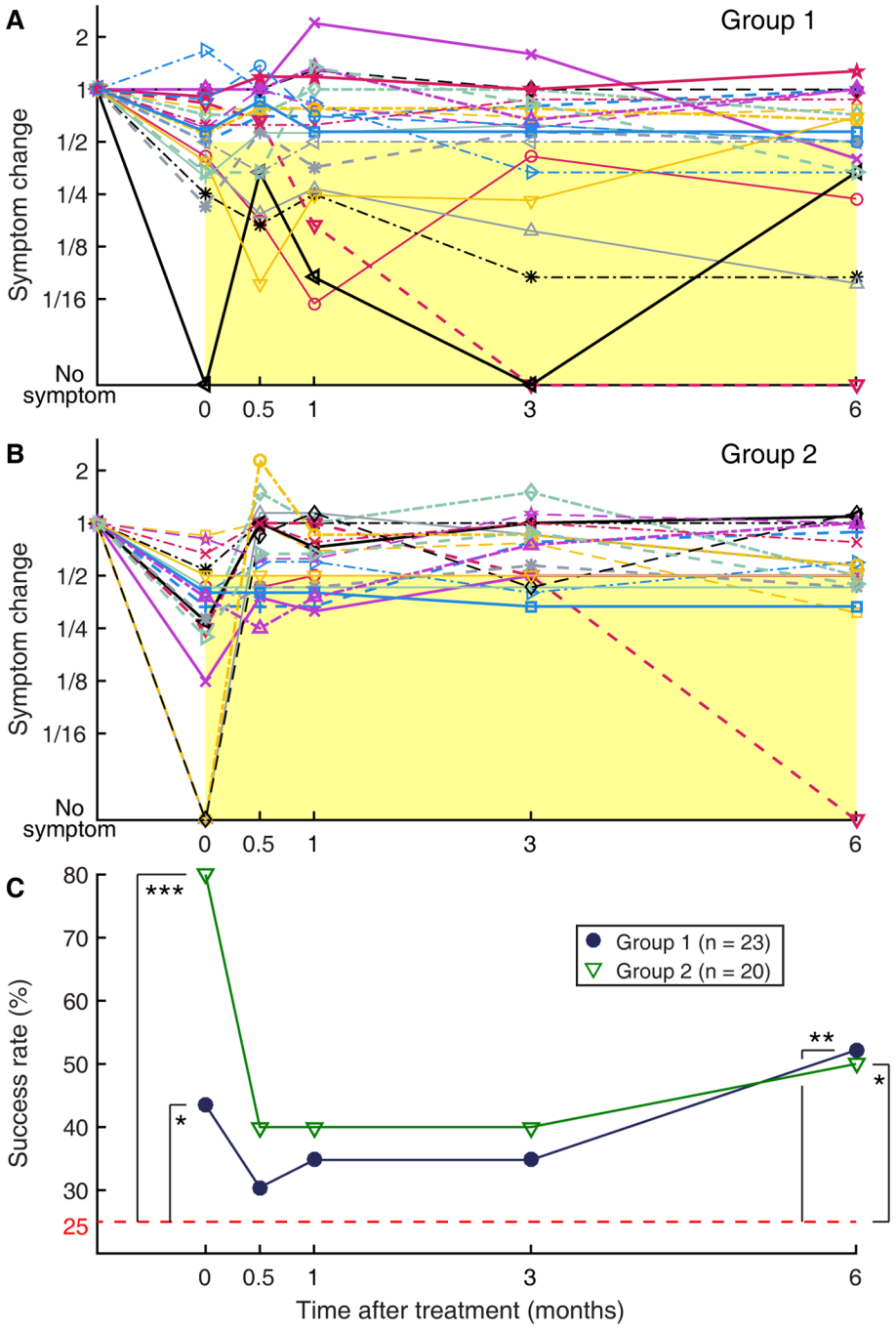

FIGURE 4
Longitudinal changes in subjective symptom rating, normalized to the pre-treatment level. (A) Group 1. (B) Group 2. Each set of connected markers indicate an individual subject. Time zero indicates immediately after the treatment. All responses are normalized relative to the pre-treatment symptom level, to which a value of 1 is assigned. Markers falling on the yellow rectangular areas indicate a successful outcome defined as more than a halving of symptom severity relative to the pre-treatment level. (C) Summary of (A) and (B) plotted as groupwise "success" rate over time. Filled circles: Group 1; open triangles: Group 2. The dashed horizontal line indicates the expected rate with random reporting of a halving of symptom severity, i.e., group-wise non-recovery. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

success rate at the two-week (0.5 months) post-treatment follow-up assessment (Figures 4B,C). Only five of the 16 subjects with initial success in Group 2 continued to experience more than a halving of symptoms relative to the pre-treatment level throughout the 6-month follow-up period. The other 11 subjects with initial success experienced a symptom rebound at some point during the 6-month follow-up period, including one who reported more than a doubling of symptom rating relative to the pre-treatment level at two weeks post-treatment, although this increase was later partially reversed. In total, there were a total of five subjects with initial success who reported a symptom rebound to the pre-treatment level or worse at two weeks post-treatment, and they

TABLE 2 Correlation between immediate post-treatment symptom rating and those in longer terms.

		2 weeks	1 month	3 months	6 months
Group 1 ($n = 22$)	rho	**0.81**	**0.64**	**0.58**	**0.49**
	p	**<0.001**	**0.001**	**0.004**	**0.020**
Group 2 ($n = 20$)	rho	−0.20	−0.25	0.06	−0.05
	p	0.394	0.278	0.806	0.823

Bold typeface indicates $p < .05$.

were all non-local participants who necessarily were exposed to prolonged passive motion on their way home after the treatment. Three of four local participants in Group 2 were initially successfully treated, and none of the three reported a symptom rebound to the pre-treatment level at two weeks post-treatment. Furthermore, in Group 2, the immediate post-treatment outcome did not predict the long-term outcome; the normalized symptom ratings at two-week through six-month post-treatment were not statistically significantly correlated with the immediate post-treatment symptom rating ($|\text{rho}| < 0.26$, $p > 0.27$) (Table 2).

Compared to Group 2, and as intended, Group 1 was more resistant to symptom recurrence. Although the overall success rate for this group dropped from 43% to 30% at two weeks post-treatment, none of the 10 subjects with initial success reported a symptom rebound to the pre-treatment level (Figures 4A,C). This result is despite that all these subjects were non-local participants and were exposed to prolonged passive motion on their way home after the treatment. Over the six-month follow-up period, only one of these 10 subjects with initial success reported that the symptoms gradually returned to the pre-treatment level, while 5 subjects reported continuing to experience significantly reduced symptoms throughout the six-month period, and the remaining 4 reported symptom fluctuations but around an overall reduced level. Subject 15, who developed a transient increase in visual sensitivity during the treatment, rated the symptom level at two weeks post-treatment as unchanged from the pre-treatment level. On the other hand, the two local participants in Group 1 turned out not to successfully respond to the treatment, and their symptoms fluctuated during the six-month follow-up period. In general, despite the fluctuations in symptom ratings over time, the immediate post-treatment outcome was predictive of those in longer terms in Group 1. The correlation with the immediate post-treatment symptom rating was very strong at two weeks post-treatment ($\text{rho} = 0.82$, $p < 0.001$), gradually reducing to a weak and statistically non-significant level at six months post-treatment ($\text{rho} = 0.38$, $p = 0.072$). However, when Subject 15 was excluded from the analysis, the correlation remained very strong to moderate and statistically significant throughout the six-month follow-up period ($\text{rho} > 0.49$, $p < 0.020$) (Table 2).

Relation between VOR characteristics and treatment responsiveness

Finally, we examined whether the responsiveness to the treatment was correlated with the VOR parameters, g_1, Tc, and g_0. However, for either group (and for Group 1, with or without Subject 15), the immediate post-treatment change in symptom rating was at best weakly, and statistically non-significantly correlated with either pre- or post-treatment values of g_1, Tc, or g_0 (median $|\text{rho}| = 0.15$, $p > 0.10$). Furthermore, despite that Group 1's visual-vestibular conflict regimen, designed to attenuate velocity storage, indeed succeeded in reducing g_0, there was no clear correlation between this change and the reported symptom change. There was also no clear correlation between changes in g_1 or Tc and that in symptoms. On the other hand, even though there was no groupwise change in any of the three VOR parameters in Group 2, a moderate correlation was found in Group 2 between reduced g_1 and reduced symptom rating ($\text{rho} = 0.57$, $p = 0.016$) and between increased g_0 and reduced symptom rating ($\text{rho} = -0.51$, $p = 0.036$). As changes in g_1 and g_0 were not correlated in this group, the implication for these correlations, spurious or not, is not clear.

Discussion

In this study, we investigated whether symptoms of MdDS could be improved by attenuating the velocity storage contribution in the central vestibular pathways by using a slightly intensified version of a vestibular habituation protocol that was previously developed for motion sickness treatment (58). Because velocity storage is thought to contribute to the perception of spatial orientation and self-motion (28, 30, 31, 39), we reasoned that spatial disorientation and false sensation of self-motion in MdDS might be curbed when the contribution of a presumably malfunctioning velocity storage mechanism was limited with this protocol. A successful outcome defined as a more than halving of the subjective symptom rating from the pre-treatment level was initially achieved in 43% of the 23 subjects who underwent this treatment regimen (Group 1). This rate of success was at an above-chance level and represented a strength of the approach. Given that MdDS was previously considered intractable (3), the treatment regimen, composed of low-frequency oscillation coupled to a conflicting visual stimulus, is a welcome addition to the emerging countermeasures to the illness (12, 22, 26, 38, 79, 80). Remarkably, the initial impact of the treatment was strongly predictive of the long-term outcome, with the majority of positive responders reporting overall reduced symptoms during the 6-month follow-up period. Thus, if initially effective, the treatment also had a long-term prophylactic effect against symptom relapse. This result is consistent with the long-term retention of velocity storage attenuation previously demonstrated in both animals and humans (55, 57, 58, 65).

We found a clear contrast in the long-term outcomes of the two treatment approaches that we delivered, one aimed to attenuate velocity storage (Group 1) and the other to correct the spatial orientation properties of velocity storage (Group 2). The latter, the VOR readaptation regimen, yielded a high initial success rate, presently at 80%, similar to those previously reported (12, 26). However, the initial impact was not predictive of the subsequent symptom reports, supporting that spatial

readaptation of the VOR is not prophylactic of symptom relapse, presumably because the treatment regimen does not change the adaptive potential of the velocity storage mechanism.

As expected from the experimental design, systematic changes in the VOR response to a velocity-step rotation were shown only in the group that underwent the modified vestibular habituation protocol (Group 1). The protocol attenuated the contribution of velocity storage by way of a reduction in the coupling gain, g_0, but not of a reduction in the rate of charge/discharge, Tc. The protocol in addition reduced the gain of the rapid VOR response, g_1. These outcomes in patients with MdDS are at odds with the original application of the protocol in a motion sickness study involving both healthy normal and motion sickness-susceptible individuals (58). In this study, the velocity storage contribution was also attenuated but by way of a reduction in Tc without a change in the VOR gain. The source of the discrepancy is presently unknown, but the training stimulus was intensified at a faster pace and to a greater degree in the present application of the protocol. In addition, as visual coupling to velocity storage has been reported to be saturated at only ≈20°/s in humans (81), the OKS may have provided incomplete counteraction to the VOR during rotation at the speed used in the present study. Also puzzling is that the induced changes in the VOR parameters, particularly g_0, did not correlate with those in symptom rating even though attenuation of velocity storage was hypothesized to cause symptom improvement. This disconnection may be because of the multifacetedness of MdDS symptomatology and individual differences in the emphasis of various symptoms when reporting the overall symptom severity. Furthermore, since the VOR was tested only during the laboratory visits, how long the changes in the VOR parameters were retained is unknown. However, g_1 presumably would have been recalibrated quickly in a natural environment independently of the velocity storage parameters (57).

What determines the natural strength of velocity storage contribution to the VOR is not well understood (59–62, 64, 82), but age is a known mediating factor such that Tc increases through early adulthood and transitions in middle adulthood toward a decrease (52, 53). We confirmed this general trend in a large data set from a historical cohort consisting of individuals without MdDS or other vestibular dysfunction known to affect velocity storage. An earlier study provided a slightly longer estimate of vestibular time constant peaking at a slightly younger age (53). However, these variations may be explained by the differences in the test paradigms, assumptions regarding the underlying structure of the response, or age distributions of the samples, whether the age-based fit had an assumed shape or was data-driven, or any combination of these or other factors. The data from the historical cohort further indicated that age might also mediate g_0, but unlike for Tc, the data-driven fit indicated stability of g_0 over much of the age span followed by a decline in senescence. The implications of these findings, in terms of functional consequences or mechanistic bases, are presently unclear.

Against this backdrop, we found no evidence to associate MdDS with abnormal Tc or g_0. That is, a naturally long Tc or high g_0 does not appear to be a risk factor for MdDS, nor does a naturally short Tc or low g_0 appear to have a prophylactic effect. There is a strange juxtaposition between this conclusion and the results that, while training with the velocity storage attenuation regimen was associated with symptom improvement and a possible prophylactic effect, a direct association between the observed training-induced reduction of g_0 and symptom improvement was not evident. Further, the VOR parameters we studied were not predictive of the treatment responsiveness in either group. Lastly, even though we expected the VOR readaptation regimen to change the orientation properties of velocity storage without changing Tc or g_0, and we indeed found no group-wise systematic change in these parameters, the interindividual variations in the Tc and g_0 changes were moderately anticorrelated. This unexpected relation may be a reflection of a complexity arising from reshaping the three-dimensional structure of velocity storage. These unsolved problems highlight that understanding malleability of velocity storage and its consequences is an important research direction.

A practical clinical implication of this study is that a therapy technique aimed at attenuating velocity storage shows promise as a lasting remedy for MdDS that can complement the VOR readaptation approach (12, 26). We cannot completely rule out the possibility of a placebo effect because treatments in our laboratory are now highly sought after, and patients may have arrived with higher expectations than other treatments that they had tried previously. Nevertheless, the contrast between the outcomes of the two approaches in both the immediate and long terms is in support of a true clinical effect. Although the VOR readaptation approach is gaining recognition as being effective, the risk of relapse may make the treatment most useful when conducted at clinics local to patients (41–44) or through telemedicine using a portable device (27). However, a significant roadblock associated with the VOR readaptation approach currently is the availability of resources and clinical expertise required for determining the stimulus parameters. On the other hand, the regimen we used in this study to attenuate velocity storage followed a rigid protocol with little interpersonal variation. Velocity storage can also be attenuated with a simple protocol that uses a large repetition of rotations in darkness or with the eyes covered, albeit perhaps with a different efficiency (55, 65). Therefore, attenuation of velocity storage is a pragmatic clinical option in the treatment of MdDS. It remains to be tested whether combining this approach with VOR readaptation, when achievable, can yield a high probability of success with robust long-term benefits.

Data availability statement

The datasets presented in this article are not readily available because the raw data were collected using custom-made software. However, the datasets will be made available by the author upon reasonable request. Requests to access the datasets should be directed to SY, sergei.yakushin@mssm.edu.

Ethics statement

The studies involving humans were approved by Institutional Review Board of Icahn School of Medicine at Mount Sinai. 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

JM: Data curation, Formal Analysis, Investigation, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. CC: Investigation, Methodology, Writing – review & editing. TR: Writing – review & editing. SY: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, 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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Case Report: Keep your eyes open! Nystagmus guides atypical BPPV

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The clinical diagnosis of benign paroxysmal positional vertigo (BPPV) is confirmed from observing the direction, intensity, and duration of nystagmus from unique head positions that advantage gravity to overcome the inertia of otoconia displaced inside the semicircular canals. This case series highlights BPPV with atypical nystagmus presentations relative to the head position. Clinicians should carefully observe symptoms and nystagmus presentations regardless of the testing position and utilize technology and rules of vestibular physiology to enhance their diagnostic acumen.

KEYWORDS

BPPV, positional vertigo, positional nystagmus, vestibular, atypical

Introduction

Variants of benign paroxysmal positional vertigo (BPPV) such as sitting up vertigo, short-arm posterior canal BPPV, and type II BPPV may present with atypical nystagmus patterns or even absent nystagmus that can be difficult for clinicians to manage and cause longer durations of morbidity (1, 2). This case series presents four cases of unique BPPV presentations that highlight the clinical means to appropriately identify the affected semicircular canal based on nystagmus patterns that include comparing the intensity of nystagmus in different head positions, changing gaze direction (eye in orbit) to accentuate vertical or torsional components, and identifying canal-specific nystagmus patterns independently of the positioning test being performed.

All patients underwent a clinical oculomotor exam (smooth pursuit, gaze stability, saccade) including fixation removed testing (VestibularFirst Broomall, PA), video head impulse testing (GN Otometrics, Denmark), and tests of labyrinthine integrity with fixation removed (tragal pressure, glottis closed Valsalva). These tests were all normal unless otherwise noted in their case.

Case 1: excitatory nystagmus in bilateral Dix–Hallpike testing from unilateral posterior semicircular canal BPPV

A 42-year-old woman with a history of vitamin D deficiency, family history of migraine, and prior episodes of successfully treated BPPV presented for re-assessment after developing her typical vertigo symptoms when rolling to the left in bed overnight, getting out of bed in the morning, and laying supine during an exercise class.

Right and left supine roll test (SRT) were negative for nystagmus and vertigo. Right Dix–Hallpike test (DHT) showed upbeating and left torsional nystagmus after a 6 s latency that then was persistent beyond 40 s (Supplementary Video S1). The patient did not report

vertigo in right DHT but felt her eyes "pulsating"—consistent with the observed nystagmus. In the left DHT, she developed an immediate onset of upbeat and left torsional nystagmus with a crescendo–decrescendo velocity pattern that was greater compared with the right side and accompanied with vertigo. Although the nystagmus persisted for more than 60 s (Supplementary Video S1), it did slow down and thus an initial treatment of a left Epley canalith repositioning maneuver (CRM) was applied. However, while in the third position of the CRM she developed a mild downbeating nystagmus with right torsion that was persistent without vertigo, suggesting cupulolithiasis of the left posterior semicircular canal. She had no nystagmus reversal upon return to sitting. Repeat testing and a second CRM produced similar results. Next, a Semont-plus maneuver was performed for the left posterior semicircular canal and she had a burst of excitatory nystagmus (upbeating with left torsion) in the initial left-sidelying position, which reversed to prolonged downbeat nystagmus in the nose down and right sidelying position that extinguished after 90 s.

The patient was scheduled for a follow-up session 5 days later but cancelled the appointment as she was no longer having symptoms, suggestive of successful treatment. She has not returned to the clinic.

Case pearls and possible mechanisms

This patient's case highlights the importance of observing the direction of the torsional component of positional nystagmus independent of the semicircular canal being tested. The patient had upbeating and torsional nystagmus in both DHT, which may confuse clinicians to diagnose bilateral posterior canal BPPV. However, careful observation revealed the left torsional component was accentuated by having the patient change her gaze (3), similarly in both the right and left DHT, consistent with excitation of the left posterior semicircular canal. Another clinical pearl for this case is the observed intensity of nystagmus and vertigo. The velocity of an excitatory cupular deflection in the left DHT (and resultant vertigo) was greater than that from the right DHT, consistent with the DHT intent of positioning the affected posterior semicircular canal in the most gravity-dependent position that should enable a more robust nystagmus (4), and resulted in a greater intensity of vertigo. The patient had no vertigo during the right DHT. Figure 1 illustrates how the left posterior semicircular canal could be excited during a right DHT.

The probable cause for the observed nystagmus in this case is left posterior canal cupulolithiasis, with otoconia adherent to the cupula explaining the persistent nature of the observed symptoms and nystagmus in both DHT and the lack of responsiveness to the left Epley CRM. Adherent otoconia would also account for the persistent downbeat nystagmus observed in the third position of the left Epley CRM and final position of the Semont-plus maneuver (7). Further clinical reminders include identifying the latency and duration of nystagmus and the fatigability of nystagmus on repeated testing (8) and deciding on the appropriate treatment strategy independent of a patient's prior BPPV diagnosis and response to treatment.

In this case, both latency and duration of nystagmus as well as repeated testing of nystagmus fatigability indicated a cupulolithiasis-type BPPV, despite the crescendo–decrescendo pattern and prior diagnosis (8).

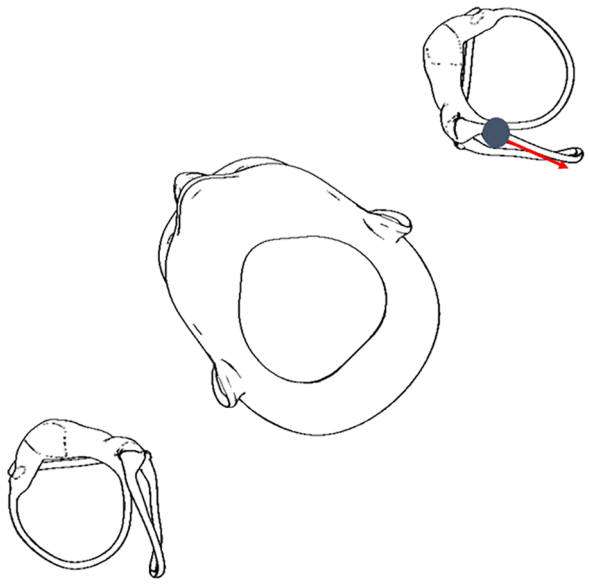

FIGURE 1
Otoconia displaced in the left posterior semicircular canal can move in an excitatory direction in a right DHT (5, 6), therefore, it is critical for clinicians to perform the DHT for both sides.

Case 2: excitatory and inhibitory nystagmus from unilateral posterior semicircular canal BPPV

A 44-year-old woman without any relevant medical history presented for evaluation of a 1-month history of episodic vertigo. The initial symptoms occurred when getting up from lying on the couch and lasted about 30 s. She reported feeling "off" and having a mild gait instability during the first day. After the initial onset, she experienced short episodes of vertigo lasting 5–10 s rising from supine and occasionally when rolling in bed. She reported that the vertical head motion would make her dizzy. She denied headaches, migraine symptoms, and any personal or known family history of migraines.

Right and left SRT were completed with no nystagmus or vertigo. Right DHT revealed downbeat and right torsional nystagmus lasting longer than 60 s (Supplementary Video S2). The patient reported generalized dizziness but not vertigo. Upon returning to sit from the right DHT, she had no nystagmus or vertigo. Left DHT revealed a robust upbeat and left torsional nystagmus lasting about 20 s with a 3 s latency consistent with a left posterior semicircular canalithiasis (Supplementary Video S2). This nystagmus then transitioned to a slow velocity downbeat nystagmus without symptoms.

The patient was treated with an Epley CRM for left posterior semicircular canalithiasis. Following treatment, repeat left DHT demonstrated a slow velocity downbeating nystagmus without

vertigo or dizziness. There was no reversal of nystagmus and no symptoms when returning to sit. Repeat right DHT was negative for both vertigo and nystagmus. The patient has not returned to the clinic but indicated she has no ongoing symptoms when consent was obtained.

Case pearls and possible mechanisms

The downbeat and right torsional nystagmus in the right DHT indicate two possibilities: (1) excitation of the right anterior semicircular canal or (2) inhibition of the left posterior semicircular canal (9). According to published diagnostic criteria for BPPV (10), anterior semicircular canalithiasis BPPV is rare and putatively can present with a predominantly vertical (downbeat) nystagmus. The addition of a straight head-hanging test position may have improved diagnostic efficiency as it has been shown to be more sensitive to true anterior semicircular canal canalithiasis (10, 11). Given the slower velocity downbeat with clearly observable right torsional nystagmus in the right DHT (consistent with an inhibitory response), coupled with a robust upbeat and left torsional nystagmus in left DHT—we reasoned the likely cause is the left posterior semicircular canal being inhibited and excited, respectively (Figure 2).

The absence of vertigo yet residual downbeat nystagmus during her repeat testing post CRM is not uncommon and has been reported to exist in 39% of patients being treated for posterior semicircular canal BPPV (12).

It is possible the otoconia from the left posterior semicircular canal were located within its short arm. Ping et al. (13) and later Ludwig and Schubert (1) reported excitatory nystagmus due to putative short-arm posterior canal BPPV. Residual otoconia in the short arm of the posterior canal following treatment could also account for the downbeat nystagmus observed in left DHT after treatment, although that is unlikely as she did not report vertigo.

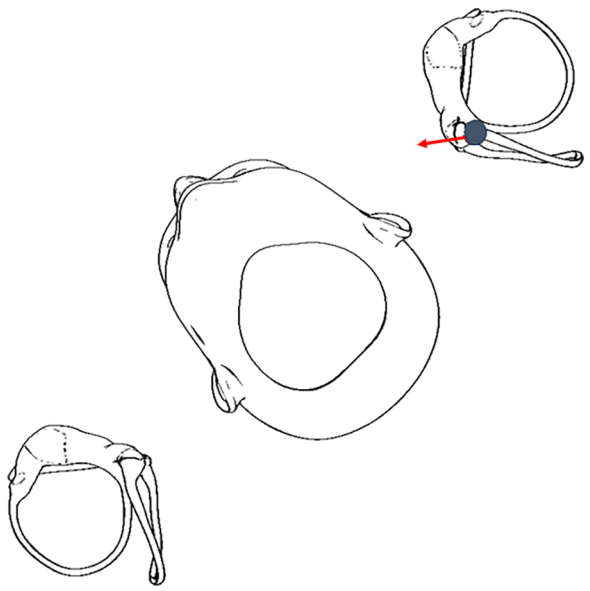

FIGURE 2
Otoconia displaced in the left posterior semicircular canal can move in an inhibitory direction in a right DHT (5, 6), therefore, it is critical for clinicians to perform the DHT for both sides.

Case 3: excitatory nystagmus from unilateral posterior semicircular canal BPPV during the supine roll test

The patient was an 80-year-old man with a history of muscular dystrophy with incomplete penetrance, atrial fibrillation, non-ischemic cardiomyopathy after pacemaker placement, Type II diabetes mellitus, hypertension, and cervical spondylosis who presented as a return patient for positional vertigo. His initial visit to the clinic occurred 1 month prior and at that time he was treated successfully for left posterior semicircular canalithiasis using an Epley CRM. The patient's cervical range of motion was limited from thoracic kyphosis that required modification of the positional testing and CRMs.

The patient was initially brought from long sitting to supine with head flexed 30° in preparation for the SRT, and after a 3–4 s latency, developed an upbeat and left torsional nystagmus. Given the patient's history of left posterior semicircular canal BPPV, the clinician decided to forego SRT and immediately changed positioning to a left DHT, where the upbeat and left torsional nystagmus continued with a crescendo–decrescendo pattern for just over 60 s.

An Epley CRM was attempted without reproduction of symptoms or nystagmus throughout the maneuver. There was no reversal of nystagmus with return to sitting. A repeat left DHT demonstrated nystagmus consistent with the initial test, although this time lasting only about 40 s. A second Epley CRM was performed with similar results as the first. The clinician considered both nystagmus and the symptoms were refractory to an Epley CRM, and hence decided to retest using the left sidelying test (14), which offered the possibility to quickly treat using a Semont maneuver if positive.

Left sidelying test revealed the same pattern, duration, and intensity of nystagmus and symptoms as the second left DHT, and a Semont maneuver was completed. There were no symptoms or nystagmus after transitioning to the final position (nose down and right sidelying) of the Semont maneuver, nor when returning to sit. A final left sidelying test and Semont maneuver produced the same positive results as the previous test. Thus, the "sleep maneuver" for posterior canal BPPV (15) was prescribed to the patient for the home program, and he was scheduled to follow-up in the clinic in 2 days; however, he cancelled the appointment due to neck discomfort. He has not returned to the clinic.

Case pearls and possible mechanisms

This patient's case highlights the importance of appropriately identifying canal-specific nystagmus patterns independently from the positional test being performed. Early identification of mixed vertical and torsional nystagmus from horizontal nystagmus in this patient with recent history of posterior semicircular canal BPPV was helpful for the treating clinician to reduce the number of test positions in this elderly patient with musculoskeletal limitations.

One possible mechanism for this patient's presentation is a typical left posterior semicircular canalithiasis BPPV, which was refractory to treatment per his musculoskeletal range of motion limits. Other possible mechanisms include a short-arm posterior canal BPPV, but further positional testing on subsequent visits would be required to explore this.

Case 4: excitatory and inhibitory nystagmus from multi-canal BPPV

The patient was a 74-year-old man with a history of hypertension, obstructive sleep apnea, and hyperlipidemia presenting for evaluation of 2-week onset of positional vertigo symptoms and gait unsteadiness. He reported positional vertigo symptoms when rolling over in bed and sitting up from supine. He also reported episodic gait instability where he had to hold onto furniture to walk and did not tolerate head movements or walking in low light environs. His oculomotor exam revealed a mild downbeat nystagmus after horizontal head shaking (fixation removed). See Table 1 for a summary of the results of positional testing and treatment across this patient's three visits.

Moving from sit to supine induced a mild downbeat nystagmus. Right SRT showed a downbeat nystagmus without symptoms, while left SRT initially showed a right beat apogeotropic nystagmus less than 5 s that transitioned to a mild downbeat nystagmus with right torsion. Right DHT showed persistent downbeat nystagmus without clear torsion in either gaze position (i.e., eye in orbit); left DHT initially showed left torsional nystagmus less than 5 s that transitioned to downbeat with mild right torsion. Upon returning to sit from left DHT, he had a more pronounced downbeat and right torsional nystagmus. He was treated with Epley for left posterior semicircular canal BPPV, with increased downbeat with mild right torsion in the third position of the Epley and his most notable symptoms of vertigo. Following treatment, repeated right and left DHT showed minimal downbeat nystagmus and no symptoms, although upon returning to sit there was prolonged crescendo–decrescendo left torsional nystagmus with mild upbeat and vertigo. Further treatment on the initial visit was deferred due to time constraints.

On the return visit 6 days later, sit to supine with head flexed 30° showed a right beat nystagmus without symptoms. Right SRT showed a mild left beat (apogeotropic) nystagmus without symptoms, and left SRT showed a fast velocity right beat (apogeotropic) nystagmus with vertigo. After 28 s, the nystagmus transitioned to upbeating with left torsion with increased vertigo that lasted 17 s, then returned to a persistent horizontal right beating apogeotropic nystagmus with diminishing symptoms lasting more than a minute (Supplementary Video S3).

Right DHT showed left beating nystagmus that was persistent, without symptoms. Left DHT showed a right beat nystagmus with vertigo that was persistent. Upon return to sit, he had mild downbeat with left torsion that then transitioned to persistent left beating with mild vertigo. Right sidelying (patient's most symptomatic position at home) showed left beating, persistent nystagmus with mild vertigo. Bow showed a left beat nystagmus without symptoms, lean showed an upbeat left torsional nystagmus with vertigo lasting about 5 s that transitioned to right beating with vertigo.

TABLE 1 Summary of observed nystagmus patterns, durations, and symptoms including responses to attempted treatments across three treatment sessions for case four.

Positional test	Visit#	Observed nystagmus	Symptoms
Sit to supine	1	Mild downbeat	None
	2	Right beat	None
	3	Upbeat, left torsion ×10 s	None
Right SRT	1	Mild downbeat	None
	2	Initial—left beat (apogeotropic), persistent	Initial—none
		After Epley—left beat (apogeotropic), persistent, mild	After Epley—No vertigo, mild nausea
	3	Right beat, geotropic ×10 s	None
Left SRT	1	Right beat (apogeotropic), then mild downbeat, right torsion	None
	2	Initial—right beat (apogeotropic)—robust, ~28 s transitions to upbeating w/left torsion ×17 s, then returns to right beat (persistent)	Initial—intense
		After Epley—right beat (apogeotropic), intense and persistent	After Epley—moderate to intense
	3	None	None
Right DHT	1	Persistent mild downbeat	None
	2	Left beat, persistent	None
	3	Right beat, ×30 s	None
Left DHT	1	Left torsional, then downbeat with right torsion (increase after return to sit)	Mild then intense during Epley (nose down position)
	2	Initial—right beat, persistent	Initial—moderate Repeat—intense, then mild
		Repeat—upbeating, left torsion ×15 s, then right beat	Repeat—intense, then mild
		After Epley—right beat	After Epley—none
	3	Initial/Repeat/first Epley—Upbeat, left torsion ×10 s, then downbeat, right torsion ×30 s	Initial/repeat/after first Epley—-mild
		After bow and yaw—upbeat, left torsion, reproduced in nose down position Epley	After bow and yaw—moderate
		After second Epley—none	None

All nystagmus instances observed were transient (<1 min duration) unless otherwise noted as persistent.

Repeat left DHT showed upbeating left torsional nystagmus <15 s that transitioned to right beat horizontal nystagmus. He was treated with a left Epley CRM with reproduction of upbeating left torsional nystagmus and vertigo in the third position (right side lie), suggestive of treatment success (16). Following the maneuver, a repeat left DHT showed right beating nystagmus without vertigo. In left SRT, his right beat (apogeotropic) nystagmus intensified and remained persistent with associated vertigo. In right SRT, he had persistent left beat (apogeotropic) nystagmus without vertigo (mild nausea). He was then treated with a modified Gufoni for a right horizontal canal apogeotropic BPPV. There was mild left beat nystagmus in the initial right sidelying position, which intensified then went away after turning the nose toward the ceiling. There was no nystagmus during return to sit.

On his third visit, sit to supine showed a slow upbeat and left torsional nystagmus lasting less than 10 s. SRT to the right showed less than 10 s of slow geotropic nystagmus without vertigo; SRT to the left was negative. Return to sit showed a slow downbeating and right torsional nystagmus lasting less than 10 s. Right DHT showed a slow velocity right beating nystagmus that lasted 30 s without reversal on returning to sit. Left DHT showed an initial upbeating left torsional nystagmus lasting 10 s with vertigo, which transitioned to a slow downbeat nystagmus lasting 30–35 s. There was no reproduction of nystagmus or symptoms throughout an attempted Epley CRM for left posterior semicircular canal BPPV, and upon returning to sit, he had 10 s of downbeat nystagmus with right torsion.

Repeat left DHT showed an initial upbeating left torsional nystagmus lasting 10 s with vertigo, which transitioned to a slow downbeat nystagmus lasting 30–35 s, although this time there was a right torsional component. The downbeating nystagmus remained unchanged in a half-DHT (17). With return to sit, there was an increased velocity downbeat and right torsional nystagmus lasting about 10 s. A bow and yaw maneuver was attempted next given the persistent downbeating with right torsional nystagmus suggestive of a short-arm posterior canal BPPV, followed by a repeat left DHT that showed excitatory upbeat and left torsional nystagmus before transitioning to a transient downbeat. A second Epley CRM was completed with reproduction of excitatory nystagmus and vertigo in the third position, suggestive of treatment success (16). Repeat DHT and SRT were negative.

Case pearls and possible mechanisms

This case similarly highlights the importance of identifying canal-specific nystagmus patterns independent of the positional test being performed and the challenge of multi-canal BPPV. This was most notable on the second day of testing when the patient initially displayed right beating apogeotropic nystagmus before transiently changing to upbeat and left torsional nystagmus while in the left SRT. The bow and lean test helped lateralize the affected horizontal semicircular canal but was also beneficial in clearly revealing a concomitant left posterior canal BPPV (18).

In this challenging case, the patient had an initial downbeat nystagmus in both DHTs yet a right torsional component developed while in the left DHT that can only be generated from inhibition of the left posterior semicircular canal when BPPV is the culprit (note that excitation of the left anterior canal would cause downbeat with left torsion). As mentioned above, anterior canal BPPV is rare and distinguishing the torsional component in many cases may be difficult (9), although it must be advantaged by asking patients to change the eye in orbit position (3). In addition, Bhandari et al. (11) showed through three-dimensional simulations that upon return to sitting in an anterior canal BPPV, otoconia continues in an ampullofugal/excitatory direction, explaining the absence of nystagmus reversal after returning to sit. This patient had a clear reversal of nystagmus upon returning to sit that further indicated this was not likely to be from an anterior canal BPPV, which led the clinician to attempt an Epley maneuver for an affected left posterior semicircular canal.

Repeated testing within and between visits revealed the otoconia location would change following testing, treatment, or a return to daily activities. While it is rare, multi-canal BPPV occurs in ~5.1% of cases (cross-sectional study of 3,975 patients with BPPV) (6). This patient responded to maneuvers for both the posterior and horizontal semicircular canals. With respect to the downbeat nystagmus observed after headshaking, Lee and Kim (19) showed 20% of patients with posterior semicircular canal BPPV can show a "perverted" vertical nystagmus. Yang et al. demonstrated that perverted post headshake nystagmus is not specific to central disorders (20).

Discussion

BPPV represents a common and typically easy to treat cause of vertigo; however, there is a growing body of evidence demonstrating numerous variants that can make its diagnosis challenging. Understanding and leveraging the rules of vestibular physiology is critical to ensuring accurate and timely diagnosis and treatment. Removing visual fixation is especially critical in peripheral vestibular disorders such as BPPV. Özel et al. (21) demonstrated that positional nystagmus was suppressed in room light by as much as 66.1% when patients with BPPV were tested without blocking fixation. Asking patients to change eye in orbit (3) can further aid the diagnostic process. Video-Frenzel recording goggles allow for re-examination of positional nystagmus after testing that is helpful to ensure diagnostic accuracy and treatment success, and if needed, share with other clinicians.

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

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

DL: Writing – original draft, Writing – review & editing. MCS: Writing – original draft, 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.

The authors declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fresc.2024.1384151/full#supplementary-material

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Wearable sensor and smartphone assisted vestibular physical therapy for multiple sclerosis: usability and outcomes

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Introduction: Vertigo, dizziness, gaze instability and disequilibrium are highly prevalent in people with MS (PwMS) and head movement induced dizziness is commonly reported. Vestibular physical therapy (VPT) is a specialised, non-invasive and effective therapy for these problems but usually involves travel for the person to a specialist center with both personal and carbon costs. The use of wearable sensors to track head movement and smartphone applications to deliver and track programs has potential to improve VPT in MS.
Methods: This study investigated the usability and effects of a commercially available digital VPT system (wearable head sensor, smartphone app and clinician software) to deliver VPT to PwMS. A pre/post treatment design was employed and the primary outcome was the System Usability Scale (SUS). Other patient reported outcomes were the Service User Acceptability Questionnaire (SUTAQ), the Patient Enablement Instrument (PEI) and the Dizziness Handicap Inventory (DHI). Physical outcomes measurements included Mini-BESTest (MB), Modified Dynamic Gait Index (mDGI), Gait Speed (GS), Dynamic Visual Acuity (DVA) and head kinematics and symptoms during exercise.
Results: Sixteen PwMS (14 female), mean age 44(±14) years were recruited to the study and twelve completed VPT. Mean adherence to exercise, measured digitally was 60% (±18.4). SUS scores were high at 81 (±14) and SUTAQ scores also demonstrated high levels of satisfaction and acceptability of the system. Statistically significant improvements in MB (mean change 2.25; $p = 0.004$), mDGI (median change 1.00; $p = 0.008$), DVA (median change −1.00; $p = 0.004$) were found. Head frequencies significantly improved with concurrent decreased intensity of dizziness during head movements (mean change across 4 gaze stabilization exercises was 23 beats per minute; $p < 0.05$). Non-significant improvements were seen in DHI ($p = 0.07$) and GS ($p = 0.15$). 64.5% of follow up visits were conducted remotely (video or phone), facilitated by the system.
Discussion: This study had two main outcomes and benefits for PwMS. Firstly, we showed that the system used was both acceptable and could be used by PwMS. Secondly, we demonstrated an improvement in a range of dizziness, balance and gait metrics with remotely delivered care. This system has the potential to positively impact on MS physiotherapy service provision with the potential to deliver effective remote care.

KEYWORDS

vestibular rehabilitation, remote monitoring, multiple sclerosis, dizziness, disequilibrium

Introduction

Multiple Sclerosis (MS) is a progressive neurodegenerative disease affecting 2.9 million individuals worldwide (1). As an autoimmune disorder, MS results in demyelination and plaque formation throughout the central nervous system. As a consequence, the cerebellum, brainstem and dorsal root entry zone of the 8th cranial nerve are common areas for plaque formation and this can be a significant factor in disequilibrium experienced by people with MS (PwMS) (2).

Numerous studies of vestibular function in MS have shown abnormalities in vestibular evoked potentials, electronystanography, static posturography (3, 4) and dynamic visual acuity (5). Furthermore, worse vestibular function is associated with greater disability (6). Vestibular dysfunction results in vertigo, dizziness, disequilibrium, and gait impairment and these are common and disabling symptoms of MS resulting in functional limitations, loss of independence, falls and an overall decreased quality of life (7–9).

Vestibular physical therapy (VPT), a specialized form of physical therapy that targets vestibular dysfunction is increasingly being employed for PwMS. In this population, VPT improves balance, quality of life and fatigue and reduces dizziness (10–13). A recent systematic review of ($n = 7$) randomized trials concluded VPT to be a safe and effective intervention in MS but acknowledged a limited evidence base (14). In most studies, VPT is delivered "face to face" in clinics for an initial assessment and for follow up visits but the treatment outcomes are thought to be dependent on a home exercise program prescribed between visits. There is currently no system for monitoring adherence and technique remotely (14).

Current evidence for VPT in peripheral vestibular dysfunction supports exercising in short bouts up to five times a day (15). With the frequency that the exercise program needs to be performed, there are unsurprisingly a number of barriers. These include, but are not limited to, motivation, lack of feedback and guidance, as well as symptom provocation (16).

An apparent paradox presents itself for the PwMS being treated, they attend VPT to improve dizziness but the exercises prescribed will generally provoke symptoms. Given the prevalance of dizziness with head movement, which is estimated to affect as many as three quarters of PwMS, an effective treatment regime is critical to improve quality of life (17).

Improving head movement and dynamic visual acuity are core aims of VPT, and the exercises most commonly prescribed are gaze stabilization exercises (15, 18, 19). These exercises involve the individual focusing on a stationary target when moving their head in either the pitch or yaw plane and are known as vestibular ocular reflex times one exercises (VORx1). They are performed with the target presented at near (N), and far (F) distances, and the frequency and duration of the exercise, as well as the position the individual exercises in (e.g., sitting, standing) are progressed as tolerated (19).

Technological advances, such as wearable technologies linked to electronic records present opportunities for addressing the problems of symptom control and improved adherence to prescribed exercise programs. Web based VPT has been shown to be effective in chronic dizziness (20, 21) but does not address the problem of accurately measuring adherence or providing biofeedback during exercise. Sensors such as accelerometers, and gyroscopes allow human physiological signals to be encoded and recorded, allowing health professionals to measure patient exercise performance and adherence in ways that were not possible previously. These forms of technology provide patients with accurate feedback of their performance which may motivate and improve rehabilitation outcomes.

There is emerging evidence that smartphone and/or wearable sensor assisted medical care for telehealth is feasible and warrants further investigation (22, 23). Loyd et al. (23) recently investigated the use of head worn inertial measurement units (IMUs) during VPT for PwMS and vestibular dysfunction. The IMUs were worn at 3 exercise sessions over a 6-week intervention period but only during clinic visits. Initial support for their ability to detect improvements in head kinematics during gaze stabilization exercises was found (23). These advances have the potential to create novel approaches to remote feedback during treatment as well as outcome metrics.

The COVID-19 pandemic highlighted the potential benefit of remotely delivered care. Prior to this as little as 4.5% of therapists reported using telehealth in VPT programs (18) but this has increased to 38% mid-pandemic (24). This provided benefits for many, in particular, PwMS embraced use of telehealth with 69.8% reporting the experience of remote care as either good or very good (25).

However, despite the clear acceptability of remotely delivered physiotherapy and prevalence of dizziness in MS, no study to date has yet investigated the provision of VPT in MS using a wearable sensor and smart phone app in the home. Therefore, the aim of this study was to address this research gap by investigating the usability of a bespoke digital vestibular rehabilitation application. The objectives of the study were threefold; firstly, to quantify the usability of the application and sensor. Secondly, to measure patient reported outcomes after VPT delivered with the system, and finally, to quantify physical outcomes.

Materials and methods

This was a usability study using a pre-treatment-post treatment design with an aim to investigate the use of a bespoke VPT system with wearable head sensor (Vertigenius^{TM}) in the delivery of VPT to PwMS. The digital VPT system consisted of a wearable head sensor, smartphone app and clinician software (Figure 1). We measured the primary study outcome using the System Usability Scale Score (SUS). We included a range of appropriate secondary outcomes measures as follows;

1. Service User Technology Acceptability Questionnaire (SUTAQ) (26)
2. Patient Enablement Instrument (PEI) (27, 28).
3. Changes in frequency of head movement and evoked dizziness during four gaze stabilization exercises (VORx1 near and far and in vertical and horizontal planes).

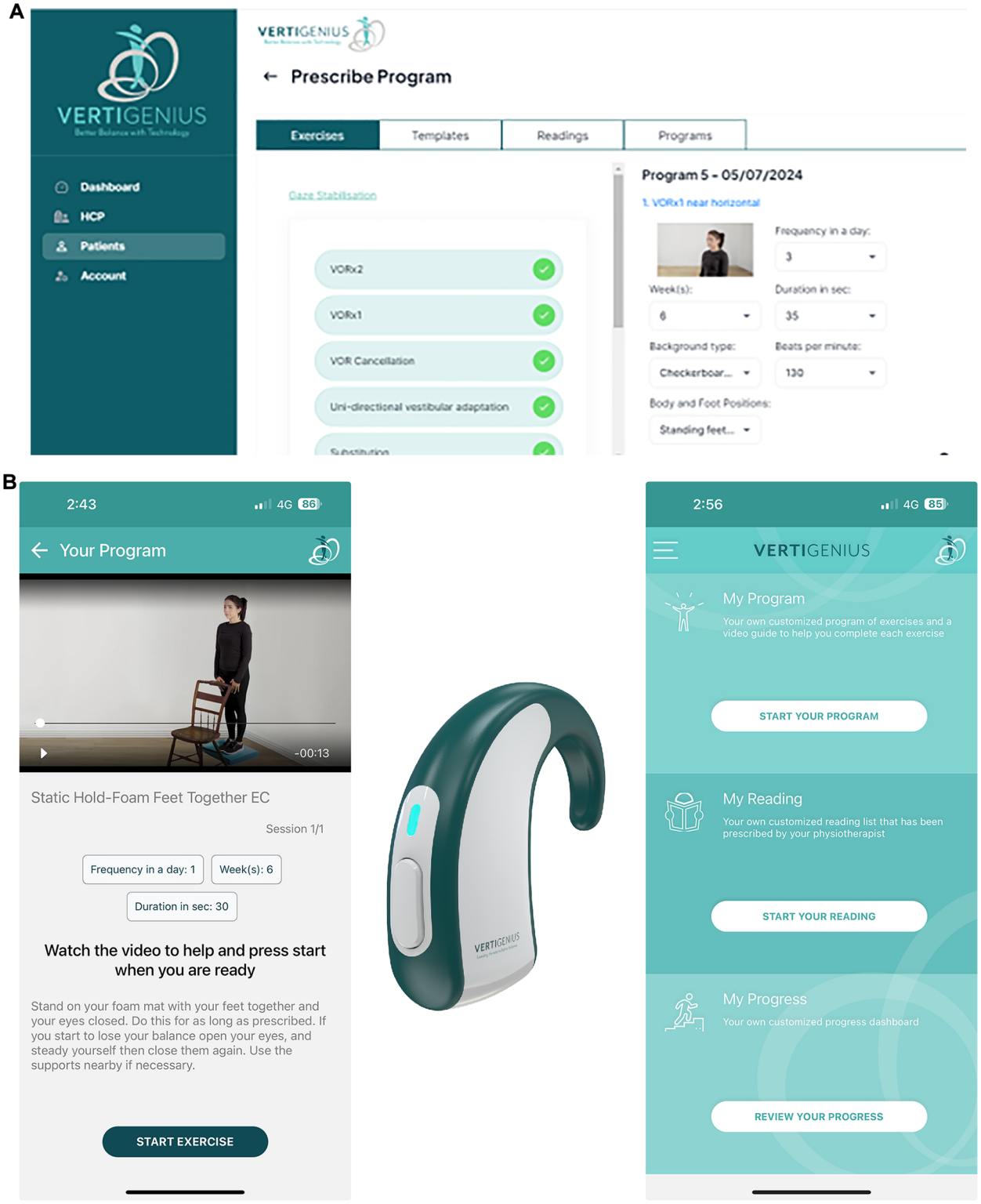

FIGURE 1
The Vertigenius™ system. Participants downloaded the application to their smartphone, which connected to the sensor which was worn behind the ear. (A) The clinician used the clinician software to prescribe, adjust and monitor exercise. (B) The head sensor information collected during exercise at home was relayed to the clinician portal and presented graphically to show whether the gaze stability exercise was performed, performed at the correct frequency in beats per minute (BPM) and dizziness symptoms before and after the exercise (not shown).

4. Dizziness Handicap Inventory Score (29).
5. Dynamic Visual Acuity (30, 31).
6. Modified Clinical Test of the Sensory Interaction on Balance (32).
7. Gait Speed (33).
8. Modified Dynamic Gait Index (34).
9. Mini-BESTest (35).
10. Adherence to the application and sensor (automatically measured by the sensor and system).
11. Daily numerical rating scale (NRS) score of dizziness, imbalance, nausea, anxiety, and oscillopsia (participant inputted via the app).
12. EQ5D5l Health Thermometer (36).

Data collection took place in the MS clinic and the physiotherapy department of a large university teaching hospital, where we identified and approved PwMS for recruitment to this study. Ethical approval was obtained from the hospital's Medical Research Ethics Committee. The study aimed to recruit 12–15 participants which is considered an adequate sample size for the primary outcome, the SUS (37, 38).

Inclusion criteria for the study were as follows: (i) diagnosis of MS (39) (ii) independently mobile with or without an aid, (iii) willing to use a smartphone/sensor health application, (iv) age >18 years, and (v) active dizziness, vertigo, or imbalance confirmed via subjective (Self report yes or no) or objective measures (balance abnormalites detected by the treating PT on the Mini-BESTest, see below). Exclusion criteria were as follows: (i) fluctuating vestibular disease (active Meniere's disease, migrainous vertigo), active benign paroxysmal positional vertigo, or other medical conditions in the acute phase (e.g., orthopaedic injury), (ii) pregnancy, (iii) MS relapse or change in disease modifying therapies in the past three months. Relapse was measured by clinical features e.g., new symptoms or change in symptoms and by MRI findings e.g., new lesions or increasing size of current lesions.

Procedure

At baseline participants underwent the following assessments recommended by either the Vestibular Evidence Database to Guide Effectiveness (VEDGE) or the Multiple Sclerosis Task Force of the American Physical Therapy Association (40).

1. Ten meter (m) walking test (33). Participants walked at their preferred speed along a 10 m track in the clinic. The instruction: "please walk to the end of the room at your normal pace" was used. A lead in of 1 m was given and the participant continued to walk past the 10 m mark. Gait speed (GS) was then calculated in meters per second (m/s).
2. The 4 item modified Dynamic Gait Index (mDGI). This is a validated four-task assessment of walking function: (i) gait at self-preferred speed, (ii) gait when changing speeds, (iii) gait with horizontal head turns, and (iv) gait with vertical head turns. It is scored from 0 to 12 with higher scores representing better gait function (34).
3. Mini-BESTest (MB). This is a balance assessment which measures dynamic balance, including: anticipatory transitions, postural responses, sensory orientation, and dynamic gait. The MB was selected over the Berg balance test for this MS study as it has demonstrated a lower ceiling effect in this context (35).
4. Dynamic Visual Acuity (DVA). This was measured using an ETDRS (Early treatment of diabetic retinopathy) chart. Static visual acuity (SVA) was first determined as the lowest LogMAR line at which participants could correctly identify 3 out of 5 optotypes. The therapist then assisted the participant to move their heads at 120BPM and asked them again to identify the optotypes. The line at which participants could correctly identify 3 out of 5 optotypes was then compared to SVA and the difference calculated in number of lines of LogMAR lost (30).
5. Dizziness Handicap Inventory (DHI). This is a patient reported outcome measure for those with vestibular dysfunction, and has been validated in MS (41). It consists of 25 questions and is scored on a Likert scale yielding a total score of 0–100 percent. Higher scores indicate higher burden of symptoms.
6. Usability and Enablement. At the conclusion of treatment, three questionnaires were administered to assess the usability (defined as acceptability, learnability, and ease of use) and enablement aspects of VPT delivered with the application and sensor.
   A. The System Usability Scale (SUS). This questionnaire was designed to subjectively assess usability of interface technologies. Levels of agreement with ten statements are scored using a five-point Likert scale anchored with "strongly disagree" and "strongly agree". The SUS provides a point estimate of percentage usability. Scores of above 70 are acceptable and highly usable products score above 90. Scores below 50 indicate unacceptably low levels of usability (37, 38).
   B. The Service User Technology Acceptance Questionnaire (SUTAQ). This questionnaire was developed to quantify patient's beliefs and expectations with regard to their acceptability of a tele-health system that included "kit", which in the case of this study was the head sensor and app. The questionnaire has 22 statements that are agreed or disagreed with on a six-point Likert Scale (ranging from strongly disagree to strongly agree). Six subscales are returned by the questionnaire measuring constructs of enhanced care, increased access, privacy and discomfort, care personnel concerns, kit as substitution and satisfaction (26).
   C. The Patient Enablement Instrument (PEI), has been used to evaluate quality of health care consultations in primary health care. It consists of six questions about change, both in patients' ability to cope with their condition, and in their understanding of their condition. It is scored on a 0–12 point scale with higher scores indicating greater enablement (27, 28).
7. Change in subjective symptoms on 0–10 numerical rating scales including change in symptoms with prescribed head frequencies during gaze stabilization exercises.

8. Percentage adherence to exercise (collected automatically by the system and duration of treatment (in weeks).
9. Care provision associated cost questionnaire. Participants filled out a questionnaire relating to cost of attending in time, distance and financial terms and were asked about falls since the previous visit.

Intervention

After baseline measures and an initial assessment by the treating physiotherapist (GQ) were completed, an individualized treatment plan was decided and discussed with the participant. Participants were onboarded to the system using a pseudonymous code. The system consists of a clinician portal where prescription of an individualized exercise program takes place and thereafter tracks exercise adherence and symptoms by electronically sending a range of subjective questionnaires.

Participants were shown how to download the app to their smartphone. Once registered on the clinician software, the treating physiotherapist selected and electronically sent their individualized program to them and showed them how to use the application. At each subsequent clinical visit and until discharge, revised and progressed exercise programs were prescribed as appropriate. The exercises prescribed included a combination of adaptation, habituation, balance and gait exercises, as would be traditionally used in VPT but delivered through the interface of the smartphone app rather than using pen and paper or an exercise print out.

Use of the app allowed the participant to watch a professional video of each prescribed exercise prior to doing the exercise and the app provided counts and timers for exercises and an audible metronome, the frequency of which was prescribed by the therapist. Examples of videos and interface may be viewed at https://www.vertigenius.com/. The app automatically progressed the participants through their exercises and measured their subjective responses to gaze stabilization exercises (vertigo/dizziness, nausea and disequilibrium) on a numerical rating scale. The app also provided digital reminders to complete the exercises and information on progress (change in vertigo, nausea, imbalance, anxiety and oscillopsia as well as head frequency during exercise, and adherence). Educational materials specific to balance and inner ear problems and tailored to the participant could also be prescribed by the portal and presented in the app.

Each participant received a head sensor (VG01; Figure 1) for use at home for gaze stability exercises. The sensor contains an inertial measurement unit (IMU) with a dual axis gyroscope, sampling at 50 Hz to measure angular velocity of head movement (degrees/s), in both yaw and pitch axis orientation. Angular velocity is used to estimate the frequency in beats per minute (BPM) of head rotation in either axis. VG01 internally processes the angular velocity of the head movement, finding a zero crossing on the head velocity and uses this to calculate BPM and subsequently sends the corresponding BPM values directly to the mobile phone app. Real-time feedback on head movement is attained by using Bluetooth technology to stream head BPM and max velocity from the head sensor to the mobile phone app at 10 Hz. The head sensor provided real time feedback on correct frequency of the head movement in relation to the prescription. The app alerted the participant through use of a traffic light system where the target on the phone screen if the participant was moving the head too fast, was red, too slow was yellow, or at the correct frequency, was green. Every second day, at one exercise session, the participant was asked to rate their symptoms of dizziness before the exercise started and after the exercise finished. This information was digitally collated and relayed back to the clinician portal, allowing the clinician to see graphs of the percentage adherence to the gaze stability exercise, the percentage time during the exercise going too fast, too slow or at the prescribed frequency and the level of symptoms before and after the exercise.

The initial assessment and final assessment were carried out in person in the physiotherapy department but for review sessions all study participants had the option of a telehealth consult (a phone or video call) if they so desired. At each session a cost analysis questionnaire was completed which collected data on time off work for the consultation, parking and transport costs, and any other costs e.g., childcare, food etc. Participants were also asked if they had missed any time off work due to vestibular symptoms since the preceding session and if they had experienced any falls or had needed a medical review due to fall related injuries.

Data analysis

Data relating to the participant's interaction with the application was processed by two of the researchers (DM and GQ). Descriptive statistics were used for the analysis of demographic data, of SUS, SUTAQ, PEI scores and cost questionnaires. Descriptive statistics were also used to analyze the number of programs and exercises prescribed and percentage adherence to the programs. Data were examined for normality using histograms and QQ plots. Paired *t*-tests and Mann–Whitney *U*-tests were used to investigate pre- and post-treatment scores in normally and non-normally distributed outcomes respectively (DHI, MB, GS, DVA, mDGI, NRS scores). Change in head frequencies during gaze stabilization exercises and change in dizziness symptoms during the four gaze stabilization exercises pre and post treatment were also examined using paired *t*-tests.

Results

A total of 16 participants (14F), mean age 44 (±14) years consented to the study, twelve completed the study. Demographics and baseline characteristics are shown in Table 1. Four withdrew from the study. Reasons for withdrawal were severe fatigue ($n = 1$), nausea ($n = 1$, not related to the intervention), moved elsewhere ($n = 1$), did not adhere to treatment with no reason given ($n = 1$).

TABLE 1 Demographics and baseline characteristics.

Variable	Mean	SD	Range
Age	44.1	13.6	25–67
Disease duration (years)	11.5	9.9	0.1–32
Expanded disability status scale (EDSS)	2.5[a]	1.1[a]	0–6
Number of falls in past year	2.1	3.05	0–10
Sex			
Male (%)	12.5		
Female (%)	87.5		
MS subtype			
Relapsing remitting (%)	93.7		
Secondary progressive (%)	6.3		
Variable	**Yes (%)**		
Mobility aid use	25		
History of falls	56.3		
Fear of falls	37.5		
Employed (FT or PT)	56.3		
Vertigo	93.8		
Dizziness	87.5		
Oscillopsia	50		
Imbalance	87.5		
Head motion intolerance	62.5		
Headache	56.3		
Fatigue	75		
Aural symptoms (any of the 3)	62.5		
Tinnitus	56.3		
Aural fullness	25		
Deafness	25		

Demographics table for $N = 16$ that have baseline and prevalence data.
For numerical values, reported as mean and SD.
For categorical, yes/no questions, reported as percentage of yes.
[a]Median and Interquartile range. FT, fulltime; PT, part time.

Treatment intervention

The duration of VPT was on average 12 (±2.2) weeks (range 7–14). A mean of 5.5 (±1.2) programs were prescribed during this time with a duration of 2.2 (±0.5) weeks. The therapist prescribed 9 (±1.2) exercises per program. Overall mean adherence to the exercises prescribed was 60.1 ± 18.4% (range 28%-88%). There was no statistically significant correlation between SUS scores and overall percentage adherence ($r = 0.32$, $p = 0.3$).

At baseline, participants reported traveling a median distance of 5.9 km to the initial session (range 1–210 km) taking a median of 25 min (0–180). Half reported being unable to fulfil a family or work role due to dizziness in the past month, and five (31.3%) reported a fall in the past month. Nine of 16 (56.3%) participants were employed and four had taken time off work to attend treatment. Of the 60 subsequent clinical consultations before the final in person assessment, 48 (64.5%) were conducted via either video or tele consult. Reasons given in support of tele/video consults were preferable to a long commute, convenient, less time consuming, had no requirement for childcare, had flexibility, and were less costly. Reasons against tele/video consults were a preference for face to face and limited technology abilities. At follow up assessments, there were eight further falls reported by $n = 4$ (25%) of participants.

Usability

Mean SUS score was 81 (±14; range 47.5–95), displayed in Figure 2. On average participants agreed strongly, or very strongly, with the statements relating to finding the system easy to use, quick to learn, and confidence using it. On average, they strongly disagreed with the statement "I thought the system was unnecessarily complex". There was less agreement with the statement "I think I would like to use the system frequently" with only 3/12 participants strongly agreeing with this statement and the remainder scoring 2/5 or 3/5 (A score of 5/5 was anchored with the statement strongly agree and 0/5 anchored with the statement strongly disagree). Only two participants scored below the accepted cut-off of 70.

Enablement scores

Mean PEI scores were 5.8/12. The majority of participants selected "better" or "much better" when answering all statements related to enablement but approximately one third reported feeling the "same or less" with regard to the six statements in the instrument (Table 2).

SUTAQ

SUTAQ sub scale scores were calculated according to Hirani et al. (26). High average scores (out of a maximum of 6, higher indicating agreement) were evident for the scales measuring whether the participant felt the kit enhanced their care (mean score 5.0), increased their access to care (mean score 4.9) or their overall satisfaction with the kit (mean score 5.5) (Figure 3). For example, on item 1 "The kit I received has saved me time in that I did not have to visit my GP clinic or other health/social care professional as often", 100% agreed with this statement and for

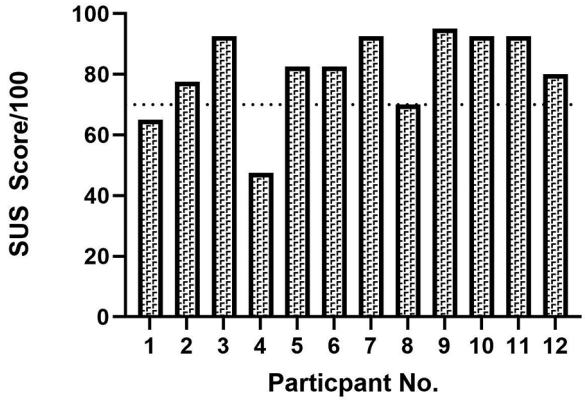

FIGURE 2
System usability scores (SUS) by participant. The SUS is scored out of 100 with higher scores representing higher usability of a given system. A cut-off of 70 (denoted by the dotted line) is the cut-off score for usability.

TABLE 2 Results from the Patient Enablement Instrument ($n = 12$).

As a result of your visit to your PT today do you feel you are?	% Scoring same or less	% Scoring better/much better
Able to cope with life	33	67
Able to understand your illness	25	75
Able to cope with your illness	25	75
Able to keep yourself healthy	25	75
Confident about your health	33	67
Able to help yourself	33	67

item 15, "The kit can be/should be recommended to people with a similar condition to me", 100% also agreed. Participants scored low on the privacy and discomfort scale indicating they had minimal concerns (mean score 2.1). They also scored very low on the care personnel concerns (mean score 1.1) i.e., they agreed the professionals providing the sensor and app and care were competent and continuity of their care was not affected by the system. There was ambiguity on the "kit as substitution" subscale (mean score 3.3); 67% of participants agreed with the statement that "the kit is not as suitable as regular face to face consultations with the people looking after me".

Physical and symptom outcomes

Statistically significant improvements were found for Dynamic Visual Acuity (median score pre-intervention of 2 lines lost vs. a post intervention score of 1 line lost, $p = 0.004$), Mini-BESTest Scores [mean score pre-intervention of 23 (± 2.8) vs. a post intervention score of 25 (±2.6), $p = 0.004$] and Modified Dynamic Gait Index scores (median score pre-intervention of 11 vs. a post intervention median score of 12 $p = 0.008$). Non statistically significant improvements (0.05 m/s) were observed for gait speed ($p = 0.15$), Dizziness Handicap Inventory scores ($p = 0.07$), Modified CTSIB scores ($p = 0.2$) and EQ5D5l Health Thermometer scores (Table 3). NRS scores for dizziness, oscillopsia, nausea and imbalance all showed statistically significant reductions (Table 3).

Head kinematics

Eleven of the 12 participants used the head sensor during their gaze stabilization exercises. One participant was unable to connect to their smartphone (an older version) but continued to use the app for exercise instruction but without the sensor feedback. This resulted in no sensor data relating to head kinematics being available for this participant. All participants were prescribed four gaze stabilization exercises (VORx1 at near and far distances and in the pitch (vertical) and yaw (horizontal) planes), except one participant who was not prescribed Vertical VORx1. Figure 4 shows subjectively rated dizziness before and after performing individual gaze stabilization exercises in the initial and final programs. Overall, symptoms were not exacerbated excessively with the exercises and, over time, symptoms of

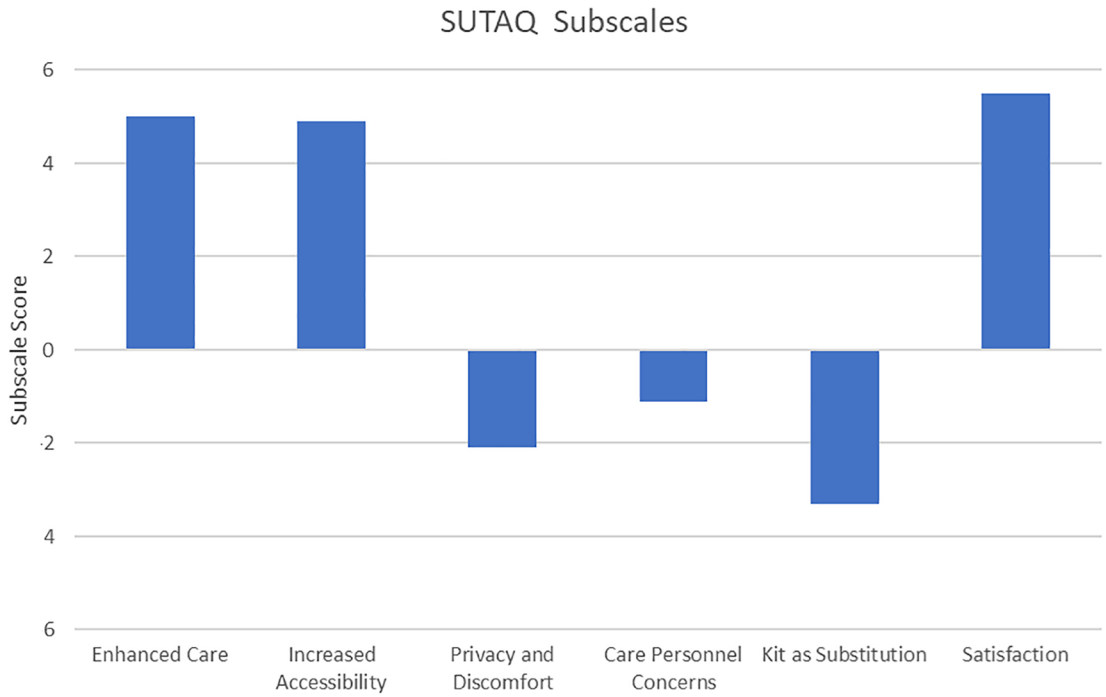

FIGURE 3
Service user acceptability technology questionnaire (SUTAQ) subscale scores. The subscales, named in the legend above had a max score of 6. The Privacy and Discomfort, Care Personnel concerns and Kit as Substitution scales are shown below the x axis as high values on these scores reflect high levels of agreement with negative aspects of the "kit".

TABLE 3 Pre and post outcomes of physical and subjective outcome measures.

Outcome	Mean T1 (SD)	Mean T2 (SD)	Diff (SD)	*P*-value	95% CI
DHI (/100)	46 (13)	37 (17)	−8.8 (15.4)	0.07	−18.6→0.96
Gait Speed (m/s)	1.3 (0.17)	1.4 (0.13)	0.05 (0.11)	0.15	−0.02→0.12
Mini-BESTest (/28)	23 (2.8)	25 (2.6)	2.3 (2.1)	0.004	0.89→3.6
Health Thermometer (/100)	67 (17)	68 (18)	1.4 (18.0)	0.79	−10.0→12.9
NRS Dizziness (/10)	3.9 (1.9)	1.5 (1.2)	−2.4 (1.8)	0.002	−3.6→−1.1
NRS Imbalance (/10)	4.0 (1.5)	1.5 (1.2)	−2.5 (1.5)	0.0003	−3.5→−1.5
NRS Anxiety (/10)	2.8 (3.4)	0.39 (0.53)	2.4 (3.2)	0.07	−5.1→0.3
NRS Oscillopsia (/10)	3.8 (1.3)	1.5 (1.1)	−2.3 (0.8)	0.0003	−3.0→−1.5
NRS Nausea (/10)	2.5 (1.1)	0.49 (0.59)	−2.0 (0.8)	0.005	−3.0→−1.0
	Median (IQR)	Median (IQR)		*P*-value	
DVA (no. of lines lost)	2 (2, 4)	1 (1, 2)	–	0.004	–
mDGI (/12)	11 (9.3, 12)	12 (11, 12)	–	0.008	–
mCTSIB (/120 s)	108 (95, 120)	116 (105, 120)	–	0.2	–

DHI, dizziness handicap inventory; m/s, metres per second; NRS, numerical rating scale; DVA, dynamic visual acuity; mDGI, modified dynamic gait index; mCTSIB, modified clinical test of the sensory interaction on balance; IQR, inter quartile range; SD, standard deviation; Diff, difference, CI, confidence interval.

dizziness showed statistically significant decreases for all four exercises. Concurrently, prescribed head frequencies increased significantly for all four gaze stabilization exercises indicating that overall participants were moving their heads at faster frequencies with less dizziness at the end of treatment.

Adverse effects

No treatment related adverse effects were reported during the study. Of eight falls reported during the study by four participants, none occurred during performance of the prescribed exercises.

Discussion

This study addressed an unmet research gap by delivering remote VPT with real-time feedback of exercise performance for PwMS. The outcomes included improvements in symptomatology, documented by a range of both subjective and objective metrics. We also found high levels of acceptability and usability of the technology in people with this chronic neurological disease that has an extremely high prevalence of dizziness. This has the potential to impact MS care by facilitating remote delivery of specialized VPT and importantly addressing barriers to adherence to the prescribed exercise where exacerbation of symptomatology is frequently encountered.

Rehabilitation is a cornerstone of management of MS, and tele-rehabilitation has previously been shown to positively affect quality of life (42). Next generation systems incorporating virtual reality and sensors, such as those used successfully in this present study have potential to augment tele-rehabilitation improving access to treatment, outcomes, and increasing understanding of dosage and effects of different exercises and approaches for dizziness in MS (23, 43, 44).

The results from this study showed that participants found the system highly usable, based on the results from two usability questionnaires (SUS and SUTAQ). SUS scores above 70 are deemed acceptable, and a mean score of 81 obtained in this present study was encouraging in this regard although two participants scored below the threshold of 70. These scores are in agreement with a previous study on the system in peripheral vestibular disorders (45). The SUTAQ more comprehensively evaluated constructs of how the "kit" was perceived and participants scored highly on the constructs of enhanced care, increased accessibility and satisfaction. The observation that 64.5% of follow up consultations were performed remotely supports the SUTAQ score; both participants and the therapist involved reported saving time as a result of the use of the system. Disagreement was evident amongst participants in the perception of whether the kit could be used as a replacement of care, with 42% of participants disagreeing that "the kit can be a replacement for my regular health or social care". This suggests that a hybrid approach to VPT in PwMS might be the most valued, but requires further study as the field of tele-rehabilitation is relatively new and equivocal results have been obtained (46). Van Vugt et al. (20) used web based VPT with or without the addition of two home visits by a therapist and compared the groups to a usual medical care group in a chronic dizziness population. No differences were found between the two intervention groups and both improved more than the usual medical care groups. Qualitative interviews supported the home visits as valued by both patients and therapists despite adding some cost to the intervention (47).

The head sensor had several functions in the delivery of VPT. Firstly, it gave real time feedback to participants during gaze stability exercises. These exercises have a good evidence base in vestibular disorders (15) but are known to increase symptoms and patients often report difficulty with performing them correctly, meeting the right head frequency and motivating themselves to exercise (16). Secondly, the head sensor tracked head frequency and coupled with the participant inputting subjective dizziness scores before and after exercises (once a day, every second day) provided the therapist with accurate real-time information on exercise performance and effects. It can be

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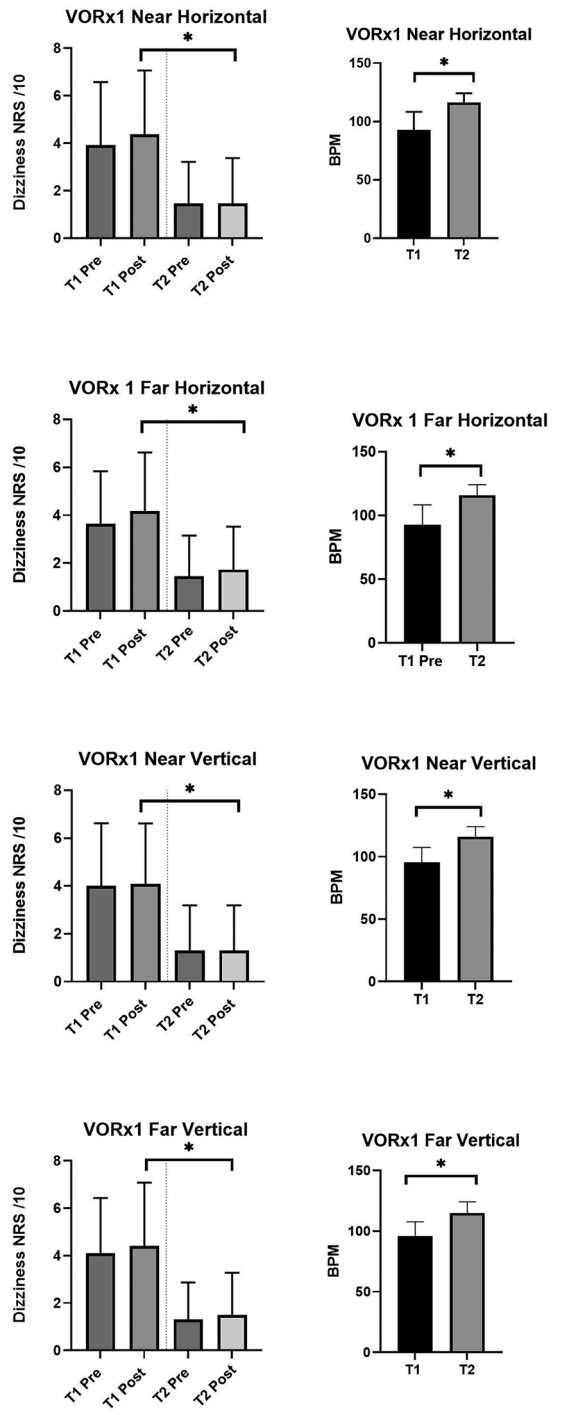

FIGURE 4
Change in dizziness numerical rating scores (out of 10) before and after the four gaze stability exercises both at time 1 and time 2. Time 1 is the first program prescribed and Time 2 is the last program prescribed. On the left It can be seen that for all exercises, the symptoms were higher at T1 than at T2. At both T1 and T2 pre and post exercise scores did not increase significantly. On the right, graphs showing the change in prescribed frequency of head movements at T1 and T2. Participants significantly increased the frequency at which they performed the exercises from T1 to T2 with concurrent decrease in symptoms. *$p <$ 0.05. VORx1 Vestibular ocular reflex times one exercise, NRS Numerical Rating Scale, T1 Time one, T2 Time 2, BPM Beats per minute (frequency at which the participant was performing the exercise with real time feedback of performance via the head sensor and app).

challenging to prescribe optimal head frequency and therapists currently use symptoms to guide prescription. This approach lacks oversight of what is happening with home exercises and therapists rely on what the patient reports and the head sensor allowed remote therapeutic monitoring and possibly aided and enhanced the proper performance of exercises at home. Clinically significant increases in the ability to move the head at progressively higher frequencies and with less dizziness were objectively measured which is encouraging. The head sensor also digitally measured exercise adherence, a metric which is acknowledged as being central to advancing knowledge of exercise dosage and effect in VPT (15). A mean exercise adherence of 60.1% was recorded which was not ideal, but similar to previous studies of VPT (48, 49). In VPT, poorer outcomes are associated with reduced adherence (50) and adherence is poorly measured in studies of exercise interventions in MS and VPT (15, 51). Percentage adherence did not correlate with SUS scores suggesting that the technology was not the reason for low adherence. Furthermore, on closer inspection, the participant with the lowest adherence (28%) in the present study had a low burden of symptoms at inception and improved quickly, which may have impacted their adherence. Future studies using wearable sensors coupled with digital exercises interventions such as the system employed in this study will be able to accurately determine adherence to exercise, whether better outcomes are possible with increased adherence and which exercises are most beneficial.

Physical outcomes

The study was not powered to assess efficacy and it is acknowledged that a randomized controlled trial is necessary for this. However, statistically significant improvements were found for balance, DVA and the mDGI. A 3 line or more loss of visual acuity is considered abnormal in DVA testing but most healthy subjects will not drop more than one line (31). All participants at baseline had a DVA loss of 2 lines or more and nine improved DVA post treatment. This suggests that the function of the vestibular ocular reflex was improved after treatment and supported by a statistically significant reduction in subjectively reported oscillopsia and lends further support to the use of gaze stabilisation exercises in PwMS. The mean increase in Mini-BESTest scores was 2.3. This did not reach published MDC scores for MS of between 3.5 and 4.7 (52), but reached the 10% MDC improvement calculated by Mitchell et al (53). mDGI scores also increased significantly, indicating better gait function. Gait speed increased by 0.05 m/s but was not statistically significant.

Subjective outcomes

One of the most commonly used subjective measures of dizziness is the Dizziness Handicap Inventory (18, 54). DHI scores reduced by 8.8 which was non-significant but similar to a report by Loyd et al (12) who reported a reduction of 8–9 when

face to face VPT was provided to a sample of PwMS. It was less than that found by Hebert et al (11) in a study of VPT in PwMS who found a clinically significant reduction of 18.7. The differences may be explained by treatment duration, VPT in the latter had a time frame of 14 weeks, and/or disease duration, which was 6 years, as opposed to 11 years in the current study. However, in the present study, dizziness measured with numerical rating scales showed significant decreases. The DHI is an overall measure with constructs of physical, emotional and functional effects of dizziness which may account for the disparity.

Limitations of the study

We included only PwMS who were able to mobilise independently with or without a gait aid, this limits the generalizability of the study to the PwMS population who may have a greater range of disability levels and disease progression. The study was powered to assess usability but was underpowered for effectiveness. Some outcomes may have not reached significance due to low numbers producing a type II error. In addition, there was no control group and a future randomized controlled trial is necessary to evaluate efficacy, particularly of the sensor and digital approach compared to conventional VPT. We did not cost an episode of care and more robust economic data is necessary before the cost-effectiveness of this digital approach can be quantified. The effects on fatigue were not formally assessed and 75% of participants reported fatigue at baseline with one dropout due to severe fatigue. A previous study found that VPT significantly improved fatigue (11) and in future studies, a daily digital NRS measure of fatigue could be incorporated to the system. We also did not include a measure of cognition which may have influenced results. Finally, the intervention duration may not have been long enough and long-term follow up of the improvements observed was not conducted.

Conclusion

This study has demonstrated high usability of a wearable head sensor combined with a digital application for VPT in PwMS. The system was well tolerated and accepted with no adverse events and reductions in dizziness at increasing head frequencies were observed with concurrent improvements in balance and gait.

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 humans were approved by St. James Hospital/Tallaght University Hospital Medical Research Ethics Committee, St. James Hospital, Dublin, Ireland. 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

DM: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. HK: Data curation, Investigation, Project administration, Resources, Writing – original draft, Writing – review & editing. SH: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. SM: Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing. GQ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

DM is the inventor of the digital intervention that was employed in the study. It is patent pending and DM is named on the patent. DM is a shareholder in Vertigenius, which is a Trinity College Dublin spinout company.

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

Publisher's note

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Innovative approaches for managing patients with chronic vestibular disorders: follow-up indicators and predictive markers for studying the vestibular error signal

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Introduction: Despite significant advancements in understanding the biochemical, anatomical, and functional impacts of vestibular lesions, developing standardized and effective rehabilitation strategies for patients unresponsive to conventional therapies remains a challenge. Chronic vestibular disorders, characterized by permanent or recurrent imbalances and blurred vision or oscillopsia, present significant complexity in non-pharmacological management. The complex interaction between peripheral vestibular damage and its impact on the central nervous system (CNS) raises questions about neuroplasticity and vestibular compensation capacity. Although fundamental research has examined the consequences of lesions on the vestibular system, the effect of a chronic peripheral vestibular error signal (VES) on the CNS remains underexplored. The VES refers to the discrepancy between sensory expectations and perceptions of the vestibular system has been clarified through recent engineering studies. This deeper understanding of VES is crucial not only for vestibular physiology and pathology but also for designing effective measures and methods of vestibular rehabilitation, shedding light on the importance of compensation mechanisms and sensory integration.

Methods: This retrospective study, targeting patients with chronic unilateral peripheral vestibulopathy unresponsive to standard treatments, sought to exclude any interference from pre-existing conditions. Participants were evaluated before and after a integrative vestibular exploratory and rehabilitation program through questionnaires, posturographic tests, and videonystagmography.

Abbreviations

AP, antero-posterior; PB, prism bar; PBc, prism bar convergence; PBd, prism bar divergence; BFI, big five inventory; CHU, University Hospital Center; CNS, central nervous system; CPV, chronic peripheral vestibulopathy; CSD, chronic subjective dizziness; DHI, dizziness handicap inventory; DVA, distance visual acuity; EC, eyes closed; EO, eyes open; EPN31, 31-item positive and negative emotionality test; Hs, hyperactive signal; iVRT, integrative vestibular rehabilitation therapy; I, inhibition without deficit; ML, medio-lateral; N, non-inhibited profile; NPA, near points of accommodation; NPC, near point of convergence; NVA, near visual acuity; OFI, ocular fixation index; P, partial contralateral inhibition; PmW, mawas board; SOT, sensory organization test; SoC, state of compensation; SF36, short form (27) health survey; SVV, subjective visual vertical; SVVdyn, dynamic subjective visual vertical; SVVstat, static subjective visual vertical; T, Total contralateral inhibition; TMJD, temporomandibular joint disorders; TVST, thomas far stereoscopic vision test; VC, visually controlled condition; VES, vestibular error signal; VNG, videonystagmography; VNGt, bithermal videonystagmography; VOR, vestibulo-ocular reflex; VOR2, double-task vestibulo-ocular reflex; VOR2g, VOR2 gain; VORg, VOR gain; VVOR, visuo-vestibulo-ocular reflex; VestiQ-VS, vestibular health questionnaire.

Results: The results indicate significant improvements in postural stability and quality of life, demonstrating positive modulation of the CNS and an improvement of vestibular compensation.
Discussion: Successful vestibular rehabilitation likely requires a multifaceted approach that incorporates the latest insights into neuroplasticity and sensory integration, tailored to the specific needs and clinical progression of each patient. Focusing on compensating for the VES and enhancing sensory-perceptual-motor integration, this approach aims not just to tailor interventions but also to reinforce coherence among the vestibular, visual, and neurological systems, thereby improving the quality of life for individuals with chronic vestibular disorders.

KEYWORDS

integrative vestibular rehabilitation, visual fusion, vestibular error signal, sensori-perceptual-motor system, monitoring indicators, predictive markers

1 Introduction

1.1 Background and justification for the study

Chronic vestibular disorders (CVS) manifest through nonspecific symptoms such as imbalances, blurred visions perceived during self or environmental movements, and disturbances in perception or even spatial memory. They pose a significant clinical challenge affecting a broad segment of the population (1, 2). While peripheral causes of these disorders are often identified initially, the impact of these peripheral impairments on the central nervous system (CNS), especially on regions associated with the vestibular system mainly multisensory related functions of the temporoparietal cortex, remains under-explored in clinical practice. This complex interaction highlights key questions about neuroplasticity of vestibular, visual and somesthetic integration, and the brain's adaptive strategies to sensory disturbances and vestibular rehabilitation techniques.

Nevertheless, the interactions and recurring complaints of visual disturbances noted in CPV are also questioned in the literature. Roberts et al. (3) highlighted a significant change in the primary visual cortex V1 in patients suffering from chronic vestibular neuritis during congruent visuo-vestibular stimulations. This discovery suggests that adaptive mechanisms associated with the primary visual cortex play a crucial role in central compensation and, by extension, in clinical outcomes in these patients. This observation is reinforced by Beh (4–7), who emphasizes the pivotal role of vestibular information in cognitive processes, particularly visuo-spatial abilities, and how vestibular disorders can lead to visuo-spatial deficits through lesions of cortical and subcortical components of the vestibular system. Finally, Cousins et al. (8) remind us that visual dependence are among the most important predictive symptoms of chronicity.

Xavier (9, 10) proposes considering the disruption of the integration of the peripheral vestibular error signal (VES), especially at a subliminal threshold level, which could influence, on one hand, short and medium-term visuo-oculomotor adaptations, and on the other hand, neuronal plasticity and the establishment of optimum compensation processes following a VES experienced by the CNS in the long term. At this stage, it's important to understand that visual fusion is a complex process that allows the human brain to combine images from both eyes into a single coherent three-dimensional image. This phenomenon, crucial for spatial perception, relies on adherence to two fundamental concepts: the horopter and Panum's area. However, this visual synergy can be compromised under pathological conditions, especially in the context of vestibular asthenopia (11). The horopter is a geometrical construct that defines the region of space where images projected onto the retinas of both eyes overlap exactly, ensuring normal retinal correspondence and optimal binocular vision for fusion and stereoscopic vision. Any deviation from this alignment leads to a discrepancy from the horopter, resulting in a perception of an image without relief, blurred, or in extreme cases, double. Panum's area, also known as the "fusion zone," is the area around the horopter where binocular fusion is still possible despite slight discrepancies between the retinal images (12). This area plays an essential role in three-dimensional perception, as it allows for some tolerance to variations in the position of the observed object. We have demonstrated that a vestibular error signal (VES) can result in a subtle adaptation of oculomotor behavior involving an anomaly in retinal correspondence. This manifests as symptoms such as visual fatigue, blurred vision, and in extreme cases, intermittent diplopia, particularly when the fixation object moves or when the individual is subjected to complex body movements. This condition is referred to as vestibular asthenopia.

It is within this research context around CPV that we conducted a retrospective study at a physiotherapy center in partnership with the Caen Hospital Center.

1.2 Vestibular error signal and research hypothesis

The "vestibular error signal" (VES) refers to a discrepancy between expected sensory information and that perceived by the vestibular system, which plays a crucial role in maintaining balance and spatial perception. This gap can result from damage

or dysfunctions at the level of peripheral or central components of the vestibular system. This concept, already present in the literature of the 1980s (13) has been enriched by numerous works done both in engineering and in the human model. Mathematical models of signal integration have allowed us to better understand the notion of error in measurement systems due to noise (unwanted signals), leading to differences and therefore errors between the output quantity and the input quantity to measure, especially in dynamic measurement situations where the mean squared errors take into account both dynamic and static errors (14).

1.2.1 Multisensory interaction and central nervous system adaptation

These numerous observations in both fundamental and clinical research indicate that the vestibular system tends to interact with visual and somatosensory events. For exemple, Angelaki & Cullen (15) emphasized how vestibular signals contribute to an astonishing range of brain functions, from spatial perception to motor coordination. Chang et al. (16) examined how the integration of auditory and vestibular signals requires their simultaneous perception despite their asynchronous arrival at the central nervous system, proposing a mechanism to explain symptoms in patients with imbalance. Ferré et al. (17) demonstrated how vestibular stimulation differently modulates two sub-modalities of the somatosensory system, increasing touch sensitivity while reducing sensitivity to nociceptive inputs. The same authors in 2015 (18) showed how vestibular stimulation interacts with visual and somatosensory events in a detection task, highlighting the vestibular role in regulating somatosensory gain.

1.2.2 Visuo-Vestibular integration and motor responses

Shayman et al. (19) explored the hypothesis that vestibular deficits could disrupt visuo-vestibular temporal integration, determining relationships between vestibular perception threshold and the temporal binding window in participants with normal and hypo-functioning vestibular function. In this context, the hypothesis of the VES playing a crucial role in maintaining certain subtle symptoms appears relevant. We know that the central nervous system processes discrepancies between expected movements and actual sensations. For instance, when a person moves or turns their head, the vestibular system anticipates changes in sensory perception based on the planned movements (15). If the actual sensory signals differ from these expectations, an error signal is generated. This error signal is then used to adjust motor responses and enhance the accuracy of future movements, as well as to update sensory perception and spatial representation (20, 21). But when facing a chronic peripheral VES, our hypothesis is that the mechanisms of sensory integrations and error signal processing are significantly altered. Alberts et al. (22) offer insights into how peripheral VES influences the noise levels of otolith and somatosensory signals depending on body tilt, leading to dynamic shifts in sensory input weights with tilt angle. This highlights a shift in sensory reliance, where otolith organs are more influential around upright positions, and somatosensory inputs become more critical at larger body tilts. Forbes et al. (23) further explored how peripheral VES affects motor responses, showing that it modifies the magnitude of muscle responses to align with the vestibular error and balance direction. This flexibility in motor command adjustments in response to vestibular disturbances points to the system's adaptability. Rideaux et al. (24) delve into the impact of peripheral VES on sensory integration, demonstrating how it leads to sensory reweighting and influences the activity balance between congruent and opposite neurons.

1.2.3 Clinical implications and rehabilitation protocol

This affects the decision-making process on whether to combine or separate multisensory signals, underlining the brain's capacity to adapt to vestibular errors for precise motion estimation. This suggests that chronic peripheral VES not only disrupts sensory integration and motor response adaptation but also impacts the ability to manage visual-vestibular mismatches, potentially leading to headaches and dizziness. Thus, following a chronic VES, the necessary adaptations for navigating and effectively interacting with our environment would be poorly adjusted, and predictions and responses based on complex and often conflicting sensory information flows would be inadequate. This mismatch can lead to a variety of persistent symptoms in CVS, including, but not limited to, dizziness, instabilities, spatial disorientations, and difficulties in executing precise and coordinated movements. The impact of these alterations on patients' daily lives can be substantial, affecting not only their ability to perform ordinary tasks but also their psychological well-being. To address these observations, we undertook the creation of a vestibular rehabilitation program based on an integrative approach involving the clinical and instrumental identification of the type of VES (irritative or deficient) and the search for tracking markers dedicated to the type of VES. iVRT addresses vestibular disorders by considering the individual as a whole, including interventions on motor, oculomotor, cognitive, and emotional systems. In addition to vestibular exercises, the treatment incorporates the assessment and rehabilitation of the cervical spine to improve sensorimotor coordination, maxillofacial approaches to reduce muscle tension and enhance proprioception, and the learning of strategies to improve dynamic balance performance and stability. Neurovisual performance, which links vision and balance, is also a focal point, with specific rehabilitative sequences if anomalies are detected. Moreover, the approach addresses psychic and emotional aspects, recognizing the impact of cognition and emotional state on physical balance and utilizing psycho-behavioral assessment and management techniques (Table 1).

iVRT is structured around four main pillars: comprehensive evaluation of the patient's abilities and dysfunctions, personalized treatment, regular monitoring to adjust the treatment, and finally, the definition of termination criteria based on indicators of success or failure. The treatment sequences detailed in Table 1 are determined following the initial assessment.

TABLE 1 Rehabilitation sequence.

Sequences	Title	Descriptions
1	Positional maneuvers	Traditionally indicated for resolving benign paroxysmal vertiginous events of peripheral positional origin. Also proposed in other settings for perceptual-sensory reweighting, notably in habituation.
2	Neurosensory reweighting	Tools and techniques aimed at creating a perceptual-sensory reweighting following a supraliminal vestibular stimulus that is incoherent.
3	Neurosensory facilitation	Tools and techniques designed to optimize the signal/noise filter by attenuating a vestibular error signal or through attentional tasks.
4	Sensory conflict induction	Tools and techniques aimed at increasing perceptual noise by artificially creating incoherence among sensory inputs.
5	Sensory integration optimization	Tools and techniques aimed at achieving a coherent response based on visual and motor context.
6	Perceptual-somatomotor and perceptual-visuo-oculomotor reweighting	In the presence of a vestibular error signal: tools and techniques aimed at optimizing perceptual-motor sensory integration through motor and/or sensory inputs to inhibit the integration of the vestibular error signal.
7	Gait and balancing performance	Tools and techniques aimed at physical conditioning and error experimentation.
8	Cognitive reweighting	Tools and techniques aimed at enhancing or optimizing cognitive-emotional and psycho-behavioral processes.

"Each treatment session is customized according to two guiding principles: addressing the patient's specific complaints and being guided by specific instrumental indicators present in the literature for which we have constructed a decision tree Figure 1, (9, 10)."This strategy adheres to the diagnostic treatment model, ensuring a targeted and responsive approach to patient care. During this care, we searched for indicators related to statistically significant changes (monitoring indicators). Finally, we evaluated retrospectively whether there are predictive markers of postural instability and predictive markers of the variation in the accuracy and precision of the subjective visual vertical (25).

2 Materials and methods

2.1 Research objectives and study design

This retrospective study aims to identify monitoring and predictive markers in patients suffering from chronic unilateral peripheral vestibulopathy unresponsive to conventional therapies for more than a year. Conducted from November 2021 to March 2022, our research focuses on key indicators derived from questionnaires and instrumental evaluations to deepen the understanding of chronic vestibular pathology. The protocol was approved by the ethics committee of the Caen University Hospital, accreditation number 2,796, and was carried out in accordance with confidentiality and consent standards.

2.2 Materials and methods

2.2.1 Participants

The study included patients with chronic unilateral peripheral vestibulopathy lasting one year or longer who had not responded to rehabilitative treatment. Rehabilitation follow-ups for these patients were conducted in a physiotherapy clinic specializing in vestibular rehabilitation located *in vitro*lles (13,127, France). To ensure the reliability and precision of the collected data, inclusion criteria were meticulously defined, relying on comprehensive clinical and instrumental evaluations.

Exclusion criteria were carefully chosen to eliminate any variables that could bias the study's results. These criteria included:

- Binocular or stereoscopic vision disorders: including neutralization, amblyopia (poor vision in an eye not corrected in childhood), anisometropia (difference in refractive power between the two eyes), and all types of strabismus, including microstrabismus, where the visual axes' misalignment is minimal but can affect depth perception.
- Psychiatric disorders diagnosed before the onset of vestibular issues to eliminate potential interferences from pre-existing psychiatric conditions that could influence vestibular symptoms or their management.
- Vascular, degenerative, and inflammatory neurological conditions affecting central functions diagnosed before rehabilitative care.
- Neurological conditions likely to impact the central nervous system and, consequently, confound the evaluation of peripheral vestibulopathy were excluded to purify the research sample from external influences that could alter the accuracy of the results analysis.

2.2.2 Experimental procedures

Participants were evaluated before and after treatment using questionnaires (Supplementary Tables S1–S5) created from vestibular patient literature to assess i/handicap and quality of life: The Dizziness Handicap Inventory [DHI (26),], the Short Form (27) Health Survey [SF36 (28, 29);], ii/personality traits with the Big Five Inventory [BFI (30);]. Also included in our questionnaire battery were the 31-item Positive and Negative Emotionality Test [EPN31 (31);] and the Vestibular Health Questionnaire we developed (VestiQ-VS; Xavier et al. 2023 in submission). Additionally, a series of instrumental examinations included: i/a sensory organization test from posturography, developed by Synapsys, including a specific analysis called sensory organization assessment (Supplementary Table S6), ii/videonystagmography (VNG thermal and kinetic) developed by

FIGURE 1
Decisional tree (Two parts). This figure illustrates the various symptoms reported by chronic vestibular patients. A comprehensive initial assessment is conducted at the beginning of treatment, and the main areas of focus are determined based on the most debilitating symptoms for the patient. At the start of each week, a screening of complaints (symptoms) is conducted. For each complaint, an evaluation is performed, and treatment is adjusted based on the results. VNGk: kinetic videonystagmography, DVA: dynamic visual acuity, VHIT: video head impulse test, VOMS: Vestibular Oculomotor Motor Screening.

Synapsys, and the study of subjective visual vertical (SVV) iii/ the following optometry tests: for the evaluation of near and far visual acuity the use of Monoyer and Parinaud scales; for the evaluation of convergence and divergence capacity the prism bar (PB); for the evaluation of fusion the Mawas Board; for the evaluation of accommodation capacities [or near point of accommodation (NPA)] and convergence [or near point of convergence (NPC)] the use of the accommodation bar; for the evaluation of distant stereoscopic vision the Thomas Stereoscopic Vision Test (TVST); and for assessing a patient's degree of binocular vision and binocular single vision the Worth four light test; all these evaluations allowing an approach that encompasses somato-

perceptual-visuo-oculomotor and somato-perceptual-motor aspects under the regulation of vestibular control (32–36).

2.2.3 Indicators under study

A detailed analysis of the following indicators was performed:

2.2.3.1 Synapsys posturography analysis

Sensory organization test (SOT) has an instrumental standard developed at the Cognitive Neuroscience Laboratory of St Charles Campus, Aix Marseille University. It is established from the Stability Limits and SOT conditions [Supplementary Tables S6 and S7 (27)].

The total energy calculation, assessing postural stability, is based on recording the trajectory of the center of pressure (CoP), representing the body's center of gravity movement on the support surface (37). The CoP speed is calculated in two directions (antero-posterior and lateral), yielding two data sets. The variance of these speeds is then calculated for each direction, and the total energy is obtained by combining these variances. A high total energy value indicates less postural stability, while a low value suggests better stability.

$$\varepsilon\text{total } (\text{mm}^2.\ \text{s}) = \text{Var(APd)} + \text{Var(MLd)}$$

Where:

Var(APd) represents the variance of the CoP speed in the antero-posterior direction (APd),

Var(MLd) represents the variance of the CoP speed in the lateral direction (MLd).

2.2.3.2 Kinetic videonystagmography (VNG) indicators

The model used includes a videonystagmography system and an electronic rotational chair (type Met4). We utilized the indicators obtained during the Met4 kinetic test in burst (sinusoidal test at 0.25 Hz) by studying the visuo-vestibulo-ocular reflex (test with the patient's eyes open without fixation; VVOR), the vestibulo-ocular reflex (test with the patient's eyes closed; VOR), the double-task vestibulo-ocular reflex [test with the eyes closed combined with a mental arithmetic task (random addition and subtraction including numbers between 1 and 100); VOR2], the ocular fixation index (test with visual fixation; OFI), and the cervico-ocular reflex [test with head stabilization (only the torso performs the sinusoidal movement); COR]. The standards are presented in the Supplementary Material, Table S8. The VNG Synapsys standards are norms developed by the manufacturer and are documented in the non-indexed internal technical documentation (38).

2.2.3.3 Bithermal videonystagmography (VNGt) indicators

The indicators recorded during the bithermal test were the absolute nystagmic preponderance, the reflectivity on the side opposite to the lesion, and the ipsilateral deficit to the lesion. Norms are available in the Supplementary Table S8 (38).

2.2.3.4 Composite indicator "state of compensation" (SoC)

We developed an indicator for this study to classify vestibular profiles via bithermal videonystagmography (VNGt), including: i/ Non-Inhibited Profile (N) with contralateral reflectivity $\geq$15°/s and ipsilateral vestibular deficit $\leq$ 30%, indicating preserved contralateral reactivity despite a minor deficit, thus without modulation of the subcortical arc; ii/ Partial Contralateral Inhibition Profile (P) when contralateral reflectivity is in the range [2°/s; 15°/s] with an ipsilateral deficit in the range [30%; 70%], showing partial compensation; iii/ Total Contralateral Inhibition Profile (T) defined by a reflectivity $\leq$2°/s and an ipsilateral deficit $\geq$70%, reflecting an almost total inhibition of contralateral peripheral input associated with maximum subcortical compensation; iv/ Inhibition without Deficit Profile (I) with reflectivity $\leq$15°/s and an ipsilateral deficit $\leq$30%, indicating a reduction in contralateral reactivity despite a minor deficit. N indicates the absence of compensation modulation in the presence of a subliminal deficient-type VES, *P* indicates moderate compensation responding to a deficient VES, T indicates strong compensation responding to a deficient VES. I indicates modulation of reflectivity in the presence of a deficient VES maintained at a subliminal level. Reflectivity in vestibulometry refers to the reflex response generated by the vestibular system during bithermal caloric stimulation. Reactivity refers to the vestibular system's ability to respond to stimulation and modulate the signals sent to the brain. In the context of vestibulometry, reactivity is often assessed in terms of vestibular compensation following a loss or deficit.

2.2.3.5 Composite indicator for the study of hyperactive signal (Hs)

Clinically, the irritative VES is identified based on three parameters: the head shaking test (HST), which triggers a nystagmus beating towards the pathological side; a kinetic test showing a preponderance towards the pathological side; and a caloric test showing an uncompensated deficit (Figure 2A). The deficient VES is identified with an HST triggering a nystagmus beating towards the healthy side, a kinetic test showing a preponderance towards the healthy side, and an uncompensated caloric test (Figure 2B).

2.2.3.6 Study of subjective visual vertical and explanatory variables of its evolution

We propose a new model of analysis for this work. The goal is to offer the community a new perspective on the examination and interpretation of the Subjective Visual Vertical (SVV; Figure 3) We chose to conduct four measurements on each side for the static test and six for the dynamic test because during our preliminary trials, we noticed that variations in measurements for certain VPC profiles, which are still poorly identified, either worsened or improved. This indicated the implementation of gravitational sensory-perceptive strategies, which we suspect are linked to somesthesia and graviception.

After averaging the measured values, we calculated for each static and dynamic condition a geometric angle (SGA and DGA, respectively) and a bisector for each angle obtained in static and

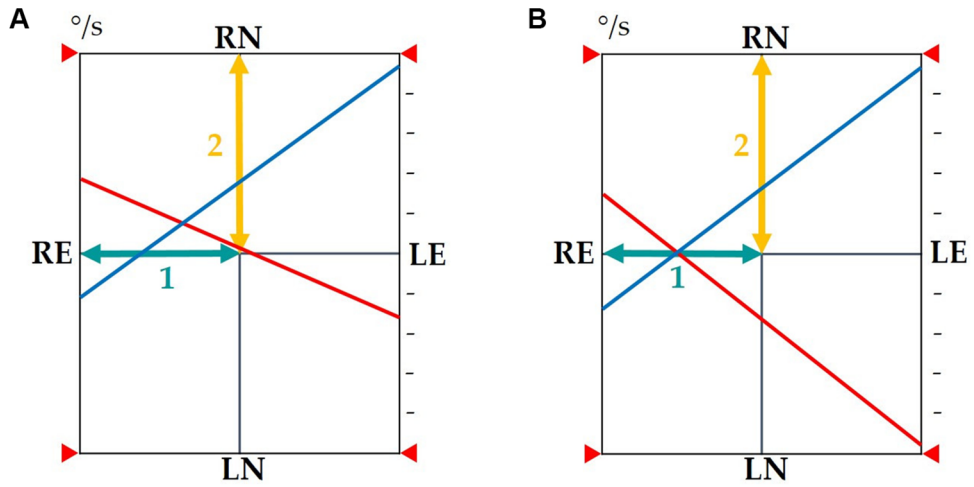

FIGURE 2
(A) In the presence of an uncompensated VES resulting from a subcortical compensation defect: The observed phenomenon will cause a shift in the intersection of the reflectivity lines along baseline 1 towards the pathological side and a shift in the intersection along baseline 2 upwards, which may indicate either an incomplete state of compensation of the vestibular nuclei during warm stimulation on the healthy side or a defect in reflectivity during cold stimulation on the pathological side. A revealed nystagmus beating towards the pathological side will be present (shift towards the upper left quadrant of the intersection point of reflectivity lines). (B) In the presence of a compensated deficient VES: The observed phenomenon will cause a shift in the intersection of the reflectivity lines towards the pathological side along baseline 1 without a parallel shift along baseline 2. The intersection of the reflectivity lines remains on the horizontal axis. A revealed nystagmus beating towards the healthy side will be present. VES, vestibular error signal; baseline 1, axis of directional preponderance; baseline 2, axis of reflectivities; red reflectivity line, results of warm stimulations of the right and left ears; blue reflectivity line, results of cold stimulations of the right and left ears; RE, right ear; LE, left ear; RN, right nystagmus; LN, left nystagmus.

dynamic conditions (SBA and DBA, respectively).

$$\theta\Delta = |\mu(\text{SVVl})^\circ\text{-}\mu(\text{SVVr})^\circ|$$

Where:

- $\theta\Delta$ = variation of the angle θ,
- μ = average of the angles in degrees (°) of the variables *SVVl* and *SVVr*,
- *SVVl* and SVVr = the set of measurements |to determine the angle SGA| taken on the right side (SVVstatr) and on the left side (SVVstatl); |to determine the angle DGA| taken on the right side (SVVdynr) and on the left side (SVVdynl), values expressed in degrees (°),

$$\theta\Delta = \frac{\boldsymbol{\mu}(\text{SVVl})^\circ + \boldsymbol{\mu}(\text{SVVr})^\circ}{2},$$

Where:

- $\theta\Delta$ = variation of the angle θ,
- μ = average of the angles taken by the bisector in the degree of inclination (°) for the values taken in SVVl and SVVr,
- SVVl and SVVr = the set of measurements |to determine the angle SBA| taken on the right side (SVVstatr) and on the left side (SVVstatl)/2 and |to determine the angle DBA| taken on the right side (SVVdynr) and on the left side (SVVdynl)/2, values expressed in degrees (°).

We modeled the geometric (Figure 3) angle obtained from the average amplitudes of the right and left test scores as representing precision (25). The bisector of the angle models accuracy. We hypothesize that accuracy is not solely linked to the internal model but also related to the integration of measurement error. In other words, two patients can have the same accuracy (represented by the inclination of the bisector relative to the vertical) but different opening angles (leading to different levels of precision: the more obtuse the angle, the lower the precision).

2.2.3.7 Optometry test indicators from visual acuity measurements

We used two visual acuity measurement scales: the Monoyer scale (39) for distance visual acuity (DVA) assessment at 3 meters and the Parinaud scale for near visual acuity (NVA) assessment at 40 cm (40).

2.2.3.8 Prismatic study (convergence and divergence) indicators

For accurate measurement of near convergence and divergence capabilities, we adopted the use of a prism bar (PB), combined with a specific measuring device (41). This device, consisting of a helmet equipped with a frontal axis on which a target is fixed at a distance of 30 cm from the nasion point, ensures uniform and reproducible measurements. The PB, with graduations extending from 1 to 40 diopters, is strategically positioned either base nasal for assessing divergence capabilities (PBd) or base temporal for examining convergence capabilities (PBc). Results are recorded in diopters.

2.2.3.9 Optometry test indicators from the mawas board examinations

The Mawas Board, known as the Mawas-Weiss plate, consists of a cardboard plate with one side printed with a white line on a black

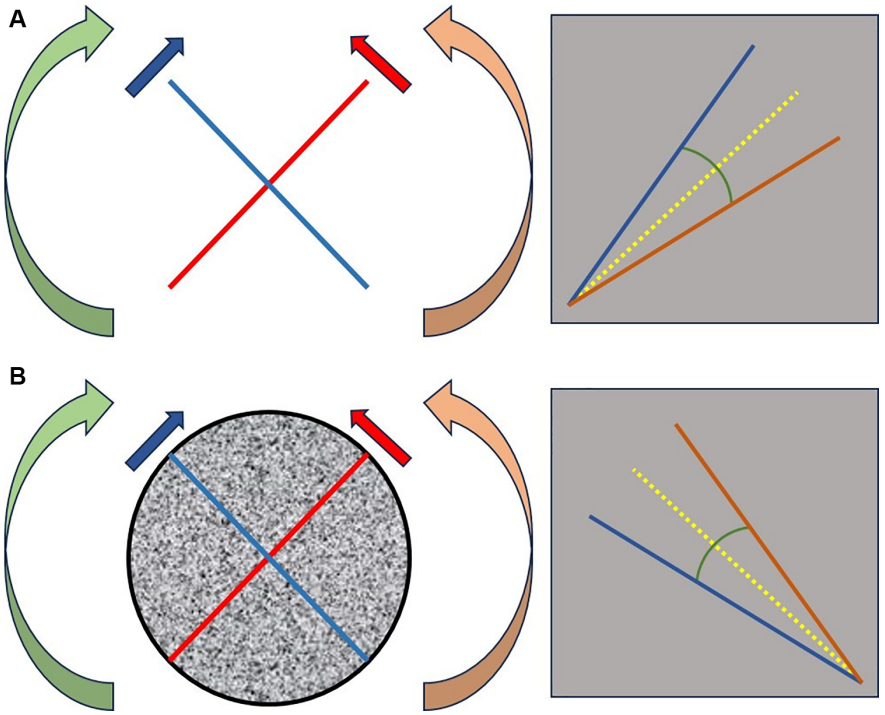

FIGURE 3
Description of the geometric angle and the bisector of the angle modeled on SVV measurements. We proceed with a random selection of the initial tilt. For example, for a right-sided selection: we perform a series of 4 measurements with the patient seated in darkness, starting from the right side [red line figure **(A)**], followed by 4 measurements from the left side [blue line figure **(A)**]. Each starting point is randomly positioned within an interval of [18°; 22°] on the right side and [−18°; −22°] on the left side relative to the vertical axis. Under dynamic conditions, optokinetic stimulation is initiated at 20°/s clockwise (green arrow) for measurements starting on the right [red line figure **(B)**], and counterclockwise (orange arrow) for measurements starting on the left [blue line figure **(B)**]. The same principles are applied except that we perform 6 measurements on each side. By averaging each series, we obtain 2 angles: one in static condition [figure **(A)**] and one in dynamic condition [figure **(B)**]. The bisector of each angle (yellow line) is then plotted. We evaluate the tracking of the geometric angle (closure = increased precision; opening = increased imprecision) and the variation of the bisector angle relative to the vertical (increased angle = decreased accuracy; decreased angle = increased accuracy).

background and the other side with a black line on a white background (42). We used this device to detect fusion disorders during vergence movements. Measurements were taken every 5 centimeters from 5 to 40 cm. A 10-s eyes-closed break was taken between each measurement to solicit a vergence movement from the rest position. Each measurement was taken randomly by drawing lots from 4 sequences for the initial assessment and 3 sequences for the final assessment (excluding the one obtained by lot during the first assessment). The goal was to closely mimic the ecological function of vergences. Fusion is considered normal when the subject visualizes a cross. Any other pattern is deemed abnormal.

2.2.3.10 Optometry test indicators from measurements of near points of accommodation (NPA) and convergence (NPC)

We used an accommodation bar to measure positive NPAs (the distance at which maximum focus accommodation is achieved) and NPCs. The distance at which vision becomes blurry indicates the positive NPA in monocular use and the NPC in binocular use (43).

2.2.3.11 Optometry test indicators from the Thomas Far stereoscopic vision test (TVST)

We assessed the patients' stereoscopic vision capabilities at distances of five and one meter, using four stereograms, based on the principle of Julesz's random dot stereograms (44). The first two, with a disparity of 250 arcs, featured images of a circle and a star, while the latter two, with a disparity of 300 arcs, depicted a cat and a car. These tests allowed measuring depth perception and the ability to distinguish spatial details at different distances.

2.2.3.12 Optometry test indicators from the Worth four dot test

In our study, the Worth lamp was used as a diagnostic tool to assess patients' binocular perception. This instrument, consisting of a specific lighting system projecting four colored points (one red, two green, and one white) at different distances, helps detect binocular vision anomalies such as diplopia or suppression of one eye. The examination is considered normal when the colors generated by the 4 lamps are perceived in the following manner: i/red, ii/green, iii/green, iv/white or mixed color (42).

2.2.4 Data preprocessing and univariate statistical analysis

The statistical analysis was conducted following an intention-to-treat strategy, where all participants were included in the analysis according to their initial allocation to the rehabilitation group. To handle missing values, we employed the mode imputation method, replacing missing values with the most frequently occurring category within our dataset, thus ensuring maximum data integrity. Data processing was performed to determine the evolution before (A1) and after (A2) rehabilitation with a threshold *p*-value of 0.05. The indicators of rehabilitation success are represented by the study of questionnaires. The search for tracking indicators is represented by the study of data from posturography, SVV, and optometry tests.

2.2.4.1 Evaluation of responses to clinical questionnaires

The Shapiro-Wilk test assessed the normality of questionnaire scores before and after intervention, allowing the use of the Student's *t*-test or the Wilcoxon signed-rank test for comparing means, depending on the data distribution.

2.2.4.2 Analysis of posturography indicators

We converted the continuous quantitative posturography scores into categorical variables, using normality thresholds defined by Synapsys. Values exceeding these thresholds were coded as "N" for normal and "AN" for abnormal. To examine the normality evolution between A1 and A2, we created four categories: "A" for variables abnormal at both A1 and A2, "B" for variables changing from abnormal to normal, "C" for those changing from normal to abnormal, and "D" for variables remaining normal. The frequencies of each category were calculated using a contingency table. The McNemar test was used to assess the statistical significance of variations.

2.2.4.3 Analysis of kinetic VNG indicators

A statistical methodology was used to analyze the evolution of several indicators, including gains and preponderances at VVOR, VOR, OFI, VOR2, COR before (A1) and after (A2) rehabilitation. Data were categorized as "N" for normal and "AN" for abnormal according to specific thresholds. A frequency analysis documented the indicator evolution before and after rehabilitation. The McNemar test examined the significance of observed changes.

2.2.4.4 Analysis of VOR2 and COR gain

A structured methodology was applied to analyze the evolution of VOR2 and COR gain, with classifications based on the improvement or deterioration of measurements. The Shapiro-Wilk tests, and depending on their results, Student's *t*-test or Wilcoxon signed-rank tests, evaluated significant differences.

2.2.4.5 Comparative analysis of VOR and VOR2 gain trends

A comparative statistical analysis of VOR gain trends and VOR2 gain was used to determine their behavior between A1 and A2. For this, we created two continuous quantitative variables named:

- varVORg using VORgA1 and VORgA2 variables according to the following equation:

$$\frac{\text{VORgA2-VORgA1}}{\text{VORgA1}} \times 100$$

varVOR2g using VOR2gA1 and VOR2gA2 variables according to the following equation:

$$\frac{\text{VOR2gA2-VOR2gA1}}{\text{VOR2gA1}} \times 100$$

Sub-groups A and D from the VOR2 gain evolution study were used to create two new categorical variables (varVORgImprovement vs. varVOR2gImprovement and varVORgDeterioration vs. varVOR2gDeterioration) coding the VOR and VOR2 gains evolution between A1 and A2 into 3 categories: category 1 where VORg < VOR2g, category 2 where VORg and VOR2g observe a slight difference IC [−5.0; 5.0], and category 3 where VORg > VOR2g.

2.2.4.6 Analysis of bithermal VNG reflectivity

To study the evolution of bithermal videonystagmography (VNGt) indicators between initial (A1) and final (A2) measurements, a two-phase statistical approach was adopted. Firstly, variations in these indicators were analyzed with statistical tests, classifying data by normality and using the McNemar test to evaluate changes in normality pre and post-rehabilitation. Secondly, evolution sub-groups ("A" for improvement, "D" for deterioration, and "I" for inversion of laterality) were formed. The Shapiro-Wilk test checked data normality, and differences were evaluated with the Wilcoxon signed-rank test. Comparisons between A1 and A2 measurements were performed to identify significant differences.

2.2.4.7 Analysis of composite indicators: state of compensation (SoC) and hyperactive signal (Hs)

We descriptively identified different groups from these two classifications.

2.2.4.8 Analysis of subjective visual vertical (SVV)

Subjects were classified according to the evolution of static (SGA) or dynamic (DGA) geometric angles between A1 and A2 into three categories: "D" for deterioration, "A" for improvement, and "S" for stagnation. This classification was also applied to the absolute values of bisector angles. If the absolute value of |static bisector angle (SBA) or dynamic (DBA) at A1| was strictly lower than |SBA or DBA at A2|, subjects were classified in the "D" category, if the absolute value of |SBA or DBA at A1| was strictly higher than |SBA or DBA at A2|, subjects were classified in the "A" category. The Shapiro-Wilk test checked the normality of distributions, with a threshold *p*-value of 0.05 to distinguish between normal and abnormal distributions. Comparisons of means between A1 and A2 for normally distributed variables were performed with the paired series Student's *t*-test, while the Wilcoxon signed-rank test was used for non-normally distributed distributions.

2.2.4.9 Analysis of explanatory variables of SVV evolution

In this study, groups were defined based on the evolution of several key indicators: the cervical-ocular reflex (COR) gain, the state of compensation assessed by thermal videonystagmography (SoC), and the presence of a hyperactive signal (Hs). To analyze data variation and concentration, two statistical tools were used: the coefficient of variation (CV) and the Gini coefficient (Cg). The CV evaluates the dispersion of data around the mean, making the comparison between distributions with different means more equitable. A higher CV indicates a greater relative dispersion. The Cg measures data concentration, with values close to 0 indicating perfect equality and values close to 1, a high concentration. The combined use of CV and Cg allows assessing variability and concentration within groups, thus facilitating the comparison of homogeneity between them.

$$CV = \left(\frac{\sigma}{m}\right)$$

Where:

- σ = standard deviation
- m = mean

$$G = \frac{A}{A + B}$$

Where:

- G is a number between 0 and 1
- A represents the area between the Lorenz line and the line of perfect equality
- B represents the total area under the line of perfect equality.

2.2.4.10 Analysis of optometry indicators

For the evolution of results obtained in the study of Near Visual Acuity (NVA), Distance Visual Acuity (DVA), prism convergence/divergence tests (PBc/PBd), Near Points of Accommodation (NPA), and Near Point of Convergence (NPC) between A1 and A2, averages were calculated. The distribution of data for normality was evaluated using the Shapiro-Wilk test. Statistical analysis of observed changes was performed using the Wilcoxon test for paired samples, suitable for non-parametric data.

The evolution of the normality state of measures in the Mawas Board examination, the Thomas Far Stereoscopic Vision Test (TVST), and the Worth test was studied, using the McNemar Chi-squared test to evaluate changes between A1 and A2.

2.2.5 Data preprocessing and multivariate statistical analysis

We employed the Ordinary Least Squares (OLS) regression model to analyze the impact of selected variables on posturographic measurements and the SVV. The OLS model, with its equation

$$B = (X^tX)^{-1}(X^tY)$$

aims to estimate the coefficients b, quantifying the influence of each independent variable X on the dependent variable Y. This method allows for the identification of causal relationships, unlike correlation analysis, which only detects co-variations. The statistical objective is to evaluate the impact of a set of explanatory factors on the variation of posturography data and the SVV angle between A1 and A2. The variation in posturography measurements was carried out according to the following model:

$$\Delta m = \frac{ma1}{ma2} \times 100 - 100$$

Where:

- Δm = variation of the measurement
- ma1 = measurement before iTRV
- ma2 = measurement after iTRV

For each evolution calculation, a quantitative variable was derived, on which linear regression was performed to measure the causality of potential explanatory factors. Predictive factors retained were all measured in the first period. Twelve variations in posturography measurements and four variations in angle measurements were thus calculated before a regression model was applied to each of them. In addition to the indicators to be explained, the study included a large set of potential explanatory variables. A selection process for these predictive factors was carried out in three steps.

First, for each variable to be explained, a univariate linear regression was performed for each potential explanatory variable. Variables from regressions with a p-value less than 25% were retained. Next, multicollinearity was examined to avoid selecting explanatory factors with a linear relationship that could explain the same variation. For this, the variance inflation factors (VIF) were calculated for each variable. Any variable with a VIF (adjusted for qualitative variables with more than two response modalities) greater than 5 was removed from the analysis. Finally, if necessary, a stepwise elimination procedure was carried out to retain only five exogenous variables. The final model retained was the one composed of five exogenous variables and presenting the lowest Akaike Information Criterion (AIC).

The quality of all models was evaluated by the coefficient of determination R^2, which indicates the proportion of variance in the variable explained by the model's explanatory variables. The overall significance of the models was estimated by the Fisher test, where the null hypothesis assumes that none of the variables have a significant effect. The fit between the dependent variable and each independent variable was assessed by a Student's t-test, which tested the null hypothesis of no linear relationship between the dependent variable and the explanatory variable.

3 Results

3.1 Cohort presentation

A total of 62 patients were included (Figure 4). Our sample consisted of 45 women (72.6%) and 17 men (27.4%), with an average age of 59.4 years and a standard deviation of 18.1 years. The sample description is provided in Table 2.

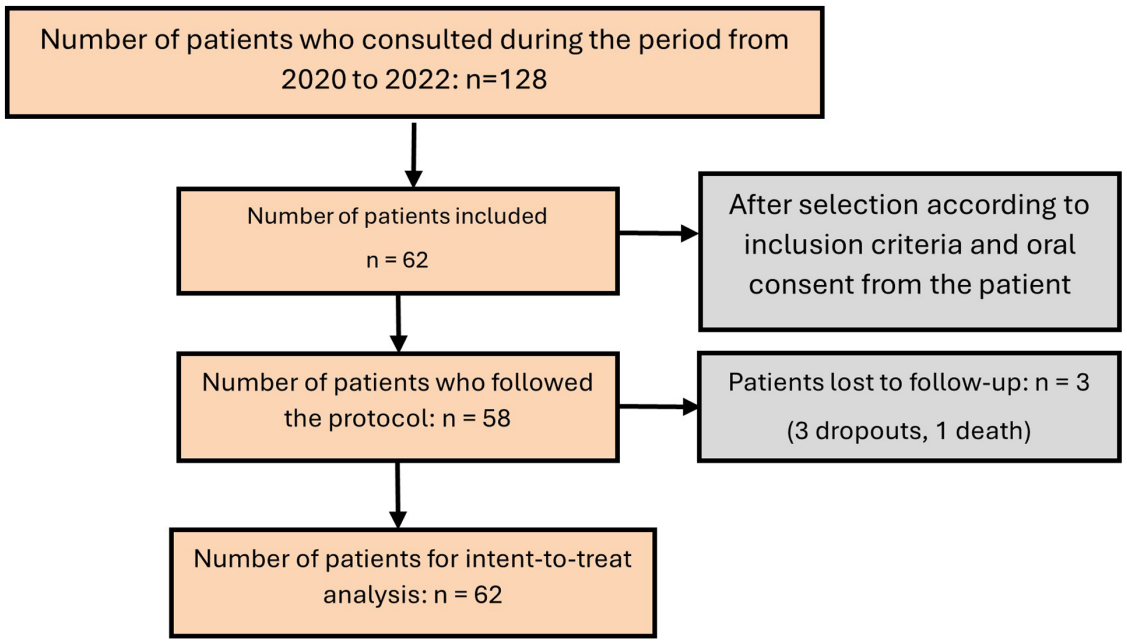

FIGURE 4
Flow chart.

TABLE 2 Study population characteristics (sample size 62).

Variables	Indicators
Year of Study Inclusion, *n* (%)	2021: 37 (59.7%), 2022: 25 (40.3%)
Follow-up Duration (months), Mean (SD)	13.0 (4.0)
Number of Sessions, Mean (SD)	86.6 (14.7)
Occupation, *n* (%)	Business Owner: 1 (1.6%), Freelance Professional: 1 (1.6%), Executive or Higher Intellectual Profession: 3 (4.8%), Intermediate Profession: 10 (16.1%), Employee: 11 (17.7%), Worker: 2 (3.2%), Retired: 29 (46.8%), Homemaker: 4 (6.5%), Student: 1 (1.6%)
Engagement in Sports Activity, *n* (%)	26 (41.9%)
Initial Diagnosis, *n* (%)	Other initial conditions: 26 (41.9%), Chronic Unilateral Vestibular Hypofunction (CUVH): 6 (9.7%), Undefined: 9 (14.5%), Recurrent Benign Paroxysmal Positional Vertigo (rBPPV): 21 (33.9%)
Diagnosis at Inclusion (A1), *n* (%)	Other: 25 (40.3%), CUVH: 16 (25.8%), Undefined: 15 (24.2%), rBPPV: 6 (9.7%)
Diagnosis at End of Care (A2), *n* (%)	Other final conditions: 28 (45.2%), CUVH: 5 (8.1%), Persistent Postural-Perceptual Dizziness (PPPD): 11 (17.7%), Functional (Psychogenic) Vertigo: 17 (27.4%), rBPPV: 1 (1.6%)

"Other" in initial diagnosis includes unilateral vestibular schwannoma, Ménière's disease. "Other" in final diagnosis includes unilateral vestibular schwannoma, Ménière's disease, vestibular migraine, Friedrich's disease; CUVH, chronic unilateral vestibular hypofunction; PPPD, persistent postural-perceptual dizziness; Functional (Psychogenic) Vertigo, psychiatric diagnosis made after the start of rehabilitative care: phobic disorders, bipolar affective disorder, anxiety disorder, major depressive disorder, post-traumatic stress disorder, and somatoform disorder; rBPPV, recurrent benign paroxysmal positional vertigo. Care: management.

The patients lost to follow-up represented 6.5% of the cohort. Among these patients, the diagnosis evolved after the start of the rehabilitative intervention: two for Canvas, five and nine months later, one for Friedrich's ataxia six months later, and one due to suicide 10 months after starting the rehabilitative follow-up. Two diagnoses of vestibular migraine were reevaluated seven months and one year later. The initial diagnosis of recurent Benign Paroxysmal Positional Vertigo (rBPPV) accounted for 33.9% but was reduced to 1.6% by the end of rehabilitation. 24.2% of undefined vestibular vertigos were defined by the end of care.

During the first crisis, 51.6% of the cohort reported experiencing rotational type visual vertigo, triggered by movement in 77.4% of cases and transient in 54.8% of cases; triggered by vision in 38.7% of cases, by Valsalva maneuver in 9.7% of cases, and by orthostatism in 9.7% of cases. Blurred vision induced by movement at the first crisis was present in 11.3% of the cohort and increased to 59.7% of the cohort at the first physiotherapy consultation. Other visual symptoms identified during the interview are presented in Table 3.

Regarding general health, 40.3% of the cohort experienced sleep disorders, and 91.9% reported abnormal fatigue that gradually set in after the first crisis. Notably, before the first crisis (one year aflter): 72.6% of the cohort had anxiety disorders, among them: 27.4% had at least one depressive episode, and

TABLE 3 Visual symptoms reported at the first physiotherapy consultation (sample size 62).

Variables	Indicators, *n* (%)
Change observed by patient since first Episode	56 (90.3%)
Fatigue when reading	24 (38.7%)
Wearing progressive glasses	21 (33.9%)
Oscillopsia	3 (4.8%)
Intermittent diplopia	7 (11.3%)
Movement-induced blurry vision	37 (59.7%)
Decrease in near visual acuity (NVA)	46 (74.2%)
Decrease in visual field while driving	32 (51.6%)
Other Symptoms	Photophobia: 6 (9.8%), Visual Vertigo While Watching TV: 17 (27.9%)

NVA, near visual acuity.

30.5% were followed for post-traumatic stress disorder. 1.61% of the cohort suffered from Temporomandibular Joint Disorders (TMJD) before the first crisis compared to 14.5% at the first consultation; 1.61% had facial nerve damage compared to 9.68%, and 3.13% had chronic neck pain compared to 25.8%, which is a quarter of the cohort.

3.2 Evaluation of iTRV: questionnaire analysis

All results are presented in Figures 5–9, and all statistical results in Supplementary Table S9 due to the data density. In an unconventional manner to facilitate data approach, we present a list from the analysis of score variation that is not significant ($p > 0.05$) for the following dimensions: SF36 pain, EPN anger, EPN surprise, BFI Extraversion, Energy, Enthusiasm, BFI Agreeableness, Altruism, Affection, BFI Conscientiousness, Control, Constraint, BFI Openness, Originality, Open-mindedness, VestiQ-VS memory, and VestiQ-VS spatial orientation.

At the end of integrative vestibular rehabilitation therapy (iVRT): 79% of patients presenting abnormal fatigue improved their scores in the fatigue dimension of the VestiQ-VS questionnaire, 78.72% of patients who presented anxiety disorders improved their emotion management score (EPN 31 questionnaire) and reported having improved their anxiety state either by decreasing medication or by resuming activities that had become anxiety-inducing before rehabilitation. Finally, 75% of patients suffering from neck pain improved their score in the pain dimension of the SF36.

3.3 Analysis of instrumental tracking indicators

3.3.1 Posturography indicator analysis

The statistical study of the variation in BOS scores gives us significant results for the evolution of i/ Vestibular score in mediolateral imbalance condition: McNemar's chi-squared = 4.00, dF = 1, p-value = 0.046; ii/ Composite score in mediolateral imbalance condition: McNemar's chi-squared = 6.13, dF = 1, p-value = 0.01.

3.3.2 Analysis of indicators from kinetic VNG tests

To assess whether rehabilitation impacted the VVOR, VOR, VOR2, COR, and OFI indicators, we examined the evolution of normality (transition to norms or not) of these indicators between two points in time: before (A1) and after (A2) for preponderance and gain. No results were statistically significant.

3.3.3 Analysis of VOR2 gain (VOR2g) and COR gain (CORg)

Three subgroups were created for the analysis of VOR2 gain as a continuous quantitative variable to assess the variation of VOR2 gain between A1 and A2. Group A: increase $n = 22$, D: decrease $n = 36$, S: stability $n = 0$.

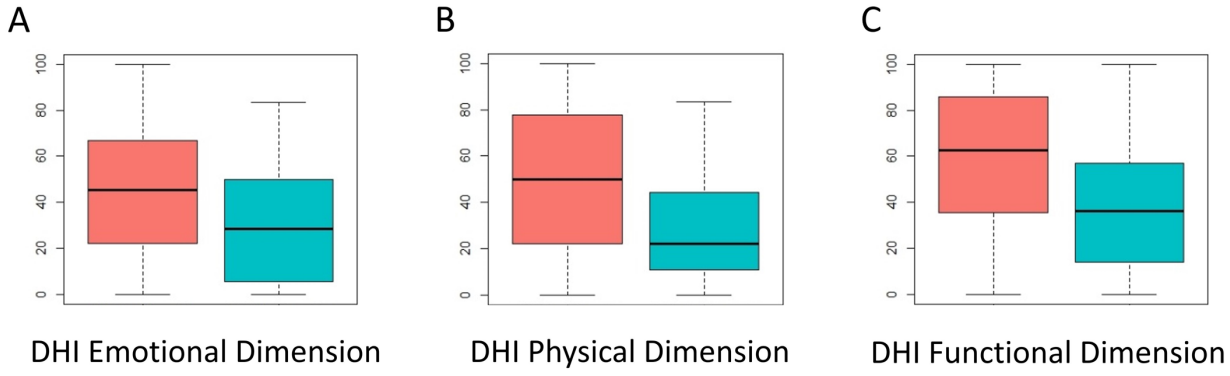

FIGURE 5
Distribution of scores across the three components of the dizziness handicap inventory (DHI). Red: scores at A1; Blue: scores at A2. Higher scores indicate a poorer state of the evaluated component.

- For subgroup A: V = 0, *p*-value = 1.93e-05 shows a significant difference between the VOR2g means at A1 and A2 in this subgroup. The mean differences (signed Wilcoxon test) suggest a significant improvement in VOR2g mean after rehabilitation for subjects in subgroup A.
- For subgroup D: t = 8.46, dF = 37, *p*-value = 3.59e-10 also shows a significant difference between the VOR2g means at A1 and A2 in this subgroup. The mean differences suggest a significant deterioration in VOR2g mean after rehabilitation.

Three subgroups were created for the analysis of numerical COR gain as a continuous quantitative variable to assess the variation of COR gain between A1 and A2. Group A: increase $n = 25$, D: decrease $n = 31$, S: stability $n = 5$.

- For subgroup A (improvement): V = 496, *p*-value = 1.22e-06. A significant difference between the CORg means at A1 and A2 for subjects classified as A is demonstrated (signed Wilcoxon test). This suggests a significant improvement in CORg after rehabilitation.
- For subgroup D (deterioration): V = 0, *p*-value = 8.752e-06 also shows a significant difference between the CORg means at A1 and A2 for subjects classified as D (signed Wilcoxon test). This suggests a significant deterioration in CORg after rehabilitation.

3.3.4 Comparative analysis of VOR (VORg) and VOR2 (VOR2g) gain trends

Among the patients with a statistically significant variation in VOR2 gain ($n = 43$), two evolution groups were observed: group A: group observing an increase in VOR2 gain, and group D: group observing a decrease in VOR2 gain.

In each group, 3 behaviors were identified:

- Group A $n = 24$: condition 1 (VORg < VOR2g) $n = 14$, condition 2 $n = 2$: VORg and VOR2g observe a slight difference IC [−5, 5], condition 3 $n = 8$: VORg > VOR2g
- Group D $n = 19$: condition 1 (VORg < VOR2g) $n = 12$, condition 2 $n = 5$: VORg and VOR2g observe a slight difference IC [−5, 5], condition 3 $n = 2$: VORg > VOR2g

3.3.5 Analysis of reflectivity from the bithermal VNG test

To study the significance of the evolution of this indicator according to its clinical interpretation, three subgroups were created: subgroup A where reflectivity improved after rehabilitation, subgroup D for which reflectivity deteriorated after rehabilitation, subgroup I where reflectivity reversed its laterality after rehabilitation.

For subgroup A and D, we compared pairs of values measured at A1 and A2 to see if the position of the medians is different from 0. This test, being conducted by pairs of values on the same variable measured at two moments, it is impossible to compare the evolution of group I, as the change in the laterality of reflectivity does not allow the statistical test to be applied.

- For subgroup A: the evaluation of right-side reflectivity gives a V = 0, *p*-value = 0.016, the evaluation of left-side reflectivity gives a V = 0, *p*-value < 0.001.
- For subgroup D: the evaluation of right-side reflectivity gives a V = 36, *p*-value = 0.008, the evaluation of left-side reflectivity gives a V = 36, *p*-value = 0.008.

These results suggest that, for each pair of variables and for each subgroup, there is a significant difference between the two variables. The alternative hypotheses indicate that the true difference in position is not equal to zero, meaning that the medians of the two groups are different.

3.3.6 Analysis of composite indicators

11.29% present a hyperactive signal (Hs) at the beginning of rehabilitation (A1), that is 7 patients, 0% at the end of care (A2).

The state of compensation (SoC) in our cohort is distributed as follows: at A1, 46.6% have normal reflectivity with a deficit ≤ 30%, 36.6% have reflectivity ≤ 15¨/s with a deficit ≥ 30%, 1.7% present bilateral areflexia (reflectivity ≤ 2¨/s with a deficit ≥ 70%), and 15% unilateral hypovalence without deficit (reflectivity ≤ 15¨/s with a deficit ≤ 30%). At A2, the proportions are 46.6% with normal reflectivity, 18.3% with reflectivity ≤ 15¨/s and deficit ≥ 30%, 6.7% with bilateral areflexia, and 6.7% with unilateral hypovalence without deficit. Between A1 and A2, 18 patients changed their SoC during rehabilitation, against 42 who did not change.

3.3.7 Evolution of geometric angles and bisectors

Three subgroups were created according to the conditions of improvement (A) or deterioration (D) of the SVV between A1 and A2. The study of the normality of variables from the analysis of the SVV with the Shapiro-Wilk test is available in the Supplementary Table S10. For each group, the following distribution is observed:

- Group A: SGA $n = 36$, SBA $n = 42$, DGA $n = 32$, DBA $n = 41$
- Group D: SGA $n = 26$, SBA $n = 20$, DGA $n = 30$, DBA $n = 31$

The statistical study of variations for each group gives the results described in Table 4.

A descriptive statistical analysis of the variation of SVV indicators (SGA, DGA, SBA, DBA) by the coefficient of variation (CV) and the Gini coefficient (Cg) was performed based on the grouping factors identified a posteriori (presence or absence of a hyperactive signal (Hs), compensation profiles either stable or evolved during iVRT (SoC) and improvement/decrease of the gain obtained at the cervical-ocular reflex(CORg). The results are presented in Tables 5, 6. The evolution of SVV measurements between A1 and A2 is available in the Supplementary Table S11.

3.3.8 Analysis of results obtained by optometry indicators

3.3.8.1 Results from the analysis of visual acuity

The evolution of Near Visual Acuity (NVA; Table 7) shows a statistically significant improvement ($p < 0.001$).

3.3.8.2 Results from prismatic analysis (PBc/PBd)

The evolution of convergence and divergence capabilities at the prism bar (PBc/PBd; Table 8) is not statistically significant.

TABLE 4 Statistical results of SVV measurement variations by group.

Population	Variable	Wilcoxon statistic	*p*-value
SGA A	Static Geometric Angle A1 vs. A2	666	<0.001***
SBA A	Static Bisector Angle A1 vs. A2	407	0.58
DGA A	Dynamic Geometric Angle A1 vs. A2	528	<0.001***
DBA A	Dynamic Bisector Angle A1 vs. A2	346	0.28
SGA D	Static Geometric Angle A1 vs. A2	−6.87	<0.001***
SBA D	Static Bisector Angle A1 vs. A2	−1.02	0.32
DGA D	Dynamic Geometric Angle A1 vs. A2	−6.10	<0.001***
DBA D	Dynamic Bisector Angle A1 vs. A2	0.66	0.52

SGA, static geometric angle; SBA, static bisector angle; DGA, dynamic geometric angle; DBA, dynamic bisector angle; A, Improvement group,;D, deterioration group.
*trend towards significance.
**moderate significance.
***strong significance.

3.3.8.3 Results from the analysis obtained at the mawas board (PmW)

The analysis of the variation in measurements obtained during the PmW examination is presented in Figure 7. A McNemar's Chi-squared test was applied to determine if the discordant pairs evolved through rehabilitative intervention:

- PmW20 A1A2 McNemar's chi-squared = 6.86, dF = 1, *p*-value = 0.01***

All results is available in the Supplementary Material section, Table S12.

3.3.8.4 Results from the analysis of measurements of near points of accommodation (NPA) and near point of convergence (NPC)

To analyze the evolution of NPA right, NPA left, and NPC values between A1 and A2, the variation in means between these two periods was examined.

- For the improvement subgroup (A) of NPA right, NPA left, and NPC values between A1 and A2, the signed Wilcoxon test shows that the differences are significant with very low *p*-values, indicating significant improvements.
- For the deterioration subgroup (D), the signed Wilcoxon test also shows significant differences with very low *p*-values, indicating significant deteriorations.

3.3.8.5 Results from the analysis of the Thomas Far stereoscopic vision test (TVST)

The analysis of the variation in measurements obtained during the far stereoscopy (TVST) exam evaluated by four figures (circle, star, cat, car) is presented in Figure 9. A McNemar's Chi-squared test was applied to determine if the discordant pairs evolved through rehabilitative intervention:

TABLE 5 Homogeneity of SVV variation by post-Hoc group formation at A1.

Variable	Group	Sample size	Static SVV geometric angle CV (Cg)	Static SVV bisector angle CV (Cg)	Dynamic SVV geometric angle CV (Cg)	Dynamic SVV bisector angle CV (Cg)
Hyperactive signal	Absent	55	0.5 (0.27)†	0.8 (0.41)	0.5 (0.26)†	1.1 (0.5)
	Present	7	0.9 (0.39)	0.8 (0.39)	0.7 (0.38)	0.4 (0.22)†
State of compensation	Constant	42	0.6 (0.29)	0.8 (0.44)	0.5 (0.29)	1.1 (0.49)
	Variable	18	0.5 (0.28)†	0.8 (0.39)	0.4 (0.21)†	1.0 (0.5)
COR gain	Increase	25	0.5 (0.26)	0.8 (0.41)	0.4 (0.24)	1.3 (0.57)
	Stable	5	0.4 (0.17)†	0.7 (0.31)	0.4 (0.19)†	1.8 (0.67)
	Decrease	31	0.7 (0.32)	0.8 (0.44)	0.6 (0.3)	0.8 (0.43)

The groups with the most homogeneity in measurement are indicated by † CV represents the coefficient of variation, and Cg stands for the Gini coefficient, both assessing the dispersion and equality of SVV variations among the groups.

TABLE 6 Homogeneity of SVV variations by post-Hoc group formation at A2.

Variable	Group	Sample size	Static SVV geometric angle CV (Cg)	Static SVV bisector angle CV (Cg)	Dynamic SVV geometric angle CV (Cg)	Dynamic SVV bisector angle CV (Cg)
Hyperactive signal	Absent	55	0.5 (0.27)†	10,9 (0,42)	0.5 (0.26)†	4,9 (0,50)
	Present	7	0.4 (0.39)		4.3 (0.44)	
State of compensation	Constant	42	0.5 (0.29)†	4,3 (0,44)	0.5 (0.29)	24,9 (0,41)
	Variable	18	0.6 (0.28)		0.5 (0.21)†	
COR gain	Increase	25	0.4 (0.28)†		0.5 (0.26)†	
	Stable	5	0.6 (0.17)		0.6 (0.186)	
	Decrease	31	0.6 (0.32)	7 (0,44)	0.6 (0.3)	31,8 (0,43)

Groups with the most homogeneous measures are indicated by †. CV denotes the coefficient of variation, and Cg is the Gini coefficient, both used to measure the dispersion and equality of SVV variations among the groups. The columns for static and dynamic SVV bisector angles are omitted due to negative values (improvement towards 0 indicates less deviation) and the challenges in interpreting CV and Cg for these measures.

TABLE 7 Visual acuity variation study from baseline (A1) to follow-Up (A2).

Data	Mean at A1	Mean at A2	Increase proportion	Decrease proportion	No change proportion	Average rate of change	*P*-value
Distance visual acuity (DVA)	8.66	7.39	4.9%	11.3%	83.8%	−4.0%	0.334
Near visual acuity (NVA)	2.83	2.4	3.3%	44.3%	52.5%	−13.0%	<0.01***

*Trend towards statistical significance (*P*-value > 0.05).
**Moderate statistical significance (0.01 < *P*-value ≤ 0.05).
***Strong statistical significance (*P*-value ≤ 0.01).
Reading Key: This table presents the changes in both distance and near visual acuity from the initial assessment (A1) to the follow-up assessment (A2), highlighting the proportions of individuals experiencing increases, decreases, or no change in visual acuity, alongside the average rate of change and their statistical significance.

TABLE 8 Study of variations in convergence and divergence (PBc/PBd) from baseline (A1) to follow-Up (A2).

Data	Number at A1	Number at A2	Mean at A1	Mean at A2	Increase proportion	Decrease proportion	Average rate of change	*P*-value
Nasal right eye (OD)	61	60	11.51	11.8	47%	32%	11%	0.561
Nasal left eye (OG)	60	60	10.98	11.43	47%	38%	14%	0.678
Temporal right eye (OD)	43	52	22.95	23.17	35%	48%	13%	0.851
Temporal left eye (OG)	44	52	23.16	23.46	33%	56%	20%	0.771

PBc, prism bar convergence; PBd, prism bar divergence.
Reading Key: Variations were not calculated for patients who had neutralization at baseline (A1) or follow-up (A2). The average rate of change is not the change in mean values from A2 compared to A1 but is the average rate of change for each patient. This table outlines the variations in convergence and divergence capabilities, as measured by the prism bar, from the initial assessment to the follow-up assessment. It includes details on the average measures at each time point, the proportion of individuals who saw increases or decreases in capabilities, and the overall average rate of change across the study population.

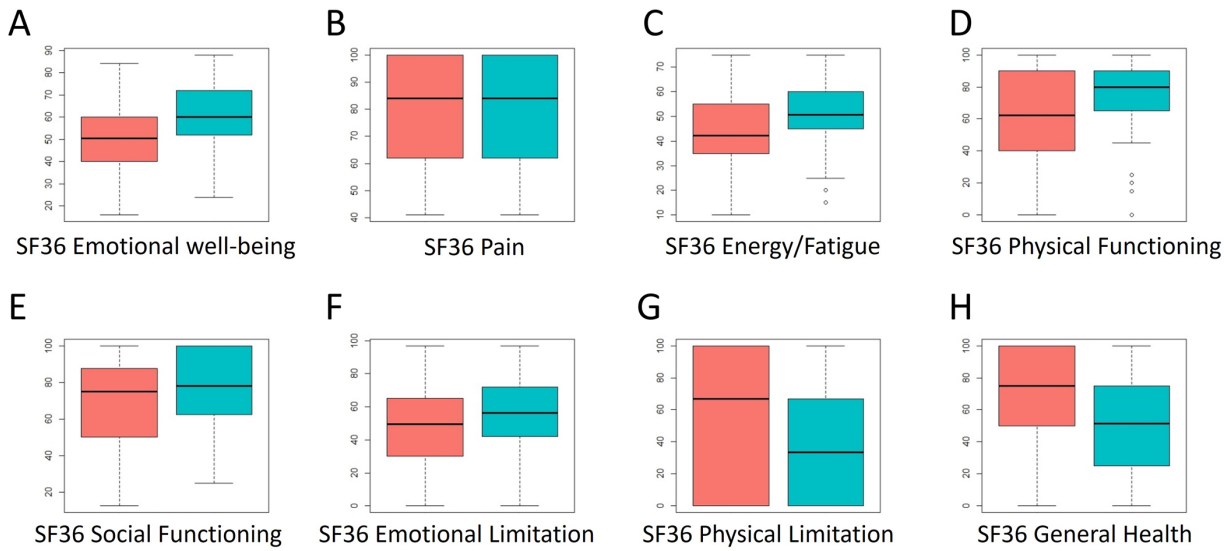

FIGURE 6
Distribution of scores across the eight dimensions of the SF36 questionnaire. Red: scores at A1; Blue: scores at A2. Higher scores indicate a better state of the evaluated component.

- Star 1 m A1A2: McNemar's chi-squared = 5.26, dF = 1, *p*-value = 0.02**
- Car 1 m A1A2: McNemar's chi-squared = 5.33, dF = 1, *p*-value = 0.02**
- Circle 5 m A1A2: McNemar's chi-squared = 5.06, dF = 1, *p*-value = 0.02**
- Star 5 m A1A2: McNemar's chi-squared = 4.08, dF = 1, *p*-value = 0.04**

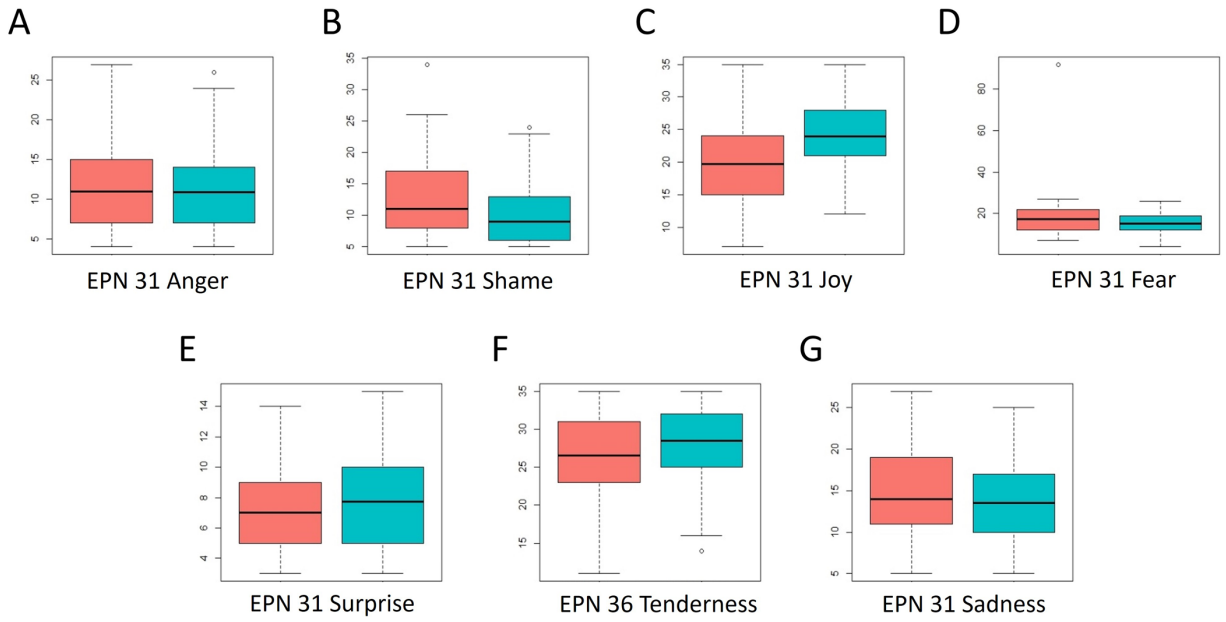

FIGURE 7
Distribution of scores across the five dimensions of the EPN-31 questionnaire. Red: scores at A1; Blue: scores at A2. Higher scores indicate that the evaluated emotional component is experienced more frequently, and vice versa.

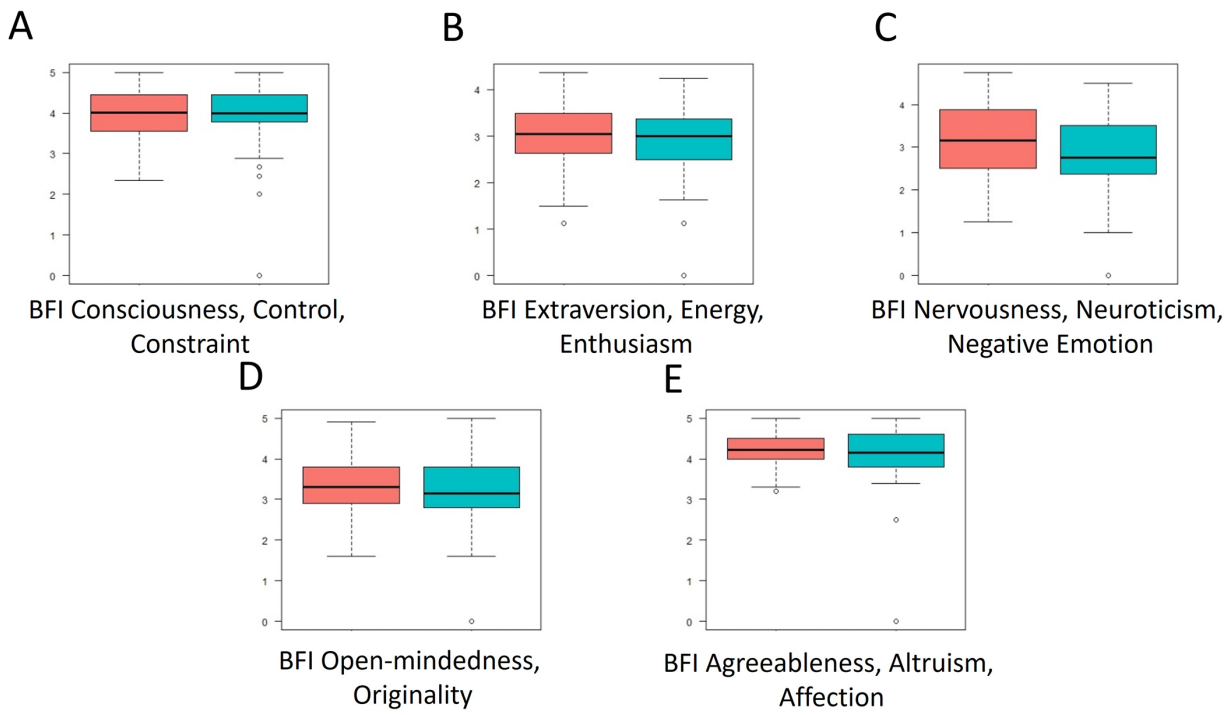

FIGURE 8
Distribution of scores across the five dimensions of the BFI questionnaire. Red: scores at A1; Blue: scores at A2. The higher the score, the more pronounced the corresponding personality trait (Extraversion, Agreeableness, Conscientiousness, Neuroticism, Openness to Experience), and vice versa.

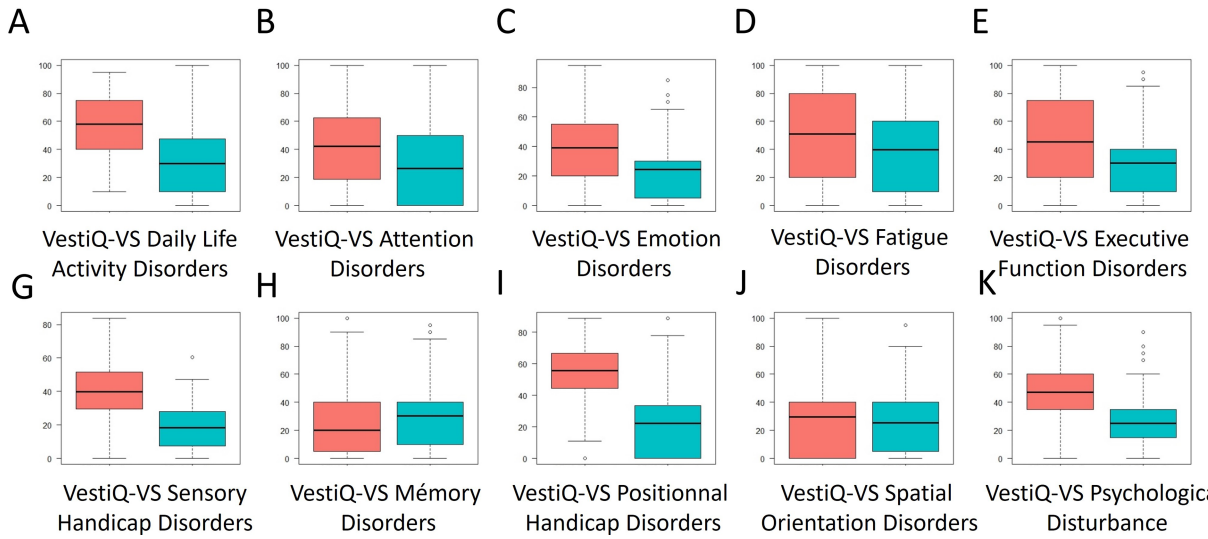

FIGURE 9
Distribution of scores across the ten dimensions of the vestiQ-VS questionnaire. Red: scores at A1; Blue: scores at A2. The higher the score, the more deteriorated the state of the evaluated component.

All results is available in the Supplementary Material section, Table S13.

3.3.8.6 Results from the analysis of the Worth test

The analysis of the variation in measurements obtained during the Worth four dot test (Table 9) shows a statistically significant change between A1 and A2 ($p < 0.01$), indicating how the perception of color and binocular vision may have changed following rehabilitation. For 26.7% of patients, we observe a restoration of retinal correspondence, and for 8.3%, an alteration of retinal correspondence ($p = 0.029$).

TABLE 9 Study of variations in convergence and divergence (PBc/PBd) measures from baseline (A1) to follow-Up (A2).

Data	Red point	Green point	Green point	White point
Number of changes from A1 to A2	0	1	0	46
Frequency of changes from A1 to A2	0.0%	1.7%	0.0%	76.7%
Frequency of accurate tests at A1	0.0%	0.0%	0.0%	13.1%
Frequency of accurate tests at A2	0.0%	0.0%	0.0%	31.1%
P-value 1	>0.99	>0.99	>0.99	<0.01***
Maintained norms from A1 to A2	0.0%	0.0%	0.0%	5.0%
Norms at A1, not at norms at A2	0.0%	0.0%	0.0%	8.3%
Not at norms at A1, at norms at A2	0.0%	0.0%	0.0%	26.7%
Not at norms at A1 and A2	100.0%	100.0%	100.0%	60.0%
P-value 2	>0.99	>0.99	>0.99	0.029**

P-value 1 evaluates whether patients changed their response (regardless of the response's correctness). *P*-value 2 compares changes in response status between the two periods, grouping incorrect responses (all but white, yellow, and orange) to assess changes from good to non-good.
PBc, prism bar convergence; PBd, prism bar divergence.
*Trend towards statistical significance (*P*-value > 0.05).
**Moderate statistical significance (0.01 < *P*-value ≤ 0.05).
***Strong statistical significance (*P*-value ≤ 0.01).
Reading Key: This table presents the variations in responses to convergence and divergence tests, highlighting the significant changes observed between the baseline and follow-up evaluations. It details the proportion of patients experiencing changes and assesses the accuracy of tests over time, providing a clear view of the shifts in visual function related to these specific tasks.

3.4 Search for predictive markers

3.4.1 Presentation of results

This section presents significant results. Twelve conditions were treated representing the six trials of the Sensory Organization Test (SOT) with each trial, the conditions of anteroposterior (AP) and mediolateral (ML) imbalance. Four models to explain posturography were retained; we did not use a method to adjust the significance threshold since our models did not include the same regressors. In addition to the significance of a factor's effect on the endogenous variable, the models allowed us to determine the explanatory power of each explanatory variable through the regression coefficients (β). Finally, one last model was retained concerning the evolution of the SVV bisector angle, but in a categorical form. The explained variable took the "improvement" modality if the angle in the second measurement approached 0 degrees, the "deterioration" modality otherwise. The objective was to evaluate the impact on the direction of the SVV bisector angle variation of the five explanatory variables: the ML-assisted posturo-static, the ML-assisted posturo-dynamic, the COR gain, the VOR preponderance, and whether the Romberg quotient (QR) was within norms or not.

To measure these potential cause-and-effect relationships, a multivariate and multinomial logistic regression was performed.

The model's adjustment was determined by calculating McFadden's pseudo-R^2, the significance of the co-factors' impact by ANOVA, and the results expressed as odds ratios.

3.4.2 Evolution of medio-lateral balance

The regression of the variation of the total energy (E) measurement in static (St) condition with eyes open (EO) for ML balance is significant ($P < 0.01$) and accounts for 31% of the variance. The model shows a causality of the dimension dBIG5A and the SoC component T at the 5% threshold. All results are presented in Table 10.

The regression of the variation of the total energy (E) measurement in static (St) condition with visually controlled condition (VC) for ML balance is significant ($P < 0.01$) and accounts for 43% of the variance. The model shows a causality of dEPN31TS and the SoC component I at the 5% threshold. All results are presented in Table 11.

The regression of the variation of the total energy (E) measurement in dynamic (D) condition with eyes closed (EC) for ML balance is significant ($P < 0.01$) and accounts for 32% of the variance. The model shows a causality of dimensions dSM, dEPN31J, and dBIG5E at the 5% threshold. All results are presented in Table 12.

TABLE 10 OLS regression analysis ΔEStEOML.

Variables	Beta Coefficient	Confidence Intervals	*P*-value
Constant	−264	[−546; 18]	0.073*
dSE (emotion dimension VestiQ-VS)	−4	[−9.2; 1.1]	0.123
dSF36SG (general health dimension SF36)	1	[−0.20; 2.3]	0.1*
dEPN31P (fear dimension EPN31)	−0.85	[−2.9; 1.2]	0.417
dBIG5A (Agreeableness, Altruism, Affection)	7.6	[1.5; 14]	0.014**
SoC			0.132
N			
I	70	[−24; 165]	0.151
P	23	[−30; 75]	0.402
T	98	[−4.2; 191]	0.047**
Model global statistics	R^2: 0.311	Fisher statistics: 3.377	Fisher test (*p*-value): 0.012**

*Trend towards statistical significance (*P*-value > 0.05).
**Moderate statistical significance (0.01 < *P*-value ≤ 0.05).
***Strong statistical significance (*P*-value ≤ 0.01).
Reading key: $\Delta EStEOML = \beta(0)+\beta1 \times dSE+\beta2 \times dSF36SG+\beta3 \times dEPN31P+\beta4 \times dBIG5A+\beta5 \times EdCI+\beta6 \times EdCN+\beta7 \times EdCP+\beta8 \times EdCT$. dSE = Emotional dimension of the VestiQ-VS questionnaire, dSF36SG = General health dimension of the SF36 questionnaire, dEPN31*P* = Fear dimension of the EPN31 questionnaire, dBIG5A = Agreeableness, Altruism, Affection dimension. State of Compensation (SoC) classifications: (N) Non-Inhibited Profile with ≥15°/s contralateral reflectivity and ≤30% ipsilateral deficit, showing no subcortical arc modulation; (P) Partial Contralateral Inhibition Profile, with [2°/s; 15°/s] contralateral reflectivity and [30%; 70%] ipsilateral deficit, indicating partial compensation; (T) Total Contralateral Inhibition Profile, with ≤2°/s reflectivity and ≥70% ipsilateral deficit, reflecting substantial contralateral input inhibition and maximal subcortical compensation; (I) Inhibition without Deficit Profile, with ≤15°/s reflectivity and ≤30% ipsilateral deficit, suggesting reduced contralateral reactivity despite a minor deficit.

TABLE 11 OLS ΔEStVCML.

Variables	Coefficient Beta	Confidence Intervals	*P*-value
Constant	222	[−1.8; 445]	0.058*
dSM	−1.4	[−4.0; 1.2]	0.3
dSE	−4.5	[−11; 2.3]	0.193
dEPN31TS	−8.4	[−17; 0.07]	0.052*
dSF36BE	18	[7.0; 30]	<0.01***
EdC			<0.01***
N			
I	171	[67; 276]	<0.01***
P	−17	[−107; 72]	0.708
T	31	[−81; 142]	0.59
Model global statistics	R^2: 0.427	Fisher statistics: 4.800	Fisher test (*p*-value): < 0.010***

*Trend towards statistical significance (*P*-value > 0.05).
**Moderate statistical significance (0.01 < *P*-value ≤ 0.05).
***Strong statistical significance (*P*-value ≤ 0.01).
Reading key: $\Delta EStVCML = \beta(0)+\beta1 \times dSM+\beta2 \times dSE+\beta3 \times dEPN31TS+\beta4 \times dSF36BE+\beta5 \times EdCI+\beta6 \times EdCN+\beta7 \times EdCP+\beta8 \times EdCT$. dSM = Memory dimension of the VestiQ-VS questionnaire, dSE = Emotional dimension of the VestiQ-VS questionnaire, dEPN31TS = Surprise dimension of the EPN 31 questionnaire, dSF36BE = Emotional well-being dimension of the SF36 questionnaire, State of Compensation (SoC) classifications: (N) Non-Inhibited Profile with ≥15°/s contralateral reflectivity and ≤30% ipsilateral deficit, showing no subcortical arc modulation; (P) Partial Contralateral Inhibition Profile, with [2°/s; 15°/s] contralateral reflectivity and [30%; 70%] ipsilateral deficit, indicating partial compensation; (T) Total Contralateral Inhibition Profile, with ≤2°/s reflectivity and ≥70% ipsilateral deficit, reflecting substantial contralateral input inhibition and maximal subcortical compensation; (I) Inhibition without Deficit Profile, with ≤15°/s reflectivity and ≤30% ipsilateral deficit, suggesting reduced contralateral reactivity despite a minor deficit.

The regression of the variation of the total energy (E) measurement in dynamic (D) condition with visually controlled condition (VC) for ML balance is significant ($P < 0.01$) and accounts for 27% of the variance. The model shows a causality of dimensions dSC, dSE, and dBIG5A at the 5% threshold. All results are presented in Table 13.

3.4.3 Evolution of the angulation of the bisector relative to verticality in the SVV examination

The regression of the bisector angle (Ab) of the dynamic subjective visual vertical (SVVd) is significant ($P < 0.01$) and accounts for 38% of the variance. The model shows causality of the instrumental indicators VORprep and CORg at the 5% threshold. All results are displayed in Table 14.

4 Discussion

4.1 Cohort presentation

The findings of this study highlight several important points regarding the population recruted, clinical follow-up their clinical significance. Patients were included over two consecutive years, with a slight predominance in 2021 (59.7%) compared to 2022 (40.3%). The average follow-up duration was 13 months, with an average of 87 rehabilitation sessions. The patients' professional distribution showed diversity, with a majority being retirees (46.8%; Table 3).

TABLE 12 OLS ΔEDECML.

Variables	Coefficient beta	Confidence intervals	*P*-value
Constant	−108	[−358; 142]	0.401
dSM	−7.2	[−0.11; 14]	0.047**
dEPN31J	−9.3	[−17; −2.2]	0.011**
dSF36FP	−1.3	[−2.7; 0.23]	0.098*
dBIG5E	13	[5.2; 22]	<0.01***
Model global statistics	R^2: 0.324	Fisher statistics: 5.270	Fisher test (*p*-value): < 0.010***

*Trend towards statistical significance (*P*-value > 0.05).
**Moderate statistical significance (0.01 < *P*-value ≤ 0.05).
***Strong statistical significance (*P*-value ≤ 0.01).
Reading key: ΔEDECML = $\beta(0)+\beta1 \times$ dSM$+\beta2 \times$ dBIG5E$+\beta3 \times$ dEPN31J$+\beta4 \times$ dSF36FP. dSM = Memory dimension of the VestiQ-VS questionnaire, dBIG5E = Extraversion, Energy, Enthusiasm dimension of the BFI questionnaire, dEPN31J = Joy dimension of the EPN31 questionnaire, dSF36FP = Physical Functioning dimension of the SF36 questionnaire. State of Compensation (SoC) classifications: (N) Non-Inhibited Profile with ≥15°/s contralateral reflectivity and ≤30% ipsilateral deficit, showing no subcortical arc modulation; (P) Partial Contralateral Inhibition Profile, with [2°/s; 15°/s] contralateral reflectivity and [30%; 70%] ipsilateral deficit, indicating partial compensation; (T) Total Contralateral Inhibition Profile, with ≤2°/s reflectivity and ≥70% ipsilateral deficit, reflecting substantial contralateral input inhibition and maximal subcortical compensation; (I) Inhibition without Deficit Profile, with ≤15°/s reflectivity and ≤30% ipsilateral deficit, suggesting reduced contralateral reactivity despite a minor deficit.

TABLE 13 OLS ΔEDVCML.

Variables	Coefficient beta	Confidence intervals	*P*-value
Constant	−108	[−364; 41]	0.401
dSF36FP	0.18	[0.46; 0.81]	0.587
dEPN31	−2.3	[−5.5; 0.89]	0.159
dSC	−4	[−7.9; 0.1]	0.044**
dBIG5A	4.9	[−2.9; 9.6]	0.037**
dSE	−5.4	[−9.9; 0.9]	0.019**
Model global statistics	R^2: 0.272	Fisher statistics: 4.114	Fisher test (*p*-value): < 0.010***

*Trend towards statistical significance (*P*-value > 0.05).
**Moderate statistical significance (0.01 < *P*-value ≤ 0.05).
***Strong statistical significance (*P*-value ≤ 0.01).
Reading key: ΔEDVCML=$\beta(0)+\beta1 \times$ dSC$+\beta2 \times$ dSE$+\beta3 \times$ dEPN31J$+\beta4 \times$ dBIG5A $+\beta5 \times$ dSF36RF. dSC = Cognition dimension of the VestiQ-VS questionnaire, dSE = Emotional dimension of the VestiQ-VS questionnaire, dEPN31J = Joy dimension of the EPN31 questionnaire, dBIG5A = Agreeableness, Altruism, Affection dimension of the BFI questionnaire, dSF36FP = Physical Functioning dimension of the SF36 questionnaire.State of Compensation (SoC) classifications: (N) Non-Inhibited Profile with ≥15°/s contralateral reflectivity and ≤30% ipsilateral deficit, showing no subcortical arc modulation; (P) Partial Contralateral Inhibition Profile, with [2°/s; 15°/s] contralateral reflectivity and [30%; 70%] ipsilateral deficit, indicating partial compensation; (T) Total Contralateral Inhibition Profile, with ≤2°/s reflectivity and ≥70% ipsilateral deficit, reflecting substantial contralateral input inhibition and maximal subcortical compensation; (I) Inhibition without Deficit Profile, with ≤15°/s reflectivity and ≤30% ipsilateral deficit, suggesting reduced contralateral reactivity despite a minor deficit.

TABLE 14 OLS regression analysis for dynamic SVV bisector angle change (ΔAbSVVd).

Variables	Coefficient beta	Confidence intervals	*P*-value
Constant	−2	[−4.6; 0.59]	0.137
VVORprep	−1.7	[−4.3; 0.87]	0.195
VORprep	1.9	[0.95; 2.9]	<0.01***
IFOg	−8.1	[−24; 7.5]	0.309
CORg	11	[4.6; 17]	<0.01***
Presence of abnormal absolute preponderance (PA)	No		0.275
	Yes	−0.99	[−2.8; 0.79]
Model global statistics	R^2: 0.375	Fisher statistics: 6.363	Fisher test (*p*-value): < 0.01***

*Trend towards statistical significance (*P*-value > 0.05).
**Moderate statistical significance (0.01 < *P*-value ≤ 0.05).
***Strong statistical significance (*P*-value ≤ 0.01).
Reading Key: ΔAbVVSd=$\beta(0)+\beta1 \times$ VVORprep$+\beta2 \times$ VORprep$+\beta3 \times$ IFOg$+\beta4 \times$ CORg$+\beta5 \times$ PAA$+\beta6 \times$ PAN. VVORprep = Preponderance observed during the sensitized burst test for the visuo-vestibulo-ocular reflex study.
VORprep = Preponderance observed during the sensitized burst test for the vestibulo-ocular reflex study.
IFOg = Gain obtained during the sensitized burst test for the study of the ocular fixation index.
CORg = Gain obtained during the sensitized burst test for the study of the cervico-ocular reflex index.
PAA = Abnormal absolute preponderance (≥2°/s) in the bithermal test.
PAN = Normal absolute preponderance (≤2°/s) in the bithermal test.

Analysis of initial and final diagnoses of patients revealed significant changes during the rehabilitative care. For instance, 8.1% of the cohort was diagnosed with central disorders after the beginning of rehabilitation, while the initial diagnosis of recurrent BPPV decreased from 33.9% to 9.7% by the end of rehabilitation. Moreover, 24.2% of unspecific vestibular vertigos were diagnosis by the end of care. These results underline the importance of clinical reevaluation to improve diagnosis according to clinical changes during rehabilitation program.

Regarding visual symptoms, the study found significant changes between the first vertigo crisis and the first integrative vestibular rehabilitation therapy (iVRT) consultation. For example, visual fatigue increased from 4.8% to 38.7% of the cohort, and movement-induced blurred vision increased from 11.3% to 59.7% of the cohort during the first iVRT consultation (Table 4). These results suggest an evolution of visual symptoms in patients with chronic vertigo (CVP), underlying compensation mechanisms. which could have significant implications for iVRT management in terms of intervention.

Finally, regarding associated syndromes such as chronic neck pain (CN) and temporomandibular disorders (TMD), 8% of the cohort suffered from CN before the first crisis compared to 13% at inclusion, and 6.5% from TMD compared to 14.5% at inclusion.

4.2 The action of iTRV: questionnaire analysis

In our study, significant improvements were observed post iVRT in various questionnaires assessing the impact of vertigo on quality of life. The DHI (Supplementary Table S9) revealed a significant decrease in emotional scores from 45.31 to 28.57 and functional scores from 50.00 to 29.17 ($p < 0.05$), indicating an improvement in the perception of handicap related to vertigo. The SF36 (Supplementary Table S9) showed improvements of

physical level (from 62.41 to 76.34) and physical health limitations (from 68.10 to 52.68), suggesting an enhancement in physical quality of life ($p < 0.05$). Particularly notable was the improvement of mental health, with an increase from 50.55 to 58.07 of the emotional well-being dimension after iVRT ($p < 0.05$). The EPN-31 results (Supplementary Table S9) indicate an improvement in joy (from 19.69 to 23.80) and a reduction in shame (from 39.87 to 18.88), demonstrating a positive impact on emotions ($p < 0.05$). Similarly, the Big Five Inventory (BFI; Supplementary Table S9) revealed an increase in extraversion after iVRT (from 3.16 to 2.76, $p < 0.05$). The VestiQ-VS (Supplementary Table S9) showed a significant improvement of psychological state (from 47.31 to 27.64) and emotional state (from 39.87 to 24.55), confirming the efficacy of iVRT on the psychological and emotional state ($p < 0.05$).

However, certain dimensions like pain in the SF36 and memory in the VestiQ-VS did not show significant change, suggesting that iVRT does not directly affect these aspects (Supplementary Table S9). Despite overall improvements, specific emotional and physical limitations persist (shown by the SF36 dimensions), possibly influenced by external factors not evaluated in this study.

4.3 Study of instrumental tracking indicators

This section discusses the relevance of tracking indicators in chronic vestibular patients (CVP) beyond the notions of normality often attributed to instrumental examinations, which are necessary in clinical conditions dealing with acute cases as well as pre- and post-surgical monitoring. However, it seems, based on our results, that CVP impacts vestibular function differently in the presence of a permanent and/or recurrent error signal. The focus of our approach is on the notion of vestibular error signal (VES), which is of paramount importance in addressing the patient in rehabilitation. We know that a supraliminal VES not only induces consequences on the behavioral performance of the VOR but also adaptive consequences through the central compensation capacities at subcortical and cortical levels (3, 45–47) and strategy of the sensori-perceptual-motor (SPM) system (23, 48). What we are beginning to understand is that a weak or subliminal VES also induces behavioral responses (9) and causes errors in spatial orientation during mental imagery tasks (46). The integration of the VES and its study appear to define subcategories of adaptation and SPM response, some of which have been recorded during our work. These are developed in the following subsections.

4.3.1 Posturography indicator analysis

Our study demonstrates significant improvements ($p < 0.05$) in vestibular function and mediolateral (ML) composite scores after iVRT, underscoring the effectiveness of iVRT on these aspects, even in older subjects. These results support the established links between vestibular function and ML balance found in the literature (49, 50). Although variations in other posturography scores were noted, they were not statistically significant, highlighting the sensitivity and potential for false positives in the algorithmic methods used for analysis. This raises questions about the specificity and interpretation of posturography measurements in CVP and suggests integrating functional tests of the vestibulo-ocular reflex for a more sensitive analysis, as recommended by Di Fabio (27). This is what we have proposed to the reader in the following sections.

4.3.2 Analysis of indicators from kinetic VNG tests

4.3.2.1 Analysis of VOR2 gain (VOR2g) and COR gain (CORg)

Regarding the indicators from kinetic VNG, the analysis showed mixed results. Not all variables studied demonstrated significant differences between A1 and A2 in terms of normalization changes, indicating that rehabilitation does not seem to have a direct impact on reflectivity (preponderance). However, the analysis of value variations according to improvement or deterioration towards normalization was significant as shown in the kinetic evaluation of the vestibulo-ocular reflex gain sensitized in a dual mental task (VOR2g) and the kinetic evaluation of the cervico-ocular reflex gain (CORg). This might support the evolution of compensation in these patients, not related to a restoration of the peripheral function of the vestibular system but indeed related to a more complex modulation of the sensori-perceptual-motor (SPM) system.

4.3.2.2 Comparative analysis of VOR (VORg) and VOR2 (VOR2g) gain trends

The interpretation of VOR2 gain depends on the value of VOR gain. Generally, an improvement in VOR2 gain could express central disinhibition in CVPs, but when it deteriorates, the interpretation becomes dependent on the clinical context. A VOR2 gain approaching the VOR gain seems to express the absence of inhibition (condition 2; Table 15).

Among the 26 patients identified in condition 1 (Table 15), 14 improved. Regarding condition 3, it is revealing for us, in chronic patients, of a plateau effect already questioned in the literature (51–54). The decrease of a gain in a dual task might indicate the presence of a cognitive task difficulty threshold beyond which the patient becomes less efficient at the vestibular level. This observation aligns with those presented by Xavier et al. (10) in patients with vestibular schwannoma. The evolution of the fatigue component of the VestiV-QS is very explicit: among the 14 patients who present an increase in VOR2 gain, fatigue improves significantly compared to the 12 patients who saw their VOR2 gain decrease. Future research should delve deeper into these observations and further explore the underlying mechanisms of these evolutions. Nonetheless, we suggest monitoring the fatigue indicator before, during, and 48 h after iVRT. However, unlike concussions where specific scales like the Post-Concussion Symptom Scale (PCSS) are commonly used to assess symptoms and fatigue, there are no standardized equivalent tools for vestibular disorders (55). Measuring neurological fatigue can be complex, as it depends on many

TABLE 15 Interpretation of gains in kinetic videonystagmography (VNGc) burst test.

Condition	Increase in VOR2g (n)	Decrease in VOR2g (n)	Gain Ratio between VOR and VOR2	Interpretation
Condition 1	14	12	VORg < VOR2g	Inhibition
Condition 2	2	5	VORg≈VOR2g	No Inhibition
Condition 3	8	2	VORg > VOR2g	Context Dependent

This table provides insights into the kinetic videonystagmography (VNGc) burst test's outcomes, categorizing patients based on the changes in their vestibulo-ocular reflex gain (VOR2g). Condition 1 indicates (in)voluntary inhibition where the gain of the reflex in a dual task (VOR2g) is lower than the standard reflex gain (VORg), suggesting a dampening effect. Condition 2 reflects a scenario with no significant inhibition, where the gains are approximately equal, indicating normal function. Condition 3's interpretation depends on the clinical context, suggesting potential overcompensation or a cognitive threshold effect where VORg surpasses VOR2g, possibly indicating an adaptive or maladaptive response to vestibular stimuli.

factors specific to each patient and their neurological condition. Health professionals may use a combination of tools and methods to assess neurological fatigue, including: (i) questioning symptoms: doctors and therapists can perform subjective clinical assessments to evaluate the patient's neurological fatigue based on their observations and the patient's reports; (ii) using measurement scales: some general fatigue measurement scales such as the Chalder Fatigue Scale (56) can be adapted for patients with chronic vestibular disorders to assess their fatigue; (iii) tracking symptoms and performance: regular monitoring of the patient's symptoms and their performance on specific tasks in iVRT can also help assess neurological fatigue.

4.3.2.3 Analysis of reflectivity from the thermal VNG test

Notable variations in reflectivity were observed in some subgroups, with significant improvements and deteriorations, indicating individual changes in reflectivity independently of the overall association with rehabilitation. Cases of reflectivity lateralization reversal after rehabilitation were noted, requiring specific analysis for their clinical implications. These findings reveal the complexity of the impact of rehabilitation on reflectivity and emphasize the importance of future studies to explore these variations in detail and identify possible beneficial interventions for vestibular patients.

4.3.2.4 Analysis of composite indicators

The analysis of the hyperactive vestibular error signal (SH) showed a resolution of this signal within the cohort studied in A2. Due to the retrospective nature of our study, we were not able to identify the origin of this signal. However, given that the studied population consists of chronic patients (i.e., presenting persistent symptoms a year after the crisis, at a minimum to be included in the study), we can suggest a multifactorial origin resolved through our integrative program.

The analysis of the evolution of vestibular compensation (SoC) through the state of reflectivity of the healthy ear when available is a relevant follow-up indicator already proven in the literature (57, 58). These articles show that VRT has a significant impact on acute vestibular patients and even on certain profiles of instrumental areflexia that can improve after treatment. However, in the context of CPV, SoC seems to evolve differently. Indeed, SoC showed discrete changes between the beginning (A1) and the end of iVRT (A2). The results revealed that 46.6% of the cohort had an absence of compensation in the caloric test (N) between A1 and A2, but, examining the details of the fluctuations, 3 among the 28 patients in this group migrated to a SoC category that may indicate the presence of a subliminal error signal (I) and 1 to a moderate compensation due to a deficient VES (P), while 2 moved from category P to N and 2 from category I to N. Additionally, 6.7% of the cohort showed strong compensation that may result from a strong deficient VES (T profile) in A2, compared to 1.7% in A1. In total, 18 patients (30%) observed fluctuation in the bithermal test, including 3 with progressive deterioration of the instrumental vestibular signal. 24 patients did not fluctuate, remaining in a SoC N category and forming a homogeneous group until A2. This last observation may indicate that over a period of iVRT management, the state of vestibular compensation of patients is not acquired for 70% of the cohort. Moreover, apart from the 3 central diagnoses corresponding to the 3 patients who shifted from an I state to a T state, other fluctuations seem impacted by iVRT. Given the restricted numbers of the subgroups, further studies are necessary to determine if the rehabilitation did not have a deleterious effect, especially for the 4 patients who exited a SoC N category: a single case study will be proposed later.

4.3.2.5 Analysis of subjective visual vertical (SVV)

The notion of precision and accuracy is an essential prerequisite in the study of somatosensory signals. The concept of precision within the framework of SVV is widely addressed in the literature (25, 59). Our innovation was to introduce the notion of precision and accuracy into the spatial modeling of our measurements. In our study, the analysis of subgroups (improvement, deterioration) reveals distinct trends. It is important to note that these results show a significant variation in the value of the geometric angle (obtained by averaging the measurements taken from the right and left tilt starting points) and not in the value of the bisector angle relative to the vertical axis. This could correspond to a modulation of precision (observed through the variation in the geometric angle) rather than a variation in accuracy between A1 and A2 (Table 4). This reinforces the idea that rehabilitation impacts the sensorimotor-perceptual (SPM) reference frame, allowing the central nervous system to integrate other information (such as somesthetic information) by modulating the weight of different sensory signals and thus optimizing precision, modeled by the reduction of the geometric angle in A2. This new SVV analysis opens perspectives for observing the establishment of multisensory integrative compensation achieved after iVRT.

Our study examined the impact of several factors on SVV in subjects undergoing iVRT, analyzing the influence of CORg, SoC profiles, and the presence of an SH (Table 5). For the composite variable SH, the coefficients of variation (CV) and Gini values (Cg)

are lower in the group without SH for the measurement of the static and dynamic SVV geometric angles. This suggests a certain homogeneity in the variations of these angles in this group. The geometric angle improvements observed in the group without SH between A1 and A2 seem to reach a higher proportion of patients compared to the deterioration group, while the group with SH, showing a higher proportion of deterioration, is mainly affected in the dynamic geometric angle measurement. In conclusion, the increase in disparities in geometric angle measurements and the degradation observed for 73% of the SH group in dynamic conditions suggest increased difficulty in SPM performance for these patients, especially when subjected to induced conflict during 20°/s optokinetic stimulation. We observe that the strategy used to resolve the imprecision is to switch to optimal accuracy performance, identified in our study by increased homogeneity of the SVV bisector angle measurement in dynamic conditions in the group where SH is present. Our hypothesis is that the central nervous system, in the context of SPM adjustment in response to a chronic hyperactive vestibular error signal (VES), would be more "rigid" and less inclined to modulate the confidence interval of the extreme SVV measurements. In other words, the strategy of optimizing precision is less effective in this context. The optimization of accuracy recruitment strategies seems more complex to modulate. Our hypothesis is that there is a strong link between accuracy and the internal model. The strategy of accuracy modulation seems useful in the presence of imprecision. However, this strategy has limits because when the internal model is biased, the strategy of enhancing precision is ineffective, as demonstrated in the case of "pushers" (60). We hypothesize that accuracy is moderately biased by the internal model in CPV patients subjected to a chronic hyperactive VES. This is why in CPV, uTRV proposes scenarios with the notion of useful error: the patient is subjected to a progression of exercises in which they experience error progressively until reaching a maximum threshold beyond which the patient will experience a return of symptoms. This is a well-known rehabilitative profile in the management of concussions (61, 62).

Patients whose SoC evolved during iVRT show more homogeneous geometric angle measurements in dynamic SVV conditions, suggesting the use of this strategy during variations in reflectivity and deficit, thus linking the quality of peripheral signal integration to that of SPM integration. For CORg, there is a clear link between the variation in COR gain and the homogeneity of the results obtained for SVV (Table 5). The values of geometric angles in static and dynamic conditions are more homogeneous in patients who did not experience a variation in COR gain during iVRT, strongly suggesting the involvement of vestibulo-collic pathways among the possible SPM compensation strategies (60–62). It appears that the recruitment of cervical proprioceptive inputs impacts the accuracy of SVV measurements in CPV patients.

4.3.2.6 Analysis of optometric indicator results

The analysis of optometric indicators yielded very interesting results. The significant improvement in near visual acuity (NVA) post-iVRT was unexpected as it has not been presented in the literature and, given the age of our cohort, was expected to show a trend towards deterioration. This highlights, for us, the potential effect of our intervention not only on balance and vestibular function but also on more global aspects such as psychic, neurovisual, and locomotor aspects. Indeed, our care has evolved with sequences (Table 1) focused on a integrative approach including osteo-articular aspects for the approach of temporomandibular and cranio-cervical dysfunctions, neurovisual for fusion disorders, and psycho-behavioral for mood disorders. This significant improvement from a statistical standpoint ($P < 0.01$) could reflect the complex interdependence between SPM integration and the notion of chronicity.

The results of prismatic analyses, although not significant, suggest that iVRT does not negatively interfere with binocular vision, a fundamental aspect for near visual acuity.

The results obtained in the Mawas board (PmW) examination show that significant variations in fusion were measured between 15 and 20 cm from nasion. The variation at 25 cm could also be considered ($p = 0.10$) and re-evaluated in another study. Here again, iVRT seems to significantly influence the neurosensory aspect of near vision.

The study of the near point of accommodation (NPA) shows a significant evolution between A1 and A2 ($p < 0.05$) with two groups either improving or diminishing in performance.

The study of distance stereograms shows a significant change in the presentation of the star, cat, and car at one meter, as well as the presentation of the circle and star at five meters. These results suggest that iVRT may impact patients' spatial perception when it integrates the use of stereograms specific to our research work.

Finally, the examination with the Worth lamp confirms these results, for which an improvement in stereoscopic vision is observed for 60% of the cohort ($p = 0.029$).

Visual fusion, dependent on the horopter and Panum's area, is an essential mechanism for three-dimensional perception. In the context of vestibular asthenopia, the associated spatial disorientation can lead to disturbances in visual fusion, exacerbating visual symptoms. Integrating the neurovisual sphere in concepts of rebalancing, facilitation, and sensori-perceptual-motor reprogramming in our treatment sequences is one of the strengths of our approach. These observations corroborate the results obtained by Xavier et al. (9) in a previous study showing that subliminal VES impacts the visuo-oculomotor component. It is highly probable that the management of chronic VES benefits from similar resolution mechanisms, impacting subtle aspects of vision such as fusion and stereoscopy.

4.4 Study of predictive markers

In this section, we discuss the predictive markers we have identified in our study. It seems useful to search for these markers to best impact the effects of physical therapy.

4.4.1 Study of predictive markers of medio-lateral stability

Vestibular signals play a crucial role in maintaining upright posture, especially under unstable postural conditions where

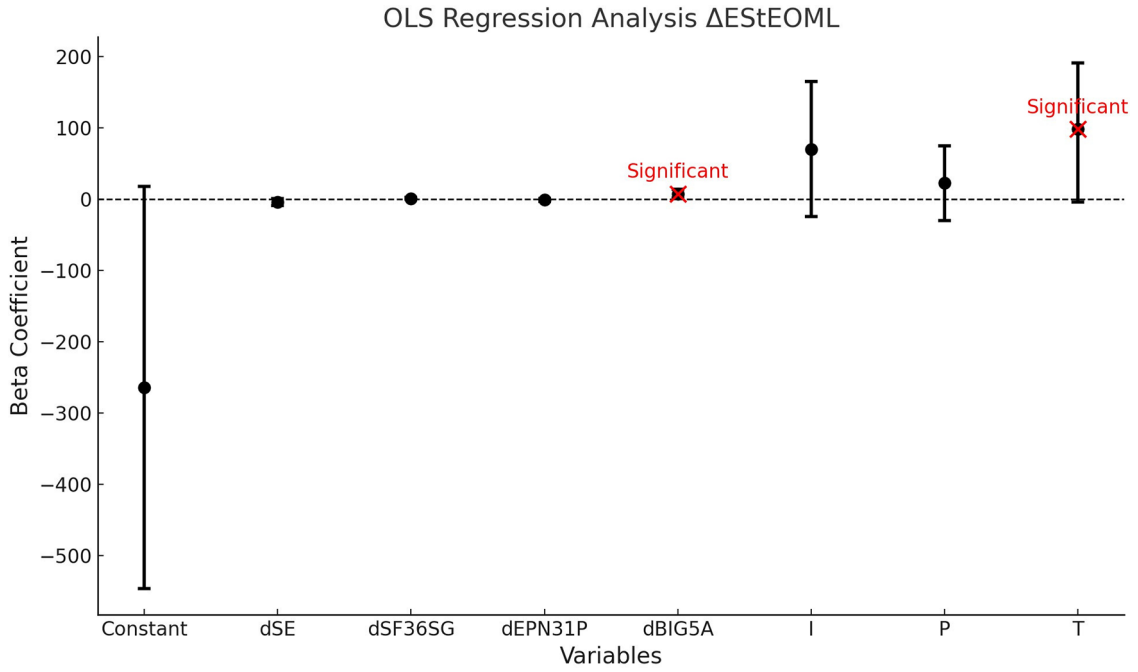

FIGURE 10
Ordinary least squares (OLS) regression analysis EStEOML. This graph shows the beta coefficients of the variables used in the OLS regression analysis for the dynamic change in the EStEOML. The beta coefficients indicate the strength and direction of the association between each variable and the dynamic EStEOML. Figure Components: • Black Dots: Each black dot represents a beta coefficient for a given variable. • Error Bars: The horizontal bars around the dots indicate the 95% confidence intervals for each beta coefficient. They show the range within which the true beta coefficient is likely to lie with a 95% probability. • Red Dots: Red dots indicate variables whose beta coefficients are statistically significant ($p < 0.05$). Significant variables are annotated with the text "Significant". • Horizontal Dashed Line at Zero: The dashed line indicates the zero value of the beta coefficient. A beta coefficient of zero means there is no association between the variable and the dynamic EStEOML How to Read the Figure: • Identify the Variables: The variables are listed on the x-axis. They include "Constant", "dSE", "dSF36SG", "dEPN31P", "dBIG5A", "I", "P", and "T". • Understand the Coefficients:The position of the black dots on the y-axis represents the beta coefficients for each variable. A positive coefficient indicates a positive association with EStEOML, while a negative coefficient indicates a negative association. Evaluate Significance: • Look at the red dots to identify significant variables. These variables have a statistically significant association with EStEOML. • Error bars that do not cross the horizontal dashed line at zero also indicate significance. Variable Definitions: dSE: Emotional dimension of the VestiQ-VS questionnaire, dSF36SG: General health dimension of the SF36 questionnaire, dEPN31P: Fear dimension of the EPN31 questionnaire, dBIG5A: Agreeableness, Altruism, Affection dimension. I: Inhibition without Deficit Profile, P: Partial Contralateral Inhibition Profile, T: Total Contralateral Inhibition Profile.

other sources of sensory information are diminished or absent. They are particularly involved in detecting and correcting rapid and significant postural movements (63). Vestibulo-spinal reflexes are modulated based on postural conditions and play a role in posture adjustment to maintain stability, especially in the ML plane (63). Studying the underlying mechanisms of ML balance is significantly important for our understanding of postural control and human mobility, especially in vulnerable populations such as patients with chronic vestibular instability and symptoms (64). Complex processes are involved in maintaining ML balance during essential tasks such as transitioning from sitting to standing or in instability situations with rapid fluctuations in the ML plane (65). Previous studies have suggested that ML balance may be more sensitive to sensory disturbances and age-related alterations than anteroposterior (AP) balance. It is known that anxiety states affect postural performance (66). Similar to studies in the field, our study was able to determine a predictive link between cognitive-emotional and psycho-behavioral health and balancing performance in the mediolateral plane. We were able to specify the impact of different factors studied through the dimensions of the questionnaires used in our study. The analysis of total energy variation in 4 ML conditions revealed several key findings under:

- Static, Eyes Open (Table 10, Figure 10): A significant relationship ($P < 0.01$) was found, with 31% of the variance explained. The emotional dimension indicates a negative correlation, suggesting that emotional deterioration is related to increased postural imbalance. Conversely, better overall state health is associated with improved stability. Fear and pleasantness dimensions did not show a significant correlation with postural imbalance.
- Static, visually controlled condition (VC; Table 11, Figure 11): A significant correlation ($P < 0.01$) was observed, with 43% of the variance explained. Emotional dysfunctions and imbalance in the experience of surprise are associated with increased instability, while better emotional well-being favors stability. Central compensation levels also influence balance, but memory disorders do not have a significant impact.

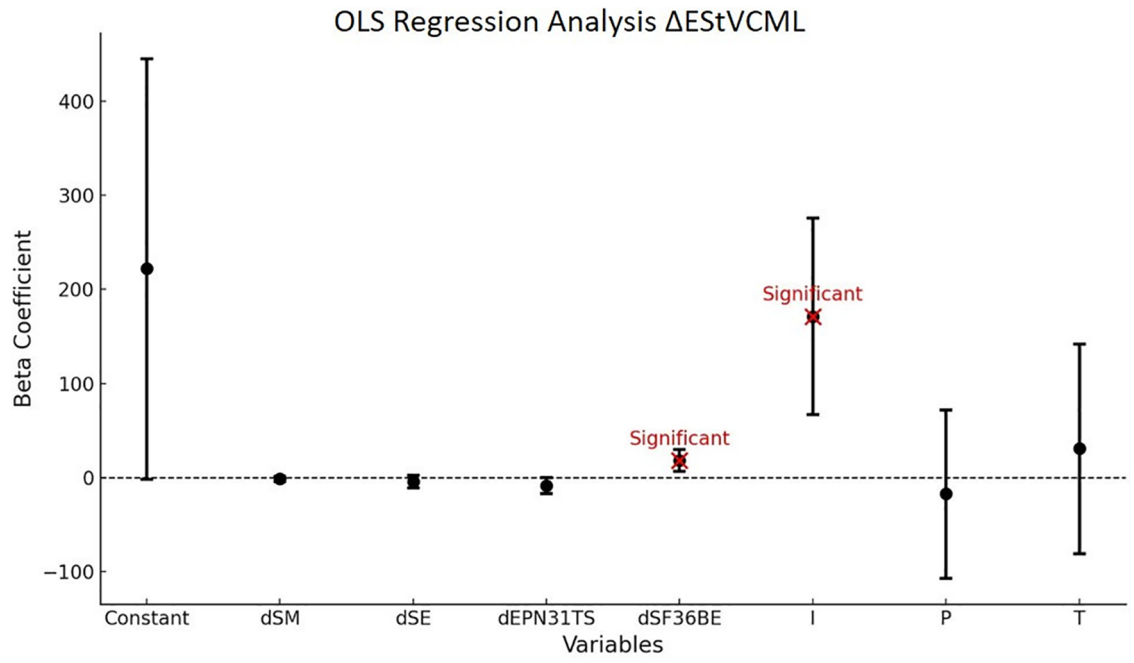

FIGURE 11
Ordinary least squares (OLS) regression analysis EStVCML. This graph shows the beta coefficients of the variables used in the OLS regression analysis for the dynamic change in EStVCML. The beta coefficients indicate the strength and direction of the association between each variable and the dynamic EStVCML. Figure Components: • Black Dots: Each black dot represents a beta coefficient for a given variable. • Error Bars: The horizontal bars around the dots indicate the 95% confidence intervals for each beta coefficient, showing the range within which the true beta coefficient is likely to lie with 95% probability. • Red Dots: Red dots indicate variables whose beta coefficients are statistically significant ($p < 0.05$). Significant variables are annotated with the text "Significant". • Horizontal Dashed Line at Zero: The dashed line indicates the zero value of the beta coefficient. A beta coefficient of zero means there is no association between the variable and EStEOML. How to Read the Figure: • Identify the Variables: The variables are listed on the x-axis. These include "Constant," "dSM," "dSE," "dEPN31TS," "dSF36BE," "I," "P," and "T". • Understand the Coefficients: The position of the black dots on the y-axis represents the beta coefficients for each variable. A positive coefficient indicates a positive association with dynamic EStVCML, while a negative coefficient indicates a negative association. Evaluate Significance: • Look at the red dots to identify significant variables. These variables have a statistically significant association with dynamic EStVCML. • Error bars that do not cross the horizontal dashed line at zero also indicate significance. Variable Definitions: dSM: Memory dimension of the VestiQ-VS questionnaire, dSE: Emotional dimension of the VestiQ-VS questionnaire, dEPN31TS: Surprise dimension of the EPN31 questionnaire, dSF36BE: Emotional well-being dimension of the SF36 questionnaire.

- Dynamic, Eyes Closed (EC; Table 12; Figure 12): A significant relationship ($P < 0.01$) with 32% of the variance explained was showed. Unimpaired memory functioning and high levels of extraversion are linked to better stability. However, an imbalance in the experience of joy is associated with increased imbalance, and physical function did not show a significant correlation.
- Dynamic, visually controlled condition (VC; Table 13; Figure 13): A significant relationship ($P < 0.01$) with 27% of the variance explained. Better cognitive abilities and high levels of pleasantness are associated with improved stability. Global emotional dysfunction is linked to increased imbalance, while fluctuations in joy and physical function did not show a significant correlation in this condition.

At this stage, it seems relevant to consider that the difficulty levels in the evaluated imbalance conditions imply different connections with cognitive-emotional (CE) recruitment for each of them. Thus, ranking the Sensory Organization Test tasks by difficulty level should also be discussed by jointly evaluating the CE recruitment capabilities specific to each patient. With the introduction of a cognitive-vestibular system (Lacroix 2021), it is suggested that each patient has a specific threshold beyond which the sensori-perceptual-motor system, and thus the balancing ability in contexts of visual deprivation, balancing performance, sensory conflict, or dual-task situations, fails. This threshold represents the limit beyond which managing balancing conditions becomes too energetically demanding for higher cognitive functions. This phenomenon indicates not only that certain patients with chronic vestibular disorders require an energy-intensive recruitment of higher cognitive functions to maintain balance but also that CE plays a significant role in managing cognitive resource allocation for balancing capabilities in complex situations. Consequently, there is a threshold beyond which managing balancing conditions is no longer ecological, highlighting the need for a personalized therapeutic approach to optimize vestibular compensation and sensory integration, emphasizing the crucial importance of the interaction between CE, the allocation of cognitive resources to the compensation of a chronic VES, and balancing capabilities.

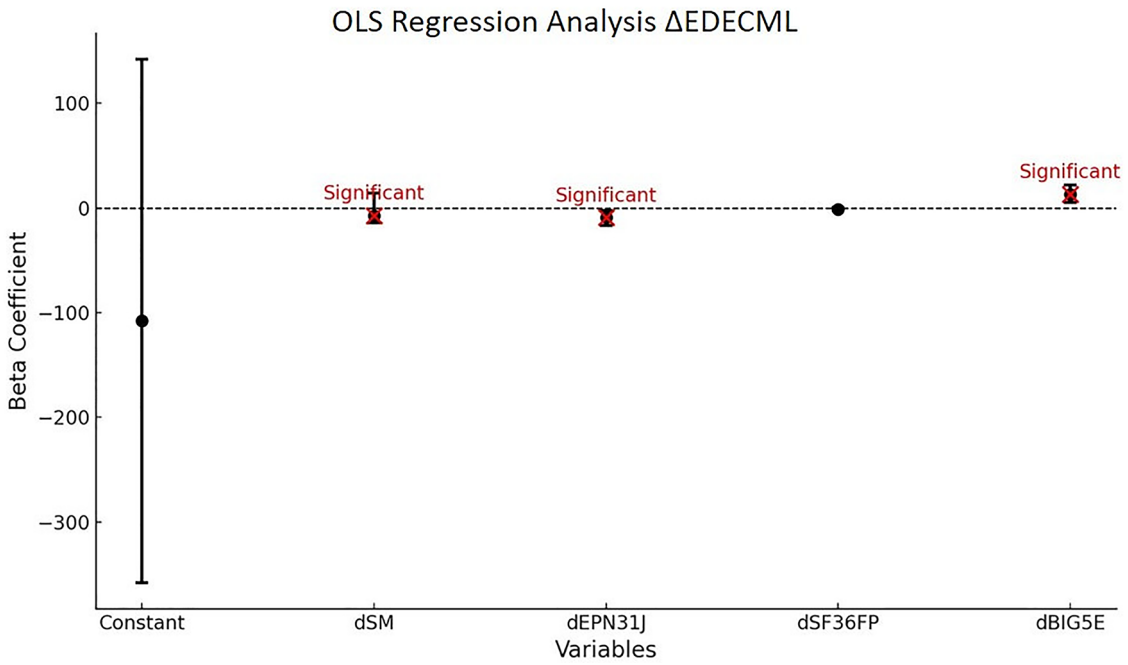

FIGURE 12
Ordinary least squares (OLS) regression analysis EDECML. This graph shows the beta coefficients of the variables used in the OLS regression analysis for EDECML. The beta coefficients indicate the strength and direction of the association between each variable and EDECML. Figure Components: • Black Dots: Each black dot represents a beta coefficient for a given variable. • Error Bars: The horizontal bars around the dots indicate the 95% confidence intervals for each beta coefficient. They show the range within which the true beta coefficient is likely to lie with a 95% probability. • Red Dots: Red dots indicate variables whose beta coefficients are statistically significant ($p < 0.05$). Significant variables are annotated with the text "Significant". • Horizontal Dashed Line at Zero: The dashed line indicates the zero value of the beta coefficient. A beta coefficient of zero means there is no association between the variable and EDECML. How to Read the Figure: • Identify the Variables: The variables are listed on the x-axis. They include "Constant", "dSM", "dEPN31J", "dSF36FP", and "dBIG5E". • Understand the Coefficients: The position of the black dots on the y-axis represents the beta coefficients for each variable. A positive coefficient indicates a positive association with EDECML, while a negative coefficient indicates a negative association. Evaluate Significance: • Look at the red dots to identify significant variables. These variables have a statistically significant association with EDECML. • Error bars that do not cross the horizontal dashed line at zero also indicate significance. Variable Definitions: dSM: Memory dimension of the VestiQ-VS questionnaire, dBIG5E: Extraversion, Energy, Enthusiasm dimension of the BFI questionnaire, dEPN31J: Joy dimension of the EPN31 questionnaire, dSF36FP: Physical Functioning dimension of the SF36 questionnaire.

4.4.2 Study of predictive markers of the variation in the inclination of the bisector relative to verticality; of the angle formed by the average of the SVV measurements in dynamic condition (optokinetic at 20°/s)

Tonal imbalances of the vestibular system, traditionally associated with unilateral peripheral vestibular lesions, have been reevaluated. These studies suggest that beyond otolithic lesions, dysfunctions at different levels of the vestibular system, including spinal, vestibular nucleus, brainstem, interstitial nucleus of Cajal lesions, as well as lesions located above the brainstem, thalamic, and cortical in the insular and temporo-parietal regions, can affect SVV and ML balance. These impairments can lead to complex dysfunctions such as visuospatial hemineglect and pusher syndrome, influencing both cognition and various sensory modalities (60). Furthermore, neural network modeling reveals that SVV inclinations result not only from otolithic imbalances but also from anomalies in the tone of vertical semicircular canals, affecting the central estimation of gravity. This model highlights the importance of the vertical semicircular canal in SVV inclinations, proposing a reevaluation of the causes of vestibular lesions, which would result from combined dysfunction of otoliths and semicircular canal input (60). In our model (Table 14; Figure 14), we also showed a significant relationship ($P < 0.01$) between the variation of the SVV bisector angle in dynamic conditions and the explanatory variables, contributing 38% to the variance. The results indicate that VOR preponderance and COR gain are positively and significantly associated with the variation of SVV inclination. This suggests a strong relationship in chronic vestibular patients between the variation of VOR preponderance and COR gain and that of the SVV angle in conditions of visual disturbance while no significant correlation is observed with VVOR, IFO, and absolute preponderance in the bithermic examination. Thus, the SPM recruitment in some of our chronic patients with instability complaints would be multimodal proprioceptive involving cervical and oculomotor proprioception according to our theory of "short" or short-latency neural networks.

4.5 Multisensory modalities

These findings prompt a reevaluation of the underlying mechanisms governing the interaction between the vestibular and

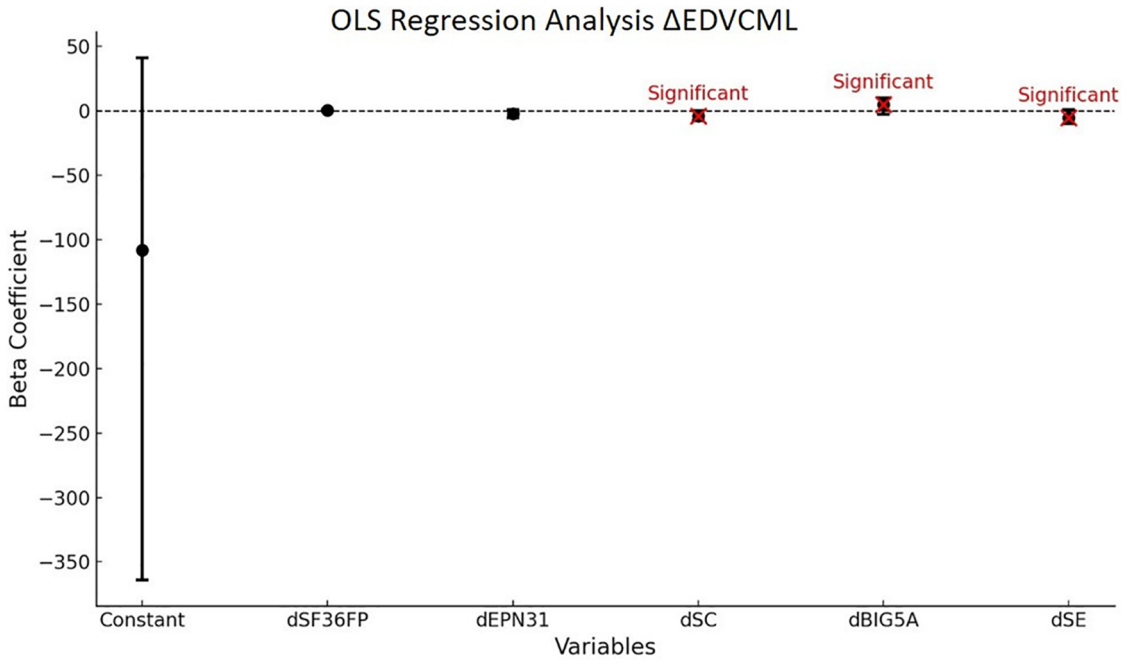

FIGURE 13
Ordinary least squares (OLS) regression analysis EDVCML. This graph shows the beta coefficients of the variables used in the OLS regression analysis for EDVCML. The beta coefficients indicate the strength and direction of the association between each variable and the outcome measure (EDVCML). Figure Components: • Black Dots: Each black dot represents a beta coefficient for a given variable. • Error Bars: The horizontal bars around the dots indicate the 95% confidence intervals for each beta coefficient. They show the range within which the true beta coefficient is likely to lie with a 95% probability. • Red Dots: Red dots indicate variables whose beta coefficients are statistically significant ($p < 0.05$). Significant variables are annotated with the text "Significant". • Horizontal Dashed Line at Zero: The dashed line indicates the zero value of the beta coefficient. A beta coefficient of zero means there is no association between the variable and the outcome measure (EDVCML). How to Read the Figure: • Identify the Variables: The variables are listed on the x-axis. They include "Constant", "dSF36FP", "dEPN31", "dSC", "dBIG5A", and "dSE". • Understand the Coefficients: The position of the black dots on the y-axis represents the beta coefficients for each variable. A positive coefficient indicates a positive association with EDVCML, while a negative coefficient indicates a negative association. Evaluate Significance: • Look at the red dots to identify significant variables. These variables have a statistically significant association with EDVCML. • Error bars that do not cross the horizontal dashed line at zero also indicate significance. Variable Definitions: dSC: Cognition dimension from the VestiQ-VS questionnaire, dSE: Emotional dimension from the VestiQ-VS questionnaire, dEPN31J: Joy dimension from the EPN31 questionnaire, dBIG5A: Agreeableness, Altruism, Affection dimension from the BFI questionnaire, dSF36FP: Physical functioning dimension from the SF36 questionnaire.

visual systems, particularly regarding the processing and integration of sensory information. Vestibular compensation appears to be influenced by two systems: the first involves a non-cognitive or low-level strategy. This strategy, primarily involving subcortical networks, seems to affect visuo-oculomotor activity under the influence of the vestibular error signal and the strong link with proprio-oculomotricity (67), and on the other hand, the vestibular nuclei and the accuracy of the SVV through the recruitment of cervical proprioceptive pathways, especially by the recruitment of COR gain, defined as accuracy in vestibular processing (25, 68). The second system, involving a cognitive or high-level strategy, entails several "possible" compensation mechanisms to influence the control of proprioceptive sensory gain, sensorimotor, cognitive-perceptual, and affective process control (6).

5 Conclusion

Our study has highlighted two main points of interest, the first being that of integrative, non-segmented therapy by a panel of paramedical practitioners. Non-pharmacological therapy should not only be responsive to dysfunctions of primary vestibular functions but should also focus on various aspects of visual function and the quality of life of chronic vestibular patients. The significant improvements in near visual acuity, visual fusion, and spatial perception underscore the importance of a real-time strategy in managing vestibular disorders. It is a true somato-perceptual-motor and cognitive-behavioral therapy, these two aspects needing to be merged in care. A second point raised by our study is the notion of new markers that must be systematically questioned before, during, and after therapy, such as neuro-visual and psycho-emotional aspects.

This study also contributes to the discussion in the existing literature (52) which posits the impact of cognitive-vestibular recruitment during compensation tasks on available resources by demonstrating that integrative vestibular rehabilitation can have extensive beneficial effects, positively impacting patients' mental health and quality of life. It underscores the importance of continuing research in this field, particularly to develop more targeted and effective rehabilitation strategies, and to better

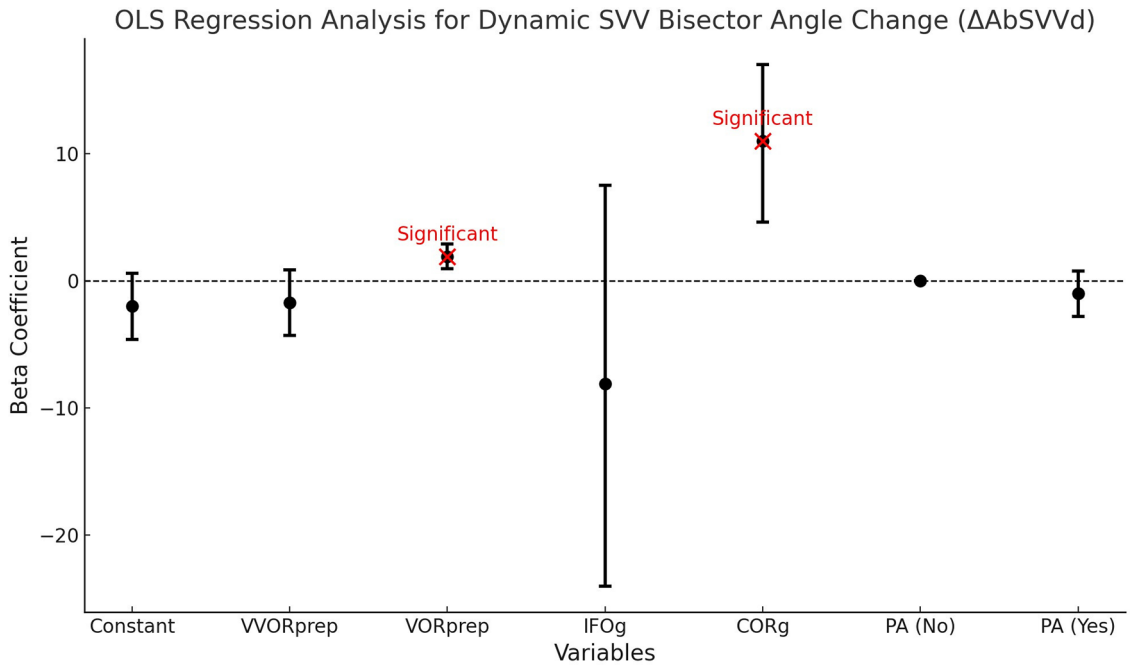

FIGURE 14
Ordinary least squares (OLS) regression analysis for dynamic SVV bisector angle change (AbSVVd). This graph shows the beta coefficients of the variables used in OLS regression analysis for the dynamic variation of the bisector angle of SVV (AbSVVd). The beta coefficients indicate the strength and direction of the association between each variable and the dynamic change in the SVV bisector angle. Figure Components: • Black Dots: Each black dot represents a beta coefficient for a given variable. • Error Bars: The horizontal bars around the dots indicate the 95% confidence intervals for each beta coefficient. They show the range within which the true beta coefficient is likely to lie with a 95% probability. • Red Dots: Red dots indicate variables whose beta coefficients are statistically significant ($p < 0.05$). Significant variables are annotated with the text "Significant". • Horizontal Dashed Line at Zero: The dashed line indicates the zero value of the beta coefficient. A beta coefficient of zero means there is no association between the variable and the dynamic bisector angle change of SVV. How to Read the Figure: • Identify the Variables: The variables are listed on the x-axis. They include measures such as "Constant", "VVORprep", "VORprep", "IFOg", "CORg", and categories of "Presence of Abnormal Absolute Preponderance (PA)". • Understand the Coefficients: The position of the black dots on the y-axis represents the beta coefficients for each variable. A positive coefficient indicates a positive association with the dynamic SVV bisector angle change, while a negative coefficient indicates a negative association. • Evaluate Significance: Look at the red dots to identify significant variables. These variables have a statistically significant association with the dynamic SVV bisector angle change. Error bars that do not cross the horizontal dashed line at zero also indicate significance. Variable Definitions: • VVORprep: Preponderance observed during the sensitized burst test for the visuo-vestibulo-ocular reflex study, • VORprep: Preponderance observed during the sensitized burst test for the vestibulo-ocular reflex study, • IFOg: Gain obtained during the sensitized burst test for the study of the ocular fixation index, • CORg: Gain obtained during the sensitized burst test for the study of the cervico-ocular reflex index, • PA (Yes): Abnormal absolute preponderance (≥2°/s) in the bithermal test, • PA (No): Normal absolute preponderance (≤2°/s) in the bithermal test.

understand central compensation mechanisms. These efforts will significantly improve the well-being and independence of individuals suffering from chronic vestibular disorders.

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 ethic commitee of the CAEN Hospital University number 2,796. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

FX: Conceptualization, Formal Analysis, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. EC: Data curation, Formal Analysis, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. BT: Validation, Visualization, Writing – review & editing. CC: Validation, Visualization, Writing – review & editing. SB: Validation, Visualization, 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fresc.2024.1414198/full#supplementary-material

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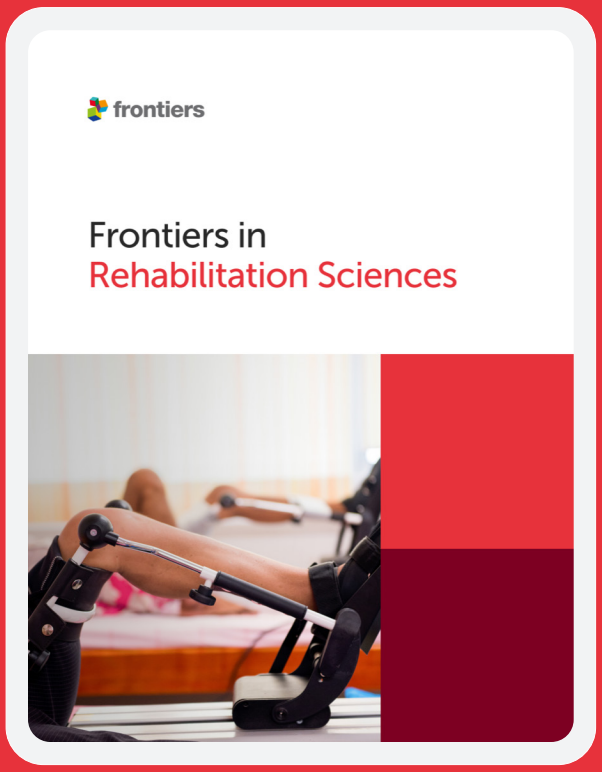

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