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Torsional vestibulo-ocular reflex during whole-body oscillation in the upright and the supine position

I. Responses in healthy human subjects

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Abstract In rhesus monkeys, the dynamic properties of the torsional vestibulo-ocular reflex (VOR) are modified by otolith input: compared with torsional oscillations about an earth-vertical axis (canal-only stimulation), the phase lead observed at frequencies below 0.1 Hz is cancelled when the animals are rotated about an earth-horizontal axis (canal-and-otolith stimulation); the gains of the torsional VOR, however, are nearly identical in both conditions. To test whether or not canal-otolith interaction in humans is similar to that in rhesus monkeys, we examined ten healthy human subjects on a three-axis servo-controlled motor-driven turntable. The subjects were oscillated in upright or supine position in complete darkness over a similarly wide range of frequencies (0.05–1.0 Hz) with peak velocities $<40^\circ/\text{s}$. Eye movements were recorded using the three-dimensional search coil technique. Compared with the torsional vestibulo-ocular gains during canal-stimulation only (earth-vertical axis), the gains obtained during combined canal-otolith-stimulation (earth-horizontal axis) were significantly higher throughout the entire frequency range ($P < 0.05$). The gain increased by 0.100 ± 0.074 (SD), independent of frequency. During the earth-horizontal axis stimulation, the phase remained always around zero, which is in contrast to the canal-stimulation only, during which one finds an increasing phase lead as frequency decreases. We conclude that, in healthy humans as in rhesus monkeys, the phase lead from the canal signals at low frequencies is effectively cancelled by the otolith input. In contrast to rhesus monkeys, however, otolith signals in healthy humans increase the gain of the torsional VOR at frequencies from 0.05 to 1.0 Hz. This normal database is crucial for the interpretation of results obtained in patients with vestibular disorders.

Key words Otoliths · Semicircular canals · Gravity · Torsion · Oculomotor · Three-dimensional eye movements

Introduction

In the supine position, the torsional vestibulo-ocular reflex (VOR) is elicited by rotation about the earth-vertical axis. This stimulation is detected mainly by the vertical canals (to a lesser degree by the horizontal canals). In the upright position, the torsional VOR is elicited by rotation about the earth-horizontal axis. In this situation, the orientation of the gravity vector changes in the frontal plane of the head, which is detected by the otolith organs that provide an additional input component for the torsional VOR. It is unclear, however, whether the canal and otolith inputs simply add or whether there is a complex frequency-dependent otolith-canal interaction.

In rhesus monkeys, the torsional VOR has systematically been tested by turntable oscillation in supine and upright position (Angelaki and Hess 1996): Over a frequency range of 0.01–1.14 Hz, the gain of the torsional VOR was not significantly different between the supine (canal-only stimulation) and the upright (combined canal-otolith-stimulation) position. At frequencies below 0.1 Hz, there was a phase lead in the supine position, which increased with decreasing frequency ($\sim 40^\circ$ at 0.01 Hz). This finding is compatible with a time constant of about 10–20 s for the velocity storage integrator in the torsional direction. In the upright position, however, there was almost no phase lead at low frequencies, which cannot be explained by simple linear summation of canal and otolith inputs. The suggested non-linearity of canal-otolith interaction in rhesus monkeys was further supported by the finding that animals with all six semicircular canals plugged had a very high torsional VOR gain in the upright position (0.8 at 0.01 and 0.02 Hz) (Angelaki and Hess 1996); with increasing frequency, the gain dropped drastically (0.2 at 0.1 Hz).

The first investigation in humans comparing torsional VOR-gains in supine and upright position on a turntable

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(passive stimulation) was restricted to a single frequency of 0.3 Hz and a single amplitude of $\pm 20^\circ$ (Tweed et al. 1994). In line with the monkey data, the authors found no significant increase of the torsional gain in the upright position.

A more recent study in healthy human subjects extended the torsional turntable oscillation in supine and upright position to different frequencies, ranging from 0.05 to 0.4 Hz (Groen et al. 1999). There was a small, but significant gain increase of about 0.1 in the upright position at all frequencies measured. Because of the strong intraindividual variability of gain values, the authors, however, did not believe that the otoliths significantly contribute to improving the gain of the torsional VOR in humans. In contrast to the monkey data (Angelaki and Hess 1996), the authors found a U-shaped function relating phase lead to frequency in the supine position, with a minimum at 0.1 Hz, while the phase lead in the upright position increased with higher frequency. At 0.4 Hz, the phase lead was more than 90° in both supine and upright positions.

In view of the contradictory results in rhesus monkeys and humans, we recorded the torsional VOR in healthy human subjects during passive roll rotation about the earth-vertical axis (canal-only stimulation) and earth-horizontal axis (combined canal-otolith stimulation) over a wider frequency range (0.05–1.0 Hz). In contrast to the

data obtained in monkeys, there was a significant increase in the torsional VOR gain by otolith input at all frequencies tested. The phase behavior in upright and supine position, however, was similar to the data reported in monkeys, but in contrast to the human data available so far. The results presented in this paper provide the reference database for a subsequent paper on the torsional VOR in patients after vestibular neuritis.

Material and methods

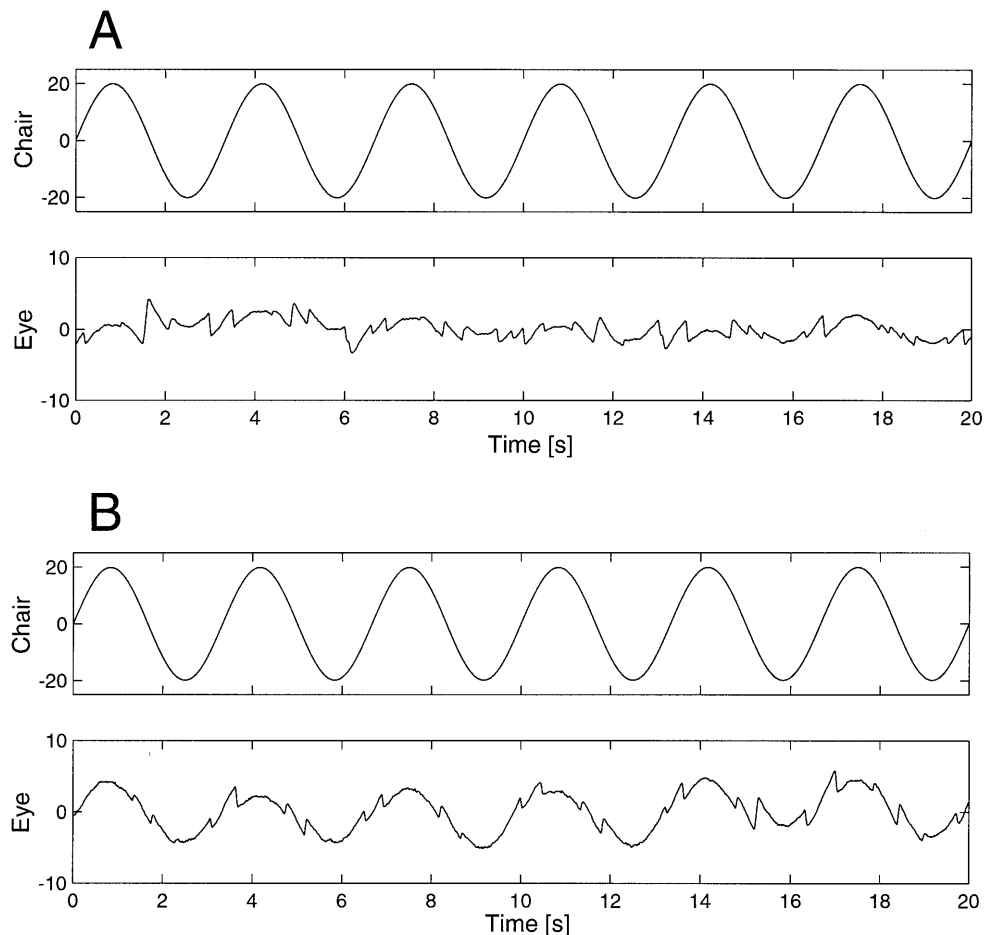
Subjects

Ten healthy human subjects (three male, seven female; 25–56 years old) participated in this study. 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.

Vestibular stimulation

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 consists of a thermoplastic material (Posicast), which can be molded to the contour of the head after being warmed in a water bath. With this device, the center of the intraaural line was positioned at the inter-

Fig. 1 Examples of raw data in a healthy subject (D.S.) during torsional chair oscillation at 0.3 Hz in supine (**A**) and upright (**B**) body positions. *Upper panels* torsional chair position, *lower panels* torsional component of eye-rotation vectors



section of the three axes of the turntable. The subjects were secured by safety belts, and movements of the body were minimized by evacuation pillows. Special care was taken to keep the subject alert by repeated encouragement and keeping the trials short with breaks in-between.

In both supine and upright positions, whole-body oscillations were performed in total darkness at six different frequencies: 0.05, 0.1, 0.3, 0.5, 0.7, and 1 Hz. The corresponding amplitudes were 40, 40, 20, 8, 4, and 2°. This resulted in peak velocities of 12.57, 25.13, 37.70, 25.13, 17.60, and 12.57°/s. To control the effect of visual fixation on the torsional VOR, we repeated the vestibular stimulation trials while subjects were continuously fixing a chair-fixed light dot straight ahead (distance: 0.8 m).

Eye-movement recording

Eye movements were recorded monocularly with dual scleral search coils (Skalar Instruments, Delft, 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 42.6, 55.5, and 83.3 kHz (Rommel type system, modified by A. Lasker, Baltimore) (Rommel 1984). For calibration, subjects were asked to fix a light dot straight ahead at the beginning of each trial. Details of the calibration procedure can be found elsewhere (Straumann et al. 1995). Eye- and chair-movement signals were digitized at a frequency of 1000 Hz with 16-bit resolution and stored on a computer hard disk for off-line processing.

Data analysis

The collected data were further processed on a PC using interactive programs written in MATLAB, version 5.3. From raw signals and calibration values of the search coil, we computed eye-rotation vectors, which describe three-dimensional ocular positions as single rotations from the reference position. Angular eye velocity vectors (ω) were calculated from rotation vectors (e) and their derivative (de) using the formula

$$\bar{\omega} = 2(de + e \times de)/(1 + |e|^2)$$

Angular eye-velocity vectors are oriented parallel to the instantaneous ocular rotation axis; their lengths denote the velocity of rotation in rad/s. For convenience of the reader, values were converted to °/s.

Individual trials of oscillatory vestibular stimulation consisted of 5–15 cycles. To obtain representative torsional eye-movement responses, we overlaid the torsional angular-velocity vectors of the cycles and computed the median value for each millisecond. In the following, we shall call this representative data set “median cycle”. By this method and by removing medians that were based on datasets with more than 20°/s standard deviation, eye-velocity signals during quick phases were discarded. Median cycles were also determined for chair-velocity traces.

The following sine function was fitted to the median cycles:

$$y = A \cdot \sin(\omega t + \phi) + c$$

where A is the amplitude, ω the frequency, ϕ the phase, and c the offset. The frequency (ω), as determined by the chair signal, was kept constant, while the amplitude (A), phase (ϕ), and offset (c) were iteratively optimized by a nonlinear least-square algorithm based on the Levenberg-Marquardt method (Matlab-function lsqnonlin.m). Half-amplitudes for clockwise (A_{cw}) and counter-clockwise (A_{ccw}) half-cycles were computed by:

$$A_{cw} = A - c, A_{ccw} = -A + c$$

To quantify the harmonic distortion of the eye-velocity signal, we also fitted the data to a sine function with two harmonics:

$$y = A \cdot \sin(\omega t + \phi) + B \cdot \sin(2\omega t + \phi) + c$$

The harmonic distortion coefficient (hd) was computed by dividing the gain of the second harmonic by the gain of the first harmonic:

$$hd = B/A$$

Results

Figure 1 shows raw position data of a healthy subject (D.S.) oscillated with 0.3 Hz (amplitude $\pm 20^\circ$) in supine (Fig. 1A) and upright (Fig. 1B) positions. In both subfigures, the upper panels depict torsional chair position and the lower panels the torsional component of eye rotation vectors. Note the enhancement of torsional eye-position amplitude during upright oscillation, which is due to otolith input.

In Fig. 2, the same data already shown in the previous figure are plotted, but this time in the velocity domain. The upper panel represents the median cycle (for a definition, see Methods) of torsional chair velocity during oscillation with the subject in the supine position (Fig. 2A). When the subject was in the upright position,

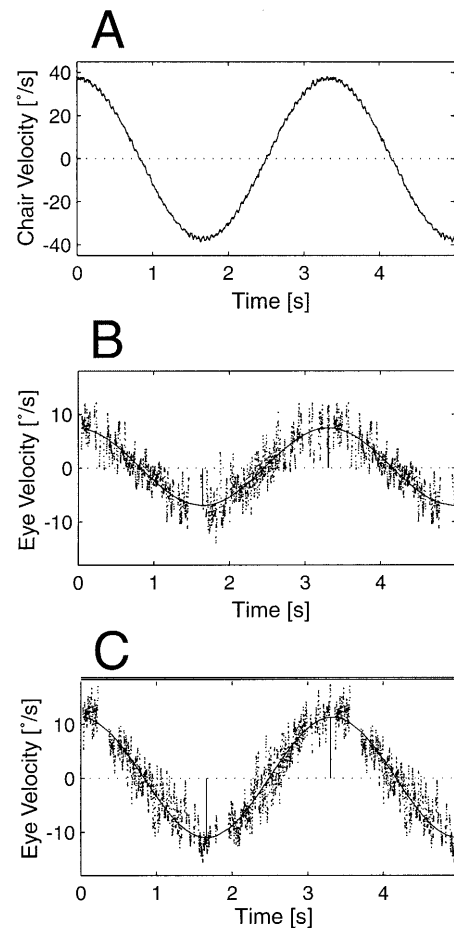
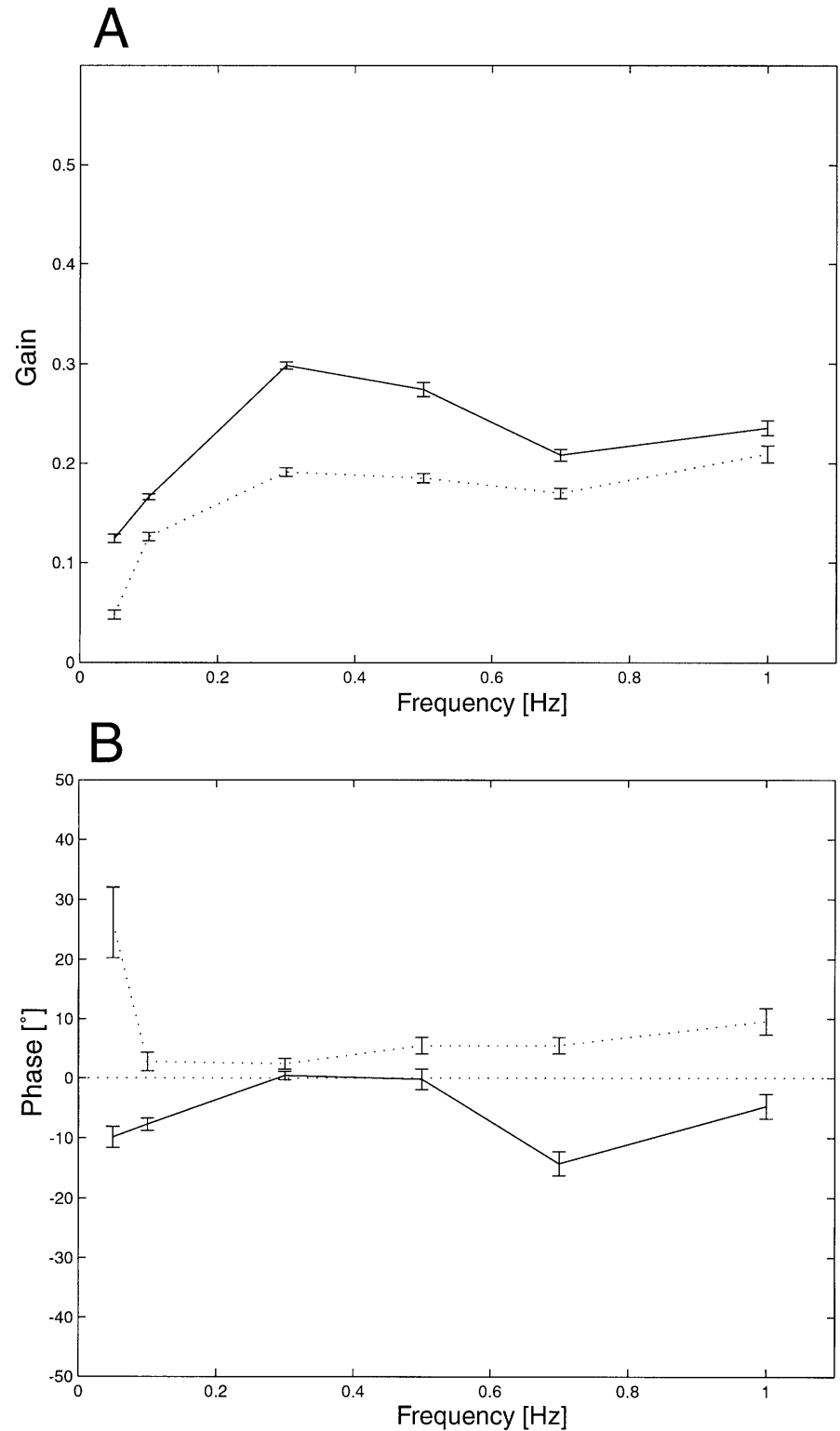


Fig. 2A–C Median angular velocities of the same data as in Fig. 1. **A** Torsional chair velocity multiplied by -1 . **B** Torsional component of angular eye velocity in the supine position. **C** Torsional component of angular eye velocity in the upright position. Solid curves Sines fitted to the data, vertical solid lines half-gains

Fig. 3A, B Data from the same subject as in the previous figures. Gain (**A**) and phase (**B**) values as a function of frequency in supine (*dotted curves*) and upright (*solid curves*) body positions



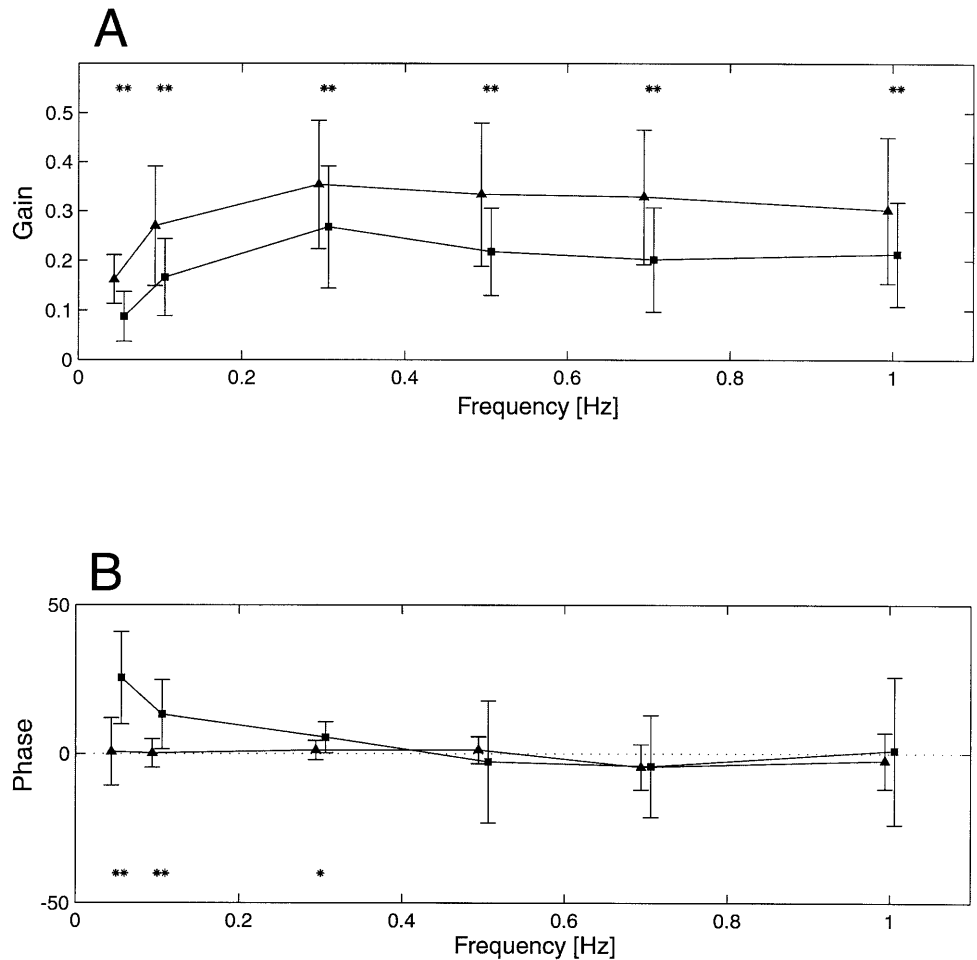
this chair signal was close to identical (not shown). The two lower subfigures depict the torsional component of angular velocity in supine (Fig. 2B) and upright (Fig. 2C) positions. Sines with a single harmonic were fitted to the data (solid curves), as described in the Methods. The gain (g) of the torsional VOR was defined as the coefficient between the torsional component of angu-

lar eye velocity (ω_e) and the velocity of the chair about the roll axis (ω_c):

$$g = \omega_e / \omega_c$$

In this example (Fig. 2), the gain in the upright position ($g_u=0.28$) was enhanced by 39% compared with the gain in the supine position ($g_s=0.17$). The definition of half

Fig. 4 Summary figure of average gain (A) and phase (B) values obtained in the supine (squares) and upright (triangles) body positions ($n=10$ subjects). Error bars indicate \pm SD. Asterisks denote the significance level of the two-tailed, paired t -test between the supine and upright data (* $P<0.05$, ** $P<0.01$)



gains based on half-amplitudes (see Methods) was analogous. In this example and the entire database of healthy subjects, there was no significant asymmetry between the half-gains in any position ($P>0.05$). In the example shown (Fig. 2), the phase difference between chair and eye movements was close to zero in both supine ($\phi=2.0^\circ$) and upright ($\phi=-0.7^\circ$) positions. The harmonic distortion coefficient (hd ; defined in Methods) was below 10% in both supine ($hd_s=0.02$) and upright positions ($hd_u=0.06$). In the entire database of healthy subjects, hd was always below 20%.

Figure 3 summarizes the gain and phase values in upright (solid curves) and supine (dotted curves) positions as a function of frequency (0.05–1.0 Hz) in a single subject (D.S.). The error bars depict the confidence intervals ($P<0.05$) of the first-harmonic sine fits through the median cycles¹. The solid lines connect the centers between the upper and lower limits of the confidence intervals. At all frequencies, gains in the upright position were significantly higher than in the supine position (Fig. 3A). Up to 0.3 Hz, gain increased with frequency in both body positions. At the lowest frequency tested (0.05 Hz), there was a large phase lead during oscillation in the supine (Fig. 3B), but not in the upright (Fig. 3A) position. At

medium frequencies (0.3, 0.5 Hz), the phase difference between supine and upright position was minimal.

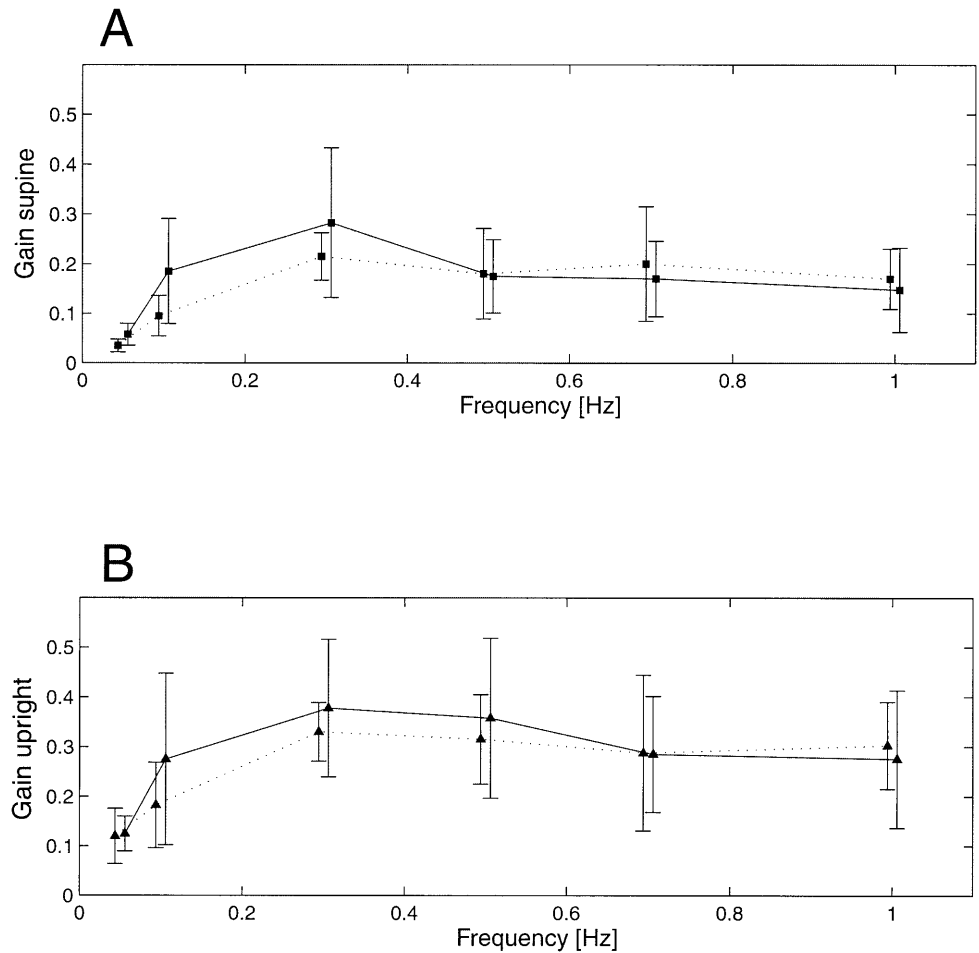
Figure 4 summarizes the gain and phase values of the torsional VOR in the ten healthy subjects tested. In Fig. 4A, the squares give the averages of the gains in the supine and the triangles the averages of the gains in the upright position. Standard deviations are plotted by error bars. The asterisks indicate the significance level of the two-tailed paired t -test between supine and upright data (*: $P<0.05$, **: $P<0.01$). At the lower frequencies (0.05 and 0.1 Hz), the gains in both supine and upright positions were smallest. At medium and high frequencies (≥ 0.3 Hz), the values did not further increase, forming a plateau ($g_s \approx 0.2$; $g_u \approx 0.3$). There was a highly significant enhancement of the torsional gain by the otolith input at all frequencies tested. The null hypothesis that the amount of the gain increase did not differ between the six frequencies could not be rejected in the two-way analysis of variance ($P=0.495$). The grand average (ten subjects, six frequencies) of gain increase was 0.100 ± 0.074 SD.

To quantify the increase in torsional gain (not shown), we defined the coefficient of relative gain enhancement (c_g). Using the formula

$$c_g = (g_u - g_s) / g_s$$

¹ Computed by the bootstrap method (Manly BFJ (1991))

Fig. 5 Average gains of torsional vestibulo-ocular reflex during supine (g_s , **A**) and upright oscillations (g_u , **B**) with (dotted line) and without (solid line) visual fixation ($n=4$)



the c_g -averages were significantly above the zero-level at all frequencies. Again, the two-way analysis of variance did not indicate that the relative gain enhancement significantly differed between the six frequencies ($P=0.065$).

In Fig. 4B, the squares give the averages of the phases in the supine and the triangles the averages of the phases in the upright position. Again, standard deviations are plotted by error bars. The asterisks symbolize the same significance levels of the t -tests as in Fig. 4A. In the supine position, there was an increasing phase lead with decreasing frequency below 0.5 Hz. This contrasts to the phase values in the upright position, which were always close to zero. The differences in phase between supine and upright position were significant between 0.05 and 0.3 Hz.

Four of the subjects were also tested during fixation of a light dot straight-ahead in otherwise complete darkness. Figure 5 summarizes the effect of visual fixation on the gain of the torsional VOR. In both supine (Fig. 5A) and upright (Fig. 5B) positions, there was no significant difference between the oscillation with (dotted curves) and without (solid curves) visual fixation ($P>0.05$).

We also compared the phase of the torsional VOR with and without visual fixation. Again, there was no significant difference between the two conditions in both supine and upright positions (data not shown).

Discussion

This study demonstrates that otolith input modifies the torsional vestibulo-ocular reflex of healthy humans in a specific way: (1) independent of frequency (0.05–1.0 Hz), the gain is enhanced by about 0.1; (2) at low frequencies (0.05–0.3 Hz), the phase lead, observed during oscillation in the supine position, is cancelled.

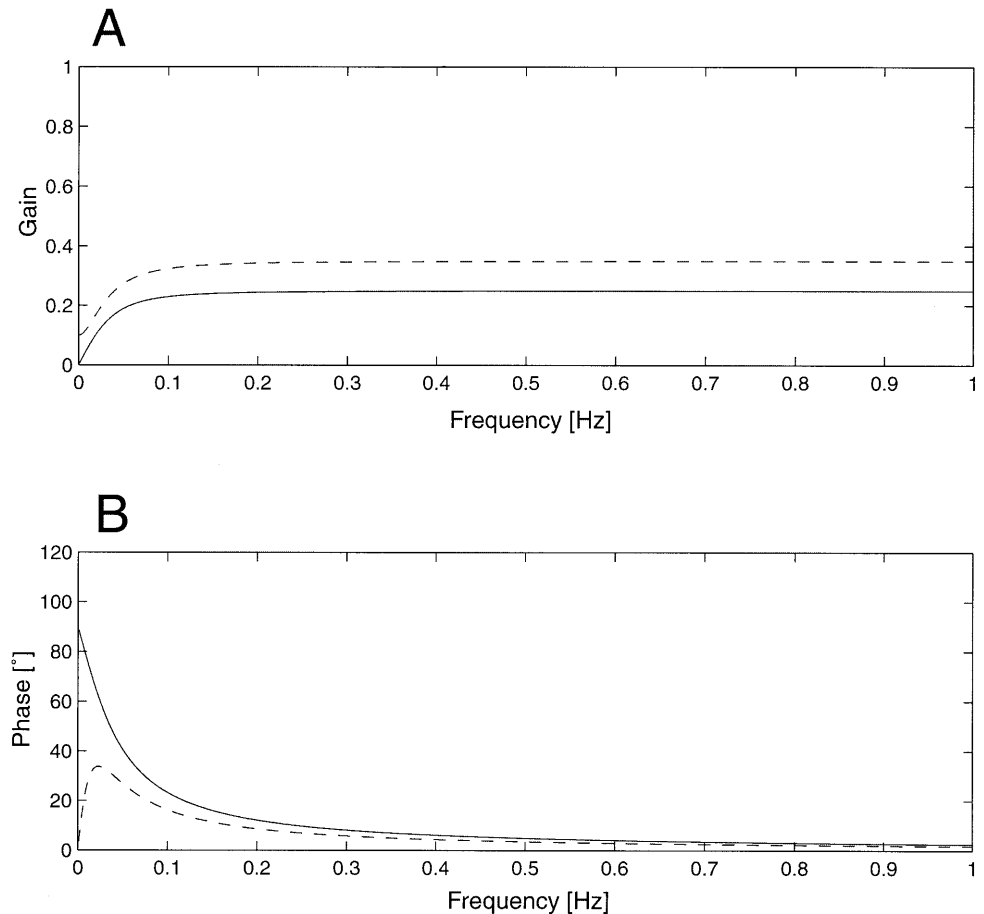
We asked whether these otolith-related effects could be explained by linear summation of torsional canal and otolith signals. Figure 6 shows a theoretical example, in which we assumed a linear interaction between canal and otolith signals. The gain of the canal signal was assumed to be 0.25. The time constant was set to 3.7 s (Seidman and Leigh 1989). For the otolith signal, we assumed a static gain of 0.1; “static” means that the eyes counterroll as a function of eye position, independent of frequency. Hence, in Laplace notation, canal-only (C only) and combined canal-otolith (C&O) stimulation are written:

$$C \text{ only: } \frac{g_1 \tau_1 s}{\tau_1 s + 1}$$

$$C \& O: \frac{(g_1 \tau_1 + g_2 \tau_2) s + g_2}{\tau_1 s + 1}$$

The solid curves depict gain (Fig. 6A) and phase (Fig. 6B) during canal-only stimulation, while the dotted

Fig. 6A, B Model of linear interaction between canal and otolith signals. Details in text. **A** Gain, **B** phase. *Solid curves* Canal-only stimulation, *dotted curves* combined canal-otolith stimulation



curves correspond to the combined canal-otolith stimulation. As expected, the amount of gain enhancement is the same over all frequencies. The phase lead at low frequencies, however, is not cancelled by the otolith signal, but only reduced. This does not correspond to our experimental data, suggesting that canal-otolith interaction is complex. In fact, there seems to be no simple linear solution that could predict the results presented in this study (see also Angelaki and Hess 1996).

There is a major discrepancy between our data obtained in healthy humans and the data reported on rhesus monkeys with intact labyrinths (Angelaki and Hess 1996): in contrast to the humans, there was no otolith-mediated torsional gain increase in the rhesus monkeys. Whether this lack of gain increase is related to the fact that the torsional gain in rhesus monkeys is more than two times higher than in humans can only be conjectured: maybe there is no need for a torsional gain enhancement in the upright position if the gain is already rather high in the supine position. In a pilot study on two rhesus monkeys, however, Tremml (1992) described a small frequency-dependent increase of the torsional gain by otolith input, which was more pronounced at lower frequencies. Hence, there might still be a slight intraindividual gain increase in rhesus monkeys, which is not detected when comparing population averages. The cancellation of the phase lead at low frequencies is present in

both rhesus monkeys and humans; thus, in this respect, there is no difference between the two species.

Groen et al. (1999) investigated the contribution of the otolith organs to the torsional VOR using a similar experimental setup as in our study. The frequency that was tested by these authors, however, was rather restricted (0.05–0.4 Hz), only five subjects were tested, and torsional eye movements were recorded by videooculography, which is inferior to the dual search-coil technique in both its spatial and temporal resolution. These factors might explain some of the following discrepancies between our results and the results reported by Groen et al.:

1. These authors suggested that there is a linear relationship between torsional gain and the logarithm of the stimulus frequency in both upright and supine position. Our data clearly suggest, however, that the gain values between 0.3 and 1.0 Hz form a plateau in both positions (Fig. 4A).
2. Groen et al. “do not believe that the otoliths contribute significantly to improve the gain of the torsional VOR in humans”. This statement contrasts with the authors’ finding that the torsional gain was significantly increased by otolith input at all frequencies tested, which is perfectly in line with our data.
3. The authors report an increase in phase lead with increasing stimulus frequency above 0.1 Hz in both

supine and upright positions. Furthermore, they found only a reduction, not a cancellation, of the phase lead in the upright position. These phase data differ widely from the curves obtained in rhesus monkeys (Angelaki and Hess 1996) and the curves from our study on healthy humans. Here, the phase lead in the supine position increased with decreasing frequency below 0.3 Hz; this phase lead was cancelled in the upright position.

Another study that compared the torsional vestibulo-ocular reflex during passive oscillation in supine and upright position was restricted to a single frequency of 0.3 Hz, but used dual search coils to measure three-dimensional eye position (Tweed et al. 1994): there was only a small, but statistically not significant increase in torsional gain due to otolith input. This might be due to the different analytical method for computing the gain values used by the authors.

In a short communication on the dynamics of the torsional VOR in the upright position over an even wider frequency range than in our study, Peterka (1992) described a monotonic gain increase with increasing frequency. Since, in this experiment, the amplitude was not proportionally decreased as frequency increased, the peak velocity of the stimulus became larger at higher frequencies. At a fixed frequency of 0.2, the author observed an increase of the VOR gain with increasing stimulus amplitude. Therefore, the monotonic gain increase observed in this study is probably a result of the nonlinear pathway of the VOR, which leads to a frequency- and velocity-dependent nonlinearity of gains, as shown in squirrel monkeys (Minor et al. 1999). In our study, peak velocity was kept below 40°/s at all frequencies tested, which is approximately in the range of the linear VOR pathway and, hence, explains the gain plateau at higher frequencies (≥ 0.3 Hz).

What could be the advantage of the otolith-induced changes on the torsional VOR, which we observed in this study? Both the frequency-independent gain enhancement and the cancellation of the low-frequency phase lead decrease the torsional slip of the visual world on the retina in the upright position. This function might be especially important during locomotion. Independent of the physiological relevance of reducing torsional reti-

nal slip, the comparison of the torsional VOR in supine and upright positions allows otolith function in healthy subjects and patients to be quantified.

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