ROLE OF INNER EAR IN SELF AND ENVIRONMENT PERCEPTION

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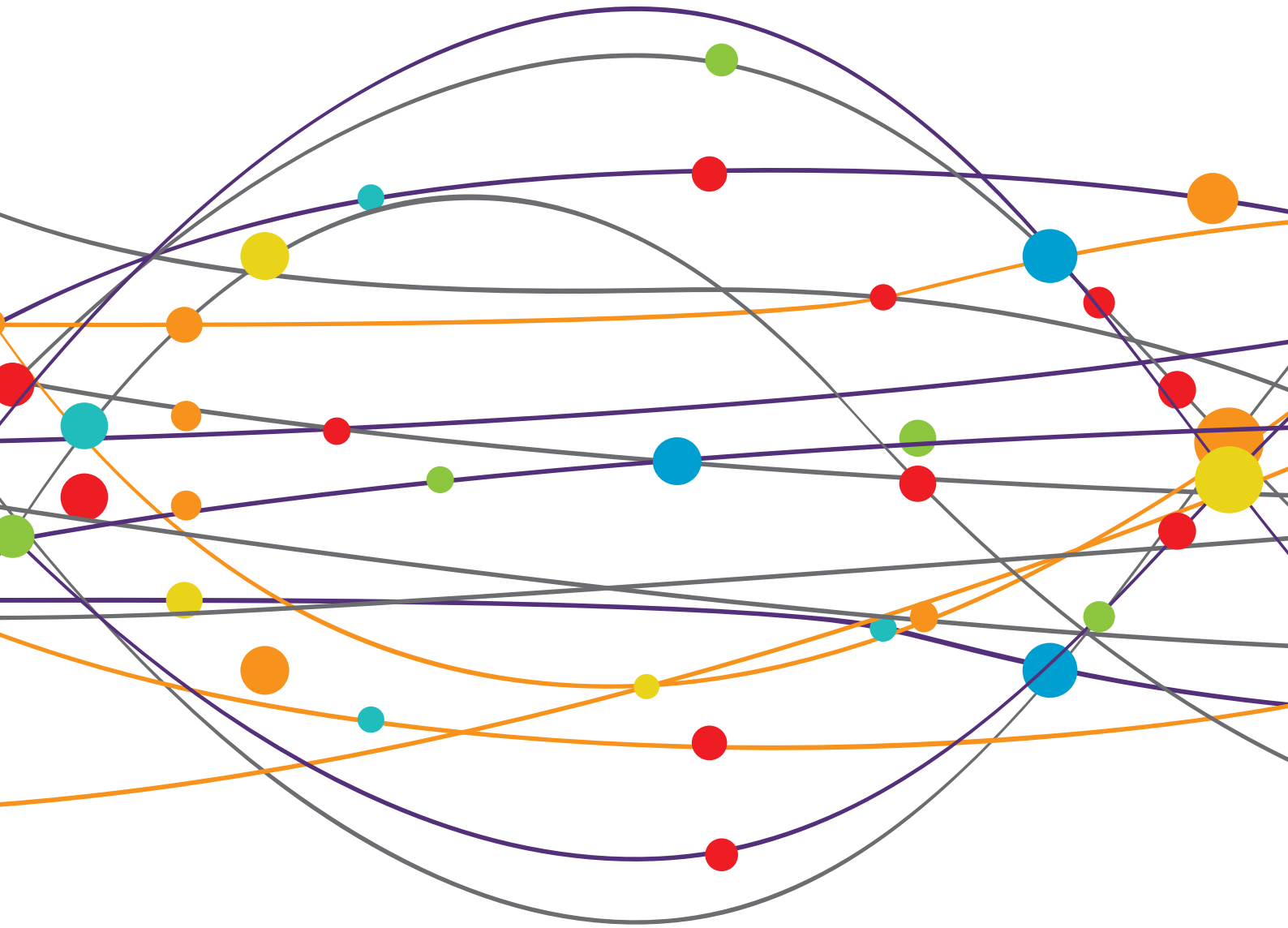

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ROLE OF INNER EAR IN SELF AND ENVIRONMENT PERCEPTION

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EDITORIAL
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Editorial: Role of Inner Ear in Self and Environment Perception

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Keywords: self-motion, vestibular system, vestibular rehabilitation, postural control, visual vertical, depersonalization and derealization, dizziness and vertigo, nystagmus

Editorial on the Research Topic

Role of Inner Ear in Self and Environment Perception

Otoneurology and vestibular neuroscience recently advanced with a better understanding of the vestibular contributions to perceptual and cognitive functions, reaching far beyond balance, and eye-movement control. Pioneering clinical observations established connections between dizziness and altered sense of self, distortions of the body schema, and symptoms resembling depersonalization and derealization (1, 2). However, studies in large samples of patients with dizziness have only recently validated the assumption that the vestibular system is the main contributor to the bodily self (3, 4). Recent epidemiological studies have also linked vestibular disorders to cognitive deficits. For example, a survey in over 20,000 adults established that individuals reporting vestibular vertigo had an eight-fold increase in the odds of reporting impaired memory and attention, limiting their activities (5). Another survey conducted in adults over 60 years revealed that vestibular impairment partially mediated the association between age and cognitive impairment. It was estimated that vestibular impairment mediates 14.3% of the effects of age on cognition and that it accelerates cognitive decline by 5 years in a visuo-spatial test (6). These studies raise the necessity to investigate more carefully the effects of vestibular impairment in dementia and several psychiatric disorders (7, 8).

Research in this area benefited from a better delineation of the human vestibular cortex. Functional MRI (fMRI) studies and meta-analyses of neuroimaging data have revealed that the cortical vestibular network is centered on the operculo-insular/retroinsular cortex (9) and that vestibular inputs also project to the temporo-parietal junction, cingulate cortex, somatosensory cortex, posterior parietal cortex, hippocampus, and frontal eye fields (10). These widespread vestibular projections to the brain were recently confirmed in whole-brain functional mapping in rodents using fMRI, local field potentials, and optogenetics (11, 12). We note that recent descriptions of functional connectivity, metabolic, and morphological brain alterations in peripheral vestibular disorders or chronic subjective dizziness [e.g., (13–15)] offer the possibility to evaluate, in a non-invasive manner, how various vestibular rehabilitation methods and drugs can improve brain plasticity. Finally, recent fMRI studies revealed the influence of cognition, emotion, and personality traits (such as neuroticism and introversion) on vestibular information processing [e.g., (16, 17)]. These observations suggest an expansion of the vestibular brain network into dimensions of emotion processing, mental health, and social cognition.

This Research Topic collection includes 17 articles combining contributions from authors with a large range of expertise in medicine and basic science, including neurology, otorhinolaryngology, neurophysiology, physiotherapy, neuropsychology, cognitive neuroscience, and bioengineering.

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This initiative brought together authors affiliated to institutions from six continents and 17 countries (Belgium, Bulgaria, Canada, France, Germany, Iran, Italy, Ivory Coast, Mexico, Netherlands, New Zealand, Russia, Spain, Switzerland, Taiwan, the United Kingdom, and the United States), showing the worldwide interest in advancing research in otoneurology, vestibular physiology, and vestibular cognition.

Altogether, contributions from this Research Topic highlight recent discoveries in otoneurology regarding (1) upright perception; (2) self-motion perception and balance control; (3) self and own-body cognition; and (4) vestibular physiopathology, testing, and rehabilitation.

UPRIGHT PERCEPTION: FROM NEUROIMAGING TO CLINICAL ASSESSMENT

An important function of the vestibular system is the perception of the visual vertical (VV), which contributes not only to own-body orientation and postural control but also to the judgment of orientation and even stability of objects in the environment. Psychophysical and clinical studies showed that vestibular signals are integrated with visual, tactile, proprioceptive, and interoceptive signals for an accurate VV perception, probably following Bayesian rules (18). In line with a developmental and multisensory perspective, Cuturi and Gori document visual, haptic, and visuo-haptic vertical perception in children and young adults tilted 90° to their side. Bayesian modeling reveals a lack of multisensory integration in children for the bimodal task.

Dieterich and Brandt offer a comprehensive overview of the pathways underpinning VV perception from the inner ear to the cerebral cortex, describing the consequences of lesions of various structures along these pathways. Using fMRI in healthy adults, Saj et al. show that VV perception involves the temporo-occipital and parieto-occipital networks (including the cuneus, lingual gyrus, and precuneus), together with areas in the cerebellum and brainstem, in accordance with observations in neurological patients (19, 20). Similar networks have been involved in navigation, balance control, and body representations, suggesting overlaps between these functions and VV perception.

Although VV perception is a widely used test of peripheral vestibular functions, it is not commonly used in neurological conditions such as vestibular migraine. Winnick et al. found that patients with vestibular migraine, but normal vestibular function, show abnormal VV when their head is tilted to the right (as if they were further tilted), whereas their VV is normal with their head upright or tilted to the left. This is corroborated by symptoms (tilting, pulling, and rotation) reported by the same patients mainly to their right side. These observations indicate abnormal multisensory integration for VV perception in vestibular migraine, consistent with abnormal self-motion perception recently measured in vestibular migraine (21).

SELF-MOTION PERCEPTION AND BALANCE CONTROL: FROM PSYCHOPHYSICS TO CLINICAL ASSESSMENT

Self-motion perception also involves several motion sensors and multisensory brain areas. Its exploration is crucial to understand self–environment interactions (22). Britton and Arshad thoroughly review human and animal studies of the relations between sensory signals and processing centers, as well as their impact on cognitive functions, such as navigation, spatial awareness, and emotions. Although many connections are to be explored, the authors present the system from an interesting perspective of integrative physiology. Kolev analyzed interindividual differences in the perception of self-motion vs. environment-motion perception after a rotatory chair stimulus. The author reports a significant effect of insinuation and sex on motion perception, opening insights into the mechanisms of motion sickness.

Two studies describe sensorimotor adaptations underpinning self-motion perception and balance control in patients with a bilateral vestibular failure (BVF). Lacour et al. show that BVF patients improve balance during fixation of a target, as well as during pursuit of a target with slow eye movements and saccades. They propose that BVF patients may use more efficiently proprioception from extraocular muscles or efference copy from the eye motor command than healthy controls. Guigou et al. explore the effect of a rotating sound on balance. A rotating sound destabilizes patients with BVF and with bilateral cochlear implants, indicating that hearing can also be used for postural control in patients with sensory deficits.

Magnetic vestibular stimulation in an MRI scanner can also evoke sensations of self-motion and horizontal nystagmus (23). Ward et al. show that visual information and continuous head rotations in the magnetic field do not influence the set-point adaptation (i.e., mechanisms attempting to inhibit unwanted nystagmus) of the nystagmus. This is in contrast with the well-known effect of vision on adaptation of the vestibulo-ocular reflex (VOR).

SELF AND OWN-BODY COGNITION

Three original research articles highlight the increasingly recognized role of the vestibular system in the sense of self and in own-body cognition. In a large sample of 319 patients with chronic dizziness, Toupet et al. show increased symptoms of depersonalization–derealization with increased levels of anxiety and depression. In addition, they show that depersonalization–derealization is associated with higher visual and vestibular hypersensitivity, migraine, and motion sickness. Aranda-Moreno et al. report that caloric vestibular stimulation and unilateral centrifugation both decreased phantom limb pain and symptoms of depersonalization–derealization reported by amputees. In an original study conducted in healthy participants, Thür et al. adapt the full-body illusion, a visuo-tactile illusion of self-identification with a virtual character (24), to include sensory conflicts between

gravitational and visual cues. Their results suggest a mutual interaction of graviceptive and other sensory signals and the individual's weighting style in defining the sense of self.

ADVANCES IN VESTIBULAR PHYSIOPATHOLOGY, TESTING, AND REHABILITATION

Vestibular dysfunctions have been associated with anxiety and hyperactivity (25), premature cognitive decline, or Alzheimer's disease (26). Other neurological disorders may also be partly related to vestibular disorders. Here, Smith summarizes recent research in humans and animals, establishing connections between the vestibular system and Parkinson's disease.

Standard otoneurological evaluation of the peripheral vestibular system now includes the video head impulse test, which is useful to detect vestibular hypofunction by testing the VOR during high-velocity head rotations (27). In a study conducted in BVF patients, Van Nechel et al. analyze the factors influencing the catch-up saccades (visible target vs. in darkness with imaginary target), which are generated to compensate deficient VOR. The authors propose that visual signals are the main trigger and parametric determinant of the catch-up saccades and that a target is necessary in most cases to generate catch-up saccades.

In addition to testing reflexive eye movements, Dupuits et al. propose that vestibular evaluation can benefit from systematic measure of vestibular perception thresholds using whole-body motion platforms, as done in standard psychophysics experiments in healthy participants (28). They measured vestibular perceptual thresholds using a hydraulic platform in the dark delivering six translations and six rotations/tilts.

In a perspective of vestibular rehabilitation, Sadeghi et al. show that unidirectional whole-body rotations toward the side of the vestibular deficit decreased VOR asymmetry even 10 min after one rehabilitation session. In a long-term study, VOR asymmetry decreased to reach normal values during the first two sessions in most patients. Finally, Idoux et al. developed a model to evoke motion sickness in mice and tested how scopolamine (a muscarinic antagonist) can prevent motion sickness at the behavioral and cellular levels. They report that both motion sickness and scopolamine decrease VOR efficacy, which might be a protective mechanism to prevent later occurrences of motion sickness. The authors set the basis for studies of motion sickness in rodents and offer translational perspectives for improving treatment of motion sickness in humans.

AUTHOR CONTRIBUTIONS

CL and AB wrote the manuscript. CL, AB, MT, and CN revised the manuscript.

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ORIGINAL RESEARCH
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How Eye Movements Stabilize Posture in Patients With Bilateral Vestibular Hypofunction

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Chronic patients with bilateral vestibular hypofunction (BVH) complain of oscillopsia and great instability particularly when vision is excluded and on irregular surfaces. The real nature of the visual input substituting to the missing vestibular afferents and improving posture control remains however under debate. Is retinal slip involved? Do eye movements play a substantial role? The present study tends to answer this question in BVH patients by investigating their posture stability during quiet standing in four different visual conditions: total darkness, fixation of a stable space-fixed target, and pursuit of a visual target under goggles delivering visual input rate at flicker frequency inducing either slow eye movements (4.5 Hz) or saccades (1.2 Hz). Twenty one chronic BVH patients attested by both the caloric and head impulse test were examined by means of static posturography, and compared to a control group made of 21 sex- and age-matched healthy participants. The posturography data were analyzed using non-linear computation of the center of foot pressure (CoP) by means of the wavelet transform (Power Spectral Density in the visual frequency part, Postural Instability Index) and the fractional Brownian-motion analysis (stabilogram-diffusion analysis, Hausdorff fractal dimension). Results showed that posture stability was significantly deteriorated in darkness in the BVH patients compared to the healthy controls. Strong improvement of BVH patients' posture stability was observed during fixation of a visual target, pursuit with slow eye movements, and saccades, whereas the postural performance of the control group was less affected by the different visual conditions. It is concluded that BVH patients improve their posture stability by (1) using extraocular signals from eye movements (efference copy, muscle re-afferences) much more than the healthy participants, and (2) shifting more systematically than the controls to a more automatic mode of posture control when they are in dual-task conditions associating the postural task and a concomitant visuo- motor task.

Keywords: bilateral vestibular hypofunction patients, static posturography, darkness, visual fixation, slow eye movements, saccades

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INTRODUCTION

Balance control in healthy subjects is the result of the integration of multisensory signals originating from three spatial references: the allocentric (vision), the egocentric (somatosensory), and the geocentric (vestibular) spatial frames. It is known since a long time that posture stability is increased with eyes open compared to eyes closed, with vision of stable space-fixed target or with full-field vision compared to darkness (1). The real nature of the visual cues for posture stabilization remains however an open debate. During quiet standing, in non-challenging conditions, fixation or pursuit of a visual target modulates balance control. Among the afferent signals inducing the visually evoked postural effects is the retinal slip, i.e., the motion of the visual images on the retina (2). On the other hand, many studies showed that eye movements *per se* modify the postural performance. Posturography recordings showed postural stability improvement during saccadic tasks compared to fixation tasks in both children (3) and adults (4–7). Execution of eye movements was however reported to decrease postural stability when healthy participants pursuit a moving target in darkness and use smooth pursuit instead of saccades (8). Explanations from the literature indicate that posture stability changes during the visual task are due either to two different modes of detection of body sway, ocular vs. extraocular (2, 8), or to sharing of the attentional resources as an effect of dual tasking condition [postural task and eye movement task; (7)].

Bilateral vestibular hypofunction (BVH) is a disorder with different clinical pictures (combined or isolated deficits of the otolith and semicircular canal functions), and it remains a diagnostic challenge since there is still no consensus about diagnostic criteria (9). Reduced or absent function of the vestibular organs and/or vestibular nerves results in impairment or loss of the major vestibular functions: posture and balance control, gaze stabilization and spatial orientation (10). Indeed, spatial disorientation, oscillopsia, and balance problems are the main deficits reported by patients with BVH, and particularly in darkness and on irregular surfaces. Vestibular rehabilitation therapy helps those patients to regain an acceptable quality of life and, when examined in the light on regular support surfaces, they show not so dramatic postural performances. Perception of the visual vertical and perception of body tilt differed only marginally in bilateral a-reflexic patients compared to age-matched controls (11). Postural equilibrium on a stable platform was improved significantly with vision (12) and light touch from a fingertip (13, 14). Augmenting sensory information by providing auditory, visual and vibrotactile bio-feedback of body sway improved also the postural performance of BVH patients (15). All the data indicate that extra-vestibular signals substitute for vestibular input in BVH patients' spatial orientation, perception and posture control (16–18). Among the main sensory inputs substituting for the missing vestibular afferents in chronic bilateral vestibular failure are however the visual cues (19, 20).

In the present study, we tried to determine how the visual input can stabilize the postural performance of chronic BVH patients. A dynamic approach with a stable force platform was used to investigate the patients' posture control system. Recordings of the Center of foot Pressure (CoP) were made during quiet standing in four conditions: eyes open in total darkness, with vision of a stable space-fixed target, and during pursuit of a moving visual target in stroboscopic light with either high (4.5 Hz) or low (1.20 Hz) flicker frequency, which called into play the smooth pursuit system and the saccadic system, respectively. Data processing of the CoP displacements was performed with the wavelet transform and the fractional Brownian-motion analysis, which constitute powerful functional describers of posture control compared to conventional methods based only on posture parameters not enough sensitive [CoP length and area, for example: see (21)].

Considering the powerful role of vision in case of BVH, we hypothesized that chronic BVH patients would use all available visual cues, provided by stable space-fixed targets as well as tracking eye movements, as substitution strategies to improve their posture stability.

METHODS

Subjects

Twenty one patients (11 female, 10 male, mean age: 62.9 years; range: 38–80 years) with BVH were included in the experiment. The history of the BVH patients showed that the disease was diagnosed several years ago (8 years on average), and that all patients had been followed by physiotherapists for intense vestibular rehabilitation therapy. When seen for the first time by the ENTs, they still complained of oscillopsia during fast head motion, with particular difficulty to read while walking, and of balance problems in the dark or on irregular surfaces. BVH was mostly idiopathic (71% of the patients). Four patients had BVH due to antibiotic ototoxicity, while bi-lateralization of Menière's disease was reported in two others. Finally, one patient reported an acute unilateral peripheral vestibular loss followed later on by another attack on the other side. Only one patient exhibited a remaining spontaneous vestibular nystagmus in the light (4.2°/s). Complete or sub-total loss of vestibular function was assessed mainly on the basis of two clinical tests: the caloric and the video head impulse test. The horizontal semicircular canal function was tested in the very low frequency part (0.003 Hz) with the caloric test (30 s irrigation of 150–200 cm^3 at 30 and 44°C). All the BVH patients showed no responses to caloric irrigation or with slow phase eye velocity in the range 0–5°/s. The total sum for the four caloric tests was <20°/s, a criteria well defining BVH according to Vibert et al. (22). In the high velocity range (video Head Impulse Test: 10° amplitude; 200°/s), the horizontal and vertical canal functions of all the BVH patients showed reduced gains of the vestibulo-ocular reflexes (<0.5) and presence of both overt and covert saccades. The otolith function was tested by recording of the vestibular evoked myogenic potentials elicited by short tone bursts (95 dB; 500 Hz) and surface EMG electrodes at the sternocleidomastoid muscles (cVEMPs). Six BVH patients showed normal cVEMPs while three others exhibited higher threshold responses on both sides. The total lack of saccular

responses was observed in two patients only and normal cVEMPs were observed on one side only in the remaining BVH patients. The oVEMPs have not been evaluated in our BVH population. The whole of the vestibular examinations indicate therefore that our population of BVH patients had absent or significantly reduced canal function in both the low and high frequency ranges, but most of them still exhibited remaining otolithic function. The data collected in the BVH patients were compared to those recorded in a control group made of 21 sex- and age-matched healthy participants (11 female, 10 male, mean age: 58.3 years; range: 32–82 years). The vestibular clinical tests have not been performed in the controls who, however, reported to be free of vestibular disorders.

All the patients and healthy controls provided informed consent before their participation. The experimental protocol was approved by the local Ethics Committee (CCPPRB Paris) and followed the recommendations of the Helsinki declaration.

Experimental Setup

Static posturography was done with a force-measuring platform (Multitest Equilibre, Framiral, Grasse, France) that records the CoP displacements (sampling frequency: 50 Hz; analog-digital converter: 16 bits) during sequences of 30 s. Patients were required to stand quietly, arms along the body, feet in natural position, and to stand as stable as possible without voluntary movements of head and body during the whole recording sessions. They were tested first with eyes open in total darkness (Dark), being instructed to look straight ahead an imaginary target located at eye level. During this recording session, and in order to reduce anxiety and stress, patients were aware that somebody located behind would take care and avoid any possible fall. In a second session, the patients had to perform the same postural task while fixating in total darkness a visual red target (Fixation) located at eye level, 1.2 m in front of them (lateral field of view: 95°). For the third and fourth sessions, the patients were instructed to follow with the eyes the visual target which was moving sinusoidally in the horizontal plane at eye level (25 degrees amplitude; 0.13 Hz frequency). During these recording sessions the patients were equipped with stroboscopic goggles, mounted on the videonystagmography goggles, that provided light flashes at high frequency (strob 1 condition: flicker frequency of 4.5 Hz; flash duration: 100 ms; 3rd session) or low frequency (strob 2 condition: flicker frequency of 1.20 Hz; flash duration: 200 ms; 4th session). Continuous perception being observed with flicker frequency higher than 4 Hz (1), slow eye movements (smooth pursuit) were done by the patients to pursuit the visual target at the high flicker frequency (Strob 1 condition), whereas saccades were observed at the low flicker frequency (Strob 2 condition) for which only partial visual stabilization was possible. Eye movements were recorded by video-oculography (Framiral, Grasse, France; lateral field of view of goggles: 50°). Calibration of the eye movements was performed at the beginning of the recordings, when the patients were standing on the platform. It consisted of red sled targets (diameter: 0.5°) presented randomly at opposite locations on a sleds bar. The four visual conditions were performed in a total dark room to avoid fixation of other stimuli, and the order of the visual tasks was not varied randomly across patients.

The **Figure 1A** shows the typical slow eye movements (strob 1 condition: smooth pursuit) and the saccadic eye movements (strob 2 condition: saccades) recorded in one representative patient at the high and low flicker frequencies, respectively.

Data Processing

The CoP displacements were computed in the antero-posterior (AP) and medio-lateral (ML) directions and used to measure the postural performance of the patients. A non-linear analysis of CoP displacements was performed in order to accurately evaluate the posture control system [see (21), for review]. It consisted of applying both the wavelet transform and the fractional Brownian-motion analysis (PosturoPro software, Framiral) to the AP and ML stabilograms.

The wavelet analysis consisted of describing body sway frequencies as a function of time, a method we have described in details in our previous papers (21, 23, 24). This method has not the limitations of the Fast-Fourier Transform and provides a time-frequency chart of body sway in three dimensional space, giving access to the changes in the body sway frequency components with time. The spectral power density was expressed as a decimal logarithm scale reported on the 3D map by a color code (cf **Figures 1B,C**). The spectral power density (SPD) contains in the whole signal as well as in the frequency part corresponding to the main contribution of vision to postural regulation (0.05–0.5 Hz) were calculated separately for the CoP displacements in the AP and ML directions. The SPD parameter is also a good estimate of the energy cost required to maintain a stable postural performance. The Postural Instability Index (PII) derived from the wavelet plots was evaluated also [see (25)]. It was calculated from both the spectral power density contained in the whole stabilogram and the time during which the spectral power of the different body sway frequencies tend to be close to zero (cancellation time) by the close-loop control mechanisms [see (21)]. The PII was computed as a global score, independently of the AP or ML directions of the CoP displacements.

The CoP trajectories were studied also as one-dimensional and two-dimensional random walks, according to stabilogram-diffusion analysis [see (26), for details]. The displacement analysis of the CoP trajectories was carried out by computing the square of the displacement between all pairs of points separated by a specified time interval Δt, then averaged over the number of Δt of the recording session, and repeated for increasing values of Δt. The analysis provides a unique plot of the mean square CoP displacement (Δr^2) vs. Δt (cf **Figure 2A**). The planar stabilogram-diffusion plots exhibit a short-term and a long-term region distinguishable on the basis of the coordinates of a critical point defined as the intersection point of the two curves fitting to these two regions. It is assumed that the spatio-temporal coordinates of this critical point approximate the region over which posture control switches from open-loop to close-loop control mechanisms.

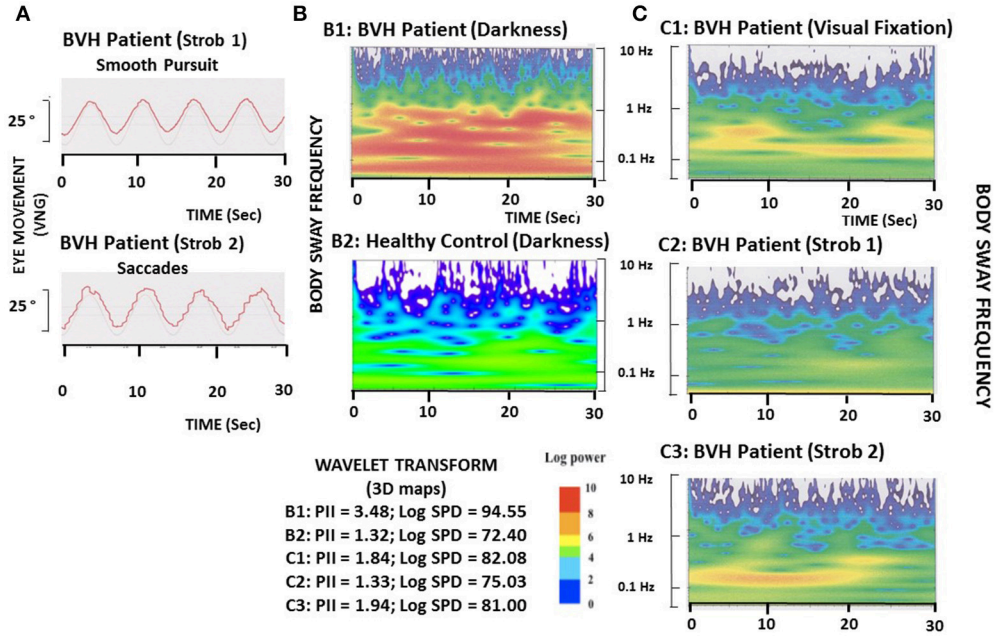

FIGURE 1 | Illustration of eye movements and postural performance in one representative BVH patient during the different visual conditions. **(A)**. The BVH patient must pursuit a visual target moving sinusoidally in the horizontal plane (25° amplitude; 0.13 Hz frequency) in stroboscopic light at either the 4.5 Hz flicker frequency, which elicits slow eye movements (smooth pursuit: strob 1), or the 1.2 Hz flicker frequency, which induces saccadic eye movements (strob 2). **(B)**. Comparison of the wavelet transform applied on the antero-posterior CoP displacements between the BVH patient **(B1)** and one representative healthy subject **(B2)** tested in total darkness. The wavelet analysis provides a 3D chart of body sway with time on the abscissae (in seconds), frequency content of the stabilogram on the ordinates (log scale in Hz), and spectral power density shown as a color code for the third dimension (expressed in decimal log). The Postural Instability Index (PII) and the spectral power density (PSD, expressed in decimal log) in the frequency range of the visual system (0.05–0.5 Hz), derived from the wavelet plots, show both higher values in the BVH patient (3.48 and 94.55, respectively) compared to the healthy control (1.32 and 72.40, respectively). **(C)**. 3D chart of the antero-posterior sway of the BVH patient tested during visual fixation of the target **(C1)**, tracking of the target with slow eye movements (**C2**: strob 1), and saccadic pursuit (**C3**: strob 2). Compared to the recording made in total darkness (**B1**), fixation, smooth pursuit, and saccades improve the BVH patient's postural stability, as shown by the strong reduction of the PII and SPD (1.84 and 82.08, 1.33 and 75.03, and 1.94 and 81.00 for the three visual conditions, respectively).

This method is particularly relevant to extract from the raw posturography data several parameters directly related to the steady-state behavior of quiet standing, or to the functional interactions with the neuromuscular mechanisms involved in the maintenance of upright stance. The amplitude of the critical point, expressed in mm^2, is a good estimate of the limits over which posture is necessary corrected by feedback mechanisms to avoid fall.

The fractal analysis is based on fundamental concepts and principles from statistical-mechanics. It is aimed at determining if two consecutive points in the stabilogram are correlated, i.e., linked by a causal relationship (CoP is moving forward because of a previous backward displacement: feedback correction; close-loop control mechanism), or if these points are not correlated (random CoP trajectory, stochastic process: open-loop control mechanism). We have calculated the number of the Hausdorff points in each stabilogram, i.e., the number of sampling points in the CoP trajectories that are not correlated each other, and the mean frequency of these points in each visual condition for the CoP displacements in the AP and ML directions. The Hausdorff frequency parameter provides another estimate of posture stability. It allows to approximate the mean time-interval during which the patient remains stable without doing any postural correction. Higher the Hausdorff frequency, shorter the mean time-interval, and more stable the subject.

Statistical Analysis

Four parameters describing body sway during quiet standing were analyzed: the global score of posture control given by the Postural Instability index (PII), the Spectral Power Density (SPD) expressed in the frequency domain of the visual system (0.05–0.5 Hz frequency part), the amplitude of the critical point (CP amplitude) and the frequency of the Hausdorff points accounted by the stochastic process of posture control. To measure the effects of visual condition on posture control, i.e., darkness, visual fixation, visual pursuit with low (saccades) and high (smooth pursuit) flicker frequencies, the four postural parameters were analyzed using a 4-way ANOVA followed by a *post-hoc* analysis with the Tuckey test (Stateview II software). Results were considered significant for $p < 0.05$.

RESULTS

The ANOVAs performed on each of the posturography parameters pointed to significant differences between the BVH

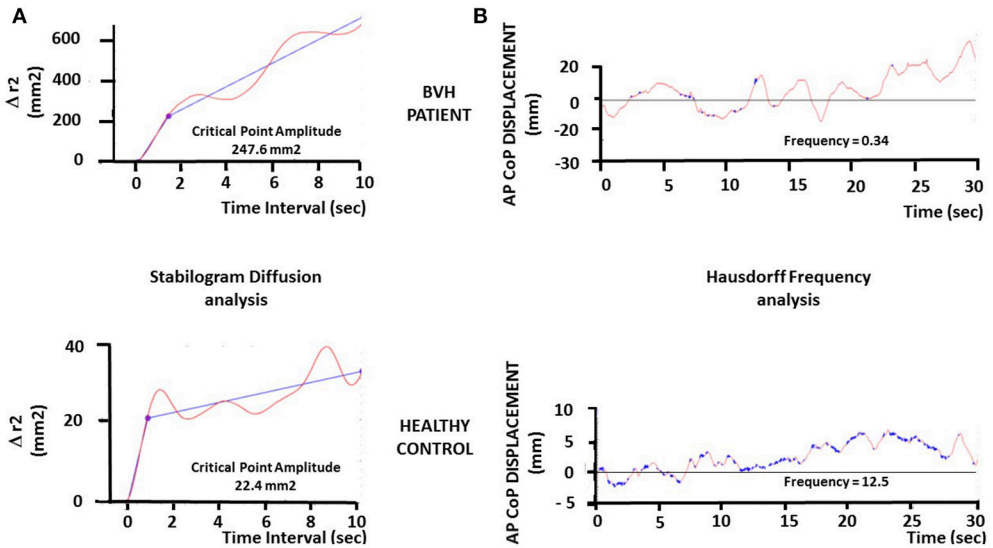

FIGURE 2 | Illustration of the stabilogram-diffusion analysis and fractal analysis in one representative BVH patient and one representative healthy subject. **(A)**. Stabilogram-diffusion analysis provides a linear-linear plot of mean square antero-posterior CoP displacement vs. time interval. Planar stabilogram plots show the critical point as the intersection of the two regression lines performed on the raw CoP displacements data. The critical point provides the critical time interval (abscissae: in seconds) and the critical mean square displacement (ordinates: Δr^2, in square millimeters). The critical time interval is similar in both the patient (upper graph) and the healthy subject (lower graph), while the critical mean square displacement is strongly increased in the BVH patient compared to the control (247.6 vs. 22.4 mm^2). **(B)** Fractal analysis applied to the antero-posterior CoP displacements of the BVH patient (upper graph) and the healthy control (lower graph), illustrating the points in the samples (Hausdorff dimension) that are not correlated each other (in blue on the plots). These uncorrelated points illustrate the stochastic process in posture regulation, i.e., the events in the stabilogram which do not induce postural corrections (open loop or automatic control). The plots show a higher number of Hausdorff points in the control compared to the BVH patient, indicating a better postural stability in the control subject.

patients and the control group. The values were [$F_{(1, 40)} = 12.54$; $p < 0.05$] for the Postural Instability Index, [$F_{(1, 40)} = 59.71$; $p < 0.001$] for the SPD recorded in the visual frequency part, [$F_{(1,40)} = 68.45$; $p < 0.0001$] for the amplitude of the critical point, and [$F_{(1, 40)} = 70.50$; $p < 0.0001$] for the frequency of the Hausdorff points.

The **Figures 1B,C** illustrates the wavelet transform applied to the stabilograms of one representative BVH patient examined in the four different visual conditions, and of one healthy control tested in darkness. Compared to the 3D map of the healthy subject, the BVH patient tested in the same visual condition exhibits a higher Postural Instability Index (PII: 3.48 vs. 1.32), and spends much more energy in the low frequency range (Log SPD = 94.5 vs. 72.40) to realize the postural task (**Figure 1B**). The figure shows also that both visual fixation and visual pursuit of a target, whatever the flicker frequency (strob 1: 4.5 Hz, slow eye movement; strob 2: 1.20 Hz, saccades), induce in the BVH patient a strong decrease of the PII. On the other hand, the spectral power density is strongly reduced compared to the task performed in total darkness, and particularly in the low frequency range of body sway (**Figure 1C**).

The **Figure 2** illustrates the stabilogram-diffusion analysis (**Figure 2A**) and the fractal analysis (**Figure 2B**) performed on the CoP displacements of another representative BVH patient (upper graphs) compared to another healthy control (lower graphs) examined in darkness. It can be seen that the amplitude of the critical point in the BVH patient is strongly increased (247.6 mm^2) compared to the control subject (22.4 mm^2) (**Figure 2A**), indicating that the control subject shifts to close-loop control mechanisms for much more lower CoP displacements ($\sim$ 4.7 mm) than the control ($\sim$ 14.7mm). Moreover, the Hausdorff frequency is much higher in the healthy control (12.5 Hz) compared to the BVH patient (0.34 Hz) (**Figure 2B**). These values correspond to mean time-intervals of posture stability without postural corrections every 80 and 2,900 ms for the control (stable) and the patient (unstable), respectively.

The ANOVA performed on the Postural Instability Index (PII) of the BVH patients showed that visual condition constituted the main fixed effects responsible for the sources of variation among subjects [$F_{(3, 60)} = 11.98$, $p < 0.00001$]. This parameter was significantly decreased in the three visual conditions (Strobe 1: $p < 0.0001$, Strobe 2: $p < 0.004$, and Gaze fixated: $p < 0.001$) compared to darkness. The more destabilizing condition was observed in darkness (PII = 2.88 $\pm$ 1.19) whereas the lowest value was found in the Strobe 1 condition (PII = 1.69 $\pm$ 0.77). No significant differences were found between Fixation and Strob 1, and Fixation and Strob 2 in the patients. For comparison, the control group showed a significantly lower PII value in darkness compared to the BVH patients (PII = 1.97 $\pm$ 0.61; $P < 0.006$). However, the PII was not significantly modified with vision of a space-fixed target or eye movements in the healthy participants.

Rather similar findings were found for the three other parameters tested in the patients' group. The ANOVAs

performed on the SPD in the visual frequency range, the amplitude of the critical point, and the Hausdorff frequency showed that visual conditions constituted the main fixed effects responsible for the variations among subjects, with [$F_{(3,57)} = 11.75$, $p < 0.0001$], [$F_{(3,57)} = 5.63$, $p < 0.01$], and [$F_{(3,60)} = 9.5$, $p < 0.00001$], respectively. These three parameters were significantly different in all visual conditions compared to darkness, at highly significant levels. The SPD and the amplitude of the critical point were significantly decreased in gaze fixation, Strob 1 and Strob 2 conditions compared to darkness, while in the same time the Hausdorff frequency was significantly increased. The highest values were always observed in darkness (Log SPD = 85.61 ± 10.59; critical point amplitude = 328.3 ± 213.5 mm^2), whereas the lowest values were found in the Strobe 1 condition (Log SPD = 76.48 ± 9.52; critical point amplitude = 100.23 ± 157.2 mm^2). The opposite pattern was seen for the Hausdorff frequency, with the highest value in Strob 1 (1.13 ± 0.63 Hz) and the lowest in darkness (0.59 ± 0.36 Hz). By contrast, the visual conditions did not change so drastically the postural performance of the control group. No significant differences were found between darkness and the other visual conditions regarding the frequency of the Hausdorff points evaluated from the AP stabilogram; this parameter was improved only during the strob 2 condition (saccades) and from the ML stabilogram ($p < 0.02$). The SPD in the visual frequency part was not statistically modified in the ML direction, but it was significantly increased in darkness compared to the other visual conditions for the AP stabilogram. The amplitude of the critical point was significantly decreased in all visual conditions compared to darkness ($p < 0.0001$).

The **Figure 3** summarizes the mean results recorded in the whole population of BVH patients and in the control group for the Postural Instability Index (PII: **Figure 3A**), the SPD in the visual frequency band (SPD: **Figure 3B**), the Amplitude of the Critical Point (CP amplitude: **Figure 3C**), and the Frequency of the Hausdorff Points (Hausdorff Frequency: **Figure 3D**). Compared to the test performed with eyes open in total darkness (dark), all four quantified postural parameters are significantly modified, attesting that posture stability was significantly improved when the patients fixated a stable space-fixed target (fixation), when they followed the moving target with smooth pursuit (strob 1 condition), and when performing saccadic eye movements (strob 2 condition). The control group exhibited postural improvement limited only to two postural parameters: the SPD in the AP direction, and the critical point amplitude, even though it remains at very low values in all visual conditions.

The comparison of the effects of visual condition on the AP and ML stabilograms in the BVH patients and in the control group is illustrated in the **Table 1**. The mean values (±standard deviation) of the SPD in the visual frequency band and of the Hausdorff points frequency are provided. **Table 1** shows similar changes in both the AP and ML stabilograms for the BVH patients, with significantly reduced SPD values ($p < 0.01$) and significantly increased Hausdorff frequency ($p < 0.01$) during fixation, strob 1 and strob 2 conditions compared to darkness. Taken together, the results point to posture stability improvement in both directions when visual stimuli or eye movements are present. By contrast, the visual conditions do not change so drastically the postural performance of the healthy participants. Significant differences are observed only for the SPD of the AP stabilogram between darkness and the other visual conditions, and between darkness and strob 2 condition (saccades) for the Hausdorff frequency evaluated from the ML stabilogram ($p < 0.05$).

DISCUSSION

It is common to say that vestibular a-reflexic patients are strongly impaired without vision, because visual cues constitute strong extra-vestibular signals substituting to the lack of vestibular information in day life situations. Our results confirm this general statement since the comparison with healthy sex- and age-matched controls points to highly significant differences between the two populations for the tests performed in darkness.

The original finding of the present study is that posture control is differentially affected by the visual conditions in the BVH patients and the healthy participants. In the control group, the global postural score is not significantly modified with fixation or eye movements compared to darkness (mean PII around 2), and the Hausdorff frequency remains at high levels (around 2 Hz), corresponding to stable body positions every 0.5 s whatever the visual conditions. The amplitude of the critical point remains very low in all conditions, in the range 30–60 mm^2, corresponding to postural corrections by the close-loop control mechanisms for CoP displacements as low as 5–8 mm. And the SPD in the low visual frequency part is significantly reduced with fixation and eye movements compared to darkness. Taken together, these data indicate that fixation of a stable space-fixed target, voluntary pursuit of a moving target and eye-tracking with saccades slightly improve the postural performance of the healthy participants mainly by reducing the energy cost to control body sway, and by increasing the efficacy of the close-loop control mechanisms.

By contrast, the BVH patients tested in darkness have significantly higher PII (2.88) and critical point amplitude (328.30 mm^2), spend more energy to control posture (higher SPD in the visual frequency part), and show lower Hausdorff frequency (corresponding to stable positions every 1.63 s). All the values recorded point to a strong degradation of posture control without vision in the BVH patients. The results clearly show however that visual input provided by fixation of a stable space-fixed target, by voluntary pursuit of a moving target with smooth pursuit, or during saccades strongly improved posture stability in the BVH patients compared to their postural performance recorded in total darkness. In these visual conditions, the patients' postural performance attested by the PII becomes quiet similar to that recorded in healthy controls. Moreover, the SPD, the critical point amplitude and the Hausorff frequency become much closer to the controls, suggesting that the BVH patients use all the sensorimotor inputs provided by their eye movements as substitution processes to improve posture control.

TABLE 1 | Comparison of the effects of the visual condition on the spectral power density and the Hausdorff frequency for the AP and ML stabilograms recorded in the BVH patients, and in the control group.

	Spectral power density (Log)		Hausdorff frequency (Hz)	
	AP CoP displacements	**ML CoP displacements**	**AP CoP displacements**	**ML CoP displacements**
BVH Patients				
Dark	85.61 (10.50)	67.95 (17.35)	0.59 (0.36)	1.21 (0.80)
Fixation	79.78 (9.25)	60.92 (13.75)	1.00 (0.72)	2.01 (1.70)
Strob 1	76.48 (9.52)	57.23 (11.97)	1.13 (0.63)	2.64 (2.14)
Strob 2	79.68 (8.90)	57.21 (12.14)	1.07 (0.73)	2.91 (1.85)
Controls				
Dark	76.41 (5.90)	59.61 (7.25)	2.06 (0.50)	2.23 (0.53)
Fixation	72.81 (6.51)	57.65 (8.25)	2.62 (0.61)	3.06 (0.88)
Strob 1	71.38 (7.15)	55.63 (7.58)	2.09 (0.71)	2.79 (0.76)
Strob 2	72.48 (7.44)	56.83 (9.12)	1.71 (0.80)	3.08 (0.67)

The mean spectral power density (decimal Log ± SD) evaluated in the visual frequency part (0.05–0.5 Hz) and the mean Hausdorff frequency (±SD) are given for each of the four visual conditions (dark, fixation, strob 1 condition: slow eye movements, and strob 2 condition: saccadic eye movements) for CoP displacements recorded in the antero-posterior (AP) and mediolateral (ML) directions.

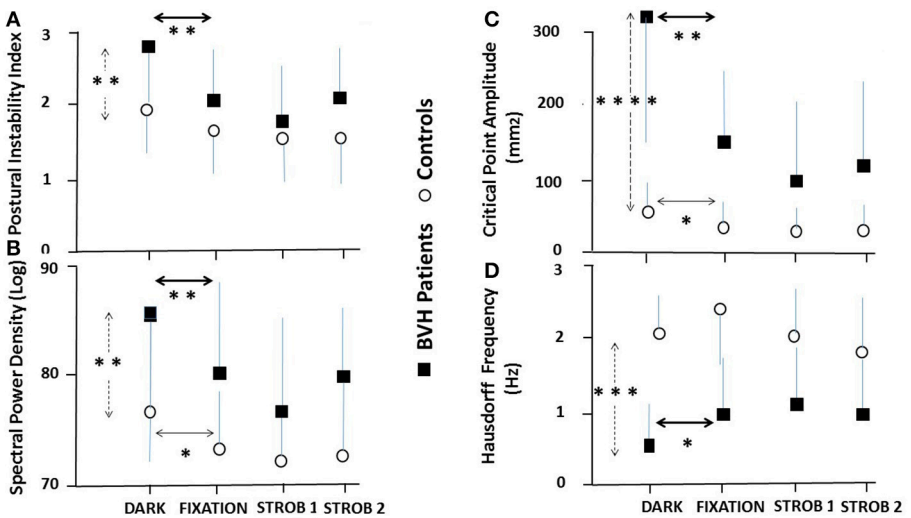

FIGURE 3 | Effect of visual input and eye movements on posture stability in bilateral vestibular hypofunction patients and healthy participants. Mean results recorded in the population of BVH patients ($N = 21$: filled squares) and the control group ($N = 21$: open circles) in the four experimental visual conditions during quiet standing. **(A)** Mean postural instability index (±SD) derived from the wavelet transform recorded in darkness, during vision of a space-fixed target, eye pursuit of the sinusoidally moving visual target in the strob 1 condition (slow eye movements) and strob 2 condition (saccades). The vertical dashed arrow indicates significant differences in total darkness between the patients and the controls, while the heavy and light horizontal arrows show significant differences between darkness and the three other visual conditions in the patients and the controls, respectively. **(B)** Mean spectral power density (±SD) in the visual system frequency part (0.05–0.5 Hz), expressed in decimal logarithm and derived from the wavelet analysis. Same conventions as in **(A)**. **(C)** Mean amplitude (±SD) of the critical point calculated with the stabilogram-diffusion analysis. Same conventions. **(D)** Mean Hausdorff frequency (±SD) derived from the fractal analysis. The frequency was evaluated by dividing the number of uncorrelated points by the recording time. A higher frequency indicates a better body stabilization. Note that all four parameters point to a better postural stability when BVH patients fixate a visual target, do slow eye movements or saccades by comparison with quiet standing in darkness. In contrast, the different visual conditions do not modify so drastically the postural parameters in the control group compared to the patients. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$.

Many studies investigated the visual contribution to postural stability in healthy subjects [(27–29), for reviews]. Visual fixation of a stationary target was reported to improve postural stability by decreasing body sway, and it has been proposed that the CNS can interpret the eye movement inputs to gain positional information (2). These authors have distinguished two modes of visual detection of body displacements. The ocular mode, based on the retinal slip (motion of the target on the retina), is very unlikely a mechanism playing a role in our experimental conditions. Indeed, retinal slip is minimized both by the smooth pursuit system and the vestibulo-ocular reflex, if any. The extra-ocular hypothesis is more likely because this second mode is based

either on ocular motor efference copy signals or proprioceptive reafferences from the extra-ocular muscles. Reduction of postural sway during fixation suppression of the nystagmus in patients with vestibular neuritis supports the role of ocular motor signals rather than that of pure visual cues elicited by retinal slip for the visual control of body sway (30).

The effect of eye movement on posture stability in healthy subject shows contrasting results in the literature. Schulmann et al. (31) concluded that tracking eye movements has a negative effect on balance, a result confirmed by Glasauer et al. (8), while smooth pursuit and saccades improved balance (32). A better postural control was also reported by Stoffregen et al. (7) and Rougier et al. (6) when subjects performed saccadic eye movements, confirming a more ancient study (5). The data suggest that saccadic and tracking eye movements have fundamentally different effects on posture; tracking with slow eye movements affect body sway but not saccades since vision is suppressed during saccadic eye movements (28, 29, 33). Of particular interest are the anatomo-histological findings showing that eye muscle fibers implicated in slow phase eye movements like smooth pursuit and nystagmus are non-twitch fibers characterized by a rich contain of neuromuscular spindles, while twitch fibers implicated in saccadic eye movements would be less richly endowed with muscle spindles (34). Our data do not show however significant differences in posture stability during saccadic or slow eye movements in our BVH patients, even though the best postural stability was always seen during tracking with smooth pursuit. In our experimental conditions, the extra-retinal signals are the major source of visual information during saccades, tracking and fixation of a stable target, suggesting that the same motor ocular factors are involved. That could explain why we found no changes in postural sway between these experimental conditions in the BVH patients.

How explaining however the discrepancy regarding the opposite effects of slow eye movements on posture control between healthy controls and BVH patients? The different postural describers used to investigate balance control could be one explanation. Most of the studies reported above have computed very simple describers (length and area of CoP displacements) that are not sensitive enough to describe precisely how posture is regulated. They do not take into account the energy cost to control posture and they ignore possible postural strategies. Our more functional parameters cannot explain however why opposite results were obtained with the same conventional postural describers used in the previous studies. The different populations tested (patients vs. controls) could be another explanation. How slow eye movements could destabilize posture in healthy subjects and unilateral vestibular loss patients, and have stabilizing effects in BVH patients. One hypothesis supported by our data is that total loss of vestibular functions induces a more power anchoring on eye proprioception compared to patients with a remaining labyrinth or healthy subjects. The BVH patients would use more than controls their eye muscle proprioceptive afferents, and/or the efference copy derived from the ocular motor command. Another one is to consider the effects of dual-tasking reported in the literature on posture control. Keeping quiet standing with a concomitant visual task is the illustration of a simple dual-task in which the visual task (fixation or pursuit of a visual target) interferes with the postural task (stand quietly). Such interactions have been reported since a long time with dual-task paradigms combining postural tasks and cognitive tasks, in which either posture or cognitive performance were altered due to the necessity to share the attentional resources between the two tasks (35). In healthy adults, it was proposed that attention is more focused on the cognitive task and, as a consequence, posture stability is improved because posture control is shifted to a more automatic mode of posture control (21, 36)]. On the contrary, deficits in the allocation of attention with aging or pathology have been suggested to explain the less efficient balance performance in dual-task conditions (21, 37, 38). The present study showed that our chronic BVH patients are more stable and spend less energy to control their posture in the visual tasks with fixation, slow eye movements and saccades. The mean age of the patients (62.9 years) being still outside the old senior population, the secondary visual tasks could indeed contribute to improve their posture stability more than in healthy controls. Indeed, not only the PII and the SPD in the visual frequency part were strongly reduced, but the Hausdorff frequency was increased, indicating that the BVH patients are more frequently stable compared to the dark condition without secondary visuo-motor task. Moreover, the amplitude of the critical point was reduced significantly, a result suggesting that the close-loop mechanisms of posture control are evoked for smaller CoP displacements.

Taken together, our data confirm that BVH patients have poor postural control in total absence of visual cues, and support that new idea that visual detection of body sway is one mechanism used by the BVH patients to improve their posture stability. The present findings strongly suggest that extra-ocular proprioceptive re-afferences or copy of the eye motor command are very likely involved, and over-used in a compensatory sensorimotor substitution process. On the other hand, when the BVH patients are in dual-task conditions, they shift to a more automatic mode of posture control that contributes also to improve their postural performance.

LIMITS OF THE STUDY

Our population of BVH patients is heterogeneous and includes patients with remaining vestibular functions regarding the otolith organs. Even though all the patients were submitted to vestibular rehabilitation therapy, the rehabilitation programs were not the same for all patients, and the history of the disease was also different in terms of duration and feeling of the handicap. The impact on the quality of life was attested in our BVH patients with regard to balance control and visual contribution to posture regulation, but not concerning the psycho-affective dimension. We tested the BVH patients on stable support only, not on foam or unstable support, another experimental condition that could provide useful information on proprioception contribution to posture control.

AUTHOR CONTRIBUTIONS

ML, CVN, and MT conceived and designed the experiments. ML, AT, SH, and ND performed the experiments. ML wrote the paper.

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Errors of Upright Perception in Patients With Vestibular Migraine

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Patients with vestibular migraine (VM) often report dizziness with changes in the head or body position. Such symptoms raise the possibility of dysfunction in neural mechanisms underlying spatial orientation in these patients. Here we addressed this issue by investigating the effect of static head tilts on errors of upright perception in a group of 27 VM patients in comparison with a group of 27 healthy controls. Perception of upright was measured in a dark room using a subjective visual vertical (SVV) paradigm at three head tilt positions (upright, ±20°). VM patients were also surveyed about the quality of their dizziness and spatial symptoms during daily activities. In the upright head position, SVV errors were within the normal range for VM patients and healthy controls (within 2° from true vertical). During the static head tilts of 20° to the right, VM patients showed larger SVV errors consistent with overestimation of the tilt magnitude (i.e., as if they felt further tilted toward the right side) (VM: −3.21° ± 0.93 vs. Control: 0.52° ± 0.70; $p = 0.002$). During the head tilt to the left, SVV errors in VM patients did not differ significantly from controls (VM: 0.77° ± 1.05 vs. Control: −0.04° ± 0.68; $p = 0.52$). There was no significant difference in SVV precision between the VM patients and healthy controls at any head tilt position. Consistent with the direction of the SVV errors in VM patients, they largely reported spatial symptoms toward the right side. These findings suggest an abnormal sensory integration for spatial orientation in vestibular migraine, related to daily dizziness in these patients.

Keywords: vestibular migraine, head tilt, subjective visual vertical, perception of upright, dizziness

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INTRODUCTION

Vestibular migraine (VM) is the most common cause of dizziness and spatial disorientation with a lifetime prevalence of about 1% in the general population (1). Currently the pathophysiology of vestibular migraine is unknown and a pathognomonic test is lacking (2). Although abnormal findings in vestibular evoked myogenic potentials (VEMP) imply disturbances of "low-level" otolithic pathways in these patients, the reduced motion detection thresholds in the roll plane and functional imaging data support the hypothesis that VM patients harbor a dysfunction of "high-level" vestibular perception (3–7).

A key aspect of our spatial perception is "orientation constancy", as we maintain a stable perception of our surroundings in upright orientation despite continuous changes in the eye, head and body positions. Patients with vestibular migraine often complain of symptoms triggered by these changes, raising the possibility of dysfunction in neural mechanisms underlying orientation constancy (1). Such perceptual dysfunction can be studied by measuring perception of upright in a psychophysical task known as the subjective visual vertical (SVV) (8, 9). Perception of upright involves integration of graviceptive signals from the otoliths with visual inputs from the retina and proprioceptive inputs encoding the head, eye, and body positions (9–11). In the upright position, where the reference frames of the eye, head, and visual world are all aligned with the direction of gravity, SVV typically remains within 2° of earth vertical (9, 12). With lateral head tilts, however, there are usually systematic SVV errors that do not correspond with the magnitude of the head tilt (9). Naturally, a lateral head tilt leads to a change in the torsional eye position in the opposite direction of the head tilt. This ocular counter-roll only partially compensates for the amount of head tilt, typically with a low gain of about 0.10–0.25 in humans (13, 14). Therefore, the reference frames for the head, eye (retina) and the visual world no longer align with the gravitational vertical, and images become tilted on the retina during head tilt. This separation of the sensory reference frames introduces a challenge for the brain, especially in the absence of visual cues, when it has to rely on information about the head (in space) and eye (in head) positions to determine upright orientation. Such processing demand is reflected by the systematic SVV errors during head tilt (9). Usually, at small head tilt angles, SVV errors are in the opposite direction of the head tilt, reflecting overcompensation for the amount of tilt and thus overestimation of upright orientation relative to the head position (known as the E-effect) (9). At large tilt angles, SVV errors are usually in the direction of the head tilt, reflecting undercompensation for the amount of tilt and thus underestimation of upright orientation relative to the head position (known as the A-effect) (9, 15, 16).

Previous studies in patients with vestibular migraine found that SVV was not altered when the head was in the upright position (17, 18). However, in these patients, errors of upright perception have not been investigated during static head tilt, when the brain has to maintain a common multisensory reference frame for orientation constancy. Thus, here we asked whether such multisensory integration is affected in vestibular migraine by investigating the effects of static head tilts on SVV accuracy and precision, and comparing the results with those of healthy controls.

MATERIALS AND METHODS

Participants

We enrolled 54 participants: 27 healthy controls with no prior history of migraine, dizziness, or other neurological disorder, and 27 patients who met the diagnostic criteria for vestibular migraine according to the consensus document of the Bárány Society and the International Headache Society (IHS) (1). The experiments were approved by the Johns Hopkins institutional review board and informed written consent was obtained from all participants.

Patients were recruited consecutively from the Johns Hopkins Outpatient Center between March 2016 and June 2017. Control participants were also recruited within the same time period. The average age for healthy controls was 41 years old (16 female) and for patients was 43 years old (19 female). All participants were right-handed by self-report, except for one left-handed patient (34 y/o, female) and one left-handed control participant (34 y/o, female). All patients met the diagnosis of vestibular migraine based on the Bárány and IHS criteria (**Table 1**). Patients with peripheral or central vestibular dysfunction on exam or with lab or imaging findings that confirmed other diagnoses were not included in this study. Absence of vestibular dysfunction or central pathology was verified by expert neuro-otological examination, brain MRI, examination of the eye-movements using video oculography, video head impulse testing (vHIT), and quantitative rotational chair testing. None of the patients had spontaneous nystagmus with removal of visual fixation or provoked nystagmus with head shaking, vibration over the mastoids, hyperventilation, Valsalva maneuver, or in the static head down positions (i.e., positional/positioning nystagmus) to indicate an underlying vestibular imbalance (19). The ocular motor evaluations including saccade, pursuit, and optokinetic responses were normal. All patients had normal balance function that included evaluations with tandem gait, standing with heels together, and standing on one leg with eyes open and closed. Fourteen patients (51.9%) were not taking any CNS-acting medication. Four patients (14.8%) were on selective serotonin or serotonin and norepinephrine reuptake inhibitors (SSRI/SNRIs), four patients (14.8%) were on tricyclic antidepressants (TCAs), and one patient (3.7%) was on trazodone. Two patients (7.4%) were taking valproic acid, one patient (3.7%) carbamazepine, and one patient (3.7%) topiramate. Four patients (14.8%) were on meclizine and three patients (11.1%) were on benzodiazepines. A dizziness questionnaire was used to probe the quality of spatial symptoms in VM patients. Specifically, patients were asked about sensation of body tilting or pulling, sensation of body rotation or spinning, dizziness when lying down on the sides, or dizziness with tilting the head laterally to the shoulders. If any of these qualities was present, they were asked to specify the direction in which they experienced symptoms as rightward, leftward, rightward and leftward, or other directions. All patients reported daily dizziness with a mean duration of 2 years (range: 3 months to 12 years, standard error of the mean: 6 months).

Experimental Setup for SVV Recordings

Participants sat upright in a completely lightproof room, fixing on a red dot (diameter 1.67 mm) at eye level, which was presented on an active matrix LED screen (2,560 × 1,600 AMOLED, Samsung Galaxy Tab S) 55 cm away in front of them. We chose this type of tablet because its pixels are not backlit, eliminating any glow from the black screen background that might provide visual cues during SVV recording. In addition, subjects could only see the screen through a round opening, as the frame of the tablet mount was also covered by gaffer's tape to avoid reflections.

TABLE 1 | Symptoms characteristics and vestibular test results in VM patients.

Characteristics of dizziness	
	***n* (%)**
Moderate intensity	6 (22.2)
Severe intensity	21 (77.8)
Lasting minutes	2 (7.4)
Lasting hours	25 (92.6)

Characteristics of headaches	
	Mean (SEM)
Age of onset (years)	30 (3.5)
Frequency (days per month)	6.5 (1.8)
Intensity (1 to 10)	5.7 (0.5)
	***n* (%)**
Lasts 4 h or more	14 (60.8)
Unilateral	12(77.3)
Pulsatile or throbbing	16 (61.5)
Aggravation by physical activity	7 (33.3)
Visual aura	11 (45.8)
Photophobia	19 (79.2)
Phonophobia	19 (79.2)
Nausea and/or vomiting	7 (29.2)

Vestibular tests results	
vHIT	**Mean (SEM)**
Gain, left	0.96 (0.02)
Gain, right	1.00 (0.02)
vHIT gain asymmetry	0.04 (0.01)
Chair rotation velocity steps	**Mean (SEM)**
60°/s gain, left	0.64 (0.03)
60°/s gain, right	0.69 (0.04)
240°/s gain, left	0.57 (0.04)
240°/s gain, right	0.59 (0.03)
60°/s TC, left	18.09 (1.30)
60°/s TC, right	17.45 (1.30)
240°/s TC, left	12.82 (1.00)
240°/s TC, right	12.99 (0.77)
60°/s gain asymmetry	0.12 (0.01)
240°/s gain asymmetry	0.07 (0.02)
60°/s TC asymmetry	0.15 (0.02)
240°/s TC asymmetry	0.07 (0.02)

All patients had chronic daily dizziness and met the diagnostic criteria for vestibular migraine. The video head impulse testing (vHIT) results show normal vestibular gains (eye velocity/head velocity) with both right and left head impulses (normal gain: 0.7–1) (20). The rotational chair results show normal vestibular gains (normal gain: 0.4–1) at both low and high velocity steps (60°/s & 240°/s). The time constant (TC), which is a measure of nystagmus duration induced by the rotational velocity step, is also within the normal range at both velocities (normal range: 8–25 s) (21). Overall, there are no significant asymmetries between the right and left vestibular gains (i.e., both vHIT and rotational chair testing) or time constants. n, Number of patients; SEM, Standard error of the mean.

Participants wore contact lenses or glasses as needed. SVV was measured in three head positions for each participant: upright (UP), 20° head tilt toward the right shoulder (right ear down or RED), and 20° head tilt toward the left shoulder (left ear down or LED). A molded bite-bar secured to a rotating tilt plate was used to passively position the head in the roll plane, and for measuring the angle of head tilt. Each participant was tested under all three head tilt positions in random succession, completing 100 SVV trials in each head position. We chose 20° head tilt because it is within the physiologic range of neck positions, and while comfortable to maintain during the recordings, it is large enough to induce SVV errors.

SVV Paradigm

We used a two-alternative forced choice task (2AFC) that was not bound by fixed probing angles to measure SVV responses. The full description of this SVV paradigm has been previously published by our group (22). At each trial, a red line (length 4 cm, width 0.75 mm) was presented at a random angle, radiating from a red dot (**Figure 1A**). The paradigm was controlled by a custom software written in Matlab (Mathworks) using Psychtoolbox (23). Stimuli were transmitted from the Matlab computer to the display tablet over the network using join.me software (LogMeIn, Inc.). In each trial, participants clicked one of two buttons on a game controller, reporting whether the line was oriented to the "right" or "left" of their perceived vertical orientation. The paradigm started with angles presented randomly from the entire 360° range. As the recording session progressed, the range of probing angles was adjusted in blocks of 10 trials by centering it around the SVV calculated from responses in previous trials (**Figure 1B**). Each block consisted of five different angle orientations in the upper visual field, and five in the lower visual field. After the sixth block, the range was kept constant at 8°. If a trial was missed when the participant did not respond within 1.5 s, that angle was presented again at a later time within the same block, ensuring that all angles were probed and the corresponding responses were obtained only once. Upon completion of 100 trials (3–5 min), an SVV value was calculated by fitting a psychometric curve to the responses from 100 trials (**Figure 1A**). The angle at which the probabilities of left and right responses were both 50%, the point of subjective equality, was taken as the SVV value. An estimate of the slope of the psychometric curve was used to calculate SVV precision. This was calculated as the difference in angle between the two points on the psychometric curve with probabilities of 50% and 75%.

Data Analysis

SVV accuracy in each head tilt position was compared between the VM patients and healthy controls using unpaired *t*-tests with the α-level adjusted to 0.0167 by Bonferroni correction.

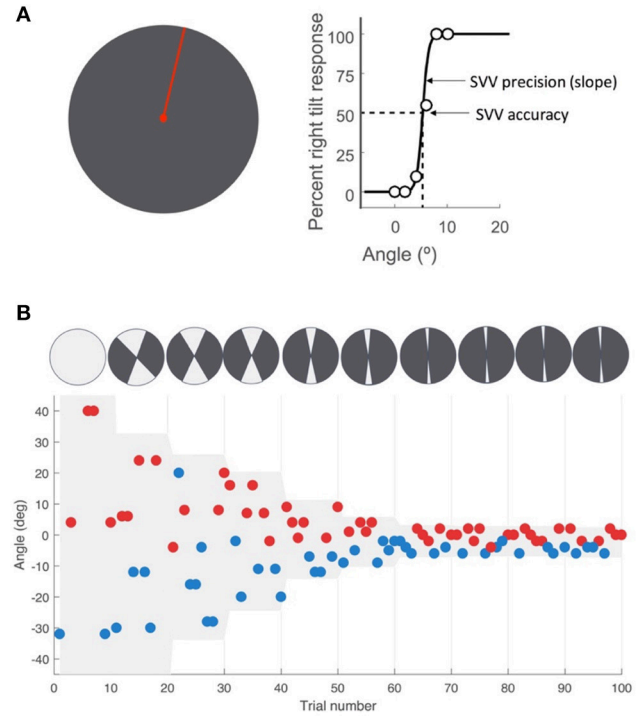

FIGURE 1 | SVV paradigm. **(A)** SVV measurement with the line stimulus (red) presented at a random orientation in each trial. As a two-alternative forced choice paradigm (2AFC), the task in each trial is to report whether the line is tilted to the right or left of perceived upright orientation. SVV is then determined by fitting a psychometric curve to the responses from all trials, and calculated as the value on the curve at which the probability of left or right responses is 50% (point of subjective equality). The SVV precision is calculated as the slope of the psychometric fit. **(B)** A sample time course of 100 trials with the participant's responses, with each point representing one trial. The y-axis shows the angle of the line presented and the color indicates the response for that trial. The left tilt responses are shown in blue and the right tilt responses in red. The line angles were presented randomly within a range that started at 360° and then adjusted based on previous responses (illustrated by the top circles with the light gray sectors). At the end of every 10 trials, the center of this range (also shown in light gray shade on the graph) was set as the SVV value calculated from the previous trials. The range was reduced in half every 10 trials until it reached 8° (±4° around the calculated center), after which it was kept constant for the remaining trials.

We used D'Agostino-Pearson omnibus test to verify the normal distribution of the SVV results. The results for SVV precision in each head tilt condition were compared similarly between the VM patients and healthy controls.

RESULTS

Accuracy of SVV responses (i.e., SVV error) in the three static head tilt positions (i.e., UP at 0°, left head tilt at −20°, and right head tilt at +20°) were compared between VM patients and healthy controls. The mean SVV error in the upright position was within the normal range (within ±2° of earth vertical) for both VM patients (mean SVV± SEM: −1.04° ± 0.43) and controls (−0.25° ± 0.38) (9, 12), and it did not differ between the two groups (Student's *t*-test with Bonferroni correction $\alpha = 0.0167$; $p = 0.17$). With the left head tilt, the mean SVV error in VM patients (0.77° ± 1.05) and controls (−0.04° ± 0.68) were not different ($p = 0.52$). With the right head tilt, the SVV error in VM patients (−3.21° ± 0.93) and controls (0.52° ± 0.70) were significantly different (Student's *t*-test with Bonferroni correction $\alpha = 0.0167$; $p = 0.002$) (**Figures 2**, **3**). Despite the difference in the SVV accuracy, the precision of SVV responses did not differ significantly between the VM patients and controls in any head tilt position (Student's *t*-test with Bonferroni correction $\alpha = 0.0167$; $p > 0.3$ for all three head positions) (**Figure 3**).

We also analyzed the number of participants in each group that showed SVV errors with "overestimation" of the head tilt (SVV error in the opposite direction of the head tilt, i.e., the E-effect) or "underestimation" of the head tilt (SVV errors in the same direction as the head tilt, i.e., the A-effect) (**Table 2**). Participants whose SVV value was 0° for a given head tilt were classified as having neither the A- nor the E-effect (only two participants among controls). For VM patients, there were 14 A-effects (mean SVV ± SEM: −3.41° ± 0.73) and 13 E-effects (5.28° ± 1.04) with the left head tilt, while there were seven A-effects (2.43° ± 0.52) and 20 E-effects with the right head tilt (−5.19° ± 0.88). For controls, there were 14 A-effects (−2.75° ± 0.52) and 11 E-effects (3.40° ± 0.65) with the left head tilt and 14 A-effects (3.34° ± 0.60) and 13 E-effects (−2.51° ± 0.54) with the right head tilt.

Overall, 21 VM patients reported dizziness induced by lateral body or head tilt or had sensations of body tilting, pulling, or rotation (**Table 3**). From these 21 patients, 16 (∼75%) reported rightward symptoms, one reported leftward symptoms, one reported both rightward and leftward symptoms, and three reported symptoms in other directions. Six other patients that did not report these symptoms had unsteadiness mainly from a sense of motion of the environment. Thus, similar to the SVV

TABLE 2 | Number of A- and E-effects for the left (LED) and right (RED) head tilt positions.

	Controls		VM patients	
	A-effect	**E-effect**	**A-effect**	**E-effect**
LED	14	11(2*)	14	13
RED	14	13	7	20

The asterisk indicates participants whose SVV value was 0° for a given head tilt, classified as having neither A- nor E-effect. Head positions: LED, left ear down; RED, right ear down.

TABLE 3 | From all VM patients who reported spatial symptoms as sensations of body tilting, body pulling, body rotation, or dizziness with lateral body or head tilt, 16 patients (∼75%) had rightward symptoms.

VM spatial symptoms			
Rightward 16	Leftward 1	Rightward & leftward 1	Other directions 3

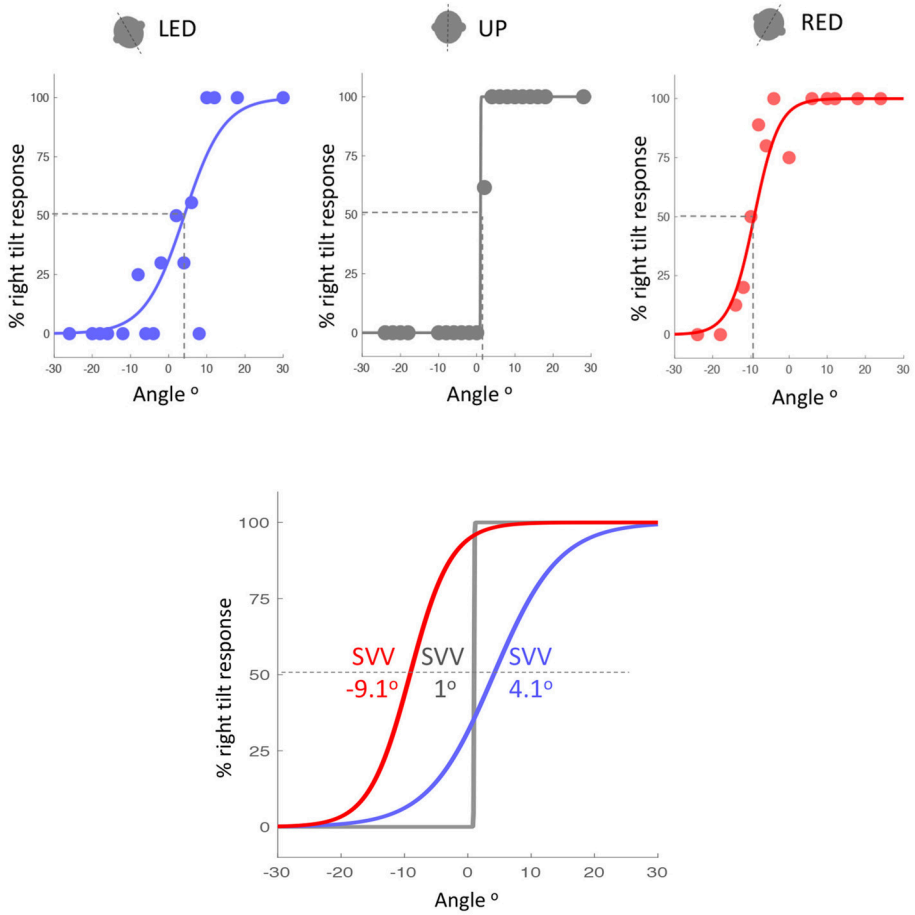

FIGURE 2 | Example of SVV accuracy in a VM patient during the left tilt (blue), upright (gray) and right tilt (red) head positions (top graphs). SVV is the point on the psychometric curves at which the probability of left or right responses is 50% (dashed lines). The psychometric curves and SVV values for the three head tilt positions are also shown together (bottom graph). Positive values indicate SVV errors towards the right side, and negative values indicate SVV errors towards the left side. SVV error is in the opposite direction of the head tilt (blue and red curves) and it is larger during the right head tilt position. LED, left ear down; UP, upright; RED, right ear down.

errors, there was an asymmetry in spatial symptoms reported by VM patients.

DISCUSSION

Patients with vestibular migraine often experience dizziness and disorientation with changes in the head and body positions. Such symptoms raise the possibility of dysfunction in neural mechanisms that subserve spatial orientation. Here we investigated SVV errors during head tilt in patients who met the diagnostic criteria for vestibular migraine. When the head is tilted, the brain has to integrate sensory information that encodes the positions of the eye, head and body in order to maintain perception of upright. Our results show that SVV accuracy in VM patients was significantly worse during the right head tilt position. The larger SVV errors in VM patients were in the opposite direction of the head tilt position, consistent with overestimation of the tilt magnitude in the process of perceiving upright orientation. There was no difference in SVV precision between the VM and control groups at any head position, showing that the poor accuracy (i.e., larger SVV errors) in VM patients cannot be related to the variability of responses across SVV trials. VM patients had no signs of vestibular or ocular motor dysfunction that could lead to abnormal SVV deviations. On this basis, SVV deviations in these patients could be linked to a "higher order" dysfunction in multisensory integration for spatial orientation (i.e., vestibular and somatosensory inputs that encode head, neck and eye positions). Such a mechanism is in line with the potential role of multisensory integration in migraine pathophysiology (24). Consistent with the larger SVV errors during the right head tilt, the majority of VM patients reported spatial symptoms towards the right side, suggesting a link between the symptoms and SVV bias in these patients.

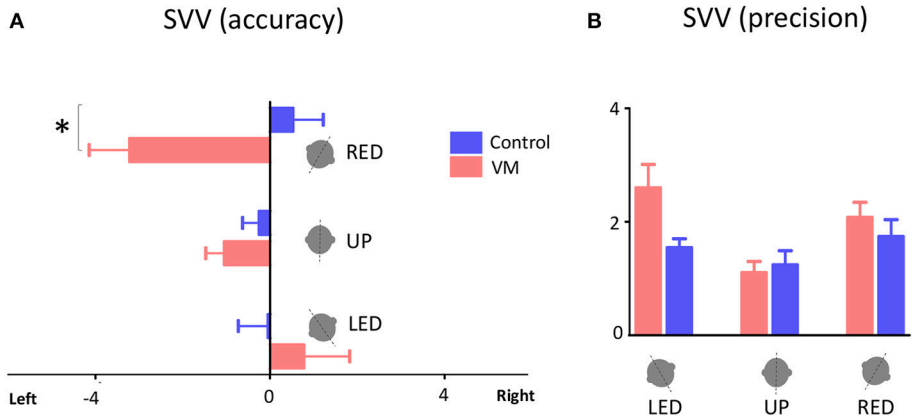

FIGURE 3 | SVV accuracy and precision. **(A)** Mean values of SVV accuracy for VM patients and healthy controls with error bars showing standard errors of the mean (SEM). Positive values indicate SVV errors toward the right side, and negative values indicate SVV errors to the left side. The asterisk indicates a significant difference in SVV errors during right head tilt in VM patients compared to controls ($p = 0.002$). **(B)** Mean values of SVV precision with error bars showing SEM. LED, left ear down; UP, upright, RED, right ear down.

Previous studies have reported no difference in SVV errors in VM patients compared to healthy controls, although there was a higher variability in VM patients (25). These measurements were only made in the upright position, even though VM patients typically complain that symptoms are triggered or worsened with changes in the head or body position. Our results show similar SVV errors in VM patients and healthy controls with the head in upright position. However, there were larger SVV errors in VM patients during head tilt, in agreement with previously-reported reduced tilt perception thresholds (i.e., motion in the roll plane) in these patients (26, 27). These findings together suggest that VM patients may be sensitive to displacements in the roll plane, and their overestimation of the tilt position may lead to larger errors of upright perception.

The asymmetric effect of head tilt on upright perception in VM patients does not conform to the known perceptual biases seen in healthy individuals, which generally do not exhibit significant asymmetries between equal head tilts in both directions (9, 22, 28). Normally, with head tilts of less than 60°, healthy individuals show SVV biases, consistent with either the A-effect or the E-effect (9, 12). Here, our patients showed significantly larger E-effect during right head tilt (i.e., tilt overcompensation error). This asymmetry in SVV errors was consistent with the direction of spatial symptoms, which was also mainly to the right side. These findings show a plausible link between the SVV bias and dizziness in these patients. With no vestibular or ocular motor dysfunction, the errors of upright perception in VM patients could be linked to neural processes within the cerebral hemispheres that contribute to spatial orientation (9). In this context, a functional laterality has been shown in vestibular processing, postural control, perception of self-motion and spatial orientation (29–33). Likewise, the asymmetry in spatial symptoms and—consistent with that—errors of upright perception in VM patients might be related to distinct abnormalities in hemispheric interactions in processing sensory information for spatial orientation (e.g., vestibular or somatosensory inputs). Currently, little is known about these multisensory neural processes and they need to be addressed in future studies. Another possibility to consider is that VM pathophysiology might involve the vestibulo-cerebellum (i.e., nodulus/uvula), where vestibular inputs are processed with respect to their underlying rotational, gravitational, and translational components (34–36). A vestibulo-cerebellar dysfunction can affect perception of head tilt position and thus result in SVV deviation (34, 35, 37, 38). In our patients, however, we did not find any clinical signs of vestibulo-cerebellar dysfunction; e.g., ataxia, head shaking induced nystagmus or abnormality in the time constant of vestibulo-ocular responses with rotational chair testing. In this study, we did not measure torsional eye position along with SVV responses. Thus, even though we did not find clinical signs of vestibular imbalance in our VM patients, we cannot entirely rule out the possibility of SVV deviations from asymmetrical changes in ocular torsion during head tilt (i.e., otolith-ocular imbalance). This is, however, less likely as the SVV errors in VM patients were larger that it could be attributed to abnormality in ocular torsion alone. Future studies will have to address this issue, using simultaneous ocular torsion and SVV measurements during head tilt. Moreover, in order to parse out sensory contributions to spatial misperception in VM patients, SVV errors should be interpreted with respect to measurements of head tilt perception using a wider range of head tilt positions.

In conclusion, here we investigated orientation constancy in patients with vestibular migraine by measuring errors of upright perception during static head tilts. Patients with vestibular migraine, compared to healthy participants, showed larger errors of upright perception that were asymmetrical and were present primarily in one head tilt direction. Consistent with these perceptual errors,

VM patients reported spatial symptoms towards the same direction. These findings, in the presence of normal vestibular function, suggest an abnormal sensory processing and integration for spatial perception in patients with vestibular migraine.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Johns Hopkins Institutional Review Board (IRB). All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Johns Hopkins IRB.

AUTHOR CONTRIBUTIONS

AW, JO-M, SS, and AK contributed to the design of the study, running the experiments, analyzing the data, and writing the manuscript. T-PC contributed to analyzing the data and writing the manuscript.

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No Gain No Pain: Relations Between Vestibulo-Ocular Reflexes and Motion Sickness in Mice

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Motion sickness occurs when the vestibular system is subjected to conflicting sensory information or overstimulation. Despite the lack of knowledge about the actual underlying mechanisms, several drugs, among which scopolamine, are known to prevent or alleviate the symptoms. Here, we aim at better understanding how motion sickness affects the vestibular system, as well as how scopolamine prevents motion sickness at the behavioral and cellular levels. We induced motion sickness in adult mice and tested the vestibulo-ocular responses to specific stimulations of the semi-circular canals and of the otoliths, with or without scopolamine, as well as the effects of scopolamine and muscarine on central vestibular neurons recorded on brainstem slices. We found that both motion sickness and scopolamine decrease the efficacy of the vestibulo-ocular reflexes and propose that this decrease in efficacy might be a protective mechanism to prevent later occurrences of motion sickness. To test this hypothesis, we used a behavioral paradigm based on visuo-vestibular interactions which reduces the efficacy of the vestibulo-ocular reflexes. This paradigm also offers protection against motion sickness, without requiring any drug. At the cellular level, we find that depending on the neuron, scopolamine can have opposite effects on the polarization level and firing frequency, indicating the presence of at least two types of muscarinic receptors in the medial vestibular nucleus. The present results set the basis for future studies of motion sickness counter-measures in the mouse model and offers translational perspectives for improving the treatment of affected patients.

Keywords: vestibular, motion sickness, scopolamine, VOR, neurons, mouse, spatial orientation, visuo-vestibular

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INTRODUCTION

Motion sickness (MS) is a disease that occurs when the brain cannot track the movement of the self in a given environment. Motion sickness is experienced by up to 15% of the humans subjects traveling by air, sea or on ground (1–3). What are the physiological causes for MS? While many theories are still debated (4, 5), it is mostly accepted that MS results from a mismatch between motion-derived neural signals, as for instance a conflict between visual and vestibular inputs experienced while reading in a moving car or on a sailing boat (6). Notably, the conflict between motion-sensitive signals can also be limited to a single sensory modality: vestibular-only motion sickness results from a conflict between semicircular canals signals and otolith signals. Vestibular-only motion sickness incapacitates the brain to integrate angular and linear acceleration in order to efficiently reconstruct the orientation of the head in space (7, 8).

To prevent the onset of motion sickness, medications have been empirically developed and documented for at least a century and probably used for much longer (9). To date, one of the most efficient drugs to prevent in particular space motion sickness (10, 11) is scopolamine (12–14), a muscarinic antagonist commonly administered through transdermal patches. While its molecular effects are well characterized, its putative action on the peripheral and/or central vestibular system, at the neuronal (15) and behavioral levels (14, 16) have still to be specified. Several studies have also tried non-pharmacological approaches to help prevent motion sickness by habituating the system to vestibular stimulation (17–20). Habituation to visual stimulation was also promising because its effects were demonstrated to be long-lasting (1).

While the interactions between the vestibular system, motion sickness and pharmacological treatments have been widely studied in humans, similar studies are conducted on animal models to understand their correlate at the cellular and molecular levels. Here we use the mouse model to investigate the interplay between vestibular reflexes, motion sickness and different counter-measures by addressing several related questions.

1. what are the consequences of motion sickness on the efficacy of the vestibular system?
2. does scopolamine protect mice against MS, as it does in humans?
3. can a non-pharmacological, preemptive adaptation reduce the occurrence of mice MS?
4. what are the direct pharmacological effects of scopolamine on the electrophysiological properties of central vestibular neurons recorded *in vitro*?

We find that motion sickness leads to a general decrease in the efficacy of vestibulo-ocular reflexes (VOR). When administrated before the occurrence of MS, scopolamine decreases the efficacy of the vestibulo-ocular reflexes and prevents the occurrence of symptoms normally associated with MS. Then, we tested the effect of a long-lasting VOR gain-down reduction protocol and validated that this reduction offers a protection against MS. At the cellular level, we demonstrate that muscarinic antagonists have heterogeneous effects on the neuron's electrophysiological parameters suggesting that the action of scopolamine on central vestibular neurons is differentially affecting subpopulations of neurons.

MATERIALS AND METHODS

Ethics

Animals were used in accordance with the European Communities Council Directive 2010/63/EU. All efforts were made to minimize suffering and reduce the number of animals included in the study. All procedures were approved by the ethical committee for animal research of the University Paris Descartes (CEEA.34).

Surgical Procedures

Surgical preparation and postoperative care for head implant surgery have been described previously (21, 22). Gas anesthesia was induced using isoflurane. The head was shaved using an electric razor. Lidocaine hydrochloride (2%; 2 mg/Kg) was injected locally before a longitudinal incision of about 2 cm was performed into the skin to expose the skull. A small custom-built head holder (3 × 3 × 5 mm) was fixed using dental cement (C&B Metabond; Parkellinc, Edgewood, NY, United States) to the skull just anterior to the lambda landmark. Following the surgery, animals were isolated and closely surveyed for 48 h. Buprenorphine (0.05 mg/kg) was provided for postoperative analgesia and care was taken to avoid hypothermia and dehydration.

Behavioral Measures

The vestibulo-ocular pathway works as an open-loop: the vestibular signals trigger compensatory eye movements to stabilize gaze in the absence of sensory feedback. As a consequence, any imbalance or modification in the vestibular inputs leads to alteration of the eye movements triggered by head movements. This makes video-oculography the main tool used in hospitals to measure vestibular function. Eye movements were therefore used as a proxy to evaluate the efficacy of the vestibular system by quantification of the vestibulo-ocular reflexes of the mice.

Video-Oculography Procedure

Eye movements were recorded using non-invasive video-oculography (23). The experimental set-up, apparatus and methods of data acquisition are similar to those previously described (22, 24). Briefly, mice were head-fixed at a ∼30° nose-down position to align the horizontal canals in the yaw plane (25, 26). Animals were placed in a custom-built Plexiglas tube secured on the superstructure of a vestibular stimulator. The VOR performance was tested in a temperature-controlled room (21°C) with all sources of light turned off except for computer screens. The turntable was further surrounded with a closed box to isolate the animal from remaining light, with a final luminance inside the box <0.02 lux.

To prevent excessive pupil dilatation in dark, a topical application of a combination of pilocarpine (inducing a miosis via local muscarinic stimulation) and Combigan (brimonidine 0.2% + timolol 0.5%, preventing the mydriasis by locally blocking the adrenergic pathways) was used. The addition of Combigan on top of the usually used pilocarpine is necessary to counteract locally the miotic effect of the systemic scopolamine injected in some protocols (cf. **Table 1**). To avoid introducing a bias between experiments with and without scopolamine, the combination of Combigan and pilocarpine was used in all experiments.

Vestibulo-Ocular Reflex Tests and Analysis

To evaluate the canalar and otolithic contributions to the VOR, different vestibular stimulations were used.

1. The eye movements evoked by an angular stimulation of the horizontal canals (aVOR) were tested. The animal was rotated around a vertical axis with sinusoidal movements at frequency of 0.2, 0.5, 1 Hz with a peak velocity of 25°/s. The angular amplitude of the movement was adjusted accordingly. At least 60 cycles were produced for each frequency. Two parameters

were extracted from the recordings: the gain (aVOR_G) and the phase (aVOR_φ). The gain is the ratio between the amplitude of the eye (response) and head (stimulus) rotations. Since the animal is head-fixed to the rotating table, head movements and table movements are identical. The phase is the temporal shift between the eye and table rotations, expressed as ratio of the sinusoidal cycle (2 pi). Details for gain and phase calculation are reported in Carcaud et al. (24).

2. The eye movements evoked by a specific stimulation of the otoliths (maculo-ocular reflexes, MOR) were tested (27) using off-vertical axis rotation (OVAR) as previously described (22). Briefly, the axis of rotation was tilted by 17° with respect to the vertical. Rotations were performed at constant speed (50°/s) for at least 10 rotations both in the clockwise (cw) and the counterclockwise (ccw) directions. Due to the inertial nature of the angular movement detection, a rotation at constant speed elicits a combined canalar and otolithic response at the beginning of the trace, however after a few seconds only the otolithic component remains (22, 28). Since gravitational acceleration acts vertically, this stimulation is equivalent to a continuous rotation (at 0.14 Hz) around the mouse head of a 17° tilted constant linear acceleration stimulus [see Figure 2B in Beraneck et al. (22)]. For horizontal OVAR responses, quick-phases were identified and removed. During rotations, the velocity of horizontal slow phases is modulated (modulation, μ) around a constant bias (β). Both parameters (μ and β) were calculated from the sinusoidal fit of eye horizontal slow-phase velocity using the least-squares optimization of the equation:

$$\mathbf{SP\,(t)} = \boldsymbol{\beta} + \boldsymbol{\mu} \cdot \boldsymbol{sin}\left[2\boldsymbol{\pi} \cdot \boldsymbol{f}_0 \cdot (\mathbf{t} + \mathbf{t_d})\right]$$

where SP(t) is slow-phase velocity, β is the steady-state bias slow phase velocity, μ is the modulation of eye velocity, f_0 is the frequency of table rotation, t_d is the dynamic lag time (in ms) of the eye movement with respect to the head movement. The bias (Maculo-ocular reflex Bias; MOR_β) is reported here as the main index of otolithic response (22, 27)

Motion Sickness Generation

Motion sickness was induced in mice using a double provocative rotation comparable to the one used in rats by Morita et al. (29). Animals were tested one at a time. Each animal was rotated for 30 min in the home-made motion sickness generating device, under room lighting (300 lux). This device is composed of one central axis rotating clockwise a 30 cm-long arm at 60°/s constant velocity. At the distal extremity of the arm is a second axis, which rotates the box containing the animal counter-clockwise with a sinusoidally-modulated speed (range 5–55°/s; **Figure 1A**). The box containing the non-restrained mouse had a padded floor. The padding was changed before each test to prevent any olfactory signaling within the box. The top part of the box was transparent.

Motion Sickness Evaluation

Kaolin is a mineral clay commonly used in animal feed. Preparation of a mix of kaolin (Sigma Aldrich #18672) and 1% w/w arabic gum (Sigma Aldrich #G9752-500G), hereafter referred to as "kaolin", was similar to that reported by Yu et al. (30). To quantify the occurrence of MS, we measured the changes in alimentary preferences observed following an aversive stimulus. Affected mice eat less of the regular food and instead turn to kaolin, which has no nutritional value.

Each mouse was housed individually for the entire time of the experiment, with *ad libitum* access to water, regular food, and kaolin. Individual consumption of food (F) and kaolin (K) was measured daily. The kaolin intake ratio (KIR) is calculated as K/(K+F) and expressed in percent.

Protective Protocols

Scopolamine dynamics

To test whether the effects of scopolamine were lasting during the entire experiment, we measured the pupil dilation under constant artificial lighting (300 lux) in a separate group of animals ($n = 12$). Animals were injected with scopolamine (Sigma Aldrich # S1875-1G; 0.3 µg/g of corporal mass, in saline solution) and the individual duration of the pupil dilation was measured. During this preliminary experiment, the scopolamine effects were found to peak within minutes and then to slowly fade: significant pupil dilatation was seen after 5–7 min and this dilation lasted for at least 90 min, i.e., longer than the duration of the experimental protocols (see **Table 1** below). No change in the pupil size was observed when animals were injected with saline in the same configuration.

Visuo-vestibular mismatch protocol

To test if decreasing the efficacy of the vestibular system is causally linked to the protective effect of scopolamine, we took advantage of a behavioral protocol recently developed [see Figure 2 in Carcaud et al. (24)] that leads to a decrease of VOR gain. A custom-built device was secured on top of the head holder for 14 days. The device consisted of a "helmet" (size: 2.2 cm width × 1.5 cm depth × 1.5 cm length; weight 2 g) that completely covered the mouse's head. The front of the device was adapted to the mouse anatomy so that the nose was not covered, and its width allowed for grooming and barbering behaviors. To preserve light-dependent physiology and nychthemeral rythm, the device was made of non-opaque plastic with a thickness of 0.3 mm. In addition, 3 mm large vertical black stripes were drawn on the external surface. When the mouse moves its head, the highly contrasted head-fixed stripes generate a visuo-vestibular mismatch (VVM). After 2 weeks, we reported a long-lasting gain-down reduction of the angular VOR of about 50% [range tested 0.2–2 Hz for velocities of 10–50°/s; see results in Carcaud et al. (24)]. Here, we take advantage of this protocol to test the interactions between the VOR and motion sickness.

Design of the Study

Different procedures were designed to test, on one hand, the functional consequences of motion sickness or of scopolamine on the vestibular system and, on the other hand, the influence of scopolamine or of the visuo-vestibular mismatch on motion sickness.

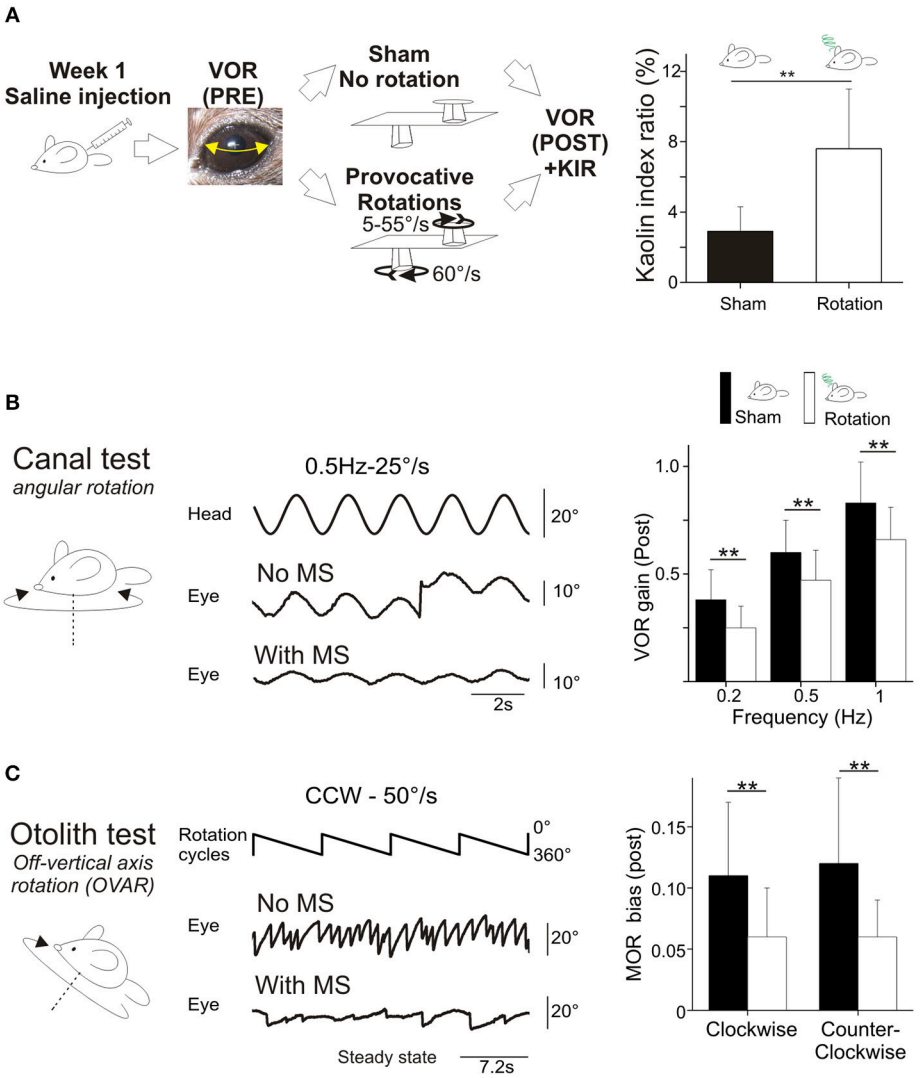

FIGURE 1 | (A) Rotation induces motion sickness. Left, scheme of the protocol designed for intra-individual comparison. Animals received saline injection and VOR was tested before and after a *sham* experiment and a provocative double-rotation. Right, *Pica* behavior quantified as a Kaolin Index Ratio was quantified before and after rotation. **(B)** Motion sickness reduces angular horizontal vestibulo-ocular reflex. Left panel, raw traces of the eye movement observed during sinusoidal rotation of the turntable after the *Sham* or provocative rotation session. Right panel, intra-individual comparison of the VOR gain measured with or without MS. **(C)** Motion sickness reduces the maculo-ocular reflex. Off-vertical axis rotation was performed at velocities of 50°/s. A sample of 4 over 10 cycles of 360° rotations at constant velocity are presented. Left, raw traces of the eye movements evoked with or without MS. Right, intra-individual comparison of the MOR gain measured with or without MS. In this and all figures, plots represent mean ± standard deviation. Asterisks indicate statistically significant differences with Holm-Bonferroni correction, $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ respectively. For table position up is left; for ease of reading, eye position is inverted (up is right).

All behavioral measures reported were performed on $n = 24$ mice. 12 additional animals were used in preliminary experiments to determine the exact parameters used but were not included in the study.

During the first week, the susceptibility of the 24 mice to *provocative rotations* was tested following an injection of a saline solution (**Figure 1A**). To account for the inter-animal variability and non-specific effects, each animal was tested in 2 sessions: vestibulo-ocular reflexes were tested a first time in the dark (aVOR and MOR testing, *pre*). Then, the animal was put into the motion sickness generating device either activated (i.e., *provocative rotation* condition) or not (*Sham* condition). Finally, the same vestibulo-ocular reflexes were recorded a second time in the dark (aVOR and MOR testing, *post*; **Figure 1A**).

The effects of scopolamine were tested in a subset of mice ($n = 16$). The mice received a scopolamine injection (0.3 µg/g of corporal mass, in saline solution). The mice were then tested again in the *Sham* and *provocative rotations* conditions (**Figure 2A**).

To test whether motion sickness could be prevented without scopolamine, the remaining 8 mice were included in the VVM gain-decrease experiment (**Figure 3A**). After the initial motion sickness tests, the helmet was put on the mouse's head for 2 weeks (see section Visuo-vestibular mismatch protocol). Following this

TABLE 1 | Experimental protocols.

Rationale	Protocol	Injection	*Provocative rotation*	VVM
Control	CTL	Saline	No (*Sham*)	No
Effect of Motion sickness	Rotation	Saline	Yes	No
Effect of Scopolamine	SCO	Scopolamine Oculomotor testing, pre	No (*Sham*) Oculomotor testing, post	No
Scopolamine protection against motion sickness	SCO + Rotation	Scopolamine	Yes	No
Behavioral protection against motion sickness	VVM + Rotation	Saline	Yes	Yes

CTL, Control; SCO, scopolamine; VVM, Visuo-vestibular mismatch protocol.

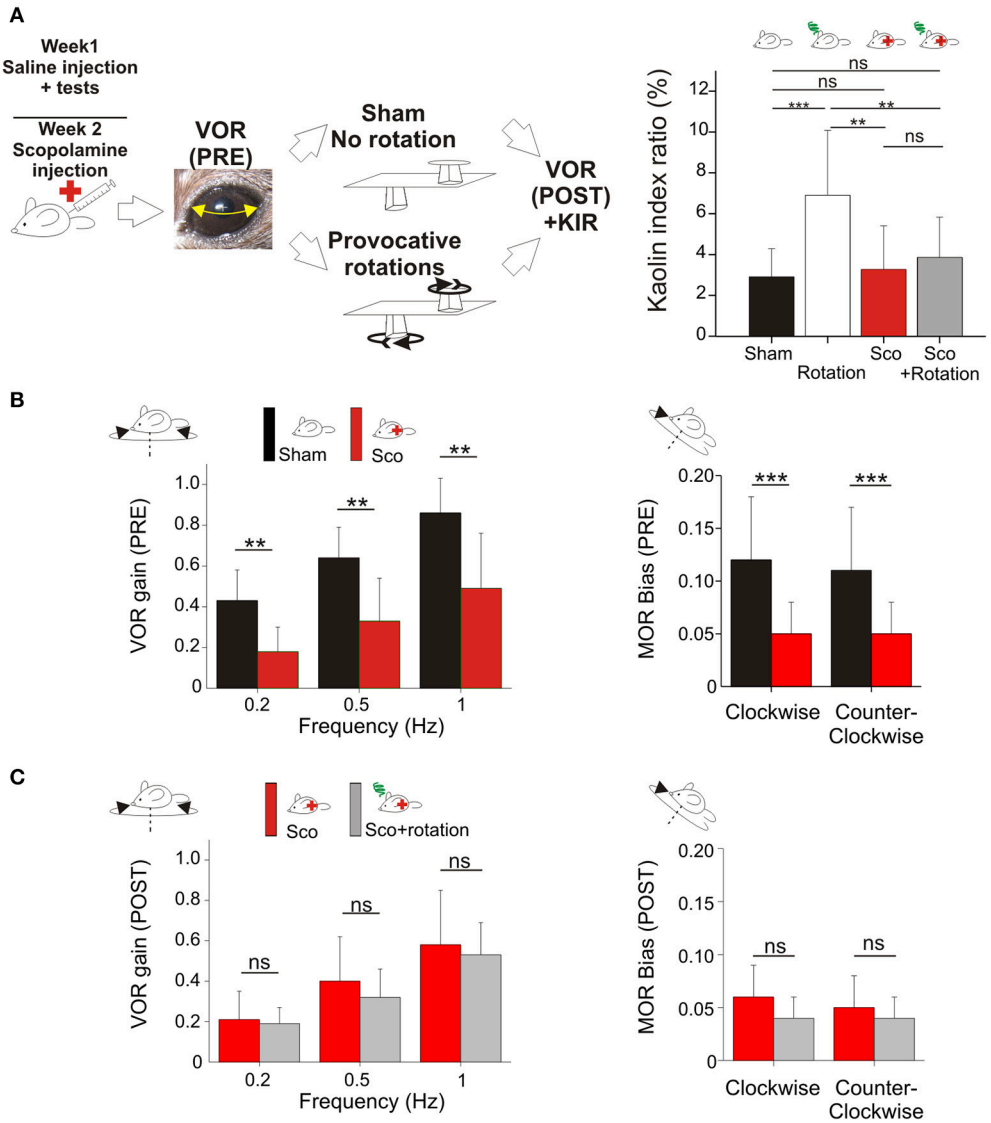

FIGURE 2 | (A) Scopolamine protects against motion sickness. Left panels, animals already tested with saline received scopolamine injection; VOR was tested before and after a *Sham* experiment and a provocative double-rotation experiment. Right, *Pica* behavior demonstrated the protective effects of scopolamine against motion sickness. **(B)** Scopolamine reduces vestibular sensitivity. Left, plots of angular VOR gain show significant reduction at all tested frequencies before provocative stimulation (Pre measurements). Right, plots of MOR bias shows significant reduction under scopolamine treatment. **(C)** No additional reduction of vestibular sensitivity was observed following provocative rotation protocol (Post measurements). Left, plots of angular VOR. Right, plots of MOR bias. Asterisks indicate statistically significant differences with Holm-Bonferroni correction, $*p < 0.05$; $**p < 0.01$; $***p < 0.001$ respectively.

perturbation period, the VOR was recorded immediately after removing the helmet, and again after the *provocative rotation* stimulation. No *sham* condition was recorded to prevent de-adaptation of the VOR.

The different protocols are summarized in **Table 1**.

Electrophysiological Experiments

To measure the neuronal effects of scopolamine, 220 μm-thick coronal brainstem slices were obtained from 5-week-old male C57BL/6J mice ($n = 18$) (24, 31). A total of 51 medial vestibular nuclei neurons (MVNn) were recorded with patch-clamp electrodes. The artificial cerebrospinal fluid (aCSF) used during the dissection and slicing is composed of (in mM): NaCl (120), $NaHCO_3$ (25), NaH_2PO_4 (1), KCl (2.5), $MgCl_2$ (3), $CaCl_2$ (0), glucose (10), sucrose (240). The recording solution differs only for NaCl (120), $MgCl_2$ (2), $CaCl_2$ (1) and sucrose (0). Analysis of resting discharge parameters, spike shape and classification of type A vs. type B neurons are similar to those previously reported (31). The intrinsic properties, as well as the responses to hyperpolarizing and depolarizing steps were compared between control conditions, or during pharmacological testing by the addition of muscarine (10 μM), or addition of muscarine (10 μM) + scopolamine (10 μM) to the bath. All chemicals were purchased from Sigma-Aldrich.

Statistics

All mice were first tested during the Control protocol (**Figure 1**), then during one of the two counter-measure protocols (scopolamine, **Figure 2**, or visuo-vestibular mismatch, **Figure 3**). This approach allowed performing statistical analyses based on within-subjects models to account for non-specific and inter-individual variations. Since not all parameters were normally distributed (as tested with a Lilliefors test), we used the same non-parametric paired-test (Wilcoxon signed-rank test) to evaluate statistical significance in all conditions. When appropriate, a one-tail version was used to account for prior knowledge about the alternative hypothesis [e.g., the effect of a treatment on the parameters as the expected reduction of the VOR gain by the VVM protocol, Carcaud et al. (24)]. The thresholds for the statistical tests were adjusted using the Holm-Bonferroni method to account for the numerosity of the planed multiple comparisons. Although adjusted p-value thresholds were used to define the level of significance of the statistical tests, for ease of reading we report in the results section the corresponding uncorrected value noted with the ¢ symbol. All results in both the text and the figures are reported as mean ± standard deviation.

RESULTS

Effect of Rotation on the Behavior of Control Mice

Induction and Quantification of MS

In response to motion sickness (MS), mice do not vomit (30, 32); however behavioral proxies can be used in rodents to assess the debilitating effects associated with MS. Following the provocative double-rotation protocol, qualitative symptoms such as urination, piloerection or tremor were observed, suggesting that MS had been induced. To quantify the occurrence of MS, we measured the "*Pica*" behavior: changes in alimentary preferences observed following an aversive stimulus (33, 34). Affected mice eat less of the regular food and instead turn to a substance referred to as "*Kaolin*" which has no nutritional value.

Mice food consumption was measured before and after their exposure to the *Sham* condition or *provocative rotation* condition (**Figure 1A**). The quantity of food and of *Kaolin* was then compared and used to calculate the Kaolin Index Ratio (KIR). As expected, the *Pica* behavior was observed in all mice ($n = 24$) following MS induction and the KIR was significantly increased (**Figure 1A**; $p < 0.01$¢; **Table 2**a,e for the different protocols).

TABLE 2 | KIR for the different protocols.

	Group 1 vs. Group 2	Group 1	Group 2	p
		Mean ± SD	Mean ± SD	
No VVM protocol; $n = 16$ mice	**a** *Sham* vs. Rotation	2.90 ± 1.39	6.90 ± 3.18	0.0014
	b *Sham* vs. SCO	2.90 ± 1.39	3.27 ± 2.14	0.2934
	c Rotation vs. SCO + Rotation	6.90 ± 3.18	3.86 ± 1.97	0.0026
	d *Sham* vs. SCO + Rotation	2.90 ± 1.39	3.86 ± 1.97	0.4627
	e *Sham* vs. Rotation	3.08 ± 1.67	9.08 ± 3.64	0.023
VVM protocol; $n = 8$ mice	**f** Rotation vs. VVM + Rotation	9.08 ± 3.64	5.13 ± 1.71	0.062
	g *Sham* vs. VVM + Rotation	3.08 ± 1.67	5.13 ± 1.71	0.117

SCO, scopolamine; VVM, Visuo-vestibular mismatch protocol; SD, standard deviation.

Sustained Rotation Decreases the Efficacy of the Vestibular Reflexes

To assess the interplay between vestibular responses and MS syndrome, various components of vestibulo-ocular reflexes were tested during passive head-fixed movements performed in the dark.

First, to determine possible non-specific effects of the protocol, mice were tested in a *Sham* condition (put in the device after saline injection, but not rotated; **Figure 1A**, left panel). There was a diminution of aVOR gain by ∼10% (15% at 0.2 Hz, $p < 0.05$¢; 9% at 0.5 Hz, $p < 0.05$¢; 5% at 1 Hz, $p > 0.1$¢) during the second measure. To account for this effect, we compare below and in **Figure 1** the different protocols from similar conditions (e.g., *Sham* Pre vs. rotated Pre; *Sham* Post vs. rotated Post).

For all tested frequencies, mice had similar angular VOR gain (aVOR_G; range 0.45 ± 0.13–0.87 ± 0.19; $p > 0.1$¢) and phase (range 20.6 ± 7.2 to −2.5 ± 5.8; $p > 0.1$¢) responses before the protocols (Pre values). Following the MS protocol however, there was a significant decrease in the aVOR gain (**Figure 1B**; $p < 0.01$¢ for all frequencies). When the responses before and after the rotation were compared, the mean decrease in aVOR gain reached about ∼30% at 0.2 Hz and ∼20% at 0.5 and 1 Hz

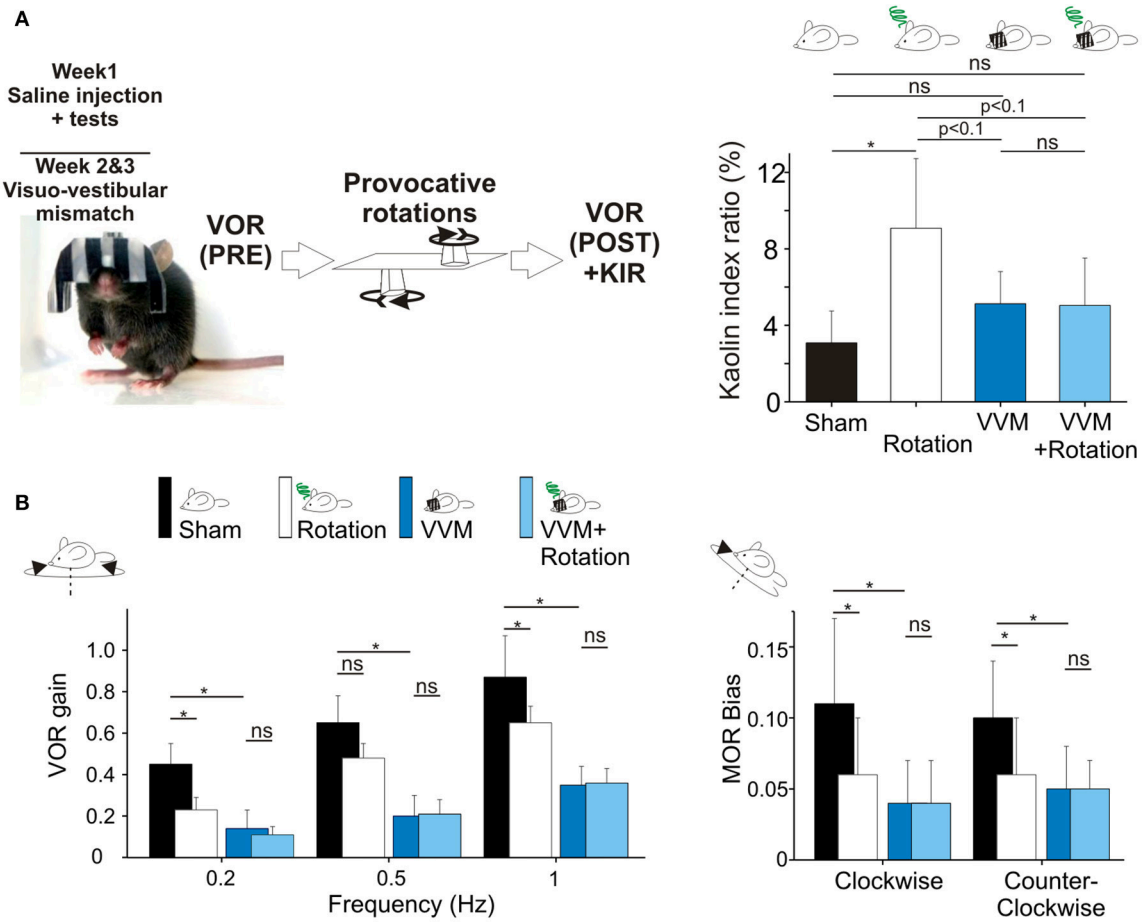

FIGURE 3 | (A) Visuo-vestibular mismatch reduces vestibular sensitivity. Left, picture of a mouse during the visuo-vestibular conflict protocol. The helmet is kept for 2 weeks. Right panel, *Pica* behavior demonstrated the protective effect of VVM protocol against MS induced by the double-rotation **(B)**. Left panels, plots of angular VOR of the $n = 8$ mice before the provocative rotations (black and deep blue bars) and after the provocative rotations (white and light blue bars). Right panels, MOR bias ratios in the same conditions. No additional reduction of vestibular sensitivity was induced by the rotation, suggesting protective effects of the VVM protocol. Asterisks indicate statistically significant differences with Holm-Bonferroni correction, $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ respectively.

(**Figure 1B**, right panel). There was also significant changes in the timing of the aVOR (aVOR_φ) toward greater phase leads, particularly for the low and middle frequencies (0.2 Hz: Δphase $= +5^{\circ}$, $p < 0.05^{\phi}$; 0.5 Hz: Δphase $= +3^{\circ}$, $p < 0.05^{\phi}$ at 0.5 Hz; 1 Hz: Δphase $= +2.5^{\circ}$, $p > 0.1^{\phi}$ at 1 Hz).

As for the angular VOR, *Sham* condition was first tested for the maculo-ocular reflex (MOR; **Figure 1C**) and no significant differences were found. Before the MS protocol, the efficacy of the MOR tested in clockwise and counterclockwise direction was similar in all mice (MOR_{β}: 0.11 ± 0.06 vs. 0.12 ± 0.07; $n = 24$).

Following the MS protocol however, a significant decrease of $\sim$50% in the efficacy of the MOR was evidenced ($p < 0.001^{\phi}$; **Figure 1C**), in both CW (MOR_{β} POST: 0.06 ± 0.04) and CCW directions (0.06 ± 0.03).

Overall, these results demonstrate that the *provocative rotation* induces motion sickness-associated behavior and affects the vestibular system by decreasing its response to motion. This decrease is observed when canal-dependent (aVOR) or otolith-dependent (MOR) reflexes are recorded; suggesting that sensitivity to angular and linear motion is affected.

Scopolamine Prevents Motion Sickness-Related Changes in the Vestibular System

Scopolamine is known to help preventing motion sickness in humans. To determine if scopolamine has a comparable effect on mice, the effect of an injection of scopolamine on VOR and motion sickness were investigated on a subset of the animals ($n = 16$).

First, the effect of scopolamine on the *Pica* behavior was measured. Injection of scopolamine did not significantly change the baseline of the KIR in *Sham* condition (**Table 2b**, **Figure 2A** black vs. red bar; $p > 0.1^{\phi}$). Then, the protective effects were tested by rotating the scopolamine-injected mice. While the rotation was efficient in provoking motion sickness in the absence of scopolamine (higher KIR with the MS protocol;

Table 2a, **Figure 2A**, white bar; $p < 0.05^{¢}$), the KIR remained low when scopolamine was preemptively administrated (**Table 2c**, **Figure 2A**, gray bar). The KIR of scopolamine-injected mice after rotation was not different from that of the Control condition (no scopolamine; no rotation; **Table 2d**, **Figure 2A** black vs. gray bars; $p > 0.1^{¢}$). Thus, while rotation provoked the *Pica* behavior in these mice, preemptive injection of scopolamine protected them against MS.

To determine the interplay between motion sickness and vestibular sensitivity, the VOR and MOR of mice injected with scopolamine was recorded. Following the injection of scopolamine, but in the absence of rotation (no MS induction), the angular VOR gain of mice was decreased ($p < 0.001^{¢}$ at all tested frequencies; **Figure 2B** left panel). The decrease was in range ∼60% at 0.2 Hz and ∼40% at 0.5 and 1 Hz. Modifications of aVOR also affected the timing of the response with a tendency toward greater phase lead at 0.2 Hz (Δphase $= +9°$, $p < 0.10^{¢}$) and 0.5 Hz (Δphase $= +15°$, $p < 0.01^{¢}$). Notably, this effect of scopolamine was consistently observed in all injected mice tested before provocative rotation. Similarly, the MOR of scopolamine-injected mice was significantly reduced in both CW and CCW direction (**Figure 2B**, right panel; $p < 0.01^{¢}$ for both directions).

Since motion sickness and scopolamine injection both induce reduction of the vestibular gain and increase in phase leads, we asked whether their combination would lead to a greater attenuation of vestibular reflexes. When scopolamine-injected animals were provocatively rotated, the gain of the aVOR was found to stay significantly lower compared to control conditions ($p < 0.01^{¢}$ at all frequencies; **Figure 2B**, left panel). However, there was no additional decrease between the scopolamine and scopolamine+rotation groups (**Figure 2C**, left panel; all frequencies $>0.05^{¢}$). A similar result was found for the MOR_{β} which was significantly decreased by the scopolamine injection (**Figure 2B**, right panel, $p < 0.001^{¢}$) but was not different in scopolamine-injected mice tested with or without rotation (**Figure 2C**, right panel). This result demonstrates that the preemptive modification of the vestibular reflexes by scopolamine injection has occluded the effects on the VOR normally observed following rotation (MS induction).

Since the scopolamine injected groups did not show any obvious sign of MS (see behavioral proxies, **Figure 2A**), we interpret that in saline-injected mice the reduction of the vestibular reflexes could be causally related to the occurrence of motion sickness following rotation. Since scopolamine-injected mice do not suffer from motion sickness, we hypothesize that the diminution of the vestibular sensitivity (by scopolamine injection in this case) could act as a protective mechanism against motion sickness.

Drugless Protection Against Motion Sickness

To test this hypothesis, we took advantage of a new methodology based on a long-lasting (14 days) visuo-vestibular mismatch (VVM, see Methods) which leads to a significant decrease in the gain of the VOR (24). Another subset of the mice ($n = 8$) was initially tested in control conditions and exposed to the provocative protocol. Before VVM, these mice had normal KIR, which again significantly increased following MS induction (**Table 2e**; $p < 0.05^{¢}$). Following these initial tests, the animals were left unperturbed for 48 h, before to start the VVM protocol. This methodology consists in putting on the head of the mouse a device which creates a visuo-vestibular mismatch. For 2 weeks, the animals were left in their home-cage with the apparatus on the head [see Figure 3A and protocol in Carcaud et al. (24)].

How does the VVM protocol affect vestibulo-ocular reflexes? As expected, the VVM protocol significantly reduced the gain of the VOR compared to pre-VVM values at all tested frequencies by >50% (**Figure 3B** compare black and dark blue bars; $p < 0.05^{¢}$). We then compared the maculo-ocular responses of mice before and after the VVM protocol. The MOR responses of the mice post-VVM were also significantly reduced compared to pre-VVM condition by about 50% in both clockwise and counterclockwise directions ($p < 0.05^{¢}$ for both directions; **Figure 3B** right panel). This result demonstrates that the VOR reduction following the long-lasting visuo-vestibular mismatch already reported for the canal-dependent pathway similarly reduces the otolith-dependent pathways, possibly through central mechanisms [see discussion in Carcaud et al. (24)].

Could the reduction of vestibular sensitivity following the VVM protocol prevent motion sickness? As expected the KIR of these mice was increased by the rotations before VVM (**Table 2e**, **Figure 3A**, right panel). After the VVM, the KIR was not significantly different from control conditions ($p > 0.1^{¢}$; compare black and deep blue bars on **Figure 3A**). When VVM mice were rotated (light blue bar), their KIR remained low, tended to be smaller compared to that of *Shams* ($p > 0.1^{¢}$) and similar to the non-rotated condition ($p > 0.1^{¢}$). The KIR in the VVM conditions tended to remain smaller from that of rotated mice ($p < 0.10^{¢}$ for both non-rotated and rotated VVM conditions), suggesting a protective effect of the VVM against MS.

To prevent de-adaptation of the reflexes, no *Sham* condition were attempted after removal of the device. VOR and MOR of the VVM mice were thus recorded immediately after removing the device (Pre values), and again immediately after MS rotation (Post values; **Figure 3A**). The effects of the provocative rotation were evaluated by comparing the PRE and POST effects (**Figure 3B** dark vs. white bars). As previously described (**Figures 1B,C**), the provocative rotation induced a reduction of angular VOR and MOR in control condition seen as a significant reduction in most tested conditions (compare black and white bars). Following the VVM protocol, rotation did no longer affect the efficacy of the vestibular reflexes, so that VOR gains and MOR bias all remained low and non significantly different between the VVM and VVM + rotated conditions (**Figure 3B**, compare blue and light blue bars).

Overall, these results show that rotations trigger in control mice MS symptoms (KIR increase) and lead to a reduction of

the aVOR gain with increased phase lead, and to a decrease of MOR bias. Scopolamine or visuo-vestibular mismatch protocols both reduce the efficacy of the reflexes and offer some protection against motion sickness symptoms.

To understand the cellular mechanisms of scopolamine, pharmacological experiments were then conducted on vestibular neurons recorded on brainstem slices.

Electrophysiological Results

Scopolamine Is Specifically Acting on MVNn Muscarinic Receptors

Thirty-two medial vestibular nuclei neurons (MVNn) were recorded in standard ACSF solution. MVNn can be segregated into subpopulations based on the characteristics of the after hyperplorization and inter-spike interval (35, 36). **Table 3** summarizes the membrane properties computed from spontaneous discharge (pacemaker activity) of the neurons, i.e., in the absence of any electrical stimulation. Here, from the 32 neurons recorded, 8 were type A neurons characterized by a single, deep afterhyperpolarization (AHP) and 24 were type B neurons characterized by a biphasic AHP. Apart from the *a priori* differences (Concavity, convexity and AHP parameters), only the firing frequency differed significantly ($p < 0.05$) between the 2 subpopulations recorded in control conditions.

Then, scopolamine (10 μM) was applied to the bath. Notably, the addition of scopolamine did not have any effect on either type A or type B neurons (**Table 3**). Since scopolamine acts as an antagonist of muscarinic receptors, and because muscarinic receptors have been reported in MVNn (38), we hypothesized that this absence of modulatory effect could be due to the *in vitro* slices recording conditions and in particular to the non-activation of the muscarinic receptors. This result suggests that the putative action of scopolamine on MVNn is specific and restricted to its action on muscarinic receptors.

Muscarine Application Can Either Depolarize or Hyperpolarize the Cells

A second set of 19 neurons (18 type B and 1 type A) was recorded in presence of cholinergic agonists (**Figure 4A**). Since only one type A was recorded, no interpretation can be made about the effects of muscarine on this subpopulation.

Muscarine depolarized 11 type B neurons by ∼3 mV. Application of muscarine strikingly modified the frequency of the spontaneous discharge which nearly doubled (**Figures 4B1,C1**). In addition, it slightly but significantly increased the amplitude of the AHP and the width of the action potential. Finally, the cellular resistance measured both in presence and in absence of action potentials significantly increased by ∼30% (**Table 4**).

Conversely, application of muscarine hyperpolarized the 7 remaining type B neurons by ∼4 mV (**Figures 4B2,C2**), while the frequency of the spontaneous discharge was almost halved and the cellular resistance measured in presence and in absence of action potentials decreased significantly by ∼40 and 30%, respectively (**Table 5**).

Scopolamine Counteracts an Activated Cholinergic System

What are the effects of scopolamine on both subpopulations? When applied on the depolarized neurons, scopolamine reversed all the effects of the muscarine application such that neurons membrane potential, frequency of discharge, spike parameters and resistance were all back to normal range and no longer statistically significantly modified compared to control condition (**Table 4**).

When scopolamine was applied on the hyperpolarized neurons, it also significantly reversed the effects of muscarine on the membrane potential, frequency of discharge, and resistance. Compared to control conditions, only the regularity of the discharge (CV) and interspike interval (Convexity) were still significantly different compared to control condition (**Table 5**).

Overall, these electrophysiological data show that (i) cholinergic stimulation has opposite effects on specific subpopulations of type B neurons, suggesting that each might express specific type of muscarinic receptors, (ii) scopolamine effects on vestibular neurons depends on cholinergic activation, is direct and specific, (iii) scopolamine acts as an antagonist which completely abolished the various cholinergic responses on all type B neurons tested.

DISCUSSION

Rodent Models for Studying Motion Sickness Using Combined Genetic, Molecular and Physiological Approaches

Motion sickness is a disease associated with discomfort, and often mistaken with the emetic reflex. While the association of MS and emesis is common in humans, it was demonstrated that rodents actually lack the brainstem neurological components responsible for emesis (32). However, the illness-response behavior known as *Pica* was identified as an analogous to vomiting, observed both in response to intoxication (33) and to provocative vestibular stimuli (29). The *Pica* behavior has since the 90's extensively been used as an index of rat motion sickness [e.g., (34, 39–41)] and was later validated in mice (42, 43). In both species, the causal relation between an intact vestibular system and the *Pica* behavior following challenging rotational stimuli was demonstrated (29, 43). Here, we have shown that in mice, *Pica* behavior can serve as a reliable index of motion sickness induced by a double-rotation paradigm similar to the one originally used in rats (29). We note that other behavioral symptoms such as piloerection, tremble, and abnormal urination were also frequently observed, although not quantified here. The stimulation protocol used is particularly efficient in generating combined canalar and otolithic overstimulation. Because of the possibility to use genetically-engineered mice and to conduct molecular studies, rodent models have recently attracted the attention of many research groups. Wang et al. (44–46) have studied in rats the inter-individual differences and the implication of the vestibulo-thalamic pathway in the habituation to *provocative*

TABLE 3 | Absence of effects of scopolamine in absence of cholinergic agonists.

	Type A ($n = 8$)			Type B ($n = 24$)		
	Control condition	**Scopolamine alone (10 μM)**	***p***	**Control condition**	**Scopolamine alone (10 μM)**	***p***
Vm (mV)	−52.76 ± 3.11	−52.69 ± 6.26	1	−51.23 ± 4.69	−50.31 ± 5.70	0.34
F (Hz)	5.61 ± 1.92	1.78 ± 1.24	0.13	13.85 ± 5.89	15.86 ± 11.98	0.57
CV	14.02 ± 8.20	35.86 ± 14.04	0.25	11.86 ± 7.55	24.93 ± 27.94	0.1
AHP (mV)	32.11 ± 7.26	32.40 ± 6.96	0.88	25.83 ± 5.20	25.35 ± 5.61	0.73
Width (ms)	1.70 ± 0.56	1.70 ± 0.52	0.88	0.78 ± 0.23	0.82 ± 0.27	0.12
Concavity (mV)	−2.79 ± 1.55	−6.16 ± 0.75	0.13	−0.05 ± 0.14	−0.62 ± 1.33	0.06
Convexity (mV)	0.31 ± 0.28	0.13 ± 0.06	0.13	0.74 ± 0.56	0.49 ± 0.64	0.38
AHPR (V/s)	0.18 ± 0.11	0.14 ± 0.06	0.38	N/A	N/A	N/A
dAHP (V/s)	N/A	N/A	N/A	6.50 ± 2.41	6.28 ± 3.32	0.85
Resistance Hyperpol. (MΩ)	522 ± 177	514 ± 164	0.38	416 ± 141	378 ± 323	0.08
Resistance Depol. (MΩ)	110 ± 52	153 ± 71	0.13	121 ± 52	120 ± 51	1

Vm, membrane potential, F, spontaneous discharge frequency, CV, coefficient of variation of the spontaneous discharge, AHP, After HyperPolarization, Width, spike width at threshold, Concavity and convexity: quantification of the shape of the interspike interval, AHPR, quantification of the AHP rectification, dAHP, quantification of the double AHP, Resistance hyperpol: slope of the IV curve in response to hyperpolarizing steps, Resistance depol: slope of the IV curve in response to depolarizing steps. For more details on how these parameters are calculated see (31, 36, 37).

TABLE 4 | Effects of scopolamine on neurons depolarized by muscarine.

Depolarized type B ($n = 11$)	**I: Control**	**II: Muscarine alone (10 μM)**	**III: Muscarine (10 μM) +Scopolamine (10 μM)**	***p*-value**		
				I vs. II	**II vs. III**	**I vs. III**
Vm (mV)	−48.37 ± 3.97	−45.08 ± 4.72	−47.89 ± 3.68	0.001	0.001	0.52
F (Hz)	13.50 ± 12.54	23.04 ± 16.71	16.48 ± 14.31	0.001	0.003	0.32
CV	24.18 ± 21.91	19.67 ± 33.44	22.31 ± 21.42	0.24	0.102	0.638
AHP (mV)	24.68 ± 4.31	25.89 ± 4.61	26.45 ± 4.87	0.042	0.175	0.0019
Width (ms)	0.81 ± 0.50	0.86 ± 0.51	0.87 ± 0.59	0.0047	0.848	0.186
Concavity (mV)	−0.91 ± 1.87	−0.39 ± 0.76	−1.36 ± 2.10	0.188	0.125	0.813
Convexity (mV)	0.73 ± 0.70	0.90 ± 0.66	0.78 ± 0.53	0.24	0.465	0.7
AHPR (V/s)	0.02 ± 0.03	0.03 ± 0.07	0.03 ± 0.08	0.625	0.625	0.625
dAHP (V/s)	6.36 ± 4.54	5.26 ± 4.13	5.51 ± 4.28	0.0014	0.432	0.105
Resistance Hyperpol. (MΩ)	362 ± 203	470 ± 277	396 ± 232	0.002	0.002	0.375
Resistance Depol. (MΩ)	101 ± 49	128 ± 54	106 ± 49	0.002	0.002	0.492

Vm, membrane potential, F, spontaneous discharge frequency, CV, coefficient of variation of the spontaneous discharge, AHP, After HyperPolarization, Width, spike width at threshold, Concavity and convexity: quantification of the shape of the interspike interval, AHPR, quantification of the AHP rectification, dAHP, quantification of the double AHP, Resistance hyperpol: slope of the IV curve in response to hyperpolarizing steps, Resistance depol: slope of the IV curve in response to depolarizing steps. For more details on how these parameters are calculated see (31, 36, 37). Statistically significant differences are highlighted in red.

rotation. They also demonstrated that otoconia-deficient mice (het) are less susceptible to vestibular MS, indicating the pivotal role of otolithic overstimulation in MS generation. Wang and colleagues (47) took advantage of the mouse model to study the genetic susceptibility to MS by generating MS-susceptible or MS-resistant mouse strains. This recent work suggests the implication of a new protein, the swiprosin-1, in the vestibular-dependent response to MS. Collectively these studies demonstrate that *Pica* behavior constitute a reliable index of MS and reveal the high potential for combined genetic, molecular and physiological approaches in rodent models of MS.

Relation Between Vestibulo-Ocular Reflexes and Motion Sickness

Many studies have investigated the correlation between VOR characteristics and the susceptibility of the subject to MS, in order to use the VOR as a predictive measurement of MS. Overall,

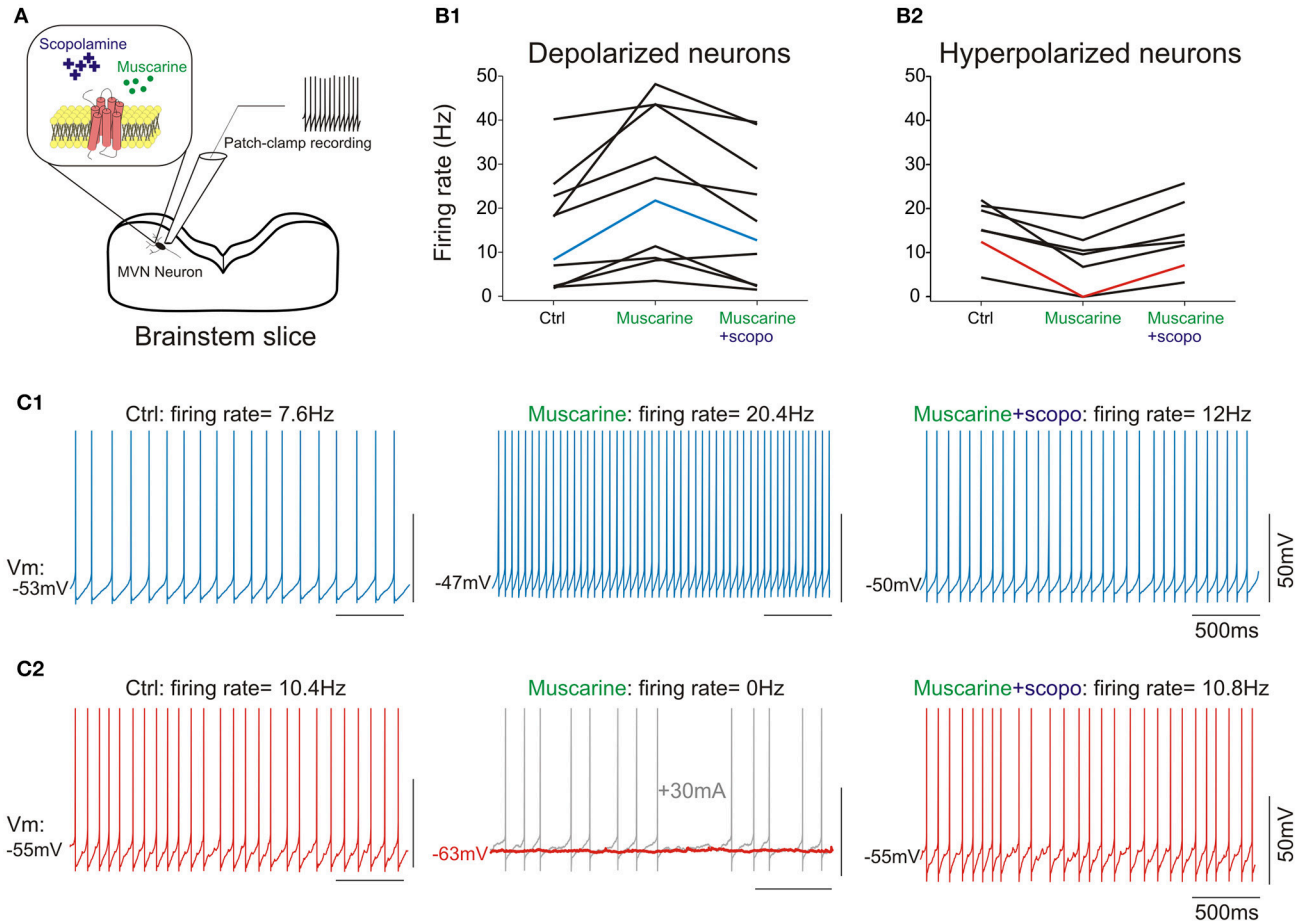

FIGURE 4 | (A) scheme of the pharmacology patch-clamp experiment. **(B1)**, cells depolarized by muscarine; **(B2)**, cells hyperpolarized by muscarine. Scopolamine counteracts muscarine effect at cellular level, irrespective of initial response to muscarine. **(C1)** Raw traces from a type B neuron in control condition (left panel), depolarized following addition of muscarine (middle panel), and re-polarized by the addition of scopolamine (right panel). **(C2)** Raw traces from a type B neuron in control condition (left panel), hyperpolarized by muscarine (middle panel) and re-polarized by the addition of scopolamine (right panel). Note that the hyperpolarization induced by muscarine silenced the neuron (middle panel, red trace). A holding current (gray trace) was injected to ensure the neuron was still correctly recorded. Neurons presented in **(C1,C2)** are highlighted in **(B1,B2)**. All numbers and statistics for the electrophysiology experiments are further reported in **Tables 3–5**.

contradictory results were reported regarding angular VOR and occurrence of MS (48, 49). Ventre-dominey and colleagues (50) reported that MS susceptibility co-occurs with decreasing time constant of the VOR and with the increasing eye velocity during otolith-specific stimulation (OVAR); however other studies contradicted this result (51) and rather suggested an implication of the velocity storage in the genesis of MS during OVAR. Recently, Clement and Reschke (52) reported a correlation between MS susceptibility and the phase lead of the VOR at low frequency, with no correlation with VOR gain. Overall, studies in humans suggest a closer relationship between MS and VOR dynamic properties (phase) rather than VOR sensitivity (gain). Notably, human studies were conducted in order to evoke some degree of discomfort, but experiments were stopped just before or as soon as the subject reached sickness (52), limiting the exposure to motion to typically few minutes, which differs from our protocol. We note also that the rotation protocol used here (combination of 2 opposite directions of rotation with sinusoidal variation in angular speed) is more challenging than the protocols used in humans. Our results suggest that a lasting provocative vestibular stimulation leading to the occurrence of MS drives a significant decrease in the gain of vestibulo-ocular reflexes associated with an increase in the phase lead. This decrease in gain similarly concerned the semi-circular canals (angular VOR) and the otoliths (Maculo-ocular reflex), compatible with the hypothesis of a central common mechanism. Reduction of motion sickness following habituation was associated with a decrease in the time constant of the velocity storage (51, 53–56) and there is evidence for angular VOR gain reduction correlated with MS reduction in expert subjects, as for instance in skaters (57) or in sailors (58). A link between a higher aVOR gain and an increase in phase lead was also suggested as an indication of higher seasickness susceptibility (48). Within this framework, the general decrease in gain and increase in phase lead in

TABLE 5 | Effects of scopolamine on neurons hyperpolarized by muscarine.

Hyperpolarized type B ($n = 7$)	I: Control	II: Muscarine alone (10 μM)	III: Muscarine (10 μM) Scopolamine (10 μM)	*p*-value		
				I vs. II	II vs. III	I vs. III
Vm (mV)	−53.68 ± 3.17	−57.81 ± 5.58	−54.51 ± 5.90	0.0016	0.0016	0.688
F (Hz)	15.64 ± 6.03	8.25 ± 6.59	13.75 ± 7.80	0.0016	0.0016	0.375
CV	11.65 ± 11.74	9.14 ± 8.25	20.52 ± 15.42	0.938	0.375	0.0016
AHP (mV)	24.90 ± 5.36	23.30 ± 6.66	23.02 ± 7.82	0.375	0.688	0.469
Width (ms)	0.82 ± 0.21	0.87 ± 0.25	0.90 ± 0.27	0.688	0.813	0.234
Concavity (mV)	−0.11 ± 0.29	−0.01 ± 0.03	−0.30 ± 0.80	1	0.5	0.5
Convexity (mV)	1.20 ± 0.86	0.66 ± 0.46	0.69 ± 0.87	0.047	0.688	0.0031
AHPR (V/s)	0.00 ± 0.00	0.00 ± 0.01	0.00 ± 0.00	0.5	0.5	1
dAHP (V/s)	3.95 ± 3.41	3.43 ± 2.97	3.58 ± 3.75	0.469	0.938	0.375
Resistance Hyperpol. (MΩ)	596 ± 300	377 ± 117	462 ± 138	0.0031	0.0031	0.156
Resistance Depol. (MΩ)	173 ± 131	123 ± 102	197 ± 159	0.0031	0.0031	1

Vm, membrane potential, F, spontaneous discharge frequency, CV, coefficient of variation of the spontaneous discharge, AHP, After HyperPolarization, Width: spike width at threshold, Concavity and convexity: quantification of the shape of the interspike interval, AHPR, quantification of the AHP rectification, dAHP: quantification of the double AHP, Resistance hyperpol: slope of the IV curve in response to hyperpolarizing steps, Resistance depol: slope of the IV curve in response to depolarizing steps. For more details on how these parameters are calculated see (31, 36, 37). Statistically significant differences are highlighted in red.

the vestibulo-ocular responses we report, putatively associated with a decrease in the general sensitivity of the vestibular system, might reduce the sensitivity to the conflicting sensory inputs, and thus putatively help preventing later occurrence of MS.

Visual and Vestibular Interactions and Motion Sickness Prevention

If interactions between the VOR main parameters and MS exist, then it might be possible to act on the reflexes to manipulate the susceptibility of the patients. Dai et al. (1) demonstrated in a group of MS-susceptible patients that a visuo-vestibular iterated training protocol could reduce MS sensitivity for several weeks following the habituation sessions. We took advantage of a long-lasting visuo-vestibular mismatch to induce a reduction in the vestibulo-ocular reflexes that again affected equally both canals- and otolith-based reflexes. We demonstrated (24) that this protocol leads to a reduction of the neural responses in the direct VOR pathway. The cellular mechanisms associated to this decrease were a reduction in the synaptic efficiency between the vestibular afferent and the central vestibular neurons and a decrease in the excitability of subpopulations of central vestibular neurons (24). In other term, the long-lasting visual perturbation reduced the brainstem sensitivity to vestibular inputs. Here, we show in mice that the visually-induced reduction in the vestibular reflexes offers a protection against MS. Our results suggest that this effect lasts for at least 3 days, although longer term effects are possible and would deserve dedicated experiments. Overall, our neural and behavioral evidence support the possibility of using visuo-vestibular protocols to habituate susceptible patients to MS induced by vestibular overstimulation or by visuo-vestibular sensory conflicts. For example, since myopic people who wear glasses (but not lenses) have lower angular VOR gains (59), it would be interesting to test whether they are less susceptible to MS than myopic people wearing lenses, and even less than hyperopic people corrected with glasses, whose angular VOR gain is enhanced because of their high positive lenses. Because changes in the efficacy of gaze stabilizing systems are often associated with oscillopsia (60, 61), it would be interesting to study if patients under anti-motion sickness treatments report greater oscillopsia during active head motions.

Scopolamine Effects on the Vestibular Reflexes and on Motion Sickness

Scopolamine is well-known as being among the most efficient anti-MS drugs in humans. It is commonly used in particular during space flight as a counter-measure against space motion sickness. In a series of experiments performed on humans in the 80's, Pyykkö et al. (62–64) demonstrated that patches of scopolamine prevented motion sickness by reducing the vestibular and optokinetic gains and suggested that the drug acted on the integrative function of the central vestibular nuclei. More recently, Werts et al. (14) reported a reduction of the angular VOR and caloric response following intranasal administration of scopolamine. Scopolamine had a depressant action on the response of the semicircular canals, postulated to be a combination of peripheral and central effects while it had little effect on the saccular reflex tested with cervico Vestibular Evoked Myogenic Potentials (cVEMP). On the other hand, Tal et al. (65) reported a significant decrease in cVEMP p13 latency following scopolamine administration. Bestaven et al. (16) demonstrated a significant reduction of ∼30% of the vestibulo-spinal reflexes following galvanic vestibular stimulation associated with a decrease in balance test and vertical perception. In cat, no direct effect of scopolamine on the VOR was found at low doses, while at high doses the effects were confounded

by sedation (66). To our knowledge, our experiments for the first time demonstrate in rodents that the prophylactic effect of scopolamine is associated with a reduction of vestibular sensitivity that concerns not only the semi-circular canal but also the otolith signals. We further show that the preemptive reduction of the vestibular reflexes by scopolamine injection can occlude the reduction of the VOR normally observed following MS. This occlusion suggests that both phenomena rely on a single mechanism or that, if the two processes are distinct, they converge on the same neuronal elements that cannot be adapted below a certain threshold.

Neuronal Mechanisms and Motion Sickness

What are the neuronal mechanisms associated with MS? Experimental evidence suggests that the processing of divergent sensory inputs in various brain areas (e.g., cerebellum; thalamus) contributes to patients' MS and also impacts the functioning of many cortical areas (67, 68). A key observation which emphasizes the instrumental role of the vestibular system may be, however, that patients with a total loss of labyrinthine function do not get motion sick [review in Lackner (5)]. In addition, in most instances it is the exposure to passive, rather than active, motion that leads to MS (69). In the vestibular nuclei and in the fastigial nuclei of the cerebellum, neurons categorized as "vestibular-only" were demonstrated to differentially encode passive and active movements (70–74). The proposed mechanism is termed "*reafference cancelation.*" It suggests that the vestibulo-cerebellum is using an internal model to predict the consequences of active, voluntary movements and substract this *reafference* signal from the signal sensed by the vestibular organs, termed *exafference* signal. As a result of the substraction of *reafference* and *exafference*, the discharge of vestibular-only neurons would represent the difference between the expected movement and the actual movement. Their discharge thus codes the "unexpected," passive part of head movements. Vestibular-only neurons are implicated in vestibulo-spinal and vestibulo-sympathic pathway and are nowadays the best candidate for motion sickness generation within the vestibulo-cerebellum (73).

The identification of vestibular-only neurons *in vitro* still remains to be done. However, recent data have suggested that type B neurons constitute the vestibular-projection neurons while type A neurons would constitute the interneurons implicated in local regulation of activity (24, 35). It was also demonstrated that VN neurons that project to the cerebellum and are implicated in vestibulo-cerebellar regulatory loops are glutamatergic, so there is a high probability that vestibular-only neurons and neurons that project on the cerebellum are dominantly type B neurons. Here, all tested type B neurons were found to be modulated by cholinergic stimulation. The presence of nicotinic and muscarinic acetylcholine receptors (mAChR) in the vestibular nucleus with high density in the medial vestibular nucleus is well documented (75–79). Two distinct populations of type B neurons were found based on their modulation by the cholinergic system. Acetylcholine had opposite effects on these subpopulations, suggesting the existence of different receptors. Zhu et al. (38) reported that among the five mAChR subtypes, M2 and M3 may be the most highly expressed in the rat MVN. Interestingly, M2 is linked to the excitatory Gq/11 proteins, while M3 is coupled to the inhibitory Gi/o proteins (80, 81), and both receptors could play distinct roles in regulating vestibular afferent activity onto MVN neurons and activity of cerebellum-projecting neurons (38). The potential of mACHR subtype-specific agonists and antagonists as counter-measures again MS should be the focus of future studies.

AUTHOR CONTRIBUTIONS

EI and MB: Designed research. EI: Performed research. EI, MT, and MB: Analyzed data and wrote the paper.

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Effect of Rotating Auditory Scene on Postural Control in Normal Subjects, Patients With Bilateral Vestibulopathy, Unilateral, or Bilateral Cochlear Implants

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Objective: The aim of this study was to investigate the impact of a rotating sound stimulation on the postural performances in normal subjects, patients with bilateral vestibulopathy (BVP), unilateral (UCI), and bilateral (BCI) cochlear implantees.

Materials and Methods: Sixty-nine adults were included (32 women and 37 men) in a multicenter prospective study. The group included 37 healthy subjects, 10 BVP, 15 UCI, and 7 BCI patients. The average of age was 47 ± 2.0 (range: 23–82). In addition to a complete audiovestibular work up, a dynamic posturography (Multitest Framiral, Grasse) was conducted in silence and with a rotating cocktail party sound delivered by headphone. The center of pressure excursion surface (COPS), sensory preferences, as well as fractal, diffusion, and wavelet analysis of stabilometry were collected.

Results: The rotating sound seemed to influenced balance in all subgroups except in controls. COPS increased with sound in the BVP and BCI groups in closed eyes and sway-referenced condition indicating a destabilizing effect while it decreased in UCI in the same condition suggesting stabilization ($p < 0.05$, linear mixed model corrected for age, $n = 69$). BVP had higher proprioceptive preferences, BCI had higher vestibular and visual preferences, and UCI had only higher vestibular preferences than controls. Sensory preferences were not altered by rotating sound.

Conclusions: The rotating sound destabilized BVP and BCI patients with binaural hearing while it stabilized UCI patients with monaural hearing and no sound rotation effect. This difference suggests that binaural auditory cues are exploited in BCI patients for their balance.

Keywords: binaural hearing, stereophony, balance, bilateral vestibulopathy, posturography, multisensory integration

INTRODUCTION

The interaction between binaural hearing and space representation has been discussed for several decades. In 1960, Hennebert studied the clinical effects of a rotating sound in healthy subjects and observed a provoked nystagmus which he called "audiokinetic." This nystagmus had a slow phase parallel to the source movement. Other reported effects were a deviation of the upper limbs during the Romberg test, deviation of vertical writing toward the sound and also neurovegetative reactions (1).

Bats are probably the most performant animals in using their hearing for the representation of their environment (2). These animals can separate auditory cues related to echolocation from those used for communication during their flight (2) and echolocation seems to be quite efficient since it does not add large energetic costs to the aerodynamic power requirements of their flight (3). After several months of training, many blind humans can also develop echolocation using tongue clicks. They use this capacity in daily life to avoid obstacles and to obtain information on the form and the size of surrounding objects (4). Echolocation is a dynamic process and uses the head-related transfer function (4–6). This ability requires stereophony with two equivalently performant ears (7). In blind experts, a separate processing of auditory source-motion and echo-motion in temporal-occipital cortex is observed and fMRI data suggest central reorganization with a possible recruitment of visual cortex (8).

Other observations on postural behavior of normal subjects submitted to static or mobile sound sources support the idea that hearing afferences could have an impact on the gait when other afferences are destroyed or ineffective (9–11). Studies in elderly patients are in line with those in experimental conditions on the role of auditory input in the balance by showing that hearing aids enhance the gait during Romberg test, decrease the risk of falls (12) and improve many aspects of quality of life related to balance (13).

In patients with a cochlear implant (CI), the effect of sound on balance has been rarely reported (14). Many bilaterally deaf patients still receive CI on one side due to its cost (15). Today, based on proven benefits of binaural hearing on global auditory performances, bilateral CI (BCI) is proposed more frequently in developed countries (16). However, BCI does not provide stereophony in all patients due to asymmetries of auditory nerve function, and to the sound coding strategies which reduce or suppress binaural time cues (17). Although the effect of BCI on sound localization has been reported (17, 18), the influence of binaural cues provided by CI on balance performances has not been investigated to our knowledge. It should also be underlined that CI has a potential impact on vestibular integrity and function. Histological lesions in the saccule and semicircular canals as a consequence of CI have been described (19). However, the functional consequences in unilateral cochlear implantees (UCI) appear to be mild (20).

Recent studies on sound-gait interaction provide different and sometimes contradicting results, but they all suggest an effect of the sound on balance performances (21–27). The contradictions are probably related to the experimental protocol, the characteristics of the subjects, the measured parameters and the fact that balance is a dynamic process which uses different sensory inputs changing in hierarchy depending on patients and on situations (28).

In order to better understand the interaction between hearing and vestibular functions, especially in patients with CI, we aimed at investigating the effect of moving sound sources on balance performances by dynamic posturography in healthy subjects, in patients with bilateral vestibulopathy (BVP), and also in UCI and BCI.

MATERIALS AND METHODS

Population

Sixty-nine subjects were included in this prospective and multicenter study from September 2015 to February 2016. The population included 37 healthy volunteers, 10 BVP, 15 UCI, and 7 BCI. The group was composed of 32 women and 37 men. The mean age was 47 ± 2.0 years [range: 23–82] in the general population, 38 ± 2.1[23–66] for controls, 63 ± 2.4 [50–74] for BVP, 53 ± 3.7[23–71] for UCI, and 57 ± 9.2[25–82] for BCI. Controls were younger than other subgroups ($p < 0.05$, ANOVA followed by Dunett).

The study was conducted in two tertiary referral centers for balance disorders. The study received the approval of the local ethical research committee (CPP Est III) and from the French National Agency of Safety for Medicine and Health Products (number 2015-A00754-45). An informed consent was signed by all patients. All patients (but not controls) underwent a vestibular assessment with caloric and rotatory tests, videonystagmography analysis of gaze, pursuit, and saccade, and finally cervical vestibular evoked myogenic potentials (cVEMP). Eye movement analysis did not show signs of central involvement in this population.

BVP was defined according to the Barany Society criteria: the horizontal angular vestibulo ocular reflex (VOR) gain on both sides <0.6 (angular velocity 150–300°/s) and/or the sum of the maximal peak velocities of the slow phase caloric-induced nystagmus for stimulation with warm and cold water on each side <6°/s and/or the horizontal angular VOR gain <0.1 upon sinusoidal stimulation on a rotatory chair (0.1 Hz, $V_{max} = 50°/s$) and/or a phase lead >68 degrees with a time constant of <5 s (29). All BVP subjects had a hearing test to confirm their normal hearing. Control subjects were asymptomatic and not tested for hearing.

In UCI group, nine patients (60%) had a normal caloric test, five (33%) had a deficit in the same side as the implanted ear, and one (7%) had a bilateral deficit. Eleven (73%) UCI had bilateral normal responses to cVEMPs, four (27%) had a deficit the same side as the implanted ear.

In BCI group, caloric stimulations were obtained in five cases. There was a bilateral deficit in three cases (60%), a unilateral deficit in one case (20%), and a normal caloric test for one patient. Four (57%) BCI had bilateral normal responses to cVEMPs, two (29%) patients had a unilateral right deficit, and one (14%) had a bilateral deficit. No UCI or BCI patient corresponded to the criteria of BVP.

In the UCI group, eight patients were implanted on the right side and seven UCI on left side. In this group, 13 patients were implanted with Digisonic SP implant and Zebra Processor (Oticon Medical Inc., Vallauris, France), one patient with Hi-Res 90K implant and Naida processor (Advanced Bionics, Valencia, CA), and one with Nucleus Freedom implant and processor (Cochlear Inc., Lane Cove, Australia). Three patients had a hearing aid on the contralateral ear. UCI were implanted 6 ± 1.2 years before the inclusion. The pure-tone average threshold of the implanted ear was 39 ± 2.0 dB HL ($n = 15$). The aided pure-tone average threshold of the contralateral ear was 95 ± 6.2 dB HL ($n = 15$).

BCI were implanted 4 ± 1.3 years before test tests for the right ears and 2.8 ± 1.06 years for the left ears. The pure-tone average threshold was 43 ± 5.2 dB HL on the right and 44 ± 3.2 dB HL on the left. In this group, six patients were bilaterally implanted with Digisonic SP implant and Zebra Processor (Oticon Medical Inc., Vallauris, France), and one with Advanced Bionics Hi-Res 90K implant and Naida processor (Advanced Bionics, Valencia, CA).

All patients were evaluated on a dynamic posturography platform. Each test was conducted in silence, with a clockwise and counterclockwise rotating sound.

Dynamic Posturography

The tests were performed on a conventional posturography plate bearing three pressure sensors (Balance Quest, Micromedical Technologies, Chatham, IL). The sampling rate was set at 50 Hz. The confidence ellipse surface containing 90% of all center of pressure positions was recorder and referred to as center of pressure excursion surface (COPS in mm^2, **Figure 1**). A value of 300 was assigned to the test in case of fall. Sensory preferences and visual dependency indexes were calculated based on COPS measurements in different posturography conditions as follows (30): visual preference (eyes open, stable platform/eyes open, sway-referenced platform), vestibular preference (eyes open, stable/eyes closed, sway-referenced platform), proprioceptive preference (eyes open, stable/eyes closed, stable), visual dependency index (optokinetic stimulation, stable + optikenitic stimulation, sway-referenced)/(eyes closed, stable + eyes closed). Each condition was measured for 30 s and a 15-s break separated each condition.

In the two most unstable conditions (eyes closed sway-referenced, EC-SR and optikenitic stimulation, sway-referenced, OK-SR), wavelet and diffusion analyses were conducted: the energy consumption was measured in two axes (mediolateral: X and anterior-posterior: Y) in three frequency bands 0.05–0.5, 0.5–1.5, and 1.5–10 Hz by wavelet analysis. Based on this measure, a postural stability index (PSI) representing the total time during which no energy consumption was measured, and a postural control index (PCI) representing the total time with postural activity were automatically calculated by the software in the three frequency bands (Posturopro ® Software, Inserm, Marseille, France). A postural instability index (PII) deduced from the two latter parameters was studied (PII = PSI/PCI). The diffusion analysis estimated the extent of oscillation around an equilibrium state and its break-point by two additional parameters: the critical time (CT, in s) and the critical amplitude (CA, in mm^2). Moreover, a Fractal analysis was conducted and the result was presented as the proportion of Hausdorff points (n/N) representing the percentage of stochastic position points among all sampled positions.

Subjects were stimulated by a rotating sound on the dynamic posturography platform in four trials (clockwise rotating sound, silence, anti-clockwise rotating sound, silence). The stimulus consisted of a rotating *Cocktail party* sound at 189°/s horizontally around the subject. The sound was delivered at 75 dB by a headphone (HD 205, Sennheiser, Wedemark, Germany) to mask the noise produced by the posturography platform. The rotating sound effect was created by CSoundQT® 3.1 Software (Pelican, Gumby Framework, New Haven, CT) based on head-relative transfer function.

In silence, control and BVP subjects were tested in a quiet room with the headphone off placed on ears. For UCI and BCI patients, the external processors and the hearing aids were removed.

Statistics

Values were expressed as mean ± SD. Linear mixed models were used to access relationship between sound and gait of different subgroups. As the age could be a significant factor for the performances on the dynamic posturography, the model was corrected for age. A robust estimator of variance was used (31). Statistical tests were conducted on Stata (StataCorp LLC, College Station, TX).

RESULTS

Posturography

Center of Pressure Excursion Surfaces and Sensory Organization Test

As expected, patients with bilateral vestibular loss had larger COPS than controls in eyes closed or optokinetic and sway-referenced conditions (**Table 1**, $p < 0.05$, Linear mixed models, $n = 69$). Interestingly, UCI and BCI had greater excursion surfaces than control subjects not only in sway-referenced conditions but also in eyes closed and stable platform condition (**Table 1**).

Rotating sound seemed to influence COPS differently in patients with bilateral vestibular loss and in those with UCI:COPS increased with sound in the bilateral vestibular loss group ($n = 10$) in EC-SR condition, indicating a destabilizing effect, while it decreased in UCI in the same environment suggesting stabilization ($n = 15$, $p < 0.05$, linear mixed model corrected for age, $n = 69$, **Table 1**).

In the optokinetic and sway-referenced condition, BCI had also larger COPS with rotating sounds (CW and CCW) than in silence suggesting a destabilizing effect ($p < 0.05$, linear mixed model corrected for age, $n = 69$, **Table 1**) while other groups did not seem to be influenced in this condition.

SOT in silence revealed a lower proprioceptive preference index in subjects with bilateral vestibular loss than in controls (**Table 2**). In contrast, UCI patients had a lower vestibular preference index than controls. In BCI subjects, both vestibular and visual preference indexes were lower than controls (**Table 2**,

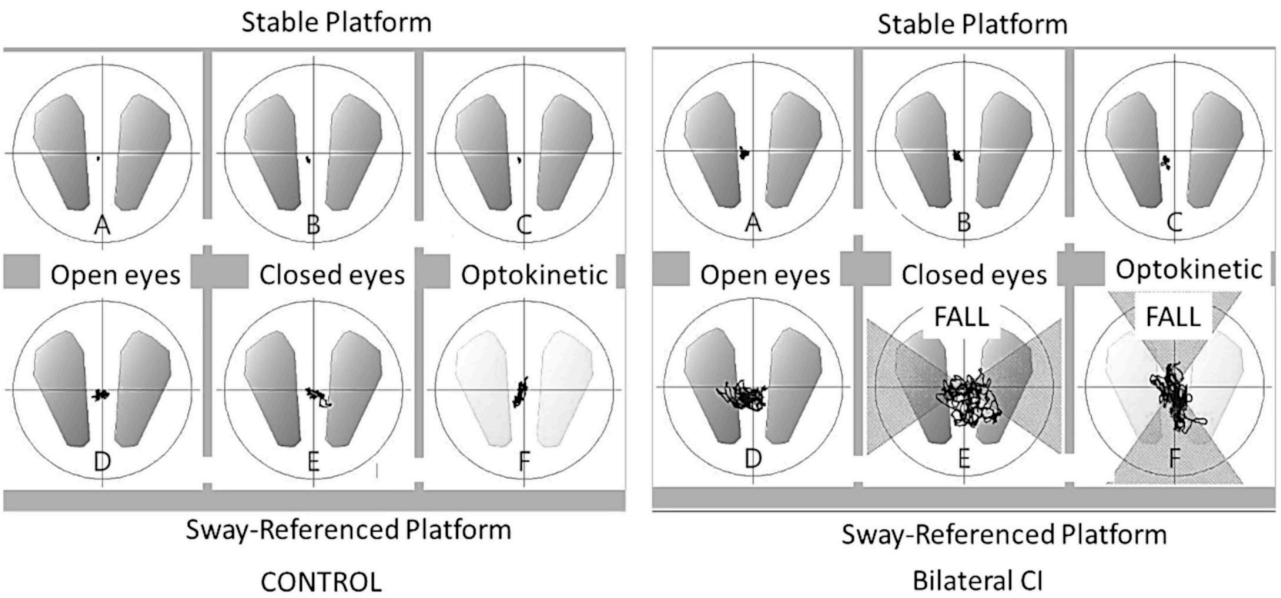

FIGURE 1 | Center of pressure excursion surface (COPS). Ellipse containing 90% of all center of pressure positions (mm²) in six conditions on dynamic posturography for a control subject and a bilateral cochlear implant patient. The line shows the movement of pressure positions during the 30 s. acquisition and "FALL" indicates patient falls during the test.

linear mixed models corrected for age, $n = 69$). Sound did not seem to influence sensory preferences (**Table 2**).

Although CIs had a COPS similar to controls in the easy condition (eyes open, stable platform), they showed greater COPS in difficult conditions (closed eyes, sway referenced), together with a reduced vestibular preference. This suggested a compensated vestibular deficit in accordance with caloric and otolithic tests.

Wavelet, Diffusion, and Fractal Analysis of Stabilometry

In silence and in EC-SR condition, PII was higher in UCI than in control suggesting more instability (**Table 3**, $p < 0.05$, Linear mixed models, $n = 69$). This difference was not observed in OK-SR condition. Other groups of patients had similar PII to the control in EC-SR and OK-SR conditions (**Table 3**, $p < 0.05$, linear mixed models corrected for age, $n = 69$). Sound did not seem to influence PII (**Table 3**).

Diffusion analysis revealed higher CAs in BVP, UCI, and BCI patients than control in EC-SR and OK-SR conditions regardless of sound conditions ($p < 0.05$, linear mixed models corrected for age, $N = 69$, **Table 4**). Critical time did not differ between groups (linear mixed models corrected for age, $n = 69$, **Table 5**).

Fractal analysis showed lower proportion of Hausdorff points in UCI and BCI subjects than in controls in Y (roll) axis in EC-SR and OK-SR conditions ($p < 0.05$, linear mixed models corrected for age, $n = 69$, **Table 6**). Sound did not seem to influence the proportion of Hausdorff points in the Y axis in any subgroup (**Table 6**). No difference between subgroups or effect of sound could be observed in the X axis (pitch, data not shown).

DISCUSSION

In this study, we showed that the hearing afferences could have an impact on the gait especially when other sensory inputs are impaired. As expected, patients with BVP, UCI, and BCI had poorer posturography performances than the control and their sensory organization was altered. Interestingly, the rotating sound reduced the COPS in patients with UCI and no stereophony but increased COPS in patients with BVP enjoying stereophony and BCI with binaural hearing in sway-referenced conditions and disturbed visual input. In contrast, control subjects did not modify their COPS under the sound effect suggesting a different hierarchy of sensory inputs in these individuals. The destabilizing effect of the rotating sound in BVL and BCI patients could be enhanced by the vestibular deficit in these subjects. This deficit might have modified the hierarchy of sensory inputs for balance.

Two limitations of our study were that the mean age of the control population was lower than other subgroups, and that although control subjects were totally asymptomatic, they were not explored by audiometry. We corrected the effect of age in our multivariate analysis, but these two aspects might limit the comparison between subgroups.

Several studies have already reported the effect of the sound on the gait or vestibular function with contradicting results: Some studies reported higher stability (9, 11–13, 32), while others described poorer balance performances (10, 21, 22). The apparent contradiction could lie in the nature of the stimulus: stable vs. moving source.

Stevens et al. (32) tested the impact of the sound on the gait by dynamic posturography in 12 control and six patients with

TABLE 1 | Center of Pressure (COP) excursion surfaces as a function of posturography conditions in silence and rotating sound.

Condition	Sound	Control ($n = 37$)	Unilateral CI ($n = 15$)	Bilateral CI ($n = 7$)	Bilat. vestibular loss ($n = 10$)
Eyes open stable	Silence	2.1 ± 2.74	3.3 ± 2.96	6.2 ± 8.21	2.4 ± 3.81
	CW	1.8 ± 1.86	3.6 ± 2.79	6.5 ± 5.92	3.5 ± 5.11
	CCW	1.6 ± 1.25	2.6 ± 1.47	5.0 ± 6.98	3.9 ± 5.74
Eyes closed stable	Silence	1.0 ± 0.86	**3.6 ± 4.79***	**4.1 ± 4.86***	32.8 ± 93.96
	CW	1.1 ± 0.94	**2.7 ± 2.05***	**2.8 ± 1.67***	6.9 ± 11.70
	CCW	1.3 ± 1.03	**3.5 ± 2.49***	**5.5 ± 5.80***	6.6 ± 11.37
Optokinetic stable	Silence	1.4 ± 1.68	6.5 ± 16.08	2.5 ± 1.66	32.1 ± 94.15
	CW	1.2 ± 1.15	22.2 ± 76.89	2.5 ± 2.03	34.0 ± 93.66
	CCW	2.3 ± 0.69	4.9 ± 1.63	3.7 ± 1.37	61.5 ± 39.75
Eyes open sway-ref.	Silence	7.0 ± 5.55	**59.8 ± 99.01***	**163.8 ± 130.21***	35.6 ± 93.18
	CW	6.4 ± 6.05	**39.2 ± 75.20***	**82.0 ± 99.10***	11.2 ± 18.51
	CCW	7.9 ± 7.89	**40.6 ± 74.57***	**110.9 ± 130.19***	14.0 ± 20.83
Eyes closed sway-ref.	Silence	18.4 ± 48.81	**220.0 ± 121.84***	**220.9 ± 135.29***	**139.3 ± 131.99***
	CW	26.2 ± 68.73	**126.8 ± 129.34*£**	**258.9 ± 108.81***	**148.0 ± 136.39*£**
	CCW	11.6 ± 21.86	**112.9 ± 119.85*£**	**227.4 ± 124.00***	**180.9 ± 144.18*£**
Optokinetic sway-ref.	Silence	35.2 ± 81.46	**135.5 ± 139.61***	**192.6 ± 134.74***	**129.1 ± 129.14***
	CW	27.0 ± 67.45	**94.6 ± 128.71***	**272.5 ± 72.87*£**	**161.8 ± 132.78***
	CCW	20.6 ± 50.41	**101.3 ± 126.31***	**257.6 ± 109.61*£**	**163.6 ± 140.44***

Surfaces include 95% of all COPs and are expressed as mean ± SD in mm^2. CW, Clockwise; CCW, Counter-clockwise; CI, Cochlear implant.
**$p < 0.05$ vs. control.*
£$p < 0.05$ vs. silence in the same condition and group, linear mixed model corrected for age, $n = 69$.
Bold values represent significant differences of the parameter in comparison to control or versus silence.

TABLE 2 | Sensory preference index based on center of pressure excursion surfaces in silence and rotating sound.

Sensory preferences	Sound	Control ($n = 37$)	Unilateral CI ($n = 15$)	Bilateral CI ($n = 7$)	Bilat. vestibular loss ($n = 10$)
Visual	Silence	0.4 ± 0.66	0.2 ± 0.16	**0.1 ± 0.10***	0.3 ± 0.23
	CW	0.5 ± 0.61	0.4 ± 0.53	**0.2 ± 0.15***	0.8 ± 1.24
	CCW	0.5 ± 1.31	0.3 ± 0.50	**0.1 ± 0.10***	0.4 ± 0.32
Vestibular	Silence	0.5 ± 1.39	**0.04 ± 0.07***	**0.1 ± 0.07***	0.2 ± 0.38
	CW	0.6 ± 1.37	**0.5 ± 1.42***	**0.1 ± 0.11***	0.1 ± 0.22
	CCW	0.7 ± 2.64	**0.1 ± 0.23***	**0.1 ± 0.10***	0.2 ± 0.45
Proprioceptive	Silence	2.3 ± 3.7	1.6 ± 1.12	2.1 ± 2.79	**0.8 ± 0.76***
	CW	2.0 ± 2.02	1.9 ± 1.97	2.0 ± 0.96	**1.0 ± 1.00***
	CCW	1.6 ± 1.38	0.9 ± 0.54	1.3 ± 0.75	**1.2 ± 0.92***
Visual dependency	Silence	3.0 ± 6.74	1.0 ± 1.86	1.1 ± 0.50	20.0 ± 59.21
	CW	1.4 ± 1.51	2.1 ± 6.00	3.7 ± 7.35	3.2 ± 6.92
	CCW	2.4 ± 4.11	1.4 ± 2.07	1.3 ± 0.82	1.4 ± 1.04

Values are expressed as mean ± SD. CW, Clockwise; CCW, Counter-clockwise; CI, Cochlear implant.
**$p < 0.05$ vs. control, linear mixed model corrected for age, $n = 69$.*
Bold values represent significant differences of the parameter in comparison to control or versus silence.

neurological diseases. They delivered a stable white noise via four earth-referenced speakers placed around the subject during the six conditions of posturography and showed that this type of stimuli decreased the COPS in both patients and controls. By comparing head-fixed stationary sound to silence, the authors did not find an improvement of the gait and concluded that the effect of an earth-fixed sound is probably based on localization cues more than on alertness. This observation was in accordance with a previous study in which stationary music delivered by a headphone did not influence the gait during posturography (26). Moreover, the stabilizing effect of earth-fixed stationary sounds were in accordance with other studies in healthy subjects evaluating gait by the Fukuda stepping test (9) and Romberg test (12).

In addition to providing cues on the distance and orientation of the body relative to earth-referenced sound sources, recent reports suggest that stable sound sources may interact with the visual input (33). Indeed, directing the gaze toward the

TABLE 3 | Postural instability index.

Postural instability index	Sound	Control ($n = 37$)	Unilateral CI ($n = 15$)	Bilateral CI ($n = 7$)	Bilat. vestibular loss ($n = 10$)
Eyes closed sway-ref.	Silence	3.2 ± 0.96	**4.6 ± 2.06***	3.9 ± 2.80	4.0 ± 2.46
	CW	3.1 ± 1.21	**4.9 ± 0.97***	4.6 ± 2.22	4.4 ± 2.22
	CCW	2.9 ± 0.98	**4.8 ± 1.07***	4.7 ± 2.24	4.4 ± 2.31
Optokinetic sway-ref.	Silence	3.4 ± 1.22	4.1 ± 1.35	3.7 ± 2.59	4.7 ± 1.78
	CW	3.3 ± 1.13	3.7 ± 1.73	4.4 ± 2.31	5.4 ± 1.51
	CCW	3.3 ± 1.19	4.2 ± 1.20	4.5 ± 2.26	4.4 ± 2.21

Values are expressed as mean ± SD. CW, Clockwise; CCW, Counter-clockwise; CI, Cochlear implant.
**p < 0.05 vs. control, linear mixed model, corrected for age n = 69.*
Bold values represent significant differences of the parameter in comparison to control or versus silence.

TABLE 4 | Critical time.

Critical time	Sound	Control ($n = 37$)	Unilateral CI ($n = 15$)	Bilateral CI ($n = 7$)	Bilateral vestibular loss ($n = 10$)
Eyes closed sway-ref.	Silence	0.8 ± 0.35	1.0 ± 0.81	0.6 ± 0.52	1.0 ± 0.72
	CW	0.9 ± 0.37	1.2 ± 0.56	1.0 ± 0.60	1.0 ± 0.50
	CCW	1.0 ± 0.59	1.0 ± 0.55	0.8 ± 0.44	1.0 ± 0.65
Optokinetic sway-ref.	Silence	1.1 ± 1.31	1.1 ± 0.50	0.9 ± 0.82	0.8 ± 0.64
	CW	1.1 ± 0.87	0.9 ± 0.61	0.9 ± 0.88	0.8 ± 0.43
	CCW	1.1 ± 0.71	1.0 ± 0.38	0.7 ± 0.35	0.9 ± 0.53

This parameter was estimated by diffusion analysis of stabilometry during dynamic posturography. Values are expressed as mean ± SD in seconds. CW, Clockwise; CCW, Counter-clockwise; CI, Cochlear implant. The was no difference between subgroups or experimental conditions (linear mixed model corrected for age, n = 69).

TABLE 5 | Critical amplitude.

Critical amplitude	Sound	Control ($n = 37$)	Unilateral CI ($n = 15$)	Bilateral CI ($n = 7$)	Bilat. vestibular loss ($n = 10$)
Eyes closed sway-ref.	Silence	350.9 ± 674.64	**2,787.5 ± 2,510.37***	**1,938.2 ± 2,782.11***	**2,608.9 ± 2,886.14***
	CW	456.2 ± 1,020.90	**2,429.0 ± 2,909.74 ***	**2,457.6 ± 2,240.32***	**2,401.5 ± 2,118.99***
	CCW	373.2 ± 1,029.16	**2,352.7 ± 3,186.51***	**2,509.7 ± 2,462.20***	**2,764.5 ± 2,601.43***
Optokinetic sway-ref.	Silence	385.5 ± 606.4	**1,220.4 ± 1,619.2***	**1,135.2 ± 1,005.7***	**1,920.1 ± 1,680.2***
	CW	456.2 ± 1,020.9	**2,429.0 ± 2,909.7***	**2,457.6 ± 2,240.3***	**2,161.3 ± 2,137.3***
	CCW	360.4 ± 681.4	**2,787.5 ± 2,510.4***	**1,938.2 ± 2,782.1***	**2,608.9 ± 2,886.1***

*This parameter was estimated by diffusion analysis of stabilometry during dynamic posturography. Values are expressed as mean ± SD (mm^2). CW, Clockwise; CCW, Counter-clockwise; CI, Cochlear implant. *p < 0.05 vs. control, linear mixed model corrected for age, n = 69.*
Bold values represent significant differences of the parameter in comparison to control or versus silence.

TABLE 6 | Proportion of Hausdorff points in Y (Roll) axis.

Exp. condition	Sound	Control ($n = 37$)	Unilateral CI ($n = 15$)	Bilateral CI ($n = 7$)	Bilateral vestibular loss ($n = 10$)
Eyes closed sway-ref.	Silence	1.6 ± 1.27	**0.6 ± 0.77***	**0.4 ± 0.43***	1.7 ± 1.08
	CW	1.7 ± 1.75	**0.7 ± 0.81***	**0.7 ± 0.51***	1.7 ± 1.17
	CCW	1.7 ± 2.03	**0.9 ± 0.88***	**0.9 ± 0.96***	1.2 ± 0.86
Optokinetic sway-ref.	Silence	1.6 ± 1.42	**0.9 ± 0.83***	**0.3 ± 0.24***	1.8 ± 1.04
	CW	1.5 ± 1.34	**0.6 ± 0.45***	**0.5 ± 0.31***	1.7 ± 1.49
	CCW	1.5 ± 2.41	**0.7 ± 0.89***	**0.5 ± 0.37***	1.3 ± 0.84

This parameter was calculated by fractal analysis of dynamic stabilometry. Values are expressed as mean ± SD. CW, Clockwise; CCW, Counter-clockwise; CI, Cochlear implant.
**p < 0.05 vs. control, linear mixed model corrected for age, n = 69.*
Bold values represent significant differences of the parameter in comparison to control or versus silence.

source without moving the head significantly enhances the detection of interaural time and intensity differences (33). This observation indicates a visual and auditory interaction possibly at the brainstem level which could also benefit to the gait.

The effect of moving sound fields has also been investigated by stabilometry in healthy subjects but with contradictory results. While some authors report that moving sounds appear to increase sway (1, 21, 22), others observe a stabilizing effect of rotatory sounds and argue that contrary to moving visual cues, mobile sound sources are easier to identify and consequently more valuable in a multisensory processing of the balance (27).

The type of sound used in the experimental protocol might also explain the discrepancies between the reports on this subject (1, 10, 34). In 1960, Hennebert stated that rotating continuous pure tone elicited little vestibular response (nystagmus, Romberg test) while discontinuous pure tones with regular interruptions at a 3–5 Hz frequency have a higher impact. Similarly, white noise or complex sounds such as music yielded better responses (1). In this report, no quantification of the effects and quantitative comparison was provided. To our knowledge, no other study has compared the effect different sounds on the gait. For our subjects, we chose a cocktail party noise in order to be realistic and close to daily-life situations.

In our study, the rotating sound algorithm provided an impression of source displacement to patients with binaural hearing (BVP and BCI) but appeared as a sound oscillating in amplitude in the implanted ear of UCI patients. Based on previous reports, this could explain the destabilizing effect of the rotating sound in BVP and BCI subjects in contrast to the stabilizing impact on the UCI patients. Our sound stimuli did not disturb the healthy subjects even in conditions where the visual and proprioceptive inputs were hampered. This observation suggests that hearing afferences have a more prominent effect on the posture when other afferences (especially vestibular) are damaged.

The impact of CI on the vestibular system is a concern among otologists, mainly because the surgical trauma of the implantation in an already fragile inner ear may partly destroy the vestibule. This possibility influences the rehabilitation strategy especially in case of bilateral implantation (35). However, few studies have focused on the potential advantage of auditory input on the gait as a result of a richer multisensory input (14, 36, 37). While the effect of an active CI is undetectable by dynamic posturography if the patient is not stimulated by sound (37), patients seem to performed better with their CI on and an earth-referenced white noise in dark in comparison to the same situation with deactivated CI (14). Similarly, patients with hearing aids appear to benefit from the enhanced auditory input for their balance performance in the presence of a stationary sound (36).

Observations on dynamic posturography are also in accordance with several publications reporting an increase in risk of falls beginning in mild hearing losses and proportional to its severity: 1.4 X for every 10 dB loss in senior population (12, 13, 38–40). Additionally, the idea that auditory input can be readily integrated in the multisensory gait control is also supported by the observation that translating hip and trunk movement into sound at delivering it to the subjects through headphone (auditory biofeedback) enhanced postural control in both BVP and healthy subjects (11).

Wavelet, diffusion, and fractal analysis of stabilometry in dynamic posturography have already been reported as meaningful indicators of balance performance and efficiency (41–43). More than instability, they are indicators of energy consumption and balance control strategy: strict correction of COP displacements requiring more energy vs. a more tolerant strategy (44). Wavelet and diffusion analysis, confirmed deductions from COPS showing lower balance performances in patients with CI and in BVP compared to controls. However, they did not indicate a significant modification of energy consumption or balance strategy under the rotating sound effect. This could be explained by large interindividual variations (especially for the CA) and the fact that dynamic posturography evaluates the balance in a standing position and not during movements (walking). Indeed, walking is probably a more ecological manner to evaluate the multisensory integration in balance (45).

Interaction between auditory and vestibular information seems to take place at the cortical level. The temporo–parietal junction, connecting the auditory, somatosensory, and visual cortices is involved in a multimodal representation of space. It occupies the posterior portion of the superior temporal plane and the superior temporal gyrus. It contains trimodal neurons with receptive fields over the head–neck–shoulder region potentially involved in head orientation (46). A recent fMRI investigation suggests that superior temporal gyrus (planum temporale) and the posterior insula are particularly involved in the processing of both auditory and vestibular information (47). Sound–movement interaction may also be processed at a subcortical level. Recent studies on the influence of gaze direction on the auditory spatial resolution suggest a multisensory integration in the brainstem, presumably in the superior colliculus (32).

In conclusion, rotating sound influences the gait and alters the balance strategy in patients with CI and in BVP. While it destabilizes patients with binaural hearing (BCI and BVP), it seems to stabilize those with monaural hearing (UCI). These observations indicate the integration of binaural auditory cues for the balance control in patients with BCI.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

AB, MT, and CG designed the study. BD, CG, MT, and AB developed the experimental setup. CG, BD, and SH evaluated the subjects. CG, SA, and AB analyzed the data and prepared the manuscript.

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REVIEW
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Vestibular Functions and Parkinson's Disease

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For decades it has been speculated that Parkinson's Disease (PD) is associated with dysfunction of the vestibular system, especially given that postural instability is one of the major symptoms of the disorder. Nonetheless, clear evidence of such a connection has been slow to emerge. There are still relatively few studies of the vestibulo-ocular reflexes (VORs) in PD. However, substantial evidence of vestibulo-spinal reflex deficits, in the form of abnormal vestibular-evoked myogenic potentials (VEMPs), now exists. The evidence for abnormalities in the subjective visual vertical is less consistent. However, some studies suggest that the integration of visual and vestibular information may be abnormal in PD. In the last few years, a number of studies have been published which demonstrate that the neuropathology associated with PD, such as Lewy bodies, is present in the central vestibular system. Increasingly, stochastic or noisy galvanic vestibular stimulation (nGVS) is being investigated as a potential treatment for PD, and a number of studies have presented evidence in support of this idea. The aim of this review is to summarize and critically evaluate the human and animal evidence relating to the connection between the vestibular system and PD.

Keywords: vestibular system, Parkinson's disease, vestibulo-ocular reflexes, vestibulo-spinal reflexes, VEMPs, striatum, dopamine

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INTRODUCTION

Parkinson's Disease (PD) is a chronic neurodegenerative disease characterized by tremor, rigidity, slowness of movement ("bradykinesia"), postural imbalance, and, ultimately, other non-motor symptoms such as cognitive impairment and depression (1). The age- and gender-adjusted incidence rate of PD is approximately 13.4 per 100,000, which rapidly increases over the age of 60 (2, 3). The fact that postural instability is a symptom of the disease, suggests the possibility that the vestibular system may be implicated. Nonetheless, conclusive evidence for vestibular dysfunction in PD has been slow to emerge.

The notion that vestibular dysfunction may occur in PD has a long and complicated history. Studies reaching back into the 1980's have suggested such a link, but several studies have reported negative results [e.g., (4); see (5) for a review]. Similarly, there has been a suggestion that vestibular information is transmitted to the basal ganglia, the striatum in particular, which loses dopaminergic input in PD. However, confirmation of such a pathway has also been slow to emerge, with apparent discrepancies between various electrophysiological and neurotracer studies [see (6) for a review]. Over the last 10 years, interest in the effects of vestibular stimulation on the basal ganglia has been amplified by studies reporting that noisy galvanic vestibular stimulation [nGVS; e.g., (7)] or caloric vestibular stimulation [e.g., (8)] can reduce the severity of some PD symptoms (see (5) for a review).

TABLE 1 | A summary of studies examining nystagmus and VOR function in PD patients.

Reichert et al. (9)	36 PD patients 316 controls	Reduced or absent caloric nystagmus
Ciparrone et al. (10)	36 PD patients 316 controls	Abnormal caloric nystagmus
Vitale et al. (11)	11 PD patients 11 controls	Unilateral vestibular hypofunction and positional and SN in patients with LTF
Lv et al. (12)	63 PD patients 56 controls	Abnormally high VOR gain

TABLE 2 | A summary of studies examining posture and VEMPs in PD patients.

Pastor et al. (4)	15 PD patients 10 controls	No difference in body sway
Pollak et al. (13)	54 PD patients 53 controls	Unilaterally absent cVEMPs 37% and unilaterally absent cVEMPs 7.4% of patients
Potter-Nerger et al. (14)	20 PD patients 10 controls	Smaller cVEMPs in patients L-DOPA increased cVEMP Amplitude
De Natale et al. (15)	14 early PD patients 19 advanced PD 27 controls	Delayed cVEMPs, mVEMPs and oVEMPs Absent VEMPs
De Natale et al. (16)	24 PD patients 24 controls	Abnormal cVEMPs, mVEMPs and oVEMPs in PD patients
Potter-Nerger et al. (17)	13 PD patients 13 controls	cVEMPS preserved in patients oVEMPS significant delay and reduced amplitude in patients
Venhovens et al. (18)	30 PD patients 14 Atypical P 25 controls	Delayed CVEMPs and oVEMPs in PD patients
Shalash et al. (19)	15 PD patients 15 controls	Absent oVEMPs and delayed cVEMPs in patients
Huh et al. (20)	25 FOG PD patients 22 no FOG PD 26 controls	Diminished sensory processing in in PD patients with FOG

From these studies it has been suggested that some form of vestibular stimulation may be a potential early adjunctive treatment for PD, that may delay the need for drug treatments such as L-DOPA and ropinirole, or at least reduce the doses needed so that higher doses of drug therapy can be "saved" for later in the course of the disease.

The objective of this review is to summarize and critically evaluate the current evidence for an interaction between vestibular function and PD, considering: (1) the evidence that vestibular symptoms are present in PD; (2) whether there is evidence for the neuropathology of PD in the central vestibular system; (3) what neural circuitry might underlie an interaction between the vestibular system and the striatum; and (4) whether vestibular stimulation can affect the severity of PD symptoms.

VESTIBULAR SYMPTOMS IN PARKINSON'S DISEASE

Many early studies of vestibular function in PD reported evidence of deficits in the vestibulo-ocular (VORs) and vestibulo-spinal reflexes (see **Tables 1**, **2**). There seem to have been relatively few VOR studies reported (**Table 1**); however, it is conceivable that deficits could appear in the vestibulo-spinal reflexes without necessarily being evident in the VORs or the perception of vertical, since the VORs and vestibulo-spinal reflexes involve relatively independent neural pathways (21). The technology for detecting vestibular deficits of various sorts has advanced enormously in recent decades and it is conceivable that in some early studies, vestibular dysfunction was present but was not detected. Of course, one of the critical factors is the stage of the PD, with vestibular symptoms perhaps more likely to be detected later in the disease. Furthermore, in some studies, PD patients exhibiting vestibular symptoms may have been excluded from the study.

Abbreviations: PD, Parkinson's Disease; GVS, galvanic vestibular stimulation; nGVS, noisy galvanic vestibular stimulation; DA, dopamine; GABA, γ-aminobutyric acid; L-DOPA, L-3,4-dihydroxyphenylalanine; VORs, vestibulo-ocular reflexes; cVEMPs, cervical vestibular-evoked myogenic potentials; oVEMPs, ocular vestibular-evoked myogenic potentials; mVEMPs, masseter vestibular-evoked myogenic potentials; fMRI, functional magnetic resonance imaging; PET, positron emission tomography.

Vestibulo-Ocular Reflex Studies

PD is well known to be associated with deficits such as hypometric saccades and abnormalities of smooth pursuit eye movement (e.g., see (22) for a review). Whether the VORs are affected is still somewhat controversial, even decades after the first studies.

Reichert et al. (9) studied bi-thermal caloric nystagmus in 36 PD patients and 316 controls and found reduced or absent nystagmus in the patients, which was associated with postural instability (**Table 1**). Ciparrone et al. (10) studied the effects of caloric-induced nystagmus in 36 PD patients and 316 controls and found abnormal nystagmus in 82.9% of the patients. However, they observed few cases of spontaneous nystagmus. In general, caloric stimulation generated an increased response in many cases (48.6%), sometimes with a directional preponderance (25.7%). Nonetheless, the abnormal nystagmus was not correlated with the clinical PD symptoms. The results for the caloric nystagmus did not appear to be analyzed statistically. Vitale et al. (11) studied vestibular function using caloric testing and video-oculography in 11 PD patients and 11 age-matched controls. They found evidence of unilateral vestibular hypofunction in all of the patients with lateral trunk flexion, a common symptom in PD. They observed spontaneous positional

jerk nystagmus with primary forward gaze, which was suppressed by visual fixation, as well as positional nystagmus. Nystagmus was increased during the head shaking test in all patients except one. The results were analyzed statistically (see **Table 1**).

Lv et al. (12) are one of the few groups to quantitatively report abnormalities in the head impulse test in PD patients. They used the video head impulse test in 63 PD patients and 56 controls. They found, somewhat paradoxically, that the VOR gain for PD patients was significantly greater than the controls (i.e., 1.2 and 1.23 for the left and right sides compared to 0.98 and 0.99 for the control group, respectively). However, this result may be consistent with the increased caloric nystagmus reported by Cipparrone et al. (11). Lv et al. (12) found no correlation between the VOR gain and age or disease duration and only a weak correlation between the VOR gain and the Unified Parkinson's Disease Rating Scale score. The authors speculated that the increased VOR gain was possibly a compensatory response which developed during the early stages of PD.

Taken together, these studies suggest that there may be VOR abnormalities in PD; however, as yet too few quantitative studies have been conducted to draw reliable conclusions.

Vestibulo-Spinal Reflex Studies

Pastor et al. (4) examined the postural response to galvanic vestibular stimulation (GVS) while standing with feet together and eyes closed, in 15 PD patients and 10 age-matched controls. They observed no significant difference in the speed or direction of body sway between the patients and controls, suggesting that a central vestibular dysfunction was not responsible for their postural instability.

Pollak et al. (13) examined the cervical vestibular-evoked myogenic potentials (cVEMPs), indicative of saccular function, in 54 PD patients and 53 controls and found unilaterally absent cVEMPs in 37% of the patients and bilaterally absent cVEMPs in 7.4%, which were statistically significant differences compared to the controls. Once again, however, there was no correlation with the disease stage. Potter-Nerger et al. (14) also studied cVEMPs in 20 PD patients (10 with and 10 without sub-thalamic electrodes) and 10 age-matched controls. They observed significantly smaller cVEMPs in the PD patients, but especially in those without the sub-thalamic electrodes. They found that administration of L-DOPA, but not sub-thalamic stimulation, increased the cVEMP amplitude.

de Natale et al. (15) studied cervical, masseter and ocular VEMPs (cVEMPs, mVEMPs, and oVEMPs) in 14 patients with early PD, 19 with advanced PD and 27 age-matched controls, and found that the VEMPs were abnormal in the PD patients, although these were different in the early and advanced patients. The mVEMP and oVEMP amplitudes were significantly smaller than controls for the late PD group and the frequency of abnormalities for each VEMP was significantly higher than controls. PD is commonly associated with sleep disorders (see (23) for a review) and the severity of this problem is often quantified using the REM Sleep Behavior Disorder Screening Questionnaire (see (24) for a review). In this study the degree of VEMP impairment was found to correlate with the REM Sleep Behavior Disorder Screening Questionnaire in both groups of PD patients and inversely with the Mini-BEST test scores (measuring postural instability) in the advanced PD patients. In a further study (16), they investigated cVEMPs, mVEMPs and oVEMPs in 24 PD patients and 24 age-matched controls and found that cVEMPS were abnormal in 41.7% of PD patients, mVEMPS in 66.7% and oVEMPs in 45.8%. For mVEMPs and oVEMPs, but not cVEMPs, the amplitudes were significantly smaller than the control group. There was also a significant correlation and a significant inverse correlation between the number of abnormal VEMPs and the scores on the REM Sleep Behavior Disorder Screening Questionnaire and the mini-BEST test, respectively. These results again suggest the possibility that VEMPs might be useful in the diagnosis of PD (see **Table 2**).

Potter-Nerger et al. (17) studied cVEMPs and oVEMPs in 13 PD patients and 13 age-matched controls. They found that the cVEMPS were relatively well-preserved in the PD patients; however, the oVEMPs, indicative of utricular function, exhibited a significant delay and a significantly reduced amplitude. Furthermore, L-DOPA treatment had no significant effect on either the cVEMPs or the oVEMPs.

Venhovens et al. (18) examined cVEMPs, oVEMPs and brainstem auditory-evoked potentials in 30 PD patients, 14 with Atypical Parkinsonism and 25 age- and sex-matched controls. In addition, they measured the subjective visual vertical and used videonystagmography with caloric and rotatory chair stimulation. They found that 27 of the 30 PD patients and all 14 Atypical Parkinsonism patients had significantly abnormal cVEMPs and oVEMPs, compared to the controls. In PD and Atypical Parkinsonism patients, brainstem auditory-evoked potentials exhibited a significant delay. Delayed latencies for oVEMPs and cVEMPs were common for the PD and Atypical Parkinsonism groups. The abnormal vestibular test results were correlated with an increased risk of falling. Once again, these results support the hypothesis that the symptomatology of PD includes vestibular dysfunction.

Shalash et al. (19) studied the relationship between oVEMPs, cVEMPs and brainstem auditory-evoked potentials in 15 patients with PD and 15 age-matched controls. They found that the PD patients exhibited significantly delayed brainstem auditory-evoked potential latencies as well as absent and delayed oVEMPs and delayed latencies for cVEMPs. The ipsilateral and contralateral cVEMPs were significantly correlated with measurements of sleep, perception, memory and cognition, as well as urinary scores. The VEMP responses were significantly correlated with cardiovascular function and sexual dysfunction.

Huh et al. (20) used the "sensory organization test" to study vestibular contributions to postural control in 25 PD patients with freezing of gait, 22 PD patients without freezing of gait and 26 age-matched controls. The sensory organization test comprises 6 conditions in which postural stability is challenged by changing visual and somatosensory input, thereby altering the dependence on vestibular input (20): (1) eyes open, floor fixed, visual surround fixed; (2) eyes closed, floor fixed, visual surround fixed; (3) eyes open, floor fixed, visual surround sway-referenced; (4) eyes open, floor sway-referenced, visual surround fixed; (5) eyes closed, floor sway-referenced, visual surround fixed; (6) eyes open, floor sway-referenced, visual surround sway-referenced.

They found that the PD patients with freezing of gait exhibited significantly worse postural sensory processing, especially the inability to use vestibular information.

Taken together, these studies suggest an emerging consensus that VEMPs become abnormal in PD.

Subjective Visual Vertical and Perception of Tilt Studies

Bronstein et al. (25) evaluated the ability to set a straight line to gravitational vertical ("subjective visual vertical") in 24 PD patients, 8 patients with bilateral vestibular loss and 24 control subjects. They used static conditions as well as changes in body position and background visual motion. They found no statistically significant differences in the subjective visual vertical in the upright position. However, while the subjective visual vertical was significantly different during visual motion for the patients with bilateral vestibular loss, the PD subjects performed similarly to the control subjects. However, Scocco et al. (26) studied 8 PD patients, 9 patients with "Pisa Syndrome," a condition in which a person exhibits a lateral deviation around the longitudinal axis for no obvious reason, and 18 controls. They tested the subjective visual vertical when the PD patients were on or off L-DOPA and found that the PD patients performed significantly worse than the controls when they were on the L-DOPA, and visual dependency was greater for the PD patients when they were inclined, during the off condition. Barnett-Cowan et al. (27) studied 12 PD patients and compared them with 13 age-matched controls and found that PD patients with left-sided initial motor symptoms, were more dependent on visual information for the subjective visual vertical, when they were taking their dopaminergic medication.

More recently, Bertolini et al. (28) examined the judgement of forward tilt in 11 PD patients and compared it to 19 age-matched controls. This was done on a motion platform in darkness in response to two consecutive forward tilt movements, and combining tilt movements with translations in order to probe multi-cue integration. They found that PD patients were significantly less accurate in judging forward tilt, but only in the multi-cue conditions, not the single cue conditions, suggesting a deficit in sensory integration.

Finally, in the most recent study published, Gandor et al. (29) studied subjective visual vertical in 30 patients with and without lateral trunk flexion and found that PD patients with lateral trunk flexion had significantly greater subjective visual vertical angles than those without lateral trunk flexion. Fourteen out of 21 patients with lateral trunk flexion exhibited abnormal subjective visual vertical while 9 out of 9 patients without lateral trunk flexion exhibited a normal subjective visual vertical.

Taken together, these studies suggest that if subjective visual vertical is abnormal in PD, it may be related to whether the patients are taking L-DOPA and whether they suffer from lateral trunk flexion. Too few studies of forward tilt have been conducted to draw reliable conclusions.

Other Studies

Montgomery et al. (30) studied orientation to a starting position in 48 PD patients (24 with mild disease and 24 with moderate disease) and 35 control subjects, passively transported in a wheelchair in a visual condition where they could see the walls and ceiling but not the floor, and a "vestibular" condition, in which they wore a blindfold. They found that the PD patients with moderate disease performed significantly worse in the visual and vestibular conditions compared to the control subjects and patients with mild PD, but that while performance in the visual condition distinguished the mild PD patients from the controls, the mild PD patients and the controls performed similarly in the vestibular condition compared to the moderate PD patients.

Putcha et al. (31) used fMRI to study cortical activation in areas involved in processing visual motion, in 23 PD patients and 17 matched controls. They examined V6, V3a and the medial temporal area, as well as two regions associated with visual-vestibular processing, the parieto-insular vestibular cortex and the cingulate sulcus visual area, stimulated with simulated optic flow motion as well as random motion. Compared to the control subjects, the PD patients exhibited significantly reduced activity in the medial temporal area and cingulate sulcus visual areas, and activation of the cingulate sulcus visual area was inversely correlated with the disease severity.

It has been suggested that the cortical field potential responses ("electrovestibulography") to vestibular stimulation might be used as a biomarker for the diagnosis of PD (32–34). Electrovestibulography is a technique in which the shape and phase of field potential signals in response to natural vestibular stimulation (e.g., tilting), are analyzed using algorithms such as the Neural Event Extraction Routine (NEER) (32–34). Classification statistical analyses such as linear discriminant analysis are then used in an attempt to classify or diagnose patients as having PD, based on the field potential data, and the results are interpreted using receiver-operating characteristic (ROC) curves, in terms of the sensitivity [i.e., true positive/(true positive + false positive)] and specificity [i.e., true negative/(true negative + false positive)] of the diagnosis. Dastgheib et al. (32–34) have described high levels of diagnostic accuracy (up to 95%) using multivariate statistical and data mining methods such as linear discriminant analysis. The same method has been used to demonstrate that treatment of PD with L-DOPA may disturb vestibular function (35, 36); see also (37).

Hwang et al. (38) conducted an interesting study of 8 PD patients in which they stood in a visual cave with optokinetic stimulation at 0.2 Hz while simultaneously receiving an 80 Hz vibratory stimulus to their Achilles tendons and a bilateral monopolar GVS stimulus at 0.36 Hz. The amplitude of the visual stimulus was varied so that the weighting of vision changed, and the gain of the proprioceptive and vestibular stimuli was also varied. In humans without PD, they found that increasing the amplitude of the visual input caused them to reduce the emphasis on visual input, as well as re-weighting visual-proprioceptive and visual-vestibular interaction effects, suggesting that they used intermodal re-weighting to adapt to the situation. By contrast, they found that PD patients had difficulty with cross-modal interaction, suggesting that they suffered from a deficit in fusing information from different sensory modalities.

Taken together, these studies suggest that PD patients may experience deficits in the way that the brain integrates

sensory information, including vestibular information, and that these changes, in terms of electrophysiological activity, could potentially form a signature of PD which might be useful in early diagnosis of the disease.

PARKINSON'S DISEASE PATHOLOGY IN THE CENTRAL VESTIBULAR SYSTEM

Seidel et al. (39) conducted a pathological study of α-synuclein, which forms Lewy bodies, in the hindbrains of 5 PD patients, 1 patient with Parkinson's Disease with dementia and 5 with dementia with Lewy bodies. In all cases they found Lewy bodies and Lewy neurites in the substantia nigra, ventral tegmental area, pedunculopontine tegmental nucleus, raphe nuclei, periaqueductal gray, locus coeruleus, parabrachial nuclei, reticular formation, dorsal motor vagal and solitary nuclei, in addition to the vestibular nucleus complex, prepositus hypoglossi, and even the root of the vestibular nerve. The subnuclei of the vestibular nucleus complex included the medial vestibular nucleus, superior vestibular nucleus and the lateral vestibular nucleus. These results suggest very strongly that the neuropathology of PD extends into the central vestibular system and is therefore likely to undermine at least some of the vestibular reflexes, as well as autonomic, limbic system and cortical projections carrying vestibular information.

Muller et al. (40) studied cholinergic terminals in the thalamus and cortex, and dopamine (DA) terminals in the striatum, in 32 males and 92 females with PD, and 10 female and 15 male age-matched controls. They used positron emission tomography (PET) for the vesicular monoaminergic transporter to image DA terminals and acetylcholinesterase for the acetylcholine terminals and related these data to data from the sensory organization test balance platform protocol. They found that reduced cholinergic thalamic innervation was related to increased center of pressure sway speed, while controlling for the effects of Parkinsonian motor deficits and cognitive impairment. However, there were no significant effects of cortical cholinergic terminal deficits or striatal DA terminal deficits. The authors suggested that PD symptomatology is modulated by connections between the pedunculopontine tegmental nucleus and the thalamus. This is very interesting since the pedunculopontine tegmental nucleus may be one of the nuclei through which vestibular information reaches the dorsal striatum (see (6) for a review). The pedunculopontine tegmental nucleus, which contains vestibular-responsive neurons (41), also undergoes significant changes in the number of cholinergic neurons following bilateral vestibular loss in rats (42). Cai et al. (43) have recently used fMRI to examine the connectivity between the pedunculopontine tegmental nucleus and other brain regions following GVS. They used 23 PD patients without evidence of freezing of gait and who were on medication (L-DOPA) and compared them with 12 controls. They reported that GVS did not have a significant effect on pedunculopontine tegmental nucleus connectivity in controls; however, in PD patients, while the baseline magnitude of pedunculopontine tegmental nucleus connectivity was inversely correlated with Unified Parkinson's Disease Rating Scale scores, both noisy and sinusoidal GVS elevated the level of pedunculopontine tegmental nucleus connectivity, increasing it with respect to the inferior parietal region. They found that noisy GVS reduced its connectivity with the basal ganglia and cerebellum. This appears to be the first study to demonstrate that GVS can modulate brain connectivity in patients with PD and therefore the results are highly relevant to those studies, reviewed later, that have used noisy or stochastic GVS in an attempt to reduce Parkinsonian symptoms.

Wellings et al. (44) recently studied the expression of non-phosphorylated neurofilament protein in the lateral vestibular nucleus (i.e., Deiters' nucleus), which are proteins whose reduced expression in the substantia nigra is known to contribute to impaired motor function. They conducted immunohistochemical analysis of the brainstems of 6 PD patients and 6 aged-matched controls and found that there was a 50% reduction in the expression of non-phosphorylated neurofilament protein in the lateral vestibular nucleus; by comparison, there was no significant difference in the facial nucleus, demonstrating that this effect was selective for the lateral vestibular nucleus. There was a similar decrease in the intensity of non-phosphorylated neurofilament protein labeling in the lateral vestibular nucleus of PD patients. They also reported an 84% increase in somatic lipofuscin in the lateral vestibular nucleus of PD patients, the significance of which is that lipofuscin deposits are known to increase with neurodegeneration. The authors suggested that these changes in the lateral vestibular nucleus are probably related to the postural deficits seen in PD.

Taken together, these studies provide substantial evidence of neuropathological changes in the vestibular nucleus complex during the development of PD. In addition to explaining some of the abnormalities in vestibular reflexes, especially VEMPs, that have been reported in PD patients, this may also explain some of the cognitive deficits that eventually develop in PD, due to deterioration of the ascending pathways from the vestibular nucleus complex to the limbic system and neocortex [see (45, 46) for a review].

NEURAL CIRCUITRY UNDERLYING EFFECTS OF VESTIBULAR STIMULATION ON PARKINSONIAN SYMPTOMS

Animal Studies

The basal ganglia are a group of nuclei in the midbrain that are responsible for the coordination of movement as well as reinforcement learning. They comprise the dorsal striatum [the caudate nucleus and the putamen; see **Figure 1**] as well as the ventral striatum (the nucleus accumbens) and the globus pallidus [see (47) for a review]. There is evidence that the vestibular system may have a substantial influence over the basal ganglia, due to the need to integrate information about self-motion with plans to initiate voluntary movement, including voluntary eye movement [see (6, 22) for reviews].

Vestibular information was first proposed to be transmitted to the striatum via the motor cortex [e.g., (48)] or the hippocampus [e.g., (49)]. However, Muskens (50, 51) suggested that it may be

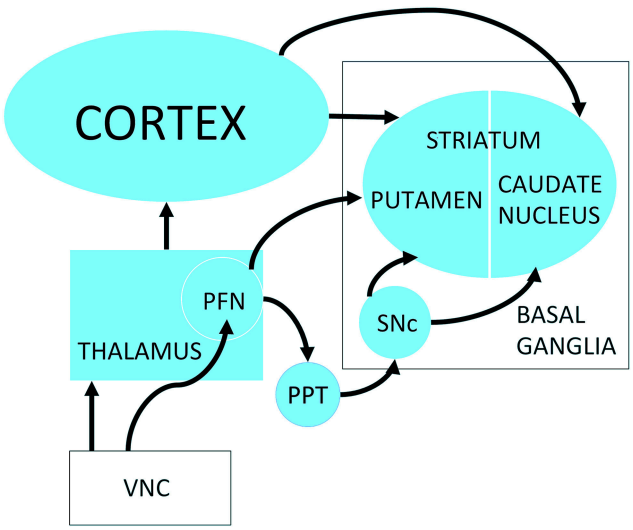

FIGURE 1 | Possible neuronal pathways connecting the vestibular nucleus complex to the striatum. PFN, Parafascicular nucleus; PPT, pedunculopontine tegmental nucleus; SNc, Substantia nigra pars compacta; VNC, vestibular nucleus complex. Reproduced from Stiles et al. (59) with permission from the publisher.

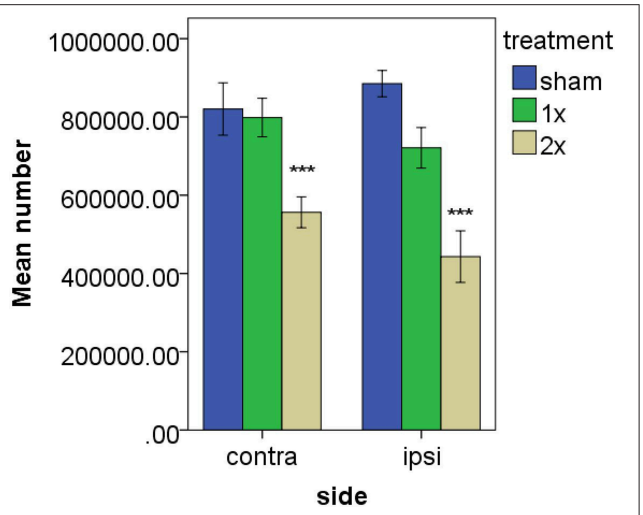

FIGURE 2 | Estimated number of c-Fos positive cells in the striatum following vestibular stimulation. $^{***}P \leq 0.0001$ for the comparison of the higher current with both the sham groups and the lower current group. From Stiles et al. (59) with permission.

transmitted via subcortical pathways. Potegal et al. (52) sought to test Muskens' hypothesis by lesioning the "vestibular cortical projection area" and recording from the caudate nucleus while electrically stimulating the vestibular nerve. If vestibular input to the caudate nucleus arose from the vestibular cortex and required it to be intact, then lesioning the latter should abolish vestibular responses in the caudate nucleus. However, they found no change in the evoked field potentials in the caudate nucleus with the vestibular cortex inactivated, suggesting the possibility of subcortical pathways between the vestibular nucleus complex and/or cerebellum and the dorsal striatum. Further field potential studies in both the caudate nucleus and putamen of the dorsal striatum demonstrated responses to electrical stimulation of the vestibular nerve [squirrel monkeys; (53)] or the lateral and medial vestibular nucleus [cats; (54)]. On the other hand, the results of single neuron studies were ambiguous. Segundo and Machne (55) reported that electrical stimulation of the vestibular labyrinth in cats resulted in an increase in the firing rate of single neurons in the putamen and the globus pallidus. By contrast, Matsunami and Cohen (56) found no change in the firing of single striatal neurons in the caudate nucleus of awake rhesus monkeys, in response to electrical stimulation of the contralateral vestibular nucleus complex, with the exception of when stimulation trains were used and the current intensity was high enough to produce movement of the limbs. More recently, Rancz et al. (46) reported that field potentials and multi-unit activity could be evoked in the striatum in rats in response to electrical stimulation of the superior vestibular nerve. They also confirmed this result using fMRI.

Striatal neurons have been demonstrated to fire in response to movement that is in phase with head velocity, suggesting the possibility of vestibular input from the vestibular nucleus complex or cerebellum (57, 58). Stiles et al. (59) have also recently reported that c-Fos expression, as a marker of cellular activation, and the firing rate of a circumscribed number of single striatal neurons, can be altered by electrical stimulation of the vestibular labyrinth in the anesthetized rat (see **Figures 2–4**). In related studies, they also demonstrated that such electrical stimulation can modulate the release of serine, threonine and taurine, as well altering DA metabolism (60).

Lai et al. (61) conducted neurotracer studies that suggested rapid pathways between the vestibular nucleus complex and/or cerebellum and the dorsolateral putamen, via the parafascicular nucleus of the thalamus (see **Figure 1**). On the basis of these results they suggested that there may be a disynaptic pathway from the vestibular nucleus complex and/or cerebellum to the striatum. Recently, Kim et al. (62) reported that polysynaptic field potentials could be evoked in the contralateral parafascicular nucleus following electrical stimulation of the horizontal semicircular canal vestibular nerve in rats. Stiles et al. (59) observed some increases in the response of single striatal neurons to electrical stimulation of the vestibular labyrinth, with latencies of approximately 50 ms, which, under urethane anesthesia, could be consistent with a disynaptic pathway (63).

Many animal studies have attempted to understand the impact of the vestibular system on the basal ganglia, by lesioning the peripheral vestibular system or by using transgenic animals lacking vestibular function. There have been reports of vestibular loss affecting the expression of DA receptors in the striatum (64). Giardino et al. (64) reported that in young and old rats, unilateral peripheral vestibular lesions resulted in a bilateral increase in D_1 DA receptors in the striatum, as well as an increase in D_2 receptors. Bilateral vestibular loss, however, did not affect D_1 receptor density in young rats while it reduced D_2 receptors. By comparison, bilateral vestibular loss resulted in increased D_1 and D_2 receptors in the striatum in old rats. However, other studies

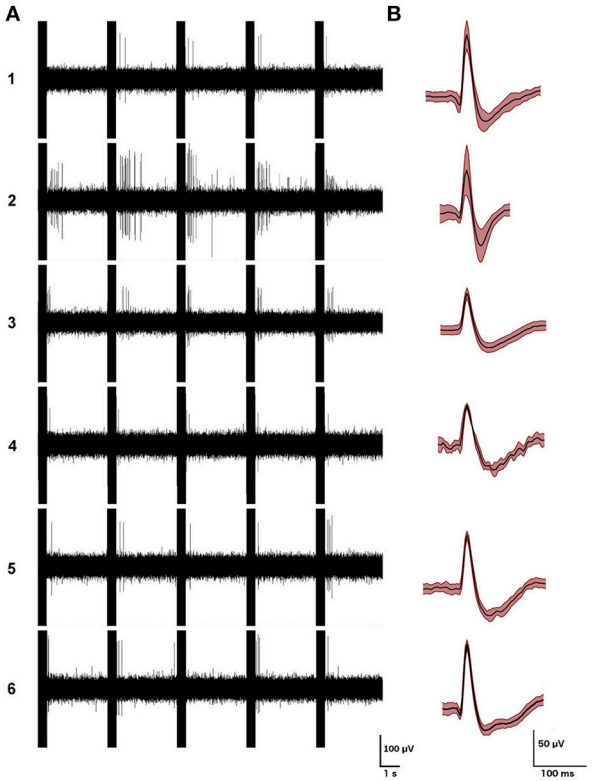

FIGURE 3 | Examples of the firing patterns of the 6 single striatal neurons responding to electrical stimulation of the vestibular labyrinth in a phase-locked manner, **(A)** with examples of their action potential waveforms (averages of 200 action potentials **(B)**; mean ± SD in red). From Stiles et al. (59) with permission.

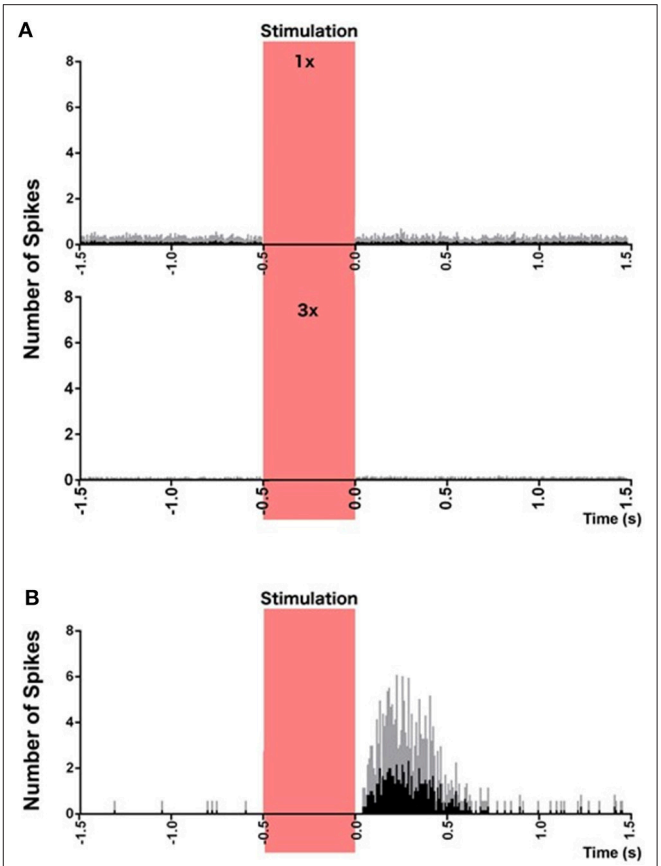

FIGURE 4 | Peri-stimulus histograms of neuronal responses to electrical vestibular stimulation. **(A)** Combined histogram of firing of all non-responsive neurons at 1× (top) and 2× (bottom) the threshold of nystagmus. **(B)** Combined firing of all 6 responsive neurons, at 3× the threshold of nystagmus, phase-locked to the stimulus. Red bar represents the stimulation period. Spikes from the stimulus artifact have been removed for clarity. Data are presented as mean (black bars) and standard deviation (gray bars). From Stiles et al. (59) with permission.

have failed to find similar changes in the number of DA receptors (65). Stiles et al. (65) reported that D_2 receptors were significantly higher in number in the right striatum than the left in both sham control and bilateral vestibular loss rats.

One of the most dramatic symptoms of bilateral vestibular loss in rodents is locomotor hyperactivity and circling behaviors (64, 65). Eugene et al. (66) studied circling behavior in the vestibular-deficient *KCNE1* mutant mouse and reported that it was associated with increased tyrosine hydroxylase expression, a marker for DA synthesis, in the striatum ipsilateral to the direction of circling, whether it was in a leftward or rightward direction. This increase in circling and locomotor activity observed in vestibular-deficient animals may suggest a change in striatal function resulting in a hyperkinetic disorder (67). The results from vestibular-deficient *ci2/ci2* rats are also consistent with this hypothesis: the specific DA D_2 receptor antagonist, raclopride, caused a decrease in locomotor hyperactivity and circling behavior (68). However, Antoine et al. (69) found no change in DA receptors in a genetic mouse model of vestibular dysfunction in which the *Sk12a2* gene was knocked out in the inner ear, specifically disrupting vestibular function. They did, however, find a significant increase in the amount of phosphorylated extracellular signal-regulated kinase 1/2 (ERK1/2) and its downstream target, phosphorylated cyclic AMP response element binding protein (pCREB), in the nucleus accumbens in the ventral striatum. The lack of change in the non-phosphorylated ERK1/2 suggested an increase in activation of the ERK1/2 pathway, which is involved in learning and memory in the basal ganglia.

A different explanation of locomotor hyperactivity associated with vestibular loss, comes from a study by Pan et al. (70), who demonstrated a correlation between induced motor hyperactivity in rats and the increased labeling of orexin A neurons in the hypothalamus following bilateral vestibular loss. Orexin, or hypocretin, is a peptide secreted by small groups of neurons in the hypothalamus, which project to various brain regions such as the cortex, basal forebrain, dorsal raphe, pedunculopontine tegmental nucleus, tuberomammillary nuclei and locus coeruleus. Orexin regulates the sleep-wake cycle and low levels of it are the cause of narcolepsy. Interestingly, orexin neurons have also been shown to project to the vestibular nucleus complex (see (71) for a review). Pan et al. (70) found that the locomotor hyperactivity caused by bilateral vestibular loss was

reduced by a type A orexin receptor antagonist. Nonetheless, the locomotor activity of the control rats was also reduced, suggesting a non-specific effect.

Other studies have found neurochemical changes in the striatum following bilateral vestibular loss in rats. Aitken et al. (72), using receptor autoradiography, reported that M_1 muscarinic acetylcholine receptors, which mediate many of the excitatory effects of acetylcholine, decreased in density in the striatum and the hippocampus at 30 days (but not 7 days) following bilateral vestibular loss induced by intratympanic injection of sodium arsanilate. In a related study, Benoit et al. (73), using flow cytometry, demonstrated that the number of neurons expressing M_2 acetylcholine receptors, which mediate many of the inhibitory effects of acetylcholine, underwent a significant increase at 30 days (but not 7 days) in the striatum and hippocampus following bilateral vestibular loss. Benoit et al. (74) have also reported that the number of striatal neurons expressing N-methyl-D-aspartate receptors exhibited a significant decrease at 7 days (but not 30 days) following bilateral vestibular loss.

Samoudi et al. (75) used hemiparkinsonian rats (the 6-hydroxy-dopamine model) to examine the effects of nGVS on motor symptoms and neurotransmitter release in the basal ganglia. They found that nGVS improved locomotor activity, measured by performance on a rotarod, and enhanced GABA release in the substantia nigra; however, DA release in the striatum was not significantly affected. The only other study to use microdialysis following high frequency stimulation of the vestibular labyrinth in rats, i.e., not GVS or nGVS, showed no significant effect on DA release in the striatum; however, there was evidence of a significant reduction in DA metabolism, as demonstrated by a reduced ratio between 3,4-dihydroxyphenylacetic acid and DA (60).

Taken together, the evidence from animal studies strongly suggests that vestibular input is transmitted to the basal ganglia, the striatum in particular. However, the nature of this input is complex and may be restricted to specific areas of the striatum. For example, the results of the available electrophysiological studies are complicated and difficult to reconcile with some of the other neurochemical data. Some of these apparent discrepancies are likely to be due to the anesthetic conditions under which the electrophysiological experiments were conducted. However, the behavioral evidence indicates that bilateral vestibular loss has major effects on motor activity in rodents.

Human Studies

Bottini et al. (76), using PET scans, reported an increase in activity in the putamen (part of the dorsal striatum) following cold water caloric vestibular stimulation in healthy subjects [see (77) for a review]. Using GVS, Bense et al. (78) obtained similar results in the putamen. Other PET and fMRI studies in humans have reported increases in activity in the putamen and the caudate nucleus, following either cold caloric vestibular stimulation or galvanic vestibular stimulation (GVS) [(79–82); see (77) for a review]. An interesting recent result is that people with persistent postural perceptual dizziness have been shown to exhibit a decrease in gray matter volume in the caudate nucleus (83).

Jansen et al. (84) investigated $D_{2/3}$ receptors in patients with bilateral vestibular loss and found that they exhibited an approximately 40% decrease in the bilateral temporo-parieto-occipital cortex, as well as in the striatum and the right thalamus. The longer the disease duration, the greater was the loss of $D_{2/3}$ receptors in the middle/superior temporal gyrus. Patients who suffered from oscillopsia exhibited reduced $D_{2/3}$ receptor availability in the right medial temporal and medial superior temporal regions.

Overall, the available human data are consistent in supporting the notion that the basal ganglia receive vestibular input, and some recent studies suggest that the striatum may undergo changes in conditions such as persistent postural perceptual dizziness. Furthermore, vestibular loss appears to alter the expression of DA receptors in the human brain.

EFFECTS OF VESTIBULAR STIMULATION ON PARKINSONIAN SYMPTOMS

Many studies have investigated the potential of vestibular stimulation to reduce the severity of Parkinsonian symptoms. Most of these studies have employed sub-threshold GVS with a Gaussian noise signal superimposed upon it—so-called "stochastic or noisy GVS (nGVS)." The principle behind its effects is known as "stochastic resonance": that a sub-threshold sensory signal may be more effectively detected by the brain if a noise signal is superimposed upon it (see (85) for a review). Having said this, the effects of nGVS upon the brain are poorly understood and there is a sense in which the application of it to neurological disorders has preceded a scientific understanding of its neural effects.

One of the first studies was by Yamamoto et al. (7), who investigated the effects of 24 h of nGVS on 7 patients with multi-system atrophy and 12 patients with L-DOPA-responsive PD or L-DOPA-unresponsive PD. They reported that nGVS appeared to increase the speed of bradykinesic rest-to-active transitions, indicated by measurements of trunk activity in the PD patients. They also found that the stimulation decreased reaction time on a continuous performance task without any increase in omission or commission error rates, suggesting that the PD patients exhibited better motor execution during cognitive tasks.

Pal et al. (86) examined the effects of nGVS on postural sway in the medio-lateral and antero-posterior planes in 5 PD patients and 20 controls. The nGVS resulted in a small but significant decrease in sway, measured using center of pressure displacement over 26 s, in the eyes closed condition in the PD patients and controls with low intensity stimulation (0.1 mA).

Kataoka et al. (87) used normal GVS applied for 20 min to 5 PD patients. They reported that 3 out of 5 patients diagnosed with PD including postural instability and/or abnormal axial posture, exhibited a reduction in postural instability following the GVS stimulus. This was measured using the anterior and lateral bending angles (captured using 2 digital video cameras) while the patients were standing with their feet 10 cm apart, and their eyes open. Okada et al. (88) also employed normal GVS to study anterior bending posture in 7 patients with PD. They measured

the patients' anterior bending angles while they stood with their eyes open or closed. They found that the GVS significantly reduced the bending angles in both conditions compared to the sham control condition. However, the degree of change in the bending angle did not significantly correlate with the Unified Parkinson's Disease Rating Scale motor score, or the disease duration or the anterior bending angles before the GVS was applied.

Lee et al. (89) examined the effects of nGVS on tracking behavior in PD patients. They studied 12 PD patients with mild to moderate symptoms while they were off medication and asked them to perform a sinusoidal visuomotor tracking task, using a joystick. They found that the nGVS significantly increased the signal-to-noise ratio in the tracking task, enhancing the patients' ability to perform the task. The authors speculated that this effect may have been due to enhanced activity in the cingulate cortex.

Samoudi et al. (90) studied the effects of nGVS on motor symptoms in 10 PD patients who were either on or off L-DOPA. Following a backward perturbation, nGVS significantly improved balance corrections and reduced the response time, measured using a force plate and dynamic perturbation test. In the static posturography conditions, the nGVS significantly reduced the total sway with eyes closed when the patients were off L-DOPA. However, the nGVS increased nausea following L-DOPA administration in 2 subjects.

In the most recent study involving normal GVS, Koshnam et al. (91) examined its effects on motor symptoms in 11 PD patients while on medication. They employed both a timed up and go task as well as a finger tapping task and quantified the behavior using accelerometers and video cameras. They found that GVS significantly improved the coefficient of variation in step duration, the tapping score, and the duration of manual motor blocks.

To date, the studies of the effects of nGVS and GVS on PD have yielded fascinating data, which suggest the promise of potential novel therapies for the motor and non-motor symptoms of PD. However, it is important to keep in mind, at this early stage of investigation, the limitations of these studies. Most of them involve small sample sizes and when they included controls, the sample sizes were sometimes unequal [e.g., (86)]. Even when the patients served as their own controls in before and after studies, the issue of small sample sizes is important. No study conducted to date meets the standards of a randomized controlled clinical trial (RCT), in which PD patients would be randomly allocated to nGVS and sham nGVS groups, for example. Such a study would probably require double-blind measurement of the dependent variables, where neither the subject nor the experimenter knows to which treatment group the subject belongs, and the sample sizes employed would need to be based on statistical power calculations. In this kind of study, it would be important to separate the vestibular contributions to balance from other contributions such as proprioceptive inputs, and to measure vestibular function more broadly, including the VOR and VEMPs. Finally, it would be ideal to include non-motor as well as motor symptoms of PD, in order to determine the effects of nGVS and GVS on cognitive function and depression.

Wilkinson et al. (8) employed caloric vestibular stimulation to examine the effects of vestibular activation in a single case study of PD. Compared to baseline and the sham condition, they observed improvements in the scores for the EQ5D (a standardized instrument for quantifying general health status), Unified Parkinson's Disease Rating Scale, the Schwab and England Activities of Daily Living Scale (a scale which measures the ability of PD patients to function independently), 2 min walk, timed up and go, non-motor symptom assessment scale for PD, Montreal cognitive assessment scale, Hospital depression scale and Epworth sleepiness scale. These changes exceeded the minimal clinically important difference thresholds for these measures. This study, although based on a single patient, suggests the possibility that noisy vestibular stimulation may not be necessary in order to achieve clinical improvement with vestibular stimulation.

The effects of nGVS have also been studied in patients with vestibular dysfunction. Iwasaki et al. (92) studied 11 patients with bilateral vestibular loss and compared them to 21 healthy controls. Using white noise GVS they measured balance in terms of the velocity, the envelopment area and the root mean square center of pressure. They reported that the nGVS improved all 3 measures in 76% of the control subjects and 91% of the bilateral vestibular loss patients. They concluded that their study constitutes Class IV clinical evidence for the efficacy of nGVS in improving postural stability in patients with bilateral vestibular loss. Schniepp et al. (93) measured vestibulo-spinal reflex thresholds in 12 patients with complete bilateral vestibular loss and 10 with some residual function. They used a 1 Hz sinusoidal GVS to determine individual vestibulo-spinal reflex thresholds and then used nGVS. None of the patients with complete bilateral vestibular loss exhibited vestibulo-spinal reflex responses, as expected. However, they found that the delivery of weak nGVS improved the detection of subthreshold vestibular stimuli and reduced the threshold in 90% of the patients with residual vestibular function.

Some studies have also investigated the effects of nGVS in subjects without PD or any other neurological disorder. Goel et al. (94) delivered nGVS in the 0–30 Hz range to 45 subjects and measured the stability of the head, trunk and whole body. They reported that the stimulus delivered in the medio-lateral, anterior-posterior and combined directions significantly enhanced balance performance, measured using a force plate with motion sensors placed on the head and trunk. Pan et al. (95) examined the effects of 24 h of nGVS on wrist activity in 14 hospitalized patients, 10 with akinesia and 4 with ataxia. They found evidence from the power-law exponent that nGVS resulted in significantly reduced akinesia.

The only study to date, to investigate the electrophysiological effects of nGVS in humans, was by Kim et al. (96), who examined its effects on EEG. They measured theta (4–7.5 Hz), low alpha (8–10 Hz), high alpha (10.5–12 Hz), beta (13–30 Hz) and gamma (31–50 Hz) EEG bands in 10 neurologically-intact subjects. They found that the main effect of nGVS was to suppress the power of gamma EEG in lateral brain regions immediately following the stimulus, and that this was followed by a delayed increase in the power of beta and gamma EEG in frontal regions of the brain. The authors suggested that nGVS modulates the synchrony of multiple EEG oscillations. They speculated that the $1/f$ power density of the nGVS stimulus that they used may

recruit more global neuronal networks at slower oscillations, which then affect higher frequency oscillations in networks of GABAergic interneurons, thus modulating many frequency bands (97).

A related question is whether vestibular stimulation through specific forms of vestibular rehabilitation, could be effective in the treatment of PD? Acarer et al. (98) studied the effects of vestibular rehabilitation in 29 PD patients and compared them to 11 control PD patients. Following 8 weeks of customized vestibular rehabilitation, they observed a significant improvement in scores in the Activities-Specific Balance (ABC) Confidence Scale (a scale measuring confidence in mobility), the Berg Balance Scale (which quantifies balance under different conditions such as standing up from a sitting position, standing on one foot etc.) and the Dynamic Gait Index (a measure of balance, gait and risk of falling). These results are consistent with those of Wilkinson et al. (8) and suggest that vestibular stimulation other than GVS or nGVS, may be useful in treating PD.

Taken together, the studies conducted in humans so far suggest that nGVS, and even normal GVS, may reduce postural instability and deficits in visual-motor control in patients with PD. There is also a suggestion that there may be some benefit to the non-motor symptoms of PD, although few studies have investigated this possibility so far. The fact that normal GVS, caloric vestibular stimulation and even vestibular rehabilitation on its own, may reduce some symptoms of PD, naturally raises the question of whether the stochastic property of nGVS is even necessary, or whether it is vestibular stimulation itself that is the key factor in any improvement. Future studies should compare these interventions under the same conditions in order to answer this question.

CONCLUSIONS AND FUTURE EXPERIMENTS

Although there are still relatively few studies of VOR function in patients with PD, there is increasing evidence that VEMPs, in particular, are abnormal. The evidence for abnormalities in the subjective visual vertical is less convincing, and much of the data supporting deficits is related to whether the patients exhibit lateral trunk flexion or whether they are on L-DOPA. There is some evidence for alterations in activity in the medial temporal area and cingulate sulcus visual area regions of the brain in response to visual motion stimulation and for abnormalities in the integration of information from different sensory modalities in PD.

There is substantial evidence for Parkinsonian neuropathological changes in the vestibular nucleus complex, including Lewy bodies (39) as well as reduced non-phosphorylated neurofilament and increased lipofuscin (44). There is also evidence for a reduction in cholinergic input to the thalamus (40), which is very interesting in light of the evidence for a decrease in pedunculopontine tegmental nucleus connectivity in the PD brain (43). The pedunculopontine tegmental nucleus is a major source of cholinergic input, contains neurons that are vestibular-responsive (41), and which undergoes significant changes in the number of acetylcholine-containing neurons following bilateral vestibular loss (42). It is very likely that the pedunculopontine tegmental nucleus is involved in the interaction between the vestibular nucleus complex, the parafascicular nucleus, which is part of the thalamus, and their connections with the substantia nigra and striatum (see **Figure 1**). Yousif et al. (99) reported that deep brain stimulation of the pedunculopontine tegmental nucleus in PD patients increased sway when going from light to darkness and also reduced vestibular perceptual thresholds.

Many imaging studies in humans have demonstrated that vestibular stimulation alters activity in the striatum (76–82). The results of electrophysiological studies in animals are more complex, especially the single neuron recording studies, of which there appear to be only three. It does appear that field potential changes are easier to record in the striatum in response to electrical stimulation of the peripheral vestibular system, at least in anesthetized rats (46, 59). Nonetheless, taken together with neurotracer studies [e.g., (61)] and other evidence from microdialysis studies (60), there is evidence for connections between the vestibular nucleus complex and cerebellum and the striatum. Certainly, more studies are needed to elucidate these connections, using selective electrical stimulation of the vestibular labyrinth and both neuronal recording and neurotransmitter microdialysis in the striatum (100, 101).

There is evidence that GVS and nGVS can reduce the severity of some PD symptoms (7, 86–91) and there is a case report that even caloric vestibular stimulation may have similar effects (8). However, more systematic studies are needed before the clinical effects of vestibular stimulation on PD become clear. Kim et al. (96) have provided fascinating data to suggest that nGVS modulates EEG activity in many frequency bands, and perhaps one of the most pressing needs in this area is the systematic investigation of the effects of nGVS on electrophysiological activity and neurotransmitter release in normal animals and also in animals exhibiting experimental Parkinsonian symptoms. These studies will elucidate the mechanism of action of nGVS in PD so that, if it is effective as an adjunctive treatment, its application can be optimized.

Finally, why is it that vestibular stimulation, in the form of nGVS, caloric vestibular stimulation or even natural vestibular stimulation, might exert beneficial effects on brain function in conditions such as PD? The answer to this question is elusive at present. However, it is conceivable that, due the evolutionary age of the vestibular system, and the otoliths in particular, their importance in detecting gravitational vertical and the widespread transmission of vestibular information across many brain regions, including many cortical areas, vestibular stimulation has some kind of "re-setting" effect on electrophysiological rhythms in the brain, which interferes with pathophysiological activity and promotes normal function (96). The precise details of how this happens and exactly what it entails will have to await further studies in animals and humans.

AUTHOR CONTRIBUTIONS

PS conceived and wrote the paper.

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Visual Input Is the Main Trigger and Parametric Determinant for Catch-Up Saccades During Video Head Impulse Test in Bilateral Vestibular Loss

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Patients with vestibular deficit use slow eye movements or catch-up saccades (CUS) to compensate for impaired vestibulo-ocular reflex (VOR). The purpose of CUS is to bring the eyes back to the visual target. Covert CUS occur during high-velocity head rotation and overt CUS are generated after head rotation has stopped. Dynamic visual acuity is improved with an increased rate and gain of CUS. Nevertheless, the trigger and the parametric determinants of CUS are still under debate. To clarify the underlying mechanism, especially the visual contribution, we analyzed the number, amplitude and latencies of the CUS in relation with the extent of VOR deficiency. The head and eye movements were recorded in 17 patients with bilateral vestibular loss (BVL) and in 33 subjects with normal VOR gain using the Video Head Impulse Test (vHIT) in two conditions: with visible target and in darkness with an imaginary target. Our study shows that in darkness without visible target the number of CUS is significantly reduced and the relationship between the amplitude of CUS and gaze position error is lost. Results showed that there is a correlation between the number of CUS and the drop in VOR gain. CUS occurring during the head movement and when the head remained still were not always sufficiently accurate. Up to four consecutive CUS could be required to bring eyes back to the visible target. A positive correlation was found between the amplitude of overt saccades with visible target and the gaze position error, namely the remaining eye movement to reach the target. These results suggest that the visual inputs are the main trigger and parametric determinant of the CUS or at least the presence of a visual target is necessary in most cases for a CUS to occur.

Keywords: vestibulo-ocular reflex, catch-up saccades, bilateral vestibulopathy, video head impulse test, covert saccade, overt saccade, dynamic vision

INTRODUCTION

One of the main mechanisms used by humans to keep a visual target on the fovea during head movements is the vestibulo-ocular reflex (VOR). The VOR moves the eyes in the direction opposite to head movement with a ratio between eye velocity and head velocity close to −1. In bilateral loss of vestibular function, the patient is unable to maintain the gaze on target during fast head movements and may experience oscillopsia, when he gets the illusion of unstable objects in the visual field. The eyes are initially carried away with the head movement, then one or several corrective saccades occur, bringing the image back on the fovea. Such saccades act as a compensatory, refixation mechanism, they are regarded as catch-up saccades (CUS). CUS have also been described during and after transient high velocity head rotations in patients with unilateral vestibular loss (1).

Two types of CUS have been described. Covert CUS occur early, while the head is still moving, most likely imperceptible by the examiner; overt CUS occur once the head impulse has stopped, visible by the observer (2). The simple bedside head impulse test allows the detection of overt CUS only (3). With the help of the search-coil recording and video head impulse test (vHIT) both types of CUS can be detected and analyzed (4).

In most cases of unilateral or bilateral VOR deficit, both types of CUS are found. Some patients present only one type (5) or even none if they blink, have a relative high VOR gain or move the head too slowly (6). CUS may also occur in subjects with normal VOR gain and their frequency increases with age (7).

There is a great disparity in the literature about the latencies of these CUS, from about 70 ms (5, 6) to 150 ms (5, 8). The trigger and parametric determinants of the CUS are still under debate. Conceptually, the relationship between the amplitude of CUS and the gaze position error (GPE) (6) could be determined by several factors, such as the residual or contralateral vestibular function, visual input or combined input from both oculomotor and cervical proprioception. The relatively short latency led some authors to suggest that an accurate CUS cannot be attributed to vision and is driven by vestibular input in unilateral vestibular deficit (6, 9). After bilateral neurectomy, the disappearance of CUS when the target is switched-off 1 s before the head impulse led other authors to promote a crucial role of the visual input for the accuracy of CUS (10). Nevertheless, Lehnen et al. (10) found similar CUS latencies in one patient with residual vestibular function compared to patients with complete bilateral vestibular loss (BVL), suggesting that residual vestibular function does not modify the triggering delay of CUS in the light. But, this patient performed efficient CUS with similar latencies in darkness and in light, suggesting that residual vestibular function provides a major contribution in the generation of the CUS in darkness.

In our practice, we observed that CUS are less accurate in bilateral than unilateral vestibular loss and some patients showed more than one CUS after the end of the head movement. This suggested that in BVL, the first overt saccades are not always accurate enough to bring the eyes back on the visual target. As shown by Weber, the amplitude of subsequent saccades becomes smaller (11). Even if CUS by themselves could not improve vision during the head movement, their occurrence is correlated with an improvement of the dynamic visual acuity (8). The preservation of the static visual acuity during head movement requires a stable image (retinal slip <4°/s) for more than 50 ms (12). The visual acuity declines progressively from the fovea out to the periphery of the retina. Early CUS bring the target image closer to the fovea. In doing so, they reduce the blurred vision and diminish the time needed to reacquire the target on the fovea (13) at the end of the head thrust. However, they cannot prevent the retinal slip which degrades the vision during a high velocity head movement. Ramaioli et al. (14) showed that the occurrence of early CUS may improve dynamic visual acuity, but the visual stimulus remained displayed when the head velocity decreased under 80°/s, allowing the eye smooth pursuit to suppress the residual retinal slip.

Head movements only rehabilitation technique has been suggested to improve dynamic vision for BVL by an increase in head impulse gain and/or an increase in compensatory saccade amplitude (15). This heterogeneity requires further insights into the mechanism triggering CUS to identify interventions promoting their occurrence for the rehabilitation of patients with BVL.

The aim of this study was to identify which factors determine the parameters of these CUS in patients with complete or partial bilateral vestibular deficit. Therefore, vHIT was performed in subjects with either BVL or normal VOR gain in standard conditions (visible target in lighted room) and in total darkness with an imaginary target in order to evaluate the influence of visual suppression on VOR gain and associated CUS.

MATERIALS AND METHODS

Participants

The study included a first group of 17 patients with BVL. BVL was mostly idiopathic in 14, caused by gentamycin toxicity in one, bi-lateralization of Menière's disease in one, and acute unilateral peripheral vestibular loss followed later by another attack on the other side in one patient.

These patients were aged between 29 and 80 years (mean 62 ± 12.9 years). The BVL was assessed based on a sum under 20°/s for the maximum slow phase velocities of the nystagmus induced by the caloric tests (30 s irrigation of 150–200 cm^3 at 30°C and 44°C) (16), and non-identifiable responses to rotatory chair test. The inclusion criteria are in accordance with the diagnosis criteria consensus of the Barany Society (17). All of them were diagnosed several years before testing (8 years on average) and were in an intensive vestibular rehabilitation program, including gaze stabilization exercises.

The second group included 35 patients who presented with vertigo or dizziness and showed normal horizontal VOR gain (>0.8) at the vHIT. These patients were aged between 17 and 92 years (mean 50 ± 14.7 years). The diagnosis was vestibular migraine (15 patients), persistent perceptual postural dizziness (6 patients), benign paroxysmal positional vertigo (5 patients), space and motion discomfort (3 patients), motion sickness (2 patients), cervical canal stenosis (1 patient), polyneuropathy (1 patient), lacunar syndrome (1 patient) and vitreous floaters (1 patient).

All the patients gave written informed consent. The study was conducted according to the Helsinki declaration. The experimental protocol was approved by the local Ethics Committee (CCPPRB Paris).

Data Collection

Head impulses were recorded with the ICS Impulse ver. 4.0® vHIT (Otometrics A/S, Taastrup, Denmark). Calibration instructions were given for each patient before the test. During calibration, the subject kept the head still while switching the gaze between two laser dots on each side of a target through a small angle about 10°, to ensure the overlapping of head and eye movements. Horizontal head impulses to each side were manually delivered with unpredictable timing and direction by the physician, standing behind the subject. At least eight accepted head impulses, with an amplitude about 10°, head velocity about 200°/s and acceleration about 2000°/s² were collected for each horizontal canal in each session.

For the first session, patients were instructed to fixate a red dot on a wall about 140 cm away from their sitting position in light (light-test).

In order to address the visual contribution to the VOR, at the end of the first session, similar head impulses were applied with the patient in total darkness, asking them to fixate an imaginary target that would be in the same position on the wall as during the test in light conditions (darkness-test). This was done because preliminary tests performed in dark conditions without any instruction for the patient gave invalid results owing to erratic eye movements. Total darkness was achieved using a vision-denied solution cup for the recorded right eye and an opaque patch for the left eye that were applied on Otometrics goggles in a completely darkened testing room. The vision-denied cup, which allows infrared light to pass while blocking light in the visible spectrum was provided by Otometrics.

Data Analysis

The gain values of the left and right horizontal VOR were used from the Otometrics ICS Impulse ver. 4.0® software. Raw data from Otometrics software were exported and further analyzed through algorithms implemented in Microsoft Excel software. These algorithms define the head and eye velocities and positions over time as well as the latency, velocity and amplitude of CUS. This allowed us to determine the contribution of each CUS to attain the eye position to target position (**Figure 1**). Only CUS that brought the eye toward the target position were analyzed, with a maximum of four saccades in a limited acquisition time interval of 800 ms. Saccades were identified by their peak velocity. The onset of the first saccade was identified manually on the velocity trace or on the cumulative amplitude curve. As shown in **Figure 1**, in case of low VOR gain, this onset is most often easy to identify. The eye end position of each catch up saccade is settled 20 ms after its peak velocity. The saccade amplitude is the difference between this eye end position and the eye end position of the previous saccade. A preliminary manual analysis has shown that the eye position 20 ms after the peak velocity provides a reliable value to determine the saccade amplitude. The relative amplitude of CUS was defined as the ratio between the amplitude of the CUS and the head rotation amplitude at the end of the CUS. Relative gaze position error was defined at the end of each CUS as the ratio between the cumulative amplitudes of eye movement to the final amplitude of the head movement. We defined the latency onset as the instant when head velocity was >5°/s. We measured the maximum velocity latency for all CUS ($n = 628$) from the beginning of the head movement for the first CUS and from the latency of the previous CUS for the following CUS. Statistical analysis of the data was done using Dell Inc Statistica 13 and Microsoft Excel 1807 software. Student test was used to compare horizontal VOR gains in light vs. darkness. The maximum velocity latency distribution in light and darkness were analyzed by the Shapiro-Wilk test. The comparison of the CUS latency in light vs. darkness was performed using a Mann-Whitney test. The relation between the number of CUS and the VOR gain were evaluated with ANOVA test. The number of CUS in light and darkness were compared with a Chi-squared test.

RESULTS

BVL Group

A total of 329 head impulses were delivered with light target and 319 with imaginary target. For light-test, average vHIT gains of right and left horizontal VOR were 0.32 ± 0.18 (range 0.08–0.79) (**Table 1**). Six out of 17 patients (80 light-test recordings) showed records with a VOR gain over 0.5 (24%) (**Figure 2**). For darkness-test, the horizontal VOR gains were significantly reduced: 0.27 ± 0.16 (range 0−0.9) (Student test for paired values, $p = 0.003$).

For the light-test, 96% of the head impulses were followed by CUS ($n = 634$). **Figure 3A** shows maximum velocity latency histogram of the first CUS ($n = 317$) for the recordings with visible target in light. The peak of the histogram is at 183 ms with onset latency about 20 ms earlier. The maximum velocity latency for all CUS showed a non-Gaussian distribution (Shapiro-Wilk $W = 0.920$ $p < 0.0001$) with a median at 183 ms. The median latencies of the first and subsequent CUS were similar:195, 171, 179, and 152 ms, respectively and the median latency, since onset of head impulse, of the second, third and fourth CUS range from 355 to 519 ms. For the vHIT in darkness ($n = 241$) the peak of maximum velocity latency of all CUS is 158 ms and the median is 195 ms (non-Gaussian distribution Shapiro-Wilk $W = 0.857$ $p < 0.0001$) (**Figure 3B**). There was a significant increase of the latency of all CUS in darkness compared to light (non-parametric test of Mann-Whitney $Z = -4.975$, $p < 0.0001$) but not for the first CUS (non-parametric test of Mann-Whitney $Z = -0.319$, $p = 0.75$), nor for the subsequent ones (non-parametric test of Mann-Whitney $Z = -0{,}932$, $p = 0.35$).

The number of CUS were plotted against the VOR gain values, showing that the number of CUS increased significantly as the gain value decreased in light-test [ANOVA $F_{(4,325)} = 17.9$ $p < 0.00001$] but not in darkness (**Figure 4**).

We assessed the relation between the relative amplitudes of covert and overt CUS (ratio between amplitude of the CUS and the head rotation amplitude) and the gaze position error (GPE). The gaze position error is the ratio between the remaining eye movement to reach the target (difference between the head rotation amplitude and the cumulative eye movement amplitude

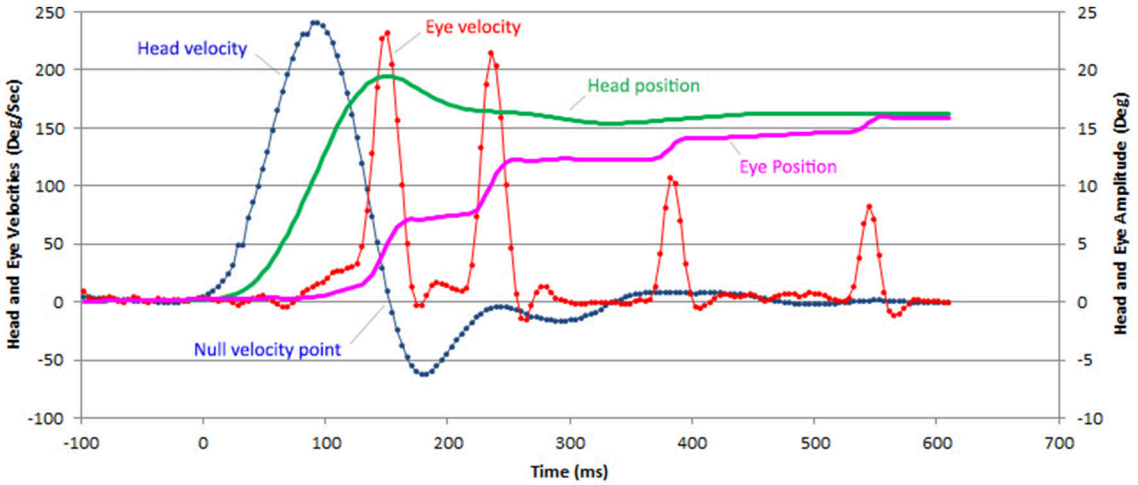

FIGURE 1 | Example of a horizontal vHIT recording with 4 CUS in a patient with BVL. The head (green line) and eye (purple line) position are computed from the head (blue) and eye (red line) velocity data provided by the recording device (ICS Impulse Otometrics). Only saccades that bring the eyes closer to the target are considered catch-up saccades. The onset of all latencies was defined when head velocity reached 5°/s.

TABLE 1 | The vHIT gains mean (range) collected with visible target and in darkness in the BVL group of 17 patients.

Patient	vHIT gAINS			
	Visible target		Darkness	
	Left	Right	Left	Right
1	0.59 (0.55–0.64)	0.39 (0.21–0.64)	0.59 (0.32–0.68)	0.31 (0.11–0.56)
2	0.24 (0.12–0.41)	0.27 (0.19–0.31)	0.35 (0.07–0.46)	0.22 (0.12–0.35)
3	0.49 (0.42–0.72)	0.69 (0.57–0.73)	0.43 (0.24–0.73)	0.58 (0.4–0.83)
4	0.58 (0.16–0.67)	0.49 (0.11–0.61)	0.61 (0.06–0.9)	0.44 (0–0.54)
5	0.16 (0.07–0.34)	0.12 (0–0.26)	0.18 (0–0.41)	0.14 (0–0.25)
6	0.30 (0.19–0.69)	0.17 (0.11–0.27)	0.22 (0–0.61)	0.27 (0.06–0.56)
7	0.58 (0.06–0.78)	0.30 (0.15–0.45)	0.28 (0.03–0.6)	0.32 (0.23–0.44)
8	0.08 (0–0.2)	0.17 (0.1–0.28)	0.07 (0–0.26)	0.10 (0–0.2)
9	0.16 (0.03–0.39)	0.22 (0.15–0.27)	0.11 (0–0.43)	0.16 (0–0.3)
10	0.40 (0.15–0.45)	0.35 (0–0.76)	0.34 (0.13–0.5)	0.27 (0.14–0.36)
11	0.17 (0.1–0.34)	0.25 (0.01–0.38)	0.17 (0.15–0.19)	0.24 (0.13–0.28)
12	0.16 (0.05–0.57)	0.19 (0–0.63)	0.29 (0–0.56)	0.17 (0–0.6)
13	0.52 (0.22–0.69)	0.50 (0.23–0.62)	0.51 (0.2–0.61)	0.48 (0.21–0.61)
14	0.28 (0.19–0.48)	0.30 (0.19–0.91)	0.23 (0.12–0.73)	0.14 (0–0.31)
15	0.32 (0.08–0.5)	0.79 (0.09–0.94)	0.28 (0.14–0.58)	−0.12 (0–0.63)
16	0.11 (0.09–0.16)	0.14 (0.1–0.24)	0.35 (0.08–0.69)	0.33 (0.12–0.55)
17	0.14 (0.09–0.18)	0.22 (0.17–0.27)	0.09 (0–0.14)	0.20 (0.09–0.38)

at the onset of the CUS) and the head rotation amplitude. **Figure 5B** shows a high correlation ($r = 0.79$ $p < 0.05$) between the amplitude of the overt saccades and the GPE in the light test. The correlation coefficient between the amplitude of the covert saccades and the GPE with visible target is 0.27 ($p < 0.05$).

In complete darkness, there is a drop of 62% of the number of CUS (241 in darkness vs. 634 with visible target). The mean reduction of saccade rate per record is 50% for the covert saccades and 65% for the overt saccades (Chi-squared = 6.58 $p = 0.01$) (**Table 2**). Furthermore, no clear relation could be noted between the relative amplitude of covert or overt saccades and the GPE for the amplitude of CUS performed in darkness-test ($R = 0.33$ and 0.55, respectively) (**Figures 5C,D**).

In the subgroup of 6 BVL patients with VOR gain over 0.5, CUS were identified in 72 out of 80 recordings (90%) in light-test and in 35 out of 76 recordings (46%) in darkness-test (Chi-squared = 34.9 $p < 0.001$). The mean gains were 0.64 ± 0.12 and 0.4 ± 36, respectively (Student test for paired values, $p < 0.001$).

Group of Patients With Normal vHIT Gain

For this group of 35 patients with normal vHIT we compared the VOR gain measured in light-test ($n = 638$) and in darkness-test ($n = 615$). The mean VOR gain for the entire group was 1.1 ± 0.14 (mean ± SD) in light-test and significantly reduced in darkness-test: 0.88 ± 0.24 (mean ± SD) (Student test for paired data $p < 0.01$). The occurrence of CUS was not significantly different in light-test and darkness-test: 9.4% vs. 8.1% (Chi-square = 0.63, $p = 0.42$) (data not shown).

DISCUSSION

These findings contribute understanding of parametric determinants of the compensatory CUS recorded during vHIT in BVL patients. Our results show significant changes of the CUS number, amplitude and latency after the suppression of visual cues in the group of BVL patients. This study suggests that visual input is the main trigger and determinant of the number, amplitude and latency of the CUS. We also confirm the hypothesis that a visible target increases the high-velocity VOR gain even in the control subjects with gains within the normal range (18).

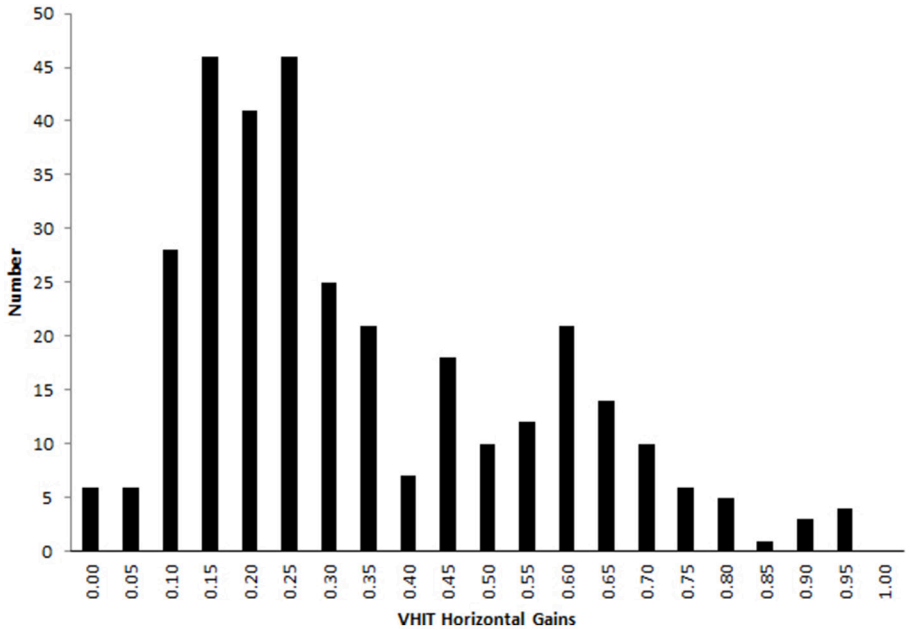

FIGURE 2 | Horizontal VOR gain during vHIT with visible target in the bilateral vestibular deficient patients group. A proportion of 23 % (76 out of 330) head impulses showed a VOR gain over 0.5 and 4% (13 out of 330) over 0.8.

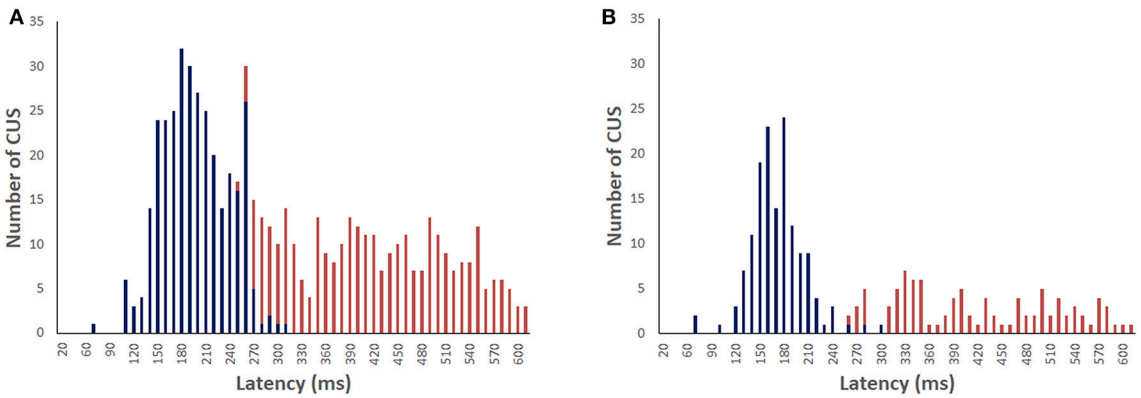

FIGURE 3 | Distribution of the covert saccades (blue) and overt saccades (red) latencies in bilateral vestibular deficient group during vHIT recordings with light target **(A)** and in darkness with imaginary target **(B)**. The median of CUS peak velocity is 183 and 195 ms, respectively.

The Required Number of CUS Increases With Low VOR Gain

We found a mean onset latency of 163 ms for the first CUS. This is consistent with other results in the literature (5, 6, 8, 10). This time interval has been established as necessary and sufficient for a refixation saccade to be organized as substitution for a deficient VOR (19). Some authors have measured latencies as short as 70 ms with skewed distribution and the mean latency of 151 ms (6). One hypothesis is that these short latencies resulted from correctly anticipated head impulse. The latencies of CUS also increase with the decline of the head impulse acceleration (6).

CUS cannot be accurate if they occur during passive head movement because the end position cannot be predicted. Therefore, they are often followed by additional CUS. These can be hypothesized to be encoded after the end of head movement to fixate the gaze on target. When the head is immobile, the saccade should be accurate enough to put the eye position on target. Overt saccades are defined as occurring after the first moment at which the head velocity become zero (the null velocity point). The null velocity point is not equivalent to the end of head movement because it is often followed by a rebound movement in opposite direction. The mean latency of the head null velocity point in our series is 150 ms and the head is motionless at

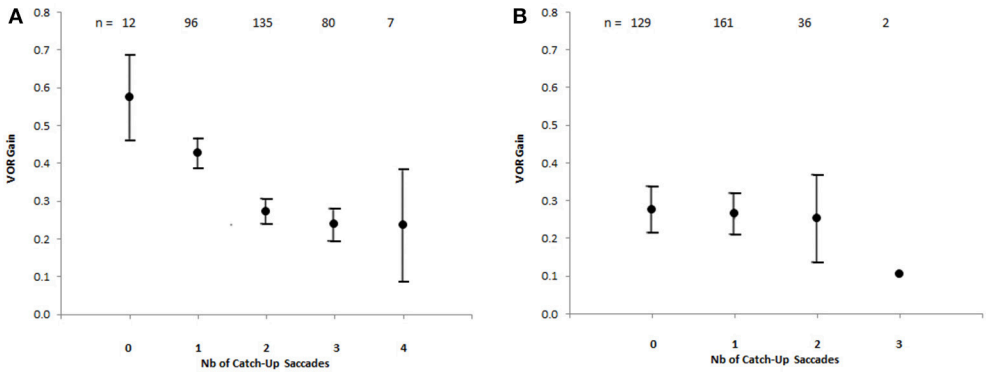

FIGURE 4 | Number of catch-up saccades per record plotted against VOR gain in the bilateral vestibular deficient group, showing the increasing number of catch-up saccades with decreasing VOR gain value [Anova $F_{(4,325)} = 17{,}9$ $p < 0.00001$] with visible target **(A)**. The vertical brackets represent 95% confidence interval. There is no similar relationship for recordings in darkness **(B)**. The values above indicate the number of records.

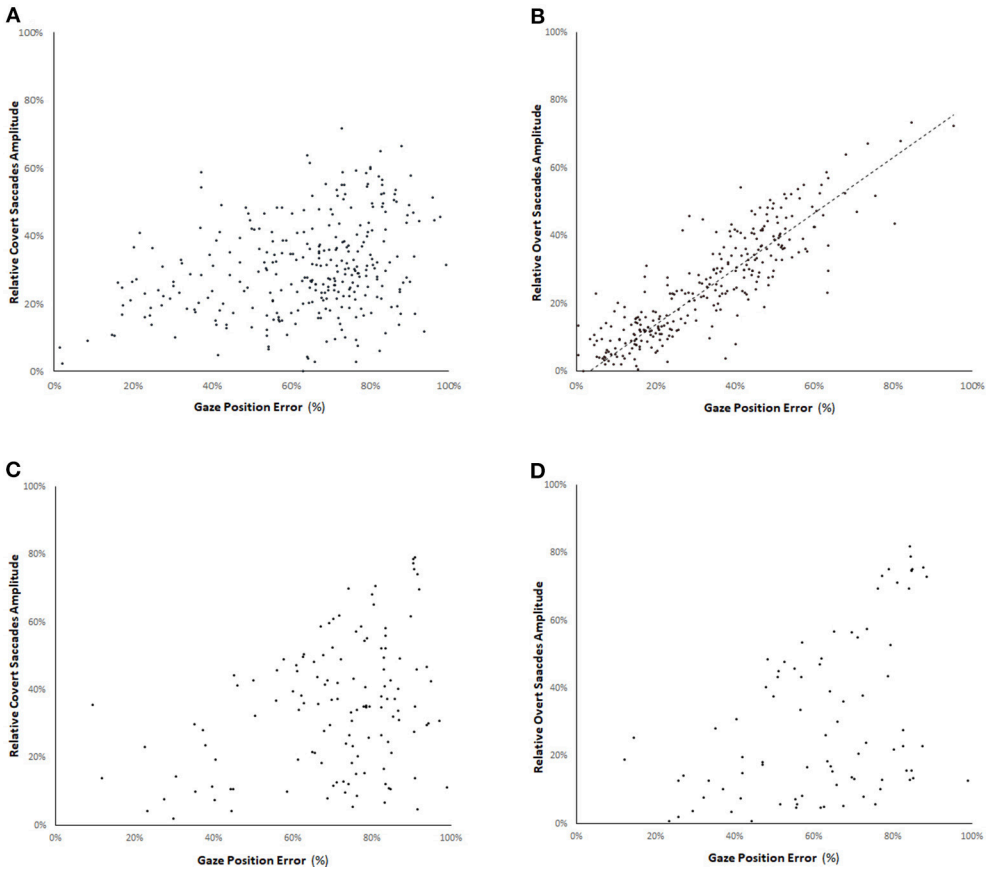

FIGURE 5 | Relation between the relative amplitude of covert saccades **(A,C)** and overt saccades **(B,D)** (ratio between the amplitude of the CUS and the head rotation amplitude) and the gaze position error in the bilateral vestibular deficient group for vHIT with visible target **(A,B)** and in darkness with an imaginary target **(C,D)**. The gaze position error is the ratio between the remaining eye movement to reach the target (difference between the head rotation amplitude and the cumulative eye movement amplitude at the onset of the CUS) and the head rotation amplitude. There is a high correlation (straight line slope = 0.82, $r = 0.79$ $p < 0.05$) between the amplitude of the overt saccades and the gaze position error with visible target. The correlation coefficient of the amplitude of overt saccades in darkness is 0.55 **(D)**.

about 250 ms. In healthy subjects, saccades remain precise despite ongoing changes in head position in space (20). So, we can assume that patients with unilateral vestibular deficit remain qualified to generate accurate CUS on target position once the null velocity point is reached. During the possible following head rebound movement in the opposite direction, the target position

TABLE 2 | The number of records, covert and overt saccades with light target and in darkness for each BVL patient.

Patient	Visible target			Darkness			Differences of saccade rate per record		
	Records	Covert saccades	Overt saccades	Records	Covert saccades	Overt saccades	Covert saccades	Overt saccades	All CUS
1	21	25	27	21	13	10	48%	63%	56%
2	24	24	38	21	1	3	95%	91%	93%
3	21	16	19	20	2	11	87%	39%	61%
4	19	12	12	22	2	9	86%	35%	60%
5	19	23	13	13	6	7	62%	21%	47%
6	19	17	20	19	2	12	88%	40%	62%
7	20	10	13	19	1	4	89%	68%	77%
8	19	25	15	22	7	8	76%	54%	68%
9	22	11	21	19	16	0	−68%	100%	42%
10	19	23	23	15	10	0	45%	100%	72%
11	17	22	11	17	9	8	59%	27%	48%
12	19	29	15	16	16	0	34%	100%	57%
13	14	10	11	15	8	1	25%	92%	60%
14	18	18	24	20	8	12	60%	55%	57%
15	20	15	11	24	5	2	72%	85%	78%
16	19	20	28	18	20	1	−6%	96%	54%
17	20	20	13	19	19	8	0%	35%	14%
Mean :							50%	65%	59%

The difference of saccade rate per record in light and darkness is expressed in %. The mean difference of saccade rate per record for the whole group is 50% for covert saccades, 65% for overt saccades and 59 % for all CUS.

is perceived as stable in space due to the efficient ipsilateral vestibular system. In case of bilateral vestibular deficit, the head has to be completely motionless before an accurate CUS could be generated. For visually guided saccades the delay between the target presentation and the start of the eye movement is about 180 ms (21). This may explain why in some of our bilateral vestibular deficient patients an accurate saccade cannot occur roughly before 430 ms. An additional time, likely due to the initial CUS, accounts for a median three or four CUS latency of 504 ms.

In this study, we also show that there is a significant relationship between the occurrence of multiple CUS and VOR gain. The number of CUS increases significantly with the drop in VOR gain, and thus with the gaze position error. Therefore, the amplitude of a single CUS, even programmed after the head movement does not systematically compensate a significant VOR gain deficit.

Only Overt Saccades in Presence of Visual Target Are Efficient

Our study showed that the corrective amplitude of overt saccades is correlated with the GPE under visible target condition (**Figure 5A**). Similar relation was shown in a group of 8 patients with complete unilateral vestibular loss and one with BVL (6). Covert saccades are elicited by a velocity signal during the retinal slip. So, their amplitude cannot be determined by the residual distance to the target. Conversely, overt saccades are refixation saccades encoded based on a stationary GPE. During passive head movement of varying amplitude, the GPE could be based on residual vestibular information, on retinal inputs or on the weighing between cervical and oculomotor proprioceptive information. By suppressing retinal information concerning the target position we assessed the role of the visual information in processing the CUS. The similarities between CUS and head-fixed saccades mean sequence responses suggest that the CUS originate from the saccadic system (22). Saccade velocities were not included in our analysis because the maximum velocity of the CUS is determined by their amplitude (6).

Less CUS in the Absence of Visible Target

Several reports reveal the high occurrence of CUS in unilateral and BVL (2, 6). In our BVL group, there is a significant drop (59%) in number of CUS in darkness-test suggesting that a visible target is a main factor for the CUS to supervene. Moreover, the lacking visual information induces the loss of relation between the residual CUS amplitude and the gaze position error (**Figures 5B, D**). This observation is in accordance with others (23) that showed an absence of CUS amplitude adaptation after reduction of VOR gain after a period of visual VOR suppression.

Literature data show that 1 year after neurectomy the ipsilateral VOR gain was 0.27+/-0.14 (1), suggesting that a gain over 0.5 is indicative of a residual vestibular function. A model proposed by Colagiorgio (24) hypothesize that covert saccades are driven by the prediction of head displacement using vestibular and extravestibular signals. For passive head impulses it is suggested that residual vestibular information may account for 80% of the estimated gaze position prediction. However, in our 6 patients with residual vestibular function the number of CUS also decreases significantly during the vHIT

recordings performed without visible target despite the further reduction of the gain. Thus, the residual vestibular function in some patients or the inference of the gaze position error from cervical and oculomotor input are less efficient to generate adapted CUS. Nevertheless, the inter-individual variability of the CUS reduction in darkness could be explained by the use of proprioceptive triggers by some patients, especially those with lower residual VOR gain. In the presence of a residual vestibular function, the opening of the VOR loop in darkness impairs the triggering and adaptation of the CUS. Peng et al. (22) showed that corrective saccades can be generated in the absence of vision by flashing off the target when the head began to move. This is more suggestive of memorized target paradigm. Even in this condition, the authors observed that the CUS did not accurately minimize the GPE. We argue that the absence of a visual cues lowers the efficiency of the substituted saccadic system probably by opening the feed-back loop that controls the occurrence and accuracy of saccades.

Visual Deprivation Lowers the VOR Gain

In both group of patients, our results showed significant decrease in VOR gain when no visual information about the target position was available. The modulation of normal VOR gain measured at high velocities by the vHIT was already addressed with variation of the gain by the target distance and the brightness of the peripheral visual field (18).

The incidence of CUS in normal subjects, measured by vHIT varies greatly in the literature, from 16.7 to 49% (7, 25). The CUS in normal subject probably compensate the hypometric characteristic of VOR, which increases with age (7). In our group with normal vHIT, we observed significant decrease of the VOR gain in darkness-test and the occurrence of CUS is 9.4 and 8.1% in light and dark conditions, respectively. The absence of significant increase in number of CUS in darkness-test despite the VOR gain reduction, could be explained by the lack of visual input.

The ocular pursuit system could be responsible for increased VOR gain with a visible target compared to dark condition. There is some evidence that the pursuit system is still necessary to enhance the VOR gain for large amplitude at low velocities (26). But, the smooth pursuit system has a latency of about 100 ms (27) and low velocities VOR gain significantly increase already during the initial 80 ms, when comparing VOR with visual fixation and in darkness (28). So, it seems unlikely that the pursuit system and the optokinetic system, which has a latency of 70 ms in humans (29), are able to increase the VOR gain during head thrusts that reach their peak velocities after about 90 ms. The target distance of 140 cm eliminates the vergence contribution during the target fixation. Attentiveness increases VOR gain (30), but we argue that the attention level do not significantly change from light condition to darkness with a precise task to imagine a visual target.

The efficiency of the VOR is powered by a visual feedback loop. Its main goal is to diminish the retinal image slip. This feedback loop modulates the activity of vestibular nuclei. This VOR gain modulation is an adaptive mechanism and the few minutes in light or darkness before the recording onset, followed by a set of at least ten recordings, allowed this mechanism to develop. Demer et al. (31) showed that VOR gain adaptation is already achieved 15 min after the wearing of magnifier spectacles, but an eventual adaptation for shorter time is not reported. Adaptation to the target distance can occur as early as 40 ms after the beginning of the head motion. (32). We argue that the VOR cannot be accurate without a constant modulation by the image stabilization feedback. The increase of VOR gain when the target is in light environment, opposite to dark environment (18) suggests that the VOR efficiency increases when an image has to be stabilized (23). We concur with Chim et al. (18) arguments in invoking the vestibular adaptation mechanisms to increase the high-frequency VOR response. The absence of oscillopsia passing from darkness to light suggests that this adaptation is a fast process. The retinal position error has been showed to increase the high-velocity VOR response (18). Conversely, the suppression of visual target opens the VOR arc, decreasing its efficiency. Similarly, to avoid the ocular pursuit interference, the low speed VOR is often evaluated in the absence of visual target. The large dispersion of normative values of VOR gain in these conditions is explained by the same mechanism (33). This raises the question about the reliability of VOR evaluation in the absence of target image on the retina.

CONCLUSIONS AND PERSPECTIVES

We found a drastic reduction in number of CUS under dark conditions, suggesting that the visual input is a main factor for a CUS to be generated, even in patients with residual vestibular function. The absence of visible target also reduces significantly the VOR gain and eliminates the relationship between the CUS amplitude and the remaining eye movement to compensate the passive head rotation.

The VOR appears to be a hypometric system (7) but the visual feedback information can modulate the VOR gain with a delay of 40 ms after the head movement (32). This short delay allows the adjustment of the VOR gain and CUS amplitude.

Further, studies are necessary for understanding the triggering of residual CUS in darkness and how CUS could bring supplementary improvement in rehabilitation techniques for the patients with vestibular deficiencies.

AUTHOR CONTRIBUTIONS

CVN, AB, UD, CH, and MT conceived and designed the experiments, wrote and revised the manuscript. CVN, AB, and UD performed the experiments. MT, CH, AB, and CVN recruited patients.

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Biases in the Visual and Haptic Subjective Vertical Reveal the Role of Proprioceptive/Vestibular Priors in Child Development

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Investigation of the perception of verticality permits to disclose the perceptual mechanisms that underlie balance control and spatial navigation. Estimation of verticality in unusual body orientation with respect to gravity (e.g., laterally tilted in the roll plane) leads to biases that change depending on the encoding sensory modality and the amount of tilt. A well-known phenomenon is the A-effect, that is a bias toward the body tilt often interpreted in a Bayesian framework to be the byproduct of a prior peaked at the most common head and body orientation, i.e., upright. In this study, we took advantage of this phenomenon to study the interaction of visual, haptic sensory information with vestibular/proprioceptive priors across development. We tested children (5–13 y.o) and adults (>22 y.o.) in an orientation discrimination task laterally tilted 90° to their left-ear side. Experimental conditions differed for the tested sensory modality: visual-only, haptic-only, both modalities. Resulting accuracy depended on the developmental stage and the encoding sensory modality, showing A-effects in vision across all ages and in the haptic modality only for the youngest children whereas bimodal judgments show lack of multisensory integration in children. A Bayesian prior model nicely predicts the behavioral data when the peak of the prior distribution shifts across age groups. Our results suggest that vision is pivotal to acquire an idiotropic vector useful for improving precision when upright. The acquisition of such a prior might be related to the development of head and trunk coordination, a process that is fundamental for gaining successful spatial navigation.

Keywords: subjective vertical, vision, haptic, development, vestibular, bayesian, multisensory

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INTRODUCTION

During development, perception of the direction of gravity (i.e., verticality) is pivotal to learn how to maintain the upright posture, the most important posture needed for locomotion and spatial navigation. In this learning process, the brain must combine information coming from different sensory modalities, crucial cues are those that signal body orientation relative to gravity (i.e., vestibular and proprioceptive) and those that inform about the orientation of objects belonging to the explored environment. Perceived verticality depends on several aspects, such as contextual information (1–3), age (4–8), and sensory loss (9, 10). In order to disclose the role of vestibular and proprioceptive sensory information on perceived verticality, much research has used a simple

paradigm in which verticality is judged when tilted in the roll-plane. In this context, uni- and multisensory contributions have been investigated by focusing on the subjective visual vertical [SVV; (11–14)], the subjective haptic vertical [SHV; (15–17)] the subjective auditory vertical (18) and the interaction of visual and haptic sensory information on perceived verticality (16).The advantage of this methodology is that it provides an indirect measurement of the perceptual readout of vestibular and proprioceptive sensory information signaling body orientation relative to gravity. The upright body orientation can indeed lead to perceptual biases such as the Aubert or A-effects that indicate perceived verticality tilted toward body tilt. This effect, first discovered in 1861 (19), has been interpreted as undercompensation for body tilt driven by an idiotropic vector indicating the most common body orientation, that is upright (11). In Bayesian terms, this scenario has been expressed with a prior model that assumes unbiased vestibular and proprioceptive sensory information about body roll tilt. The percept is represented by the posterior probability distribution and can be calculated as the product between sensory information (i.e., likelihood probability distribution) and a prior peaked at the upright position (20–22). The influence of the prior has been shown to change depending on subjects' body tilt, showing that modeled sensory variability for the encoding modality of perceptual verticality increases as the tilting angle increases (21). In this context, A-effects are interpreted as the byproduct of a system that functionally improves precision around the upright orientation for small head and body tilts (22, 23). Opposite to the A-effect, the E-effect (with "E" indicating Entgegengesetzt, that is "opposite" in German) is observed when verticality estimates are biased away from body tilt (24) thus indicating overcompensation of body tilt. Such effect has been observed for tilts of a few degrees (21) and >135-150° (25, 26); a possible interpretation of the E-effect is related to how precision based on otolith sensory information varies depending on head orientation (27).

Regardless of the involved sensory modality, perception of verticality changes depending on the developmental stage. Children in scholar age (6–11 y.o.) are less precise than adults in judging visual verticality when standing upright and postural performance follows a similar pattern as it improves after 8–9 y.o. (5, 7). These findings indicate a non-negligible role of the developmental stage in gaining functional and fine balance control. However, less is known about the interaction of the balance system with other sensory modalities in this ontogenetic process.

In adulthood, the brain is able to combine sensory information provided by different sensory modalities leading to more precise estimates, for instance when combining visual with haptic (28) or with vestibular information in discrimination tasks (29–32). However, studies on children have found that multisensory integration appears later in development (33, 34), leading to different sensory weighting depending on the investigated perceptual feature. In particular, vision seems to have a prominent role in calibrating multisensory brain processes underlying object orientation discrimination (33), spatial navigation (34), and generally postural control [for a review (26)]. Relatively to the perception of verticality, the presence of vision since birth has a strong role in providing the brain with the means to build an idiotropic vector whose influence on perceived verticality is absent in congenitally blind individuals (15). With the study presented here, we intended to investigate how visual and haptic sensory readout of verticality are influenced by vestibular/proprioceptive priors across childhood. Research on priors across childhood mostly focused on within modality priors, showing developmental trends for the interaction between light from above and convexity priors (35) and more generally for lighting direction (36). To our knowledge, no studies investigated the use of priors during development on the perceptual readout of visual and haptic sensory information. To fill this gap in the literature, we took advantage of a simple object orientation discrimination task performed by subjects tilted on their left-ear side. We allowed participants to use either vision, touch or a combination of both modalities for providing the response. We tested children from 5 to 13 y.o. and adults older than 22 y.o. in order to investigate how head and body roll tilt affects visual and haptic readout of vestibular information across the main developmental stages. We found that the youngest group of children are biased in judging verticality across both modalities and in the bimodal condition showing A-effects. Older children and adults show no strong A-effects in the haptic modalities and in some cases a tendency to E-effects whereas they always show A-effects for visual judgments of verticality. Our results are nicely predicted by a Bayesian model that allows vestibular sensory information (i.e., likelihood) to vary depending on subjects' age and the prior to shifting position between upright and upside-down, thus shifting the estimate to indicate either A- or E-effects.

MATERIALS AND METHODS

Participants

In this study, we had 90 subjects participating in the experiments. Twenty-nine children were excluded from the analysis because they could not perform the task properly as they were constantly distracted and unstill during the task (17 out of 29) or because their psychometric fit did not converge properly (12 out of 29). The remaining 61 subjects (29 females, age range 5–37 y.o.) were divided into 7 subgroups depending on the age: 6 y.o. ($n = 6$; 3 females; it includes one child of 5 y.o.); 7 y.o. ($n = 7$; 3 females); 8 y.o. ($n = 10$; 2 females); 9 y.o. ($n = 8$; 5 females); 10 y.o. ($n = 15$; 7 females); 11 y.o. ($n = 7$; 5 females; it includes 2 children of 13 y.o.); >22 y.o. ($n = 8$; 4 females; age range, 22–37 y.o.). All subjects performed the three experimental conditions except for 4 children who performed only visual and haptic conditions. All participants or their legal representatives provided signed informed consent before starting the test. This study was approved by the ethics committee of the local health service (Comitato Etico, ASL 3, Genova, Italy) and it was performed in accordance with the Declaration of Helsinki.

Stimuli

During the experiment, subjects laid over a memory foam matrass on their left-ear side, a pillow was added under

their head in order to maintain head and body roll-tilted 90° counterclockwise relative to gravity (see **Figure 1A**). Two identical 3d printed white plastic bars (length: 1.5 cm; width: 1.2 cm; height: 17 cm) fixed over a black circle were used to deliver the stimuli to be judged. In both bars, a section of 2 cm at one of the bar's ends had a texture rougher than the rest of the bar thus signaling the top. Both bars were fixed over two independent computer-controlled motors. The whole experiment was controlled via MATLAB with the use of the Psychtoolbox (37). Motor's sound potentially cueing bar's rotation was masked by sound played between trials for 2.5 s; for children, we use a music theme in order to make the task amusing. The sound was played through two speakers positioned behind the setup, not visible by the participant. At the end of the played sound, the trial could start and the experimenter asked the participant to perform the verticality task to avoid any attentional and performance decay. In the visual condition, an array of LEDs was installed underneath the bar and lighten up to show the visual stimulus. Subjects viewed the luminous bar through a shroud (length, 40 cm; diameter, 12.5 cm) thus the visual stimulus subtended ∼17° and no other contextual visual cue could influence the response. A blurring film was placed over the shroud's aperture close to the bar in order to blend neighboring LEDs into one luminous strip. Bar's top end was visually signaled by a dotted pattern.

Procedure

All experiments were conducted in a darkened room. In all conditions subjects performed a two-alternative forced choice task and were asked to indicate in which direction the bar was tilted. In details, subjects were asked to tell the experimenter toward which side away from the vertical the bar was tilted by using the room's features as references (i.e., position of the window in the room was used to indicate stimulus orientation toward body tilt whereas door's position was used to indicate stimulus orientation away from body tilt). The experimenter then would record the response by pressing a key on the computer controlling bars' orientation via MATLAB. We decided to use a discrimination task because it has been shown to be less vulnerable to artifacts compared to other methods as the adjustment task (6). In all conditions, subjects were asked to look through the shroud. In the haptic condition, shroud's aperture was covered by a dark gray cardboard in order to avoid visual cues of any sort. In the haptic and bimodal conditions, the haptic bar was positioned ∼40 cm away from subjects' body as this was the minimum distance allowed because of the shroud presence. In the bimodal condition, subjects were told they were touching and seeing identical bars with matching orientation and were asked to base their response on the orientation information provided by both sensory modalities. In the haptic and bimodal conditions, subjects used their right hand to explore the bar (see **Figure 1**). Each experimental condition was run on a single block of 100 trials for adult participants and 50 trials for children. Block order between the visual and haptic condition was alternated whereas the bimodal condition was always presented as the last block of trials in order to avoid any influence of multisensory integration processes on the unimodal conditions. Experimental blocks were presented over a period of maximum 2 days to avoid that fatigue or attentional decay could influence subjects' performance. Breaks were taken between blocks of trials.

Psi Method

Stimulus orientation was determined by the PSI adaptive procedure (38), implemented using the PAL_AMPM routine from the Palamedes toolbox (39). The adaptive procedure algorithm was given an initial PSE estimate of 0° corresponding to no biased estimate. Stimulus orientation ranged between −45° and 45 degrees and changed at each trial based on the response given at the previous trial following the adaptive procedure. By using a Bayesian criterion, this method minimizes the uncertainty associated with the parameter estimates of the psychometric function (i.e., mean and standard deviation of the cumulative Gaussian fit). For each condition and subject, we fit a cumulative Gaussian to the data using the PAL_PFML_Fit routine from the Palamedes toolbox (39) which finds the best fit in a maximum likelihood sense. The point of subjective equality (PSE) is represented by mean of the distribution and it provides a measure of the orientation at which the bar is

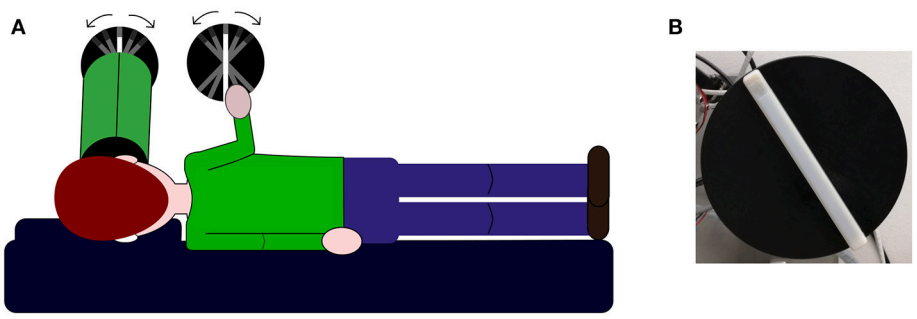

FIGURE 1 | Experimental set-up. **(A)** Illustration of the set-up used to deliver visual and haptic stimuli and participants body orientation during the task. The first disk from the left represents the visual stimulus looked through a shroud represented as the green tube in front of participant's face (see methods section for details). The second disk represents the haptic stimulus and it is explored by participants with their right hand. In the bimodal condition, subjects are instructed to look through the tube and touch the haptic bar at the same time. **(B)** Picture showing the bar used in the experiments.

perceived to be vertical. Deviations of the PSE from 0° represents a biased estimate of verticality, therefore they will be referred as "bias" throughout the manuscript. The just noticeable difference (JND) is the standard deviation extrapolated from the cumulative Gaussian fit and it is used as a measure of precision associated with the estimate (see **Figure 2**).

Statistical Analysis

In order to test whether there is an effect provided by the sensory modality used to encode stimulus orientation, either visual, haptic or bimodal, and by participants' age, we ran a linear mixed model ANOVA with the experimental condition and subjects' age (subjects are divided into 7 subgroups: up to 6, 7, 8, 9, 10, 11 y.o. and adults) as factors. The relationship between age and bias magnitude was tested by correlation analysis corrected for multiple comparisons (Bonferroni correction). *Post-hoc* analysis was conducted to test significance level in subgroups defined by age using one-tailed one sample *t*-tests corrected for multiple comparisons (Bonferroni correction). Comparison of biases between age subgroups and for each experimental condition was done by means of one-tailed paired *t*-tests corrected for multiple comparisons (Bonferroni correction). As our hypothesis predicts an A-effect for all sensory modalities in children and a reduced or absent bias in adults we used the one-tailed *t*-test that assumes biases to be >0.

Multisensory Integration

Integration of visual and haptic sensory cues is tested by using an MLE prediction Bayesian model as previously used in several studies (28, 40). We used the following equation to calculate precision associated with the bimodal estimate:

$$\sigma_{VH}^2 = \frac{\sigma_V^2 \ \sigma_H^2}{\sigma_V^2 + \sigma_H^2} \tag{1}$$

where σ_V and σ_H are the sigma for the visual and haptic modality given by the psychometric fit respectively, and represent precision associated with the estimate. The MLE calculation assumes that the optimal bimodal estimate of the PSE ($\hat{S}_{VH}$) is given by the weighted sum of the independent visual and haptic estimates ($\hat{S}_V$ and $\hat{S}_H$).

$$\hat{S}_{VH} = w_V \hat{S}_V + w_H \hat{S}_H \tag{2}$$

Where each sensory modality's weight is calculated as follows:

$$w_V = \frac{1/\sigma_V^2}{1/\sigma_V^2 + 1/\sigma_H^2}, w_H = \frac{1/\sigma_H^2}{1/\sigma_V^2 + 1/\sigma_H^2} \tag{3}$$

Two-tailed paired *t*-tests corrected for multiple comparisons (Bonferroni correction) are used in order to compare predicted accuracy and precision (i.e., PSE and JND of the psychometric fit) in children (age 6–11 y.o.) and in adults. The model predicts that when the two sensory modalities are combined, precision improves. If the model fails in predicting this pattern, e.g., by predicting higher precision than observed in the behavioral measurement, a probable explanation would be that multisensory integration is not yet accomplished.

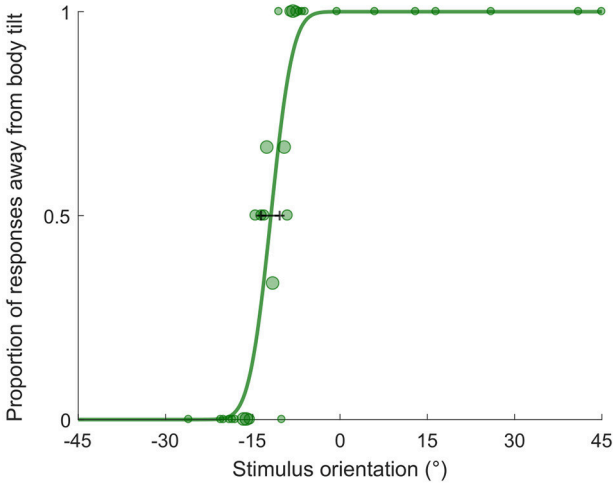

FIGURE 2 | Example psychometric fit. The plot represents performance of participant aged 9 y.o. in the bimodal condition. The shift of the PSE (−11.88°) indicates the bias in perceived verticality, negative bias indicates an A-effect. The JND (2.94) represents the variability associated with the estimate. The size of dots is proportional to the number of repetitions for each stimulus value.

Bayesian Prior Model

Prediction of potential biases following the A- or the E-effects in verticality estimation were modeled by using a Bayesian modeling approach. We used this approach to test whether prior information or experience could influence the estimate of verticality depending on subject's age. Therefore, we modeled the prediction of our results based on a maximum likelihood estimation approach (MLE) where the peak of the posterior distribution represents the predicted estimate. The posterior distribution reflects the influence of the prior on the likelihood distribution which in turn represents the sensory information associated with the stimulus and it is assumed to be unbiased. We allowed three parameters to vary in order to find the best fitting prediction (in the least squares sense) to the behavioral results. The sigma of the likelihood distribution is varied depending on subjects' age by using the following Equations (4, 5). In particular, similar to previous work (21), we first calculated σ_a as:

$$\sigma_a(\rho) = a_0 + a_1 \rho \tag{4}$$

with a_0 the offset and a_1 the coefficient that defines how σ_a changes with age (indicated by ρ). Based on previous behavioral results (5), we allow σ_a to vary either increasing or decreasing depending on participants' age. To this aim, a_1 is allowed to have positive and negative values. However, a negative sigma cannot be used in the model, therefore we adjust σ_a by using the following equation:

$$\sigma_{b=} \sigma_a + \min(\sigma_a) + \varepsilon \tag{5}$$

with ε a constant added to avoid that the function equals 0 and the shift of the function is provided by adding the minimum of σ_a. This is done to keep the decreasing relationship in case

of negative values of a_1 and by maintaining σ_b values always positive. Equation (5) allows to test an increasing or decreasing function whose starting point is always defined by $a_0$and it is the same for each value of a_1.

We also varied the sigma of the prior distribution (σ_p) in order to test whether the prior influenced the estimate or not. Indeed, a flat prior would lead to no shifts of the posterior thus predicting no biases. Moreover, considering the controversial findings on the haptic perception of verticality showing either A- or the E-effect, we varied where the prior distribution is centered either toward or away from the upright orientation of head and body. Considering the pattern of biases as a function of age, our results seemed roughly consistent with a prior distribution that could change its peak depending on age or could maintain the same pattern of biases (A- rather than E-effects) across age. Moreover, the development of priors across age would be consistent with previous findings that show priors to depend on visual experience [(15) see Discussion]. Thus, we used four different possibilities for the prior distribution. First, as a control we used a flat prior that does not influence the estimate, thus the posterior is equal to the likelihood distribution. Second, a prior peaked at 0°, i.e., the upright position parallel to gravity that would lead to A-effects across all ages. Third, a prior peaked at 0° for children and a flat prior for adults and, fourth, a prior peaked at 0° for children and −180°, i.e., opposite to the direction of gravity thus leading to E-effects, for adults. These last possibilities assume that the prior shifts across development.

RESULTS

PSE Analysis

Verticality estimates show biases depending on subjects age and the sensory modality used to encode stimulus orientation. As shown in **Figure 3**, in the visual condition, verticality estimates are negative, that is they are biased toward body tilt for all ages with peaks for adult participants. In the haptic condition, the youngest participants (6 y.o.) show biases toward body tilt, whereas older children show less pronounced biases and adults show a shift to the positive sign, indicating biases away from the body tilt. The bimodal condition mostly shows biases toward the body tilt both in children and adults. Linear mixed model ANOVA shows a significant effect of experimental condition [$F_{(2,\ 106)} = 15.13$, $p < 0.0001$], no significant effect given by age group [$F_{(6,\ 55)} = 0.38$, $p = 0.88$] and a significant interaction between condition and age group [$F_{(12,\ 106)} = 3.66$, $p < 0.001$].

Post-hoc analysis (one-tailed *t*-tests corrected for 21 comparisons) reveal significant biases in the visual condition for the following age subgroups 6 y.o. ($p < 0.01$), 9 y.o. ($p < 0.01$), 10 y.o. ($p < 0.0001$) and >22 y.o. ($p < 0.001$) and a tendency for the age of 7 y.o. ($p = 0.056$); significant biases in the haptic condition only for children aged 6 y.o. ($p = 0.03$) and a tendency for the age of 8 y.o. ($p = 0.08$); in the bimodal condition biases are significant for children aged 10 y.o. ($p < 0.001$) and for adults ($p < 0.01$). Correlation analysis shows that age and biases are not significantly correlated in the bimodal condition (rho = −0.04, $p = 1$); whereas there is a significant negative correlation between age and haptic biases (rho = 0.42, $p < 0.01$) and a tendency for a negative correlation in the visual condition (rho = −0.31, $p = 0.07$).

Multisensory Integration

Bimodal estimates of verticality show consistent biases across all ages. In the youngest group of subjects, biases are in the same direction across all conditions whereas in older children and adults biases are in between visual and haptic estimates values. The behavioral data are compared with the Bayesian integration predictions: predicted biases match the behavioral data across all ages as showed by paired *t*-tests which did not report any significant difference. Considering variability, there are no differences between adults and children for each unimodal condition that is both for the visual and haptic modality. In this case, we analyzed only the data from the subjects who did all conditions including the bimodal condition. This was done to allow us to compare bimodal and Bayesian integration prediction with the data for the unimodal conditions. The comparison between behavioral bimodal variability and the prediction shows that predicted variability matches behavioral data for the adult group (non-significant paired *t*-tests) but not for children ($p < 0.01$) (see **Figure 4**).

Bayesian Prior Model

In our model, we multiplied the likelihood with the prior in order to calculate the posterior distribution. By following the MLE approach, we consider the peak of the posterior as the predicted bias. We allowed 3 parameters to vary to find the best fitting model: where the prior is centered or a flat prior that does not influence the estimate; sigma of the prior (σ_p); offset (a_0) and coefficient (a_1). The last two parameters (a_0 and a_1) are used in equation (4) to calculate the sigma of the likelihood distribution (σ_b). For the visual modality, we found that the best fitting model corresponds to a prior centered at the upright position (0°) whereas in the haptic modality, the prior shifts from 0° for children and −180° for adults. Regarding σ_p, variability changes depending on the encoding sensory modality, that is 24.7° for the visual modality and 28.3° for the haptic modality. We observe a different scenario regarding the parameters that define the sigma for the likelihood. For the visual modality, we observe that the best fitting offset (a_0) equals 5.3 and the coefficient (a_1) equals 0.16, thus indicating that a slightly increasing sigma depending on age is the one that provides the best fit ($R^2 = 0.1$; see **Figure 5**). Regarding the haptic modality, we find that the best fitting offset (a_0) equals 0.3 and the coefficient (a_1) equals −0.16. This means that the best fit is provided by a decreasing trend of the sigma depending on participants' age ($R^2 = 0.18$; see **Figure 5**).

DISCUSSION

In this work, we tested children and adults in a subjective vertical task. Participants were tilted on their left-hand side and had to discriminate the tilt of a bar in three conditions, visual, haptic and bimodal. Although previous research has shown effects given by gender in the perception of body orientation (41), we tested this aspect in our study and observed no influence of gender (see **Supplementary Materials**). Our results show biases that reflect

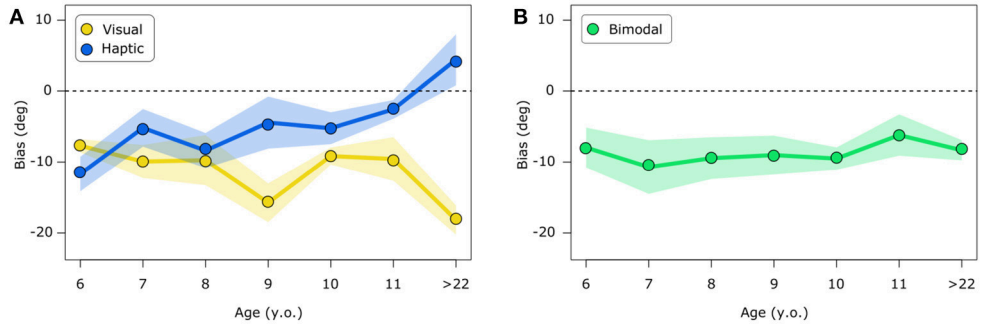

FIGURE 3 | Visual and haptic biases **(A)** and bimodal biases **(B)**. Biases represent the bar's tilt in degrees at which the bar is perceived to be vertical. Positive values indicate an estimation of verticality away from body tilt, negative values represent biases toward body tilt. The first ones can be interpreted as overcompensation of body tilt whereas the latter show undercompensation of body tilt. Bimodal biases are presented separately for visualization purposes. In both figures **(A)** and **(B)**, shaded areas represent standard error.

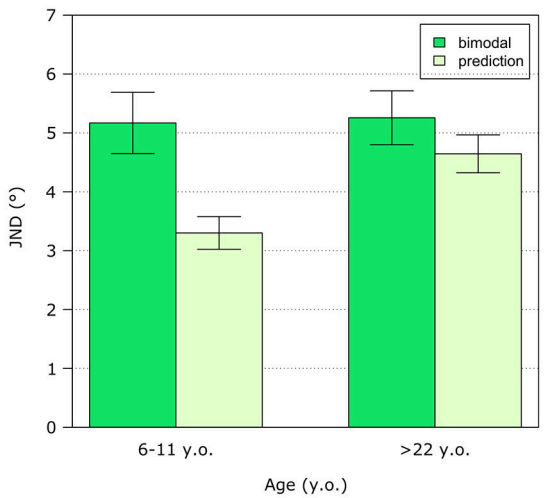

FIGURE 4 | Bimodal vs. predicted variability. Variability is represented as the mean JND across subjects divided into two groups: children of primary school age (6–11 y.o.) and adults (>22 y.o.). Error bars show standard error.

undercompensation or overcompensation of body tilt depending on the encoding sensory modality and subjects' age. The former phenomenon is known as A-effect and in Bayesian terms can be interpreted as the influence of a prior set at the most common head and body orientation relative to gravity that is upright (i.e., an idiotropic vector). In the visual modality, bias direction is consistent at all ages showing A-effects of similar magnitude. In the haptic modality, on the other hand, the pattern of biases is modulated by subjects' developmental stage, this is confirmed by significant biases toward the tilt for the youngest group of children (i.e., 6 y.o.) as well as by a negative correlation between haptic biases and age.

In order to better understand the nature of these biases in verticality perception, we compared behavioral results with those predicted by a Bayesian model. In this context, perceptual biases have often been linked to a Bayes-optimal mechanism for which the percept depends on the influence of prior information on the readout of sensory information (42–45). Biases can indeed be interpreted as the side effect of a system that functionally takes advantages of priors in order to improve precision and generally perception. In particular, we observe that model's prediction of visual verticality is quite steady across age, that is the prior is centered at the upright position for all ages and there is a slight increase of variability in the likelihood as age increases. This happens because we did not allow prior variability to vary depending on subjects' age; therefore, we cannot exclude that prior rather than sensory variability changes with age. Regarding the haptic modality, we observed a different scenario. As we allowed the model to vary where the prior is centered with respect to participants' age, we observe that there is a shift of the prior across age, not observed instead in the visual condition. Specifically, children' biases in haptic verticality are nicely predicted by a prior centered at the upright position, thus indicating the presence of A-effects. Biases in adults, instead, are better explained by a prior centered in the opposite position, thus suggesting the presence of E-effects. However, our behavioral data do not show significant E-effects. Moreover, variability associated with sensory information about body orientation in space has a decreasing trend. These results are in line with previous findings showing that haptic orientation judgements at the early stages of development are less reliable as vision dominates for the readout of such object properties (33). In other words, we observe that haptic readout of proprioceptive and vestibular information about body orientation in space is less precise in children than in adults. In children, there is a trend to improve the precision with age and this is shown by a weaker influence of the prior as age increases.

Provided that haptic judgments of verticality have been linked to the body rather than the head reference (16, 46), our results suggest that at the early stages of development the brain is yet to disambiguate head and body references. In this sense, children are influenced by the prior as head and body are processed within the same representation of coordinates. Later in development, the two references might disambiguate thus inducing the brain to selectively access different references (e.g., priors peaked at different positions). Along these lines, previous research has shown that the ontogenesis of locomotor balance control follows a similar progression across age (47). Specifically, up to 7 years

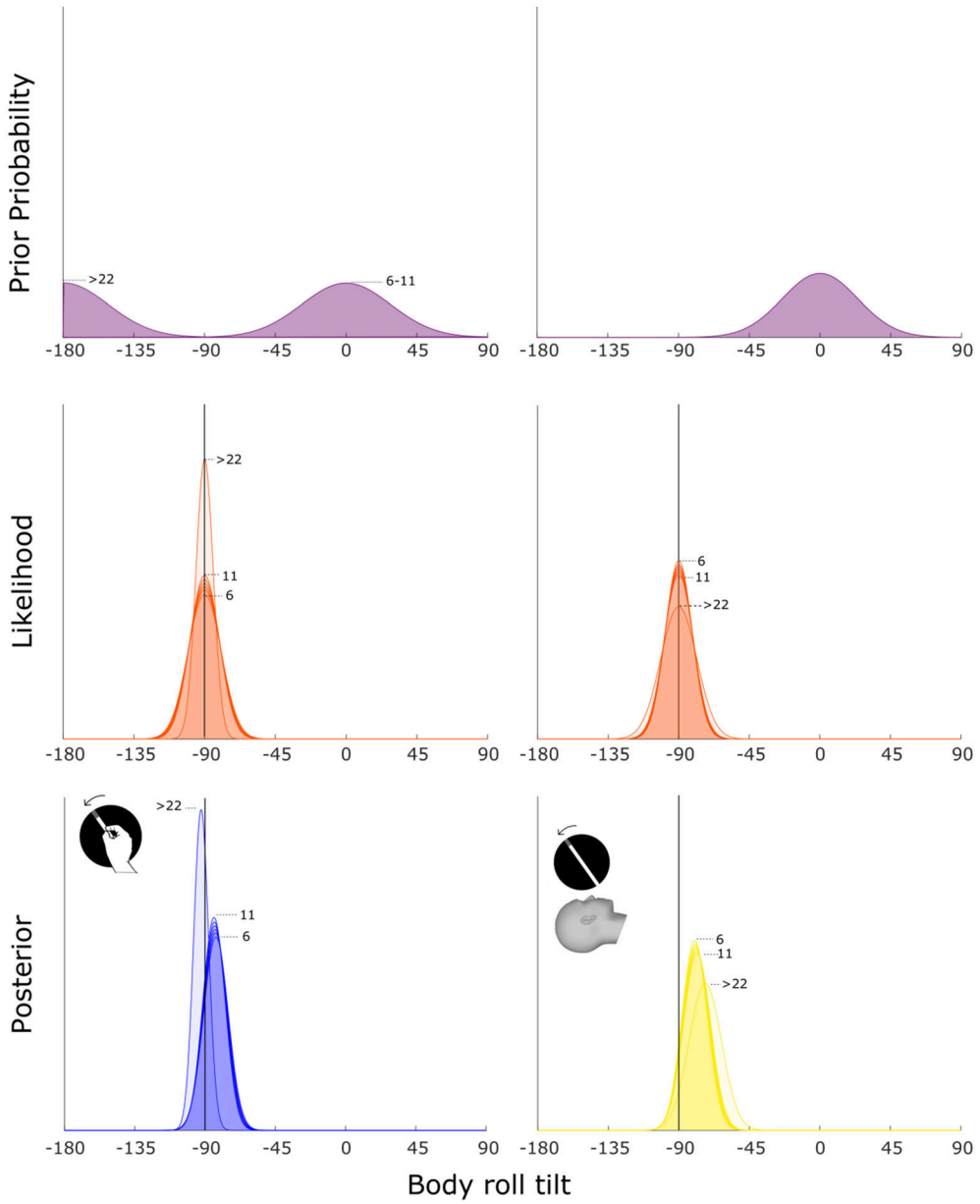

FIGURE 5 | Bayesian prior model for body tilt estimation. The left and right columns show the best fitting model in a least-squares sense for the haptic and visual modality respectively. The posterior (third row) is calculated as the product between prior (first row) and likelihood (second row) distributions. The position of the posterior's peak defines whether the model predicts over- (between −180 and −90°) or undercompensation (between −90 and 0°) of body tilt. The numbers on the side of the curves indicate the age group related to each curve. For illustration purposes, age groups between 7 and 10 y.o. are not indicated.

old children use an "en bloc" strategy according to which head and trunk are used as a unique block of reference frames (48). The use of such a global representation is also shown in the coordination of forearm and trunk in simple motor tasks and can be interpreted as a prominent use of egocentric reference (49). Later in development, children tend to use a different strategy by independently moving neck and trunk to maintain balance, namely an "articulated mode" (48). In this sense, the biases in perceptual verticality presented here can be considered as the byproduct of the development of a balance control system that is rougher in the youngest and it increases in complexity and articulation as age increases.

In a recent study (15), we investigated haptic perception of verticality in early and late blind adults when tilted counterclockwise. The results show that early blind individuals have no consistent biases in perceiving verticality whereas late blind subjects show an A-effect. Interestingly, such effect is not present in sighted people (see Introduction). Therefore, it is

possible that the development of an idiotropic vector signaling the most important posture we need for spatial navigation might be based on the visual input at the first stages of development. Along these lines, the results reported here show that the same prior influences both visual and haptic readout of verticality at the first stages of development. As subjects' age increases, the prior maintains its influence in the visual modality whereas haptic sensory information (represented by the likelihood distribution) seems to increase in precision and the prior position might shift thus provoking a bias reduction or even inversion of bias direction, i.e., E-effects. This might represent the most important result of this research as it indicates that vision is very useful for balance control and that both haptic and visual information are used at the early stages of development to code the upright prior. However, more studies in this direction would be need to better disclose the relationship of a visually mediated prior and blindness especially if since birth. In this context, it can be proposed that a training based on haptic verticality may provide the brain with the experience necessary to build the upright prior, thus possibly improving balance and posture control in visually impaired children.

Bimodal judgments of verticality are strongly influenced by vision at all ages and Bayesian integration models do not match the behavioral data in children as previously observed [(33), for a review: (50)]. This result is true when we consider precision in verticality discrimination: children do not take advantage of the availability of both modalities to judge object orientation. Adults instead seem to be the only ones who can benefit in terms of precision in the bimodal condition. Surprisingly, although we observe no differences between adults and children when comparing precision for each individual sensory modality (i.e., vision and touch), the model predicts higher precision in the bimodal condition for children compared to adults. A slightly higher precision in one or both of the unisensory modalities for children might have led to such higher predicted bimodal precision in children. This difference might be due to individual differences in the unimodal conditions that should have been maintained also in the bimodal condition thus leading to improved precision in this condition as predicted. Since this is not the case, the reduced capability of children integrating unisensory information might underlie the observed difference between groups. On the other hand, bias prediction matches the behavioral measurement both in children and adults, thus indicating that accuracy is predicted by a Bayesian cue combination model. The reason behind the difference between precision and accuracy might rely on the fact that both visual and haptic biases in children are toward the same direction, therefore both sensory modalities are influenced by the same prior and this is maintained when both sensory modalities are available.

In adults, biases are predicted by a prior that shifts peak position depending on the involved sensory modality. This result is in line with the abovementioned lack of integration in children: on the one hand, the brain is yet to integrate the two sensory modalities, on the other hand, the sensory readout is dictated by priors that are peaked at the same body orientation, that is upright. In other words, the lack of multisensory integration and the absence of sensory specialization in possibly referring to different body coordinates (e.g., head and body) might require a similar prior to influence sensory readout to improve precision. From the model perspective, the posterior distribution representing the percept is given by the product of the prior and sensory information (i.e., the likelihood), and this product generates by definition a more skewed distribution thus representing a more precise estimate. Therefore, since precision cannot improve by multisensory integration, the brain might use a similar prior for both sensory modalities in order to maintain a functional representation of the upright, that is the most important posture the body needs to successfully move in space.

To our knowledge, our research represents the first attempt to combine Bayesian priors and multisensory integration to study the development of perception across childhood, particularly focusing on visual and haptic perceived verticality. Our findings posit visual sensory information to be pivotal not only in gaining functional perception of object orientation but also in influencing a proprioceptive/vestibular prior regarding head and body orientation relative to gravity. Moreover, we show that during the first years of development vision and touch seem to equally provide the information necessary to maintain an upright posture as both modalities are influenced by the same proprioceptive/vestibular prior. This information is useful in the context of adapting rehabilitation tools and techniques for orientation and mobility at different stages of development in people suffering of difficulties in maintaining an upright posture and avoiding falls. Rehabilitation programs may benefit from the results presented here as we show that a proprioceptive/vestibular upright prior is already acquired at the age of 6 y.o. and its influence on vision and touch depends on the developmental stage. In this sense, rehabilitation protocols might be shaped on patient's age considering the conveying sensory modality that is influenced by the upright prior, touch and vision for the youngest whereas the older ones mostly take advantage of vision.

AUTHOR CONTRIBUTIONS

LC and MG conceived and designed the project. LC performed experiments. LC analyzed data. LC and MG wrote and edited the manuscript. All authors gave final approval for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.01151/full#supplementary-material

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Rebalancing the Vestibular System by Unidirectional Rotations in Patients With Chronic Vestibular Dysfunction

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Introduction: Vestibular dysfunction is a common disorder that results in debilitating symptoms. Even after full compensation, the vestibulo-ocular reflex (VOR) could be further improved by using rehabilitation exercises and visual-vestibular adaptation. We hypothesized that in patients with asymmetric vestibular function, the system could be rebalanced by unidirectional rotations toward the weaker side (i.e., a pure vestibular stimulation).

Methods: Sixteen subjects (5 female and 11 male, 43.2 ± 17.0 years old) with chronic vestibular dysfunction that was non-responsive to other types of medical treatment were recruited for the study (ClinicalTrials.gov Identifier: NCT01080430). Subjects had VOR asymmetry quantified by an abnormal directional preponderance (DP) with rotation test and no previous history of central vestibular problems or fluctuating peripheral vestibular disorders. They participated either in the short-term study (one session) or the long-term study (7 visits over 5 weeks). Rehabilitation consisted of five trapezoid unidirectional rotations (peak velocity of 320°/s) toward the weaker side. Care was taken to slowly stop the rotation in order to avoid stimulation in the opposite direction during deceleration. To study the short-term effect, VOR responses were measured before and 10, 40, and 70 min after a single unidirectional rotational rehabilitation session. For long-term effects, the VOR gain was measured before and 70 min after rehabilitation in each session.

Results: We observed a significant decrease in VOR asymmetry even 10 min after one rehabilitation session (short-term study). With consecutive rehabilitation sessions in the long-term study, DP further decreased to reach normal values during the first 2 sessions and only one subjects required further rehabilitation after week 4. This change in DP was due to an increase in responses during rotations toward the weaker side and a decrease in VOR responses during rotations in the other direction.

Conclusion: Our results show that unidirectional rotation can reduce the VOR imbalance and asymmetry in patients with previously compensated vestibular dysfunction and could be used as an effective supervised method for vestibular rehabilitation even in patients with longstanding vestibular dysfunction.

Keywords: compensation, unidirectional rotation, vestibulo-ocular reflex, directional preponderance, rehabilitation

INTRODUCTION

Normal vestibular function is essential for proper balance control and gaze stabilization during head movements during natural activities. Vestibular dysfunction results in imbalance between inputs from the two sides, leading to symptoms such as vertigo. Vestibular disorders have a prevalence of ∼35% in Americans above 40 years of age (1). The dysfunction has considerable impact on daily activities, requiring sick leaves in ∼80% of cases and puts a large burden on health costs. Vestibular system's great adaptive properties are exploited during vestibular compensation, a process that includes changes in the vestibular periphery (2), vestibular nuclei (3, 4), commissural connections between the two nuclei (5) and extravestibular inputs (6–8).

Evidence from previous studies suggest that natural vestibular compensation strategies do not use the full capacity of the system. Training programs that use visual-vestibular training in the form of bidirectional (9) or unidirectional (10) rotations in the presence of a visual surround further improve the vestibulo-ocular reflex (VOR) in animals with compensated unilateral lesions.

In order to improve compensation in patients with chronic vestibular symptoms, the multisensory nature of the vestibular compensation can be exploited through sets of rehabilitation exercises (11–15). Originally, vestibular rehabilitation was performed as group activities and a hierarchy of exercises with different difficulty levels (16). Later, more specific approaches were used based on physiological or behavioral rationales, which were more effective in decreasing the magnitude of symptoms experienced by patients and increasing their independence during daily activities (17, 18). Recently, it has been shown that customized and supervised exercises are more beneficial than unsupervised (e.g., performed alone at home) or general fitness exercises (19–24).

Here, we describe a new rehabilitation method that solely targets the vestibular pathway through a specific vestibular stimulation. The rehabilitation consists of unidirectional rotations in the dark in the direction of the less responsive (LR) side. The hypothesis behind this original idea was formalized by one of the authors (NR) and tested by pilot (unpublished) studies about 20 years ago. Basically, this hypothesis was based on changes in commissural pathways and vestibular nuclei during compensation and suggested that unidirectional rotation toward the side with lower VOR responses results in excitation of that side and simultaneous inhibition of the other side (i.e., the side with higher VOR responses). This could result in an adaptive change, leading to an increase in responses of the weaker side and a new balance between the two sides. This effect could be due to changes in the vestibular nuclei and commissural pathways or at the peripheral level, or both. A confounding and counterproductive effect most likely also exists due to the habituation of responses resulting from repeated rotations, as shown by previous studies in normal animals and humans (25–30). We provide evidence that a pure unidirectional rotation in patients with vestibular asymmetry could effectively reduce the VOR asymmetry, with effects lasting for several weeks. In some, but not all cases, this was accompanied by a long-term subjective sense of improvement in balance.

METHODS

This study was performed as a sequential double blinded clinical trial on 16 patients (5 females and 11 males, 25–64 years old). There was no sex or age limitation for selecting the patients. Regarding the etiology of the vertigo, during our initial assessment, we only asked questions to rule out any known central etiology, such as tumor or surgery (since it would interfere with compensation process) or any history of fluctuating disorders such as Meniere's or BPPV with asymptomatic periods (which would be inappropriate for studying the rehabilitation effects). Typically, subjects' symptoms were not alleviated by previous medical treatment and none of the subjects used any medication during the study. Subjects had a proven and documented history of vestibular dysfunction for 1–8 years and an abnormal asymmetric VOR response during rotation test, as evidenced by a directional preponderance (DP) >10% during rotation (see below). In the initial session, a complete vestibular examination was performed, which included saccadic, smooth pursuit, optokinetic, gaze holding, rotation, and caloric tests. We used caloric DPs as supplementary evidence of asymmetry (DP < 20%) initially. However, caloric DP was not required to be abnormal for inclusion in the study. Caloric DPs were positively correlated with rotation DPs ($R^2 = 0.69$). The research protocol was then explained to patients and those who agreed to participate in the study, gave written informed consent in accordance with the Declaration of Helsinki. Subjects were free to drop out of the study at any time. All tests were performed in the Audiology Center of Day General Hospital, Tehran, Iran and each patient's primary care physician or otolaryngologist was informed of their participation in this research. This study (ClinicalTrials.gov Identifier: NCT01080430) was carried out in accordance with the recommendations of the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran

and the protocol was approved by the Institutional Review Board of the University.

Quantifying the VOR Asymmetry

Eye movements were measured by electronystagmography during rotation (Nicolet Spirit). Rotations were performed at peak velocity of 40°/s and 0.2 Hz. Patients were in complete darkness with eyes open during the test. The head was positioned 30° nose down, so that the horizontal canal was in its maximum plane of activation. All recordings were done while the subjects performed mental arithmetic to increase their state of alertness.

As a measure of vestibular compensation (10, 31, 32), VOR symmetry was quantified by calculating the directional preponderance (DP) as:

$$DP = \frac{V_{HR} - V_{LR}}{V_{HR} + V_{LR}} \times 100$$

where V_{HR} and V_{LR} represent peak eye velocities during rotations toward the side with higher responses (HR) and lower responses (LR), respectively. The HR and LR sides were determined on the first test for each subject and were not changed during the course of the study. In this way, a change in the direction of DP would be represented by negative values. The normal range of DP for the test as performed by our equipment was <8% as measured in 52 normal subjects. Patients with initial DP values of >10% were included in the study.

We used DP of responses to whole-body sinusoidal rotations as a measure of asymmetry to quantify the effect of our intervention. Comparison of rotation DP to caloric test has shown that it is a reliable measure of diagnosis of vestibular imbalance in routine vestibular clinical practice and follow up (33, 34). It also has the additional benefit that its measurement is fast and relatively comfortable for patients (35). Furthermore, whole body rotation provides reliable results that are comparable to head-on-body rotations during head shaking (36) or head impulse test (HIT) (35, 37). Finally, while both HIT and whole body rotations reliably track ipsilesional VOR recovery, whole body rotations are better for following contralesional compensatory changes over time (37).

Short-Term and Long-Term Unidirectional Rotational Rehabilitation Protocol

The unidirectional rotation comprised of a velocity trapezoid, with acceleration of 80°/s^2 over 4 s to reach a maximum velocity of 320°/s and then slowly decelerate at 10°/s^2 to stop over approximately 30 s. The slow deceleration was particularly important in order to have a smooth end of rotation since a sudden stop could function as a stimulation in the opposite direction. Each session comprised of 5 such rotations, with 1 min intervals in between. The whole session was completed in ∼7 min. Rotations were performed in the dark with the subjects' eyes open and heads positioned 30 degrees nose down.

In each session of the study, subjects first underwent an initial DP assessment by rotation test. After 3–4 min, the unidirectional rotational rehabilitation was performed as described above. Eight subjects participated in a short-term study, for which the subjects were kept in the rotation chair and DP was assessed by sinusoidal rotation test 10, 40, and 70 min after the end of rehabilitation. VOR asymmetry was originally evaluated by rotation and caloric tests, but for further evaluations we only used rotational testing since it was less bothersome for patients and more practical for serial evaluations. Another 8 subjects participated in a long-term study. In this case, subjects were asked to rest for 1 h in a calm place in the hospital without using stimulating beverages (e.g., coffee) and post rehabilitation DP was measured only 70 min after the unidirectional rotation. The rehabilitation was performed two times a week for the first 2 weeks and once a week for the second 2 weeks, providing a total of 6 sessions in 4 weeks. One week after the last session, a sinusoidal rotation test was performed for a final DP measurement. During the course of the study, if the DP measured at the beginning of any session was in the normal range or reversed, the patient was not subjected to any additional unidirectional rotations and would be instructed to return for follow up in the next session. We did this as an ethical issue since the unidirectional rotation in a subject with normal DP was not necessary and could theoretically result in an imbalance in the opposite direction.

Evaluation of Subjective Improvement of Symptoms

To document symptoms of all patients before the beginning of the study in the first session, they were evaluated by one of the researchers (NGS) using a questionnaire. In particular, they were asked to specify when their vestibular symptoms (e.g., vertigo, falling to one side, oscillopsia) have started, whether they had a sensation of rotation (i.e., true vertigo) or imbalance, the frequency and duration of symptoms, any accompanying auditory problems, and any precipitating factors. Subjects that participated in the long-term study were also asked to fill in a form in order to report any occasions of vestibular symptoms and their specificities (e.g., duration, intensity, …) during the days between the rehabilitation sessions.

RESULTS

We tested the effect of unidirectional rotational rehabilitation on 16 patients (5 female and 11 male) with confirmed chronic vestibular dysfunction for 1–8 years (3.5 ± 2). All patients had a history of some level of auditory problem, with some degree of hearing loss. Mean age of subjects was 43.2 ± 17.0 (range: 25–64) years old. For the short-term study (n = 8 subjects, 3 female, 5 male), data was collected at 10, 40, and 70 min after rehabilitation. For the long-term study (n = 8 subjects, 2 female, 6 male), data was collected over 6 sessions (4 weeks), before and 70 min after rehabilitation in each session (see Methods for details). None of the patients had jobs or participated in activities that resulted in intense head movements in between sessions and none had performed rehabilitative physical exercises.

Short-Term Effect of the Unidirectional Rotation

For each of the 8 subjects that participated in the short-term study, eye velocities were measured during sinusoidal rotations and VOR responses were evaluated for half cycles to the right and left and a DP was calculated. DPs calculated for rotation and caloric tests were linearly related to each other (slope = 0.7) and on average, were not different (26.5 ± 6.5% vs. 30.1 ± 6.0%, paired *t*-test, $p = 0.36$). Based on the initial rotation test (i.e., before rehabilitation), the two sides were labeled as "low response" (LR) and "high response" (HR). The unidirectional rotational rehabilitation was then performed with rotations toward LR as described in the Methods. **Figure 1A** shows the VOR response for one of the subjects with an initial asymmetric VOR, with smaller responses during rotations to the right. As such, the right side was labeled as LR and rehabilitation for this subject consisted of unidirectional rotations to the right. At 10 min after the end of rehabilitation, there was an increase in responses for rotations in both directions. For this subject, HR responses gradually decreased over time, while LR responses remained slightly larger than initial values.

Average eye velocities for all patients in the short-term study showed a similar trend (**Figure 1B**). While VOR responses for both sides increased slightly 10 min after rehabilitation, this change was not significant (repeated measures ANOVA, $n = 8$, $p = 0.08$) and decreased at 40 min and 70 min for both directions of rotation. While the increase in eye velocity for LR rotations could be attributed to the unidirectional rotation (i.e., our hypothesis), the increase for HR half cycles at 10 min was unexpected and could be a rebound phenomenon after the inhibition due to the fast unidirectional rotation. The general trend of these changes was in a way that the asymmetry between the two sides decreased over time as calculated by the DP value (**Figure 1C**). This effect was observed even 10 min after rehabilitation (repeated measure ANOVA, *post hoc* Tukey test, $p = 0.016$ re initial value) and continued up to 70 min ($p = 0.003$). Seventy minutes after rehabilitation, DP was normalized in half of the patients, while the other half showed a decrease in DP. In 2 subjects with DP (post-rotation) to within the normal range, the direction of DP changed (i.e., negative DP) at 40 min and in one of them remained so even at 70 min.

Together, these results suggest an effective improvement in VOR asymmetry up to 70 min after one session of the unidirectional rotational rehabilitation. We next investigated whether this effect could be preserved for longer periods.

Long-Term Effect of the Unidirectional Rotation

Eight patients (2 female and 6 male) participated in the long-term study, which required 7 visits over a period of 5 weeks. Note that these subjects were different from those in the short-term study and have not had any previous experience with the unidirectional rotation. Of these, 2 female subjects only participated in the first session and dropped out of the study for personal reasons. For the other 6 subjects, we measured VOR responses at the beginning of each session and 70 min after the rehabilitation in that session.

In the first session, similar to that observed for subjects in the short-term study, VOR responses showed a decreasing trend for HR peak eye velocity and an increasing trend for LR peak eye velocity (**Figure 2A**), the changes were not significant for HR (35.0 ± 3.6 vs. 26.0 ± 4.4°/s, paired *t*-test, $p = 0.15$) or LR (25.0 ± 2.2 vs. 26.75 ± 5.3°/s, paired *t*-test, $p = 0.23$). All of the long-term patients also showed a decrease in their DP values 70 min after rehabilitation in the first session and the average DP decreased from 21.2 ± 4.1% initially to 1.4 ± 4.2% (paired *t*-test, $p = 0.02$). When data of all 16 subjects were pooled together, the decrease at 70 min became more pronounced (**Figure 2B**, 24.7 ± 3.7% vs. 7.7 ± 4.1%, paired *t*-test, $p = 0.0006$).

When VOR responses at the beginning of all sessions were pooled (**Figures 3A,B**), the eye velocities for rotations in the two directions were significantly different (33.8 ± 2.0°/s vs. 23.5 ± 1.5°/s, *t*-test, $p = 0.003$). At 70 min after rehabilitation, the pooled data showed no significant difference between the two sides (31.0 ± 2.3°/s vs. 27.15 ± 2.8°/s). The decreasing (non-significant) trend for HR rotations and the increasing (non-significant) trend for responses to LR rotations were opposite to that expected from simple habituation to a unidirectional rotation observed in normal subjects, which resulted in a decrease in the responses of the side ipsilateral to rotation and no change in the opposite side (38). Differences between responses in normal conditions and in asymmetric (compensated) conditions could be due to compensatory changes in vestibular nuclei neurons and commissural pathways and will be further addressed in the Discussion. As a result of these changes in responses of the two sides, average DP values decreased (**Figures 3C,D**) from 14.1 ± 2.2% at the beginning of sessions to 2.4 ± 2.2% at 70 min after rehabilitation (paired *t*-test, $p = 0.002$). This change is comparable to that observed for the short-term study (**Figure 1C**).

In the majority of cases, DP decreased to within the normal range in the first few sessions. On average, DP was in the normal range at the beginning of the second session and showed no significant change up to the last session, about 4 weeks later (**Figure 4A**). Note that when patients showed normal DPs they did not receive rehabilitation and were only followed up in the next session. Similar to the short-term effect, average VOR responses as measured by peak eye velocity did not show a significant change over time (**Figures 4B,C**, ANOVA, $p > 0.05$). Again, there was a non-significant decreasing trend over time in responses to rotations toward HR and a non-significant increasing trend for responses to LR rotations, which were enough for a significant decrease in asymmetry and DP over time. Also, notice that all 4 subjects who returned for the last final DP measurement (with no rehabilitation rotation) had symmetric VOR responses with minimal DP values. For 3 of these subjects, the symmetry was accompanied by near normal responses (i.e., ∼40°/s) for rotations in both directions. Although a significant clinical finding, this should be considered with caution since only 4 subjects participated in the last session and 3 of them had LR peak eye velocities close to normal at this point (**Figures 4B,C**, last points).

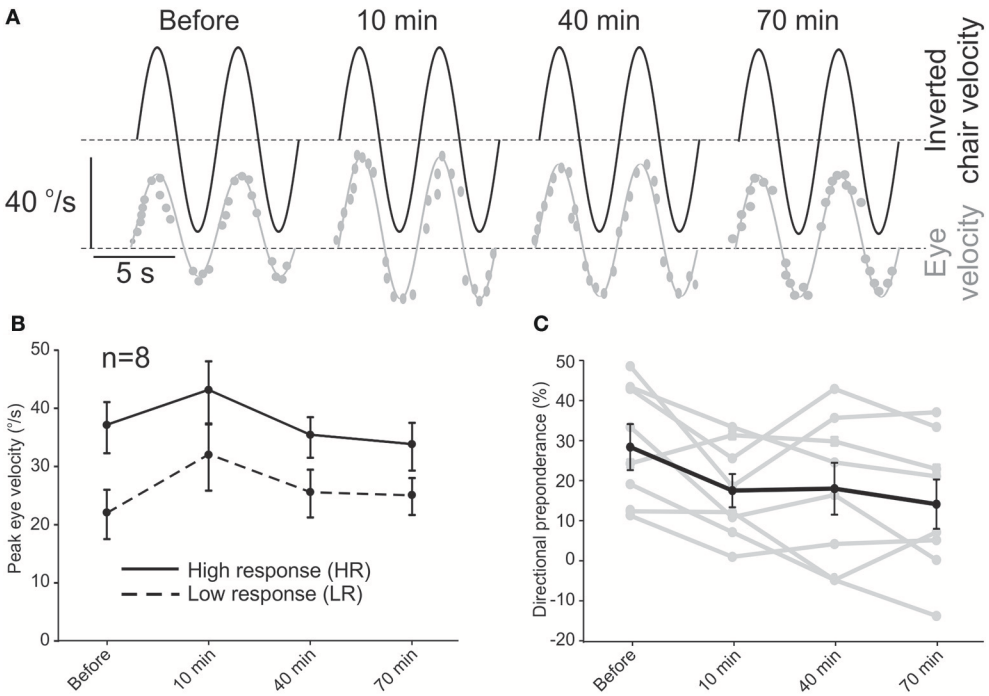

FIGURE 1 | Short-term effect of the unidirectional rotational rehabilitation on VOR asymmetry. **(A)** Example of an asymmetric response to sinusoidal rotation in one of the subjects and its improvement after rehabilitation. Dashed lines show 0°/s. **(B)** Average peak eye velocity ($n = 8$ subjects) for rotations in the two directions before and after rehabilitation. The side that has larger responses is designated as the side with "higher activity" or HA and the other side as "lower activity" or LA. **(C)** Directional preponderance as a measure of VOR asymmetry decreased over time. The change is significant between the initial value and all other values (repeated measure ANOVA, $p < 0.01$). Data for each subject is shown by gray lines.

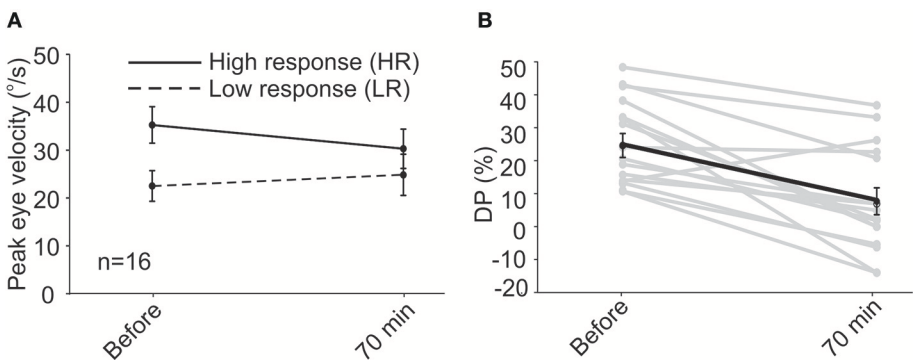

FIGURE 2 | Following unidirectional rotational rehabilitation, VOR response to HA rotations decreased by ∼16% and responses to LA rotations increased by ∼14% when all 16 patients (short-term and first session of long-term group) were pooled together **(A)**. Although average changes were not significant 70 min after rehabilitation, they resulted in a significant change in DP **(B)**, decreasing from 24.7 ± 3.7% to 7.7 ± 4.1% (paired t-test, $p = 0.0006$) and bringing it to normal values.

For all subjects, the last recorded DP—either session 7 or the last session that they participated in—was lower than the original value, measured before the rehabilitation on the first session. In fact, all final DPs were within the normal range (**Figure 5A**). The average DP decreased significantly (paired t-test, $p < 0.05$) from 14.8 ± 3.8 to -2.2 ± 4.4. Notably, the rehabilitation had no effect on 2 subjects with near normal initial DP values (**Figure 5A**). On average, DP decreased by up to 80% over the first 3 sessions. On the fourth session, 3 patients had normal DP values and were not subjected to the unidirectional rotation. For the last 2 sessions, only two of the patients showed initial abnormal DP values and were thus subjected to the unidirectional rotation. As such, the rehabilitation was effective in all cases and in most cases only required less than 3 sessions.

To investigate whether the effect of the rehabilitation was preserved between sessions, we compared the 70 min post-rehabilitation DP of each session with the initial DP of the next session (**Figure 5B**). As mentioned before, average initial DPs at

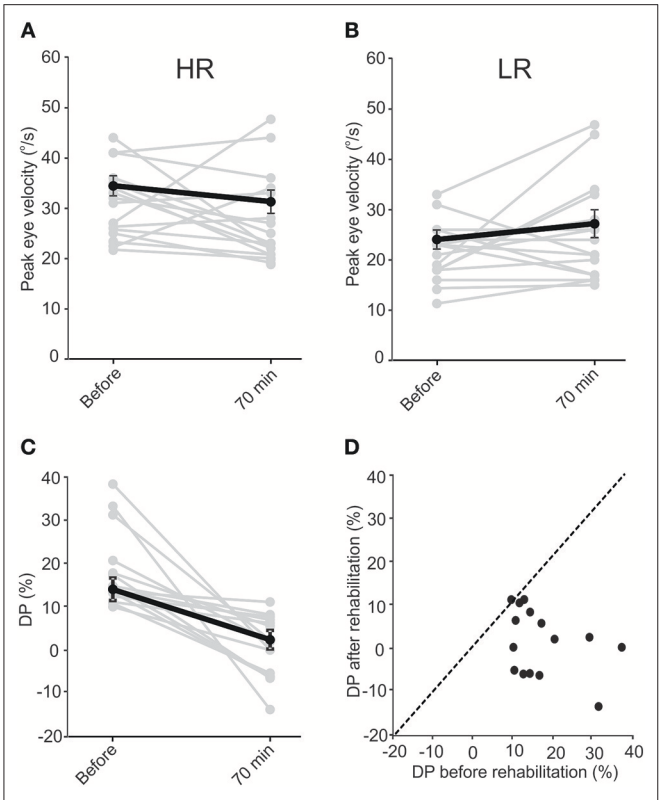

FIGURE 3 | Data pooled from all sessions of subjects in the long-term study. "Before" data is from the initial values collected before rehabilitation in each session. "After" data is collected 70 min after rehabilitation in each session. VOR responses for LA and HA rotations were different "before" rehabilitation (paired *t*-test, $p = 0.003$). Similar to the short-term study, in the majority of instances rehabilitation resulted in a decrease in VOR responses during HA rotations **(A)** and an increase in responses during LA rotations **(B)**, resulting in the responses to rotations in the two directions to be similar after rehabilitation (paired *t*-test, $p = 0.85$). While the change in response averages were not significant for HA (paired *t*-test, $p = 0.33$) and LA (paired *t*-test, $p = 0.11$) responses, the average DP **(C)** still decreased significantly (paired *t*-test, $p = 0.002$). Except in one session for one of the subjects, DPs either decreased or did not change after rehabilitation. This is shown by the points lying below the dashed identity line in **(D)**.

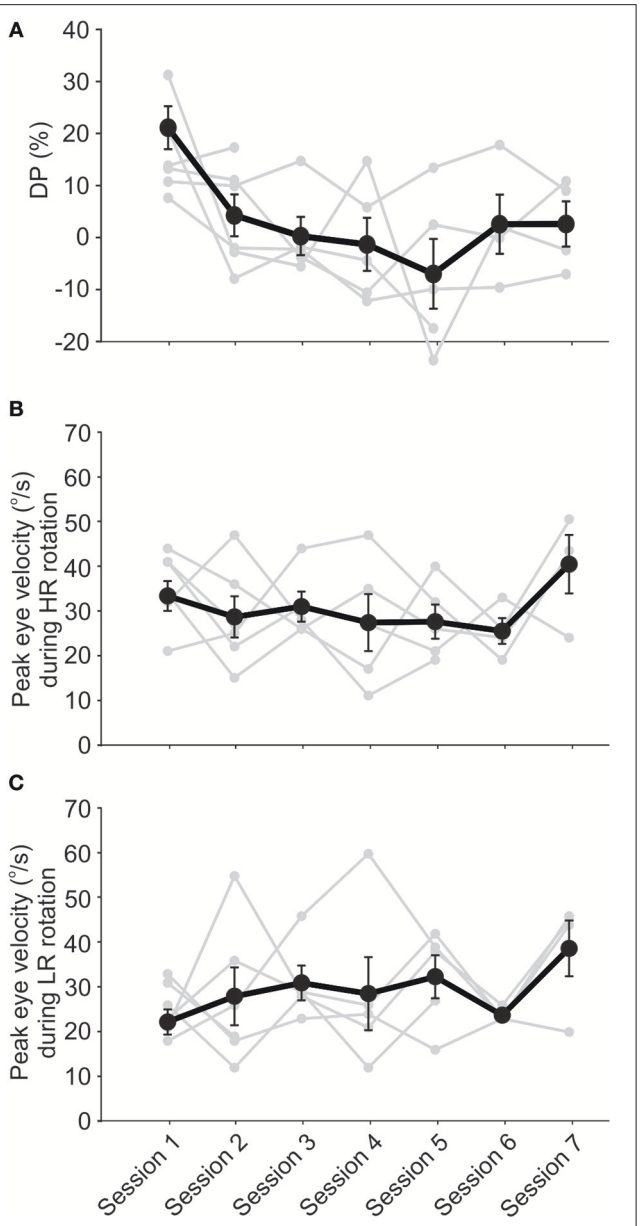

FIGURE 4 | Unidirectional rotational rehabilitation resulted in long-term improvement of VOR asymmetry. Data points are from subjects who participated in at least 2 session ($n = 6$) and the initial values measured before rehabilitation are shown for each session. DP decreased over time for the majority of these subjects **(A)**. The only significant change is between the DP for the first session compared to other sessions (ANOVA, $p < 0.01$), suggesting that the decrease in asymmetry occurs in the first couple of sessions for most subjects. This decrease was due to a decrease in VOR responses to HA rotations **(B)** as well as an increase in responses to LA rotations **(C)**. Changes in VOR responses (i.e., eye velocities or gains) were not significant, but were enough to result in a highly significant improvement in VOR symmetry, as quantified by DP. Note the increase in VOR responses for both sides in the final session, reaching close to normal values (~40°/s).

the beginning of each session (i.e., before rehabilitation in that session) showed a decrease over time (**Figure 4A**). Interestingly, these average initial values were similar to after rehabilitation DPs from the previous session (**Figure 5B**, repeated measure ANOVA, $p = 0.1$), suggesting that the effect of rehabilitation was retained and did not substantially diminish between sessions. The seemingly larger differences between DPs (and larger variabilities) after session 4 are probably due to the longer times between sessions (i.e., twice weekly for the first 4 sessions and weekly for sessions 5 and 6).

Effect of Unidirectional Rotational Rehabilitation on Subjective Symptoms

Six of the eight subjects that participated for more than 1 session in the long-term study reported on subjective changes in their symptoms over time. At the beginning of this study, two of the patients experienced only mild imbalance, while others had true vertigo or severe imbalance. However, these 2 patients showed other signs of vestibular dysfunction, such

as falling toward one side in the dark. In all subjects, the sense of imbalance was aggravated by rapid head movements. All subjects also experienced associated autonomic symptoms during vertigo. Interestingly, the 2 subjects with the least response to the unidirectional rotation (**Figure 5A**) were the ones with a history of mild imbalance. All 6 subjects reported decrease in the intensity and frequency of dizziness/imbalance symptoms and felt more confident participating in social and daily activities.

DISCUSSION

Unidirectional Rotational Rehabilitation Improves VOR Symmetry

The results of the present study show that training by a purely unilateral vestibular stimulation could decrease the asymmetry of the VOR response in patients with chronic vestibular dysfunction. We used a unidirectional rotational stimulation in the dark (i.e., without any visual stimulation) and showed that this could be an effective rehabilitation method for decreasing the DP of patients with chronic vestibular dysfunction. In most cases, the vestibular imbalance decreased by ∼10 min after the rehabilitation was applied and the effect lasted for weeks. Although chronically elevated DPs are harder to change (39), we found that all subjects showed an improvement in their DPs with this rehabilitation method.

Repeated unidirectional rotations have previously been shown to result in habituation of vestibular responses and a decrease in VOR gain and time constant in different animals as well as humans (27–29, 38, 40). Indeed, with unidirectional stimulations, the gain of the stimulated side decreased over time while the opposite side showed no change in response (38). In our study, we observed the opposite effect: rotations toward the LR side resulted in an increase in their responses, while those of HR side slightly decreased. We believe that the difference between our results and those of previous studies is due to two factors. First, we used a purely unidirectional rotation and took special care to have a very slow deceleration in order to avoid any reversal of stimulation at the end of rotation. This is in contrast to previous studies where step stimuli were stopped abruptly and in fact the stimulus was considered to be the deceleration part of the movement (28, 40). As such, in previous studies subjects received vestibular stimulation in both directions, corresponding to the acceleration and deceleration parts of the movement. Second, our subjects were patients with asymmetric responses and some level of compensation. Previous studies during compensation have shown changes in properties of vestibular nuclei neurons (3, 4), inputs to the vestibular nuclei (6–8, 41), and commissural connections between the two sides (5). Because of the asymmetry and the above changes at the cellular, synaptic, and network levels, it is conceivable that repeated stimuli could have different effects (i.e., inducing a homeostatic change in the activity of vestibular nuclei to reach a new balance between the two sides) compared to normal conditions (i.e., habituation and a decrease in response).

It has been shown that the naturally occurring compensation could be improved further by specific goal-directed training exercises. Such rehabilitation exercises typically use the multisensory nature of vestibular compensation to further improve balance and gaze stability in patients. Animal studies have shown compensatory changes in the vestibular nuclei (VN) neuron responses, changes in extravestibular inputs (such as neck proprioception and efferent copy of neck motor command) to the VN (6–8) as well as changes at the peripheral level (2). Consistent with these studies, patients with vestibular dysfunction use compensation strategies that include changes in neck reflexes (42, 43), preprogramming of compensatory eye movements (44–46), and generation of multiple catch-up saccades (47–49). Visual inputs play a major role in vestibular compensation so that when animals were kept in darkness for 4 days after unilateral lesion, they did not show improvement in spontaneous nystagmus, which was recovered once they were moved to a lighted area (50). Studies on animals with compensated asymmetric VOR responses after unilateral labyrinthectomy have shown that further general VOR adaptation could be attained to raise the gain of the VOR with repeated visual-vestibular interaction training. These studies used bidirectional rotations while viewing a patterned background (9) or unidirectional visual–vestibular training (i.e., providing retinal slip only during ipsilesional head rotations) (10) and showed that ipsilesional VOR gain could be selectively enhanced. The findings of these previous studies suggest that vestibular compensation does not reach its maximum capacity by spontaneous/natural recovery processes and the VOR gain could be further increased by visual–vestibular training after compensation.

The goal of rehabilitation exercises is to use visual and other extravestibular inputs as well as other balance cues to further compensate for the lack of vestibular inputs. Previous studies have shown a 70–80% improvement in patients using different rehabilitation protocols. One study found that 28% of patients showed complete resolution of symptoms within 1 year and 54% showed some degree of improvement (51). The unidirectional rotational stimulus that we used for rehabilitation was designed based on the theoretical and experimental observations showing that changes in the commissural pathway between the two vestibular nuclei (VN) contributes to vestibular compensation (5, 52–55). We expected that a purely vestibular stimulation would activate Hebbian plasticity mechanism in these pathways [i.e., cells that fire together wire together (56)]. During rotation, ipsilateral receptors are stimulated and contralateral ones are inhibited. At the VN level, the interaction between the two sides increases this imbalance. Type I excitatory neurons that are stimulated by ipsilateral inputs from the nerve, innervate contralateral type II inhibitory neurons, which project to and inhibit type I neurons on the same side. As such, unidirectional rotations toward the LR side will stimulate this weaker side and inhibit the stronger HR side, rebalancing the two sides. This suggests an increase in VOR gain for rotations in one direction and a decrease in VOR gain for rotations in the opposite direction. Indeed, recent studies have shown independent VOR gain adaptation to right and left rotations in normal humans (57–59). Initially, we were hoping to see a stronger effect

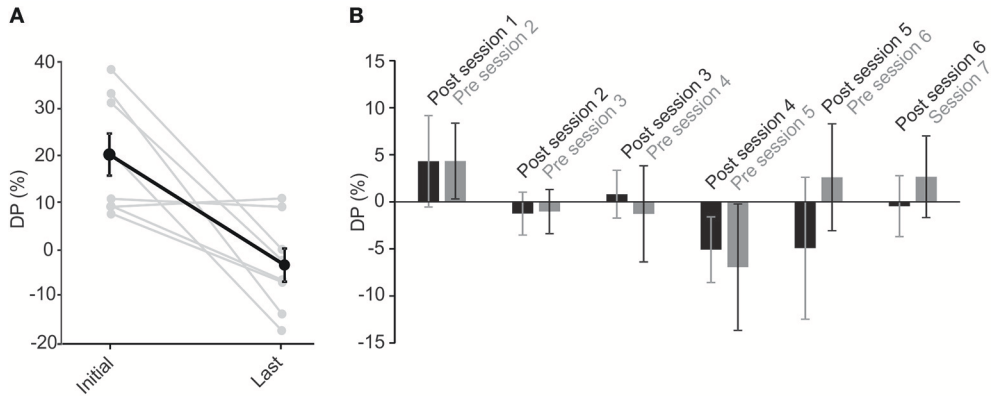

FIGURE 5 | Unidirectional rotational rehabilitation results in long-term effects. **(A)** Comparison of DP values between the initial DP calculated on the first session (i.e., before the first unidirectional rotational rehabilitation) and DP on the last session that a subject participated in the long-term study. Most of the subjects (6 out of 8) showed a decrease in DP after rehabilitation. Although DP in two subjects who had initial near normal DP values, did not change after rehabilitation, average DPs showed a significant decrease (paired *t*-test, $p = 0.008$). **(B)** The effect of rehabilitation was retained in between sessions. Bar graphs show initial values measured at the end of each session 70 min after rehabilitation (black, "post session") and those at the beginning of the next session before rehabilitation (gray, "pre session"). Differences between values were not significant for each group (repeated measures ANOVA, $p > 0.1$ for all), suggesting that the effect of rehabilitation lasted until the next session.

on the LR and an improvement in the VOR response (gain) after rehabilitation. However, the VOR response became more symmetric (i.e., lower DPs) due to a non-significant decrease in VOR response to HR rotation and a non-significant increase in LR responses. It is possible that the increase in LR response was diminished by a concomitant habituation to repeated rotations, as suggested by previous studies in normal subject [e.g., (38)].

Mean values of DP during the 6 sessions show reductions and even reversals, demonstrating the effect of the rehabilitation to reduce the vestibular imbalance. Most of the changes were observed in the first session with about 80% decrease in DP measured 70 min after the rehabilitation. This is similar to the results of Ushio et al. (10), where a significant change was observed immediately after their unidirectional visual–vestibular adaptation paradigm in animals after unilateral labyrinthectomy. We observed that in most cases even 2–3 such unidirectional rotations (albeit in the dark) would result in normal DPs. Note that this normalization of DP is partly mediated by an increase in the response of LR side, thus improving the overall vestibular function (**Figures 2A**, **3B**, **4B,C**). Furthermore, the effect of rehabilitation did not seem to be dependent on the initial DP value. From the 6 subjects, 4 were sensitive and showed a decrease of >100% (i.e., a change in the direction of DP) by the last session. Two other patients showed very little change (i.e., ∼15%) over the 6 sessions, yet had initial DP values close to those of 2 of the patients that were sensitive to the rehabilitation.

We observed a retention of the rehabilitation effect for days to weeks in most patients. This is in contrast to results of Ushio et al. (10), where the unidirectional visual–vestibular training effect was preserved only for faster movements (i.e., during the acceleration period of their velocity trapezoid test rotation) 3 days after the last session. This apparent discrepancy could be due to multiple factors. The most important difference is the adaptation pathways used in the two studies. This previous study used visual-vestibular adaptation that is mediated through the cerebellum and floccular target neurons in the VN as part of the "modifiable VOR pathway" (60–63). We used rotation in the dark, which should affect all VN neurons regardless of their type. Furthermore, the dynamics of our stimulus were very different from that used by Ushio et al. (10). In our study, unidirectional rotations reached a peak velocity of 320°/s, which is higher than the 150°/s used in the previous study. For our purposes, it was critical to have a slow deceleration (10°/s^2) in order to avoid stimulation in the opposite direction when stopping the rotation. This is very different from the 1,000°/s^2 acceleration/deceleration used by the previous study. It was suggested that the training provided by the previous study most likely affected the irregular/phasic pathway (10). In contrast, we believe that the present study most likely affected the tonic pathway, with stronger long-term effects when tested by slow sinusoidal rotations. Whether we also affected the phasic pathway (i.e., response to faster head movements) was not tested due to the limitation of ENG (rather than VNG) testing and safety issues of rotation of human subjects by the chair at high frequencies and velocities. Using the head impulse test with VNGs could address this point more clearly in future studies. Finally, there could be species differences between humans (present study) and monkeys used in the previous study.

While both the visual–vestibular training (10) and the unidirectional rotation introduced in our study show similar efficiency in increasing the vestibular compensation, because of different pathways involved, the two methods could have different clinical applications. The visual–vestibular training functions through the adaptation pathway and as such, is not appropriate for patients with damage to areas such as the cerebellum. In contrast, our unidirectional rotation in the dark most likely affects neurons in the vestibular nuclei and the commissural pathway (rather than the cerebellum). Consistent

with this notion, previous studies on habituation of responses to repeated rotations in normal subjects have concluded that changes occur mainly in the velocity storage, which is part of the vestibular nuclei (27). The unidirectional rotations described in the present study also have the benefit of being simpler to perform and require simpler equipment, with no visual stimulation.

Effect of Unidirectional Rotation on Subjective Symptoms

To evaluate the subjective improvement of symptoms, we used a simple questionnaire. The patients were required to report the frequency and intensity of symptoms that they mentioned on the first session, as well as any new symptoms developed during the study. Surprisingly, although previous studies have shown that DP is a good measure of the degree of compensation in the vestibular system (34, 64, 65), we found a discrepancy between improvement in DP values and subjective improvement following vestibular rehabilitation. Only 6 out of 16 patients reported subjective improvement in symptoms during the rehabilitation program. However, it is important to note that the rehabilitation and rotation tests did not result in aggravation of any of the symptoms.

Previous studies have shown that training and adaptation in one direction of movement does not necessarily transfer to other types of movements (66–68). As a result, patients with major problems in the horizontal rotation response would have benefited the most from the present rehabilitation. In the present study, we only measured the function of the horizontal VOR responses. Future studies for measurement of responses to roll, pitch, or linear movements are required to directly study whether the effect of this rehabilitation in the horizontal plane could transfer to any of these other directions of movement.

It should be noted that in the present study, rather than the available standardized questionnaires, we used a simple form for following up the symptoms in our subjects. Standard questionnaires are detailed and long and while they are excellent for initial careful validation of symptoms in vestibular patients, they are cumbersome for using multiple times over a short period of time. We used a short form between visits to simply verify any change in the progression of patients' imbalance as they conceived it. However, it should be noted that since our questionnaire was not validated by a large number of patients, response variability could be higher and potentially be a source of discrepancy between subjective and objective results. Future studies that include quantification methods (such as Likert scale) on standardized tests are required to further evaluate the subjective effect of this rehabilitation and a comparison to other methods such as the vestibular-visual training.

In general, one of the shortcomings of subjective measures is that their value is reduced due to their intrinsic variability. The observed discrepancy between the subjective and objective improvement could be related to psychological factors (e.g., fear of movement) and personal characteristics (e.g., age, sex, income, educational level, comorbidities, and motivation) (69, 70). It has been shown that the fear of recurrences is at the root of the psychosocial disabilities associated with vertigo and there is a strong relationship between the severity of such disability and the accompanying somatic anxiety (71–73). Since 2014, new criteria have been set to diagnose psychological consequences or causes of chronic dizziness as "persistent postural-perceptual dizziness" (PPPD), which includes anxiety, panic attacks, and depression (74). It has been shown that PPPD caused by vestibular problems can be decreased by vestibular rehabilitation. On the other hand, it has also been demonstrated that there is no correlation between the frequency of symptoms and the degree of disability in patients, as some patients who experience permanent instability may be significantly less affected in their daily lives than patients who suffer from dizziness less often (75). Future studies with larger number of patients over a longer period of time and by taking into account recent criteria for identification of different etiologies and psychological factors as identified by the International Classification of Vestibular Disorders (76) in individual subjects are required to more accurately investigate any direct relationship between subjective and objective measures of improvement after rehabilitation.

AUTHOR CONTRIBUTIONS

NR conceptualized the original idea and hypothesis behind the unidirectional rotational rehabilitation. NR and SGS designed the study, analyzed the data, and wrote the manuscript. NGS designed the study, performed the experiments, analyzed the data, and wrote the manuscript. BS designed the study and performed the experiments.

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Visual Fixation and Continuous Head Rotations Have Minimal Effect on Set-Point Adaptation to Magnetic Vestibular Stimulation

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Background: Strong static magnetic fields such as those in an MRI machine can induce sensations of self-motion and nystagmus. The proposed mechanism is a Lorentz force resulting from the interaction between strong static magnetic fields and ionic currents in the inner ear endolymph that causes displacement of the semicircular canal cupulae. Nystagmus persists throughout an individual's exposure to the magnetic field, though its slow-phase velocity partially declines due to adaptation. After leaving the magnetic field an after effect occurs in which the nystagmus and sensations of rotation reverse direction, reflecting the adaptation that occurred while inside the MRI. However, the effects of visual fixation and of head shaking on this early type of vestibular adaptation are unknown.

Methods: Three-dimensional infrared video-oculography was performed in six individuals just before, during (5, 20, or 60 min) and after (4, 15, or 20 min) lying supine inside a 7T MRI scanner. Trials began by entering the magnetic field in darkness followed 60 s later, either by light with visual fixation and head still, or by continuous yaw head rotations (2 Hz) in either darkness or light with visual fixation. Subjects were always placed in darkness 10 or 30 s before exiting the bore. In control conditions subjects remained in the dark with the head still for the entire duration.

Results: In darkness with head still all subjects developed horizontal nystagmus inside the magnetic field, with slow-phase velocity partially decreasing over time. An after effect followed on exiting the magnet, with nystagmus in the opposite direction. Nystagmus was suppressed during visual fixation; however, after resuming darkness just before exiting the magnet, nystagmus returned with velocity close to the control condition and with a comparable after effect. Similar after effects occurred with continuous yaw head rotations while in the scanner whether in darkness or light.

Conclusions: Visual fixation and sustained head shaking either in the dark or with fixation inside a strong static magnetic field have minimal impact on the short-term

mechanisms that attempt to null unwanted spontaneous nystagmus when the head is still, so called VOR set-point adaptation. This contrasts with the critical influence of vision and slippage of images on the retina on the dynamic (gain and direction) components of VOR adaptation.

Keywords: magnetic vestibular stimulation, MRI, vision, fixation, labyrinth

INTRODUCTION

People working around strong magnetic resonance imaging (MRI) machines have reported transient sensations of rotation (1–3). A key to understanding the physiology underlying this effect is observed when visual fixation is removed. A horizontal nystagmus was first reported in a 1.5T magnetic field when fixation was removed (4) and a persistent, higher-intensity horizontal (and torsional) nystagmus is seen in humans when in darkness in magnetic fields of higher strengths [3-7T (5, 6)]. Although the sensation of rotation fades away within several minutes, some nystagmus persists inside the MRI up to the longest time tested thus far of 90 min (7, 8). This nystagmus induced by the magnetic field of the MRI can be suppressed with visual fixation upon a target. A key feature of a nystagmus that originates from labyrinthine imbalance is suppression of the nystagmus during visual fixation.

The proposed mechanism for the MRI-induced nystagmus and vertigo is a Lorentz force, generated by interactions between the flow of ions through inner ear endolymph into utricle hair cells and the strong static magnetic field of the MRI machine (6). This Lorentz force is proportional to the strength of the magnetic field, the net current flowing into hair cells and the height over which the current travels. As long as the subject remains in the MRI, the Lorentz force displaces the cupula of the lateral and superior semicircular canals (6), causing vertigo and nystagmus and creating an effect similar to constant acceleration of the head (8).

Many agonist/antagonist systems exist within the body that allow quick responses to environmental changes; and these systems operate around a balanced level of tonic activity—the set-point—providing, a stable platform from which they generate a response. Set-point adaptation is the process by which the brain modifies a system's tonic activity in response to a sustained change in the environment. As an agonist/antagonist system the vestibulo-ocular reflex (VOR) operates around a stable set-point. By inducing a constant displacement of the semicircular canal cupulae and observing the dynamics of the VOR, we can study set-point adaptation (9). Over time in the MRI the nystagmus slowly but only partially decays, implying incomplete adaptation. Upon exiting the magnetic field an after effect appears in which the nystagmus and sense of rotation reverse direction. The presence of the after effect reflects adaptation that has occurred in the MRI. We previously showed that the time course of adaptation to magnetic vestibular stimulation (MVS) can be described by a set of adaptation operators of increasing time constants working in parallel (8). It is unknown, however, what error signals are responsible for driving these different adaptation processes.

In the case of adaptation of the dynamic components of VOR [e.g., (10)] retinal slip (motion of the images upon the retina) is an important error signal that informs when the eye has moved an incorrect amount to compensate for the head movement. In the case of set-point adaptation during MVS with visual fixation, retinal slip could also indicate a wrong set-point when there is a nystagmus. However, because the nystagmus is greatly suppressed retinal slip might not be an explicit error signal for set-point adaptation. Instead the mechanisms that suppress the nystagmus, e.g., the motor commands that enable steady fixation, may interact with the adaptation processes.

Multiple systems can use visual information and contribute to the suppression or cancellation of an undesired nystagmus due to an imbalanced vestibular system. The smooth pursuit system generates eye movements that maintain the image of a moving object of interest on the center of the fovea. The optokinetic system monitors full-field visual motion to generate eye movements that work in concert with the VOR to maintain a stable retinal image during head movements. Both systems could cooperate to suppress the nystagmus although there might also be a specific fixation system that keeps the eyes still (11).

Here we sought to determine whether visual fixation influences the early phases of VOR set-point adaptation in order to infer where along the neural pathway the components of set-point adaptation are occurring. Because of spontaneous nystagmus, the obvious error signals to drive set-point adaptation are retinal slip, and the brain's attempt to eliminate it. Hence, we first asked if visual fixation would hasten the rate of adaptation.

METHODS

Eye movements were tracked using video oculography on six individuals before, during and after exposure to a 7T MRI scanner (Philips Research, Hamburg, Germany). There were four men, two women; ages 33 to 71 years. In all experiments subjects were supine on the MRI table and entered the MRI bore in the head-first position. The magnetic field vector B of the MRI in this study was directed from the subject's head toward the feet when entering the MRI head-first. Eye movements were recorded with infrared illumination using the RealEyes xDVR system (Micromedical Technologies Inc.) and custom software to measure binocular eye position in three dimensions (12). As part of this system, video is recorded at 100 Hz using separate cameras for each eye (Firefly MV, Point Grey Research Inc., Richmond, BC, Canada). During dark conditions, vision was

occluded with a double layer of black felt to ensure complete darkness. During visual fixation conditions, after entering the magnet in darkness subjects removed the black felt, the MRI bore lights were turned on, and the subject was instructed to fix their gaze at the intersection of a vertical and horizontal black line (21.6 × 27.9 cm) on the inside surface of the magnet bore (distance of approximately 30 cm). To assess whether there were differences with the type of visual stimulus used, additional experiments were performed with a rich visual stimulus of yellow dots (each 2 cm diameter) randomly positioned on a black background that filled most of the visual field (55.9 × 71.1 cm). Following the fixation portion of the trial, the lights were turned off, and subjects replaced the black felt over their eyes.

Trials began with the subject supine on the MRI table with their head near the bore in a neutral position, and eye movements were recorded for 2 min outside the MRI. Subjects entered the MRI at a fixed-speed of 10.8 cm/s over the 2 m travelled to the center of the bore. Eye movements were recorded for 5, 20, or 60 min and then subjects exited the MRI and recording continued for an additional 4, 15, or 20 min. For each subject the trial was then repeated entering the magnetic field in darkness, followed by light with visual fixation, beginning 60 s after entering the magnetic field. Subjects were placed in darkness again 10 s before exiting the bore (30 s in the 20- and 60-min trials). All subjects performed visual fixation with intersecting lines. Three subjects also underwent trials with the full-field stimulus. To assess whether fixation had an impact on later components of adaptation, three subjects underwent five trials lasting 20 min in the MRI and one subject underwent a trial lasting 60 min. **Figure 1** shows an example of eye movement recording during a 20-min visual fixation trial.

Additionally, a subset of subjects ($n = 2$) performed the above series of experiments, except that instead of the second series of trials using a visual fixation stimulus, yaw head rotations (∼2 Hz) in the dark while inside the MRI were performed, starting 60 s after entering the magnetic field and stopping 10 s prior to exiting the MRI bore. Head rotations were kept at a constant rate using the periodic noise of the MRI machine (∼2 Hz) as a metronome. These trials of yaw head rotations were repeated in the light with subjects fixing on a full-field stimulus.

The velocity of the slow-phase component of nystagmus (SPV) was calculated in 1 s windows. First, we identified outliers in the eye movement recordings due to blinks and other eye tracking artifacts as portions of the data with large and fast changes in estimated pupil size (more than 10% around a 5 s average), too high velocities (1,000 deg/s), or accelerations (50,000 deg/s^2). Then, we detected and removed quick-phases to calculate the SPV. In a first pass we detected quick-phases as portions of the eye velocity with speeds above 100 deg/s. Then, we removed those portions of data with an additional 30 ms before and calculated a smooth version of the velocity using a median filter (4 s window). Next, we subtracted this smooth version of the velocity from the original eye velocity and ran a second pass of quick-phase detection, this time with a more sensitive 10 deg/s threshold. After removing the newly detected quick-phases (and 30 ms before and after) from the raw velocity we applied another median filter (1 s window) on the remaining data to obtain the slow-phase velocity. Finally, we averaged the slow-phase velocity of the two eyes and applied an additional median filter to reduce the effect of potential noise present in only one eye. Eye movements when the head was rotating were removed and not analyzed.

The amplitude of the after effects were compared for all subjects between trials with visual fixation and those in darkness by calculating the area under the curve of the after effect within a 3 min window after exiting the magnet (7 min window for 20 min trials). Statistics were performed using a paired t-test and a p-value of <0.05 was considered significant. For graphs of averages across subjects, SPV traces were first normalized by dividing the SPV by the peak SPV during the corresponding dark condition for that subject. Experiments were approved by the Johns Hopkins institutional review board and written informed consent was obtained from all participants.

RESULTS

As prior studies, all subjects developed a horizontal, and torsional nystagmus when entering the magnetic field in the head-first position in darkness. The nystagmus slowly, but incompletely faded in the MRI, and reversed direction upon exiting the magnetic field (**Figure 2**, blue traces). With visual fixation in the MRI, all subjects could suppress the spontaneous nystagmus that had been observed in darkness (**Figure 2**, red traces) down to a slow-phase velocity of -0.6 ± 0.3 deg/s. When subjects removed fixation while still within the magnetic field, a horizontal and torsional nystagmus resumed, and upon exiting the magnetic field there was an after effect. The amplitude of the after effect, reflecting adaptation inside the MRI was slightly increased with fixation in the short duration trials ($N = 5$, $p = 0.007$ **Figures 3A,B**), but not in the longer duration trials ($N = 3$, $p = 0.5$, **Figures 3D,E**) or the trials using a full-field visual stimulus ($N = 4$, $p = 0.06$, **Figures 3G,H**). The time constant of the decay of the after effect was not different between trials with and without visual fixation in the short duration trials ($N = 5, p = 0.8$, **Figure 3C**), the long duration trials ($N = 3, p = 0.07$, **Figure 3F**), nor in the trials using a full-field visual stimulus ($N = 4, p = 0.3$, **Figure 3I**).

For subjects that performed the sustained head rotations inside the MRI, the velocity of nystagmus at the time of stopping head movements and the after effect after exiting the magnetic field were the same as from trials in which the subjects lay in the field in darkness and also the same as trials in which subjects performed sustained head rotations with the lights on and a full-field visual stimulus (**Figure 4**).

There are multiple ways in which visual information can affect adaptation, depending on when the suppression of the nystagmus occurs relative to adaptation and on whether visual information itself can interact with the adaptation processes. To test which of the scenarios better corresponded with our data, we simulated the system under different configurations using a control-systems approach (see **Supplementary Table 1** and **Supplementary Figure 1**). We started with a model of MVS set-point adaptation (8) and added a mechanism for

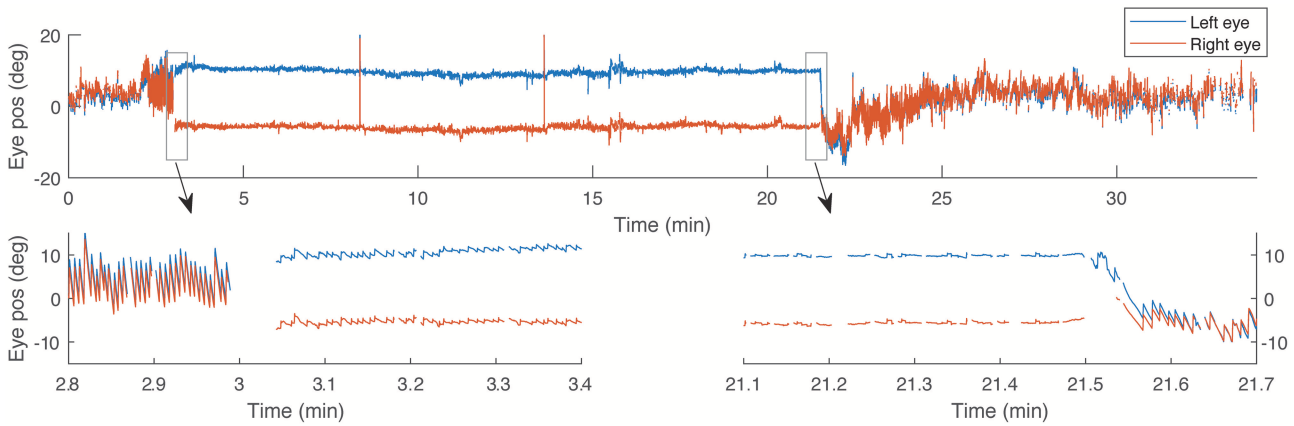

FIGURE 1 | An example recording of horizontal eye position during a 20-min trial with visual fixation. Bottom panels show details of 30-s time periods around the times when the light turns on and off, respectively. Gaps in the data correspond with eye blinks.

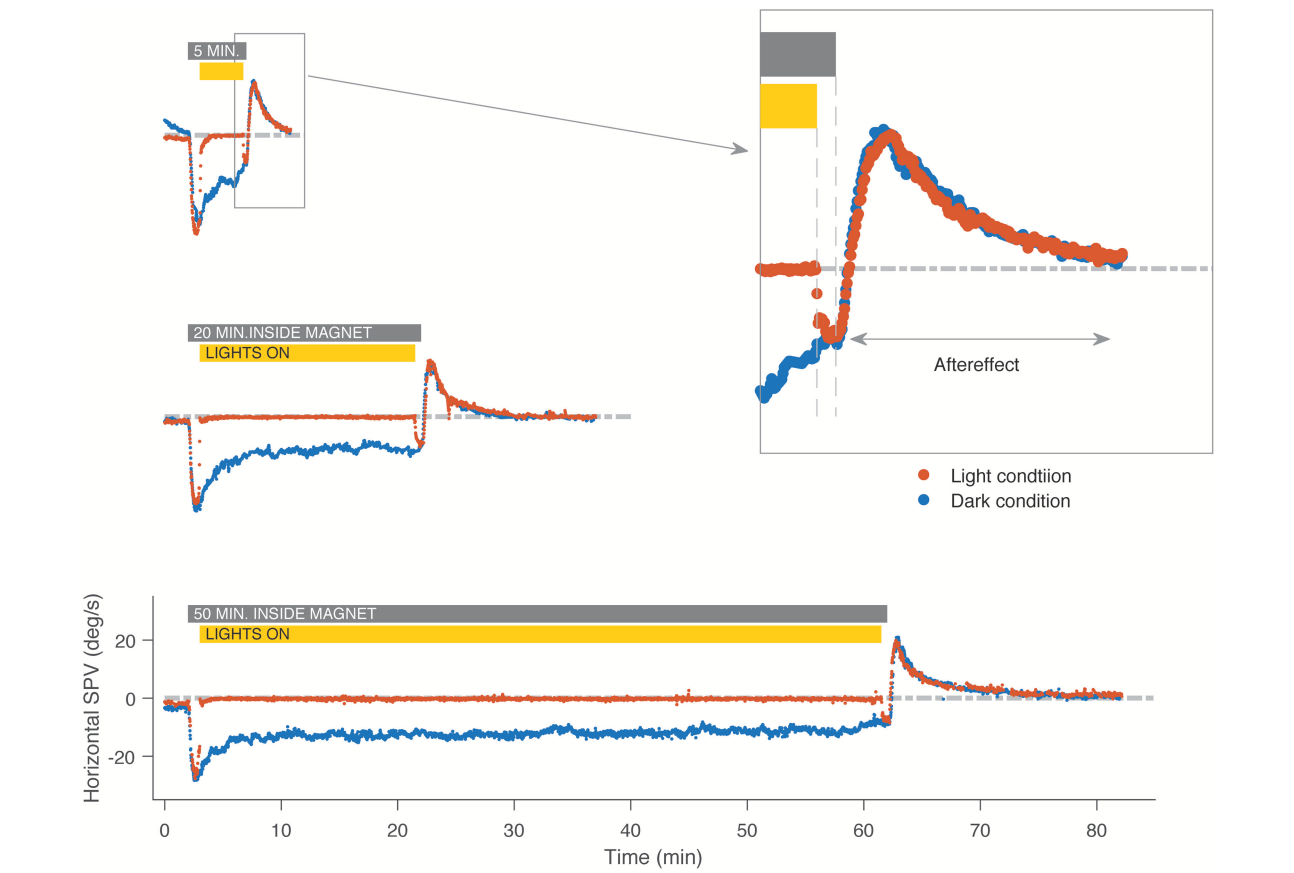

FIGURE 2 | An example subject's horizontal slow-phase nystagmus eye velocity in the MRI. The blue traces represent trials in darkness without visual fixation and the red represent trials where the subject enters the MRI in darkness, lights are turned on for visual fixation, and then turned off before exiting from the MRI. In darkness, a pattern of first fast then slow adaptation occurs, followed by an after effect in the opposite direction. Aside from the period of visual fixation, the slow-phase velocity is similar, regardless of whether lights were on or off, or of the duration in the MRI. Gray bar indicates the time the subject was inside the magnet for both trials in darkness and with visual fixation, and yellow bar indicates duration of exposure to visual fixation in the light for trials with fixation only. SPV, slow-phase eye velocity.

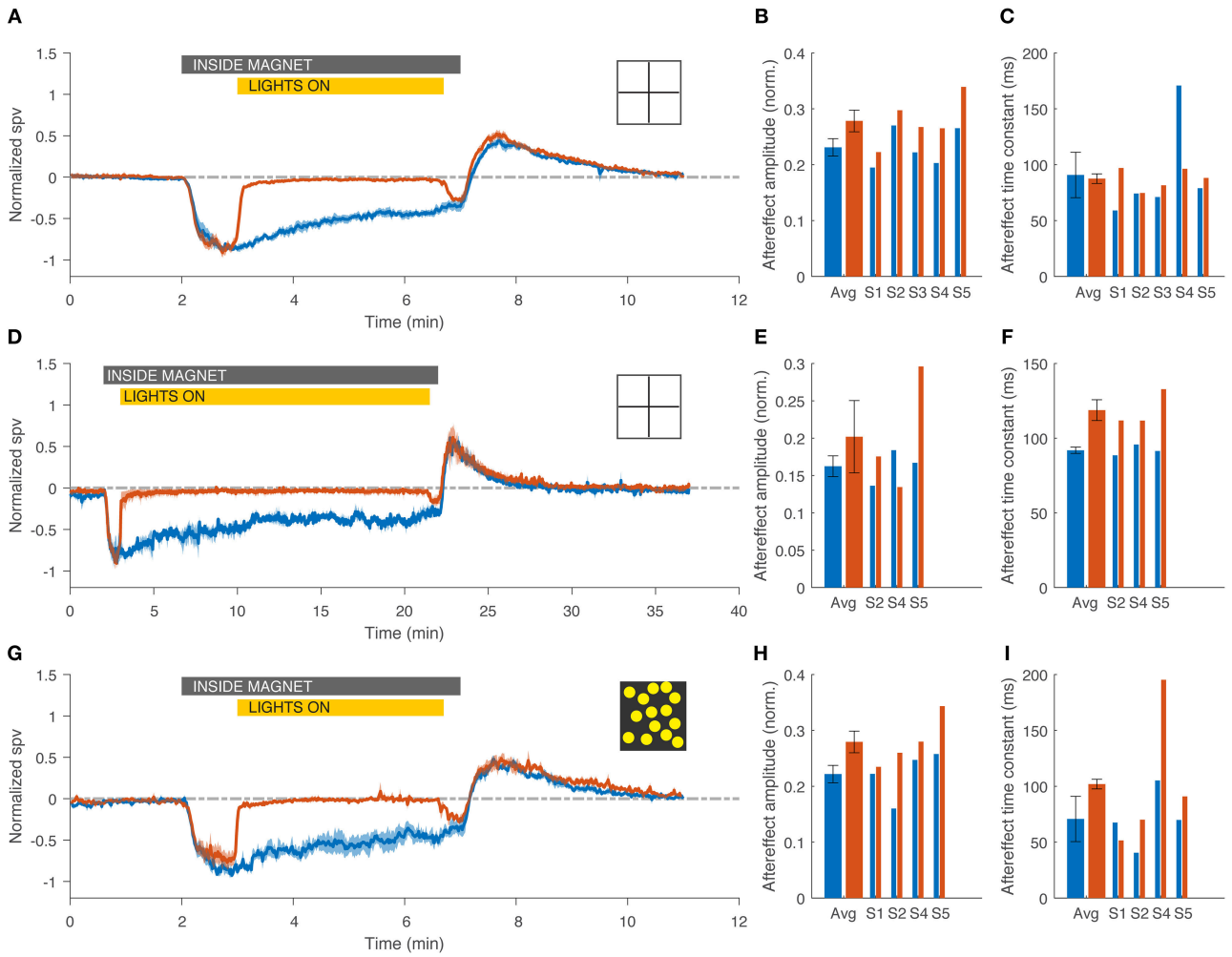

FIGURE 3 | Visual fixation had little impact on the adaptation to the magnetic vestibular stimulus, regardless of the duration of fixation (top and middle rows, 5 and 20 min) or the visual fixation stimulus (top and bottom rows, 5 min, simple cross and rich full field stimulus). **(A,D,G)** Average normalized slow-phase velocity (SPV) across subjects for fixation (red) and darkness (blue) conditions. Note the different time scale on the abscissa for the graph in **D**. **(B,E,H)** Amplitude of the after effect, calculated for each subject as the area under the curve during the after-effect period (3 min after exiting the magnet for the 5 min trials and 7 min for the 20 min trials). **(C,F,I)** Time constant of the decay of the after effect, calculated with an exponential fit starting at the maximum SPV during the after effect. Gray bar indicates the time the subject was inside the magnet for both trials in darkness and with visual fixation, and yellow bar indicates duration of exposure to visual fixation in the light for trials with fixation only. Bar graphs show average and individual results. Errors bars and shaded area represent standard error of the mean (SEM).

visual suppression of nystagmus based on a simple smooth pursuit system that cancels the retinal slip of the fixation target (Figure 6) from Robinson et al. (13). Then, we compared the simulated slow-phase velocity for conditions equivalent to our MVS recordings under different model configurations. First (**Figures 5A,B**), adaptation occurs at an earlier stage than cancellation of nystagmus by the VOR. Second (**Figures 5C,D**), adaptation occurs after the cancellation of nystagmus by the VOR. Third (**Figures 5E,F**), adaptation occurs earlier than the cancellation of the nystagmus by the VOR but it is also enhanced when visual information is available. These simulations suggest our data are consistent with visual fixation suppressing the nystagmus at a later stage than adaptation and with little or no interaction between visual suppression and the adaptation operators.

DISCUSSION

We found that adaptation to a magnetic field-induced, static vestibular imbalance and the adaptation after effect when the subject came out of the magnetic field, were nearly superimposable regardless of whether the eyes were fixing on a target or the subject was in darkness while in the MRI machine. This occurred regardless of whether a relatively simple target or a rich visual stimulus occupying the entire visual field was used. Likewise, head rotations while in the MRI machine did not influence the adaptive process. A magnetic vestibular stimulus, generated by the interactions of a strong static magnetic field and the natural ionic currents of the inner ear, is thought to induce a constant displacement of the semicircular canal cupulae (5, 6, 14). This stimulus generates eye movement responses

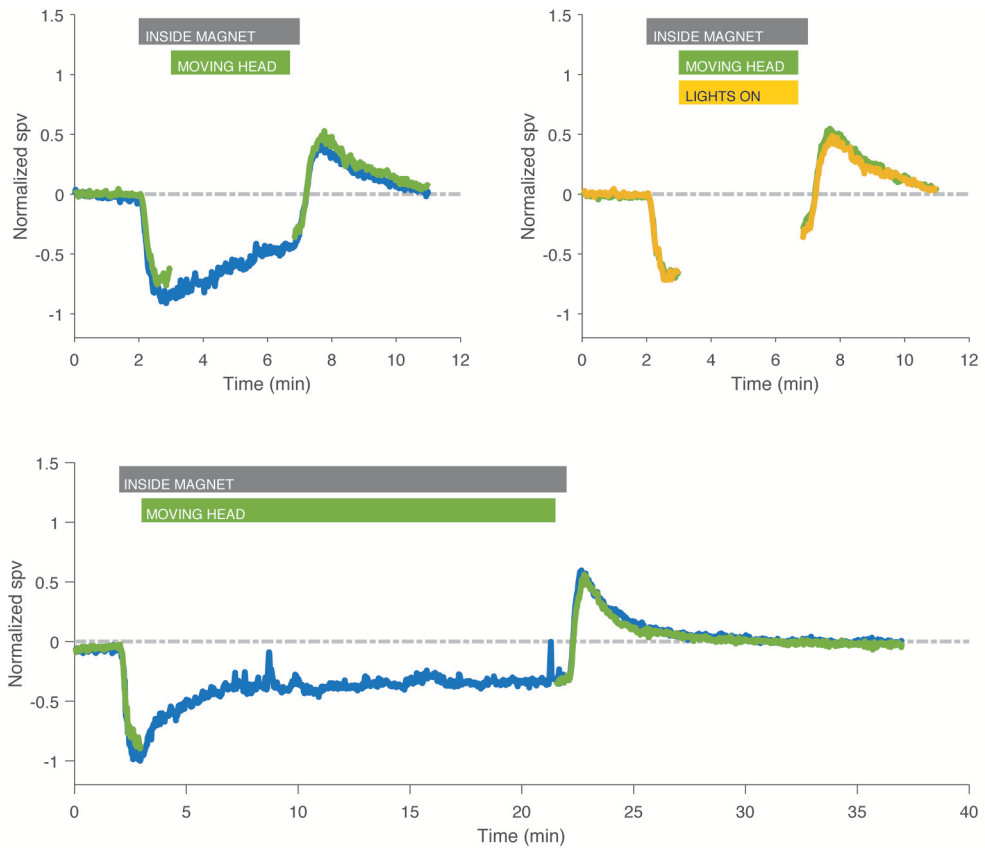

FIGURE 4 | Recordings with head rotations at ~2 Hz in the MRI while in darkness (green) or with fixation (yellow) compared to control experiment in darkness without head movement (blue) in two different subjects. Eye movements during the head shaking have been removed for clarity. Head rotations, either in darkness or with fixation, had no effect on the after effect compared to lying still in darkness, nor was there any effect that might have been superposed from a head-shaking induced nystagmus. Gray bar indicates the time the subject was inside the magnet for both trials in darkness and with visual fixation, green bar indicates the time the subject was moving the head, and yellow bar indicates duration of exposure to visual fixation in the light for trials with fixation only.

similar to those expected for a constant acceleration stimulus (8). A nystagmus of peripheral origin is suppressed by visual fixation and becomes apparent when visual fixation is eliminated. The finding here of consistent suppression of the nystagmus with visual fixation supports a peripheral origin for magnetic vestibular stimulation. Perhaps surprisingly, the presence of vision, while suppressing the nystagmus response, had little impact on the rate or amplitude of adaptation, or on the after effect, suggesting that the early process that monitors asymmetric vestibular input is occurring largely independent of vision. Jareonsettasin et al. found that the two early components of adaptation to a static vestibular imbalance have time constants of 1 to 2 min and 10 to 20 min while the late component has a time constant of more than 1 h (8). Our combined results for 5, 20, and 60 min suggest that the presence of vision does not impact either of the first two components of adaptation.

MVS as a Technique to Explore Set-Point Adaptation

In dynamic vestibular adaptation of the gain of the VOR, motion of an image on the retina is thought to be the error signal used by the cerebellum to recalibrate the VOR to ensure a clear image during head movements. After a lesion to the peripheral vestibular system, this restoration of the gain of the VOR toward normal tends to gradually occur over time (15). Similarly, for static, set-point adaptation of the VOR, there must exist a mechanism that monitors the spontaneous neural discharge occurring at the vestibular nuclei in order to rebalance activity between the two sides. For example, in the case of a patient who undergoes a labyrinthectomy or vestibular neurectomy, a spontaneous nystagmus will develop that will adapt slowly over days to weeks (16, 17). Normal subjects show adaptation that occurs within minutes during a sustained, constant-velocity or constant acceleration rotation of the head (18, 19). The nystagmus generated by magnetic vestibular stimulation also adapts slowly but incompletely in the longest tested trial of 90 min (8). Presumably the nystagmus would eventually disappear over a longer time period. The after effect observed after trials of magnetic vestibular stimulation, is proportional to the duration of adaptation that has occurred when in the MRI, and is absent for short duration exposures (6). Magnetic vestibular stimulation therefore is a useful, and in many

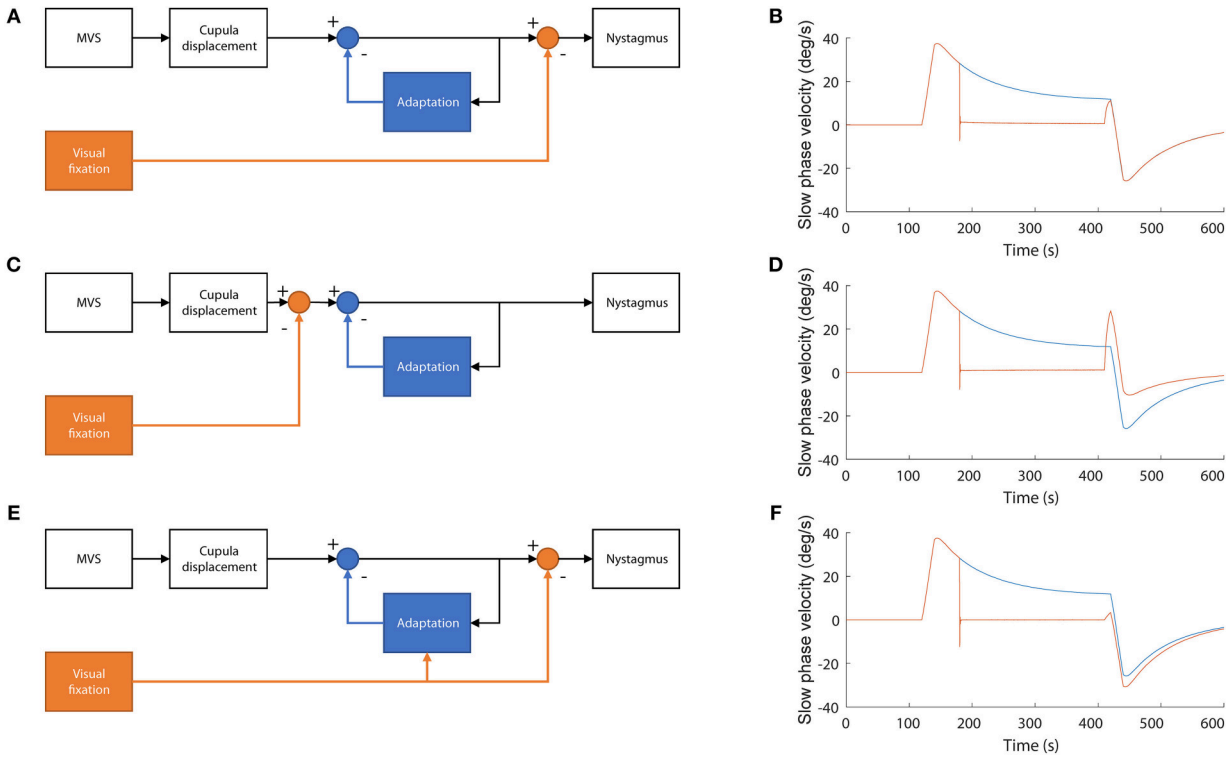

FIGURE 5 | Simulations of alternative models of the interaction between adaptation and the cancellation of nystagmus by visual fixation. **(A,B)** Visual information is used to cancel nystagmus at a stage of processing later than adaptation. In this model adaptation is not affected by the presence of visual fixation while in the MRI. This simulation accords best with our data **(C,D)** Visual information is used to cancel the nystagmus at a stage before adaptation occurs. In this case, no adaptation occurs during fixation and thus the after effect is smaller, only due to the initial first minute of adaptation in darkness, **(E,F)** Visual information is used to cancel nystagmus after adaptation occurs but also to enhance adaptation. In this case, adaptation is stronger, and the after effect is larger.

ways ideal model to explore the mechanisms of the relatively early phases of adaptation to a static vestibular in both normal human subjects and patients with vestibular lesions.

The Role of Vision in VOR Set-Point Adaptation

By assessing the influence of vision on set-point adaptation to a vestibular imbalance, we can infer where along the adaptation pathway vision might have an effect. Despite vision and motion of images on the retina being critical signals for adaptation of the dynamic components of the VOR, our data show they have little if any have little if any effect upon the early components of VOR set-point adaptation. After acute unilateral labyrinthectomy in the monkey, an absence of vision does not prevent the eventual disappearance of the spontaneous nystagmus (20). Furthermore, occipital lobectomy in monkeys affects the dynamic component of vestibular adaptation, but not the static component (21), supporting not only that vision is unnecessary for adapting to a static vestibular imbalance, but also that the mechanism of set-point adaptation may be occurring earlier, in the brainstem or cerebellum. In the cat, however, Courjon et al. suggested that spontaneous nystagmus after a hemi-labyrinthectomy may fade more quickly if the cat is exposed to light; however, much of the nystagmus subsided even when the cats were kept in darkness (22).

The Cerebellum in Set-Point Adaptation

The cerebellum may be involved in the process of static vestibular adaptation (23) and examples such as control of posture, pointing, and alignment of the eyes have suggested that the cerebellum facilitates set-point adaptation (24–26). Some insight can be gained from studies of what is called Bechterew's phenomenon, a spontaneous nystagmus that develops when a patient or animal loses labyrinthine function, first on one side, and then, after an interval, on the other side (27, 28). Without the presence of peripheral vestibular input, individuals develop a spontaneous nystagmus after injury to the second side that reflects the adaptation that had occurred between the injuries. The Bechterew's phenomenon can be found in decerebrate animals and in animals in which the cerebellum was removed, and is thought to reflect adaptation at the level of the vestibular nuclei (29).

The Importance of the Vestibular Nucleus in Set-Point Adaptation

Additional animal studies also have suggested that set-point adaptation is occurring in the vestibular nucleus. After a vestibular lesion, numerous processes occur at the vestibular nucleus ranging from changes in gene expression, levels of neurotransmitters, inflammatory responses, and synaptic activity, among others (30). A loss in excitatory input from the

lesioned vestibular afferents leads to a decrease in discharge at the level of the ipsilateral vestibular nucleus (31). A candidate location for the mechanism that rebalances activity is therefore at the level of the commissural system interconnecting the vestibular nuclei (20, 32). The commissural system contributes further inhibition to the ipsilateral vestibular nucleus, and as the resting discharge at the vestibular nucleus increases, behavioral compensation occurs (33). McCabe et al. performed a systematic series of lesion studies to determine the site responsible for rebalancing afferent activity of the medial vestibular nuclei, ultimately concluding that cerebellum, cerebrum, spinal cord, contralateral vestibular nuclei, and ipsilateral superior and lateral vestibular nuclei were unlikely to be the source, suggesting that the adaptation is happening early in the pathway, perhaps in the ipsilateral vestibular nucleus (34). Their findings support earlier work by Spiegel and Demetriades that the ipsilateral vestibular nucleus is critical for this rebalancing process (29). Duensing and Schaefer identified neurons in the vestibular nucleus that behaved differently from peripheral vestibular afferents, responding in the same way to head rotations to either side (35). Whether such neurons could be associated with set-point adaptation is unknown, but the characteristics of their responses are what would be needed to compare activity between the vestibular nuclei on both sides. Vestibular efferent neurons in frogs also respond in a similar manner, being excited in response to angular rotation to either side (36). Although the role of the vestibular efferents in monkeys and humans is unclear, there is some evidence in mice that they participate in compensation (37) and may help resolve spontaneous nystagmus in mice (38) and cats (39). Finally, there is likely some adaptation in the vestibular periphery which may also contribute to rebalancing (40, 41).

Horizontal Head Rotations Have Minimal Impact on Set-Point Adaptation

In a few of our experiments subjects continuously rotated their head in the yaw plane at ∼2 Hz both while in darkness and in light with visual fixation. These head rotations did not affect the adaptive response, supporting the idea that the mechanism underlying set-point adaptation can extract and compensate for a persistent static bias in the face of changing dynamic vestibular signals. We also wondered if our normal subjects would show an effect on adaptation of a post head-shaking induced nystagmus much as shown by patients with a pathologically-induced asymmetry in vestibular tone. For head-shaking to cause a nystagmus the velocity-storage system must also be functioning (16). Thus, the lack of an effect of head shaking on adaptation could be due to a change in the velocity-storage mechanism during adaptation. Another possibility is that our subjects did not develop sufficient additional asymmetries in vestibular tone for the post head-shaking effect to be seen in our data.

Limitations and Caveats

The results of this study only apply to the early components of set-point adaptation in healthy adults with intact labyrinths. There may be different neural substrates for the different components of set-point adaptation, some of which might be more influenced by visual fixation. The stimulus in magnetic vestibular stimulation is bilateral, affecting both labyrinths at the same time. The response of the brain to a constant stimulus when there is only one labyrinth, for example, after a labyrinthectomy, may differ compared to the responses seen during MVS. Finally, patients with a chronic, pathological imbalance in vestibular input may also behave differently from the healthy adults used here. Nevertheless, our results overall were remarkably consistent and suggest that the immediate adaptation to a vestibular imbalance occurs at an early stage, and likely at the level of the vestibular nuclei.

Another consideration is that there are many vestibular nuclei neurons (e.g., vestibular only (VO) neurons) that have vestibulospinal projections and probably drive vestibulospinal reflexes (42). Eye-head (EH) cells or flocculus target neurons (FTN) in the vestibular nucleus respond to both eye and head movements (43). Perhaps an explanation for the lack of an effect of vision or of head rotations on the early adaptation seen here is the fundamental need of the organism for vestibulospinal balance in order to maintain upright posture, regardless of vision or nystagmus. Another potential confound in our data is that during the periods of fixation subjects had to look at a near target that required them to converge their eyes to a different position than when they were in the dark. The similar after effects we observed with and without fixation suggest that any difference in eye positions did not have an effect on adaptation.

CONCLUSIONS

In sum, these data support a model in which the effect of visual fixation and of sustained head rotations on spontaneous nystagmus are introduced only after vestibular set-point adaptation has taken place. We have previously shown that set-point adaptation of VOR in response to an MRI occurs over multiple time courses of increasing duration that can be approximated with multiple time constants of increasing amplitude (8). The findings here suggest that vision or head rotations have little impact on early (seconds to minutes) vestibular set-point adaptation. Whether or not vision influences the later (hours to days) components of set-point adaptation is unknown. Furthermore, these different adaptive processes may occur in different anatomic locations or by different mechanisms. Future knowledge on the substrates of adaptation may lead to ways to alter the time courses of adaptation favorably, allowing new treatments for human disease.

ETHICS STATEMENT

Experiments were approved by the Johns Hopkins institutional review board and informed consent was obtained from all participants.

AUTHOR CONTRIBUTIONS

BW, DZ, MS, and JO-M designed the study. BW, DR, MS, and NP-F collected the data. JO-M and DZ developed the mathematical modeling. BW and JO-M wrote the initial drafts of the manuscript. All authors were involved in approval of the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.01197/full#supplementary-material

Supplementary Figure 1 | To simulate different possible scenarios of the interaction between MVS and visual fixation we implemented a model in Simulink. The model only includes the horizontal canals and combines the left and right sides as a single control system that can encode positive and negative firing rates. The dynamics of the cupula include two force inputs: inertial force due to head acceleration (set to zero in this simulations) and the magnetic field induced Lorentz force. Then, there are two forces that counteract the movement of the cupula: viscous drag, proportional to velocity of the cupula and endolymph, and elastic force, proportional to the displacement of the cupula. The output of the cupula converted into firing rate units receives a positive feedback loop from the velocity storage system and two negative feedback loops from the adaptation operators. The output of the model is eye velocity which can be fed back to a simple system that attempts to cancel retinal slip (smooth pursuit or fixation system). We simulated three different configurations in this system: (1) if S1 switch is closed the eye velocity will be canceled by visual fixation after the adaptation occurs, (2) if S2 is closed the cancelation will occur before adaptation, and (3) if S3 is closed the visual system will enhance the vestibular adaptation by increasing its gain. The parameters of the simulations are included in **Supplementary Table 1**.

Supplementary Table 1 | Simulation parameters.

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Influence of Visual and Vestibular Hypersensitivity on Derealization and Depersonalization in Chronic Dizziness

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Objective: The aim of this study was to investigate the relation between visual and vestibular hypersensitivity, and Depersonalization/Derealization symptoms in patients with chronic dizziness.

Materials and Methods: 319 adult patients with chronic dizziness for more than 3 months (214 females and 105 males, mean age: 58 years, range: 13–90) were included in this prospective cross-sectional study. Patients underwent a complete audio-vestibular workup and 3 auto questionnaires: Hospital Anxiety and Depression (HAD), Depersonalization/Derealization Inventory (DDI), and an in-house questionnaire (Dizziness in Daily Activity, DDA) assessing 9 activities with a score ranging from 0 (no difficulty) to 10 (maximal discomfort) and 11 (avoidance) to detect patients with visual and vestibular hypersensitivity (VVH, a score > 41 corresponding to mean $+ 1$ standard deviation).

Results: DDI scores were higher in case of VVH (6.9 ± 6.79, $n = 55$ vs. 4.2 ± 4.81, $n = 256$ without VVH, $p < 0.001$, unpaired t-test), migraine (6.1 ± 6.40, $n = 110$ vs. 4.0 ± 4.42, $n = 208$no migraine, $p < 0.001$, unpaired t-test), and motion sickness (6.8 ± 5.93, $n = 41$ vs. 4.4 ± 5.11, $n = 277$ no motion sickness, $p < 0.01$, unpaired t-test). Women scored DDI higher than men (5.1 ± 5.42, $n = 213$ vs. 3.9 ± 4.91, $n = 105$, respectively, $p < 0.05$, unpaired t-test). DDI scores were also related to depression and anxiety. DDI score was also higher during spells than during the basal state.

Conclusion: During chronic dizziness, Depersonalization/Derealization symptoms seem to be related to anxiety and depression. Moreover, they were prominent in women, in those with visual and vestibular hypersensitivity, migraine, and motion sickness.

Keywords: chronic vertigo, persistent postural-perceptual dizziness, migraine, optic flow vertigo, motion sickness, anxiety, depression, depersonalization/derealization disorder

INTRODUCTION

Chronic dizziness in patients with a unilateral stable vestibular weakness or even normal inner ear function and no neurological abnormality is a diagnostic and therapeutic challenge. In an attempt to define at least a part of this population, a syndrome designated as phobic postural vertigo was proposed to define those with a hypersensitivity to visual stimuli and movements (1). Other medical terms such as optic flow vertigo (2), chronic subjective dizziness (3), and more recently persistent postural-perceptual dizziness (PPPD) have been employed to describe nearly the same group of patients (4). It appears that all these syndromes represent a group with ill-defined borders. Hypersensitivity to visual stimuli and motion is also strongly associated to migraine and motion sickness (5), and thus, defining the extent of this phenomenon in chronically dizzy patients with a vestibular dysfunction is an important issue to consider.

Chronic dizziness is typically associated with anxiety and depression, but whether balance disorders are a consequence, or a contributing factor to these disorders remains unclear (3, 6). Psychological repercussions of long-term vertigo seem to extend beyond anxiety or depression and include depersonalization/derealization disorder (DRD) (7). Depersonalization is the subjective experience of detachment or estrangement from one's own self. Derealization is the equivalent subjective experience as applied to one's surroundings, animate or inanimate. Since these two experiences are often associated and there is no evidence to distinguish their nature, a single classification, namely DRD, has been adopted in DSM-5 (8). DD symptoms are typically observed in psychiatric illnesses, especially panic disorder and depression, and also in neurological disorders but may also represent a primary disorder (9, 10).

Depersonalization/Derealization (DD) symptoms as evaluated by DRD inventory (DDI) (11), are present in a higher proportion of individuals with vestibular disorders in comparison to healthy controls (6, 7, 12). Also, DDI scores appear to be related to anxiety and depression in patients with balance disorders (7). Finally, caloric vestibular stimulation increases the DDI scores in healthy adults (7) suggesting a direct link between vestibular inputs and DD symptoms.

Identifying subgroups of patients with chronic vertigo who are present DD symptoms will potentially lead to a better understanding of the phenomenon and targeted therapeutic actions. To our knowledge, the relation between visual and vestibular hypersensitivity (VVH), and DD symptoms has not been studied. We hypothesized that patients with chronic dizziness and VVH had higher anxiety, depression, and DDI scores.

The principal objective of this study was to investigate the relation between VVH and DD symptoms. In addition, we also analyzed the relation between several clinical parameters (especially age, sex, motion sickness, migraine, Hospital Anxiety, and Depression scale) and the extent of VVH and DD symptoms.

MATERIALS AND METHODS

This cross-sectional study included 319 consecutive patients with a spontaneous dizziness. The group was selected from a population of 500 consecutive patients examined for balance disorders in one tertiary referral center during 5 months. The study was conducted during a routine follow-up and data acquisition and analyses were not blinded. The inclusion criteria were: patients complaining of spontaneous dizziness according to International Classification of Vestibular Disorders I (ICVD-I V 1.0) (13) lasting for more than 3 months after the last acute episode of a possible triggering event, French-speaking patients capable of responding to questionnaires. Adults and teenagers were included regardless of their age. Two patients with bilateral vestibular loss were excluded due to possible confusion between symptoms due to the peripheral deficit and those related to central processing. Patients presenting with vertigo in addition to spontaneous dizziness were also excluded. The study was reviewed and approved by our institutional ethical committee (CPP Est III), and all patients provided their informed and written consent. The population comprised 214 females and 105 males with a mean age of 58 $\pm$ 17.4 years (range: 13–90 years). The mean delay between the triggering event and the inclusion was 4.1 $\pm$ 6.43 years. Initially, all patients underwent a thorough clinical examination, a caloric test, evaluation of oculomotricity, and subjective visual vertical. Based on this workup, 167 (52%) patients fulfilled the diagnostic criteria for persistent postural-perceptual dizziness [PPPD, (14)]: Unsteadiness $>$ 3 months, exacerbation by upright position, self- or visual environment movements, significant functional handicap, and symptoms not better explained by any other disorder. This group included 125 women (74%) and 42 men (26%) with a mean age of 56 $\pm$ 17.4 years.

The possible triggering disease was classified into the following categories:

- Recent benign paroxysmal positional vertigo (3–12 months before inclusion, BPPV according to von Brevern et al. (15): $n = 58$ (18%)
- Cured BPPV (>12 months before inclusion): $n = 85$ (26%)
- Stress defined by anxiety or traumatic stress associated to spontaneous dizziness without abnormality of clinical and instrumental vestibular examination (16): $n = 36$ (11%)
- Probable Ménière's disease according to the Ménière's disease diagnostic criteria (17): $n = 33$ (10%)
- Vestibular migraine according to Barany Society criteria (18): $n = 30$ (9%)
- Otolithic dysfunction defined as vertigo or postural unsteadiness, normal canal function, and abnormality of sacculocolic or utriculoocular myogenic evoked potentials (19): $n = 11$ (3%)
- Unilateral vestibular loss defined by a canal paresis on bicaloric test (>30% asymmetry of the sum of 2 the stimulations measured by the slow-phase velocity of the nystagmus on videonystagmography) and video Head Impulse test (vHIT, gain < 0.7 on at least one canal on the same side): $n = 8$ (3%)

- Central disorders were defined as vertigo, dizziness, or unsteadiness associated to abnormal ocular pursuit control and/or gaze nystagmus and/or dysmetric saccades, and/or absent ocular fixation, and/or abnormalities of central vestibular pathways on MRI (20): $n = 11$ (3%)
- Age-related dizziness defined by age >75 years-old and spontaneous dizziness, and no evident deficit of canal or otolith function, and no identifiable neurologic abnormality: $n = 8$ (2%)
- Vestibular paroxysmia was diagnosed according to Strupp et al. (21). In this group patients were treated by carbamazepine with no acute vertigo: $n = 3$ (1%)
- Perilymphatic fistula diagnosed according to Portmann et al. (22). In this group patients were surgically treated with no more triggered vertigo or dizziness (13): $n = 4$ (1%)
- Drug-related group defined by patients with orthostatic dizziness, no clinical or instrumental signs of vestibular deficit and anti-hypertensive medication (23): $n = 2$ (1%).
- Undetermined triggering event: $n = 30$ (10%).

In addition to this routine workup, patients responded to 3 self-assessment questionnaires: Dizziness in Daily Activity (DDA), Hospital Anxiety Depression Scale (HAD) (24), and DDI (11).

In the DDA questionnaire, the patients were asked if they were dizzy in the 9 following situations: (1) Rapid head movements when dish-washing; (2) Sport and house-keeping; (3) Looking both ways before crossing the street; (4) Moving visual scene (e.g., crowd, traffic, malls, public transportation); (5) Climbing or coming down (e.g., stairs, pavement borders, bus); (6) Moving images on screens; (7) Undergoing acceleration and break (e.g., lift, car, train, speedwalk); (8) Bending forward (e.g., tying shoes, plugging a device, picking up an object from the ground); (9) Open spaces (e.g., parks, beaches, embankments). For each item, the patient indicated whether he/she was concerned by the activity and scored the dizziness from 0 (none) to 10 (maximal discomfort). A score of 11 was assigned to the activities which were avoided due to unbearable discomfort. A global score was calculated as the sum of the scores ranging from 0 to 99.

HAD scale comprised 14 questions pertaining to anxiety ($n = 7$) and depression ($n = 7$). Each item was scored from 0 to 3. A score was calculated for anxiety (aHAD) and depression (dHAD) separately ranging from 0 to 21. Characterized anxiety and depression were defined as a score > 8/21 for each subgroup of questions (24).

DDI included 28 questions. One point was assigned to each positive answer. The global score ranged from 0 to 28. Patients were asked to fill in the DDI concerning their status at the basal level and during a past vertigo spell. Information concerning migraine and motion sickness were also recorded.

Statistical Tests

We tested the a priori hypothesis of a relationship between DDA score reflecting VVH in one hand and age, sex, the triggering disease, migraine, motion sickness, anxiety, depression, and DD symptoms on the other hand.

Data were analyzed by Statview (SAS Inc., Cary, NY). Values were expressed as mean ± SD. Continuous variables were analyzed by a paired or an unpaired *t*-test for 2 subgroups and ANOVA followed by a Bonferroni's test for multiple comparisons. A Mann-Whitney test was employed for the comparison of 2 groups when the normal distribution of the variable was not insured. A Fisher's exact test was used to compare categorical variables in 2 subgroups. $P < 0.05$ was considered as significant.

TABLE 1 | Dizziness in daily activity questionnaire.

Items	Score	Not concerned (%)	Avoidance (%)
Dish washing	1.4 ± 2.70 (277)	20	11
Sport and house-keeping	3.9 ± 4.06 (292)	10	40
Crossing street	2.1 ± 3.06 (299)	6	10
Crowd	3.3 ± 3.56 (304)	4	17
Stairs	2.8 ± 3.26 (304)	4	10
Screens	2.8 ± 3.53 (298)	6	19
Acceleration	2.6 ± 3.32 (302)	4	15
Bending forward	3.5 ± 3.36 (308)	2	9
Open spaces	0.9 ± 2.43 (283)	27	10
Global score	22.2 ± 19.45 (312)		

The questionnaire was submitted to 319 patients. Patients rated their dizziness during the activity from 0 (none) to 11 (avoidance due to unbearable dizziness).

RESULTS

Dizziness in Daily Activity Score

In total, 312 patients responded to the DDA questionnaire (**Table 1**). All the proposed items appeared to concern the majority of the patients. Women had a higher DDA score than males (25.6 ± 20.51, $n = 210$ vs. 15.2± 14.84, $n = 102$, $p < 0.0001$, unpaired *t*-test). The rate of avoidance was also higher in women (90 among 1,794 questions in women, 5% vs. 20 among 908 in men, 2%, $p < 0.001$, Chi-2 test). Age and etiology categories were similar in these subgroups and did not appear as confounding factors (data not shown).

DDA score was also higher in migraineurs (27.9 ± 21.88, $n = 111$ vs. 19.1 ± 17.23, $n = 201$ patients without migraine, $p < 0.001$, unpaired *t*-test). The effect of migraine on the score appeared to be separate from the effect of sex (**Figure 1A**, $p < 0.05$ for the effect of migraine, $p < 0.0001$ for the effect of sex and no significant interaction, 2-way- ANOVA).

An acquired motion-sickness also appeared to increase DDA score (28.8 ± 20.45, $n = 41$ vs. 21.2 ± 19.08, $n = 273$ patients without motion sickness, $p < 0.05$, unpaired *t*-test). This effect appeared to be independent from the effect of sex (**Figure 1B**).

Age did not seem to influence the DDA score. Indeed, there was no correlation between age and DDA score ($R = 0.08$, simple regression analysis, not significant, ANOVA), and there was no difference of DDA scores between younger (<60 years) and senior patients (23.5 ± 20.65, $n = 155$ vs. 21 ± 18.2, $n = 157$, respectively, not significant, unpaired *t*-test). Similarly, etiology categories did not seem to influence DDA assessment (data not shown).

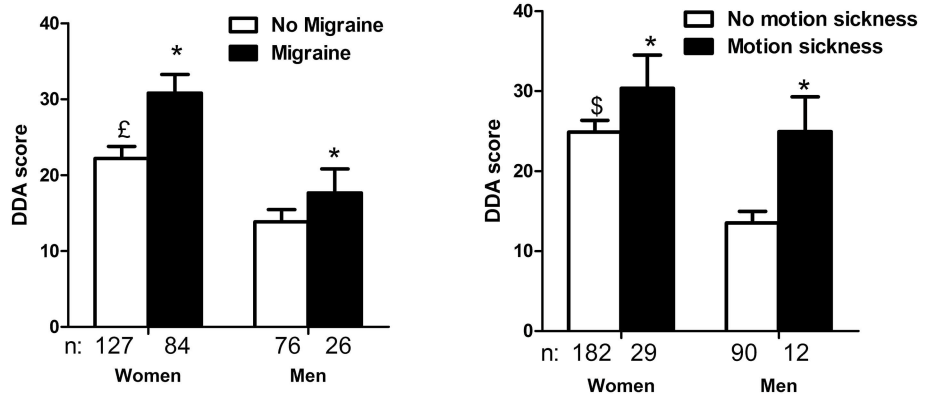

FIGURE 1 | Dizziness in Daily Activity (DDA) scores as a function of sex, migraine history **(A)** and motion sickness **(B)**. Females had higher DDA scores than males. A personal history of migraine **(A)** and acquired motion sickness **(B)** also increased the scores without interaction with the effect of sex (*$p < 0.05$ for the effect of migraine, and motion sickness, $^{£}p < 0.0001$ and $^{\$}p < 0.05$ for the effect of sex, interaction not significant, 2-way ANOVA).

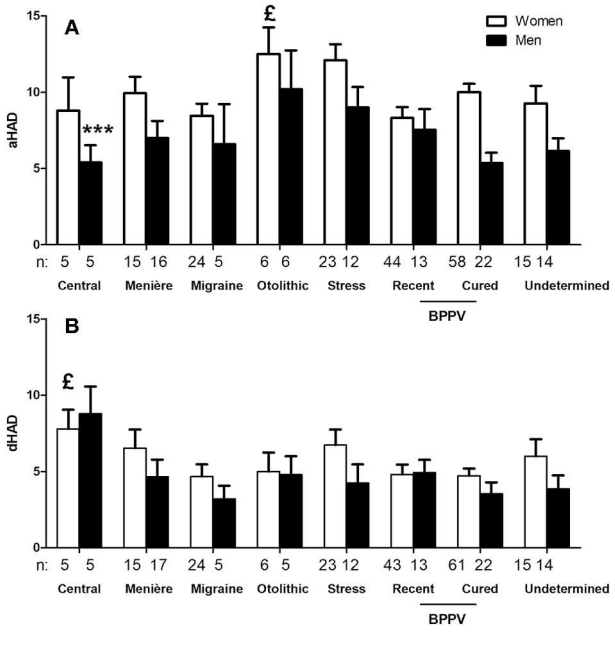

FIGURE 2 | Hospital Anxiety and Depression (HAD) questionnaire anxiety scores as a function of sex and triggering disease. Only subgroups with $n > 3$ are represented. Sex and triggering disease both influenced the anxiety scores **(A)**, $^{£}p < 0.05$ for the effect of triggering disease and $^{***}p < 0.0001$ for the effect of sex, not significant for interaction, 2-way ANOVA). Only etiology influenced depression scores **(B)**, $^{£}p < 0.05$ for the effect of triggering disease and not significant for the effect of sex, 2-way ANOVA). Central dizziness had higher depression scores ($P < 0.001$, Bonferroni post-test).

Forty-one patients (13%) declared no discomfort for all proposed activities (global score = 0). This group was composed of 20 males and 21 females with a mean age of 61 ± 16.1 years. This group was more masculine in comparison to the group scoring > 0 on DDA (49% vs. 30% of men, respectively, $p < 0.05$, Fisher's exact test). The group scoring 0 on DDA did not include any case of motion sickness while this symptom was noted in a significantly higher proportion of individuals among those with a DDA score above 0 (41 out of 273, $p < 0.01$, Fisher's exact test).

Hospital Anxiety and Depression Scale

Anxiety (aHAD) score in our population with chronic dizziness was 8.6 ± 4.54 ($n = 305$).This score was higher in women (9.5 ± 4.42, $n = 203$ vs. 6.9 ± 4.24, $n = 102$ for men, $p < 0.0001$, unpaired *t*-test) and in young patients (9.4 ± 4.45, $n = 153$ in patients <60 years vs. 7.8 ± 4.50, $n = 152$ in > 60 years, unpaired *t*-test, $p < 0.01$). Etiology also seemed to influence the anxiety scores. Higher scores were recorded in stress-related dizziness and otolithic syndrome (**Figure 2**).

Patients with a history of migraine reported higher anxiety levels than others (9.7 ± 4.64, $n = 106$ vs. 8.1 ± 4.37, $n = 199$, respectively, $p < 0.01$, unpaired *t*-test). Similarly, those with acquired motion sickness had higher aHAD ratings (9.5 ± 4.52, $n = 39$ vs. 8.5 ± 4.53, $n = 266$, $p < 0.05$, unpaired *t*-test).

Depression (dHAD) score in the population was 5.0 ± 3.94 ($n = 308$). There was no difference between men and women (4.5 ± 3.71, $n = 104$ vs. 5.3 ± 4.05, $n = 204$ not significant, unpaired *t*-test). In the same manner as aHAD, scores in young patients tended to be higher than those in senior patients (5.3 ± 4.08, $n = 153$ vs. 4.6 ± 3.77, $n = 155$, respectively, mean difference = 0.7, $p = 0.08$, unpaired *t*-test). dHAD did not seem to be influenced by a history of migraine or acquired motion sickness (data not shown).

Patients with characterized anxiety or depression (scores > 8) had higher DDA scores than those with scores below 8 (**Figure 3**), suggesting a relation between daily activity discomfort and anxiety/depression levels.

Depersonalization/Derealization Inventory

The average score for DDI was 4.7 ± 5.28 ($n = 318$). Women scored higher than men (5.1 ± 5.42, $n = 213$ vs. 3.9 ± 4.91, $n = 105$, respectively, $p < 0.05$, unpaired *t*-test). Also, patients below 60 years had higher scores than seniors (5.4 ± 6.04, $n = 156$ vs. 4.0 ± 4.35, $n = 162$,

respectively, $p < 0.05$, unpaired t-test). As for the HAD questionnaire, etiology also affected DDI score independently from the sex with higher levels in central disorders and in women (**Figure 4**).

Patients with a personal history of migraine also provided higher DDI ratings in comparison to those without a migraine history (6.1 ± 6.40, $n = 110$ vs. 4.0 ± 4.42, $n = 210$, respectively, $p < 0.001$, unpaired t-test). Patients with acquired motion sickness had also higher DDI scores than those who did not suffer from it (6.8 ± 5.93, $n = 41$ vs. 4.4 ± 5.11, $n = 279$, respectively, $p < 0.01$, unpaired t-test).

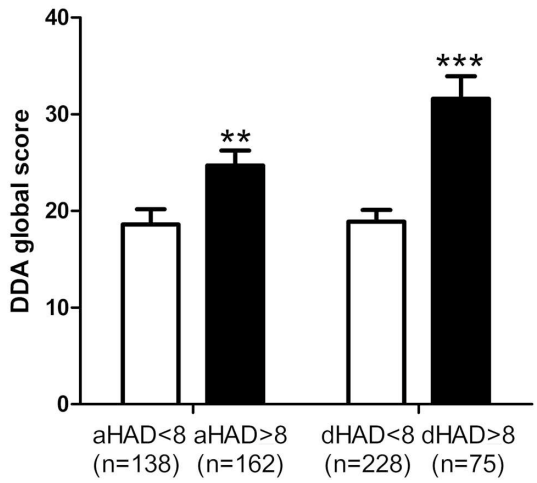

FIGURE 3 | Relation between Dizziness in Daily Activity (DDA) and Hospital Anxiety and Depression (HAD) scores. Subjects with a characterized anxiety (anxiety score on HAD, aHAD > 8) and depression (depression score on HAD, dHAD > 8) had higher DDA scores. Bars represent mean ± SEM. $^{**}p < 0.01$, $^{***}p < 0.001$, unpaired t-test.

Patients with characterized anxiety and depression (aHAD and Dhad > 8) had higher DDI scores (6.0 ± 5.75, $n = 167$ for aHAD ≥ 8 vs. 3.0 ± 4.11, $n = 139$ for aHAD< 8, $p < 0.0001$, and 7.6 ± 6.66, $n = 79$ for dHAD ≥ 8 vs. 3.6 ± 4.33, $n = 230$ for dHAD< 8, $p < 0.0001$, unpaired t-test).

The analysis of the parameters which influenced DDA score in our population by a multiple regression model showed that the combination of dHAD, aHAD, DDI, and age as independent factors were correlated to DDA (Adjusted $R = 0.52$, $p < 0.0001$, ANOVA, $n = 296$).

When asked to score their perception during past vertigo spells by the DDI, patients estimated their DD symptoms higher than the one at the basal state (9.6 ± 6.67, $n = 312$ vs. 4.7 ± 5.28, $n = 318$, respectively, $p < 0.0001$, paired t-test). This significant increase concerned 25 items out of 28 (**Figure 5**). The mean variation of the score was 4.9 ± 5.98 ($n = 311$, range: -8 to 26). Younger patients (<60 years) had higher DDI score shifts during the spells than the seniors (6.4 ± 6.22, $n = 154$ vs. 3.5 ± 5.40, $n = 157$, $p < 0.0001$, unpaired t-test). But the sex did not seem to influence the amplitude of the shift (4.5 ± 5.60, $n = 103$ for men vs. 5.0 ± 6.14, $n = 207$ for women, not significant, unpaired t-test). History of migraine and acquired motion sickness did not influence the amplitude of the shift (5.4 ± 6.47, $n = 107$ for migraineurs vs. 4.6 ± 5.67, $n = 203$ for non-migraineurs, and 5.0 ± 6.09, $n = 270$ for motion sickness vs. 4.4 ± 5.00, $n = 40$ for no motion sickness, not significant, unpaired t-test). Etiology did not seem to alter the DDI score shift during spells (**Figure 6**).

DISCUSSION

In this study, we showed that patients with chronic balance disorder complaining from vestibular and visual discomfort in daily life activities were frequently young women with a history of migraine or acquired motion sickness. The extent of the

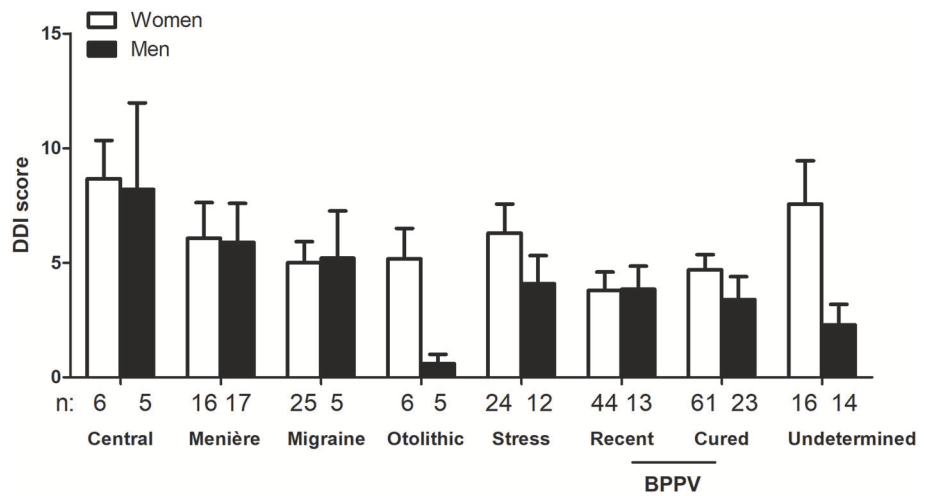

FIGURE 4 | Influence of sex and triggering disease on Depersonalization/Derealization Inventory (DDI) scores. Sex and triggering disease both influenced DDI scores ($p < 0.05$ for the effect of sex and $p < 0.05$ for the effect of etiology, not significant for interaction, 2-way ANOVA). Only triggering disease groups with $n > 3$ for men and women are represented. Bars represent mean ± SEM. BPPV: Benign paroxysmal positional vertigo.

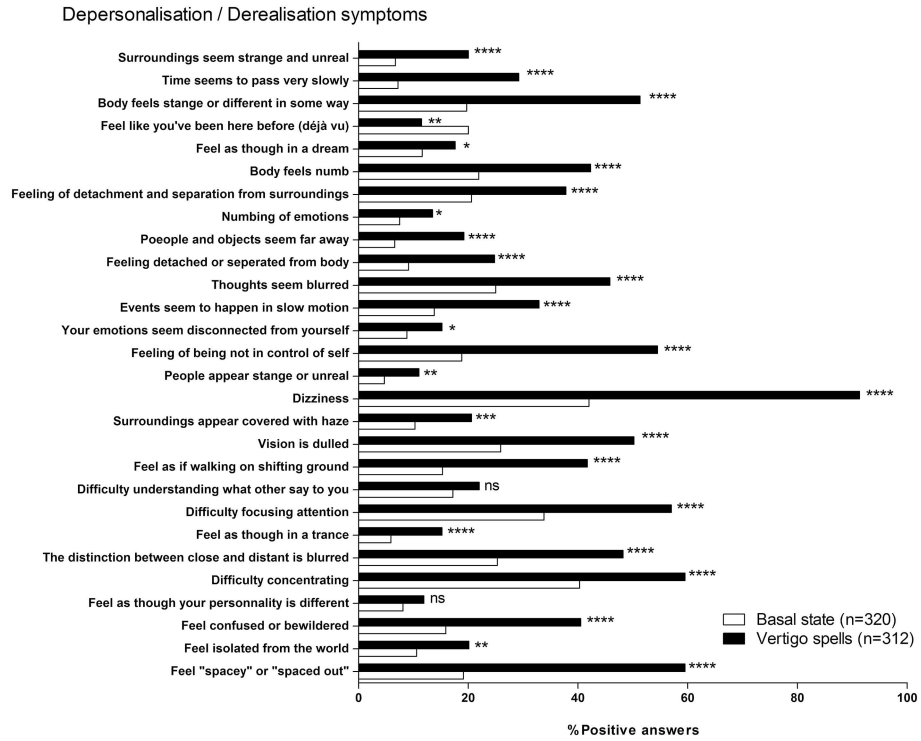

FIGURE 5 | Depersonalization/Derealization Inventory (DDI) at basal state and during vertigo spells. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$, ns, not significant; Khi-2 test vs. basal state.

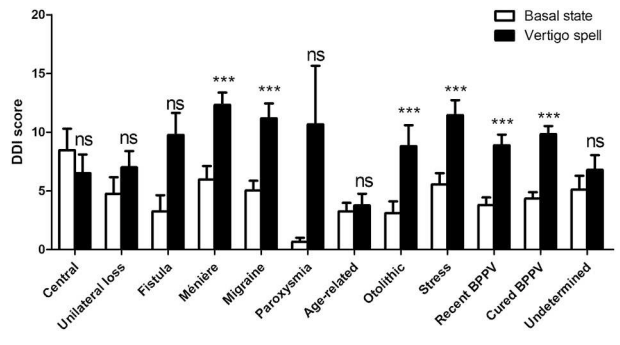

FIGURE 6 | Depersonalization/Derealization Inventory (DDI) scores at basal state and during vertigo spells as a function of triggering disease. Both triggering disease and vertigo spells influenced the score ($p < 0.0001$ for the effect of vertigo spells, not significant the effect of triggering disease and for interaction, 2-way ANOVA). Bars represent mean ± SEM. Ns, not significant, ***$p < 0.001$, Bonferroni's post-test vs. basal state. BPPV, Benign paroxysmal positional vertigo.

discomfort was related not only to depression and anxiety levels, but also to the depersonalization/derealization sensations. The intensity of these latter increased during vertigo spells suggesting the impact of vertigo on the perception of self, environment, and time.

The relation between anxiety, depression, and vertigo has been already reported in several studies (25). This association is probably explained by the close connections between the vestibular and the limbic systems (26). In our study, other symptom related to the triggering event such as headaches, tinnitus, and hearing loss could also interfere with anxiety and depression, or even depersonalization/derealization. However, it is very difficult to estimate this participation. Vertigo decreases in the majority of cases, even if the initial disorder persists (e.g., vestibular neurectomy), via a neuronal reorganization at the level of the brainstem but also thalamic and cortical centers leading to the central vestibular compensation (27). However, if the vestibular function fluctuates, or if the rehabilitation exercises are insufficient, monotonous, or late the central process cannot accomplish a complete compensation (27). Interestingly, psychological factors seem also crucial in the compensation: passivity, depression, and avoidance largely influence balance performances (27). Our results suggest that other subgroups of patients may also encounter difficulties to compensate their vestibular dysfunction. Female patients appeared to present with more vestibular and visual discomfort than males independently from other possible confounding factors (age, migraine, motion, sickness).

An extensive literature has suggested the sex difference in the integration of visual inputs into the balance function and motion sickness (28, 29). Women are more frequently subject to motion sickness and exhibit higher scores at motion sickness susceptibility questionnaire (29). This susceptibility seems to decrease in senior patients (29). In addition, posturography shows that women tend to couple their sway to the moving environment in a less extent than men (28). Although, the

explanation for this difference is unclear, the influence of sex hormones on the fluctuation of vestibular function could explain the pronounced discomfort in female patients (30).

The same female preponderance has been observed for the incidence of migraine (31). In this disease, the role of estrogen has been well-documented (31). A close relationship between migraine, motion sickness, and vestibular disorders has also been established. In a recent study, Ghavami et al. showed that migraine, sensitivity to visual motion, light and sound, head motion, smells, weather changes, or medication was present in 95% of all patients with definite Menière disease and that this population was predominantly feminine (70%) (32). These observations are in accordance with our results showing higher vestibular and visual discomfort in females, in migraineurs and in those suffering from motion sickness.

Current questionnaires evaluating vertigo such as Dizziness Handicap Inventory do not assess VVH (33). Situational Characteristics Questionnaire (SCQ) focuses more on VVH and is validated in Canadian French (34). However, its use in France would have necessitated adaptation and validation since the two languages and every-day life habits are different. While car and bus trips are very detailed, many other situations which we explore are not taken into account (e.g., screens, dish-washing). Moreover, patients who are not concerned by the proposed activities are not recorded and the avoidance due to extreme stress is not considered in SCQ.

Consequently, to the aim of investigating the relation between VVH and DD symptoms, we designed an in-house questionnaire especially targeting situations in which VVH is incapacitating and assessed the handicap by a Likert scale. The validity of the Likert method as a psychometric tool has been demonstrated in many domains specially in chronic vertigo (35) The addition of avoidance as an indicator of extreme handicap in some activities appeared to us as crucial. Likert scales remain valid with 11 levels (36). However, this questionnaire needs to be further investigated for validity and reliability.

The relation between self-awareness and vestibular function was investigated as early as the beginning of twentieth century (37). Since its first description, this relation has been largely studied with complex experimental paradigms in normal subjects and in patients with vestibular loss (38). Vestibular stimulations modulate the sense of owning a body and anchors the self to the body (39). Negative emotions enhance self-motion detection (40).

The relation between DD symptoms and vestibular disorders has been previously reported by Sang et al. (7). These authors investigated the basal DD symptoms level and the effect of a caloric vestibular stimulation in healthy subjects and in patients with peripheral vestibular disorders (unilateral canal paresis, BBPV) by the DDI. This study showed that DD symptoms were more intense in patients with a vestibular disorder (with and without recent symptoms) than in normal subjects. Patients with recent vestibular symptoms had also higher DDI scores than those with past symptoms. They also observed that DDI scores increased during a vestibular caloric test in normal individuals. These results are in accordance with our observations and suggest a strong link between the vestibular network and the centers regulating the self-awareness. In addition to the previously reported results, we showed that women had tendency to score higher on DDI. Similarly, patients below 60 years of age, those suffering from migraine, and motion sickness reported higher DDI scores. This observation provides a possible link between the above-mentioned observations on migraine, motion sickness, vestibular disease, and the possible role of sex hormones. We also showed that DDI scores increase during the past vertigo spells. This result is also in accordance with the increase of DDI in normal individuals during caloric stimulation (7). The amplitude of the score shift during the spells was significantly greater in young patients. This information underlines the relation between the vestibular input and the perception of the environment and the self.

In conclusion, chronic dizziness can entail not only anxiety and depression but also sensations of depersonalization, and derealization independently from the etiology. The observation that DDI scores increase during vertigo spells suggests that balance disorders enhance depersonalization and derealization. This possible causality can be explained by the disturbances of our internal body scheme and the environment representation during vestibular disorders, and the uncertainty on the validity of sensory inputs that they generate. DD complaints were more frequent and intense in young female patients and in those suffering from migraine and motion sickness. These patients also reported incapacitating symptoms related to visual and vestibular hypersensitivity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

MT and AB analyzed data and prepared the manuscript. CV, CH, and UD participated in the study design. MT, AC, and SH included and examined the patients.

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Functional Neuroanatomy of Vertical Visual Perception in Humans

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Vertical representation is central to posture control, as well as to spatial perception and navigation. This representation has been studied for a long time in patients with vestibular disorders and more recently in patients with hemispheric damage, in particular in those with right lesions causing spatial or postural deficits. The aim of the study was to determine the brain areas involved in the visual perception of the vertical. Sixteen right-handed healthy participants were evaluated using fMRI while they were judging the verticality of lines or, in a control task, the color of the same lines. The brain bases of the vertical perception proved to involve a bilateral temporo-occipital and parieto-occipital cortical network, with a right dominance tendency, associated with cerebellar and brainstem areas. Consistent with the outcomes of neuroanatomical studies in stroke patients, The data of this original fMRI study in healthy subjects provides new insights into brain networks associated with vertical perception which is typically impaired in both vestibular and spatial neglect patients. Interestingly, these networks include not only brain areas associated with postural control but also areas implied in body representation.

Keywords: vertical perception, posture, fMRI, visual orientation, vestibular system

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INTRODUCTION

The transition to bipedalism in man had many implications on orientation and navigation skills. The vertical position freed the hands, modified the perception of the environment (with a largest horizon) and of the body, and drastically changed social interaction (1). Based on multisensory integration of visual, vestibular and somesthetic origin (2–4), the representation of the vertical makes it possible to reference the positions and displacements of our body as well as surrounding objects with respect to gravity. There is clinical evidence of deficits in verticality perception after peripheral vestibular loss (5–7) or central lesions (8–10). Neuroimagery performed in brain damaged patients suggested that several cortical regions could participate in a cortical network of vertical perception. Indeed, impaired vertical judgments were reported in patients with damage of the posterior parietal and temporal cortices (9, 10) or of the posterior insula (11, 12). Though the studies carried out in brain damaged patients certainly provided precious data, the issue remains poorly explored in healthy participants and the precise functional neuroanatomy of vertical perception is still uncertain. To our knowledge, only one study using high-density electrical neuroimaging showed an early potential map specific to the visual judgement of the vertical in the right temporal-occipital cortex, followed by a bilateral map in the temporal-occipital and parietal-occipital cortices (13).

In the present study, we use functional magnetic resonance imaging (fMRI) in order to describe, with a better spatial precision and in healthy participants, the brain areas involved in the visual

judgment of the vertical. For this purpose, a special set of stimuli was designed that could be used in a main verticality judgment task and in a control color judgment task as well.

METHODS

Subjects

Sixteen healthy volunteers (mean age: 25.7±5.8 yr; 6 males and 10 females) were recruited from the general population. All participants signed an informed consent according to the ethics rules of the University Hospital of Geneva. Exclusion criteria were: past history of cerebral disease, epilepsy, head trauma, vestibular disorders or major psychiatric illness; visual acuity below 20/40; left handedness; pregnancy; claustrophobia or contraindication to magnetic field exposure (pacemaker, metallic prosthesis, dental apparatus, etc.); addiction or intake of any drug interfering with neuronal activity or cerebral blood flow.

Behavioral Design

The tasks were designed to assess the perception of the verticality. On each trial, a vertical line (height = 10°) was presented. The thickness of the line (1°) was sufficient to be clearly visible. The vertical line was presented 24 times straight (0°) and 36 times tilted by −30°, −25°, −20°, −15°, −10°, −5°, 5°, 10°, 15°, 20°, 25°, or 30° (3 times each). A circle and an irregular frame were also presented on the screen so as to avoid systematic strategies and frame effects (14).

The line was presented for 1,500 ms and followed by an inter-trial interval of 1,500–3,000 ms (pseudo-randomly jittered). All visual stimuli were projected on a screen in the MRI scanner and seen through a mirror mounted on the head coil.

All stimuli configurations were shown in two tasks requiring a similar binary response (yes / no) indicated by a key-press: a line verticality (LV) task, in which the participants judged whether the line was aligned with the true vertical and a line color (LC) task, in which they judged whether the line was red or green (control task).

Procedure

Before acquiring fMRI data, the perceived vertical was compared in supine (like in the MRI device) and in sitting positions. In both postural conditions, the percentage of correct responses and the response times were analyzed for LV and LC tasks. Here, the aim was to determine whether, in the present experimental conditions, the body position (supine or sitting) differentially affected the performance in the two tasks.

During fMRI acquisition**,** the two tasks were administered in a blocked design to maximize signal-to-noise ratio and to minimize attentional demand. Each block lasted 24 s and included 6 stimuli. In a given fMRI run, five blocks of each task were presented in a pseudo-random order, with brief resting periods (total duration 5 min). Two fMRI runs were obtained in each participant (duration 2 × 5min), separated by a brief pause (**Figure 1**). The positions and tilts of the stimuli were equally distributed between the tasks.

Acquisition of fMRI Data

MRI data were acquired in the Brain and Behavior Laboratory at the University Medical Center, using a 3-T whole-body TRIO system (Siemens) with the standard head-coil configuration. Functional T2*-weighted images were obtained using echoplanar imaging (EPI) with axial slices (TR/TE/Flip = 2,200 ms/30 ms/85°, FOV = 235 mm, matrix = 128 × 128). Each functional volume was comprised of 32 contiguous 3.5 mm-thick slices, parallel to the inferior surface of occipital and temporal lobes. For each patient, a high-resolution anatomical image was also acquired after the functional scans, using a 3D-GRE T1-weighted sequence (FOV = 250 mm, TR/TE/Flip = 15 ms/5.0 ms/30°, matrix = 256 × 256, slice-thickness = 1.25 mm). This anatomical image was used for co-registration with functional images and subsequent normalization procedure.

Analysis of Behavioral Data

In the first part (before fMRI), behavioral data (percentage of correct responses and response time) were analyzed using a two-way repeated-mesures analysis of variance (ANOVA, Statistica software) with the task (LV, LC) and body position (sitting, supine) as within-subjects factors. In the second part (during the fMRI), a one-way ANOVA was performed on the task (LV, LC).

The alpha risk was fixed at $p < 0.05$.

Analysis of fMRI Data

All fMRI data were processed and analyzed using the general linear model for event-related designs in SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Functional images were realigned, corrected for slice, normalized to an EPItemplate (re-sampled at a voxel-size of 3 mm), spatially smoothed (8 mm FWHM), and high-pass filtered (cutoff: 180 s). Statistical analyses were performed on a voxelwise basis across the whole-brain, using a mixed blocked and event-related design (15).

Individual visual events were modeled by a standard synthetic haemodynamic response function (HRF). This HRF was estimated at each voxel by a General Linear Model (GLM) using a least-square fit to the data, for each condition, and each individual participant. Statistical maps (SPM[t]) generated from comparisons between conditions in individual subjects were then included in a second-stage random-effect analysis, using one-sample *t*-tests (16). The resulting maps SPM[t] were thresholded at conventional statistical values (voxel threshold at $P < 0.001$ and cluster threshold of $P < 0.05$), using standard parameters similar to previous imaging studies in our group (17). Main comparison was performed between vertical and control tasks. Thus this analyse enabled us to identify the neural networks that are selectively responsible for vertical coding.

RESULTS

Behavioral Data

The first ANOVA carried out on the data obtained before fMRI runs showed no main effect of task on the rate of correct responses ($p = 0.72$), no main effect of body position ($p = 0.82$) and no interaction (LV: supine = 95 ± 2%, sitting = 96 ± 3%,

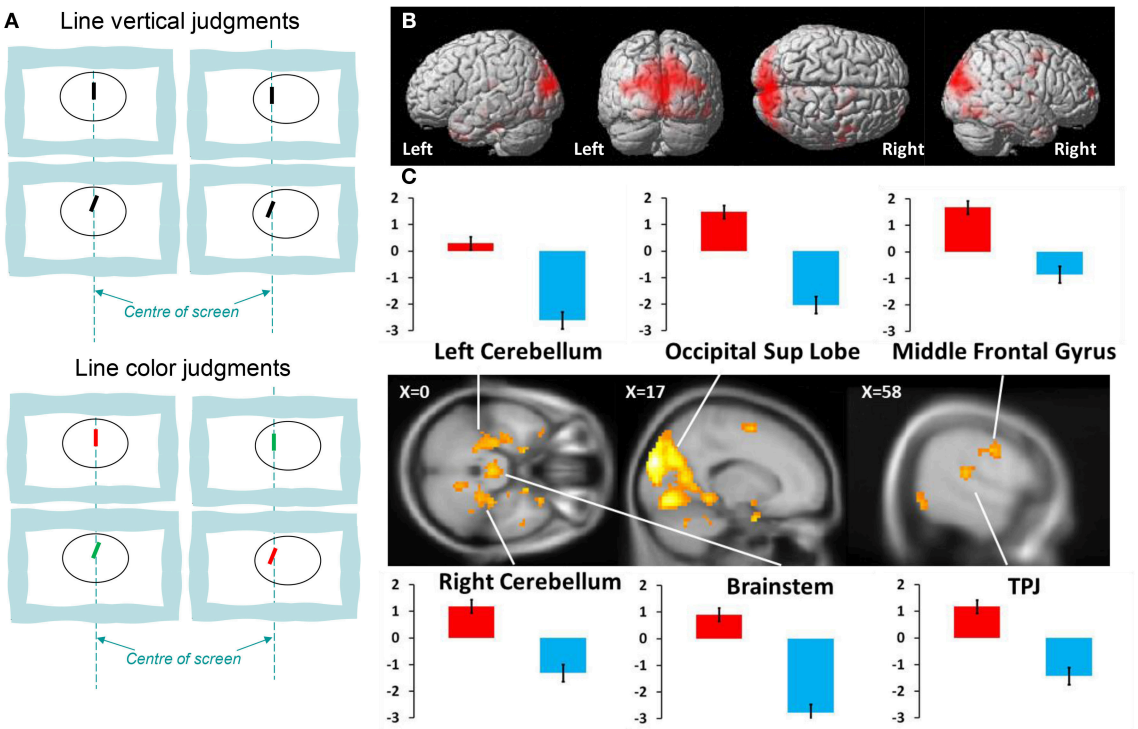

FIGURE 1 | (A) Examples of stimuli for Line Verticality (LV) judgment and Line Color (LC) judgment; **(B)** activation in the whole group ($n = 16$) during LV vs. LC control tasks ($P < 0.001$ uncorrected; cluster size > 10); **(C)** fMRI analyses for vertical task. Activated brain regions are projected on a standard anatomical template. Parameter estimates of activity (beta value, in arbitrary units, averaged across responsive voxels in each cluster) are shown for main peaks in each task condition. Red bars, vertical task; blue bars, control task; TPJ, temporo-parietal junction.

LC: supine = 97 ± 2%, sitting = 98 ± 1%,). Similarly, the second ANOVA performed on the response times showed no effect of task ($p = 0.77$), no effect of body position ($p = 0.75$) and no interaction (LV: supine = 669 ± 52 ms, sitting = 717 ± 81 ms; LC: supine = 602 ± 79 ms, sitting = 580 ± 54 ms). The body position (supine or sitting) did not differentially affected the performance in the two tasks.

Behavioral data obtained during fMRI scanning did not show any effect of the task ($p = 0.79$ neither for the rate of correct responses (LV: 96 ± 3%; LC = 98 ± 1%) nor for response times (LV: 698 ± 47 ms; LC: 550 ± 65 ms).

Neuroimagery Data

The data from brain imaging are shown in **Figure 1** and listed in **Table 1**. The brain activations during verticality judgment relative to the control task were localized principally in both temporo-occipital cortices, with a right dominance tendency. We then directly compared the two tasks against each other. The contrast LV > LC showed strong bilateral activations within the superior occipital gyrus, the parietal lobe, the middle and superior temporal gyrus and the supplementary motor areas. Specific activations occurred in the right hemisphere for the inferior parietal lobe, the thalamus and the anterior part of the cerebellum (dentate, nodulus peduncles) and the midbrain. In the left hemisphere, specific activations were located in the parahippocampal gyrus and the brainstem. We then directly compared the two spatial tasks against each other. The contrast LC > LV showed selective activity in the left inferior temporal gyrus (xyz = −60 −16 −26, $Z = 3.47$, $P < 0.001$).

DISCUSSION

This study in healthy participants shows that the neuroanatomical substrates of the judgment of the visual vertical involves a wide cortical network distributed bilaterally. This network includes mainly the occipital cortex, with the cuneus and the lingual gyri, the precuneus, the cerebellum and the brainstem. That these regions played a role in the judgment of verticality is in agreement with the results of previous studies which showed that the lingual gyrus and the cuneus are involved in orientation discrimination tasks (18). Recently, these brain regions have been shown to be involved in the treatment of vestibular information (19). In this fMRI study, the regions specifically activated during galvanic vestibular stimulation were the vestibular cortex, the inferior parietal lobe, the superior temporal gyrus and the cerebellum.

The role of these areas specifically activated during vertical judgment has also been mentioned in studies of vertical perception in stroke patients (9, 10, 20). The posterior temporo-parietal areas closely corresponded to those found by Lopez

TABLE 1 | Activation peaks (Montreal Neurological Institute coordinates) obtained for Line Vertical judgment > Line Color judgment ($P < 0.001$ uncorrected; cluster size > 15).

Area	MNI			Z
	x	y	z	
RIGHT HEMISPHERE				
Superior occipital gyrus	18	−91	25	6.15
Middle occipital gyrus	9	−94	10	5.9
Supplementary motor area	9	8	58	4.28
Precentral gyrus	30	−4	49	3.86
Superior frontal gyrus	21	−7	58	3.82
Precuneus	9	−52	52	4.15
Superior temporal gyrus	30	23	−26	3.46
Midbrain (red nucleus)	36	11	−32	3.4
Parietal lobe (postcentral)	63	−16	22	3.36
Middle frontal gyrus	30	65	13	3.7
Middle temporal gyrus	48	2	−35	3.68
Cerebellum anterior lobe	48	5	55	3.62
Inferior parietal lobule	24	−28	49	3.28
Thalamus	42	−43	52	3.24
LEFT HEMISPHERE				
Middle occipital lobe	−21	−91	19	3.98
Precuneus	−3	−52	49	3.56
Brainstem	0	−28	−29	4.13
Parahippocampal gyrus	−18	5	−26	3.98
Middle temporal gyrus	15	−61	−32	3.6
Supplementary motor area	3	−4	4	3.54
Parietal lobe (postcentral)	60	−1	10	3.23
Superior temporal gyrus	−66	−22	22	3.42

et al. (13). Their EEG study in normal subjects revealed a bilateral activity in the temporo-occipital and parieto-occipital regions during a vertical estimation task. Moreover, the present data are compatible with monkey studies showing that neural populations in the ventral and dorsal streams respond to orientation discrimination (21, 22). In addition, they are in agreement with the perceptual data reported in brain-damaged patients as deviation of vertical have been reported after a damage of the temporo-parietal junction, including the superior temporal gyrus and inferior parietal lobe (9, 10). Moreover, a recent study in patients suffering from unilateral vestibular neuritis who underwent resting state F-FDG PET showed, in the acute phase, a deviation of the vertical that was associated with a metabolic response in main cortical vestibular areas similar to those we evidenced here (23). In this study, the authors also found a metabolic response in the cerebellum for patients with left neuritis. In support of these data, a lesion of the inferior peduncle has been shown to bias the subjective visual vertical (24). In our study, the cerebellar activation appeared restricted to its anterior part. Though no strong activation of the vermis was expected in healthy participants lying on their back, our data are compatible with an involvement of the caudal and rostral parts of the vermis, where the lower part of the body is represented. This would suggest that, even when lying, the body remains a reference for verticality judgments. However, the activation of this anterior region and of midbrain could also sign an activity in cognitive/visuospatial loops including the ventral dentate nucleus (25, 26).

It is noteworthy and of the greatest clinical relevance that the brain areas involved in vertical visual perception in the healthy subjects largely overlap those reported in the studies of verticality disorders. More specifically, the current study identified clusters in the cerebellum, the brainstem, right inferior parietal lobe that overlapped with lesioned sites typically associated to pathological tilt of vertical (9, 20, 27, 28). Keeping in mind that the present study is grounded on a paradigm that was firstly shown to yield similar behavioral performance in supine and in sitting positions, we have to consider that perception of verticality is not influenced by the body position. In fact, in supine position, the participants could refer the visual stimulus to a bodily horizontal axis, or project their main body axis in the vertical plane to judge the verticality of the stimulus (29, 30). Finally, one can note that brain and vestibular damaged patients with an altered perception of verticality are usually older than the participants tested here.

To conclude, the present fMRI study indicates that during vertical judgments activation spreads to the temporo-occipital and parieto-occipital cortices, and also to the cerebellum and the brainstem. Recently, these regions have been claimed to be also implicated in the body representation (17), the balance control (31) and the spatial navigation (32). All in all, the data obtained here from healthy participants clarify the neural substrate of these functions that all require a continuously updated representation of the vertical.

AUTHOR CONTRIBUTIONS

AS: study concept and design, analysis and interpretation of data, and drafting the manuscript; LB: interpretation of data, revision of the manuscript for intellectual content; JH: interpretation of data, revision of the manuscript for intellectual content.

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ORIGINAL RESEARCH
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Stimulation of the Semicircular Canals or the Utricles by Clinical Tests Can Modify the Intensity of Phantom Limb Pain

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Background: After amputation, phantom limb pain may be produced by the multisensory processes underling the experience of an intact body. Clinical evidence has shown that cold caloric vestibular stimulation may modify the perception of phantom limb pain. However, it is yet unknown if this effect can be observed after the mild vestibular stimulation given by the clinical caloric test, or after utricle stimulation by centrifugation. Additionally, there are no studies on the association between the report of altered perceptions or experience of the self or the environment (depersonalization/derealization symptoms) and phantom limb pain.

Objective: To assess the influence of unilateral stimulation of the horizontal semicircular canals by clinical caloric test, and the utricles by unilateral centrifugation on the intensity of phantom limb pain, and to explore the association between phantom limb pain and symptoms of depersonalization/ derealization.

Methods: 34 patients (56 ±7 years old, 23 men) accepted to participate after 3 to 23 months of unilateral supracondylar amputation, secondary to type 2 diabetes mellitus. After assessment of vestibular function and symptoms of common mental disorders, using a cross-over design, in 2 separate sessions with 1 week in between, vestibular stimulation was delivered by right/left caloric test (30 or 44°C) or right/ left centrifugation (3.85 cm, 300°/s peak). Before and after each vestibular stimulus, the intensity of phantom limb pain and depersonalization/derealization symptoms were assessed, with a daily follow-up of pain intensity during 1 week.

Results: Either caloric stimulation or unilateral centrifugation decreased phantom limb pain ($p < 0.05$), along with decrease of symptoms of depersonalization/derealization ($p < 0.05$). One third of the patients reporting pain decrease immediately after stimulation also reported no pain at least for 1 day.

Limitations: No sham condition was included.

Conclusions: Vestibular stimulation by the clinical caloric tests or by unilateral centrifugation may decrease the intensity of phantom limb pain, with decrease of perceptions of unreality. These effects might be related to an update of the immediate experience of the body, given by the sensory mismatch induced by asymmetrical vestibular stimulation.

Keywords: vestibular, otoliths, phantom limb pain, despersonalization, body image

INTRODUCTION

Perception of head acceleration and orientation in space is sustained by right/left asymmetry of the input from each of the bilateral 5 vestibular organs, with crossing inhibitory/excitatory connections in the vestibular pathway; the three semicircular canals measure how the head rotates in space, while the utricle and the saccule measure how the body translates in space, and how it is positioned relative to gravity (1, 2).

Until the twenty-first century, selective stimulation of each vestibular organ was feasible just at some research facilities. Currently, the most widely used method to stimulate and assess the vestibular function is to modify the spontaneous discharge from each (right or left) horizontal semicircular canal by the clinical caloric tests, where water either at 44°C (excitatory) or at 30°C (inhibitory) is introduced into the external ear canal, with the head positioned 30°arc from the earth horizontal (3). Also, to modify the spontaneous discharges of both ears simultaneously, rotational testing is performed by active or passive movements of the head only or the whole body (4). In addition, mainly for research, galvanic vestibular stimulation is used to stimulate the entire vestibular nerve, via polarization effects (5).

However, since human beings have evolved under the gravitational field, gravity is central to orient the body as well as the objects in space (6). In the last two decades, significant advancements have been made for the assessment of the graviceptors (4). Among other tests of the utricular function, unilateral centrifugation on a rotating chair can be performed when the subject is shifted either to the right or to the left. Then, the center of rotation is located directly over one utricle, while a centripetally displaced g-force is applied over the eccentrically displaced utricle, with a sheering effect as if the displaced utricle was undergoing a static head tilt (7).

Pain is an interpretation of nociceptive input, influenced by memories, emotional, pathological, genetic, and cognitive factors (8). Phantom limb pain refers to the pain perceived in a part of the body that is no longer present. Independently from the general characteristics of the patients, a combination of cortical and peripheral mechanisms may interact to result in the experience of phantom limb pain (9). Evidence suggest that phantom limb pain emerges through altered afferent input from the affected limb and dorsal root ganglia, together with disrupted sensory processing and derangement of body representation at the supra-spinal and cortical level [for review see (10, 11)].

Body image and body schema are terms used to describe the body representation. The body image refers to the concept of the shape, the size and the mass of the body and its parts (12); while the body schema can be defined as a dynamic representation of the relative positions of the body parts derived from multiple sensory and motor inputs (e.g., proprioceptive, vestibular, tactile, visual, efference copy) that interacts with motor systems for movement and action (13, 14). Behavioral studies demonstrate that vestibular signals, including the graviceptors, contribute to continuously update the body schema and to control the interactions with objects in the environment [for review see (15)]. Consistently, vestibular stimulation in healthy subjects and vestibular disease in patients may trigger feelings of unreality of both the body and the environment (depersonalization/derealization symptoms) (16–18).

In healthy subjects, experimental evidence has shown that semicircular canal stimulation may change the instantaneous representation of the body segments (19). Also, in microgravity, mental transformation of one's own body or body parts becomes more difficult (20). In patients, caloric vestibular stimulation, rotation or galvanic vestibular stimulation may modify certain illusions of body representation, such as somatophrenia (a tendency to imagine or exaggerate body ills), hemi-body neglect, or phantom limb (21–23). In amputees, caloric vestibular stimulation may even evoke phantom limb illusion (24).

Caloric vestibular stimulation may also reduce experimental pain (25, 26) as well as clinical central pain (27, 28). In healthy subjects cold left caloric vestibular stimulations may elicit a modulation of both nociceptive processing and pain perception. Using laser pulses for selective stimulation of the left hand skin nociceptors, before and after left cold caloric vestibular stimulation, showed that vestibular stimulation induced a transient decrease of subjective pain intensity, which was associated with reduced amplitude of all laser evoked potential components, including the first arrival of nociceptive input to primary somatosensory cortex (26). In several chronic pain conditions, caloric vestibular stimulation may temporarily ameliorate pain (29). It may decrease chronic central post-stroke pain, along with reduction of somatic delusions (30). In 2 of 4 patients with pain following spinal cord injury, caloric vestibular stimulation had an analgesic effect (31). In a group of 10 patients with phantom limb pain, caloric vestibular stimulation was related to pain reduction in all of them (24). In patients with a variety of pain conditions including phantom limb pain, spinal cord injury and complex regional pain, a significant analgesic effect was observed after cold caloric vestibular stimulation, compared to a control stimulation (ice-pack to forehead) (32).

The effect of vestibular stimulation on nociception has been usually assessed by strong cold stimulation of the left horizontal semicircular canal. However, irrigation of the external ear canal

with a strong cold stimulus can be painful, and it could activate inhibitory nociceptive pathways (33). Yet, in patients with limb amputation, a moderate cold stimulus with water at 20°C have been used to evoke phantom perception as well as to decrease phantom limb pain, either ipsilateral or contralateral to the amputation side, supporting that caloric stimulation seems to have general activation effects on the neural mechanisms underpinning the representation of the body (24). This finding suggests that the mild caloric vestibular stimulation used in the clinical setting could have an effect on phantom limb pain. In addition, the influence of altered graviception by utricle stimulation on the perception of phantom limb pain has not been assessed. Moreover, there is a lack of information on the possible association between the perception of phantom limb pain and altered perceptions or experience of the self or the environment (symptoms of depersonalization/derealization).

The Aims of the Present Study Were:

- To assess if the mild caloric stimulation of the horizontal semicircular-canals, given by any of the stimuli comprising the clinical caloric tests, could have an effect on the intensity of phantom limb pain similar to the effect already reported for cold caloric vestibular stimulation.
- To assess if utricular stimulation by unilateral centrifugation could have an effect on the intensity of phantom limb pain, similar to the effect of caloric stimulation.
- To explore the association between changes on phantom limb pain and the report of altered perceptions or experience of the self or the environment, by probing for depersonalization/derealization symptoms simultaneously with phantom pain intensity, just before and after vestibular stimulation.

In order to partially control for inter-subject variability, the study was performed in a homogeneous group of patients, all of them had unilateral supracondylar amputation, secondary to complications of type 2 diabetes mellitus, and a cross over design was used to test semicircular canal stimulation and utricle stimulation, with a week in-between, including a daily follow-up of pain intensity after each vestibular stimulus.

MATERIALS AND METHODS

Participants

The research protocol was approved by the Research and Ethics Committees of the Institution (IMSS. R-2015-785-050).The study was carried out in accordance with the Declaration of Helsinki and its amendments.

Thirty four patients (56 ± 7 years old, mean ± standard deviation; 23 men) gave their informed consent to participate in the study. All of them reported phantom limb pain after 3–23 months of unilateral supracondylar amputation (median 5 months) (**Table 1**). None of them wore prosthetic devices, or had history of otology or balance disorders or prolypherative retinopathy or advanced renal disease. Patients with a history of migraine or other neurological or psychiatric disorders (submission to psychiatric care or psychopharmacological treatment) were not included in the study. Three patients received the first vestibular stimuli, but did not come back for the second stimuli due to unavailability of adequate transportation or personal circumstances unrelated to the study or the phantom limb pain.

TABLE 1 | General characteristics of 34 patients with unilateral supracondylar amputation of a lower limb, secondary to type 2 diabetes mellitus.

CHARACTERISTIC	
Amputated limb (right/left)	18/16
Handiness (right/left)	32/2
LATTINEN SCORE (RANGE & MEDIAN)	
Total score	2–13 (7)
Pain intensity	1–3 (1.5)
Pain frequency	1–4 (2)
Need of medication	0–3 (1)
Handicap	0–3 (1)
FEATURES OF PHANTOM PAIN (FREQUENCY)	
Electric shocks	91%
Painful cold	50%
Burning	20%
ASSOCIATED SYMPTOMS (FREQUENCY)	
Pins & needles	76%
Numbness	76%
Tingling	73%
Itching	50%
SYMPTOMS OF COMMON MENTAL DISORDERS(FREQUENCY)	
GHQ12 score ≥3	47%
Zung anxiety score ≥45	17%
Hamilton score ≥8	82%
Dissociative experiences score ≥8	61%

The sample size was calculated in order to identify the already reported general effect of caloric vestibular stimulation on phantom limb pain, with a pain intensity decrease in 90% of the participants, precision of ±0.10 and 2 sided type I error of 0.01.

Procedures

Evaluations Prior to Vestibular Stimulation

The diagnosis of phantom limb pain was confirmed by an independent surgeon within the week before vestibular stimulation. Then, adequate ear function was verified by quantitative testing, using tympanometry (Interacoustics AT235, Assens), audiometry (Orbiter 922 Madsen, Otometrics, Taastrup), eye movement recordings and rotational tests at 0.16 Hz and 1.28 Hz (I-Portal NOTC, Neuro Kinetics, Pennsylvania). Within the same day of the first vestibular stimulation, pain characteristics were assessed using the Lattinen index (34) and the DN4 questionnaire (*Douleur Neuropathique 4 Questions*) (35); and symptoms of common mental disorders were evaluated using the General Health Questionnaire of 12 items (36), the Zung Instrument for Anxiety Disorders (37), the 17-items Hamilton Depression Rating Scale (38), and the Dissociative Experiences Scale (39). Additionally, handiness was assessed by the Edinburg inventory (40).

The Lattinen Index is a tool for measuring chronic pain. It comprises 4 dimensions: Pain intensity, Pain frequency, Analgesic consumption, Functional Ability, and Hours of Sleep. In Spanish, the overall score as well as the individual dimensions have been validated, showing positive correlation with the Visual Analog Scale and the McGill Pain Questionnaire, among other scales. The internal consistency and test-retest assays have shown coefficient values of alpha > 0.7 and intra-class correlation > 0.85, respectively (34).

The DN4 is a questionnaire for identification of chronic pain associated to a lesion in the nervous system. It includes 10 items. The first seven items are related to the quality of pain (burning, painful cold, and electric shocks) and its association to abnormal sensations (tingling, pins and needles, numbness, and itching). The other 3 items are related to neurological examination in the painful area (touch hypoesthesia, pinprick hypoesthesia and tactile allodynia) (35).

The 12 item General Health Questionnaire (GHQ-12) comprises 12 items to identify symptoms of depression and anxiety. It was scored using the "GHQ method" of 0-0-1-1 (range 0–12) (36).

The Zung Instrument for Anxiety Disorders is a 20-item scale, with some of the items keyed positively and some negatively, on a four-point scale ranging from 1 "none or a little of the time" to 4 "most or all of the time." The final score range from 20 to 80, a score between 20 and 44 is considered in the normality range (37).

The 17 item-Hamilton Depression Rating Scale evaluate depressed mood, vegetative and cognitive symptoms of depression, and co-morbid anxiety symptoms (23, 24). The 17 items were rated on a 5-point (0–4) with a rating of 0 = absent; 1 = doubtful to mild; 2 = mild to moderate; 3 = moderate to severe; 4 = very severe. The final score range from 0 to 48, a score between 0 and 7 points is considered in the normality range (38).

The Dissociative Experiences Scale comprises a broad range of dissociative experiences including disturbances in memory, identity, and cognition, and feelings of derealization, depersonalization, absorption, and imaginative involvement. Scores on each of the 28 items could range from 0%, "This never happens to you," to 100%, "This always happens to you," using multiples of ten (e.g. 10, 20, 30%,. . .). The total score is calculated by dividing the sum of the individual scores by 28 (range 0 to 100%). A cutoff of 8 is considered in the low normal range (39).

Vestibular Stimulation

A cross over design was used to administer 2 vestibular stimuli by an independent investigator, with a follow-up of pain intensity for 7 days after each stimulus. Since the effect of vestibular stimulation was expected to be transitory, the follow-up was intended just to verify the return to baseline before the next stimulation.

During the first visit, patients were assigned by a random number list either to caloric stimulation of the right or the left horizontal semicircular canal, at 30°C or 44°C (20) (ICS NCI 480, Otometrics, Taastrup), or to unilateral centrifugation at 3.85 cm right or left (300°/s peak velocity; I-Portal NOTC, Neuro Kinetics, Pennsylvania). During the second visit, patients who already received caloric stimulation were assigned to centrifugation and *visceversa,* with random stimulation of the right or the left ear. The intensity of phantom limb pain, by the pain intensity subs-core of the Lattinen Index (34), and depersonalization/derealization symptoms (41) were assessed before and after delivering vestibular stimulus.

After caloric vestibular stimulation all participants showed horizontal nystagmus and reported vertigo; while during centrifugation, the deviation of the visual vertical was consistent with the side of the stimulus.

After each stimulation session, patients received instructions to daily record the intensity of phantom pain on a printed version of the pain intensity sub-score of the Lattinen Index for each day, and every day, they received a standardized phone call remaining them to register the intensity of pain.

To facilitate self-report of pain intensity, since the selected type of patients usually has a variety of visual deficiencies, the pain intensity dimension of the Lattinen Index was preferred among other instruments. This subs-core includes both numeric and simple descriptors that are organized vertically, and it is rated on a 5-point scale from 0 to 4, with a rating of 0 = no; 1 = mild; 2 = moderate; 3 = severe; 4 = unbearable (34).

The 28 item depersonalization/derealization inventory is a tool designed to assess symptoms of depersonalization/derealization in clinically anxiety states, more than in a dissociative disorders context. The severity of each item is coded on a scale where 0 = does not occur, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe. The total score is calculated by adding-up all the points (range 0–112). The higher scores are related to a higher frequency and/or severity of the symptoms, no cutoff score has been suggested (41).

Analysis

Statistical analysis was performed on coded data to assess the immediate responses to vestibular stimulation and the effect of confounding variables, using paired "t" test, Cohen's h and Cohen's d, and analysis of covariance (CSS, Statsoft, Tulsa),

TABLE 2 | Mean and standard deviation of the mean of the sub-score of pain intensity (from 0 to 4) of the Lattinen index, reported by the patients with pain before and after each type of vestibular stimulation.

Vestibular stimuli	Number	Pain intensity score		*p*	Effect size
		Before	After		Cohen's d
CALORICS					
Right 30°C	7	1.2 ± 0.4	0.5 ±0.7	**0.008**	1.75
Left 30°C	6	1.5 ±0.8	0	**0.007**	1.87
Right 44°C	1	1	0	NA	NA
Left 44°C	5	1.6 ± 0.5	0.2 ±0.4	**0.025**	2.8
CENTRIFUGATION					
Right	11	1.4 ±0. 6	0.2 ±0.4	**0.001**	2
Left	9	1.7 ±0.8	0.5 ±1	**0.002**	1.5

Significant values are given for "t" test for dependent samples. The p values > 0.05 are highlighted.

with a 2 sided significance level of 0.05. In addition, since just before vestibular stimulation, some patients reported the absence of phantom pain, discriminant function analysis (CSS, Statsoft, Tulsa) was used to assess the association between the report of specific symptoms of depersonalization/ derealization and the report of phantom limb pain.

Discriminant function analysis is used to determine which variables discriminate between two or more naturally occurring groups. In this study, it was used to determine which symptoms of depersonalization/derealization could discriminate between patients with/without phantom limb pain just at the moment of vestibular stimulation, as well as between those who reported or not a decrease of phantom limb pain after stimulation.

RESULTS

Phantom Limb Pain

The characteristics of phantom limb pain reported by the patients are described in **Table 1**. Although, all the patients reported phantom limb pain during the clinical evaluation, at the moment of the first vestibular stimulation, 28 patients reported pain and 6 had no pain. At the moment of the second vestibular stimulation (day 8), 11 patients reported phantom limb pain, 20 patients had no pain and 3 patients did not come back.

According to the type of stimuli, since 3 patients received just one stimulus, 32 patients received caloric stimulation (8 right/8 left at 30°C; 7 right/9 left at 44°C) (**Table 2**), and 33 patients received centrifugation (19 right/14 left) (**Table 2**). After any stimuli, there was a decrease of pain intensity, with a very large size effect (**Table 2**). However, among those who received right caloric stimulation at 44°C, just one patient reported phantom limb pain at the moment of vestibular stimulation, which decreased after the stimulus, while the other 6 patients reported no pain at the moment of vestibular stimulation.

The frequency of pain decrease after either caloric stimulation or centrifugation was similar (**Table 2**), the size effect between the 2 stimuli was small (Cohen's h = 0.35). The first time, 92% (12/13) and 80% (12/15) of the patients reported pain decrease after caloric stimulation and centrifugation, respectively, the 6 patients with no pain reported no change (**Figure 1**). The second time, 80% (4/5) and 66% (4/6) of the patients reported pain decrease after caloric stimulation and centrifugation respectively, the 20 patients with no pain reported no change (**Figure 1**). The two times, one third of the patients who reported pain decrease immediately after stimulation had no pain at least for 1 day (**Figure 1**).

According to the report of phantom limb pain before and after vestibular stimulation, pain intensity scores are shown in **Figure 2**. Among the 24 patients who reported pain decrease after the first vestibular stimulation, 21 patients received the second vestibular stimulation, of whom 13 patients reported no pain and 8 reported pain. The 3 patients who received just the first vestibular stimulation reported pain decrease after stimulation, which lasted for 1 or 2 days. At the moment of the 2 vestibular stimulations, 5 patients reported no phantom limb pain. Their general characteristics were similar to the characteristics of the whole group of patients. Contrary, two patients reported persistent phantom limb pain, before and after the 2 vestibular stimulations. They were women aged 53 and 58 years, with recent amputation (3 and 4 months, 1 right/1 left); the 2 of them had a GHQ12 score $\geq$3, with symptoms suggestive of depression, and a dissociative experiences score $\geq$8.

The frequency of symptoms of common mental disorders is described in **Table 1**. Multivariate analysis showed no influence of the report of symptoms of common mental disorders on the Lattinen Index total score attained at the clinical evaluation, or the pain intensity sub-score reported before any of the 2 vestibular stimuli ($p > 0.05$). However, these results may have been influenced by the low frequency of symptoms of anxiety, and the high frequency of symptoms of depression that were reported by the participants.

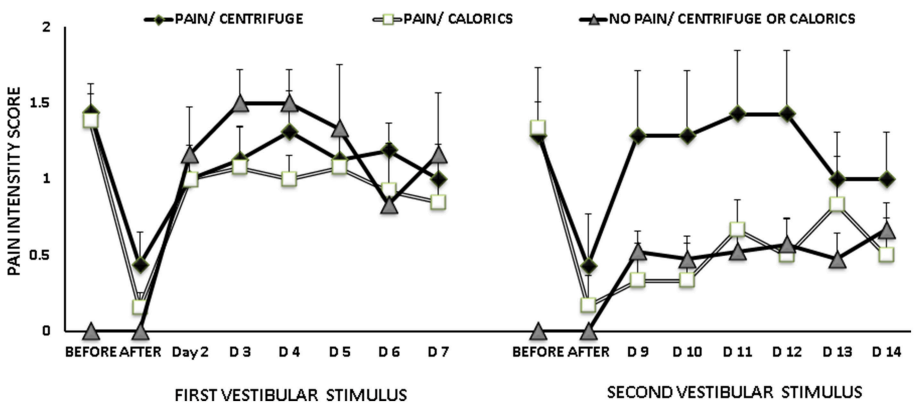

FIGURE 1 | Mean and standard error of the mean of pain intensity scores, before and after vestibular stimulation, according to the report of phantom limb pain at the moment of vestibular stimulation and the type of stimuli, either caloric stimulation or unilateral centrifugation. At the second stimulation, patients who already received caloric stimulation were assigned to unilateral centrifugation and *visceversa*. At the first vestibular stimulation, among 28 patients with phantom pain 13 received caloric stimulation and 15 received unilateral centrifugation, while 6 patients reported no phantom pain. At the second vestibular stimulation, among 11 patients with phantom pain 5 received caloric stimulation and 6 received unilateral centrifugation, while 20 patients reported no phantom pain.

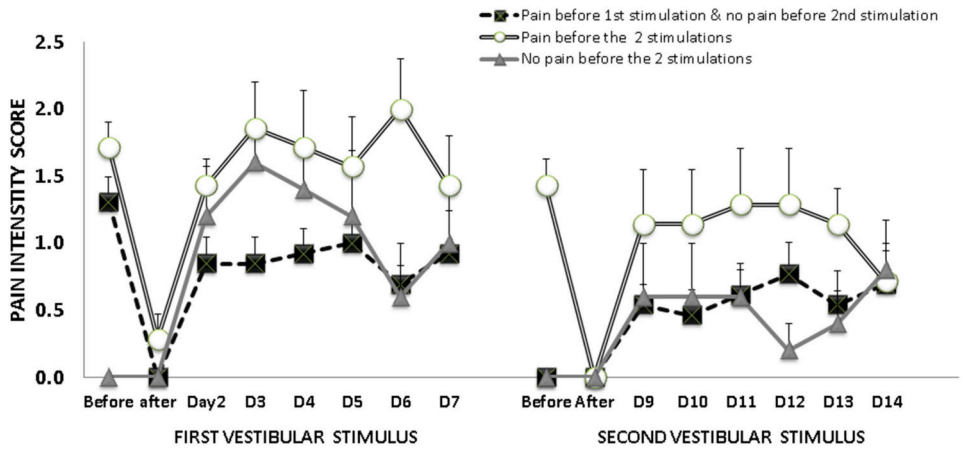

FIGURE 2 | Mean and standard error of the mean of pain intensity scores, before and after vestibular stimulation, according to the report of phantom pain at the moment of each vestibular stimulation 13 patients reported phantom pain just before the first vestibular stimulation, but no phantom pain before the second stimulation; while 7 patients reported phantom pain before the 2 stimulations and 5 patients reported no phantom pain before either stimulation.

Symptoms of Depersonalization/Derealization

Depersonalization/derealization symptoms reported by the patients are described in **Table 3**.

After the first vestibular stimulation, the total score of depersonalization/derealization symptoms decreased in all patients (18 ± 15 vs. 10 ± 8; Cohen's d = 0.53) (paired "t" test, $t = 3.4$, $p = 0.001$), including those who had pain (18 ± 14 vs. 10 ± 6; Cohen's d = 0.57) (paired "t" test, $t = 3.2$, $p = 0.003$). After the second vestibular stimulation the score also decreased in all patients (16 ± 13 vs. 11 ± 10; Cohen's d = 0.38) (paired "t" test, $t = 3.0$, $p = 0.005$), but almost significantly in those who had pain (19 ± 13 vs. 12 ± 8; Cohen's d = 0.53) (paired "t" test, $t = 2.15$, $p = 0.056$).

Before any stimulation, the symptom "Body feels strange or different in some way" was reported by circa 80% of all the patients, which decreased after either stimulus to circa 55% ("t" test, after either stimulus $t \geq 2.9$, $p \leq 0.005$). Other symptoms that decreased after either stimulus were: "Feeling of detachment or separation from surroundings," "Feeling detached or separated from your body," "Your emotions seem disconnected from yourself," "The distinction between close and distant is blurred," and "Feel isolated from the world" ("t" test, after either stimulus $t \geq 2.3$, $p \leq 0.02$).

Discriminant function analysis showed that the combination of the symptoms "Body fells numb," "Vision is dulled," and "Feel as though in a trance," before vestibular stimulation, discerned 81% of the times those who had phantom pain, and 50% of those with no pain (Malahanobis distance 1.07, $F = 5.2$, $p = 0.002$). In addition, "Feel as though in a trance," before vestibular stimulation, discerned 82% of the times the decrease of the intensity of phantom pain after vestibular stimulation and 57% of no decrease (Malahanobis distance 1.13, = 5.6, $p = 0.02$).

DISCUSSION

In this study, mild caloric stimulus of the horizontal semicircular canals, by clinical test, as well as unilateral stimulation of the utricles, by centrifugation, were related to temporary decrease of phantom limb pain, in association to decrease on the report of symptoms of depersonalization/ derealization.

The finding that stimulation of either the semicircular canals or the utricles (right or left) may have an effect on phantom limb pain, further supports the hypothesis by Andre et al. (24), that vestibular stimulation may have general effects on the neural mechanisms underpinning the representation of the body. However, to assess this hypothesis, further functional imaging studies on multisensory integration are needed, taking into account the effect of magnetic vestibular stimulation (42). In addition, it is important to ponder that, in this study, the stimulation provided by the two stimuli was asymmetric and not physiological. During unilateral caloric stimulation each labyrinth is activated separately; while during eccentric acceleration in a fixed earth vertical attitude, the fast rotation of the direction of the resultant linear acceleration is not accompanied by a tilt velocity signal of the semicircular canals [for review see (43)]. Then, the sudden discrepancy between the discordant sensory input and the reference frame given by individual experiences could also have had an influence on the change of the immediate experience of the body in the environment.

Interestingly, the report of general feelings of unreality, like "Feel as though in a trance" showed the greatest association with the report of phantom limb pain before stimulation, as well as with pain decrease after vestibular stimulation. The biological viability of these associations may be supported by the contribution of the vestibular inputs to the conscious experience of the body (19). Since the vestibular system is phylogenetically

TABLE 3 | Frequency and score range of each of the depersonalization/derealization symptoms (42) reported by the patients before and after vestibular stimulation.

Depersonalization/ derealization symptoms	Centrifuge (*N* = 33)		*p*	Calorics (*N* = 32)		*p*
	Before frequency (score range)	After frequency (score range)		Before frequency (score range)	After frequency (score range)	
1. Surroundings seem strange and unreal	33.3% (0–3)	30.3% (0–3)	0.17	37.5% (0–3)	31.3% (0–3)	0.5
2. Time seems to pass very slowly	54.5% (0–4)	45.5% (0–2)	**0.02**	53.1% (0–3)	43.8% (0–3)	0.14
3. Body feels strange or different in some way	78.8% (0–4)	57.6% (02)	**0.0007**	81.3% (0–4)	53.1% (0–3)	**0.005**
4. Feel like you've been here before (déjà vu)	18.2% (0–2)	15.2% (0–2)	0.74	21.9% (0–3)	25.0% (0–3)	0.82
5. Feel as though in a dream	30.3% (0–4)	51.5% (0–2)	0.72	40.6% (0–4)	40.6% (0–3)	0.30
6. Body feels numb	69.7% (0–4)	48.5% (0–2)	**0.0004**	68.8% (0–3)	56.3% (0–3)	0.19
7. Feeling of detachment or separation from surroundings	33.3% (0–3)	21.2% (0–2)	**0.02**	43.8% (0–4)	15.6% (0–2)	**0.009**
8. Numbing of emotions	54.5% (0–3)	48.5% (0–2)	0.13	59.4% (0–3)	37.5% (0–2)	**0.007**
9. People and objects seem far away	30.3% (0–3)	18.2% (0–2)	**0.03**	40.6% (0–4)	25.0% (0–2)	0.07
10. Feeling detached or separated from your body	27.3% (0–4)	12.1% (0–3)	**0.02**	40.6% (0–4)	25.0% (0–2)	**0.02**
11. Thoughts seem blurred	30.3% (0–2)	36.4% (0–2)	0.78	50.0% (0–3)	28.1% (0–2)	**0.005**
12. Events seem to happen in slow motion	15.2% (0–2)	48.5% (0–2)	**0.005**	31.3% (0–3)	21.9% (0–3)	0.16
13. Your emotions seem disconnected from yourself	36.4% (0–4)	18.2% (0–2)	**0.03**	43.8% (0–3)	28.1% (0–3)	**0.02**
14. Feeling of not being in control of self	39.4% (0–2)	27.3% (0–2)	0.32	46.9% (0–3)	25.0% (0–2)	**0.02**
15. People appear strange or unreal	15.2% (0–1)	6.1% (0–1)	0.08	21.9% (0–2)	6.3%% (0–2)	0.09
16. Dizziness	39.4% (0–2)	60.6% (0–4)	0.06	40.6% (0–2)	71.9% (0–3)	0.09
17. Surroundings appear covered with a haze	18.2% (0–2)	33.3% (0–1)	0.21	28.1% (0–3)	25.0% (0–2)	0.35
18. Vision is dulled	75.8% (0–4)	63.6% (0–3)	**0.01**	81.3% (0–4)	68.8% (0–3)	0.11
19. Feel as if walking on shifting ground	21.2% (0–2)	24.2% (0–2)	0.74	21.9% (0–2)	18.8% (0–3)	0.78
20. Difficulty understanding what others say to you	48.5% (0–4)	18.2% (0–1)	**0.0004**	50.0% (0–3)	37.5% (0–2)	0.16
21. Difficulty focusing attention	33.3% (0–3)	21.2% (0–2)	0.09	46.9% (0–3)	34.4% (0–2)	**0.02**
22. Feel as though in a trance	27.3% (0–2)	36.4% (0–2)	0.18	18.8% (0–3)	21.9% (0–1)	0.71
23. The distinction between close and distant is blurred	60.6% (0–4)	45.5% (0–2)	**0.008**	59.4% (0–3)	50.0% (0–2)	**0.04**
24. Difficulty concentrating	45.5% (0–3)	24.2% (0–1)	**0.016**	46.9% (0–3)	37.5% (0–2)	0.13
25. Feel as though your personality is different	51.5% (0–3)	42.4% (0–3)	0.21	56.3% (0–3)	34.4% (0–2)	**0.001**
26. Feel confused or bewildered	36.4% (0–3)	30.3% (0–3)	0.49	43.8% (0–3)	28.1% (0–2)	**0.02**
27. Feel isolated from the world	36.4% (0–3)	15.2% (0–1)	**0.007**	43.8% (0–4)	28.1% (0–1)	**0.01**
28. Feel "spacy" or "spaced out"	9.1% (0–1)	12.1% (0–3)	0.25	15.6% (0–3)	15.6% (0–1)	0.42

Significant values are given for "t" test for dependent samples. The p values > 0.05 are highlighted.

ancient, and its connectivity has prevailed in many networks, contributing to the internal representation of the self (44, 45); while, nociception contributes to subtend the most primitive forms of somatosensation (46), and it also contributes to the multisensory representations that underlie the sense of one's own body and of peripersonal space (25).

In this study, participants were asked to report phantom limb pain intensity immediately before and after vestibular stimulation, with a daily follow-up. Patients with no pain just at the moment of vestibular stimulation reported no change after stimulation, but during the following days they reported their usual experience of phantom pain. Then, half of the patients experienced phantom limb pain only before one vestibular stimulation, which decreased after stimulation, and they reported no pain and no change after the other vestibular stimulation. This finding advocates for an authentic report of phantom limb pain before and after vestibular stimulation. Of note, just 16% of the patients reported no pain before the two vestibular stimulations. This fluctuation of pain intensity is consistent with epidemiological studies showing that patients with persistent phantom limb pain may report that pain is usually intermittent (47, 48). In a survey of 255 lower extremity amputees several months or years after amputation, 81% of those reporting phantom limb pain stated that it was episodic in nature (49). Similarly, in a group of 92 patients with lower extremity amputation only 37% of the group who reported phantom limb pain experienced it more than half of the time (50).

Among the patients with phantom limb pain who reported pain decrease following the first vestibular stimulation, a week later, just 33% of them reported phantom limb pain again. This finding suggests that vestibular stimulation might also have an influence on the clinical evolution of phantom limb pain intensity. However, this study cannot test such hypothesis, which would require a different study design. On the other hand, 2 of the patients participating in the study reported persistent phantom limb pain, with no decrease after vestibular stimulation. Several factors may have conditioned the persistence of pain, including a possible influence of the distress related to grief (51). Also, in amputees, epidemiological evidence suggests that depressed mood may contribute to the experience of chronic pain, including phantom limb pain (52). Of note, all the participants of this study have type 2 diabetes mellitus, which doubles the odds ratio for comorbid depression (53).

The main limitation of the study is the lack of a sham stimulus. Since there was no previous study on the effect of mild stimulation of the semicircular canals by the stimuli comprising the clinical caloric tests or a possible effect of utricular stimulation on phantom limb pain, the study was designed to assess these effects in a selected group of patients with intricate diabetes complications. Then, care had to be taken to minimize exposure to conditions with uncertain benefit to the patient. Another limitation was the unsuitability of the majority of patients with type 2 diabetes mellitus to fulfill the stringent selection required to participate in the study, which limit the generalizability of the findings. Another limitation of the study was the failure to test the 4 stimuli included in the clinical caloric tests, since the majority of the patients exposed to warm caloric stimulus of the right ear reported no pain at the moment of stimulation. Then, the study cannot support or deny differences between warm stimulation of the right semicircular canal vs. any of the other 3 stimuli (right-cold, left-warm, & left-cold).

CONCLUSION

The results show that the mild unilateral vestibular stimulation used for clinical tests, of either the horizontal semicircular canals or the utricles, might modify the intensity of phantom limb pain along with decrease on the report of altered perceptions or experience of the self or the environment. These effects might be related to an update of the immediate experience of the body, given by the sensory mismatch induced by asymmetrical vestibular stimulation.

DATA AVAILABILITY

Full data is available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

KJ-R: conceived and designed the study and the vestibular stimuli, analyzed and interpreted the data, and wrote the manuscript. CA-M: supervised the selection of participants, performed the stimuli, collected the data, and revised the manuscript. JR-E: selected and evaluated the participants and revised the manuscript. AA-G, AB-S, and LG: performed a preliminary assessment and invited the candidates to participate, and revised the manuscript.

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Self-Motion Versus Environmental-Motion Perception Following Rotational Vestibular Stimulation and Factors Modifying Them

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Motion perception following rotational vestibular stimulation is described either as a self-motion or as an environmental-motion. The purpose of the present study was to establish frequency of occurrence of both sensations in healthy humans; what other sensations they experience and how factors insinuation and visual cues modify them. Twenty-four healthy subjects were rotated with constant velocity of 80°/s in four combinations of opened and closed eyes during the rotation and after a sudden stop. After the cessation of the rotation they reported their spontaneous or insinuated illusory motion. During spontaneous perception after sudden cessation of rotation and with the subject's eyes open, the illusory sensations of self- and environmental-motion were almost equally presented. There was no simultaneous illusory perception of self-motion and environmental-motion. Insinuation modified the perception of motion; presence or absence of visual cues prior to the cessation of the rotation and the presence or absence of visual cues immediately after the cessation of the rotation changed the motion sensation. There is a gender effect in motion perception. This finding might be of benefit in further exploring the gender difference in the susceptibility to motion sickness.

Keywords: self-motion, environmental-motion, perception, insinuation, vestibular, visual

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INTRODUCTION

The vertigo in which a subject inappropriately experiences the perception of motion is generally due to a dysfunction of the vestibular system or its unusual stimulation. The vertigo is used to describe two different types of motion: "external" vertigo—false sensation that the visual surround is moving, and "internal" vertigo—false sensation of self-motion (1, 2).

Vertigo, with its two types, is unique due to the fact that, unlike other pathological symptoms, it may be experienced by healthy humans during strong stimulation of the vestibular system in their life activities, e.g., repetitive spinning, known as a physiologic vertigo (3). Physiologic vertigo occurs with the physiological stimulation of any of the three stabilizing sensory systems: vestibular, visual or somatosensory. It is induced by intersensory or intrasensory mismatches (4). Unlike in most cases of vestibular pathology, in healthy humans it is caused by symmetrical stimulation of both labyrinths. In one, generating excitatory impulses, in the other—inhibitory impulses.

Numerous articles describe the characteristics of vertigo in pathology (5–7). This sensation belongs to so called derealization symptoms, which is discussed in previous articles not only in vestibular pathology but also in psychiatric practice, for instance anxiety [see in (8)]. However, to understand the pathology better, as well as to understand the physiological vertigo, importantly linked to the development of devices for enjoyment and human transportation—especially aircrafts and spacecrafts where spatial disorientation caused by motion illusions may lead to accidents (9, 10), we need to know how this sensation is experienced by healthy humans.

The search in the literature shows that there are very few publications in this field (11–20) which are mostly focused on self-motion perception. An earlier study on illusory self-motion perception shows that it significantly varies when strong unilateral caloric vestibular stimulation is applied in healthy humans (12, 21). However in the study the illusory environmental-motion perception was not investigated. Besides the subjects were either in supine position or their head was tilted backward so that the lateral semicircular canals were in the vertical plane therefore their afferentation interferes with the signal from the otoliths due to the effect of the gravity.

In a previous investigation (11) it has been shown that at threshold level of vestibular or visual stimulation the insinuation changes motion perception in healthy humans. Therefore it is of interest to know whether and in which way the insinuation during supra-threshold stimulation will change the perception.

This study aimed to establish which sensation between self- and environmental-motion predominates in healthy humans when the body is suddenly stopped after vertical axis rotation, what other sensation is experienced, the direction of motion with respect to the stimulus direction, and how the perception is influenced by different conditions of vestibular-visual interaction. We also aimed to establish whether insinuation influences the perceived motion and is there a gender effect. We hypothesize that perception for motion in healthy humans will not be equal for all humans but supposedly exists dominating perception of what is moving and its direction, indicating inter-individual difference; the visual-vestibular interaction and insinuation will change specifically the perception; a gender effect exists mainly in insinuation.

SUBJECTS AND METHOD

Twenty-four healthy volunteers (12 men and 12 women with the same age range: from 23 to 35 years) took part in the present study. Their vestibular and visual systems were examined prior to the study in order to exclude any disease affecting these systems. The subjects in seating position were rotated on a Barany chair surrounded with a stationary optokinetic pattern with vertical black and white stripes in an illuminated room. The rotation was 12 cycles with a constant velocity of 80°/s−54 s. totally, twice to the left and to the right randomized between the subjects. After a sudden cessation of the rotation they had to describe their sensation of motion.

Twelve experimental series randomized between the subjects were conducted. Three randomized questions were asked: (1) What is moving and in what direction? (spontaneous perception); (2) Are you moving and in what direction? (insinuated perception); (3) Is the environment moving and in what direction? (insinuated perception). In the insinuated series the subjects were instructed to attend to, and to report the occurrence of either self-motion (self-motion task) or environmental-motion (environmental-motion task). We aimed to investigate, with the last two tasks, the effect of the insinuation factor (11). The tasks were performed under four conditions with respect to the visual input factor, randomized between the subjects, in order to understand the effect of the integration of the vestibular signal with the visual one. These four conditions can be summarized as follows:

1. Eyes open during rotation and after the sudden stop
2. Eyes closed during rotation then eyes open after the sudden stop
3. Eyes open during rotation then eyes closed after the sudden stop
4. Eyes closed during rotation and after the sudden stop.

When the subjects had their eyes open they were instructed to look straight ahead. For the purpose of the analysis, the reports were divided into four possible groups with respect to the presence and the direction of motion. The groups were as follows: (1) rotation in the opposite direction to the chair rotation, (2) rotation in the same direction as the chair, (3) perception of some motion without clear discrimination of the direction of the motion or what is moving, (4) lack of perception of motion. The gender effect was also investigated. The *Chi-square test* was used for statistical analysis. A $p < 0.05$ was accepted as significant.

The study was approved by the local Bioethics Committee of the Institute of Neurobiology of The Bulgarian Academy of Sciences, Sofia. It was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all subjects of this study.

RESULTS

The results of the spontaneous perception under each of the four visual-vestibular interaction conditions are presented in **Figure 1**. The results show that the motion under four visual-vestibular interaction conditions varies among the subjects indicating inter-individual difference (**Figure 1**). A part of the subjects perceive self-motion, while another part—environmental-motion. That varies depending on the visual-vestibular condition. Under open eyes during rotation and after the stop condition illusory rotation (self and environmental) in the direction opposite to that of the chair rotation dominates ($p < 0.001$). There is no significant difference between perception of the self- and the environmental-motions. The self- and environmental-motion perception in the direction of the chair rotation is experienced in 6.2% ($SE = 3.5\%$) of the trials. While under open eyes during rotation and after the stop condition the visual afferentation is integrated with the

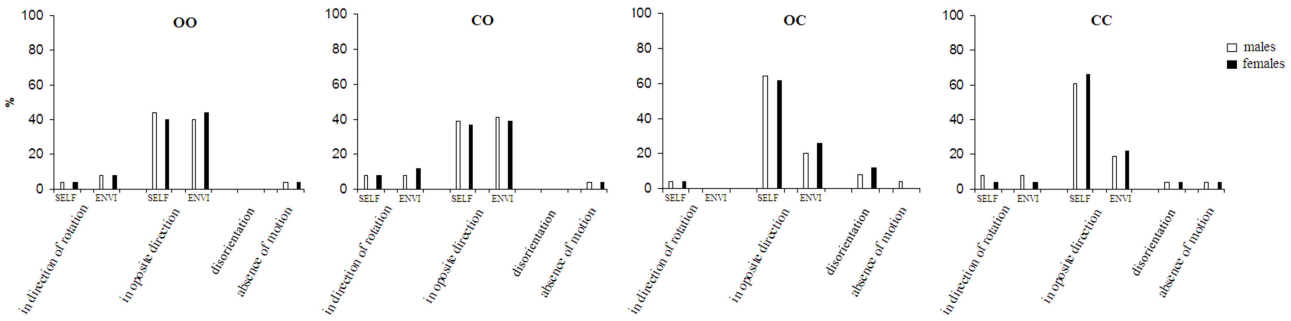

FIGURE 1 | Spontaneous perception of motion after sudden stop of rotation. OO, eyes opened during the rotation and after the sudden stop; CO, eyes closed during the rotation and opened immediately after the sudden stop; OC, eyes opened during the rotation and closed immediately after the sudden stop; CC, eyes closed during the rotation and after the sudden stop; SELF, perception of self-motion; ENVI, perception of environmental-motion.

vestibular one, under closed eyes during rotation and after the stop condition the subjects had total visual deprivation. In the latter condition the perception of self-motion in the direction opposite to that of the chair rotation increased ($p < 0.01$). However, 16.7% ($SE = 5.4\%$) of the subjects had a feeling of environmental-rotation, although they do not see it. Under this condition, the perception of self- or environmental-rotation in the direction of the chair rotation was rare–6.2% ($SE = 3.5\%$) of the trials. In conditions of partial visual deprivation—closed eyes during rotation and open eyes after the stop condition and open eyes during rotation and closed eyes after the stop condition, different effects showed. In the former there is no significant difference between perceptions of the self- and environmental-motion perception in the direction opposite to that of chair rotation. In the latter, the perception of self-motion was higher and the perception of environmental-motion lower compared to both conditions with open eyes after the stop—closed and open during the rotation ($p < 0.01$). That is, in closed eyes during rotation and closed after the stop condition the results are closer to open eyes before and after the stop condition, while open eyes during the rotation and closed eyes after the stop condition shows results closer to closed eyes before and after the stop condition. Self- and environmental-motion perception in the direction of the chair rotation were rare experienced–6.2% ($SE = 3.5\%$) of the trials.

Under the two conditions with closed eyes after the cessation of the rotation a third, unclear sensation appeared. Subjects described it as a spatial "disorientation." By description it corresponds partly to "visually-induced dizziness" of the Barany Society classification (22). Disorientation dominates in open eyes during rotation and closed after the stop condition ($p < 0.05$).

In the spontaneous perception series, the gender effect was not significant.

The effect of the factor of insinuation on the perception of self-motion and environmental-motion is shown in **Figures 2**, **3**. Generally, in the insinuation series the sensation referred to as disorientation becomes consistently more pronounced ($p < 0.001$) and the absence of motion as well ($p < 0.001$). **Figure 2** presents the effect of the insinuation of self-motion on the motion perception. Under the first condition (open eyes before and after the stop) the perception of self-motion in a direction opposite to the direction of the chair rotation predominates over that in the direction of the chair rotation ($p < 0.001$). The experience of disorientation appears under this condition unlike in to the spontaneous series. Absence of motion consistently increased compared to the spontaneous series ($p < 0.001$) and it is dominating sensation in this condition. Under the condition of total visual deprivation the perception of self-motion in the direction opposite to that of the chair rotation increases nearly doubly compared to the first condition ($p < 0.001$). It strongly dominates all other sensations ($p < 0.001$). The disorientation sensation decreases almost doubly ($p < 0.001$), while the absence of motion sensation decreases nearly three times ($p < 0.001$). Compared to open eyes before and after the stop condition the insinuation of self-motion during partial visual deprivation, i.e., eyes closed during the body rotation and open after the stop or open during rotation and close after the sudden stop, shows different perceptual changes. In the former, the absence of the perception of motion dominates ($p < 0.01$), whereas in the latter, the perception of self-rotation in the direction opposite to that of the chair rotation dominates ($p < 0.01$). The disorientation sensation is present in both conditions but dominates under the condition with closed eyes after the sudden stop ($p < 0.01$).

Figure 3 presents the effect of the insinuation of environmental-motion on the motion perception.

Under the first condition, the perception of the environmental-motion in the direction opposite to that of the chair rotation significantly dominated all other sensations ($p < 0.01$) followed by absence of motion, motion in the direction of chair rotation and disorientation. Under the condition with total visual deprivation, although only in 8.3% ($SE = 3.5\%$) of the trials there were reports of a perception of environmental-motion in a direction opposite to that of the chair rotation; however, nobody reported perception of environmental-motion in the direction of the chair rotation. Here, like the first condition there were reports of a disorientation sensation–14.6% ($SE = 5.1\%$) of the trials. The absence of motion sensation strongly dominates under this fourth condition ($p < 0.001$) [79.2% ($SE = 6.1\%$) of the trials]. With respect to the two conditions with partial

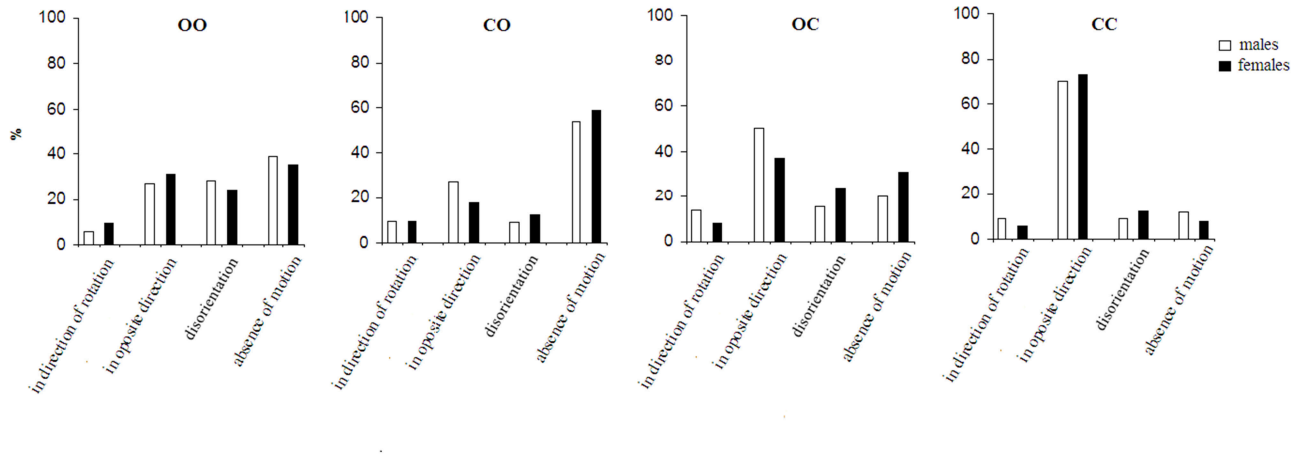

FIGURE 2 | The perception of motion under conditions for the insinuation of self-motion. For the abbreviations see **Figure 1**.

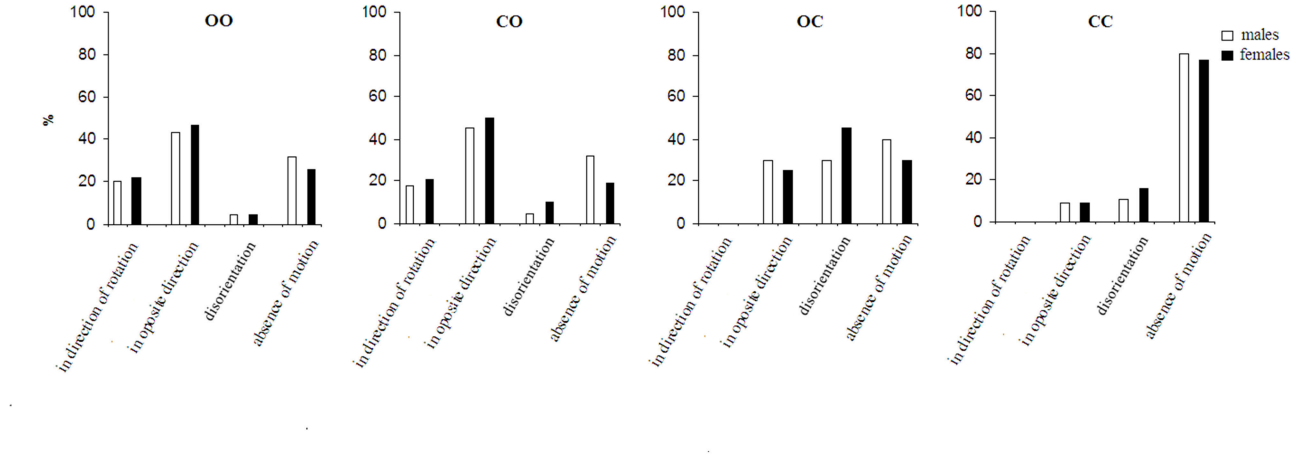

FIGURE 3 | The perception of motion under conditions for the insinuation of environmental-motion. For the abbreviations see **Figure 1**.

visual deprivation—eyes closed during the rotation and opened after the stop and eyes open during the rotation and closed after the stop, the results of the former were close to the condition with open eyes before and after the stop. That is, perception of environmental-motion in a direction opposite to that of the chair rotation dominated ($p < 0.01$). Under the latter condition eyes open during the rotation and closed after the stop in a significant percent ($p < 0.01$) of trials–27% ($SE = 4.4\%$), the subjects had a feeling of environmental-motion although they were with closed eyes. Under this condition the disorientation sensation slightly, insignificantly dominates, followed by an absence of any sensation of motion and environmental-motion in the direction opposite to chair rotation. Environmental-motion in the direction of the chair rotation was not experienced under this condition.

When both insinuation series are compared, it is seen that the insinuation effect differs significantly ($p < 0.01$) in the appearance of the insinuated motion perception (self- or environmental), as well as in the disorientation and the perception of an absence of motion. Under the most natural condition: with open eyes during and after the rotation, the insinuation modifies both perceptions in different ways. While in the spontaneous perception series there is no significant difference between the self- and environmental-motion perceptions under this condition, in the insinuation series the perception of environmental-motion dominates over self-motion ($p < 0.05$). This tendency of domination of environmental-motion is expressed more under the second condition—eyes closed during the rotation and opened after the stop ($p < 0.01$), while in the spontaneous series the effect is almost the same. Under the third condition—open eyes during the rotation and closed after the stop, there is an inversion of the effect: the self-motion perception dominates over the environmental-motion perception ($p < 0.01$). This perception dominates also, and is even more expressed, under the same condition, in the spontaneous series ($p < 0.01$).

Under the last condition: total visual deprivation, the perception of environmental-motion consistently decreases, while the perception of self-motion correspondingly increases ($p < 0.001$). In the spontaneous series, respectively, the tendency is the same.

The disorientation perception significantly ($p < 0.01$) differs between the two insinuation series showing different tendencies across the four conditions. In the insinuation of self-motion it dominates under the first condition—open eyes before and after the stop ($p < 0.01$) but is more present in the insinuation of environmental-motion under the third condition—open eyes during the rotation and closed after the stop ($p < 0.01$). In the spontaneous perception series, the sensation is less expressed ($p < 0.05$).

With respect to the sensation of an absence of motion it also differs significantly between the two insinuation series. In the insinuation of self-motion it dominates under the second condition—closed eyes during the rotation and open after the stop over the other conditions ($p < 0.01$). However, in insinuation for environmental-motion it is most pronounced under the fourth condition—visual deprivation ($p < 0.001$).

The two insinuation series showed gender difference significant ($p < 0.05$) in both partial visual deprivation conditions (**Figures 2**, **3**). It is pronounced for disorientation sensation—dominating in females, and absence of motion—dominating in males.

DISCUSSION

The present study found that after a sudden stop of constant velocity rotation humans with open eyes spontaneously perceive nearly equally either self- or environmental-motion, never both simultaneously. Presence or absence of visual cues prior or after the stop change the perception. Insinuation modifies the perception. There is a gender effect.

Self- and environmental-motion perceptions were investigated in different aspects using either vestibular—caloric or rotational, or visual stimuli [e.g., (11–14, 16–21, 23)]. When thresholds for motion were studied mostly sinusoidal visual and vestibular stimuli were used. Our previous studies (11, 13) showed how visual-vestibular interaction and the insinuation change the threshold for self-motion and object/visual scene motion perception during different frequencies sinusoidal rotation, to establish the frequency effect.

In the present study we used constant vestibular suprathreshold stimulus caused by sudden stop of constant velocity combined with different visual stimuli to establish the percent frequency of occurrence of perception for self- and environmental-motion.

This study shows that in healthy humans spontaneously under open eyes before and after the stop condition both types perceptions are presented almost equally. Our hypothesis is that the "egocentric" perception dominates in the brain of some humans while the perception of the external world (exocentric) dominates in others. We assume that it is possible for the mechanism to function at "a chance level" in some of the subjects (11). That is to say, their attention, at a particular moment, may be directed either toward the external world or toward themselves. The present study shows also that there are other factors which contribute to which type of perception is evoked. These are insinuation and the afferentation of visual cues integrated with vestibular afferentation.

It is interesting to note that even under total visual deprivation an environmental-motion perception can be created. One hypothetical explanation is Eigengrau/Eigenlicht phenomenon, more commonly referred to as visual noise. It is considered to be result of spontaneous discharge of the receptors in the retina which creates images (24). Supposedly such visual images contribute for motion perception. A second hypothesis, especially for open eyes during the rotation and closed after the stop condition, is that it is possible afterimage effect to facilitate the appearance of this perception. A recent study at threshold level indicates that afterimage lowers the threshold for self-motion perception (14). It might be at suprathreshold level this phenomenon to contribute for evoking perception of environmental-motion. We suppose that efference copy signal could probably contribute for evoking perception for the described environmental-motion. It provides the only extraretinal signal about eye position that is available without delay, and it is shown to be the most important extraretinal source of information for perceptual localization and motor activity. Efference copy accompanies all voluntary eye movements and some involuntary ones, including pursuits, saccades, and the fast phases of vestibular and optokinetic nystagmus (25). It could be admitted also that in the absence of visual afferentation from the external world an imaginary environmental image may exist in the brain, probably due to the short-term visuospatial residual memory for which the right parietal eye field and frontal eye fields play a key functional role as show several experiments (26–28). It is possible this perception to be generated by a combination of the proposed mechanisms.

The two types of partial visual deprivation used in this study showed different effects. The explanation could be that in the first case the visual signal is uninterruptedly moving with constant velocity along the retina while in the other this motion is caused by eye balls motion with decreasing velocity from the vestibuloocular reflex (VOR) which generates oculogyral illusion (29).

The effects of the insinuation on the perceptions of self- and environmental-motion are different depending on the condition which is in an agreement with our previous findings on threshold level in different experimental conditions of vestibular-visual interaction (11, 13). The evoked perception of environmental-motion dominates over the evoked perception of self-motion under the open eyes during rotation and after the stop condition, when the brain receives full visual afferentation in conjunction with those of the vestibular and the somatosensory ones. It dominates also, and is even more expressed, under the condition of reduced visual afferentation—closed eyes during the rotation and open after the stop, when the eyes are closed during rotation and opened after the sudden stop. Probably, the modulating influence of the insinuation has a stronger effect on the perception of environmental-motion than on that of self-motion. Probably to some extent this is constitutionally influenced as for

instance the susceptibility to motion sickness (30) in which the vestibular and the visual systems are also involved (31, 32). In agreement with this hypothesis is that human behavioral genetic methods indicate individual behavioral difference with a genetic base (33).

It is interesting to note that the perceptions of self-motion and environmental-motion in the insinuated series do not dominate over the same perceptions in the spontaneous perception series. Even under the first three conditions they are slightly less perceived than that in the spontaneous perception series. This indicates that the insinuation influences mainly on the other two sensations: disorientation and absence of motion.

For the greater part of the trials the direction of the perceived two rotations is based on the functioning of vestibulospinal and vestibuloocular reflexes. However, in a small number of the trials there was a perception of rotation in the opposite direction. This probably is due to a perceptual signal intensity which, in this case, is close to the motion perception threshold but below to that for determining direction which, together with the existing noise in the system, causes an erroneous conclusion for motion direction (11, 19). In those who perceive "disorientation," obviously the afferentation for motion perception is close but below the threshold for a definite motion. The signal is ineffective for the brain to define the motion.

Another interesting finding in this study is that nobody reported an appearance of both sensations simultaneously. The hypothetical explanation is that the motion perception mechanism is organized in such a way that probably only one perception can operate at a time especially when it is illusion. Once one illusory motion perception, evoked by suprathreshold motion stimulus, occupies the brain's perceptual mechanism, it does so completely until the sensory afferentation is changed. The phenomenon vection [described in number of studies, e.g., recent ones (34, 35)] supports this hypothesis. Once one is in vection it is so powerful illusory perception that he cannot stop this illusory motion perception. We hold that the phenomenon we describe belongs to the class of the Necker cube phenomenon, where perceptual interpretations tend to switch between two states. There exists a model that correspondingly describes the mechanism (36, 37). This class of models is called visual-vestibular conflict models. One may experienced a similar phenomenon also in the train illusion where one sits in a train and the one on the other track is moving, evoking a self-motion illusion that can switch back to feeling oneself stationary. There is a tendency that once one gets trapped into the illusion, it may be difficult to get out again. What is characteristic of such perceptions is that one can have only one or the other.

The results of the present study indicate that in human's brain perception there is significant gender effect in conditions of insinuation for motion. In agreement with this finding is that other human perceptive reactions also show a gender difference e.g., in neurosensory systems adaptation [to space in astronauts (38)]. The brain exhibits sex difference in responses to stress or other environmental cues (39), sensation and perception (40). Also in mental processes like mental rotation (41–43).

While in disease vertigo as a symptom is an indication for structural damage or alteration in the homeostasis, its biological meaning in healthy humans is unclear. The vestibular system and its interaction with the other systems in the brain are phylogenetically imperfectly created to function, thus evoking vertigo in healthy humans which in many situations is not useful, e.g., when appear oculogyral illusions (29), and in some cases even unpleasant.

Certainly, with the development of the transportation industry and especially astronautics and aviation, the importance of, and the necessity to understand, the nature of vertigo and its related sensations in healthy humans will increase; as will the need to manage them with new aproaches and devices due to the big problem of accidents caused by the human factor—spatial disorientation for motion, position, or attitude, especially in military aviation with loses, not only material, but also of human lives (9, 10). For instance the approach for creating artificial gravity by centrifuge for long-term space flights concerns the perception for motion (44).

The limitation of the present investigation is that the suprathreshold effect was studied for one suprathreshold stimulus only. In a next experiment it would be interesting to establish how increasing strength of suprathreshold stimuli affects the trend of the perception.

In conclusion, in healthy humans, after sudden cessation of rotation and with the subject's eyes open, the spontaneous illusory sensations of self- and environmental-motion are nearly equally presented; there is no simultaneous perception of illusory self- and environmental-motion; presence or absence of visual cues prior to the cessation of the rotation and immediately after the cessation of the rotation influence the perception of motion; there is an inter-individual difference in the motion perception; insinuation for either motion modifies the perception of motion; there is a gender effect.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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REVIEW
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Vestibular and Multi-Sensory Influences Upon Self-Motion Perception and the Consequences for Human Behavior

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In this manuscript, we comprehensively review both the human and animal literature regarding vestibular and multi-sensory contributions to self-motion perception. This covers the anatomical basis and how and where the signals are processed at all levels from the peripheral vestibular system to the brainstem and cerebellum and finally to the cortex. Further, we consider how and where these vestibular signals are integrated with other sensory cues to facilitate self-motion perception. We conclude by demonstrating the wide-ranging influences of the vestibular system and self-motion perception upon behavior, namely eye movement, postural control, and spatial awareness as well as new discoveries that such perception can impact upon numerical cognition, human affect, and bodily self-consciousness.

Keywords: self-motion perception, vestibular system, cerebellum, cortex, behavior

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INTRODUCTION

Despite the vestibular system being evolutionarily ancient (1), it has long been overlooked as a primary sensory organ, notably by Flourens who, whilst identifying that pigeons with peripheral vestibular lesions suffered from imbalance, concluded that the semi-circular canals were involved in generating motor responses for head and eye movements (2). The inner ear itself was first recorded in the 1,500 s by Andreas Vesalius and Gabriele Fallopio, reviewed by Weist (3). Initial research into the mechanics behind how acceleration can be detected took place in the 1870s by three independent scientists: Josef Breuer, a Viennese doctor, Ernst Mach, a professor of physics and Alexander Crum Brown, who worked as a chemist having received degrees in medicine and chemistry. They identified the semi-circular canals as the organs for motion sensation, suggested relative inertial motion of endolymph to the bony skull as the method of transduction, and observed that the semi-circular canals and otoliths might work in combination to differentiate between linear motion and tilt, and whose work forms the basis of our current understanding, well-reviewed by Weist and Baloh (4) and Weist (3). The vestibular system is found in different forms across the animal kingdom and is reviewed by Lowenstein (5) and Beisel et al. (6).

The paired vestibular organs consist of three semi-circular canals and two otoliths, which together sense rotational and linear accelerations and are responsible for maintaining both stable vision during head movements [via the vestibular-ocular reflex (VOR)] and a stable posture (via vestibular-spinal reflexes). Furthermore, they also contribute to an awareness of our movement in space as demonstrated by the ability of a subject to report passively applied movements whilst seated in a rotating chair in darkness. In everyday life, vestibular stimuli are integrated with

visual, somatosensory, auditory, and motor efference inputs to derive estimates of self-motion. Perhaps the reason for the omission of vestibular perception from the traditional human senses is that, compared with the perceptual times for other senses, vestibular perceptual awareness is relatively slow (70–160 ms) and less sensitive (7, 8). Accordingly, during daily life we are often unaware of workings of the vestibular system until it fails. Patients with vestibular disorders suffer not only from difficulties with balance but also report head-movement induced oscillopsia and difficulties during complex behaviors such as self-motion perception and navigation (9). This review will examine the role of the vestibular system in the perception of self-motion and explore how self-motion perception can modulate other behaviors.

SENSING MOTION

The vestibular organs are our motion detectors and consist of the otoliths and the semi-circular canals. These detect changes in velocity via stimulation of the hair cells which contain cilia projections from their apical surface. The cilia are named according to their length: the longest being the kinocilium, the others, the stereocilia. Even in the absence of any stimulation, they exhibit a low level of tonic activity (10–12). Hair cells depolarise when the stereocilia deflect toward the kinocilium and hyperpolarise when the deflection of the stereocilia is directed away from the kinocilium (13–15). Depolarisation leads to release of neurotransmitters onto first-order vestibular neurons. Such deflections occur due to the relative inertia of the endolymph in the semi-circular canals into which the cilia project: when the head accelerates, the lag of this fluid deflects the cilia. The hair cells also receive efferent synapses which can modulate the activity of the hair cells (16). The utricle and saccule are the two otoliths and detect linear accelerations in the axial and coronal planes, respectively. Their hair cells project into a gelatinous layer which is covered with calcium carbonate crystals. The anterior, posterior, and horizontal canals work in pairs to sense rotations in the sagittal (pitch), coronal (roll), and transverse (yaw) planes, with an increase in impulse discharge during ipsilateral rotation and a reduction seen during contralateral rotation (11) [it might be added here that the semi-circular canals have also been shown to respond to tilting and linear acceleration, albeit with a much greater threshold (17)]. Two distinct types of afferent neurons, categorized by the regularity of their resting activity spike pattern, carry signals from the hair cells to the vestibular nuclei (12). For canal afferents, regular fibers, which have smaller axon diameters, are thought to predominantly transmit information about head motion over time whereas the irregular fibers are more sensitive to motion, exhibiting higher gain (18, 19). Both fibers respond similarly to active and passive head motion (20). Otolith afferents are similarly formed of regularly- and irregularly-firing neurons (21).

THE VESTIBULO-OCULAR REFLEX

The vestibulo-ocular reflex (VOR) serves to stabilize visual input on the retina during short, fast head movements by driving the eyes with a velocity of equal magnitude and in opposite direction to the head movement. It was first described by Andreas Hoegyes who demonstrated that each semi-circular canal was connected to the appropriate extra-ocular muscle (22). The canal afferents, having tonic discharge that is modulated according to the direction of rotation (10, 11), work in pairs, such that stimulation of one side occurs whilst the other side is inhibited (23). Similar mechanisms exist for translational head movements, which result in a linear VOR (24, 25). The VOR is fittingly fast, operating with latencies of 5–6 ms (26), which is in keeping with the short three-neuron pathway involved: the primary afferent neuron of the vestibular nerve, an interneuron, and a motor neuron to the corresponding extra-ocular muscle (27–29). The functional importance of which was first recognized by Lorente de No, who discovered that feedback pathways within the neuronal arc are involved in the VOR, a concept extended by Raphan et al. in their description of the velocity storage mechanism (30, 31). Furthermore, the VOR is sensitive, and can respond, to changes in the relationship between vestibular signals and the visual field: wearing magnifying lenses leads to adaptive increases in VOR gain whilst left-right reversing Dove prisms lead to adaptive decreases in the gain of the VOR (32–34). The mechanism for these adaptations appears to be via long-term depression in the cerebellar flocculus (35, 36). [Note that removal of the vestibulocerebellum does not abolish the VOR (34)]. Following unilateral vestibular loss, there is an impressive recovery of the VOR, revealing the importance of multimodal input integration, in particular, proprioceptive, and motor efferent inputs (37, 38). Nystagmus arises when there is slow, continuous movement of the head, with the slow, vestibular, component in the opposite direction of the motion, and a fast, "catch-up" saccade in the same direction [note that nystagmus can, of course, arise in other circumstances, namely: physiological nystagmus (optokinetic and end-point); infantile nystagmus and pathologic nystagmus, reviewed by Abadi (39)]. Early work carried out by Lorente de No established the importance of the role of the reticular nuclei in these reflexes: in rabbits with lesions of the raphe nuclei of the pons and the medulla oblongata, thus severing the axons of the reticular nuclei, the fast component of nystagmus disappeared (40, 41).

WHAT IS SELF-MOTION PERCEPTION AND HOW DOES THE VESTIBULAR SYSTEM AND ASSOCIATED CENTRAL PROCESSING GIVE RISE TO IT?

Perception of Angular Motion

Perception of passive self-rotation can be quantified in terms of the minimum (or threshold) rotation required for perceptual awareness and by a subject's estimates of angular velocity and/or displacement. Vestibular perceptual thresholds are dependent upon the axis of rotation, with thresholds for whole-body rotations about the vertical axis (yaw) being significantly lower than those for roll and pitch (42). Additionally, perceptual thresholds improve as the frequency of sinusoidal rotation increases up to 0.2 Hz, and plateau beyond 0.5 Hz, findings that suggest that vestibular signals undergo high-pass filtering

(see **Figure 1**) (43). Vestibular perception thresholds for yaw rotations in young healthy subjects are significantly greater at 1.18 deg/s^2 compared with the angular acceleration required for nystagmus (0.51 deg/s^2) (44).

Eye movements can also be used to indicate perceived rotation by implementing a paradigm in which participants are either asked to hold a given direction of gaze in the dark during angular rotation (which requires both the vestibular-ocular reflex and a compensatory saccade), or are instructed to make a saccade back to a previously seen visual target after having been rotated in the dark (vestibular memory-contingent saccade) (45). Subjects perform marginally better in the latter, possibly secondary to interference between the VOR and the rotation being estimated during the former task (46). As with threshold perceptions, yaw rotations yield the best accuracy (46). Labyrinthine-defective patients are unable to produce any structured response as would be expected of a task designed to test vestibular perception (47).

The ability to estimate and reproduce rotational *displacement* is another method to probe vestibular perception. Metcalfe and Bronstein examined the ability of patients with labyrinthine disease and healthy controls to re-orientate themselves using a self-controlled motorized Barany chair after passive displacement in the dark in a "go-back-to-start" paradigm (48). Controls demonstrated high accuracy with low degrees of variation (5–15° for 30–180° displacements). Patients with acute unilateral vestibular failure (within a month of symptom onset) demonstrated an inability to accurately perceive rotations in either direction, consistently underestimating magnitude of displacement toward the lesion and exhibiting highly variable responses to rotation in the opposite direction. The study followed the patients up for several months, by which time there was partial restoration of perception and the symmetry of the responses had been restored, suggesting compensatory central mechanisms.

More recently, Panichi et al. sat subjects in a head-fixed rotating chair in darkness and asked them to fixate on the location of a previously seen target (presented straight ahead prior to rotation) (49). The chair rotated in an asymmetric sinusoidal pattern, with a fast component in one direction and a slow, restoring component in the opposite direction, an arrangement previously shown to selectively bias central vestibular perceptual processing (50). They found that patients with acute vestibular neuritis have a large deficit in vestibular perception during conditions in which the slow-phase acceleration was toward the lesioned side and that whilst this improved over the 1-year follow-up period, it did not return to normal. Notably, this asymmetry of self-motion perception correlated with patients' dizziness handicap inventory score. It has been well-documented that clinical outcomes in patients with chronic dizziness correlate poorly with low-level brainstem reflexes (i.e., VOR) (51–53) and much better with cortical processes including visual dependence and anxiety and depression (54, 55). These observations provide support for the theory that there exist different central mechanisms for compensation of VOR and vestibulo-perceptual responses, with the latter higher-level processes affording better predication of prognosis following vestibular dysfunction.

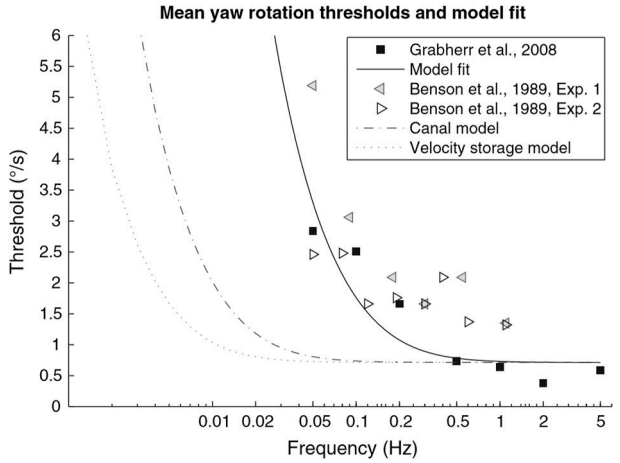

FIGURE 1 | From section Perception of angular motion. This figure, modified from Grabherr et al. (43). Graph showing velocity thresholds as a function of sinusoidal motion frequency, where velocity is the peak velocity achieved in each cycle of sinusoidal acceleration. Black squares represent mean data from Grabherr et al. (43), $n = 7$. Left and right pointing triangles from Benson et al. (42), $n = 6$ and $n = 8$, respectively. Solid black line represents the fitted model for the high-pass filter $K_{TS}/(TS + 1)$.

Perception of Linear Motion

Linear accelerations are sensed by the otolith organs, and the double integral of their signal can be used to estimate passive linear displacement in the absence of other sensory inputs (56, 57). In their study, Israel et al. found that whilst subjects were unable to spontaneously produce a passive linear displacement of two meters when blindfolded, they were able to reproduce the distance traveled, peak velocity, and velocity profile following passive displacement and that, in this paradigm, reproduction of parameters relating to velocity appeared to have been processed independently of the reproduction of displacement (56). Regarding vestibular perception of linear motion, lateral movements have lower thresholds than anterior-posterior movements: in one study using a sinusoidal stimulus of frequency 1 Hz, thresholds for accelerations were 6.5 cm/s^2 and 8.5 cm/^{2} for lateral and anterior-posterior movements, respectively, whilst thresholds for velocity were 10.4 and 13.5 cm/s (58). Vertical linear movements have a perceptual threshold greater than that for lateral movements but less than that for anterior posterior motion (59). Using single acceleration steps, Gianna et al. found acceleration thresholds of 4.84 cm/s^s and velocity thresholds of 7.93 cm/s for lateral movements (60). Other movement profiles with linear and parabolic ramping of the acceleration resulted in higher thresholds, thereby supporting the view that large acceleration gradients facilitate perception (see **Figure 2**). The study also examined the thresholds of patients with impaired vestibular function. Although their average thresholds were worse than healthy controls, there was overlap between the two groups, suggesting that somatosensory cues were also used in the task. A recent paper examined the effects of a central (vestibular migraine) and peripheral (Menière's disease) vestibular dysfunction on linear motion perception, finding that perceptual thresholds were higher for patients with Menière's

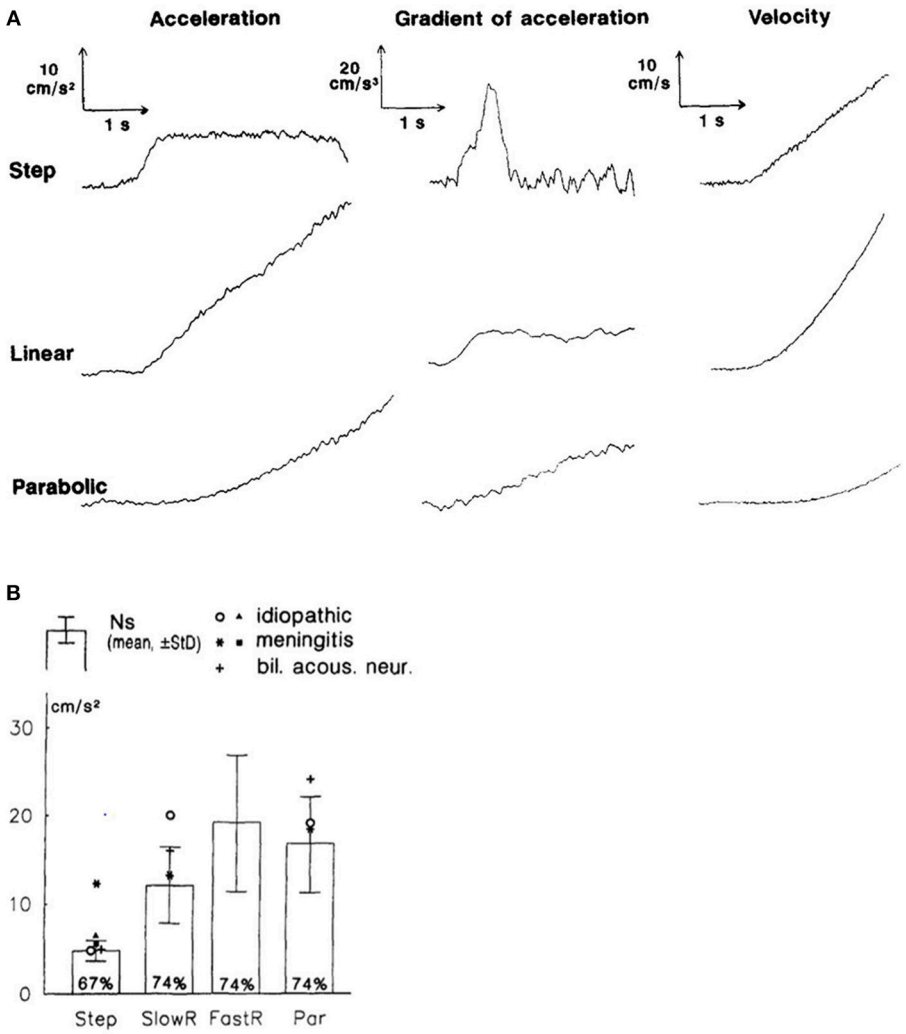

FIGURE 2 | From section Perception of linear motion. This figure, modified from Gianna et al. (60). **(A)** Motion profiles for acceleration steps and corresponding rate of change of acceleration and velocity. **(B)** Acceleration thresholds for normal subjects (Ns) (mean +/− standard deviation) and individual subjects with vestibular impairment in the different conditions: step accelerations, low linear ramp (SlowR), high linear ramp (FastR), and parabolic acceleration (Par).

disease but not significantly different for vestibular migraine patients compared with controls (59). These findings contradict recent findings of abnormal tilt thresholds in vestibular migraine patients (61).

Perception of Heading

The ability to estimate one's direction of translation is termed heading perception and the vestibular system plays an important role in this process. For example, in macaques heading discrimination thresholds in the dark increase 10-fold after bilateral labyrinthectomy (62). Regarding the relative contribution of the visual and vestibular systems in heading estimation tasks, it appears that when subjects are asked to point out the heading direction, the visual system enables more precise determination (63), but when asked to perform a discrimination task (forced choice of two), thresholds are similar for the two senses (62). Interestingly, body position relative to gravity can modify vestibular heading perception, but visual heading perception is unaffected by changes in body position (64).

Calculating Self-Motion Relative to the World

Signals generated by the vestibular system create an egocentric reference of self-motion: to be useful for guiding our movements and behavior relative to the external world, a transformation to an earth-referenced frame of self-motion is required. To create an earth-referenced model of self-motion, two difficulties need to be overcome. Firstly, the signal from the semi-circular canals does not vary with the attitude of the head in space, for example, a raw rotation generates the same signals at the level of the hair cells whether the subject is upright or supine. Secondly, the otoliths alone cannot distinguish linear acceleration from head

tilt relative to gravity (65). These difficulties can be overcome through integration of vestibular signals with additional inputs including visual and proprioceptive stimuli (reviewed below). However, even when undergoing passive motion in a dark room, a solution can theoretically be computed by combining information from the canals and the otoliths. To resolve these problems, it has long been hypothesized that the brain calculates an estimate of the attitude of the head relative to gravity using multisensory inputs, including canal signals, a value that can then be used to resolve the above issues (66). In monkeys undergoing passive movements, some cerebellar nodulus/uvula Purkinjie cells respond preferentially to translation (or rather, to the vector perpendicular to gravity) (67) whereas others respond to tilt (68). These neurons project to the vestibular nuclei and the fastigial nucleus, and from there to the thalamus, which also demonstrates varying degrees of separation of movement types relative to gravity (69, 70). Modeling work suggests a similar mechanism exists in humans (71).

Differentiating Between Actively-Generated and Passively-Applied Motion

An unaddressed question is how we differentiate active vs. passive motion. In life, we experience a combination of actively-generated and passively-applied motion. Yet the relative movement of the endolymph, and the subsequent deflection of the hair cells, is identical during both active and passive movements of a given profile and acceleration. The question arises as to how changes in sensory signals due to external variables (exafference) vs. those resulting from our own actions (reafference) can be distinguished. An in-built mechanism would be to use a copy of any motor commands against which to compare sensory stimuli: this exists in the form of discharge corollaries, also known as motor efference copies. Subtraction of the actual sensory signal from the predicted sensory result of an action theoretically leaves the signal from any additional passive motion.

As noted previously, in alert primates, semi-circular canal afferents respond identically to actively- and passively-generated head movements (20). In contrast, vestibular nuclei neurons show differential activation to passive and active head movements, with reduced responsiveness to vestibular afferents during actively-generated movements (72–74). In an experiment designed to probe the mechanism for such modulation of vestibular neurons responsiveness, Roy et al. compared the activity of medial vestibular nuclei neurons during a range of tasks including: passive whole-body rotations; active head movements; passive body rotations, controlled by the monkey using a steering wheel to drive a turntable, with an earth-fixed head (to activate neck proprioceptors); and, head restrained monkeys actively trying to turn their heads (motor commands but no corresponding proprioceptive signals) (75). Only during the actively generated head movements did the authors observe a reduction in vestibular nuclei neuron responsiveness to vestibular afferent signals. Furthermore, in the paradigm where the monkeys were attempting but unable to move their heads (i.e., there was muscular activation but not a corresponding change in muscle length and joint movement), there was minimal modulation of vestibular nuclei neuron responsiveness. Taken together, these observations suggest that motor efference copies and not proprioceptive signals nor prior knowledge of the movement that lead to suppression of vestibular neuron responses during actively generated movements, and that only when the motor efference copy matches the proprioceptive input does reafference occur. As a neural correlate of this, during active self-motion, neurons in the fastigial nucleus continually compare predicted and actual sensory stimuli (76) and respond only to unexpected self-motion (77). Neurons in the posterior parietal cortex also exhibit a differential response to active and passive movements, although the responses of individual neurons to different types of movement here is more complicated than that observed for the vestibular nuclei neurons, perhaps reflective of more complicated cortical processing (78).

Prolonging Self-Motion Perception: the Velocity Storage Mechanism

The use of the relative motion of the endolymph to the bony canals as an indicator of head motion works well for short, fast head movements. However, with prolonged head movements, friction reduces the relative motion of the endolymph, leading to a decay in the signal generated. When the head is rotating at constant velocity, the signal from the semi-circular canals falls to 1/e of its maximum after 3–7 s: i.e., the time constant of the canals lies between 3 and 7 s (79, 80). However, it is conceivable that it might be physiologically disadvantageous for vestibular reflexes and perception to exhibit a similar decay curve, and indeed measured time constants for the VOR and vestibular perception are on the order of three to four times greater than that of the canals (30, 81). The network responsible for prolonging the time constant of the VOR and perception and thus sustaining behavioral responses beyond the time when the endolymph has ceased to move relative to the head is called the velocity storage mechanism. It can be modeled as a leaky integrator with reversal of the sign of the signal and works as a form of imperfect positive feedback on the canal signal to the nuclei (30). The integrator is leaky to prevent inappropriate propagation of noise. The velocity storage network is thought to reside in the cerebellum. Whilst there has been some debate as to whether the VOR and vestibular perception use the same velocity storage network, most work now supports the theory that they share the mechanism. In healthy subjects, there were no differences in perceived rotational velocity and the slow-phase response of the VOR after suddenly stopping yaw and pitch rotations in the dark (82); time constants of the VOR and perceived rotation co-varied in patients with chronic vestibulo-cerebellar degeneration and healthy controls (83); and, when measuring post-rotational nystagmus and perceived rotation using a hand-driven wheel connected to a tachometer, intra-subject group decay time constants for the two variables were the same for healthy controls (16 s), and patients with congenital nystagmus (7 s) (see **Figure 3**) (84). It is worth noting at this point that the velocity storage network is not the only mechanism

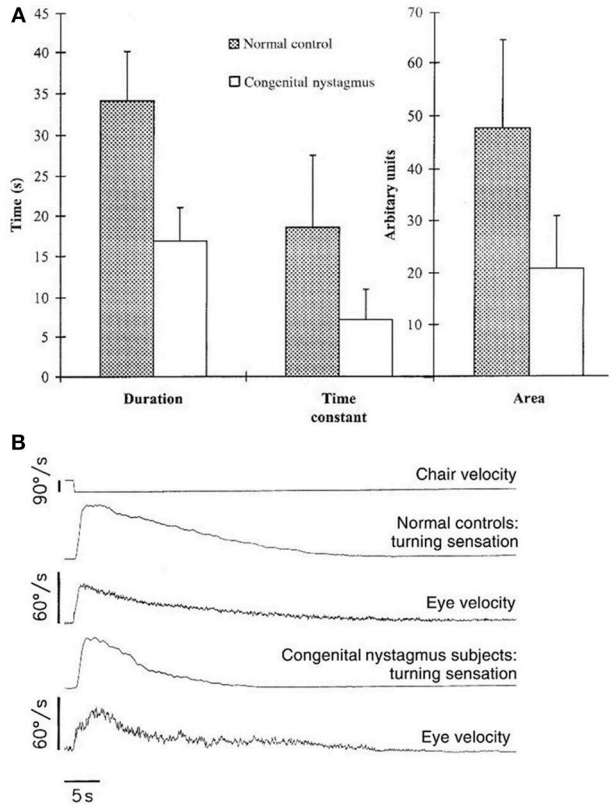

FIGURE 3 | From section Prolonging self-motion perception: the velocity storage mechanism. This figure, from Okada et al. (84). **(A)** Eye velocity and vestibular sensation averaged across subjects (normal, $n = 31$, and congenital nystagmus, n = 14) after suddenly stopping whole-body passive rotations in the dark. **(B)** Mean duration, time constant and area under the curve of turning sensation in subjects with congenital nystagmus and healthy controls.

responsible for prolonged self-motion perception: the visual system also plays an important role. In general, initial, short-latency responses to self-motion are generated by the vestibular system, whilst responses of greater duration and latency are produced predominantly from visual flow inputs (85).

Cognitive Cueing

Cognitive, top-down influences are important for many neural processes: self-motion perception is no different. When subjects were asked to imagine themselves rotating in a chair prior to actual rotation, when the imagined and real rotations were in the same direction, vestibular perceptual thresholds were lower and, interestingly, so were thresholds for the VOR (86). Conversely, the ability to generate and manipulate mental images itself relies upon an intact vestibular system: subjects with vestibular impairment performed worse than healthy controls in object-based mental transformations (87). Furthermore, vestibular stimulation can facilitate mental transformations (88), with improved performance during congruent inertial motion (89). Such cognitive cueing is also evident during traditional passive linear self-motion tasks: with sufficient acceleration, one might expect subjects to experience tilt due to the somatogravic illusion. However, this is generally not reported by participants. Wertheim et al found that when subjects have prior knowledge that they will be accelerated from rest during an experiment, they do not report tilt, but that up to 50% of participants report tilt when they have no prior knowledge, suggesting that the sensation of tilt is suppressed in the former group (90).

SO WHERE IS SELF-MOTION PERCEPTION PROCESSED?

Traditionally, perception was thought to be the preserve of the cortex, with sensory inputs passing first through the thalamus and then to a unimodal area of primary cortex before reaching higher association areas to be combined with other sensory inputs. However, this view is changing: more recent findings suggest that multisensory processes occur in primary sensory cortices and recognize the role of non-cortical areas (91). No specific unimodal vestibular cortical area has been identified; rather, cortical neurons that are modulated by vestibular stimuli also respond to visual, proprioceptive, and motor efference inputs. Therefore, the perception of self-motion is believed to be processed by a network of different structures and regions, centered on the lateral fissure and the parieto-insular "vestibular" cortex and including the vestibular nuclei, cerebellum and other cortical areas, a theory that is supported by the multiple areas found to be involved in self-motion perception in animal and human studies. Having a distributed network is of evolutionary benefit as it reduces the risk that a focal brain lesion leads to a significant defect in self-motion perception. **Figure 4** summarizes the main components of this vestibular network.

The Vestibular Neurons and Their Projections

The vestibular fibers, whose cell bodies are found in Scarpa's ganglion, run to the four principal vestibular nuclei in the dorsolateral pons and medulla and directly innervate the posterior cerebellum, as well as projecting to other central structures (92). These nuclei are also interconnected. Many second order vestibular neurons receive convergent inputs from otolith and canal afferents, thus providing a mechanism for early integration of the two signals (93–95). For vestibular-only neurons, so-called as they respond only to change in head attitude and not to eye movement, this appears to occur physiologically in the form of sub-additive integration, with canal afferents more heavily weighted at lower frequencies and otoliths at higher frequencies (72). As an aside, this may be the basis for a correlate seen in human psychophysical experiments, in which perception of combined passive linear and rotational motion cannot be predicted as the simple sum of the two components (96). Vestibular neurons at this level are also modulated by visual and proprioceptive stimuli and from central, top-down inputs (97). The nuclei project to the spinal cord via the lateral vestibulospinal tract and descending medial longitudinal fasciculus; to the autonomic nervous system; to the extra-ocular nuclei via the ascending medial longitudinal fasciculus; to the cerebellum; and, to the thalamus from where there are connections to the cortex

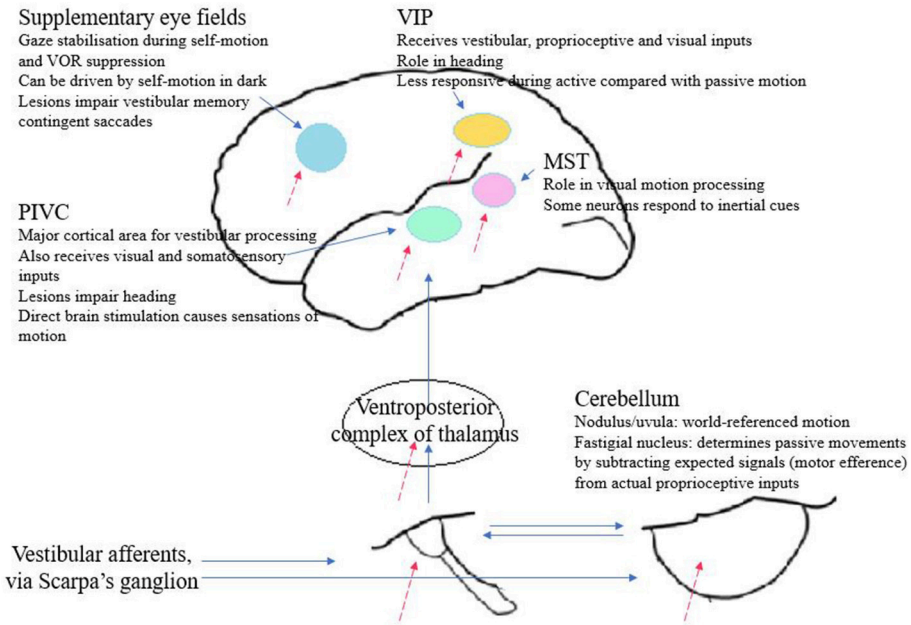

FIGURE 4 | From section So where is self-motion perception processed? Diagram summarizing the main vestibular projections and brain regions contributing to self-motion perception. Dashed arrows indicate integration with extra-vestibular inputs.

(92). A study of patients with acute posterolateral thalamus lesions using positron emission tomography during caloric vestibular stimulation (CVS), demonstrated reduced vestibular temporo-parietal cortex activation on the side ipsilateral to the lesion but did not find any significant effect on motion perception (98).

Cerebellar Contributions to Self-Motion Perception

Recently, the role of the cerebellum has been recognized as extending beyond the traditional confines of motor control of the eye movements and posture to include sensory discrimination and self-motion perception (99, 100). Anatomically, the nodulus/ uvula and fastigial nucleus of the cerebellum receive significant input from the vestibular system: a smaller contribution is of primary afferent fibers projecting to the ipsilateral uvula and nodulus and a larger proportion of secondary fibers from the vestibular nuclei (101). The vestibular nuclei are reciprocally innervated by the cerebellum. As described above, in monkeys the nodulus/ uvula appear to be important in generation of a world-referenced frame of self-motion (67, 68), whereas the fastigial nucleus generates signals of unexpected self-motion by comparing motor efference signals and actual proprioceptive feedback from movement (76, 77).

In humans, psychophysical studies on subjects with cerebellar degeneration have yielded informative observations: patients with midline cerebellar lesions, when rotated in the dark, showed impairment in multiple parameters compared with healthy controls, including the duration of self-motion perception and the perceptual time-constant (see **Figure 5**) (102), findings replicated in a subsequent study of patients with chronic degeneration of the vestibulo-cerebellum (83). A further study investigated the vestibular perceptual thresholds of two patients with cerebellar agenesis, finding them to be globally elevated, particularly for movements which only activated the otoliths (103). These observations support the view that the cerebellum has a role in extracting information about self-motion from multiple signals generated by both self and passive movements, and from background noise.

Cortical Processing of Self-Motion Perception

From the brainstem and cerebellum, vestibular inputs pass through the thalamus, predominantly via the main somatosensory nucleus, the ventroposterior complex, to the cortex. At the thalamus, it has been proposed that information flows in two channels, one encoding head motion, the other body motion (104). Many vestibular-sensitive neurons are already multi-sensory, being modulated by visual, proprioceptive and motor efference signals (105). There are two major cortical areas implicated in the processing of vestibular information for the perception of self-motion: the ventral intraparietal area (VIP) and the parieto-insular vestibular cortex (PIVC). A third, the medial superior temporal area (MST), is critical for visual motion perception but also receives vestibular inputs. The supplementary eye fields appear to be important in the control of eye movements during self-motion: the neurons here are modulated by vestibular stimuli (106); and, patients with lesions of the supplementary eye field exhibited worse accuracy during a vestibular memory-contingent saccade (107, 108).

Neurons in the MST respond predominantly to visual stimuli, and in particular to visual motion stimuli. Several

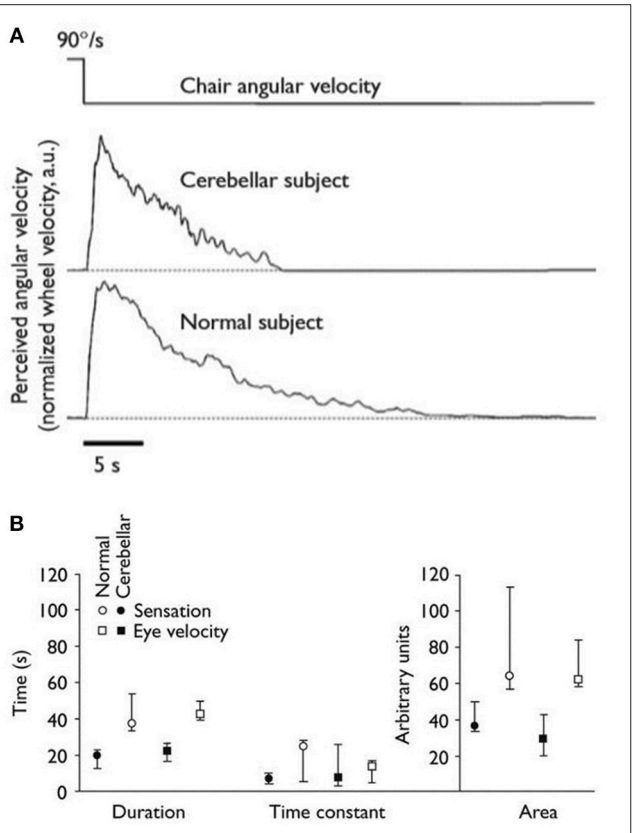

FIGURE 5 | From section Cerebellar contributions to self-motion perception**.** This Figure, from Bronstein et al. (102). **(A)** Graphs of representative individuals for perceived angular velocity after suddenly stopping rotations in the dark. **(B)** Median duration, time constant and area under the curve for sensation and eye velocity in patients with midline cerebellar degeneration ($n = 8$) and healthy controls ($n = 8$).

studies have confirmed the importance of this area in visual heading perception (109–112). It has also been shown that a subset of MST neurons are modulated by passive whole-body translations [a response that is not seen following bilateral labyrinthectomy (62)] albeit with smaller and less directionally selective responses than for optic flow stimuli. Combining vestibular stimulation with congruent and incongruent optic flows varied the amplitude and direction-selectivity of these neurons (113). These findings were since extended to show that the response of MST neurons to inertial motion cues was correlated with heading discrimination (62) and that visual and vestibular cues were summed in neurons with congruent heading preferences (114). However, it remains likely that vestibular cues only have a minor influence over the MST area, a theory that is supported by the finding that inactivating MST using muscimol, a $GABA_A$ agonist, had little effect on vestibular heading thresholds, but did impair visual thresholds (111). Humans with MST lesions display great difficulty in navigation and have impaired visual motion perception (115).

VIP neurons respond reliably to vestibular, visual and somatosensory inputs (116, 117) and receive inputs from MST (118, 119). Compared with MST, VIP neurons are modulated to a greater extent by vestibular stimuli and show greater correlation with perceptual decisions (120). Subgroups of neurons show preferential response to different types of inertial motion, a characteristic that is invariant with respect to head attitude and gaze direction. It is worth noting that responses to active motion are generally smaller than those to passive motion (116), thus raising the question as to the role the VIP cortex plays in distinguishing active vs. passive motions and coordinating appropriate behavioral responses.

Around two-thirds of PIVC neurons respond to vestibular stimulation (121). Vestibular-responsive neurons are more strongly activated by semi-circular canal inputs compared with those from the otoliths. Of those neurons modulated by canal signals, there were subgroups which preferentially encoded rotations in a specific plane. As noted above, the PIVC is multisensory, and neurons there also respond to somatosensory and (particularly large-field) visual stimuli (122, 123). In primates, lesions of the PIVC led to impaired heading perception (124). In humans, whilst direct stimulation of this cortical area during craniotomies led to a range of vestibular sensations including movement of the world and vertigo (125), cerebral infarctions affecting the PIVC are reported to cause an impairment in subjective vertical (126). Functional magnetic resonance imaging studies have revealed activation of the PIVC and posterior insular cortex during caloric vestibular and direct galvanic stimulation (127–129). During this series of experiments, some conditions required subjects to keep their eyes closed, whilst in others they viewed random movement or a fixation cross. The posterior insular cortex responded strongly to visual motion, whereas in the PIVC there was a trend for visual motion to reduce activity (130). The role of the posterior parietal cortex in self-motion perception is demonstrated in a series of psychophysical experiments. Repetitive transcranial magnetic stimulation to this region impairs performance on a whole-body displacement task that required angular path integration based only on vestibular inputs (131). The same stimulation applied to the right posterior parietal cortex also worsened a motion-reproduction task (i.e., one not requiring path integration) when applied *during* the motion reproduction, although it had no effect when applied during the initial rotation (encoding phase) (132).

The role of the posterior parietal cortex in top-down vestibular perception (as defined by vestibular perceptual thresholds) has also been established: transcranial direct current over the temporoparietal junction (TPJ) alters vestibulo-perceptual and VOR thresholds (133, 134). Nigmatullina et al. found that in ballerinas, who are typically trained to perform multiple pirouettes, display remarkable vestibular adaptation, compared with rowers, who are physically active but not trained to tolerate numerous rotations, there is differential white matter volume in the TPJ bilaterally (135). Lesion studies demonstrate a split in processing dependent upon the nature of the task: subjects with parieto-occipital lesions perform well in "low level" tasks such as discriminating the direction of moving stimuli, but poorly when asked to judge heading direction; the reverse is true for patients with occipital lesions (136). Further studies support this theory

of split cortical processing for parallel channels carrying different information about motion (137, 138).

Lateralisation of Vestibular Cortical Processing

Vestibular stimulation activates both cerebral cortices, but it is recognized that there is a right hemisphere dominance in right-handed individuals, and an even stronger left-sided bias in left-handed subjects (139). Although this asymmetry has been shown to lead to differential effects on both vestibular low-level reflex behaviors including the VOR (140) and on vestibular-sensitive cognitive processes [for example, as recently proposed, anxiety (141)], the effects, if any, on self-motion perception remained to be fully explored. As discussed above, repetitive transcranial magnetic stimulation to the posterior parietal cortex can differentially impair perceived whole-body angular displacement, with worse performance when the right hemisphere is stimulated (affecting leftward rotations) compared with left hemisphere rotations (132). Future work could explore whether control of self-motion perception is more commonly the result of asymmetric or symmetric cortical activity.

INTEGRATION OF VESTIBULAR AND NON-VESTIBULAR CUES IN SELF-MOTION PERCEPTION

Whilst the vestibular system clearly plays an important role in self-motion perception, it is far from the only system that can provide such information. This is important because:

a) The human body is not rigid and can move with several degrees of freedom, as explored in a novel paradigm establishing relationships in movement between different body parts (142). Thus, the vestibular system alone is insufficient to provide a complete representation of self-motion.
b) Using one sensory input alone to perceive self-motion would leave one vulnerable to illusions and false interpretations (for example, the somatogravic illusion in which aviators, deprived of adequate visual stimuli, sense linear forward acceleration as a backwards tilt of the head, potentially leading to the dangerous situation of pitching the nose of their aircraft) and to loss of information (constant velocity is not encoded by vestibular system).
c) When using one input, accuracy is worse than can be achieved by integrating multiple inputs.
d) Comparison of sensory inputs with motor efference copies enables discrimination between self-generated and passive motion, as described above.

The vestibular system is unusual in that it receives early input from multiple other systems including visual, somatosensory and motor efference signals [reviewed here (97)]. These multisensory inputs enable refinement of self-motion estimates and thereby attune behavioral responses (143). In general, multisensory processing is a skill which improves over time, and self-motion is no different. Supporting this view are recent findings that demonstrate older adults are able to improve their performance in a driving task by a greater margin than younger adults when additional vestibular cues were added to the visual stimulus (144).

Integration of Visual and Vestibular Inputs

The visual system contributes to self-motion perception, with optic flow-induced perception being highly accurate and precise. Studies in primates reveal that they rely predominantly on the visual system for navigation in three-dimensional space (145). Visual-vestibular interactions occur as early as the vestibular nuclei, although this is mostly seen in neurons involved in the VOR, not in vestibular-only neurons, and thus such interactions are unlikely to be involved in self-motion perception (146, 147). Indeed, Bryan and Angelaki show that VOR neurons in the vestibular and deep cerebellar nuclei cease to respond to optic flow once the OKN was suppressed (by requiring the animals to fixate on a head-fixed target) (147). At higher levels, visual-vestibular input is integrated in cortical areas traditionally associated with visual processing, including the MST and VIP areas. In these regions, there are neurons that respond both to motion in darkness and to optic flow, and the former response is abolished following bilateral labyrinthectomy (62, 148, 149). This may be the neural substrate to explain how combined visual-vestibular stimuli improves self-motion perception compared with either stimulus alone.

When examining the relative contributions of the visual and vestibular systems to self-motion perception, it has become clear that they vary depending upon the experimental conditions rather than having some pre-defined weighting. In a study in which subjects experienced linear acceleration, visual cues enabled more precise determination of heading than vestibular cues (150), whereas in a separate experiment, in subjects undergoing roll rotations, vestibular perception was better at frequencies of sinusoidal motion >2 Hz and visual perception better at frequencies <1 Hz (151). Kolev et al. rotated supine subjects about the earth-vertical axis, i.e., they underwent roll without otolith stimulation (152). Whilst it is unsurprising that coherent, simultaneous visual-vestibular signals improve perceptual thresholds, the authors found that even conflicting visual-vestibular signals, generated when the subjects fixated on a visual target that rotated with them, yield lower perceptual thresholds than seen with vestibular-alone stimulation (152). The study also demonstrated a frequency-dependence of perceptual thresholds. However, experiments designed to probe the sensation of self-motion as induced by moving visual fields reported visual dominance despite the presence of conflicting vestibular stimulation. That is, in subjects undergoing yaw rotations whilst watching visual fields that were rotating in the same direction but at different velocities, the reported magnitude of self-motion appeared to relate to that of the incongruent visual stimuli (153). In a similar setup, subjects reported self-motion perception in the opposite direction to actual whole-body rotation during prolonged periods of yaw rotation during which the visual field rotating in phase and in the same direction as the vestibular rotation (154). These apparent discrepancies are

likely to reflect dynamic reweighting of visual and vestibular cues under different conditions, perhaps reflecting the unlikelihood that information from the visual system is incorrect in daily life.

There is additional cross-talk between the two systems beyond the mere computing self-motion: perceptual learning, as measured by an improvement in vestibular motion discrimination thresholds performed in the dark, occurs when training rotations occur in the light, but not when subjects are blindfolded during training (155).

Integration of Proprioceptive, Somatosensory, and Vestibular Inputs

Proprioception is another important sensory input used alongside vestibular signals to calculate self-motion. Anatomically, integration of the proprioceptive and vestibular systems occurs directly (dorsal root axons innervate vestibular nuclei) and indirectly (via second order neurons and via the cerebellum) [reviewed in (156)]. Functionally, vestibular-only neurons are modulated by passive neck rotations in squirrel monkeys (157) and in cynomolgus monkeys (158), leading to reduced neuronal activity during head only motion compared with whole-body motion. The latter study found that during passive vestibular and proprioceptive stimulation signals underwent linear summation, but that sub-additive integration occurred during active head movements and during gaze shifts. Such differential processing under different experimental conditions might explain the apparently conflicting finding that during passive movements of the head of the rhesus monkey no modulation of vestibular-only neurons was seen (74). The authors hypothesized that this might be a reflection of the arboreal habitats of squirrel and cynomolgus monkeys compared with the predominantly ground-dwelling rhesus monkey. Proprioceptive-vestibular interactions are also documented in the thalamus, primary somatosensory cortex and ventral intraparietal region (159, 160).

The role of the proprioceptive system in self-motion perception in humans is well-established. During a remembered-target task, subjects performed better when there were combined vestibular and neck proprioceptive inputs compared with the vestibular-alone condition (161). In a similar setup, reducing the stimulus amplitude reduced gain in the vestibular-only condition, but not in proprioceptive conditions (47); the study also found that detection of head turns was predominantly determined by somatosensory inputs (47); and that proprioceptive afferents can reliably encode head on body rotations even when there is no vestibular stimulation (162).

This relationship between the vestibular and somatosensory systems is to some degree reciprocal. Vestibular activation improves sensitivity to tactile stimuli (153, 163–167), possibly via a non-linear mechanism that is only in effect once a certain threshold of self-motion perception has been achieved, and this occurs independently to changes in attention (168). Furthermore, vestibular activation can transiently reverse hemianesthesia secondary to brain lesions, possibly due to altered neuronal dynamics in the putamen, insula and secondary somatosensory cortex (169, 170).

Optimal Integration

As discussed above, the precision of self-motion perception is greater when more than one sensory input is used. Recently there has been interest into the way in which multi-sensory cues deriving from a common cause are integrated. Across sensory systems, including the vestibular system, data from experiments appear to suggest that inputs are integrated in a Bayesian optimal way, i.e., the weight of each cue is proportional to its reliability (1/variance) (171). Regarding self-motion perception, visual and vestibular cues appear to be optimally integrated during heading discrimination and rotational movements (151, 172–174). Furthermore, the brain can dynamically change the relative weights of cues to reflect changing conditions (173) and can even integrate conflicting sensory cues in a statistically optimal way to minimize variance (172, 175). Recordings from multi-sensory neurons in the dorsal medial superior temporal area point to its role in visuo-vestibular cue integration, with evidence of near-optimal processing (114, 176).

Aftereffects: Evidence for Shared Hardware to Process Different Stimuli

A method to probe to what degree the same neuronal networks are used to process information from different sensory inputs is to examine cross-modal aftereffects. Aftereffects are the sensations that occur following cessation of the initial stimulus. In the case of motion perception, they typically occur in the opposite direction, thereby shifting perception of subsequent stimuli. For example, in the waterfall illusion, after watching the water drop down toward earth for some time, stationary rocks and trees appear to drift upwards (177, 178). Cross-modal aftereffects refer to sensations that occur in a different modality to the initial stimulus and are thought to represent recalibration rather than a fatigue-induced process as is evidenced by the lack of aftereffects to visual stimuli when they are presented with an appropriate vestibular stimulus (179). When the lights are extinguished following prolonged exposure to a rotating drum, subjects experience self-motion in the opposite direction, an effect which is accompanied by an "after-nystagmus" (180, 181). If the stimulus is not sufficiently long, no aftereffects are experienced: whilst exposure to optic flow inducing a sensation of linear self-motion for 15 s resulted in a shift in perception, shorter durations of up to 7 s had no such effect, even though the onset of vection had occurred by this time (182, 183).

VECTION: AN ILLUSION OF SELF-MOTION

First described in the nineteenth century by Mach (184) and Wood (185), vection is the false perception of self-motion induced by sufficiently large stimuli moving across the retina in the absence of any true acceleration as signaled by the vestibular system. Today, vection is perhaps most recognizably experienced whilst sitting as a rail passenger, looking out of the window and believing that one's own carriage is leaving early, only to realize that it is rather a train on an adjacent platform that is pulling away. The illusion is widely exploited in virtual reality, theme park rides and I-Max cinemas, but it also remains of

interest in neuroscience as it reveals details of the relationship of different sensory inputs in the generation of self-motion perception (vection is not solely generated by visual inputs: proprioceptive and auditory stimuli have also been shown to provoke the illusion (186, 187).

Vection is typically experienced several seconds after the onset of the stimulus. For visually-generated vection, there are some general precepts that have been established, with the following all increasing the credibility of the illusion: greater velocity up to a point, previously suggested as 120 degrees/s for a rotating stimulus (188); larger stimulus size (188–190); increased density of moving objects (190); and, circular and curvilinear rather than linear motion (191). Furthermore, Brandt et al. established that it is predominantly the peripheral vision that is responsible for vection: whilst masking the central visual field with black disks, diameters of up to 120° exerted minimal effect on the generation of vection, but when blocking the peripheral vision, central visual stimuli of up to 30° diameter fail to induce self-motion perception; and, when the central and peripheral visual stimuli are of equivalent area, it is the peripheral stimulus that dominates (188). And the perception is remarkably compelling: Brandt et al also demonstrated that subjects still experienced circular vection when the rotating stimulus accelerated at $15^\circ/s^2$ (188).

During vection there is a conflict between incoming visual, somatosensory and vestibular information, with corresponding deactivations in the PIVC during rotational vection (192, 193). In contrast, during linear vection functional magnetic resonance imaging found only activations in various cortical areas with no PIVC or any other cortical deactivations (194). A further study attempted to correlate the intensity and duration of vection with brain activity in different regions. Whilst no correlation was found with PIVC, enhanced activity of the cerebellar vermis and parieto-occipital areas amongst others was reported (195). The authors concluded that this might represent a "dorsal stream" responsible for the intensity of vection. As might be expected given the hypothesized role of the cerebellar nodulus, there is increased activity during periods of reported self-motion illusion compared with object motion (193). Experimentally, subjects with bilateral impaired vestibular function report vection sooner, for longer and more compellingly than healthy controls (196, 197). Such a process of reciprocal inhibition might be explained physiologically as a consequence of a system of flexible dominant sensory weights given to incoming signals which enables self-motion perception during periods of incongruent information (for example, after prolonged rotation when the relative motion of the endolymph has ceased).

As with many perceptions, visual vection can be modulated by the presence or absence of additional inputs. Whilst proprioceptive stimuli alone do not reliably induce vection in all subjects, they can enhance vection. For example when small vibrations are applied to the subjects' seat at the time of onset of visual stimuli (198) or during auditory self-motion illusions (199). Proprioceptive stimuli can also enhance vection induced by auditory stimuli (200) and even static leaning of the upper body can enhance vection (201). In addition, the role of top-down processing and expectation should not be underestimated. It is common practice to "prime" subjects by demonstrating that actual self-motion is possible, even if it will not occur. Work in children demonstrated that linear vection is felt earlier is when a chair is placed on rollers compared with directly on the ground (202).

HOW VESTIBULAR FUNCTIONING AND SELF-MOTION PERCEPTION CAN MODULATE BEHAVIOR

Perception of self-motion is critically important for many human behaviors, including heading and navigation and control of body and eye movements. Therefore, it is not surprising that self-motion perception should modulate such behaviors. This section will review the effects of the vestibular system and self-motion perception upon eye movement, postural control and spatial awareness and more abstract behaviors including numerical cognition, human affect and bodily self-consciousness.

The Relationship Between Self-Motion Perception and Visually-Induced Postural Responses

Lee and Lishmann (203) demonstrated that visual information is important for the control of stance, and visual motion stimuli can induce postural sway (visually-evoked postural response, VEPR). The VEPR is known to be influenced by stimulus size and displacement across the retina (204) and it would appear logical that information containing cues regarding self- vs. object-motion would also modulate sway. Using transient movements of a visual scene to induce a postural response, Guerraz et al. (205) showed that sway was reduced when the subject could control some aspect of the stimulus motion compared with the uncontrolled condition. Moreover, in an oscillating room paradigm, when participants are aware that there is object-motion rather than self-motion, not only do they sway less than subjects who are unaware, they also do not show any change in sway as this distance between them and the wall increases (206). The authors also observe that the variability within each subject group was the same, and concluded that the prior information leads to a reweighting of different sensory cues in the control of posture. In further experiments, (static) subjects viewed a horizontally-translating background with either a head-mounted or earth-fixed LED at the center of a luminescent window frame (207). In these scenarios, the direction of postural sway depends upon the nature of the foreground, being in the direction of the background motion for the head-fixed display and transiently reversed in the earth-fixed case, whilst vection only occurred in one direction (opposite to that of the background motion). Subjects experienced vection sooner and for longer in the head-fixed condition. As vection is delayed compared with the VEPR, and as it is unidirectional compared with the bidirectional VEPR, it is likely that the two are processed differently. However, when subjects were experiencing self-motion there was significantly greater sway in both conditions as measured by displacement at C7 level, an effect that preceded vection onset (as indicated by pushing a button) by ∼1 s. The authors argued that there

may be a dual system at work, similar to that governing the eyes and reviewed here (85), in which as short-latency, brief VEPR (responsive to parallax) is subsequently replaced by a longer-latency visuo-postural response that can be enhanced by vection and might control posture during prolonged body displacements.

Self-Motion and the Detection of Movement

Whilst freely walking, one perceives the world to be stationary despite its projection moving across one's retina, and additionally, moving objects are perceived as moving, the result of subtracting expected inputs from actual inuts, discussed above and reviewed by DeAmgelis and Angelaki (208). The thresholds at which object motion can be detected, as well as the reaction times for such visual perception, are, however, increased during self-motion as compared with when the subject is stationary (209). Conversely, the threshold for vestibular perception are increased when subjects simultaneously view a moving visual pattern (189). Furthermore, when viewing a bistable rotating Necker cube, participants perceived the cube to be rotating in a congruent direction with their own passive whole-body rotation (210), and when viewing a bistable plaid, in which the observer perceives either two gratings moving across each other, or a single percept moving coherently, self-motion modified the dominance of each percept such that when self-motion and the global coherent percept were in opposite directions, the dominant percept was of a coherent image, and when self- and global percept- motion were orthogonal, subjects were more likely to view the image as two gratings moving independently (congruent motion had no effect) (211). The authors of the latter study suggest that this occurs as a result of an interaction between the visual motion and self-motion vectors at the stage of motion integration.

Self-Motion Perception and Spatial Awareness

Spatial representation within the brain has been the focus of much research over the last 70 years, and the vestibular system plays an important role in tracking and updating one's location in space reviewed by Moser et al. (212, 213) and Fyhn et al. (214). It might be noted here that this role is not limited to space as defined by visual inputs: the construct of auditory space is also dependent upon self-motion and it was recognized in 1940 that, despite movement of the head, human subjects can perceive a stable auditory environment and use it to accurately localize sounds (215). More recently, experiments have demonstrated that auditory space can be distorted by passive and active self-motion, with constructed space shrinking during forward acceleration (i.e., subjects indicate that sounds are located as being physically further away from them during periods of forwards acceleration compared with the stationary scenario, a phenomenon that has a dose-dependent relationship) (216, 217). For the purposes of this review, we will focus on the role of the vestibular system in: the perception of vertical, the modulation of visuospatial attention, with particular reference to patients experiencing visuospatial neglect, and visuospatial memory and navigation.

The Perception of Vertical and Vestibular Dysfunction

Verticality can be perceived through via visual, somatosensory and vestibular cues, and it follows that such perception can be affected by vestibular dysfunction. Following peripheral vestibular lesions, humans tilt their head, and shift their center of mass toward the side of the lesion (218, 219). Vestibular lesions have dissociative upon the perception of verticality dependent upon the experimental paradigm: whilst the subjective visual vertical was strongly deviated toward the side of the lesion in patients, the subjective seated postural vertical was not significantly different between the patient and control groups (220) [perception of the static visual vertical typically returns around 1 year after the insult (221, 222)]. The deviation in visual vertical is likely explained by altered inputs from the otoliths, leading to an altered representation of the gravitational vector and disturbance of the subjective visual vertical (223), and indeed, patients with bilateral peripheral vestibular dysfunction have been observed to have normal subjective visual vertical (224). This latter patient group also have a preserved postural vertical, although the sensitivity of this is reduced in patients who have a fluctuating (as opposed to stable) abnormality in vestibular dysfunction (225), suggesting that proprioceptive and somatosensory inputs are important in this perception, with the vestibular system refining the estimate for verticality. Subjective visual vertical can be improved, although not normalized, by the presence of visual cues for horizontal and vertical, for example as are found in an ordinary room (226). In the same experiment, Borel et al. found that the postural tilt toward the size of the lesion was reversed in the condition when visual cues were provided. Estimates for visual vertical also improve when subjects are balancing in a precarious position, for example on a beam, leading to the hypothesis of the "dynamics of balance," that is, that we have a heightened awareness of our orientation the more unbalanced we are (227). These findings are reviewed by Lopez et al. (228), who propose that the changes seen in relation to patients' perception of verticality following peripheral vestibular lesions are adaptive and might be explained in terms of changing the frame of reference (gravitationally-, egocentrically- or allocentrically-orientated) and of higher postural constraints. The neural substrate underpinning such reference frames is suggested to be a distributed neural network including the premotor cortex, premotor cortex, inferior parietal lobule, posterior parietal cortex, insula, and the temporo-parietal junction (228).

The Effect of Self-Motion Perception on Gaze Direction and Optokinetic Nystagmus

During self-motion perception, as compared with visual field motion without self-motion perception, there is a shift of the mean gaze direction toward the incoming visual stimulus, which reverts when the perceptual state reverts to object motion (229, 230). The change in mean gaze direction may be viewed as a shift in visuospatial attention during times of perceived self-motion (230). It is worth noting that this shift in gaze toward the incoming visual stimulus is seen when subjects are instructed to passively stare at the rotating stripes [in contrast, subjects actively pursuing the visual stimulus undergo a shift of mean gaze in

the direction the stimulus is moving toward (231)] and thus the subtleties of human behavior modulation, reflecting underlying perceptual strategies, are revealed.

Thilo et al. (230) also found that shifts in perceptual state were also linked to changes in the slow-phase gain of optokinetic nystagmus (OKN), with self-motion associated with reduced gain, possibly as a result of conflict between the need to accurately pursue the visual stimulus (moving in one direction) and the drive of the eye toward the incoming visual field (in the other direction). Additionally, slow-phase gains were generally decreased when the subjects were supine compared with upright (all subjects viewing the same stimulus rotating about their longitudinal axis). This is the opposite finding to earlier work that showed enhanced slow-phase gains in the supine position compared with the upright position when the optokinetic stimulus was rotating about the subjects' naso-occipital axis, generating a torsional OKN (232). The authors postulate that this differential response is a result of the presence or absence of conflict between information arising from the otoliths and the visual system: in times of conflict, the otoliths may exert an inhibitory influence on the OKN.

Visuospatial Neglect and the Vestibular System

Neglect is the clinical phenomenon whereby patients fail to respond to, report or orient toward stimuli on the contralesional side (233). It can be multimodal and includes visuospatial, auditory, and somatosensory neglect. In one study, Bisiach and Luzzatti found the neglect can even affect internal visualization: in patients asked to recall the Piazza del Duomo in Milan, when imagining the scene with their backs to the cathedral, they were observed to omit places on the left side of the scene, places that they subsequently named without prompt when asked to imagine the same scene from the other side of the piazza, facing the cathedral (234). Neuroanatomically, neglect is particularly associated with lesions of the right posterior parietal cortex, including the TPJ (235). Perhaps it is not so surprising then that stimulation of the vestibular system, which is intricately linked with the TPJ, can modulate neglect. First reported in 1941, left-cold and right-warm CVS temporarily alleviates left visuospatial neglect, an effect which appears to be related to shift of spatial attention to the left and facilitation of left lateral gaze (236–238), and functional MRI during left-cold stimulation does demonstrate activation of the right hemisphere (239). Galvanic vestibular stimulation appears to have a similar effect, with right-cathodal stimulation most effectively improving line bisection error in patients with neglect (240). These findings have been extended by work demonstrating that optokinetic stimuli can also improve performance in behavioral tests of neglect (241–243), improvements that have been reported to last for up to 2–4 weeks after treatment (244, 245). However, whilst performance on behavioral tasks might improve following optokinetic stimulation in patients with neglect, there is evidence to suggest that such stimulation does not correct the suspected underlying asymmetry of spatial representation in the brain. Leftwards optokinetic stimulation improved performance in line bisection, but accentuated the leftward bias that patients had when asked to construct a line of known length on the basis of a given "midpoint" (246).

Vestibular Dysfunction, Visuospatial Memory and Navigation

That the vestibular system might play a role in spatial memory is suggested by neuro-anatomical studies which demonstrate connections between various vestibular centers and the hippocampus, where so-called place cells are found, (9, 247) and supported by functional MR imaging during CVS (248). And whilst it is evident that the vestibular system is responsible for simple navigation tasks in the absence of other cues (for example, estimation of passive rotational and linear displacements in silence and in dark), it has only been more recently demonstrated that such impairments extend to more complex navigational tasks. Peruch et al. allowed subjects to explore a path using either proprioceptive-vestibular, visual-vestibular, or visual-alone inputs and then asked them to reproduce or reverse it or to take a "shortcut" back to the start in the same environment (249). Patients with unilateral vestibular impairment did much worse in the visual-alone and visual-vestibular conditions, the deficit being more marked the more complex the task. The fact that performance is impaired even in the visual-alone paradigm is perhaps surprising: patients with vestibular impairment might have been expected to perform better than their healthy peers in view of upregulated visual pathways to compensate for their vestibular loss. Yet the findings have been replicated in an experiment using a virtual Morris water task to test spatial memory and navigation, and furthermore that patients with bilateral vestibular loss have significant specific hippocampal atrophy compared with healthy controls (9) and also in animals (250, 251), lending further evidence that the vestibular system is important in spatial memory and navigation. Adding to this evidence is the observation that left-cold CVS significantly improved performance in an object-location-recall task (252).

The Vestibular System and a Sense of Self

Bodily self-consciousness, which comprises of self-location, self-identification and first-person perspective, is one of the higher-order functions influenced by the vestibular system. Bodily self-consciousness is thought to be the summation of different sensory and motor efference inputs, including that of the vestibular system, that allows for the construct of personal space (i.e., the space occupied by the body and the space immediately surrounding the body) and of extrapersonal space, reviewed by Blanke (253). Evidence for the role of the vestibular system in the construct of bodily self-consciousness also comes from patients with vestibular impairment: it is well-recognized that patients with vestibular dysfunction can experience a range of abnormal sensations, from distorted body image and schema to depersonalization, derealisation and out-of-body experiences, observations that were first recorded a century ago by Bonnier (254) [republished (255)] and Schilder (256). The role that the vestibular system plays in each of these symptoms is reviewed by Lopez and by Pfeiffer and for a fuller account the reader is directed to (257, 258).

Altered bodily self-consciousness has been linked with changed perception of body parts: patients with vestibular impairment reported changes in how various body parts feel during episodes of dizziness (254, 256) and caloric and galvanic vestibular stimulation has been observed to modify healthy subjects' perception of hand size (259, 260). Additionally, body integrity image disorder, which describes a syndrome in which patients complain of a mismatch between how they feel and how they physically are, with the result that they often request limb amputation, and somatoparaphrenia, in which patients, following a right parietal stroke, reject their left arm as being alien, can be improved temporarily by CVS (261, 262).

Depersonalization, the sensation of being detached from oneself, and derealisation, that of being detached from one's surroundings, are also thought to be a consequence of disturbed bodily self-consciousness. Not only have these symptoms been documented in patients with vestibular dysfunction, but Jáuregi-Renaud et al. found that the depersonalization/derealisation scores of patients as measured by Cox and Swinson's questionnaire were correlated with their error in estimation of passive whole-body rotation (263, 264). Symptoms of depersonalization and derealisation can also be induced in healthy controls by CVS (265). Although the neural correlate of such symptoms has yet to be conclusively identified, the superior temporal gyrus and TPJ seem to be the strongest candidates: electrical stimulation of this area caused subjects to report that they felt strange [for review, see (266)]; patients with depersonalization/derealisation symptoms had altered metabolism here on positron emission tomography (267); and, repetitive transcranial magnetic stimulation of the right TPJ has been reported to alleviate these symptoms (268).

Out-of-body experiences are also associated with disturbed bodily self-consciousness. Such experiences typically have three characteristics: the person feels that they are in an illusory body that is removed from their physical body and that they have a first-person perspective of looking back at their physical body. They have been linked with a TPJ dysfunction, most often affecting the right side (269, 270). Sufficiently strong electrical stimulation of that region of the cortex also induces the illusion, with lower levels of stimulation inducing a sensation of falling or sinking (271). Out-of-body experiences have been observed to occur most typically when subjects are in a non-upright position (272), which is proposed to be due to visual-vestibular conflict, the otoliths, by signaling the direction of gravity, normally being important for forming a strong world-referenced image of oneself (273). Out-of-body experiences can also be induced by combined visual-vestibular-somatosensory conflict, for example, in healthy subjects watching the back of a virtual body being stroked whilst feeling a synchronous stroking on their own back (274). In such cases, interfering with TPJ functioning using transcranial magnetic stimulation abolished the illusion, yet the ability to imagine transformations of external objects was unaffected, suggesting that the TPJ performs a specific role in the processing of self in space and of bodily self-consciousness (275).

Interestingly, patients with schizophrenia have been observed to have a degree of vestibular dysfunction and reduced functional connectivity of the vestibular system (276–278). Schizophrenia can be thought of as a disease of impaired multisensory processing with symptoms of depersonalization, derealisation, distorted first person perception, and loss of agency. The onset of psychosis is often preceded by a period of social withdrawal and sub-delusional detachment from reality. The psychotic period of the illness was defined historically by the presence of Schneider's first rank symptoms of delusional perception, auditory hallucinations, and delusions of thought interference and passivity. The TPJ has been implicated in auditory hallucinations (279, 280), with reported symptom improvement following repetitive transcranial magnetic stimulation (281) and reduced TPJ-hippocampal connectivity has been associated with poorer social performance and negative symptoms (282, 283), reviewed by Wible (284). CVS has been recorded as improving insight into illness in schizophrenia (285) and reducing delusions in schizoaffective disorder (286).

The Vestibular System and Human Affect

Patients with vestibular impairment have been observed to suffer from a high burden of psychiatric disease, particularly affective disorders such as anxiety and depression (287–290). Moreover, patients with psychiatric disease and no diagnosis of vestibular impairment have been found to have abnormal behavioral responses in tests known to rely upon intact vestibular functioning, including postural control (291) and vestibulo-oculo-motor tasks (292), and even in healthy subjects, mood state modifies balance control (293). It is thought, therefore, that the increased burden of psychiatric disease amongst patients with vestibular impairment compared with the general population might be explained by more than just the observation that chronic disease can negatively impact upon mood. Neuro-anatomically, there are cortical areas that are known to process vestibular information and to be involved in the regulation of mood and affect, including the anterior cingulate cortex (ACC) (294, 295). CVS has been shown to modify activity in the ACC and left-cold stimulation has been shown to increase risk estimation (and reduce unrealistic optimism) (296), improve anosognosia (a syndrome in which patients with evident disability deny any illness) (296) and modulate affective control and mood (297). Furthermore, positron emission tomography has revealed increased activity in the ACC of patients with mania associated with bipolar disorder and euthymic controls (298), and CVS has been reported to temporarily reduce the symptoms of mania in such patients (286, 299). The role of the ACC and vestibular stimulation in depression has yet to be fully investigated, although one might note that there are reports of abnormal eye movement control in depressed subjects (300). Chronic pain, itself associated with changes in mood and affect, is thought to be partly mediated by C-nociceptor input to the ACC, and in some patients, CVS has been reported to reduce symptoms (301, 302).

Self-Motion Perception and Recovery From Vestibular Dysfunction

After an insult to the vestibular system, it is usual for there to be abnormalities of low-level vestibular functions, such as the VOR, as well as of higher-order functions, such as motion

perception. In such patients, and after a certain delay, it has been observed that whilst vestibular perception may have returned to normal or near-normal, the lower-level functions may remain abnormal, so-called perceptuo-reflex uncoupling, suggesting that, under optimal circumstances, higher-order processing can compensate for vestibular dysfunction (48, 135). Such compensation need not be the preserve of recovery from illness: as mentioned above, ballerinas who are accustomed to performing multiple pirouettes demonstrate similar perceptuo-reflex uncoupling (135), an uncoupling that has been proposed to occur via cerebellar sensory gating (77, 135, 303). [The reverse, symptoms of dizziness without abnormal VOR is, of course, a well-known phenomenon seen in brainstem infarction, epileptic seizures and electrical stimulation (126, 304). It is possible that in patients who go on to develop chronic symptoms after an initial vestibular insult, there is an impairment in such central compensatory processing. Such patients typically demonstrate poor correlation between VOR function (which is often unremarkable on clinical testing) and their symptoms (52). Research suggests that factors for good recovery from vestibular lesions include anxiety, visual dependence, autonomic arousal, depression, and fear of bodily sensations (54), and whilst some of these might be viewed as contributing to a psychological component to their symptoms, as summarized above, the co-existence of vestibular disorders and anxiety may point to shared central pathways. A better understanding of these might improve identification of such patients and clinical management of their disease.

The Effect of Self-Motion Perception on Numerical Magnitude Allocation

Other more abstract influences of self-motion on behavior include the relationship between numerical magnitude allocation and perception of self-motion. This is interesting not least because, at first consideration, the two processes might appear to be relatively independent. It is worthwhile acknowledging here that the exact relationship between numerical representation in the brain and visuospatial attention is debated (305, 306). Nevertheless, various experiments investigating the effect of self-motion on magnitude allocation have been carried out. Evidence supporting the hypothesis that numerical magnitude allocation can be influenced by self-motion includes: the bidirectional relationship between numerical magnitude and self-motion perception thresholds observed in subjects undergoing whole-body linear motion (307); modulation of the spontaneous number generator by lateral head turns and galvanic vestibular stimulation (308, 309); and, in stroke patients with visuospatial attentional biases (who have been shown to have concomitant biases in numerical estimations (310) viewing a visual stimulus moving toward the side of the neglect temporarily reversed the numerical bias (311, 312). In a recent study examining the effect of perceptual state of self during motion on a mental number-pair bisection task (estimating the mid-point between two numerical values), it was found that: vestibular-alone stimulation exerted no differences in number-pair bisection compared with baseline; when the subject perceives the world to be moving and themselves stationary, rightwards motion reduced the magnitude of estimates compared with baseline and leftwards motion increased the magnitude; and, during vection, both leftwards and rightwards vection elicited the same increase in magnitude of estimates as leftwards world motion, a finding explained by the inhibition seen in the right vestibular cortex during vection and thus leading to left hemisphere dominance and biasing toward larger numbers (see **Figure 6**) (306).

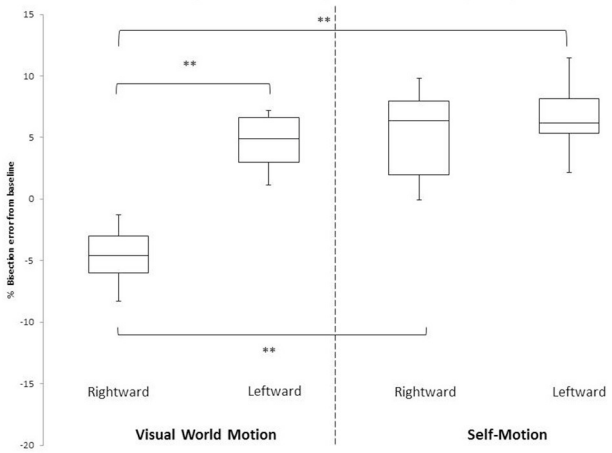

FIGURE 6 | From section, The effect of self-motion perception on numerical magnitude allocation. This Figure, modified from Arshad et al. (306). Graph showing percentage error in the number bisection task (normalized to 0% error by subtracting the baseline) for the four perceptual conditions: world motion right and left and self-motion (vection) right and left. Box-plots represent the median and interquartile range with whiskers denoting 10th and 90th percentile. **Marks significance at $p < 0.01$.

Self-Motion Perception and Economic Decision Making

Related to the role of the vestibular system in numerical magnitude allocation are the recent findings that implicate vestibular stimulation in economic decision making (297). Purchase decision making describes the motives and considerations involved in buying a product and include the desirability of that product as well as its cost and the maximum the individual is willing to pay (313–315). In their experiment, Preuss et al. had subjects choose to buy or not to buy products (listed at 20% of the market price) either during sham or left-cold CVS. In the second half of the experiment, subjects ranked the desirability of products and their own "willingness to pay" for those products when the products were displayed at a range of prices, up to 100% of the market price. During left-cold CVS, subjects were less likely to buy products, and they also rated products as being less desirable. In contrast, the willingness of the subjects to pay for those products was not significantly different during sham and stimulation conditions.

Also probing the effects of the vestibular system on economic and prosocial decision making, Arshad et al. (316)

used a modified version of the dictator game and a non-numerical prosocial questionnaire probed the effects of vestibular stimulation and binocular rivalry on participants' strategies. They found that there exists a correlation between inherent number-pair bisection error and the mean amount of money a subject donated to an unknown stranger, and that modulating numerical magnitude perception through combined CVS and binocular rivalry led to congruent changes in the mean amount donated, and that this occurred in a proportional manner. The intervention had no effect on the results of the altruism questionnaire, suggesting that the effect was mediated via numerical magnitude. The neural mechanism for such behavior remains to be determined, although a role for the ACC has been hypothesized (316).

CONCLUSION

The vestibular system may have developed as an organ to sense movement and coordinate postural and eye reflexes designed to stabilize the body, but its role in the generation of perception of self-motion, though less well-recognized, is equally important. Our understanding of the neurophysiology of self-motion perception has increased over the past few decades through a multitude of electrophysiological studies, psychophysical experiments, and observations from clinical medicine. Vestibular afferents undergo early processing and integration with somatosensory, visual and motor efference inputs in the vestibular nuclei. Such processing is evident throughout the vestibular network including in the cerebellum where it contributes to generation of world-framed motion and unexpected motion and in the PIVC and VIP where heading perception is processed. Future work might focus on the effects of different perceptual states on higher cognitive processes, perhaps examining the role, if any, that vestibular cortical lateralisation plays, and in doing so discover better tests for the monitoring of patients with central and peripheral vestibular disorders which may open up new avenues for the treatment of these diseases.

AUTHOR CONTRIBUTIONS

ZB conceptualized and wrote the manuscript. QA conceptualized and edited the manuscript.

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REVIEW
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Perception of Verticality and Vestibular Disorders of Balance and Falls

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Objective: To review current knowledge of the perception of verticality, its normal function and disorders. This is based on an integrative graviceptive input from the vertical semicircular canals and the otolith organs.

Methods: The special focus is on human psychophysics, neurophysiological and imaging data on the adjustments of subjective visual vertical (SVV) and the subjective postural vertical. Furthermore, examples of mathematical modeling of specific vestibular cell functions for orientation in space in rodents and in patients are briefly presented.

Results: Pathological tilts of the SVV in the roll plane are most sensitive and frequent clinical vestibular signs of unilateral lesions extending from the labyrinths via the brainstem and thalamus to the parieto-insular vestibular cortex. Due to crossings of ascending graviceptive fibers, peripheral vestibular and pontomedullary lesions cause ipsilateral tilts of the SVV; ponto-mesencephalic lesions cause contralateral tilts. In contrast, SVV tilts, which are measured in unilateral vestibular lesions at thalamic and cortical levels, have two different characteristic features: (i) they may be ipsi- or contralateral, and (ii) they are smaller than those found in lower brainstem or peripheral lesions. Motor signs such as head tilt and body lateropulsion, components of ocular tilt reaction, are typical for vestibular lesions of the peripheral vestibular organ and the pontomedullary brainstem (vestibular nucleus). They are less frequent in midbrain lesions (interstitial nucleus of Cajal) and rare in cortical lesions. Isolated body lateropulsion is chiefly found in caudal lateral medullary brainstem lesions. Vestibular function in the roll plane and its disorders can be mathematically modeled by an attractor model of angular head velocity cell and head direction cell function. Disorders manifesting with misperception of the body vertical are the pusher syndrome, the progressive supranuclear palsy, or the normal pressure hydrocephalus; they may affect roll and/or pitch plane.

Conclusion: Clinical determinations of the SVV are easy and reliable. They indicate acute unilateral vestibular dysfunctions, the causative lesion of which extends from labyrinth to cortex. They allow precise topographical diagnosis of side and level in unilateral brainstem or peripheral vestibular disorders. SVV tilts may coincide with or differ from the perception of body vertical, e.g., in isolated body lateropulsion.

Keywords: vertical orientation, subjective visual vertical, subjective postural vertical, vestibular system, graviception, hemispatial neglect, pusher syndrome

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INTRODUCTION

The perception of verticality in the roll and pitch planes is based on an integrative graviceptive input from the vertical semicircular canals and otolith organs. This input is mediated by a bilateral central circuitry connecting the vestibular nuclei with integration centers for vertical and torsional eye-head coordination located in the rostral midbrain tegmentum (interstitial nucleus of Cajal, INC; rostral interstitial nucleus of the medial longitudinal fascicle, riMLF) and the thalamus (in particular, the paramedian and dorsolateral subnuclei). The vestibular input has to be integrated with visual and somatosensory information about vertical orientation of the three-dimensional space relative to the earth-centered gravitational force. Especially, the visual and the vestibular systems provide us with information about vertical orientation. Its coordinates have to be matched by convergence to create the actual global percept of up and down, right and left, and fore and aft. This percept may apply to either the egocentric orientation of surrounding targets or to the allocentric orientation of body position within the environment. The sensory modalities involved cannot perceive different verticals at the same time independently—a visual and a vestibular one. This multisensory input establishes an internal model of space and verticality, which is updated via bottom-up and top-down processes (1, 2). Other models use Bayesian spatial-perception (3–5) and an inverse probabilistic approach based on an optimal observer theory (6).

With respect to orientation in space, vestibular input from the otolith organs in stationary subjects enables a two-dimensional (egocentric) spatial orientation, input from the semicircular canals and otolith organs in mobile subjects contributes to a three-dimensional (allocentric) spatial orientation. The novelty of such a concept is that two reference frames—"egocentric and allocentric"—are attributed to two operational modes—"static and dynamic" (7). An explanation involving a strictly dichotomous separation, however, is too simple, since both reference frames and modes of operation have to be integrated according to the particular task in natural environments. Thus, tests of vestibular function (in virtual or real environments) involve a static, two-dimensional and a dynamic, three-dimensional mode of action, respectively (7).

In the current clinical review we focus on psychophysical adjustments of the subjective visual vertical (SVV) and the subjective postural vertical (SPV) for balance control in a three-dimensional space. Depending on the method employed, different sensory systems come into play when the subjective vertical is assessed. The clinical examination of body orientation in space is performed in heterogeneous ways of measuring the body vertical (e.g., a moving chair on a platform or the three-axes space curl), the haptic vertical (metal rod), and the visual vertical (with several devices, e.g., use of spectacles or adjustments of visual lines at some distance in front of the body). These different approaches aim to quantify the input of different senses such as the somatosensory sense from the trunk and the lower limbs (body postural vertical, haptic vertical), the vestibular sense (subjective visual vertical without visual cues for orientation), and the visual sense. However, no known measure can be solely attributed to only one sensory system. The brain seems to use Bayesian inference to integrate noisy multisensory signals to reduce perceptual uncertainty by weighting the signals in proportion to their reliability (6, 8).

Other modalities can in part substitute for the deficit of patients with disorders of a particular sensory function. For example, patients with spinal cord injuries (lacking somatosensory input from the lower body) perceive verticality without any significant directional bias in orientation, both in haptic and postural tests, but they are more uncertain than control subjects (9). Similar findings were reported for patients with peripheral vestibular disorders (10, 11). Thus, humans create and update internal models of verticality on the basis of convergence and integration of vestibular, somatosensory, and visual graviceptive cues. The posterolateral thalamus seems to play a crucial role in this process of integration of vestibular and somatosensory input (12). It is increasingly acknowledged that the role of the thalamo-cortical system with its widespread connectivities is much broader. The thalamus has even been termed a multisensory and cognitive integrative hub that encompasses spatial orientation and motion perception (13, 14).

Abbreviations: SPV, subjective postural vertical; SVV, subjective visual vertical; OTR, ocular tilt reaction; INC, interstitial nucleus of Cajal; PSP, progressive supranuclear palsy; NPH, normal pressure hydrocephalus; riMLF, rostral interstitial nucleus of the medial longitudinal fascicle.

METHODS OF VERTICALITY PERCEPTION

Subjective Postural Vertical (SPV)

To assess the *postural vertical* the subject sits on a tilting device in darkness and adjusts himself in a vertical position. For example, the seat of the blindfolded participants is tilted to the left or right relative to gravity and they are then asked to adjust the tilt of the motion base until they feel upright (10, 15–18). Another method in which the subject stands is the space curl, a three-axis system similar to a gyroscope (19). This device was also used for rehabilitation of verticality perception [e.g., in pusher syndrome (20)].

To assess the *subjective haptic vertical*, a subject sitting in the dark adjusts a rotatable bar by his tactile sense until it is vertical (21).

Subjective Visual Vertical (SVV)

Measurement of the perceived visual vertical discloses acute unilateral vestibular dysfunction when the device used provides no cues to visual spatial orientation as in darkness or with a random dot pattern background (22–24). A systematic review of visual vertical assessment methods showed a great heterogeneity of the parameters, settings, and procedures. Only a few are suitable for standardization so as to limit errors and improve interpretation of the results (25). This review assessed data of 61 studies (1,982 patients) on SVV measurement procedures for hemispheric ($n = 43$), brainstem ($n = 18$) or cerebellar ($n = 8$) strokes (25). SVV assessment procedures varied in paradigm, type of stimulus, patient posture, number of trials and results. Therefore, the authors recommended that the SVV be assessed

in darkness and in an even number of trials (6 to 10) with the body in an upright position. Then, normal SVV orientation (mean of SVV adjustments) can be considered to range from −2.5 to 2.5° and is reliable for clinical use and research studies. This corresponds to the normal ranges for measurements with a hemispheric dome (22).

In the *hemispheric dome* method (22), patients sit in front of a device which covers the entire visual field and its inner surface presenting a random pattern of colored dots that provides no cues to true vertical orientation. Participants are asked to move a linear target located at random offset positions into a vertical position in the center of the dome.

In the *bucket test* (26, 27) the subjects evaluate the vertical orientation by properly aligning a straight line visible on the inner bottom of the bucket which the examiner rotates at random. On the outer bottom surface of the bucket an angular protractor provides the examiner to readout the tilt angle.

In the computerized *Visual-Spatial Perception Program* (28) the SVV procedure expects the subject to vertically orient a tilted white line on a dark background.

Differentiation of Vestibular and Peripheral Ocular Motor Disorders

Some caution is required in choosing the appropriate device for SVV measurements. In certain studies the visual vertical was measured by using glasses similar to a Maddox double rod *directly in front of the eyes*. The problem of this technique, adopted from ophthalmologic labs, is that it determines the subjective perception of the cyclorotation of one eye, for example, in extraocular eye muscle palsies, rather than the perceived vertical of the visual environment. Measurements with the monocularly and binocularly determined SVV using a device in front of the body, the subjective perception of ocular torsion, or the objective determination of ocular torsion with fundus photographs yielded different results [for review see: (29)]. For example, the monocular SVV of the right eye of a patient with an acute right third nerve palsy showed a pathological tilt of +19°, whereas the SVV of the left eye and the binocular SVV were both normal (−1.6°, −2.0°). The Maddox double rod gave a right excyclotropia of 4°-5°, and the fundus photographs, an excyclotropia of 8° right (normal) and 7° left (normal). This example clearly demonstrates that a valid way of distinguishing between central vestibular lesions and extraocular eye muscle paresis (third or fourth nerve palsy) is the dissociated occurrence of SVV tilts and ocular torsion in both the non-paretic and the paretic eye. The SVV tilts of patients with eye muscle pareses occur only during monocular testing; tilts are normal during binocular testing (29, 30). Thus, monocular vs. binocular measures of SVV tilt allow us to differentiate vestibular from peripheral ocular motor disorders.

Disorders of the Postural Vertical

Misperception of the postural body vertical is critical for hemispheric and thalamic disorders such as the pusher syndrome (17, 18, 31) and the idiopathic normal pressure hydrocephalus (NPH)(32) as well as brainstem disorders such as the progressive supranuclear palsy (PSP) syndrome (33, 34) and the dorsolateral medullary Wallenberg syndrome (35). A misperception in the frontal roll plane is typical for the *pusher syndrome* which also includes lateral falls (17, 18). Such patients have a severe misperception of their body's orientation and experience it as "upright" although it is tilted. The thus afflicted patients actively push the body away with the unparalysed arm or leg to the contralateral side. Patients with pusher syndrome cannot correctly indicate their own body's upright. However, they appear to have no difficulty to determine the vertical orientation of the visual surrounding (17, 18).

The perception of upright body orientation in the pusher syndrome was also investigated while the patient was standing in the space curl device. The study revealed that these patients adjusted their body with an ipsilateral lateral tilt in the roll and also in the pitch plane, an adjustment that decreased with decreasing severity of the condition (36). Their uncertainty in the perception of verticality in both roll and pitch planes indicates a global misperception of verticality.

Causative lesion sites may include the thalamus and—perhaps more likely—the posterior insula (31, 37). Components of the multisensory cortical vestibular network are located at these sites. The right hemispheric dominance in this network corresponds to the significantly higher frequency of the pushing syndrome in strokes of the right hemisphere (38), an observation that explains the clinical experience of physical therapists, that recovery from pushing behavior takes longer after right- compared to left-hemispheric strokes (39).

A misperception of body verticality in the sagittal pitch plane is typical for patients with idiopathic *normal pressure hydrocephalus (NPH)*. Such misperception was considered a potential diagnostic tool (and a therapeutic predictor) for these patients before and after cerebral spinal fluid drainage. A correlation was found between the backward tilt of the subjective body vertical and a ventricular enlargement of the frontal horns neighboring the thalamic nuclei. Thus, such a disturbance in the pitch plane might indicate a bilateral vestibular dysfunction of the thalamus; it promises to increase diagnostic accuracy of suspected NPH (32).

Postural instability in the pitch plane has also been documented in neurodegenerative *progressive supranuclear palsy* (PSP), especially the occurrence of backward falls in early stages of the disease (34). In addition to early postural instability with falls, PSP is defined by supranuclear vertical gaze palsy, bilateral akinesia and muscle rigidity as well as frontal and subcortical dementia with pseudobulbar palsy (33, 40). Postural instability leads to gait abnormalities like freezing that can be quantitatively characterized (41, 42). Patients who self-monitored the frequency of falls, underwent a standardized clinical investigation, posturographic analysis of balance during experimentally modified sensory input, and a [18F]FDG-PET. Further, they performed an fMRI paradigm that involved mental imagery of upright stance. Compared to age-matched controls sway path values were higher and the frequency of falls was associated with decreased cerebral regional glucose metabolism (rCGM) of the thalamus, but increased rCGM of the precentral gyrus. In the fMRI mental imagery of stance induced a decreased activation of the mesencephalic brainstem tegmentum and the

thalamus in those patients with postural imbalance causing falls. Thalamic dysfunction of postural control was most evident when balance was assessed during modification of the actual sensory input (41). The results support the view that reduced thalamic activation by ascending brainstem projections causes postural instability in PSP (34). Thus, gait impairment in PSP indicates dysfunction of the indirect, prefrontal-subthalamic–pedunculo-pontine loop for control of balance and locomotion. The stereotyped, direct locomotor loop connecting the primary motor cortex and the spinal cord (with rhythmic cerebellar drive) revealed an increased activity in PET during walking (42). This can be explained as an attempted compensation or a contribution to the stereotyped gait pattern in PSP.

In quantitative gait analyses patients with PSP are more sensitive to perturbations performing dual tasks than patients with NPH. Cognitive dual-tasks caused a more pronounced reduction of gait velocity in PSP. Motor dual-tasks resulted a dissociation in locomotion performance in both disorders: it worsened considerably in PSP patients, but tended to improve in NPH patients (43).

Isolated Body Lateropulsion

The phenomenon of *axial body lateropulsion* occurs when the body is pulled toward the lesion side and there is a tendency to fall down. It is a well-recognized transient feature of a lateral medullary syndrome (44–46) and axial body lateropulsion may occur in some patients even without vestibular and cerebellar dysfunctions (isolated body lateropulsion). They suffer from a caudal medullary lesion of the spinocerebellar tract, the descending lateral vestibulospinal tract, the ascending vestibulo-thalamic and dentatorubro-thalamic pathways, or the thalamocortical fascicle (44, 45, 47, 48). The isolated symptomatology of lateropulsion can be attributed to lesions below the network of the vestibulo-ocular reflex (VOR), which links the extraocular eye muscles and contributes to the perception of gravitational vertical. In very rare cases cortical strokes of the parietal lobe can also cause isolated or predominant body lateropulsion like those of the posterior cingulate and/or precuneus (49).

More often patients with acute lesions of the medullary brainstem, especially dorsolateral medullary infarctions (i.e., Wallenberg syndrome including the vestibular nuclei) present with lateropulsion and additional vestibular signs such as a deviation of the SVV, skew deviation of the eyes, and ocular torsion, all of which are directed to the ipsilateral side (38, 50). It is striking that these patients in the postacute phase do not experience subjective vertigo, despite their strong tendency to fall sidewards (35). This can be explained by postural regulation, which aims to adjust the body to the tilted vertical. Lateropulsion can be interpreted as a postural compensation of an erroneously

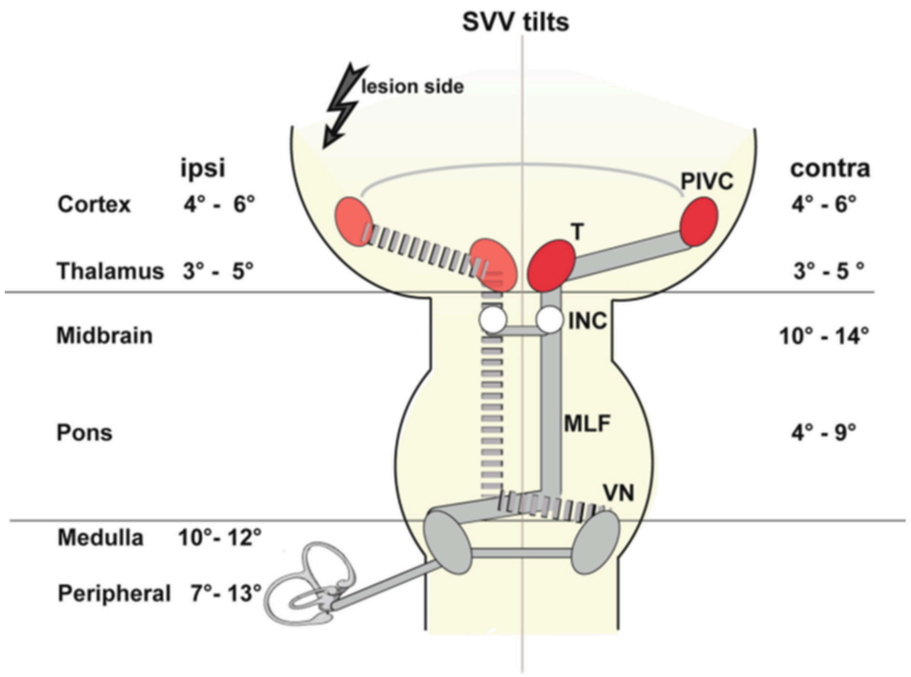

FIGURE 1 | Schematic graviceptive pathways together with the amount of SVV tilt (in deg) for ipsilateral (ipsi) and contralateral (contra) lesions depending on the level of acute unilateral vestibular damage. The range of the mean values was calculated from a total of 15 published studies (see **Table 1** for reference numbers). The four major messages are as follows: (i) In peripheral and pontomedullary brainstem lesions SVV tilts are ipsilateral. (ii) In pontomesencephalic vestibular pathway lesions up to the INC, SVV tilts are contralateral. (iii) In vestibular thalamic and cortical lesions, SVV tilts may be either ipsilateral or contralateral with an intraindividual consistency and an equal distribution interindividually. (iv) The amount of SVV tilt is maximal in complete peripheral lesions (mean up to 13 deg) and in brainstem lesions (mean up to 12–14 deg), and less in lesions of the vestibular thalamus and cortex (mean up to 5–6 deg). INC, interstitial nucleus of Cajal; MLF, medial longitudinal fascicle; VN, vestibuar nucleus [From Glasauer et al. (2)].

TABLE 1 | SVV tilts in acute unilateral vestibular lesions at different lesion sites from labyrinth to cortex (i, ipsilateral tilt; c, contralateral tilt).

	TSL [days]	No. of Patients	Amount of SVV tilt [deg] Mean/median		(Range)	References
			ipsi	contra		
Cortex	1–7	54			(i −8.7; c −7.5)	(37)
	2–12	52	i 4	c 3.4–6.2	(2.7–15)	(55)
	4–10	82	i 5.4	c 5.3		#
Thalamus	1–9	37	i 3.4	c 5.1		(57)
	1–7	17	i 3	c 4		(54)
Midbrain	1–9	14		c 13.5		(54)
	1–15	28			(6–29)	(22)
Ponto-mes.*	−14	14	i 4.1		(2.7–6.6)	(58)*
Pons	1–15	47	i 9.3		(5–15)	(22)
Medulla	1–5	36	i 11		(5–22)	(35)
	1–15		i 12.4			(22)
	1–10	50	i 9.8		(−28)	(59)
	1–2	43	i 7.9			(60)
Brainstem in total	i 1–19 c 2–8	82	i 7.0	c 4.2		(53)
	3–9	79	i 4.5	c 4.2	(2.3–9.6)	(52)
	1–10	111	i/c 8.1		(2.7–26)	(22)
LABYRINTH/NERVE						
Neuritis	1–11	50	i 7		(−25)	(59)
Neuritis	1–2	40	i 7.3			(60)
Neuritis	3–4	5	i 12.2		(5.5–33.3)	(61)
Neuritis	1–14	20	i 6.8		(0.2–33.0)	(62)
Neurectomy	1–10	13	i		(10–30)	(63)
Neurectomy	1–7	5	i 8.5		(7–10)	(10)
Neurectomy	4–10	13	i 11.9		(6.6–22)	(64)
Neurectomy	1–14	15	i 12.4		(4.8–21.4)	(62)
Labyrinthect.	1–7	6	i		(4–21)	(65)
Zoster	1–7	4	i 10.4		(3.2–17.2)	(62)

TSL time since lesion onset; ipsi=i=ipsilateral tilt; contra=c=contralateral tilt.

** tilts in ponto-mesencephalic lesions are typically due to an affection of the medial longitudinal fascicle (MLF) which crosses midline above the vestibular nuclei and therefore show contralateral directions of tilts, skew deviation and ocular torsion. One exception from that rule has been described for rare anteromedian pontomesencephalic lesions close to and within the medial lemniscus which manifested with isolated ipsilateral SVV tilts [without skew deviation and ocular torsion; Zwergal et al. (58)].*

#, Baier et al., unpublished.

perceived body tilt contralateral to the side of the lesion. Despite the thus elicited postural imbalance and the conflicting true vertical, the posture is continuously pushed toward what the central nervous system wrongly computes as being vertical (50). The extent of the damage of vestibular structures can certainly vary; in single cases a combination of isolated axial lateropulsion with only ipsilateral SVV tilts was reported in small caudal medullary lesions (46).

Disorders of the Visual Vertical

Tilts of SVV are the most frequent sign of an *acute tone imbalance* of the bilateral vestibular system in the roll plane. They occur with acute unilateral lesions of the graviceptive pathways that originate from the otolith organs and the vertical semicircular canals and travel via the vestibular nuclei and the vestibular subnuclei of the thalamus to the parieto-insular vestibular cortex, PIVC (**Figure 1**). Adjustments of SVV are ipsilateral in peripheral and caudal ponto-medullary brainstem lesions but contralateral in ponto-mesencephalic lesions (2, 22, 23, 25, 51–53). Lesion sites along the brainstem pathways were confirmed more recently by voxel-wise lesion-behavior mapping techniques in MRI (52, 53). In contrast, unilateral lesions of vestibular thalamus or cortex areas manifest with smaller tilts of SVV, and—importantly—can be either ipsilateral or contralateral (2, 25, 54–56) (**Figure 1**, **Table 1**).

Cerebellar lesions may also cause vestibular dysfunction in the roll plane. Acute unilateral lesions of the vestibulo-cerebellar loop induce either ipsilateral or contralateral SVV tilts depending on the cerebellar lesion site (66). However, the amount of tilt is larger than in thalamo-cortical lesions and more in parallel to those of medullary brainstem lesions and have an identical time course (67). MRI lesion mapping in patients showing contralateral SVV tilts (in some patients a complete OTR) disclosed the dentate nucleus as the causative structure. In contrast, ipsilateral tilts

indicated lesions in the biventer lobule, the middle cerebellar peduncle, the tonsil and the inferior semilunar lobule, sparing the dentate nucleus (66).

The *spontaneous course* of SVV tilts indicates that they are due to an *acute* vestibular dysfunction. They most often decrease and normalize over time within a few weeks. In patients with a unilateral lesion of the dorsolateral medulla affecting the vestibular nucleus the deviations recovered within about 4 weeks (22, 35, 59). A comparable time course of SVV tilts was seen in patients with an acute vestibular neuritis, now termed acute vestibular syndrome (59). Patients with an acute unilateral cerebellar infarction also had a spontaneous recovery within 2–4 weeks (67). The MRI of some patients who had a pathological deviation of the perceived vertical lasting several months or years revealed damage to the cerebellar structures necessary for compensation and recalibration (68).

SVV Tilts and Associated Vestibular Motor Signs

Tilts of the visual vertical are often associated with the components of an ocular tilt reaction (OTR, an eye-head synkinesis); all tilts are in the same direction in the roll plane. The OTR consists of head tilt, skew deviation (upward deviation of one eye, downward deviation of the other), and ocular torsion combined with SVV tilts. Tilts of SVV toward the head tilt suggests that this is the perceptual correlate of perceived body tilt. The consequence is a compensatory motor response and adjustment of SVV in the opposite direction, i.e., in parallel to the direction of eye-head tilt (**Figure 2**). OTR was first described in monkeys (69) elicited by electrical stimulation of the unilateral mesodiencephalic structures. However, OTR can occur along the vestibular pathways from the labyrinth to the upper midbrain, but not in the thalamus and cortex (**Figure 3**). Due to the crossing of the graviceptive pathways in the pons the OTR is—like the SVV tilts—ipsilateral in unilateral pontomedullary lesions and contralateral in unilateral pontomesencephalic lesions, especially in those of the INC (23, 38, 52, 53).

Clinically there are two types of OTR (70): an "*ascending*" medullary type and a "*descending*" mesencephalic type. An OTR due to ponto-medullary vestibular nucleus lesions (Wallenberg syndrome) reflects a tone imbalance of the VOR in roll plane (**Figure 4**), whereas OTR caused by INC lesions (paramedian midbrain infarctions) reflects a tone imbalance of the neural integration center for vertical and rotatory eye-head coordination (54). The midbrain center not only integrates eye and head velocity for position (i.e., maintaining eye-head position in space at the end of the movement), it also adjusts vestibular reflex responses to cortical voluntary eye movements (54, 70, 71). The different manifestations of the ascending VOR type with monocular or disconjugate eye torsion indicate dysfunction of nerve fibers from the posterior, anterior, or both semicircular canals (**Figure 4**). If the crossed ponto-mesencephalic pathways are affected unilaterally—rostral to the downward–branching of vestibulo-spinal pathways—tilts of SVV and ocular skew-torsion occur without head tilt (23, 35). The descending mesencephalic type of OTR primarily manifests with a binocular ocular torsion.

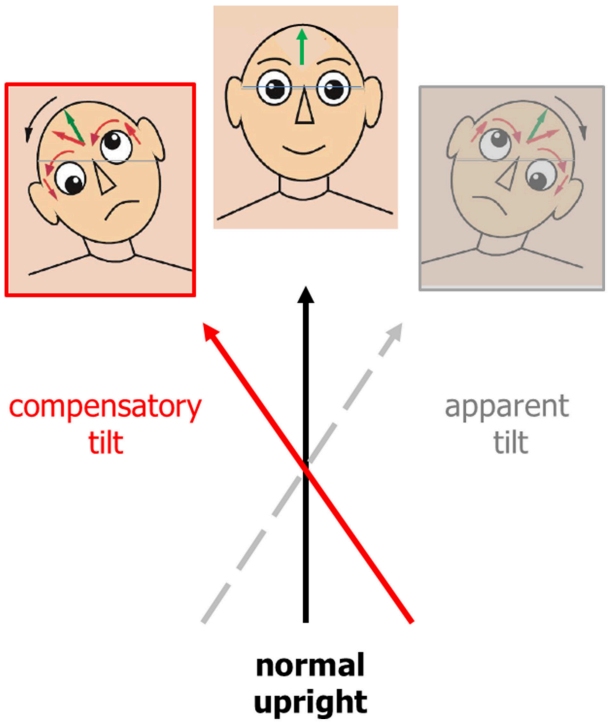

FIGURE 2 | Ocular tilt reaction (i.e., triad of head tilt, vertical divergence, and ocular torsion of both eyes) and deviation of subjective visual vertical (green arrow = normal upright) represented as a "motor compensation" (in red) of a lesion-induced perception of eye-head tilt (in gray). The compensatory tilt is opposite in direction to the apparent tilt. Eyes and head are continuously adjusted to what the lesioned brain computes as being vertical.

However, due to an additional damage of the trochlear or oculomotor nerve fascicles inducing monocular torsion of the ipsilateral (N. III) or contralateral eye (N. IV) the conjugate torsion can become disconjugate or monocular (30).

SVV Tilts in Thalamic and Cortical Lesions

It is well recognized that lesions of the *thalamus*, especially of the posterolateral nuclei, induce ipsilateral or contralateral SVV tilts combined with unsteadiness of gait (54, 72). Patients with acute unilateral infarctions of these nuclei exhibit mild SVV tilts of 4–6° without any other components of OTR, i.e., without ocular torsion or skew deviation (54). Another study of the perception of verticality in 86 stroke patients reported that the thalamus is mainly involved in postural vertical perception; some of the patients manifested with pusher behavior (73). However, a specific thalamic lesion location analysis was not conducted.

To determine the distinct thalamic subnuclei associated with contralateral or ipsilateral SVV tilts, statistical lesion behavior mapping was applied in 37 stroke patients with acute circumscribed thalamic lesions (57). Two distinct regions for graviceptive processing were found: (i) Contralateral SVV tilts were caused by lesions of the nuclei dorsomedialis, intralamellaris, centrales thalami, posterior thalami, ventrooralis internus, ventrointermedii, ventrocaudales and superior parts of the nuclei parafascicularis thalami. (ii) Ipsilateral SVV tilts were

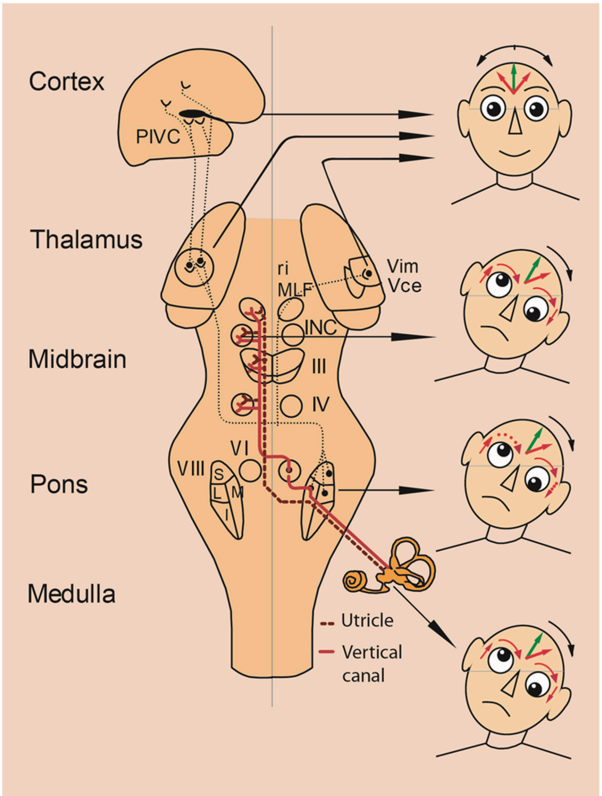

FIGURE 3 | Vestibular lesions manifesting with SVV tilts and ocular tilt reaction. Pathways from the utricles and vertical semicircular canals mediate graviceptive function in the frontal roll plane. These pathways ascend from the vestibular nuclei (VIII) to the ocular motor nuclei, including the trochlear nucleus (IV), oculomotor nucleus (III) and abducens nucleus (VI). From here, they travel to the supranuclear centers of the interstitial nucleus of Cajal (INC), and the rostral interstitial nucleus of the MLF (riMLF) in the midbrain tegmentum. This circuitry is the basis for the vestibulo-ocular reflex, and is connected with vestibulospinal reflexes to control eye, head, and body posture. Projections via the thalamus (Vim, Vce) to the parieto-insular vestibular cortex (PIVC) subserve perception of verticality. Unilateral lesions of the graviceptive vestibular pathways cause vestibular tone imbalance in the roll plane. Patients with such lesions can present with an ocular tilt reaction—an eye—head synkinesis with vertical divergence of the eyes (skew deviation), ocular torsion, head tilt, and tilt of the subjective visual vertical. Right-hand images depict the resulting vestibular syndromes according to the level of the unilateral graviceptive pathway lesion. These pathways cross at the pontine level, so the direction of tilt is ipsiversive with peripheral or pontomedullary lesions (bottom two heads) and contraversive with pontomesencephalic lesions above the crossing (head at midbrain level). In thalamic and vestibular cortex lesions, there are no eye and head tilts, and tilts of the subjective visual vertical are contraversive or ipsiversive (top head). Head images: green arrows in the forehead represent objective visual vertical; red arrows represent pathological subjective visual vertical; and red arrows around the eyes represent pathological vertical deviation and torsion of the eyes. I, inferior; L, lateral; M, medial; S, superior subnuclei of the vestibular nucleus (VIII). [Modified from Brandt and Dieterich (23)].

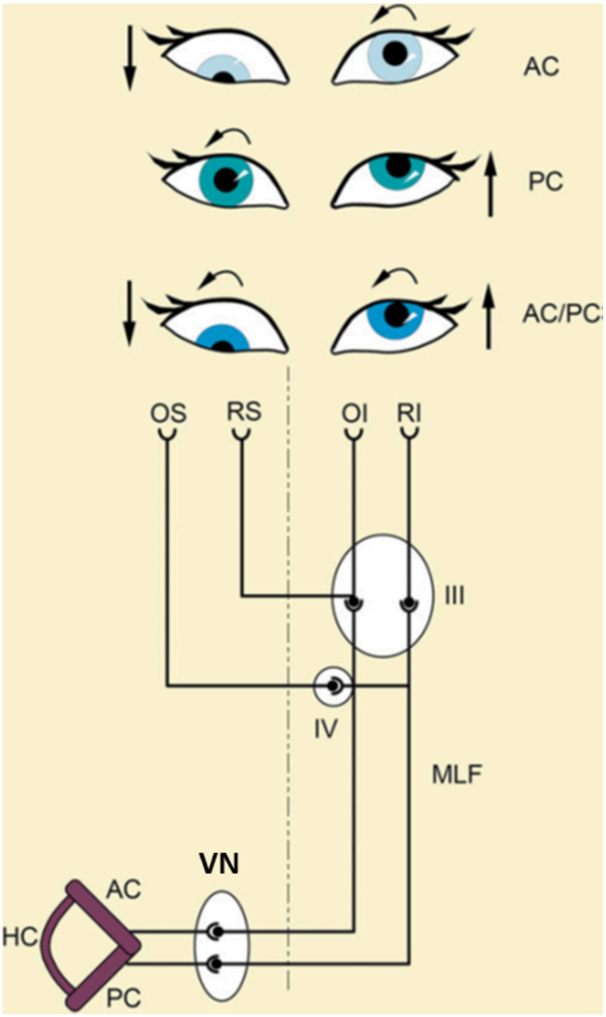

FIGURE 4 | Schematical explanation of different types of ocular tilt reaction (OTR) according to the input of the affected semicircular canals. The ascending-VOR type of OTR is characterized by monocular or dysconjugate skew torsion of the eyes depending on whether input from fibers of the posterior (PC), anterior (AC), or both semicircular canals (AC/PC) to the extraocular eye muscles are affected. An excitatory ascending pathway projects from the AC to the ipsilateral superior rectus (RS) and the contralateral inferior oblique (OI) muscle. A lesion of this pathway causes a hypotropia of the ipsilateral eye and an incyclotropia of the contralateral eye (AC type; **top**). An excitatory ascending pathway is linked from the posterior semicircular canal to the ipsilateral superior oblique (OS) and the contralateral inferior rectus (RI) muscle. A lesion of this pathway causes excyclotropia of the ipsilateral eye and hypertropia of the contralateral eye (PC type; **middle**). A combination of both canals (AC/PC) induces a complete OTR (**bottom**). III, oculomotor nucleus; IV, trochlear nucleus; VN, vestibular nucleus; MLF, medial longitudinal fascicle [Modified from Brandt and Dieterich (23) and Dieterich and Brandt (35)].

caused by more inferiorly located lesions, including the nuclei endymalis thalami, inferior parts of the nuclei parafascicularis thalami, and also small parts of the junction zone of the nuclei ruber tegmenti and brachium conjunctivum (57). These data suggest separate graviceptive structures in the vestibular network which—when damaged—cause either contralateral or ipsilateral SVV tilts (57). This is in line with data from combined structural and functional connectivity mapping by means of diffusion tensor imaging combined with functional connectivity magnetic resonance imaging in right-handed volunteers (74). A link was observed between the vestibular nuclei and the ipsilateral and

contralateral parieto-insular vestibular cortex (PIVC). There were five separate and distinct vestibular pathways, three of which run ipsilaterally, whereas the other two revealed a crossing at pontine or midbrain level. Of the three ipsilateral projections two run through the posterolateral or paramedian thalamic subnuclei; the third bypassed the thalamus to directly project to the inferior insular cortex (74, 75). The two contralateral pathways traveled through the posterolateral thalamus.

The disorder *thalamic astasia* is characterized by a transient postural imbalance associated with a strong tendency to fall, while motor weakness or sensory loss are absent (76). This results in lateropulsion or retropulsion. It was described in acute lesions of the posterolateral or centromedian thalamic subnuclei (54, 77, 78) and was interpreted to be a vestibular tone imbalance (54). In the few patients examined it was joined by contralateral SVV tilts (38, 78).

SVV deviations of about 4–6° were also seen in patients with acute *cortical* infarctions of the middle cerebral artery territory, which chiefly affected the posterior insula and the temporal gyri (55). Ocular torsion and skew deviation were not associated. With the use of voxel-based lesion behavior mapping in MRI it was possible to more precisely localize the infarction in the posterior insular cortex (e.g., long insular gyrus IV) (37, 79, 80) (**Figure 5**). The cortical site of the infarction causes misperception of verticality in the acute stage of stroke, thus agreeing with imaging data of patients with an acute peripheral vestibular neuritis. In the latter patients SVV tilts correlated positively with the regional cerebral glucose metabolism for the posterior insula and retroinsular region bilaterally—more so in the right hemisphere than in the left hemisphere—and for the middle temporal gyrus bilaterally (82). These studies in patients with vestibular neuritis together with the imaging data on healthy participants during galvanic vestibular (83) or visual motion stimulation, which induced circular vection (84), allowed to attribute the processing of certain aspects of the vestibular stimulus to particular parts of the vestibular thalamo-cortical network.

Investigations of the SVV and the haptic vertical at later stages after right hemispheric stroke (during rehabilitation, mean day 43) showed that the lesions correlated to the SVV tilts, which occurred more centrally on the temporo-occipital junction and the posterior part of the middle temporal gyrus. The lesions correlating to the haptic tilts were located more anteriorly in the superior temporal gyrus and sulcus (21). In contrast, B. Baier from our group was able to demonstrate in patients with *acute* unilateral strokes of the right hemisphere that the lesioned areas associated with SVV tilts were found in the insular cortex, the rolandic operculum, the inferior frontal gyrus, and the frontal inferior operculum (**Figure 6**). Similar lesion sites were also seen in lesions associated with tilts of the haptic visual vertical located in the insular cortex, rolandic operculum, superior temporal gyrus, pallidum, Heschl's gyrus, superior longitudinal fascicle, and the corona radiate (**Figure 6**). An affection of insular regions and the superior temporal gyrus was also found earlier in patients with middle cerebral artery infarctions presenting with contraversive pushing (31, 37) (**Figure 7**).

Polysynaptic pathways and multisensory convergence link the bilaterally organized central vestibular network with cerebellar, hippocampal, limbic, and non-vestibular cortex structures to mediate *"higher" vestibular (cognitive) functions*. The cortical disorders *spatial hemineglect* and *pusher syndrome* have characteristics which can be explained by the hemispheric dominance of the vestibular network, i.e., of the right hemisphere in right-handers (85, 86).

Spatial hemineglect results from a disturbed awareness of the visual surroundings in the egocentric hemifield contralateral to an acute temporoparietal lesion (87). Stroke studies on spatial hemineglect showed that the right superior temporal cortex and the insula are preferred lesion sites (88, 89). The latter areas are parts of the distributed cortical vestibular network. Indeed, patients with spatial hemineglect exhibit systematic tilts of the SVV (90, 91). The magnitude of tilts were modulated by factors that mediate the perception of gravity and head-orientation in space (92). Neglect patients—as distinct to brain-damaged control patients—showed a counterclockwise tilt of their SVV judgments. SVV judgments were modulated by the orientation of a visible frame. If the frame was tilted counterclockwise, the spatial bias of neglect patients increased, whereas in clockwise tilts of the frame, the spatial bias decreased or even reversed in larger frame tilts (92). This enhanced rod-and-frame effect might be due to a pathologically enhanced effect of contextual visual features on SVV due to impaired processing of gravitational information (92).

Studies with vestibular caloric stimulation transiently improved spatial awareness, a finding that underlines the important contribution of cortical vestibular function in hemineglect (93, 94). When galvanic vestibular stimulation was combined with vibration of the neck muscles, the horizontal deviation of the neglect border combined linearly (95). Therefore, the spatial neglect was considered a disorder of *multisensory vestibular cortex* function (89). However, multiple sensory modalities are involved in hemineglect as well as sensorimotor control, attention, and cognition which requires multisensory integration (96). The same is true for the pusher syndrome in which somatosensory, vestibular, and visual modalities have to be integrated. Accordingly, the adjustments of SVV are influenced by the visible space and body position (97).

Mathematical Modeling of Vestibular Function in the Roll Plane

Traditionally, the effect of unilateral peripheral vestibular lesions on SVV was attributed to a tone imbalance of the otolith system (98). Use of a neural network model focusing on the direction of SVV tilts in the roll plane in upright and tilted body positions allowed comparison of the data from model simulations with clinical data (**Figure 8**). This recently revealed that the SVV tilt is also caused by a tone imbalance of semicircular canal input which significantly contributes to the central estimator of gravity (2). This model concept nicely confirms the earlier hypothesis that a combined dysfunction of otolith and semicircular canal input is the underlying pathomechanism of, for example, ocular tilt reaction and SVV tilt in the Wallenberg syndrome (35).

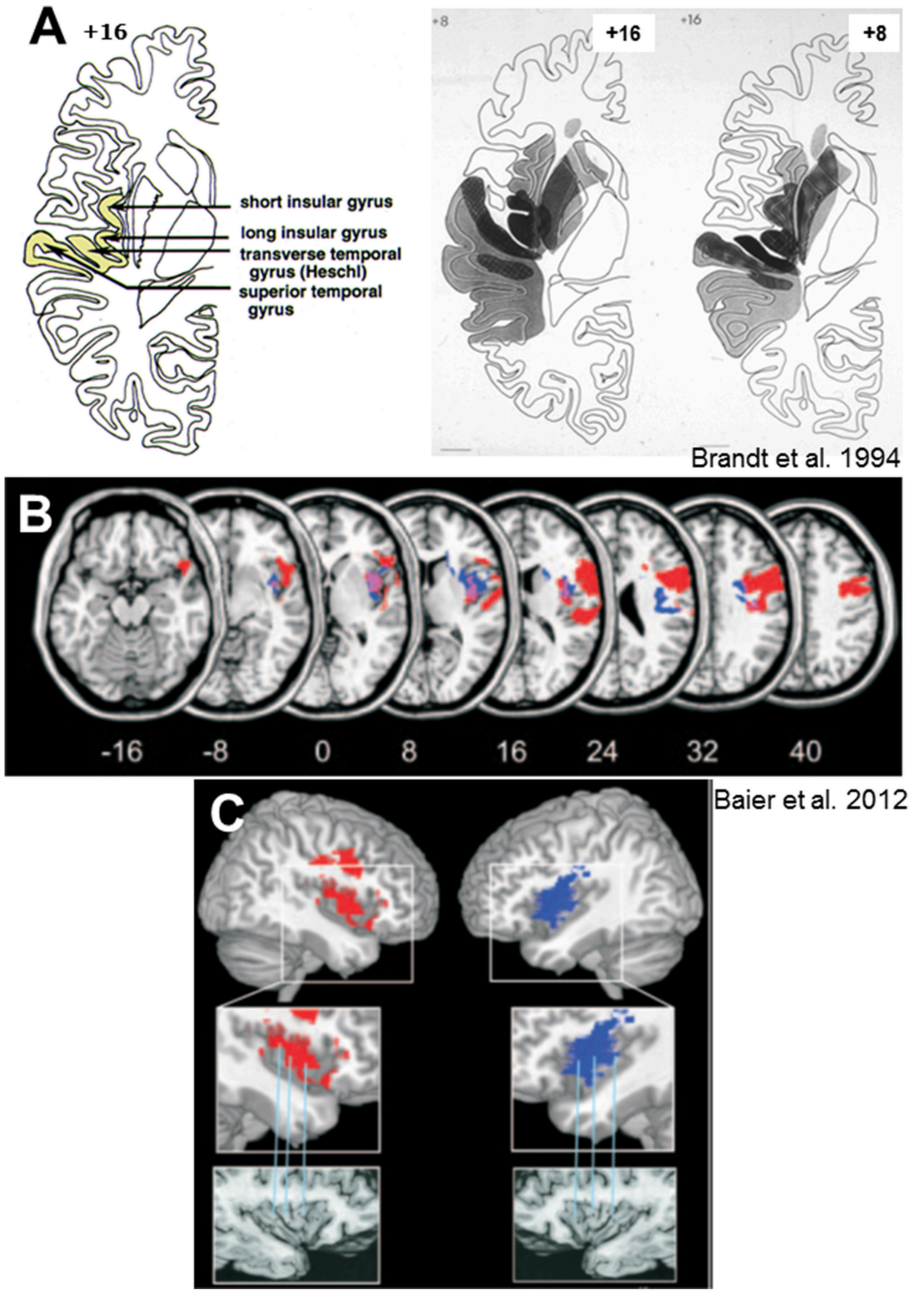

FIGURE 5 | Lesion sites of hemispheric infarctions that cause tilts of subjective visual vertical. **(A)** Collective presentation of infarcted areas taken from MRI scans and projected onto sections of the atlas of Duvernoy (81) in 7 patients with clearly demarcated infarctions of the middle cerebral artery which caused significant contralateral SVV tilts. Overlapping areas of infarctions (7 of 7 in black) are centered at the posterior part of the insula, involving the short and long insular gyri, the transverse temporal gyrus, and the superior temporal gyrus [from Brandt et al. (55)]. **(B)** Statistical voxelwise lesion-behavior mapping (VLBM) analysis comparing 32 patients with acute right-sided infarctions (RBD) and 22 patients with acute left-sided infarctions (LBD) with respect to absolute tilt of subjective visual vertical (*t*-test statistic). Presented are all voxels that survived a correction for multiple comparisons using a 1% false discover rate cutoff threshold. Overlay of the statistical map from LBD patients (blue color), flipped to the right hemisphere, and the statistical map of the RBD patients (red color). Overlapping regions are shown in violet. From Baier et al. (79) **(C)** Illustration of the affected parts of the insula using the atlas of Duvernoy (81). Right insular lesions in red, left insular lesions in blue. Affected are the circular insular sulcus, central insular sulcus, short insular gyrus, and long insular gyrus [From Baier et al. (79)].

The pattern of dissociated ocular torsion and skew deviation in Wallenberg patients was explained by the connections of the posterior and anterior semicircular canals with their respective plane-specific set of extraocular eye muscles (100) (**Figure 4**). Moreover, also the tonic ocular torsion during prolonged galvanic stimulation can be best attributed to semicircular canal

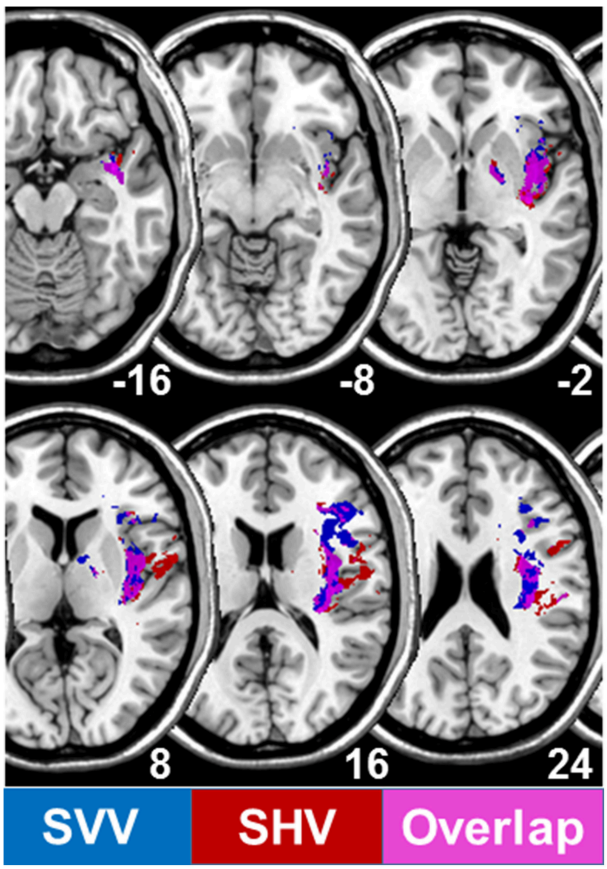

FIGURE 6 | Overlapping lesion plots of 82 patients with an acute unilateral infarction of the right hemisphere. Statistical VLBM analysis comparing the 82 right brain damaged patients with respect to absolute tilts of subjective visual vertical (SVV) and subjective haptic vertical (SHV) (*t*-test statistic). Presented are all voxels that survived a correction for multiple comparisons using a 5% permutation rate correction cut off threshold. Lesions associated with SVV tilts are given in dark blue, those associated with SHV tilts in red, overlap of both in pink/violet.

activation (101). Thus, all these data allow the assumption that SVV tilts are caused by vertical semicircular canal imbalance rather than solely by an otolith imbalance. This led us to use the term "vestibular graviceptive pathways" (35).

Mathematical modeling helps understand systemic vestibular function. It requires knowledge of the neuronal circuitry, specific function of various vestibular cell systems (such as head angular velocity cells, head direction cells, or grid cells) and reliable quantitative clinical data of SVV tilts at specific lesion sites. Models should not only confirm but predict the effects of circumscribed lesions within the vestibular circuitry. Two approaches may serve as typical examples for the translational application. The first model addressed the question of why rotational vertigo is regularly caused by ponto-medullary vestibular lesions but only rarely by mesencephalic lesions (102). The second asked the question of how the different directional tilts of SVV along the ascending vestibular pathways can be explained, especially the direction-specific (ipsilateral or contralateral) tilts along the brainstem but the bilateral tilts at thalamic and cortical levels (54, 55).

The first model focused on a retrospective analysis of the frequency of rotational vertigo in acute unilateral midbrain strokes ($n = 63$) that involved the vestibular and ocular motor systems (102). Unilateral pontomedullary brainstem lesions often caused rotational vertigo, while midbrain lesions rarely caused rotational vertigo (14%) which occurred only transiently (<1 day). Swaying vertigo or unspecific dizziness (22%) and postural imbalance (31%) were typical for upper midbrain lesions. The prevailing signs were that of a vestibular tone imbalance in the roll plane in form of SVV tilts (89%), skew deviation (81%), and an incomplete or complete OTR (73%). Upper midbrain and meso-diencephalic strokes manifested chiefly with swaying or unspecific vertigo. These different manifestations were attributed to the anatomical distribution of two distinct vestibular cell systems based on semicircular canal function. The coding for head direction is performed by so-called angular head-velocity cells and head direction cells. In rodents angular head-velocity cells have been identified preferably in the lower brainstem and less frequent in the midbrain, whereas head direction cells were located mainly at midbrain and thalamic level and including cortical areas (103). The cell specific coding determines the clinical manifestation of dysfunctions of the angular velocity cell system with the sensation of body rotation and of the head direction cell system with swaying dizziness and unsteadiness. It was possible to simulate, predict, and confirm the clinical findings by mathematical modeling neural network function of the head direction cell system (102).

A subsequent model approach was used to explain the different directions of SVV tilts in the roll plane (2) (**Figures 1**, **3**, **8**). Patient studies resulted in the following topographic diagnostic rules: (i) OTR or its components are seen in unilateral lesions from the peripheral labyrinth to the midbrain including the INC. Therefore, reflexive ocular motor control by the vestibulo-ocular reflex, the head and the body by vestibulo-spinal reflexes are mediated at lower brainstem and cerebellar level (71). (ii) Lesions of the centromedial or posterolateral vestibulo-thalamic subnuclei or the parieto-insular vestibular cortex cause SVV tilts only. (iii) Lesions of thalamic or cortical vestibular areas induce both, ipsilateral or contralateral SVV tilts (54, 57, 79). These tilts are constant in a single patient, but vary interindividually (about 50% ipsilateral, 50% contralateral). (iv) It is remarkable that the degree of SVV tilts is less in thalamic and in cortical disorders as compared to peripheral or lower brainstem lesions (**Figure 1**, **Table 1**).

Other groups developed different models based on transfer functions to dynamic Bayesian inference (3–5). Here, we only refer briefly to these articles for further reading. Our review is addressed to general neurologists who are usually not educated to understand the mathematics of such an overarching conceptual model framework. The inverse probabilistic approach by Clemens and co-workers (6) is most instructive. It shows that a forward approach is difficult to implement when the different sensory inputs cannot be

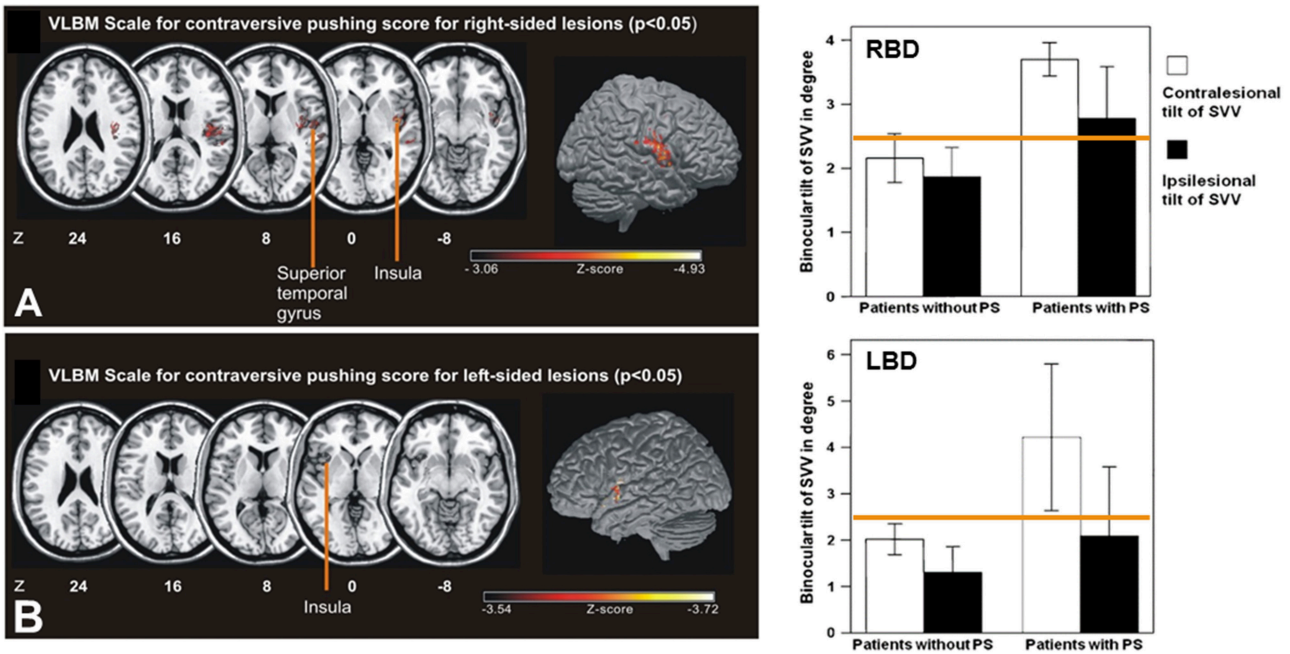

FIGURE 7 | Lesion sites of acute hemispheric infarctions that cause pushing behavior. Left: Statistical voxelwise lesion-behavior mapping (VLBM) multiple regression analysis of the right-sided lesion patients (**A**: RBD; top) and left-sided lesion patients (**B**: LBD, bottom) with predictors including the Scale for Contraversive Pushing (SCP) and lesion size. The key areas of the lesion covered the posterior insular cortex, the superior temporal gyrus, and white matter in RBD. The key areas in LBD associated with the extent of contraversive pushing were the anterior insular cortex as well as parts of the operculum and the internal capsule reaching to the lateral thalamus (not shown here). Talairach z-coordinates of each transverse section are given. Right: Mean amplitude of SVV in RBD and LBD without and with pusher syndrome (PS). Significance was not obtained ($p > 0.05$) for either the contra- or the ipsilesional tilt of SVV. Error bars indicate standard error of the mean. Yellow line indicates normal range for SVV measurement [adopted in part from Baier et al. (37)].

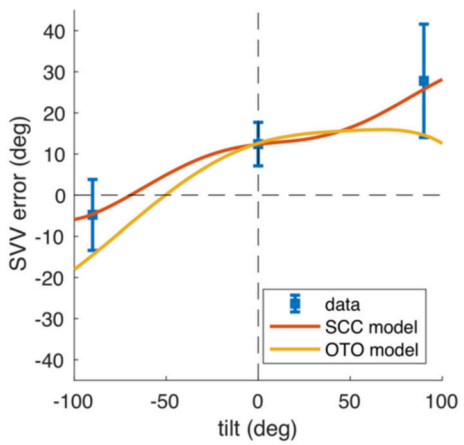

FIGURE 8 | Mathematical model data predicting and simulating tilts of subjective visual vertical (SVV). SVV data from Merfeld et al. (99) obtained in patients with unilateral vestibular nerve section (blue, error bars denote SD) and model simulations of the SVV adjustments (red and yellow) in upright and tilted (right ear down, left ear down) body positions. The OTO model (yellow) assumes unequal distribution of hair cells with opposite tuning on the utricular macula (Ewald's law for otolith organs). The SCC model (red) assumes that the afferent input of vertical semicircular canals is processed centrally by the gravity estimation mechanism. After a lesion, the semicircular canal bias causes a perceptual error of gravity direction that becomes visible as SVV tilt [From Glasauer et al. (2)].

studied in isolation. Their model predictions are based on the derived noise properties from the various modalities (6). They found that the accuracy of orientation estimates of subjective body and visual vertical in healthy subjects can be linked to a reference-frame-dependent weighting of sensory signals (6). This reverse-engineering approach in the healthy subjects was consistent with published data of two patients groups with acquired neurological or vestibular disorders (10, 11), which led them to speculate on the clinical relevance of such models. Furthermore, recent experiments emphasize the role of vestibular cerebellar function for gravity perception (104).

Why do SVV tilts at thalamic and cortical levels differ from those at brainstem level? One explanation could be that a partial crossing of the ascending pathways in the midbrain at the level of the INC provides the thalamus and the cortex with graviceptive input from both labyrinths (74). This enables the bilateral thalamocortical networks to operate separately in the right and left hemisphere because there is no direct interconnection between the two thalamic nuclei complexes (14, 105). An alternative or supplementary explanation could be based on different neuronal coding principles for graviceptive input due to the different vestibular cell systems, according to the discussed head direction cell system for the horizontal yaw plane (103). Findings in the macaque monkey concerning the tuning of gravity in anterior

thalamic neurons (106) confirm this view. An analysis of 15 studies (2) on the effects of unilateral peripheral or central vestibular lesions on the direction and amount of SVV tilts showed the following findings (see **Table 1**): acute unilateral labyrinthine or eighth nerve lesions caused ipsilateral SVV tilts in upright head and body position. Maximal tilts were found in complete vestibular loss caused by labyrinthectomy or neurectomy (**Figure 1**).

The gravity coding which changes from a peripheral or brainstem vectorial representation in otolith coordinates to a coding of distributed population at thalamic and cortical levels is compatible with the affects of unilateral thalamic and cortical lesions that variably effect the perceived verticality. This population-coding network for the perception of the gravity vector implements the elements that are required for the described perceptual underestimation of the SVV in tilted body positions, i.e., the Aubert effect (2) (**Figure 8**).

CONCLUSION

Thus, it is the level of the lesion of graviceptive vestibular pathways which is critical for the control of verticality perception and the position of eye, head, and body relative to gravity in the roll plane. It explains all features of OTR including postural instability:

- Medullary lesions may cause lateropulsion.
- Vestibular nucleus lesions cause ipsilateral "VOR-OTR" with monocular or disconjugate ocular torsion.
- Brainstem lesions between the vestibular nucleus and the rostral midbrain cause SVV tilts and ocular skew-torsion.
- INC lesions cause "integrator OTR" with binocular conjugate ocular torsion.
- Unilateral vestibular lesions above brainstem level from meso-dienecephalic vestibular structures to the cortex as a rule manifest with perceptual rather than motor dysfunctions.
- Lesions at thalamic level cause SVV tilts without associated ocular motor signs; rarely vestibular thalamic astasia may occur.
- Lesions of the insular and temporo-parietal cortex cause mild ipsilateral or contralateral SVV tilts and in exceptional cases transient vertigo.

Patients with cortical lesions of the vestibular system may also present with higher vestibular dysfunctions such as visuospatial hemineglect and pusher syndrome. Higher vestibular dysfunctions involve cognition and more than one sensory modality. They involve multisensory convergence and sensorimotor interaction for spatial memory, spatial orientation, navigation, and attention. Based on the clinical data, mathematical models have been developed which are able to simulate and predict the deficits of gravity perception in patients with neurological and otoneurological disorders.

AUTHOR CONTRIBUTIONS

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

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The Tilted Self: Visuo-Graviceptive Mismatch in the Full-Body Illusion

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The bodily self is a fundamental part of human self-consciousness and relies on online multimodal information and prior beliefs about one's own body. While the contribution of the vestibular system in this process remains under-investigated, it has been theorized to be important. The present experiment investigates the influence of conflicting gravity-related visual and bodily information on the sense of a body and, vice versa, the influence of altered embodiment on verticality and own-body orientation perception. In a full-body illusion setup, participants saw in a head-mounted display a projection of their own body 2 m in front of them, on which they saw a tactile stimulation on their back displayed either synchronously or asynchronously. By tilting the seen body to one side, an additional visuo-graviceptive conflict about the body orientation was created. Self-identification with the seen body was measured explicitly with a questionnaire and implicitly with skin temperature. As measures of orientation with respect to gravity, we assessed subjective haptic vertical and the haptic body orientation. Finally, we measured the individual visual field dependence using the rod-and-frame test. The results show a decrease in self-identification during the additional visuo-graviceptive conflict, but no modulation of perceived verticality or subjective body orientation. Furthermore, explorative analyses suggest a stimulation-dependent modulation of the perceived body orientation in individuals with a strong visual field dependence only. The results suggest a mutual interaction of graviceptive and other sensory signals and the individual's weighting style in defining our sense of a bodily self.

Keywords: full-body illusion, vestibular system, multisensory integration, out-of-body experience, bodily orientation, haptic vertical

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INTRODUCTION

The continuous representation of the own body and its relation to the external world is an important part of the daily experience of our self. Such representations are thought to be based on a probabilistic integration of body signals from various sensory systems and prior beliefs about the body (1). The sense of our bodily self, which includes the feeling of body ownership, self-location, and first-person perspective (2), is thus surprisingly plastic and constantly updated by the current sensory signaling. Over the last years, experimental setups that systematically present synchronous but conflicting inputs from different sensory modalities have been developed to alter and study such updating processes.

In the seminal rubber hand illusion (3), synchronous but conflicting information about where a tactile event is seen (on a rubber hand in front of the participant) and where it is felt (on the real hand of the participant, hidden from sight) induces a temporary illusory sense of ownership over the rubber hand. Such a subjective change in the bodily self corroborates various perceptual and physiological measures, such as drops in skin temperature recorded on the participant's hand (4) [but see Ref. (5) for a critical view]. In this setting, the spatially conflicting information is thus presented in a body-centered reference frame (i.e., the visual and bodily information about the tactile event concerning the hand locations differs in relation to the rest of the body). The information about the position and orientation of the body in space with respect to gravity remains stable. Related illusions have been developed to investigate more global body representations (6), in which the conflicting information is spatially presented in an allocentric reference frame (i.e., the position of the full body in space). Consequently, in these full-body illusions, vestibular and other graviceptive (proprioceptive and interoceptive) systems might play an important role, as they both encode self-orientation in relation to gravity (7, 8). Recent theoretical and empirical work shows that vestibular signals importantly contribute to higher-level space and body perception (9–11) and bodily self-awareness [see, e.g., Refs. (12, 13) for extensive reviews]. Yet, very few studies have directly investigated the mutual interactions between visuo-graviceptive conflicts and bodily self-consciousness [for exceptions, see Refs. (14–18)].

Here, we set out to test how conflicting visual and graviceptive signals in a full-body illusion and resulting perceptual changes might affect perceived body and gravity orientation. For this, we created a full-body illusion, in which participants see a video of their own body in a head-mounted display (HMD), as if it were projected 2 m in front of them [for details, see Ref. (6) and **Figure 1A**]. Tactile stroking was applied to their back while participants saw their own back in front of them being touched synchronously (to increase self-identification with the seen body) or asynchronously (as a control condition) to the felt touch. Importantly, to additionally create a visuo-graviceptive conflict about the body orientation in space, we displayed the seen body and its surroundings in an orientation that is either congruent with the participant's body orientation (upright, 0°) or incongruent with the participant's body orientation (tilted 30° counter-clockwise relative to gravity).

We measured self-identification with the seen body using questionnaires (3, 6) and skin temperature. Previous studies showed that skin temperature drops during illusory self-identification and might thus be an implicit measure of self-identification with the seen body (16, 19). To test our main hypothesis that illusory self-identification with a tilted body changes the perception of gravity and/or the perceived own-body orientation in space, we measured subjective haptic vertical and subjective body orientation.

In line with previous literature, we expect synchronous visuo-tactile stroking to increase self-identification with the seen body, with an associated decrease in skin temperature (19). During synchronous stroking in the tilted condition, we expect that self-identification with a seen tilted body will bias vertical perception and own-body orientation perception. It is well-known that actual body tilt in the roll plane changes visual vertical perception, leading to an A-effect (i.e., under compensation for large body tilts) or an E-effect (i.e., over compensation for small body tilts) (20). For haptic vertical perception of small body tilts, Schuler et al. (21) found a slight overcompensation in subjective haptic vertical judgment. This result is in line with earlier findings, which found a slight overcompensation up to 90° body tilt (22) and an overcompensation of 5° at a 35° body tilt (23). If participants identify with the seen 30°-tilted body, we expect them to overcompensate their haptic vertical judgment and to align their body orientation perception in the direction of the tilted body shown in the HMD.

As sensory weighting strategies have been previously shown to influence self-location in a variant of the full-body illusion (9, 13), we expect that individuals with a stronger visual field dependence, as measured by the rod-and-frame test, will show a stronger illusion and a more strongly altered verticality judgment.

Alternatively, the additional mismatch between visual and graviceptive information in the tilted conditions might also decrease illusory embodiment. Previous research testing the limits of plasticity in the rubber hand illusion paradigm showed that an additional spatial misalignment between the real and the rubber hand (a rotation next to the shift) decreased the illusion (24), even for small rotations (25).

MATERIALS AND METHODS

Participants

Forty participants were recruited, but three participants were excluded for technical reasons and two due to cybersickness. The remaining sample included 35 healthy, right-handed participants (aged 18–41 years, mean ± SD: 22.9 ± 4.3 years, 10 males). All participants were naive to the study aims, had normal or corrected-to-normal vision, and declared no history of psychiatric, neurological, or vestibular diseases. They were recruited through the psychology mailing list of the University of Zurich and received study credits. The protocol was approved by the Ethics Committee of the Faculty of Arts and Social Sciences at the University of Zurich (Approval number 17.12.15), and all participants gave written informed consent prior to inclusion in the study.

Experimental Procedures

Familiarization With the Protocol

Informed consent was obtained and demographic data were gathered. Following this, participants were familiarized with the procedures and the haptic device, and completed a practice trial. After making sure that they understood the task, the experiment started.

The Full-Body Illusion

Procedures

To induce the full-body illusion, we adapted the paradigm [detailed in Ref. (6)]. Participants were instructed to stand straight and not move during the experiment. In order to

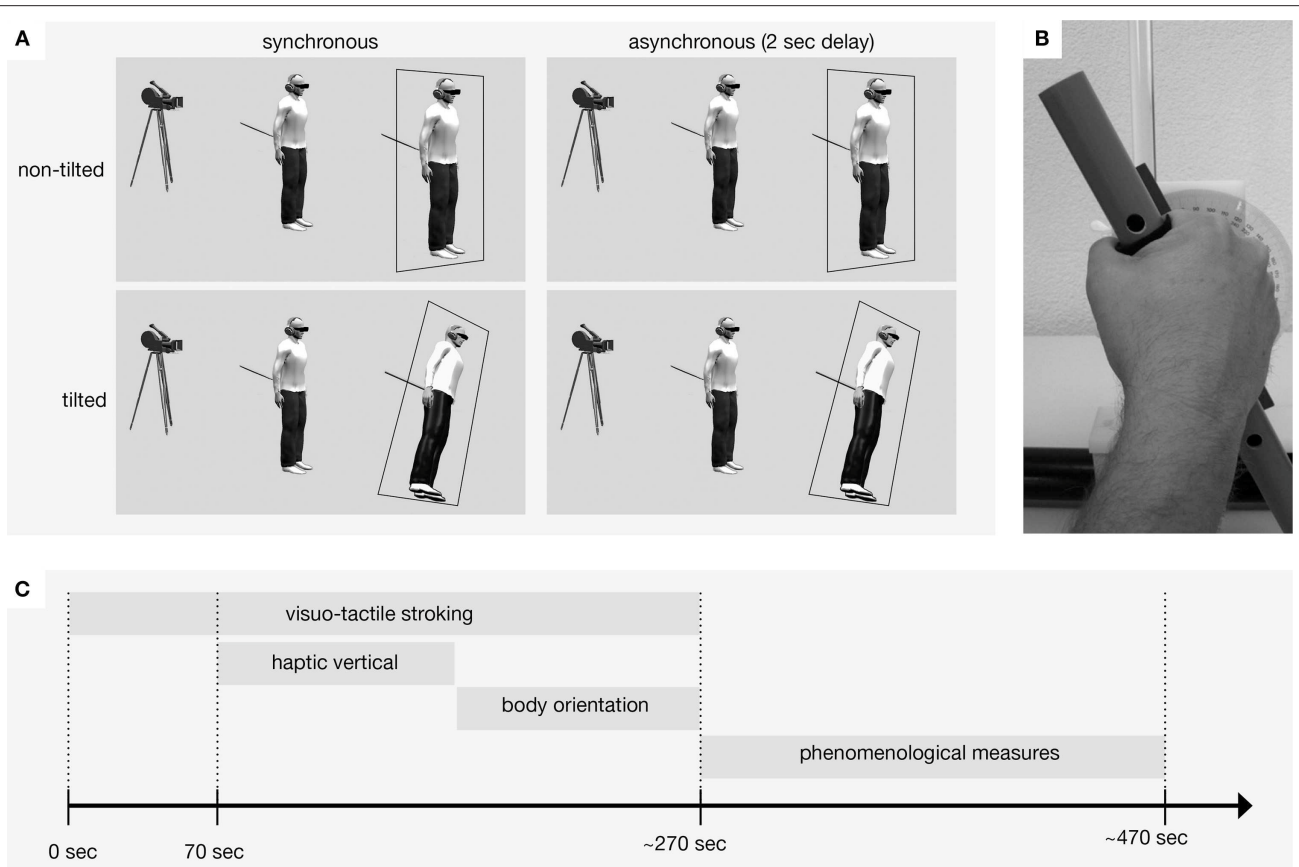

FIGURE 1 | Experimental setup and procedure. **(A)** Illustration of the four experimental conditions: Participants were seeing on the HMD their own body in front of them either in an upright position or in a tilted position, and the stroking on the back was shown either synchronously or asynchronously with the felt stroking. **(B)** Device that was used to measure subjective haptic vertical and subjective body orientation. **(C)** Procedure of one condition. First, the stroking was applied to induce the illusion, then while still experiencing the multisensory stimulation, participants completed the haptic vertical and the subjective body orientation task. Afterwards, the stimulation was halted and participants filled out a questionnaire on the phenomenological aspects of the illusion.

verify how much the participants moved, the head movements where tracked using the HMD (Oculus Rift; Oculus VR, Irvine, CA, USA) that was used for the visual presentation [see Supplementary Online Material for methods and results (see **Table S1**) of the head tracking]. The participant's body was filmed from behind at a 2 m distance with a Logitech c930e webcam (Logitech, Lausanne, Switzerland). The video was mapped to a digital 3D object, approximately matching the distortion of the webcam, and then projected on an HMD, using software developed in Unity 2017.3.0. The participants were touched on their back with a wooden stick. An experimenter, who was located outside the visual field of the camera, applied the touch manually. Stroking was applied on the back in an unpredictable way (which has been suggested to increase the illusion), at a rate of about one stroke per second. Four conditions were designed; the felt touch could be seen either synchronously (with an intrinsic system delay of approximately 135 ms measured at a rate of 240 Hz, thus below detectable threshold) or asynchronously (a constant delay of 2 s in addition to the intrinsic delay) on the seen body, which could be seen either upright or tilted with the virtual environment by 30° to the left (**Figure 1A**). Each condition was presented once in a counterbalanced order between participants. Each of the four trials (see **Figure 1C**) consisted of a stimulation period of 70 s, in which participants were instructed to focus on the visual scene and the tactile stimulation. Then, eight consecutive beeps instructed the participants to make judgments about their haptic vertical (see below for details). After that, another eight consecutive beeps instructed the participants to judge their own-body orientation with respect to gravity (see below for details). These two tasks took about 100 s, each depending on speed of answer. Importantly, the stroking and the visual input continued throughout these tasks. After that, the stroking was stopped, and participants answered a questionnaire shown on a black background on the HMD before the next trial started. One trial took ∼5 min.

Measures

Subjective haptic vertical and body orientation. After 70 s of stroking, an auditory signal instructed participants to start with the verticality judgment. A motor-driven haptic vertical device (see **Figure 1B**) was used for the judgment [for further information about the device, see Ref. (26)]. The device was fixed in front of the participants at a height of 120 cm, and the rod was calibrated to 0° before every experiment. Participants were

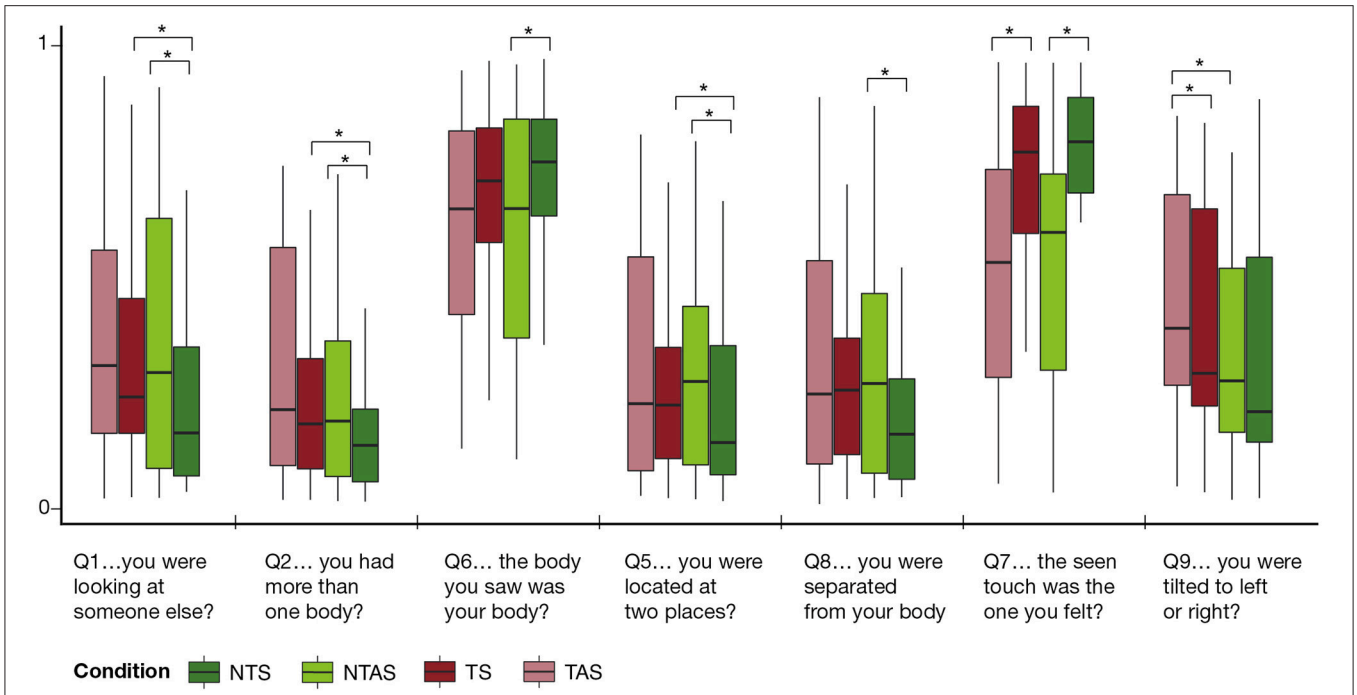

FIGURE 2 | Results of the questionnaire. For all items that revealed a significant effect of Condition, the medians and interquartile ranges for each condition are plotted. Significance bars refer to the results of the Bonferroni-corrected *post hoc* Wilcoxon tests. * indicates a significant effect. NT, non-tilted; T, tilted; S, synchronous stroking; AS, asynchronous stroking.

instructed to align the rod with the perceived direction of gravity ("subjective haptic vertical," eight times) and thereafter with their foot-head axis ("subjective body orientation," eight times). The rod position was sampled at 200 Hz using Labview (National Instruments). After each judgment, the rod automatically moved to a new random position between ±75° from upright.

Questionnaire. After the haptic judgment tasks, a German version of a questionnaire adapted to a previous full-body illusion questionnaire (6), including additional items about the vestibular perception, was presented in the HMD. For clarity, the questionnaire was subdivided into four categories based on the content of the questions (see **Table 1**). The questions were answered on a visual analog scale ranging from 0 ("not at all") to 1 ("very strongly") by controlling a continuously moving cursor with head movements. Once the cursor was at the selected position on the visual analogue scale (VAS) scale, participants answered by selected with the cursor an OK button and the answer was recorded using Unity. This way, participants did not have to remove the HMD between the conditions or use an extra controller.

Skin temperature. During the stroking period, we continuously measured skin temperature with a sampling rate of 2 Hz with an HH309A Data Logger Thermometer (Omega, Stamford, CT, USA), through four sensors (16). Two sensors were placed in camera field of view, i.e., one at the back of the neck and one at the back of the left arm. A third sensor was placed on the collarbone, which was not visible in the HMD, as previous studies indicated a drop in temperature only for seen body parts (16). A forth measured changes in the room temperature.

The Rod-And-Frame Test

At the end of the experiment, visual field dependence was measured with the rod-and-frame test (27). MATLAB R2017b was used for presentation of the rod-and-frame test and for recording responses. A white dotted line (8.6 cm in length) was presented on the screen. Participants were asked to adjust the line inside a square to a vertical position. The initial position in which the line was shown was either tilted counter-clockwise (four trials) or clockwise (four trials) at a randomly chosen angle (in the range of ±4° with respect to the gravitational vertical). The frame was tilted 20° clockwise eight times and was upright eight times. The order of the two conditions was counterbalanced. The room was completely dark and a round frame covered the screen edges, so the participants could not refer to vertical objects around them.

Data Processing and Statistical Analysis

Preprocessing

Subjective haptic vertical and body orientation

For each of these two measures, we calculated the mean and standard deviation of the eight repetitions. One participant was excluded for technical reasons.

Skin temperature

For each condition, the mean value of the first 1.5 s (three measure points) was used to calculate a baseline. The baseline-corrected values of the data points from the following 70 s were

TABLE 1 | The table shows the results of the Friedman tests for all dependent variables and *post hoc* Wilcoxon comparisons for the significant effects.

Results	Friedman-test		NT (S vs. AS) (Illusion-effect upright)	T(S vs. AS) (Illusion-effect tilt)	S (NT vs. T) (Tilt-effect synchronous)	AS (NT vs. T) (Tilt-effect asynchronous)
QUESTIONNAIRE						
Ownership related questions						
Q1: …You were looking at someone else?	x^2 =14.7	$p = 0.002$*	$p = 0.003$*	$p = 0.31$	$p = 0.002$*	$p = 0.94$
Q2: …You had more than one body	$x2 = 13.5$	$p = 0.004$*	$p = 0.002$*	$p = 0.14$	$p = 0.004$*	$p = 0.16$
Q6: …The body you saw was your body?	$x2 = 12.2$	$p = 0.007$'	$p < 0.001$*	$p = 0.20$	$p = 0.10$	$p = 0.40$
***Disembodiment related* questions**						
Q5: …You were located at two places?	$x^2 = 14.1$	$p = 0.003$*	$p = 0.011$*	$p = 0.80$	$p = 0.002$*	$p = 0.80$
Q8: …You were separated from your body (as if yourself and body were localized at two different places)?	$x2 = 13.1$	$p = 0.005$*	$p = 0.003$*	$p = 0.33$	$p = 0.039$	$p = 0.63$
Referral of touch related question						
Q7: …The seen touch was the one you felt?	$x^2 = 31.6$	$p < 0.001$*	$p < 0.001$*	$p < 0.001$*	$p = 0.16$	$p = 0.79$
***Balance, stability and orientation related* questions**						
Q3: …You were swaying back and forth?	$x^2 = 8.0$	$p = 0.047$*	$p = 0.15$	$p = 0.66$	$p = 0.02$	$p = 0.70$
Q4: …You lost balance?	$x^2 = 2.6$	$p = 0.47$				
Q9: …You were tilted to left or right?	$x^2 = 10.7$	$p = 0.014$*	$p = 0.96$	$p = 0.012$*	$p = 0.15$	$p < 0.001$*
Q10: …You were floating?	$x^2 = 1.3$	$p = 0.72$				
Q11: …You felt sick?	$x^2 = 2.5$	$p = 0.48$				
VERTICALITY						
Subjective haptic vertical	$x^2 = 4.0$	$p = 0.26$				
Subjective body orientation	$x2 = 24.8$	$p < 0.001$*	$p = 0.88$	$p = 0.23$	$p < 0.001$*	$p < 0.001$*
SKIN TEMPERATURE						
Electrode neck	$x^2 = 2.65$	$p = 0.45$				
Electrode collarbone	$x^2 = 1.66$	$p = 0.65$				
Electrode left arm	$x2 = 2.09$	$p = 0.55$				

**indicates significance level. For Friedman tests, it was set to 0.05, and for the post hoc tests, it was set to p = 0.0125 according to the Bonferroni correction. NT, non-tilted; T, tilted; S, synchronous stroking; AS, asynchronous stroking.*

then averaged. Finally, the baseline-corrected room temperature was subtracted from all temperature averages. Four participants were excluded for technical reasons.

The rod-and-frame test was analyzed by calculating the mean of the eight trials for each condition (tilted frame/upright frame). A hierarchical cluster analysis was used to form two groups based on their visual field dependence/independence (28). For this, Ward's aggregation method was used (SPSS 24), and the Euclidean distance between participants was calculated based on the values of the tilted and the upright frame and a hierarchical tree was formed. The tree was divided at the maximum of dissimilarity into two clusters of visual-field-dependent and visual-field-independent participants. Two participants were excluded for technical reasons.

Statistics

Statistical analysis was performed using R 3.5.0 GUI 1.70. First, the Shapiro–Wilk test revealed non-normally distributed data for most of the dependent variables. We thus used non-parametrical tests, by first testing the effect of Condition (synchronous/tilted, asynchronous/tilted, synchronous/non-tilted, asynchronous/non-tilted) using Friedman tests. For significant effects only, we used Wilcoxon tests to compare the effect of Synchrony (synchronous vs. asynchronous visuo-tactile stroking) for the tilted and non-tilted conditions, separately. In addition, we compared the effect of Tilt (non-tilted vs. tilted) separately for the synchronous and asynchronous conditions. We used a Bonferroni-corrected p value to account for the number of comparisons for each dependent variable ($n = 4$, corrected p-value: 0.0125).

To test the effect of visual field dependence on the variables of interest (i.e., the relative differences between synchronous and asynchronous stroking in the two different tilts, and the relative differences between the two different tilts in both types of stroking), we calculated the relative values by subtracting the asynchronous from the synchronous conditions and the non-tilted from the tilted conditions. To compare relative dependent variables between visual-field-dependent and -independent participants, we used Mann-Whitney U-tests.

RESULTS

Explicit Measures of the Illusion: Questionnaire

Table 1 shows all questionnaire items and results of the Friedman test, as well as *post hoc* comparisons for the significant effects. The Friedman test revealed a significant effect of Condition for questions related to ownership (Q1, Q2, and Q6), disembodiment (Q5 and Q8), touch (Q7), and balance and orientation-related questions (Q3 and Q9) ($p < 0.047$, $\chi^2 > 8.0$, see **Figure 2**). The Friedman test was not significant for the other vestibular-related questions Q4, Q10, and Q11 ($p > 0.47$, $\chi^2 < 2.6$).

Embodiment-Related Questions

The *post hoc* comparisons (see **Figure 2**) showed that in the non-tilted condition, ownership was higher in the synchronous than in the asynchronous condition. This was evidenced by a stronger feeling that the seen body was felt as their own (Q6), a lower sensation of looking at someone else (Q1), and a feeling that they had more than one body (Q2). Similarly, the referred sensation of touch (Q7) was stronger in the synchronous than in the asynchronous condition, and the feeling of disembodiment (Q5 and Q8) was stronger in the asynchronous than in the synchronous condition.

For the tilted conditions, of all these effects, only the one for referral of touch (Q7) was significant. This is further corroborated by the significant difference in the synchronous conditions between non-tilted and tilted for questions Q1, Q2, and Q5.

Body Orientation and Stability-Related Questions

The only item that revealed significant differences in the *post hoc* comparison was the question whether participants felt tilted (Q9) and suggested that they felt more tilted during asynchronous stroking than during synchronous stroking.

Implicit Measures: Skin Temperature, Verticality, and Subjective Body Orientation Judgment

Skin Temperature

The Friedman test revealed no significant effect of Condition on baseline-corrected skin temperature measured on the neck ($\chi^2 = 2.65$, $p = 0.45$), collarbone ($\chi^2 = 1.66$, $p = 0.65$), and left arm ($\chi^2 = 2.09$, $p = 0.55$).

Subjective Haptic Vertical

The Friedman test did not reveal a significant effect of Condition on the subjective haptic vertical ($\chi^2 = 4.0$, $p = 0.26$). A further analysis of the effect of Condition on the standard deviation of the haptic vertical was also not significant ($\chi^2 = 2.3$, $p = 0.5$).

Subjective Body Orientation

The Friedman test showed a significant effect of Condition ($\chi^2 = 24.8$, $p < 0.001$). **Table 1** shows the significant *post hoc* comparisons. The perceived own-body orientation was significantly more tilted to the left (thus in the direction of the seen body) in the tilted compared to the non-tilted conditions, for both synchronous ($p < 0.001$) and asynchronous ($p < 0.001$) visuo-tactile stroking. The analysis of the effect of Condition on the standard deviation of subjective body orientation was not significant ($\chi^2 = 7.55$, $p = 0.06$).

Modulatory Effect of Visual Field Dependence

Hierarchical clustering revealed a group of visual-field-dependent participants ($n = 13$, mean value non-tilted $= -0.05°$, mean value tilted $= 1.55°$) and a group of visual-field-independent participants ($n = 20$, mean value non-tilted $= -0.13°$, mean value tilted $= -0.30°$). There was a significant effect of Group for both the relative subjective body orientation and the relative subjective haptic vertical.

Subjective Haptic Vertical

A Mann-Whitney test indicated that visual-field-dependent participants aligned their subjective haptic vertical more to the seen body in the tilted condition compared to the non-tilted condition during synchronous stroking (Mdn $= -1.70°$) than did visual-field-independent participants (Mdn $= -0.10°$, $U = 186$, $p = 0.02$).

Subjective Body Orientation

A Mann-Whitney test indicated that in the tilted condition, visual-field-dependent participants aligned their subjective body orientation more toward the seen body during synchronous relative to asynchronous visuo-tactile stroking (Mdn $= -1.37°$) than did visual-field-independent participants (Mdn $= -0.03°$, $U = 183$, $p = 0.02$). Similarly, during synchronous visuo-tactile stroking, visual-field-dependent participants aligned their subjective body orientation more strongly in the direction of the seen body in the tilted relative to the non-tilted condition (Mdn $= -3.37°$) than did visual-field-independent participants (Mdn $= -0.50°$, $U = 181$, $p = 0.03$, see **Figure 3**).

DISCUSSION

This study investigates illusory self-identification and self-orientation perception in a multisensory stimulation paradigm. Participants saw in an HMD a projection of their own body 2 m in front of them and felt tactile stimulation on their back either synchronously or asynchronously to the seen touch [full-body illusion setup (6)]. We exposed participants to an additional visuo-graviceptive conflict by presenting them with the projected body in an orientation that was congruent (upright) or incongruent (tilted) with the participant's actual upright body orientation. The study revealed three main findings. First, while we replicated self-identification with the seen body during synchronous stroking on a phenomenological level, questionnaire data suggest, in line with the alternative hypothesis, a decrease in the illusion strength during additional visuo-graviceptive conflict about the body orientation in space with respect to gravity. Second, we did not find a modulation of the perceived vertical and own-body orientation for the tilted body by synchrony of the stroking at the group level. Third, an analysis accounting for idiosyncratic strategies in multisensory integration (29) suggests a stimulation-dependent modulation of the perceived body orientation only in individuals with a visual field dependence.

Effect of Visual-Otolithic Conflict on the Full-Body Illusion

Our data show that the full-body illusion, as determined by explicit measures, is attenuated by the static visuo-graviceptive conflict from body orientation. While we replicated enhanced self-identification with the seen body during synchronous as compared to asynchronous visuo-tactile stroking in the upright position (6), this difference was no longer significant in the tilted

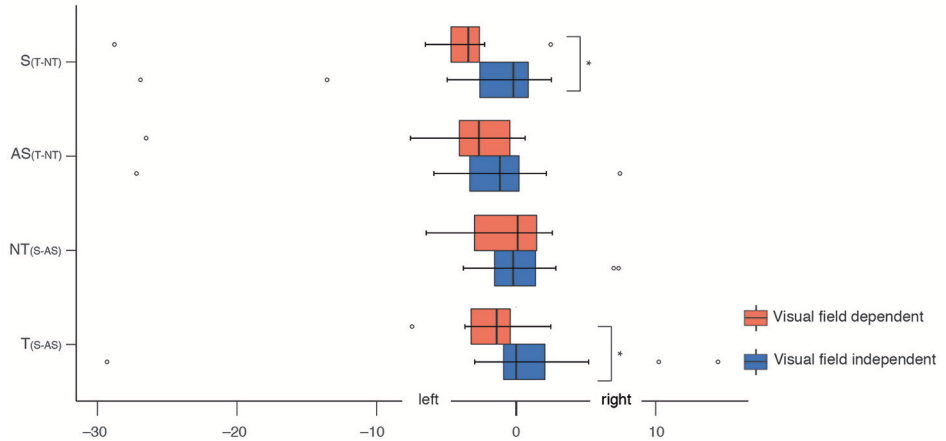

FIGURE 3 | Results of the effect of visual dependence on haptic subjective body orientation. Medians and interquartile ranges for the relative values of the subjective body orientation are plotted for the visual dependent group and the not visual dependent group. Significance bars refer to the results of the Mann-Whitney tests. *indicates significant effects. $S_{(T-NT)}$ indicates the relative values for the synchronous tilted as compared to the synchronous non-tilted condition. $AS_{(T-NT)}$ indicates the relative values for the asynchronous tilted as compared to the asynchronous non-tilted condition. $NT_{(S-AS)}$ indicates the relative values for the non-tilted synchronous as compared to the non-tilted asynchronous condition. $T_{(S-AS)}$ indicates the relative values for the tilted synchronous as compared to the tilted asynchronous condition.

condition, as shown in questions tapping into body ownership and disembodiment.

Attenuation of illusory ownership due to an additional static visuo-proprioceptive conflict has been extensively studied in the rubber hand illusion. While the rubber hand is typically placed 10–15 cm to the side of the participant's hand, studies have presented the rubber hand rotated in yaw, e.g., 10–30° (25), with respect to the real hand. These data generally show a weaker illusion for increasing angles (30), especially if the rubber hand is rotated to an anatomically implausible position [angle of 135°, 180°, and 225° to the real hand; see Ref. (31)]. Yet, differences have been found between implicit and explicit measures regarding tolerance to this mismatch. Holle et al. (30), for example, showed a significant proprioceptive drift toward the rubber hand (implicit measure), while the questionnaire (explicit measure) suggested no illusion for a rubber hand rotated by 180°.

The attenuation of the full-body illusion reported here might be in line with these findings and importantly extends them from a body-centered toward a gravity-centered reference frame (32). On a more conceptual level, the attenuation of the illusion could be explained either by an influence of top-down knowledge about the body—e.g., anatomical plausibility or prior knowledge about body posture (31, 33)—or additional multisensory mismatches in the bottom-up process. This latter view is supported by data from the rubber hand illusion suggesting that even a slight angular mismatch, i.e., 10–30° rotation of the rubber hand, reduces illusory ownership over the rubber hand (25).

In contrast to previous studies (4, 16, 19), skin temperature, as an implicit measure of self-identification, was not significantly modulated by visuo-tactile synchrony. The validity of skin temperature as an index of self-identification with an external body has been debated (34), and null results have been found in several related studies (35, 36). This null finding stresses the need for other, more appropriate implicit measures, such as vertical perception.

Vertical and Body Orientation Perception During the Full-Body Illusion

A main aim of this study was to test whether self-identification with a body that is tilted in relation to gravity would alter subjective haptic vertical perception and subjective body orientation perception [see Ref. (18) for a similar approach from a first-person perspective]. During illusory self-identification with the seen body in the tilted condition, we expected participants to align their subjective body orientation to the seen body. As a consequence, we expected them to adapt the perceived verticality by overcompensating (21). Both measures could serve as a useful implicit measure of the illusion (see above).

However, in the overall sample, we did not find a significant effect of Condition on haptic vertical perception. There are two possible reasons for the lack of a main effect of synchrony, which cannot be disentangled by the current protocol. First, the illusion in the tilted conditions may have been too weak to have a significant influence on haptic vertical and subjective body orientation perception. Indirect evidence for this hypothesis comes from our findings that visual-field-dependent participants actually do show a modulation of the haptic body orientation and verticality judgment (see below). Alternatively, the results could suggest that the measure is not sensitive to this modulation, which could be due to a very accurate gravity representation in an upright position (21) or a general strong role of non-visual signals on gravity perception, especially in the context of own-body perception. Yet, there are both physiological and behavioral measures showing that visual signals might overrule other graviceptive ones (37). Furthermore, against this hypothesis, we found a main effect of tilt on subjective body orientation, with the feeling of being more tilted toward the left, irrespective of visuo-tactile synchrony, which is in line with literature suggesting that looking at a tilted room alters perceived self-orientation (38).

Effect of Visual Field Dependence/Independence on Visuo-Vestibulo-Tactile Integration

It is long known that individuals differ in the weight they put on various sensory systems during multisensory integration tasks, such as the rod-and-frame test (27). As expected, we found that visual field dependence influences perceived body orientation as a function of the synchrony of the stroking. Visual-field-dependent participants adapted their subjective body orientation more in the direction of the seen body in the synchronous than in the asynchronous visuo-tactile stroking condition. Furthermore, they adapted the subjective haptic vertical in the same direction. Although this result has to be interpreted with caution due to the small sample size, it suggests that visual field dependence influences implicit (but not the explicit) measures of the illusion, in line with previous literature (39, 40). Several studies showed that visual field dependence modulates illusory body perceptions. David et al. (41), for example, found a significant positive correlation between visual field dependence and proprioceptive drift in the rubber hand illusion. Moreover, visual field dependence was a good predictor of the perceived first-person perspective in a full-body illusion (17).

Our results show a selective adaptation of body orientation and verticality perception for visual-field-dependent individuals. These individuals showed stronger adaptation of the perceived body orientation during synchronous visuo-tactile stroking. Such adaptation of body perception to reduce the multisensory conflict could go in two directions: either participants perceive the visual body as closer to their own graviceptive reference (i.e., less tilted, which might be indicated by our findings in the questionnaire suggesting a stronger sensation of tilt in the asynchronous condition) or they perceive their own-body orientation as closer to the visual body (i.e., more tilted in line with our initial hypothesis). The fact that participants, irrespective of the type of stroking, adapted their body orientation to the seen body and room might give further evidence to the former hypothesis.

CONCLUSIONS AND LIMITATIONS OF THE STUDY

This study showed an attenuation of the full-body illusion during visuo-graviceptive conflict, providing empirical evidence for the importance of vestibular and other graviceptive cues in the moment-to-moment construction of our sense of a bodily self. The fact that only visual-field-dependent participants adapted the perceived body and gravity orientation to the seen and synchronously stroked body, further demonstrates the importance of individual weighting of sensory input in defining our bodily self. Future studies should further investigate such mutual interactions between body orientation in space and illusory self-identification. Since a 30° tilt in our study diminished the illusion, future studies should look at smaller orientation mismatches to be able to define the threshold and describe the effect of illusory tilt in the full sample. Furthermore, a limitation of our study was that we manipulated the orientation of the seen body and its surroundings. Future studies should try to disentangle the influence of the room tilt and the body tilt by rotating the two independently. Finally, it would be interesting to change the participant's actual orientation in space. It has been shown that verticality perception is less accurate (21) in positions different from upright, and illusory self-orientation and position in the room are more frequent in tilted positions in healthy participants and in epileptic and otoneurological patients (42, 43). Such manipulation would further allow inducing uncertainty in the prior belief about the participant's body orientation.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Ethics Committee of the Faculty of Arts and Social Sciences at the University of Zurich with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Faculty of Arts and Social Sciences at the University of Zurich.

AUTHOR CONTRIBUTIONS

CT, MR, and BL designed the experiment. CT, MR, and CB programmed the experiment. CT recorded the data. CT and BL analyzed the data. CT and BL drafted the manuscript. All authors reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00436/full#supplementary-material

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A New and Faster Test to Assess Vestibular Perception

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Objective: Clinical vestibular testing mainly consists of testing reflexes, but does not routinely include testing for perceptual symptoms. The objective of this study was to investigate a new and faster test for vestibular perception, and to compare its results with previous studies.

Methods: Fifty-five healthy subjects with no prior vestibular complaints were included and divided into three age groups. Vestibular perceptual thresholds were measured using a hydraulic platform in the dark. The platform delivered 12 different movements: six translations (forward, backward, right, left, up, and down) and six rotations/tilt (yaw left, yaw right, pitch forward, pitch backward, roll left, and roll right). The subject had to report the correct type and direction of movements. Thresholds were determined by a double confirmation of the lowest threshold. General trends in thresholds like relative interrelationship and the influence of age were analyzed and compared with values reported previously.

Results: Mean thresholds of age groups ranged between 0.092 and 0.221 m/s^2 for translations, and between 0.188 and 2.255°/s^2 for rotations. The absolute values differed from previous reports, but the relative interrelationship of thresholds between type and direction of motion remained. An association between age and vestibular thresholds was found, similar to previous reports.

Conclusion: This new and faster test for vestibular perception showed comparable patterns in perceptual thresholds when compared to more research oriented, lengthy tests. This might pave the way for establishing vestibular perception testing protocols useful for the clinic.

Keywords: vestibular perception, vestibular perceptual function, perceptual threshold, perceptual threshold measurement, vestibular function, vestibular function disorders

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INTRODUCTION

The vestibular organ consists of three semicircular canals (lateral, anterior, and posterior) and two otolith organs (saccule and utricle). Three major vestibular functions are gaze stabilization, spatial orientation, and balance. These essential functions also rely on the contribution of other multiple senses, such as the visual and somatosensory system (1). In case of vestibular failure, contributions of the visual and somatosensory system increase in order to

maintain balance (sensory substitution). Concurrently, readjustments of brainstem vestibular processing and adaptation occur (2, 3).

Current diagnostics for the vestibular system mainly rely on the evaluation of reflexes, such as the vestibulo-ocular reflex (VOR) and the vestibulo-collic reflex. However, one third of patients with dizziness or imbalance have normal vestibular results on these tests (4). This illustrates that perceptual symptoms cannot always be addressed with current vestibular tests, and is probably related to the fact that vestibular perception utilizes other sensory pathways than vestibular reflexes (5). In general, perceptual thresholds have high sensitivity and specificity, since it is not easy to adapt to deficits caused by threshold-level stimuli. Therefore, there is a real clinical need to go "beyond reflexes" and measure vestibular perception, which could provide important additional information in the diagnostic process (4). Until now, vestibular thresholds have proven to be useful in identifying specific peripheral deficits and in diagnosing central disorders such as vestibular migraine (6–8). However, the clinical value of tests for vestibular perception is not yet fully determined. For example, they might develop into the equivalent of the "speech audiogram" for vestibular disorders (3, 6).

Vestibular perception has been tested previously with a platform capable of producing different motion profiles: yaw rotations, combined translational and rotational movements (5, 9), roll tilt (6), and lacked pitch movements (1, 8). The tested subject had to perceive and identify the type and/or direction of the movements. Next to this, differences between vestibular and visual thresholds were measured, and the effect of combining both was also evaluated (10, 11). However, these vestibular perception tests take considerable time: up to 3 h (6). This not only increases the burden for the patient, but might also decrease the attention of the patient during the test. These factors can significantly influence reliability and reproducibility of the results. Therefore, there is a need to develop a clinically oriented test for vestibular perception that is sensitive and specific, but less time-consuming.

The objective of this study was to investigate the application of a simplified and shorter paradigm for testing vestibular perception and to compare its results with those obtained in previous, research oriented studies. This new paradigm might be used in the future for multiple purposes, including clinical evaluation of the vestibular implant and diagnosis of vestibular perceptual deficits (4, 12).

It should be noted that vestibular perceptual tests are not purely testing the vestibular system (peripheral and central), since other sensory systems like proprioception are also involved in detecting movements. The brain integrates all these different inputs. Therefore, the vestibular perceptual thresholds can be considered as a functional outcome of the whole system, in which the vestibular system plays a major role (4).

METHODS

Participants

Fifty-five healthy subjects with no prior vestibular complaints were included in this study. Ages ranged from 21 to 81 years old (median age 55 years, mean age 49 years). Twenty-four males and 31 females participated. Exclusion criteria comprised current vestibular disease, and inability to sit in the testing chair for at least 1 h. Patients with migraine or using vestibulosuppressants were also excluded because both these factors are known to influence vestibular function (7). All included subjects were able to complete the whole experiment.

Perception Platform

Vestibular perceptual thresholds were measured using the hydraulic CAREN platform combined with the D-flow 3.22.0 software from Motek Medical BV (Amsterdam, The Netherlands). The platform delivered 12 different smooth, controlled movements: six translations (forward, backward, right, left, up, and down) and six rotations or tilt (yaw left, yaw right, pitch forward, pitch backward, roll left, and roll right). Each of the 12 thresholds was measured independently of others, which implies that no (major) effect should be expected from one movement on the thresholds of other movements.

Preparations

The subject was informed about the testing paradigm. All subjects were tested by the same technician (BD). The subject was seated in a chair mounted on the platform, and then fastened with a seatbelt for security purposes and to limit information provided by the body sliding on the chair. The test was performed in complete darkness and a blindfold was put on to avoid any visual cues. An infrared camera was used to monitor the subject during the experiments. Subjects wore a headset for communication with the technician and to mask the surrounding noise of the platform by playing a mix of previous sound recordings of the platform. First, a practice run was performed to verify understanding of the testing paradigm and subject compliance. Then, the testing paradigm was carried out. The technician continuously checked and maintained attention of the patient by communicating via the headset.

Testing Paradigm

The objective of the testing paradigm was to measure perceptual thresholds for angular and translational motions. Movements were applied in a random order and started at the highest possible accelerations. For each movement, the platform was first positioned and then the "test movement" was performed. After that, the platform returned to its neutral position. Then, the subject had to immediately report the direction and type of movement to the technician using the headset. Both the direction and type of movement had to be correct, in order for the response to be validated by the technician (i.e., to lower the acceleration for that specific movement). Translation accelerations were lowered in steps of 0.1 m/s^2, rotation accelerations in steps of $10°/s^2$. In case of an incorrect or absent response, a step up of respectively, 0.05 m/s^2 or $5°/s^2$ was used. If the response remained incorrect, the accelerations were increased again by 0.02 m/s^2 and $2°/s^2$, respectively. The perceptual threshold for each movement was determined by a double confirmation of the lowest threshold, plus two times an absent response at the acceleration one step below the threshold.

Stimulus

A special motion stimulus profile was developed to quantify perceptual thresholds for translational (six directions) and rotational (six directions) accelerations. The motion profile for translational stimuli are illustrated in **Figure 1**. The rotational stimuli had the same profile. They were composed of a smoothly increasing acceleration phase (low jerk) until constant acceleration was obtained for a fixed duration (plateau phase). This was followed by a smooth decrease of the acceleration (low jerk) down to zero. After each stimulus the platform moved with a subthreshold acceleration and jerk to the starting position needed for the next chosen stimulus. By this procedure, patients did not feel any movement or tilt between the subsequent stimuli, by which it was not possible to anticipate on the type or direction of the next stimulus. A random sequence of all possible 12 stimuli was used. Due to the limitations of the platform, the range of translational movements was restricted up to 0.4 m, and the range of rotational movements up to 30°. This stimulus profile was chosen to provide a constant acceleration at a certain magnitude, for a given duration, defined by the investigator. All non-linear parts of the stimulus were sinusoidal to smoothly reach the plateau phases of the acceleration. The sine parameters (amplitude and frequency) depended on the magnitudes of acceleration (a) and jerk (j) and varied for each separate motion stimulus. Therefore, every stimulus was controlled by three parameters: maximum range, acceleration magnitude, and jerk magnitude. Minimum acceleration was 0.01 m/s^2 for translations and 0.1°/s^2 for rotations. Maximum acceleration was 0.4 m/s^2 for translations and 40°/s^2 for rotations.

Data-Analysis

IBM SPSS Statistics Version 24 was used for data-analysis. In order to compare the type of movements, results were grouped into the same type of movement (e.g., translations and rotations), same type of translation (translation left and right, forward and backward, up and down), and same type of rotation (yaw, pitch forward and backward, roll left and right). To be able to statistically evaluate the influence of age, age groups were made for ages 21–39, 40–59, and 60–81 years. Mean thresholds of movements were calculated for the whole population of tested subjects, as well as for each age group separately. Paired t-tests were performed between all types of translations and between all types of rotations, to evaluate possible significant differences between them. Scatterplots were made for every movement tested by the platform to visualize the relation between perceptual thresholds and age. To further investigate the influence of age and gender, multiple regression analyses were performed for mean perceptual thresholds. The mean threshold of all movements, the mean threshold of all translations and the mean threshold of all rotations were used as dependent variables. Age and gender were used as independent variables. P-values below 0.05 were considered significant. Regarding the multiple regression analysis, Cooks distances were determined and a multicollinearity test was performed, showing no multicollinearity. In order to compare thresholds from previous literature (6) presented in velocity units (v), with the thresholds in this study presented in acceleration units (a), peak velocities were converted into peak accelerations by $a_{peak} = v_{peak}\pi f$, where f was the motion frequency. Since both studies differed in terms of paradigm (determining thresholds differently, not all type of movements the same) and stimulus (different profile shape, duration, and frequencies), no statistics were applied to compare both datasets. However, general trends in thresholds like relative interrelationship and the influence of age were analyzed separately and compared between these studies.

Ethical Considerations

The procedures in this investigation were in accordance with the legislation and ethical standards on human experimentation in the Netherlands and in accordance with the Declaration of Helsinki (amended version 2013). Approval was obtained from the ethical committee of Maastricht University Medical Center (NL52768.068.15/METC). All procedures were performed at the Maastricht University Medical Center. All subjects provided written informed consent.

RESULTS

Perceptual Thresholds for Translations and Influence of Age and Gender

Thresholds for translations varied widely within and between age groups (**Figures 2**, **4**). Mean thresholds of age groups ranged between 0.092 and 0.221 m/s^2 (**Table 1**). Thresholds of the upward-downward plane were significantly higher than those of

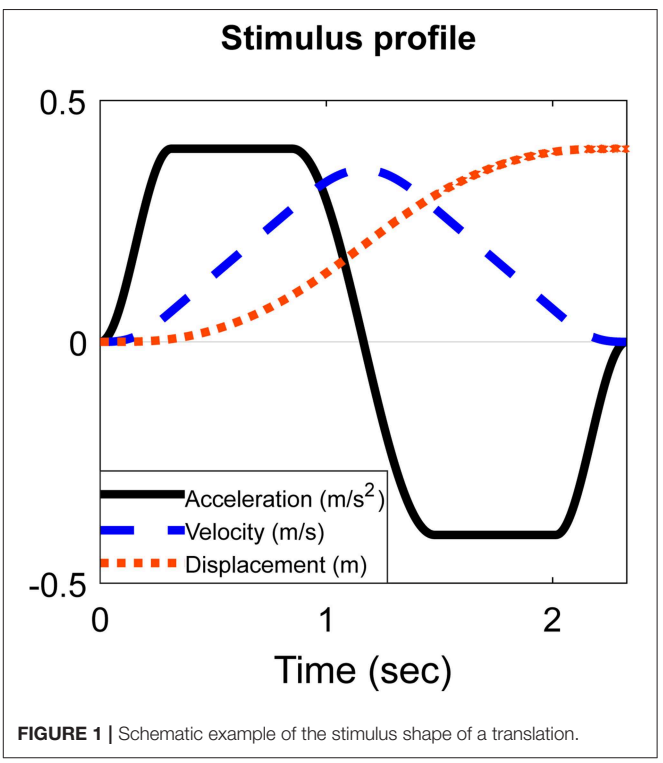

FIGURE 1 | Schematic example of the stimulus shape of a translation.

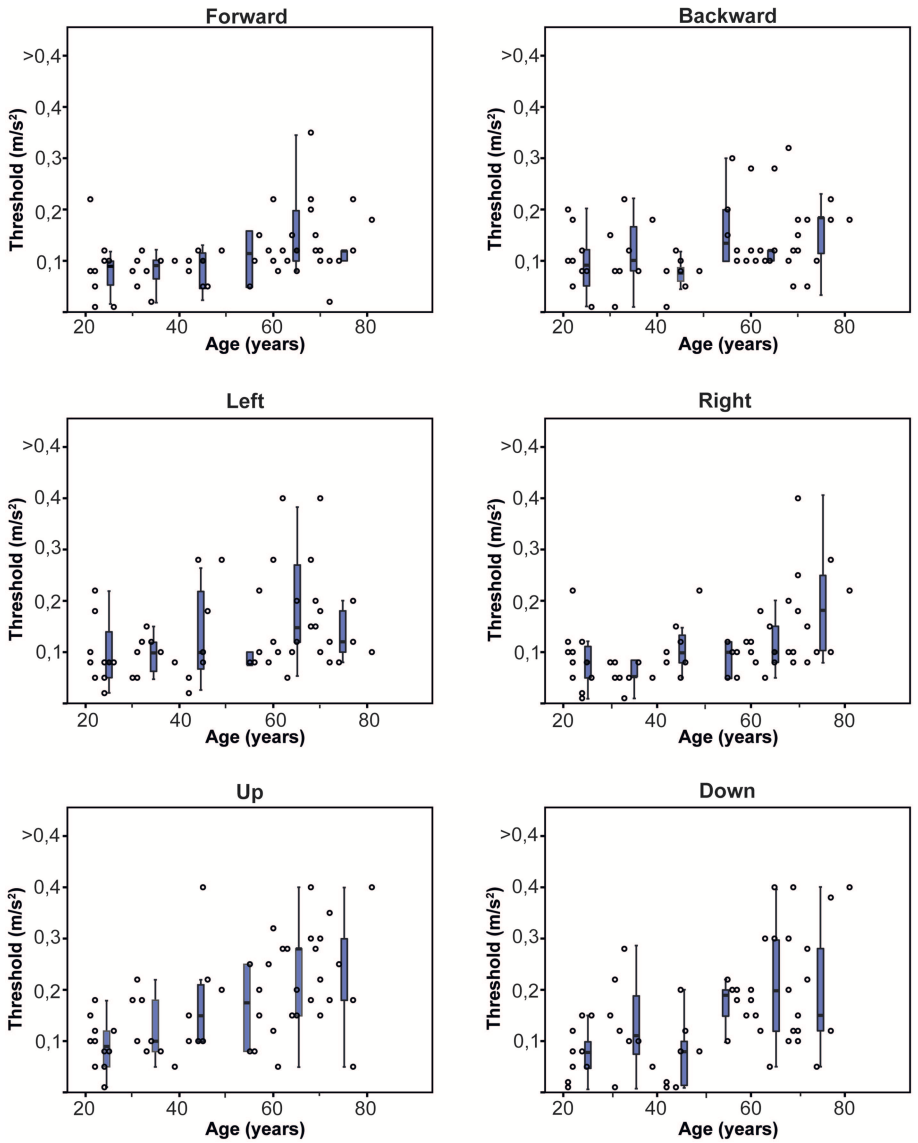

FIGURE 2 | Normative thresholds for each direction of translation, obtained in 55 healthy subjects of different ages. Each dot represents the threshold of one subject for a specific translation. Each box plot represents the 25–75 percentiles of thresholds per decade, whiskers the 95 percentiles and bold black lines the median.

the forward-backward plane ($p = 0.03$; **Table 1**). No significant differences were found between the other translations. Mean thresholds increased with age group, except for leftward and rightward translations. A multiple regression was run to predict the mean perceptual threshold of all translations from age and gender [$F_{(2, 52)} = 12{,}480$, $p < 0.0005$, $R^2 = 0.324$]. Age added significantly to the prediction ($p < 0.001$), not gender ($p = 0.240$).

Perceptual Thresholds for Rotations and Influence of Age and Gender

Thresholds for rotations showed less variability within and between age groups than thresholds for translations (**Figures 3**, **4**). Mean thresholds of age groups varied between 0.188 and 2.255°/s^2 (**Table 1**). Perceptual thresholds for yaw rotations were significantly higher than for pitches and rolls ($p = 0.016$; **Table 1**). No significant difference was found between the pitches and rolls ($p = 0.242$). Mean thresholds increased with each age group for yaw and pitch rotations, but not for roll rotations. A multiple regression was run to predict the mean perceptual threshold of all rotations from age and gender [$F_{(2, 52)} = 8{,}644$, $p < 0.005$, $R^2 = 0.250$]. Again, only age added significantly to the prediction ($p < 0{,}001$), not gender ($p = 0.297$).

Comparison of Perceptual Thresholds With Previous Literature

Figure 5 presents the perceptual thresholds for y- and z-translations and yaw and roll rotations in this study, compared to

TABLE 1 | Mean thresholds for translations and rotations, presented for each age group, with standard deviation between brackets.

Age (in years)	No. of subjects	Translations forward + backward	Translations left + right	Translations up + down	Yaw rotations left and right	Pitches forward+ backward	Rolls left + right
All	55	0.12 (0.05)	0.14 (0.11)	0.16 (0.09)	1.62 (1.59)	0.61 (0.89)	0.44 (0.85)
20–39	20	0.09 (0.04)	0.12 (0.15)	0.10 (0.05)	0.82 (0.56)	0.19 (0.24)	0.22 (0.55)
40–59	13	0.11 (0.04)	0.11 (0.06)	0.15 (0.07)	1.79 (1.67)	0.52 (0.52)	0.81 (1.42)
60–81	22	0.14 (0.05)	0.16 (0.08)	0.22 (0.09)	2.26 (1.89)	1.04 (1.20)	0.42 (0.55)

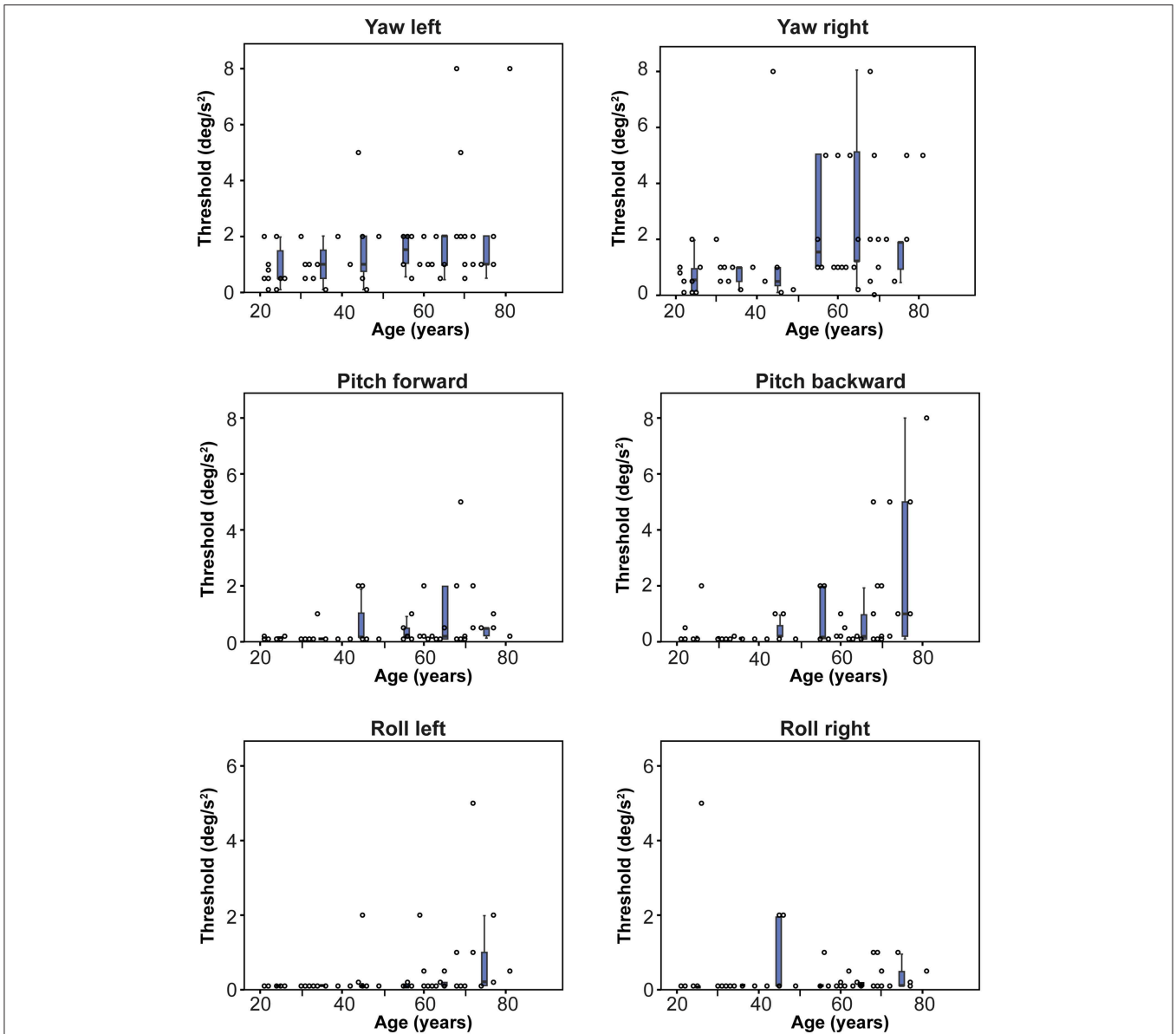

FIGURE 3 | Normative thresholds for each direction of rotation, obtained in 55 healthy subjects of different ages. Each dot represents the threshold of one subject for a specific rotation. Each box plot represents the 25–75 percentiles of thresholds per decade, whiskers the 95 percentiles and bold black lines the median. Note that y-axes are optimized for each specific movement. Dots on the x-axis have a value of 0.01°/s^2.

those in previous literature (6). Although the absolute thresholds varied between these studies, the relative interrelationship of thresholds between movements remained: y-translations and roll rotations showed lower mean thresholds than z-translations and yaw-rotations, respectively. Thresholds for roll rotations around 0.1 Hz in this study were close to those previously measured at 0.2 Hz. A significant age effect on thresholds was found in both studies (6).

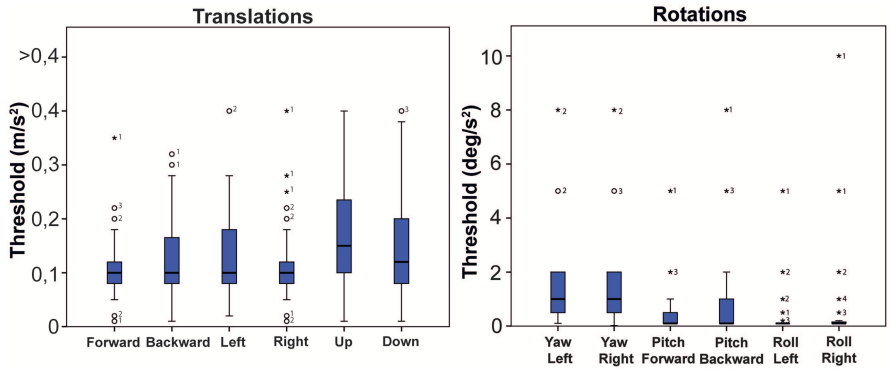

FIGURE 4 | Normative values of all translations combined and all rotations combined. Bold black lines in the boxes represent medians, boxes the 25–75 percentiles, whiskers the 95 percentiles. Outliers are represented by an open circle, extreme outliers by an asterisk. Numbers next to a dot indicate the amount of dots with the same value.

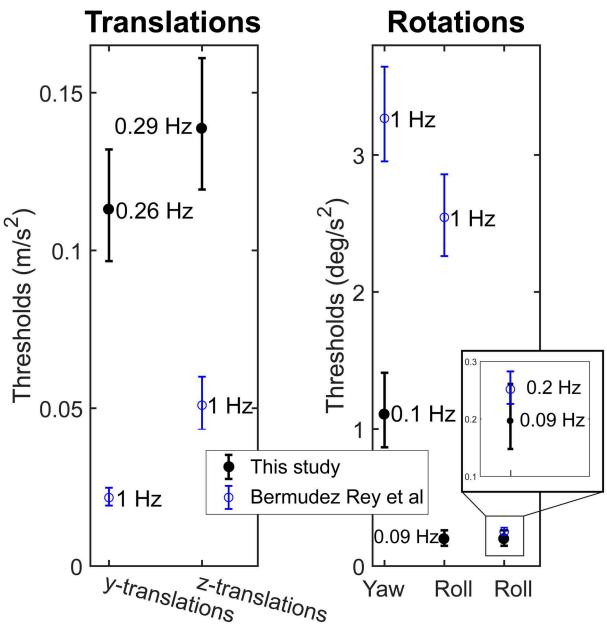

FIGURE 5 | Mean and 95% confidence intervals of perceptual thresholds for translations and rotations in this study ($n = 55$), compared to those in previous literature (6) ($n = 79$). For each mean value, the frequency of the stimulus is given.

DISCUSSION

This study was the first step in evaluating a clinically oriented test for vestibular perception. Perceptual thresholds in a group of healthy subjects were obtained and thresholds significantly increased with increasing age. Gender did not have a significant effect. These findings were congruent with a previous study, despite of this study using a different testing paradigm and different type of stimulus, and including more directions (6).

This testing paradigm differed from more research oriented studies in several ways. Firstly, it was devised to be relatively fast and complete, in order to have a test more suited for clinical settings. Testing time was substantially reduced from ∼3 h to less than 1 h (45–60 min). This reduced burden for the patient, costs of testing, and might have improved attention of the patient. The latter is particularly relevant, since after a long testing session attention is more likely to decrease, resulting in less reproducible and reliable results (13). Testing time was reduced by using fewer motions to determine the thresholds. Reliability of thresholds was therefore ensured by adding pitches forward and backward to the types of movement, and by randomly presenting all stimuli in the same session, without the subject being aware of the type of movement. This reduced the possibility of reporting the right threshold by chance. Secondly, this testing paradigm used different stimuli than previously reported. It was based on a stimulus with the longest possible duration of constant peak acceleration (plateau phase) and varying frequencies, instead of a fixed frequency with a sinusoidally shaped acceleration profile. This new profile was chosen to have a longer exposition of the subject to the main parameter of the stimulus of interest and the main stimulus for the vestibular system: acceleration. However, due to the limitations of the platform, the frequency of the stimulus had to differ for each acceleration. This is a potential limitation, since frequency-dependency of the system is more difficult to evaluate. Next to this, it prevented comparison of the absolute thresholds of this study with previously reported ones. After all, the frequency-dependency of the vestibular system implies that testing at difference frequencies might yield different results (5, 6). Nevertheless, this could mainly explain the differences between the absolute values of thresholds between the studies. Thirdly, in this paradigm continuous interactive communication between the technician and the patient was added. In extensive preliminary trials, this strategy was found to be superior to using a joystick to indicate thresholds, without any significant communication. Communication also improved attention, reduced anxiety (since the patients sat in a dark room), and facilitated verification whether the reported thresholds were representative or not (e.g., a lack of attention at the moment of testing a certain threshold). If an unreliable threshold was

suspected, the threshold was determined again. Fourthly, not all skin surfaces were covered to reduce somatosensory input as much as possible. Whether covering of all skin surfaces has any beneficial effects in this paradigm proposed, should still be determined.

More dispersion was observed in the thresholds for translations, than for rotations, pitches, and rolls. This was in accordance with previous literature (6) and could be attributed to a higher contribution of somatosensory input during these movements. Regarding the group of translations, thresholds of the vertical plane were significantly higher than those of the forward-backward plane. Regarding the group of rotations, thresholds for yaw rotations were significantly higher than those for pitches and rolls. It could be hypothesized that these two movements were less affected by somatosensory input, compared to the other movements in their group. For instance, a translation in the vertical plane will cause less activation of the somatosensory system, including neck proprioception (14), than translations in other planes, since the body remains in line with gravity. Also, a rotation in yaw plane does not include any tilt with respect to gravity, in contrast to pitches and rolls. These two movements appear therefore to be those that most purely test the thresholds for translations and rotations of the peripheral vestibular system, with the least interference of the somatosensory system.

The contribution of the somatosensory system implies that vestibular perceptual tests are not purely testing the vestibular system (peripheral and central), since somatosensory cues are also involved in detecting movements. The brain integrates all these different inputs. Therefore, the vestibular perceptual thresholds can be considered as a functional outcome of the whole system, in which the vestibular system plays a major role (4). This also implies that this test is not specifically designed to detect a peripheral or central vestibular deficit, but to demonstrate the vestibular perceptual functionality of a patient at a given time.

Limitations

Many subjects could still hear some movements of the platform (e.g., translations downward) in spite of the masking noise on the headphones. Platform sounds were almost the same for each movement. Therefore, the sounds might have indicated that the platform was moving, but could not help in distinguishing between direction and type of movements (e.g., translations vs. rotations, upwards vs. downwards). Since the thresholds of movements were defined by the right type and direction of movements, it was hypothesized that sounds might have not significantly influenced the thresholds. However, the platform sounds should be taken into consideration when refining this testing paradigm.

Perceptual thresholds significantly increased with increasing age. Since the vestibular function of the healthy controls was not measured but only screened with a questionnaire, it cannot be determined whether the increasing thresholds with age were mainly influenced by age, or other factors. For example, age-related decline in vestibular function (presbyvestibulopathy) as well as clinically asymptomatic vestibulopathies could account for the decline of vestibular perception. This needs to be determined in future studies.

Future

Next step is to investigate this testing paradigm in patients with unilateral and bilateral vestibulopathy. If this succeeds, it might pave the way for routinely measuring vestibular function "beyond reflexes." It might be used in clinic, in which it should be noted that this test is relatively expensive regarding time and equipment, compared to other vestibular tests. Therefore, it is hypothesized that it will probably first be suited for tertiary referral centers that have the resources and interest to investigate vestibular perceptual threshold deficits in patients (regardless of the etiology), or to use it to demonstrate perceptual changes after rehabilitation. It could also be used in research settings to e.g., evaluate the effect on perceptual thresholds of future therapies, for example the vestibular implant (12, 13, 15–17). For the latter, it should be noted again that vestibular perception is the end-result of detection and processing of movements by the whole vestibular system (see above): peripheral and central. This process is susceptible to multisensory integration and many other factors (e.g., adaptation, compensation, and cognition) (18). Therefore, vestibular perception should be used in the future as an outcome measure by itself, and not purely as a marker of vestibulopathy.

CONCLUSION

This new and faster test for vestibular perception showed comparable patterns in perceptual thresholds when compared to more research oriented, lengthy tests. This might pave the way for establishing vestibular perception testing protocols useful for the clinic.

ETHICS STATEMENT

The procedures in this investigation were in accordance with the legislation and ethical standards on human experimentation in the Netherlands and in accordance with the Declaration of Helsinki (amended version 2013). Approval was obtained from the ethical committee of Maastricht University Medical Center (NL52768.068.15/METC). All procedures were performed at the Maastricht University Medical Center. All subjects provided written informed consent.

AUTHOR CONTRIBUTIONS

BD: author and research conductor. FL: co-author and research conductor. NG, AP, JG, and HK: checking the writing and research. MP: co-author and checking the writing and research. RvdB: co-author, conducting the research, and checking the process.

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