

Velocity storage in the human vertical rotational vestibulo-ocular reflex

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Received: 10 September 2010 / Accepted: 2 December 2010 / Published online: 19 December 2010
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Abstract Human horizontal rotational vestibulo-ocular reflex (rVOR) has been extensively investigated: the horizontal semicircular canals sense yaw rotations with high-pass filter dynamics and a time constant (TC) around 5 s, yet the rVOR response shows a longer TC due to a central processing stage, known as velocity storage mechanism (VSM). It is generally assumed that the vertical rVOR behaves similarly to the horizontal one; however, VSM processing of the human vertical rVOR is still to be proven. We investigated the vertical rVOR in eight healthy human subjects using three experimental paradigms: (1) per- and post-rotatory around an earth-vertical axis (ear down rotations, EDR), (2) post-rotatory around an earth-horizontal axis with different stopping positions (static otolith stimulation), (3) per-rotatory around an earth-horizontal axis (dynamic otolith stimulation). We found that the TC of vertical rVOR responses ranged 3–10 s, depending both on gravity and on the direction of rotation. The shortest TC were found in response to post-rotatory earth-horizontal stimulation averaging 3.6 s, while they were prolonged in EDR stimulation, i.e. when the head angular velocity vector is aligned with gravity, with a mean value of about 6.0 s. Overall, the longest TC were observed in per-rotatory earth-horizontal stimulation, averaging 7.8 s. The

finding of longer TC in EDR than in post-rotatory earth-horizontal stimulation indicates a role for the VSM in the vertical rVOR, although its contribution appears to be weaker than on the horizontal rVOR and may be directionally asymmetric. The results from per-rotatory earth-horizontal stimulation, instead, imply a role for the otoliths in controlling the duration of the vertical rVOR response. We found no reorientation of the response toward earth horizontal, indicating a difference between human and monkey rVOR.

Keywords Vertical rVOR · VSM · Pitch VOR · Gravity · Directional asymmetry

Abbreviations

ANOVA	Analysis of variance
EDR	Ear down rotation
OKN	Optokinetic nystagmus
OKAN	Optokinetic after-nystagmus
OKR	Optokinetic reflex
OVAR	Off-vertical axis rotation
rVOR	Rotational vestibulo ocular reflex
SCC	Semicircular canals
SPV	Slow phase velocity
TC	Time constant
VSM	Velocity storage mechanism

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Introduction

The rotational vestibular ocular reflex (rVOR) is known to stabilize gaze to ensure clear vision during head rotations. It rotates the eyes in a direction that compensates for the

head movements sensed by the semicircular canals (SCC). The three SCC in each labyrinth are roughly orthogonal to each other and thus sense rotational head accelerations in three dimensions. The rVOR behaves as a high-pass filter of head angular velocity with a very short latency (<10 ms) (Minor et al. 1999; Angelaki and Hess 1995; Gizzi et al. 1994), making it the earliest sensory information available to respond to head perturbations.

The time constant of the exponential decay of the slow-phase eye velocity (SPV) in the horizontal plane typically ranges from 15–20 s, which is longer than that of vestibular afferents from the SCC (presumably around 5 s) (Cohen et al. 1981). Such prolongation is due to a stage of central processing of the afferent signals, commonly known as velocity storage mechanism (VSM), which is believed to involve the nucleus prepositus hypoglossi and the medial vestibular nuclei; see Leigh and Zee (2006) for a review. Several studies have provided evidence that such central processing stage is likely to be a site involved in the implementation of an internal model of self motion (Merfeld et al. 1993, 1999; Angelaki et al. 2004; Green et al. 2005; Green and Angelaki 2010), contributing to the production of both perceptual and reflex responses and integrating sensory information of different origins, rather than simply the VSM of the VOR. Yet, in the following, we will refer to it as VSM, since it is the name with which the process is best known in the field of vestibular physiology and ocular motor control.

The horizontal rVOR has been extensively investigated, and different models of the VSM in the horizontal plane have been proposed (Robinson 1977; Raphan et al. 1977). Based on the similar structure of the three SCC, the results of studies performed in the horizontal plane are generally, at least to some extent, considered valid also for the other rotation axes. Yet, the vertical rVOR (i.e. evoked by rotations around the interaural axis) has been much less studied, especially in human subjects, so that a role for the VSM in the human vertical rVOR is still to be proven.

Monkey (Cohen et al. 1999; Angelaki and Hess 1994) and human (Fetter et al. 1992; Benson and Bodin 1965) studies have shown that the prolongation of the time constant of the SPV during the horizontal rVOR is strongly influenced by the angle between the head angular velocity vector and the gravity vector, and is maximum when the two vectors are aligned. Monkey studies have also shown that in response to optokinetic stimulations around a body vertical axis, the eye velocity vector tends to align with gravity (cross-coupling of optokinetic after-nystagmus (Raphan and Cohen 1988; Dai et al. 1991; Raphan and Sturm 1991). Indeed rVOR and OKR are believed to be different facets of the same neurologic system, coupled through the VSM (Robinson 1977). Although no cross-coupling of OKAN has been found after vertical OKN with the animal upright, horizontal–vertical and horizontal–

torsional components of eye velocity were found following post-rotatory tilt toward upright after roll and pitch rotations around an earth vertical axis, respectively (Angelaki and Hess 1994; Hess et al. 2005). These findings led to the hypothesis that the activity of the VSM is influenced by the perception of gravity, which is mediated by otolith signals since the SCC are insensitive to linear accelerations (Raphan and Cohen 2002; Gizzi et al. 1994; Angelaki and Hess 1995). One suggested explanation for such findings (Raphan and Cohen 1988; Angelaki and Hess 1994) is that by prolonging the eye velocity component that is aligned with gravity, the VSM aims at forcing the eye movements to occur around the gravity vector.

Monkey studies on the role of the VSM in producing vertical responses have analyzed both the vertical post-rotatory rVOR (Matsuo and Cohen 1984; Angelaki and Hess 1994) and the vertical optokinetic nystagmus (OKN) and after-nystagmus (OKAN) (Matsuo and Cohen 1984). Post-rotatory rVOR showed a directional asymmetry when the animals were lying on their side, i.e. the axis of rotation is aligned with gravity, with downward (beating) nystagmus (upward SPV) lasting significantly longer than the upward counterpart (downward SPV).

Post-rotatory responses evoked when the animals were tilted toward the upright position after being rotated around the earth-vertical interaural axis (i.e.: while lying on the side) showed reduced or no asymmetries, and the duration of the nystagmus was significantly shortened (Angelaki and Hess 1994), so that the SPV time constant could be even shorter than the value expected for the canal afferents. Experiments in monkeys before and after a complete nodulo-uvulectomy, i.e. the ablation of one of the anatomic parts believed to be relevant in the VSM neural circuitry, have shown a post-surgery reduction of the duration of vertical responses for both OKAN and rVOR, and an almost complete cancellation of the up/down asymmetry (Wearne et al. 1998).

Vertical VSM studies in humans are mainly based on OKN-OKAN (Clement 2003; Clement and Lathan 1991). These experiments confirm the up/down asymmetry found in monkeys only in terms of gain. However, these results are less straightforward, as other researchers (Baloh et al. 1983) found a reversed, yet non-significant, asymmetry. Vertical rVOR studies are usually limited to passive rotations with the subject lying on his side (Baloh et al. 1983) or to active head movements with the subject upright (Clement 2003).

To our knowledge, the only human study of per-rotatory nystagmus evoked by constant velocity rotations around the earth-horizontal interaural axis was carried out by Wall and Petropoulos (Wall and Petropoulos 1993). This study reported a higher gain for downward than upward SPV and a longer upward SPV time constant. In a previous study (Bertolini et al. 2008a), we examined the per-rotatory

rVOR response to constant-velocity rotations around the earth-horizontal interaural axis in three healthy subjects, accelerating them at $10^\circ/s^2$. The estimated time constants ranged from 6–9 s.

The frequency response of the human horizontal, vertical, and torsional VOR was recently studied using sinusoidal oscillations at different orientations with gravity (Bockisch et al. 2005). The gain of vertical and torsional VOR responses was found to increase when dynamic otolith stimulation was present (i.e. when the head angular velocity vector was orthogonal to gravity).

Taken together, current literature studies suggest that the VSM contributes to vertical rVOR responses in monkeys, that its contribution is gravity dependent and that even directional asymmetries may be due to a modulation of its contribution. Based on these considerations, we reasoned that empirically showing the influence of the direction of gravity on the time constant of the SPV during vertical rVOR would be a crucial point for determining the processing of the VSM in humans, if any.

Therefore, the present work further investigates the vertical rVOR by recording the eye movements evoked by head angular velocity steps around the pitch axis (i.e. the inter-aural axis) in a group of eight healthy human subjects. In order to assess the influence of gravity on the vertical rVOR in humans, we studied responses to rotations around axes that were either parallel (ear down rotations—EDR) or orthogonal (off vertical axis rotations—OVAR) with respect to gravity.

Materials and methods

Subjects

We studied a total of eight healthy human subjects (five men and three women, 26–46 years old) using three different experimental paradigms. All subjects participated in the first and in the second paradigm, but only four of these were able to carry out the third paradigm without being affected by motion sickness. The three paradigms were recorded on different days (a few weeks apart).

All subjects had normal vestibular function and no known eye movement abnormalities when they participated in the recordings. Written consent of all subjects was obtained after full explanation of the experimental procedure. The experimental protocol was approved by a local ethics committee and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Recording of eye movements

Eye movements were recorded monocularly with dual scleral search coils (Skalar Instruments, Delft, The

Netherlands) (Robinson 1963; Collewijn et al. 1985; Ferman et al. 1987) after anesthetizing the conjunctiva with Oxybuprocaine 0.4%. The head was surrounded by a chair-fixed coil frame (side length 0.5 m), which produced three orthogonal magnetic fields with frequencies of 80, 96, and 120 kHz (Rommel type system, modified by A. Lasker, Baltimore) (Rommel 1984). Eye- and chair-movement signals were digitized at a frequency of 1,000 Hz with 16-bit resolution and stored on a computer hard disk for off-line processing. The calibration procedure was carried out before each subject wore the coil, using a mechanical device to rotate it in the three different planes to get maximum output values. Details of the coil calibration procedure can be found elsewhere (Bockisch et al. 2005).

Subjects were seated on a turntable with three servo-controlled motor-driven axes (prototype built by Acutronic, Switzerland). The head was restrained with an individually adjusted, three-point mask (Sinmed BV, The Netherlands). This mask consisted of a thermoplastic material (Posicast), which can be molded to the contour of the head after being warmed up in a water bath. With this device, the center of the interaural line was positioned at the intersection of the three axes of the turntable. The subjects were secured by safety belts, and movements of the body were minimized by evacuation pillows.

Experimental paradigms

We studied three different vestibular stimulation paradigms evoking vertical rVOR responses:

- Pitch rotations around the earth-vertical axis (per- and post-rotatory EDR).
- Pitch post-rotatory stimuli around the earth-horizontal axis (post-rotatory OVAR).
- Pitch per-rotatory stimuli around the earth-horizontal axis (per-rotatory OVAR).

Within each paradigm, the sequence of trials was pseudo-randomized in terms of rotation direction and, in the post-rotatory OVAR paradigm, in terms of stopping position as well. All experimental paradigms were carried out in complete darkness. Short breaks in-between the trials (2 min) were used to limit the discomfort of the subjects; during rest times, the light was switched on to reduce darkness adaptation.

Per- and post-rotatory EDR

We recorded the ocular motor responses to constant-velocity ($60^\circ/s$) pitch rotations around the earth-vertical interaural axis (left and right ear down rotations—EDR), both in the forward and backward direction (Fig. 1, panel a). The turntable was accelerated and decelerated at $90^\circ/s^2$.

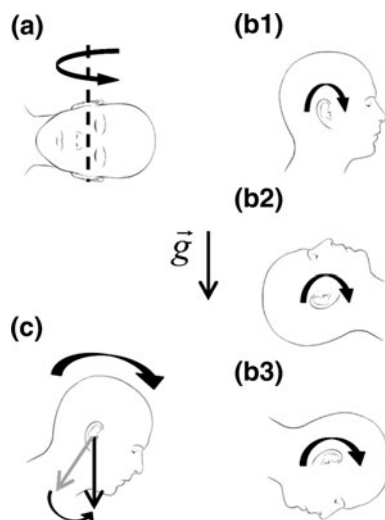


Fig. 1 Graphical representation of the three experimental paradigms, showing the orientation of the gravity vector: **a** EDR; **b1** post-rotatory OVAR after stopping upright; **b2** post-rotatory OVAR after stopping supine; **b3** post-rotatory OVAR after stopping prone; **c** per-rotatory OVAR, showing the rotation of the gravity vector in a head fixed reference system

The duration of the rotations was 12 s. One subject repeated the experiment increasing the rotation time to 24 s to control for effects of rotation duration. A laser dot on a screen in front of the subject was switched on 5 s before the onset of the chair movement and switched off 4 s later, to impose the same initial position of the eyes for all trials.

Post-rotatory OVAR

We recorded the ocular motor responses of each subject to three different post-rotatory stimuli corresponding to different stopping positions ($+90^\circ$ —supine, 0° —upright, -90° —prone, Fig. 1, panels b1–b3) after either forward or backward constant velocity ($60^\circ/\text{s}$) pitch rotations around the earth-horizontal interaural axis (off vertical axis pitch rotations—OVAR). In each trial, the turntable was decelerated at $90^\circ/\text{s}^2$, stopping in less than 1 s; thus, the stimulus for the vestibular system was close to a step of angular velocity. To avoid the dizziness potentially induced by the per-rotatory OVAR (the rotation prior to the stimulus), the chair was decelerated after two complete rotations (12 s), even if the per-rotatory nystagmus had not yet vanished. The eye movements were recorded until the end of the post-rotatory response. Five subjects repeated the experiment increasing the rotation time: one to four rotations (24 s) while the other four were rotated for up to 1 min.

Per-rotatory OVAR

Subjects were seated upright and were rotated either forward or backward around the earth-horizontal interaural

axis (OVAR) at a constant velocity of $60^\circ/\text{s}$ for 1 min (Fig. 1, panel c). Each subject was rotated three times in each direction. The turntable was accelerated at $90^\circ/\text{s}^2$. Special care was taken to reduce episodes of motion sickness by breaking the whole paradigm in three non-consecutive days (i.e. two trials per day) and instructing the subject on a breathing technique to avoid the dizziness (Yen Pik Sang et al. 2005). As with the first paradigm, a laser dot on a screen in front of the subject was used to impose the same initial position of the eyes for all trials.

Data analysis

The collected data were processed on a PC using interactive programs written in MATLAB (The Mathworks, Natick, MA), version 7.1. From the raw signal and calibration values of the search coil, we computed eye positions as 3-D rotation vectors in a head-fixed coordinate system. Noise was removed by low pass filtering the eye position with a Butterworth filter with cut-off frequency at 40 Hz. Eye velocity was computed using rotation vectors as detailed in (Schmid-Priscoveanu et al. 2000). To reconstruct the slow-phase velocity (SPV), the fast phases of the response were interactively marked using a custom program allowing to manually adjust the indices of the beginning and the end of each automatically identified saccade. Saccades were then removed from the velocity signal, and missing data points were not interpolated.

Considering that our study aims at quantifying the differences in the time course of the vertical rVOR in response to stimuli involving different orientations with respect to gravity, and that the vertical SPV responses did not show any evident initial eye velocity plateau (Raphan et al. 1979), we chose to fit the experimental SPV data using a first-order model of the rVOR (Robinson 1977) in which the VSM is represented as a positive feedback loop around the vestibular nuclei, arranged so that the time constant of the SCC is centrally replaced by the time constant of the VSM. We therefore fit the SPV response to a step of angular velocity using a single exponential decay.

In the following, we will present the different procedures that, due to the differences between the experimental conditions tested, were applied to pre-process the eye movement data.

Per- and post-rotatory EDR and post-rotatory OVAR

Responses to per- and post-rotatory EDR stimuli were recorded within the same trials, with the initial acceleration and the following constant velocity rotation providing the per-rotatory stimulus, and the sudden stop of the chair providing the post-rotatory one. In fitting these data we therefore allowed separate response parameters for the two

directions of stimulation and interpreted directional differences in the response time constants as due to the VSM processing (Matsuo et al. 1979; Matsuo and Cohen 1984). The gain of the per-rotatory response is the ratio of the peak per-rotatory eye velocity over that of the chair, while the gain of the post-rotatory response was estimated as the ratio of the change in eye velocity caused by the stopping of the chair over the corresponding change in chair velocity.

A clearly distinguishable post-rotatory response was not always present after OVAR. We chose to fit only responses reaching peak slow-phase velocities of at least 5°/s, since noise would reduce the reliability of the estimates with lower eye velocities. With this constraint, roughly 26% of trials were discarded.

Per-rotatory OVAR

Per-rotatory OVAR stimuli involve a continuously changing orientation of the head with respect to gravity and therefore a modulation of the input to the otoliths, i.e. the inner ear sensor for linear accelerations. During OVAR, they sense rotation as the projection of the gravity vector on the saccular and utricular maculae (Fig. 1, panel c), and their stimulation produces a sinusoidally modulated vertical eye velocity with a bias. Such response lasts as long as does the rotation, while the rVOR response, evoked by the constant velocity stimulation of the SCC, decays with time as shown in the eye velocity trace of a representative subject in Fig. 2. Many models of the SCC-otolith interaction have been proposed in literature (Raphan and Cohen 2002; Glasauer 1992; Paige and Seidman 1999; Seidman et al. 2002; Kushiro et al. 2002; Crane and Demer 1999); however, the physiology of such mechanism is still under debate. Due to the relatively small amount of data, compared to that which may be obtained in monkey studies, that we were able to collect on our subjects in this demanding paradigm, we have preferred a simpler approach to data analysis than the estimate of all the parameters of a full VOR model. Therefore, in order to provide a reliable quantity describing the behavior of SPV decay time constant, our analysis considers the SPV during OVAR as the linear sum of an exponential response originated from the canals and of a sinusoidal one from the otoliths (Gianna-Poulin and Peterka 2008; Crane and Demer 1999).

The fit of the responses therefore considers one expression for the eye movement driven by sensory information provided by the SCC and another expression for the eye movement driven by the otoliths (Bertolini et al. 2008b) as in Eq. 1:

$$y = A_1 \cdot e^{-t/\tau} + A_2 \cdot \sin(2\pi ft + \varphi) + c \quad (1)$$

where A_1 is the amplitude and τ the time constant of the rVOR response, while A_2 is the amplitude, f the frequency, φ the phase, and c the offset of the otolith-produced sinusoidal response. The frequency (f) was kept constant at 0.16 Hz (corresponding to a chair angular velocity of 60°/s), while the other parameters (A_1 and A_2 , φ , c and τ) were iteratively optimized using a nonlinear least-squares algorithm.

The approximation introduced by considering a constant bias does not affect the validity of the estimate of the TC of the SPV if, as it is commonly thought, the bias is due to the VSM (Green and Galiana 1998; Angelaki et al. 2001) and its charging time constant is that of the VSM itself. If, on the other hand, such hypothesis does not hold, our approach introduces an error in the estimate of the SPV TC; yet, mathematical simulations show that the error in the estimate is attenuated by a factor of 0.33, i.e. if the actual TC for loading the bias was 10% shorter than that of the VSM, then the our approach would overestimate the SPV TC by 3.3%.

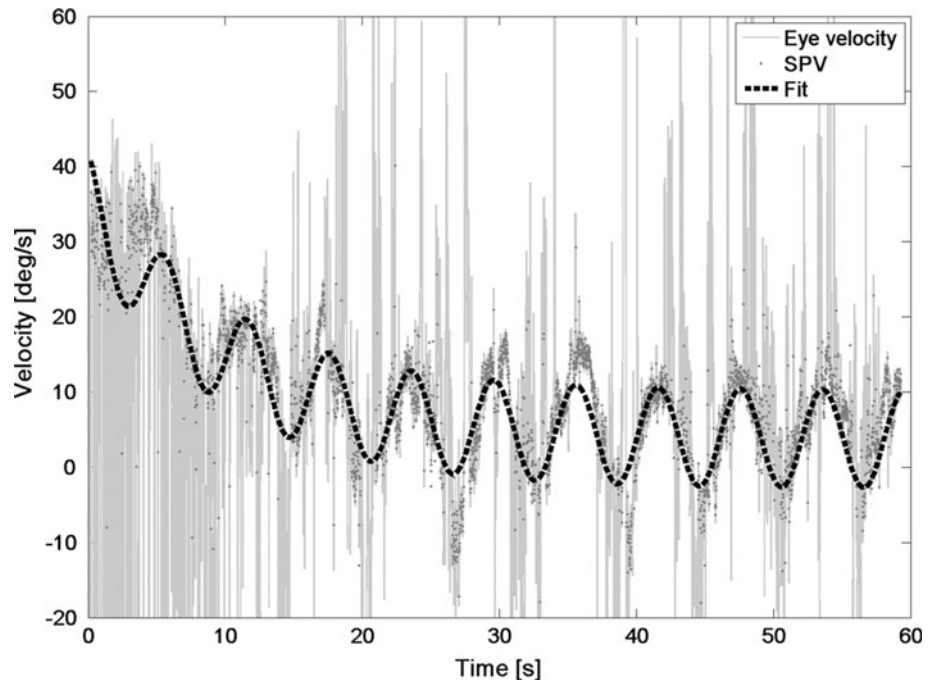
The gains of the per-rotatory responses can be evaluated as the ratio of the sum of the two amplitudes $A_1 + A_2$ (Eq. 1) to chair velocity. Indeed the bias is zero at the onset of head rotation; thus, the peak eye velocity is due only to the rVOR. Due to the different nature of the otolithic stimulation (linear acceleration) and of the system output (rotation of the eye in the orbit), no otolithic gain can be evaluated (Ramat et al. 2001).

An example of the described procedure is shown in Fig. 2 where the fit in Eq. 1 was applied, after the removal of saccades, to a representative trace of OVAR per-rotatory responses recorded in subject 8.

Statistical analysis

Gains and TCs of each subject estimated from EDR and per-rotatory OVAR responses were first investigated for normal distribution with Lilliefors test. Repeated measures N-way analysis of variance (ANOVA) was then performed on values estimated from EDR and per-rotatory OVAR trials on a subject by subject basis. We used positions (right ear down and left ear down), directions of the resulting eye movements (upward and downward SPV) and stimulus type (per-rotatory and post-rotatory) as factors for EDR, while only direction was considered for per-rotatory OVAR responses. The same approach could not be applied to post-rotatory OVAR estimates since five subjects were tested only twice for each stopping position in each direction and three subjects only once. To confirm that the effect of a factor found to be relevant for individual subjects was significant across the whole population, we performed repeated measures N-way analysis of variance

Fig. 2 Representative example of raw data, SPV and the corresponding fit using Eq. 1 from a per-rotatory OVAR trial. The resulting fitting parameters in this example were $A_1 = 32.42^\circ/s$, $A_2 = 6.05^\circ/s$, $c = 4.72^\circ/s$, $f = 1/6$ Hz, $\varphi = 2.0$ rad, $\tau = 9.30$ s



considering within-subjects data (Trujillo-Ortiz et al. 2006) by pooling subjects and using the same factors mentioned above. The same test was also performed on post-rotatory OVAR data using stopping positions (upright, supine, and prone) and directions (upward and downward SPV) as factors.

Once the relevant factors were identified, mean gains and TCs of each subject were then computed for each paradigm pooling the non-relevant factors. Lilliefors test was used to investigate for normal distribution of the subjects' means. One-way ANOVA was then performed pooling all subjects' means to confirm the effect of the relevant factors and to compare the different paradigms.

Results

As a result of the processing described in the “Methods” section, the study of all experimental conditions led to the analysis of the time constant and gain of the exponentially decaying vertical SPV. Eye movements around axes other than the vertical one were not studied as no horizontal or torsional transient response was evoked in any paradigm. A weak sinusoidal modulation was instead present in both the horizontal and the torsional traces during per-rotatory OVAR.

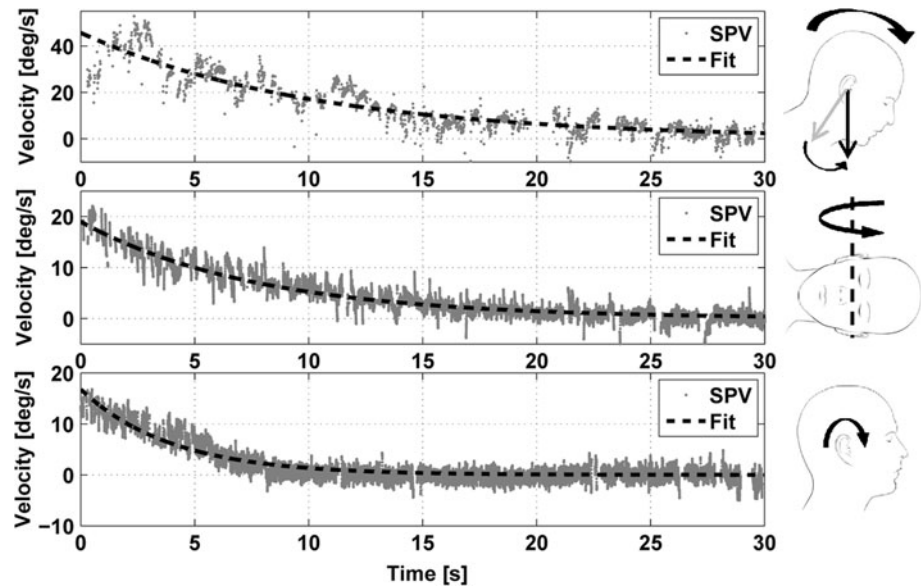
We found no significant differences in the values of the parameters estimated from responses to the different durations of head rotation described in the “Experimental paradigms” section (12, 24 s and 1 min) and their results are therefore pooled in the following description.

Due to the differences between the three paradigms of vestibular stimulation (see Methods), their results are presented in separate sections, followed by an inter-paradigm comparison section.

Per- and post-rotatory EDR

Eight subjects were recorded in this paradigm. A representative example of the data acquired in this experimental condition is shown in Fig. 3, center panel. We compared time constants on a subject-by-subject basis using repeated measures three-way ANOVA to evaluate effects of different factors. No significant difference was found between positions (right ear down and left ear down) and stimulus type (per-rotatory and post-rotatory). However, six of eight subjects showed a significant difference between the SPV time constants based on the direction (upward SPV and downward SPV) of the resulting eye movements ($P < 0.05$). Five of them had a longer time constant in upward SPV, while one showed a longer time constant in downward SPV. A second set of experiments was carried out on this subject a few months apart, and the reversed asymmetry finding was confirmed. The remaining two subjects also showed a longer upward SPV time constant, yet their asymmetry was not statistically significant. Since the asymmetry found for the subject with longer downward SPV time constant was highly significant ($P = 0.003$, $F = 9.97$), we considered our data in terms of “preferred” direction, which we established as the one showing the longer time constants for each subject. We therefore tested the time constants of the whole population of subjects using repeated measures three-way ANOVA

Fig. 3 Representative SPV data and exponential fit recorded in one subject in the three tested paradigms. *Top panel* Per-rotatory OVAR during backward rotation (TC estimate = 10.27 s). *Center panel* Post-rotatory left EDR after backward rotation (TC estimate = 7.26 s). *Bottom panel* Post-rotatory OVAR stopping upright after forward rotation (TC estimate = 3.79 s)



considering within-subjects data (Trujillo-Ortiz et al. 2006), with subject position, stimulus type and direction (in terms of “preferred” and “non-preferred” direction) as factors. Only the difference between directions was significant ($P = 0.017$, $F = 9.56$).

When considering each subject’s mean value, no significant difference was found between per-rotatory and post-rotatory time constants (6.2 ± 1.6 and 5.8 ± 1.2 s (mean \pm SD) respectively, $P = 0.55$, $F = 0.37$) and between right ear down and left ear down time constants (6.1 ± 1.4 and 6.0 ± 1.4 s, respectively, $P = 0.86$, $F = 0.03$). Thus, in the following we will pool the parameters estimated from per- and post-rotatory responses, based on the direction of their SPV.

Pooling subjects based on such criterion, we found that the mean time constant in the “preferred” direction was 6.9 ± 2.1 s, which proved significantly ($P = 0.034$, $F = 5.2$) longer than that in the “non-preferred” direction (5.1 ± 0.9 s).

The same tests were applied on gain values. None of the factors showed significant differences between gains both within subjects and pooling them. Considering each subject’s mean value, the mean gains over the entire population of subjects were 0.50 ± 0.11 and 0.41 ± 0.13 for “preferred” and “non-preferred” directions, 0.44 ± 0.10 and 0.47 ± 0.09 for per-rotatory and post-rotatory conditions and 0.46 ± 0.10 and 0.45 ± 0.09 for right ear down and left ear down positions, respectively. The overall mean gain in EDR position was 0.45 ± 0.09 .

Post-rotatory OVAR

A total of 20 (out of 78) responses were discarded from the analysis because they were either absent or the peak SPV

did not reach the $5^\circ/\text{s}$ threshold (see “Data analysis” section). Considering stopping positions (i.e. prone, upright and supine) and direction of the resulting eye movements as factors of a repeated measures two-way ANOVA for within-subjects analysis, we found a relevant influence of the different stopping positions on the time constant of the responses ($P = 0.017$, $F = 5.56$). On the other hand, we found no significant directional asymmetry of the rVOR time constants both comparing upward SPV and downward SPV ($P = 0.46$, $F = 0.62$) and “preferred” and “non-preferred” directions, defined according to EDR results ($P = 0.53$, $F = 0.44$). Data relative to rotations in the two directions were therefore pooled, on the basis of their stopping position. The bottom panel in Fig. 3 shows a representative post-rotatory response after stopping with the subject upright.

Considering each subject’s mean value, the mean (of means) time constant for upward and downward SPV were 4.54 ± 1.60 and 4.14 ± 1.25 , respectively. Their differences were not significant ($P = 0.31$, $F = 1.10$). The mean time constant in supine position (4.7 ± 1.2 s) was not significantly different ($P = 0.85$, $F = 0.04$) from that in prone position (4.5 ± 1.6). However, the mean time constant recorded after stopping in upright position was only 3.6 ± 0.7 s, significantly shorter ($P = 0.036$, $F = 9.51$) than that in the supine position, and near the significance cutoff ($P = 0.056$, $F = 3.61$) from that in the prone position. Considering that supine and prone positions are similar in terms of head orientation with respect to gravity, i.e. gravity aligned with the naso-occipital axis, while different from the upright position, i.e. gravity aligned with the rostro-caudal axis, we chose to pool the data from the responses recorded in supine and prone positions. Their mean time constant was 4.6 ± 1.2 s, which was

significantly longer ($P = 0.05$, $F = 4.56$) than that after stopping upright.

Statistical analysis of the gain values using repeated measures two-way ANOVA considering within-subjects data revealed a significant effect ($P = 0.004$, $F = 8.13$) of rotation direction, but no differences due to stopping positions ($P = 0.08$, $F = 4.03$). Considering each subject's mean value, the grand mean of gains after stopping in the upright position was 0.28 ± 0.13 , while that after stopping in supine and prone positions was 0.37 ± 0.09 ; such difference was not significant ($P = 0.12$, $F = 2.77$). Pooling the stopping positions, we found a significant ($P = 0.03$, $F = 5.89$) directional asymmetry between post-rotatory gains, with mean values of 0.38 ± 0.11 and 0.25 ± 0.10 for “preferred” and “non-preferred” direction, respectively.

Per-rotatory OVAR

An example of per-rotatory SPV trace is shown in the top panel of Fig. 3 after saccade removal. Only four of our subjects were able to complete the per-rotatory OVAR trials. Comparing time constants on a subject-by-subjects basis, only one of these showed a significant directional asymmetry ($P = 0.007$, $F = 26.89$), although all subjects showed a larger time constant in the forward direction (i.e. upward SPV). The subject with reversed asymmetry in the first paradigm was not able to perform the per-rotatory paradigm due to motion sickness. We compared the time constants using repeated measures one-way ANOVA considering within-subjects data, but did not find any significant directional asymmetry ($P = 0.4$, $F = 1.07$).

Similarly, pooling each subject's mean value based on the direction of the resulting eye movements, we found no significant asymmetry ($P = 0.39$, $F = 0.83$), although the mean time constant of upward (7.8 ± 2.1 s) was longer than that of downward SPV (6.3 ± 2.6 s). Gain comparison did not show any significant difference both within subjects and pooling them. The gains were respectively 0.65 ± 0.20 and 0.53 ± 0.22 for upward and downward SPV. Their difference was also not significant ($P = 0.45$, $F = 0.65$).

Comparison

Pooling mean results calculated over each subject on a directional basis, we found no significant differences between the time constants in EDR and per-rotatory OVAR ($P = 0.54$, $F = 0.40$ and $P = 0.24$, $F = 1.58$ for “preferred” and “non-preferred”, respectively). Per-rotatory OVAR “preferred” was instead significantly longer than EDR “non-preferred” ($P = 0.009$, $F = 10.62$). The latter was not significantly longer than post-rotatory OVAR supine and prone ($P = 0.52$, $F = 0.43$), yet it was significantly longer than post-rotatory OVAR upright ($P = 0.004$, $F = 11.58$) (Table 1).

The longest time constants were found when the axis of rotation was aligned with gravity (EDR) and during per-rotatory OVAR, while they were shorter when the subjects were stopped after rotation around an earth horizontal axis (OVAR).

The shortest rVOR time constants in our set of experiments were found in post-rotatory trials when the axis of rotation was perpendicular to the gravity vector (OVAR) and the subject was stopped upright. In this condition, we found a mean value of 3.6 ± 0.7 s and no significant directional asymmetries. An overall comparison of the time constants estimated in the different tested paradigms is shown graphically in Fig. 4.

Among the different conditions considered in our study, the gain of the vertical rVOR reached values above 0.5 only in response to rotations around the earth-horizontal interaural axis (forward and backward per-rotatory OVAR) and to rotations in the “preferred” direction around the earth vertical axis (“preferred” direction EDR). There were no significant differences among these three conditions. A mean gain of roughly 0.4 was found in “non-preferred” direction EDR and “preferred” direction post-rotatory OVAR, which were significantly lower than those in forward per-rotatory OVAR ($P = 0.03$, $F = 6.65$ and $P = 0.01$, $F = 9.26$, respectively). The responses elicited by post-rotatory OVAR stimuli in the “non-preferred” direction showed a mean gain of only 0.25, which was significantly lower than all the other tested paradigms ($P < 0.03$). Figure 5 shows the gains estimated in the different experimental conditions.

Table 1 Mean values and standard deviations for the rVOR time constant (seconds) in the different experimental conditions together with their respective gains

	Per OVAR preferred	EDR preferred	Per OVAR non-preferred	EDR non-preferred	Post OVAR supine-prone	Post OVAR upright
Time constant	7.8 ± 2.1 s	6.9 ± 2.1 s	6.3 ± 2.6 s	5.1 ± 0.9 s	4.6 ± 1.2 s	3.6 ± 0.7 s
Gain	0.65 ± 0.20	0.50 ± 0.11	0.53 ± 0.22	0.41 ± 0.13	0.37 ± 0.09	0.28 ± 0.13

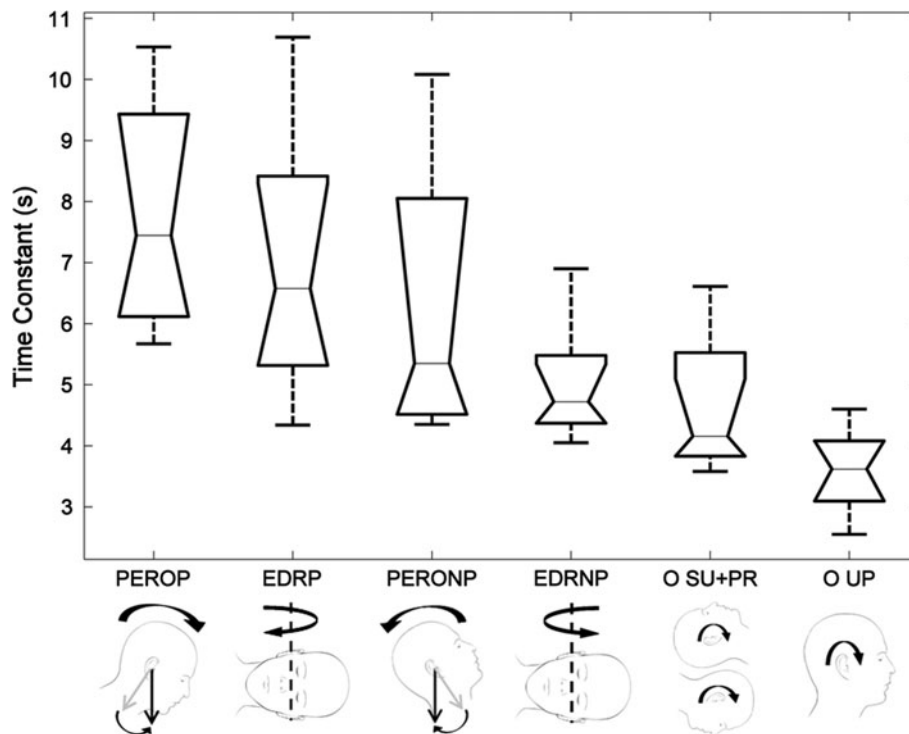


Fig. 4 Graphical representation of the statistical comparison between the time constants estimated from the three main paradigms, separately considering the most relevant grouping parameter for each one. PEROP: Per-rotatory OVAR preferred direction. EDRP: Ear down rotations preferred direction. PERONP: Per-rotatory OVAR non-preferred direction. EDRNP: Ear down rotations non-preferred direction. O SU + PR: Post-rotatory OVAR stopping supine and prone. O UP: Post-rotatory OVAR stopping upright. The *lower* and *upper lines* of each “box” are the 25th and 75th percentiles of the

sample. The distance between the *top* and *bottom* of the *box* is the inter-quartile range. The *line* in the *middle* of the *box* is the sample median. The “whiskers” (the *lines* extending above and below the *box*) show the extent of the rest of the sample. The notches in the *box* are a *graphic* representation of the confidence interval about the median of a sample. It provides a graphical way to determine which groups have significantly different medians. The symbol “+” identifies the outliers

Discussion and conclusions

To assess the contribution of the VSM to the vertical rVOR in humans, we analyzed the eye movements evoked by steps of angular velocity around the interaural axis in eight healthy human subjects. Previous studies have shown the relevance of the direction of gravitational acceleration with respect to that of the head angular velocity vector in determining the VSM contribution during yaw rotations (Angelaki and Hess 1994; Cohen et al. 1999; Raphan et al. 1992). We therefore chose to study pitch head rotations during which head angular velocity was either aligned with or orthogonal to gravity. We reasoned that a modulation of the vertical rVOR response time constant would be an indicator of the changing contribution of the VSM. Therefore, we considered pitch head rotations with the interaural axis being either earth-vertical (EDR) or earth-horizontal (OVAR). To our knowledge, this is the first human study comparing the responses of the vertical rVOR to steps of angular head velocity around different axes.

The SPV of the vertical rVOR showed a quick rise followed by an exponential decay, and was therefore similar to that of horizontal rVOR responses elicited by similar stimuli. During rotations involving the stimulation of the otolith organs, i.e. when the axis of rotation was earth-horizontal, a sinusoidal modulation and a bias were superimposed on the decaying response. Analysis of the eye velocity around the horizontal and the torsional axes did not show any significant transient response. Thus, no evident cross-coupling was evoked by pitch rotations in humans. Although no cross-coupling from vertical to horizontal eye velocity has been reported in OKAN studies in the monkey (e.g. Dai et al. 1991), the stimuli used in this paper are more similar to the post-rotatory tilt after ear down pitch rotations tested by Hess and colleagues (Hess et al. 2005; Angelaki and Hess 1994), which did lead to cross-coupling. Therefore, this finding may be an indicator of the existence of significant differences in the 3D behavior of the vestibulo-ocular reflexes between monkeys and men; a hypothesis which should be further investigated considering the substantially different nature of the

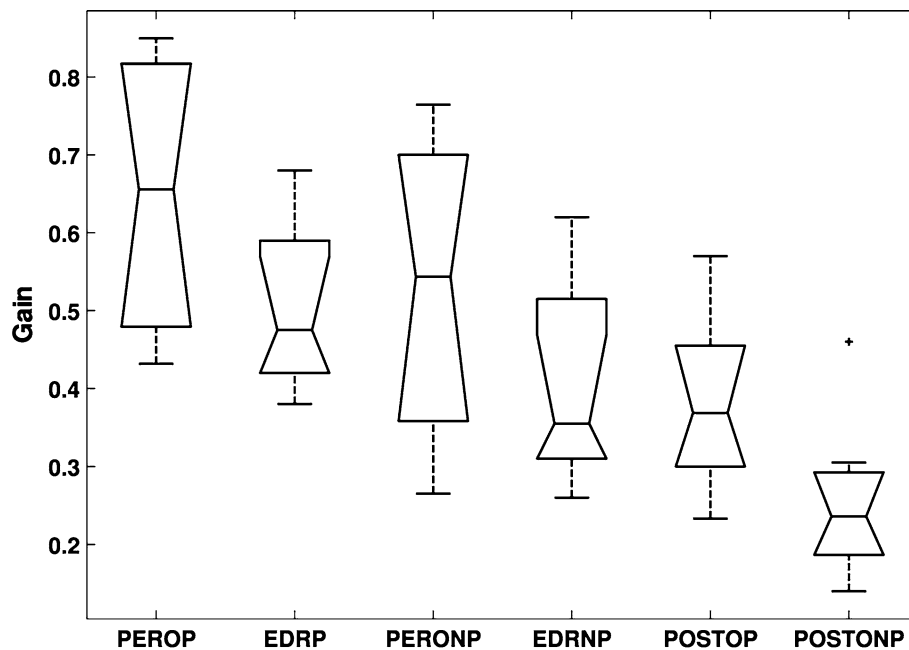


Fig. 5 Graphical representation of the statistical comparison between the gain values estimated from the three main paradigms, grouped considering the most relevant grouping parameter for each one. Note that although during EDR non-significant directional asymmetry was found. Here, the values from *upward* and *downward* SPV are separated for ease of comparison with Fig. 4. *PEROP* Per-rotatory

OVAR preferred direction. *EDRP* Ear down rotations preferred direction. *PERONP* Per-rotatory OVAR non-preferred direction. *EDRNP* Ear down rotations non-preferred direction. *POSTOP* Post-rotatory OVAR preferred direction. *POSTONP* Post-rotatory OVAR non-preferred direction. Symbols as in Fig. 4

exposure to vestibular stimuli during the life of individuals in the two species, due to both posture and natural activities.

We analyzed the vertical SPV responses by fitting them with a first-order model of the rVOR (Robinson 1977) and studied the resulting estimates of the rVOR parameters.

In all tested paradigms, we found that the vertical rVOR has a significantly shorter time constant than the 15–20 s usually found for the horizontal rVOR (Leigh and Zee 2006).

In sum, considering the entire set of experimental conditions tested, we found a variety of vertical rVOR time constants ranging from less than 4 s to over 9 s. These results suggest that indeed there is a central processing of the vertical angular velocity signal, and that the VSM may modulate its contribution to the vertical rVOR response, depending both on the orientation with respect to gravity and on the direction of rotation. Our results show that the VSM contribution to the vertical rVOR is weaker than that to the horizontal one. This finding may explain why periodic alternating nystagmus, a condition related to the alteration of the VSM function (Cohen et al. 1987; Furman et al. 1990), is commonly limited to the horizontal plane.

The finding that the longest rVOR time constants in response to post-rotatory stimuli were those in EDR is in agreement with previous studies on monkeys (Angelaki and Hess 1994); it suggests that gravity is a key factor in

determining the level of VSM activity also for the vertical rVOR, and notably that its alignment with the angular head velocity vector prolongs such activity.

The vertical rVOR time constant in EDR is asymmetrical with respect to the direction of rotation, with most of the tested subjects showing a markedly “preferred” direction, in which the prolongation is greater than in the other. This “preferred” direction usually coincides with upward SPV, as previously found in OKN and OKAN studies (Clement 2003; Clement and Lathan 1991), although one subject had a reversed asymmetry. Our findings are in agreement with the hypothesis that the marked directional asymmetry found in the EDR condition is most probably due to the VSM processing itself (Matsuo et al. 1979; Matsuo and Cohen 1984), since it is absent during post-rotatory OVAR stimuli stopping upright i.e. the condition corresponding to the shortest overall rVOR time constants.

Importantly, we found that the rVOR time constant was longest in response to per-rotatory OVAR stimuli and shortest in response to the corresponding post-rotatory ones. Therefore, the explanation for this finding implies a role of the otolith organs, whose saccular and utricular maculae are continuously swept by the projection of the gravity vector during per-rotatory OVAR stimuli. Thus, the information provided by the otoliths may be used by the CNS to infer the continuous rotation. If, as suggested by

Green and Galiana (1998; Angelaki et al. 2001), the otolith signal is carried to the VSM, and considering that previous studies have shown that OVAR stimuli induce no bias in the absence of VSM (Wearne et al. 1997; Darlot et al. 1988), we hypothesize that during continuous OVAR the otolith signal may act to increase the activity of the VSM beyond the level involved in the post-rotatory condition. The long time constants found during per-rotatory OVAR could then reflect an activation of the VSM mechanism being sustained by otolith-related signals. Such experimental finding is in agreement with a previous study on the frequency response of the rVOR to sinusoidal oscillations around different axes (Bockisch et al. 2005), which reported a lower corner frequency for pitch rVOR responses when the otolith organs are dynamically stimulated by gravity. The existence of a contribution of an otolith-perceived angular head velocity signal to the estimate of head rotation is also in agreement with current models of otolith-canal sensory fusion (Bos and Bles 2002; Mergner and Glasauer 1999; Zupan et al. 2002).

Indeed pitch rotations of the head involving an activation of the SCC being consistent with the otolith-perceived change in orientation with respect to gravity is a common condition during everyday movements. Such increase of the time constant could have a functional meaning if interpreted in terms of an increased sensitivity to the low-frequency canal information triggered when changing head orientation with respect to gravity. In natural conditions, this could occur when one leans forward to reach for an object on a low surface or on the floor. Such movement would change the position of the body center of mass and challenge one's ability to maintain balance. Special care must then be taken to avoid falling, and low-frequency rotational information, combined with otolith input, would be especially relevant for proper control of balance.

With respect to the duration of the SCC time constant, our experimental findings cannot provide a straightforward answer, as their time constant is masked by that of the overall response with our fitting approach. Yet, the lowest values we found deserve some consideration. In fact at least two hypotheses can be considered to explain the range of time constants found experimentally. First, it can be hypothesized that the shortest time constants we found represent the activity of the canal afferents alone and that different levels of VSM contribution are present in the other conditions. Second, we could hypothesize that the minimum value we found results from the dumping of the rVOR response, which in some conditions (in monkeys) was reported to reduce the duration of the response below that of the activity of vestibular afferents (Angelaki and Hess 1994). The real value of the canal time constant would therefore lie between the minimum and the maximum values we found.

In favor of the first hypothesis would be the fact that our shortest estimates (post-rotatory OVAR upright) are similar to what is commonly considered for vestibular afferents both in monkeys (Fernandez and Goldberg 1971; Correia et al. 1992) and humans (Cohen et al. 1981), and to what has been proposed for the cupular time constant based on modeling studies (Dai et al. 1999; Gizzi and Harper 2003).

Following the second hypothesis, instead, our lowest estimates would be interpreted as the effect of the dumping of rVOR activity possibly triggered by the recognition, mediated by otolith signals, of a well-known static postural condition, i.e. upright. This interpretation would be in agreement with the observation that bilateral macular ablation in the monkey prolongs the decay time constant of the SPV in post-rotatory OVAR experiments as reported by Igarashi and colleagues (Igarashi et al. 1980). In such scenario, the other post-rotatory data could be interpreted assuming the dumping system is less efficient when gravity is aligned with the naso-occipital axis (a less common condition for high angular accelerations of the head compared to upright).

The distribution of gain values in the different conditions tested seems to qualitatively mirror the one shown by the time constants (Fig. 5). However, no significant differences were found between the different stopping positions during post-rotatory OVAR, and no relationship between such positions and the absence of post-rotatory responses could be inferred from our data. The possibility that the absence of post-rotatory response might be due to motion sickness or habituation seems unlikely since our subjects did not report particular discomfort and the sequence of trials was randomized. Nevertheless, a thorough analysis of the effects of rotation direction and stopping position on the gains of the vertical rVOR would need a larger data set. The finding of higher gains during per-rotatory OVAR is in agreement with previous results on the frequency response of the rVOR (Bockisch et al. 2005), reporting a higher gain at all frequencies when the otolith organs are dynamically stimulated by gravity.

In conclusion, in order to investigate the contribution of the VSM to the vertical VOR, we studied the per- and post-rotatory SPV of the vertical rVOR in response to pitch rotations around axes being either aligned or orthogonal to gravity. We found that the TC of rVOR responses ranged from 3–10 s, depending both on gravity and on the direction of rotation. Our results indicate a role for the VSM in the vertical rVOR, although its contribution appears to be weaker than on the horizontal rVOR and may be directionally asymmetric.

The shortest TC were found in response to post-rotatory earth-horizontal stimulation, while they were longer in EDR stimulation, i.e. when the head angular velocity vector is aligned with gravity. Overall, the longest TC were

observed in per-rotatory earth-horizontal stimulation, thus implying a role for the otoliths in the activation of the VSM.

Conflicts of interest The authors have reported no conflicts of interest.

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