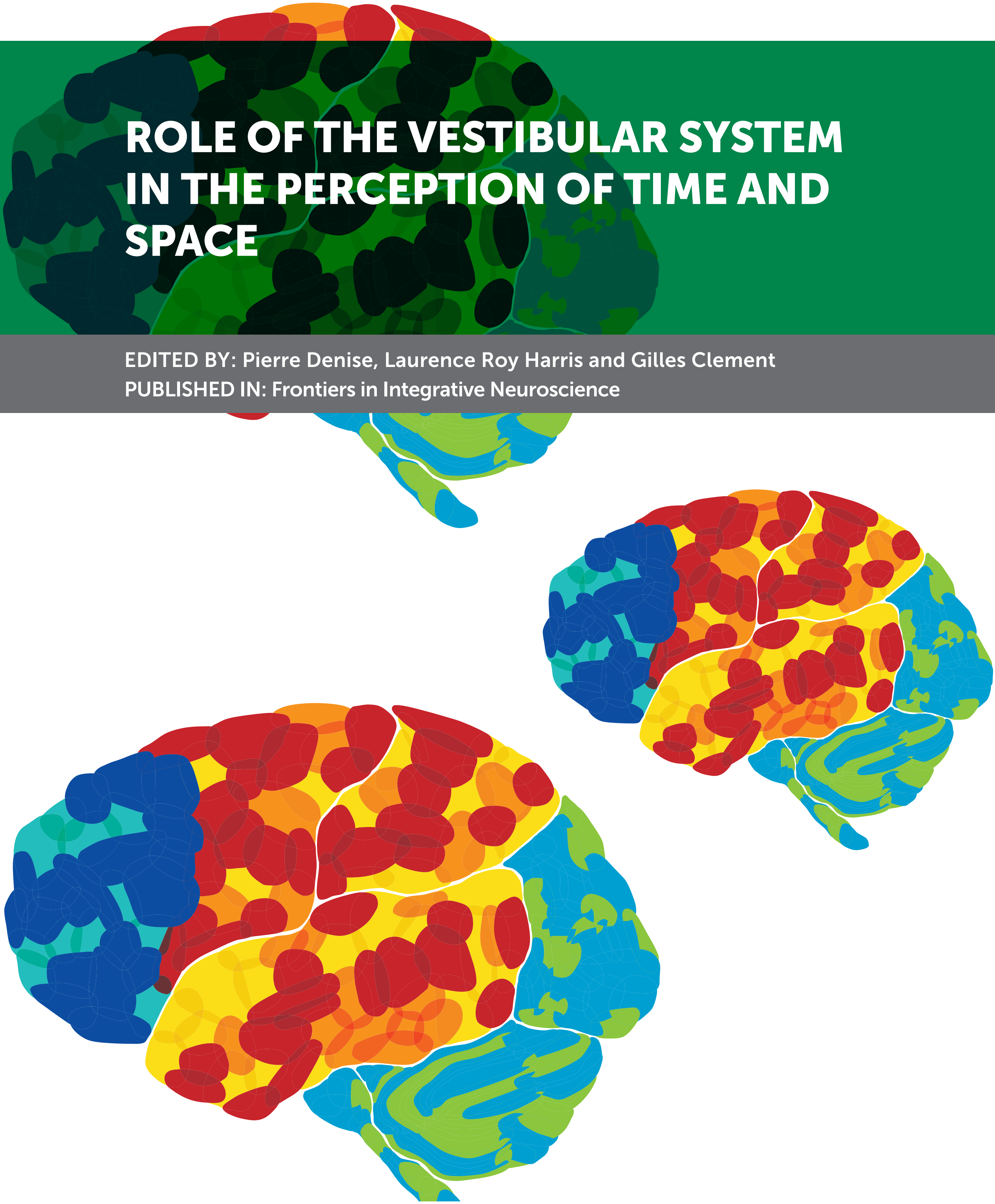

# ROLE OF THE VESTIBULAR SYSTEM IN THE PERCEPTION OF TIME AND SPACE

**EDITED BY:** Pierre Denise, Laurence Roy Harris and Gilles Clement
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frontiers Research Topics

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# ROLE OF THE VESTIBULAR SYSTEM IN THE PERCEPTION OF TIME AND SPACE

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# Editorial: Role of the vestibular system in the perception of time and space

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KEYWORDS

**time perception and vestibular system, time perception, spatial cognition, weightlessness, hypergravity**

Editorial on the Research Topic
Role of the vestibular system in the perception of time and space

The aim of this Research Topic was to address the influence of the vestibular system on time perception and spatial cognition, as well as how they are linked (Figure 1). Accurate time perception is required for higher level cognitive abilities, such as planning, decision making, communication, and effective coordination. Spatial cognition includes body motion, perception of the self, verticality, and distance perception combined with spatial learning and memory. Spatial cognition supports our capability for balance, orientation, and navigation in the terrestrial environment through integration of vestibular information into central multi-sensory processing. Since time perception is an inseparable part of spatial cognition, there is a growing interest in the role of vestibular inputs to subjective time. This Research Topic attracted a wide range of submissions across the spectrum of this theme. With this editorial, we intend to discuss the submitted contributions within the broader context of this growing field.

Navigation, i.e., the ability to estimate our position and track and plan our path in our topographical environment, relies not only on detection and perception of our own motion but also on evaluation of the duration of this motion. Thus, it is no wonder that recent studies suggest that the representations of space and time share the same metrics and cortical network, presumably located in the right temporal-parietal junction (TPJ) (Delle Monache et al.). There is growing, but still scarce, evidence of links between spatial processing and time perception. For example, subjects who observe downscaled environments experience an underestimation of duration that is proportional to the scale-model environments being observed (Senna et al., 2021).

The vestibular system signals head movements and gravity, but its influence is not restricted to balance reflexes at the brainstem level as recent evidence shows that vestibular processing is involved in spatial cognition and time perception. Self-motion perception relies mainly on visual, vestibular, and somatosensory cues. In darkness, or in an impoverished environment in visual cues, the processing of vestibular cues is critical for spatial cognition (Stapel and Medendorp). However, the vestibular system signals head angular velocity (semicircular canals) and head linear accelerations, inertial

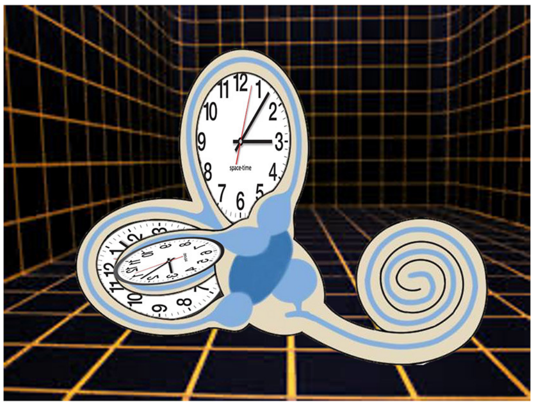

FIGURE 1
Artistic representation of the link between the perception of time and the vestibular system. Credit: Laurence Harris, York University.

or gravitational (otolith organs), while spatial orientation relies on position (angular and linear); thus, those vestibular signals need additional processing, i.e., time integration, in order to derive head angular position from head velocity and head linear position from head linear acceleration (Wagner et al.).

The TPJ continuously processes data from the visual, vestibular, and somatosensory channels for updating our spatial maps. However, the TPJ is also involved in time perception (Arshad et al.). As we know from experiments, patients with lesions of the TPJ display a correlated deficit in vestibular spatial perception and motion duration perception suggesting that temporal integration of self-motion velocity occurs in the TPJ and providing an explanation as to why a time perception deficit could lead to spatial disorientation (Utegaliyev et al.).

Changes in the level of gravity affect the vestibular system due to an increase or decrease in tonic otolith inputs. Therefore, alterations in time perception and space orientation are seen in subjects during whole body rotation (Alcantara-Thome et al.), head tilt (Bernard-Espina et al.), whole body tilt (Tekgün and Erdeniz), exposed to microgravity, and hypergravity (Clément, 2018), as well as in patients with mal de debarquement (Yakushin et al.) or vestibular disorders (Kwon et al.).

## Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

## Acknowledgments

We sincerely thank the authors who have contributed to the success of this Research Topic. Their articles demonstrate the growing popularity of the field of time perception and point to promising discoveries of the functioning of the vestibular system.

## 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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ORIGINAL RESEARCH
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# Anxiety and Motion Sickness Susceptibility May Influence the Ability to Update Orientation in the Horizontal Plane of Healthy Subjects

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Few studies have evaluated the influence of idiosyncrasies that may influence the judgment of space-time orientation after passive motion. We designed a study to assess the influence of anxiety/depression (which may distort time perception), motion sickness susceptibility (which has been related to vestibular function, disorientation, and to the velocity storage mechanism), and personal habits on the ability to update orientation, after passive rotations in the horizontal plane. Eighty-one healthy adults (22–64 years old) accepted to participate. After they completed an in-house general health/habits questionnaire, the short Motion Sickness Susceptibility Questionnaire, the Hospital Anxiety and Depression Scale (HADS), the Pittsburgh Sleep Quality Index, and the short International Physical Activity Questionnaire, they were exposed to 10 manually driven whole-body rotations (45°, 90°, or 135°), in a square room, with distinctive features on the walls, while seated in the normal upright position, unrestrained, with noise-attenuating headphones and blindfolded. After each rotation, they were asked to report which wall or corner they were facing. To calculate the error of estimation of orientation, the perceived rotation was subtracted from the actual rotation. Multivariate analysis showed that the estimation error of the first rotation was strongly related to the results of the orientation test. The magnitude and the frequency of estimation errors of orientation were independently related to HADS anxiety sub-score and to adult motion sickness susceptibility, with no influence of age, but a contribution from the interaction of the use of spectacles, the quality of sleep and sex. The results suggest that idiosyncrasies may contribute to the space-time estimation of passive self-motion, with influence from emotional traits, adult motion sickness susceptibility, experience, and possibly sleep quality.

**Keywords: orientation, vestibular, anxiety, motion sickness, adults**

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## INTRODUCTION

Behavior in the environment requires a dynamic updating of the perceptions of the body and the surroundings of the body. The spatial updating of self-to-object directions and distances (egocentric relations) that takes place concurrently with the change of spatial relations independent of the position of the perceiver (allocentric relations) depends upon the availability of multisensory information (Klatzky, 1998). Evidence suggests that humans update egocentric, internalized versions of the surroundings to orient themselves as they move (Wang and Spelke, 2000). Though, from an ecological approach to perception and action (Gibson, 1966), perception may not be based on patterns of stimulation available to individual perceptual systems, but may take advantage of "higher order relations" between them (Stoffregen and Riccio, 1988).

During active movements, comparison between the internal prediction of the proprioceptive consequences of self-motion to the actual resultant feedback, input carried by vestibular afferents may be canceled in conditions where there is a match between predicted and actual proprioceptive feedback (Cullen, 2011). Neurons in the vestibular nuclei differentially encode active versus passive head motion; during active movements, distinct classes of neurons allow for reduction of vestibular signals in order to redirect gaze or to stabilize head in space (for review Cullen and Roy, 2004). However, it is unknown yet how this differential processing of head velocity at the vestibular nucleus contributes to other vestibular functions.

In the absence of vision, vestibular signals may update self-orientation in the environment (Crum-Brown, 1875; Mach, 1875). Throughout passive motion, perception of displacement is derived from the same signal that determines perception of velocity, by integration over time (Mergner et al., 1996); while space-time relativity seems to be independent of whether velocity, distance derived by path integration, or both variables are stored in spatial working memory (Glasauer et al., 2007). Besides, vestibular perception of passive rotation in the horizontal plane can be independent of whether subjects are standing or sitting during rotation (Becker et al., 2000); while moving on to active behavior, displacement perception may be modified by proprioceptive and efferent signals, as well as the vestibular afferents at the pace of stepping (Jürgens et al., 1999).

After whole body passive rotations around an earth-vertical axis, without visual cues, subjects can indicate their orientation in space with respect to their initial orientation, while they update their actual orientation with respect to the surroundings (Israël et al., 1996; Wang and Spelke, 2000; Jáuregui-Renaud et al., 2008). Using simultaneous measurement of oculo-motor and perceptual measures of the vestibular time constant has shown that the perception of angular velocity is based on signals subserved by the velocity storage mechanism (Okada et al., 1999). This mechanism lengthens the time constant of the oculo-motor response to constant head rotation when no vision is available (Raphan et al., 1979), in such a way that the vestibulo-ocular response and the perception of self-motion outlast the duration of the response from the semicircular canals (Grunfeld et al., 2000; Bertolini et al., 2012).

The velocity storage mechanism has also been related to motion sickness susceptibility (for review Cohen et al., 2019). However, there are many theories of motion sickness, and some reject explanations in terms of velocity storage (Stoffregen and Riccio, 1988).

In addition, during passive rotation in the dark, updating orientation is dependent on vestibular inputs and processing in the central nervous system, with no opportunity to anticipate motion (for review see Behrendt, 2013; Eichenbaum, 2017). Then, both unpredictability and uncertainty may enable emotional responses during updating orientation in the dark (for review see Lake and LaBar, 2011);

The accuracy to judge angular displacements is highly variable among healthy subjects (Guedry et al., 1971), and overestimation of rotation is more frequent than underestimation (Israël et al., 1995; Marlinsky, 1999; Jáuregui-Renaud et al., 2008; Anson et al., 2021). It may decrease in old age (Anson et al., 2021), but other individual factors are poorly documented. We designed a study to assess the influence of individual factors on the vestibular contribution to update orientation, after passive rotations in the horizontal plane in young and middle-aged adults.

We selected the following factors that may influence time perception or space-time perception, as well as personal habits that could influence performance: common mental symptoms (anxiety/depression), which have been related to distortions on the awareness of time (Droit-Volet, 2013); susceptibility to motion sickness (in cars, boats, planes, trains, funfair rides), which is related to vestibular function (for review Money, 1970), to disorientation (for review Yardley, 1991), and which could be related to the velocity storage mechanism (for review Cohen et al., 2019); as well as physical activity (Rogge et al., 2021), quality of sleep (Martínez-Gallardo et al., 2020), the use of spectacles (Demer and Crane, 1998), and alcohol/tobacco use (Hafström et al., 2007).

# MATERIALS AND METHODS

## Participants

After approval by the Research and Ethics Committees, 81 subjects (mean age 40.0 years ± standard deviation 11.0 years) accepted to participate. All the participants denied having a history of dizziness, vertigo, unsteadiness, migraine, hearing loss, and neurological or psychiatric disorders (submission to psychiatric care of psychopharmacological treatment); none of them had evidence of vestibular dysfunction assessed by neuro-otology evaluation with caloric/rotational tests, and all of them were naive to the study protocol and to the orientation test.

Once they have completed questionnaires to assess the individual factors, they performed an updating orientation test.

## Questionnaires

An in-house questionnaire of general health and personal habits.

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), which is a self—report screening scale that contains 14—items with a Likert scale, seven for anxiety and seven for depression. It has been used to identify possible and probable cases of anxiety disorders in samples from the general population, general practice and psychiatric patients (Bjelland et al., 2002). It is scored by summing the ratings for all the items to yield a total score, and by summing the ratings for the seven items of each subscale to yield two separate sub-scores, which range from 0 to 21. A cut-off score of $\geq 8$ for both subscales gives sensitivities and specificities in the range of 0.70–0.90 (Zigmond and Snaith, 1983; Bjelland et al., 2002),

**TABLE 1 |** General characteristics and questionnaire scores of the 81 adults participating in the study.

| Variables | Percentage (number) |
|---|---|
| Handness | |
| Right | 86.4% (70) |
| Left | 4.9% (4) |
| Ambidextrous | 8.6% (7) |
| Education | |
| High school | 2.4% (2) |
| College | 28.3% (23) |
| University graduate | 46.9% (38) |
| University post-graduate | 12.3% (10) |
| Occupation | |
| Health workers | 56.7% (46) |
| Administrative workers | 33.3% (27) |
| Other occupation | 8.6% (7) |
| Tobacco and alcohol | |
| Tobacco smokers | 11.1% (9) |
| Alcohol use | 53.0% (43) |
| Corrected Myopia /Astigmatism | 35.8% (29) |
| | **Median (Q1–Q3)** |
| Pittsburgh sleep quality index | |
| Sleep Efficiency | 2 (1–3) |
| Sleep Latency | 1 (0–2) |
| Sleep Quality | 3 (2–4) |
| Total score | 6 (3–8) |
| International Physical Activity Questionnaire (met-minutes per week) | |
| Vigorous activity | 240 (0–1200) |
| Moderate activity | 120 (0–720) |
| Walking | 495 (157–1287) |
| Total activity | 1386 (480–3576) |
| Hospital Anxiety and Depression Scale | |
| Anxiety score | 3 (1–7) |
| Depression score | 1 (0–3) |
| Total score | 5 (2–10) |
| Motion sickness susceptibility questionnaire | |
| Before age 12 | 2 (0–4.5) |
| Over the last 10 years | 1 (0–3) |
| Total score | 3.6 (0–7.5) |
| Updating Orientation Test | |
| Estimation error | |
| First set of rotations | 18° (9°–27°) |
| Second set of rotations | 18° (9°–27°) |
| All rotations | 18° (9°–22.5°) |
| 45° rotations | 11.2° (0°–22.5°) |
| 90° rotations | 18° (9°–27°) |
| 135° rotation | 0° (0°–45°) |
| Total Correct Estimations | 7 (5–8) |

**TABLE 2 |** Median, Quartile 1 (Q1) and Quartile 3 (Q3) of the Pittsburgh sleep quality index, International Physical Activity Questionnaire, Hospital Anxiety and Depression Scale, Motion Sickness Susceptibility Questionnaire, and updating orientation results by age (young adults ≤40 years *versus* middle age >40 years).

| **Comparisons by age group** | | | | |
|---|---|---|---|---|
| | **≤40 years (*n* = 42) Median (Q1–Q3)** | **>40 years (*n* = 39) Median (Q1–Q3)** | ***Z* value** | **Bilateral *p* value** |
| Pittsburgh sleep quality index | | | | |
| Sleep Efficiency | 1 (1–2) | 2 (1–3) | −2.216 | **0.030** |
| Sleep Latency | 1 (0–2) | 1 (0–2) | −0.325 | 0.759 |
| Sleep Quality | 3 (2–3) | 3 (2–5) | −2.275 | **0.025** |
| Total score | 5 (3–7) | 6 (4–9) | −2.270 | **0.023** |
| International Physical Activity Questionnaire (met-minutes per week) | | | | |
| Vigorous activity | 960 (0–1920) | 80 (0–960) | 1.377 | 0.191 |
| Moderate activity | 360 (0–840) | 0 (0–720) | 1.685 | 0.113 |
| Walking | 693 (198–1386) | 380 (99–693) | 1.707 | 0.089 |
| Total activity | 2492 (678–4095) | 990 (405–3135) | 1.722 | 0.086 |
| Hospital Anxiety and Depression Scale | | | | |
| Anxiety score | 3.5 (1–6) | 3 (0–7) | 0.418 | 0.682 |
| Depression score | 1 (0–2) | 1 (0–3) | −0.616 | 0.556 |
| Total score | 4.5 (2–9) | 5 (1–11) | 0.123 | 0.906 |
| Motion sickness susceptibility questionnaire | | | | |
| As a child (before age 12) | 3 (1.1–5.1) | 1.1 (0–4) | 2.635 | **0.008** |
| Over the last 10 years | 2 (0–3.3) | 0 (0–1.8) | 2.924 | **0.004** |
| Total score | 4.75 (2–9) | 2 (0–5.5) | 2.964 | **0.002** |
| Updating Orientation Test | | | | |
| Average estimation error | | | | |
| First set of rotations | 18° (9°–27°) | 18° (9°–27°) | 0.587 | 0.575 |
| Second set of rotations | 18° (9°–27°) | 18° (9°–27°) | 0.222 | 0.832 |
| All rotations | 18° (9°–22.5°) | 13.5° (9°–27°) | 0.497 | 0.628 |
| 45° rotations | 11.2° (11.2°–22.5°) | 11.2° (0°–22.5°) | −0.468 | 0.655 |
| 90° rotations | 18° (9°–27°) | 18° (9°–18°) | 0.722 | 0.489 |
| 135° rotation | 22.5 (0°–45°) | 0° (0°–45°) | 0.179 | 0.876 |
| Total correct estimations | 7 (5–8) | 7 (5–8) | −0.311 | 0.759 |

*Comparisons were performed using Mann-Whitney U test. Significant values are highlighted in bold.*

and Cronbach's alpha coefficient varying from 0.67 to 0.93 (Bjelland et al., 2002).

The short from of the Motion Sickness Susceptibility Questionnaire (Golding, 2006b), which is a self—report screening scale that contains 18—items, divided into two parts: part A assessing motion sickness during childhood and part B assessing motion sickness during adulthood. It predicts individual

**TABLE 3 |** Median, Quartile 1 (Q1) and Quartile 3 (Q3) of the Pittsburgh sleep quality index, International Physical Activity Questionnaire, Hospital Anxiety and Depression Scale, Motion Sickness Susceptibility Questionnaire, and updating orientation results by sex.

| **Comparisons by sex** | **Women ($n$ = 52) Median (Q1–Q3)** | **Men ($n$ = 29) Median (Q1–Q3)** | **$Z$ value** | **Bilateral $p$ value** |
|---|---|---|---|---|
| Pittsburgh sleep quality index | | | | |
| Sleep Efficiency | 2 (1–3) | 1 (1–2) | 1.675 | 0.105 |
| Sleep Latency | 1 (0–2) | 1 (1–2) | −1.663 | 0.111 |
| Sleep Quality | 3 (2–4.5) | 3 (1–4) | 0.517 | 0.613 |
| Total score | 6 (3–8.5) | 6 (3–7) | 0.460 | 0.648 |
| International Physical Activity Questionnaire (met-minutes per week) | | | | |
| Vigorous activity | 0 (0–1200) | 960 (0–2000) | −1.988 | 0.057 |
| Moderate activity | 0 (0–540) | 240 (0–1200) | −1.877 | 0.076 |
| Walking | 495 (149–990) | 693 (165–1386) | −0.814 | 0.419 |
| Total activity | 1056 (396–3247) | 2506 (809–6008) | −2.298 | **0.021** |
| Hospital Anxiety and Depression Scale | | | | |
| Anxiety score | 4 (1–7) | 2 (0–5) | 1.538 | 0.128 |
| Depression score | 2 (0–3) | 0 (0–2) | 1.465 | 0.161 |
| Total score | 5 (2–10.5) | 3 (0–7) | 1.706 | 0.089 |
| Motion sickness susceptibility questionnaire | | | | |
| As a child (before age 12) | 2 (0–4.5) | 2 (0–5.1) | −0.354 | 0.728 |
| Over the last 10 years | 1.1 (0–3.1) | 1 (0–2) | 0.745 | 0.477 |
| Total score | 3.3 (0.5–8.2) | 3.6 (1.1–6) | −0.049 | 0.964 |
| Updating Orientation Test | | | | |
| Estimation error | | | | |
| 1st set of rotations | 18° (9°–27°) | 18° (9°–18°) | 0.805 | 0.441 |
| 2nd set of rotations | 18° (9°–27°) | 18° (9°–18°) | 0.615 | 0.553 |
| All rotations | 18° (9°–27°) | 13.5° (9°–22.5°) | 0.872 | 0.390 |
| 45° rotations | 11.2° (0°–22.5°) | 11.2° (11.2°–22.5°) | −0.241 | 0.818 |
| 90° rotations | 18° (9°–27°) | 9° (9°–18°) | 1.027 | 0.324 |
| 135° rotation | 22.5° (0°–45°) | 0° (0°–45°) | 0.681 | 0.546 |
| Total correct estimations | 7 (5–8.1) | 7 (6–8) | −0.648 | 0.527 |

*Comparisons were performed using Mann-Whitney U test. Significant values are highlighted in bold.*

differences in motion sickness caused by a variety of stimuli (e.g., cars, boats, planes, trains, funfair rides). Each score ranges from 0 (no susceptibility) to 27 (maximal level of susceptibility) and gives a total score from 0 to 54, with a Cronbach's alpha coefficient of 0.87 (Golding, 2006b).

The Pittsburgh Sleep Quality Index (Buysse et al., 1989), which is a self-rated questionnaire to assess sleep quality and sleep disturbances. Nineteen items generate seven scores on: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The combination of these sub-scores also generates three separate factors to assess (Jia et al., 2019): sleep efficiency; sleep latency and sleep quality. A total score $>5$ can be considered as bad quality of sleep (Buysse et al., 1989), with Cronbach's alpha coefficient varying from 0.70 to 0.83 (Mollayeva et al., 2016).

The short form of the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003), which is a self-report instrument to assess the frequency and duration of vigorous, moderate and walking activities, as well as the average sitting time on a weekday during the last 7 days. Although the overall scale tends to overestimate the amount of physical activity, it has shown acceptable correlations with objective measures of activity to assess walking (Lee et al., 2011).

## Updating Orientation Test

To assess self-orientation relative to the distinctive features of an unfamiliar room, participants were seated in the normal upright position, unrestrained on a hydraulic barber's chair (with a gyroscope on the headrest), in the center of a squared room (2 × 2 m), which contained fixed features positioned in the middle of each wall, in such a way that the features and corners subtended 45° with respect to the subject. They were asked to remember the location of each of the features while they were rotated in the light, and faced each of the walls. Then, blindfolded and wearing noise-attenuating headphones, they were exposed to two sets of five manually driven whole body rotations of 45° (2 s) or 90° (3 s) or 135° (4 s), to the right or to the left, in an unpredictable sequence, balanced for amplitude, direction, and order, with 10 s in-between (to allow post-rotatory sensations to fade). After the first set of five rotations and return to the start position, the eye mask was removed and the subject had a short rest of 1–2 min before commencing the second set of rotations. The actual rotation sequence included five rotations to the right and five rotations to the left (four rotations of 45°, five rotations of 90°, and 1 rotation of 135°); the sequence of small and large rotations and vice versa were similar to the right than to the left; whenever the first rotation of the first set was to the right, then the first rotation of the second set (after the rest) was to the left, and vice versa. Participants were instructed to report which wall or corner they were facing at the moment, just after each rotation (Jáuregui-Renaud et al., 2008).

The estimation error of each rotation was computed by subtracting the reported rotation from the actual rotation. Average estimation errors were calculated for all rotations and for each rotation size (error magnitude), and the number of correct estimations (error frequency) was also considered. All participants were tested during the morning and early afternoon.

## Analysis

Statistical analysis was performed using STATISTICA software (Tulsa, OK., StatSoft Inc.). According to data distribution (Kolmogorov Smirnov test), the results are described using median and quartiles 1 and 3 (Q1–Q3). The exploratory bivariate

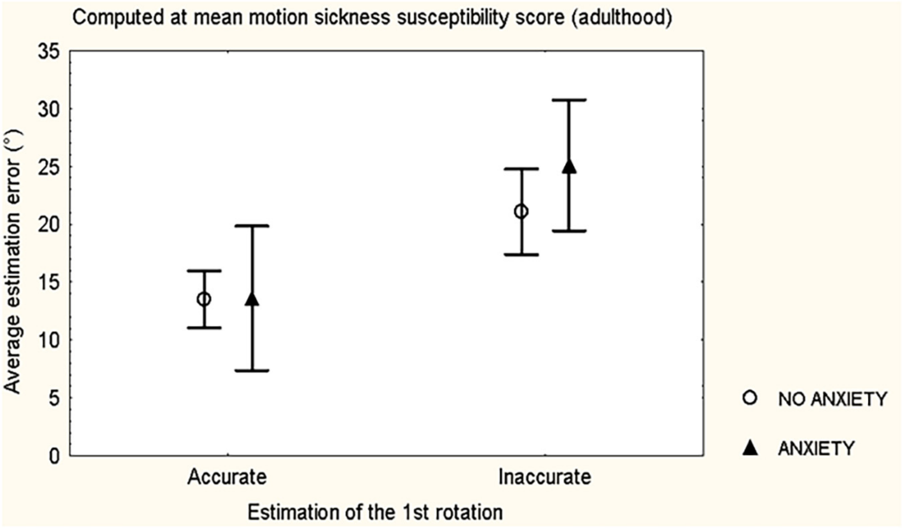

**FIGURE 1 |** Mean and standard error of the mean of the average estimation error during the updating orientation test, according to accuracy/inaccuracy of the estimation of the first rotation and evidence of Anxiety/No anxiety (HADS anxiety sub-score ≥8), of 81 healthy volunteers.

analysis was performed using Pearson correlation coefficient to assess linear correlations, and Mann Whitney *U* test to compare subgroups by age (≤ or >40 years old), by sex, and by HADS anxiety sub-score ≥8. To further assess linear correlations, analysis of covariance was performed. Considering the data distribution and plausible not linear effects, to assess the contribution of each independent variable to predict the estimation errors and correct estimations, after controlling for all other independent variables, a multivariable analysis was performed using a Generalized Linear Model with Wald test (Lindsey, 1997). The significance level was set at 2-tailed 0.05.

# RESULTS

## General Description

The characteristics of the participants and the scores on the Motion Sickness Questionnaire and the HADS are described in **Table 1**. The majority of participants was right-handed and had a university degree; circa half of them were health workers and a third of them were administrative workers. The report of physical activity was varied: 27.1% ($n = 22$) reported low physical activity, 29.6% ($n = 24$) reported moderate physical activity and 43.2% ($n = 35$) reported high physical activity. The use of alcohol was frequent but moderate (53%, $n = 43$) as well as the report of bad quality of sleep (Pittsburgh Sleep Quality Index >5) (51%, $n = 42$).

The results of the orientation test are shown in **Table 1**. Inaccurate estimation of orientation was observed after 34.3% of all rotations, with a typical error of 45°; overestimation of rotation was more frequent than underestimation of rotation (85.3% versus 14.7%). The median estimation error for all rotations was 18° (Q1–Q3 = 9°–22.5°); it was the same for the two sets of rotations (18°, 9°–27°), and it was consistent with the median estimation error for the 90° rotations (18°, 9°–27°). The median of the total correct estimations was 7 (5–8).

## Exploratory Bivariate Analysis

Comparisons by age are shown in **Table 2**. Compared to young adults (21–40 years old), middle-aged participants (41–64 years old) showed the lowest scores on the Motion Sickness Susceptibility Questionnaire total score and sub-scores ($p \leq 0.008$), and the highest scores on the Pittsburgh Quality of Sleep Index total score and sub-scores ($p \leq 0.03$), with no differences between subgroups on the average estimation error or the correct estimations.

Comparisons by sex are shown in **Table 3**. Although men spent more energy on physical activity (met-minutes per week) than women ($p = 0.021$), there were no other differences by sex.

Comparison by HADS anxiety sub-score showed that participants with a sub-score ≥8 reported fewer accurate estimations ($Z = -2.013$, $p = 0.044$) and larger overestimation of rotation ($Z = 1.985$, $p = 0.047$) than those with a sub-score <8.

Weak linear correlations were observed between the results of the orientation test and the HADS score and sub-scores (anxiety sub-score and depression sub-score) (Pearson's $r < 0.3$, $p < 0.05$), as well as the motion sickness total score and adult sub-score (Pearson's $r < 0.3$, $p < 0.05$) (**Appendix 1**). The strongest linear correlations were observed between the estimation error of the first rotation and the average estimation error, the total correct estimations and the estimation error for the 90° rotations (Pearson's r from 0.48 to 0.67, $p < 0.00001$) (**Appendix 1**).

Further covariance analysis confirmed that inaccurate estimation of the first rotation was linearly related to increased average estimation error, independently from HADS anxiety sub-score ≥8 and from the motion sickness susceptibility adult sub-score ($F = 15.630$, $p = 0.0001$) (**Figure 1**); while no

**TABLE 4 |** Coefficient estimates and standard error (S.E.) of the estimates are described with Wald statistic and *p* values for the average estimation error and the total correct estimations without including the first rotation estimation error **(A)** and including it **(B)**.

| | **Estimation error**<br>*Estimate ± S.E.* | **Correct estimations**<br>*Estimate ± S.E.* |
|---|---|---|
| **A** | | |
| Intercept | 2.410 ± 0.121 | 2.057 ± 0.039 |
| Wald Statistic (*p* value) | 396.890 (**<0.0001**) | 2650.439 (**<0.0001**) |
| Adult Motion sickness score | 0.054 ± 0.019 | –0.030 ± 0.013 |
| Wald Statistic (*p* value) | 7.744 (**0.0005**) | 5.096 (**0.023**) |
| HADS Anxiety score | 0.0290 ± 0.011 | –0.018 ± 0.007 |
| Wald Statistic (*p* value) | 6.654 (**0.009**) | 7.194 (**0.007**) |
| Sex | 0.082 ± 0.095 | –0.009 ± 0.027 |
| Wald Statistic (*p* value) | 0.741 (0.389) | 0.1344 (0.713) |
| Use of spectacles | 0.173 ± 0.095 | –0.057 ± 0.027 |
| Wald Statistic (*p* value) | 3.318 (0.068) | 4.400 (**0.035**) |
| Quality of sleep | 0.107 ± 0.097 | –0.050 0.028 |
| Wald Statistic (*p* value) | 1.237 (0.265) | 3.134 (0.076) |
| Sex * Use of spectacles * Quality of Sleep | 0.245 ± 0.095 | –0.094 ± 0.027 |
| Wald Statistic (*p* value) | 6.533 (**0.010**) | 12.202 (**0.0004**) |
| **B** | | |
| Intercept | 2.351 ± 0.110 | 2.091 ± 0.037 |
| Wald Statistic (*p* value) | 451.183 (**<0.0001**) | 3160.707 (**<0.0001**) |
| Adult Motion sickness score | 0.025 ± 0.018 | –0.026 ± 0.012 |
| Wald Statistic (*p* value) | 1.871 (0.171) | 4.290 (**0.038**) |
| HADS Anxiety score | 0.0233 ± 0.010 | –0.0121 ± 0.006 |
| Wald Statistic (*p* value) | 5.317 (**0.021**) | 3.464 (0.062) |
| 1st Rotation Estimation error | 0.009 ± 0.002 | –0.005 ± 0.001 |
| Wald Statistic (*p* value) | 15.496 (**<0.0001**) | 17.717 (**<0.0001**) |
| Sex | 0.045 ± 0.086 | 0.012 ± 0.024 |
| Wald Statistic (*p* value) | 0.276 (0.598) | 0.268 (0.604) |
| Use of spectacles | 0.134 ± 0.085 | –0.046 ± 0.024 |
| Wald Statistic (*p* value) | 2.475 (0.115) | 3.533 (0.060) |
| Quality of sleep | 0.064 ± 0.087 | –0.024 ± 0.026 |
| Wald Statistic (*p* value) | 0.536 (0.463) | 0.852 (0.355) |
| Sex * Use of spectacles * Quality of Sleep | 0.235 ± 0.086 | –0.090 ± 0.024 |
| Wald Statistic (*p* value) | 7.480 (**0.006**) | 14.036 (**0.0001**) |

*Significant values are highlighted in bold.*

significant linear interaction between these two variables was observed ($F = 0.672$, $p = 0.4$).

## Multivariable Analysis

The Estimates with their Standard Error and the Wald statistic with *p* values for all the variables included in the model are shown in **Table 4A**. The anxiety sub-score of the HADS and the adult sub-score of the Motion Sickness Susceptibility Questionnaire had independent contributions to both the average estimation error ($p \leq 0.009$), and the total correct estimations ($p \leq 0.023$), with a contribution of the use of spectacles on the total correct estimations ($p \leq 0.035$), but no influence was observed from age, physical activity, smoking, or alcohol use. In addition, in men, the use of spectacles and bad quality of sleep was related to larger average estimation error ($p = 0.010$) and less total correct estimations ($p = 0.0004$).

To confirm the independent contribution of the estimation error of the first rotation to the overall results of the orientation test, including plausible no linear effects, a second multivariable analysis was performed including this variable (despite collinearity). The Estimates with their Standard Error and the Wald statistic with *p* values for all the variables included in the model are shown in **Table 4B**. A highly significant relationship was observed between the estimation of the first rotation and the overall results of the test ($p < 0.0001$); participants who made an accurate estimation of the first rotation had lower average estimation error than those who made an inaccurate first estimation.

## DISCUSSION

In young and middle-aged healthy subjects, assessment of the influence of individual factors on updating orientation during passive rotations in the horizontal plane showed contributions from anxiety and adult motion sickness susceptibility (in cars, boats, planes, trains, funfair rides), as well as an interaction among the use of spectacles, the quality of sleep and sex, with no independent influence from age or sex. Estimation of the first rotation was related to the accuracy in updating orientation during the following rotations.

The finding of an association between HADS anxiety sub-score and the results of the orientation test is consistent with the relationship between emotion and vestibular function (Balaban and Thayer, 2001; Viaud-Delmon et al., 2011; Preuss et al., 2014; Coelho and Balaban, 2015). The spectrum of this relationship comprises from the dizziness related to psychiatric disorders (for review see Viaud-Delmon et al., 2011) to the neural network of vestibular inputs (Balaban and Thayer, 2001; Balaban, 2002). However, in this study we also considered the influence of affective states on the subjective estimation of time (Pariyadath and Eagleman, 2007; Tanaka and Yotsumoto, 2017). Since anxiety has been related to distortions of the awareness of time, including overestimation of short time intervals (for review see Droit-Volet, 2013).

In agreement with previous reports using the same or a similar orientation task (Israël et al., 1995; Marlinsky, 1999; Jáuregui-Renaud et al., 2008; Anson et al., 2021), in this study, overestimation of rotation was more frequent than underestimation. The orientation test design included rotations of increasing amplitude/duration, this allowed overestimation of duration to be easily interpreted as increased amplitude, which could give rise to overestimation errors. Participants with a HADS anxiety sub-score ≥8 were prone to overestimate the rotations. We propose the hypothesis that distortion of the duration of rotation could have influenced the percept of displacement. However, variation of the velocity among rotations (11°/s) could have interfered with this result.

The association of motion sickness susceptibility (in cars, boats, planes, trains, funfair rides), with errors on updating

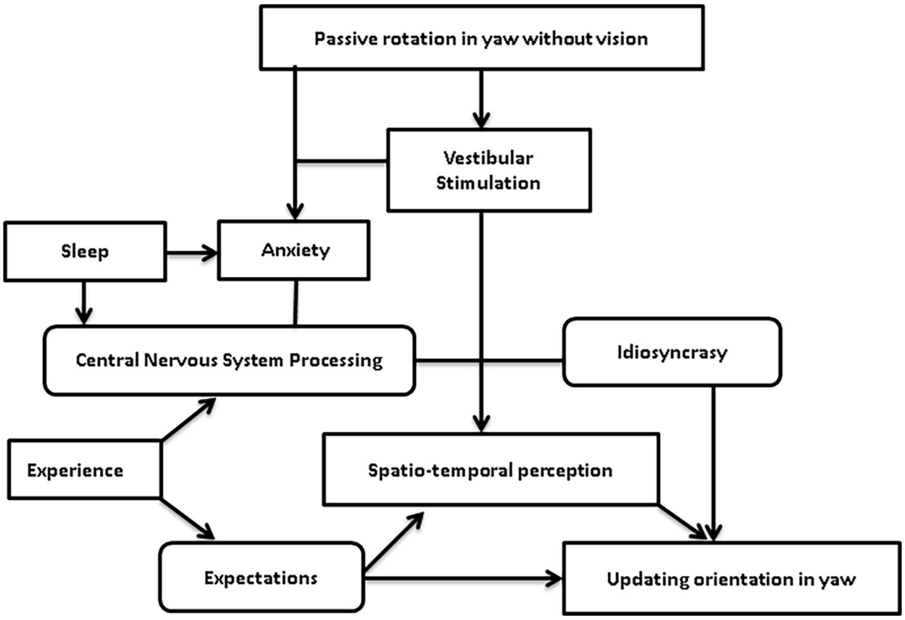

**FIGURE 2 |** Theoretical model of the interaction among individual factors during passive rotation without vision to update orientation in the horizontal plane.

orientation suggests that the unknown idiosyncrasy related to the variability of motion sickness susceptibility among subjects (Lentz and GuedryJr., 1978; Golding, 2006a) may also contribute to distortions on the space-time perception of passive rotations. We suggest that a link between these two variables could be the velocity storage mechanism and its processing, by means of the source signal to perceive both displacement and duration of rotation. The finding of lower motion sickness susceptibility scores in participants older than 40 years is consistent with the report of its decline with age, in both healthy subjects and vestibular patients (Paillard et al., 2013; Jones et al., 2019).

The independent contribution of motion sickness susceptibility and trait anxiety (by HADS anxiety sub-score) to the estimation error of orientation is in agreement with the report that the relationship between trait anxiety and motion sickness susceptibility can be weak in healthy subjects and not evident in patients with vestibular disease (Paillard et al., 2013).

The relationship between the estimation accuracy observed during the first rotation of the orientation test and the performance during the whole test could be explained by the test itself. Since participants were blindfolded, and they had no opportunity to contrast or reset their space-time perception of rotation with other sensory cues, they had to rely on their vestibular inputs and use the memory trace of their initial motion perception as they rotated to face each new direction. In addition, the strongest correlation with the estimation error of the 90° rotations could have been influenced by the reference axis. During passive rotations without vision, evidence suggests that the spatial framework used to organize the egocentric space orientation may include an orthogonal system related to the frame of the human body, with an ideal angle of 90° for subjective estimations of turns in the range of 15°–165° (Sadalla and Montello, 1989).

Several factors may have contributed to the finding that the use of spectacles and bad quality of sleep were related to larger average estimation error and less correct estimations, particularly in men. In healthy subjects, visual conditions can modify the vestibular responses (Gonshor and Jones, 1976). In laboratory situations, including passive head rotation, the wearing of telescopic spectacles can modify the gain of the vestibulo-ocular reflex (Demer and Crane, 1998). However, an objective evaluation of the corrected refraction errors would be required to adequately assess this factor. On the other hand, sleep disturbances have been related to several deficits including attention, memory, cognitive processes and emotional reactivity (for review see McCoy and Strecker, 2011); likewise, they can alter vestibular responses (Collins, 1988; Quarck et al., 2006; Martin et al., 2018) and they can affect the perception of motion during magnetic vestibular stimulation (Martínez-Gallardo et al., 2020). Evidence supports that, after sleep deprivation, the vestibulo-ocular reflex gain may increase in response to velocity steps (Quarck et al., 2006), or the responses may decrease according to the time of sleep deprivation (Collins, 1988). Moreover, in this study, since participants were blindfolded, we cannot disregard the effect of darkness on the alertness of subjects with bad quality of sleep (de Zeeuw et al., 2019). In addition, recent evidence suggests that sleep deprivation could have a stronger effect on balance (i.e., postural stability) in men, compared to women (Ołpińska-Lischka et al., 2021).

In agreement with previous reports (Jáuregui-Renaud et al., 2008; Anson et al., 2021), the analysis of this study showed no independent influence of sex on updating orientation after passive rotations in the horizontal plane. This finding was consistent with the observed lack of influence of physical activity on the performance of the orientation test, given that men reported more physical activity than women. Previous reports support that men may out-perform women on virtual navigation tasks (Astur et al., 1998) and way-finding outdoors (Silverman et al., 2000). However, men may prefer an allocentric strategy to orient them-selves (Dabbs et al., 1998), while women may prefer a landmark-based strategy (Choi et al., 2006). Albeit the orientation test of this study implied a combination of egocentric and allocentric strategies, an egocentric framework may have been used to update object position while rotating. This is consistent with the evidence supporting that the ability to accurately locate objects in small-scale environments appears to depend on the perception of the current egocentric distances and directions of objects, with a continuous update of these perceptions relative to the environment geometry through time, which can be used as a source for reorienting over motion (for review see Cheng et al., 2013), while path integration using the head as a reference is egocentric by nature. Moreover, in this study, the reported localization was not by chance; which supports that egocentric spatial perceptions persisted over orientation/disorientation.

We also observed no significant correlation between the age of the participants and the average estimation error or the total correct estimations. Young and middle-aged adults showed similar results on the orientation test, despite clear differences on the motion sickness susceptibility scores. These findings support that the decline in spatial orientation that has been observed in the elderly could be attributed to factors that may develop late in life (Anson et al., 2021), but may not be evident yet in young and middle-aged subjects (Jáuregui-Renaud et al., 2008).

An interaction among these variables is represented in **Figure 2**. The results suggest that updating orientation in the horizontal plane during passive rotations, without vision, would be the result of the space-time perception of the stimuli, in the context of individual expectations and idiosyncrasy. However, to estimate both displacement and duration of motion, idiosyncrasy may play a part in central integration of the sensory inputs; while anxiety and bad sleep may influence this processing, in the context of individual experiences and expectations.

The main limitation of this study was its cross-over design. Repeated measures would allow less individual cofactors increasing the variance, and better assessment of age effects on performance; though performing a known task would have an effect on the results. A second limitation of the study is the reliance en self-report instruments; also, the apparent lack of influence of alcohol/tobacco use that is not conclusive, due to the low frequency of smokers and the moderate alcohol consumption among participants. Another limitation was that the manually driven rotations of the orientation test introduced velocity variability among the three amplitudes tested (11°/s), precluding an accurate assessment according to the space-time characteristics of the stimuli. However, the consistent findings open new research questions to study the influence of individual factors in the perception of self-motion, including the possibility that distortion of time perception might interfere with displacement perception, as well as the influence of the immediate perception of motion on updating space-time orientation.

In conclusion, in young and middle-aged healthy adults, susceptibility to motion sickness and anxiety may influence the space-time perception of earth-vertical passive rotations in the horizontal plane, with influence from individual traits and experiences, and possibly sleep quality.

## 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 Comité Local de Investigación en Salud y Ética en Investigación no. 3601 del Instituto Mexicano del Seguro Social. The participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

KJ-R conceived and designed the study and the vestibular stimuli, supervised the selection of participants, analyzed and interpreted the data, and wrote the manuscript. MA-T selected and evaluated the participants, performed the stimuli, collected the data, and revised the manuscript. JM-P coordinated the evaluation of participants, validated and administered the data, and revised 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.

# APPENDIX 1

**TABLE 1 |** Correlation matrix between the updating orientation test results and the age, the first rotation estimation error, the Motion Sickness Susceptibility Questionnaire and the Hospital Anxiety and Depression Scale (HADS) total scores and sub-scores.

| | **Age** | **1st rotation error** | **Motion sickness susceptibility** | | | **Anxiety and Depression (HADS)** | | |
|---|---|---|---|---|---|---|---|---|
| | | | **Childhood** | **Adult** | **Total** | **Anxiety** | **Depression** | **Total** |
| Average estimation error | −0.006, *p* = 0.953 | **0.486, *p* < 0.0001** | 0.199, *p* = 0.076 | **0.254, *p* = 0.023** | **0.244, *p* = 0.029** | **0.270, *p* = 0.015** | **0.240, *p* = 0.031** | **0.270, *p* = 0.015** |
| 45° rotations | 0.034, *p* = 0.765 | 0.0644, *p* = 0.570 | 0.107, *p* = 0.343 | 0.084, *p* = 0.456 | 0.103, *p* = 0.361 | 0.095, *p* = 0.399 | 0.121, *p* = 0.282 | 0.110, *p* = 0.328 |
| 90° rotations | −0.044, *p* = 0.696 | **0.676, *p* < 0.0001** | 0.175, *p* = 0.120 | **0.233, *p* = 0.037** | **0.22, *p* = 0.047** | **0.280, *p* = 0.012** | **0.241, *p* = 0.031** | **0.278, *p* = 0.012** |
| 135° rotation | 0.006, *p* = 0.953 | 0.173, *p* = 0.123 | 0.131, *p* = 0.243 | **0.235, *p* = 0.035** | 0.193, *p* = 0.085 | 0.177, *p* = 0.115 | 0.115, *p* = 0.307 | 0.158, *p* = 0.160 |
| Total correct estimations | −0.016, *p* = 0.887 | **−0.514, *p* < 0.0001** | −0.196, *p* = 0.081 | **−0.267, *p* = 0.016** | **−0.249, *p* = 0.025** | **−0.287, *p* = 0.010** | **−0.274, *p* = 0.014** | **−0.295, *p* = 0.008** |

*Significant values are highlighted in bold.*

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# Panoramic Uncertainty in Vertical Perception

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Judgments of the orientation of a visual line with respect to earth vertical are affected by panoramic visual cues. This is illustrated by the rod-and-frame effect (RFE), the finding that the perceived orientation of a luminous rod is biased by the orientation of a surrounding squared frame. In this study, we tested how the uncertainty of frame orientation affects the RFE by asking upright or tilted participants to psychometrically judge the orientation of a briefly flashed rod contained within either a circular frame, a squared frame, or either of two intermediate frame forms, called squircles, presented in various orientations. Results showed a cyclical modulation of frame-induced bias across the range of the square and squircular frame orientations. The magnitude of this bias increased with increasing squaredness of the frame, as if the more unequivocal the orientation cues of the frame, the larger the reliance on them for rod orientation judgments. These findings are explained with a Bayesian optimal integration model in which participants flexibly weigh visual panoramic cues, depending on their orientation reliability, and non-visual cues in the perception of vertical.

**Keywords: multisensory integration (MSI), subjective visual vertical (SVV), Bayesian, vision, vestibular, rod-and-frame**

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## INTRODUCTION

Many of our daily activities, such as walking, standing, or gaze control, rely on estimates of head and body orientation in space. These estimates are inferred not only from sensory inputs, such as visual and vestibular cues but are also based on motor feedback and prior expectations. As a measure of spatial orientation, experimentalists often assess the percept of vertical, i.e., the perceived orientation of a visual line relative to gravity ($\tilde{L}_G$), which can computationally (**Figure 1A**) be inferred by combining the orientation estimates of the head ($\tilde{H}_G$), eye-in-head ($\tilde{E}_H$), and line-on-retina ($\tilde{L}_E$), according to $\tilde{L}_G = \tilde{H}_G + \tilde{E}_H + \tilde{L}_E$. How do visual cues contribute to the perception of vertical? Rich visual scenes typically contain various panoramic cues, such as houses, trees, or the horizon. These cues unambiguously indicate which direction is up and hence can provide the brain with information about gravity direction (van der Schaaf and van Hateren, 1996; Coppola et al., 1998; Girshick et al., 2011; Pomante et al., 2021). More impoverished visual scenes, lacking clear panoramic cues, also affect the percept of vertical (Ebenholtz and Callan, 1980; Li and Matin, 2005a). For example, the perceived orientation of an earth-vertical line is biased when surrounded by a tilted squared frame (Witkin and Asch, 1948; Alberts et al., 2016; Niehof et al., 2019), an effect known as the rod-and-frame effect (RFE; Witkin and Asch, 1948). The magnitude of this RFE cyclically changes as the frame rotates across a 90° range (Wenderoth, 1973; Alberts et al., 2016). In fact, even a single peripheral line could induce such a bias, with the same 90° periodicity (Vingerhoets et al., 2009). Matin and Li (1995) explained the RFE as an indirect contribution of the visual frame to the internal estimate of head orientation. In turn, this visual signal, in combination with vestibular and other non-visual head orientation signals, then affects the perceived orientation of the rod (see **Figure 1A**). Rules of Bayesian inference dictate that the most precise estimate (estimate with the lowest variance) of head orientation is achieved by integrating the sensory signals and prior expectations according to their reliability (Laurens and Droulez, 2007; MacNeilage et al., 2007; De Vrijer et al., 2008, 2009; Tarnutzer et al., 2009; Clemens et al., 2011; Alberts et al., 2016; Kheradmand and Winnick, 2017; De Winkel et al., 2018, 2021). This means that more reliable information weighs in heavier in the combined head orientation estimate than less reliable information. Alberts et al. (2016), building on the work of Vingerhoets et al. (2009) and Clemens et al. (2011), provided a Bayesian model of the RFE, involving a precision-dependent weighting of vestibular and visual frame signals. They experimentally validated their model by showing that lowering the vestibular reliability by tilting the head (Tarnutzer et al., 2009) increased the RFE and that reducing the visual frame reliability by increasing viewing distance reduced the RFE.

Noteworthy, the manipulation of viewing distance in the study by Alberts et al. (2016) affected the quality of the whole visual scene; the global frame and the local rod. Therefore, it remains elusive whether changes in the retinal size of the rod, the frame, or both caused the alteration of the RFE effect. Recent findings of Pomante et al. (2019) suggest that visual uncertainty of rod orientation is not central. The authors manipulated the orientation reliability of the rod by replacing it with ellipses differing in their polarization from near-circular to strongly polarized. Polarization of the ellipse did not alter the RFE, suggesting that the rod does not function as a head orientation cue (**Figure 1A**). In the current study, we further tested the role of visual frame reliability in the RFE and its interaction with changes in vestibular reliability.

In contrast to the unambiguous cue to the gravity direction provided by rich visual scenes, a squared visual frame provides less certainty by delivering four ambiguous cues. Heuristically, a circular frame provides no cues to gravity direction, but frames intermediate a square and circle could be expected to differ in the reliability of their implicit cues to the gravity direction. Here, we employed this type of manipulation by contrasting the effects of a square and a circle with two intermediate forms known as *squircles* (see **Figure 1B**; Weisstein, 2011). A squircle, which is a superellipse with equal length semi-axes, can be specified as:

$$\left|\frac{x-a}{r_a}\right|^n + \left|\frac{y-b}{r_b}\right|^n = 1 \tag{1}$$

where, $r_a$ and $r_b$ represent the length of the semi-axes, and $a$ and $b$ quantify the offset with respect to the origin. In a squircle, $r_a$ and $r_b$ are equal, and the larger the $n$, the more square-like the form. In the current study, the RFE of a squared frame was compared to a squircular frame with $n = 2.4$, a more circular squircle with $n = 2.2$, and a full circular frame ($n = 2$), under two physical orientations of the head (upright and rightward tilted by 30°).

Reasoning based on the Bayesian model described above, we expected the magnitude of the RFE – the bias – to increase with the squaredness of the frame and with decreasing vestibular reliability (**Figure 1C**). Likewise, the impact of frame orientation on the response variability was expected to be larger with increasing squaredness and more strongly so when the vestibular reliability was reduced.

## MATERIALS AND METHODS

### Participants

Data of 12 participants (mean age = 20.5 years, *SD* = 2.9 years, eight women) naïve to the study purposes were included in the final analyses. All included participants finalized two experimental sessions, which took them 2 h per session. Ten additional participants were recruited but excluded from the analyses, for failing to finish the first session ($n = 3$), not returning at the second session ($n = 3$), or not following the task instructions ($n = 4$). All participants had normal or corrected-to-normal vision and no known (history of) neurological disorders. Participants were recruited from a participant database of Radboud University. They provided written informed consent prior to taking part and received either gift vouchers (€20 per 2 h session) or study points for participation.

### Experimental Setup

Participants were seated in a chair that was mounted on a height-adjustable frame. After adjusting the height of the chair and table, the researcher locked the position of the chair. Two custom-made vertical foam-padded headrests were mounted to the frame. The headrests were adjustable in height and position, such that these could be aligned with and gently enclosing the ears of the participant. The headrests stabilized the head either in an upright or in a 30° tilt position.

The participants looked through a tube (length: 70 cm, diameter: 31.5 cm) in front of them toward an OLED TV screen (LG 55EA8809, 123 × 69 cm, 1,920 × 1,080 pixels, refresh rate 60 Hz) in a darkened laboratory. The advantage of an OLED screen is that pixels set to black do not emit light. A tunnel of cloth connected the head of the participant with the front of the tube. Both cloth and tube were used to prevent potential remaining external light to reach the eyes of the participants. Participants had to indicate with a handheld button-box whether the rod was rotated clockwise (CW) or counterclockwise (CCW) relative to the earth vertical.

### Experimental Procedure

The participants performed a rod-and-frame task, in which they judged whether a rod presented against a background of a frame was rotated CW or CCW with respect to the gravitational vertical. Each trial started with a gray frame (square: 15 × 15 cm, circle and squircles: diameter of 15 cm, 12.2° visual angle) presented on a black background. After 200 ms, a gray rod (length: 12 cm, 9.8° visual angle, width: 1 px) was presented in the center of the frame for 33 ms, and then the rod was removed again. The frame remained on the screen until the participant had responded

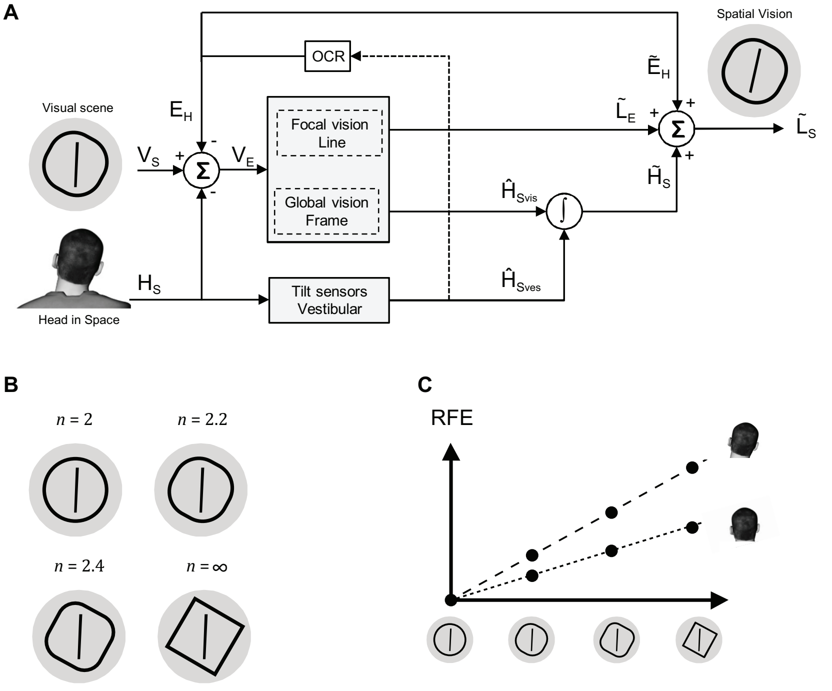

**FIGURE 1 | (A)** A schematic of the Bayesian model. **(B)** The four frame forms used: circle (*n* = 2), squircle 2 (*n* = 2.2), squircle 1 (*n* = 2.4), and square (*n* = ∞). **(C)** Hypothesized relation between frame form, head orientation, and magnitude of the rod-and-frame effect.

by pressing one of the two available buttons. Between trials, the screen was black for 400 ms.

The orientation of the rod and the orientation of the frame were varied independently. The rod's orientation was randomly selected from a set of nine rod orientations centered around the gravitational vertical (−7°,−4°,−2°,−1°, 0°, 1°, 2°, 4°, or 7°), and the frame was displayed in an orientation randomly chosen from a set of 15 angles between −35° and 35°, in steps of 5°. Four different frame forms were used: a square, a circle, and two squircles (see **Figure 1B**). Except for the circle, all possible combinations of frame form, frame orientation, and rod orientation were used. Because a circle has no orientation, only the rod orientation was varied in the circle condition. This led to 414 unique trials, together constituting a sequence. The experiment was split into two sessions and each session consisted of 10 trial sequences. A session thus consisted of 4,140 trials and typically took about 2 h including breaks. The trial order was randomized within each sequence. Head orientation was either held upright or tilted 30° to the right within a session. The order of head orientation conditions was counterbalanced across participants. Both sessions started with 10 practice trials. The performance of participants was monitored during practice trials, and, if needed, another practice round was included.

## Data Analyses

The data analyses, which will be explained in more detail below, included a number of steps. First, psychometric curves were fitted to the data, and a summary statistic describing the goodness-of-fit (the Bayesian information criterion, BIC) was calculated. The psychometric fits provided a model-free benchmark for comparison with the Bayesian model. Next, the Bayesian model was fitted to the data and the same summary statistic was obtained. Subsequently, the Bayesian model was validated and evaluated by means of a bootstrapping procedure and a parameter recovery analysis. Finally, the goodness-of-fit of the Bayesian model was compared to the psychometric model-free benchmark.

## Model-Free Benchmark

Clockwise frame and rod orientations were defined positively. Per participant, session, frame form, and frame orientation, a cumulative Gaussian was fit to the proportion of CW responses as a function of rod orientation (Wichmann and Hill, 2001):

$$P(x) = \lambda + (1 - 2\lambda)\frac{1}{\sigma\sqrt{2\pi}}\int_{-\infty}^{x} e^{-(y-\mu)^2/2\sigma^2}dy \quad (2)$$

where $x$ represents the rod orientation in space and $\lambda$ the lapse rate, accounting for individual stimulus-independent errors. The mean $\mu$ and the SD $\sigma$ of the Gaussian account for the perceived orientation of gravity of participants [i.e., the systematic bias or point-of-subjective equality (PSE)] and response variability, respectively. A Matlab search routine called "fminsearch" was used to find the fit that maximized the likelihood estimation, through searching for the minimum of the negative log likelihood.

## Model Fitting

A Bayesian optimal integration model was fitted on the responses of the participants. This model has been described in full detail in a previous paper (Alberts et al., 2016). In short, the model describes that how a line-on-retina estimate can result in a line-in-space estimate via a few steps. First, the line-on-eye estimate is combined with the eye-in-head estimate, producing a line-relative-to-head estimate. This line-relative-to-head estimate can then be combined with the head-in-space estimate to result in a line-in-space estimate. According to the model, the head-in-space estimate results from optimally integrating (extra)vestibular cues, the visual contextual cues, and the prior on head orientation, following:

$$P(\widetilde{H}_s|\widehat{H}_s, \widehat{\theta}_R) = P(\widehat{H}_s|H_s) \cdot P(\widehat{\theta}_R|H_s) \cdot P(H_s) \tag{3}$$

where $P\ (\hat{H}_s \mid H_s)$ is the vestibular likelihood, $P\ (\hat{\theta}_R \mid H_s)$ is the contextual likelihood, and $P\ (H_s)$ is the prior head orientation. The head-in-space estimate with the highest probability given the sensory evidence is utilized: the *maximum a posteriori* (MAP). The vestibular likelihood is based on the (extra)vestibular cues, which are assumed to be veridical but contaminated with noise. The vestibular noise parameter is operationalized as an offset ($\beta_{HS}$) plus a noise component that scales linearly with the tilt angle of the head relative to the upright position ($\alpha_{HS}$). The prior on head orientation relative to the earth vertical was modeled as a Gaussian centered at 0° (upright) with SD $\sigma_{HP}$. The contextual likelihood is described in the model as a function that strongly relies on the sensory inputs from the cardinal directions of the frame. The sensory input is expressed here in retinal coordinates and we accounted for the uncompensated ocular counterroll in the head-tilted condition by including a parameter $A_{OCR}$, which cannot be established empirically. To remove ambiguity in the fitting of the present data, we fixed the $A_{OCR}$ at 14.6 based on previous findings (Clemens et al., 2011; see Alberts et al., 2016 for mathematical details). The contextual probability distribution is modeled as the normalized sum of four von Mises distributions, with one von Mises distribution peaking at the veridical frame orientation, and the others peaking at 90° intervals. As previous work demonstrated that vertical perception more strongly relies on the (near) vertical frame lines than on the (near) horizontal lines (Alberts et al., 2016), the variance in the vertical direction ($\sigma^2_{ver}$) was allowed to vary independently from the variance in the horizontal direction ($\sigma^2_{hor}$). Additionally, changes in frame orientation will also change the dependence on the cardinal axes, with equal importance for the horizontal and vertical at a frame orientation of 45° and a lessening importance of the horizontal for more upright frames. The change in dependence on the different cardinal axes was modeled as a free parameter $\tau$ .

The described model had seven free parameters ($\sigma_{HP}$, $\alpha_{HS}$, $\beta_{HS}$, $\sigma_{ver}$, $\sigma_{hor}$, $\tau$, and $\lambda$), with $\lambda$ denoting the lapse rate. All data were first symmetrized per participant and condition (as in Clemens et al., 2011; Alberts et al., 2016), based on the responses of the participants to the head upright square frame condition. Then, the model was fit per participant on the data of the square frame fitting both vestibular conditions simultaneously. Subsequently, the obtained parameter values were fixed and used to fit the data of the squircles, with only one free parameter, namely, a gain factor. The gain factor, $g_1$ for squircle 1 and $g_2$ for squircle 2, scaled the variability in visual context probability distribution such that a gain of one implied that $\sigma_{ver}$ and $\sigma_{hor}$ in the squircle condition were equal to those in the square condition, whereas, a gain factor larger than one implied increased variability in comparison to the squared frame.

Model fitting was performed in Matlab 2015b (Mathworks) using the function "fmincon" to minimize the log likelihood of the data given the parameter values. Random initial parameter values were used, and the routine was repeated five times to ensure a global rather than a local minimum would be found.

## Model Evaluation

Hundred bootstrap runs were performed to obtain the SD of the fitted parameter values. Per run, 1,350 stimuli (15 frame orientations × 9 rod orientations × 10 repetitions) and accompanying responses were randomly sampled with replacement from the original data.

To validate our fitting procedure, we performed a parameter recovery analysis to ensure that they can be inferred well given our experimental design and analysis pipeline (see Perdreau et al., 2019 for further details; here, bootstrapped parameter values were used). We determined to what extent the recovered parameter values could be predicted from the initial parameter values by means of linear regression analyses. The variance explained by the regression ($R^2$) was taken as an indicator of the validity of the Bayesian fitting procedure.

The model was furthermore evaluated by comparing the bias and variability obtained from fitting the cumulative Gaussian with the bias and variability data obtained through forwarding modeling using the parameter values resulting from the bootstrapping. As an indication of the quality of the model fits, the BIC (Schwarz, 1978; Raftery, 1995) was computed for both the full model fits and the psychometric fits (as a descriptive account of the data). The BIC for the psychometric fits included both head orientations, three frame forms, and all 15 frame orientations, resulting in 186 free parameters, to allow a comparison with the BIC values of the full model, which had seven free parameters for fitting the data of the square, and one free parameter for fitting the data of each squircle (hence nine free parameters in total). The BIC trades off the likelihood of a model given the data and the number of free parameters, following:

$$BIC = \ k \log(n) - 2\log(\hat{L}) \tag{4}$$

where $k$ is the number of free parameters, $n$ is the number of observations, and $\hat{L}$ is the maximum likelihood of the data given the model. The BIC is useful for comparing models which differ in the number of free parameters. Lower BIC values indicate a better fit. We also subjected the gain factors of the three frame forms (all except the circle) to a statistical comparison.

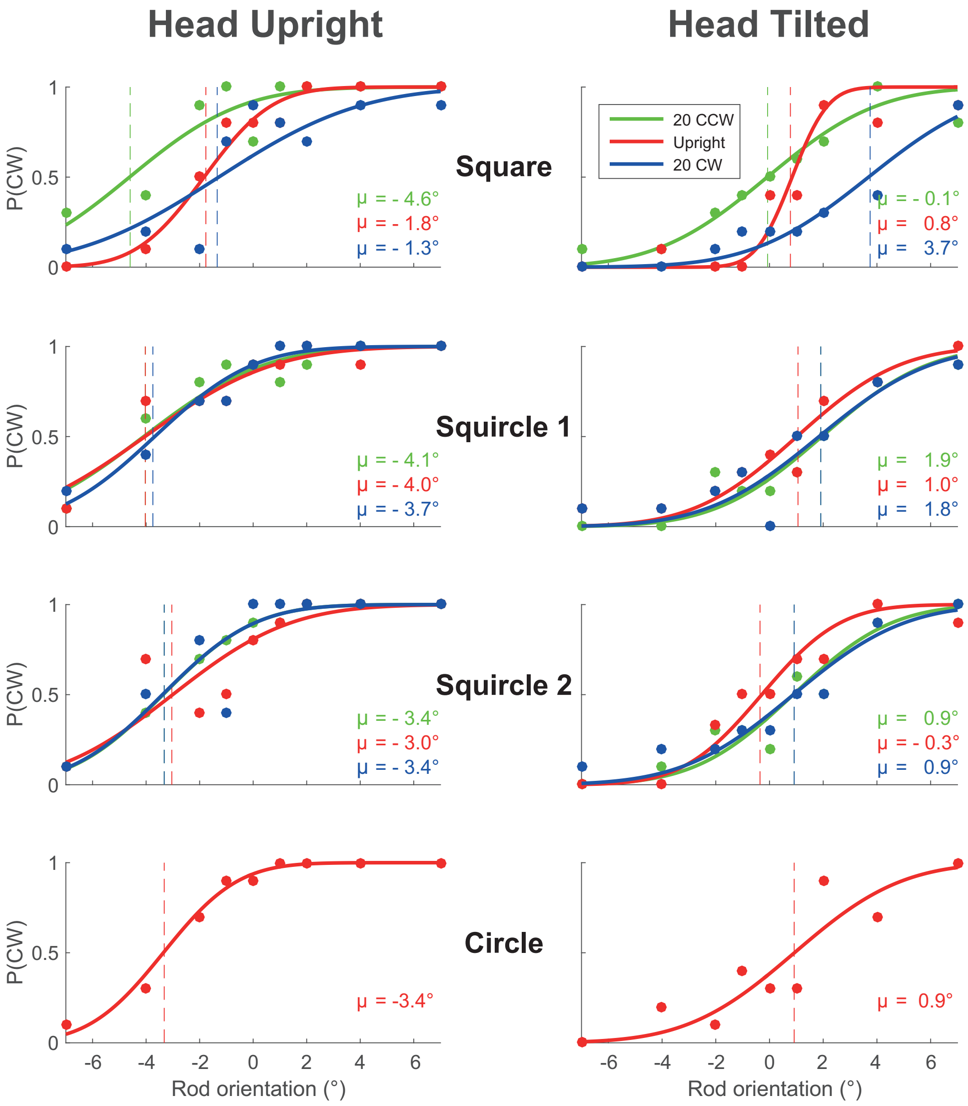

**FIGURE 2 |** The lines represent the psychometric curves that best fit the data of one of the participants. The raw data points (proportion of CW responses) are shown as circles. Panels on the left correspond to the head upright condition, to the right to the head tilted condition. The panels from top to bottom correspond to the used frame forms: square, squircle 1, squircle 2, and circle. The different colors represent different frame orientations (green, 20 degrees CCW; red, 0 degrees; blue, 20 degrees CW). CW, rotated clockwise; CCW, counterclockwise.

## RESULTS

**Figure 2** shows the data of a single participant as the proportion of CW responses at each rod orientation for the squared frame and the two squircles in three exemplar frame orientations: 20°CCW, 0° and 20°CW, and the circular frame, during the head upright (left) and head tilted (right) condition. We fitted psychometric curves based on the obtained bias and variability of the responses (see section "Materials and Methods"). In the first row, depicting data for a squared frame, three central characteristics of the RFE can be observed. First, the bias shifts with the orientation of the frame: the dotted red line, representing the point of subjective equality for the upright frame (i.e., the orientation of the rod for which an equal number of CW and CCW responses was given) is located to the right of the dotted green line, which represents the PSE for the 20° CCW-oriented frame, and to the left of the blue line, which represents the 20° CW frame. Second, the red curve is steeper than the blue and green curve, which indicates that the rod orientation estimate is more precise when the frame is upright rather than tilted. A third characteristic of the RFE can be found when comparing the upper left and the upper right panel, namely, that the PSE shifts with head tilt.

The effect of frame form on the RFE follows from the comparison among the different rows of panels. As shown, the shift in the PSE due to the frame orientation appears to be more substantial for the squared frame than for the two squircular frames, conform our expectation that the RFE is stronger for more square-like forms. Furthermore, the difference in steepness between the colored lines seems more pronounced in the square frame condition than in the squircular frame conditions. This is again in line with the expectation that the effect of the frame is stronger for squared compared to squircular frames.

**Figure 3** illustrates the observed and modeled PSE of the square-like frames as a function of frame orientation, as an average across participants. If the PSE is zero, the rod orientation judgments are unbiased, whereas, when the PSE is systematically off from zero, there is a bias. With a squared frame (upper panels), a clear cyclical pattern is visible in the measured bias, which is the classic observation about the RFE, the bias is negative for CCW-oriented frames and positive for CW frames. Furthermore, the modulation of the systematic error appears stronger when the head is tilted (panels on the right) compared to when the head was upright (panels on the left). The cyclical pattern seen with squared frames is reduced for squircle 1, and even more strongly so for squircle 2. In other words, the RFE appears to reduce with increasing roundness of the frame form, as predicted. The plots further show that tilting the head led to a larger bias in rod orientation judgments in the presence of the squircular frames.

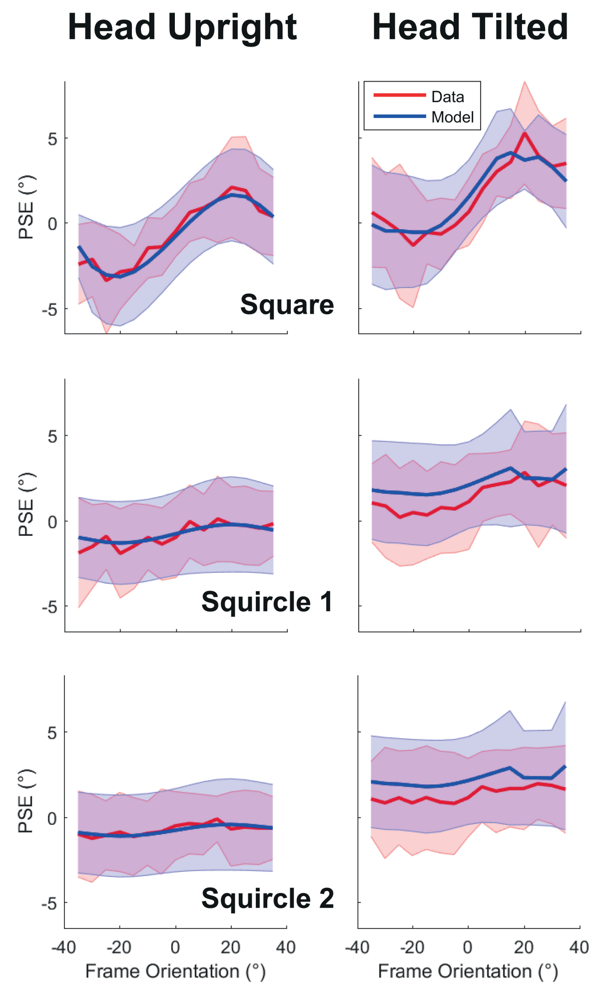

**FIGURE 3 |** Point-of-subjective equality as a function of frame orientation. Panels on the left correspond to the head upright condition, to the right to the head tilted condition. The panels from top to bottom correspond to the used frame forms: square, squircle 1, and squircle 2. Grand averages are plotted as lines, standard deviation over participants as shaded regions. In red the observed data, in blue the results of the best-fit model. PSE, point-of-subjective equality.

**Figure 3** further shows a relatively close overlap between the model and the data, suggesting that the model performed well in capturing the biases of the participants. The model fitted best for the systematic data from the square frame (mean BIC = 2,539), followed by squircle 1 (mean BIC = 2,903) and squircle 2 (mean BIC = 2,913). Moreover, the full model provided a better fit with the data than a purely descriptive account of the data (i.e., by fitting separate psychometric curves to the data, see **Table 1**).

**Figure 4** displays the observed and modeled variability for each frame form as a function of frame orientation. For the squared frame, a V-shaped pattern can be observed in the data with the lowest variability around upright, closely resembling earlier findings (Alberts et al., 2016; Niehof et al., 2019). Head tilt appeared to lead to a stronger modulation of variability by frame form. This was expected: an ideal observer should rely more strongly on frame orientation because the vestibular derived orientation cues are noisier when the head is tilted. Furthermore, as predicted, the impact of frame orientation decreases dramatically with increasing roundness of the frames, and the pattern in the variability data is flatter for squircles 1 and 2 than for the square. The model does not perfectly capture the trends in the observed response variability. The reason is that the model overestimates variance to allow some wiggle room for fitting the systematic error in the responses.

**Table 2** lists the bootstrapped derived parameter values (± SD) for each participant. The model was first fitted on the data of the squared frame, fitting both head tilt conditions simultaneously (see section "Materials and Methods"). While there is some variability across participants, on average the parameters ($\sigma_{HP}$, $\alpha_{HS}$, $\beta_{HS}$, $\sigma_{ver}$, $\sigma_{hor}$, and $\tau$) match fairly well with earlier reports (Clemens et al., 2011; Alberts et al., 2016). With these parameters

**TABLE 1 |** Delta BIC values ($BIC_{psy} - BIC_{full}$).

| Participant | Psychometric fits – Full model |
|---|---|
| P1 | 1,048 |
| P2 | 664 |
| P3 | 985 |
| P4 | −662 |
| P5 | 720 |
| P6 | 1,272 |
| P7 | 1,191 |
| P8 | −51 |
| P9 | 1,265 |
| P10 | 109 |
| P11 | 1,156 |
| P12 | 1,123 |
| Overall | 14,100 |

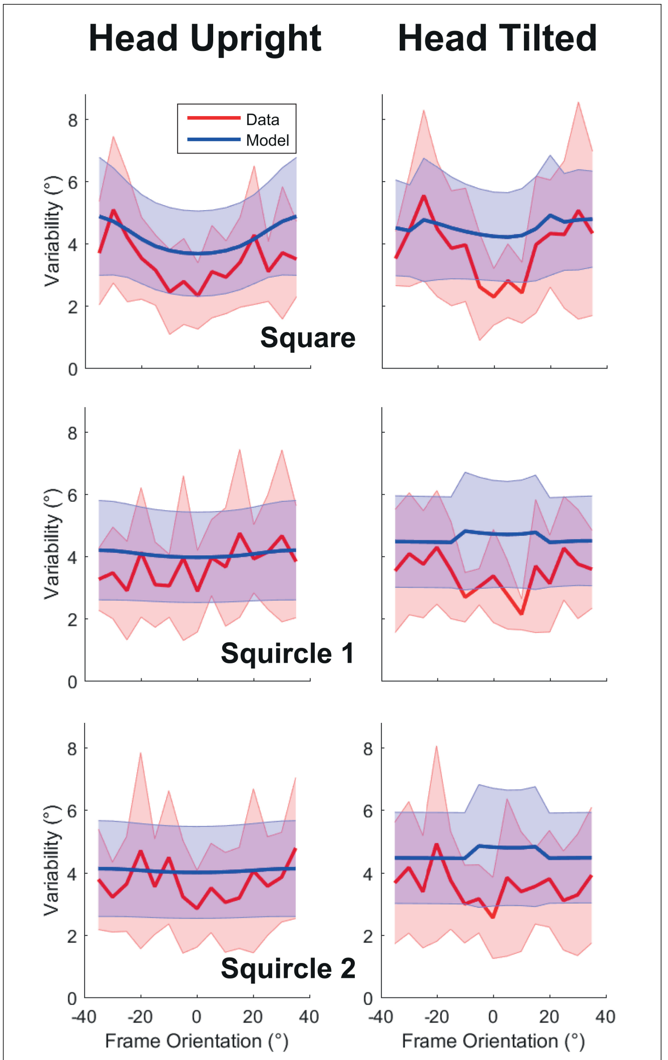

**FIGURE 4 |** Response variability as a function of frame orientation. Panels on the left correspond to the head upright condition, to the right to the head tilted condition. The panels from top to bottom correspond to the used frame forms: square, squircle 1, and squircle 2. Grand averages are plotted as lines, standard deviation across participants as shaded regions. In red are the observations, in blue, the results of the best-fit model.

established, we fitted the gain factors, $g_1$ for squircle 1 and $g_2$ for squircle 2, which scaled the variances in visual context probability distribution to that of the squared frame. While there was some variability across participants, the gain factor of squircle 1 was significantly larger than 1 ($M = 32.6$, $SD = 23.1$; $t(11) = 4.745$, $p = 0.001$; Cohen's $d = 1.4$), indicating that the variance of the visual context was higher for squircle 1 compared to the squared frame. In other words, rounding the square reduced the precision of the panoramic cue, as expected. Similarly, the gain factor was higher for squircle 2 compared to squircle 1 in 9 of the 12 participants, suggesting that rounding the frame has a parametric impact on panoramic cue precision.

Linear regression analyses were used to assess how closely the recovered parameter values matched the parameter values derived from the bootstrapping procedure. The variance explained ($R^2$) by the linear regression analyses ranged between 83 and 99% for the square frame. For the squircles, the explained variances were 38% (squircle 1) and 45% (squircle 2) for the gain factors (see **Table 2** for a complete list).

## DISCUSSION

In the current study, we manipulated frame form to investigate the impact of panoramic uncertainty on the vertical perception of a visually presented line. Orientation of the frame was found to (cyclically) bias the subjective visual vertical (SVV), and tilted frames were associated with larger variance in the responses, both indicative of a standard RFE. Furthermore, we replicated earlier findings on the effect of head tilt, demonstrating that roll-tilt of the head leads to a larger RFE. In addition to these replications, we found that rounder frame forms – which increase the uncertainty about the panoramic orientation – diminish the RFE. The modulation of the RFE by frame form was gradual in the sense that the intermediate steps from circle to square led step-by-step to a larger RFE.

With a squared frame, a clear RFE was observed, both in the bias and in the variability of the responses. When the frame was tilted leftward or rightward, the point of subjective equality was shifted, respectively, to the left or to the right, replicating many previous studies on the RFE (Witkin and Asch, 1948; see for a review: Medendorp et al., 2018). Responses to tilted frames were more variable than responses to the upright frame, in line with previous findings (Alberts et al., 2016; Niehof et al., 2019). Both effects, a bias and increased variance, were predicted based on the optimal Bayesian multisensory integration (MSI) account, which suggests that the prior experience of the observer that lines often match the cardinal axes will pull the vertical judgment toward the orientation of peripheral lines, and frame rotation leads to larger visual context uncertainty. Furthermore, congruent with optimal Bayesian MSI and in line with previous findings (DiLorenzo and Rock, 1982; Corbett and Enns, 2006; Vingerhoets et al., 2009; Alberts et al., 2016; De Winkel et al., 2021), the current study found a stronger RFE when participants had their head tilted by 30°compared to when they held their head upright.

Besides the classic SVV manipulations of varying the frame and head orientation, we manipulated frame form. The role of frame form on the RFE has historically been studied from the perspective of holistic processing in which different visual features could lead to the same gestalt (Koffka, 1935) and hence potentially to a similar RFE. The idea of the frame as a unitary stimulus, in terms of a gestalt, was reflected in the major axes hypothesis (Beh et al., 1971). According to this hypothesis, a major frame axis was defined as a line intersecting with the center of the frame which splits the frame into two symmetrical parts. The frame was thought to pull the vertical judgment of the rod by means of the major axis that was closest to the gravitational line. The major axes hypothesis was studied using triangular and hexagonal frames (Beh and Wenderoth, 1972). However, the

**TABLE 2 |** Parameter values of the model, including a measure of how well the parameter values could be recovered ($R^2$).

| Participant | $\sigma_{HP}$(°) | $\alpha_{HS}$ (°/°) | $\beta_{HS}$(°) | $\sigma_{ver}$ (°) | $\sigma_{hor}$(°) | $\tau$ | $\lambda$ | $g_1$ | $g_2$ |
|---|---|---|---|---|---|---|---|---|---|
| P1 | 19.2 ± 2.9 | 0.31 ± 0.04 | 5.6 ± 1.5 | 4.9 ± 1.1 | 159 ± 41 | 0.75 ± 0.05 | 0.06 ± 0.05 | 1.6 ± 0.0 | 2.0 ± 0.0 |
| P2 | 3.9 ± 0.3 | 0.00 ± 0.00 | 3.4 ± 0.3 | 5.3 ± 2.1 | 159 ± 48 | 0.76 ± 0.13 | 0.04 ± 0.02 | 47.8 ± 19.3 | 57.4 ± 5.3 |
| P3 | 8.1 ± 0.8 | 0.00 ± 0.00 | 6.2 ± 0.8 | 107.4 ± 71.2 | 33 ± 52 | 0.75 ± 0.38 | 0.07 ± 0.05 | 53.8 ± 13.4 | 14.9 ± 12.6 |
| P4 | 4.4 ± 0.4 | 0.05 ± 0.01 | 2.5 ± 0.4 | 2.8 ± 1.1 | 127 ± 57 | 0.71 ± 0.03 | 0.11 ± 0.02 | 45.1 ± 25.0 | 47.4 ± 24.0 |
| P5 | 7.4 ± 0.6 | 0.01 ± 0.01 | 4.1 ± 0.4 | 7.8 ± 1.6 | 92 ± 63 | 0.84 ± 0.10 | 0.04 ± 0.02 | 8.8 ± 11.8 | 12.6 ± 14.3 |
| P6 | 16.8 ± 2.4 | 0.00 ± 0.00 | 7.8 ± 0.9 | 22.0 ± 6.1 | 124 ± 66 | 0.54 ± 0.37 | 0.14 ± 0.04 | 11.4 ± 14.5 | 13.8 ± 12.3 |
| P7 | 13.4 ± 3.6 | 0.07 ± 0.03 | 5.1 ± 0.7 | 8.7 ± 0.8 | 97 ± 58 | 0.76 ± 0.15 | 0.12 ± 0.05 | 59.2 ± 2.3 | 55.4 ± 5.7 |
| P8 | 6.2 ± 0.5 | 0.04 ± 0.02 | 3.7 ± 0.6 | 6.6 ± 2.0 | 119 ± 75 | 0.75 ± 0.15 | 0.15 ± 0.01 | 45.4 ± 20.2 | 50.9 ± 17.1 |
| P9 | 7.8 ± 0.5 | 0.01 ± 0.01 | 3.1 ± 0.2 | 7.0 ± 0.9 | 19 ± 28 | 0.97 ± 0.08 | 0.02 ± 0.01 | 7.8 ± 13.5 | 4.4 ± 8.5 |
| P10 | 7.5 ± 0.8 | 0.00 ± 0.01 | 7.8 ± 1.1 | 8.7 ± 1.7 | 164 ± 27 | 0.75 ± 0.12 | 0.15 ± 0.00 | 47.1 ± 11.5 | 48.5 ± 7.7 |
| P11 | 6.1 ± 0.7 | 0.07 ± 0.01 | 2.6 ± 0.4 | 4.2 ± 1.7 | 143 ± 58 | 0.78 ± 0.11 | 0.11 ± 0.03 | 57.5 ± 5.1 | 58.9 ± 3.2 |
| P12 | 8.1 ± 0.7 | 0.06 ± 0.03 | 5.3 ± 1.0 | 6.1 ± 1.1 | 175 ± 3 | 0.80 ± 0.05 | 0.06 ± 0.03 | 5.7 ± 10.3 | 7.0 ± 10.6 |
| Mean ± *SD* | 9.1 ± 1.2 | 0.05 ± 0.02 | 4.8 ± 0.7 | 16.0 ± 7.6 | 118 ± 48 | 0.76 ± 0.14 | 0.09 ± 0.03 | 32.6 ± 12.2 | 31.1 ± 10.1 |
| $R^2$ | 0.985 | 0.993 | 0.975 | 0.948 | 0.987 | 0.825 | 0.823 | 0.382 | 0.451 |

idea of the frame functioning as a unitary stimulus was later abandoned as illusory shapes did not necessarily evoke an RFE (Ebenholtz, 1985), and independent lines (Li and Matin, 2005a,b; Vingerhoets et al., 2009) could function as visual context as well. As such, a frame is a specific instantiation of a set of peripheral lines that provide panoramic information about orientation. Frame form can thus affect the RFE not necessarily as a unitary stimulus, but through the degree to which its components have a clear orientation that can be mapped onto the cardinal axes (van der Schaaf and van Hateren, 1996; Coppola et al., 1998; Girshick et al., 2011).

Here, the employed frame form manipulation functioned as a means to alter the uncertainty of the orientation cue provided by the visual context. Reasoning from a Bayesian MSI account, a more uncertain visual cue should be assigned less weight in the head-in-space estimate and hence lead to a smaller impact on the visual context. This was indeed found. First, the results showed that increasing roundness reduced the RFE. Second, the modeling demonstrated that the rounder frame forms led to a larger panoramic uncertainty, as the gain factor was larger than one for both squircles. This indicates that the variability parameters belonging to the visual context were larger for the squircular frames compared to the squared frame. Indeed, for 9 of the 12 participants, the gain factor was higher for the rounder squircle compared to the more square-like squircle. In close connection, the study by Alberts et al. (2016) demonstrated that increased viewing distance could be modeled as an increase in visual context uncertainty through ramping up the gain factor. However, the reduced RFE for larger viewing distances that they found could be the result of uncertainty about the frame orientation, the rod orientation, or both. To address part of this issue, Pomante et al. (2019) showed that manipulating the orientation uncertainty of the central stimulus – ellipses with various eccentricities were used instead of rods – does not affect the bias in an ellipse-in-frame task, indicating that the central stimulus does not interact with the frame in global visual processing. These findings suggested that the result from Alberts et al. (2016) was probably indeed the result of increased uncertainty about the frame orientation and not about the rod. The current empirical and model findings provide further support that uncertainty about the orientation of the visual context impacts the perception of the earth vertical.

In terms of the model fits, the present model fitted the data better than a model-free description based on psychometric fits (ΔBIC across all subjects, **Table 1**). The model fit could likely be improved by measuring a larger range of rod orientations. **Figure 2** indicates that the currently used range of rod orientations may have been too restricted. In earlier work using the same model, the same (−7 to 7°; Alberts et al., 2016), but also larger ranges have been utilized (−12 to 12°, Alberts et al., 2019; −15 to 15°, Alberts et al., 2018). Here, we opted for a restricted range to allow us to measure all four frame forms under a specific head orientation within one measurement session, accepting the limitations that come with such a restricted range.

A large part of the current study forms a replication of earlier work. Applying the same model to data collected under the same conditions led to parameter values within the same range as the earlier studies (Clemens et al., 2011; Alberts et al., 2016, 2018, 2019), emphasizing the robustness of the model, and replicability of the observed effects. The condition of interest, such as the manipulation of panoramic reliability with the use of squircular frames, was captured in the model by the gain parameter. While Alberts et al. (2016) reported an average gain of 1.31, we reported an average gain of 32.6 and 31.1, respectively, for squircles 1 and 2. These higher gain factors indicate that the uncertainty about the orientation of the visual context can more effectively be altered by changing the roundness of the frame form than by increasing the viewing distance. Large individual differences were observed in the gain factors, which may be a direct result of the large individual differences in $\sigma_{vert}$ and $\sigma_{hor}$, which accounted for the reliability of the vertical and horizontal context information, respectively. Alberts et al. (2016) also observed large individual differences in these measures, with $\sigma_{vert}$ ranging between 1.8 and 10.2° and $\sigma_{hor}$ ranging between 30.2 and 104.6°. It could be argued that some individuals are more sensitive to visual context than others, in line with findings going back even to the early work of Witkin and Asch (1948). Indeed, older people, whose vestibular system is less sensitive than that of younger people, have been found to rely more strongly on a visual context in the rod-and-frame task (Alberts et al., 2019), which led to higher in $\sigma_{vert}$ and $\sigma_{hor}$ values in the model. Future research could reveal whether the impact of turning a square into a squircle is larger for the elderly or other populations experiencing vestibular loss.

The degree to which a sensory signal weighs into the final percept depends on its reliability, and on the reference frame of the task (Clemens et al., 2011, see also De Winkel et al., 2021). The maximum bias induced by the visual frame was 9.8°, comparable to the maximum bias observed by De Winkel et al. (2021). However, there were substantial individual differences [the smallest bias we observed was 1.9° (*SD* = 2.0°)], which are also reflected in the individual differences in sensory weights (see also Alberts et al., 2018, 2019). The weight of the prior on head orientation ranged between 0.03 and 0.38 (Mean = 0.20), the visual weight ranged between 0 and 0.47 (Mean = 0.24), and the vestibular weight ranged between 0.32 and 0.74 (Mean = 0.57). These values are very comparable to the weights found by Alberts et al. (2018, 2019). With increasing roundness of the frame, the prior on head orientation gained slightly in weight, the vestibular weight increased and the visual weight decreased. Although the size of these changes varied between participants, the pattern was found in every individual.

Our findings provide further evidence for the notion that vertical perception is the result of Bayes-optimal MSI, in which weights are assigned to each cue relative to its reliability. In the real world, the visual context often contains many lines and polarity cues, and hence as a next step, we propose to investigate how visual context reliability as assessed by the model relates to the orientation of a multitude of line segments in the periphery. If the context solely consists of randomly oriented lines, it no longer can function as head orientation, and hence a verticality cue, and thus will have a reliability of zero. If the context purely consists of vertical lines, its reliability as a verticality cue is maximal but will decrease if more randomly oriented lines are intermixed.

To conclude, the current study demonstrated that panoramic uncertainty, manipulated through changes in frame form, altered the RFE. The RFE bias was stronger for a fairly square-like squircle compared to a rounder squircle, and a regular square had a stronger impact than both squircles. The weaker the orientation cues conveyed by visually presented abstract frame form, the smaller the impact of this visual context on vertical judgments of a visual line, congruent with the Bayesian ideal observer model.

## DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in an online repository. The name of the repository and accession number can be found below: https://doi.org/10.34973/kbzc-ng08.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee Social Science, Radboud University Nijmegen. The participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

JCS and WPM: conceptualization, methodology, and modeling. JCS: data collection, analyses, and writing – original draft. WPM: writing – review and editing. Both 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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REVIEW
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# Watching the Effects of Gravity. Vestibular Cortex and the Neural Representation of “Visual” Gravity

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Gravity is a physical constraint all terrestrial species have adapted to through evolution. Indeed, gravity effects are taken into account in many forms of interaction with the environment, from the seemingly simple task of maintaining balance to the complex motor skills performed by athletes and dancers. Graviceptors, primarily located in the vestibular otolith organs, feed the Central Nervous System with information related to the gravity acceleration vector. This information is integrated with signals from semicircular canals, vision, and proprioception in an ensemble of interconnected brain areas, including the vestibular nuclei, cerebellum, thalamus, insula, retroinsula, parietal operculum, and temporo-parietal junction, in the so-called vestibular network. Classical views consider this stage of multisensory integration as instrumental to sort out conflicting and/or ambiguous information from the incoming sensory signals. However, there is compelling evidence that it also contributes to an internal representation of gravity effects based on prior experience with the environment. This *a priori* knowledge could be engaged by various types of information, including sensory signals like the visual ones, which lack a direct correspondence with physical gravity. Indeed, the retinal accelerations elicited by gravitational motion in a visual scene are not invariant, but scale with viewing distance. Moreover, the “visual” gravity vector may not be aligned with physical gravity, as when we watch a scene on a tilted monitor or in weightlessness. This review will discuss experimental evidence from behavioral, neuroimaging (connectomics, fMRI, TMS), and patients’ studies, supporting the idea that the internal model estimating the effects of gravity on visual objects is constructed by transforming the vestibular estimates of physical gravity, which are computed in the brainstem and cerebellum, into internalized estimates of virtual gravity, stored in the vestibular cortex. The integration of the internal model of gravity with visual and non-visual signals would take place at multiple levels in the cortex and might involve recurrent connections between early visual areas engaged in the analysis of spatio-temporal features of the visual stimuli and higher visual areas in temporo-parietal-insular regions.

**Keywords: internal model, vestibular network, neuroimaging, TMS, connectomics, psychophysics, insula, temporo-parietal junction (TPJ)**

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# INTRODUCTION

Gravity represents a physical invariant of the Earth environment to which all species, including ours, have adapted through evolution. A clear exemplification of such adaptation is represented by the lack of conscious effort with which gravity effects are taken into account when controlling most motor behaviors, ranging from the seemingly simple task of maintaining balance during gait to the complex motor skills performed by professional athletes, acrobats, and ballet dancers. Moreover, gravity cues provide an absolute spatial reference, crucial for navigation and, more generally, for spatial perception (Jeffery et al., 2013; Angelaki et al., 2020). Information about gravity is relayed to the Central Nervous System (CNS) by multiple sensory sources, namely, the vestibular organs, the retina, skin, muscle, tendon, and visceral receptors (Mittelstaedt, 1992). In particular, vestibular otolith organs (saccule and utricle) are considered the main graviceptors. Hair cells in the neuroepithelium of their maculae are stimulated by gravito-inertial accelerations, thereby signaling head accelerations due to linear inertial motion as well as to changes of head orientation relative to gravity (Fernández and Goldberg, 1976). Remarkably, this ambiguity about the nature of the accelerative force inherent to the otoliths' afferent signals is tackled early in the processing of vestibular information. In fact, during dynamic head tilts, gravito-inertial accelerations signaled by the otoliths can be disambiguated by filtering the otolith signals (Mayne, 1974) and/or combining them with signals from the semicircular canals in the vestibular nuclei and the cerebellum (Glasauer, 1992; Angelaki et al., 1999; Merfeld et al., 1999; Mackrous et al., 2019). Thus, Purkinje cells in the caudal vermis integrate otolith and semicircular canal inputs during passively applied self-motion (see Angelaki and Cullen, 2008). A subset of these neurons represents head orientation relative to gravity, whereas another subset preferentially encodes translational self-motion (Laurens et al., 2013). The gravity-driven responses are canceled for self-generated movements, indicating that the brain builds a dynamic prediction of the sensory consequences of gravity to ensure postural and perceptual stability (Mackrous et al., 2019). Information from the vestibular nuclei and cerebellum is relayed and processed in several regions of the brain and spinal cord, giving rise to sensations and movements (Angelaki and Cullen, 2008).

Although vestibular signals may be combined with visual and somatosensory information as early as in the vestibular nuclei (Waespe and Henn, 1978; Carleton and Carpenter, 1983; Büttner-Ennever, 1992; Barmack, 2003; Shinder and Taube, 2010; Cullen, 2012), vestibular only neurons, projecting from the vestibular nuclei to the thalamus/cortex, do not receive under normal conditions visual and/or somatosensory inputs. These latter inputs, however, can be un-masked along with efference copy signals after labyrinthectomy (Cullen et al., 2009; Sadeghi et al., 2009, 2011, 2012). Instead, more extensive multisensory integration takes place at a higher processing level, within several interconnected subcortical structures (such as the thalamus) and cortical areas around the sylvian sulcus, namely, the insula, the retroinsula, the parietal operculum, the temporo-parietal junction, forming the so-called vestibular network (Guldin and Grüsser, 1998; Lopez and Blanke, 2011). One particular functional aspect of the multisensory integration process occurring in the vestibular network, which the present review article will focus on, is inherent to the notion that visual, as well as somatosensory signals, can embed information about gravity. In this respect, the contribution of the somatosensory system to graviception can be inferred by considering the upright stance condition where the effects of gravity on the body determine the distribution of pressure forces on the feet soles, sensed by cutaneous receptors, and that of limb extensor muscles loads, sensed by Golgi Tendon Organs. On the contrary, for the visual system, there are several factors that make extracting gravity-related information from retinal signals a less straight-forward process. First, despite the fact that gravitational acceleration is quasi-constant on Earth (its magnitude varies by $<1\%$ and its vertical deflection by $<0.05°$ at different latitudes or altitudes), retinal accelerations elicited by visual targets moving along the fronto-parallel plane under gravity are hardly constant since they scale inversely with viewing distance. Secondly, for motion-in-depth, such as when an object accelerated by gravity approaches the viewer (i.e., projectile motion), the retinal speed (rate of change of image size, elevation, and disparity) is related non-linearly to the object speed in world coordinates. Thirdly, besides differences in magnitude between physical and retinal accelerations, the direction of "visual" gravity is not invariably aligned with that of physical gravity, as in the case of watching a scene on a tilted monitor or in weightlessness. Finally, as a further complication, the visual system is poorly sensitive to arbitrary accelerations, especially over short time windows (Bennett et al., 2007). Thus, for both fronto-parallel motion (Werkhoven et al., 1992; Brouwer et al., 2002) and motion in depth (Trewhella et al., 2003; Lee et al., 2019), the Weber fractions of acceleration discrimination (i.e., the ratio of just noticeable difference to the absolute value of acceleration, and thus a measure of perceptual precision) are more than five times worse than those of speed discrimination.

Unsurprisingly, the motor system generally does not account well for arbitrary visual accelerations, as shown by manual interceptive responses to targets moving along a horizontal line with different positive or negative accelerations (Port et al., 1997; Benguigui et al., 2003) or by ocular tracking responses to accelerated targets (Bennett and Barnes, 2006). In these situations, spatial and temporal errors tend to be relatively small for low accelerations but increase steeply with increasing accelerations. It is worth noting that the motion accelerations imposed to the visual targets in these experiments were considerably lower than the gravity acceleration and, by extrapolating these results, one might expect timing errors of about 400 ms for targets accelerated by gravity!

However, people exhibit remarkable accuracy and precision when interacting with targets accelerated by gravity. In fact, small timing and spatial errors are generally observed when subjects catch or punch a ball in free-fall from different heights (Lacquaniti and Maioli, 1989; Zago et al., 2004, 2011a,b; Indovina et al., 2005; Katsumata and Russell, 2012; Brenner and Smeets, 2015) or approaching in projectile motion (Russo et al., 2017). Interestingly, the greater accuracy at intercepting targets accelerated by gravity is also evident when a substantial portion of the target path is occluded from vision, implying that visual extrapolation mechanisms take into account natural gravity effects on objects' motion (Bosco et al., 2012; La Scaleia et al., 2015). Alike manual interception studies, ocular tracking experiments have shown significantly greater accuracy following target motion modeled according to natural kinematics (gravity and air drag) compared to arbitrary kinematics (hypo- or hypergravity; Diaz et al., 2013a,b; Delle Monache et al., 2015, 2019; Jörges and López-Moliner, 2019; Meso et al., 2020). Visual effects of gravity are taken into account, although with variable precision (see below), also in perceptual tasks that do not necessarily involve the production of motor response timed to the target motion, such as the discrimination of motion duration for targets shifting along the vertical (Moscatelli and Lacquaniti, 2011; Torok et al., 2019; Gallagher et al., 2020), time-to-passage estimation during virtual self-motion (Indovina et al., 2013a), visuomotor synchronization (Zhou et al., 2020), naturalness judgments of motion under gravity (La Scaleia et al., 2014, 2020; Ceccarelli et al., 2018), speed discrimination of targets moving in different directions (Moscatelli et al., 2019), and interpretation of biological motion (Chang and Troje, 2009; Maffei et al., 2015).

How does the visual system account for gravity acceleration, given that image accelerations are poorly discriminated (see above)? According to a current hypothesis, an internal model mimics the expected gravity effects on visual targets (Lacquaniti and Maioli, 1989; Tresilian, 1997; Zago et al., 2008, 2009; Lacquaniti et al., 2013, 2014, 2015; Jörges and López-Moliner, 2017). Compatible with this idea, erroneous expectations of Earth's gravity effects are evident in the timing of interceptive responses to visual targets moving vertically downward at a constant speed, due to either real weightlessness in a spacelab (McIntyre et al., 2001) or simulated weightlessness in the laboratory (Zago et al., 2004; Bosco et al., 2012; Russo et al., 2017; La Scaleia et al., 2020). These findings suggest that the brain is able to build an *a priori* knowledge of gravity effects based on innate mechanisms and/or learning with daily experience. Thus, in order to produce accurate response timing when intercepting targets accelerated by gravity, this internal model of gravity effects is combined with online visual signals about the target position and velocity (Zago et al., 2008, 2009; Lacquaniti et al., 2013, 2014, 2015). Moreover, in order to map visual information between retinal and world coordinates, the visual effects of gravity on a moving target can be interpreted by combining information about the rate of change of retinal image with binocular (stereo, vergence) and monocular (familiar size, vertical and horizontal scene contours, perspective, shading, texture gradient, lighting, etc) cues (Zago et al., 2009).

We mentioned earlier that the direction of visual gravity is not always coincident with that of physical gravity. Some insight on how this discrepancy is dealt with has come from the work of Zago et al. (2011a). This study manipulated the alignment between the visual gravity vector and stationary visual cues, as well as relative to the orientation of the observer and of the physical gravity vector. Participants pressed a button, which triggered a hitter to intercept targets moving with constant acceleration, scaled to the visual scene so as to be congruent with Earth gravitational acceleration. A factorial design assessed the effects of scene orientation (normal or inverted) and target gravity (normal or inverted). Interception scores were significantly higher when scene direction was concordant with target gravity direction, irrespective of whether both were upright or inverted (**Figure 1A**). Therefore, the combined influence of visible gravity and structural visual cues can outweigh both physical gravity and viewer-centered cues, yielding to rely instead on the congruence of the apparent physical forces acting on people and objects in the represented visual scene. In another study (Moscatelli and Lacquaniti, 2011), observers judged the duration of motion of a target accelerating over a fixed length path in one of the different directions. The visual motion was presented to participants either over a pictorial scene or a uniform background and while either standing upright or tilted by 45° relative to the computer display and Earth's gravity. In another experimental condition, observers were upright and the scene was tilted by 45°. Results of these experiments indicated again that the effects of virtual gravity can be represented with respect to a pseudo-vertical direction concordant with the visual scene orientation and discordant with the direction of Earth's gravity (**Figures 1B,C**). By applying the model of the vision group at York University (Jenkin et al., 2004; Dyde et al., 2006) to their data, Moscatelli and Lacquaniti (2011) found that a weighted sum of the observer orientation, target motion orientation, and pictorial scene orientation relative to physical gravity could account for the estimated downward of visual gravity, with weighing coefficients of 43, 37, and 20%, respectively. These weightings, however, vary considerably as a function of the specific task and context.

Current evidence indicates that the internal model of gravity effects is qualitative and does not comply with physics exactly. Indeed, as mentioned above, people systematically underestimate the motion duration of constant speed targets descending along the vertical and activate their arm muscles too early to intercept them (McIntyre et al., 2001; Zago et al., 2004). The precision of perceptual judgments of the duration of parabolic motions is independent of whether the target moves according to natural gravity or it shifts at a constant speed (Jörges et al., 2021). A general heuristic that assumes that descending targets or moving as projectiles are affected by gravity might provide information that is generally good enough while requiring much less cognitive processing or visual resources than exact models of physics (Zago et al., 2008; Vicovaro et al., 2021). However, as remarked above, motor actions on targets accelerated by gravity can be strikingly accurate, presumably because of the integration with online sensory information about target motion.

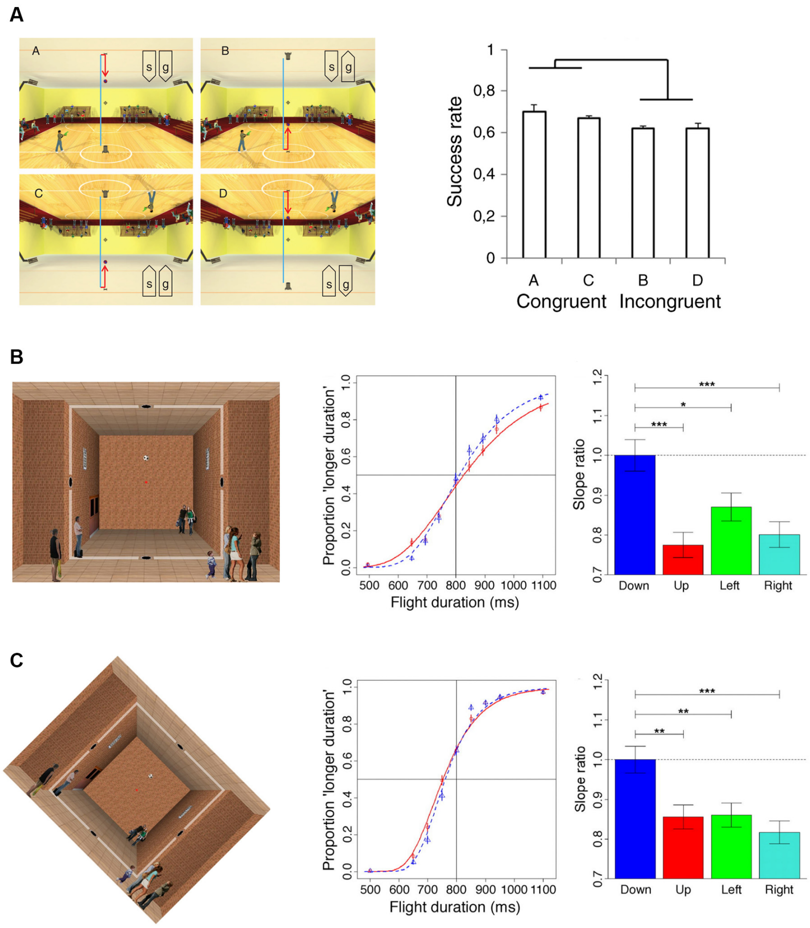

**FIGURE 1 |** Results of psychophysical experiments manipulating the direction of the "visual" gravity vector relative to physical gravity. **(A)** The four panels on the left side illustrate the scenarios (indicated with "a", "b", "c", "d") employed in Experiment 1 of Zago et al. (2011a). A ball was launched vertically and bounced back hitting the opposite side. The ball decelerated until bouncing (blue trajectory), and then it accelerated (red trajectory). Participants pressed a button to trigger the standing character to shoot a bullet to hit the ball at the interception point (indicated by the crosshair). The orientation of the scene ("s") and the direction of the simulated gravity acting on the target ("g") were manipulated in different blocks of trials: (upper left, scenario "a") normal scene orientation and gravity, (upper right, scenario "b") normal scene orientation but inverted target gravity, (lower left, scenario "c") both scene and gravity were inverted, and (lower right, scenario "d") inverted scene and normal target gravity. The panel on the right side illustrates the interception scores (success rates) observed for the four scenario conditions described above. **(B)** The leftmost panel illustrates the background scene and the visual target of Experiment 1 of Moscatelli and Lacquaniti (2011). The soccer ball moved at constant acceleration between two holes located on opposite sides of the room and, in different blocks of trials, along four possible directions: downward, upward, rightward, or leftward. Ball kinematics was congruent with the effects of gravity only in the downward direction. Participants maintained fixation throughout the trial on the red dot at the center of the scene. The middle panel illustrates the psychometric functions for downward (blue) and upward motion (red), obtained by pooling data of the seven participants of Experiment 1. The rightmost panel shows the precision of discrimination for the four directions of motion quantified by the slope of a Generalized linear mixed model fitted to the subject population data. Slopes were normalized to the values obtained for the downward direction. Error bars refer to ± 1 SD; ***, ** and * denote significant differences at $p < 0.001$, $p < 0.01$ and $p < 0.05$ level, respectively. **(C)** The leftmost panel illustrates the visual scene used for Experiment 6 of Moscatelli and Lacquaniti (2011), which was identical to Experiment 1, except for the 45 degrees clockwise rotation of the computer display. The middle and rightmost panels illustrate the results of this experiment with the same format as the corresponding panels in **(B)**.

## BEHAVIORAL EVIDENCE ABOUT VESTIBULAR AND SOMATOSENSORY CONTRIBUTIONS TO MODELING THE EFFECTS OF GRAVITY ON VISUAL TARGET MOTION

In line with the principle, visual processing of gravitational motion could be independent of the vestibular and somatosensory processing of physical gravity. There is, however, behavioral evidence that this is not the case, since vestibular and somatosensory cues about the head and body orientation help construct a gravity reference for intercepting visual targets. A number of studies have shown that the participant's posture relative to gravity direction contributes to providing a sense of Up and Down in the interception of targets moving along the vertical (Senot et al., 2005; Le Séac'h et al., 2010; Baurès and Hecht, 2011). In these studies, subjects intercepted a ball approaching from above or below in a virtual scene presented with a head-mounted stereoscopic display. Above (below) was obtained in sitting subjects (Senot et al., 2005) who pitched the head backward (forward) so as to look up (down) toward a virtual ceiling (floor), or in lying subjects (Le Séac'h et al., 2010; Baurès and Hecht, 2011) who looked up (down) while supine (prone). Interception responses were significantly earlier for downward than upward moving targets, consistent with an expectation that downward motion is faster than upward motion under gravity (Senot et al., 2005; Le Séac'h et al., 2010; Baurès and Hecht, 2011). This expectation is naïve because it violates Newtonian mechanics, according to which downward and upward displacements under gravity along a given vertical path have the same duration (in fact, with air resistance, upward is actually faster than downward motion, Timmerman and van der Weele, 1999). Interestingly, also targets shifting downward at constant speed are perceived as moving faster than the same targets moving at the same speed upward or rightward (Moscatelli et al., 2019).

A direct role for vestibular inputs has been shown with parabolic flight experiments where upward and downward motion were tested in weightlessness and on the ground. These experiments showed that the response bias (i.e., earlier responses for downward compared to upward motion) reversed sign between the weightlessness and the ground condition, mirroring the sign reversal of otolith signals at the transition from the hypergravity to the hypogravity phase of the parabolic flight (Senot et al., 2012). Moreover, sound-evoked stimulation of the otolith receptors interferes with the anticipation of gravity effects during visually simulated self-motion in the downward direction (Indovina et al., 2015), and unloading of the otoliths in the weightless conditions of space flight affects Up/Down asymmetries in the perception of self-motion (De Saedeleer et al., 2013).

A quantitative assessment of the role of vestibular and somatosensory cues about the head and body orientation on interception timing was reported by La Scaleia et al. (2019). In their experiment, participants hit a ball rolling in a gutter towards the eyes, resulting in image expansion. The scene was presented in a head-mounted display, without any visual information about gravity direction. In separate blocks of trials, participants were pitched backwards by 20° or 60°, while ball acceleration was randomized across trials to be compatible with rolling down a slope of 20° or 60°. Initially, the timing errors were large, independent of the coherence between ball acceleration and pitch angle, consistent with responses based exclusively on visual information (since visual stimuli were identical at both tilts). At the end of the experiment, however, the timing errors were systematically smaller in the coherent conditions than the incoherent ones. Therefore, practice with the task led to the incorporation of information about head and body orientation relative to gravity for response timing. Such information could have been extracted by combining signals from at least two sources: (1) the background activity and dynamic sensitivity of otolith regular afferents, which are related to the component of the gravitational shear force acting in the plane of the maculae, changed by the static head tilt; and (2) signals from somatosensory (cutaneous, muscle, and tendon) and visceral receptors (in the kidneys, vena cava), which monitor contact forces between the body and the environment, thereby contributing a sense of body orientation.

Visual gravity and information about the actual body posture interact to provide a gravity reference. Purely visual cues from the inclination of the support surface in virtual reality induce locomotor adaptations to counter expected gravity-based changes similar to what happens with real inclinations (Cano Porras et al., 2019). When the task requires aligning a visual line to the vertical in the dark, the so-called subjective visual vertical or SVV (Lacquaniti et al., 2015; Kheradmand and Winnick, 2017), the direction of gravity is estimated by combining retinal cues about the line orientation with vestibular and somatosensory cues about the head and body orientation, plus the prior assumption of an upright head orientation (Mittelstaedt, 1983; Bringoux et al., 2003, 2004; Dyde et al., 2006; MacNeilage et al., 2007; De Vrijer et al., 2008; Zago, 2018).

Observers typically present a strong bias toward the direction of body rotation in estimating the orientation of a visual bar when their body is tilted >60° in the roll plane and in the absence of visual background information (the A-effect, Aubert, 1861). This deviation of SVV results from the under-compensation of body tilt (Van Beuzekom and Van Gisbergen, 2000). A static visual reference frame can reduce such bias in the perceived vertical (Haji-Khamneh and Harris, 2010). Moreover, also dynamic information about visual motion can reduce the bias contributing to SVV estimates. In one experiment, observers were presented with projectile motions of a visual target along parabolic trajectories with different orientations relative to physical gravity (Balestrucci et al., 2021). Participants were either upright or lying horizontally on their sides. When they were tilted, the bias in SVV was significantly reduced following the interception of parabolas aligned with the physical vertical.

Finally, vestibular stimulation resulting from increases of the gravito-inertial force (up to 1.4 *g*) with a short-radius centrifuge disrupts the time course of representational gravity, that is, the phenomenon in which the remembered vanishing location of a moving target is displaced downward in the direction of gravity, and more so with increasing retention intervals (De Sá Teixeira et al., 2017).

## A NEURAL REPRESENTATION OF "VISUAL" GRAVITY IN THE VESTIBULAR CORTEX

The evidence that somatosensory and vestibular signals can influence the visual perception of gravity-related information, raises the issue about the nature of the multimodal processing of sensory information taking place in the vestibular network. Until not long ago, the common view was that multisensory integration in the vestibular cortex would help resolve the ambiguities in the sensory signals. This could be instrumental to several higher-level processes afforded by vestibular information, such as spatial navigation, learning, and memory (Taube et al., 1996;

Brandt et al., 2005; Taube, 2007; Gurvich et al., 2013; Smith and Zheng, 2013; Cullen and Taube, 2017), perceptual and motor decision making (Medendorp and Selen, 2017), mental imagery and mental rotation (Mast et al., 2006, 2014; Falconer and Mast, 2012), or bodily self-consciousness (Lopez, 2015, 2016).

Results of recent studies combining psychophysical and neuroimaging approaches have provided a complementary perspective on the function of the vestibular cortex by suggesting that multisensory processing in the vestibular network is directly concerned with gravity-related information. In an early study, Indovina et al. (2005) asked participants undergoing functional MRI scanning to perform a manual interception task with moving targets either congruent or not with natural gravity. Subjects' interception timing was compatible with the use of *a priori* knowledge of gravity effects on the target motion (see above), and, most interestingly, fMRI data showed that visual targets congruent with natural gravity engaged preferentially cortical areas belonging to the vestibular network, as assessed by intersecting the statistical activation maps resulting from the contrast between the fMRI activations for natural and non-natural gravity with those obtained following vestibular caloric stimulation (**Figure 2A**). This result represented the first evidence that vestibular cortex activity can reflect processing of an internal representation of gravity effects on visual motion. Subsequent studies confirmed this result by integrating the visual paradigm used in Indovina et al. (2005) with manipulations of the visual background (Miller et al., 2008) and with apparent motion stimuli (Maffei et al., 2010). Two other studies by the same group extended the evidence to visual processing of self-motion, by showing that vestibular network areas could be activated, during visually simulated rollercoaster rides, by vertical motion congruent with gravity (Indovina et al., 2013b), as well as during a path integration task employing the same rollercoaster visual stimulation (Indovina et al., 2016). Finally, significant preferential activations of the posterior insular cortex have been reported for vertical compared to horizontal hand movements, particularly with the arm loaded so to enhance the effect of gravity on the hand motion (Rousseau et al., 2016). **Figure 2B** provides a graphical synopsis of these findings with a brain activation map obtained by performing an activation likelihood estimation (ALE) meta-analysis (Turkeltaub et al., 2002, 2012; Eickhoff et al., 2009) of 88 activation foci reported in these six studies (Indovina et al., 2005, 2013b, 2016; Miller et al., 2008; Maffei et al., 2010; Rousseau et al., 2016).

A particularly interesting aspect emerged from the aforementioned study by Miller et al. (2008), in that fMRI results indicated some of the vestibular network regions that may be specifically involved in extracting gravity cues from visual information. In these experiments, interception of vertical motion either congruent or not with the effects of gravity was performed with two visual scenarios, either a neutral background or a quasi-realistic scene incorporating static graphic elements, which provided reference and metric cues to scale the motion of the visual target to the overall scene size. It was found that the visual scene containing naturalistic pictorial cues facilitated the adoption of *a priori* knowledge of gravity to time the interception of the visual targets and that this process was associated with increased activity of the vestibular nuclei, of the nodulus and posterior cerebellar vermis. Thus, the extraction of gravity-related information from visual cues (which would help interpret the causality of the target motion to control predictively the timing of the interceptive action), might occur at rather early processing stages where vestibular and visual signals are first combined (see the introductory paragraph dealing with multisensory integration in the vestibular nuclei).

The extraction of gravity cues from visual signals can also be instrumental for the interpretation of biological motion. The neural correlates of this process have been investigated by an fMRI study, in which participants viewed intact or scrambled stick-figure animations of walking, running, hopping, and skipping recorded at either natural or reduced (Moon) gravity (Maffei et al., 2015). As was the case with inanimate object motion, the temporo-parietal junction (TPJ) and insular cortex were activated more strongly by viewing stick-figure animations recorded at natural compared to reduced gravity, supporting a role for these cortical regions in extracting gravity cues also from visual information related to biological motion. Cortical regions sensitive to biological motion configuration in the occipito-temporal cortex (OTC) showed a higher BOLD signal for reduced gravity compared to natural gravity, but with intact stick-figures only. Interestingly, connectivity analysis indicated significant modulation of the bi-directional connections between OTC and the peri-silvian regions involved in the internal representation of gravity, implying further that biological motion interpretation could depend on predictive coding of gravity effects (Maffei et al., 2015).

## FUNCTIONAL PARCELLATION OF THE VESTIBULAR NETWORK AND PROCESSING OF "VISUAL" GRAVITY

The neuroimaging evidence discussed above underlines the complexity and heterogeneity of the brain areas comprising the vestibular network, hinting, in some cases, (see, for example, Miller et al., 2008) at potential differential functional properties with respect to the processing of gravity-related information. In fact, both anatomical and functional studies in the monkey brain indicate that the vestibular network may comprise at least two core regions, the parieto-insular vestibular cortex (PIVC), responding primarily to vestibular inputs, and the visual posterior sylvian area (VPS), which responds to both visual and vestibular inputs (Guldin and Grüsser, 1998; Chen et al., 2010). The putative human homologs of monkey PIVC and VPS have been identified, respectively, in the OP2 (Eickhoff et al., 2006)—a parietal operculum subregion responding mainly to vestibular and somatosensory stimuli, but also to visual motion in a small posterior subregion adjacent to the retroinsula (Mazzola et al., 2012; zu Eulenburg et al., 2012; Ibitoye et al., 2021)—and in a region of the supramarginal gyrus responding to vestibular and visual inputs, named posterior insular cortex (PIC; Sunaert et al., 1999; Beer et al., 2009; Frank et al., 2014; Frank and Greenlee, 2018). Although OP2 and PIC have been often considered a single functional region, generically labeled as human PIVC

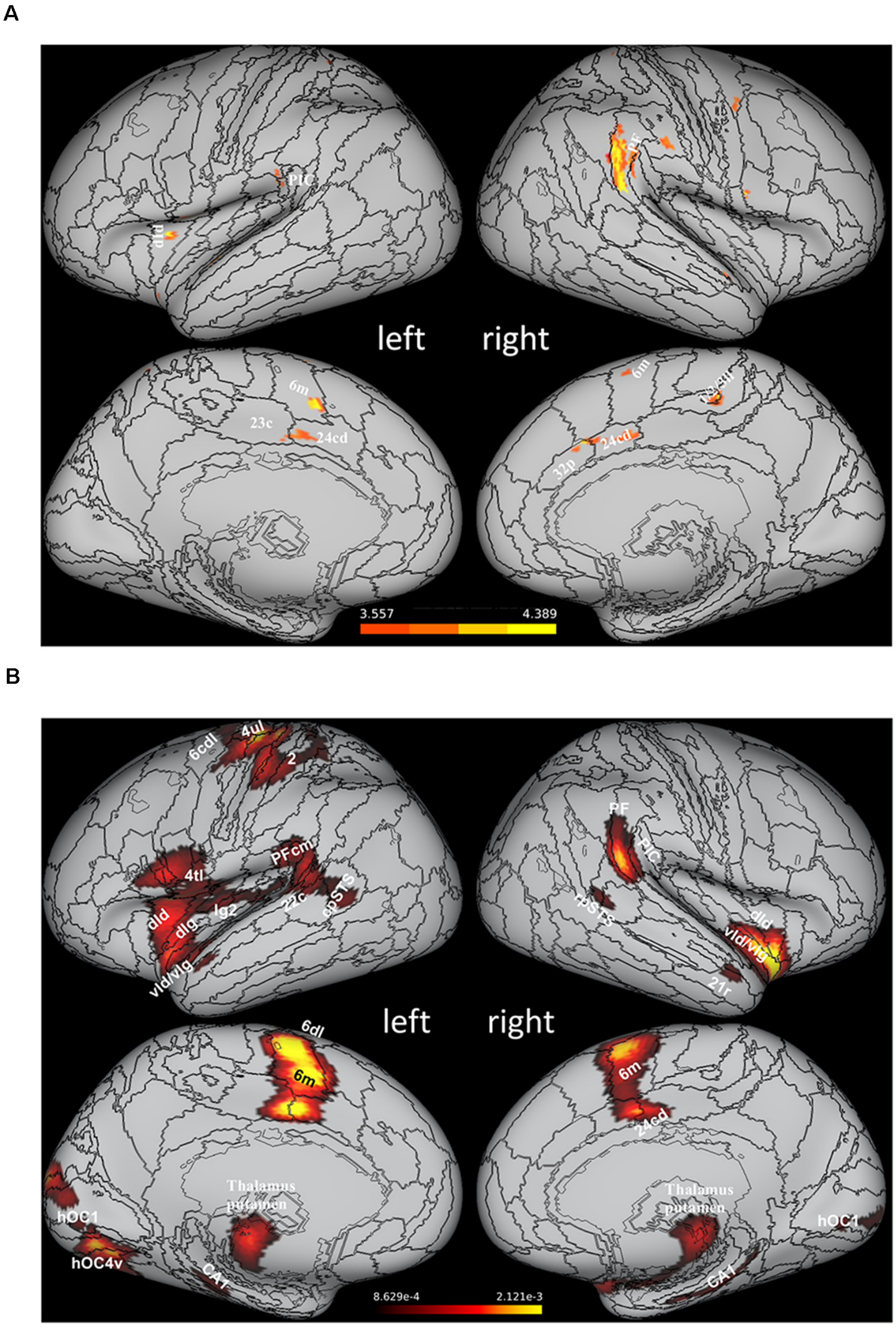

**FIGURE 2 |** Areas of the vestibular network activated preferentially by stimuli congruent with the effects of gravity. **(A)** Statistical activation map resulting from the intersection of the brain activation map evoked by caloric stimulation and that derived by the statistical contrast between the activity evoked by visual motion congruent (1 *g*) and non-congruent (−1 *g*) with gravity (data from Indovina et al., 2005 replotted on the Conte69 inflated brain template). **(B)** Statistical activation map obtained with an ALE meta-analysis of 88 activation foci drawn from six studies reporting preferential fMRI activations in response to stimuli congruent with effects of gravity (Indovina et al., 2005, 2013b, 2016; Miller et al., 2008; Maffei et al., 2010; Rousseau et al., 2016). The activation map, overlapped onto the Conte69 inflated brain template (Glasser et al., 2016), was thresholded at voxel level ($p < 0.05$) and corrected at cluster level at $p < 0.05$ (Eickhoff et al., 2012). Given the limited number of foci and the compliant statistical thresholds used for the meta-analysis, this activation map should be considered for illustrative purposes rather than statistical ones in a strict sense. Labels correspond to: rostroventral area 40 (PIC), area supramarginalis (PF), area supramarginalis columnata magnocellularis (posterior; PFcm), ventral dysgranular and granular insula (vld/vlg), dorsal granular insula (dlg), dorsal dysgranular insula (dld), dorsal granular insula (dlg), granular insula 2 (lg2), caudal dorsolateral area 6 (6 cdl), medial area 6 (6 m), area 4 (upper limb region, 4ul), area 4 (tongue and larynx region, 4tl), area 2 (2), caudal area 22 (22 c), caudal dorsal area 24 (24 cd), caudal area 23 (23 c), caudal dorsal area 24 (24 cd), posterior area 32 (32p), area1/2/3 (lower limb region, 1/2/3ll), rostral posterior superior temporal sulcus (rpSTS), caudal posterior superior temporal sulcus (cpSTS), cornu ammonis 1 (CA1), rostral area 21 (21r), human V1 (hOC1), human ventral V4 (hOC4v). PIC, posterior insular cortex.

(Cardin and Smith, 2010; Riccelli et al., 2017a), recent evidence indicates that these two regions can be separated functionally at an individual subject level based on their fMRI responses to caloric vestibular stimulation and visual motion (Frank et al., 2016), implying that also the human vestibular network may comprise functionally distinct hubs.

The results of a structural connectivity study by Indovina et al. (2020) are compatible with this view. By drawing data from 974 subjects of the repository of the Human Connectome Project, it was found that the structural connectivity pattern of PIC was consistent with a prominent role in visuo-vestibular processing, whereas that of OP2 was consistent with the integration of mainly vestibular, somato-sensory, and motor information (**Figure 3**). From the analyses reported in that article, in fact, PIC showed bilateral connections with the medial superior parietal regions including VIP (7r, 7ip) and with most of the thalamus, and ipsilateral connections with the insula, peri-sylvian regions, frontal premotor regions, occipital and temporal areas, the posterior cingulate cortex, and the rostral hippocampus. Conversely, OP2 showed ipsilateral connections with the rest of the insula and the peri-sylvian region, the superior parietal cortex including VIP (A7r, A7ip), and the somatosensory cortex. Furthermore, the brain areas connected with PIC were more diffuse and bilateral compared to the brain areas connected with OP2. Remarkably, these structural connectivity patterns are in line with those reported by neuroanatomical tracing studies in the squirrel monkeys for VPS (area T3) and PIVC, respectively. Indeed, in these monkeys, VPS shows strong connections with parieto-occipital and parieto-temporal regions (area 19), the upper bank of the temporal sulcus (STS-area), anterior cingulate gyrus, and parts of the posterior parietal area 7, while PIVC is connected primarily with Brodmann's areas 8a, 6, 3a, 3aV, 2, and posterior parietal area 7ant (Guldin et al., 1992).

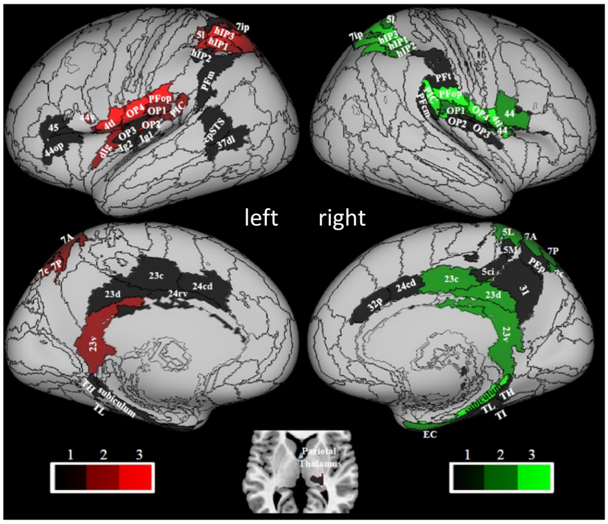

**FIGURE 3 |** Hubness within the vestibular network computed by using data of 794 right-handed individuals drawn from the Human Connectome Project repository. PIC and OP2 are among the vestibular areas with the strongest hubness index. Red and green colors relate to regions in the left and right hemispheres, respectively. Brain regions are mapped onto the Conte69 inflated brain. Labels correspond to: parietal opercula 1, 2, 3, 4 (OP1, 2, 3, 4), caudal posterior superior temporal sulcus (cpSTS), area 4 tongue and larynx region (4 tl), granular insula 2 (Ig2), granular insular 1 (Ig1), Area supramarginalis opercularis (PFop), rostroventral area 40 (PIC), area supramarginalis columnata magnocellularis (posterior; PFcm), area supramarginalis tenuicorticalis (PFt), area supramarginalis magnocellularis (PFm), caudal posterior superior temporal sulcus (cpSTS), dorsolateral area 37 (37 dl), human intraparietal 1, 2, 3 (hIP1, 2, 3), lateral area 5 (5l), intraparietal area 7 (7ip), superior parietal lobe (5 ci), area 31 (31), dorsal area 23 (23 d), caudal area 23 (23 c), ventral area 23 (23v), caudodorsal 24 (24 cd), pregenual area 32 (32p), ventral area 44 (44v), rostral area 45 (45), opercular area (44op), dorsal granular insula (dIg), granular insula 2 (Ig2), hippocampotemporalis (TH), subiculum, latero posterior parahippocampal gyrus (TL), temporal agranular insular cortex (TI), entorhinal cortex (EC). Figure drawn from Indovina et al. (2020).

Aside from the identification of these two main hub regions, another aspect of the organizational scheme of the vestibular network considered by Indovina et al. (2020), was the possible lateralization of vestibular functions, as PIC and OP2 structural connectivity patterns were found to be lateralized to the left hemisphere, whereas those of the posterior peri-sylvian supramarginal and superior temporal gyri were lateralized to the right hemisphere. Moreover, these lateralization effects did not depend on handedness. Evidence in the literature with respect to the lateralization of the fMRI responses observed in vestibular areas following vestibular stimulation and of their functional connectivity, however, appears far from conclusive. Early studies indicated that vestibular fMRI activations following vestibular stimulation may be lateralized to the right hemisphere in right-handed individuals and to the left hemisphere in left-handed people (Dieterich et al., 2003; Janzen et al., 2008; Lopez et al., 2012; Kirsch et al., 2018). Along these lines, an ALE meta-analysis of fMRI activations evoked by caloric, galvanic, and sound-evoked vestibular stimulation showed larger activation volumes in the parietal, temporal, and insular cortices of the right hemisphere during stimulation of the right ear than in the left hemisphere following stimulation of the left ear (Lopez et al., 2012). However, because of the low spatial resolution of the ALE meta-analysis technique, laterality differences in the posterior peri-sylvian cortex could not be assessed. Furthermore, a recent study on OP2 connectivity and fMRI activation following caloric stimulation in healthy subjects and patients affected by vestibular neuritis failed to show any lateralization in OP2 functional connectivity or in its response to caloric stimuli. Nevertheless, it pointed out that the effects of the peripheral vestibular disease were asymmetrical and the relationship between activity and dizziness/visual dependence was observed only in the right hemisphere, suggesting right lateralization of higher-order vestibular functions (Ibitoye et al., 2021). Conversely, a systematic review of the clinical outcomes of insular infarction concluded that despite vestibular-like syndromes being reported more often after right insular stroke, a clear lateralization has not yet clearly emerged for the Vestibular-like Syndrome (Di Stefano et al., 2021). Overall, this fragmented evidence in the literature for lateralization patterns may indicate another level of anatomo-functional compartmentalization within the vestibular network, but further studies are still needed to draw definite conclusions on the degree and type of lateralization of vestibular functions.

The functional parcellation within the vestibular network in relation to the strong hubness shown by PIC and OP2, instead, may suggest a potential role in the processing of gravity-related visual information for the component of the vestibular network integrating mainly visual and vestibular information, that is, the nodal area PIC and its interconnected areas. The results of three studies involving transcranial magnetic stimulation (TMS) of cortical sites in TPJ of the visual-vestibular network provide further support to this idea (Bosco et al., 2008; Delle Monache et al., 2017; De Sá Teixeira et al., 2019). In the first two studies, TPJ activity, as well as that of visual motion area hMT/V5+ and of the intraparietal sulcus (IPS), involved in visuomotor control, was disrupted by means of various online and off-line TMS paradigms, while healthy participants intercepted target motion either congruent or not with the effects of natural gravity (**Figure 4**). In the first study, targets moved vertically downward either accelerated by gravity or decelerated by the same amount (Bosco et al., 2008). In the second study, participants intercepted computer-simulated baseball fly-ball trajectories, which could be perturbed or not with the effects of altered gravity (either constant velocity, 0 *g*, or accelerated 2 *g*) and occluded 500 ms after the perturbation until landing (Delle Monache et al., 2017). A common finding across studies was that TPJ stimulation affected selectively the timing of the interceptive responses to visual motion congruent with the effects of gravity. Conversely, TMS applied on area hMT/V5+ altered the interceptive responses to all types of motion (not shown in **Figure 4**). Interestingly, the effects of stimulation of both cortical sites on the timing of the interceptive responses were restricted to specific temporal windows during the target motion trajectory. In Bosco et al. (2008), two TMS pulses (dpTMS) were delivered either 100 or 300 ms after the onset of the vertical trajectories (trajectory durations comprised between 700 and 890 ms), and significant effects of TPJ and hMT/V5+ stimulation were evident only for the earliest time window, implying that processing of visual information about the very beginning of the target trajectory in these two cortical areas is causally related to the timing of the interceptive action (see **Figure 4B**). With respect to the specific contribution of TPJ to the interceptive timing, the selectivity of the effects of its disruption for target motion congruent with natural gravity goes along with the idea that this cortical region is responsible for processing gravity-related visual information and contributes to an internal representation of gravity effects. This interpretation is supported also by the results of the second study with ballistic trajectories. In these experiments, three TMS pulses (tpTMS) were delivered 100 ms after either the perturbation or the occlusion of the visual motion on TPJ, hMT/V5+, and IPS sites. Once again, TPJ stimulation affected selectively the timing of the interceptive responses to unperturbed fly-ball trajectories, which were congruent with the effects of gravity and air friction, whereas stimulation of visual motion area hMT/V5+ altered the interceptive timing regardless of the type of motion trajectory. Remarkably, statistically significant stimulation effects for these two cortical regions were evident only when tpTMS was delivered at the onset of the trajectory perturbation (or at corresponding time frames in the unperturbed trajectories), with the target visible, but not when tpTMS was delivered just after the target disappearance (see **Figures 4C,D**). This result, while strengthening the idea that TPJ activity is causally related to the processing of gravity information embedded in visual signals, makes it unlikely that it may be also engaged in motion extrapolation. Instead, consistent with previous electrophysiological and neuroimaging evidence indicating a putative role of IPS in motion extrapolation (Assad and Maunsell, 1995; Lencer et al., 2004; Olson et al., 2004; Ogawa and Inui, 2007; Shuwairi et al., 2007; O'Reilly et al., 2008; Beudel et al., 2009; Makin et al., 2009), IPS stimulation was effective at both temporal windows, however altering the timing of the interceptive responses only for trajectories incongruent with natural gravity (Delle Monache et al., 2017). Therefore, it remains unclear which neural structures, likely belonging to the vestibular network, may participate in the extrapolation of natural gravitational motion, at least within the behavioral context examined by these studies.

The third TMS study, carried out by De Sá Teixeira et al. (2019), extended to the perceptual domain the evidence regarding the putative role of TPJ in the processing of the internal representation of gravity. The experiments were aimed at elucidating the potential neural basis for the observed phenomena of representational momentum and representational gravity, that is, the forward and the downward perceived vanishing location of a moving target (Freyd and Finke, 1985; Hubbard, 1990). To this end, offline continuous theta-burst stimulation (cTBS) was used to depress the excitability of TPJ and visual motion area hMT/V5 before the execution of a standard spatial localization task. The study reported an increase in representational gravity following disruption of hMT/V5+ activity and an increase of representational momentum following TPJ stimulation. These results are compatible with a push-pull mechanism between the relative contributions of area hMT/V5+ and TPJ. Accordingly, the spatial localization responses might be determined by the reciprocal balance between perceived kinematics and anticipated dynamics (i.e., the effects of gravity acceleration).

Overall, these three TMS studies have established a causal relationship between the activity of TPJ and the use of *a priori* knowledge of gravity engaged by visual motion information.

## WHAT CAN BE LEARNED FROM PATIENTS' STUDIES?

Further insight on the role of the vestibular cortex in the processing of gravity-related information has come from studies involving stroke patients with lesions of the peri-sylvian areas belonging to the vestibular network. Blood supply to the vestibular network largely depends on branches of the middle cerebral artery (MCA), a vessel frequently involved in acute stroke (cf. Ng et al., 2007). Common vestibular symptoms like vertigo, dizziness, and postural instability have often been reported following MCA infarction, particularly if lesions include the putative human homolog of PIVC (Marsden et al., 2005; Eguchi et al., 2019; Di Stefano et al., 2021). In addition,

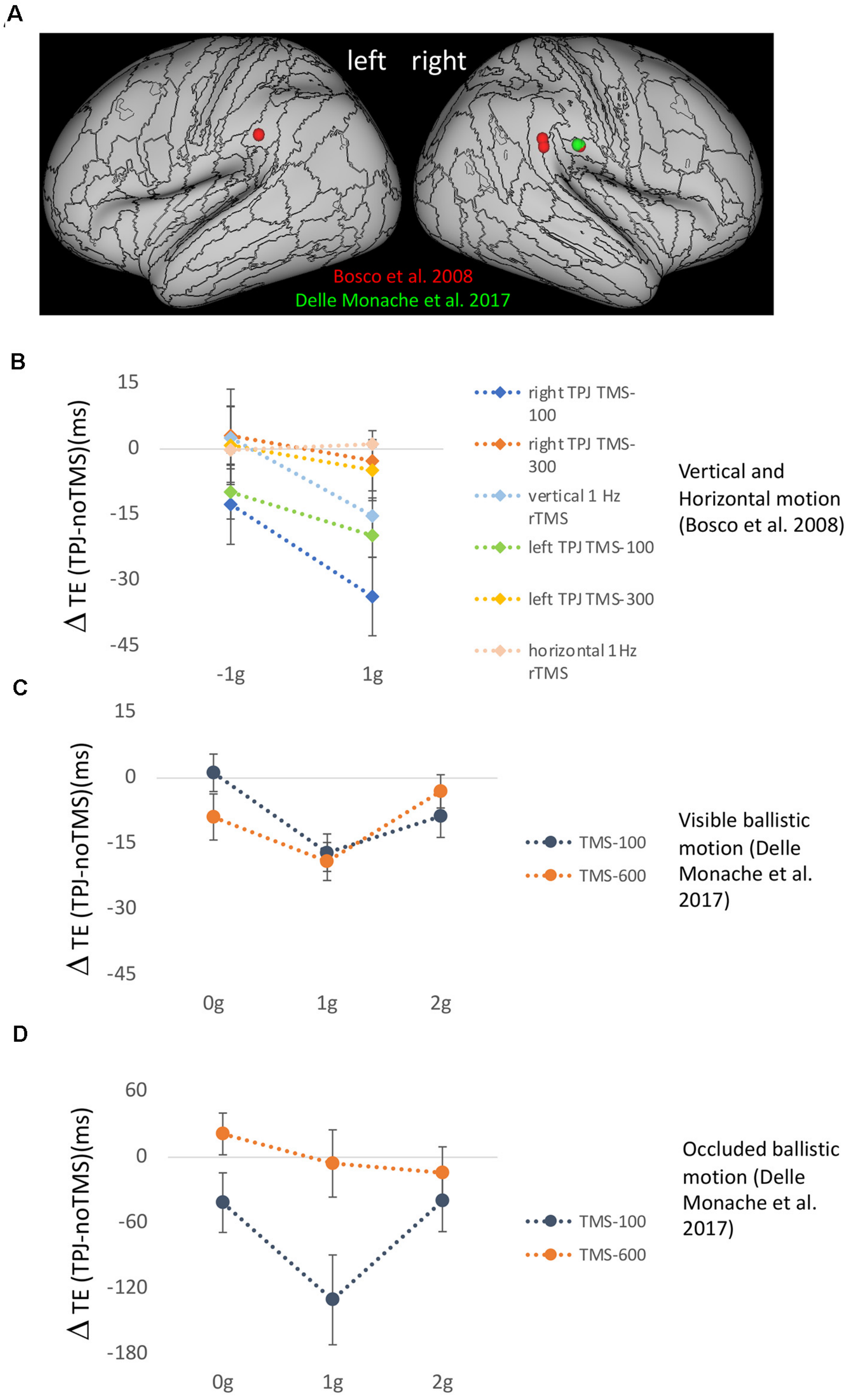

**FIGURE 4 | (A)** Effects of transcranial magnetic stimulation (TMS) of temporo-parietal junction (TPJ) on the timing of manual interception responses. **(A)** Anatomical location of the mean stimulation sites on TPJ reported for the experimental protocols of Bosco et al. (2008) (red) and Delle Monache et al. (2017) (green). **(B)** Mean timing error differences (±SEM) observed following TPJ stimulation compared to trials without TMS, for 1 *g* accelerated and decelerated motion in the six experimental protocols of Bosco et al. (2008). All conditions involved vertical target motion except that labeled horizontal 1 Hz rTMS. **(C)** Mean timing error differences (±SEM) observed following TPJ stimulation compared to trials without TMS for unperturbed 1 *g* and perturbed 0 *g* and 2 *g* ballistic trajectories, which were visible throughout their extent (Experiment 2 of Delle Monache et al., 2017). **(D)** Mean timing error differences (±SEM) observed following TPJ stimulation compared to trials without TMS, for unperturbed 1 *g* and perturbed 0 *g* and 2 *g* ballistic trajectories, which were occluded 500 ms after the perturbation until landing (Experiment 1 of Delle Monache et al., 2017).

strokes involving the insula and TPJ have been linked to deficits of awareness, in line with the role played by these regions in providing an anchor for self-location and first-person perspective (Pfeiffer et al., 2014; Ferrè and Haggard, 2016; Lopez, 2016).

Functionally, many symptoms associated with damages to the vestibular network can be interpreted as failures to process or integrate information derived from multiple sensory sources and/or to reconcile these inputs with prior information resulting from a lifelong experience with gravity. In consequence of these unsolved conflicts, brain-damaged patients can experience pathological tilts in perceived verticality (Karnath, 2007; Baier et al., 2012; Pérennou et al., 2014; Dieterich and Brandt, 2019) or more complex sensations such as paroxysmal tilts of the visual scene, (e.g., room tilt illusion, Tiliket et al., 1996; Malis and Guyot, 2003; Sierra-Hidalgo et al., 2012) and altered sense of embodiment (Blanke et al., 2004; Bünning and Blanke, 2005; Lopez et al., 2008). Paradigmatic conditions are cases when patients refer to transitory and often dramatic perturbations of the perceived upright posture, which is felt as no longer aligned with the gravitational vector and/or the subjective sense of self. In contraversive pushing, for example, patients spontaneously sit or stand with their longitudinal body axis tilted toward the paretic side, and actively use the non-paretic limbs to push away from the non-paretic side (cf. Davies, 1985; Karnath, 2007; Pérennou et al., 2008; Baier et al., 2012). This unusual behavior mainly emerges in cases of damage to regions involved in processing body perception and graviceptive information, such as the posterior thalamus and parts of the insula, the superior temporal gyrus, and post-central gyrus (Karnath, 2007; Pérennou et al., 2008; Baier et al., 2012). The capacity to determine the vertical orientation of the visual surrounding is often spared, suggesting that pushing could reflect the patient's attempts to compensate for a mismatch between the perceived postural and visual vertical (Karnath et al., 2000) or to align the body with the verticality reference (Pérennou et al., 2008). On the other hand, lesions extending to TPJ have been associated with feelings of disembodiment, i.e., the paradoxical, temporary sensation of being localized elsewhere with respect to one's physical body (Blanke et al., 2004; Bünning and Blanke, 2005). These out-of-body experiences (OBEs) are often accompanied by vestibular sensations such as feelings of flying or floating (Blanke et al., 2004), and are likely linked to two disturbances: a failure to integrate inputs relative to the body from different sensory channels, and vestibular dysfunction. The former would cause what has been described as "disintegration" in personal space and could explain the illusory reduplication of the experient's body. The latter would further affect the integration between the central representations of the body and extra-personal space (possibly at the TPJ), producing the experience of seeing oneself from an elevated position (Blanke et al., 2004).

In contrast to the many descriptions of altered perception of verticality and/or body orientation, less is known about how lesions to the vestibular network affect interactions with moving objects. As reviewed above, successful planning of interception movements takes advantage of an internal model of gravity effects stored in the vestibular cortex, which is used to supplement the continuous flux of information conveyed by the sensory channels (McIntyre et al., 2001; Indovina et al., 2005). To explore this issue, one study investigated the capacity to efficiently intercept a moving target in patients diagnosed with MCA infarction (Maffei et al., 2016), by employing a similar task to the one used in Indovina et al. (2005). Maffei and collaborators considered the DeltaT, i.e., the relative difference between timing errors of the responses to the two types of target motion (1 $g$, $-1$ $g$), as an indicator of whether patients' interceptive responses reflected or not *a priori* assumptions of gravity effects. In fact, if 1 $g$ and $-1$ $g$ trials were to be correctly discriminated, DeltaT would be expected to be small, timing errors being similarly small in both conditions. Conversely, if priors about gravitational acceleration are being applied to both types of motion, responses to $-1$ $g$ trials should be anticipated (Zago et al., 2004) producing an increase in DeltaT. Consistent with these assumptions, an abnormally large DeltaT was found in a subgroup of patients. Correlation with neuroanatomical data *via* voxel-based lesion-symptom mapping VLSM (Bates et al., 2003) and lesion subtraction analyses showed an association with damage to peri-sylvian areas, centered in the parietal operculum. In healthy subjects, this same region has been found activated in fMRI studies comparing 1 $g$ and $-1$ $g$ motion (Maffei et al., 2010), suggesting a role of this region in discriminating between motions that either obey or violate gravity (**Figure 5A**). On this basis, it has been postulated that, by losing this ability, stroke patients could not detect the mismatch between incoming sensory signals and expectations based on stored models of gravity, thus failing to apply the correct model to each type of motion. Remarkably, this study reported also that patients with large DeltaT showed a relatively intact verticality perception. Compared to interception, estimation of the subjective visual vertical (SVV) requires aligning the perceived vertical estimation with the veridical vertical, i.e., it involves spatial rather than temporal processing of gravity information, two operations that may not rely on the same neural substrates (**Figure 5B**). In fact, SVV impairments are more frequently reported following strokes to the posterior insula (Brandt et al., 1994; Baier et al., 2013; Maffei et al., 2016) as are the postural disturbances associated (Dieterich and Brandt, 2019), suggesting again possible dissociations as to where and how gravity information is processed. Indeed, in the afore-mentioned study by Maffei et al. (2016), VLSM analysis indicated that greater deviations of SVV were associated preferentially with lesions mainly centered on the posterior insula, that is, in a site distinct from the parietal operculum, which was preferentially associated with impairment of discrimination of gravitational motion.

Another clinical disorder providing insights on the study of the internal representation of gravity in the vestibular cortex is functional dizziness, that is, chronic dizziness without an organic cause. This disorder has recently been defined as persistent postural-perceptual dizziness or PPPD (Staab et al., 2017). One of the possible causes of PPPD might be the behavioral maladaptive shift to visual dependence, with greater reliance on visual rather than vestibular information for spatial orientation, which persists even after the resolution of the acute vestibular problem (Cousins

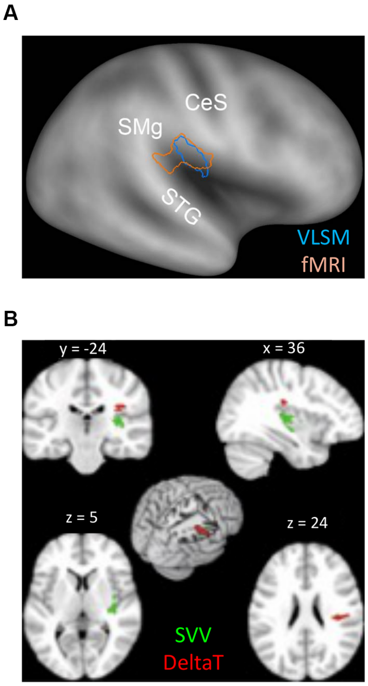

**FIGURE 5 | (A)** Overlap between the peri-sylvian region activated by the contrast (1 *g* > −1 *g*) in the fMRI study on healthy subjects (pink contour) and the lesion map resulting from the VLSM analysis performed by Maffei et al. (2016) (see text), which considered the lesioned brain regions associated with higher DeltaT values (blue contour). Contours are plotted onto the PALS inflated human brain template (Caret). CeS, Central Sulcus; STG, Superior Temporal Gyrus; SM, Supramarginal Gyrus. **(B)** Lesion Subtraction Map reported by Maffei et al. (2016). Red voxels were found to be damaged more frequently (>65%) in patients with the highest values of DeltaT (*n* = 7) than in the seven patients with the smallest DeltaT values. Green voxels were found more frequently damaged (>65%) in patients with altered SVV estimation than in the five patients showing the smallest DeltaT values and intact SVV estimation. The MNI coordinates are reported on top of each brain section. Modified from Maffei et al. (2016). Cortex with permission of Roopa Lingayath, Senior Copyrights Coordinator ELSEVIER. SVV, subjective visual vertical.

et al., 2014). One possibility entertained by a recent fMRI study (Riccelli et al., 2017b) is that this greater reliance on visual information by PPPD patients might be paralleled by a lower reliance on *a priori* information about gravity stored in the vestibular cortex. Thus, fMRI signals were acquired during visually simulated rollercoaster rides along vertical and horizontal directions in 14 patients with PPPD secondary to an acute peripheral vestibular episode, like vestibular neuritis (VN) or benign paroxysmal positional vertigo (BPPV), as well as in healthy controls (Riccelli et al., 2017b). PPPD patients who had suffered from vestibular neuritis underwent caloric testing in the acute stage of the peripheral vestibular disease and 6 months later to evaluate the extent of their recovery. Patients who experienced benign paroxysmal positional vertigo as a trigger for PPPD had no symptoms or signs of active positional vertigo at the time of entry in the study. Statistical comparisons between the fMRI activation maps observed during the vertical vs. the horizontal self-motion bouts showed a significant decrease of the BOLD signal in the right middle insula in the group of PPPD patients as compared with the healthy controls. In the light of the consistent reports that the insular cortex is activated preferentially by visual motion congruent with the effects of gravity (see above, and also **Figure 2**), this result appears to be in line with the idea that PPPD patients rely to a lesser extent than healthy subjects on internalized gravity-related information. However, it is also worth noting that this result has been obtained by collapsing data for the direction of motion (vertical vs. horizontal) regardless of the kinematics (accelerated/decelerated at 1 *g*, constant speed), Thus, more controlled studies are needed to disentangle whether this decrease in the activity of the right insula shown by PPPD patients is related to the internal representation of gravity, for example by combining neuroimaging and psychophysical approaches in these patients in order to measure both interception and fMRI responses to visual motion either coherent or incoherent with gravity effects.

## CONCLUDING REMARKS

We reviewed experimental evidence gathered from behavioral, neuroimaging, and patients' studies in support of the hypothesis that an internal model estimating the effects of gravity on visual objects is constructed by transforming vestibular estimates of physical gravity, processed in the brainstem and cerebellum, into an internalized supramodal representation of gravity stored in the vestibular network. The integration of the internal model of gravity with visual and other non-vestibular signals can take place at multiple levels in the areas of the vestibular network and might be instrumental in extracting gravity cues from sensory signals, such as retinal ones, that may not relate directly to physical gravity. This process would afford the implicit interpretation of a virtual reproduction of the physical world, like that rendered by a movie. Although it seems reasonable to consider this process as distributed among the brain areas belonging to the vestibular network, we suggest that brain regions more closely associated with PIC could provide a stronger contribution, by virtue of their denser reciprocal connectivity with cortical areas engaged in the processing of spatio-temporal features of the visual stimuli (Indovina et al., 2020).

## AUTHOR CONTRIBUTIONS

SD, II, MZ, ED, FL, and GB drafted the manuscript. All authors contributed to the article and approved the submitted version.

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# Impact of Canal-Otolith Integration on Postural Control

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Roll tilt vestibular perceptual thresholds, an assay of vestibular noise, have recently been shown to be associated with suboptimal balance performance in healthy older adults. However, despite the strength of this correlation, the use of a categorical (i.e., pass/fail) balance assessment limits insight into the impacts of vestibular noise on postural sway. As a result, an explanation for this correlation has yet to be determined. We hypothesized that the correlation between roll tilt vestibular thresholds and postural control reflects a shared influence of sensory noise. To address this hypothesis, we measured roll tilt perceptual thresholds at multiple frequencies (0.2 Hz, 0.5 Hz, 1 Hz) and compared each threshold to quantitative measures of quiet stance postural control in 33 healthy young adults (mean = 24.9 years, SD = 3.67). Our data showed a significant linear association between 0.5 Hz roll tilt thresholds and the root mean square distance (RMSD) of the center of pressure in the mediolateral (ML; $\beta = 5.31$, $p = 0.002$, 95% CI = 2.1–8.5) but not anteroposterior (AP; $\beta = 5.13$, $p = 0.016$, 95% CI = 1.03–9.23) direction (Bonferroni corrected $\alpha$ of 0.006). In contrast, vestibular thresholds measured at 0.2 Hz and 1 Hz did not show a significant correlation with ML or AP RMSD. In a multivariable regression model, controlling for both 0.2 Hz and 1 Hz thresholds, the significant effect of 0.5 Hz roll tilt thresholds persisted ($\beta = 5.44$, $p = 0.029$, CI = 0.60–10.28), suggesting that the effect cannot be explained by elements shared by vestibular thresholds measured at the three frequencies. These data suggest that vestibular noise is significantly associated with the temporospatial control of quiet stance in the mediolateral plane when visual and proprioceptive cues are degraded (i.e., eyes closed, standing on foam). Furthermore, the selective association of quiet-stance sway with 0.5 Hz roll tilt thresholds, but not thresholds measured at lower (0.2 Hz) or higher (1.0 Hz) frequencies, may reflect the influence of noise that results from the temporal integration of noisy canal and otolith cues.

**Keywords: vestibular, semicircular canal, otolith, noise, perception, sway, balance, postural control**

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## INTRODUCTION

Current models of postural control have implicated sensorimotor noise as one of the principal determinants of postural sway during quiet stance, with increases in sway attributed to increases in sensorimotor noise (Maurer and Peterka, 2005). While postural control has sensory and motor contributions, each with independent sources of noise, recent efforts in computational modeling suggest that postural sway is predominantly influenced by sensory noise, with limited contributions from noise in the motor pathways (van der Kooij and Peterka, 2011). Additionally, postural sway, even in conditions of impoverished visual cues, is under the influence of multiple sensory systems, including vestibular and proprioception. The influence of vestibular sensory noise on models of postural control has however been estimated to be approximately 10-times larger than the effect of noise in the proprioceptive system (van der Kooij and Peterka, 2011). Consistent with this notion, a recent empirical study of healthy older adults found that vestibular noise, assayed using vestibular roll tilt perceptual thresholds, was strongly correlated with the ability to complete a categorical (i.e., pass/fail) balance task (i.e., "eyes closed, standing on foam" Bermúdez Rey et al., 2016; Karmali et al., 2017); the mechanism underpinning the specific association between vestibular thresholds and reduced postural control has yet to be fully revealed.

Sensory noise denotes irregularities in neural activity which impairs one's ability to perceive the accompanying afferent signal (Faisal et al., 2008). Vestibular afferent signals encode motion of the head in six degrees of freedom, with the semicircular canals encoding angular velocity (Fernandez and Goldberg, 1971) and otolith organs encoding gravitoinertial force (i.e., translation, and tilt; Fernandez and Goldberg, 1976). Due to imprecision in the transduction and subsequent transmission of the vestibular afferent signal (Faisal et al., 2008) the precision of self-motion estimates diminish as the signal to noise ratio decreases (Merfeld, 2011). Vestibular perceptual thresholds measure the size of a stimulus needed to exceed the baseline level of noise in the sensory system to enable reliable perception and thus have become a standard method for quantifying the level of vestibular sensory noise (Grabherr et al., 2008; MacNeilage et al., 2010; Merfeld, 2011; Valko et al., 2012; Agrawal et al., 2013; Bermúdez Rey et al., 2016; Crane, 2016; Kobel et al., 2021).

During dynamic roll tilt (**Figure 1A**), the canals and otoliths are each stimulated as the head rotates about an earth horizontal axis, with the otoliths encoding the resultant net gravitoinertial force. However, consistent with the behavior of all linear accelerometers (Einstein, 1907), on the basis of the afferent otolith signal alone, the brain cannot independently differentiate if the stimulus was due to a tilt (i.e., changing orientation relative to gravity) or translation (i.e., due to a linear acceleration inertial force) of the head (Angelaki et al., 1999). During roll tilt, angular velocity estimates derived from the vertical canals $\hat{\omega}$ must be temporally integrated ($\hat{G} = \int (-\hat{\omega} \times \hat{G})dt$) to yield a relative estimate of the orientation of gravity ($\hat{G}$) relative to the head (Glasauer, 1992; Merfeld et al., 1993, 1999; Angelaki et al., 1999; Merfeld and Zupan, 2002). Therefore, perceptual precision during roll tilt is reliant on the dynamic temporal integration of the canal signal with the otolith-derived estimate of gravity, with higher roll tilt vestibular thresholds indicating greater noise following this temporal integration. Accordingly, it has been proposed that the previously observed correlation between 0.2 Hz roll tilt thresholds and balance performance (Karmali et al., 2017; Beylergil et al., 2019) may represent the influence of noise resulting from the temporal integration of noisy canal and otolith signals on postural sway; however, this relationship has yet to be fully explored.

Earlier studies have compared categorical (i.e., pass/fail) balance assays, such as the "eyes closed, on foam" condition of the modified Romberg balance test (Agrawal et al., 2009), to roll tilt thresholds measured at 0.2 Hz and 1 Hz (Karmali et al., 2017, 2021). Due to unique dynamics associated with the processing of otolith (i.e., tilt; Fernandez and Goldberg, 1976) and canal (i.e., angular velocity; Fernandez and Goldberg, 1971) signals, their integration during such tasks is dependent upon the frequency of the roll tilt stimulus (Lim et al., 2017). In the absence of otolith cues, perceptual thresholds for earth vertical roll rotations (measured in supine) were found to plateau at frequencies above approximately 0.44 Hz (Lim et al., 2017); this behavior is qualitatively similar to the high pass filter characteristics of semicircular canal afferents (plateauing at approximately 0.03 Hz), with the higher cut off frequency for perception presumably reflecting an added influence of the central vestibular pathways mediating self-motion perception (Grabherr et al., 2008) or decision-making (Merfeld et al., 2016). Conversely, the perception of static tilt, as primarily mediated by the otoliths, is invariant with frequency (Lim et al., 2017), with sensitivity being proportional to the sine of the tilt angle (Fernandez and Goldberg, 1976; Jamali et al., 2019). As a result, for a fixed velocity, the otolith organs are stimulated to a greater extent at lower frequencies as the displacement is larger at lower frequencies of tilt (**Figure 1B**).

For dynamic roll tilt, Lim et al. (2017) used an optimal Kalman filter model to show that rotation cues and static tilt cues, presumably of canal and otolithic origin respectively, were optimally integrated at frequencies between 0.2 and 0.5 Hz, as measured thresholds were lower than predicted on the basis of a static combination of unimodal rotation and tilt cues (Lim et al., 2017). Accordingly, roll tilt thresholds within this range (i.e., 0.2–0.5 Hz) reflect contributions of noise associated with the canals, otoliths, and their dynamic temporal integration.

Here we measured roll tilt thresholds at the lowermost (0.2 Hz) and uppermost (0.5 Hz) ends of this range to assess the relative contributions of the canal and otolith cues. Due to the dependency of the otoliths on the amplitude of tilt, rather than frequency, their relative influence on roll tilt perception would be expected to be increased at 0.2 Hz, relative to 0.5 Hz, due to the increased displacement for a given velocity threshold (**Figure 1**). For 0.5 Hz roll tilt, the tilt amplitude decreases, and the higher frequency angular velocity cue leads to an increased reliability of vertical canal cues, due to the high pass nature of rotation perception. Thus, 0.2 Hz and 0.5 Hz roll tilt thresholds reflect noise resulting from canal otolith integration but differ in the relative precision of canal and otolith cues. We also assessed thresholds using a 1 Hz roll tilt stimulus to provide a measure of vestibular noise that resulted primarily from the vertical canals with minimal contributions from the otolith organs.

Our goal was therefore to determine if postural control is preferentially influenced by noise associated with the temporal integration of noisy canal and otolith cues (i.e., 0.2 and 0.5 Hz roll tilt). To address this question, we compared sensitive quantitative measures of quiet stance postural control to roll tilt vestibular

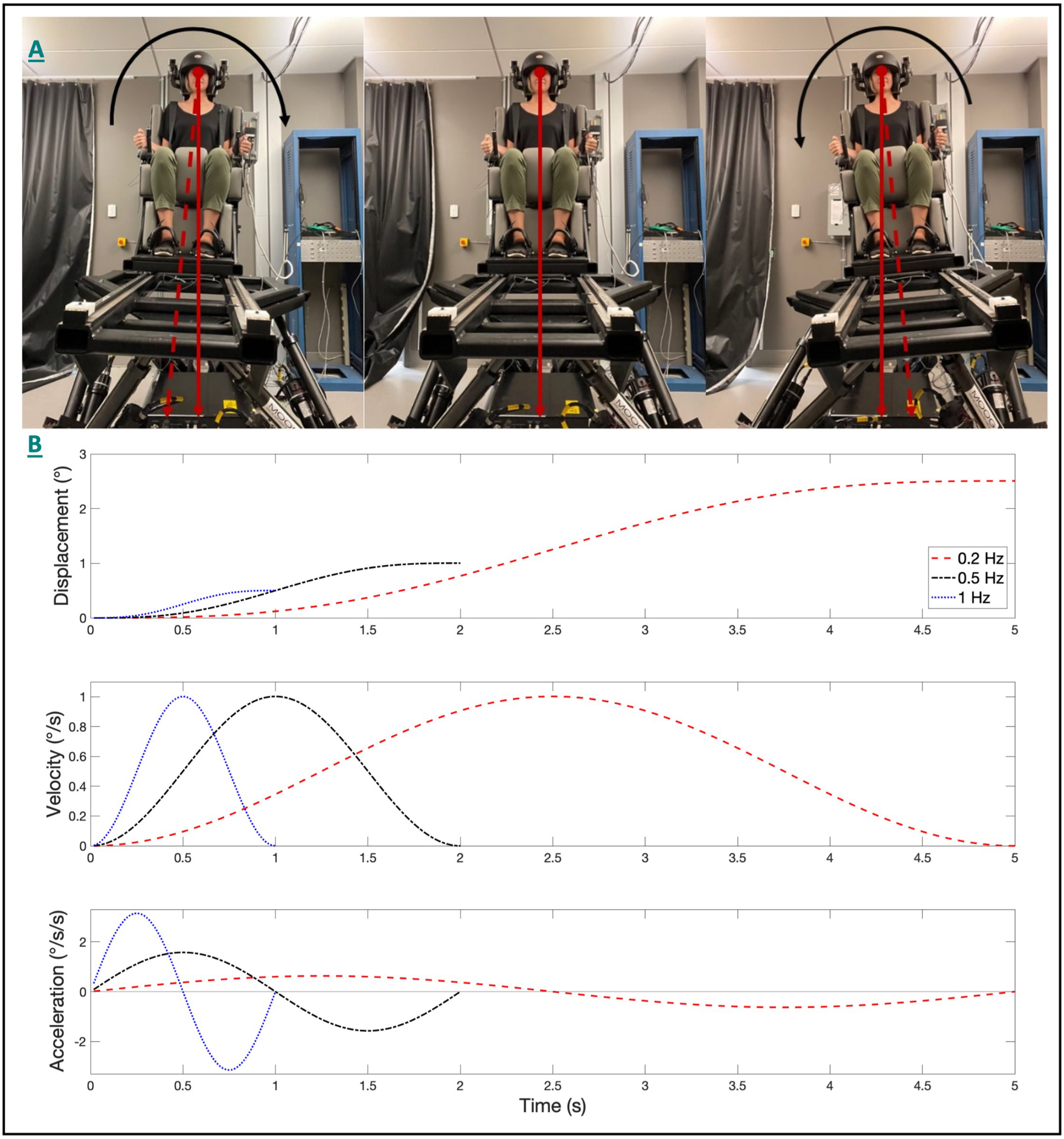

**FIGURE 1** | The 6DOF motion platform set up and the head-centered roll tilt motion is shown **(A)**. The angular displacement (top), velocity (middle), and acceleration (bottom) trajectories for single cycle acceleration stimuli are shown **(B)** for each of the three frequencies of roll tilt. The peak angular velocity was held constant at 1°/s for each condition. Note that for identical peak velocities, that displacements decreased, and peak accelerations increased as the frequency increased.

thresholds measured at the frequencies previously used by others (0.2 Hz and 1 Hz; Bermúdez Rey et al., 2016; Karmali et al., 2021), as well as at 0.5 Hz, to determine if the frequency, and therefore relative influence of canal (0.5 Hz) and otolith (0.2 Hz) cues, influenced this relationship. We hypothesized that increased roll tilt noise, resulting from the temporal integration of noisy canal and otolithic cues, as represented by 0.2 and 0.5 Hz roll tilt perceptual thresholds, would be positively correlated with measures of postural instability measured in the corresponding mediolateral plane.

# METHODS

## Participants

Since aging could impact balance *via* multiple age-related sensory and motor degradations, we tested only healthy young individuals so that we could quantify correlations between sway and tilt thresholds independent of the effects of aging. This substantially reduces the chance of a correlation between sway and tilt thresholds arising from any unmeasured age-related variation (e.g., age-related CNS declines) that might contribute to age-related changes in both tilt thresholds and sway. Data were collected on 33 healthy young adult volunteers (Mean 24.9 ± 3.67 years old, Range 20–32; 22/33 Female; **Table 1**). These individuals were recruited as part of a separate intervention trial, with a recruitment target of 30 participants. During this effort, two subjects dropped out during the intervention phase and were replaced, and due to time constraints, an additional subject agreed to only complete the baseline testing for the intervention trial; hence we report the baseline data here from 33 healthy participants. Each participant completed a health screening questionnaire prior to enrollment and denied any history of vestibular, neurologic, or alternative major medical comorbidity. The study was approved by the Ohio State University Institutional Review Board and each subject provided written informed consent prior to participation. All ethical standards set out in the Declaration of Helsinki were followed.

**TABLE 1** | Demographic information of participants and summary statistics for variables of interest.

| N = 33 (22 female) | Mean | SD | 95% CI | |
|---|---|---|---|---|
| Age (years) | 24.9 | 3.67 | 23.60 | 26.21 |
| Vestibular Thresholds (°/s) | | | | |
| 0.2 Hz | 0.51 | 0.24 | 0.42 | 0.59 |
| 0.5 Hz | 0.74 | 0.31 | 0.63 | 0.85 |
| 1 Hz | 0.86 | 0.35 | 0.74 | 0.99 |
| Vestibular Bias (°/s) | | | | |
| 0.2 Hz | 0.018 | 0.12 | −0.33 | 0.34 |
| 0.5 Hz | 0.044 | 0.24 | −0.55 | 0.58 |
| 1 Hz | 0.02 | 0.21 | −0.67 | 0.63 |
| CoP—EC Foam | | | | |
| ML RMSD (mm) | 11.62 | 3.18 | 10.50 | 12.75 |
| ML MV (mm/s) | 33.23 | 8.93 | 30.06 | 36.39 |
| ML MF (Hz) | 0.36 | 0.12 | 0.32 | 0.40 |
| AP RMSD (mm) | 11.36 | 3.82 | 10.00 | 12.71 |
| AP MV (mm/s) | 32.64 | 9.24 | 29.37 | 35.92 |
| AP MF (Hz) | 0.35 | 0.14 | 0.30 | 0.40 |
| CoP—EO Firm | | | | |
| ML RMSD (mm) | 4.25 | 1.38 | 3.76 | 4.74 |
| ML MV (mm/s) | 9.52 | 2.42 | 8.66 | 10.38 |
| ML MF (Hz) | 0.33 | 0.10 | 0.30 | 0.37 |
| AP RMSD (mm) | 4.54 | 1.72 | 3.93 | 5.15 |
| AP MV (mm/s) | 8.53 | 1.60 | 7.97 | 9.10 |
| AP MF (Hz) | 0.23 | 0.096 | 0.20 | 0.27 |

*Vestibular perceptual thresholds and biases for head-centered roll tilt motions representing the standard deviation and mean of the fitted cumulative distribution function, respectively. Mean CoP parameters for both the ML and AP directions are presented for each of two balance conditions of interest, "eyes closed, foam" and "eyes open, firm". AP, anteroposterior; CoP, Center of Pressure; EC, eyes closed; EO, eyes open; ML, mediolateral; MF, mean frequency; MV, mean velocity; RMSD, root mean square distance.*

## Vestibular Thresholds

Vestibular self-motion perceptual thresholds were used to quantify vestibular perceptual noise (Merfeld, 2011). Subjects were positioned in a custom-made chair atop a 6DOF Moog (Elma, NY) motion platform (**Figure 1A**). A five-point seatbelt and a helmet were used to secure the subject to the chair and to mitigate unintended head movement while testing. Given the goal to quantify vestibular contributions to motion perception, all testing occurred in the dark to eliminate visual cues; directional auditory cues were masked with 60 dB SPL of white noise during each test motion.

Each of three test conditions consisted of 100 trials with the subject being tilted about a head-centered naso-occipital axis (**Figure 1A**) at a single discrete frequency (0.2, 0.5, or 1 Hz). The subject was instructed to indicate the perceived direction of the tilt stimulus (e.g., left or right) by pressing buttons held in the right and left hands (i.e., forced choice, direction recognition task). No feedback was provided, and subjects were instructed to make their best guess if unsure of the motion direction. Practice was provided until the subject reported feeling comfortable with the task. After each motion, a 3-s delay was provided prior to the next test motion to reduce the potential influence of motion after-effects (Crane, 2012). Due to the attentional demands of the task, subjects rested a minimum of 5 min between tests.

Consistent with past studies of vestibular perception (Grabherr et al., 2008; MacNeilage et al., 2010; Agrawal et al., 2013; Bermúdez Rey et al., 2016), we used single cycles of sinusoidal acceleration (**Figure 1B**) as the test stimulus. Dynamic roll tilts performed at 0.2 Hz, 0.5 Hz, and 1 Hz, therefore, correspond to motion stimuli having durations of 5, 2, and 1 s respectively. Single cycles of acceleration [$(a(t) = A\sin(2\pi ft) = A\sin(2\pi t/T)$; A = peak acceleration, $f$ = frequency (i.e., the inverse of the duration (T) of the motion)] provide stimuli without discontinuities that mimic typical stimuli experienced during naturalistic human motion. The peak velocity ($v_{\text{peak}} = AT/\pi$) and peak displacement ($D = AT^2/2\pi$) are proportional to the peak acceleration (A).

For the majority of trials, a standard four-down/1-up (4D/1U) adaptive staircase procedure was used in which the magnitude of the motion stimulus decreased each time the subject correctly reported the motion direction four times in a row ("4 down"), and the motion magnitude increased anytime the subject incorrectly reported the motion direction ("1 up"; Leek, 2001). A 2D/1U staircase was used until the first incorrect response to reach near-threshold stimulus levels more efficiently. Step sizes were selected using parameter estimation by sequential testing (PEST) rules (Leek, 2001). Using pilot data, we set the staircase to start at 5.5 degrees to ensure that each subject started at a suprathreshold stimulus.

Thresholds were calculated by fitting the binary subject responses (left/right) and the corresponding motion stimuli (direction and magnitude) to a Gaussian cumulative distribution function (CDF) defined by two parameters, the standard deviation (i.e., "threshold") and the mean (i.e., "bias"). The threshold parameter represents the "one-sigma" vestibular threshold, as has been commonly reported (Valko et al., 2012; Bermúdez Rey et al., 2016; Karmali et al., 2021; Kobel et al., 2021), and represents: (1) the standard deviation of the underlying distribution function and (2) the stimulus level that would be expected to yield 84.1% accuracy in the absence of bias (Merfeld, 2011). Bias or "vestibular bias" (Merfeld, 2011) describes the displacement of the CDF along the abscissa; for example, a bias of +0.5°/s signifies that the individual would, on average, have an equal probability of reporting a right (negative) and a left (positive) rotation when the stimulus delivered is +0.5°/s (to the left; Merfeld, 2011). Estimates of threshold and bias were derived from a maximum likelihood estimate (Wichmann and Hill, 2001) using a bias-reduced generalized linear model (Chaudhuri and Merfeld, 2013) and probit link function. These methodological details have been published (Merfeld, 2011; Lim and Merfeld, 2012; Chaudhuri and Merfeld, 2013) and have been used extensively (Bermúdez Rey et al., 2016; King et al., 2019; Suri and Clark, 2020; Karmali et al., 2021; Kobel et al., 2021). We highlight that our bias reduced method accounts for the known serial dependency associated with staircase methods that have previously been shown to underestimate thresholds (Kaernbach, 2001; Klein, 2001; Chaudhuri and Merfeld, 2013). Given the attentional demands of the task, we also accounted for attentional lapses, defined as incorrect responses that occur independent of the magnitude of the motion stimulus, through the use of a lapse-identification algorithm using a standard delete-one jackknife when fitting the psychometric function (Clark and Merfeld, 2021).

## Postural Control

Center of pressure (CoP) data were collected from a tri-axial force plate (AMTI, Watertown, MA) at a sampling rate of 100 Hz. Subjects stood on a foam pad with the eyes closed and with feet in a narrow stance (i.e., medial border of the feet touching) for a duration of 63 s, with the first 3 s removed from the analysis to allow for the subject to accommodate to the conditions of the task; we used the same medium density (5 lb/ft$^3$) foam pad (SunMate, 16"x18"x3") that was used in the National Health and Nutrition Examination Survey (NHANES; Agrawal et al., 2009) and in the preliminary data relating roll tilt thresholds to "pass/fail" balance performance (Karmali et al., 2017). A secondary condition was captured where subjects were allowed to stand with their eyes open on a firm surface (while still in a narrow stance) for 33 s (with the final 30 s being analyzed). Alternative test conditions were performed as part of a larger data collection effort, however, our analysis focuses on these two tasks to provide: (1) a description of postural control when vestibular cues are known to dominate (eyes closed on foam), and (2) a control condition to determine if associations between vestibular noise and balance dissipate when vestibular cues are down-weighted in favor of visual and somatosensory cues (eyes open on a firm surface).

Maurer and Peterka (2005) found that CoP metrics aggregate into three independent groups—displacement, velocity, and frequency measures (Maurer and Peterka, 2005). To capture unique aspects of the postural control system, while also limiting the number of analyses, we *a priori* chose to focus our analyses on a single parameter from each of these three COP metric categories.

Root mean square distance (RMSD) is equivalent to the standard deviation of the zero-mean CoP tracing (Prieto et al., 1996); thus, it reflects the amount by which the CoP is displaced in a given plane of motion [anteroposterior (AP) or mediolateral (ML)], providing a quantitative metric of spatial control. Each measure was calculated separately in the ML and AP planes. In Equation 1, n is the total number of samples (60 s × 100 Hz = 6,000) and *x* represents the CoP displacement after removal of the mean (Equation 1).

$$x_{CoP} = CoP_{disp} - \left(\frac{1}{n}\sum_{i=1}^{n} CoP_{disp}\right);$$

$$RMSD = \sqrt{\frac{1}{n}\sum_{i=1}^{n}[x_{CoP}(i)]^2} \tag{1}$$

Mean velocity (MV) describes the average instantaneous velocity of the CoP and is calculated by differentiating the CoP displacement signal (Equation 2).

$$MV = \frac{1}{n-1}\sum_{i=1}^{n-1}|\dot{x}_{CoP}(i)| \tag{2}$$

Mean frequency (MF) uses the CoP velocity and displacement data to describe the oscillatory behavior of the CoP reflected as the number of cycles of CoP displacement per second (Hz; Equation 4). MD represents the mean distance of the CoP from the zero-meaned center of the CoP trajectory (Equation 3).

$$MD = \frac{1}{n}\sum_{i=1}^{n}|x_{CoP}(i)| \tag{3}$$

$$MF = \frac{MV}{(2\pi MD)} \tag{4}$$

As a secondary analysis, we set out to examine the relationship between the frequency content of the postural sway and the frequency of the roll tilt stimulus. We computed the one-sided power spectral density (PSD) of the mediolateral CoP data using Welch's method (*pwelch*; MATLAB R2020b). The CoP tracing was divided into eight segments with adjacent segments overlapping by 50%; each segment was then windowed using a Hanning window. To avoid the influence of measurement noise, a frequency range of 0.01–20 Hz was used. The area under the PSD curve was calculated and the frequency at which 95% of the power fell below was determined. In addition to the individual PSD's, a median PSD was also found by taking the median power at each discrete frequency.

## Data Analysis

For our primary analyses, each of the three principal CoP metrics (RMSD, MV, and MF) from the "eyes closed, on foam" condition was regressed on each of the three vestibular threshold measures (0.2, 0.5, 1 Hz), yielding nine univariate regression models. A Bonferroni correction was used to account for multiple comparisons ($\alpha = 0.05/9 = 0.006$). In order to determine the effect of individual thresholds while controlling for shared elements of perceptual noise, we then constructed multivariable regression models whereby each of the three CoP metrics was regressed on all three threshold measures, in addition to age, yielding three regression models. The primary analyses focused on CoP metrics quantified only in the mediolateral plane given the shared direction with the roll tilt stimulus. However, to determine the directional specificity of the relationship between roll-tilt thresholds and mediolateral sway, the above analyses were repeated for CoP data in the anteroposterior plane.

Secondary regression analyses were completed to assess the relationship between the significant predictors of sway in the "eyes closed, on foam" condition and balance performance in an "eyes open, firm standing" condition, where vestibular contributions are minimal (Fitzpatrick and McCloskey, 1994). This was done to further test our central hypothesis that noise resulting from canal-otolith integration influences postural control in conditions where vestibular cues are prioritized (eyes closed, on foam) rather than in conditions where alternative sensory systems are known to dominate (eyes open, on firm).

Several studies have log transformed vestibular perceptual thresholds to achieve normality (Benson et al., 1989; Grabherr et al., 2008) prior to analysis. However, quantile-quantile normal probability plots and the Shapiro-Wilk test of normality showed that the residuals from each of our regression models failed to deviate significantly from a normal Gaussian distribution, so we did not transform our data. All analyses were completed using Stata (v 16.1, College Station, TX).

## RESULTS

Mean vestibular perceptual velocity thresholds and velocity biases, as well as our CoP parameters of interest for each condition (eyes closed, foam and eyes open, firm), are listed in **Table 1**. Overall, roll-tilt vestibular perceptual velocity thresholds increased with increasing frequency (**Figure 2**) consistent with past reports (Valko et al., 2012; Bermúdez Rey et al., 2016; Lim et al., 2017). At all frequencies, confidence intervals for measured biases included zero, showing no evidence of directional asymmetry.

In the "eyes closed, standing on foam" balance task, univariate linear regression models showed a significant linear association between mediolateral RMSD of the CoP and 0.5 Hz roll tilt thresholds ($\beta = 5.31$, $p = 0.002$, 95% CI = 2.1–8.5; **Figure 3**). While a positive association can be observed between 0.5 Hz roll tilt thresholds and the mediolateral MV, this effect failed to reach statistical significance ($\beta = 9.13$, $p = 0.072$, CI = −0.87–19.1). No significant relationship was seen between 0.5 Hz thresholds and the mediolateral MF ($\beta = -0.09$, $p = 0.2$, 95% CI: −0.22–0.05).

Thresholds measured at 0.2 Hz (**Figure 4**) and 1 Hz (**Figure 5**), where otolith and canal cues respectively are more reliable, were not significantly associated with mediolateral MV (0.2 Hz: $\beta = 2.7$, $p = 0.69$, CI −11.1–16.6; 1 Hz: = 5.26, $p = 0.256$, CI −4–14.5), or mediolateral MF (0.2 Hz: $\beta = -0.16$, $p = 0.065$, CI −0.34–0.01; 1 Hz: $\beta = -0.0222$, $p = 0.72$, CI −0.15–0.1). A positive trend was seen between both 0.2 Hz and 1 Hz thresholds and mediolateral RMSD, however, these associations did not reach statistical significance (0.2 Hz: $\beta = 4.13$ $p = 0.083$, CI −0.57–8.83; 1 Hz: $\beta = 3.12$, $p = 0.053$, CI: −0.045–6.3; **Figures 4**, **5**, respectively).

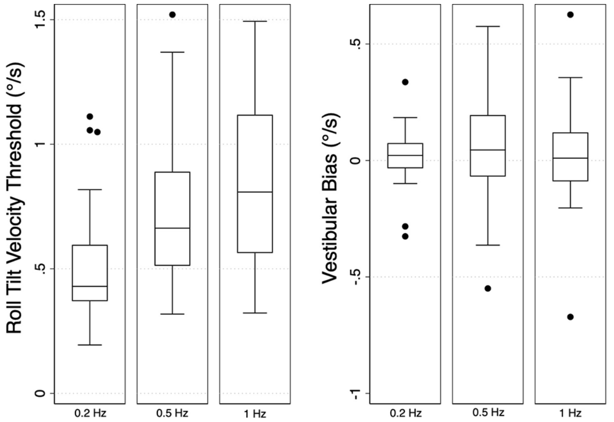

**FIGURE 2** | Box plots showing the median values and distributions of vestibular thresholds (left) and biases (right) for each frequency of head-centered roll tilt ($N = 33$). Velocity thresholds were found to increase with increasing frequency, while bias was similar at each frequency. Error bars represent ±1.5 times the first (Q1; 25th percentile) and third (Q3; 75th percentile) quartiles [interquartile range (IQR) = Q3 − Q1]. Outliers, defined as points greater than 1.5x the IQR, are shown as filled black circles.

After correcting for multiple comparisons, postural sway in the anterior-posterior plane orthogonal to the plane of motion for roll tilt thresholds was not associated with roll tilt perceptual thresholds at any frequency ($\alpha > 0.006$; **Figures 3–5**). However, there was a positive linear trend between 0.5 Hz roll tilt thresholds and anterior-posterior RMSD of the CoP ($\beta = 5.13$, $p = 0.016$, CI: 1.03–9.23) that was not statistically significant.

To ascertain if the relationship between postural control and 0.5 Hz thresholds was driven by elements shared between the three threshold measures (including individual elements of canal and otolith noise) multivariable regression analyses were completed. The significant positive relationship between 0.5 Hz thresholds and mediolateral RMSD persisted ($\beta = 5.44$, $p = 0.029$, CI = 0.60–10.28), while no significant relationship was seen for 0.2 Hz or 1 Hz thresholds (**Table 2**); this finding may reflect an association between postural control and the noise inherent to the temporally integrated canal-otolith signal. Similar to the univariate analyses, a positive trend between 0.5 Hz thresholds and mediolateral MV was observed but did not reach statistical significance (**Table 3**). Neither 0.2 Hz nor 1 Hz roll tilt thresholds showed a significant effect on any of the postural control measures (**Tables 2–4**) except a statistically significant relationship between the mediolateral MF and both 0.2 Hz thresholds and age was identified (**Table 4**). However, as both effects were small, and 0.2 Hz thresholds were negatively

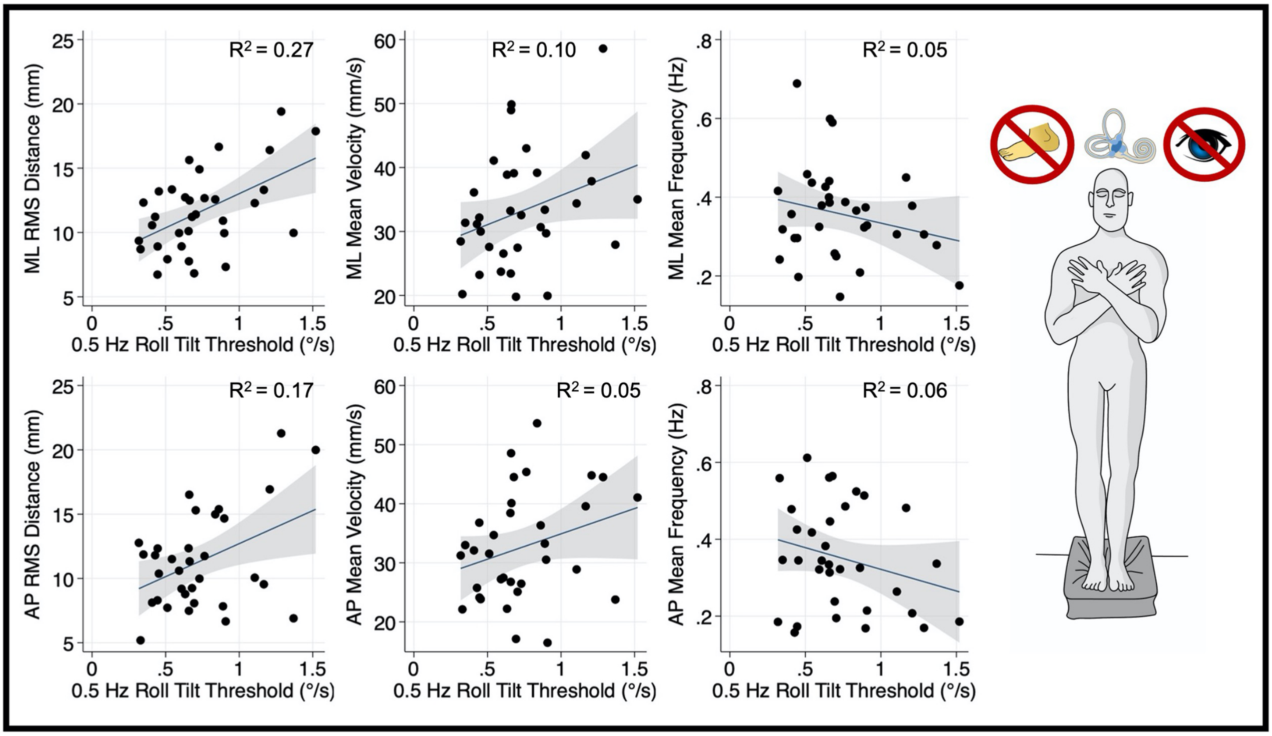

**FIGURE 3 |** Relationship between 0.5 Hz roll tilt thresholds and RMSD, mean velocity, and mean frequency for both the mediolateral plane (top) and anteroposterior plane (bottom) during an "eyes closed, on foam" balance task. To the right of the plots, the task and relevant balance control systems are displayed, showing a dominance of vestibular cues in the "eyes closed, foam" condition. Each data point represents one individual's performance. The blue line shows a linear fit with the 95% CI depicted by the gray shaded region. A statistically significant relationship between RMS distance and 0.5 Hz roll tilt was seen (upper left); not one of the five other associations plotted here was statistically significant. RMSD, root mean square distance.

associated with mediolateral MF, the importance is unclear. In addition, larger samples have shown that thresholds are stable under age 40, and thus, the weak, positive effect of age may result from sampling variability. When compared to CoP data measured in the AP direction, similar to the univariate analyses, no significant effects were observed between any of the threshold measures when regressed on each of the CoP metrics. While not significant, there was a positive relationship between 0.5 Hz roll tilt thresholds and AP RMSD ($\beta = 5.91$, $p = 0.057$, 95% CI = −0.2–12.03).

Our primary univariate analyses that assessed the relationship between vestibular noise, which we posit results from canal-otolith integration (i.e., 0.5 Hz roll tilt thresholds) and mediolateral postural sway were repeated for a balance task that relies minimally on vestibular cues (i.e., eyes open, firm surface; **Figure 6**). This focused analysis allowed us to assess if the statically significant relationship between vestibular perceptual thresholds at 0.5 Hz and postural sway is constrained to conditions where vestibular cues are prioritized for postural control. Unlike the "eyes closed, on foam" condition, for the CoP metrics calculated from the "eyes open, firm surface" condition, 0.5 Hz roll stilt thresholds did not demonstrate a statistically significant correlation with the mediolateral RMSD ($\beta = 0.028$, $p = 0.49$, 95% CI: −0.05–0.11), MV ($\beta = 0.017$, $p = 0.45$, 95% CI: −0.029–0.064), or MF ($\beta = 0.41$, $p = 0.45$, 95% CI: −1.5–0.68). This is consistent with the hypothesis that 0.5 Hz roll tilt thresholds and postural sway, when assessed in the presence of degraded visual and proprioceptive information, are each influenced by a shared noise source.

Finally, to determine if the relationship between 0.5 Hz roll tilt thresholds and postural sway was instead the result of a shared dominant frequency (i.e., 0.5 Hz), we performed a spectral analysis of the mediolateral and anteroposterior "eye closed, on foam" CoP data. Power spectral density (PSD) of the ML and AP CoP traces revealed that 95% of the power in the CoP signal resided below 0.11 ± 0.011 and 0.12 ± 0.018 Hz respectively (**Figure 7**). This supports the supposition that the correlative relationship between the perception of 0.5 Hz tilt stimuli and postural sway was not reflective of a shared dominant frequency, but instead supports that both share a common underlying physiologic element, herein hypothesized to be noise resulting from the temporal integration of noisy canal and otolith cues.

## DISCUSSION

Our data show that vestibular noise demonstrates a significant, positive association with postural sway variability. Specifically, increases in 0.5 Hz roll tilt thresholds, which quantify vestibular perceptual noise, were accompanied by increases in sway. As

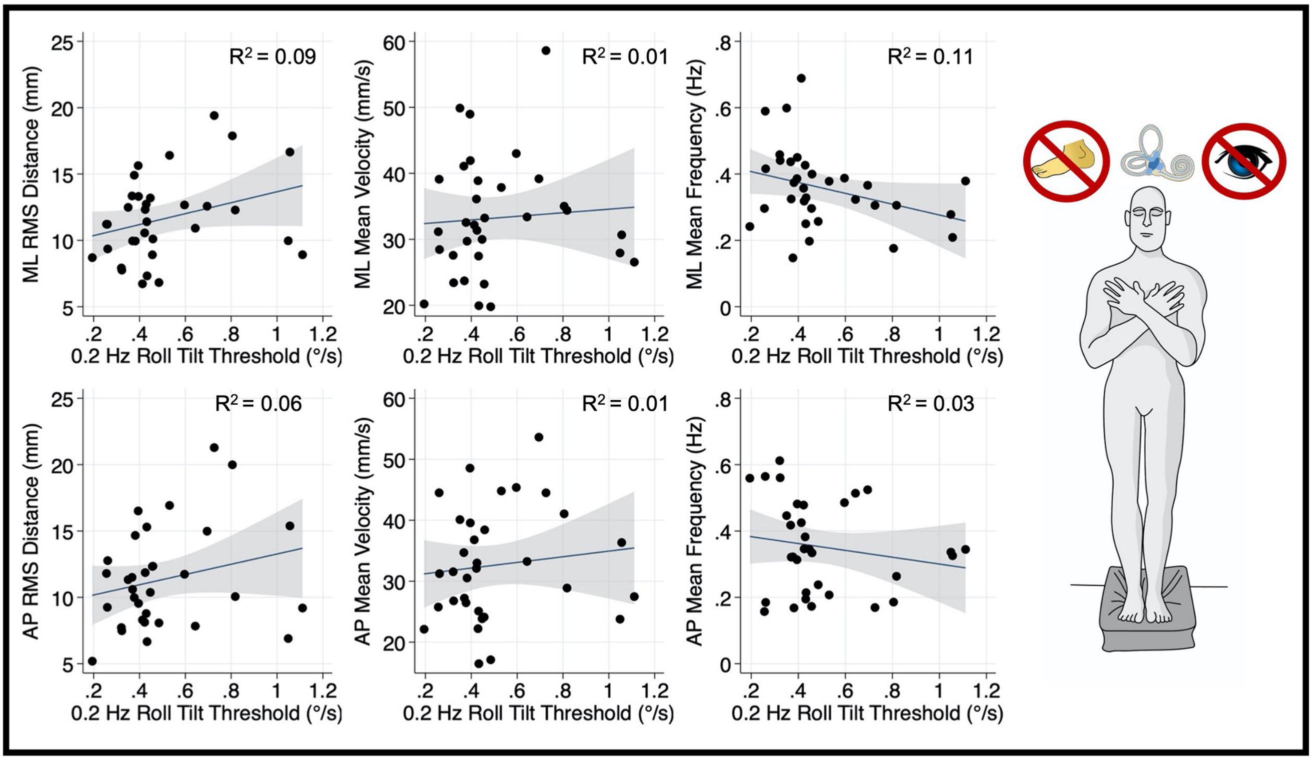

**FIGURE 4 |** Relationship between 0.2 Hz roll tilt thresholds and RMSD, mean velocity, and mean frequency for both the mediolateral plane (top) and anteroposterior plane (bottom) during an "eyes closed, foam" balance task. To the right of the plots, the task and relevant balance control systems are displayed, showing a dominance of vestibular cues in the "eyes closed, foam" condition. Each data point represents one individual's performance. The blue line shows a linear fit with the 95% CI depicted by the gray shaded region. No statistically significant relationships were seen between 0.2 Hz thresholds and postural sway. RMSD, root mean square distance.

**TABLE 2 |** Results of a multivariable linear regression model.

| ML RMSD | β | SE | t | p | 95% Conf. Interval | | Sig. |
|---|---|---|---|---|---|---|---|
| 0.2 Hz Roll Tilt | −0.48 | 2.791 | −0.17 | 0.865 | −6.197 | 5.238 | |
| 0.5 Hz Roll Tilt | 5.442 | 2.361 | 2.30 | 0.029 | 0.605 | 10.278 | * |
| 1 Hz Roll Tilt | 0.065 | 1.941 | 0.03 | 0.974 | −3.91 | 4.04 | |
| Age | 0.107 | 0.145 | 0.74 | 0.464 | −0.189 | 0.404 | |
| Intercept | 5.122 | 3.72 | 1.38 | 0.179 | −2.498 | 12.742 | |

*Controlling for 0.2 Hz and 1 Hz roll tilt thresholds, as well as age, 0.5 Hz roll tilt thresholds displayed a significant positive effect on the mediolateral RMSD in the "eyes closed, foam" condition. RMSD, root mean square distance; ML, mediolateral. *Significant at alpha < 0.05.*

**TABLE 3 |** Results of a multivariable linear regression model.

| ML MV | β | SE | t | p | 95% Conf. Interval | | Sig. |
|---|---|---|---|---|---|---|---|
| 0.2 Hz Roll Tilt | −9.747 | 8.408 | −1.16 | 0.256 | −26.969 | 7.476 | |
| 0.5 Hz Roll Tilt | 12.874 | 7.112 | 1.81 | 0.081 | −1.695 | 27.443 | |
| 1 Hz Roll Tilt | 0.483 | 5.845 | 0.08 | 0.935 | −11.491 | 12.457 | |
| Age | 0.598 | 0.436 | 1.37 | 0.181 | −0.295 | 1.491 | |
| Intercept | 13.348 | 11.205 | 1.19 | 0.244 | −9.605 | 36.301 | |

*None of the roll tilt threshold measures were found to have a significant effect on the mediolateral MV in the "eyes closed, foam" condition. MV, mean velocity; ML, mediolateral.*

this positive correlation with roll tilt thresholds was observed only at 0.5 Hz, it suggests that the association between postural sway and vestibular noise may be due to the shared influence of noise resulting from the temporal integration of noisy canal and otolith signals. In addition, this relationship appears to be greatest when: (1) the sway plane is concordant with the direction

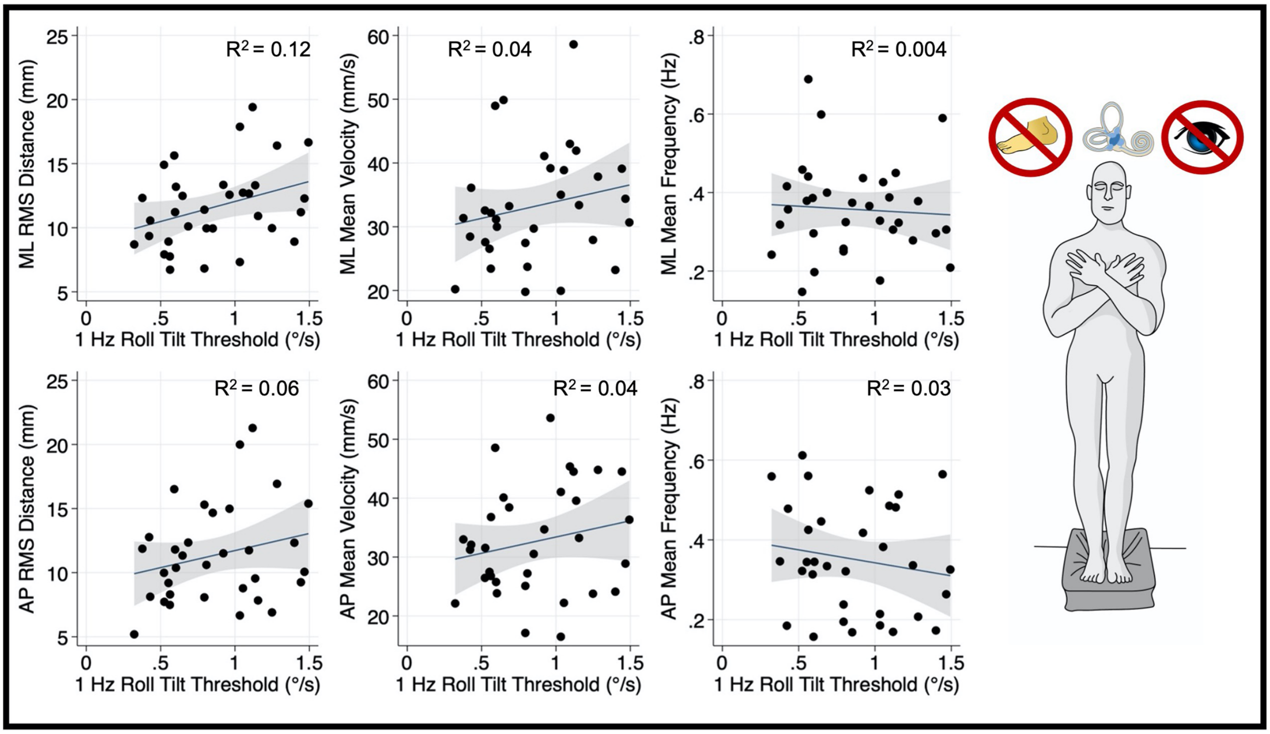

**FIGURE 5 |** Relationship between 1.0 Hz roll tilt thresholds and RMSD, mean velocity, and mean frequency for both the mediolateral plane (top) and anteroposterior plane (bottom) during an "eyes closed, foam" balance task. To the right of the plots, the task and relevant balance control systems are displayed, showing a dominance of vestibular cues in the "eyes closed, foam" condition. Each data point represents one individual's performance. The blue line shows a linear fit with the 95% CI depicted by the gray shaded region. No statistically significant relationships were seen between 1.0 Hz thresholds and postural sway. RMSD, root mean square distance.

**TABLE 4 |** Results of a multivariable linear regression model.

| ML MF | β | SE | t | p | 95% Conf. Interval | | Sig. |
|---|---|---|---|---|---|---|---|
| 0.2 Hz Roll Tilt | −0.223 | 0.106 | −2.10 | 0.045 | −0.441 | −0.006 | * |
| 0.5 Hz Roll Tilt | −0.035 | 0.09 | −0.39 | 0.697 | −0.219 | 0.149 | |
| 1 Hz Roll Tilt | 0.059 | 0.074 | 0.80 | 0.43 | −0.092 | 0.211 | |
| Age | 0.012 | 0.006 | 2.17 | 0.039 | 0.001 | 0.023 | * |
| Intercept | 0.148 | 0.142 | 1.04 | 0.306 | −0.142 | 0.438 | |

*None of the roll tilt threshold measures were found to have a significant effect on the mediolateral MF in the "eyes closed, foam" condition. MF, mean frequency; ML, mediolateral.*
**Significant at alpha < 0.05.*

of the roll tilt threshold stimulus, implying an influence of roll tilt vestibular noise on the spatial control of posture, and (2) quiet stance balance conditions where vestibular cues are prioritized and visual and proprioceptive cues are degraded (i.e., standing on foam with eyes closed). Finally, it appears that variability in the displacement of the body in space (i.e., RMSD) is most affected by vestibular noise, as statistically significant relationships were not apparent when the mean velocity (MV) or the mean frequency (MF) of the CoP were regressed on roll tilt thresholds.

## Temporal Integration and Spatial Control of Posture

An underappreciated role of the vestibular system is its capacity to provide a gravity-referenced estimate of one's position in space during complex, dynamic tasks (Merfeld, 1995; Glasauer and Merfeld, 1997; Angelaki and Cullen, 2008). The dynamic nature of vestibular function implies a temporal requirement whereby the vestibular system must sense the motion, integrate multiple self-motion cues, and continuously generate an appropriate behavioral output. As a result, the direction recognition task described herein inherently requires the vestibular system to possess the capacity to account for changes in stimulation over time in order to generate a precise estimate of the self-motion cue. Our results show that during a dynamic 0.5 Hz roll tilt motion, lasting two seconds, the precision by which the vestibular system integrates velocity cues from the canals with gravitational cues from the otoliths contributes significantly to one's ability to control their body in space during an "eyes closed, on foam" balance task where vestibular cues dominate. The implications for this finding are notable, as it suggests that the imprecision in these complex, time-dependent computations may contribute to the control of balance and may have implications for alternative

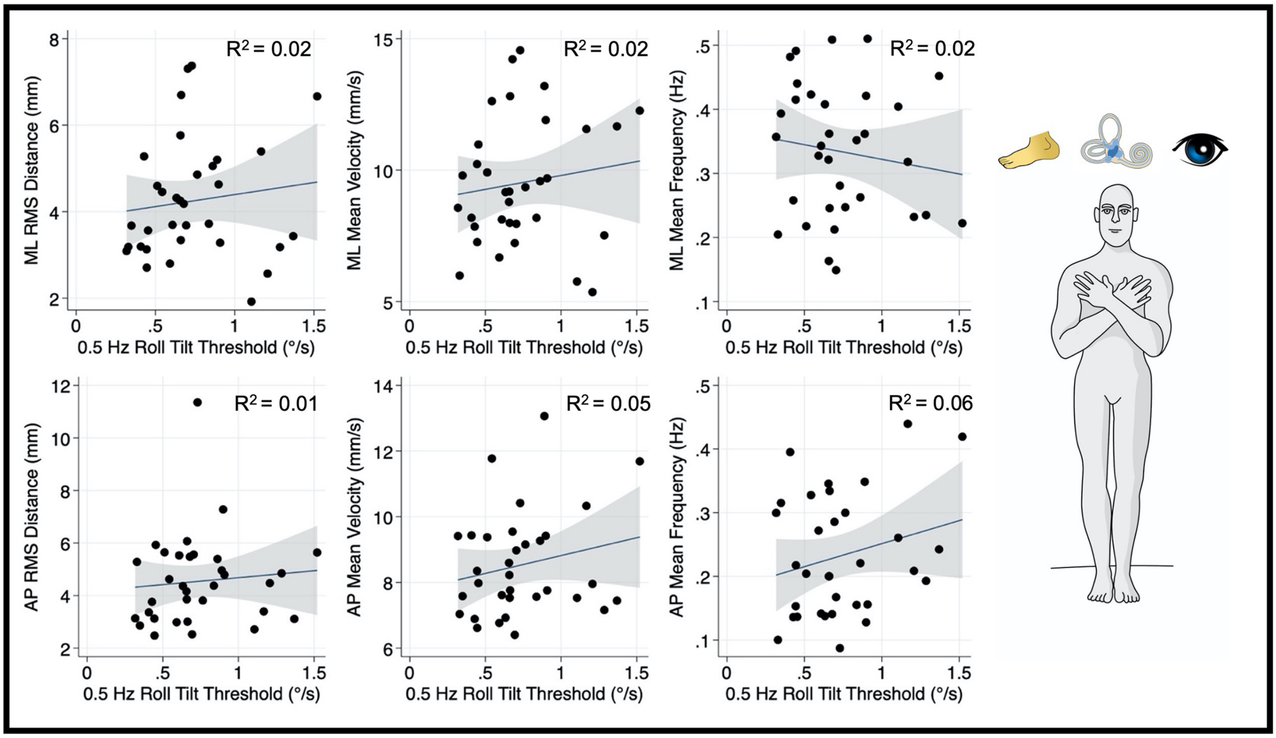

**FIGURE 6 |** Relationship between 0.5 Hz roll tilt thresholds and RMSD, mean velocity, and mean frequency for both the mediolateral plane (top) and anteroposterior plane (bottom) during an "eyes open, firm" balance task. To the right of the plots, the task and relevant balance control systems are displayed, showing the presence of proprioceptive and visual, as well as vestibular, cues in the "eyes open, firm" condition. Each data point represents one individual's performance. The blue line shows a linear fit with the 95% CI depicted by the gray shaded region. Unlike the "eyes closed, foam" condition, no significant linear effects were observed between RMSD, MV, or MF and 0.5 Hz roll tilt thresholds. MF, mean frequency; MV, mean velocity; RMSD, root mean square distance.

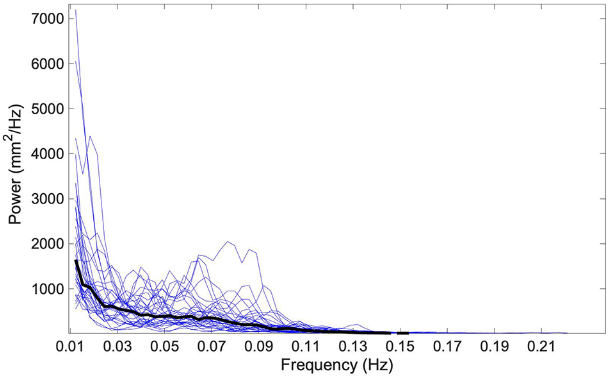

**FIGURE 7 |** The one-sided power spectral density (PSD) of the ML CoP tracing is shown using blue traces for each of the 33 subjects. The median spectral density calculated at each discrete frequency is shown by a solid black line. 95% of the power in the CoP signal is housed below 0.11 Hz; this is below the frequency for any of the roll tilt perceptual thresholds that were measured (0.2, 0.5, and 1 Hz). CoP, Center of Pressure; ML, mediolateral.

sequalae of vestibular impairment such as gaze instability, cognitive impairment, and autonomic dysregulation. Further, in our multivariable regression models where we controlled for elements common to the three threshold frequencies (e.g., cognition, tactile inputs from the motion device), we still found a significant relationship between 0.5 Hz thresholds and mediolateral postural sway, suggesting that noise associated with the temporal integration of noisy canal and otolithic cues may represent a critical element contributing to variability in postural sway when visual and kinesthetic cues are unreliable, degraded, or unavailable.

## Interpretation of the Frequency Effect

Lim et al. (2017) showed that on average, the dynamic angular velocity cue from the canals, and the tilt cue from the otoliths were optimally integrated during roll tilt at frequencies between 0.2 Hz and 0.5 Hz using an optimal Kalman filter model. Our finding that 0.5 Hz thresholds correlated with postural sway suggests that noise following the temporal integration of noisy canal and otolithic cues may affect postural control. The absence of a significant correlation between postural sway and 0.2 Hz thresholds, where canal-otolith integration presumably still occurs, suggests that the relative reliability of otolith and canal cues may influence this relationship.

At 0.2 Hz, the amplitude of tilt for a given velocity threshold is increased relative to 0.5 Hz (**Figure 1**), and as a result, 0.2 Hz roll tilt leads to greater stimulation of the tilt-sensitive otolith organs. The increased use of the otolith-derived tilt cue at 0.2 Hz is likely also accentuated by the decreased perceptual sensitivity to the canal-derived rotation cues at frequencies below

0.44 Hz (Lim et al., 2017). Therefore, we posit that the selective correlation between postural sway and roll tilt thresholds at 0.5 Hz, suggests that postural control is preferentially influenced by noise resulting from the temporal integration of noisy otolith and canal signals, rather than the noise in the otolith signal alone. The absence of a correlation between postural sway and 1 Hz roll tilt thresholds supports the supposition that the association between 0.5 Hz thresholds and postural sway reflects the influence of noise resulting from the integration of canal and otolith signals, rather than the central processing of the canal signal. Further, our data showing that more than 95% of the power in the postural sway signal was below 0.5 Hz (**Figure 7**), suggests that the selective relationship of 0.5 Hz thresholds was not simply reflective of a shared dominant frequency between the two tasks.

## Comparison to Past Empirical Studies

This effort represents one of only three datasets to compare balance to measures of vestibular perceptual noise, as quantified by vestibular thresholds. Karmali et al. (2017) analyzed data collected by Bermúdez Rey et al. (2016) and showed that 0.2 Hz roll tilt thresholds were significantly associated with the likelihood of completing the same "eyes closed, on foam" balance task (Bermúdez Rey et al., 2016; Karmali et al., 2017). While we similarly found a correlation between roll tilt thresholds and balance performance, we did not identify a significant effect for 0.2 Hz thresholds and only saw a relationship at 0.5 Hz. This may reflect differences in the study populations as we only enrolled young healthy adults, while the previous dataset assessed a wide age range (18–89 years) to capture the effects of healthy aging. Another difference, which may also reflect this difference in age of the populations, is that all 33 subjects in our study could complete the "eyes closed, on foam" balance task for 60 s, whereas Bermúdez Rey et al. (2016) reported that only 70/99 could stand in this same condition for 30 s (Bermúdez Rey et al., 2016). The difference in findings between our results and those of Karmali et al. (2017) may also have been due to the methods used to quantify balance performance. While we assessed continuous measures of the CoP quantified using a force plate, Bermúdez Rey et al. (2016) did not utilize a force plate, instead using a categorical "pass/fail" measure (Bermúdez Rey et al., 2016). Thus, 0.2 Hz thresholds may correlate specifically with age-related imbalance or may be reserved for more severe balance impairment, as represented by the inability to complete the aforementioned balance task.

In a more recent publication, Karmali et al. (2021) compared an expanded battery of vestibular thresholds to static postural sway, as well as computerized dynamic posturography, in a sample of healthy adults (21–61 years old; Karmali et al., 2021). They found that only interaural translation thresholds (performed at 1 Hz) were significantly correlated with postural sway (Karmali et al., 2021). A relationship between roll tilt thresholds and postural control was not identified; however, roll tilt thresholds were only quantified at 0.2 and 1 Hz, and not 0.5 Hz, and thus their findings are consistent with the findings reported here. Additionally, analogous to the selective correlation shown here between 0.5 Hz roll tilt and sway during the "eyes closed, on foam" condition, Karmali et al. (2021) similarly showed that correlations between thresholds and sway were strengthened in the conditions where proprioceptive cues were degraded.

The common directionality between interaural (left/right) translation thresholds and dynamic roll tilt, with both occurring in the mediolateral direction, is also worthy of consideration. While we showed that the effect of 0.5 Hz roll tilt was specific to postural sway in the mediolateral direction, Karmali et al. (2021) instead showed that interaural translation thresholds also correlated with postural sway in the anteroposterior direction. Thus, noise associated with the processing of otolith-derived linear acceleration signals, as reflected by interaural translation thresholds, may more generally influence the postural control system, whereas noisy canal-otolith integration may be specific to the spatial control of the body in the corresponding plane of motion. We do note that while the association between 0.5 Hz roll tilt thresholds and AP RMSD in our study was not significant, we did see a positive linear association which may have reached significance with a larger sample size, and thus we cannot rule out that roll tilt thresholds may also more generally predict postural sway in alternative planes.

We also highlight that the findings of Karmali et al. (2021) are not incongruent with the proposed mechanism linking canal-otolith integration to impaired postural control. During interaural translations, the otolith organs encode the net change in gravitoinertial force but cannot discern if the acceleration cues resulted from the effects of gravity, such as during a tilt of the head to the right, or due to a linear acceleration of the head to the left. Thus, the semicircular canals, yielding a signal that indicates an absence of rotation about an earth horizontal axis (i.e., no tilt), are required, analogous to during dynamic roll tilt, to dynamically update internal models within the central nervous system to permit the appropriate perception of the translation stimulus.

## Comparison to Theoretic Noise Parameters

Maurer and Peterka (2005) used simulations of CoP data to compare the traditional postural sway metrics reported here (i.e., RMSD, MV, and MF) to model parameters derived from a closed loop model of postural control. They found significant correlations between the noise parameter from their model (i.e., a Gaussian signal disturbing the balance system) and the RMSD and MV, but not MF, of the CoP (Maurer and Peterka, 2005). Here, we show that empirical measures of vestibular noise similarly display a significant association with the RMSD and no significant association with the MF of the CoP; however, unlike the theoretical model, none of our vestibular threshold metrics were significantly correlated with the MV, despite a positive association ($p = 0.079$) between 0.5 Hz thresholds and mediolateral MV. As these simulations by Maurer and Peterka were based on the performance of older adults, the effects of vestibular noise on CoP velocity may be emphasized by aging, which might have been tempered in our analysis of young healthy adults. While speculative, we posit that the correlations of both the empirical data (reported herein) and model-based noise parameters (Maurer and Peterka, 2005) with similar CoP metrics (RMSD, MV) suggest that postural control and roll tilt thresholds are influenced by a shared source of vestibular noise and that the selective correlation to 0.5 Hz roll tilt thresholds suggests that the common element is noise resulting from the temporal integration of noisy canal and otolith cues required to best estimate tilt.

### Limitations

Here we define self-motion perceptual thresholds as measures of vestibular sensory noise, however, we acknowledge the presence of extra-vestibular inputs during these tasks. The notion that direction recognition thresholds rely predominantly upon vestibular cues is supported by past data showing that perceptual thresholds were 2.5–56.8 times higher in patients with absent bilateral vestibular function (due to bilateral labyrinthectomy/neurectomy; Valko et al., 2012). Due to time constraints (i.e., limiting the battery to <2 h) we only captured thresholds across a narrow range, and thus future studies would benefit from utilizing both higher (>1 Hz) and lower (<0.2 Hz) frequencies to better isolate canal and otolith noise relative to the centrally integrated canal-otolith signal. As well, future studies could further explore the directional specificity of the relationship between canal-otolith integration and postural sway by quantifying vestibular thresholds in additional planes of motion (e.g., pitch tilt). As a final limitation, to avoid "fishing", we pre-selected only three of the many (>15) possible metrics commonly used to describe the CoP (Prieto et al., 1996). Yet, we highlight that previous data (Maurer and Peterka, 2005) has shown that CoP metrics naturally separate into three distinct groups of highly correlated variables. To avoid redundant analyses and associated "fishing" for statistically significant findings, we a priori chose to only use one CoP measure from each category [i.e., displacement (RMSD), velocity (MV), and frequency (MF)] in this study.

## CONCLUSION

Our data showed that vestibular noise resulting from the temporal integration of noisy canal and otolith signals is significantly and positively associated with the amount of variability in postural sway in the corresponding mediolateral plane. These findings suggest that the precision by which the vestibular system integrates canal and otolith signals over time significantly impacts the ability to control the position of the body in space.

## 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. 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

AW, MK, and DM conceptualized the experiment. AW and MK collected the data. AW analyzed the data and wrote the initial draft of the manuscript. MK 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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# Contributions of Body-Orientation to Mental Ball Dropping Task During Out-of-Body Experiences

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Out-of-body experiences (OBEs) provide fascinating insights into our understanding of bodily self-consciousness and the workings of the brain. Studies that examined individuals with brain lesions reported that OBEs are generally characterized by participants experiencing themselves outside their physical body (i.e., disembodied feeling) (Blanke and Arzy, 2005). Based on such a characterization, it has been shown that it is possible to create virtual OBEs in immersive virtual environments (Ehrsson, 2007; Ionta et al., 2011b; Bourdin et al., 2017). However, the extent to which body-orientation influences virtual OBEs is not well-understood. Thus, in the present study, 30 participants (within group design) experienced a full-body ownership illusion (synchronous visuo-tactile stimulation only) induced with a gender-matched full-body virtual avatar seen from the first-person perspective (1PP). At the beginning of the experiment, participants performed a mental ball dropping (MBD) task, seen from the location of their virtual avatar, to provide a baseline measurement. After this, a full-body ownership illusion (embodiment phase) was induced in all participants. This was followed by the virtual OBE illusion phase of the experiment (disembodiment phase) in which the first-person viewpoint was switched to a third-person perspective (3PP), and participants' disembodied viewpoint was gradually raised to 14 m above the virtual avatar, from which altitude they repeated the MBD task. During the experiment, this procedure was conducted twice, and the participants were allocated first to the supine or the standing body position at random. Results of the MBD task showed that the participants experienced increased MBD durations during the supine condition compared to the standing condition. Furthermore, although the findings from the subjective reports confirmed the previous findings of virtual OBEs, no significant difference between the two postures was found for body ownership. Taken together, the findings of the current study make further contributions to our understanding of both the vestibular system and time perception during OBEs.

**Keywords: out-of-body experience (OBE), vestibular system, virtual reality (VR), mental ball dropping (MBD) task, full-body ownership illusion**

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## INTRODUCTION

Out-of-body experiences (OBEs) are a type of autoschopic phenomena characterized by a sense of disembodiment (Blanke and Arzy, 2005). During OBEs, most people experience themselves in an elevated position, and this feeling is usually followed by the sensation of floating or flying localized in an extracorporeal space (Blanke et al., 2004; Bradford, 2005; Pfeiffer et al., 2014b). In the literature, OBEs were reported in various situations, including during seizures (Devinsky et al., 1989), after artificial brain stimulation (Blanke et al., 2002, 2004), and after damage to certain brain regions [i.e., the temporoparietal junction (TPJ)] (Blanke and Mohr, 2005; Blondiaux et al., 2021). Additionally, findings from the transcranial magnetic stimulation studies on the TPJ and galvanic vestibular stimulation provide further evidence for vestibular system involvement contributing to changes in visuo-spatial perspective and self-location during OBEs (Blanke et al., 2005; Lenggenhager et al., 2008). Based on these findings, it was suggested that the brain regions involved in OBEs are not only involved with vestibular processing, but are also engaged with information from different sensory modalities (Blanke et al., 2002; Ionta et al., 2011a) and related to a variety of cognitive processes, including perspective change (Palla and Lenggenhager, 2014; Deroualle et al., 2015; Pavlidou et al., 2018) and time perception (Clément, 2018; Huberle and Brugger, 2018).

Over the last decade, OBE-like experiences were also reported in healthy people (Braithwaite et al., 2011, 2013; Smith and Messier, 2014), and were experimentally induced through multisensory conflict using virtual reality techniques (Ehrsson, 2007; Lenggenhager et al., 2007, 2009; Bourdin et al., 2017). The experimental setups used during these OBE-like experiences were adapted from the original rubber-hand illusion (Botvinick and Cohen, 1998) and later used to study full-body ownership illusion (Blanke and Metzinger, 2009). Here, during a full-body ownership illusion experiment, the participants received simultaneous (synchronous) stroking to their physical body and were asked to see the visual stimulus applied to the same body location over the fake body, leading them to report an increased feeling of ownership over the fake body and to feel closer to it (Ehrsson, 2007; Lenggenhager et al., 2007). Over the years, studies employed full-body ownership illusion to study not only changes in the body-ownership but also used it to study changes in self-location (Ehrsson, 2007; Lenggenhager et al., 2007; Ionta et al., 2011b; Guterstam et al., 2015a). In fact, within the scope of the present article, a previous study by Tekgün and Erdeniz (2021) showed that full-body ownership illusion can be induced in a supine body position, providing support for the influence of vestibular signals on illusionary ownership and changes in self-location (Lenggenhager et al., 2009; Pfeiffer et al., 2014b; Pavlidou et al., 2018). Thus, it was suggested that the vestibular system and its significant role in body orientation is the main modulator of multisensory processing (Lopez et al., 2009; Lopez and Blanke, 2011; Kaski et al., 2016). This was evidenced by a wide range of experimental studies revealing that body orientation influences different aspects of bodily self-consciousness, such as perspective and self-location change (Lopez et al., 2008b, 2015; Lenggenhager et al., 2009; Thür et al., 2019; Tekgün and Erdeniz, 2021). In line with such findings, the supine body position (body-orientation in pitch axis) was shown to be associated with less accurate verticality judgments compared to sitting or standing positions (Templeton, 1973; Lichtenstein and Saucer, 1974; Goodenough et al., 1981; Tekgün and Erdeniz, 2021). This difference was supported by an early study by Saj et al. (2005), showing that patients with spatial neglect improved their performance in verticality judgments in the supine position, due to reduced asymmetrical otolith inputs. These differences are likely explained by the reduced vestibular signals available when in the supine position (Lopez and Blanke, 2010; Lenggenhager et al., 2015), similar to findings observed in microgravity environments (Lackner, 1992; Oman, 2003; Clément and Reschke, 2008; Erdeniz and Tükel, 2020; Meirhaeghe et al., 2020) and space flight analog studies, involve bed-rest (Moore et al., 2011; Koppelmans et al., 2013; Mulavara et al., 2018).

Therefore, one of the main assumptions inherent in the concept of multisensory weighting is that the supine position decreases in weight for vestibular inputs in favor of other sensory modality inputs (Lenggenhager et al., 2015). Of interest, previous studies also demonstrated that OBEs are more frequently experienced by those in the supine position (i.e., lying in bed) compared to standing (Blackmore, 1982; Irwin, 1985; Blanke et al., 2004). This difference was confirmed in around 73% of healthy individuals (Green, 1968) and 80% of patients with the neurological problem (Blanke and Mohr, 2005). Additionally, individuals' reports of the feeling of flying and floating during these experiences provided further evidence for the association between real life OBEs and altered vestibular functioning (Lopez and Blanke, 2010).

Given this evidence and the fact that OBEs occur more frequently in the supine position (Lopez and Blanke, 2010), we hypothesized that participants would show greater changes in self-location in the supine position compared to the standing position. For this purpose, in a within-group experimental design, we manipulated participants' physical body orientation (standing and supine), measuring changes in self-location before and during a virtual OBE. Similar to previous studies (Lenggenhager et al., 2009; Bourdin et al., 2017), in the current experimental setup, the participants were first introduced to a full-body ownership illusion (embodiment phase), during which a visual stimulus on the virtual body was applied synchronously with a tactile stimulus on the physical body. Following that, in the OBE phase (disembodiment phase), participants' visuo-spatial perspective switched to a third person view point, which moved to a higher location in the virtual room. Our main hypothesis on self-location was tested with a mental ball dropping (MBD) task in which the participants estimated the duration of an imaginary ball falling to the ground from their imagined location in their out-of-body experience. In this study, the MBD task allowed us not only to interpret changes in self-location during a virtual OBE but also to speculate about the changes in participants' time perception ability. Moreover, participants' subjective experiences on body-ownership and self-location were measured with a questionnaire after the embodiment and disembodiment phases. We expected an increased feeling of ownership during the former phase compared to the latter.

# MATERIALS AND METHODS

## Participants

Based on studies similar to the current experimental setup (Lenggenhager et al., 2007, 2009; Aspell et al., 2009; Bourdin et al., 2017), *a priori* sample size calculation was performed for an effect size of 0.8 at 0.05 alpha level by using G*Power software (Faul et al., 2007). Based on that, for a one-tailed Wilcoxon signed-rank test for matched pairs (i.e., supine duration > standing duration), a required total sample size of 12 was considered necessary to reach 80% of power (Hintze, 2008). In the present study, the participants were a total of 30 volunteers (11 men, 19 women) between the ages of 19 and 39 ($Mage = 24$, $SD = 3.93$), all recruited from Izmir University of Economics. No participants reported any previous history of psychological, psychiatric, or neurological disorder, and all had normal or corrected to normal vision. Additionally, based on our demographic questionnaire, none of the participants reported experience of dizziness, ringing in the ears, vertigo, or a postural imbalance prior to the experiment. Before the experiment, the participants signed a written informed consent form and completed a questionnaire about demographic information, including their age, sex, and education levels. The present study was approved by the ethics committee of the Izmir University of Economics (No: B.30.2.IEU.0.05.05-020-066) and conducted according to the Helsinki regulations.

## Equipment and Setup

To create a wide field of view, PIMAX 5K plus head-mounted display (HMD) (https://pimax.com/about-us/) was used to present the virtual environment (200° field of view, 120 Hz). The environment was built using the game development platform UNITY 3D (https://unity.com/) version 2019.1. Two virtual characters, a male and a female avatar, were created to match the participants' gender, using Make Human software (http://www.makehumancommunity.org/). Previous studies used either real or virtual characters seen from 3PP in a dark virtual environment (Ehrsson, 2007; Lenggenhager et al., 2007, 2009) or virtual characters seen from 1PP in a virtual environment with contextual cues (i.e., virtual furniture) (Bourdin et al., 2017). In the present study, we combined the elements from the previous studies by presenting the participants with a virtual character seen from a 1PP in a dark virtual environment (refer to **Supplementary Movies 1, 2**). Here, the virtual environment was totally darkened, and the participants could see only their virtual body and its reflections on a full-height virtual mirror in front of them (González-Franco et al., 2010; Blom et al., 2014). Considering our focus on investigating the contribution of the vestibular system, we created the virtual characters both in the supine and standing positions, congruent with participants' physical body position. Based on that, the participants completed the experimental procedure both in the standing and supine positions on a stretcher with head supported by a yoga block to compensate for the pressure from the neck (Trousselard et al., 2003; Bringoux et al., 2018) and to minimize the proprioceptive and vestibular signals coming from the neck muscles (Mergner et al., 1997; Pettorossi and Schieppati, 2014). To account for differences in participants' height, the height of the stretcher in the supine position was calibrated to the distance of each participants' hand above the ground in the standing position (refer to **Supplementary Figure 1**). To animate participants' movements into virtual bodies, two HTC VIVE controllers and the Final IK asset (https://assetstore.unity.com) were used during the adaptation period of the full-body ownership illusion. To induce full-body ownership illusion, a synchronous visuo-tactile stimulation was applied with the controllers. The tactile stimulus was delivered to the abdomen of the physical body, and a spatially and temporally matched visual stimulus was seen on the corresponding location of the virtual body. OBEs were induced by manipulating the position of the virtual camera in UNITY, providing 3PP by moving the camera to an elevated position (14 m from the virtual floor) outside the virtual body, and slightly rotating it around the body x-axis, similar to the method by Bourdin et al. (2017). This perspective transformation followed a diagonal path until it reached a height of 14 m with the velocity of the camera adjusted to 0.18 m/s. Here, it is important to note that the height of 14 m was calculated not based on the relative initial camera position but is based on the absolute difference between the virtual floor and the final camera position. During the transition from 1PP to 3PP, the virtual body was stationary, but the camera rotation attached to the head of the virtual body was still under participants' control. These manipulations were based on the previous reports of OBE (Blackmore, 1982; Metzinger, 2009) and adapted from previous experimental setups (Bourdin et al., 2017). Furthermore, participants' accuracy in time perception was measured by a time reproduction task before each experimental session. For that, audacity (https://www.audacityteam.org) was used to create five auditory stimuli (sinus wave 440 Hz) with different durations (1.355, 1.916, 2.346, 2.709, and 3.029 s) which were presented through the participants' headphones. Then, changes in self-location were compared using MBD, in which the participants were asked to hold down the mouse button for the duration of the estimated time taken between the ball being released from the hand and it hitting the floor (refer to section Measurements for details). To ensure accuracy, Python 3.7 was used to record mouse button presses in both the time reproduction task and MBD task.

## Procedure

Each participant took part in two experimental sessions, which included embodiment and disembodiment phases, each including standing and supine positions. Before the experiment, it was ensured that the order of the standing and supine positions was counterbalanced, and the participants were randomly assigned to one condition. After putting on the headphones and holding the mouse in their right hands, in the standing position, the participants began the experiment with the time reproduction task, using the mouse to replicate five different fall durations with eyes closed, and without the head-mounted display.

After the headphones were retrieved, the participants were instructed about the MBD task, which they completed five times with their eyes closed in the standing position. After the mouse was retrieved, the participants were fitted with the HMD and given the VR controllers to hold. During the 1-min adaptation period, the participants were familiarized with the virtual body as they observed their head and arm movements, while their feet remained stationary (Tekgün and Erdeniz, 2021). Following that, the experimenter retrieved the controllers and returned the mouse to the participants, who were asked to wait for instructions before using it. Then, the full-body ownership illusion was induced for 1 min through visuo-tactile stimulation by tapping and stroking participants' physical body synchronously with a visual stimulation on the virtual body. During the illusion, the participants were instructed to make no bodily movements, but to focus on the visual stimulus on the virtual body by looking either directly from 1PP or in the virtual mirror reflection (Tekgün and Erdeniz, 2021).

After the full-body ownership illusion, the virtual OBE phase was initiated, in which participants' 1PP began to elevate as though gliding slowly upward, giving the impression of being 14 m above the virtual body. During this time, the virtual body was stationary, but the camera rotation was still under participants' control. When looking down, the participants saw the virtual body in a position congruent with their physical body (refer to **Supplementary Movies 1, 2**). After the visuo-spatial perspective transition in the OBE phase, the participants performed the MBD task five times while seeing their virtual body 14 m below them. HMD was then removed, and the participants completed the subjective report on illusory full-body ownership experiences and OBEs. The HMD was reattached, and the same experimental procedure was implemented for the other body position condition, except for the time reproduction task. After the experiment, the participants were thanked and debriefed; their questions about the experiment were answered. **Figure 1** illustrates the experimental design.

## Measurements

### Time Reproduction Task

At the beginning of the experiment, a time reproduction task was given to measure participants' time reproduction skills (Kitamuraa and Kumarb, 1984; Mioni et al., 2014). The participants listened to five different randomly presented auditory stimuli (1.355, 1.916, 2.346, 2.709, or 3.029 s) corresponding to free-fall times of an imaginary ball falling from different heights (9, 18, 27, 36, or 45 m). The durations were calculated based on the law of free fall (no air resistance) and calculated by the following equation (refer to Bratzke and Ulrich, 2021 for details):

$$h(t) = 1/2\, gt^2$$

According to this equation, $h$ corresponds to height, $t$ denotes fall time, and $g$ refers to acceleration factor (9.807 $m/s^2$). Before listening, the participants closed their eyes and were informed that the sounds were associated with a ball dropped from a certain height. Here, the reason for emphasizing the need to reproduce the duration of a falling object is the ability of the participants to achieve accurate measurement in the time reproduction task by facilitating their mental imagery (Taatgen et al., 2007; MacPherson et al., 2009; Hargreaves, 2012), as well as to prepare them for the MBD task. However, in order to prevent the participants from learning these height-duration associations, they were not informed about the actual heights. After hearing each sound, they were asked to replicate its duration by pressing and releasing the mouse button. This measurement allowed us to note any serious impairment in time reproduction skills.

### Mental-Ball Dropping Task

In the present study, as an implicit measure of self-location, we used MBD task in which the participants imagined the duration of the fall of the imaginary ball from their hand to the ground (Lenggenhager et al., 2009; Ionta et al., 2011b; Salomon et al., 2013; Bourdin et al., 2017). Two MBD tasks were administered in different phases of the experiment. First, in the baseline phase (*base-MBD*), the participants performed the MBD task with their eyes closed without HMD. For this measurement, it was particularly emphasized that the task should be performed from a ground level in the physical room. Following that, after the OBE phase (*obe-MBD*) in the virtual environment, the participants performed the second MBD task while watching their virtual body 14 m below them. For this measurement, particular emphasis was placed on the need for those participants to complete the task relative to their perception of the experienced ground level. In each phase, the MBD task was performed 5 times, resulting in 10 MBD measurements for each body orientation condition (supine and standing), thus in total 20 MBD measurements (10 per condition) were collected from each participant.

### Self-Report Questionnaire

After the experiment, the participants were presented with an adapted version of the questionnaire from previous studies (Botvinick and Cohen, 1998; Lenggenhager et al., 2007). The questionnaire was presented in two parts: the first included items about full-body ownership illusion, and the second, items about OBE. The full-body ownership illusion was assessed by 2 items focusing on body ownership (*FBI1*), and self-location (*FBI2*). For the OBE phase, 5 items, such as body-ownership (*OBE1*), disembodiment (*OBE2*), vestibular sensations (*OBE3*), elevated visuo-spatial perspective (*OBE4*), and connection with the body (*OBE5*) were, respectively, tested. A paper-based questionnaire with a total of 8 items was presented on the visual analog scale (VAS) consisting of a 10 cm line with "strongly disagree" on the extreme left and "strongly agree" on the extreme right. **Table 1** shows all the items in the questionnaire.

## Data Processing and Statistical Analysis

Statistical analysis was performed with SPSS 20. First, to evaluate participants' time reproduction ability, and its deviations from the ideal free-fall model, we performed a linear regression

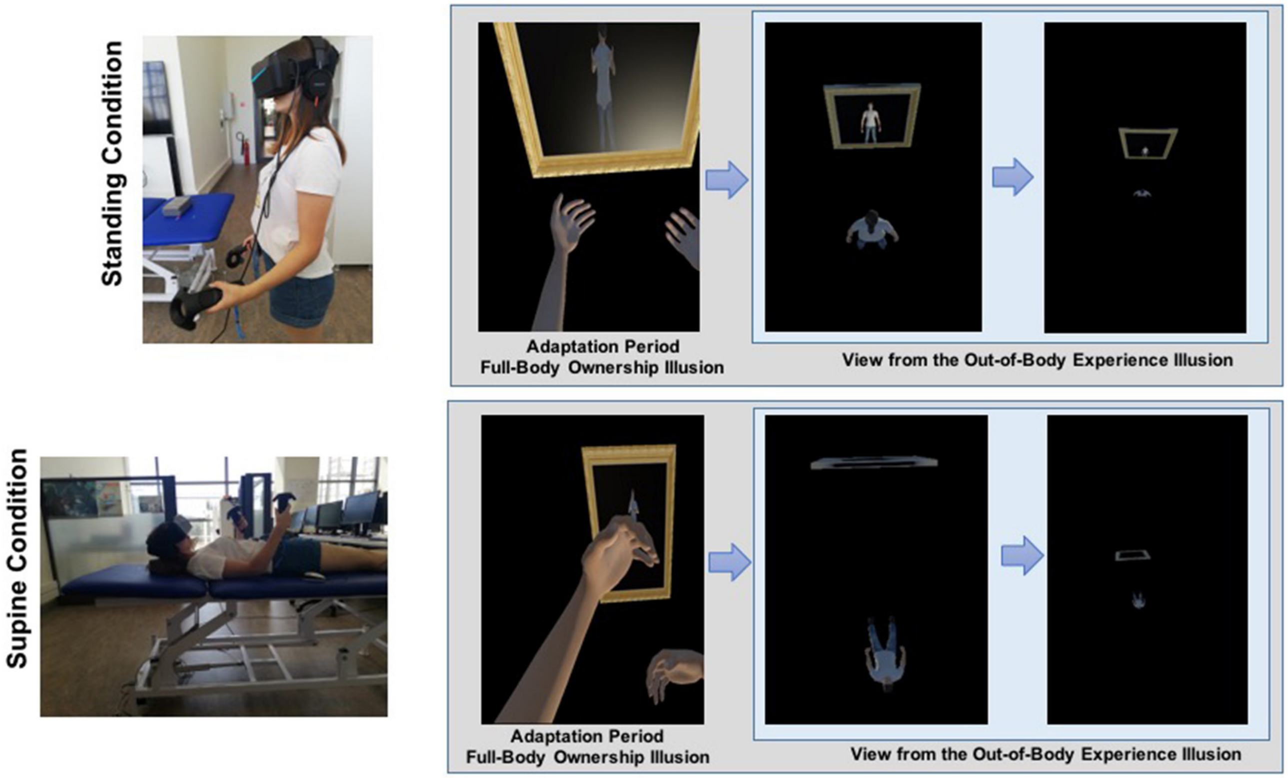

**FIGURE 1 |** Illustration of the experimental design. **(A)** Standing condition and **(B)** supine condition. During the full-body ownership illusion, participants experience the virtual body from the first-person perspective (1PP) while being subjected to synchronous visuo-tactile stimulation. In the virtual out-of-body experiences, 1PP of participants is shifted toward up, 14 m above the virtual body.

**TABLE 1 |** The list of self-report questionnaire items for full-body ownership illusion and out-of-body experience (OBE).

| Item names | Item statements |
|---|---|
| **Immediately after the time of seeing the virtual body was stroking synchronously with your physical body and reflected onto the virtual mirror** | |
| Ownership (FBI1) | I felt as if the virtual body was my own body. |
| Self-location (FBI2) | I felt as if my body was located at where the virtual body was. |
| **Immediately after the experience of watching the room from above** | |
| Ownership (OBE1) | I felt as if the virtual body was my own body. |
| Disembodiment (OBE2) | I felt out of my virtual body. |
| Vestibular sensation (OBE3) | I felt as if I was floating in air. |
| Visuo-spatial perspective (OBE4) | I felt as if I was in an elevated position in the room. |
| Body connection (OBE5) | I felt a connection with the virtual body as if I was looking down at my virtual body. |

analysis on the time reproduction data. Second, we performed Shapiro–Wilk-test to check for normality assumption, which showed that the data was normally distributed for the Self-Report Questionnaire but not for the MBD task. Therefore, for the MBD task, we used a non-parametric test, the one-sided Wilcoxon signed-rank test, to compare changes in *obe-MBD* and *base-MBD* times in the standing position to those in the supine position. We also computed the average changes in MBD times for each body orientation by subtracting *base-MBD* times from *obe-MBD* (Bourdin et al., 2017) and compared these using Wilcoxon signed-rank test. Thus, to test whether answers to questions differ across the standing and supine body positions, we analyzed the Self-Report Questionnaire using a paired-sample *t*-test.

# RESULTS

## Time Reproduction Task

To analyze participants' accuracy of time reproduction, for each participant, we investigated estimated durations associated with

**TABLE 2 |** Descriptive statistics results of the time reproduction task.

| | Auditory Stimuli | | | | |
|---|---|---|---|---|---|
| | **1355 (ms)** | **1916 (ms)** | **2346 (ms)** | **2709 (ms)** | **3029 (ms)** |
| Mean (ms) | 1,342.20 | 1,692.43 | 2,245.80 | 2,713.86 | 2,967.50 |
| SE (ms) | 78.77 | 70.71 | 137.81 | 103.33 | 100.75 |

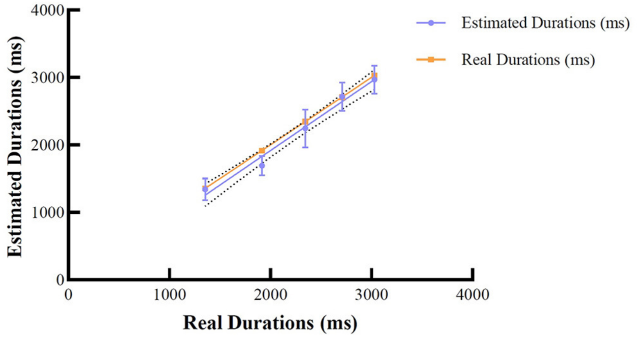

**FIGURE 2 |** Means for the estimated durations and real durations based on the law of free fall. Error bars represent 95% CIs.

the ideal free-fall time (real durations) (Bratzke and Ulrich, 2021). To achieve this, we first calculated participants' mean durations (refer to **Table 2**) and fitted a linear regression model with ideal durations based on the law of free fall as the predictor, and estimated durations as the dependent variable. Overall, the results demonstrated a good model fit ($R^2 = 0.546$). The result revealed that the slopes were not significantly different, $F_{(1,296)} = 0.086$, $p = 0.769$. That is, the means of the estimated durations were similar to the real durations, i.e., the participants were capable of reproducing time durations (pooled slope equals 1.011). **Figure 2** illustrates the linear fit model for the mean of estimated durations corresponding to each real duration. The mean duration estimates for each type of auditory stimuli can be seen in **Table 2**.

## Mental-Ball Dropping Task

First, to verify the effect of OBEs on the MBD task, we used Wilcoxon signed-rank test to compare MBD scores between the standing-baseline/supine-baseline and standing-OBE/supine-OBE positions. Exploration of MBD task times revealed that participants' baseline MBD times were on average 960 ms in the standing position (*Mdn* = 655.5) and 970 ms in the supine position (*Mdn* = 792), and as expected, the difference was not significant, $T = 309.5$, $z = -1.58$ $p = 0.06$, $r_B = -0.331$. Regarding the MBD times during OBEs, estimations of MBD times were on average 1,348 ms in the standing position (*Mdn* = 1,107), whereas estimations were about 1,517 ms in the supine position (*Mdn* = 1,285). The statistical analysis showed a significant difference between the standing and supine positions, $T = 322$, $z = -2.26$ $p = 0.01$, $r_B = -0.480$. Furthermore, supine-OBE and standing-OBE durations were compared against the law of free fall for 14 m that corresponds to 1,689 ms. Here, the supine-OBE ($z = 161$ $p = 0.144$, $r_B = -0.305$) position showed no significant difference from 1,689 ms. The standing-OBE ($z = 112 = p = 0.013$ $r_B = -0.518$) durations showed significantly shorter times than 1,689 ms. This suggests that during OBEs, the participants experienced more elevated self-location, as measured by MBD response times, in the supine position as compared to the standing position. A figure representing the results is available in **Supplementary Figure 3**. To clearly show the shift in self-location, we analyzed the difference between *base-MBD* times and *obe-MBD* times for each body position using Wilcoxon signed-rank test. The changes in MBD times in the supine position were on average 547 ms (*Mdn* = 347) compared to an average of only 388 ms (*Mdn* = 215) in the standing position. The statistical analysis revealed that the changes in MBD estimations were significantly smaller in standing compared to supine positions, $T = 319$, $z = -1.78$, $p = 0.038$, $r_B = -0.372$ (**Figure 3**).

## Self-Report Questionnaire

**Figure 4** shows the results of paired sample *t*-test. For items related to full-body ownership illusion, there was no significant difference between the standing and supine positions. On average, participants' ratings for body-ownership (*FBI1*) in the standing position ($M = 61.1$, $SE = 3.86$) were not statistically different from the ratings in the supine position ($M = 62.8$, $SE = 3.77$), $t_{(29)} = -0.433$, $p = 0.67$. For ratings on self-location (*FBI2*), the difference between standing ($M = 64.9$, $SE = 4.3$) and supine positions ($M = 60.8$, $SE = 3.73$) was also non-significant, $t_{(29)} = 0.11$, $p = 0.23$. During OBEs, the participants reported similar body-ownership (*OBE1*) experience in standing ($M = 47.8$, $SE = 4.83$) and supine positions ($M = 47.1$, $SE = 4.77$), the difference was non-significant, $t_{(29)} = 0.11$, $p = 0.46$. The difference of disembodiment ratings (*OBE2*) between standing ($M = 48.9$, $SE = 4.96$) and supine positions ($M = 49.2$, $SE = 4.04$) was also non-significant, $t_{(29)} = -0.04$, $p = 0.52$. However, two of the items related to OBE phase revealed significant differences between standing and supine positions. The results for vestibular sensations (*OBE3*) revealed a significant difference between standing and supine positions, $t_{(29)} = 1.84$, $p = 0.04$, $d = -0.37$. That is, participants reported stronger vestibular sensations during OBE phase in the standing position ($M = 58.6$, $SE = 4.61$) compared to the supine position ($M = 49.2$, $SE = 4.34$). Similarly, the experience of elevated visuo-spatial perspective (OBE4) was stronger in the standing position ($M = 66.1$, $SE = 4.47$) compared to the supine position ($M = 49.1$, $SE = 4.98$), and the difference was statistically significant, $t_{(29)} = 2.40$, $p = 0.01$, $d = 0.44$. Rating for body connection item (OBE5) revealed that feeling of connection with the body was non-significant between the two positions, $t_{(29)} = 1.68$, $p = 0.052$. Participants rated OBE5 item on average with 55.7 points ($SE = 5.09$) in the standing position and 47.1 ($SE = 4.49$) in the supine position.

Additionally, to verify that full-body ownership illusion induced the illusory ownership of the virtual body, we used paired sample *t*-tests to compare the ratings of ownership items after the illusion with those after OBE, in both standing and supine positions. The results showed that participants experienced stronger feeling of ownership following the illusion both in the standing position, $t_{(29)} = 3.08$, $p = 0.005$, $d = 0.562$, and supine position, $t_{(29)} = 2.63$, $p = 0.014$, $d = 0.48$. On average, ownership ratings after the full-body ownership illusion were 14.48 points higher than the ratings after OBE, suggesting a successful induction of the illusion of body ownership and mild disembodiment during OBE as observed in the literature (Bourdin et al., 2017). A figure representing the results can be found in **Supplementary Figures 2**, **3**.

## DISCUSSION

Blanke and Mohr (2005) suggested that OBEs are characterized by three different subjective experiences: "the feeling of being outside one's physical body (or disembodiment); the presence of a distanced and elevated visuo-spatial perspective (or perspective); and the seeing of one's own body (or autoscopy) from this elevated perspective" (p. 186). On the basis of this characterization, we investigated the influences of the body-orientation on OBEs with a virtual OBE illusion set-up inspired by previous studies (Ehrsson, 2007; Lenggenhager et al., 2007, 2009; Bourdin et al., 2017). This was achieved by manipulating the physical body position and by comparing time estimations in the MBD task as an objective measure for quantifying the changes in self-location during the OBE illusion. Here, it is important to remember that the fundamental purpose of including the supine position was to create a condition with decreased vestibular input, and thus, bring about a modification of the sensory weighting strategies (Lopez and Blanke, 2010; Tekgün and Erdeniz, 2021), which might potentially increase the durations recorded in this position. In order to achieve this, first, the participants performed a time reproduction task with different durations corresponding to free-fall times of an imaginary ball falling from different heights. The results of this task showed that participants, on average, can successfully reproduce these durations and the mean durations have a good model fit based on the ideal free fall model. Furthermore, in order to explore the subjective changes in OBE, we adapted the questionnaire of Bourdin et al. (2017). The results of the questionnaire on body ownership showed no significant difference between the supine and standing positions, either during the full-body ownership illusion phase or during the out-of-body phase. However, a comparison of the main effect of ownership before (FBI1) and after the out-of-body phase (OBE1) (regardless of the body position) showed a significant fall in the body ownership scores for both conditions. This finding provides support for the successful induction of the sense of embodiment during full-body ownership illusion, which was lost during the OBE phase. Regarding our initial hypothesis related to self-location, the data from the MBD task showed increased MBD durations in the supine position compared to the standing position, suggesting greater changes in self-location in the former position. In summary, these

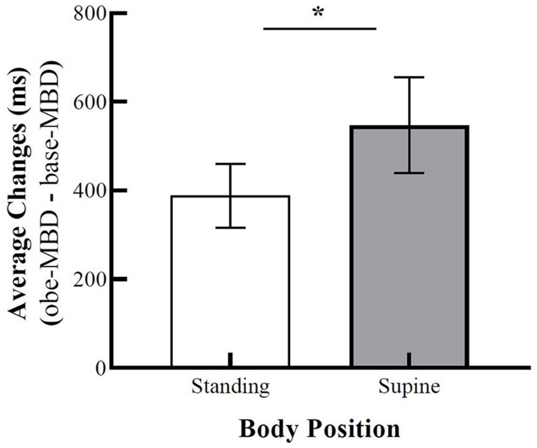

**FIGURE 3 |** Average changes in a mental ball dropping (MBD) task between baseline and OBE phases based on standing and supine conditions. Error bars represent SEM. Asterisk denotes a significance level of $p < 0.05$.

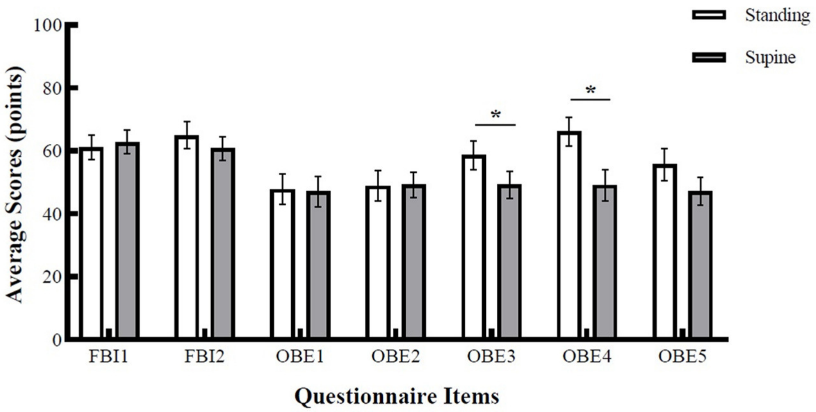

**FIGURE 4 |** Average scores of the self-report questionnaire. Error bars represent SEM. Asterisk denotes a significance level of $p < 0.05$.

results extend earlier findings regarding a stronger out-of-body experience in the supine position, and we discuss below possible explanations and alternative theoretical frameworks underlying these.

The first explanation related to increasing in MBD duration in the supine position is highlighted in studies showing that the vestibular system is involved in a multitude of functions, including spatial orientation (Brandt, 1999; Clément and Reschke, 2008; Clemens et al., 2011), perspective-taking (Deroualle et al., 2015; Lopez, 2016), mental imagery (Falconer and Mast, 2012; van Elk and Blanke, 2013), and time perception (Davis et al., 2009; Kaski et al., 2016). This explanation is based on the theory that the brain regions involved in OBEs and MBD have common neural origins in the TPJ and surrounding brain areas, covering parieto-insular areas (Blanke et al., 2004; Ionta et al., 2011b; Shinder and Newlands, 2014; Smith and Messier, 2014; Lopez and Elzière, 2018; Rousseau et al., 2019; Blondiaux et al., 2021). Here, it is important to note that, despite the debate over the exact cortical location of the vestibular system (Lopez and Blanke, 2011; Lopez et al., 2012; Frank and Greenlee, 2018), from its cortical interaction, it is considered that vestibular and other sensory signals with respect to the body orientation are likely to draw on shared neural resources, as well as computations carried out by adjacent or overlapping brain regions (Van Beuzekom and Van Gisbergen, 2000; Zupan et al., 2002; MacNeilage et al., 2006; Vrijer et al., 2008). In fact, a study by Kaski et al. (2016) showed that patients with TPJ lesions have impaired deficits in time estimation (motion duration) and position perception. It can be argued that different mental functions (i.e., mental imagery, spatial orientation, and timing) might share neural resources and that decreased vestibular input might lead to increased computational resources for other functions (Walsh, 2003; Huberle and Brugger, 2018), potentially increasing the estimated durations during the supine position. Referring to our results, MBD time during supine-OBE showed no significant difference from the ideal free fall estimate, while standing-OBE showed significantly shorter durations. According to the above explanation, one can argue that during supine OBE, the vestibular system (which is idle) and other related sensory systems can make more accurate estimations on the temporal changes related to bodily movements (Lacquaniti et al., 2015), by encoding the changes in the body and head movements in relation to gravity. This could then provide increased information about self-motion during the supine OBE, which could contribute to the accuracy of estimations regarding the changes in self-location and self-orientation in space (Seemungal, 2014). Therefore, in relation to its specific role in calculating the internal model of gravity, it can be argued that the vestibular system plays an important role in estimating the timing of spatiotemporal actions (McIntyre et al., 2001; Zago et al., 2004; Zago and Lacquaniti, 2005), even during virtual OBEs. In fact, there is evidence for this explanation from functional neuroimaging and transcranial magnetic stimulation studies showing that several areas in temporoparietal regions covering TPJ are involved in OBE (Blanke and Mohr, 2005; Blondiaux et al., 2021) and in time perception (Indovina et al., 2005, 2013; Bosco et al., 2008; Miller et al., 2008; Lacquaniti et al., 2013, 2015; Kheradmand et al., 2015). Indeed, it was shown that time duration estimations were impaired by both vestibular stimulation (Capelli et al., 2007) and weightlessness (Semjen et al., 1998).

Another line of research suggests that body orientation manipulation might also change the internal model gravity (Van Beuzekom and Van Gisbergen, 2000; Lopez et al., 2009), possibly tying it to a coordinate system (i.e., 3PP) other than egocentric coordinates (Moscatelli and Lacquaniti, 2011). Accordingly, in the present study, in the standing position, the gravitational up and bodily up were aligned, but in the supine position, they were orthogonal. In that case, weighting more on vision to resolve the conflict in the supine position might then lead to a stronger experience of being located at the 3PP, and this could explain the longer time estimations in the MBD task. This argument is supported by previous studies showing disruption in the normal time course of representational gravity when the body is not aligned with the environmental gravity axis (de sá Teixeira et al., 2017). For example, it was shown that participants produce longer temporal duration in 0 g compared to 1 g environments (Clément, 2018). All these studies suggest that orientation perception relative to the external environment alters the uncertainty regarding the direction of "down," with a potentially significant effect on the MBD duration estimations (de sá Teixeira, 2014; de sá Teixeira and Hecht, 2014; de sá Teixeira et al., 2017).

Further possible explanations for the current findings involve two changes that occur during OBEs: (i) in self-location ("Where am I in space?") and (ii) in perspective ("From where do I perceive the world?"). According to this explanation, during OBEs, participants in the supine position might experience an increased feeling of altitude (i.e., change in self-location), which might then lead to longer MBD durations. Evidence for this is provided by previous studies showing that self-location and 1PP are intricately connected (Maselli and Slater, 2013; Pfeiffer et al., 2014a; Guterstam et al., 2015b), and therefore, the definition of self-location was extended further to address the collective contribution of body-location and location of 1PP (Huang et al., 2017). In this relationship, the vestibular system is considered as a core binding mechanism that critically maintains the integrity between visuo-spatial perspective and the body (Lopez et al., 2008b; Lopez and Blanke, 2010), and indirect evidence for such a relationship is also seen in the influence of artificial vestibular stimulations on tasks that require the mental rotation of one's own body (Mast et al., 2006; Lenggenhager et al., 2008; Falconer and Mast, 2012; van Elk and Blanke, 2013). Accordingly, during the supine OBE, the participants might experience a greater disruption in relations between self-location and visuo-spatial perspective, possibly leading to the increased feeling of altitude and longer MBD durations. According to this explanation, multiple brain areas, one of which is the hippocampus, may be jointly responsible for coding self-location (Guterstam et al., 2015a,b, 2020), and also, for coding the relation between time and distance (Kraus et al., 2013), and this signal may also be integrated into the parieto-insular areas, possibly including TPJ (Craig, 2009; Wittmann, 2009). Further evidence is also provided by studies showing that changes in self-location can affect distance estimations (Harris and Mander, 2014).

An alternative, and more plausible explanation, is that spatial representations for computing time are affected by the changes in the visual perspective (i.e., egocentric and allocentric). Previous studies showed that TPJ activity was not only modulated by the visuo-tactile synchrony of stroking, but was also, differently influenced by perspective-taking (Slater et al., 2010; Ionta et al., 2011a). This aligns with a previous study suggesting that perspective-taking is a strongly embodied process and that longer reaction time may relate to the incongruence between the posture of the participant's actual body and that of a distant avatar (Kessler and Rutherford, 2010; Kessler and Thomson, 2010; Deroualle et al., 2015). Further evidence is provided by a series of behavioral studies, in which Kessler et al. showed that participants were more ready to adopt the viewpoint of an avatar when it matched their body posture (Kessler and Rutherford, 2010; Kessler and Thomson, 2010). This line of research emphasizes the key role of the switch from 1PP to 3PP, suggesting that the vestibular signal might disintegrate when the contribution from 1PP is lost (Brugger et al., 1997; Blanke et al., 2002, 2004; Blanke and Mohr, 2005; Lopez et al., 2008b; Lopez and Blanke, 2010; Ionta et al., 2011b). This interpretation is consistent with the perceived self-motion and perceived self-orientation function of the vestibular system (Kaski et al., 2016). Taken together, these results could explain the increased estimations of time following the change from the 1PP to 3PP in the supine position.

Questionnaire results showed that for both conditions, the strong body ownership illusion during the embodiment phase (FBI1) became weaker during the OBE phase (OBE1). Moreover, the disembodiment question (OBE2) also showed a significant decrease for both standing and supine conditions during OBE but with no significant difference between the two conditions. This emphasizes the possibility that the change from the egocentric viewpoint to 3PP may have created similar amounts of dis-ownership over the virtual body during OBE for both body positions. In fact, this finding is in line with the studies suggesting that OBEs are not directly characterized by complete dis-ownership of the physical body, but rather, by the localization in and the attribution of the self to an illusory body, which corresponds to the particular perspective (Lopez et al., 2008a). Moreover, the questionnaire results regarding vestibular sensations (OBE3) and elevated visuo-spatial perspective (OBE4) showed that participants reported stronger vestibular sensations and more elevated visuo-spatial perspective in standing compared to the supine body position. However, as we discussed earlier, the MBD task indicated that participants experienced being more elevated in the supine compared to the standing position. As further discussed below, this apparent contradiction might be associated with the management of sensory information (i.e., vestibular and proprioceptive). Accordingly, for the MBD task results, the experience of being more elevated in the supine position might be explained by the decrease in vestibular and proprioceptive signals (i.e., decreased input from the feet, and the more relaxed muscles). According to this argument, the decrease in vestibular and proprioceptive signals might possibly increase weight in vision, resulting in the stronger experience of being in the location of the visuo-spatial perspective, as indicated by longer estimation times. This finding is supported by the recent study by Beauchet et al. (2018), showing that the supine position is associated with more accurate mental chronometry. They argued that the decrease of vestibular and proprioceptive signals in the supine position might enhance the mental imagery process, possibly leading to more accurate duration estimations. Overall, we suggest that longer estimated times in the supine position compared to the standing position may stem from the absence of interfering vestibular and proprioceptive signals, leading to a greater reliance on vision, allowing for a focus on mental imagery during the MBD task. However, regarding vestibular sensations (OBE3) and elevated visuo-spatial perspective (OBE4) questions, stronger vestibular sensations and elevated visuo-spatial perspective in the standing position might be equally well-explained by the active perception of orientation during standing (Peterka, 2002). According to this argument, in the standing position, unlike in the supine position, the constant force experienced from the ground serves to stabilize and maintain body orientation. The body, therefore, is not motionless but generates compensatory actions based on the information from lower body parts (Stoffregen and Riccio, 1988). As a result, one possible interpretation for the questionnaire findings might be related to the involvement of the additional proprioceptive information available while standing. Such that, when standing, active proprioceptive stimulation may overcome vestibular uncertainty (i.e., about the elevation during OBE when the physical bodies were in the standing position), and thus, the sense of visually perceived elevated perspective is enhanced with the sensation of floating. Similarly, there is also the possibility that the natural tendency to sway and lean in the standing position may have enhanced sensitivity to graviception, resulting in increased vestibular sensations.

Finally, as mentioned above, it is also important to note that the vestibular system is closely associated with the perception of self-motion and spatial orientation (Day and Fitzpatrick, 2005; Angelaki et al., 2009; Fetsch et al., 2009; Pfeiffer et al., 2014b). Accordingly, several studies revealed the contribution of the vestibular system to the spatial aspect of bodily self-consciousness, specifically, to the egocentric viewpoint (Ionta et al., 2011b; Pfeiffer, 2015; Pavlidou et al., 2018; Deroualle et al., 2019). For example, Pavlidou et al. (2018) clearly showed that vestibular stimulation boosts the egocentric viewpoint, and if this is the case (Peterka, 2002; Chiba et al., 2016; van Kordelaar et al., 2018), during standing, the active vestibular system might attempt to maintain the egocentric perspective based on the point of view of the physical body during OBE phase, and as a result of this mismatch (i.e., similar to motion sickness), participants might experience stronger vestibular sensations and elevated visuo-spatial perspective in the standing position.

## Limitations

The findings of the current study are naturally subject to some limitations. First, previous studies showed the close relationship between the perception of time and space (Glicksohn, 1992; Kraus et al., 2013; Lacquaniti et al., 2015; Clément, 2018; Huberle and Brugger, 2018), and that the perception of time is significantly influenced by scale model environments and altered sensory environments (Glicksohn, 1992; Riemer et al., 2014; Mitchell and Davis, 2016; Glicksohn et al., 2017). Thus, in the current study, the deliberate use of a dark virtual environment without boundaries (i.e., walls) might have significantly influenced the results. For future research, it is important to replicate the current findings in different model environments. Second, despite calibrating the height of the bed to match the participant's hand distances from the floor in the supine posture, the calibration might have been inaccurate, and participants might have confused their height from the floor with their height from the stretcher. Thus, although there is no indication of such a scenario based on the baseline MBD durations, caution is needed when replicating our experimental design and using height-adjustable stretchers. Finally, a few previous studies have shown that the participant's posture relative to gravity direction contributes to a sense of "upwards" and "downwards" during the calculation of gravitational motion (Senot et al., 2005; Le Séach et al., 2010; Baurès and Hecht, 2011). In the current study, during the virtual OBE illusion phase, participants were able to freely move their head "upwards" or "downwards," as well as sideways, and we did not control for such gravitational direction effects. For future research, while creating virtual OBE illusion, it is important to include a control condition with a fixated direction of gaze (i.e., looking upward to the ceiling or downward to the virtual body) to eliminate any gravitational direction effect.

## CONCLUSION

In the current study, it was shown that virtual OBE illusion can be induced both during standing and supine body positions. The present data, based on participants' subjective reports, showed no significant differences between the two positions in terms of the feeling of disembodiment. Moreover, the subjective reports revealed stronger feelings of floating and elevation in the standing position, although it should be noted that the results of the implicit measurement suggest that longer MBD durations were often experienced in the supine posture. Thus, the results of the current study, we believe, provide important insight into the understanding of vestibular contributions on experiencing OBEs, as well as time perception during OBEs.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Izmir University of Economics (No: B.30.2.IEU.0.05.05-020-066). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

ET and BE contributed equally to conception, design, statistical analysis and writing of the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnint.2021.781935/full#supplementary-material

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REVIEW
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# Magnitude Estimates Orchestrate Hierarchal Construction of Context-Dependent Representational Maps for Vestibular Space and Time: Theoretical Implications for Functional Dizziness

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Maintaining balance necessitates an accurate perceptual map of the external world. Neuro-physiological mechanisms of locomotor control, sensory perception, and anxiety systems have been viewed as separate entities that can on occasion affect each other (i.e., walking on ice). Emerging models are more integrated, that envision sensory perception and threat assessment as a fundamental component of balance. Here we present an empirically based theoretical argument that vestibular cortical areas construct magnitude estimates of our environment *via* neural integration of incoming sensory signals. In turn, these cortically derived magnitude estimates, construct context-dependent vestibulo-spatial and vestibulo-temporal, representational maps of the external world, and ensure an appropriate online scaling factor for associated action-perceptual risk. Thus, threat signals are able to exert continuous influence on planning movements, predicting outcomes of motion of self and surrounding objects, and adjusting tolerances for discrepancies between predicted and actual estimates. Such a process affects the degree of conscious attention directed to spatial and temporal aspects of motion stimuli, implying that maintaining balance may follow a Bayesian approach in which the relative weighting of vestibulo-spatial and vestibulo-temporal signals and tolerance for discrepancies are adjusted in accordance with the level of threat assessment. Here, we seek to mechanistically explain this process with our novel empirical concept of a Brainstem Cortical Scaling Metric (BCSM), which we developed from a series of neurophysiological studies illustrating the central role of interhemispheric vestibulo-cortical asymmetries for balance control. We conclude by using the BCSM to derive theoretical predictions of how a dysfunctional BCSM can mechanistically account for functional dizziness.

**Keywords: vestibular cortex, functional dizziness, space perception, time perception, interhemisphere asymmetry**

## OVERVIEW

Patients with psychosomatic vestibular conditions (i.e., functional dizziness) have been extensively studied over the last four decades. Various terms have emerged to describe these patients including phobic postural vertigo (Brandt, 1996), space-motion discomfort (Jacob et al., 1993), visual-vertigo (Bronstein, 1995), and chronic subjective dizziness (Ruckenstein and Staab, 2009). A new umbrella term has emerged to describe patients with functional dizziness, namely, Persistent Postural Perceptual Dizziness (PPPD) (Staab et al., 2018). The definition of PPPD was promulgated by an international panel of experts convened by the Bárány Society and is included in the 11th edition of the International Classification of Diseases (ICD-11; WHO, 2015a,b; Staab et al., 2018).

Clinically, patients with PPPD present with two key fluctuating or continuous symptoms; (a) a dizzy, not-truly vertiginous sensation, with patients reporting that their head is swimming and/or (b) unsteadiness, such that patients report swaying, rocking, or jelly legs. Symptoms can be exacerbated in visually complex environments, during upright posture and head movements. Typically, PPPD is triggered by an acute disruption to normal balance function; however, the development of PPPD is not attributable to the degree of otological dysfunction or failed ear recovery. Rather, psychological risk factors (anxiety-related personality traits) and shifts in psycho-physical functioning (space-motion perceptual style and visual dependence) are strong predictive factors for determining which patients will develop PPPD following vestibular dysfunction (Cousins et al., 2017). This is in line with clinical histories that illustrate symptom severity is modulated by factors such as introspection, distraction, fatigue, and alertness.

Such a clinical picture gives rise to the notion that functional dizziness is in essence a perceptual disorder, as illustrated by the schematic (**Figure 1**) of the putative pathophysiological mechanisms implicated for functional dizziness. Indeed, our vestibular signals are critical for facilitating the detection of body motion *via* spatial and temporal perceptual mechanisms. Elucidating the neurobiological basis of functional dizziness is clinically pertinent, especially when considering its high prevalence (20% of dizzy patients in general neurology clinics; 40% in specialized dizziness centers; 5% of general population), as well as the considerable functional (80% limiting daily social activities), occupational (41% take time off work), and cognitive impairment imparted (Dieterich et al., 2016; Xue et al., 2018; Staibano et al., 2019; Adamec et al., 2020; Kim et al., 2020).

Despite emerging evidence, which we shall review here, exactly how the brain derives vestibulo-spatial and vestibulo-temporal perceptual maps of the external world remains unclear. Furthermore, whether distorted representational maps of space and time can account for symptoms in functional patients that exhibit disordered vestibular perception, remains unclear. To address these questions, in this review, we shall consider emerging research regarding how vestibular-related brain mechanisms code for space and time and their associated implications for movement and balance in healthy individuals. Consequently, this will enable us to make theoretically derived predictions of how balance and movement are impaired in the pathophysiological state.

## PROPOSITION

We propose that the pathophysiological mechanisms underlying PPPD involve alterations in processing of multi-modal (i.e., vestibular, visual, proprioceptive, auditory) motion stimuli (brainstem to cortical pathways), changes in conscious awareness of motion, and reduced tolerance for both perceived postural instability (intra-cortical networks) and resulting adjustments to locomotor control strategies (cortical to brainstem and spinal cord pathways). These bottom-up and top-down alterations in functioning are affected by over-vigilant threat assessments (i.e., high trait anxiety and excessive body vigilance) which in turn induce greater physiological and psychological reactivity to discrepancies between actual and perceived motion (**Figure 1**). Based on such a model, one would predict that patients with functional dizziness will exhibit, (a) altered interhemispheric brainstem-cortical functional connectivity, (b) perceptually biased estimates of space and displacement, and (c) erroneous predictions of self-motion perception. Furthermore, abnormalities (a–c) would be correlated with psychological measures such as trait anxiety to ensure the scaling factor is maintained and proportionate. Indeed, such a proposition is broadly consistent with other models of functional neurological disorders, that posit abnormal integration between top-down and bottom-up brain systems that monitor and regulate behavior (Edwards and Bhatia, 2012; Edwards et al., 2012; Stone and Edwards, 2012).

## MAGNITUDE–SPACE–TIME

Testing the proposition of abnormal integration between brainstem and cortical processes is challenging owing to gaps that exist in vestibular neuroscience regarding how these processes principally interact. Brainstem mechanisms are posited to construct magnitude estimates of self-displacement by mathematically integrating angular and linear head velocity signals *via* a process that can be viewed as an extension of "velocity storage" and "neural integration" (Cohen et al., 1981). These bottom-up vestibular transformations and their subsequent sensory integration feed into the vestibulo-cortical network to maintain spatial orientation. Thus, the vestibular cortex must resolve spatial and temporal ambiguity that requires the ability to formulate an internalized magnitude estimate and/or judgment, for example, "am I moving or are objects moving around me," and "how long have I been moving"? Consideration of these spatial- and temporal-based questions highlights a key commonality across the dimension of space and time that the brain must extract and utilize in order to resolve perceptual ambiguity, which we propose is magnitude perception (Walsh, 2003).

Our emerging data implicate the vestibular cortex in setting the parameters of the dimensional entities of representational

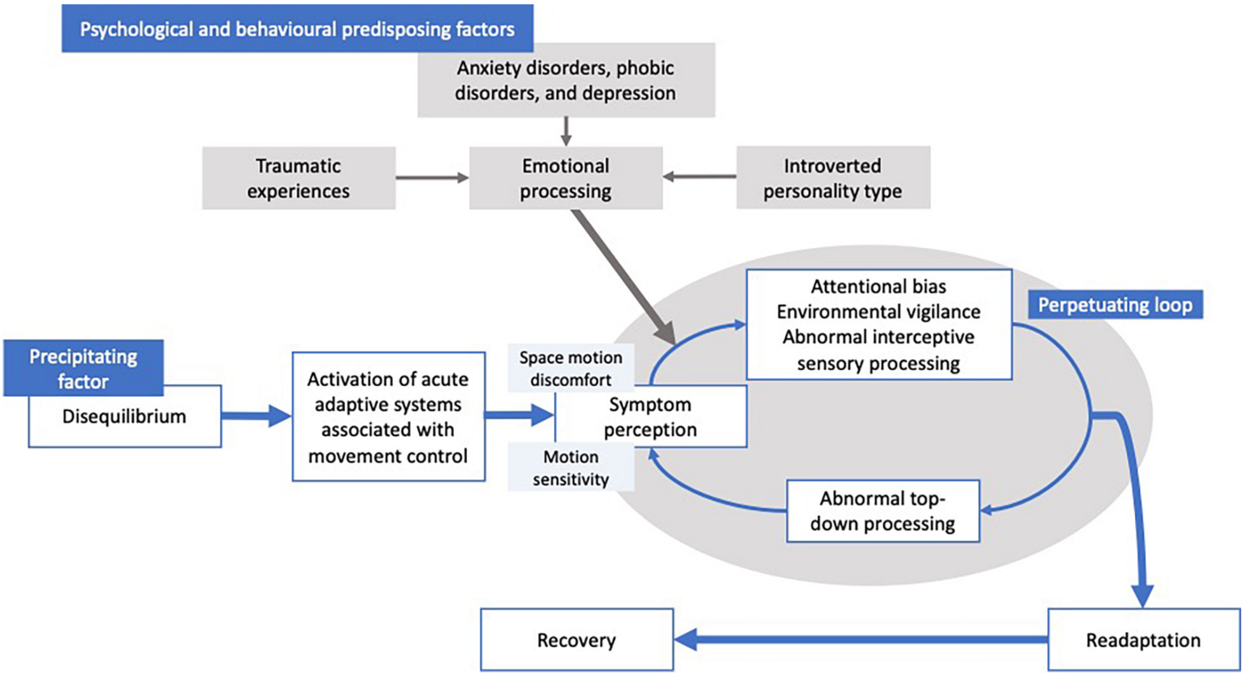

**FIGURE 1 |** Graphical depiction of the mechanisms suggested to be involved in functional dizziness. That is, a participating factor (i.e., vestibular loss, medical cause, and anxiety) causes disequilibrium, leading to a transient distortion of vestibular perception impairing cognitive control of movement and balance. Psychological factors and behavioral co-morbidities (i.e., anxiety, phobia, emotional trauma, and personality types) are suggested to increase the likelihood of the transient perceptual distortions to persist, resulting in a perpetuating loop causing a failure of re-adaptation.

magnitude, space, and time in a set hierarchal pattern, with dynamic interhemispheric competition representing the control mechanism. This is supported by our data that illustrates numerical magnitude perception (i.e., estimating the midpoint between two intervals; 23–87) can be selectively biased toward smaller or larger magnitudes in a hemispheric dependent fashion, and that such biasing can disrupt the construction of representational space and time (Arshad et al., 2016; Kaski et al., 2016). Central to this proposition is that vestibulo-cortical control, magnitude allocation, and spatial attention are subject to dynamic interhemispheric competition, implying a common cortical control mechanism (Kinsbourne, 1977; Dieterich et al., 2003; Arshad et al., 2016). Indeed, data from patients with cortical lesions, which disrupt normal interhemispheric interactions, have illustrated the presence of cortical and brainstem mediated biases in both the vestibulo-spatial and vestibulo-temporal domains (Rubens, 1985; Ventre-Dominey et al., 2003). Of note, the functional relevance of interhemispheric interactions is provided by data that demonstrate that non-invasive modulation of the healthy hemisphere in stroke patients can ameliorate the pathological biases following stroke (Sparing et al., 2009). Functionally speaking, such cortical co-arrangement facilitates the integration of information across the physical dimensions of magnitude, space, and time, allowing for the utilization of expected vestibular signals to construct the intended trajectory of self-locomotion compared to vestibular feedback indicating the accuracy of actual movement. To provide empirical data for this proposition, we have developed novel neurophysiological techniques to disrupt interhemispheric interactions in healthy individuals and adapted experimental paradigms for use in patients with vestibular lesions.

## EXPERIMENTAL TECHNIQUES TO PROBE THE BRAINSTEM-CORTICAL SCALING METRIC

One of the techniques we developed to disrupt interhemispheric interactions involves combining binocular rivalry (RIV) (different images simultaneously presented to each eye which cannot be fused resulting in the eyes competing for perceptual dominance) with vestibular stimulation (i.e., caloric irrigations with either cold (30°C) or warm (44°C) water irrigations), referred to as CAL+RIV stimulation. Notably, this paradigm can selectively induce interhemispheric competition when rivalry is combined with caloric irrigations that preferentially implicate the left hemisphere [i.e., right-ear cold (RIGHTCOLD + RIV) and left-ear warm (LEFTWARM + RIV)] (**Figure 2**). No conflict or biases occur when caloric irrigations preferentially implicate the same (i.e., right) hemisphere as the rivalry stimulus [i.e., left-ear cold irrigations (LEFTCOLD + RIV) or right-ear warm irrigations (RIGHTWARM + RIV)]. Indeed, experimental application of this technique reveals an ability, during the conflict conditions, to bias cognitive processes and vestibular processing [namely suppression of the brainstem mediated vestibular-ocular reflex (VOR)] in a manner consistent with that

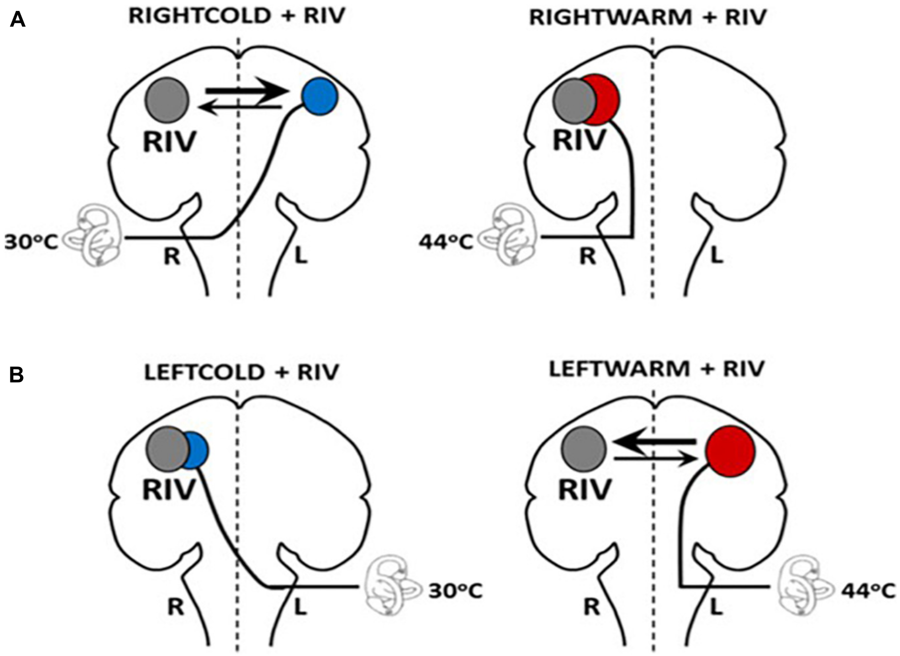

**FIGURE 2 |** Schematic model illustrating hemispheric activation during CALORIC + RIV stimulation: perceptual switching during binocular rivalry activates the right hemisphere (gray circle). Hemispheric activations following caloric stimulation are shown by the red circle following warm irrigations or by blue circles following cold irrigations. The labyrinth represents the side of the caloric irrigation. The size of the circles illustrates the relative degree of the activation. **(A)** During RIGHTCOLD + RIV, the hemispheres are in conflict; however, the right hemisphere exerts a predominant effect (as shown by the relative thickness of the arrows). No interhemispheric conflict occurs during either RIGHTWARM + RIV as both stimuli activate the right hemisphere. **(B)** Similarly, no conflict is present in LEFTCOLD + RIV condition, whereas during the LEFTWARM + RIV condition, conflict presents, but critically here the left hemisphere exerts a greater influence.

expected following unihemispheric inhibition (see the section below for further details) (Arshad et al., 2016).

The second technique involves modulating vestibulo-cortical excitability over the posterior parietal cortex (PPC), with transcranial direct current stimulation (tDCS). Application of unipolar cathodal tDCS over the left PPC induces top-down modulation of the VOR. Right hemisphere cathodal stimulation does not modulate the VOR, despite housing the predominant vestibular representation. This lack of modulation following (right hemisphere) cathodal stimulation can be accounted for by an on-going functional interhemispheric asymmetry (i.e., in right handers, for spatial/vestibular functions the right hemisphere is more dominant) between the parietal cortices enabling the right hemisphere to exert greater inhibition over the left, in right-handed individuals. Accordingly, cathodal tDCS of the left PPC not only inhibits its ability to process vestibular signals but also potentiates right hemispheric dominance (**Figure 3**; Arshad et al., 2014).

Both techniques reviewed above, namely CAL + RIV stimulation and tDCS, suppress the VOR *via* top-down vestibulo-cortical mechanisms. Specifically, the suppression in the amplitude of elicited vestibular nystagmus reflects the degree of interhemispheric modulation using either CAL + RIV stimulation or tDCS, and thus reflects the brainstem contribution to the proposed Brainstem Cortical Scaling Metric (BCSM). Quantification of this brainstem component is made by calculating the nystagmus suppression index (NSI) which is the percentage change (before vs. after CAL + RIV or tDCS) in the peak slow phase velocity of the VOR (Arshad et al., 2015).

## SIGNIFICANCE OF THE BRAINSTEM-CORTICAL SCALING METRIC ON MAGNITUDE, SPACE, AND TIME PERCEPTION

Using the techniques reviewed above to disrupt interhemispheric interactions not only disrupts low-level vestibular function (i.e., suppression of brainstem mediated VOR) but can additionally bias magnitude, spatial, and temporal percepts in a proportional manner (Arshad et al., 2015, 2016; Nigmatullina et al., 2016). That is, biased percepts are correlated with the extent of the VOR suppression (i.e., NSI), ensuring modulated brainstem estimates of head displacement match perceptual ("cortically based") estimates. For example, RIGHTCOLD + RIV stimulation when compared to the corresponding caloric alone condition (RIGHTCOLD) biases numerical magnitude estimates (mid-point between two numbers) toward smaller magnitudes, mediated by a right-hemisphere predominant response following interhemispheric conflict, as corroborated by lesion data (Zorzi et al., 2002). LEFTWARM + RIV stimulation, when compared to the corresponding caloric alone condition (LEFTWARM), biases magnitude estimates toward

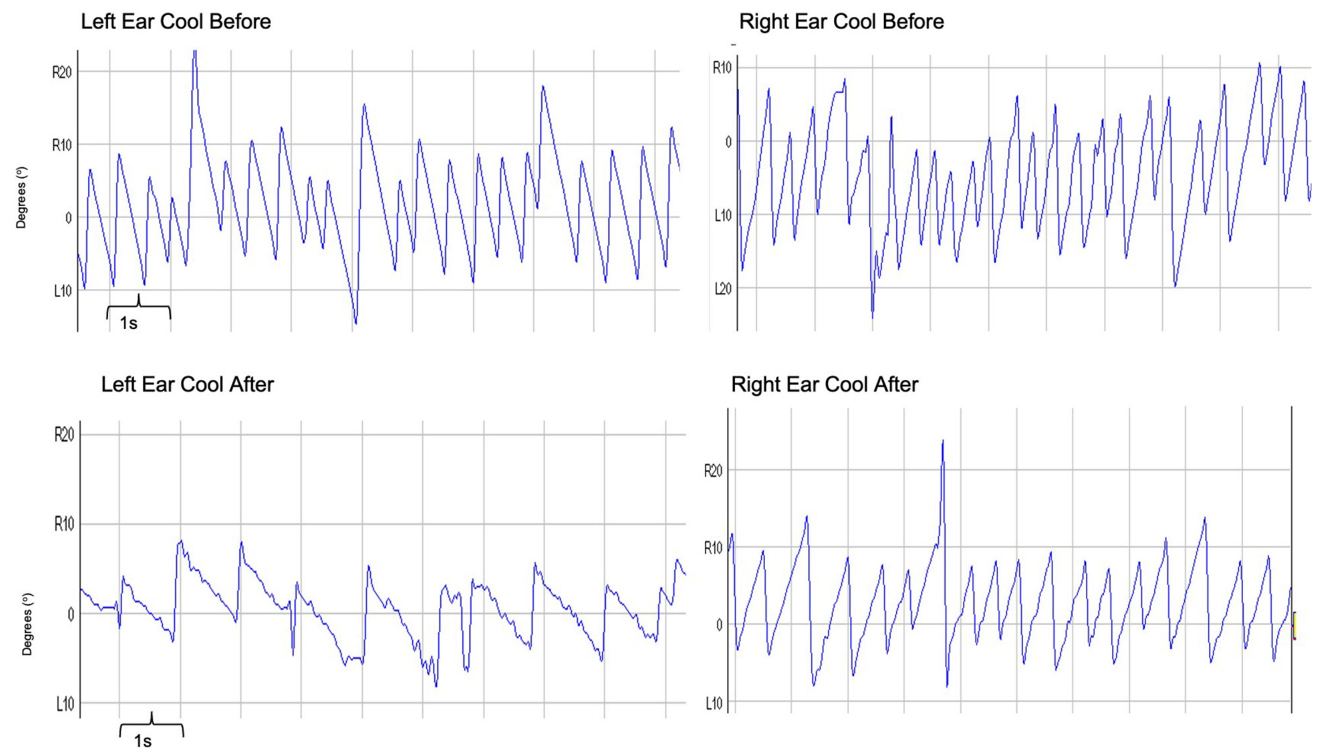

**FIGURE 3 |** Trace depicting caloric-induced vestibular nystagmus: Raw traces obtained before and after the application of left hemisphere cathodal tDCS. Right-ear cold irrigations are represented in the right panel, whereas left-ear cold irrigations in the left panel. The recordings before tDCS are on the top with after tDCS traces represented on the bottom. The *x*-axis represents time, with one large square representing 1 s. The *y*-axis represents the degrees of eye movement either right (R) or left (L) from the center (0°). To measure the slow phase velocity of a nystagmus, one utilizes the slope of the nystagmus in its slow phase. In these recordings, one can clearly see a less steep slope, and therefore a suppressed slow phase velocity of the nystagmus following cathodal tDCS – for both right and left ear cold irrigations.

larger magnitudes, mediated by a left-hemisphere predominant response (Arshad et al., 2016). To explore the influence of these magnitude biases upon representational space, we asked subjects to draw numerical (magnitude-dependent, 1–12) or alphabetical (magnitude-independent, A–L) clock faces with their eyes closed. Lateral distortions were observed only for the numerical, but not the alphabetical clock drawings. Critically, these occurred in the

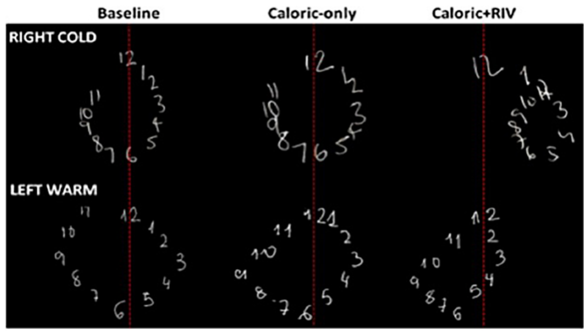

**FIGURE 4 |** Representative numerical clock drawings from a single subject during CALORIC + RIV stimulation: upper panel shows the drawings for the baseline condition (darkness), following RIGHTCOLD caloric only and RIGHTCOLD + RIV. Note the rightward lateral displacement of the numerical clock drawing following RIGHTCOLD + RIV. The lower panel shows the drawings for the baseline condition (darkness), following LEFTWARM caloric only and LEFTWARM + RIV. Note the leftward lateral displacement of the numerical clock drawing following LEFTWARM + RIV.

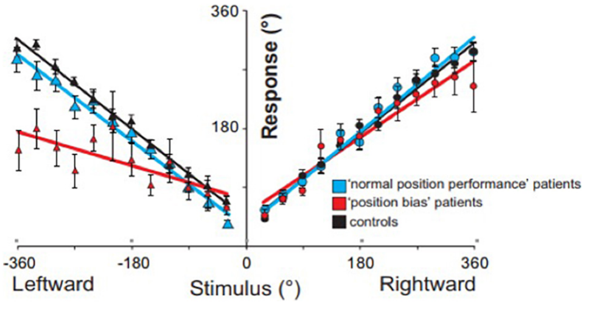

**FIGURE 5 |** Position task results: grouped response–stimulus position performances are shown for patients with a position bias (red; 'patients), patients with normal performance (blue; control patients), and age-matched controls (black line). Position bias was calculated for each stroke patient from the subjective response–stimulus position performance regressions, by dividing the leftward regression slope by the rightward regression slope. Vertical bars represent standard errors of the mean.

opposite direction to that predicted by a hemispheric-mediated spatial biasing account, implying that magnitude supersedes the representational construct of space (**Figure 4**; Arshad et al., 2016).

Regarding temporal biasing, right hemispheric lesions bias magnitude percepts toward larger magnitude (Zorzi et al., 2002). Based on the above findings, we predicted that if right-hemispheric lesion patients were asked to imagine a clock face, it would disrupt temporal estimates of self-displacement inside an imagined clock face due to an associated expansion of leftward representational space. As shown in **Figure 5**, stroke patients underestimated their perceived displacement during leftward rotations despite having normal motion perception, due to the fact that they felt as though they traveled less distance in the same time (i.e., expanded space) (Kaski et al., 2016).

Taken together, our findings imply that disrupting interhemispheric interactions alters vestibulo-cortical functioning in turn biasing magnitude percepts that subsequently

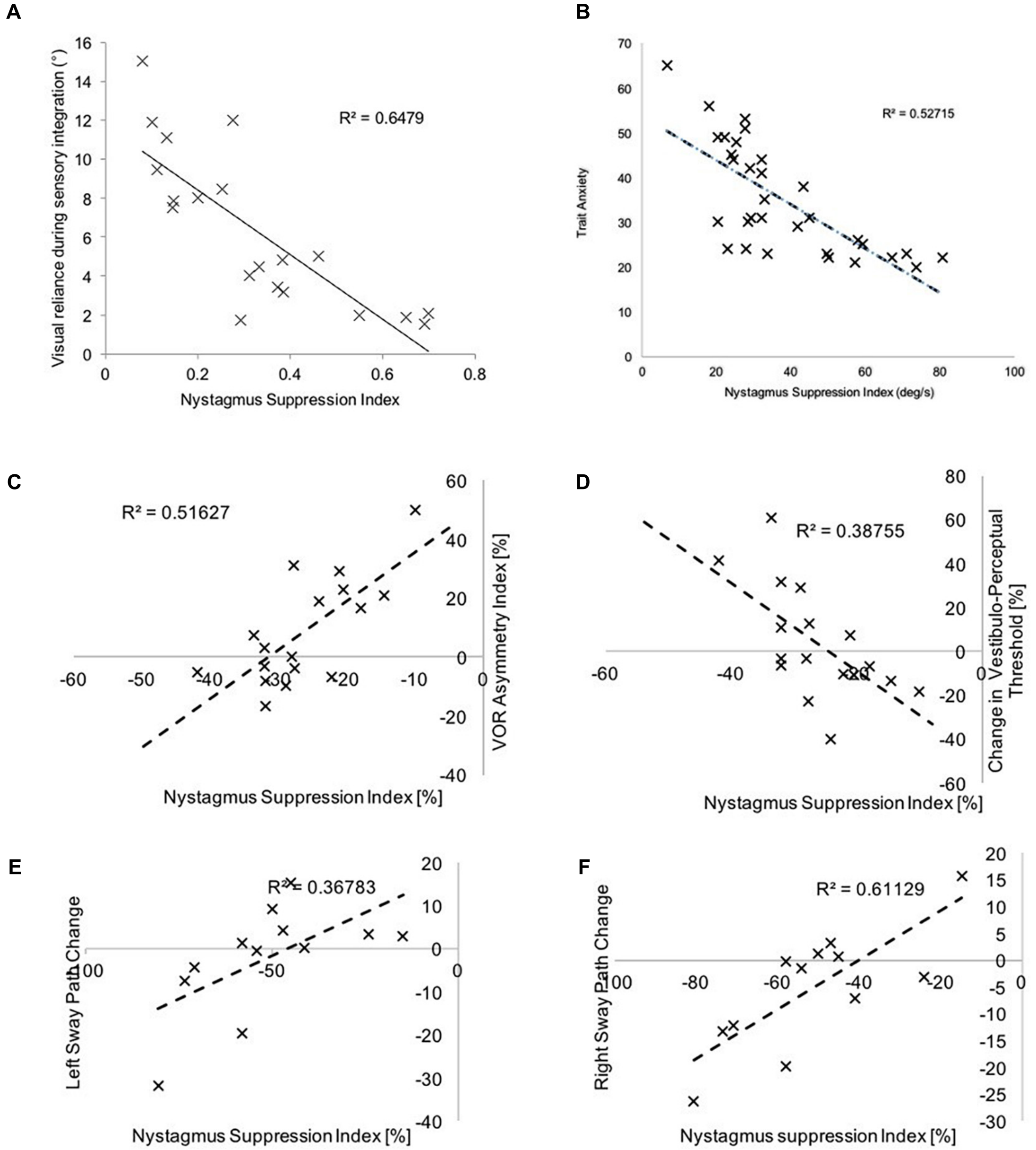

**FIGURE 6 |** Here we represent the relationship between the NSI (following left PPC cathodal stimulation) and **(A)** visual dependency-assessed using the rod and disk task, **(B)** trait anxiety assessed using the Spielberger questionnaire, **(C)** vestibulo-ocular thresholds during yaw rotations, **(D)** vestibulo-perceptual thresholds during yaw rotations, **(E)** sway velocity during leftward body motion and, **(F)** sway velocity during rightward motion. Greater NSI indicates increased right-hemispheric vestibulo-cortical dominance, and this is associated with **(A)** reduced reliance upon visual cues during sensory integration, **(B)** reduced trait anxiety, **(C,D)** reduced motion detection thresholds, and, **(D,E)** reduced sway velocity.

distorts the coding of representational space and time. Indeed, we have proceeded to demonstrate that such distortion of space and time impairs control of body motion as illustrated by our recent findings in healthy individuals.

## RELEVANCE AND PREDICTIONS FOR FUNCTIONAL BALANCE AND MOVEMENT DISORDERS

Our data in healthy individuals (**Figure 6**), illustrates that following cathodal stimulation of the left PPC, increased right hemispheric vestibulo-cortical dominance (i.e., a good vestibular inertial system as reflected by greater NSI) is associated with (1) reduced visual dependency (Arshad et al., 2019), (2) lower trait anxiety (Bednarczuk et al., 2018), (3) reduced motion sensitivity (Arshad et al., 2019), and (4) increased postural stability (Castro et al., 2019). These factors are suggested to reduce the risk factors for developing functional dizziness. Thus, we postulate that in right-handers, increased right hemispheric vestibulo-cortical dominance is likely to protect against the development of functional dizziness.

Accordingly, we postulate that patients with functional dizziness will exhibit reduced right-lateralized vestibulo-cortical dominance manifesting distorted representations of space and time attributable to biased percepts toward larger magnitudes. In turn, the BCSM's ability to properly scale estimates of displacement and duration is altered, thereby throwing off internal predictions of space and time, which in turn impairs accurate assessment of errors between predicted and actual motion, resulting in sensations of disconnectedness from self and surroundings (mild depersonalization and derealization). These minor dissociative symptoms are consistently experienced by patients with chronic dizziness, including functional dizziness, and by normal individuals exposed to strong vestibular stimuli (Jáuregui-Renaud et al., 2008; Aranda-Moreno and Jáuregui-Renaud, 2016). Such sensations of foggy headedness or indistinct feelings of not being well planted in space disrupt normal reflexive processes. That is, under normal circumstances, humans are largely unaware of the details of sensory integration, motion perception, and locomotor control, which operate outside of executive processes (fully conscious perception and action). These sensorimotor functions may transiently intrude into consciousness as when traversing an icy pavement, but even then,

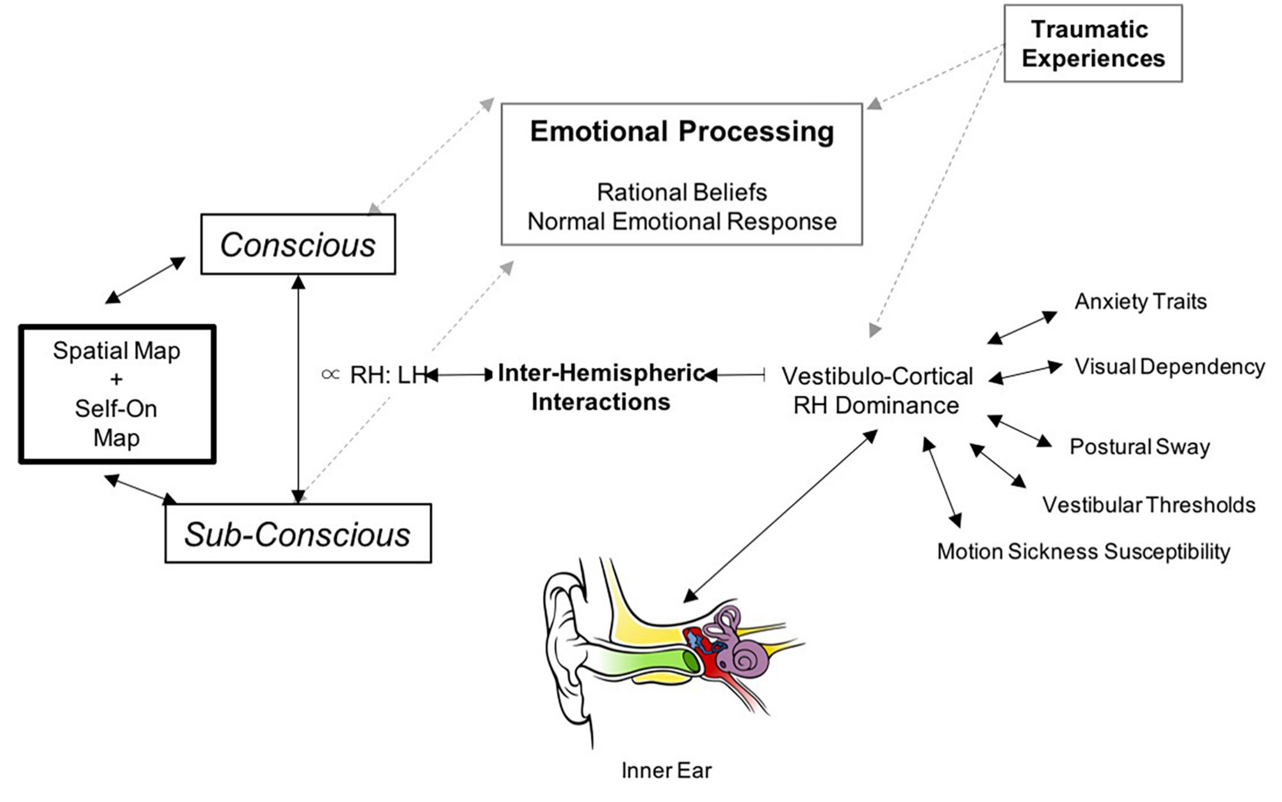

**FIGURE 7 |** Schematic illustration of our proposed neurobiological model for PPPD: The central component in the model is the interhemispheric interactions in the vestibulo-cortical network that determines its dominance and in-turn influences risk factors for developing PPPD including lower motion perceptual thresholds, increased sway during postural control, increased motion sickness susceptibility, higher visual dependence, and anxiety. These interhemispheric interactions can also be influenced by predisposing emotional trauma (non-vestibular). This cortical network receives signals from bottom-up vestibular transformations provided by the vestibular system. The net result of the cortical system is to generate perceptual vestibulo-spatial and vestibulo-temporal maps of the world, and this is cross-referenced with physical signals from the accelerometers (balance organ) in our inner ear. If there is a mismatch as in the case of PPPD – this subsequently opens up feed-forward pathways to emotional networks.

most aspects of locomotor dynamics (e.g., individual muscle movements) remain outside of direct executive control. Patients with functional dizziness, however, experience a consistently heightened, conscious awareness of space and motion stimuli, particularly an increased sense of error between predicted (conscious) and actual (subconscious) motions. Driven by their anxious temperaments, functional dizzy patients exert unnecessarily increased executive control over locomotion, altering reflexive postural dynamics and normal weighting of sensory inputs, a mismatched behavioral response that paradoxically reduces the effectiveness of lower-level systems. Research on heuristics in decision-making has well described the adverse effects of undue emphasis on risk and the influences of emotional states induced by perceptual biases (Kahneman, 2003).

## THEORETICALLY DERIVED PREDICTION

The outlined conceptual principles above require a pathophysiological model of functional dizziness that can tie together threat assessment, risk tolerance, perceptual bias, and functional shifts in space-motion processing and locomotor control. Accordingly, we propose the following theoretical hypothesis and schematic model as depicted in **Figure 7**. Namely, in patients with PPPD, reduced right hemispheric vestibulo-cortical dominance, (1) alters cortical processing of brainstem mediated head velocity signals, thereby distorting interhemispheric representations of the magnitudes–space–time continuum, biasing dynamic perceptual maps of body position and motion in the physical world and (2) concurrently heightens threat assessment and reduced risk tolerance from an anxious temperament. In turn, this disrupts the normal process of detecting errors between predicted (conscious) and actual (subconscious) movement, which intrusively and unnecessarily rises to the level of conscious awareness and impacts upon emotional networks. Such multi-level changes in brain functioning account for the primary symptoms of functional dizziness that patients experience, including a diminished sense of agency about control of locomotion. Future research and experimental data will determine the validity of the proposed theoretical predictions made herewith.

## AUTHOR CONTRIBUTIONS

QA conceptualized and wrote the manuscript. YS provided the technical contributions and edited the manuscript. MS edited the manuscript and drafted the figures. DK and JS conceptualized and edited the manuscript. All authors contributed to the article and approved the submitted version.

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# How Tilting the Head Interferes With Eye-Hand Coordination: The Role of Gravity in Visuo-Proprioceptive, Cross-Modal Sensory Transformations

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To correctly position the hand with respect to the spatial location and orientation of an object to be reached/grasped, visual information about the target and proprioceptive information from the hand must be compared. Since visual and proprioceptive sensory modalities are inherently encoded in a retinal and musculo-skeletal reference frame, respectively, this comparison requires cross-modal sensory transformations. Previous studies have shown that lateral tilts of the head interfere with the visuo-proprioceptive transformations. It is unclear, however, whether this phenomenon is related to the neck flexion or to the head-gravity misalignment. To answer to this question, we performed three virtual reality experiments in which we compared a grasping-like movement with lateral neck flexions executed in an upright seated position and while lying supine. In the main experiment, the task requires cross-modal transformations, because the target information is visually acquired, and the hand is sensed through proprioception only. In the other two control experiments, the task is unimodal, because both target and hand are sensed through one, and the same, sensory channel (vision and proprioception, respectively), and, hence, cross-modal processing is unnecessary. The results show that lateral neck flexions have considerably different effects in the seated and supine posture, but only for the cross-modal task. More precisely, the subjects' response variability and the importance associated to the visual encoding of the information significantly increased when supine. We show that these findings are consistent with the idea that head-gravity misalignment interferes with the visuo-proprioceptive cross-modal processing. Indeed, the principle of statistical optimality in multisensory integration predicts the observed results if the noise associated to the visuo-proprioceptive transformations is assumed to be affected by gravitational signals, and not by neck proprioceptive signals *per se*. This finding is also consistent with the observation of otolithic projections in the posterior parietal cortex, which is involved in the visuo-proprioceptive processing. Altogether these findings represent a clear evidence of the theorized central role of gravity in spatial perception. More precisely, otolithic signals would contribute to reciprocally align the reference frames in which the available sensory information can be encoded.

**Keywords: multisensory integration, cross-modal transformation, gravity, reaching/grasping movement, eye-hand coordination, vision, proprioception, otolith**

## INTRODUCTION

When reaching to grasp an object, arm proprioceptive signals and the visually acquired object position/orientation must be compared. A typical situation in which visuo-proprioceptive communication is strictly necessary is at the beginning of the reaching movement if the hand is out of sight. There are, however other common situations where cross-modal transformations, i.e., the encoding of visual information in a proprioceptive space and vice-versa, is necessary during the whole reaching movement: for instance, when trying to insert a bolt from beneath a plate on which the threaded hole location is visually identified from above. There is also evidence that the visuo-proprioceptive interaction is performed even when it is not strictly necessary, that is even when object and hand can be both seen, or both sensed through proprioception, before the movement onset (Sober and Sabes, 2005; Sarlegna and Sainburg, 2007, 2009; Sarlegna et al., 2009) and during movement execution (Tagliabue and McIntyre, 2011, 2013, 2014; Cluff et al., 2015; Crevecoeur et al., 2016; Arnoux et al., 2017).

It has been shown that tilting laterally the head when seating interferes with the communication between visual and proprioceptive systems (Burns and Blohm, 2010; Tagliabue and McIntyre, 2011) and we demonstrated that this phenomenon is independent from the phase of the movement during which the head is tilted (Tagliabue et al., 2013; Tagliabue and McIntyre, 2014). These studies, however, did not allow understanding whether the neck on trunk lateral flexion *per se* (the signals originating from the neck muscles), or the head misalignment with respect to the vertical (gravitational signals), interferes with cross-modal transformations. The first option, that we call here the *Neck Hypothesis*, would be consistent with the contribution of the neck flexion angle information to the kinematic chain linking the hand to the eyes and that may be thus used to compute visuo-proprioceptive transformations (Sabes, 2011). This hypothesis has two possible variants: "Neck1 Hp," wherein the lateral neck flexions *per se* interferes with eye-hand transformation, because of the rarity of adopting such neck postures when performing reaching/grasping tasks; "Neck2 Hp," wherein lateral neck flexions require an increase of the muscle activations to support the weight of the head, resulting in increased signal-dependent noise that would interfere with eye-hand transformations (Abedi Khoozani and Blohm, 2018). An alternative option, called here the *Gravity Hypothesis* (Gravity Hp), is related to the idea that gravity might play a fundamental role in the reciprocal calibration between visual and proprioceptive senses (Paillard, 1991), since it can be both seen (the visual environment provides information about the vertical) and felt (mechano-receptors detect gravity action). The head-vertical misalignment might hence perturb the ability of using gravity as reference for visuo-proprioceptive transformations. This could be due to an increase of the otolithic noise with the lateral head tilt (Vrijer et al., 2008) or to the fact that eye-hand coordination tasks are more commonly performed with the head straight and sensorimotor precision has been shown to be proportional to the task usualness (Howard et al., 2009).

To discriminate between these hypotheses, we performed a first virtual reality experiment in which the subject had to perform in a *Seated* and in a *Supine* position the same cross-modal task: align the hand to "grasp" a visual target with the unseen hand (Tagliabue and McIntyre, 2011; Tagliabue et al., 2013). To test the effect of the neck flexion, the subjects are asked to laterally tilt the head between the target acquisition and the hand movement onset. If "*Neck1 Hp*" is correct, the subjects' performance should not change notably between postures, because the tasks performed in the seated and supine condition do not significantly differ in terms of lateral neck flexion. On the other hand, "*Neck2 Hp*" predicts an improvement of the precision when supine, because, thanks to a special head support, in this position the neck muscles never have to sustain the head weight, resulting in spindle-noise reduction (Abedi Khoozani and Blohm, 2018). Neck proprioceptive degradation is not to be expected with the head-support, because there is evidence that a decrease of the muscle tone, as experienced by astronauts in weightlessness, does not reduce the sensitivity of the muscle receptors (Roll et al., 1993). Finally, "*Gravity Hp*" will be supported by a decrease of precision when supine, because when lying on their back the subject's head is misaligned with respect to gravity during the whole task and not only during the response phase, as in the seated configuration.

Two control experiments were performed to test whether potential effect of posture observed in the cross-modal task could be due to an effect of posture on visual and/or proprioceptive perception, and not on the sensory transformations. In the first control experiment the subjects performed a unimodal visual task: only vision could be used for both target acquisition and response control. In the second control experiment a unimodal proprioceptive task was tested: both target and response could be sensed through proprioception only.

In order to compare the *Neck* and *Gravity Hypotheses* predictions with the measured subjects' precision and sensory weighting, we applied our "*Concurrent Model*" (see below) of multisensory integration (Tagliabue and McIntyre, 2008, 2011, 2012, 2013, 2014; Tagliabue et al., 2013; Arnoux et al., 2017; Bernard-Espina et al., 2021) to the cross- and uni-modal tasks tested here.

To confirm our interpretation of the first set of results, we performed an additional experiment in which the subjects were tested seated and supine, but without lateral neck flexions. The goal was to specifically test the effect of the modulation of the gravitational information without interference from neck muscle-spindles' signals.

## MATERIALS AND METHODS

### Ethics Statement

The experimental protocol was approved by the Ethical Committee of the University of Paris (N° CER 2014-34/2018-115) and all participant gave written informed consent in line with the Declaration of Helsinki.

### Experimental Setup and Procedure

The setup is very similar to what used in our previous studies (Tagliabue and McIntyre, 2011, 2012), consisting of the following components: an active-marker motion-analysis system (CODAmotion; Charnwood Dynamics) used for real-time recording of the three-dimensional position of 19 infrared LEDs (sub-millimeter accuracy, 200-Hz sampling frequency). Eight markers were distributed ~10 cm apart on the surface of stereo virtual reality goggles (nVisor sx60, NVIS) worn by the subjects (field of view: 60°, frame rate: 60 Hz, resolution: 1,280 × 1,024 pixels, adjustable inter-pupillary distance); eight on the surface of a tool (350 g, isotropic inertial moment around the roll axis) that was attached to the subjects' dominant hand; and three attached to a fixed reference frame placed in the laboratory. Custom C++ code was developed by the research team to optimally combine the information about the three-dimensional position of the infrared markers and the angular information from an inertial sensor (IS-300 Plus system from InterSense) placed on the VR headset to estimate in real-time the position and the orientation of the subject's viewpoint and thus to update accordingly the stereoscopic images shown in the virtual reality goggles. For tracking the hand movement only infrared markers were used.

The three-dimensional virtual environment shown to the subjects through the head mounted display consisted of a cylindrical tunnel (**Figure 1**). Longitudinal marks parallel to the tunnel axis were added on the walls to help the subjects to perceive their own spatial orientation in the virtual word. The fact that the marks went from white in the "ceiling" to black on the "floor" facilitated the identification of the visual vertical.

### Experimental Paradigm

The task consisted of three phases: (1) memorization of the target orientation, 2) lateral neck flexion, and (3) alignment of the tool to the remembered target orientation. As in our previous studies (Tagliabue and McIntyre, 2011, 2012, 2013, 2014; Tagliabue et al., 2013; Arnoux et al., 2017), we took advantage of the head rotation to introduce a sensory conflict with the subjects not noticing it (see below). The target could be laterally tilted with respect to the virtual vertical of −45°, −30°, −15°, 0°, +15°, +30° or +45°. The subjects had 2.5 s to memorize its orientation. After the target disappeared, the subject was guided to laterally tilt the head 15° to the right or to the left by a sound with a left-right balance and a volume corresponding to the direction and the distance from the desired inclination. If the subject was unable to extinguish the sound within 5 sec, the trial was interrupted and repeated later on, otherwise a go signal was given to indicate that he/she had to reproduce the target orientation with the tool. The subject clicked on the trigger of a trackball held in the hand to validate the response.

In order to quantify the sensory weighting in each experimental condition a sensory conflict was artificially introduced (Tagliabue and McIntyre, 2011): tracking the virtual reality goggles was normally used to hold the visual scene stable with respect to the real world during the lateral head tilt, but in half of the trials, a gradual, imperceptible conflict was generated such that, when the subjects laterally flex the neck, they received visual information corresponding to a larger head tilt. The amplitude of the angle between the visual vertical and subject body axis varied proportionally (by a factor of 0.6) with the actual head tilt, so that for a 15° lateral head roll a 9° conflict was generated. When, at the end of the experiment, the subjects were interviewed about the conflict perception, none of them reported to have noticed the tilt of the visual scene.

Each subject was tested in two postural conditions: Seated and Supine (**Figures 1A,B**). In order to compensate for possible learning effects, half of the subjects were tested first seated and then supine, and the other half in the opposite order. When the subjects performed the task in the supine position, they lay in a medical bed with their head supported by an articulated mechanical structure allowing for lateral neck flexions (**Figure 1B**). When the subject performed the task in a seated position the same head support was fixed to the back of the chair to restrain the head movements in a way similar to the supine condition (**Figure 1A**). Since the main axis of the virtual tunnel always corresponded to the anterior-posterior subject direction, it was horizontal and vertical in the Seated and Supine Condition, respectively.

As detailed below, the first three experiments presented in this study differed only by the sensory information available to acquire the target and to control the tool during the response (**Figure 1C**). The task used in the fourth, additional experiment was the same as for the main cross-modal experiment with the exception that the subject always kept the head aligned to the body.

#### Cross-Modal Experiment

The target was presented visually and during the response the tool orientation could be controlled through arm proprioception only (V-P task). As shown in the top part of **Figure 1C**, the target consisted of parallel beams blocking the tunnel in front of the subject. In the response phase, subjects raised their hand and reproduced the memorized beams orientation by prono-supinating the palm. The subjects' hands were represented in the virtual environment as a capsule with the same main axis so that all its degrees of freedom except the roll (hand prono-supination) could be visually controlled. It follows that only arm proprioception could be used to control the alignment task.

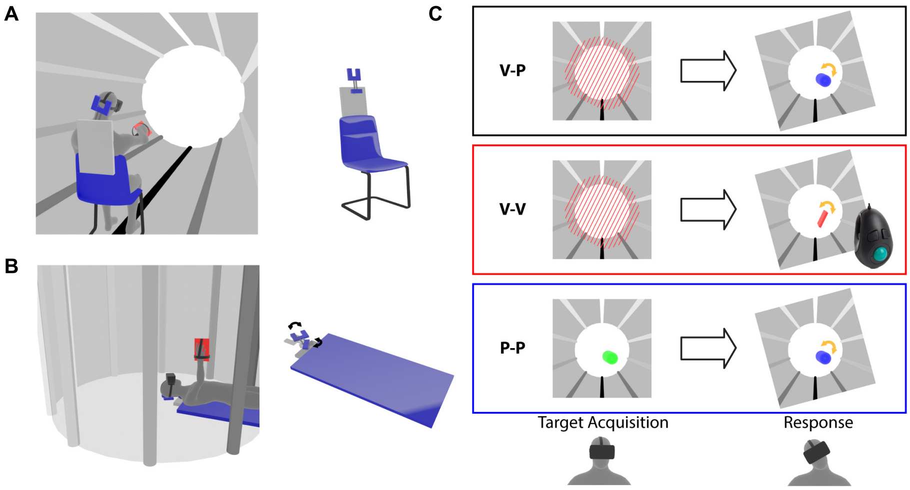

**FIGURE 1 |** Virtual reality experimental paradigm. Representation of the **(A)** Seated and **(B)** Supine conditions. The subjects wear a virtual reality headset and a tool is fixed to their hand. The left images illustrate the virtual tunnel in which the subject perform the task. The configuration of the rotating head support (forked structure) is shown for the two postural conditions. **(C)** Target presentation (left) and response modality (right) for the three experiments. The tilted frames in the response phase represent the lateral neck flexion that the subjects perform after the target memorization. For the cross-modal (V-P) task the target is represented by tilted red bars and during the response the subject hand movements are applied to a blue capsule, which provides visual feedback about the pointing direction in pitch and yaw, but no visual cues about the prono-supination of the hand used to reproduce the target orientation. For the unimodal visual (V-V) task the target is presented as in the V-P task, but a virtual hand-tool (red rectangle) controlled by a trackball is used to reproduce the target orientation. During the target acquisition of the unimodal proprioceptive (P-P) task the color of the capsule representing the subject hand changes from red to green when the hand approaches the target orientation. The response modality is the same as in the V-P task.

### Uni-Modal Visual Experiment

Both target acquisition and tool control orientation could be performed by using vision only (V-V task). The target was represented by the beams as in Experiment 1. For the response, subjects did not move the hand, which was kept next to the body. A virtual representation of the tool fixed to the subject hand appeared in front of their eyes with a random roll orientation (see middle part of **Figure 1C**). They used a trackball to change its roll angle and to align it to the memorized beams. In this way only visual information could be used to evaluate the task achievement.

### Uni-Modal Proprioceptive Experiment

Both target and tool orientation could be sensed through proprioception only (P-P task). The beams were not shown to the subjects. To sense the target orientation, they raised the hand, which was represented by a capsule, as in the response phase of Experiment 1. In this phase the color of the capsule changed as a function of the hand roll turning from red to green as the hand approached the target roll angle. Thus, subjects had to pronate or supinate the hand to find the target orientation. After 2.5 s with the correct hand orientation an audio signal instructed the subject to lower the arm. The only information available to memorize the roll orientation of the target was the proprioceptive feedback related to forearm pronation–supination. The target orientation was in this way presented proprioceptively, without any visual feedback about the desired orientation. The response was controlled using proprioception only, as in Experiment 1.

In total 54 subjects were tested, 18 for each experiment (average age: V-P 26.5 ± 9; V-V 30 ± 6; P-P 24.5 ± 6). The number of male and female participants was balanced and about 17% of the subjects were left-handed. The subjects performed two trials for each combination of target orientation, head inclination and sensory conflict, for a total of 56 (= 2 × 7 × 2 × 2) trials per posture. The order of the trials was randomized.

### Neck Straight Experiment

The task is very similar to the one tested in the "Cross-modal Experiment" except that the subjects were not asked to laterally flex the neck after the target memorization. Twelve subjects participated to the experiment (age: 38.5 ± 8). Half of them performed the Seated condition before the Supine condition, the other half did the opposite to compensate for possible learning effects. As for the previous experiment, each target orientation was tested twice per postural condition, for a total of 28 (= 2 × 2 × 7) responses. The head mounted display used for these tests was an Oculus Rift (field of view: 90°, frame rate: 90 Hz, resolution: 1,080 × 1,200 pixels, adjustable inter-pupillary distance). As for the main experiments, a custom C++ code was developed by the research team to integrate optical (Codamotion system) and inertial (embedded in the Oculus-Rift) sensors and to update the stereo images provided in virtual reality headset.

## Data Analysis

The subjects' performance was analyzed using Matlab (MathWorks, RRID: SCR_001622) in terms of the lateral inclination (roll) of the tool when they validated the response. In order to describe the variability of the subject responses, we computed the root mean square of the difference, *RMSd*, between

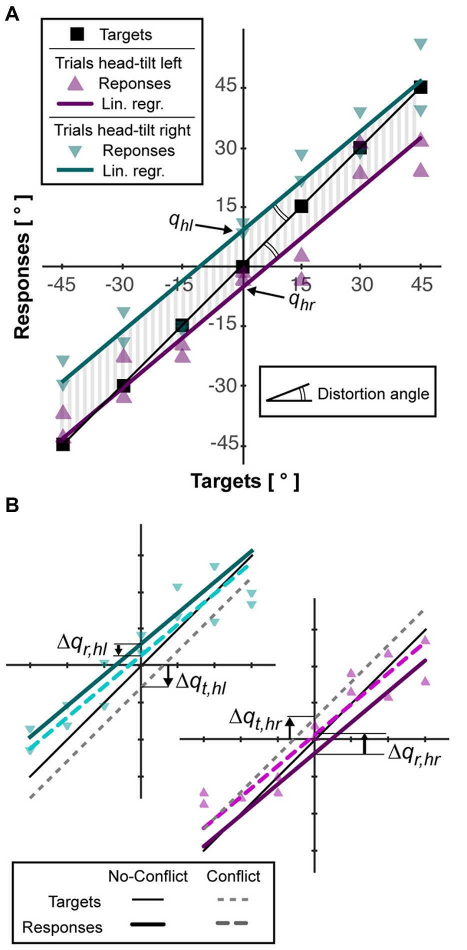

**FIGURE 2 |** Example of subject responses and associated analysis. **(A)** The responses for trials without conflict (triangles) are linearly interpolated as describe in "Materials and Methods" section (colored lines). The area (vertical gray bars) between each interpolation line and the line joining the targets (squares) is used to compute accuracy, *Acc*. The angle between the interpolation lines and the targets line is used quantify the distortion, *Dist*, of the responses. The intersections between the vertical axis and the lined interpolating the responses after left and right neck flexion ($q_{hl}$, $q_{hr}$) are used to quantify the response bias induced by the head roll (Aubert-Müller effect, *AMe*). **(B)** For the trials with conflict, that is, rotation of the visual scene, the responses after left and right flexion of the neck are interpolated separately (see "Materials and Methods" section) and represented by dotted, colored lines. To estimate the relative importance given to the visual information, the vertical distance between the lines interpolating the response with and without conflict, $\Delta q_{r,hl}$ and $\Delta q_{r,hr}$, is computed and compared to the theoretical deviation of the targets, if they assumed to move together with the visual scene, $\Delta q_{t,hl}$ and $\Delta q_{t,hr}$.

the two responses, $r$, to each combination of target, $t$, and head, $h$, inclination in the trials without conflict.

$$RMSd = \sqrt{\frac{\sum_{h=1}^{2}\sum_{t=1}^{7}\left(r_{t,h,1} - r_{t,h,2}\right)^2}{14}} \tag{1}$$

To describe the characteristics of the average behavior of the subjects, the linear regression lines of their responses after tilting the head to the right and to the left were computed imposing their parallelism (see **Figure 2A**). Each of the two regression lines have the form $r = mt+q_i$, where $r$ and $t$ are the response and target orientation, respectively. The parameter "$m$," common for the two lines, represents their slope. The intersection with the response axis "$q_i$" is different for the trials with rotation of the head to the right ($i = hr$) and to the left ($i = hl$). The parameters of the lines were used to quantify the following variables:

- The *accuracy (Acc)*, that is average response-target distance, was represented by the average absolute distance between the regression lines and the line passing through the targets position (vertical gray lines in **Figure 2A**).
- The *Aubert-Müller effect (AMe)*, corresponding to the global response bias due to the lateral neck flexion (Guerraz et al., 1998), was quantified as half of the algebraic distance between the intersection point of the two regression lines with the vertical axis: $AMe = (q_{hl} - q_{hr})/2$.
- The *distortion (Dist)*, representing possible over/under-estimation of the distance between two targets' orientation (McIntyre and Lipshits, 2008), is represented by the angle between the regression lines and the line passing through the targets' orientations: $Dist = \text{atan}(m)$-45° (double arcs in **Figure 2A**). Positive and negative values of *Dist* correspond to a global over- and under- estimation of the angular distances, respectively.

## Sensory Weighting Quantification

To quantify the specific effect of the sensory conflict in each condition we linearly interpolated the responses of the conflict-trials with right and left neck flexion constraining the lines to be parallel to regression lines of the no-conflict-trials (see **Figure 2B**). This procedure provides the responses-axis intercepts for the conflict trials. Subtracting to these parameters the corresponding values in the no-conflict-trials we obtain the average deviations of the response due to the tilt of the visual scene: $\Delta q_{r,hi}$. In order to convert the response deviation into the percentage weight given to visual information, we computed, for each conflict trial, the virtual displacement of the target expected if only visual information was used to code its orientation, which corresponds to $t$ - $head\_angle \times 0.6$. We linearly interpolated these theoretical responses for right and left neck flexion separately, constraining the lines to be parallel to the one joining the targets ($m = 1$) and we obtained the response-axis intercepts (see **Figure 2B**). Subtracting from these parameters the intercept of the line joining the target in the no-conflict trials ($q = 0$), we obtain the average target deviation expected in case of fully visual encoding of their orientation: $\Delta q_{t,hi}$. The percentage weight given to the visual information, $\omega_V$, can be then computed as it follows:

$$\omega_V = \frac{1}{2}\sum_{i=l,r}\frac{\Delta q_{r,hi}}{\Delta q_{t,hi}} \cdot 100\% \tag{2}$$

## Statistical Analysis

For each experiment, we assessed the effect of the subject posture on the subject performances by performing mixed model ANOVAs on the *AMe*, *Dist*, *Acc*, *RMSd,* and $\omega_V$ dependent variables, with the *Posture* (Seated, Supine) and *Order* (Seated-First and Supine-First) as within- and between- subjects independent variable, respectively. No between-experiment comparisons were performed, because they do not correspond to the goal of this study. Since we performed three distinct experiments, we applied a Bonferroni correction ($n$ = 3) to the resulting p-values to reduce the probability of type I errors (false positive). Therefore, in the following, $p < 0.05/3$ ($\simeq$0.0167), $p < 0.01/3$ ($\simeq$0.0033), and $p < 0.001/3$ ($\simeq$0.00033) will be indicated with "*," "**," "***," respectively. For the straight-neck experiment, we specifically wanted to test the "*Gravity Hp*," that is whether the Supine position increased the subjects' variable and constant errors. We therefore performed one-tail Student's *t*-tests on *RMSd* and *Acc*. Since the subjects did not rotate their head, no conflict could be generated and no quantification of the sensory weighting was possible. All statistical analyses were performed using the Statistica 8 software (Statsoft, SCR_014213).

## Optimal Integration of Non-independent Sensory Signals Based on the Maximum Likelihood Principle

In order to quantify the predictions associated with the *Gravity* and *Neck* Hypotheses and compare them with the experimental results, we apply our *Concurrent Model* of optimal sensory integration (Tagliabue and McIntyre, 2011, 2014) to describe the information flow associated with the Seated and Supine postures for each of the three experiments. An illustration of the general model structure is reported in **Figure 3A**.

This model is based on the assumption that the target and hand position are compared in the visual and proprioceptive space concurrently ($\Delta$V and $\Delta$P) and then these two parallel comparisons are combined based on the Maximum Likelihood Principle (Ernst and Banks, 2002). From this optimality principle it follows that the relative weight, $W_{\Delta V}$ and $W_{\Delta P}$, given to each comparison depends on their variance $\sigma^2_{\Delta V}$ and $\sigma^2_{\Delta P}$ as it follows:

$$W_{\triangle V} = \frac{\sigma^2_{\triangle P} - cov(\triangle V, \triangle P)}{\sigma^2_{\triangle V} + \sigma^2_{\triangle P} - 2cov(\triangle V, \triangle P)}$$

$$W_{\triangle P} = \frac{\sigma^2_{\triangle V} - cov(\triangle V, \triangle P)}{\sigma^2_{\triangle V} + \sigma^2_{\triangle P} - 2cov(\triangle V, \triangle P)} \tag{3}$$

which corresponds to the minimal achievable variance of motor vector estimation $\Delta$

$$\sigma^2_{\triangle} = \frac{\sigma^2_{\triangle V}\sigma^2_{\triangle P} - cov(\triangle V, \triangle P)^2}{\sigma^2_{\triangle V} + \sigma^2_{\triangle P} - 2cov(\triangle V, \triangle P)} \tag{4}$$

In Equations 3 and 4 the covariance between $\Delta$V and $\Delta$P, *cov($\Delta$V,$\Delta$P)*, is used to take into account the situations in which the two concurrent comparisons are not fully independent (Tagliabue and McIntyre, 2013). The application of MLP to multi-sensory integration therefore assumes that the brain can estimate the variability of the signals to be combined ($\sigma^2_{\triangle V}$ and $\sigma^2_{\triangle P}$) and to which extent they are independent ($cov(\triangle V, \triangle P)$). Although it is not clear whether, and how, the brain would actually estimate these specific parameters, perceptive and behavioral studies have shown that human sensory weighting is clearly modulated by signals' variability as predicted by the MLP (Ernst and Banks, 2002) and that performances cannot be improved by combining two fully dependent signals (Tagliabue and McIntyre, 2013-2014), as expected if their covariance is taken into account.

For the cross-modal task without head rotation (**Figure 3B**), the model predicts a reconstruction of the proprioceptive target representation from the visual information and of a visual hand representation from the proprioceptive feedback (green arrows). These cross-modal transformations, which introduce additional errors, are associated to specific variance terms $\sigma^2_{V\to P}$ and $\sigma^2_{P\to V}$, and, as show in section 1 of **Supplementary Material**, Equations 3 and 4 become:

$$W_{\triangle V} = \frac{\sigma^2_{V\to P}}{\sigma^2_{V\to P} + \sigma^2_{P\to V}} \qquad W_{\triangle P} = \frac{\sigma^2_{P\to V}}{\sigma^2_{V\to P} + \sigma^2_{P\to V}}$$

$$\sigma^2_{\triangle} = \sigma^2_{T_V} + \sigma^2_{H_P} + \frac{\sigma^2_{V\to P}\sigma^2_{P\to V}}{\sigma^2_{V\to P} + \sigma^2_{P\to V}} \tag{5}$$

As illustrated in **Figures 3C,D**, the model predicts no cross-modal reconstructions for the unimodal tasks (Tagliabue and McIntyre, 2013): in these tasks, the direct comparison between the available information about the target and the hand fully covaries with any comparison reconstructed from the available cues. From equation 4 it follows that the reconstruction of concurrent comparisons cannot improve the precision of $\Delta$ and using equations 3 it results that the predicted sensory weights and the motor vector variance are:

$$W_{\triangle V} = 1 \quad W_{\triangle P} = 0 \quad \sigma^2_{\triangle} = \sigma^2_{T_V} + \sigma^2_{H_V} \tag{6}$$

$$W_{\triangle V} = 0 \quad W_{\triangle P} = 1 \quad \sigma^2_{\triangle} = \sigma^2_{T_P} + \sigma^2_{H_P} \tag{7}$$

for the visual and proprioceptive task, respectively.

For all tasks, once the motor vector is estimated, the motor system generates the muscle activations necessary to displace the hand in the defined direction and distance. This step introduces some additional noise, that we will call motor noise, $\sigma^2_m$, so that the variance of the movement execution is $\sigma^2_{ME} = \sigma^2_{\triangle} + \sigma^2_m$. There might be additional factors, as the concentration and fatigue levels of the subject, that can contribute to the movement execution variability. For sake of simplicity, the present version of the model does not include them separately and they are all combined together in the $\sigma^2_m$ term.

To simulate the effect on the information processing of head inclination with respect to gravity, or of the neck flexion, in these three tasks, the variance, $\sigma^2_N$, is added to the $\sigma^2_{V\to P}$, $\sigma^2_{P\to V}$ terms. This extra noise is added to the cross-modal sensory transformations performed with the neck flexed, with neck muscle acting against gravity or with the head misaligned with respect to gravity, depending on the hypothesis to be tested.

In order to test which hypothesis, between the "Neck1," "Neck2," and "Gravity," better predicts the experimental results, we compare the observed effect of posture on the subjects'

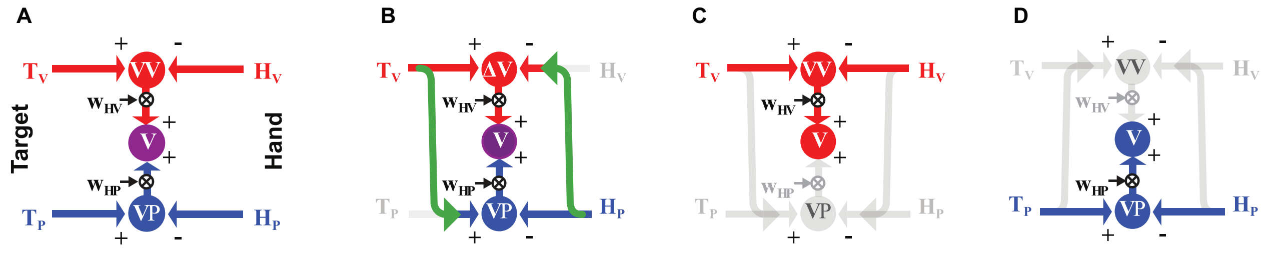

**FIGURE 3 |** Concurrent Model of multisensory integration. **(A)** Graphical representation of the sensory information flow when the target, T, to be reached (on the left) and the hand, H, used to perform the movement (on the right) can be both sensed through vision, V (red), and proprioception, P (blue). ΔV and ΔP represent the concurrent representations in the visual and proprioceptive space of the movement to be performed to reach the target. The weights $W_{\Delta V}$ and $W_{\Delta P}$ (see Equation 3) allow one to optimally combine the concurrent representations and maximize the precision of the final motor vector estimation (Δ). **(B)** Application of the model to the cross-modal task of reaching a visual target with an unseen hand. Missing sensory cues are gray. The green arrows represent cross-modal transformations, that is, the encoding of an information coming from the visual system in the reference frame associated to the proprioceptive sensory system, V→P, or vice-versa, P→V. **(C,D)** Model application to uni-modal visual and proprioceptive tasks, respectively, where no cross-modal transformations are predicted.

responses' variability, $DMSd = RMSd^2_{Supine} - RMSd^2_{Seated}$, and on the response deviation due to visual scene rotation, $D\omega_V = \omega_{V,Supine} - \omega_{V,Seated}$, with corresponding parameters of the model: the difference between the Supine and Seated posture predicted by the model for the movement execution variability, $D\sigma^2_{ME} = \sigma^2_{ME,Supine} - \sigma^2_{ME,Seated}$, and for the weight associated with visual representation of the task, $DW_{\Delta V} = W_{\Delta V,Supine} - W_{\Delta V,Seated}$.

As shown in **Supplementary Material (sections 3** and **4)**, the theoretical predictions depend only on two main parameters: the variance associated to the cross-modal sensory transformation, $\sigma^2_{P\leftrightarrow V}$, and to the noise added to these transformations when performed with the head misaligned with respect to gravity and/or the body, $\sigma^2_N$. In order to reduce even further the degrees of freedom of the model, and thus the possibility of overfitting the experimental data, the value of $\sigma^2_{P\leftrightarrow V}$ is set to $23.19^{\circ 2}$; a value that is computed from the results of Tagliabue and McIntyre (2011) in section 4.2 of **Supplementary Material**. To statistically test whether the predictions of the various hypotheses differed from the experimental data, a multivariate Hotelling's $T^2$ test is performed with six dependent variables ($D\omega_V$ and $DMSd$ for each of the three experiments) and the six corresponding model predictions ($DW_{\Delta V}$ and $D\sigma^2_{ME}$) as reference values.

## RESULTS

The subjects' average responses in the three main experiments (Cross-modal, Unimodal Visual and Unimodal Proprioceptive tasks) for the two tested postures (Seated and Supine) are depicted in **Figure 4A**, where specific deviations of the responses away from the target can be seen for each task and each posture. The statistical analyses show that none of the analyzed parameters were significantly affected by the posture *Order* and that the *Order* did not significantly interact with the *Posture* effect. Neither did *Posture* appear to have had a significant effect on the average error (accuracy) in any of three experiments (**Figure 4B**). More detailed analyses of the pattern of errors, however, reveal some specific effects of *Posture* (see statistics reported on **Table 1**): the global response deviation in relation with the lateral neck flexion, close to zero in the Seated condition, significantly increased in all three experiments when the subjects were Supine (Aubert-Müller effect in **Figure 4C**). The effect of posture on the perceptive distortion appears to have differed among the three experiments (**Figure 4D**): a significant modulation, but in opposite directions, for cross-modal and unimodal proprioceptive tasks and no difference for the unimodal visual experiment. In conclusion, subjects' posture appears to affect some specific aspect of the average response patterns, but the average error (accuracy) does not significantly change when supine.

On the other hand, the variability of the responses RMSd, reported in **Figure 5A**, appears to have been affected by the subject's posture: in the cross-modal experiment the subjects were significantly less precise when supine, but this was not the case in the unimodal visual and proprioceptive experiments. The change, or lack thereof, in response variability was accompanied by a similar modulation of the sensory weighting shown in **Figure 5B**: only in the cross-modal task did the visual weight significantly increase in the supine posture.

Overall, these results suggest that the use of sensory information during the cross-modal paradigm differs from that of unimodal tasks, and that this weighted processing is significantly affected by posture.

### Analysis of Between-Subjects Differences

To go beyond average responses, we then assessed whether inter-individual variability can provide more insight on the sensory processing underlying the responses observed in the three experiments.

For the Seated condition of the unimodal visual and proprioceptive experiments, the concurrent model predicts, respectively, a negative and positive correlation between the visual weighting and the variability of the motor vector estimation. In fact, a visual weight smaller than 100% in the V-V task, or the larger than 0% in the P-P task, would both correspond to suboptimal solutions and thus to an increase of the variability of the motor vector estimation (see **Supplementary Material, section 2**). The correlation between visual weighting and the variability of the motor vector estimation measured in inter-individuals is reported in **Table 2**.

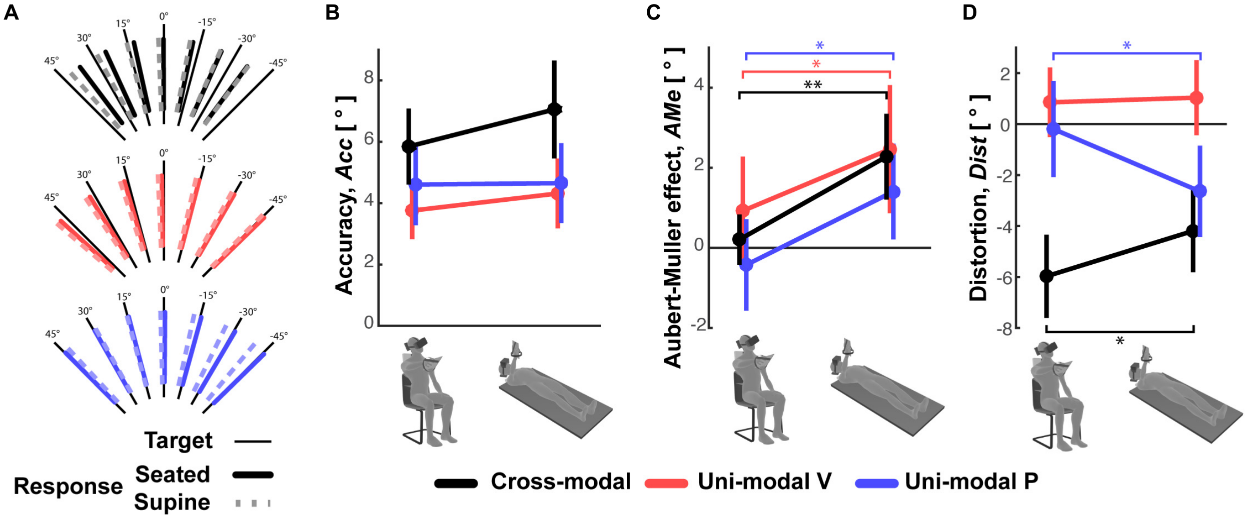

**FIGURE 4 |** Average subject responses. **(A)** For the three experiments, the mean orientation of the subjects' responses to each target orientation is represented for the Seated and Supine conditions. The three parameters representing **(B)** the response accuracy, **(C)** Aubert-Müller effects, that is the global bias of the responses due to lateral neck flexion. Positive values correspond to deviations toward the head direction. **(D)** Response distortions are reported for the Seated and Supine conditions of the three experiments. Vertical whiskers correspond to 95% confidence intervals. * and ** represent $p < 0.05/3$ and $p < 0.01/3$, respectively, and their color represents the experiment to which they refer.

**TABLE 1 |** For each of the experiments (cross-modal, V-P; unimodal visual V-V; unimodal proprioceptive, P-P) the ANOVA main effect of Posture, posture Order and the interaction between these two factors are reported for the Aubert-Müller effect, AMe, the response distortion, Dist, accuracy, Acc, and variability, RMSd, as well as for the relative weight associated to visual information, $\omega_V$.

| | | **Effects** | | |
|---|---|---|---|---|
| **Exp** | **Param.** | **Posture** | **Order** | **Posture x Order** |
| V-P | AMe | $F_{(1,16)} = 12.7$, $\boldsymbol{p = 0.0026}$ | $F_{(1,16)} = 0.18$, $p = 0.67$ | $F_{(1,16)} = 0.01$, $p = 0.89$ |
| | Dist | $F_{(1,16)} = 10.6$, $\boldsymbol{p = 0.0049}$ | $F_{(1,16)} = 0.23$, $p = 0.63$ | $F_{(1,16)} = 0.61$, $p = 0.44$ |
| | Acc | $F_{(1,16)} = 0.97$, $p = 0.34$ | $F_{(1,16)} = 0.97$, $p = 0.33$ | $F_{(1,16)} = 0.34$, $p = 0.57$ |
| | RMSd | $F_{(1,16)} = 15.3$, $\boldsymbol{p = 0.0012}$ | $F_{(1,16)} = 0.01$, $p = 0.91$ | $F_{(1,16)} = 1.41$, $p = 0.25$ |
| | $\omega_V$ | $F_{(1,16)} = 23.9$, $\boldsymbol{p = 16{\bullet}10^{-5}}$ | $F_{(1,16)} = 0.00$, $p = 0.97$ | $F_{(1,16)} = 0.57$, $p = 0.46$ |
| V-V | AMe | $F_{(1,16)} = 9.16$, $\boldsymbol{p = 0.0080}$ | $F_{(1,16)} = 0.19$, $p = 0.67$ | $F_{(1,16)} = 2.91$, $p = 0.11$ |
| | Dist | $F_{(1,16)} = 0.01$, $p = 0.93$ | $F_{(1,16)} = 0.20$, $p = 0.65$ | $F_{(1,16)} = 2.49$, $p = 0.13$ |
| | Acc | $F_{(1,16)} = 1.63$, $p = 0.22$ | $F_{(1,16)} = 0.42$, $p = 0.52$ | $F_{(1,16)} = 0.86$, $p = 0.37$ |
| | RMSd | $F_{(1,16)} = 0.10$, $p = 0.76$ | $F_{(1,16)} = 0.07$, $p = 0.79$ | $F_{(1,16)} = 0.85$, $p = 0.37$ |
| | $\omega_V$ | $F_{(1,16)} = 2.36$, $p = 0.14$ | $F_{(1,16)} = 0.25$, $p = 0.62$ | $F_{(1,16)} = 3.54$, $p = 0.08$ |
| P-P | AMe | $F_{(1,16)} = 10.9$, $\boldsymbol{p = 0.0044}$ | $F_{(1,16)} = 0.98$, $p = 0.34$ | $F_{(1,16)} = 2.11$, $p = 0.16$ |
| | Dist | $F_{(1,16)} = 10.7$, $\boldsymbol{p = 0.0048}$ | $F_{(1,16)} = 0.01$, $p = 0.92$ | $F_{(1,16)} = 6.93$, $p = 0.018$ |
| | Acc | $F_{(1,16)} = 0.01$, $p = 0.93$ | $F_{(1,16)} = 4.94$, $p = 0.04$ | $F_{(1,16)} = 0.04$, $p = 0.83$ |
| | RMSd | $F_{(1,16)} = 0.85$, $p = 0.37$ | $F_{(1,16)} = 2.89$, $p = 0.11$ | $F_{(1,16)} = 0.98$, $p = 0.33$ |
| | $\omega_V$ | $F_{(1,16)} = 0.02$, $p = 0.89$ | $F_{(1,16)} = 0.71$, $p = 0.41$ | $F_{(1,16)} = 4.31$, $p = 0.054$ |

*The significant results after the Bonferroni correction ($p < 0.05/3$) are reported in bold fonts.*

Although not statistically significant, the tendency to a negative correlation in the unimodal visual task reported in **Table 2**, is consistent with the model prediction, while the absence of correlation in the P-P experiment is not. This could be due to a significant contribution of the motor noise to *RMSd* in this task, because both memorization and response require active hand movements. Motor noise affects the response variability but not the sensory weight, thus it might hide an existing correlation between the variability of motor vector estimation and the sensory weighting. The potential influence of motor noise is supported by the fact that the expected correlation seems to exist for the V-V task, where the motor component should be irrelevant.

For the V-P task no clear correlation between $\omega_V$ and *RMSd* is to be expected, because, as shown in Equation 5, the sensory

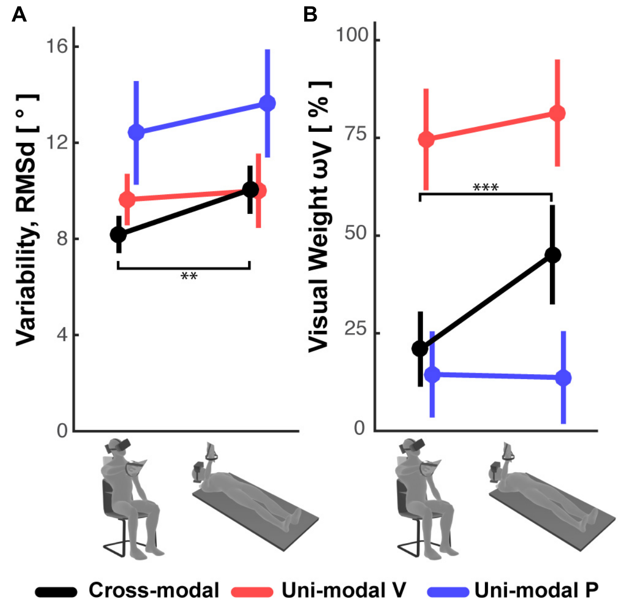

**FIGURE 5 | (A)** Subjects' response variability and **(B)** visual weight observed in the Seated and Supine conditions for the cross-modal and the two uni-modal (visual and proprioceptive) experiments. Vertical whiskers correspond to 95% confidence intervals. ** and *** represent $p < 0.01/3$ and $p < 0.001/3$, respectively, and their color represents the experiment to which they refer.

**TABLE 2 |** Coefficient of correlation R (and associated p-value) between the variability, RMSd, and visual dependency, $\omega_V$, in the Seated condition of the three experiments (Exp).

| Exp | *R* | *p* |
|---|---|---|
| V-P | 0.11 | 0.65 |
| V-V | −0.41 | 0.09 |
| P-P | 0.17 | 0.51 |

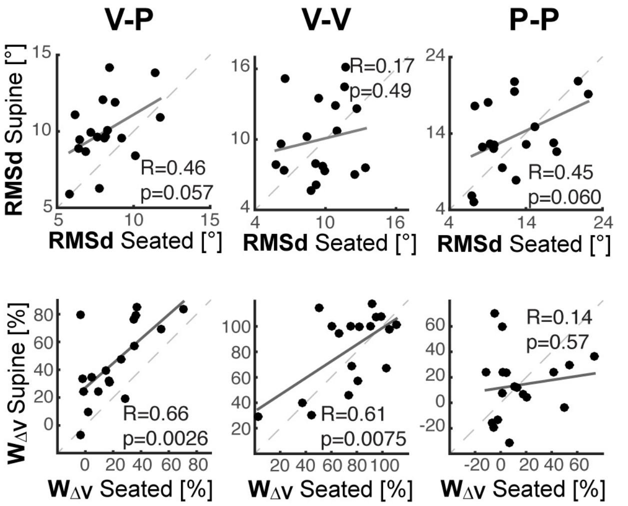

**FIGURE 6 |** Inter-individual analyses. For each of the three experiments cross-modal (left), unimodal visual (middle) and unimodal proprioceptive (right), individual performance in the Supine condition are shown as a function of the performance in the Seated condition, in terms of response variability (top row) and visual dependency (bottom row). Dashed lines correspond to the identity line. Solid lines correspond to the linear interpolation of the data. "R" is the coefficient of correlation between the Seated and Supine data and "p" represents the corresponding statistical significance.

weight theoretically depends only on the noise attributed to the cross-modal sensory transformations, whilst the response variability depends also on the subject's visual and proprioceptive acuity. Moreover, motor noise could play a role, as in the P-P task.

In order to understand whether between-subject differences while seated would affect an individual's performance when supine, we evaluated the correlation between the individual performance in the Seated and Supine conditions. As shown in **Figure 6**, we evaluated the performance in terms of response variability, *RMSd*, and visual weight, $\omega_V$.

The top part of **Figure 6** shows that the ranking of the subject in terms of response precision in the Seated condition tends to be preserved when Supine, but only in the tasks with relevant proprioceptive and motor components (V-P and P-P). Consistent with the results of **Table 2**, this finding suggests that the individual motor noise contributes to the observed response variability and tends to be preserved between postures. The bottom part of **Figure 6** show that in the tasks with a relevant visual component (V-P, V-V), the subjects that are most visuo-(in)dependent when seated, remain the most visuo-(in)dependent when supine. These correlations suggest that, although different levels of visual-dependency can be observed among the subjects, their visual-dependency ranking was not altered by posture. It follows that the effect of the postural change in the cross-modal task was quite consistent among all of participants.

## Model Predictions

**Figure 7A** graphically represents the model predictions associated with the hypotheses that the lateral neck flexion per se (Neck1 Hp), the increase of the noise in the neck muscles-spindles (Neck2 Hp) or the head misalignment with respect to gravity (Gravity Hp), interferes with the ability to perform cross-modal transformation (detailed model equations are presented in **Supplementary Material, section 3**). Their quantitative comparison with the experimental results is shown in **Figure 7B** in terms of differences between the Seated and Supine condition. Focusing these predictions on the effect of the postural change has two main advantages: first, it compensates for a possible role of individual motor precision or sensory acuity that, as we have shown above, might increase between-subject variability. Second, it simplifies the model by allowing a significant reduction of the number of parameters estimated.

**Figure 7B** show that the "Neck1 Hp," which predicts no changes between Seated and Supine postures for all three, Cross-Modal, Unimodal Visual and Unimodal Proprioceptive tasks, is significantly different from the experimental observations [Hotelling's test: $T^2 = 93.0$, $F_{(6,12)} = 10.9$, $p = 0.0003$]. The "Neck2 Hp" prediction also significantly differs from the experimental

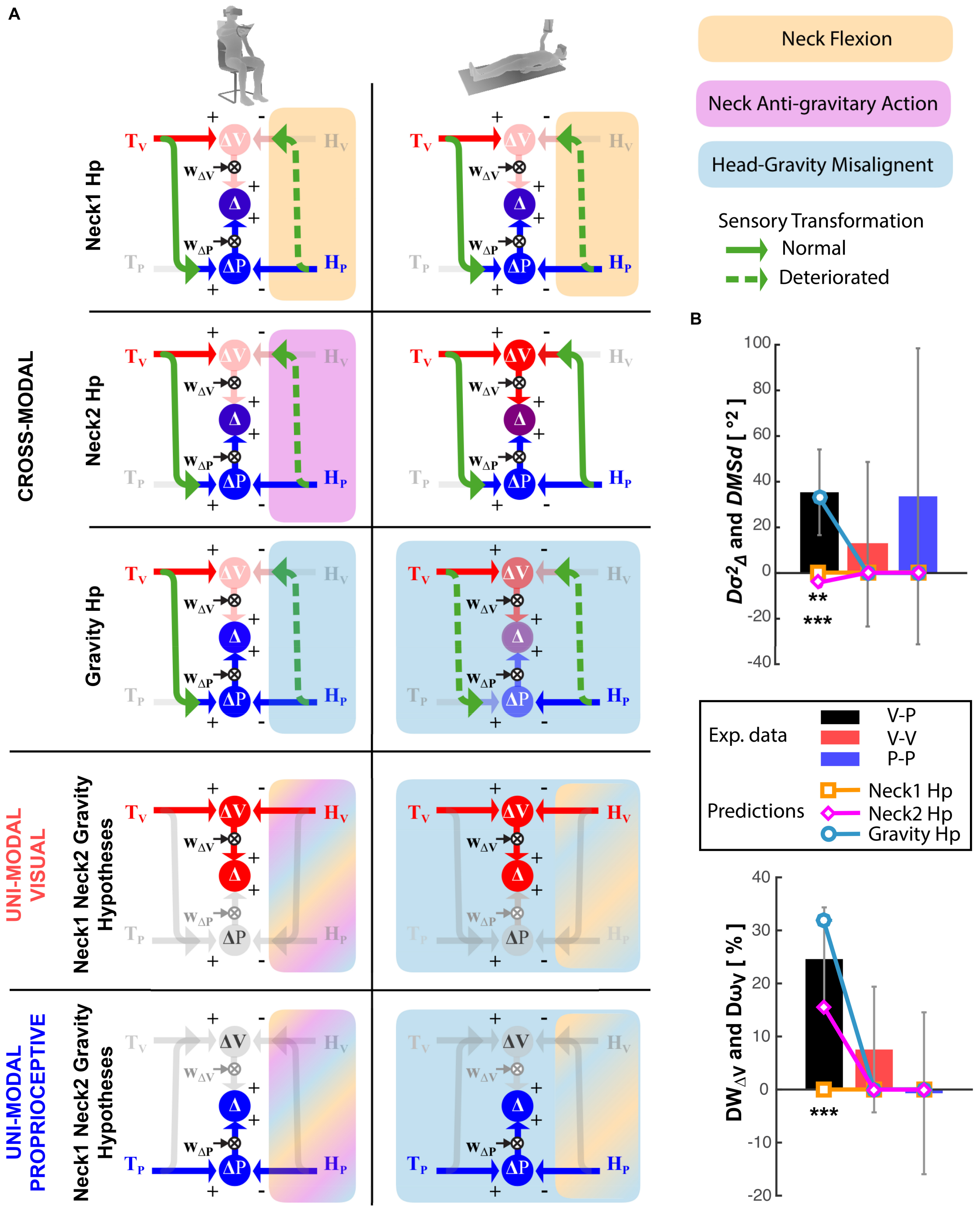

**FIGURE 7 |** Model predictions. **(A)** Graphical representation of the sensory information flow in the Seated (left) and Supine (right) conditions for the cross-modal, unimodal visual and unimodal proprioceptive experiments. For the cross-modal task the predictions for the Neck1, Neck2, and Gravity hypotheses are represented separately. For the unimodal visual and proprioceptive tasks, the three hypotheses are identical and thus represented together. The model structures and the graphical conventions are the same as in **Figure 3**. In addition, dashed green arrows represent perturbed cross-modal sensory transformations; faded arrows and circles are associated with a noisy information. For each tested theory the colored rectangular areas include the cross-modal transformations perturbed by the hypothesized disrupting factor: orange, violet and cyan represent the neck flexion, the neck muscles action against gravity and the head-gravity misalignment, respectively. Since for the unimodal tasks the three hypotheses are represented together, multicolor areas illustrate the cross-modal transformations affected by more the one disrupting factor. **(B)** Comparison between the experimental results and the predictions of the three hypotheses, in terms of modulation of the response variance (upper panel) and visual weight (lower panel) due to postural change (Supine-Seated). Vertical whiskers represent the 95% confidence interval of the experimental data. ** and *** represent statistical difference ($p < 0.01$ and $p < 0.001$) between the model predictions and the experiments results for each experiment and each parameter separately. The color of the stars indicates the tested hypothesis.

observations [Hotelling's test: $T^2 = 34.93$ $F_{(6,12)} = 4.11$, $p = 0.017$]. Indeed, although this hypothesis appears to better match the increase of the visual weight when supine, it cannot account for the increase in response variability; since in the Supine posture the neck muscles never act against gravity the model must predict a decrease of the response variability with respect to task performed with the Seated posture, which require a neck muscles' activation during the response phase to support the tilted head.

"Gravity Hp" appears to well capture the fact that the Supine posture increases both the response variability and the visual weight in the cross-modal task only [Hotelling's test: $T^2 = 9.65$, $F_{(6,12)} = 1.13$, $p = 0.40$]. The matching between the Gravity Hp prediction and the experimental data is obtained with $\sigma_N^2 = 81^2$, which means that the variance associated with the cross-modal transformation would increase by about 3.5 times when the head is not aligned with gravity.

## Straight-Neck Experiment

To confirm the role of the head-gravity alignment on the visuo-proprioceptive transformations (experimental results and the model prediction of **Figure 7**) the precision and the accuracy of the subjects' responses was compared between the Seated and Supine conditions of a cross-modal task performed without lateral neck movements. **Figure 8** shows that, as for the main Cross-Modal Experiment, when supine the subjects are significantly less precise [one-tailed $t$-test: $t_{(11)} = 3.42$, $p = 0.04$] and less accurate [one-tailed $t$-test: $t_{(11)} = 2.79$, $p = 0.009$] than when seated.

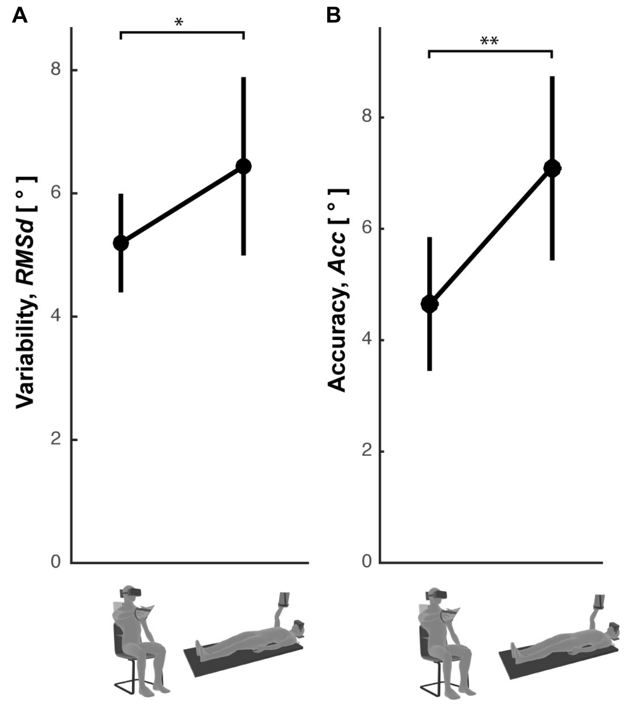

**FIGURE 8 |** Response errors in the Straight Neck Experiment. Subjects' response **(A)** variability and **(B)** accuracy observed in the Seated and Supine conditions for the cross-modal task without lateral neck flexions. Vertical whiskers correspond to 95% confidence intervals. * and ** represent $p < 0.05$ and $p < 0.01$, respectively.

# DISCUSSION

We have performed experiments to try to understand why lateral neck flexions appear to interfere with the visuo-proprioceptive transformations used during reaching/grasping movements (Burns and Blohm, 2010; Tagliabue and McIntyre, 2011, 2014; Tagliabue et al., 2013). This type of cross-modal transformation consists of encoding retinal visual signals into a proprioceptive joint space and, vice-versa, encoding the position/orientation of the hand sensed through joint proprioception in a visual space.

Our first working hypothesis was that neck flexion might perturb the sensory information coming from the eye-hand kinematic chain, which can be used for computing the cross-modal transformation (Sabes, 2011). The lateral neck flexion interference could have two main origins: the rarity of performing eye-hand coordination tasks with such neck configuration (Neck1 Hp) or degradation of the proprioceptive neck information due to the muscle effort necessary to sustain the head's weight (Neck2 Hp). "Neck1 Hp" is related to the difficulty of interpreting correctly the "unusual" sensory signals coming from the flexed neck. As observed for different tasks, motor performance appears indeed to correlate with the relative incidence of the type of movement during everyday life (Howard et al., 2009). "Neck2 Hp" is based on the signal-dependent nature of noisiness of the neck muscles spindles (Abedi Khoozani and Blohm, 2018). An alternative hypothesis, one that does not involve the eye-hand kinematic chain, was that head misalignment with respect to gravity, and not lateral neck flexion, would mainly interfere with visuo-proprioceptive transformations (Gravity Hp). This hypothesis is based on the fundamental role that gravity would have in reciprocal calibration of the retinal and proprioceptive reference frame (Paillard, 1991).

To test which of these hypotheses better describe the actual functioning of the human central nervous system (CNS) we asked volunteers to perform a virtual-reality task requiring cross-modal transformations, i.e., matching with an unseen hand a memorized visual target orientation, as to grab it, after a lateral neck flexion. The subjects performed this task both in a Seated and Supine position.

The expected effect of changing posture is very different for the three hypotheses. To try to formalize and quantify these predictions we applied an optimal theory of multi-sensory integration to the above-described task. This statistical model, in which the task is concurrently represented in the visual and proprioceptive space (Tagliabue and McIntyre, 2008, 2011, 2012, 2013, 2014; McGuire and Sabes, 2009; Tagliabue et al., 2013; Arnoux et al., 2017; Bernard-Espina et al., 2021) allowed to compute the effects of changing posture in terms of subjects' responses variability and in terms of the relative importance given to the visual and proprioceptive encoding of the information.

The model results show that the "Neck1 Hp" predicts no significant changes in subject precision nor in sensory weighting, because the lateral neck flexion is the same in the two postural conditions. If the "Neck2 Hp" is correct a decrease of the response variability and an increase of the importance given to visual encoding is to be expected, because when supine a special head support always sustained the head, reducing the neck muscles activation, and hence the neck proprioceptive noise. The "Gravity Hp" predicts an increase of both response variability and weight associated to visual space, because when supine the subject head is always misaligned with respect to gravity, continuously perturbing cross-modal transformations. The results of the "Cross-Modal Experiment" show a significant increase of the response variability and visual weight when supine, so that the "Gravity Hp" prediction is the closest to the experimental observations. With the "Neck-Straight Experiment," which does not involve lateral head rotations, we were able to disentangle even further the role of gravitational afferences from those generated by neck movements, such as neck muscle spindles and semi-circular canals signals. The persistence, in this experiment as in the task with head rotations, of an increase of subject errors in the supine posture confirms and reinforce the importance of the gravity-head alignment. Overall, these results clearly support the hypothesis of a fundamental role of gravity in the ability of performing cross-modal transformations. More precisely, these findings are consistent with the idea that a misalignment of the head with respect to gravity interferes with the ability of performing cross-modal transformations, that is the encoding a visual information in the proprioceptive space and vice-versa.

Although the present results support the central role of the external gravitational reference, a role of the neck and of the rest of eye-hand kinematic chain, which is associated with an egocentric processing of the information, should not be fully discarded. We have indeed already reported evidence supporting the coexistence of ego- and exo-centric information processes (Tagliabue and McIntyre, 2012, 2014). Moreover, a role of the visual vertical in the ability to perform cross-modal sensory transformations cannot be excluded, as it has been shown that the vertical direction perception is a highly multisensory process, with gravity, body and scene information interacting (Dyde et al., 2006).

The posture effect on the cross-modal transformations reported here, however, is ascribable to gravitational signals, because in all used experimental paradigms the head/body axis information and the visual information contributing to the vertical perception were identical in the seated and supine condition and the only factor that changed was the misalignment with respect to the gravitational vector.

To be able to exclude the hypothesis that the observed effect of the posture in the cross-modal task could be ascribed to a degradation of the visual or proprioceptive acuity *per se* and not of the sensory transformations, we added two control experiments in which the subjects performed visual and proprioceptive tasks not requiring sensory transformations. The lack of significant differences between the seated and supine condition in terms of response variability and sensory weighting in these uni-modal experiments suggests that the head misalignment with respect to gravity does not significantly alter the unimodal sensory precision *per se*, and thus supports the idea of a specific effect of posture/gravity on the sensory transformations. The different effect of the posture on the response precision between the cross-modal and unimodal tasks is perfectly in line with the results of the orientation reproduction experiment of McIntyre and Lipshits (2008). They showed indeed that laterally tilting the whole body of subjects by 22.5° clearly increases their response errors in a cross-modal (haptic-visual) task, and not so in two unimodal tasks (visual-visual and haptic-haptic). The consistency with the present results also suggests that the head tilt effects are independent of the tilt axis (pitch or roll).

In our three first experiments we observed that posture also influences some features of the average pattern of subjects' responses. Although our theoretical framework does not provide predictions on this aspect of the subjects' performance, it is interesting to note that the response shifts due to the lateral neck flexion (Aubert-Müller effect) significantly increased when supine, in all three experiments. This result suggests that gravity direction would also contribute to the encoding of the target and response orientation, no matter the modality of the information. This is consistent with Darling and Gilchrist (1991) study on hand orientation reproduction tasks showing that gravitational information influences the encoding of the hand roll. Similarly, the disappearance of the oblique effect when the subject' whole body is laterally tilted in purely visual (McIntyre et al., 2001) and cross-modal (McIntyre and Lipshits, 2008) orientation reproduction tasks was interpreted as an evidence of the use of gravity as a reference to encode orientation cues. In addition to its role in perception, gravity was shown to contribute also to motor encoding, since lateral tilts affected the perception of hand movements direction (Darling et al., 2008) and the control of eye saccades (Pelt et al., 2005).

## Inter-Individual Differences

The analyses of the between-subjects differences suggest that the effect of the head-gravity misalignments on cross-modal transformations is quite robust, since it does not appear to depend on individual characteristics such as visual dependency or precision, which can vary significantly between subjects. The observed inter-subject variability in the Seated condition also suggests that not all subjects perform optimally, in the "Maximum Likelihood" sense (Ernst and Banks, 2002), that is, some subjects sub-optimally combine the visual and proprioceptive representations of the task. As expected, however, those subjects who deviate from the theoretical optimal sensory weighting tends to show larger level of variability.

Lastly, the inter-subject analyses also suggest that the noise of the motor component of the task, which can be different between participants, might represent a relevant part of the performance variability. These observations confirm the rationale of basing our conclusions on within-subject comparisons.

## Vestibular Pathways to Cortical Networks Involved in Visuo-Proprioceptive Transformations

The present section aims at discussing whether the behavioral findings reported here are compatible with the current knowledge about the anatomy and physiology of the central nervous system. First, the brain areas involved in visuo-proprioceptive transformations will be presented. Second, it will be discussed how the signals related to head orientation with respect to gravity might interact with these brain areas and hence with the cross-modal processing.

The idea that the brain performs cross-modal transformations is supported by several electrophysiological and brain imaging studies. For instance, the encoding of visual stimuli in somatosensory space is consistent with the observation that brain regions such as the somatosensory areas (S) and Broadman's Area 5 (BA5), which are known to encode the hand grasping configuration and the position of tactile stimulation in the peripersonal space (Koch and Fuster, 1989; Deshpande et al., 2008; Lacey et al., 2009), are activated also by visual stimuli such as images of glossy and rough surfaces, which a have a strong "tactile content" (Sun et al., 2016), and by images of familiar manipulable objects (Vingerhoets, 2008). Similarly, the encoding of haptic/proprioceptive information in visual space is fully compatible with the finding that the visual area in the Lateral Occipital Complex, called LOtv, is activated not only by 3D objects images (Moore and Engel, 2001), but also when sensing familiar objects with the hand (Deshpande et al., 2008; Lacey et al., 2009).

A brain area which appears to be a good candidate for performing cross-modal transformations is the Intra-Parietal Sulcus (IPS) which has been shown to have neural activation compatible with the computation of visuo-tactile transformations in monkey (Avillac et al., 2005) and which is known to be involved in the visuo-motor transformations performed during grasp movements (McGuire and Sabes, 2011; Janssen and Scherberger, 2015). Monkey experiments have shown that, in this brain area, the information can be reencoded from the retinal space to the somatosensory space, and vice-versa, thanks to recurrent basis function neural networks (Pouget et al., 2002) which would use the sensory signals relative to the eye-body kinematic chain to "connect" the two sensory spaces. In humans, the Anterior part of IPS is strongly activated when comparing visual to haptic objects, and vice-versa (Grefkes et al., 2002) or when reaching a visual target without visual feedback of the hand (Beurze et al., 2010). Virtual lesions of this area through TMS interfere with visuo-tactile transformations, but not with uni-modal, visual and tactile, tasks (Buelte et al., 2008). The planning of cross-modal tasks, such as reach-and-grasp visual objects with an unseen hand, also appears affected by TMS of the anterior IPS (Verhagen et al., 2012).

Focusing on the main finding of the present study, one can ask through which neural pathway the head-gravity misalignment can affect the visuo-proprioceptive transformations occurring in the IPS. At the peripheral level, the information about the head orientation with respect to gravity is mainly provided by a complex integration of the signals from different areas of the otolithic organ (Chartrand et al., 2016) arising from both the left and right organs (Uchino and Kushiro, 2011). Semi-circular canal and neck proprioception, which are combined to otolithic information already at the level of the vestibular nuclei (Gdowski and McCrea, 2000; Dickman and Angelaki, 2002), can also contribute to the head orientation estimation. However, since in the Straight Neck Experiment the posture effect was also observed when no head rotations, nor neck flexions, occurred, we can conclude that the otolithic signals are sufficient to affect visuo-proprioceptive transformations. At the central level, it is known that the vestibular-otolithic information can reach the parietal cortex through the posterior vestibular thalamocortical pathway (Hitier et al., 2014; Cullen, 2019). Specific otolithic afferences have been indeed observed in the IPS: otolithic stimulations activate neurons of Ventral IPS in monkeys (Schlack et al., 2002; Chen et al., 2011), with half of the neurons in this area which receive vestibular inputs (Bremmer, 2005), and human fMRI studies also show IPS activations resulting from saccular stimulations (Miyamoto et al., 2007; Schlindwein et al., 2008). Electrical stimulations of the anterior-IPS have also been reported to elicit linear vestibular sensations in a patient (Blanke et al., 2000). Since head-gravity misalignment modulates the otolithic inputs and the otolithic system projects to the IPS, it is plausible that gravitational information would be integrated in the recurrent basis-function neural network of this brain areas (Pouget et al., 2002; Avillac et al., 2005) to "connect" the visual and the proprioceptive space. As a consequence, it is reasonable that an alteration of the otolithic gravitational input due to the head tilt can alter cross-modal transformations.

There are other neural structures involved in motor control, such as the cerebellum, that receive otolithic inputs (Büttner-Ennever, 1999), and could therefore contribute to the effect of the head-gravity misalignment observed here. However, the predictive functions of the cerebellum (Blakemore and Sirigu, 2003), which is fundamental for the control of rapid movements, probably plays only a marginal role in the slow, quasi-static, movements tested here.

## Otolithic Signal-Dependent Noise or Unusualness?

Once we have established that the head-gravity misalignment affects visuo-proprioceptive transformations and which neural circuits could be responsible for this phenomenon, the following question remains open: "How does tilting the head interfere with the cross-modal sensory processing?" At least two possible explanations exist: first, the unusualness of performing eye-hand coordination tasks with the head tilted; second, a possible signal-dependent increase of the otolithic noise with the head tilt.

Some studies have been able to correctly predict the effect of tilting the head on subjective vertical experiments by assuming that the noise of the otolithic signals linearly increases with the signal amplitude (Vrijer et al., 2008), hence the second hypothesis appears reasonable. To our knowledge, however, there are no electrophysiological studies clearly supporting the signal-dependent modulation of the otolithic noise (Fagerson and Barmack, 1995; Yu et al., 2012), therefore, the fact that unusual tilt of the head could interfere with cross-modal sensory transformations should not be "*a priori*" discarded. The "usualness effect" appears consistent with IPS recurrent neural networks functioning (Pouget et al., 2002) in which the synaptic weights necessary to perform visuo-proprioceptive transformations are learnt through experience. Since the upright position is largely the most common head orientation in our everyday life, it is possible that these neural networks become "optimized" for such head position and significantly less effective when otolithic afferences signal a head tilt for which we have a limited experience. A way to test this hypothesis could be to perform experiments on subjects that are in a tilted position, or in weightlessness, for a long period of time and see whether they can learn to perform cross-modal transformations as effectively as in the upright position, despite the altered or lacking otolithic signals.

## CONCLUSION AND PERSPECTIVES

The results of the present study show the relevant role of the head-gravity alignment in the ability of performing visuo-proprioceptive transformations necessary to correctly reach and grasp objects. This finding suggests that the neural networks in the parietal cortex involved in the cross-modal processing of sensory information are more efficient when the otolithic afferences correspond to an upright head position.

This finding has interesting implications: for instance, the application of this idea to the clinical field suggests that vestibular pathologies might perturb not only equilibrium and eye movements, but also the eye-hand coordination, which is rarely assessed in these patients. Our findings might be beneficial also to healthy subjects, in that they can contribute to the ergonomic principles used when conceiving a new working station: avoiding visuo-manual tasks when the operator is tilted would indeed maximize their execution precision. Finally, there are potential space-related applications: the astronauts' eye-hand coordination might be perturbed in weightlessness, because of the lack of the gravitational reference used for visuo-proprioceptive transformations. To prevent potential deterioration of performances in delicate visuo-manual tasks, as controlling robotic-arms or piloting space vehicles, specific training performed in "altered" posture could therefore be beneficial.

## 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 CER Université de Paris. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

MT conceived and supervised the experiments, performed the final data analysis, and wrote the first draft of the manuscript. JB-E performed the experiments and data analyses. DD developed the experimental setup and performed the experiments. All authors contributed to manuscript revisions, read and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnint.2022.788905/full#supplementary-material

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# Vestibular Stimulation Causes Contraction of Subjective Time

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As the cerebellum is involved in vestibular and time-keeping processes, we asked if the latter are related. We conducted three experiments to investigate the effects of vestibular stimulation on temporal processing of supra-second durations. In Experiment 1, subjects had to perform temporal productions of 10- and 15-s intervals either standing on both feet or while being engaged in the difficult balancing task of standing on one foot with their eyes closed (or open for control purposes). In Experiment 2, participants were required to produce intervals of 5, 10, 15, and 20 s while standing on both feet with their eyes open or closed, which constituted an easier balancing task. In Experiment 3, we removed the active balancing; temporal productions of the same four durations had to be performed with the eyes open or closed during the passive vestibular stimulation induced by the oscillatory movements of a swing. Participants produced longer intervals when their eyes were closed, but active balancing was not the culprit. On the contrary, temporal over-production was particularly pronounced during the passive vestibular stimulation brought about by the swing movements. Taken together, the experiments demonstrate that the contraction of the subjective time during balancing tasks with closed eyes is most likely of vestibular origin.

**Keywords: time perception, subjective duration, vestibular system, postural load, balancing, temporal production vestibular system and time perception**

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## INTRODUCTION

Time perception is one of the integral components of human consciousness and experience. Being able to time events, judge their durations, and establish their temporal order is of central importance to adaptive behavior, outcome judgment, and effective decision-making. However, the subjective duration of an event, in addition to its actual physical duration, can be affected by a variety of external factors, such as emotional content of the stimulus (Grommet et al., 2011), intensity of the sensory signal (Wearden et al., 2007), and attentional allocation (Brown, 1997). The present study focuses on the role of vestibular stimulation in time perception, which has thus far received little attention.

A successful model in the field of time perception, at least during prospective timing, where subjects are informed in advance that the duration of the stimulus or the event should be judged, is the Scalar Expectancy Theory (SET). According to this model, there is a hypothetical internal clock consisting of a pacemaker, an accumulator, and a switch (Treisman, 1963; Gibbon et al., 1984). The pacemaker emits pulses at a certain rate, the accumulator encodes the emitted pulses, and the switch connects the pacemaker and the accumulator. When a duration is to be produced or estimated, the switch closes, which allows the pulses from the pacemaker to be collected by the accumulator. When a to-be-timed interval is over, the switch opens, thus cutting the connection between the pacemaker and the accumulator. The number of pulses collected by the accumulator serves as an estimate of how much time has elapsed during the interval. Finally, the collected pulses representing subjective time are compared against duration representations stored in the long-term memory, and the duration judgment is made (Matthews and Meck, 2016). The more pulses collected by the accumulator during a given actual time period, the longer the subjective duration of the to-be-timed interval is perceived to be (Wearden, 2005). Even though the neurobiological basis for such an internal clock has remained elusive, SET continues to be an effective theoretical model for the explanation of various phenomena of subjective temporal experience (Buhusi and Meck, 2005).

Physiologically and/or emotionally arousing events have been demonstrated to reliably accelerate the rate at which the pacemaker emits pulses, thus leading to the lengthening of subjective time. Stimuli containing more intense perceptual stimulation are judged to be longer in duration. For instance, filled auditory intervals are perceived to last longer than empty intervals (Thomas and Brown, 1974; Wearden et al., 2007). Likewise, auditory and visual stimuli preceded by trains of clicks (Penton-Voak et al., 1996) and flickering visual stimuli (Kanai et al., 2006) were overestimated in duration compared to their counterparts with less sensory intensity. Regarding emotional content, it has been shown that people overestimated the durations of faces depicting intense emotional expressions such as anger or happiness (Droit-Volet et al., 2004) and pictures evoking fear (Grommet et al., 2011). A similar effect was found with emotional auditory stimuli; people overestimated the duration of negative sounds compared to positive ones (Noulhiane et al., 2007). Additionally, more direct manipulations of physiological arousals, such as the administration of dopaminergic agents (Lake and Meck, 2013) or increasing the body temperature (Wearden and Penton-Voak, 1995), have led to the elongation of subjective time. Within the SET framework, the standard explanation of these effects is that the state of higher arousal increases the number of pulses generated by the pacemaker during a given physical unit of time, causing subjective temporal dilation.

The allocation of attentional resources between a timing task and a non-temporal secondary task also influences perceived subjective duration, which has been demonstrated in a number of experiments, where subjects had to perform a timing task and a concurrent non-timing secondary task. The more cognitively demanding and resource-intensive the task to be performed simultaneously with the temporal task, the more variable and shorter time estimations were (Thomas and Weaver, 1975; Zakay and Block, 1996). For example, with increasing levels of workload and complexity, produced time intervals became shorter and less accurate when subjects had to reproduce the duration of a text passage to which they were listening (Brown and Boltz, 2002). Likewise, being engaged in cognitive and motor tasks with increasing levels of difficulty leads to shorter estimates of perceived time in prospective paradigms (Brown, 1985, 1997; Zakay, 1998). The reasoning behind these findings is that as less attention is dedicated to the timing task, fewer pulses are encoded by the accumulator, which in turn results in shorter perceived durations. Note that also task-irrelevant information in the timing task itself can reduce accumulator performance (Thönes et al., 2018). Conversely, as more resources are allocated to temporal processing, the more pulses reach the accumulator, thus leading to temporal expansion.

What has come to play a prominent role in time perception research are theories of embodied cognition (Wittmann, 2014). Embodied cognition assumes that mental representations are situated in or referenced with respect to the body of the perceiver, and thus bodily changes of the latter should affect these representations (Leitan and Chaffey, 2014). For instance, still photographs depicting people, animals, and abstract images that are suggestive of dynamic motion were judged to be longer in duration compared to images with a standing posture, suggestive of a stationary body (Yamamoto and Miura, 2012). Similar effects of temporal overestimation were found with moving geometric forms, compared to stationary forms (Brown, 1995), with images of dancing sculptures featuring different intensities of implied dynamic motion (Nather and Bueno, 2011), and with animated drawings of a human walking at different speeds (Karşılar et al., 2018). This implies that the manipulation of visible body postures accelerates the rate of the pacemaker, which in turn produces more frequent pulses, thus dilating temporal experience.

In contrast to these examples of implied body motion, the investigation of the equivalent direct effects of actual bodily experience of the observer has received only limited attention in the time perception literature. A notable exception is a study where subjects had to wear a weighted backpack while performing a timing task of a visual stimulus. Perceived time was lengthened compared to the no-backpack condition, but note that this effect was observed when the to-be-timed stimulus was that of a backpack (Jia et al., 2015). The effect of the self-referential bodily experience on time perception was also demonstrated when subjects experienced an extended bodily discomfort induced by the submersion of the hand into cold water (Rey et al., 2017). Directing attention to oneself and/or the unpleasant bodily experience lengthened subjective time.

Considering the influence of physiological, attentional, and proprioceptive factors on subjective time, it is likely that the vestibular system likewise affects the pacemaker or the accumulator. In fact, the cerebellum, the subcortical brain structure, which is primarily responsible for motor coordination and vestibular control of balance, has been implicated in timing functions. Patients with damage to the cerebellum were more variable and less accurate in the production of rhythmic finger tapping and had poorer performance in duration discrimination tasks (Ivry and Keele, 1989). Similarly, Nichelli et al. (1996) reported impaired temporal discrimination for both sub-second and supra-second durations in patients who suffered from cerebellar degeneration. Consistent with these findings, repetitive trans-cranial stimulation over the left lateral cerebellum resulted in the overproduction of intervals in the sub-second range (Koch et al., 2007). When it comes to longer time intervals, however, the picture is less clear. Koch et al. (2007) failed to find similar effects for intervals in the supra-second range, whereas another study on patients with cerebellar lesions revealed that damage in the middle and superior cerebellum can lead to overproduction and underestimation of temporal intervals in this range, suggesting that impaired cerebellar activity slows down the pacemaker (Gooch et al., 2010). However, cerebellar involvement in the processing of supra-second durations awaits replication. Additionally, brain imaging studies suggested cerebellar activation during temporal processing tasks. Left lateral cerebellar activation was found to be prominent in fMRI studies, when participants were engaged in the temporal discrimination tasks of sub-second durations (Schubotz et al., 2000; Lewis and Miall, 2003).

Since the cerebellum is involved in the processing of vestibular and proprioceptive afferences (Rochefort et al., 2013), it seems plausible that vestibular activation or load would affect the mechanisms of time-keeping. Indeed, vestibular stimulation has been shown to affect temporal performance in a number of studies. One of the earlier studies on this topic exposed subjects to gravitational stress. They were seated in a cabin at the end of a centrifuge arm, pivoting in such a way that the force along the body's $g_z$-axis could be increased to 3 g. They had to reproduce temporal intervals of auditory tones of durations between 1 and 20 s by pressing and releasing a button. The reproduced intervals fell short of the stimulus durations in the 1 g control condition, and even more so under the gravitational stress induced by centrifugation (Frankenhaeuser, 1960). The author attributes the effect to reduced memory retention during centrifugation. Note that SET cannot easily explain this result. Changes in the pacemaker or accumulator should cancel out in reproduction tasks since perception and production should be equally affected. It appears that g-loading made subjects more impatient, if not forgetful, across the board.

A less complicated effect was found during otolith unloading, as tested in microgravity on three astronauts during a spaceflight mission. They first had to tap in synchrony with a metronome at inter-tap-intervals between 350 and 530 ms, which they successfully did. Then the metronome was turned off while they continued to tap. In microgravity the taps were faster than on the ground as if the pacemaker had sped up; additionally, it also led to increased variability of the inter-tap intervals (Semjen et al., 1998). More recently, the effect of vestibular stimulation on time perception was addressed by Capellia and colleagues (Capelli and Israël, 2007; Capelli et al., 2007). In one of their experiments, subjects were instructed to produce 1-s intervals by tapping a button before, during, and directly after being rotated by a mobile robot. The rotation could be at a constant angular velocity, at accelerating, or at decelerating rotation rates, and rotation would stop altogether between rotation phases. Inter-press intervals were not affected by the rotation *per se* or by the different velocity profiles; however, the intervals produced were more variable in all rotation conditions. The same observation was reported in another experiment using the same task of pushing a button each second, during the linear movement. Despite the clear effect of the vestibular stimulation on the accuracy of timed motor production, no systematic bias of pacemaker or accumulator was found in these studies. Furthermore, the increase in variability can not only be attributed to vestibular otolith stimulation but also to stress or changes in memory or motor response execution induced by the rotation, which occurred at maximally 60°/s.

Experiments where vestibular stimulation was induced by asking subjects to assume different bodily postures brought contradictory results as well. In a recent study conducted by Lo et al. (2021), subjects were instructed to produce durations with button presses of 3, 5, and 7 s while adopting body postures that signaled different levels of action (e.g., standing still, running). The temporal productions were shorter when assuming postures that signal action, which suggests that the dynamic posture has sped up the pulse rate of the pacemaker. In a study conducted by Schreuder et al. (2014), subjects had to produce considerably longer temporal intervals of 1.33, 1.58, and 2.17 min while assuming an upright or a supine posture and while at the same time being exposed to different odors: rosemary, peppermint, and no odor. Subjects exposed to rosemary odor under produced durations compared to peppermint and no odor condition. However, no effect of body posture was found, although it effectively had induced arousal measured by skin conductance response and heart rate. Thus, the potentially arousing effects of rosemary cannot account for its ability to speed up the clock.

As research on the influence of vestibular stimulation on time perception in supra-second durations is limited and has not always found a clear effect, other than increasing variability with vestibular excitation, we sought to take a closer look at supra-second time estimates in the face of vestibular engagement. Rather than stressing the vestibular system, we decided to add common balancing tasks to a temporal production task. Additionally, to minimize memory effects, we asked our subjects to produce a time interval of a given length rather than reproducing a previously perceived interval. The vestibular engagement was brought about by a difficult active balancing task (Experiment 1), an easier balancing task (Experiment 2), and a passive oscillatory movement induced by a swing (Experiment 3), which provided continuous vestibular acceleration stimulation without active balance control. In Experiment 1, subjects had to perform temporal production tasks of either 10 or 15 s while balancing on one foot with eyes closed or open. One-foot balancing is a challenging task. It requires the integration of information from vestibular and somatosensory sources to identify the position of the body in the environment prior to the execution of appropriate motor responses (Cherng et al., 2001). The absence of the visual information ordinarily used for fine-tuning makes this task rather challenging. Thus, the vestibular and proprioceptive cues necessary for balancing were either supplemented with visual information or not. In Experiment 2, temporal productions of 5, 10, 15, and 20 s were performed with eyes open or closed while standing on both feet. This is a much easier balancing task, which nevertheless introduces postural sway requiring an active balance maintenance (Era et al., 2006). It should significantly reduce the vestibular load and thus allow for an assessment of this information when comparing the results to those of Experiment 1. Finally, in Experiment 3, in contrast to the experiments above, the vestibular stimulation was induced passively. Subjects performed temporal productions of the same durations as in Experiment 2 while comfortably lying on a nest swing (see

**Figure 1**) either when it was brought into an oscillatory motion or when it was at rest. Thus, it removed active postural control altogether. Within the SET framework, if the rate of the pacemaker is excited by the vestibular stimulation alone, we expect relative underproductions of temporal intervals during the balancing task. We also expect relative underproductions when subjects are in swinging motion compared to the stationary control. These effects should be more pronounced in the absence of visual information across all three experiments.

# EXPERIMENT 1

## Methods

### Subjects

Forty-four subjects (27 female and 17 male) aged from 19 to 61 years ($M$ = 28.68, SD = 9.88) voluntarily participated in the experiment. The subjects, mostly students, were recruited by approaching them as they walked across the campus of the University of Mainz. All of them followed instructions of the experiment and were included in the data analysis. Informed consent was obtained beforehand verbally from all subjects, and they were debriefed after the experiment.

### Design

The study was a field experiment with a multifactorial within-subjects-design to investigate the influence of a difficult balancing task on time perception. The subjects had to perform a temporal production task for intervals of either 10 or 15 s (time interval), with their eyes either open or closed (visual condition), and while standing either on one foot or on both feet (balance condition). These three factors were fully crossed. The visual condition was blocked, that is either all trials with open eyes or all trials with closed eyes were performed first. Within each visual condition, subjects first completed the two trials of the one balance condition, then those of the other. Per subject, the order of the balance conditions was held constant in both visual conditions. Likewise, the order of the two- time intervals was set constant for a given subject and counterbalanced among subjects, such that one-half of the subjects started each combination of visual condition and balance condition with the 10-s interval, and the other half with the 15-s interval. Each subject completed eight trials, one for each combination of visual condition, balance condition, and time interval.

### Procedure

The data collection took place during 3 days in the period starting from September 14 to 20, 2021. All subjects were approached individually on campus. After being instructed that they would perform a time estimation task eight times while having their eyes open or closed, and while standing on one foot or on both feet, they gave their verbal consent. For the one-foot stand, they were instructed to lift the leg of their choice so that the foot was clearly off the ground. The length of the time interval to be produced was communicated verbally. Once this was done, after a few seconds, the experimenter gave the start signal, the German equivalent of "Ready-steady-go!" ("Auf die Plätze, fertig, los!"), at which time the stopwatch was started on a smartphone (iPhone). Subjects were asked to say "stop" out loud when they thought the predefined time interval had elapsed. For each trial, the experimenter recorded the duration of the produced time interval as indicated by the stopwatch. After completion of the last trial, demographic information and ratings concerning task difficulty experienced when balancing on one foot were obtained. Finally, the subjects were debriefed about the nature and the purpose of the experiment.

## Results and Discussion

We analyzed the produced time intervals in terms of the relative estimation error, which is given by

$$\frac{interval_{\text{produced}} - interval_{\text{to-be-produced}}}{interval_{\text{to-be-produced}}} \cdot 100\ [\%]$$

where $interval_{\text{produced}}$ is the duration of the produced time interval, and $interval_{\text{to-be-produced}}$ is the actual duration of the to-be-produced time interval in units of seconds, respectively. The resulting unit is %.

We calculated a time interval × visual condition × balance condition repeated-measures ANOVA on the relative estimation error using a univariate approach. **Figure 2** shows the mean relative estimation error as a function of the to-be-judged time interval, visual condition, and balance condition. The effects of visual condition and balance condition were clearly not significant, $F_{(1,43)} = 0.396$, $p = 0.533$, $\eta_p^2 = 0.009$ and $F_{(1,43)} = 0.139$, $p = 0.711$, $\eta_p^2 = 0.003$. The visual condition × balance condition interaction was not significant, $F_{(1,43)} = 3.044$, $p = 0.088$, $\eta_p^2 = 0.066$. However, an interesting trend can be observed in the data. As can be seen in **Figure 2**, there is a trend for the visual condition to have an effect during the two-feet stand but not the one-foot stand. When standing on both feet, subjects produced longer durations with their eyes closed compared to open, $\Delta_{\text{mean}} = 2.82\%$, $SE_{\Delta} = 1.75\%$, Cohen's (1988) $d_z = 0.242$. When standing on one foot, the effect of the visual condition was considerably attenuated and opposite, $\Delta_{\text{mean}} = -1.00\%$, $SE_{\Delta} = 1.87\%$, $d_z = -0.081$. The effect of the time interval was significant, $F_{(1,43)} = 5.182$, $p = 0.028$, $\eta_p^2 = 0.108$. On average, the relative estimation error was larger for the 10 s interval than for the 15 s interval. Descriptively, the effect of the time interval was more pronounced when standing on one foot. However, in the rmANOVA the time interval × balance condition interaction was not significant, $F_{(1,43)} = 2.897$, $p = 0.096$, $\eta_p^2 = 0.063$. Neither were the remaining effects, $F \leq 0.431$, $p \geq 0.515$. Across all conditions, subjects slightly overproduced the given time intervals ($M = 5.12\%$, $SE_M = 3.86\%$).

Our results show a trend towards longer interval productions with eyes closed compared to open when subjects were standing on both feet. In the one-foot condition, the visual condition had virtually no effect. We assume the following aspects to be responsible for this inconclusive pattern of results. First, the high strain in the one-foot condition may have made the estimates in both conditions less precise. This is more of a challenge than one may think. Many of our subjects had great difficulty balancing on one foot for the required durations, in particular with their eyes closed. Most subjects had to use their second foot briefly

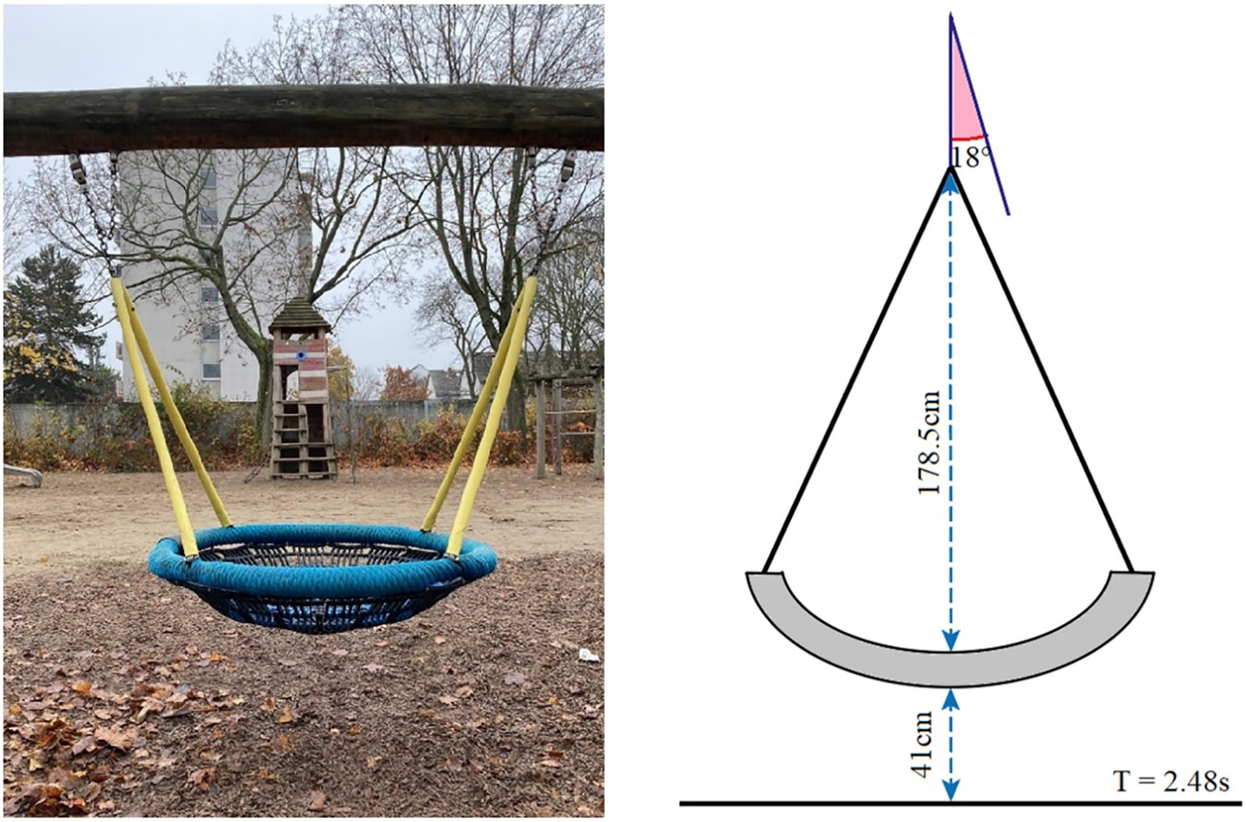

**FIGURE 1 |** Nest swing used in Experiment 3.

in between to keep their balance. Note that based on the trial sequences used in Experiment 1, we cannot perform an analysis devoid of a potential carry-over effect of the one-foot stand on the two-feet condition. Additionally, a physically demanding task such as this might have increased the level of the physiological arousal that is known to affect time perception (Droit-Volet et al., 2004; Grommet et al., 2011; Kroger-Costa et al., 2013; Rey et al., 2017). Second, our subjects performed only two trials per combination of visual condition and balance condition. Thus, also for the two-feet stand, for which we found a quite promising trend, we could only measure the effect of the visual condition rather coarsely. For these reasons, we conducted a second experiment in which we focused on the two-feet stand and collected twice the number of interval productions per visual condition.

# EXPERIMENT 2

## Methods

### Subjects

Forty-eight subjects (22 female, 26 male) aged from 17 to 63 years (*M* = 26.13, SD = 8.99) participated in the experiment. The recruitment procedure was the same as in Experiment 1. None of the subjects had participated in Experiment 1 and none had to be excluded from the data analysis. The experimenter obtained verbal informed consent beforehand and debriefed the subjects after the experiment.

### Design and Procedure

The data collection took place during 3 days in the period from October 1 to October 7, 2021. The design of the experiment was similar to Experiment 1 and investigated the influence of balancing on time perception using an easier balancing task. Subjects were instructed to perform temporal productions of intervals of either 5, 10, 15, and 20 s (time interval) with their eyes open and closed (visual condition) while standing on both feet. The visual condition was blocked. One half of the subjects first completed all trials with their eyes open and then the other half with their eyes closed. The order of the four intervals to be judged was the same for the two blocks for a given subject but was counterbalanced between subjects, so that two subjects were assigned to each of the 24 possible orders. In total, each subject completed eight trials. In all other respects, the procedure was identical to that of Experiment 1.

## Results and Discussion

We ran a time interval × visual condition rmANOVA using a univariate approach with Huynh and Feldt (1976) correction for the degrees of freedom (correction factor ε). **Figure 3** shows the mean relative estimation errors (calculated as in Experiment 1) as a function of the duration of the to-be-produced time interval

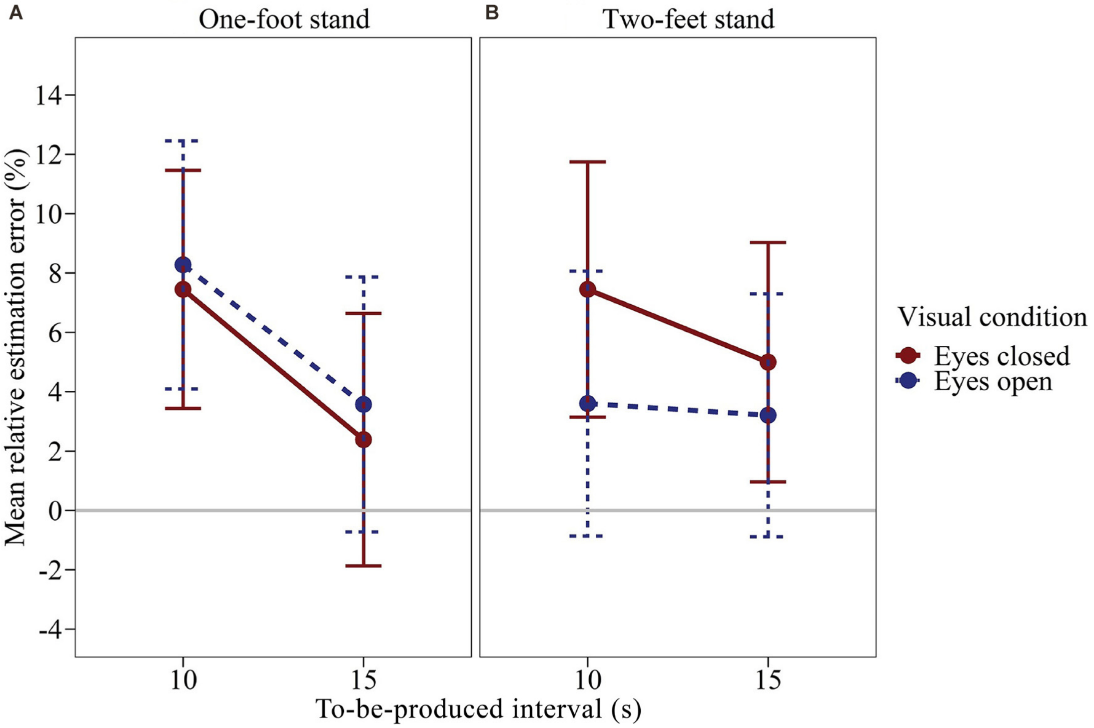

**FIGURE 2** | Mean relative estimation error of to-be-produced intervals by visual condition for each balance condition of Experiment 1. **(A)** One-foot stand condition, **(B)** two-feet stand condition. Error bars represent ±1 standard error of the mean (SEM). Values above 0 indicate relative overproduction of the interval.

and the visual condition. The effect of the visual condition was significant, $F_{(1,47)} = 5.719$, $p = 0.021$, $\eta_p^2 = 0.108$. Subjects produced longer time intervals with their eyes closed compared to open eyes, $\Delta_{\text{mean}} = 2.88\%$, $SE_\Delta = 1.21\%$, $d_z = 0.345$. The effect of the time interval was not significant, $F_{(3,141)} = 2.503$, $p = 0.089$, $\eta_p^2 = 0.051$, $\varepsilon = 0.642$, accompanied by a significant visual condition × time interval interaction, $F_{(3,141)} = 2.717$, $p = 0.047$, $\eta_p^2 = 0.055$, $\varepsilon = 1.00$. As illustrated in **Figure 3**, the mean relative estimation error slightly decreased with increasing interval duration, especially in the interval productions with closed eyes. As in Experiment 1, averaged across all conditions, subjects slightly overproduced the given time intervals ($M = 6.52\%$, $SE_M = 2.81\%$).

Taken together, the results of Experiments 1 and 2 show that in an easy active balancing task, i.e., standing still on both feet, subjects with their eyes closed produced longer intervals compared to the eyes open condition. How can this effect be explained? The active balancing task, which we perform casually and without notice in everyday life, becomes somewhat of a challenge when we close our eyes. The increased effort that is involved in the motor control, as well as the increased postural sway that goes along with balancing in the dark (Era et al., 2006; Hansson et al., 2010), and the involvement of the vestibular afferent information could be responsible. Note, however, that the overproduction is opposite to the above-mentioned finding that time productions in microgravity are underproduced (Semjen et al., 1998). To remove the potential effects of physical effort and attention to the motor control task from the equation, we decided to forego active balancing in a third experiment. We placed subjects on a swing to isolate the potential effect of passive vestibular stimulation on time perception.

# EXPERIMENT 3

## Methods

### Subjects

Forty-eight subjects (30 female, 18 male) aged from 18 to 58 years ($M = 28.73$, SD = 9.85) participated in the experiment. They were recruited by approaching them at a public playground, near a student accommodation, or as they were walking by. None of the subjects had to be excluded from the data analysis. As before, informed consent was obtained verbally, and they were debriefed after the experiment.

### Design

In Experiment 3, we investigated the influence of the passive vestibular stimulation on the interval production task used in Experiments 1 and 2. The design was identical to that of Experiment 2, with the exception that instead of the active balancing task, vestibular stimulation was induced purely passively. Subjects were instructed to relax comfortably into a large swing, which was brought into motion by the experimenter (**Figure 1**). The swing chosen for the experiment was a playground nest swing that could comfortably accommodate an adult person. The subject assumed a lying posture, such that the

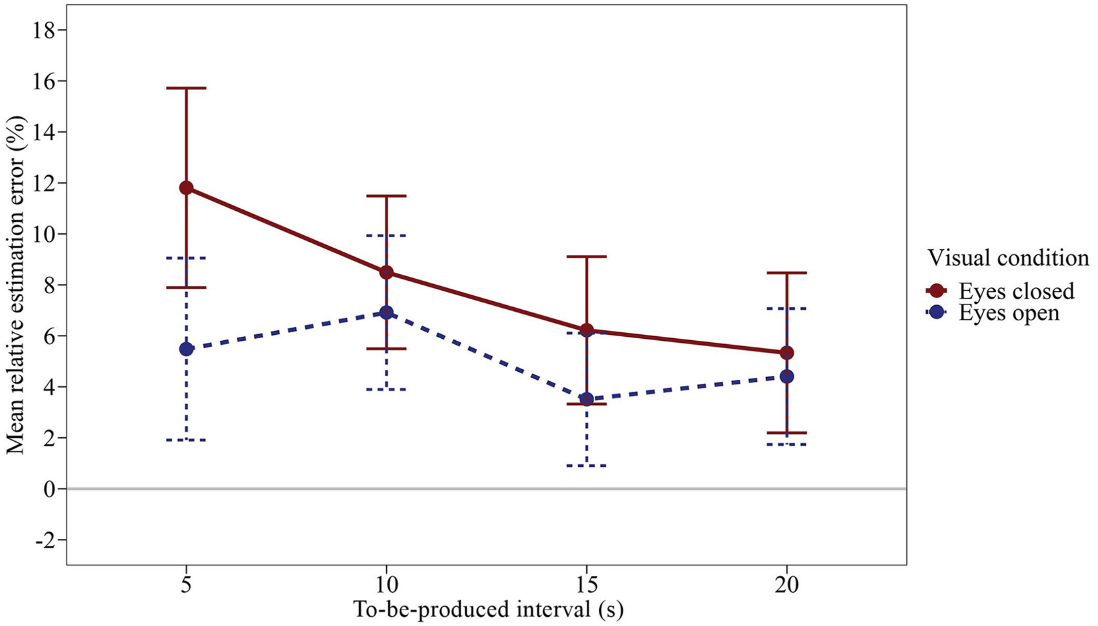

**FIGURE 3 |** Mean relative estimation error of to-be-produced intervals by visual condition of Experiment 2. Error bars represent ±1 standard error of the mean (SEM). Values above 0 indicate relative overproduction of the interval.

main body axis was aligned with the swing plane. The distance of the nest from the ground was 41 cm, and it was suspended at a radial distance of 178.5 cm from the fulcrum on a supporting beam. For the vestibular stimulation, upon embarkation of the subject, the experimenter moved the swing to a starting position of 18° from the resting position, such that a full oscillation cycle spanned an amplitude of 36° and took 2.48 s to complete. The pushes were always given from behind (i.e., outside the subject's field of view) in the direction of oscillation. Subjects performed the same temporal production task of intervals of either 5, 10, 15, or 20 s (time interval) with their eyes either open or closed (visual condition), as in Experiment 2. They were instructed to relax and lie still in the nest of the swing. The experimenter could either hold the swing still or swing it (vestibular stimulation). These three factors were fully crossed. The swing motion was blocked, that is either all trials lying still in the nest or all trials with the movement were performed first. Within each of these blocks, one half of the subjects first completed all trials with their eyes open and the other half with their eyes closed. For the combinations of vestibular stimulation and visual condition, the order of the four intervals to be judged was set constant within a given subject and counterbalanced among subjects. Apart from that, the procedure was identical to that of Experiment 2. In total, Experiment 3 consisted of 16 trials.

## Procedure

The data collection took place for 5 days between October 25 and November 6, 2021. As before, the length of the time interval to be produced was communicated verbally, as were the experimenter's start and the subject's stop signals. Regardless of the swing motion condition, subjects had to maintain the same relaxed position for the entire experiment, which lasted approximately 10 min. During the movement of the swing, subjects were only given slight booster pushes between the single trials to maintain the 36°- amplitude. Thus, the pushing did not interfere with the time estimation. For each trial, a second experimenter recorded the produced time as stopped with the stopwatch.

## Results and Discussion

We computed a time interval × visual condition × vestibular stimulation rmANOVA using the same specifications as in Experiment 2.The effect of vestibular stimulation was significant, $F_{(1,47)} = 7.818$, $p = 0.007$, $\eta^2_{\mathrm{p}} = 0.143$. **Figure 4** shows the mean relative estimation error for the produced time intervals (calculated as before) as a function of the time interval, visual condition, and vestibular stimulation. Averaged across all combinations of visual conditions and time intervals, subjects produced longer intervals when the swing was in motion (see **Figure 4**), $\Delta_{\mathrm{mean}} = 9.86\%$, $SE_{\Delta} = 3.53\%$, $d_z = 0.404$. The effect of the visual condition was not significant, $F_{(1,47)} = 2.605$, $p = 0.113$, $\eta^2_{\mathrm{p}} = 0.053$. However, there was a significant visual condition × vestibular stimulation interaction, $F_{(1,47)} = 4.809$, $p = 0.033$, $\eta^2_{\mathrm{p}} = 0.093$. To investigate this interaction in more detail, we compared the mean estimation error for eyes closed vs. eyes open separately for each of the two levels of vestibular stimulation by means of a paired-samples t-test (two-tailed). When the swing was at rest, the effect of visual condition was significant, $t_{(47)} = 2.365$, $p = 0.022$. In contrast, when the swing was in motion, the effect of visual condition was clearly not significant, $t_{(47)} = -0.262$, $p = 0.795$. As illustrated in **Figure 4**, when the swing was at rest, subjects produced longer time intervals with their eyes closed compared to open, $\Delta_{\text{mean}} = 6.69\%$, $SE_{\Delta} = 2.83\%$, $d_z = 0.341$. In contrast, when the swing was in motion, the interval productions were largely unaffected by the visual condition, $\Delta_{\text{mean}} = -0.57\%$, $SE_{\Delta} = 2.16\%$, $d_z = -0.038$. In the rmANOVA, all remaining effects were not significant, $F \leq 1.562$, $p \geq 0.213$. Across all conditions, subjects overproduced the given time intervals more clearly than in Experiments 1 and 2 ($M = 13.76\%$, $SE_M = 5.56\%$).

In sum, the results of Experiment 3 show that passive vestibular stimulation equally leads to longer interval productions. In addition, as in Experiment 1 (although not significantly there), we found that otherwise vestibular stimulation modulated the effect of the visual condition. When the nest swing was at rest, subjects produced longer time intervals when their eyes were closed compared to open. When, however, the swing was in motion, the effect of the visual condition was eliminated completely.

## GENERAL DISCUSSION

We have conducted three experiments to investigate the effect of vestibular stimulation on temporal productions of supra-second time intervals. It is exceedingly difficult, if not impossible, to isolate vestibular influence, and the time range of the stimuli is often critical. Often, the vestibular stimulation is potentially confounded by other factors such as tactile and postural stimulation, physical and/or physiological stress, memory effects, or the choice of the motor actions that are used to signal a temporal judgment. Previous research on this topic has remained inconclusive, and the number of studies that have used supra-second intervals is rather limited. In order to examine the influence of the vestibular system on time perception in the supra-second range, we started with a most demanding active balancing task in Experiment 1 and then made the task easier in Experiment 2, and finally provided mere passive vestibular stimulation in Experiment 3. We have covered the range from balancing on one foot with eyes closed to being gently rocked back and forth by the oscillatory movement of a swing. To minimize the potential effects of memory and motor response as far as possible, we employed a task in which subjects verbally produced predetermined supra-second time intervals in the range of 5–20 s duration. By and large, vestibular stimulation caused an overproduction of the time intervals.

Let us now take a closer look at the SET model outlined in the introduction. An over-production can be attributed to a slowing of the pacemaker or to the accumulator missing some of the pulses produced by an unchanged pacemaker. In Experiment 1, participants had to perform the temporal productions while engaged in an active balancing task requiring tactile and vestibular motor control, with their eyes closed or open. This task was exceedingly difficult for most of our subjects when their eyes were closed. Thus, it seems safe to assume that the strain of the balancing task should have stimulated the pacemaker and thus increased the rate at which it generated pulses. Accordingly, one would have expected shorter temporal productions in the one-foot condition compared to two-feet condition as well as with eyes closed compared to open. However, this was not the case. Note that the expected shorter interval productions and the associated accelerated passage of subjective time presuppose an unchanged accumulator. More pulses are emitted (and properly accumulated) per physical unit of time, which should lead to an overestimation of time passed and, thus, to shorter productions. Yet again, we found no such effect of the balancing task. Nor did the availability of visual input matter, maybe with the exception of a tendency for an interaction between balance and visual condition. When standing on both feet, participants tended to overproduce temporal intervals with eyes closed compared to eyes open. This runs opposite to the expected increase in pacemaker arousal. Thus, if one were to interpret this trend, one would have to attribute it to attention on the part of the accumulator. However, if balancing strain would have caused the accumulator to miss pulses, there should have been an effect of vision in particular in the one-foot condition. This was not the case.

Considering that the one-foot balancing task in Experiment 1 was overly difficult and because of its difficulty surely has introduced a lot of postural sway (Era et al., 2006; Hansson et al., 2010), we sought to reduce variability in Experiment 2. Subjects stood on both legs while making temporal productions over a wider range of time intervals with eyes closed or open. Here, once again, subjects overproduced the instructed durations, but they did more strongly so when their eyes were closed, as compared to open. In other words, the everyday task of seemingly trivial active balancing, which is involved in standing upright with eyes closed, led to a contraction of subjective time. How can this finding be explained? Within the framework of the SET model, our results would be compatible with both a reduced pacemaker rate and a reduced recording of pulses by the accumulator. In the following, we will elaborate on why we consider a reduced recording by the accumulator to be the most likely explanation. To start on the side of the pacemaker, higher physiological arousal due to the more demanding balancing task in the condition with eyes closed may have influenced the rate of the pacemaker. However, based on the results of Experiment 1, we deem the level of physiological arousal unlikely to account for the pattern of results. Moreover, when considering upright posture maintenance with eyes closed as a more arousal-inducing physical activity than standing upright with eyes open, one would expect an acceleration in the pulse rate of the pacemaker when the eyes are closed, which in turn should lead to shorter rather than longer interval productions. In line with this conclusion, physical stress, such as through induced muscle tension (Warm et al., 1967), pedaling on a cycle ergometer (Vercruyssen et al., 1989), or running on a treadmill (Kroger-Costa et al., 2013), all are associated with dilation of subjective time, that is an overestimation of temporal durations. If physical stress or arousal of this kind were at the heart of our balancing tasks, we should have found underproduction rather than overproduction of the instructed intervals. Thus, our results cannot be explained by pacemaker arousal.

In contrast, on the side of the accumulator, our results could be attributed to the diversion of attentional resources

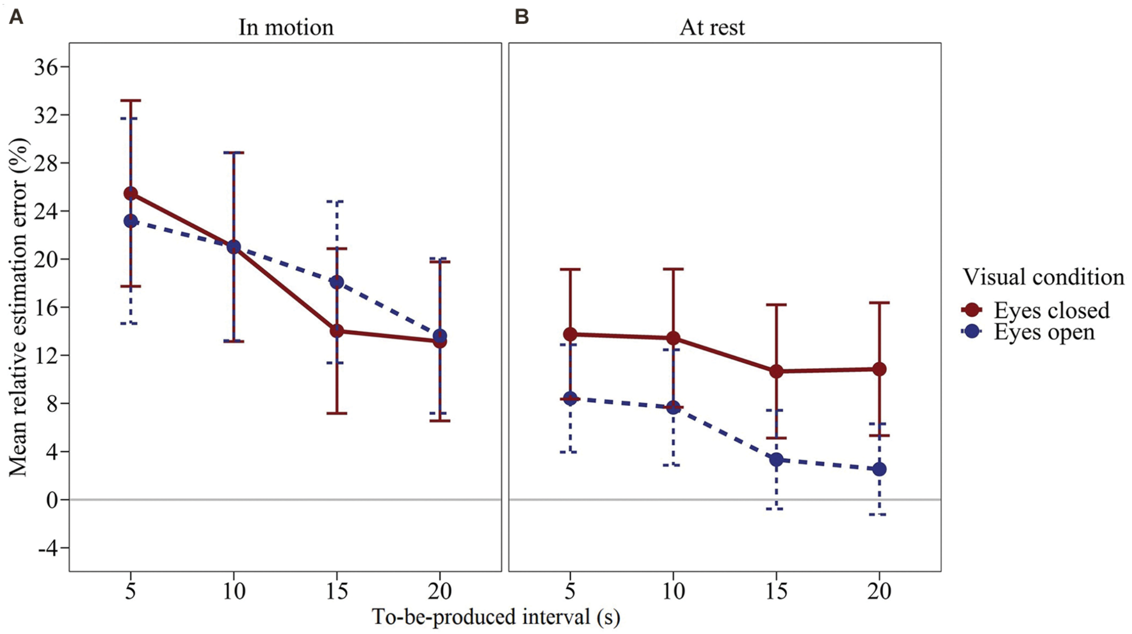

**FIGURE 4 |** Mean relative estimation error of to-be-produced intervals by visual condition for each vestibular stimulation condition of Experiment 3. **(A)** Swing in motion, **(B)** Swing at rest. Error bars represent ±1 standard error of the mean (SEM). Values above 0 indicate relative overproduction of the interval.

(Brown, 1997) or a comparable inefficiency in the way the pacemaker pulses are counted. When performing the timing task while balancing, attentional resources might be allocated between the timing and secondary non-timing tasks. As more resources are dedicated to the secondary task, fewer resources are available for timing, which leads the accumulator to miss pulses emitted by the pacemaker (Zakay and Block, 1996). Is this a likely explanation? At first sight, this does seem so. For instance, it has been reported that subjects overestimated durations following interoceptive mindfulness meditation (Kramer et al., 2013), which focuses attention. In the same vein, interoceptive awareness and attention to one's own heartbeat were associated with longer produced time intervals in the range of 8–20 s (Meissner and Wittmann, 2011). As already mentioned in the introduction, participants tended to underestimate the durations of events when engaged in secondary tasks requiring a greater amount of attentional and cognitive resources (Thomas and Weaver, 1975; Zakay and Block, 1996; Brown and Boltz, 2002). Balancing with eyes closed can be regarded as a secondary task that diverted attention away from the accumulator, which could then have caused temporal overproduction. In other words, the criterion of the instructed duration was reached later as the accumulation of the arriving pulses built up more slowly because some pulses were missed by the accumulator. Thus, reduced attention caused by the balancing task is compatible with the findings of Experiment 2. Note, however, that in Experiment 1, the exceedingly difficult one-foot balancing task should have demanded the most attentional resources but did not produce longer time estimates than the much easier two-feet balancing task.

Could the effects be attributed to the engagement of the motor system with or without negligible vestibular contribution? In a recent study, Castellotti et al. (2022) found that a secondary cognitive task led to an underestimation of a given time interval between 15 and 120 s. This could be an attention effect. Walking on a treadmill, as opposed to sitting while solving arithmetic tasks, led to even more pronounced underestimation. When assuming that no further attention was needed to walk on the treadmill, this could be a mere motor effect. This is consistent with our results, but note that together with the results of our third experiment, it is unlikely that the mere motor exertion is responsible here. Lying in the swing required neither attention nor motor exertion. Thus, vestibular stimulation appears to have been critical in Castellotti et al.'s walking condition.

Could mere vestibular stimulation have slowed the pacemaker or distracted the accumulator? To further investigate the role of vestibular load in timing, Experiment 3 examined the effects of vestibular stimulation through passive oscillatory movements induced by a swing. Here, participants produced longer intervals during pronounced passive vestibular stimulation compared to when the swing was at rest. Interestingly, eye closure had no effect when the swing was in motion. In contrast, when the swing was at rest, participants produced longer temporal intervals with their eyes closed compared to open, which replicates the findings of Experiment 2. Also, the effect of the vestibular stimulation was larger than that of eye closure at rest. Taken together, this does indeed suggest a direct vestibular effect on the timing network. Within the SET framework, and given that active balancing with eyes closed is strenuous and should—if anything—speed up the pacemaker, the vestibular effect suggests that the accumulator has missed pulses rather than the pacemaker having produced fewer pulses. Accumulator misses are the most likely explanation for the overproduction of temporal intervals under the conditions of vestibular stimulation.

Given the existing research on the vestibular system and the cerebellum, we could make tentative claims regarding the brain regions involved in the temporal processing of supra-second intervals. When considering the crucial role of the cerebellum in the functions of vestibular control and proprioception, the results of Experiments 2 and 3 are in line with the findings of Gooch et al. (2010), who found that cerebellar damage led to the contraction of subjective time for supra-second intervals. However, cerebellar involvement in this range needs to be replicated, which so far has only been established for sub-second intervals (Schubotz et al., 2000; Koch et al., 2007). That said, it could be argued that the tasks used in our experiments do not only affect cerebellar activation but also other brain regions further downstream, such as the basal ganglia. The basal ganglia have also been implicated in vestibular and motor control functions (Stiles and Smith, 2015). An fMRI study reported the activation of the basal ganglia in duration discrimination tasks (Rao et al., 2001). Pathology of these brain regions in patients with Parkinson's disease has likewise been linked to overestimation and underproduction of supra-second time intervals (Pastor et al., 1992). However, other brain regions are involved as well, for instance, dorsolateral pre-frontal cortex (Lewis and Miall, 2003) to which the basal ganglia have extended connections (Alexander et al., 1986). Further brain imaging and stimulation studies are needed before we can pin down the brain regions associated with vestibular timing tasks.

In sum, the results of Experiments 1–3 demonstrate the influence of vestibular stimulation on temporal processing. Note that the degree of over-production, up to 25% for the 5-s interval, was larger for the vestibular stimulation used in Experiment 3, as compared to the more or less strenuous balancing tasks used in Experiments 1 and 2. We can be reasonably certain, that memory encoding differences can be ruled out as explanations of our results. Time intervals that were encoded at rest and reproduced during the stress of running on a treadmill were under-produced, as is compatible with an accelerated pacemaker during exercise (Sayalı et al., 2018). By using pre-defined interval lengths and by the absence of balancing effects, memory encoding cannot explain our results. Neither can arousal on the side of the pacemaker. Mere stimulation of the vestibular system, accompanied by those tactile and proprioceptive cues that are necessarily confounded with it, distorted time perception in the direction of subjective temporal contraction. Vestibular stimulation prompted our subjects to produce lengthened time intervals, which can be interpreted as an impact on the accumulator that lets it miss pulses. Thus, vestibular activation can be said to perceptually shorten a given time interval.

It is important to note, however, that the methods employed in the current experiments were rather crude. We used a stopwatch in a field setting, which forced us to focus on long time intervals of up to 20 s and may have introduced a degree of inaccuracy, especially for the shortest intervals. Despite this limitation, the effects on temporal performance that we did find in the field, provide strong support for the involvement of the vestibular system in timing functions. Future studies in a controlled laboratory setting should extend this finding to shorter intervals and control for arousal to further specify the involvement of the vestibular system in temporal processing. Furthermore, taking into account the inconsistent findings of the previous studies regarding the role of the vestibular system and the cerebellum, in particular, brain imaging and stimulation studies are crucial for further research on their involvement in time perception. For instance, the application of peripheral electrical stimulation could be thought of as distracting noise in the system. Thus, we might predict that with galvanic stimulation, the effect of vestibular stimulation found here will disappear as the noise leads to a down-weighting of the vestibular signal. An opposite effect might arise from cerebellar stimulation. Additionally, by applying systematic classical galvanic stimulation to the mastoid regions (see e.g., Day, 1999), one could stimulate vestibular afferents to generate percepts that are similar to those generated by the movement of the swing in our third experiment. If we find comparable effects of time contraction with such galvanic stimulation in the stationary observer, that is in the absence of the dynamically changing proprioceptive information or changes in the positions of the body present during the oscillatory motions of the swing, the role of the vestibular system in time production could be isolated and pinpointed further. This line of research is worth future investigation since it has important implications for tasks and activities that require spatial navigation and orientation, where accurate temporal estimation is essential, such as during the operation of a vehicle or an aircraft.

On a final note, if the effect of time contraction is not a maladaptive side-effect but rather has adaptive functionality, what could it be? During rapid body accelerations, the body is typically at higher risk to bump into things and in more immediate need to initiate swift action or corrective posture changes. The subjective time contraction could bear witness of a sharpened perceptual state which is induced by the vestibular stimulation. Be this as it may, the interaction between the vestibular system and time perception opens up a few interesting questions for future research.

## DATA AVAILABILITY STATEMENT

The raw data of Experiments 1–3 can be retrieved from: https://osf.io/z7fg2/?view_only=1b665a41ca8144268e1b48ed0832eeca.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

All authors were involved in designing the experiments. CC processed the data and performed the analysis. All authors interpreted the data and discussed the results. NU and CC wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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# Treatment of Gravitational Pulling Sensation in Patients With Mal de Debarquement Syndrome (MdDS): A Model-Based Approach

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Perception of the spatial vertical is important for maintaining and stabilizing vertical posture during body motion. The velocity storage pathway of vestibulo-ocular reflex (VOR), which integrates vestibular, optokinetic, and proprioception in the vestibular nuclei vestibular-only (VO) neurons, has spatio-temporal properties that are defined by eigenvalues and eigenvectors of its system matrix. The yaw, pitch and roll eigenvectors are normally aligned with the spatial vertical and corresponding head axes. Misalignment of the roll eigenvector with the head axes was hypothesized to be an important contributor to the oscillating vertigo during MdDS. Based on this, a treatment protocol was developed using simultaneous horizontal opto-kinetic stimulation and head roll (OKS-VOR). This protocol was not effective in alleviating the MdDS pulling sensations. A model was developed, which shows how maladaptation of the yaw eigenvector relative to the head yaw, either forward, back, or side down, could be responsible for the pulling sensation that subjects experience. The model predicted the sometimes counter-intuitive OKS directions that would be most effective in re-adapting the yaw eigenvector to alleviate the pulling sensation in MdDS. Model predictions were consistent with the treatment of 50 patients with a gravitational pulling sensation as the dominant feature. Overall, pulling symptoms in 72% of patients were immediately alleviated after the treatment and lasted for 3 years after the treatment in 58% of patients. The treatment also alleviated the pulling sensation in patients where pulling was not the dominant feature. Thus, the OKS method has a long-lasting effect comparable to that of OKS-VOR readaptation. The study elucidates how the spatio-temporal organization of velocity storage stabilizes upright posture and how maladaptation of the yaw eigenvector generates MdDS pulling sensations. Thus, this study introduces a new way to treat gravitational pull which could be used alone or in combination with previously proposed VOR readaptation techniques.

**Keywords: MdDS, velocity storage, orientation-vector, gravitational pull, rocking, swaying, bobbing, vestibular only (VO) neurons**

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## INTRODUCTION

Mal de Debarquement Syndrome (MdDS) is a debilitating neurological condition characterized by non-spinning vertigo akin to being on a boat (Brown and Baloh, 1987; Cha, 2015). Patients have described the symptoms as rocking, swaying, bobbing, walking on a trampoline or walking on sponges (non-spinning vertigo), which are often associated with anxiety, depression, and cognitive issues (Hain et al., 1999; Cha et al., 2008). In a large number of instances, there is also a gravitational pulling sensation (Dai et al., 2017). MdDS symptoms are generally triggered by boat, plane, or car rides and have been referred to as motion-triggered MdDS (MT). A phenotypically similar disorder includes these symptoms, but the onset is due to non-motion triggers or comes on spontaneously. This has been referred to as "non-motion triggered - motion oscillating vertigo by the International Consensus of Vestibular Disorders (Cha et al., 2020). For our purpose, we will refer to this entity as non-MT MdDS". MdDS is differentiated from other vestibular disorders because there is symptom relief when re-exposed to passive motion. Non-spinning vertigo persists while sitting, standing, and lying down long after the triggering event. Patients also report a sensation of gravitational pulling in one or several directions (Dai et al., 2017; Yakushin et al., 2020). These sensations were commonly accompanied by sensitivity to moving visual stimuli, loud noise, and fluorescent lighting, ear fullness, head pressure, brain fog, fatigue, and sensitivity to head movement. Patients often had cognitive complaints such as an inability to multitask, impaired concentration, and slower speech (Dai et al., 2017; Cha et al., 2020). The perceptions of motion (rocking and swaying) have been hypothesized to represent centrally induced maladaptation of the spatiotemporal coordination present in normal subjects (Dai et al., 2014; Cohen et al., 2018). When the non-spinning vertigo improved by readaptation, the cognitive symptoms immediately improved (Dai et al., 2017). However, the underlying deficiencies in pulling sensation, have not been addressed, and an effective treatment protocol has not been developed.

In the past, MdDS patients had up to 19 but on average 2–5 visits to physicians before being accurately diagnosed (Macke et al., 2012; Mucci et al., 2018a). The accuracy of an MdDS diagnosis depends on the awareness of the medical and research community of this syndrome. Lately, due to the internet, many patients are self-diagnosed and then confirm their condition with a specialist familiar with MdDS (Dai et al., 2017). The options for MdDS are therefor limited. Vestibular physical vestibular rehabilitation, benzodiazepines, and migraine medications can improve the quality of life in some patients, but symptoms remain in many others (Cha, 2012; Hain and Cherchi, 2016; Ghavami et al., 2017; Cha et al., 2018). The disruption of the inappropriate activity in a neural functional-connectivity network using non-invasive brain stimulation methods during several days may reduce symptoms (Cha et al., 2016, 2019; Ahn et al., 2021); however, the long-term outcome of this treatment is unknown.

Dai et al. (2014) proposed an effective therapy of MdDS based on the readaptation of the functional component of the vestibulo-ocular reflex (VOR) called velocity storage. The treatment concept was based on several experiments investigating the spatial orientation of velocity storage in the monkey (Raphan and Cohen, 2002; Cohen and Raphan, 2004). It was hypothesized that roll velocity storage eigenvector had become misaligned with the head roll axis during exposure to complex vestibular and visual stimuli, triggering inappropriate nystagmus and oscillating vertigo. The protocol developed was designed to counteract the roll eigenvector maladaptation by activating velocity storage in the direction opposite to what induced the contextual maladaptation. This readaptation is proposed to be induced by the OKS while rolling the head at the frequency of the patient's oscillatory vertigo (OKS-VOR) (Dai et al., 2014). Roll readaptation treatment was effective initially in 75% MT and in 50% non-MT MdDS patients (Dai et al., 2017). A 1-year follow-up of these patients determined that the success rate for both MT and non-MT MdDS was identical at 50% (Dai et al., 2017).

A weakness in the OKS-VOR treatment was the lack of a placebo arm, although the effectiveness of this readaptation treatment has been independently confirmed by several investigators (Hain, 2018; Mucci et al., 2018b; Schenk et al., 2018). Furthermore, Mucci and colleagues (Mucci et al., 2018b) demonstrated that OKS-VOR readaptation is more effective than placebo. The original studies by Dai et al. (2014, 2017), as well as replications using this protocol (Hain, 2018; Mucci et al., 2018b; Schenk et al., 2018), demonstrated similar success rates regardless of slight variations in treatment setups and protocols. A subset of cases that initially worsened or did not respond to the treatment, later improved by reversing OKS stimulus, supporting Dai's hypothesis that countering velocity storage should improve symptoms and that readaptation in the direction of velocity storage should increase MdDS symptoms (Schenk et al., 2018; Yakushin et al., 2020). This strengthened the argument that the results of Dai's studies were not due to placebo and that velocity storage was at the root of the various syndromes associated with MdDS.

Since 2014, 591 MT and non-MT MdDS patients were treated at Icahn School of Medicine at Mount Sinai with the original VOR readaptation method (Dai et al., 2017). Among them were 50 patients treated only with a modified method of treatment for the gravitational pulling sensation. These 50 patients are the core of this study. The sensation of gravitational pulling, however, did not seem to improve with the original OKS-VOR readaptation protocol (Dai et al., 2014; Yakushin et al., 2020). We, therefore, worked on modifying the original treatment based on the idea that the yaw and pitch eigenvectors could have become maladapted. To accomplish this goal, this study retrospectively examined data from patients whose dominant debilitating syndrome was the gravitational pull sensation and was treated with OKS in a specific direction keeping the patient's head stationary upright. An extension of the velocity storage model was then considered to explain how proprioception affects velocity storage. The main questions that we wished to answer was whether this model predicted how the gravitational pulling sensation might be induced by a maladaptation of spatial and temporal coding of the yaw axis eigenvector of velocity storage. We also wished to determine if the model predicted the orientation of OKS stimuli that would optimally re-adapt the eigenvector to alleviate the symptoms of the pulling sensation. Finally, we wished to determine whether the model predictions agreed favorably with the data on pulling directions and whether the alleviation of pulling sensations were alleviated by OKS, independent of whether the pulling sensation was a dominant feature of the debilitation or was only a component embedded in other features of MdDS.

## MATERIALS AND METHODS

### Patient Selection

All MdDS patients seeking treatment with the VOR readaptation protocol at MSSM were screened with an intake form and a brief interview. Patient eligibility criteria were the same as for the subjects who were recruited in our previous studies (Dai et al., 2014, 2017; Yakushin et al., 2020). The inclusion criteria were (1) continuous rocking, swaying, bobbing, and/or gravitational pulling, which had persisted for at least 3 weeks, with or without a trigger. (2) Subjects reporting improvement in symptoms when in a moving vehicle (i.e., a car) and return of symptoms when stopped (Cha et al., 2020). (3) No history of head or neck trauma, Lyme disease, serious peripheral vestibular disease, or other major neurological disorders. There was no age limitation in this study. The patients were categorized as MT MdDS if the oscillating sensation began less than 2 days after a motion event and as non-MT MdDS if a motion event did not precede the onset of oscillating sensation or it took place more than 2 days after a motion event. Subjects were referred by physicians, physiotherapists, former patients, or were self-referred. Many had completed neurologic and otologic workups, including MRIs that were unremarkable. Institutional Review Board (IRB) approved a review of the records at Icahn School of Medicine at Mount Sinai under the grant listed in the acknowledgments.

### The Treatment Procedure for Gravitational Pull

Among 591 treated patients, 50 experienced a dominant sensation of gravitational pull. They were therefore treated with OKS to alleviate this symptom. Patients were seated upright in an enclosed cylindrical chamber. Horizontal optokinetic nystagmus was induced by rotating the projector about the vertical axis. The projector was located above the patient's chair (Dai et al., 2014, 2017). The thickness of the stripes was 70 mm for the projected light and 110 mm for the shadows (**Figure 1A**). The projector could be tilted by 90°, to induce vertical optokinetic nystagmus (**Figure 1B**). Because the chamber was cylindrical, the horizontally projected stripes were slightly curved, and the widths of white and gray stripes varied 80–120 mm and 110–140 mm, respectively. Based on our previous study (Dai et al., 2017) a velocity of 5°/s and a brightness of 2 lux were used. The OKS stripes were administered for 1 min, and patients were required to stare at a point on the wall.

After each OKS, the patient was asked whether the postural stability improved, remained the same, or worsened. If the patient reported improvement or no change, the treatment time was increased. If the patient reported worsening of pulling, the direction of the treatment was reversed and given for 1 min. If subjects reported alleviation of symptoms, the velocity could be increased to 10°/s, and brightness increased to 3 lux as tolerated. A treatment session of 5–60 min was provided once a day.

### Quantitative and Qualitative Analyses of the Treatment Effectiveness

Subjective quantitative evaluation of improvement was evaluated with an eleven-point numerical Likert-like scale, where 0 represented "no MdDS symptoms" and 10 represented the severest symptoms the patient could imagine (Likert, 1932). The treatment was continued until the overall subjective symptoms score was improved by 50% or until no further improvements were reported. Thus, an average treatment for gravitational pull sensation over 4–5 days was 30 min, varying from 1 to 178 min. After each OKS exposure, patients were asked whether the symptoms improved, worsened, or had no effect. This qualitative response was used as a guideline for the next OKS treatment.

### Static Posturography

Static posturography for stability was performed using a Wii board (Dai et al., 2017). The dominant oscillating frequency of rocking or swaying was determined from the power spectra of the recorded center of pressure (COP) (Demura et al., 2008). Posture was recorded in several positions: feet 27 cm apart with eyes open, feet apart with eyes closed, feet together with eyes closed. Prior to 2017, to express an internal sensation of motion, subjects were asked to move their arm attached to an acceleration sensor at the frequency of the internally sensed movement (Dai et al., 2014). From 2017 onward, subjects were asked to move their bodies in the direction of perceived movement to exaggerate postural shifts while standing on a Wii board instead of using the arm. Postural data for comparisons were collected from recordings that were not exaggerated on the first day prior to the treatment and after the last treatment. Data were also collected at other times if subjects had difficulty determining the type of motion experienced and whether symptoms were improving or worsening. Again, these data were from recordings that were not exaggerated.

We define symmetrical body oscillation about the upright position in the for-aft plane (pitch) as rocking and side-to-side (roll) as swaying. Patients with gravitational pull sensations typically had asymmetrical body motions between upright and direction of pull. They also perceived their body motion, like oscillations in the plane of pull combined with resistance to pull.

To compare the postural stability after individual treatments, the displacement of COP over a 20-s period was computed as well as the root mean square (RMS) of the postural displacement along roll RMS, swaying, and pitch axes (pitch RMS, rocking) (Dai et al., 2017). Since body motion for the majority of patients in this study was not symmetrical and sinusoidal, the trace duration over 20 s was considered as the most reliable measure.

### Long Term Follow-Up

To determine the long-term effects of the treatment, all former patients were contacted first with a follow-up announcement

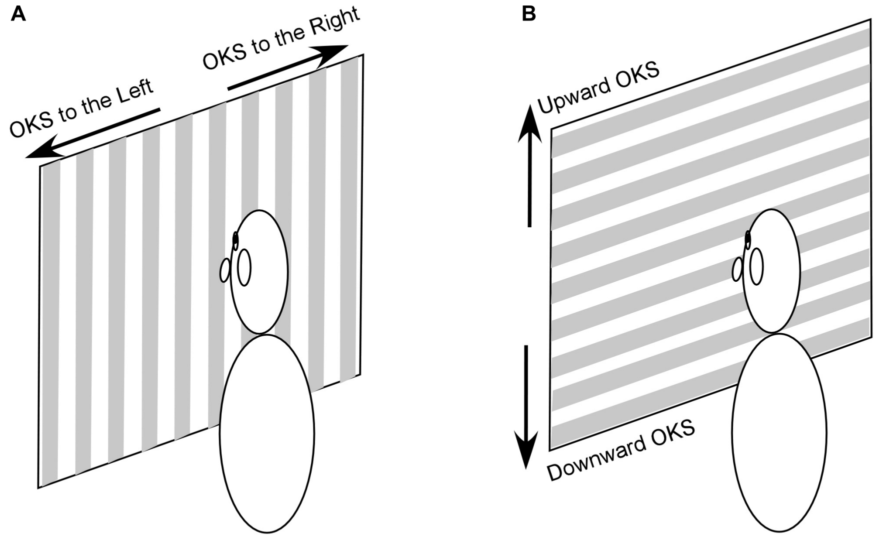

**FIGURE 1 |** OKS stimulation used to induce horizontal **(A)** and vertical **(B)** optokinetic nystagmus. It should be noted that the chamber wall is cylindric and stripes in **(A,B)** are curved and wider at the periphery. See text for a detailed description of the stimulus.

letter. All patients who did not wish to participate in follow-up were excluded. Furthermore, all patients that were diagnosed with severe neurological problems since the treatment were also excluded. Among 50 patients with only gravitational pull sensation, one refused to participate in the follow-up. The follow-up forms include overall and individual symptom scores immediately after treatment, 2 weeks, and 1, 3, 6, and 12 months after treatment, as well as scores at the time of the follow-up (varied among patients). Follow-up forms also included VVAS, SVQ, DHI, BAI, and STAI to evaluate sensitivity to visual (VVAS) and physical (SVQ) motions, disability level (DHI), and the level of anxiety (BAI, STAI). To normalize individual physical, emotional and functional disability with DHI, which varies with the number of elements in each sub-scale, we used average individual scores which vary from 0 to 3.

## Other Relevant Data

Among the remaining 541 patients that experienced rocking and swaying, gravitational pull was reported by 376 patients (59 male). Because exposure to OKS can potentially trigger migraine-like symptoms (Dai et al., 2017), the treatment protocol for MdDS patients was designed to reduce major symptoms of MdDS within the shortest amount of time. We targeted the next most prominent symptom if the most bothersome symptoms (rocking, swaying, gravitational pull) resolved or resulted in no improvement. Thus, the original VOR-OKS readaptation protocol in these patients was combined with treatment for gravitational pull. To verify whether the treatment of gravitational pull was effective in these patients, we analyzed whether patients felt qualitative changes in symptoms. The long-term follow-up was not performed on these patients because it was not possible to determine whether OKS-VOR readaptation or OKS treatment was more effective in overall symptoms improvements in these patients.

## Statistical Analyses

Two groups of data were compared with a standard Chi-Square test. Multiple groups of data were compared by ANOVA using the Bonferroni *post hoc* test (Keppel, 1991). Sinusoidal fit through the data was performed using a least-square fit algorithm. Mean and standard deviations were presented as **a(b)**.

# RESULTS

## The Theoretical Basis for the Onset of Mal de Debarquement Syndrome and Its Treatment

Under normal circumstances, head and body posture is maintained so that the yaw axis of the head is aligned with the spatial vertical, which is opposite to that of gravity (**Figure 2A**; Horak, 2009; Ivanenko and Gurfinkel, 2018). Because the body center of mass (COM) is about 100 cm above the center of pressure (COP) at the foot and has a small base of support, it behaves as an inverted pendulum when standing and thus represents an unstable equilibrium (Nashner et al., 1989; Horak, 2009). It is, therefore, necessary for the central nervous system (CNS) to combine sensory information from the visual system, vestibular system, and proprioception to activate a neural controller to minimize body sway and maintain equilibrium (**Figure 2B**).

Much work has been done to characterize the neural control for maintenance of upright body posture by tilting the surface of the support and visual world tilt as part of a feedback control system and studying the effects on body sway (see Horak, 2009; Ivanenko and Gurfinkel, 2018 for review). A number of studies have included pulling the body for-aft as another important input, which can perturb upright stance

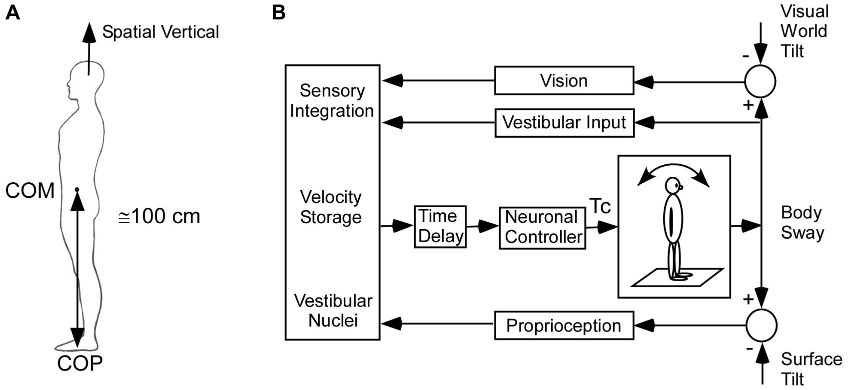

**FIGURE 2 |** Model of the postural control. **(A)** Inverted pendulum model. COM – center of mass, COP – center of pressure. **(B)** Model of sensory integration of visual, vestibular, and proprioceptive inputs [modified from Horak (2009)]. This model includes the low frequency postural adjustments contributed by velocity storage.

and requires multisensory control to stabilize upright posture (Peterka, 2002, 2003; Mergner et al., 2003; Maurer and Peterka, 2005; Cnyrim et al., 2009). The aim of the control models was to focus on the multisensory control that contributes to postural stability and predict the changes in postural control when there is vestibular loss compared to normal (Mergner and Rosemeier, 1998; Mergner and Glasauer, 1999; Mergner et al., 2003; Maurer and Peterka, 2005). However, this kind of control accentuates the upper frequency (0.05–0.4 Hz) "rapid postural responses" that maintain upright posture and equilibrium and is not consistent with the slow oscillations and pulling characteristic of MdDS. Neither, do these models consider how the spatio-temporal or orientation properties of velocity storage maintain upright postural stability or how their maladaptation contributes to MdDS.

The basis of our model and treatment protocol for MdDS comes from the hypothesis that the cause of the MdDS disorder is a disruption of the velocity storage mechanism, which initially was shown to store information about Head Velocity relative to space in the central vestibular system (Cohen et al., 1977; Raphan et al., 1979; **Figure 3**). It was subsequently shown that velocity storage has strong input from proprioceptive mechanisms that maintain posture during locomotion (Solomon and Cohen, 1992a,b; **Figure 3**, Proprioceptive Velocity). Velocity storage of motion information has orientation properties that are related to positions of the head relative to gravity (Sturm and Raphan, 1988; Dai et al., 1991; **Figure 4**) and its maladaptation could induce the slow postural adjustments readjustments. Normally, the head coordinate frame (**Figure 4A**, blue arrows) has the eigenvectors of H aligned with the head frame (**Figure 4B**, red arrows), with the H matrix being diagonal (**Figure 4D**). When the H matrix is non-diagonal, having a $h_{yr}$ component, the Yaw eigenvector is pitched forward or back (**Figure 4E**). When the H matrix has a $h_{yp}$ component, the eigenvector is rolled to the side (**Figure 4F**). In general, the H matrix can have all components, inducing a non-orthogonal basis for velocity orientation, which are not aligned with the head roll, pitch, and yaw axes (**Figure 4G**). Moreover, the orientation vectors that characterize velocity storage can be adapted by conflicting motion environments (Dai et al., 2009). Thus, velocity storage is a critical mechanism for converting central velocity coding and orientation from the vestibular system and inducing slow compensatory ocular and the postural response of the orientation vectors of velocity storage during long-term vestibular stimulation on sea voyages.

## Determining the OKS Direction to Treat Gravitational Pull

The model suggests that the mechanism of treatment for the gravitational pulling sensation is the adaptation of the yaw axis eigenvector of velocity storage (**Figure 5**) to align with the yaw axis of the head. When the yaw axis eigenvector maladapts to having a positive roll component (counterclockwise rotation), then the yaw axis of the head is tilted back relative to the yaw eigenvector (**Figure 5A**). We hypothesize that there is a cross-product computation of the head yaw vector with the yaw eigenvector, which, using the right-hand rule, encodes a vector coming out of the left ear, which is an orientation back (**Figure 5A**, blue circle with dot). This creates an internal sensation of pulling back. The treatment for adapting the yaw eigenvector so that it aligns with the head would be an upward OKS stimulus, which opposes the maladapted orientation using the right-hand rule (**Figure 5A**, a gray area, circle with x). This is counter-intuitive to the notion that a downward OKS is necessary for a backward pulling sensation. Similarly, a maladapted tilt back of the Yaw eigenvector (**Figure 5B**) induces an orientation back and a pull forward sensation as the head yaw axis is down relative to the yaw eigenvector (**Figure 5B**, a circle with x). Again, the treatment would be a counter-intuitive OKS down, which would produce a vector opposite to the orientation of the pull forward vector according to the right-hand rule (**Figure 5B**, a gray area, a circle with dot).

A somewhat similar approach can be taken to explain the treatment for pulling to the right or left. If the yaw eigenvector maladapts by tilting to the right, then the yaw axis of the head is rotated left ear down relative to the eigenvector, giving a pull to the left side (**Figure 5C**). To cancel out the vertical component of the yaw eigenvector, the OKS stimulus should be opposite to the pull. This should be OKS to the right against the gravitational pull (**Figure 5C**; Raphan and Cohen, 1988). When

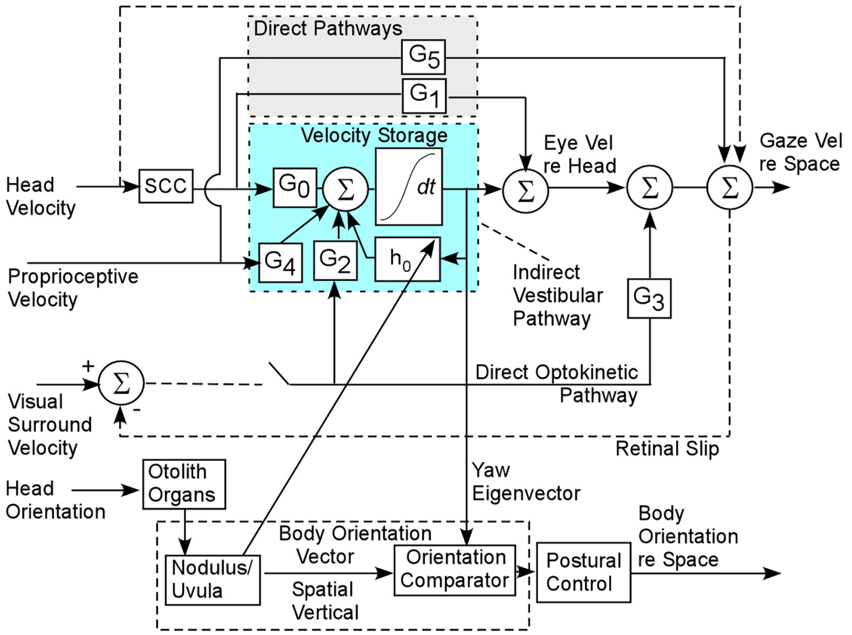

**FIGURE 3 |** Gaze and body postural control contributed by the velocity storage integrator. $G_0$ is the gain coupling matrix from the semicircular canals (SCC) to velocity storage. $G_2$ is the gain matrix coupling the optokinetic velocity input to velocity storage. $G_4$ is the gain coupling matrix from the proprioceptive velocity input to velocity storage. $G_1$ and $G_3$ are the direct pathway gain matrices from the semicircular canals and optokinetic input and are responsible for the rapid responses to head and optokinetic movement. There is also a rapid proprioceptive pathway ($G_5$), but these are assumed not to play a role in the maladaptation leading to MdDS.

the yaw eigenvector is maladapted by rotation counterclockwise, the pull is right ear down (**Figure 5D**). To cancel out the vertical component of the eigenvector, the OKS adaptation should be OKS to the left (**Figure 5D**). We predict from the direction of the maladaptation that roll (torsional) OKS stimuli, which would oppose the pull orientation, would perhaps be more efficient in the treatment of the lateral pulls. In addition, the model has not considered how alterations of the eigenvectors of velocity storage affect perception, which has been considered during off-vertical axis rotation and its effects on motion sickness (Dai et al., 2010). The incorporation of motion sickness into this model and how it is controlled by perception would clarify some of these issues.

We further assumed that magnitude of the vector could also play a role in MdDS symptoms. To account for up and down pulling, we hypothesize that this is caused by a maladaptation of the magnitude of the yaw eigenvector. A reduction in the magnitude would induce a floating sensation, while an increase in magnitude would induce heaviness. The appropriate adaptation is upward OKS for the floating sensation to increase the magnitude of the yaw eigenvector and downward OKS for the heaviness to decrease the magnitude of the eigenvector.

## Treatment of Patients With Gravitational Pull Sensation as the Dominant Symptom

Based on the above model predictions, we compared the use of upward OKS to treat gravitational pulling back and up, downward OKS to treat pulling forward and downward, leftward OKS to treat pulling right, and rightward OKS to treat pulling left. Of the 50 patients with dominant symptoms of gravitational pull sensation, 41 were females (82%). The age of the MdDS patients with dominant pulling sensation was 49 (12) for females and 31 (15) for males ($p = 0007$). MT onset of MdDS symptoms was reported by 33 patients and 17 had non-MT MdDS symptoms. There was no difference in the average duration of MdDS from the onset time until the time of treatment for both groups 3.2 (6.2) years, varying from 3 weeks to 30 years. The most common triggers for MT MdDS were cruises (36%), boating (36%), flight (18%), and car rides (10%). Among non-MT MdDS, 6 patients associated the onset of MdDS with vertigo attacks (35%). Among the other triggers were brushing teeth, massages, and elevator rides (one of each). The majority (47%) were unable to identify the event associated with symptom onset. There was a high number of males in non-MT (35%) vs. MT MdDS (9%). The average subjective symptom scores based on the Likert scale prior to treatment did not vary between MT and non-MT MdDS and was 5.5 (2.3). Besides the gravitational pull sensation, patients also reported non-dominant sensations of rocking, swaying, bobbing, trampoline walking, and other symptoms commonly reported by patients with MdDS (**Table 1**). Immediate responses to treatment for gravitational pull sensations in different directions are shown in **Figures 6–8**.

## Posturography Analysis of Pulling Backward Sensation Before and After Treatment

The static posturography measurement of a patient who experienced a dominant gravitational pulling back sensation had minimal roll oscillations but substantial pitch oscillations with a dominant frequency of ≈0.27 Hz (**Figure 6A**, black

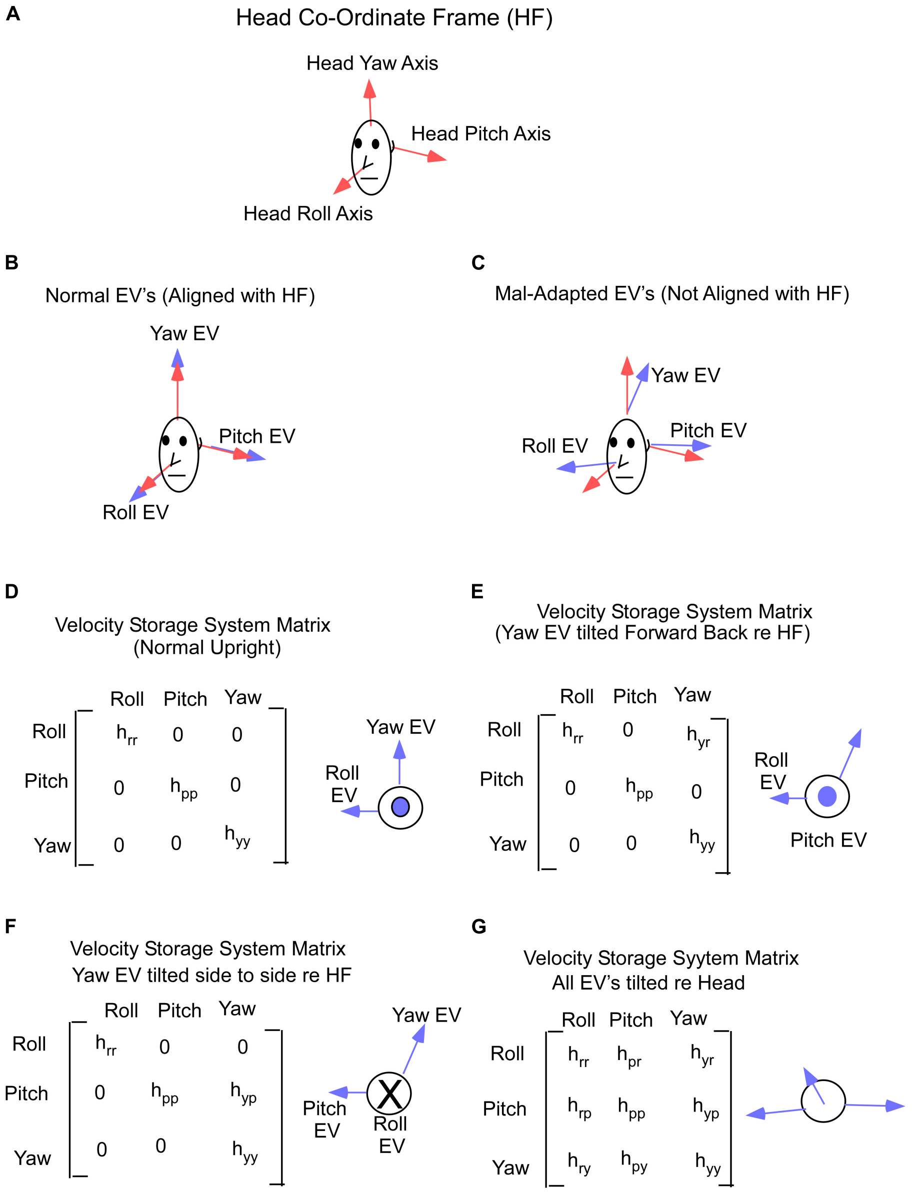

**FIGURE 4 | (A)** Head coordinate frame used in this study. **(B)** Yaw, pitch and roll eigenvectors in normal non-adapted states and are aligned with the head axes. **(C)** Yaw, pitch and roll eigenvectors shifted from their normal orthogonal orientations due to maladaptation of the velocity storage system matrix. **(D)** Gain matrix of velocity storage in normal state, when yaw, pitch, and roll eigenvectors are aligned with the head axes. **(E,F)** Gain matrix of velocity storage with yaw eigenvector shifted forward **(E)** or sideways **(F)**. **(G)** Gain matrix of velocity storage when all 3 eigenvectors are shifted from their normal **(D)** orientations. Insets in **(D–G)** on the right from gain matrices are a top view of the head. EV – eigenvector.

trace). The pitching oscillations were not symmetrical, with larger amplitudes and faster pitching backward, which corresponded to a sensation of backward pulling that was resisted by the patient leaning forward (**Figure 6B**, black trace).

Postural stability improved after upward OKS at 5°/s for 1 min (**Figures 6A,B**, blue traces). Plots of roll vs. pitch COP show the phase relationship of body motion as well as the power of any pulling offset before and after treatment (**Figures 6C,D**). Before treatment, the power (RMS) and stability (Trace) of the upright posture were trace 20s = 2,061 mm, roll RMS = 5 mm, pitch RMS = 71 mm. After treatment, trace 20s = 347 mm, roll RMS = 4 mm, pitch RMS = 12 mm, which is an 83% improvement in stability (Trace). Patients also reported a subjective improvement in backward pulling.

## Posturography Analysis of Pulling Lateral Sensation Before and After Treatment

Treatment of a patient that experienced a sensation of gravitational pull to the left is shown in **Figure 7** (**Figure 7A**,

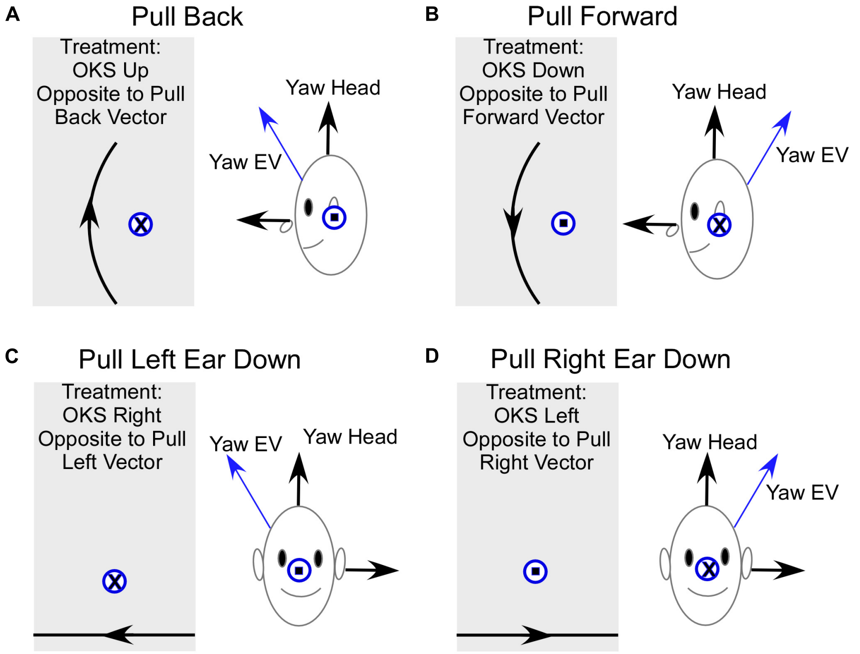

**FIGURE 5 |** Summary of the model-based predicted treatment protocol for gravitational pulling sensation. EV- Eigenvector. **(A)** Sideview of the pulling back sensation. The Yaw EV is shifted forward so the head yaw is back relative to the EV. The vector representing this pulling back sensation is the cross product of Yaw Head with Yaw EV and according to a right-hand rule, this is a vector out of the left ear (circle with a dot). The OKS treatment is OKS up, which re-adapts the Yaw EV toward Yaw Head. The direction of rotation of OKS represented by a circle with an x, opposite to the maladapted vector rotation. **(B)** Sideview of the pulling forward sensation. The Yaw EV is maladapted back re the Yaw Head, inducing a forward pulling sensation. The vector for this rotation is into the left ear (circle with an x) and the OKS stimulus to readapt is down and represented by a vector out of the left ear. **(C)** Pull Left ear down. This occurs when the Yaw EV is rotated right. The appropriate treatment using horizontal OKS is toward the right, which because of the known cross-coupling of velocity storage would adapt the Yaw EV toward the Yaw Head. It should be noted that the model predicts that a more potent OKS stimulus to re-adapt this shift in the EV would be a counterclockwise roll OKS from the subject viewpoint, which would be a vector opposing the rotation of the Yaw EV relative to the Yaw Head. **(D)** Pull Right Ear down. This occurs when the Yaw EV is rotated left relative to the Yaw Head. The appropriate treatment using horizontal OKS is toward the left, which because of the known cross-coupling of velocity storage would adapt the Yaw EV toward the Yaw Head. In this instance, the model predicts that a more potent OKS stimulus to re-adapt this shift in the EV would be a clockwise roll OKS from the subject viewpoint, which would be a vector opposing the rotation of the Yaw EV relative to the Yaw Head. Front view. Gray rectangles – screens with OKS stimulus. The direction of OKS is indicated by arrows. The direction of the OKS vectors for side down pulling sensation is consistent with previously studied cross-coupling when the head is tilted side down.

black trace). The patient constantly resisted the pull by bringing the body back to an upright position, which generated oscillations at ≈0.3 Hz. This was accompanied by small irregular roll oscillations (**Figure 7B**, black trace). On static posturography, it appeared that there were constant oscillations ≈ ± 15 mm in all directions (**Figure 7C**, trace 20s = 387 mm, roll RMS = 7 mm, pitch RMS = 5 mm). After rightward horizontal OKS at 5°/s for 2 min, leftward pulling was not present (**Figure 7A**, blue trace) and was not reported subjectively. Irregular rocking remained the same (**Figure 7B**, blue traces). Static posturography revealed a reduction of leftward pulling (**Figure 7D**, trace 20s = 189 mm, roll RMS = 1 mm, pitch RMS = 3 mm). The pitching oscillations were about the same (roll RMS = 5mm vs. 3 mm). The trace length was reduced by 51%.

## Posturography Analysis of Pulling Forward Sensation Before and After Treatment

The typical example of treatment for forward pulling is shown in **Figure 8**. The patient did not experience any swaying (**Figure 8A**, black trace), but reported forward pulling (**Figure 8B**, black trace). The patient resisted the pulling creating non-sinusoidal body oscillations ≈0.12 Hz. The static posturography confirmed this oscillation at ± 30 mm (**Figure 8C**, trace 20s = 310 mm, roll RMS = 3 mm, pitch RMS = 13 mm). The patient was exposed to downward OKS at 5°/s for 2 min. After this treatment, sway was minimal (**Figure 8A**, blue trace), and rocking was reduced (**Figure 8B**, blue trace). The static posturography confirmed this improvement (**Figure 8D**, trace 20s = 184 mm, roll RMS = 3 mm, pitch RMS = 5 mm). The trace length was improved by 41%.

## Treatment of Pull-Up and Pull-Down Sensation

The treatment effect for gravitational pull-up and down sensations could not be revealed with static posturography and was justified only qualitatively. Because the direction of gravitational pull could change on different days, data from the 50 subjects treated for various gravitational pulls were analyzed to determine the effectiveness of the treatment with sex and

**TABLE 1 |** Symptoms reported by 50 MdDS patients with gravitational pull as the dominant sensation of motion.

| Symptom | Occurrence |
|---|---|
| Rocking | 62% |
| Swaying | 78% |
| Bobbing | 40% |
| Trampoline walking | 52% |
| Migraine | 28% |
| Tinnitus | 36% |
| Brain fig | 66% |
| Head pressure | 44% |
| Fullness of the ears | 44% |
| Anxiety | 76% |
| Depression | 54% |
| Fatigue | 68% |

trigger as variables rather than comparing the effectiveness of the treatment of individual pull directions.

Treatment was initially successful in 36 (72%) patients (73% MT and 71% non-MT MdDS). Body motions were larger with eye-closed conditions and significantly reduced in successfully treated patients from 727 (682) mm to 406 (433) mm (44%, $p = 0.03$). The postural improvement with the eye-opened condition was insignificant (39%, $p = 0.089$). In patients who did not report significant symptoms improvement after the treatment, postural stability significantly improved with eye-opened [411 (230) vs. 234 (68), 43%, $p = 0.017$] but not with eye-closed ($p = 0.940$). This indicates that postural stability is not a major factor in the overall severity of MdDS as judged by patients.

Since resistance to gravitational pulls produces body oscillations similar to sinusoidal motion, we compared available data of the rocking and swaying frequencies of 47 patients who experienced dominant gravitational pull sensations with the sensations obtained from 541 MdDS patients where the pulling sensation was not dominant. The rocking frequency of patients with dominant gravitational pull sensations was comparable to that of other MdDS patients [0.27 (0.14) Hz vs. 0.25 (0.17) Hz, $p = 0.568$]. The same was true for the swaying of patients with the sensation of pull only [0.33 (0.19) Hz vs. 0.31 (0.19) Hz, $p = 0.619$]. Thus, the body oscillations of patients who experienced dominant gravitational pull sensations were similar to those of the patients with dominant rocking and swaying sensations.

## Follow-Up Study

Thirty-four of 49 patients treated for dominant gravitational pull responded to the follow-up questionnaire, with 16 providing only an overall symptoms score. Since patients were treated at different times, the follow-up was performed 2.8 (1.3) years after the treatment. There were 20 (20/34) patients who reported improvement, and 11 (11/34) reported no improvement at the time of follow-up. Thus, 59% (20/34) of patients treated only for gravitational pull remained improved 3 years later (54% MT, 57% SO). Two more MT patients (2/34) did not respond to the treatment, but about a year later, one started clonazepan, and another changed their diet, and by the time of the follow-up, symptoms were significantly improved. One other non-MT (1/34) patient was diagnosed with a small fiber neuropathy which caused severe pain and it could not be determined which symptoms were due to MdDS.

Among patients who reported improvements at follow-up, 15 (15/20) had improvement immediately after the treatment and remained improved. Five others (5/20) did not respond to the treatment immediately and, most likely, recovered spontaneously at the time of follow-up. Finally, among the patients who did not report improvement at the last follow-up, 8 (8/11) initially responded to the treatment, but symptoms returned after traveling home. Thus, we could conclude that all the patients that improved immediately and maintained improvement after travel home continued to have benefits up to 3 years later.

Individual symptoms were analyzed to determine whether long-term treatment effectiveness could be predicted based on the data obtained immediately after treatment (**Table 2**).

Detailed analyses of individual symptoms score indicate that the was no difference in individual scores of successfully treated and not successfully treated groups ($p > 0.127$). The most commonly experienced symptoms were rocking, gravitational pull, and anxiety. It was not surprising that all patients also reported improvement in rocking since they perceived the gravitational pull sensation as fore-aft rocking. What was surprising was that 100% of successfully treated patients reported improvement in fuzzy vision and ear fullness, while only ≈55% in the unsuccessfully treated group improved. The second-largest improvement in successfully treated patients was the brain fog (83%) and sensitivity to fluorescent lights (75%). Improvement of all other symptoms was only slightly larger in the successfully treated group. Interestingly, while the overall score in the unsuccessfully treated group was not improved, the treatment improved the sensation of gravitational pull in 64% of the unsuccessfully treated group. Twenty-seven percent in that group also reported improvement of the rocking sensation. Thus, we can speculate that when postural improvements are associated with reduction of fuzzy vision, ear fullness, brain fog, and sensitivity to lights, overall improvement will remain. Data also indicated that when sensitivity to lights remained high, symptoms will be re-triggered after successful treatment of MdDS.

We performed quantitative analyses of sensitivities to visual stimuli (VVAS) and physical motion (SVQ) in 2 groups. Only 1/7 patients had high sensitivity to visual stimuli (VVAS = 3.8) in the successfully treated group, while the remaining 6 had low sensitivity (av VVAS = 1.5). In the non-successfully treated group, 1/10 had extreme sensitivity (VVAS = 8.7), three patients had high sensitivity (av VVAS = 4.5), and six patients had low sensitivity (av VVAS = 1.6). Sensitivity to the physical motion was moderate in two groups, with 71% successfully and 55% not-successfully treated patients remained sensitive to motion, while the remaining patients were not sensitive to motion. Regardless of differences in sensitivities to moving visual stimuli and to physical motion, patients with higher visual sensitivity were

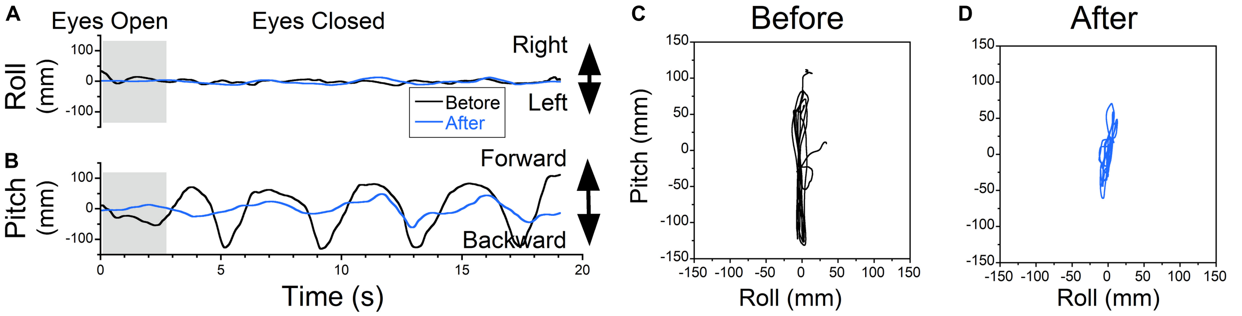

**FIGURE 6 |** The COP changes as a function of time (Static posturography). **(A)** Side-to-side (swaying) body oscillations. **(B)** Forward-back (rocking) body oscillations. Static posturography of a 52-year-old female with MdDS triggered immediately after a flight. Prior to treatment, the patient had no swaying (**A**, black trace) but reported strong backward gravitational pulling (**B**, black trace). The shaded areas in **(A,B)** are intervals when the patient had her eyes open. **(C,D)** Trajectory plots of COP before **(C)** and after **(D)** exposure of upward OKS at 5°/s for 1 min. After treatment, postural stability increased (**A,B,D** blue traces).

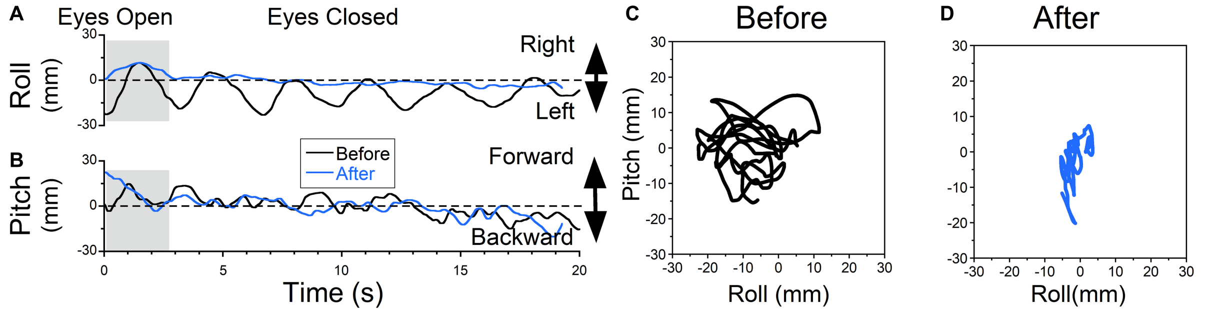

**FIGURE 7 |** Static posturography of a 48-year-old female with MdDS triggered immediately after a cruise. Details of individual plots are described in **Figure 6**. The patient experienced a sensation of gravitational pulling to the left (**A**, black trace) and some rocking (**B**, black trace). When the eyes were closed, the patient's body gradually drifted to the left. When the posture reached a certain deviation from upright, to gain stability patient quickly moved her body back to the upright position. This is different from body swaying when oscillation is sinusoidal and body deviations are symmetrical about upright. After exposure to OKS to the right at 5°/s for 2 min, the sensation of gravitational pulling to the left was reduced (**C**, blue traces). As a result, side-to-side body oscillations were no longer observed. Minimal forward-back body oscillations remained unchanged (**D**, blue traces). **(D)** Trajectory plots of COP before **(C)** and after **(D)** treatment. After treatment, postural stability increased (**A,B,D** blue traces).

more likely to be sensitive to physical motion (MLR, $p < 0.05$). General disability was lower in the successfully treated group (DHI = 26.4 vs. 40.9). The same was true for physical (0.9 vs. 1.4), emotional (0.9 vs. 1.4), and functional (1.3 vs. 1.9). Thus, the physical and emotional disabilities remain high in the non-successfully treated group.

Anxiety level was verified by several different scales STAI Y1 and STAI Y2, BAI. STAI indicates moderate anxiety in both groups (45 of 80, where < 40 is normal). Anxiety was severe in the majority (86%) of successfully treated patients but mild in the majority (70%) of the unsuccessfully treated as determined by BAI. Similarly, the anxiety level was abnormal in 60% of successfully treated and only in 20% of unsuccessfully treated patients as determined by HADS(a). Thus, if the patient with high anxiety responded to treatment initially, the high anxiety was not a significant factor in long-lasting treatment success.

## Qualitative Analyses of Gravitational Pull Sensation Treatment in 591 Patients

Data from 50 patients with dominant sensation of gravitational pull and 376 patients that experience gravitational pull as one of several other motion sensations were combined (376 + 50 = 426). The most common direction of the gravitational pulling was backward (52%) and sideways (32%). Pulling forward (11%), down (5%), and up (3%) were less frequent. Thus, backward gravitational pulling was the most frequent, dominant sensation. During the 4-day treatment, some patients experienced a pulling sensation only in one specific direction, while other patients experienced pulling sensations for which the direction of pull varied over time.

A backward gravitational pulling sensation was reported by 307 patients (307/426, 72%). The backward only pulling sensation was exclusively experienced by 57%, whereas 35% experienced a backward pulling sensation and one other additional pulling direction, 5% experienced two other additional pulling directions, and 3% experienced three other additional pulling directions.

The majority of patients with gravitational pull-back sensation reported improvement of postural stability after exposure to upward OKS (96%, 296/307), similar to that shown in **Figure 6**. Six patients (6/307, 2%) did not report any postural changes after upward OKS. The five remaining (5/307, 2%) patients reported improvement after downward OKS but no improvement after

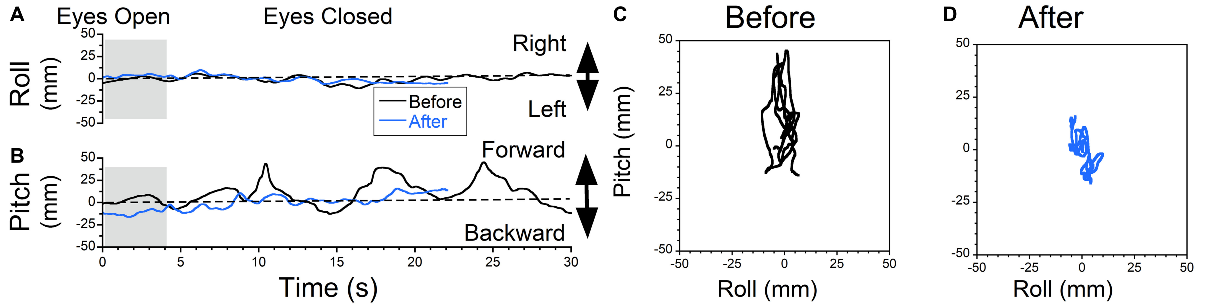

**FIGURE 8 |** Static posturography of a 71-year-old female with MdDS triggered immediately after a cruise. Details of individual plots are described in **Figure 6**. The patient reported a sensation of forward gravitational pulling. Body deviation side-to-side were minimal (**A**, black traces). When the patient closed her eyes, the body was gradually falling forward, but when deviation reached certain level, it was pulled back toward upright position (**B**, black trace). After exposure to downward OKS at 5°/s for 2 min, the swaying remained minimal (**C**, blue trace) and forward body deviation was reduced **(D)**. Self-score of overall symptoms prior to treatment was 7/10, and after treatment was 4.5/10.

**TABLE 2 |** Frequency of individual symptoms at long-term follow-up in successfully and unsuccessfully treated groups.

| Symptoms | Successfully treated | | | Not successfully treated | | |
|---|---|---|---|---|---|---|
| | **Experienced** | **Score** | **Improve** | **Experienced** | **Score** | **Improve** |
| Overall | 100% | 6.3 (2.2) | 100% | 100% | 5.9 (2.5) | 0% |
| Rocking | 100% | 7.2 (1.6) | 100% | 100% | 6.1 (2.7) | 27% |
| Gravity pulling | 100% | 6.9 (1.7) | 100% | 100% | 5.6 (2.8) | 64% |
| Brain fog | 86% | 5.1 (2.5) | 83% | 100% | 4.1 (2.9) | 50% |
| Light's sensitivity | 57% | 3.4 (3.5) | 75% | 67% | 3.7 (3.8) | 50% |
| Noise sensitivity | 71% | 3.9 (3.2) | 60% | 56% | 2.7 (2.8) | 40% |
| Anxiety | 83% | 5.3 (3.1) | 60% | 100% | 6.7 (2.5) | 44% |
| Depression | 83% | 5.3 (3.7) | 60% | 83% | 4.6 (3.8) | 44% |
| Fatigue | 83% | 5.9 (4.3) | 40% | 89% | 6.1 (3.2) | 50% |
| Fuzzy vision | 17% | 0.2 (0.4) | 100% | 56% | 2.2 (3.0) | 40% |
| Head pressure | 83% | 4.3 (3.3) | 60% | 78% | 2.7 (2.7) | 57% |
| Ear fullness | 50% | 2.9 (3.8) | 100% | 56% | 1.9 (3.2) | 40% |

*Experienced: present of patients who experience this symptom. Score: severity of that symptom on 0–10 self-score prior to treatment. Improve: percent of patients who reported at least 50% improvement of that symptom. Score is presented as mean (SD).*

upward OKS. None of 307 patients reported worsening of their symptoms after upward OKS. Thus, backward pulling was reduced after upward OKS in 96% of patients who experienced this sensation.

The mean treatment time for backward pulling was 17 (19) min, varying from 1 to 135 min over a week of treatment. There was no difference in treatment times for patients who experienced only back pull or pull in multiple directions ($p = 0.420$, ANOVA with Bonferroni adjustment).

Lateral pulling was reported by 190 patients (89 left, 101 right). Only 26% experienced pulling in one direction. The majority (63%) experienced pulling in two directions, while 9 and 2% experienced pulling in three and four directions, respectively. Thus, pulling in two directions was the most common sensation in patients who experienced lateral pulling. Data were found where lateral pulling, patients were exposed to OKS in the direction opposite to the sensation of pulling (**Figure 5**). The average treatment time was 15 (21) min for leftward pulling and 18 (25) min for rightward pulling. The results were combined because there was no difference in treatment duration ($t$-test, $p = 0.502$). The average treatment time for lateral pulling of 188 patients was 17 (23) min varying from 1 to 171 min over a week of treatment.

The treatment for lateral pulling was effective in 95% of patients (181/190). Seven patients (4%, 7/190) did not report any improvement. One patient reported improvement after OKS was induced in the same direction as pull (1/190), and another after OKS was induced in either direction (1/190).

Forward pulling was reported by 66 patients (66/426, 15%). Forty-eight percent reported pulling only in one direction, while 30% had it in two, 11% in three, and 11% in four directions. Thus, similar to gravitational pull backward, gravitational pulling forward was frequently the only direction of pull experienced by patients. The average treatment duration was 10 (12) min, varying from 1 to 65 min over a week of treatment.

The treatment for gravitational pull forward was effective in 94% (62/66) of patients. Two patients (3%, 2/66) reported improvement after upward and downward OKS, and 2 other patients (3%, 2/66) did not report significant improvement.

Upward pulling was reported by 18 patients (18/426, 4%). Patients frequently described this sensation as floating above the ground or not being grounded. Thirty-three percent of patients experienced isolated upward pulling. Many patients had additional pulling directions (28% in two, 28% in four, and 11% in three). The average treatment duration was 10 (13) min over a week of treatment. Seventeen patients (94%, 17/18) reported improvement after this treatment, and one (6%) reported no significant changes.

Downward pulling was reported by 33 patients (33/426, 8%). These patients frequently reported that their legs were heavy. Thirty-four percent reported isolated downward pulling. The majority (41%) reported additional pulling in one more direction. Pulling in 3 directions was reported by 19% and in 4 directions by 6% of patients. The average duration of treatment was 19 (33) min, varying from 1 min to 154 min over a week of treatment. Eighty-five percent (28/33) of patients reported improvement after downward OKS.

Thus, while the average duration of treatment for gravitational pulling in different directions varied from 10 to 17 min, this difference was not significant ($p = 0.120$, ANOVA). Pulling in only one direction was most common for backward pulling (57%) and forward pulling (48%) sensations. Pulling in all other directions was multidirectional.

## Effects of Pull Sensation Treatment in the Wrong Direction of OKS

The model predicted that the treatment of backward and forward pulling sensation with forward and backward OKS, respectively, would exacerbate the symptoms. We experimentally verified the effect of OKS in the wrong direction. We found data where downward OKS for 1 min was used to treat backward pull in 26 patients. Twenty of 26 (77%) reported worsening of the pull sensation. The remaining 6 of 26 did not report any changes. Thus, downward OKS was ineffective in treatment gravitational pull backward, confirming that treatment for yaw eigenvector correction is following the right-hand rule as predicted by the model (**Figure 5**).

Similarly, to test whether hypotheses derived direction of effective treatment is correct (**Figure 5**), 2 patients with lateral pull sensations were exposed to OKS in the same direction and reported symptoms worsening.

To test whether downward pulling could be treated with upward OKS, it was applied to 6 of 33 patients with that pulling sensation. In one patient, 1 min exposure to upward OKS increased the sensation of downward pulling. The other 5 (5/33) reported improvement after upward and downward OKS.

Thus, using short 1 min OKS in the direction which is opposite to that predicted by the model is typically worsening the sensation of pulling.

## Treatment of Oscillating vs. Pulling Vertigo

In some instances, patients failed to distinguish the difference between lateral pulling, swaying, forward/backward pulling, and rocking. In many cases, the gravitational pulling can be determined by posturography. Body rocking and swaying were typically sinusoidal at a specific frequency (Dai et al., 2014, 2017). Thus, posturography was helpful in identifying gravitational pulling when it revealed non-sinusoidal, somewhat nystagmus oscillations with varying frequencies, such as that shown in **Figures 6–8**. Moreover, rocking and swaying typically had equal amplitude in both directions from the upright center position. In the case of gravitational pulling, posturography typically revealed oscillations away and back to the upright center position (**Figures 7A**, **8B**, dashed lines).

A more complicated case is shown in **Figure 9**. The patient did not experience any swaying (**Figure 9A**, gray trace) but had substantial fore = aft body rocking at ≈0.1 Hz (**Figure 9B**, gray trace). Oscillations were not very consistent but were symmetrical about the upright center position (trace 20s = 812 mm, roll RMS = 4 mm, pitch RMS = 27 mm) (**Figure 9C**). We first attempted to treat the patient for fore-aft rocking. Rightward OKN was induced at 5°/s, while the head was rolled side-to-side at 0.1 Hz for 3 min. Following treatment, the patient had no changes in swaying (**Figure 9A**, blue trace) but reported a stronger rocking sensation (**Figure 9B**, blue trace). Static posturography revealed oscillations at 0.15 Hz (trace 20s = 716 mm, roll RMS = 6 mm, pitch RMS = 54 mm). The roll RMS values were close to zero before and after that treatment. The pitch RMS, however, increased by 100%. Since trace duration was about the same in both cases, an increase in pitch RMS indicates that this treatment induced the fore-aft rocking. Based on this result, the treatment was reversed to eliminate induced rocking, and the forward pulling was successfully treated (not shown). This indicates that the original protocol using VOR-OKS readaptation (Dai et al., 2014) may not be appropriate for treating gravitational pull sensations.

# DISCUSSION

This study has shown that the sensation of gravitational pulling experienced by MdDS was related to the maladaptation of the orientation of the yaw axis eigenvector of velocity storage. As such, patients could be treated by OKS in a specific direction determined by the direction of pulling as predicted by the model according to the right-hand rule (**Figure 5**). The pulling sensation could be alleviated regardless of whether it was the dominant symptom or was part of the symptoms experienced by MdDS patients whose dominant features were pitch or roll oscillations. Treatment was effective in 72% of patients immediately after the treatment, and symptoms remained improved 3 years after the treatment at 58% of patients. This indicates that OKS itself is a robust treatment for the gravitational pull and is further evidence that maladaptation of velocity storage, which is accessed by OKS is the root cause of MdDS.

The eigenvectors of velocity storage represent a central vestibular motion reference of space (Dai et al., 1991; Raphan and Sturm, 1991; Raphan and Cohen, 2002; Cohen and Raphan, 2004). Lengthy exposure to conflicting vestibular environments might induce “false” coding of space, especially the spatial vertical, which is defined by the acceleration of gravity (Raphan and Cohen, 2002; Cohen and Raphan, 2004). Based on this false

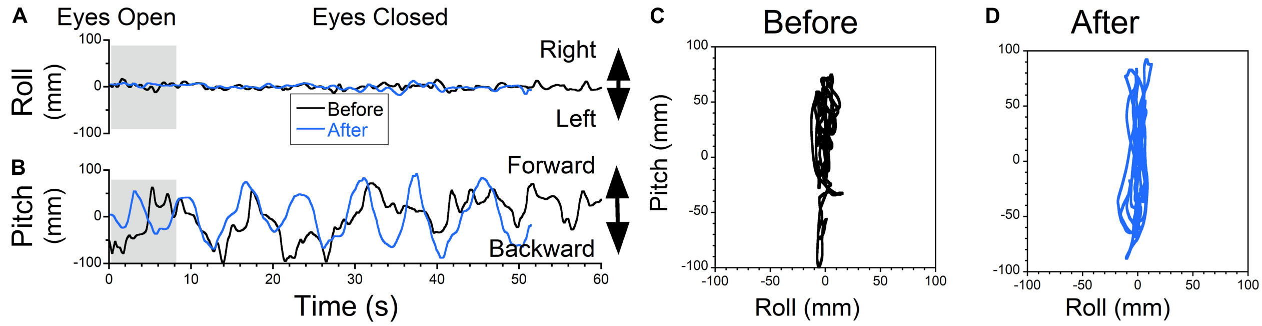

**FIGURE 9 |** Static posturography of a 52-year-old female with MdDS of unknown origin (possibly swimming). Details of individual plots are described in **Figure 6**. The patient did not experience any swaying (**A**, black trace) but reported a sensation of rocking and backwards gravitational pulling (**B**, black trace). Forward-back motion was irregular but deviations forward and back were of similar amplitude. Thus, static posturography did not have a typical pattern of rocking or gravitational pull sensation forward or backward. After exposure to OKS to the right at 5°/s while rolling the head at 0.1 Hz for 3 min (treatment for rocking), swaying remained minimal (**A**, blue trace) but rocking became stronger and regular at 0.15 Hz (**D**, blue traces). The patient reported worsening of her symptoms. At the same time fore-aft oscillations became regular **(C,D)**. The appropriate treatment should have been upward OKS for the pulling back sensation. This shows that inappropriate treatment, based on some "intuitive" notion and not model-based could have deleterious consequences.

coding, the eigenvectors of velocity storage adapt and become embedded as the representation of space (Dai et al., 2014). Thus, an internal mismatch of the orientation vectors of velocity storage, i.e., its eigenvectors, with that of the direction of the head axes induces a disequilibrium. This disequilibrium may cause the body to oscillate or experience a pulling sensation. The basis of the treatment described in this study is that the time constant of velocity storage and its eigenvectors can be adapted by countering conflicting visual-vestibular input, oscillations or pulling sensations induced by MdDS can be corrected. This forms the basis of the protocols tested for eliminating the symptoms of MdDS.

The original treatment of MdDS, was based on the idea that the roll eigenvector of velocity storage had maladapted toward pitch during cross-axis stimulation (Dai et al., 2009, Dai et al., 2014). Therefore, the protocol developed for treatment was to use a combined OKS and vestibular stimulus, which presumably re-aligned the eigenvectors with the head axes (Dai et al., 2017; Yakushin et al., 2020). This protocol, however, could not explain the sensation of pulling experienced by some MdDS patients (Dai et al., 2017; Yakushin et al., 2020) and was not effective in treating this symptom. In this study, we demonstrated that maladaptation of the yaw eigenvector alone predicts the direction of the pulling sensation by a misalignment of the yaw eigenvector with the head yaw axis and that an OKS stimulus that aligns the yaw eigenvector with the head yaw axis is effective in the treatment of pulling.

The model-based directions of the OKS that promote effective treatment are important because when the treatment is in the opposite direction, it may exacerbate the pulling sensation problem. For example, according to the model, a pull sensation backward is due to the yaw eigenvector being maladapted forward, causing a misalignment with the head yaw axis. A readaptation strategy should therefore be upward to re-align the yaw eigenvector toward the head yaw axis. This is seemingly "counter-intuitive," since the OKS is in the same direction as the pulling. However, it is the yaw eigenvector that is being readapted toward the head yaw axis, which is the therapeutic direction. A downward OKS would exacerbate the pulling and cause more problems. A similar argument can be given for the downward pulling sensation. We have used horizontal OKS to treat side-down pulling sensation. This is effective because there is considerable cross-coupling from the yaw to roll, which corresponds to a side-down pulling sensation (Raphan and Cohen, 1988). However, other directions of OKS, such as roll OKS, could be more effective for side down pulling sensation, but this needs further study.

Another important aspect of this model-based study was that it showed that the OKS stimulus was effective in treating the pulling sensation regardless of whether it was the dominant feature of the MdDS or was embedded in rocking and swaying as the dominant features. As explained before, the gravitational pull sensation could also be mistakenly interpreted as oscillations (**Figure 9**). However, treatment for gravitational pull alone is different from OKS-VOR readaptation treatments of oscillatory vertigo. Furthermore, this study indicates that treatment of the gravitational pull by OKS with the head stationary does not cause significant symptoms to increase, while OKS combined with the head motion when OKS is in the wrong direction may significantly increase MdDS symptoms. Thus, when it is unclear whether the patient is experiencing the gravitational pulling or body oscillations, it is safe to test whether posture improves by first treating the gravitational pulling sensation. This suggests that patients in whom OKS-VOR readaptation is ineffective may benefit from OKS alone.

A model-based analysis of how specifically misalignment of the eigenvectors might cause the rocking and swaying in MdDS has not been developed. Our own studies and studies from the other laboratories indicate that 25% of patients with motion-triggered and 50% of patients with spontaneous onset of MdDS do not respond to OKS-VOR treatment (Dai et al., 2014, 2017; Hain, 2018; Mucci et al., 2018b). Furthermore, body side-to-side oscillations frequently experienced by MdDS patients (Dai et al., 2017), could be only explained by pitch eigenvector maladaptation as is proposed in the present study. This may indicate that while passive transportation is commonly affected by roll eigenvector orientation, possible maladaptation of yaw and pitch eigenvectors should also be considered. It further suggests that either yaw, pitch, or roll OKS treatment protocol may be effective in helping alleviate some symptoms because it has alleviated the pulling sensations. This goes along with an even lower success rate of spontaneous MdDS when either eigenvector has equal chances of becoming maladapted. Thus, developing a clearer model-based analysis of postural and eye movement dynamics may lead to improved treatment protocols for yaw and pitch eigenvector readaptation that may improve treatment outcomes.

How velocity storage is realized in three dimensions is not known. However, there is evidence that velocity storage integration comes about because of interconnections across the midline as well as connections among various types of vestibular-only (VO) neurons on each side (Cohen et al., 2018). The weights of the interconnections could form a large scale recurrent neural net (Raphan et al., 2019) that implements the system matrix and encodes the eigenvectors. Early experiments from our laboratory support this idea, showing that velocity storage and its spatial properties were coded by VO neurons (Reisine and Raphan, 1992; Yakushin et al., 2017). These VO neurons had been known to receive multiple convergent inputs from various semicircular canals and otoliths (Dickman and Angelaki, 2002; Yakushin et al., 2006; Eron et al., 2008b). We recently demonstrated that cross-coupling from horizontal to vertical and roll components of VOR were also coded by canal-otolith convergent VO neurons (Yakushin et al., 2017). Polarization vectors of VO neurons are flexible and tend to align their orientation with gravity (Eron et al., 2008a, 2018), even when animals were in complete darkness without any specific training stimulus. This is distinct from polarization vectors coded by Eye-Head-Velocity (EHV) and Position-Vestibular-Pause (PVP) neurons that project to oculomotor neurons and therefore are part of the direct VOR pathway (Kolesnikova et al., 2011). There is also a distinct group of central otolith-only neurons that provide a rigid reference frame for head orientation (Schor et al., 1984, 1985; Angelaki et al., 1993). These neurons do not adapt their polarization vectors (Eron et al., 2009). Thus, the neural machinery exists that when the body is in the upright position a maladapted yaw eigenvector in MdDS patients can be misaligned with those neurons that encode the direction of gravity aligned with the yaw axis of the head.

The estimate of the direction of gravity in MdDS patients, however, largely relies on the polarization vector provided by VO neurons (the eigenvectors). The discrepancy between this estimate of gravity and the fixed co-ordinate frame provided by the otolith-only neurons could cause the sensation of gravitational pulling in that direction. A cross product, which gives the magnitude and direction of the misalignment of the vectors can also be implemented by another layer of the neural network, which gives the perception of pulling studied in this paper (**Figure 4**). We speculate that treatment with OKS has a strong corrective effect on the eigenvectors provided by VO neurons. As a result, coordinate frames provided by the two groups of neurons could be taught to align, which minimizes the sensation of gravitational pulling. In the present study, we demonstrated that exposing patients to full-field OKS that has a component whose vector is opposite to the cross product, corrects the gravitational pulling.

The majority of MdDS patients reported high sensitivity to the motion of their visual environment or to moving objects (visually induced dizziness, VID) (Dai et al., 2017; Mucci et al., 2018b). However, treatment of MdDS with readaptation of velocity storage (Dai et al., 2014, 2017) is based on patients' exposure to a full field OKS, to which patients reported discomfort. Thus, treatment time was minimized to achieve a positive effect (Yakushin et al., 2020). Determining whether a patient is actually rocking or is pulling forward or backward with postural correction can minimize treatment time and side effects. The same is true in distinguishing the difference between the lateral pull and sway. Patients frequently fail to distinguish the difference between two sensations. Static posturography is also not always reliable in making the distinction between pulling and oscillating vertigo. Furthermore, while posturography seems to be a very attractive objective measure of MdDS, this study demonstrates that subjective severity of the overall MdDS symptoms which is accepted by most clinicians and researchers does not correlate with postural improvements.

How long does it take to induce improper learning, and why does that learning last so long? Previous studies of our laboratory indicate that when angular VOR is adapted in the context of gravity over 1 h, the contextual change can be observed for several days (Yakushin et al., 2003). Other laboratories have confirmed our findings and demonstrated that long-lasting changes of gravitational context could occur within several minutes (Schubert et al., 2008). Recent studies also indicate that otolith context plays a critical role in spatial perception, and 5 min of learning could significantly affect the perception of the spatial vertical axis (Tarnutzer et al., 2013, 2014). We speculate that MdDS is another example of long-lasting learning of a gravitational context. The correction back to normal did not occur spontaneously because it required exposure to the same context. This speculation is confirmed by several patients treated in our laboratory since 2014, who reported that another air flight or boat ride cured their symptoms. We further speculate that maladapted learning occurs on the level of the brainstem. Cortical areas are also involved since the majority of MdDS patients are suffering from anxiety, depression, fatigue, head pressure and headaches, cognitive impairment, and visual disturbance (Cha et al., 2012, 2021; Cha and Chakrapani, 2015). Involvement of the cortical areas may be due to brainstem input based on the neural pathways involved during full-field OKS exposure (Dai et al., 2017).

Though the above results are promising in improving the treatment of MdDS, there were several aspects of this study that need further work. First, there was no uniform treatment protocol for each patient. As mentioned above, the protocol was adjusted depending on the patient's response. Although there was much variability, the predetermined direction of OKS based on symptoms was consistent for over $> 90\%$ of the patients with good results. Second, there was no placebo arm. However, a small subset of cases worsened when the stimulus was provided in the "wrong" direction, supporting the conclusion that the effect was more than placebo. Third, posturography, unfortunately, was not consistently performed on all patients, and subjective improvement was used as the outcome measurement. Lastly, the putative pathophysiology of MdDS in humans were based on animal studies that focused on the brainstem and cerebellum, and we cannot exclude concomitant cortical processes, which have been demonstrated in other studies (Cha and Chakrapani, 2015; Yuan et al., 2017; Cha et al., 2021). Despite these shortcomings, the study included a sound specific model as well a large number of patients with a significant response that agreed with model predictions.

Falling backwards, which could be related to a backward pulling sensation has been reported in groups of patients, including patients with cerebellar ataxia (van de Warrenburg et al., 2005). It is also well documented that backward falling is frequently reported by subjects with the bilateral vestibular loss (Ewald, 1892; Magnus, 1924). These conditions responded to treatment with upward and downward OKS (Vitte et al., 1994; Tsuzuku et al., 1995). We do not know whether OKS will provide any symptom relief in other groups of patients. However, this study clearly demonstrates that OKS alone has the potential to be a powerful tool in the correction of gravitational pulling in MdDS patients through a model-based analysis. If such treatment is useful in other diseases that manifest as gravitational pulling sensation, standardization of treatment is feasible. Further studies are required to determine the durability of the response and establish to what extent the treatment is reproducible. Thus, while there is more work to be done to develop the model and the model based analysis, the present study has established the foundation for how space and time is encoded in velocity storage through the eigenvectors and eigenvalues and how they might maladapt in diseased states. It also establishes a foundation for developing a sound protocol for alleviating pulling sensation symptoms, which do not exacerbate the MdDS problem.

## DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data are in a proprietary format (VMF) and are read only by a proprietary program written for this purpose. Requests to access these datasets should be directed to SY, sergei.yakushin@mssm.edu.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the IRB of the Mount Sinai School of Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

SY contributed to the design of the experiments, MdDS treatments, data acquisition, and writing of the manuscript. TR contributed to the conceptual framework and data analysis that allowed for the comparison of the data to model predictions and to the organization and writing of the manuscript. CC contributed to the clinical evaluation of the patients as well as the writing of the manuscript. All authors approved the submitted version.

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# Impaired Duration Perception in Patients With Unilateral Vestibulopathy During Whole-Body Rotation

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This study aimed to evaluate vestibular perception in patients with unilateral vestibulopathy. We recruited 14 patients (9 women, mean age = 59.3 ± 14.3) with unilateral vestibulopathy during the subacute or chronic stage (disease duration = 6 days to 25 years). For the evaluation of position perception, the patients had to estimate the position after whole-body rotation in the yaw plane. The velocity/acceleration perception was evaluated by acquiring decisions of patients regarding which direction would be the faster rotation after a pair of ipsi- and contra-lesional rotations at various velocity/acceleration settings. The duration perception was assessed by collecting decisions of patients for longer rotation directions at each pair of ipsi- and contra-lesional rotations with various velocities and amplitudes. Patients with unilateral vestibulopathy showed position estimates and velocity/acceleration discriminations comparable to healthy controls. However, in duration discrimination, patients had a contralesional bias such that they had a longer perception period for the healthy side during the equal duration and same amplitude rotations. For the complex duration task, where a longer duration was assigned to a smaller rotation amplitude, the precision was significantly lower in the patient group than in the control group. These results indicate persistent impairments of duration perception in unilateral vestibulopathy and favor the intrinsic and distributed timing mechanism of the vestibular system. Complex perceptual tasks may be helpful to disclose hidden perceptual disturbances in unilateral vestibular hypofunction.

**Keywords: vestibular perception, unilateral vestibulopathy, whole-body rotation, duration perception, spatial navigation**

## INTRODUCTION

The vestibular apparatus anchored in the inner ear generates neural signals related to acceleration, velocity, and duration of head motion (Angelaki and Cullen, 2008; Diaz-Artiles and Karmali, 2021). In the brain, the vestibular signals interact with other sensory cues such as vision and proprioception, thereby enabling the motion perception and spatial representation of the head

(Seemungal, 2014; Diaz-Artiles and Karmali, 2021). In addition, the vestibular signals generate ocular, spinal, and autonomic reflexes (Angelaki and Cullen, 2008; Kwon et al., 2021). Therefore, with vestibular dysfunction, the motion perception and spatial representation of the head may become disturbed along with the appearance of various clinical signs. Clinically, acute unilateral vestibulopathy is one of the most common vestibular dysfunctions. Patients usually report compelling vertigo (false motion sense) and show nystagmus, postural imbalance, and autonomic disturbances (Bronstein and Dieterich, 2019; Kim, 2020). The symptoms and signs decrease over time, but there may be substantial individual differences in the timing and extent of recovery (Best et al., 2009; Halmagyi et al., 2010). In fact, many patients have persistent dizziness and imbalance in the subacute and chronic stages, symptoms related to the vestibulo-perceptual (VP) pathway, without other objective signs in the vestibulo-ocular and vestibulo-spinal reflex pathways (Staab et al., 2017).

Hence, there have been several attempts to characterize the VP in those patients distinct from healthy individuals. In vestibular threshold tests, healthy individuals had a higher threshold for VP than for VOR (Seemungal et al., 2004). Patients with acute unilateral vestibulopathy had increased VP and VOR thresholds in the acute phase (i.e., they become less sensitive to vestibular stimulation) (Cousins et al., 2013). Both tended to recover over time, but the threshold of VP regained a symmetricity between the rotation toward the lesion side and the healthy side, while that of VOR did not (Cousins et al., 2013). In position estimation tests with rotational vestibular stimuli, healthy individuals tended to underestimate with a gain of about 0.8–0.9 (Kaski et al., 2016; Choi et al., 2021). In a similar experimental setting, patients with unilateral vestibulopathy also had a position estimate comparable to healthy individuals in both acute and chronic stages (Cohen et al., 2017). Regarding duration perception, a decreased duration perception for motion in the acute phase of unilateral vestibulopathy nearly recovered in the chronic phase (Cousins et al., 2013). These results may imply a strong resilience of the VP pathway but may not account for the long-lasting perceptual disturbance of patients with unilateral vestibulopathy, so further studies are warranted.

Patients with vestibulopathy may still have minor perceptual errors, which may have worked together with risk factors, such as visual dependence and psychological disturbances, to cause persistent vertigo (Best et al., 2009; Cousins et al., 2017). In fact, a recent study with a more complex rotational task, e.g., a repetitive asymmetric rotation task, revealed a biased spatial representation of the head (Panichi et al., 2017). On the contrary, the neural noise in VP and VOR pathways is proportional to the stimulus intensity (Nouri and Karmali, 2018). Therefore, the perceptual disturbance may partly be owed to the amplified noisy signals after recovery from illness, and this point of view highlights the need for precision evaluation for vestibular perception. Of interest, the precision of duration perception in the complex task was significantly altered, especially for elderly patients (Choi et al., 2021). However, further studies on patients with unilateral vestibulopathy are necessary to verify the explanation. In these backgrounds, this study investigated the characteristics of VP in patients with unilateral vestibulopathy after recovering from acute illness.

## MATERIALS AND METHODS

### Standard Protocol Approvals, Registrations, and Patient Consent

The Institutional Review Board of Seoul National University Bundang Hospital approved this prospective experimental study (B-1908-556-301), and written informed consent was taken from all patients before the experiment.

### Patients and Controls

From September 2019 to February 2020, we recruited 14 patients (9 women, mean age = 59.3 ± 14.3) with unilateral vestibulopathy in the subacute and chronic stages (with a symptom duration ranging from 6 to 25 years, median = 25 days). Patients underwent complete neurological and neuro-otological examinations. We defined unilateral vestibulopathy as the patients having a positive unilateral head impulse test (video head impulse gain $< 0.7$) or unilateral caloric paresis ($>20\%$ on bithermal caloric test). For the included patients, the mean ipsilesional head impulse gain was 0.60 ± 0.26, and the mean caloric paresis was 64.6% ± 30.75%. They had no abnormal symptoms or signs indicative of central nervous system disorders. All patients underwent a mini-mental state examination (mean score = 28.9 ± 1.7). The clinical characteristics of the included patients are presented in **Table 1**. For the comparison, we made a control set comprised of 14 age-matched healthy subjects evaluated with the same experimental protocols (Choi et al., 2021).

### Experimental Apparatus

For the experiments, we adopted the motorized chair, rotating at various constant velocities with 0.15 s of fixed acceleration and deceleration periods. According to the targeted velocity, the acceleration and deceleration ranged from $100°/s^2$ to $800°/s^2$. The amplitude and duration of rotation were predetermined according to the experimental paradigms, and the experimenter entirely controlled the chair.

### Tasks for Vestibular Perception

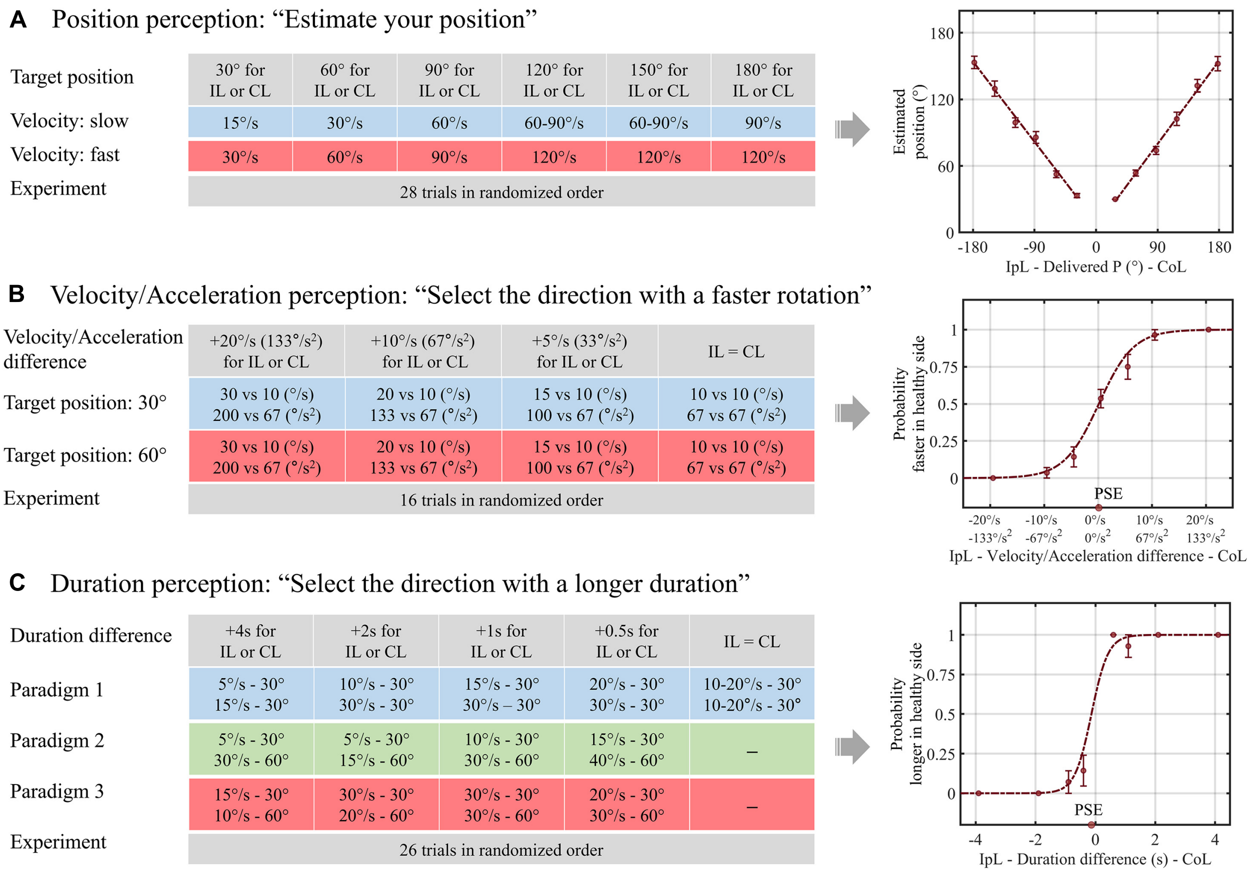
All patients sat in a chair with a safety belt fastened and underwent rotational experiments while wearing covered goggles and headphones with white noise to prevent visual and auditory cues. After receiving guidance on the method and purpose of each task, patients underwent the experiments in the order of position, velocity/acceleration, and duration tasks.

In the position task, we collected a positional estimate of the patients after whole-body rotation. The design of the position task was as follows: the amplitude of whole-body rotation was between 30° and 180° in 30° steps to the right or left, and each rotational position was delivered at two or three velocities ranging from 15 to 120°/s (**Figure 1A**). After each rotation, patients reported their estimated rotational position and then

**TABLE 1 |** Clinical characteristics of included patients.

| Patient | Age | Sex | Lesion location | Cause of vestibulopathy | Duration | Head impulse gain | | Caloric paresis |
|---|---|---|---|---|---|---|---|---|
| | | | | | | CLHC | ILHC | |
| 1 | 65 | M | Left | Vestibular schwannoma | 3 years | 1.31 | 0.58 | −68 |
| 2 | 69 | F | Left | Vestibular Neuritis | 17 days | 1.11 | 0.58 | −58 |
| 3 | 73 | M | Left | Vestibulopathy | 1 year | 0.98 | 0.36 | −100 |
| 4 | 82 | F | Left | Vestibulopathy | 6 days | 1.05 | 0.93 | −93 |
| 5 | 48 | F | Left | Vestibulopathy | 9 days | 1.16 | 0.64 | −39 |
| 6 | 72 | F | Left | Vestibulopathy | 6 days | 0.91 | 0.66 | −9 |
| 7 | 59 | M | Left | Vestibulopathy | 3 months | 0.88 | 0.43 | −100 |
| 8 | 65 | F | Left | Vestibular schwannoma | 5 years | 1.06 | 1.01 | −49 |
| 9 | 48 | M | Right | Vestibular Neuritis | 1 month | 0.71 | 0.31 | N/A |
| 10 | 40 | F | Left | Vestibulopathy | 6 months | 1.18 | 1.14 | −41 |
| 11 | 69 | F | Left | Vestibulopathy | 14 days | 0.96 | 0.29 | −89 |
| 12 | 30 | F | Left | Vestibular Neuritis | 7 days | 0.89 | 0.44 | N/A |
| 13 | 55 | F | Left | CPA tumor | 15 days | 0.85 | 0.65 | N/A |
| 14 | 55 | M | Left | Vestibulopathy | 25 years | 0.90 | 0.40 | N/A |

*N/A, data not available; CPA, cerebellopontine angle; CLHC, contralesional horizontal canal; ILHC, ipsilesional horizontal canal. A negative value in caloric paresis indicates left side caloric paresis, whereas a positive one refers to right side caloric paresis.*



| | | | | | | |
|---|---|---|---|---|---|---|
| Target position | 30° for IL or CL | 60° for IL or CL | 90° for IL or CL | 120° for IL or CL | 150° for IL or CL | 180° for IL or CL |
| Velocity: slow | 15°/s | 30°/s | 60°/s | 60-90°/s | 60-90°/s | 90°/s |
| Velocity: fast | 30°/s | 60°/s | 90°/s | 120°/s | 120°/s | 120°/s |
| Experiment | 28 trials in randomized order | | | | | |

| | | | | |
|---|---|---|---|---|
| Velocity/Acceleration difference | +20°/s (133°/s$^2$) for IL or CL | +10°/s (67°/s$^2$) for IL or CL | +5°/s (33°/s$^2$) for IL or CL | IL = CL |
| Target position: 30° | 30 vs 10 (°/s)<br>200 vs 67 (°/s$^2$) | 20 vs 10 (°/s)<br>133 vs 67 (°/s$^2$) | 15 vs 10 (°/s)<br>100 vs 67 (°/s$^2$) | 10 vs 10 (°/s)<br>67 vs 67 (°/s$^2$) |
| Target position: 60° | 30 vs 10 (°/s)<br>200 vs 67 (°/s$^2$) | 20 vs 10 (°/s)<br>133 vs 67 (°/s$^2$) | 15 vs 10 (°/s)<br>100 vs 67 (°/s$^2$) | 10 vs 10 (°/s)<br>67 vs 67 (°/s$^2$) |
| Experiment | 16 trials in randomized order | | | |

| | | | | | |
|---|---|---|---|---|---|
| Duration difference | +4s for IL or CL | +2s for IL or CL | +1s for IL or CL | +0.5s for IL or CL | IL = CL |
| Paradigm 1 | 5°/s - 30°<br>15°/s - 30° | 10°/s - 30°<br>30°/s - 30° | 15°/s - 30°<br>30°/s – 30° | 20°/s - 30°<br>30°/s - 30° | 10-20°/s - 30°<br>10-20°/s - 30° |
| Paradigm 2 | 5°/s - 30°<br>30°/s - 60° | 5°/s - 30°<br>15°/s - 60° | 10°/s - 30°<br>30°/s - 60° | 15°/s - 30°<br>40°/s - 60° | – |
| Paradigm 3 | 15°/s - 30°<br>10°/s - 60° | 30°/s - 30°<br>20°/s - 60° | 30°/s - 30°<br>30°/s - 60° | 20°/s - 30°<br>30°/s - 60° | – |
| Experiment | 26 trials in randomized order | | | | |

**FIGURE 1 |** Schematics of the experimental design and data analysis for vestibular perception. **(A)** In paradigm 1 of the duration task, the duration difference was created by delivering equal amplitude rotations with different velocities. In paradigms 2 **(B)** and 3 **(C)**, longer and shorter rotation durations were assigned for larger rotational amplitudes, respectively. IpL, ipsilesional; CoL, contralesional; P, position; PSE, point of subjective equality.

passively returned to the initial position. There was a 30-s pause between each rotation to prevent the effect of post-rotational cues. All patients were given a practice trial for six rotational positions, with rotations ranging from 30° to 180° in 30° steps. For each practice rotation, patients had auditory feedback on their estimates. Then, each patient underwent 28 rotations without feedback in random order during the position task.

In the velocity/acceleration task, we acquired patients' choices about the direction of the faster rotation after a pair of left-right rotations. The patients were rotated either rightward or leftward, returned to the initial position, and then rotated in the opposite direction. The rotation velocity was 10, 15, 20, or 30°/s for one direction and 10°/s for the other direction, thereby creating velocity differences of 0, 5, 10, and 20°/s. After each pairwise rotation, the participants reported the "faster" direction. In our experiment, the target velocity reached 0.15 s, so the acceleration was proportional to the velocity. We named it the velocity/acceleration task because it was unclear whether the participants used the velocity or acceleration cues to determine the faster direction. We performed this task at two different rotation amplitudes, namely, small (30°) and large (60°). After two practice trials with feedback for correctness, patients underwent 16 experimental trials without feedback (**Figure 1B**).

In the duration task, the patients reported the direction of the longer rotation after a pair of left-right rotations. The differences in rotation duration were 0, 0.5, 1, 2, and 4 s. In addition, as introduced in the previous study, we adopted three different paradigms to evaluate whether the interaction between the amplitude and duration of motion would change the duration perception. Therefore, in a pair of left-right rotations of paradigm 1, we applied the same amplitude rotation with different velocities to create a difference in duration. In paradigm 2, we adopted different velocities and amplitudes to assign longer rotation durations for smaller rotational amplitudes, e.g., 0.5 s longer for the rightward rotation was designed by applying 30° rightward rotation at a velocity of 15°/s and 60° leftward rotation at a velocity of 40°/s. Finally, in paradigm 3, we assigned a longer rotation duration to the larger rotational amplitude, e.g., 0.5 s longer for rightward rotation of 60° at a velocity of 30°/s and leftward rotation of 30° at a velocity of 20°/s. Patients had six practice trials with auditory feedback for the duration perception and underwent 26 experimental trials without feedback (**Figure 1C**).

## Data Management and Statistical Analyses

To investigate the perceptual characteristics of the patient group, we merged the patient data with age-matched control data and treated the group (patients vs. control) as a nominal variable. Due to the limited number of rotations per given stimulus, we analyzed the relationship between actual stimuli and the perceptual responses *via* a generalized linear model (GLM) using pooled group data. In the position data analysis, we adopted a GLM with a linear fit. The slope of regression, β, represents the change of the position estimate in response to a change in the actual stimulus. We compared β during ipsi- and contralesional rotations between the patient and control groups.

In contrast, for the velocity/acceleration and duration tasks, we used a GLM with a logit fit. The intercept value of the regression equation represents the probability of selecting "contralesional rotation was faster or longer" in the rotation without a velocity/acceleration or duration difference between ipsi- and contralesional rotations. β is the change in the logarithm of the odds, $\ln(p/1-p)$ in response to the velocity/acceleration or duration difference change. Therefore, the ideal intercept and β values indicate the accuracy and precision of the discriminative ability. Specifically, we analyzed the duration task through two statistical models. Model 1 included only the duration difference (actual stimulus) and group (patient vs. control) as variables, whereas Model 2 further included the velocity difference, creating the duration difference. A $p$-value of less than 0.05 was defined as the level of statistical significance. For the multiple comparisons, we set the $p$-value using the Bonferroni correction.

# RESULTS

## Position Task

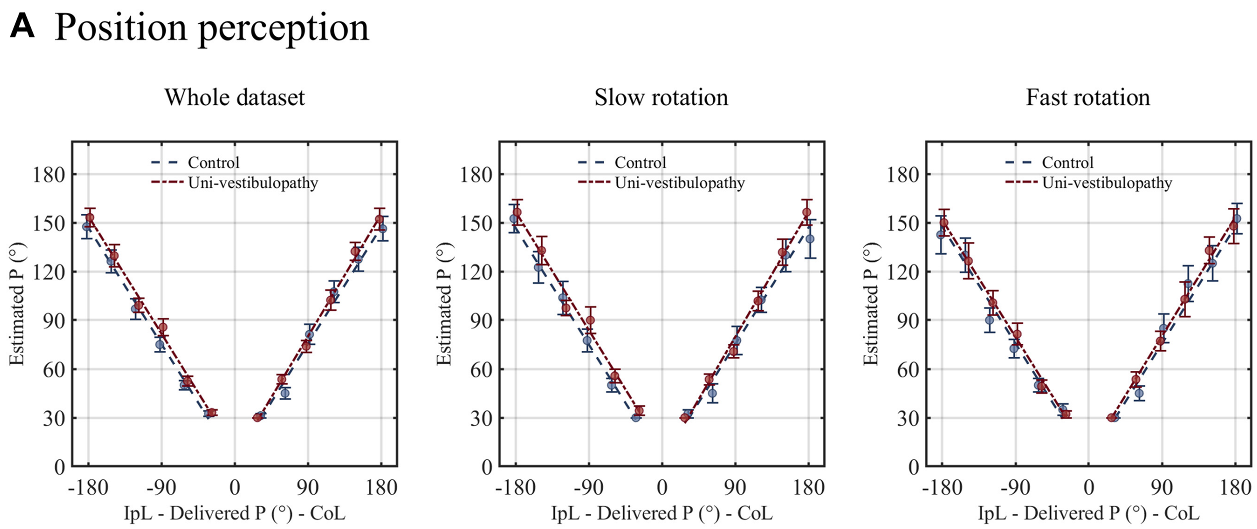
The results of the position task are presented in **Figure 2**. For the whole dataset, the GLM with linear fit showed that the regression slope of the patient group was 0.81 for ipsilesional rotation and 0.83 for contralesional rotation. Compared with the control group, the regression slope was not different regardless of the rotational direction ($p$-values for ipsilesional and contralesional rotation were 0.53 and 0.47, respectively). This pattern was reaffirmed in the subgroup analyses according to the adopted velocity (slow vs. fast) for rotation. The regression slopes during the slow or fast rotation paradigm were not different between the patient and control groups, irrespective of the rotational direction (all $p > 0.05$).

## Velocity/Acceleration Task

The results of this task are presented in **Figure 3**. The GLM with a logit fit for the whole dataset showed that the intercept and β values were −0.04 (−0.48–0.40) and 0.31 (0.21–0.41), respectively. Hence, the probability of selecting "contralesional rotation was faster" was 0.49 (0.38–0.60) when equal velocity/acceleration was applied in both directions. The intercept and β values were not different from those of the control group ($p$ = 0.48 and 0.12). The findings were similar in small and large amplitudes of rotation (intercept = 0 and –0.09; β = 0.27 and 0.38), which were not different from the control group (all $p > 0.05$).

## Duration Task

The results of the duration task are presented in **Figure 4** and **Table 2**. In statistical model 1 for the whole dataset, an intercept was 0.26 (0.01–0.51), and the β value was 0.46 (0.33–0.60). The probability of selecting "contralesional rotation was longer" was estimated to be 0.57 (0.50–0.63) when equal velocity was applied in both directions. Statistically, the intercept tended to be different from that of the control group ($p$ = 0.08), while the β value was significantly lower than that of the control



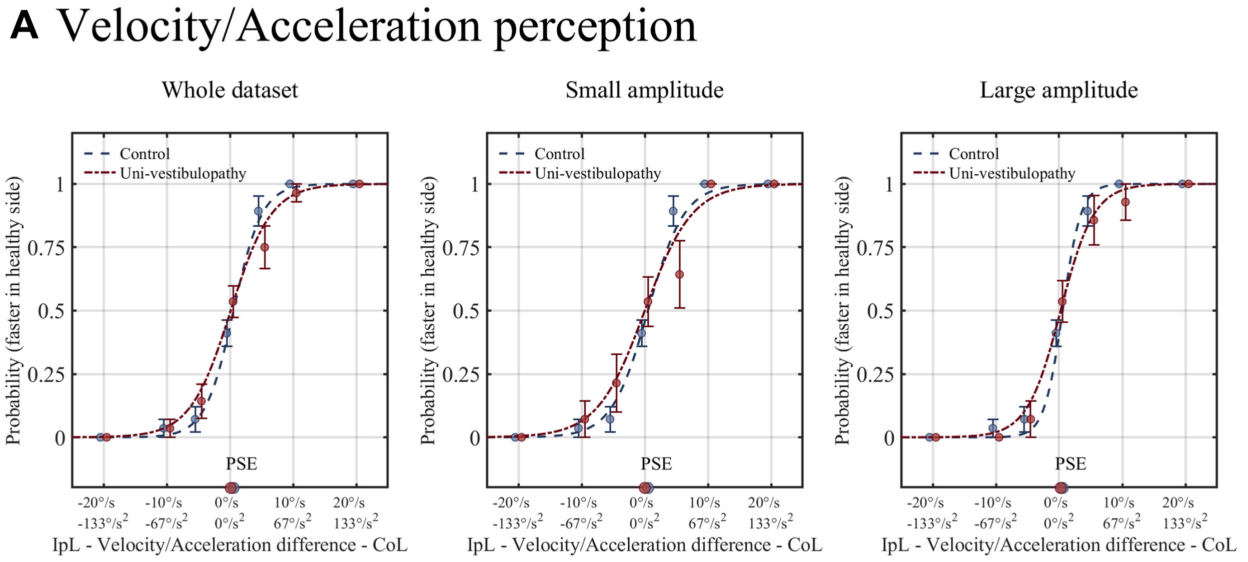
**B** Statistical results

| | Patients | Controls | *P* |
|---|---|---|---|
| Whole dataset | | | |
| *Ipsilesional β* | 0.81 (0.75 - 0.86) | 0.78 (0.72 - 0.84) | 0.527 |
| *Ipsilesional intercept* | 7.75 (1.19 - 14.31) | 6.39 (-0.16 - 12.95) | 0.763 |
| *Contralesional β* | 0.83 (0.78 - 0.89) | 0.81 (0.75 - 0.86) | 0.468 |
| *Contralesional intercept* | 3.18 (-3.00 - 9.36) | 5.07 (-1.11 - 11.25) | 0.656 |
| Slow rotation | | | |
| *Ipsilesional β* | 0.81 (0.73 - 0.89) | 0.81 (0.73 - 0.89) | 1.000 |
| *Ipsilesional intercept* | 9.50 (-0.21 - 19.21) | 5.21 (-4.50 - 14.92) | 0.492 |
| *Contralesional β* | 0.86 (0.77 - 0.94) | 0.79 (0.71 - 0.88) | 0.293 |
| *Contralesional intercept* | 0.93 (-9.43 - 11.29) | 5.57 (-4.79 - 15.93) | 0.486 |
| Fast rotation | | | |
| *Ipsilesional β* | 0.80 (0.72 - 0.88) | 0.75 (0.67 - 0.83) | 0.364 |
| *Ipsilesional intercept* | 6.00 (-3.69 - 15.69) | 7.57 (-2.12 - 17.26) | 0.798 |
| *Contralesional β* | 0.81 (0.72 - 0.90) | 0.82 (0.73 - 0.91) | 0.885 |
| *Contralesional intercept* | 5.43 (-5.00 - 15.86) | 4.57 (-5.86 - 15.00) | 0.897 |

**FIGURE 2 |** The results of the position task. **(A)** The results from the patient group (red line) are presented above the regression results from the age-matched control group (blue line). **(B)** The results of statistical analyses performed for the position task. Statistical analyses were performed using the generalized linear model with a linear fit. For clarity, the statistical model presented in this figure did not include velocity covariates. β indicates the change in the position estimate in response to the change in the actual stimulus. The intercept value indicates the static positional bias. IpL, ipsilesional; CoL, contralesional.

group ($p$ = 0.003). In addition, the regression results differed significantly by the experimental paradigm.

In paradigm 1, where the velocity difference created the duration difference, the patient group showed a significantly different intercept from the control (0.85 vs. −0.15, $p$ = 0.008), while the β value did not ($p$ = 0.07). Hence, the patient group had a higher probability of selecting "contralesional rotation was longer" than the control group when equal velocity was applied in both directions (0.70 vs. 0.44). In paradigm 2, where a longer duration was assigned to rotation with a small amplitude, the patient group showed an intercept similar to the value of the control group ($p$ = 0.68), while the β value significantly differed ($p$ = 0.008). The regression slope was inverse of the control group (−0.09 vs. 0.23), indicating that patients with subacute and chronic unilateral vestibulopathy had a loss of precision in estimating duration differences. In paradigm 3, where a longer



**B** Statistical results

| | Patients | Controls | *P* |
|---|---|---|---|
| Whole dataset | | | |
| *β* | 0.31 (0.21 - 0.41) | 0.44 (0.29 - 0.60) | 0.119 |
| *Intercept* | -0.04 (-0.48 - 0.40) | -0.26 (-0.75 - 0.24) | 0.481 |
| Small amplitude | | | |
| *β* | 0.27 (0.13 - 0.41) | 0.35 (0.16 - 0.54) | 0.375 |
| *Intercept* | 0.00 (-0.70 - 0.70) | -0.18 (-0.94 - 0.59) | 0.663 |
| Large amplitude | | | |
| *β* | 0.38 (0.17 - 0.59) | 0.69 (0.18 - 1.20) | 0.152 |
| *Intercept* | -0.09 (-0.87 - 0.69) | -0.38 (-1.32 - 0.55) | 0.539 |

**FIGURE 3 |** The results of the velocity/acceleration task. **(A)** The results from the patient group (red line) are presented above on the regression results from the age-matched control group (blue line). **(B)** The results of statistical analyses for the velocity/acceleration task. Statistical analyses were performed using the generalized linear model with logit fit. IpL, ipsilesional; CoL, contralesional; PSE, point of subjective equality, which is the stimulus amplitude that corresponds to the 0.5 probability point.

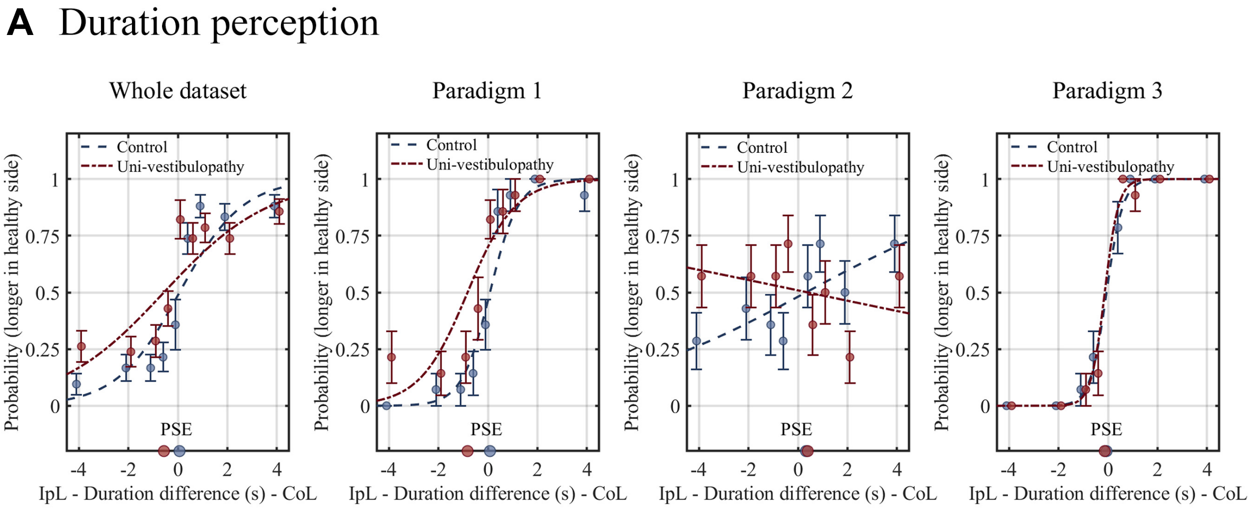
duration was assigned to rotation with a large amplitude, the intercept and β values were similar between the patient and control groups. In addition, the tendency to increase precision compared to paradigm 1 was also similar between groups.

Statistical model 2, which included velocity differences (ranged from −25°/s to + 25°/s) as a covariate, showed similar results to Model 1, except for paradigm 1, where velocity difference was found to dominate the duration perception (**Table 2**).

## DISCUSSION

This study evaluated position, velocity/acceleration, and duration perception during whole-body rotation in patients with subacute and chronic unilateral vestibulopathy. There were two main observations.

The first observation was that the patient group showed normal position and velocity/acceleration perception. A previous experiment with repetitive rotations from 90° to 360° with a 90° interval showed that patients with acute and chronic unilateral vestibulopathy had intact position estimates in ipsilesional and contralesional rotations (Cohen et al., 2017). Therefore, the position estimation in this study using more fractionalized intervals reaffirmed the previous findings. Regarding velocity/acceleration perception, the threshold testing with a stepwise rotational velocity increasing paradigm revealed that patients with acute unilateral vestibulopathy recovered the sensitivity only when the vestibular loss was mild (Cousins et al., 2013). However, both in mild and severe cases of



**B** Statistical results

| | Patient | Control | *P* |
|---|---|---|---|
| Whole dataset | | | |
| *β** | 0.46 (0.33 - 0.60) | 0.79 (0.60 - 0.97) | 0.003 |
| *Intercept* | 0.26 (0.01 - 0.51) | -0.05 (-0.33 - 0.22) | 0.078 |
| Paradigm 1 | | | |
| *β* | 1.03 (0.56 - 1.5) | 1.76 (0.95 - 2.57) | *0.067* |
| *Intercept* * | 0.85 (0.25 - 1.45) | -0.15 (-0.79 - 0.5) | 0.008 |
| Paradigm 2 | | | |
| *β** | -0.09 (-0.3 - 0.11) | 0.23 (0.02 - 0.45) | 0.008 |
| *Intercept* | 0.04 (-0.43 - 0.5) | -0.08 (-0.56 - 0.4) | 0.680 |
| Paradigm 3 | | | |
| *β* | 3.6 (1.64 - 5.55) | 3.03 (1.48 - 4.57) | 0.575 |
| *Intercept* | 0.47 (-0.77 - 1.72) | 0.18 (-0.87 - 1.24) | 0.663 |

**FIGURE 4 |** The results of the duration task. **(A)** The results from the patient group (red line) are presented above the regression results from the age-matched control group (blue line). **(B)** The results of statistical analyses for the duration task. Statistical analyses were performed using the generalized linear model with logit fit. For clarity, the statistical model presented in this figure did not include velocity covariates. An asterisk (*) indicates the parameters with statistical significance. The level of statistical significance was set at 0.05 for the whole dataset and 0.0167 for the paradigms 1–3. IpL, ipsilesional; CoL, contralesional; PSE, point of subjective equality, which is the stimulus amplitude that corresponds to the 0.5 probability point.

vestibular loss, the asymmetry of velocity perception disappeared at the chronic stage (Cousins et al., 2013). The finding was also consistent with the results in this study's discriminative velocity/acceleration task.

Of interest, the VOR pathway remained compromised in previous and current studies (Cousins et al., 2013; Cohen et al., 2017), which could support that the recovery of the VP pathway is more robust than that of the VOR pathway. The VP and VOR pathways have been known to share a velocity storage circuit (Bertolini et al., 2012). The similarity between VP and VOR imprecision, known to be proportional to stimulus intensity, is another piece of evidence to support a common neural pathway (Nouri and Karmali, 2018). Therefore, the dissociation between the VP and VOR pathways suggests that the perceptual pathway may have additional compensatory neural connections above the brainstem level. In fact, the parietoinsular cortex, the area for vestibular motion perception (Ventre-Dominey, 2014), forms diverse reciprocal connections with cortical and

**TABLE 2 |** Statistical analyses for duration perception.

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | **β with 95% CI** | ***P*** | **β with 95% CI** | ***P*** |
| Whole dataset | | | | |
| Intercept | −0.05 (−0.32–0.21) | 0.691 | −0.09 (−0.37–0.20) | 0.544 |
| Group (control to patients) | 0.31 (−0.05–0.67) | 0.079 | 0.31 (−0.05–0.67) | 0.085 |
| ΔDuration | 0.79 (0.61–0.97) | <0.001 | 0.85 (0.64–1.05) | <0.001 |
| ΔVelocity | | | −0.01 (−0.03–0.00) | 0.127 |
| Group× Δduration | −0.32 (−0.54–−0.10) | 0.003 | −0.34 (−0.56–−0.11) | 0.003 |
| ΔDuration× Δvelocity | | | 0.00 (−0.01–0.01) | 0.519 |
| Paradigm 1† | | | | |
| Intercept | −0.15 (−0.73–0.44) | 0.589 | −0.28 (−1.03–0.46) | 0.405 |
| Group (control to patients) | 0.99 (0.20–1.79) | 0.008 | 1.29 (0.32–2.27) | 0.004 |
| ΔDuration | 1.76 (1.02–2.49) | <0.001 | 0.54 (−0.05–1.14) | 0.047 |
| ΔVelocity | | | 0.13 (0.07–0.18) | <0.001 |
| Group× Δduration | −0.73 (−1.58–0.12) | 0.067 | −0.16 (−0.82–0.49) | 0.588 |
| ΔDuration× Δvelocity | | | 0.01 (−0.02–0.05) | 0.514 |
| Paradigm 2 | | | | |
| Intercept | −0.08 (−0.50–0.35) | 0.696 | −0.19 (−0.75–0.38) | 0.455 |
| Group (control to patients) | 0.11 (−0.48–0.71) | 0.680 | 0.11 (−0.50–0.72) | 0.697 |
| ΔDuration | 0.23 (0.04–0.43) | 0.008 | 0.23 (−0.02–0.47) | 0.040 |
| ΔVelocity | | | 0.00 (−0.02–0.02) | 0.907 |
| Group× Δduration | −0.33 (−0.59–−0.06) | 0.007 | −0.33 (−0.60–−0.06) | 0.007 |
| ΔDuration× Δvelocity | | | 0.00 (−0.01–0.02) | 0.483 |
| Paradigm 3 | | | | |
| Intercept | 0.18 (−0.76–1.12) | 0.671 | 0.20 (−0.95–1.35) | 0.704 |
| Group (control to patients) | 0.29 (−1.16–1.74) | 0.663 | 0.30 (−1.22–1.83) | 0.657 |
| ΔDuration | 3.03 (1.65–4.40) | <0.001 | 2.86 (1.40–4.31) | <0.001 |
| ΔVelocity | | | 0.03 (−0.08–0.13) | 0.572 |
| Group× Δduration | 0.57 (−1.64–2.78) | 0.575 | 0.53 (−1.64–2.69) | 0.589 |
| ΔDuration× Δvelocity | | | −0.00 (−0.20–0.20) | 0.983 |

*We adopted a generalized linear model with a logit fit for the statistical analyses. In model 1, the included variables were the group (control vs. patient) and duration difference (Δ) with an interaction term. In model 2, velocity difference (Δ) was also included as a covariate.*

*† Note that statistical model 2 in paradigm 1 showed the Δvelocity had the most significant p-value, indicating the duration perception depends on Δvelocity rather than Δduration. In contrast, Δvelocity was revealed not to affect the duration perception in other paradigms. The level of statistical significance was set at 0.05 for the whole dataset and 0.0167 for paradigms 1–3, according to Bonferroni correction.*

subcortical structures and the contralateral cortex (Brandt et al., 2012; Kirsch et al., 2016), which could play a compensatory role (Dieterich and Brandt, 2015).

The second finding was impaired duration discrimination in the patient group. A previous experiment quantitatively evaluating the duration perception reported a robust resilience of duration perception in patients with unilateral vestibulopathy. Unlike the VOR, the duration perception maintained the symmetricity of duration perception in acute and chronic stages (Cousins et al., 2013). However, our result in paradigm 1 of the duration task in which the velocity difference created the duration difference was different. The probability of selecting "contralesional rotation was faster" was about 0.7 when the duration difference did not exist, suggesting significant inaccuracy in duration perception. In the complex task, where the longer duration rotation was assigned to a larger rotation amplitude (paradigm 3), the duration perception became more precise, as in the control group. However, in the task where the longer duration was assigned to a smaller rotation amplitude (paradigm 2), the precision was significantly lower and worsened than in the control group. Hence, our findings suggest that patients with subacute to chronic unilateral vestibulopathy have an impaired perception of duration in terms of accuracy and precision.

Of interest, there was a noticeable effect of velocity difference or position amplitude in the duration task. The velocity difference was the main factor dominating the duration perception of paradigm 1. The impairment and improvement of duration discrimination in paradigms 2 and 3 would also reflect the effect of position amplitude. These results imply a mathematical equation-like relationship between perceptions of position, velocity, and duration and suggest a duration task's usefulness in assessing all elements of vestibular perception.

There may be an argument that the findings discussed thus far conflict. Since the temporoparietal cortex has been suggested to compute position from the velocity and duration signals (Kaski et al., 2016), the position estimate cannot be accurate in the impaired duration perception. However, in this study, position perception was evaluated semi-quantitatively, while duration and velocity/acceleration perceptions were evaluated by forced binary choice. Therefore, the errors in the duration perception observed in this study may have been insufficient to cause errors in the positional estimation. In fact, the contralesional duration bias with intact velocity/acceleration perception in this study can explain the contralesional positional bias reported in more complex tasks, such as the repetitive asymmetric rotation paradigm (Panichi et al., 2017).

Clinically, patients with chronic unilateral vestibulopathy often have reported isolated dizziness and spatial misperception without a false motion sense (Bisdorff et al., 2009). Because duration errors without velocity/acceleration misperception can lead to spatial misperception, the study findings may be partly meaningful in interpreting the dizzy symptoms. Although we did not evaluate the velocity and duration perceptions in the same way, there may be a way to determine the error in velocity perception. In that case, we may explain patients with a false motion sense without other signs. Additionally, in this context, different experimental paradigms may also be required to evaluate the VP pathway, like complex VOR testing (e.g., head shaking and skull vibration maneuvers), adopted to reveal the hidden imbalances (Koo et al., 2011; Choi et al., 2016).

Finally, in the previous study on normal subjects, the duration perception was changeable, especially in the elderly, according to the interaction between the amplitude and duration of motion (Choi et al., 2021). This finding may favor the existence of an intrinsic timing mechanism distributed in the vestibular system (Burr et al., 2007) and explain the higher prevalence of dizziness (spatial disorientation without a sense of false motion) in the elderly (Furman et al., 2010). Furthermore, a recent study with the neuropsychological vertigo inventory showed that patients with vestibular disorders had impaired time perception (Xie et al., 2021). Therefore, the altered accuracy (contralesional bias) and precision in duration perception among patients with unilateral vestibulopathy may further support the intrinsic and distributed timing mechanism of the vestibular system.

Our study had several limitations. First, the suprathreshold acceleration could affect vestibular perception. Though the acceleration period adopted in our experiments was set at 0.15 s, the short duration of rotation (e.g., 1 s rotation) would not be completely free from the effect. Second, this study had a small sample size, so further studies must verify our result. Third, we analyzed the regression fit based on the group data due to limited rotation trials per given stimuli. Though we fitted the regression after averaging the response (probability) at each given stimulus first to minimize the large and abnormal effects of a few subjects with poor performance, the results are limited for application to individual patients with vestibular pathology. Further study will be needed to identify and characterize the impaired vestibular perception in vestibulopathy at the individual level. Fourth, the finding could not reflect the specific disease condition because we included patients with variable disease duration and etiology. We can also test our paradigm in the acute and recovery stages of vestibulopathy in future studies. Finally, in the position task, we guided participants to report position estimates at 30° intervals. This prior information may have affected the position estimates and masked small biases in patients. In addition, the simplicity of rotational stimuli could not reveal a small bias. Likewise, the simple velocity/acceleration task protocol might have been insufficient to discover the hidden bias of velocity perception. The rotation signal decays over time despite the velocity-storage compensation. In the velocity/acceleration task, the vestibular signal from low-velocity rotations (10°/s for 30° and 60°) attenuated more than for high-velocity rotations, so participants would have been able to discern the velocity difference more easily. Therefore, developing and applying a more complex protocol in the position and velocity/acceleration tasks is required.

## CONCLUSION

Vestibular perception may be persistently impaired in the duration domain in patients with unilateral vestibular hypofunction, even when the other domains, such as position and velocity/acceleration perception, remain intact. Complex perceptual tasks may disclose the hidden errors of vestibular perception and partly account for persistent perceptual disturbances in patients with unilateral vestibular hypofunction.

## 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/s.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1908-556-301). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

EK analyzed, interpreted the data, and wrote the manuscript. J-YL, J-MS, H-JK, and J-HL performed the experiments and collected the data. J-YC and J-SK designed, conceptualized the study, interpreted the data, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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# Acute unilateral vestibular neuritis contributes to alterations in vestibular function modulating circumvention around obstacles: A pilot study suggesting a role for vestibular signals in the spatial perception of orientation during circumvention

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**Background:** Walking among crowds avoiding colliding with people is described by patients with vestibular disorders as vertigo-inducing. Accurate body motion while circumventing an impeding obstacle in the gait pathway is dependent on an integration of multimodal sensory cues. However, a direct role of vestibular signals in spatial perception of distance or orientation during obstacle circumvention has not been investigated to date.

**Materials and methods:** We examined trunk yaw motion during circumvention in patients with acute unilateral vestibular loss (aUVL) and compared their results with age-matched healthy controls (HCs). Subjects performed five gait tasks with eyes open two times: walk 6 m in total, but after 3 m, circumvent to the left or right, as closely as possible, a cylindrical obstacle representing a person, and then veer back to the original path; walk 6 m, but after left and right circumvention at 3 m, veer, respectively, to the right, and left 45 deg; and walk 6 m without circumvention. Trunk yaw angular velocities (YAVs) were measured using a gyroscope system.

**Results:** Yaw angular velocity peak amplitudes approaching to, and departing from, the circumvented object were always greater for patients with aUVL compared to HCs, regardless of whether passing was to the aUVLs' deficit or normal side. The departing peak YAV was always greater, circa 52 and 87%, than the approaching YAV for HCs when going straight and veering 45 deg ($p \leq 0.0006$), respectively. For patients with aUVL, departing velocities were marginally greater (12%) than approaching YAVs when going straight ($p < 0.05$) and were only 40% greater when veering 45 deg ($p = 0.05$). The differences in departing YAVs resulted in significantly lower trajectory-end yaw angles for veering trials to the deficit side in patients with aUVL (34 vs. 43 degs in HCs).

**Conclusion:** The results demonstrate the effects of vestibular loss on yaw velocity control during the three phases of circumvention. First, approaching an obstacle, a greater YAV is found in patients with aUVL. Second, the departing YAV is found to be less than in HCs with respect to the approaching velocity, resulting in larger deficit side passing yaw angles. Third, patients with UVLs show yaw errors returning to the desired trajectory. These results could provide a basis for rehabilitation protocols helping to avoid collisions while walking in crowded spaces.

KEYWORDS

**vestibular loss, object circumvention, vestibular-spinal reflex, spatial orientation, vestibular-ocular reflex**

## Introduction

Walking and navigating among crowds require accurate estimates of one's own position and angular orientation in space, as well as the associated velocities, relative to those of other people standing or moving nearby (Olivier et al., 2013).

Walking among crowds trying to avoid colliding with people is described by patients with vestibular disorder as vertigo-inducing. This is one particular situation where 45% of patients with chronic vestibular disorders, as reported by several clinical centers, noted difficulties with (Whitney et al., 2016), presumably for three reasons: First, finely controlled trunk yaw angular rotations of the patients and linear distances to the obstacle are required to avoid bumping into someone (Vallis and McFadyen, 2003; Olivier et al., 2013); second, the head and trunk rotate in phase (Vallis and McFadyen, 2003), permitting easier use of the lateral semi-circular canal signals to control trunk velocities; third, compounding the first two reasons because the lateral vestibular semi-circular responses providing yaw control signals are more commonly affected by acute unilateral vestibular neuritis than the vertical canals (Allum and Honegger, 2020a).

It has been suggested that when avoiding an obstacle in the gait path, a new trajectory is accomplished by first turning the head in yaw motion, followed by a yaw and roll motion of the trunk (Patla et al., 1999; Hollands et al., 2001). However, Vallis and McFadyen (2003) found no difference in the onset of trunk and head motion in yaw during circumvention. Furthermore, they found no change in roll motion during circumvention with respect to control trials (no obstacle avoidance). These authors argued that moving the head and trunk segments together simplified the control task for the CNS and reduced the risk of unstable veering behavior. Restricting the degrees of freedom in the yaw plane would have a major advantage for "top-down" sensory integration: First, the peripheral vestibular sensory deficit caused by vestibular neuritis is predominant in the yaw plane (Taylor et al., 2016; Allum and Honegger, 2020a) and would presumably benefit from such a restriction and, second, allow top-down higher order compensation for the dynamic VOR imbalance *via* gaze control of the visual system (Robins and Hollands, 2017). Also, the vestibular deficit could then presumably be more easily compensated for at the level of the brainstem mediated by higher cortical network structures involved in spatial orientation (Lopez et al., 2012; Huang et al., 2015; Kaski et al., 2016), apart from brainstem circuits acting directly to compensate for VOR asymmetries.

Bearing these sensory integration and central compensation processes in mind, it is noteworthy that the effects that peripheral vestibular loss would have on object circumvention have not been investigated to date. In fact, most investigations into the effect of vestibular loss on postural control have either been restricted to the pitch and roll planes (Carpenter et al., 2001; Matjačić et al., 2001; Allum and Adkin, 2003; Allum et al., 2008; Sienko et al., 2012) or been involved with fixed angular turns in the yaw direction (Glasauer et al., 2002; Péruch et al., 2006), whereas circumvention involves continuous turning in the yaw plane ((Vallis and McFadyen, 2003; **Figure 1**). Nonetheless, Glasauer et al. (2002) and Péruch et al. (2006) did establish that subjects with vestibular loss had difficulty judging the required turn angle on triangular gait courses when blindfolded. Based on the notion, vestibular loss might provide crucial information on the vestibular-based perception of yaw motion when walking in crowds, we investigated the effect of this loss on circumvention yaw plane motion in patients with acute unilateral vestibular loss by comparing instability of these patients with yaw motion of age-matched healthy control subjects. We specifically included patients with acute vestibular neuritis for the study as these patients generally do

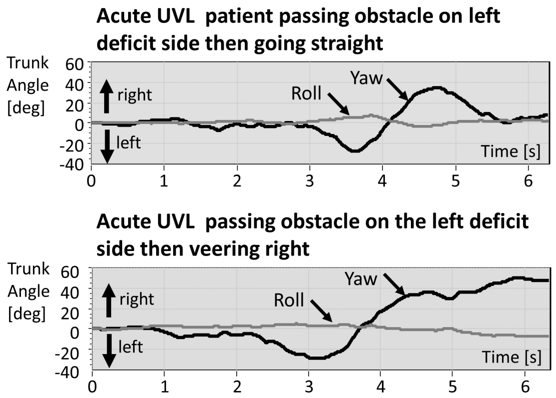

FIGURE 1
Example traces of trunk yaw and roll of a patient with acute unilateral vestibular loss (aUVL) walking straight **(upper traces)** and veering right **(lower traces)**. The obstacle is passed at approximately 4 s after the start of the recording. Rightward deflections of the yaw traces about a vertical axis perpendicular to the transverse plane are plotted positive, and leftward deflections are plotted negative. Likewise, rightward deflections of the roll traces about horizontal axis perpendicular to the frontal plane are plotted positive, and leftward deflections are plotted negative. Note the amplitudes of roll are smaller than those of yaw angles.

not have preceding vestibular problems such as those with a neurectomy to alleviate intractable Meniere's disease (e.g., see Péruch et al., 2006) or those with a cerebellar pontine angle tumor (e.g., see Glasauer et al., 2002). All three groups of patients do, however, have an ipsi-deficit dynamic vestibular ocular reflex (VOR) loss, which can be identified using video head impulse tests (vHITs), and a static imbalance present as a spontaneous nystagmus (Halmagyi et al., 1990; Taylor et al., 2015; Allum and Honegger, 2020a).

Given that deficits in roll (VOR) responses measured by vHITs are weakly correlated ($R \leq 0.55$) with deficits in roll postural control and less well correlated for deficits in pitch postural control (Allum and Honegger, 2020b), we were particularly interested in whether, in addition, a new test of vestibulo-spinal function encompassing the yaw direction could result from a study of vestibular loss on circumvention trunk responses. Thus, we also examined, for example, as control conditions, whether yaw plane instability was greater or less than that obtained with walking while rotating the head side-to-side or during normal walking.

It should be borne in mind that the current study of object circumvention (see **Figure 2**) is a simplified version of the real-life crowd situation, where two persons walking toward one another interact to control the timing and space between themselves when passing one another. Nonetheless, in the real-life and simplified versions, linear and angular measures must be perceived and controlled to avoid a possible collision. Thus, the minimum linear predicted distance between the middle of the shoulders of each person (Olivier et al., 2013) and the yaw angle of the trunk must be controlled so that the shoulders do not touch. This report is focused on yaw angular velocities during circumvention.

# Materials and methods

## Subjects

Patient data collected at the Division of Neuro-otology and Audiology, ORL Clinic, at the University Hospital Basel, were examined retrospectively for this study, which was approved by the Ethics Committee of Northwest and Central Switzerland (EKNZ), approval 2014-026, principal investigator JHJ Allum. A total of four male subjects with a mean age of 60.2 ± 16.4 (±sd) years with acute unilateral peripheral vestibular loss (aUVL) were selected on the basis of a loss greater than 75% for the lateral canal paresis (CP) as measured by caloric testing (mean CP 82.2 ± 7.9%, normal upper limit 30%). The loss was diagnosed as presumably being due to vestibular neuritis (VN) because of the presence of a pathological lateral vHIT gain on the side of canal paresis (mean 0.43 ± 0.13, normal lower limit 0.74, contralateral mean gain 0.85 ± 0.07), the presence of a spontaneous nystagmus (mean at the time of the CP measurements 8.5 ± 3.2°/s) beating toward the healthy ear, nausea, and the constant presence of symptoms over hours. Measurements were taken from caloric testing, vHIT, and balance control trials just after the acute onset of the UVL (on average 3.8 ± 1.1 days after the patient's diagnosis of VN was established). All the patients were treated intravenously with methylprednisolone (125 mg Solu-Medrol$^{TM}$ per day) and then discharged with oral medication 4–5 days after entry as an in-patient. Data of the patients with aUVL were compared with those of four age-matched healthy controls (HCs), with a mean age of 59.8 ± 17.8 years. Written informed consent was obtained from the patients and HCs for using their data anonymously. Patients with comorbid balance problems due to other causes, for example, peripheral lower leg neuropathy, were excluded from this study.

## Measurement systems

### Caloric testing

Canal paresis or unilateral weakness was determined using a bithermal (44 and 30°C) caloric test. The differences in average eye slow-phase velocity (SPV) over the culmination phases of nystagmus were compared for the left and right ear irrigations. If R equals the difference between the levels of SPV for the right ear irrigated with 44°C and then with 30°C and L with 30°C, and L the corresponding difference for the left ear, then CP was defined as [(R-L)/(R+L)] × 100%.

## Video head impulse test

To measure VOR function in response to high angular accelerations (above 2,000°/$s^2$), a video head impulse test (vHIT) system was used (ICS system from GN Otometrics, Natus Medical Inc., Taastrup, Denmark). The system was used according to the protocol described by Macdougall et al. (2013), with head angular velocities reaching 100–250°/s by 100 ms. At least 15 head rotations with artifact-free responses in each canal plane were performed.

All vHIT tests were performed by the same person (FH). During the head movements, the patient was seated with gaze fixed on a small target 3 m away. For the vertical canals, the head was first turned 45°, and up or down head rotations were performed in the plane of the canals. Sections of the data with covert saccades and artifacts were removed from the recordings prior to gain calculations by the vHIT manufacturer's software. Gains were calculated based on the quotient of the areas under the eye and head velocity impulse responses. The interval used started 100 ms prior to peak head velocity and ended when head velocity first crossed zero after this peak.

## Balance control tests

Participants' balance control during standard clinical stance and gait trials (Allum and Carpenter, 2005; Hegeman et al., 2007) as well as during object circumvention trials was measured with a SwayStar$^{TM}$ system (Balance International Innovations GmbH, Switzerland). This gyroscope system was attached to the trunk at L1-3 using a converted motorcycle belt. It measured angular velocities in pitch and roll planes for the clinical balance tests. For the circumvention trials, measurements were taken in the yaw and roll planes. Angular displacements were calculated on-line from the measured angular velocities using trapezoid integration. The same standard protocol of 14 stance and gait tasks was used to measure balance control, as described before (Allum and Adkin, 2003). Tasks were performed by the participants without shoes. Stance tasks consisted of standing on one and two legs with eyes open and closed. All stance tasks were ended after 20 s, or when the participant lost balance, or when the non-stance foot touched the ground. Standing on one leg trials were performed on the preferred leg. All stance tasks, except the standing on one leg eyes closed trial, were also repeated on a foam support surface (thickness 10 cm, width 50 cm, length 150 cm, and density 25 kg/$m^3$). A semi-stance gait-like task, walking eight tandem steps, was performed on a normal floor and on the foam support system with the participants observing their feet while walking. The following five gait tasks were all performed at the subjects' preferred gait speed: Three consisted of walking 3 m with either eyes closed, or with eyes open while rotating the head left and right, or while pitching the head up and down. The fourth gait task was to walk over four low barriers, each 24 cm high and spaced 1 m apart. The final task was to walk up and down a set of stairs consisting of two upward and two downward steps, each of height 23 cm.

The circumvention trial procedure is described in **Figure 2**. The subjects were asked to walk 6 m approaching at 3 m an air-filled obstacle with stabilizing water in its base. The obstacle was 30 cm in diameter and 140 cm in height. The subjects were told that the obstacle represented a person who was to be passed as closely as possible on the left or on the right. On passing the obstacle, the participants were either asked to continue on the same straight trajectory for another 3 m, or veer to the left after passing to the right, or veer to the right after passing to the left (see **Figure 2**). A brick placed on the floor was used to mark the end of the 6-m trajectory. We used the veering trials to determine if the obstacle departing movement strategy altered the obstacle approaching movement strategy.

During all trials, one or two spotters, as necessary, stood or moved next to the participant to prevent a fall in case of a loss of balance. The duration of each gait trial was the time needed to complete the task or to when the subject lost balance. All balance and circumvention tests were carried out by one of two persons (FH or JHJA).

# Data analysis

As measures of balance control for the clinical stance and gait tasks, we used the peak-to-peak range of angular displacement and velocity in the roll and pitch directions from each trial as well as trial durations. These were combined into a single value, the balance control index (BCI) (Hegeman et al., 2007), as follows:

$$\begin{aligned}\mathrm{BCI} &= 2*\mathrm{s2ecf}_{\mathrm{pv}}+\mathrm{tan8}_{\mathrm{ra}}+1.5*\mathrm{w3ec}_{\mathrm{pv}}\\ &\quad +20*\mathrm{w3ec}_{dur}+1.5*\mathrm{w3hp}_{pv}+12*\mathrm{stairs}_{ra} \quad (1)\end{aligned}$$

where s2 stands for standing on 2 legs, ec for eyes closed, f for foam, *pv* for peak-to-peak pitch velocity, tan8 for eight tandem steps, *ra* for peak-to-peak roll angle, w3 for walking 3 m, *dur* for duration, and hp for head pitching.

For the circumvention trials, we measured in addition to peak-to-peak yaw angular velocity, the peak amplitude of approaching yaw velocity as marked by the vertical line in **Figures 3**, **4**, the following peak yaw angle, and the peak departing yaw velocity following the peak yaw angle. The end-of-trial yaw angle was calculated based on last five samples in the trial once trials had been aligned with the peak approaching yaw angular velocity and any offsets at trial onset corrected for. Values from the two identical circumvention trials were averaged together. As three of the four subjects with aUVL had the deficit on the left side, we counted this side as the deficit side and inverted the values of the other patient with a right deficit before computing population averages as in **Figures 3**, **4** or performing statistical tests of population differences.

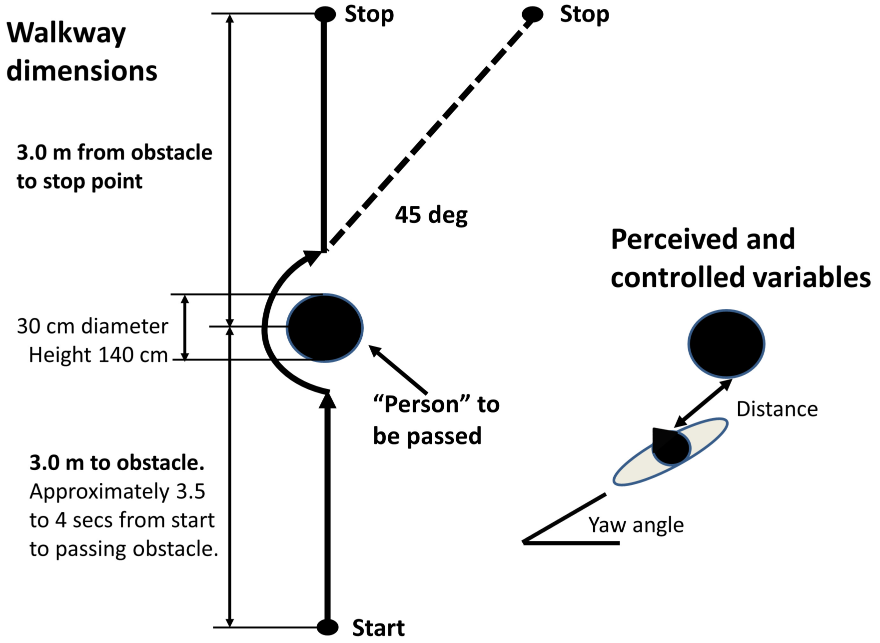

FIGURE 2
Schema of experimental task. Left walkway dimensions. Right perceived and controlled variables to avoid a collision distance and trunk yaw angle. The subject was requested to walk 3 m toward a cylindrical obstacle, to pass it on the left or right as closely as possible as instructed immediately before the trial, then continue straight, or veer to the right 45 deg, if the obstacle was passed to the left (veering left if the obstacle was passed to right), before stopping 3 m past the obstacle in front of a brick.

We were unable to apply a general linear MANOVA model for repeated measures to the data as there were too few samples. Instead we used univariate ANOVA. For these analyses, participant scores were defined to be dependent on the two fixed effects: two population types (patients with aUVL or HCs) and the four test types [go straight or veer (pass normal or deficit side)]. In order to allow effects to vary across entities, "participants" were set as random effects. For this analysis, R was used (R Core Team, 2020). *Post-hoc* data were compared using parametric *t*-tests in Excel, provided the ANOVA effects were significant ($p \leq 0.05$). The *post-hoc* analyses described in the "Results" section were corrected for multiple comparisons using a Bonferroni correction.

# Results

## Differences in standard clinical stance and gait tasks

The balance control index (BCI) summary values were significantly different between the populations ($p = 0.0014$). The mean and standard deviation values were 554 ± 44 and 345 ± 16 for patients with aUVL and HCs, respectively. The upper value (95th percentile) of normal BCI values is 460 for persons of the average age of our participants, 60 years.

## Differences in circumvention measures

Circumventing an object leads to characteristic yaw angle and angular velocity profiles, both of which are different depending on whether the subject is asked to continue going straight or asked to veer off to one side after passing the obstacle. As **Figure 1** shows, for going straight, the yaw movement is biphasic with the moment of passing by the obstacle corresponding to the zero-crossing of yaw angle motion between the two phases (**Figure 1**; Vallis and McFadyen, 2003). When the task was to veer off to the opposite direction to that used to pass by the obstacle, a change of motion with respect to going straight was observed just after the second, departing, peak yaw angular motion. The amplitudes of simultaneous roll motion were considerably less than those of yaw motion (see **Figure 1**; Vallis and McFadyen, 2003) and, therefore, not analyzed in this study.

Population effects were achieved in the ANOVA for both approaching variables, peak velocity and peak angle ($F > 6.2$, $p < 0.05$). A borderline effect was noted for departing peak velocity ($F = 5.7$, $p = 0.054$). There was a test type effect observed for approaching angle ($F = 5.1$, $p = 0.01$) and departing velocity ($5.65$, $p = 0.007$), but not for approaching velocity.

Our most striking result was a highly significant difference ($p < 0.001$–$0.05$) in peak approaching YAV between the subjects with aUVL and healthy controls (HCs) across circumvention

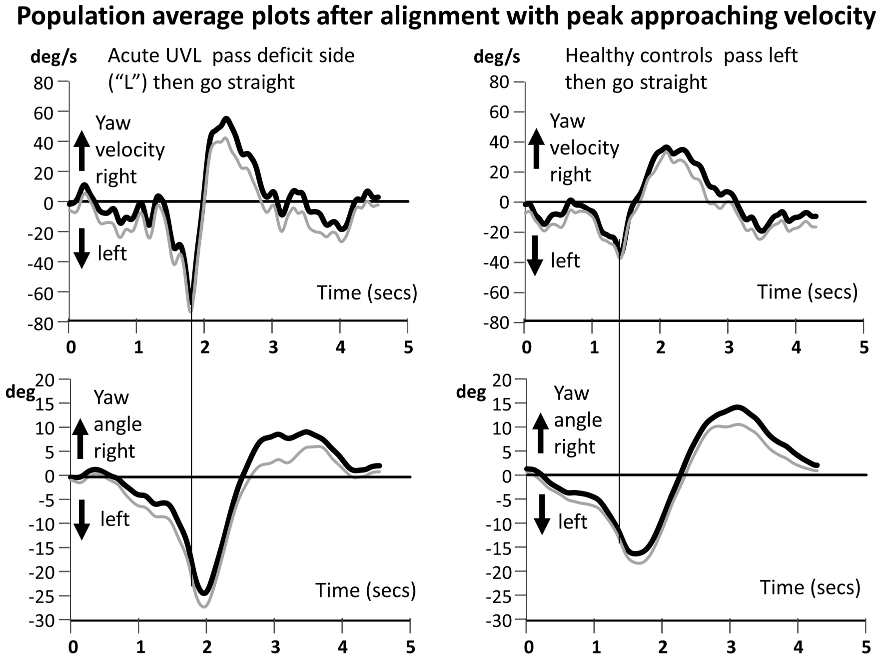

FIGURE 3
Population yaw angular velocity and yaw angle average plots for the circumvention task of walking to the obstacle, passing it on the acute unilateral vestibular loss side, and then going straight (left traces are for aUVL patients). In the majority of cases, the deficit side was on the left. Therefore, the plots of healthy controls **(right traces)** are shown for passing the obstacle on the left. All traces have been aligned at the peak approaching yaw angular velocity prior to averaging. The population average traces have been filtered with a zero-phase shift second-order Butterworth filter with a cutoff at 5 Hz. The average peak angular velocity and the corresponding time on the yaw angle plots **(lower traces)** are marked by a vertical line. In each panel, the thick black trace is the mean trace (two repetitions of four subjects), and the thin gray line is the mean minus the standard error of the mean (SEM). Note the larger yaw velocities for the subjects with aUVL.

protocols (see Figures 3–5). Furthermore, for each population, the instruction to veer off to one side, rather than going straight, after passing the obstacle had no influence on the amplitude of the peak yaw angular velocity (YAV) approaching the obstacle (Figures 3–5). Also, there was no difference observed in peak approaching YAV if patients were asked to go around the obstacle to the deficit vs. the non-deficit side (Figure 5).

Given the aforementioned increase in the YAV of patients with aUVL compared to that in the HCs on approaching the obstacle, two expectations can be formulated for the YAV amplitude of patients with aUVL departing from the obstacle if a stable yaw angle trajectory is to be maintained and the end angles are 0 and 45 degs reached without significant deviation, respectively, for the straight and veered trajectories. First, the departing YAV amplitudes of patients with aUVL should be greater than those of HCs, and second, the ratios of departing to approaching YAVs should be similar to those of HCs; that is, the departing YAVs of UVLs should be proportionally larger than the approaching YAV amplitudes as the departing YAV amplitudes are for approaching YAVs of HCs. Figures 6, 7 illustrate that neither of these conditions are fulfilled. Figure 6 shows that departing aUVL YAV amplitudes in patients are greater than those in HCs but only significantly greater for the straight trajectories ($p \leq 0.04$). Figure 7 shows that the departing YAVs of HCs are significantly greater than approaching YAVs ($p \leq 0.0006$) for both the straight and veering tasks with ratios of departing/approaching YAV amplitudes equal to 49.5% and 87%, respectively, whereas the ratios of the UVLs are not significantly greater for the straight trajectories (11.8%) and of borderline significance ($p = 0.05$) for the veered trajectories (39.4%). Despite these differences in the pattern of approaching and departing YAV velocities, the maximum angle deviation of yaw deviation was only significant greater for passing on the deficit side (straight, $p = 0.05$, and veering trajectories, $p = 0.009$). When stopping at the end of the walkway, the end angles only significantly ($p = 0.04$) varied between aUVLs and HCs for the task of passing on the deficit side and veering 45 deg to the normal side [mean end angle aUVLs 34.6 ± 5.4 (sd), HCs 43.0 ± 3.8]. This lack of a general trajectory error suggests that other sensory inputs mostly compensated for the acute vestibular loss after passing the obstacle.

There were no statistical differences between trial durations even though those of the subjects with aUVL tended to be slightly longer. For example, durations for the veering trials were on average 6.05 secs for the HCs and 6.45 for the subjects with

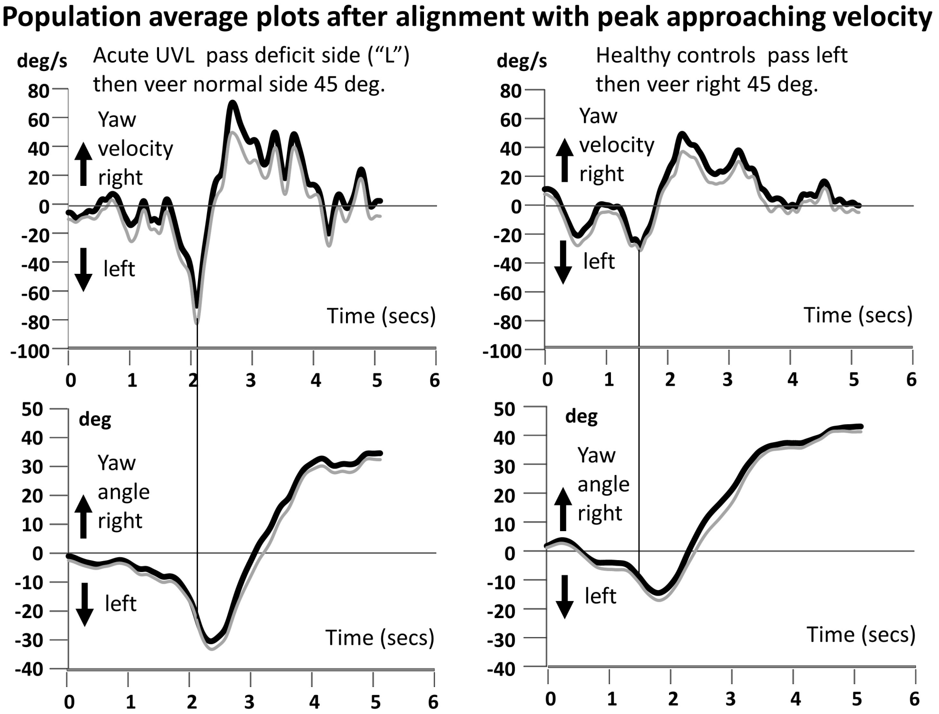

FIGURE 4
Population average yaw velocity plots for the circumvention task of walking to the obstacle, passing it on the aUVL side, and then veering to the right (left traces). On the right are the traces of the healthy controls. The angle traces in the lower plots show the veering trajectories. Details of the plots are described in the legends to Figures 1, 3.

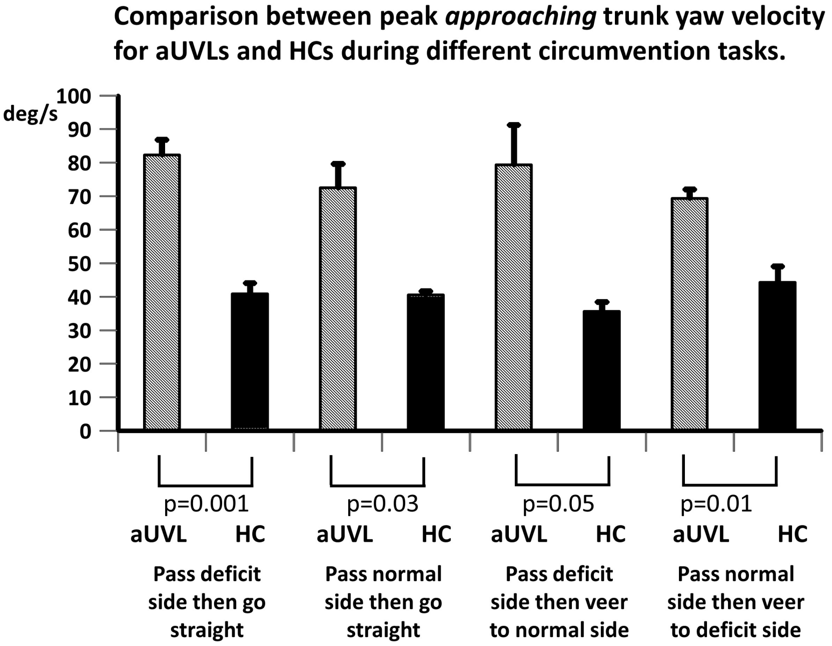

FIGURE 5
Comparison between mean peak yaw angular velocity approaching toward the obstacle. Peak yaw angular velocities for patients with aUVL and HCs during different circumvention tasks, as listed below the column plots, are displayed. The height of the column represents the mean population value, and the vertical bar, the SEM. The pair-wise levels of significant differences are indicated below the columns.

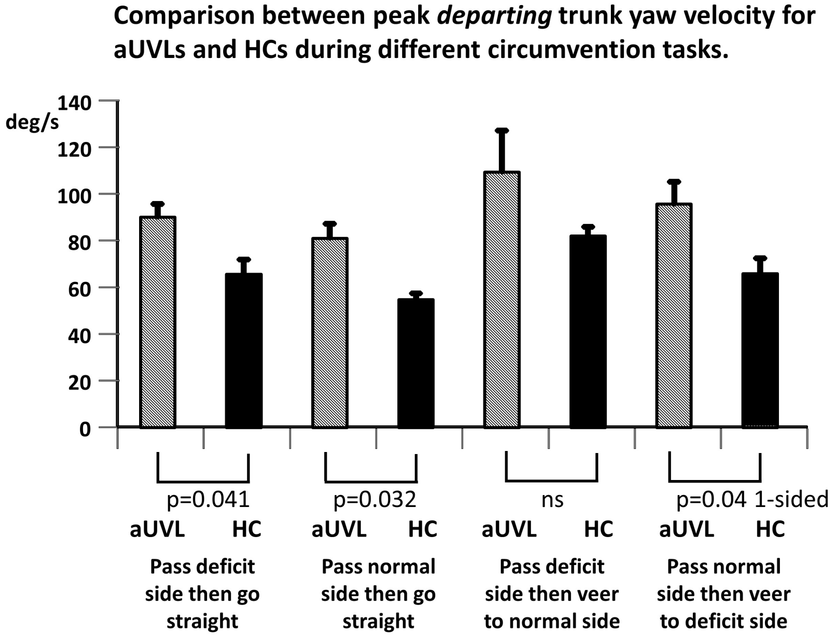

FIGURE 6

Comparison between mean peak departing from the obstacle peak yaw angular velocities for patients with aUVL and HCs during different circumvention tasks, as listed below the column plots. The height of the column represents the mean population value, and the vertical bar, the SEM. The pair-wise levels of significant differences are indicated below the columns. Note the differences between populations are most significant for the tasks continuing along the same trajectory (no veering).

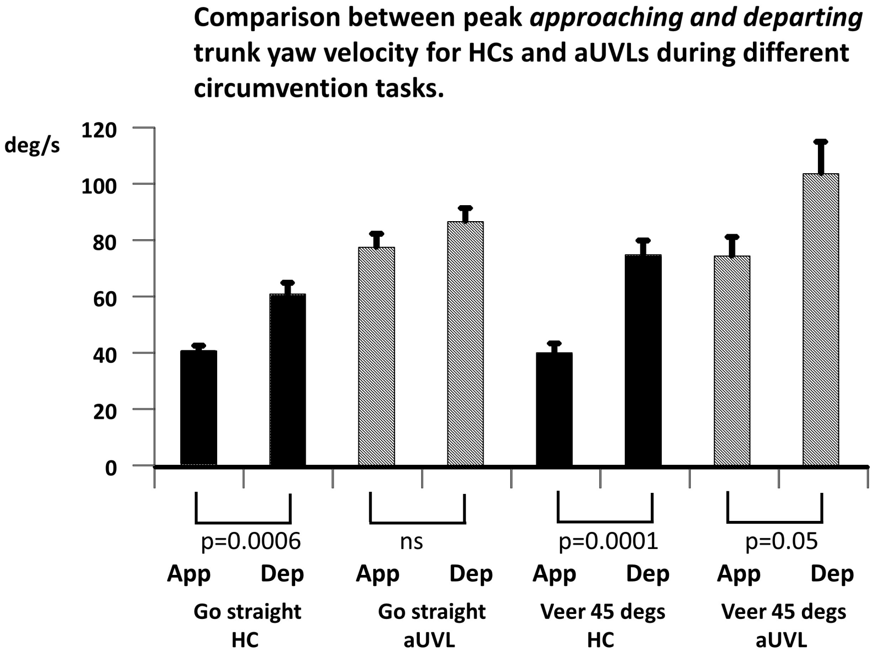

FIGURE 7

Comparison between mean peak yaw angular velocities approaching toward and departing from the obstacle peak for patients with aUVL and HCs during different circumvention tasks, as listed below the column plots. The height of the column represents the mean population value, and the vertical bar, the SEM. The pair-wise levels of significant differences are indicated below the columns. Note that the HCs show the most significant differences.

aUVL. Over the 6 m of the required trajectory, these gait speeds can be considered as being at preferred and slow gait speeds, respectively (Goutier et al., 2010).

## Comparisons with other gait tests of vestibular function

Based on the results described earlier, it is possible that the circumvention task also provides a superior test of vestibular influences on gait than currently used clinical tests. Such tests include walking 3 m while rotating the head from side in the yaw plane and walking 3 m with eyes closed (Allum and Adkin, 2003; Allum and Honegger, 2020b). Furthermore, it should be established whether simply walking 6 m provided more significant differences in yaw velocities between patients with aUVLs and HCs than during circumvention tasks. **Figure 8** shows that the peak-to-peak YAV amplitudes during the circumvention task of passing on the deficit side then going straight provide the most significant population differences ($p = 0.008$). However, the population differences for the task of walking 3 m while rotating the head from side to side were only slightly less significant ($p = 0.009$). Furthermore, the differences within each population were greatest for the circumvention task, pass deficit side then go straight, compared to the walking task, walking 3 m while rotating the head from side to side ($p = 0009$ for aUVLs, $p = 0.0015$ for HCs). Walking 6 m produced less significant differences between the patients with aUVL and HCs than the circumvention task, as illustrated in **Figure 8** ($p = 0.05$ vs. $p = 0.008$).

# Discussion

The current study of object circumvention is a simplified version of the real-life crowd situation where two people walking toward one another interact to control the timing and space between them as they pass one another. The simplified situation is similar to the situation where one of the two people is stationary. In both situations, the minimum predicted distance is controlled to avoid a possible collision (Olivier et al., 2013). In addition, the yaw angle of the trunk must also be controlled. The major simplification we used, as used in previous studies (Vallis and McFadyen, 2003), was to have the stationary person replaced by a model figure towards which subjects were instructed to walk around as closely as possible. Our subjects were those with acute unilateral vestibular loss (aUVL), due to vestibular neuritis, and healthy controls as we were interested in assessing the role of vestibular inputs in this gait task by quantifying how the vestibular dynamic imbalance alters yaw angles and angular velocities during object circumvention. As far as we are aware, this is the first time that vestibular signals have been shown to influence this collision avoidance task. The changed vestibular signals could theoretically be divided into two types, tonic imbalance as measured by the level of spontaneous nystagmus and dynamic imbalance as measured by vHIT gains. Furthermore, the effect of the changed signals could be at two levels, the perception of yaw angles and angular velocities, and the execution of motor commands in yaw. We explore these possibly different effects later. However, it should be borne in mind that our findings are based on preliminary data of few subjects.

## Changes in yaw movement strategies and direct vestibulo-spinal feedback with aUVL

Perhaps the most interesting finding of our study was that the trunk peak yaw velocities of patients with aUVLs approaching the model figure obstacle were equally larger than those of HCs, regardless of whether the object-approaching turning motion of the trunk was to the deficit side or not, and regardless of whether, on passing the obstacle, the desired trajectory was to continue straight or veer off to one side. It is an open question whether the 30–40°/s differences in approaching peak yaw velocities between subject populations are due to an altered perception of yaw velocity due to the level of spontaneous nystagmus or to a reduced vestibulo-spinal feedback gain concomitant with reduced VOR gains seen in vHIT responses.

There are three possible explanations of our preliminary findings that the planned post-obstacle trunk yaw trajectory of aUVLs did not influence the obstacle-approaching peak yaw turning velocity. Either the planned approaching trajectory yaw velocity is set by patients with aUVL to a larger preprogrammed yaw velocity than that set by HCs to ensure a collision does not occur, or, the same velocity is set by the subjects with aUVL as set by HCs, but larger velocities result because the feedback vestibulo-spinal gain countering trunk rotation velocities is too strong, that is, destabilizing, or, third, a combination of the effects occur in patients with aUVL. For the vestibulo-spinal gain explanation to be valid, the equal effect of unilateral vestibular loss on yaw velocities for turning away from the deficit vs. the non-deficit side would be divergent from the clearly asymmetric responses seen in vestibulo-ocular reflexes (Halmagyi et al., 1990; Palla and Straumann, 2004; Allum and Honegger, 2020a). Vestibulo-spinal influences on trunk muscles are inhibitory. Reducing the inhibition leads to a larger muscle response. For pitch plane rotations, the vestibulo-spinal influences on trunk paraspinal and external oblique muscles are laterally equally inhibitory (Carpenter et al., 2001; Allum et al., 2008). Thus, when this influence is absent, increased muscle activity is observed (Carpenter et al., 2001; Allum et al., 2008). Here, we consider the most parsimonious explanation for this common effect on obstacle approaching velocities for all

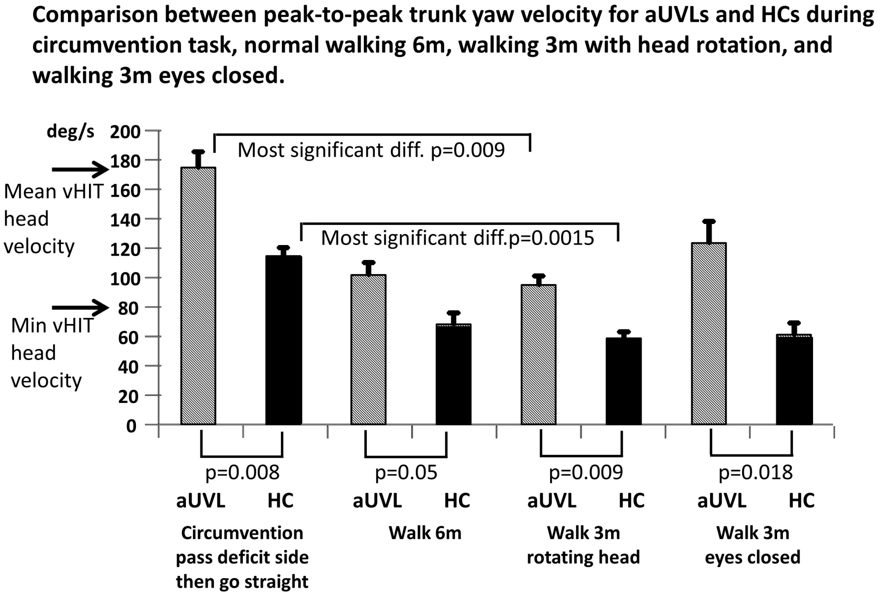

FIGURE 8

Mean peak-to-peak yaw angular velocities for the circumvention task showing the most significant differences (after Bonferroni correction) between subjects with aUVL and HCs, compared to peak-to-peak differences, for the clinic gait tasks of walking 6 m, walking 3 m with simultaneous head rotations, and walking 3 m with eyes closed. Horizontal arrows on the trunk yaw angular velocity ordinate indicate the minimum acceptable and mean yaw head velocity used for video head impulse tests of the yaw vestibular ocular reflex (data from Cleworth et al., 2017).

circumvention protocols we used is that the minimum perceived yaw angle and distance to the obstacle to avoid a collision are set larger by the patients with aUVLs; that is, the same strategy (velocity profile) is used by the patients with aUVL and HCs (as shown in **Figure 3**), but the required amplitude is set larger by patients with aUVLs and is further enhanced by excitatory (dis-inhibited) vestibulo-spinal influences. This is in contrast to the reduced yaw angle executed when patients with a unilateral neuronectomy are asked to complete a triangular gait course (Glasauer et al., 2002; Péruch et al., 2006) possibly because of the continuous yaw angle estimation required with circumvention and also because no possible collision could occur with the triangular course. Future studies should investigate the changes in yaw velocity due to strategy amplitude changes and the changes brought about by dis-inhibited vestibulo-spinal gains.

In order to turn the trunk back to the desired trajectory on passing the obstacle, we expected that the departing peak yaw angular velocity would be greater than the approaching peak yaw velocities for going straight and even larger for the veered trajectories because the yaw motion must be braked and then programmed to move in the opposite direction. This was the case for the HCs whose velocities were 50 and 87% larger, respectively. This was not the case for the patients with aUVL whose departing angular velocities were only 12 and 39% larger, respectively. Again the most parsimonious explanation for this result is that the aUVLs reduced the relative size of the departing angular velocity in order to have a larger minimum perceived obstacle-passing distance. The alternative argument that the dis-inhibited vestibulo-spinal gain that led to instability does not fit with the lowered ratio between departing and approaching velocities observed for the patients with aUVL in comparison to the HCs.

Despite the differences between the yaw velocity characteristics of the patients with aUVL and HCs described earlier, there was little difference between the amplitudes of yaw trajectories at the end of the 6-m walkway, except for the task of walking past the obstacle on the deficit side and then veering 45° to the normal side for which a deviation of 8 deg was observed. Given that approximately 3 s was available to correct the trajectories after passing the obstacle, a variety of sensory inputs, specifically proprioceptive and visual, could be used in this correction process, especially as lower leg proprioceptive, and not vestibular inputs are known to trigger balance corrections (Bloem et al., 2002). Visual inputs, especially those of virtual reality, are known to have a role in modulating circumvention movements (Souza et al., 2018) and balance corrections (Horlings C. et al., 2009). Thus, given the important triggering function of proprioceptive inputs, future experiments should determine the effect of proprioceptive loss on object circumvention particularly after the obstacle is passed.

We measured the yaw motion of the lower trunk at the level of lumbar 1–3, close to the center of gravity. Vallis and McFadyen (2003) measured the upper trunk and head motion and showed that these two segments moved in phase.

A weakness of the current study is that head motion was not recorded. Knowing the trajectory characteristics of the head might enable a link to be made between vHIT vestibular ocular responses during head impulse testing and lower trunk yaw angular velocities during circumvention trajectories. Based on previous reports of low-frequency movements (<0.7 Hz) for pitch and roll during stance (Horlings C. G. et al., 2009; Honegger et al., 2012), we would expect that head, and upper and lower trunk yaw motions would also move in phase during circumvention. As can be noted in **Figures 1**, **3**, **4**, the yaw angular motion has frequency components predominately below 0.7 Hz.

Regarding ankle and knee joint movements, the question arises if there is a difference in trunk yaw velocities depending on whether the lead leg is the inside or outside leg when passing the obstacle? As we did not measure foot placement, ankle and knee joint motion and, Vallis and McFadyen (2003) did not measure trunk yaw velocities, this question cannot be answered currently. However, it appears from the data of Vallis and McFadyen (2003) that trunk yaw velocity is higher for lead leg inside, rather than outside, even if the amplitude of yaw angle is similar. Thus, future studies should investigate whether the choice of leg to pass the object with is dependent on the side of the side of unilateral vestibular loss and whether this leads to a difference in ankle and knee joint flexion velocities.

## Study limitations and caveats

As mentioned previously, a limitation of the current study is the low number of patients with aUVL tested. This was because we imposed clearly pathological clinical vestibular test results as inclusion criteria. The canal paresis values had to be greater than 75% (the upper normal limit is 30%), the deficit side vHIT gain needed to be less than 0.65 (lower normal limit is 0.74), and the patients needed to be tested within 5 days of diagnosis to minimize the effects of central compensation prior to testing. With these criteria, we obtained clearly significant differences with respect to HCs, as illustrated in **Figures 5–8**. It should be noted, however, that our results could change with increased numbers of subjects being considered. Furthermore, while power calculations indicated that we had 90% power for the results, as given in **Figures 5–8**, it should be noted that in case our pilot data were revealing false-positive differences between subjects with vestibular loss and healthy controls, the calculated power would be mistakenly high. Another limitation of this study is the underlying assumption that deficits in vHIT responses in the yaw plane would be directly related to trunk instability in the same plane. As we did not measure head rotations, it is possible that subjects with aUVL rotate the head on the trunk differently from controls during circumvention. Nonetheless, recently, it has been determined that during clinical stance and gait tasks, trunk yaw rotations are strongly correlated ($R = 0.61$) with deficit side vHIT gains of subjects with aUVL (Allum et al., 2022).

## Control of linear distance and trunk yaw angle rotation

It has been emphasized in this report that two variables need to be controlled during obstacle avoidance, the linear distance between the passing person and the obstacle and the yaw angle of the trunk. The former measure was taken as the distance between the midpoint of the shoulders by Olivier et al. (2013). The latter measure, if correctly sensed and programmed, ensures that the shoulders are cleared past the obstacle. In this report, we demonstrated that trunk yaw velocities are altered by acute vestibular loss due to vestibular neuritis with both a tonic and a dynamic imbalance. This result is not surprising, given the greater yaw plane than roll and pitch plane VOR asymmetries (40 vs. 22%) following aUVL due to vestibular neuritis as based on video head impulse test (vHIT) responses (Allum and Honegger, 2020a) and the greater yaw than roll and pitch movements of the trunk during circumvention trials, as we, in this report, and others (Vallis and McFadyen, 2003) have demonstrated. Although we did not measure linear motion of the trunk, we would expect that this would be affected by unilateral vestibular loss because linear accelerations in the transverse plane sensed by the utricles would be affected by the type of vestibular loss our patient participants had. Following the onset of vestibular neuritis, it is common that both the lateral canal (sensing yaw head motion) and utricle responses are affected (Manzari et al., 2011) as these sensory systems are served by the same superior vestibular nerve (Gianoli et al., 2005).

## Use of sensory substitution to aid perception of linear distance and yaw angle rotation

If indeed vestibular and other sensory inputs play an important role in the control of circumvention body movements, the question arises if sensory substitution devices with artificial sensory inputs would be effective in the control of trunk movements during circumvention. There are two ways to approach this question: providing distance information from the obstacle or providing information on trunk angular motion. The first approach appears to work well for visual inputs. When blind individuals were provided with vibro-tactile devices using echo-techniques to indicate the distance to an object to be circumvented, they generally performed better than normal-sighted persons that were blindfolded (Kolarik et al., 2017). According to Kolarik et al. (2017), the better performance of the blind than that of blindfolded sighted participants is consistent with the perceptual enhancement hypothesis that persons with severe visual deficits develop improved auditory abilities to compensate for visual loss. It is also consistent with the evidence that postural control improves when a sound source is present (Anton et al., 2021). The alternative approach providing vibro-tactile feedback of trunk angular motion works well for vestibular loss patients, improving trunk sway in the pitch and roll directions (Honegger et al., 2013; Sienko et al., 2017; Kingma et al., 2019), but it has not been employed for the yaw direction presumably because of coding difficulties with yaw-directed vibro-tactile feedback. Nonetheless, it would be of interest to know which approach vibro-tactile feedback of trunk yaw velocity or obstacle distance or both brought the most perceptual and motor improvement for patients with sensory loss, be it visual, proprioceptive, or vestibular.

## Circumvention as a clinical gait task

Given the significant differences illustrated in **Figure 5**, it was of interest to us to determine whether a circumvention test could supplant some of the clinical gait tests currently used to differentiate patients with vestibular loss from healthy normal subjects (Allum and Adkin, 2003; Cohen et al., 2012). When developing a new test of vestibular function, a number of criteria should be fulfilled. Most important is that test results should show a clear difference between those of subjects with vestibular loss and healthy, age-matched controls. Ideally, the biomechanical response amplitudes of the trunk should be related to the functional vestibular ocular reflex (VOR) loss, as determined by either high-frequency vHIT responses or low-frequency rotating chair results. Significant correlations have been observed between vHIT roll and yaw response asymmetries and trunk roll and yaw asymmetries, respectively, during various gait tasks (Allum and Honegger, 2020b; Allum et al., 2022). Ideally, the test task should be similar to an everyday task that causes difficulties for subjects with vestibular loss. There are a number of gait tests that have be used to identify the effect of vestibular loss on gait performance (Allum and Adkin, 2003; Cohen et al., 2012). The test most commonly used to induce pathological performance in the yaw plane is walking while rotating the head from left to right (Cohen et al., 2012). For the typical patient with unilateral vestibular neuritis, the range of peak-to-peak yaw trunk velocity is 110 deg/s over 8.5 deg during walking with head rotation compared to 210 deg/s over 63 deg for circumventing an object (see **Figure 8**). Thus, the possible instability is greater with circumvention than with walking with head rotation. Furthermore, depending on the coupling between the head and trunk, the resulting head motion should be more similar to that imposed on the head during the vHIT (see arrows on the ordinate of **Figure 8**). During vHITs, motion of the head reaches 150–200 deg/s (Cleworth et al., 2017; Pogson et al., 2019). Thus, the higher yaw velocities present in circumvention trials also provide a better basis for comparing vestibular ocular reflex responses provided by vHIT, with the biomechanical measures of vestibular spinal reflex responses.

## Data availability statement

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

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Northwest and Central Switzerland (EKNZ), approval 2014-026, principal investigator JA. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

FH and JA carried out the data collection and analyzed the results. JA wrote the first draft of the manuscript, which was edited by HR. All authors contributed to the article and approved the submitted version.

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We thank Barbara Wenger for editorial assistance.

## Conflict of interest

JA and FH have worked as consultants for the firm manufacturing some of the equipment used in this study.

The remaining author declares 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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