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Torsional vestibulo-ocular reflex during whole-body oscillation in the upright and the supine position: II. Responses in patients after vestibular neuritis

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Abstract. In a recent study we demonstrated that otolith input modifies the torsional angular vestibulo-ocular reflex (torVOR) of healthy human subjects: Compared to turntable oscillations in supine position, oscillations in upright position increased the gain of torVOR by 0.1 and cancelled the phase lead originating from low-frequency semicircular canal signals. We asked whether these otolith-related changes of torVOR are still present in patients after vestibular neuritis (VN). Eight patients were sinusoidally oscillated about their naso-occipital axis in supine (canal-only stimulation) and upright (canal-and-otolith stimulation) position. Three-dimensional eye movements were recorded with dual search coils. The patients showed similar otolith-related gain and phase changes of the torVOR as healthy subjects: the gain increased by about 0.1 ($p < 0.05$) and the low-frequency phase lead from semicircular canal signals was abolished. These results indicate that otolith function after VN is still sufficient to interact with semicircular canal signals to optimize torsional gaze stabilization when the head is upright.

1. Introduction

Vestibular neuritis (VN) is a sudden unilateral deficit of vestibular function without auditory symptoms. Often the posterior semicircular canal function is spared [7]. The inflammation of the vestibular nerve or labyrinth is probably of viral origin [17], and most likely consists of a reactivitation of latent herpes virus type I [1–3,9,18].

After VN, the gain of the torsional vestibulo-ocular reflex (VOR) for roll head impulses toward the affected side is reduced in the acute phase, but becomes normal again over time. Average gains for horizontal head impulses towards the affected side and head impulses in vertical directions (up or down), however, remain subnormal [14]. Based on these results, we hypothesized that the torsional gain recovery was due to a compensation mechanism by way of spared ipsilateral otolith afferents. Alternatively the normalization of the torsional VOR could be the result of a compensatory functional re-organization of afferents from the contralateral utricle, a mechanism that was suggested by Lempert et al. [11]: Off-directional responses from lateral hair cells of the remaining utricle could take over the function of the deficient utricle. The presumptions of ipsilateral (spared fibres) or contralateral (intact utricle) otolith compensation was further corroborated by the finding that, in most patients, the static ocular counterroll, which was unilaterally reduced in the acute phase of vestibular neuritis, also became normal in the chronic phase [14].

Data from the head impulse testing in the patients after VN did not allow quantifying the amount of otolith-

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related recovery of the torsional VOR, because – for technical reasons – it was not possible to apply torsional head impulses with the same dynamical properties in both upright and supine positions. In fact, the contribution of the otolith input during high-frequency torsional VOR in upright human subjects is unknown. For medium- and low-frequency torsional stimuli, however, one can utilize a motor-driven turntable that allows rotating subjects in supine (canal-only stimulation) and upright (combined canal-and-otolith stimulation) position with identical dynamical parameters. By comparing the torsional gain and phase values between supine and upright position, the contribution of the otoliths can directly be determined [16]. These data show that, in healthy subjects, the torsional VOR gain during canal-only stimulation (earth-vertical axis) was significantly lower than the gain obtained during combined canal-and-otolith stimulation (earth-horizontal axis) between 0.05 and 1 Hz. During the earth-horizontal axis stimulation, the phase remained always around zero, thus the phase lead originating from low-frequency semicircular canal signals was abolished by the otolith signals. In patients after VN, we expected that, in analogy to the findings obtained with head impulses and static head roll, the otolith-mediated enhancement of torsional VOR in upright position would still be effective in the chronic state, despite a possible transient impairement in the acute phase.

2. Material and methods

2.1. Subjects

Eight patients (3 female, 5 male; 29–59 years old) with clinically diagnosed vestibular neuritis participated in this study. The clinical examination was performed by experienced neuro-otologists, and the clinical diagnosis was based on the patients' history and the bedside testing. The unilateral peripheral vestibular hypofunction was verified by dual search-coil head impulse testing [15]. All patients showed an abnormal head impulse test to the affected side (inclusion criteria).

Patients were tested one month to one year after the onset of vestibular symptoms [7 weeks, 1, 1, 3, 8, 8, 12 and 12 month(s)]. The control group consisted of the same ten healthy subjects (3 male, 7 female; 25–56 years old) that were described in a previous study [16]. 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.

2.2. Vestibular stimulation

The subjects were oscillated about the torsional (= naso-occipital) axis of the head in upright and supine position in total darkness on a motor-driven turntable with three servo-controlled motor-driven axes (prototype built by Acutronic, Switzerland). The head was restrained with an individually adjusted 3-point-mask (Sinmed BV, The Netherlands). This mask consists of a thermoplastic material (Posicast$^{\mathrm{TM}}$) that can be molded to the contour of the head after warming up in a water bath. With this device the center of the intraaural line was positioned at the intersection of the three axes of the turntable. The subjects were secured by safety belts. Evacuation pillows minimized movements of the body. Special care was taken to keep the subject alert by repeated encouragement and keeping the trials short with breaks in-between. Eye movements were monitored in three dimensions with dual search coils. While the healthy subjects were tested at six different frequencies (0.05, 0.1, 0.3, 0.5, 0.7, and 1.0 Hz), only four frequencies (0.05, 0.3, 0.5, and 0.7) were applied to the patients to reduce the examination time and strain. The corresponding amplitudes were 40, 20, 8, 4 and 2 °.

2.3. Eye movement recording

Eye movements were recorded monocularly with dual scleral search coils (Skalar Instruments, Delft, Netherlands) [5,6,13], after anesthetizing the conjunctiva with Oxybuprocaine 0.4%. The head was surrounded by a chair-fixed coil frame (side length 0.5 m) that produced three orthogonal magnetic fields with frequencies of 42.6, 55.5, and 83.3 kHz (Remmel type system, modified by A. Lasker, Baltimore) [12]. For calibration, subjects were asked to fix on a light dot straight ahead at the beginning of each trial. Details of the calibration procedure can be found elsewhere [19]. 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.

2.4. Data analysis

Collected data were further processed on a PC using interactive programs written in MATLAB$^{\mathrm{TM}}$. 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

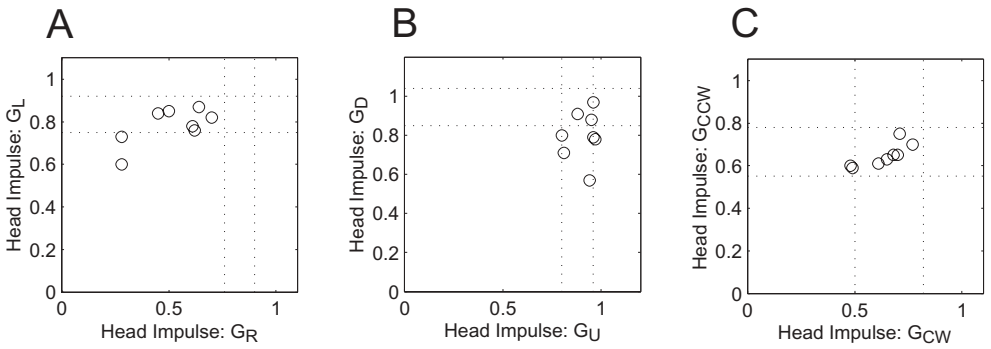

Fig. 1. Gain values of the VOR at maximal head velocity during rightward (G_R) and leftward (G_L) horizontal head impulses (A), vertical head impulses (B) in the upright (G_U) and downward (G_D) direction and torsional head impulses (C) during clockwise (G_{CW}) and counterclockwise (G_{CCW}) head rotation in the eight patients tested. The dotted lines represent the range of normal gain values of the Zurich lab (average $\pm$ 2 SD from ten healthy subjects).

derivative (de) using the formula

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

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 a standard deviation of 20°/s, eye velocity signals during quick phases were discarded. Median cycles were also determined for chair velocity traces.

The following sine function (y) was fitted to the median cycles of eye and chair velocity as function of time (t):

$$y = A \cdot \sin(2 \cdot p \cdot \omega \cdot t + \varphi) + c$$

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), the phase (φ), and the offset (c) were iteratively optimized by a nonlinear least-square algorithm based on the Levenberg-Marquardt method (Matlab-function lsqnonlin.m).

2.5. Quantitative head-impulse testing

Dual search coils were also used to record three-dimensional eye and head movements during head impulse testing. One search coil was placed on the right eye around the cornea; the other was tightly fixed on the forehead with adhesive tape. During experiments, subjects were seated with the head upright inside the magnetic frame (side length: 1.4 m). Care was taken to position the center of the interpupillary line in the center of the magnetic frame. While the subject was fixing a light dot 1.24 m straight ahead, horizontal, vertical, and torsional head impulses (amplitude: 15–25°; duration: 150–200 ms; peak velocity: $\sim$ 250 °/s; peak acceleration $\sim$ 10'000 °/s^2) were applied by the investigator standing behind the subject. The starting position of the head was always well inside a range of 5°. Directions of impulses were pseudo-randomly intermingled; five head rotations were applied to each side. Subjects were instructed to keep gaze on the light dot straight ahead.

2.6. Side of vestibular lesion

Among the eight patients with vestibular neuritis 4 patients were affected on the right and 4 on the left side. For convenience, all left-sided lesions were mirrored to the right side, thus in these patients, data obtained from vestibular stimulations in the horizontal and torsional, but not vertical, planes were multiplied by (-1).

3. Results

Figure 1 characterizes the high-frequency performance of the vestibulo-ocular reflex (VOR) in the patients. The three panels depict the results of the head impulse test in the horizontal (Fig. 1A), vertical (Fig. 1B), and torsional (Fig. 1C) movement planes.

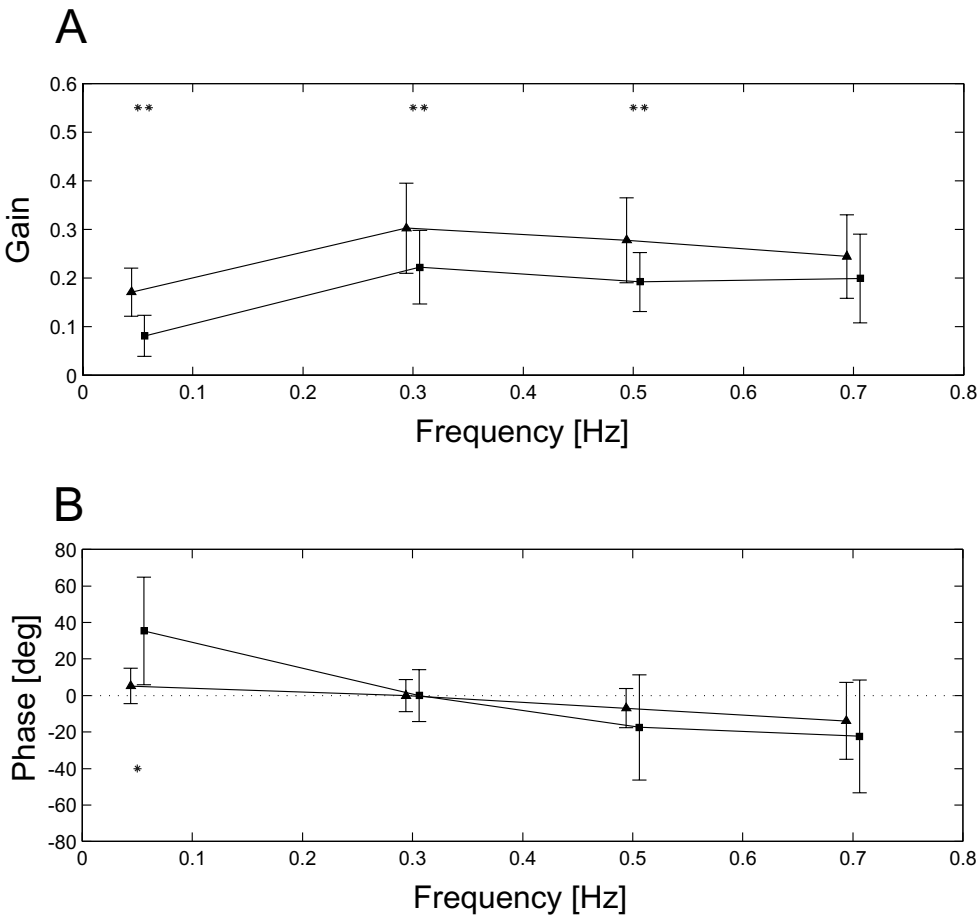

Fig. 2. Average gain (A) and phase (B) values of the torsional VOR in the supine (squares) and upright (triangles) condition in the eight patients tested. Errorbars indicate $\pm$ 1 SD. Asterisks denote the significance level of the two-tailed paired t-test between the supine and upright data (*: $p < 0.05$, **: $p < 0.01$). Symbols for the different head orientations are offset in frequency for clarity.

Symbols denote the average gains of the vestibulo-ocular reflex to both sides at maximal head velocity. The dashed lines contain the normal values (average $+/-$ 2 SD) obtained from healthy subjects ($N = 10$) that were measured in the identical experimental setup.

According to the inclusion criteria, all patients showed a gain reduction of the horizontal vestibulo-ocular reflex during head impulses to the affected (right) side (Fig. 1A). The horizontal gains to the contralateral side were within normal limits, except in two patients. Decreased vertical gains were only present in the downward (5 of 8 patients), but not in the upward direction (Fig. 1B). The gains of the vestibulo-ocular reflex during roll head impulses were nearly symmetrical and within the normal range, except in two patients (Fig. 1C). This pattern of gain reductions during three-dimensional head impulse testing agreed with a previous study on a different population of patients after vestibular neuritis [14]. Hence, the population included in the present study appeared to be typical.

Figure 2 summarizes the gain (Fig. 2A) and phase (Fig. 2B) values of the torsional VOR velocity during turntable oscillations at four different frequencies (0.05, 0.3, 0.5, 0.7 Hz) in the 8 patients. Averages of the gains are shown in the supine (squares) and in the upright (triangles) positions (errorbars: $\pm$ 1 SD). Two-tailed paired t-tests between the supine and upright data were performed (*: $p < 0.05$; **: $p < 0.01$).

At frequencies of 0.05 Hz, both the gains in supine (g_s) and upright (g_u) position were smallest (Fig. 2A). At higher frequencies ($>$ 0.3 Hz), the gain values did not further increase, forming a plateau (supine: $g_s \approx 0.2$; upright: $g_u \approx 0.3$). Except at 0.7 Hz, the torsional gain was significantly higher in upright than in supine body position. The null hypothesis, however, that the amount of the increase in gain by the otolith input did

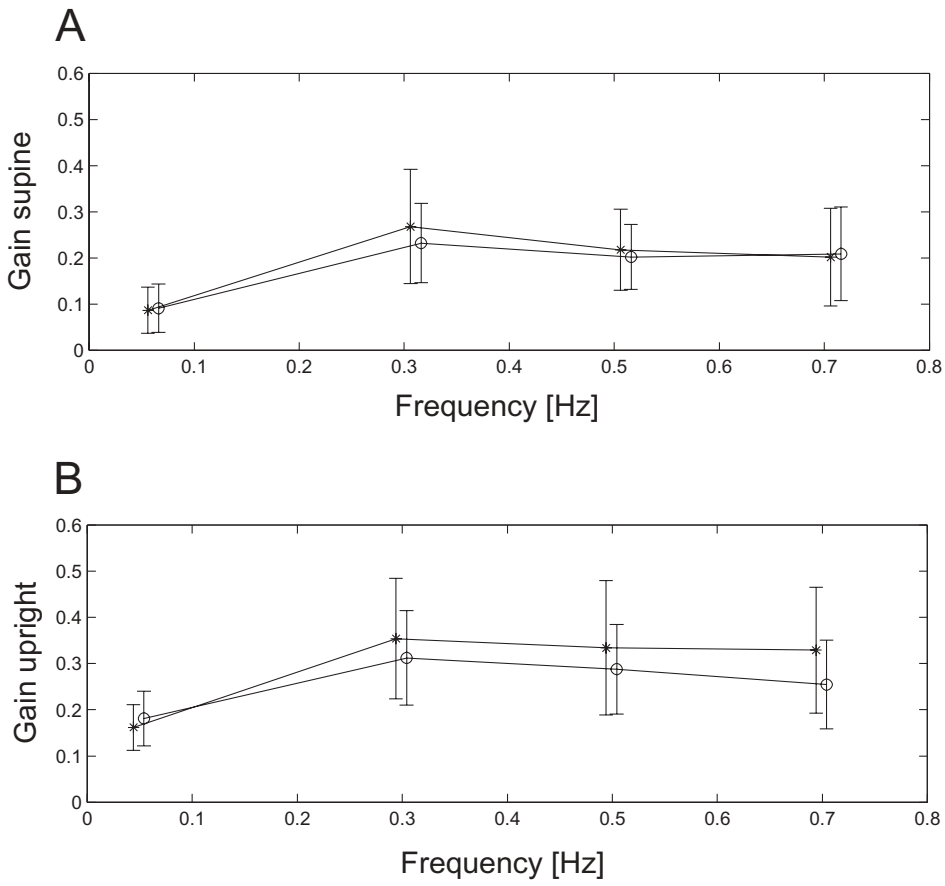

Fig. 3. Average gain values of the torsional VOR in the supine (A) and upright (B) position in the patients (circles) and healthy subjects (asterisks). The error bars indicate $+/-$ 1 SD.

not differ between the four frequencies tested could not be rejected in the two-way analysis of variance ($p = 0.8171$). The grand average of gain increase in the patients was 0.085 ± 0.021 SD.

In supine position, there was a phase lead of almost 40° at 0.05 Hz (Fig. 2B). This contrasts to the phase values in upright position, which showed practically no phase lead at this frequency. Above 0.3 Hz, there was a tendency for an increasing phase lag. This phase lag was more pronounced in supine than in upright position. The phase differences, however, between supine and upright position were only significant at 0.05 Hz.

Figure 3 compares the gain values of the patients (circles) in supine (Fig. 3A) and upright (Fig. 3B) position with the values obtained in the control group (asterisks) of 10 healthy subjects. For both body positions there were no significant differences between the patients and the healthy subjects at all frequencies tested (t-test and Wilcoxon signed-rank test).

Figure 4 compares the phase values of the patients (circles) in supine (Fig. 4A) and upright (Fig. 4B) position with the values obtained in the control group (asterisks). In contrast to the control group, patients tended to have a phase lag at frequencies above 0.3 Hz during supine (Fig. 4A) and – to a lesser degree – during upright (Fig. 4B) stimulation. Note, however, that the phase differences between patients and healthy subjects were not significant at all frequencies tested in both body positions (t-test). A cancellation of the phase lead at 0.05 Hz in upright position (Fig. 4B) was observed in both the patients and the healthy subjects.

The average offsets (not shown here) in both body positions were not significantly different between the two groups at all frequencies tested.

4. Discussion

The aim of this study was to assess the effect of vestibular neuritis (VN) on the low- and medium-

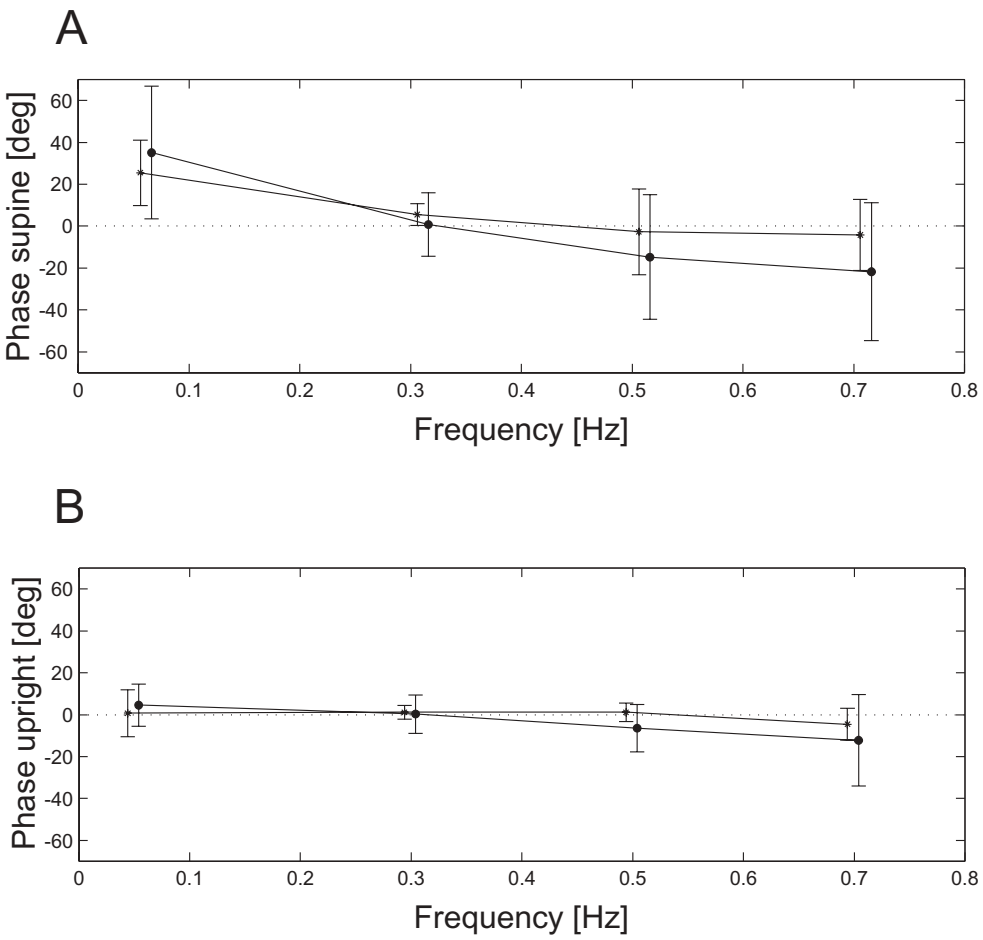

Fig. 4. Average phase values of the torsional VOR in the supine (A) and upright (B) position in the patients (circles) and healthy subjects (asterisks). The error bars indicate $+/-$ 1 SD.

frequency torsional vestibulo-ocular reflex (torVOR) with (oscillation in upright body position) and without (oscillation in supine body position) otolith input. Patients with unilateral vestibular hypofunction were tested one month to one year after VN. During turntable oscillations in both supine and upright body positions, the average gain of the torsional VOR was not significantly different between the patients and the healthy subjects at all frequencies tested (0.05, 0.3, 0.5, 0.7), although gains of the patients were below the average gains of the healthy subjects. This non-significant decrease could be due to a permanent, but small effect of VN on the torsional VOR. Without a paired comparison between prelesional (not available in this study) and postlesional data we cannot exclude significant intraindividual gain decreases of torsional VOR.

The main finding of this study was that, in the patients with unilateral vestibular hypofunction after VN, the otolith-related gain enhancement of the torsional VOR was still present and of a similar magnitude (about 0.1) as in healthy subjects. Similarly, the canal-related low-frequency phase lead was effectively cancelled by the otolith input. Compared to the group of healthy subjects, however, the group of patients, showed a tendency for a steeper decrease of the low-frequency phase lead with rising frequencies. In the patients, the low-frequency phase lead turned into a phase lag earlier (already above 0.3 Hz) and was more pronounced than in healthy subjects. This phase lag, which was present in both supine and upright body positions, can be predicted from a reduction of the velocity storage time constant of the torsional VOR, if modeled with both a high-pass and a low-pass filter.

Our data corroborate recovery of otolith function after vestibular neuritis. For high-acceleration VOR, earlier investigations in patients with acute and chronic

unilateral vestibular hypofunction after VN already showed a normalization of the initially reduced ipsitorsional gain during head impulses in upright body position, while a downward gain reduction, indicating a hypofunction of anterior canal signals, was still present [14]. In addition, at the very low end of frequencies, i.e. during static head tilt, recovery of otolith function after vestibular neuritis could be demonstrated by the regained symmetry of ocular counterroll.

In our study, we used whole-body roll oscillations, which exclude the possibility that the normalization of the torsional VOR is due to an upregulation of the cervico-ocular reflex. Thus this gain normalization can only be otolith-mediated. Two mechanism of otolith recovery are conceivable: (1) Otolith receptors or afferents are partly spared by the vestibular neuritis, hence the remaining fibers can still be used to re-install otolith symmetry by central adaptation. (2) The contralateral utricle is functionally depolarized such that off-directional responses from lateral hair cells can be used for compensation [11]. Presently, no data are available to decide between the two hypotheses.

In conclusion, the gain and phase of the torsional VOR in chronic patients after vestibular neuritis is similar to healthy subjects, probably due to otolith recovery after the acute phase. This might explain why, in general, there is a rapid improvement of postural side-to-side stability in patients despite the often permanent reduction of high-acceleration semicircular canal functions on the side affected by the vestibular neuritis.

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