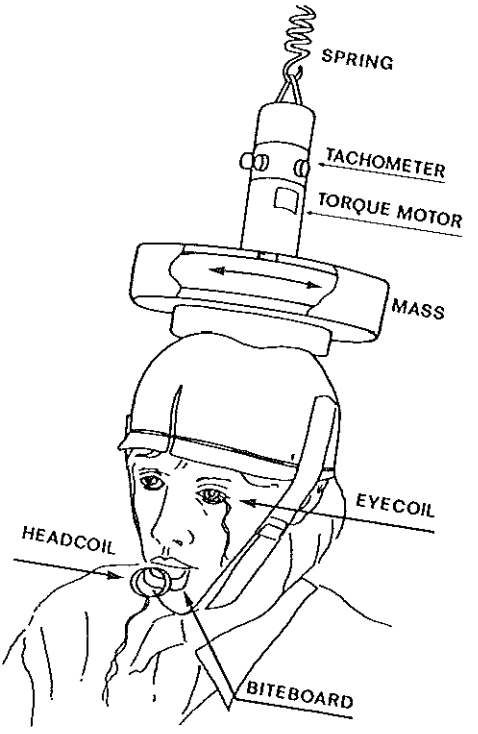
THE HUMAN VESTIBULO-OCULAR REFLEX (VOR) EVALUATED WITH A REACTIVE TORQUE HELMET



THE HUMAN VESTIBULO-OCULAR REFLEX (VOR) EVALUATED WITH A REACTIVE TORQUE HELMET

DE VESTIBULO-OCULAIRE REFLEX VAN DE MENS GEMETEN MET EEN REACTIEVE TORQUE-HELM

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR AAN DE ERASMUS UNIVERSITEIT ROTTERDAM OP GEZAG VAN RECTOR MAGNIFICUS

PROF. DR P.W.C. AKKERMANS M.A.

EN VOLGENS BESLUIT VAN HET COLLEGE VOOR PROMOTIES. DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP

WOENSDAG 29 JANUARI 1997 OM 15.45 UUR.

DOOR

SYLVIA TABAK

GEBOREN TE ROTTERDAM

PROMOTIECOMMISSIE:

PROMOTOR:	PROF. DR H. COLLEWIJN
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	PROF. DR C.J. ERKELENS
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Aan Frank
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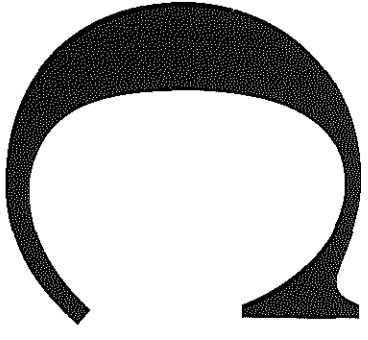

Contents

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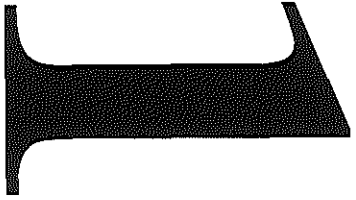

General introduction

1.1 Introduction

The vestibulo-ocular reflex (VOR) generates eye rotations that compensate for head movements. Head movements include rotations and translations (linear displacements). Linear acceleration during translational movement, as well as the gravitational acceleration, signalling head orientation is sensed by the otolith organs. For the image of a distant object to remain upon the fovea of the retina during head rotation, an equal but opposite eye rotation must be generated. This ocular reflex, which originates in the semicircular canals, probably evolved early in vertebrate evolution, since it serves the important function of allowing animals to see and move at the same time. It was so successful that it has changed very little since its origin, and the same basic design is found in widely divergent species of birds, mammals and fish.

It is possible to divide species roughly into two broad oculomotor categories depending on whether or not they have a fovea. This term is used here to denote any specialized region of the retina with such a high photoreceptor density that it is used preferentially for seeing. Afoveate animals are not very concerned with the position per se of images on the retina, and most of their subsystems, such as the vestibulo-ocular reflex (VOR), cervico-ocular reflex (COR) and optokinetic reflex (OKN), simply try to prevent the images of the visual surround from slipping about on the retina. Higher mammals, like humans, have developed a fovea and have added other eye movement systems like the pursuit, vergence, and saccadic systems. These eye movements are designed to hold or bring selected images on the fovea. The stabilization of gaze appears to be necessary for maintaining good visual acuity. In man, visual acuity is degraded when retinal image velocities exceed 2.5 deg/s (Westheimer and Mckee 1975, Murphy 1978).

The greatest potential source of image slip in daily life is self-rotation. During locomotion, head rotations can reach frequencies in the range of 0.5 to 5.0 Hz (Grossman et al. 1988, King et al. 1992); the highest-frequency head rotations are in the pitch (vertical) plane. One important property of the VOR making it possible for the brain to generate eye movements to compensate for such high-frequency head rotations is its small latency of action of less than 16 ms (Lisberger 1984, Maas et al. 1989, Gauthier and Vercher 1990). This is much below the latency of onset of visually mediated eye movements such as smooth pursuit, the smallest values being about 75 msec (Gellman et al. 1990). Another important feature of the smooth pursuit system is

the rapid degradation of its effectiveness at target frequencies above 0.5 Hz (Martins et al. 1985). Furthermore, the head perturbations that occur during locomotion are characterized by randomness (Grossman et al. 1989); this property will limit the brain's ability to generate eye movements in anticipation of these head movements.

1.2 Why investigate the human VOR at high frequencies?

The efficacy of the compensatory response can be characterized by assessing two features of the stimulus/response relationship. One is the gain, or amplitude ratio, between eye movement and head movement, which should be unity for perfect compensation. The other is the phase relationship which measures the temporal shift between stimulus and response; this should be zero for compensation. However, measurements of the VOR have conventionally been performed in darkness in order to isolate the reflex from visually-mediated eye movements. In these studies the frequencies of oscillation were usually below 0.5 Hz and the gain of the response was highly variable and generally less then unity (see Collewijn 1989 for a review). Contrary, the gain of the VOR in the horizontal and vertical planes during walking is close to unity and the phase differs little from zero (Grossman et al. 1989); this presumably more physiological gain is at least 20 % greater than values typically reported on the basis of conventional testing carried out in clinical laboratories. This discrepancy is probably due to the conditions of testing. A major factor is that the rotational stimuli applied routine clinical testing of the VOR have much lower frequencies than those occurring during locomotion (Mathog 1972, Fischer and Oosterhuis 1990). This low frequency range appears to be inadequate since the performance of the vestibulo-ocular system is far from optimal in this frequency range (Meiry 1971, Baarsma and Collewijn 1974, Barr et al. 1976). Thus, it seems that the VOR only performs at the level required for good vision during test conditions that correspond to natural activities; at these higher frequencies of head rotations, other mechanisms (visual tracking) that generate compensatory eye movements are comparatively inadequate.

Many authors have shown that the VOR gain can be strongly influenced by the visual system during low frequencies of head movements (Barnes et al. 1978, Benson and Barnes 1978, Hydén et al. 1982, Barnes and Edge 1984, Baloh et al. 1992). Even when there is no visual information (total darkness), it is known that attempted fixation of an imaginary visual target in darkness influences the VOR at lower frequencies (Barr et al.

1976). By measuring eye movements at higher frequencies, it should be possible to assess the VOR in isolation since the range of contamination by visual tracking reflexes would be surpassed. Such measurements have not been possible in the past due to torque limitations of rotating motors combined with the large total mass of rotating chair and body of the patient.

One technique that has been used to apply higher-frequencies stimuli is for the subject to actively generate head movements (Tomlinson et al. 1980, Fineberg et al. 1987, Grossman and Leigh 1990, O'Leary and Davis 1990, O'Leary et al. 1991). Unfortunately, this technique also has limitations. Normal subjects can generate anticipatory eye movements to compensate for active head rotation (Vercher and Gauthier 1990), and patients who lose vestibular function can use predictive mechanisms to generate compensatory eye movements (Kasai and Zee 1978, Bronstein and Hood 1987, Halmagyi and Curthoys 1987). These findings raise questions about the reliability of studies using rotational stimuli applied in a predictable manner, especially active, self-generated head movements (Collewijn et al. 1983, Fineberg et al. 1987). Another disadvantage is that patients with vestibular symptoms like dizziness or nausea are not easily inclined to shake their head very rapidly.

A more reliable method for testing the VOR is to apply high-frequency, passive, sinusoidal head oscillations or passive, rapid step displacements of the head. Due to mechanical limitations of power, as well as safety considerations, it is not feasible to apply whole-body movements to humans at frequencies exceeding 5 Hz (Kasteel-Van Linge and Maas, 1990). However, we developed a method to move the human head passively at frequencies up to 20 Hz by means of a reactive torque helmet. This stimulation technique, in combination with the accurate and precise measurement technique using sensor coils in an a.c. magnetic field for the recording of eye and head movements, forms the basis for the experiments described in this thesis.

1.3 Short outline of the present thesis

The reactive torque helmet technique is presented in chapter 2. Vestibulo-ocular responses to oscillatory and step movements of the head are described for a first group of normal subjects and a small number of patients with clinically diagnosed bilateral vestibular defects. The feasibility and usefulness of the technique are demonstrated.

Chapter 3 deals extensively with the abnormalities of vestibulo-ocular responses in two groups of patients, compared to a normal control group. The largest and most uniform patient group consists of subjects with a total unilateral vestibular defect after surgery for acoustic neuroma. A second, smaller and less uniform group contains patients with bilateral vestibular defects. Characteristic findings for each of these groups (and some subgroups) are described.

The effects of long-standing vestibular defects on the setting of the subjective vertical are outlined in chapter 4. It is shown that unilateral vestibular defects often lead to - apparently permanent- tilt of the subjective vertical towards the defective side.

Chapter 5 presents a series of experiments addressing modulation of the vestibulo-ocular responses during the execution of gaze-saccades. Probing of the VOR with oscillation or steps of the head, superimposed on the gaze-shifts, shows (partial) suppression of the VOR during the saccadic gaze-shifts, with a supra-normal period in the wake of the saccade.

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Human vestibulo-ocular responses to rapid, helmet-driven head movements

2.1 Abstract

High-frequency head rotations in the 2-20 Hz range and passive, unpredictable head acceleration impulses were produced by a new technique, based on a helmet with a torque-motor, oscillating a mass. Head and eye movements were recorded with magnetic sensor-coils in a homogeneous magnetic field, with the head unrestrained. To analyze the influence of the visual system on the vestibulo-ocular reflex (VOR) we measured in three conditions: 1) a stationary visual target; 2) darkness with the subject imagining the stationary target and 3) a head-fixed target. The results in 15 healthy subjects were highly consistent. At 2 Hz, VOR gain was near unity; above 2 Hz, VOR gain started to decrease, but this trend reversed beyond 8 Hz, where gain increased continuously toward 1.1 - 1.3 at 20 Hz. Phase lag increased with frequency, from a few degrees at 2 Hz to about 45 degrees at 20 Hz. Above 2 Hz, VOR gain was not significantly different for the 3 conditions. Head acceleration impulses produced a VOR with near-unity gain in both directions. We also tested three subjects with a clinically total bilateral loss of labyrinthine functions. These labyrinthine defective subjects showed, in comparison to the normal subjects, strikingly lower gains and much longer delays of the VOR during sinusoidal and step-like head movements. The results suggest that our new driven-helmet technique is an effective, safe and convenient device, enabling the assessment of the VOR at relatively high frequencies where visual and mental influences are minimized.

2.2 Introduction

The vestibulo-ocular reflex has evolved in order to guarantee a clear and stable view of the environment during activities that entail head movements. Normally (except for close targets) eye movement should be equal but opposite to head movement, i.e., gain (the ratio of eye angular motion to head angular motion) should be unity. Ideally, the phase of the compensatory eye movement with respect to the head movement should be within a few degrees of exact compensation, i.e. close to 180 deg. For convenience, this ideal phase relation for the VOR is usually designated as zero phase.

In daily life the head undergoes rotations, especially in the sagittal plane, that have frequencies of up to 5 Hz during locomotion and even higher during running

(Grossman et al. 1988; Pozzo et al. 1990; Leigh et al. 1992). Despite the relatively high frequency of these perturbations, peak velocities do usually not exceed about 200 deg/s, which is within the operating range of the VOR (Pulaski et al. 1981). The very important role of the VOR in everyday life becomes apparent from reports of patients who have lost the function of their vestibular labyrinths. Most of these patients have head-movement dependent oscillopsia (J.C. 1952).

The contribution of both the visual and the vestibular system to gaze stability has been the subject of extensive research. Efficient visual pursuit of a moving target has generally been found at frequencies not higher than 1-2 Hz. Martins et al. (1985), using stimuli with small amplitudes and recording with high resolution, found that the effectiveness of smooth pursuit already declined at target frequencies above 0.5 Hz. At frequencies above 3 Hz, smooth pursuit was totally ineffective in reducing retinal image speed. Thus, gaze stability during head movements in the higher natural frequency range must depend critically on the vestibular component. It would, therefore, be desirable to test VOR function especially in this high frequency range, but in the routine clinical setting this has not been achieved until now. The caloric test is, at best, qualitative and has no definable input/output relation. Even in normal subjects the results of this test are highly variable due to anatomical factors. A more quantitative, clinically used, test is the measurement of eye movements in subjects seated on a rotating chair undergoing low-frequency sinusoidal angular oscillation in the dark. One of the problems of the use of these slowly swinging movements is, that the results are strongly influenced by the mental state of the subject (attention, instructions etc.), as first described by Barr et al. (1976).

Attempts to assess the human VOR at higher frequencies have remained fairly scarce and mostly limited to normal subjects. Skavenski et al. (1979) generated whole body rotations up to 3 Hz and head-on-body oscillations up to 15 Hz, using a helmet to which a modified loudspeaker was attached. Vibrations of the cone of the speaker, which was loaded with extra mass, moved the helmet by reaction forces; neither helmet nor head were rigidly connected to any other structure. Mean gain in total darkness was in the range of 0.25-0.75 over the entire frequency range. Gain values that were consistently higher in the light than in the dark, indicating an influence of the visual system on the compensatory eye movements, were found only below 3 Hz. Gauthier et al. (1984) generated horizontal head rotations by connecting the head through a bite-board to an earth-fixed vibrator. In the range of 0.5-30 Hz, they found a gain near unity at 2 Hz, above which gain started to decrease. They reported a gain of 0.8 between 4

and 6 Hz, regardless of visual information. Beyond 8 Hz the trend of the gain curve reversed and gain increased toward 3-4 at 25-30 Hz. Stott (1984), using a somewhat similar head-oscillating technique in vertical direction, reported a gradual increase in gain with a peak value of 3.0 at 70 Hz (range 1.2-4.9) for a near target condition. The peak gain value for a target viewed at infinity was 2.1, also at 70 Hz. Clearly, motion applied to the head alone, such as described above, can be realized at comparatively high frequencies. For passive whole-body rotations, the practical upper limit is probably about 5 Hz, which was reached by Kasteel-van Linge et al. (1990). At 5 Hz the latter authors found a gain of about 0.9, independent of visual conditions.

An alternative method for eliciting relatively fast head-oscillations is the use of active, voluntary head-shaking by the subject, also known as the vestibular autorotation test (VAT). Tomlinson et al. (1980), Fineberg et al. (1987) and O'Leary et al. (1990, 1991) described the use of this method in a frequency range up to 6 Hz. Eye movements were recorded with electro-oculography (EOG) and head angular velocity was recorded with an angular rate sensor or a potentiometer attached to an adjustable light-weight headband or a biteboard. Tomlinson et al. (1980) reported a near-unity gain (0.9-1.1) at all but the highest frequencies (5-6 Hz), at which a small decrease in gain was seen. Phase was constant at zero within EOG resolution. Fineberg et al. (1987) and O'Leary et al. (1990, 1991) found gains slightly below unity (0.9) for the lower frequencies, decreasing with the increase in frequency to 0.7 at 6 Hz. Mean phase lags increased from about 6 deg at 2 Hz to 10 to 14 deg at 6 Hz.

In addition to high frequency, sinusoidal head oscillations, unexpected step displacements of the head can be used to elicit the VOR. Such head movements have, in principle, a frequency spectrum that contains high frequencies. Halmagyi et al. (1990) applied this kind of stimulus by manually displacing a subject's head. They found reproducible VOR responses (in darkness) which were evidently asymmetrical in subjects with a unilateral vestibular neurectomy, even one year after the lesion.

We developed a helmet containing a motor-driven mass, which applied a reactive torque to the head when actuated, without any rigid attachment to other structures. In combination with search-coil recording techniques, this device enabled us to measure the VOR reliably for oscillations in the range 2-20 Hz and for step-displacements.

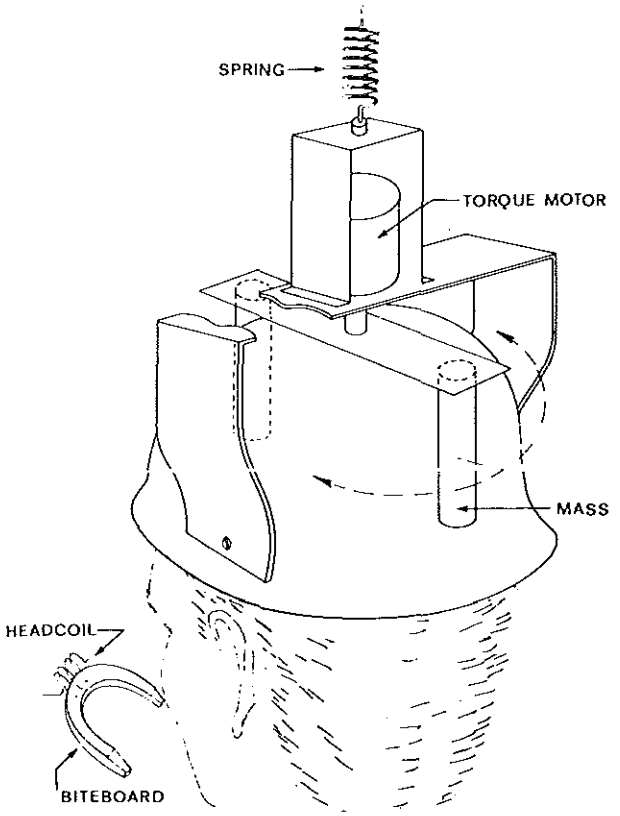

Fig. 1 Schematic diagram of the torque-driven helmet as used in the present experiments.

2.3 Materials and methods

2.3.1 Stimulation technique

Passive, horizontal head rotations were generated by a helmet, placed on the subject's head, with on top a torque motor. The helmet was a simple, standard protective device consisting of a hard plastic outer layer, connected to a softer internal construction of plastic bands that could be adjusted to fit the head snugly. The torque motor (print motor, type pmed-12 CBL, D.C.I. 2V, 5A, 2100 R/W, 26W) was rigidly mounted on the outer helmet by an aluminum frame. This motor rotated an eccentric mass (2 x 300 g, each at 11.5 cm eccentricity; moment of inertia 39.68 x 10^3 g.cm^2); rotation was unimpeded and could continue through any number of revolutions (for details see Fig. 1). The weight of the helmet with attachments was balanced by suspending it from a spring to the ceiling; this left the subjects free to translate and rotate their head in the sagittal and horizontal plane. The torque motor was powered by a driver (Soprel/Milano Transdriver (I) DB 425 W/R), which received a sinusoidally or stepwise changing voltage as the control signal. Control signals were generated by a DEC PDP 11/73 computer in conjunction with the data-acquisition protocol. The applied frequencies could be easily changed with the aid of the computer. The torque motor could produce passive horizontal head oscillations up till frequencies of 20-30 Hz but the maximum head amplitudes that could be achieved decreased with increasing head frequency to, typically, about 0.1-0.2 deg at 20 Hz (Fig. 2). To avoid marginal signal-to-noise ratios, we did not extend our measurements beyond 20 Hz. Apart from these sinusoidal head movements, sudden, unexpected step displacements of the head with peak velocities of 100-200 deg/s and amplitudes of 10-50 deg were generated by applying voltage steps instead of sinusoids to the helmet driver. We reached maximum head accelerations between 700 and 1300 deg/s^2.

2.3.2 Recording technique

Horizontal rotations of the eye and the head were recorded with the scleral coil technique, relative to an earth-fixed, homogeneous magnetic field. The ocular sensor coils (Skalar, Delft) consisted of 9 turns of fine copper wire embedded in an annulus of silicone, molded to adhere to the eye by suction (Collewijn et al. 1975). To record the head movements, a second coil was firmly attached to a biteboard with an impression

of the teeth in dental impression material to ensure a firm connection between the skull and the head coil.

The sensor coils were connected to high quality lock-in amplifiers (Princeton Applied Research, model 5210) to obtain the horizontal positions, following Robinson's (1963) amplitude detection technique. The sensitivity of the eye and head coils was calibrated prior to every experimental session with a protractor. The system's resolution was better than one minute of arc.

The recordings should reflect only rotations and be invariant for any translations. To achieve this, the magnetic field was made homogeneous in strength and direction over a space including any possible head position, using the five-coils configuration first described by Rubens (1945; see Collewijn 1977).

2.3.3 Visual targets

In the *first* set of measurements we measured in three conditions: 1) visible, stationary target (LED, distance about 120 cm), 2) darkness, with the subject imagining the same, stationary target and 3) head-fixed target (light carbon fibre stick of 40 cm, attached to the biteboard, with at the end a LED).

The measurement of veridical VOR responses requires, in addition to invariance of the recording of *gaze, eye and head angles* for head translation (described above), also invariance of the viewed *angular direction of the target* for head translation (Rodenburg et al. 1987). The latter can be achieved by placing the target at optical infinity. As real infinity is difficult to realize in laboratory conditions, optical infinity was implemented by positioning the targets in the focal plane of a Fresnel lens (size 94 x 70 cm; focal length 118 cm) in the *second* set of measurements. The calibration device contained a sight in which a visual target, placed at optical infinity by the Fresnel lens, was exactly centered when all angular position and electric outputs were zero. By sliding the calibration device sideways along a ruler, it was confirmed that translation affected neither the angular viewing direction of the target nor the electric outputs of the recording system.

Based on the results in the first set of measurements, only two conditions were investigated further in the second set: 1) visible, earth fixed target; 2) darkness, with

the subject imagining the same target. To determine if the Fresnel lens significantly affected the VOR-gain, 9 out of the 15 normal subjects were measured in the same experimental session with and without the Fresnel lens.

2.3.4 Data processing

Each signal was digitized at 500 samples per second after anti-alias low-pass filtering at 125 Hz and stored into a DEC PDP 11/73. In off-line analysis saccades were removed from the eye signal and the signal was interpolated to a cumulative smooth eye-movement signal.

Eye-in-head position was computed by subtraction of head position from smooth gaze position. Bias and trend were removed from eye and head position signals and the data for each 8 s record were reduced by a factor 2 to 2048 samples, as appropriate for the subsequent transformation with a fast Fourier routine.

Gain and phase were then computed from the cross-and auto-spectral densities of the FFT signals. Because the energy was contained in several adjacent frequency bins, a Hanning window was used.

2.3.5 Subjects

We recorded 15 healthy subjects who had no known ocular or vestibular pathologies. The protocol was approved by the local Medical Ethics Committee and all subjects gave informed consent. We also measured three subjects with clinically almost total, bilateral loss of labyrinth-function after meningitis. Two of these labyrinthine-defective (LD) subjects were known to have received gentamycine for the treatment of the meningitis. These two subjects had severe disabilities in daily life. LD subject nr 1 (man, age 63) could not walk without support because of severe unsteadiness and had to move in a wheelchair. (LD subjects are usually not chairbound, indicating that this subject had additional problems in central vestibular pathways). LD subject 1 showed a bilateral loss of caloric responses, even after stimulation with ice water. LD subject 2 (woman, age 74) had oscillopsia, especially in the vertical direction, during walking. Only some sporadic nystagmus beats could be seen after caloric stimulation with ice water. LD subject 3 (woman, age 27) had meningitis in early childhood. She was

mildly unsteady while walking in darkness but experienced no vestibular symptoms otherwise. Data about her caloric responses were not available but in a clinical report it was stated that she did not show any responses during low-frequency rotation chair measurements.

2.3.6 Protocol

The subject was seated in the magnetic field, viewing the target binocularly and with the head in what was felt as the "natural central position". All experiments were conducted in complete darkness, except for the point target. Each of 5 sinusoidal head rotation frequencies (2, 4, 8, 14 and 20 Hz) was applied, in random order, 4 times in each of 3 target conditions. Consequently, there were 60 measurements (5x4x3), each lasting 8 s.

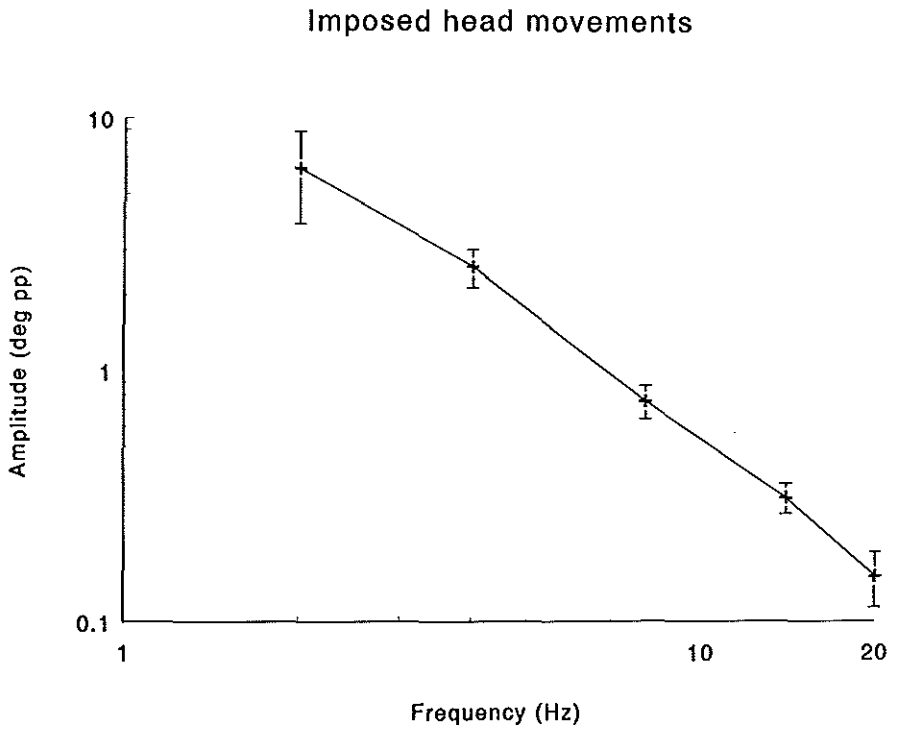

Fig. 2 Mean and SD of maximum head oscillatory peak-to-peak amplitudes achieved at different frequencies.

The visual target conditions were alternated in a fixed sequence. Horizontal step displacements of the head were applied in 4 measurements, each lasting 80 s, during which 20 head displacements in each direction (left and right) were generated. To reduce predictability, the interval between these head impulses was varied randomly between 1.3 and 2.3 s.

2.4 Results

2.4.1 Characteristics of induced oscillatory head movements

Fig. 2 shows the characteristics of the head movement amplitudes as a function of increasing frequency. Means and S.D. of peak-to-peak head excursions as a function of driving frequency are given for 14 subjects in log/log scales; in this format the relation is linear. At 20 Hz, peak-to-peak head amplitudes were only 0.1-0.2 deg (corresponding to peak accelerations of about 1500 deg/s^2), but these small amplitudes were well resolved in our recordings (see Fig. 3).[1]

2.4.2 Normal responses to sinusoidal oscillation

We first applied the sinusoidal head rotations to 7 normal subjects in three conditions: earth-fixed target, darkness and head-fixed target. Examples of representative recordings obtained are shown in Fig. 3 for the condition earth-fixed target. At 2 Hz, most subjects showed smooth compensatory eye motions with occasional anticompensatory saccades for all 3 conditions. With a visible target, most subjects saw a stable, punctiform target for head rotations below 4 Hz. At higher frequencies the target appeared elongated in the horizontal direction. From this first series of measurements it was established that a difference in performance between the 3 conditions occurred only at 2 Hz, where gain was near unity in darkness, slightly higher with the earth-fixed target and somewhat lower with the head-fixed target. At 4 Hz and higher frequencies, eye movements were identical for the 3 conditions. As our interest was mainly in this higher frequency range, and suppression of the VOR was not of

[1] In the next chapters the 25 W torque-motor was replaced by a 75 W torque motor to increase the amplitude of the head movements. Although this was successful for the lower frequencies (increase by a factor 2-3 for 2-8 Hz), the increase in amplitude at 14 and 20 Hz was only marginal.

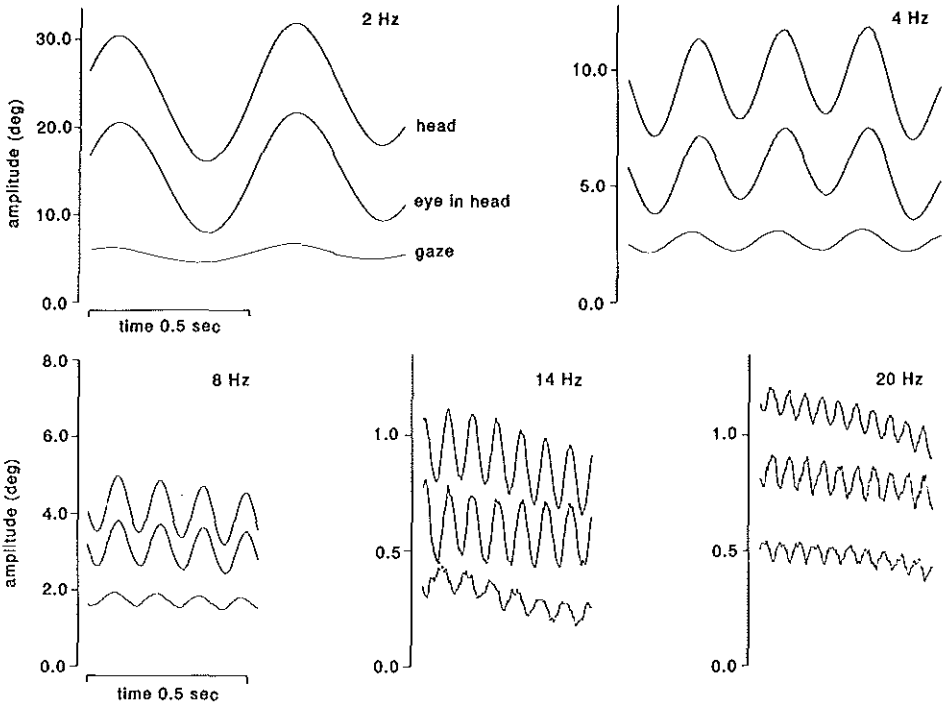

Fig. 3 Examples of head (upper trace), eye-in-head (middle trace) and gaze (lower trace; without saccade removal) recordings. The eye-in-head signal was obtained by subtracting head signal from gaze signal (after saccade removal). For clarity we inverted the eye-in-head signal. The plots relate to one healthy subject with a stationary target at optical infinity. Time scales are the same for each plotted frequency.

special interest in the present experiments, we omitted the head-fixed target condition in the later measurements, and collected data only for the conditions earth-fixed target and darkness. Interlacing these conditions kept the subjects alerted to a fixation task and also prevented cumulative off-center deviation of head and gaze. Fig. 4 shows the mean gain and phase as a function of frequency for 15 normal subjects, obtained in the second set of measurements. The bars (+ and - 1 S.D.) represent the variability between subjects (for the condition darkness). There was no significant difference between the conditions earth-fixed target and darkness. At 2 Hz, VOR gain was 0.88 (SD 0.04) in darkness and 0.92 (SD 0.07) with the stationary target. Above 2 Hz,

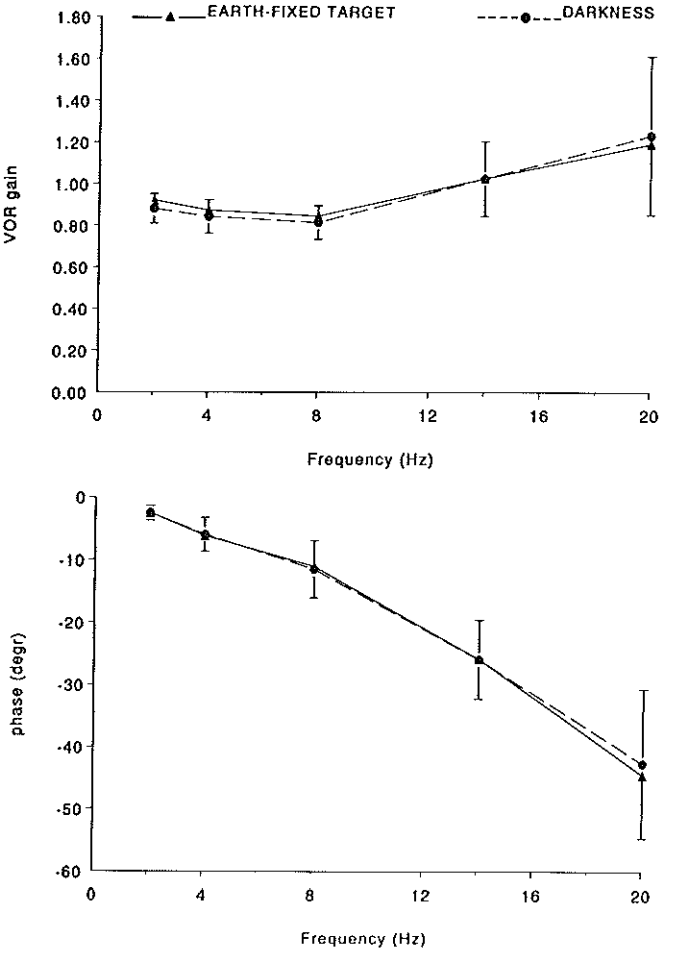

Fig. 4 Mean VOR-gain and corresponding phase lag values (during high frequency sinusoidal head oscillations) with ± 1 SD of 15 normal healthy subjects for the two experimental conditions of the second experimental set (earth-fixed target and darkness). For clarity we plotted the SD for only one experimental condition (darkness); the values in the condition with stationary target were similar.

VOR gain started to decrease, but this trend reversed beyond 8 Hz, where gain increased again, toward about 1.2 (SD 0.36) at 20 Hz. To get an impression of the intra-individual variability we calculated SD of two persons who were tested three times in different experimental sessions. The SD of the data obtained in these three experimental sessions (condition darkness) were again much higher at 20 Hz (0.15 and 0.24) than at 2 Hz (0.03 and 0.06). The phase graphs in Fig. 4 show a lag, increasing

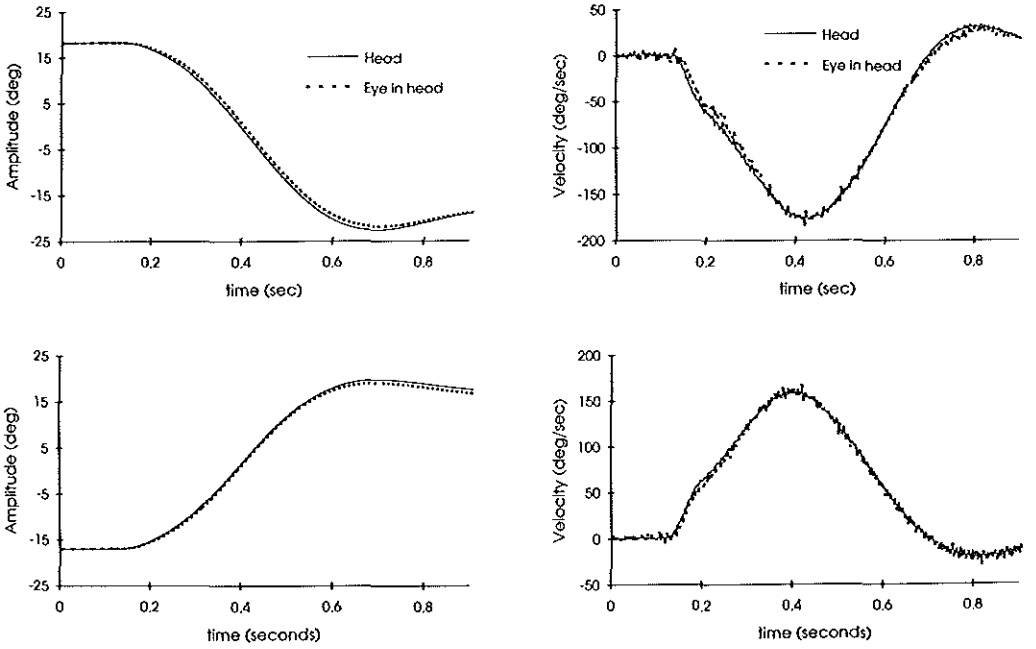

Fig. 5. Average compensatory eye movements of one healthy subject during step displacements of the head. Each graph represents the mean of about 40 step displacements of the head. Upward deflection represents a head movement to the left. For clarity we inverted the eye-in-head signal. The two left panels represent the average position recordings of one healthy subject in total darkness; the right panels represent the corresponding velocity plots.

with frequency, from 2.5 degrees at 2 Hz to about 43.5 degrees at 20 Hz. Expressed in time, the lag was 3.5 ms at 2 Hz; 4 ms at 4 and 8 Hz; 5 ms at 14 Hz and 6 ms at 20 Hz. Nine out of the 15 subjects were measured with and without the Fresnel lens in the same experimental session. Within the standard deviation, virtually no difference between the results for these two different optical conditions of the target was found, suggesting that optical infinity was not a critical factor in our experiments.

2.4.3 *Normal responses to steps*

Fig. 5 shows a representative example of the mean position and velocity response to horizontal step displacements of the head in the condition darkness (1 subject, 2 movement directions). Each plot is the mean of about 40 step displacements, obtained in a period of 160 seconds. As was expected, we found almost symmetrical responses, with near-unity gain for the condition stationary target. Gain, averaged across 15 subjects, was 0.966 ± 0.04 (S.D.) for leftward movement and 0.957 ± 0.06 for rightward movement. For the condition "darkness" (with the stationary target imagined) mean gain for leftward and rightward movements was 0.905 ± 0.106 and 0.902 ± 0.095, respectively. We calculated the VOR-gain from the plots as shown in Fig. 5 (two left panels) by dividing the maximum amplitude of eye-in-head position by the maximum amplitude of head position. One-tailed paired t-test analysis showed a significant difference in VOR-gain between both measurement conditions (p-value = 0.0150; t-value = 2.416; mean difference = 0.065). To assess reproducibility of the results in a same subject, one subject was measured on four occasions. Mean position gains across these sessions for leftward and rightward movements were 1.016 ± 0.036 and 0.998 ± 0.034 (S.D.), respectively, with the target visible. In darkness these values were 0.989 ± 0.057 and 0.975 ± 0.045. These results suggest that intra-subject variability over time does not exceed about 5%. The velocity plots in Fig. 5 show that there was a close correspondence between the velocity profiles of the head and the eye-in-head (with inverted sign). Characteristically, there was a short delay in the rising phase of the eye velocity. Peak eye velocity was slightly lower than peak head velocity. In the falling phase of velocity, eye and head velocity were almost coincident in amplitude and time for 14 of the 15 subjects. Only one person showed a slower decrease of eye-in-head velocity than head velocity, which resulted in a slightly higher eye velocity than head velocity during the last 15-20 ms of the head movement. We estimated the delay between the eye-in-head and head movement from the plots as shown in Fig. 5 (two right panels) of the 10 subjects (out of 15) who had the best signal-to-noise ratios. For this purpose, we plotted the initial part of the responses on an expanded time scale, and hand-fitted parallel straight lines through the early rising phases of head and eye velocities. Examples of such velocity plots with expanded time scale for one normal subject and for LD subject 2 are shown in Fig. 6. The horizontal distance between these lines was taken as representative for the response delay of the VOR. With the target visible, the mean delay was 6.9 ± 1.6 (S.D.) ms for leftward movement and 8 ms ± 1.5 for rightward movement (n=9). Mean delay in darkness was

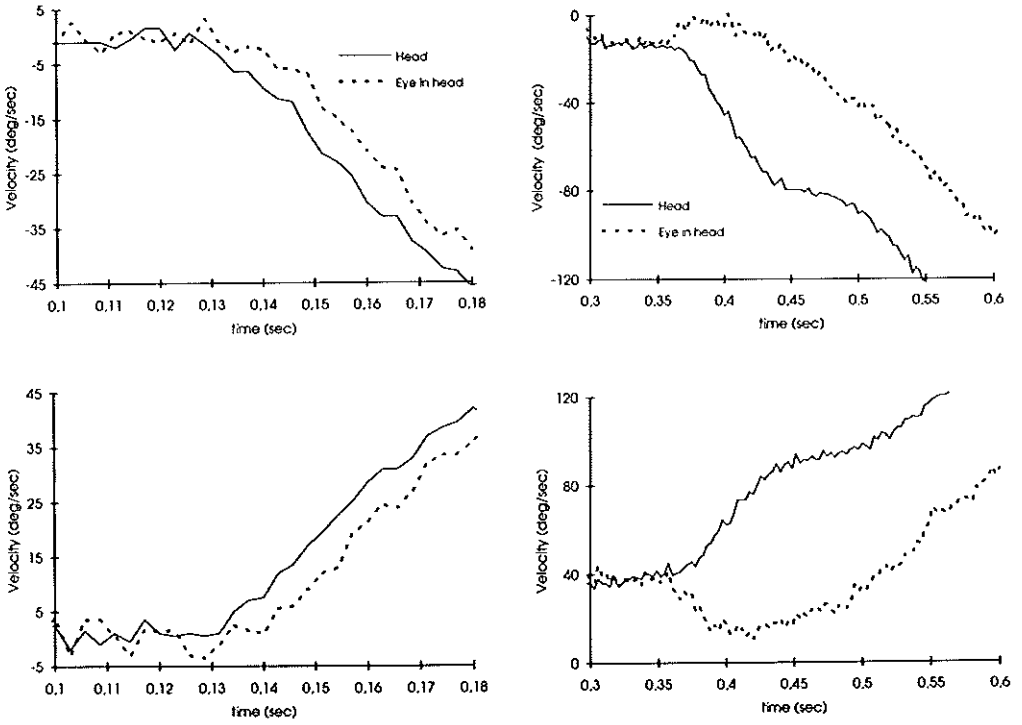

Fig. 6 Mean velocity plots, with expanded time scales, for a normal subject (two left panels) and LD subject 2 (two right panels), to show response latencies. Each graph represents the mean of about 40 step displacements of the head in total darkness. Upward direction reflects a head movement to the left. For clarity we inverted the eye-in-head signal.

respectively 7 ± 1.4 ms and 8.0 ± 1.4 ms (n=10). The average delay in darkness across both movement directions was 7.5 ± 1.4 ms. This value agrees within computational error with the delay found in the response to sinusoidal head oscillations, for which we found a phase lag of about 43.5 degrees at 20 Hz, corresponding to a delay of 6 ms.

The head acceleration reached in the example shown in Fig. 5 was about 1000 deg/s^2; values for head acceleration varied between 700 deg/s^2 and 1300 deg/s^2 among the 15 normal subjects.

2.4.4 *Control experiments*

Several control experiments were done to exclude artifacts, conceivably caused by the recording system or the helmet with torque-motor. In particular, we wished to validate VOR-gain values at the highest frequencies because the amplitudes of the head movements were very small at these frequencies.

In the first control experiment, we glued the eye coil on the head coil instead of attaching it to the subject's eye and followed the usual protocol. This situation simulated the eye standing still in the orbit during the head oscillations, thus VOR-gain should be zero. The mean VOR-gain values obtained in this experiment varied between 0.01-0.02 for the lower frequencies and 0.02-0.04 for the two highest frequencies (14 and 20 Hz). This control experiment also showed that the torque-motor did not disturb the Robinson-type magnetic field.

In the next control experiment, we attached the eye coil to the calibration device just in front of the subject. The biteboard with the head coil was, as usually, in the subject's mouth. This situation simulated the eye standing perfectly still in space during the head oscillations, thus VOR-gain should be unity. The mean VOR-gain measured in this condition varied between 0.99-1.01 for all frequencies.

In addition, we excluded artifacts originating from vibrations of the lead-wire of the eye coil during the high frequency head rotations. To this purpose we repeated the previous experiment while leading the wire from the eye coil (with the latter mounted on the calibration device) in a loop to the moving head. The VOR-gain values did not change in comparison with the previous experiment.

We also excluded ocular position noise as a spurious source of energy in the analyzed frequency band by recording the eye positions while a subject fixated an earth-fixed stationary target without head movements, and correlating these signals with the head movement signals obtained in a different session, again simulating a VOR-gain near unity for all frequencies. The calculated VOR-gain values were indeed very close to unity (0.99-1.01) for all frequencies.

Finally, we simulated a calibration error of the eye coil of 10%, and found that this hardly affected the high VOR-gain values. This result is explained by the fact that our

system records gaze (eye in space) position directly, and that VOR gain is calculated as:

(Gaze - Head) / Head

Because gaze movements are normally much smaller than head movements (by a factor of about 10), small calibration errors of gaze will only marginally affect this quotient. Thus, the calculation of VOR gain is robust against inaccuracies of calibration within a

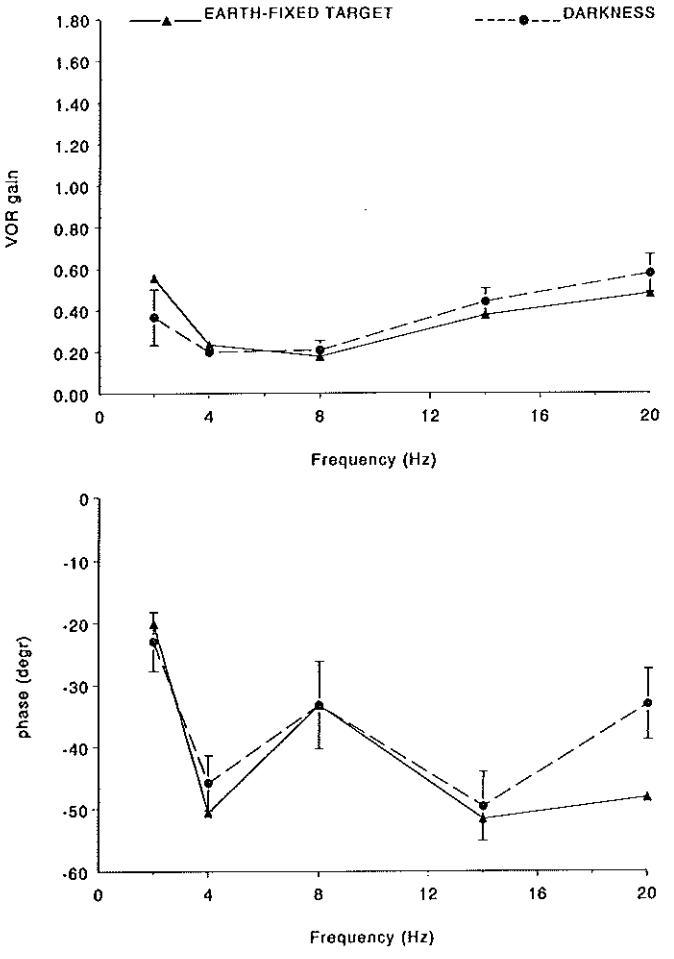

Fig. 7 Mean VOR-gain and corresponding phase lag values (during high frequency sinusoidal head oscillations) ± 1 SD of LD subject 2 for two experimental conditions (earth-fixed target and darkness). For clarity we plotted the SD for only one experimental condition (darkness).

range that is likely to occur in our procedures; we estimate that such calibration errors will rarely exceed 1-2%. Admittedly, this argument only applies to subjects with a VOR gain near unity and not to subjects with a defective VOR.

2.4.5 Responses in LD subjects

In Fig. 7 gain and phase data for sinusoidal head rotation for one of the three LD subjects are shown (LD subject 2; see Methods). The other two LD subjects showed similar trends, but as the deficits varied between individuals we prefer not to show data averaged across LD subjects. LD subject 3, who had only mild vestibular symptoms in daily life, showed better VOR-gain values than LD subject 1 and 2. In addition we also detected an asymmetry in LD subject 3 with the aid of sinusoidal head oscillations, especially during the higher frequencies: gaze in this subject had a tendency to drift to the right, which was repeatedly corrected by a saccade to the left. Consequently, it seemed also to be possible with our method to get an impression of the severity of the vestibular loss in these kind of subjects. The values of the VOR-gain for all three LD subjects were clearly lower than in normals in the 2-8 Hz frequency range. However, the graphs of the VOR-gain are of the same general form as in normal subjects: VOR gain decreased in the range from 2 Hz to 8 Hz but increased above 8 Hz. All three LD subjects showed larger phase lags than normals for all frequencies.

Fig. 8 shows the mean position and velocity responses of LD subject 2 to step displacements of the head in darkness; the changes compared to normal responses are also representative for LD subject 1. There was a clearly lower gain than normal for LD subjects 1 and 2 in both directions, also when there was a visible target. In all velocity plots the latencies of the eye-in-head movements were much longer than in normal subjects. In addition, peak eye-in-head velocities did not reach values close to peak head velocities. Fig. 6 (two right panels) shows the responses to about 40 head movements to the right and left of LD subject 2 in complete darkness, at an extended time scale. Delays for rightward and leftward head movements were both about 95 ms in darkness and about 75 ms in the presence of the fixation target. Delays for LD subject 1 were about 35 ms for all measurement conditions and both movement directions. For LD subject 3 responses to step displacements of the head had particularly low gains in complete darkness. Delays for this subject for rightward and leftward head movements were 19 ms and 17 ms, respectively, for the condition complete darkness and 25 ms and 19 ms in the presence of a stationary target. In

addition there was a clear difference in the build-up of eye velocity, especially in complete darkness, between the response on rightward and leftward step displacement of the head. Head movements to the left produced a better build-up of eye velocity than movements to the right. This asymmetry corresponds to the asymmetry found with the aid of sinusoidal head oscillations. Based on the evidence found here it is more likely that this subject, although clinically diagnosed as a LD subject, belongs to the category of subjects with a unilateral vestibular loss. Further details on a larger group of subjects with bilateral or unilateral vestibular dysfunction will be reported in a separate article (see chapter 3).

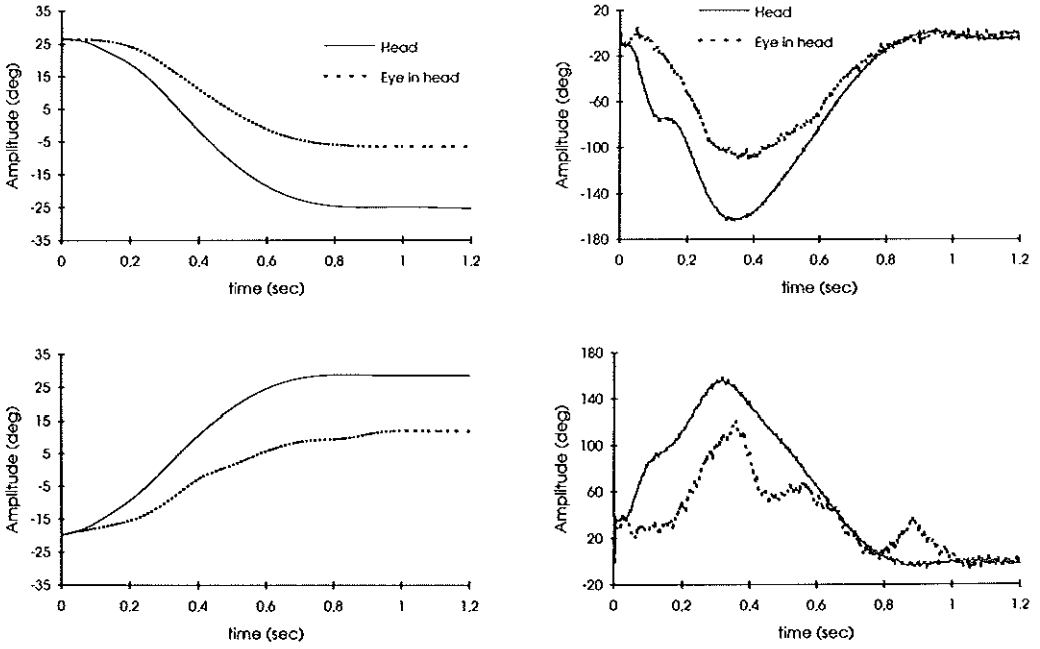

Fig. 8 Averaged responses of LD subject 2 to step displacements of the head. Each graph represents the mean of about 40 step displacements of the head. Upward direction reflects a head movement to the left. For clarity we inverted the eye-in-head signal. The two left panels represent the mean position plots of patient 1 in total darkness; the right panels represent the corresponding velocity plots.

2.5 Discussion

The new method used in the present investigation appears to have several advantages. First of all, our method is inexpensive in comparison to high frequency rotation chairs and is very safe. In addition, the method was easy to carry out in practice, with minimal strain to the subjects. The method allows the application of high frequency sinusoidal head movements and abrupt step displacements of the head with convenient electronic control of timing and shape of the stimuli. Because of the symmetrical distribution of the mass that loads the motor, the force applied to the head is a pure torque about the axis of the motor, without translational components. In this way, our method minimizes head translations and any contribution of the linear VOR. Such translations are much more likely to occur if rotations are generated indirectly by driving one eccentric point on the head (e.g. a biteboard) with a linear actuator (e.g. Gauthier et al., 1984).

The results from normal, healthy subjects were consistent for the sinusoidal head rotations up to frequencies of 14 Hz. As expected, we found in the high frequency range from 4 to 20 Hz hardly any differences in VOR-gain values between the three tested visual conditions. These results suggest that for high frequency rotations, the VOR can not be significantly modulated by visual inputs and instructions to the subjects. We found a phase lag between compensatory eye movements and head movements, almost linearly increasing with head oscillation frequency.

Experiments with active headshaking up to 6 Hz frequency by Tomlinson et al. (1980) and Fineberg et al. (1987) yielded comparable phase lags and VOR gains in the frequency range from 2 up to 6 Hz. O'Leary and colleagues (1990, 1991) found approximately the same VOR-gains but zero phase lags in the same frequency range. Considering the differences in methodology (active vs. passive head shaking; EOG vs. search coil) the overall results of the active head shaking test appear to agree with our present results within the margin of measurement error. However, a possible contribution to compensatory eye movements by efference copy signals or synergic generation of motor commands during active head movements cannot be easily excluded. Direct comparative tests of active and passive head rotations in single sessions might be illuminating in this respect, especially in LD subjects, but such tests are beyond the scope of our present paper.

One limitation of our method is the decreasing head movement amplitude with increasing oscillation frequency, resulting in a less favorable signal-to-noise ratio for the highest frequencies. This may account for the high standard deviations of the responses to the higher frequencies (14 and 20 Hz). Therefore, prudence is called for in the interpretation of the VOR-gain values for the highest frequencies. Replacing the 25 W torque-motor by a 75 W torque motor to increase the amplitude of the head movements was only successful for the lower frequencies. Possibly, further improvement for the highest frequencies might be reached by a stiffer connection between the torque-motor and the skull of the subject, resulting in a more direct transmission of the oscillations to the skull.

As already mentioned above, the interpretation of the rise in VOR-gain beyond 8 Hz to a mean value above unity at 20 Hz is difficult. Grossman et al. (1988) found that, during walking and running in place, predominant frequencies of horizontal and vertical rotations were all within a 0.6-8.2 Hz range. The highest frequency components were particularly associated with running and mainly found in the vertical plane. It seems possible that for frequencies higher than 14 Hz, which hardly occur in daily life, the VOR is not calibrated optimally.

Another possible contribution to the high gain values at 20 Hz is passive, mechanical ocular resonance (Vercher et al. 1984; Dupuis and Hartung 1980). In our experiments we have the situation of a damped oscillator (the ocular plant) with the presence of a periodic driving force (head oscillations imposed by the torque-motor). This passive oscillating system will appear to have a virtual, positive VOR-gain if the amplitude of the eye movements in space (gaze) is smaller than the amplitude of head movements. According to the physics of oscillators (Serway 1983) this occurs only for frequencies above the natural frequency ω_0 of the system. The value for ω_0 can be calculated easily from $\omega_0=\sqrt{(k/m)}$. In this formula m equals the moment of inertia and k the stiffness (one of the passive visco-elastic elements of the eye). When we substitute the values for the fast or slow passive visco-elastic elements given by Robinson (1964) we get natural frequencies of 174 Hz and 306 Hz, respectively. Influence of the inertia of the eye ball mass, leading to a positive pseudo-VOR-gain, starts to become important only above the resonance frequency, thus far above the frequencies used in our experiment.

It is conceivable that the visco-elastic properties of the orbital apparatus can be changed by paralysing the extra-ocular muscles by injection of a small volume of highly concentrated lidocaine. This has been done in monkeys by Vercher et al. (1984)

in order to prove the hypothesis of mechanical ocular resonance in the 12-30 Hz range as an explanation for the high VOR-gains found in this frequency range. They observed non-conjugate eye oscillations occurring in bursts of variable duration, with maximum amplitudes not being reached until several seconds after steady head oscillation had been reached. In our experiments the high frequency eye oscillations were constant for at least 8 s and the maximum amplitudes were reached immediately after the head started to oscillate. Neither Vercher et al. (1984) nor Dupuis and Hartung (1980) report the phase relationship between eye and head movement, which can be informative when one suspects mechanical ocular resonance.

On the other hand it seems entirely plausible for a real VOR to be functioning at these higher frequencies. After all, the elementary reflex arc of the VOR is a very short, disynaptic one with a latency ranging in the literature from 10 to 14 ms (Lorento de Nó 1933; Szentágothai 1950; Wilson and Melvill Jones 1979; Lisberger 1984; Schwarz 1986). The phase graph of Fig. 4 shows a mean phase lag of 43.5 degrees at 20 Hz, corresponding to a delay of 6 ms, which is even shorter than the above mentioned values of 10-14 ms. In addition, the fusion frequency of the extra-ocular muscles is in the order of 350 Hz (Cooper and Eccles 1930) and ocular tremors have frequencies in the range of 30-80 Hz (Ditchburn and Ginsborg 1953).

While mechanical *resonance* in the frequency range applied by us appears unlikely, the possibility of a passive component in the responses to large, passive head accelerations cannot be entirely discounted. Khater et al. (1993), using head velocity steps with accelerations of 4000 deg/s^2, observed substantial transient, zero-latency pseudo-VOR responses in the cat, even after bilateral labyrinthectomy. In our experiments, in which accelerations had peak values lower by a factor 4 than those of Khater et al., and possibly different higher-order components (jerk), we did not observe such a passive, zero latency component during head steps (Fig. 6).

Another potential source of compensatory eye movements during head-on-trunk oscillation is the cervico-ocular reflex (COR). The role of the COR in normal humans is still uncertain. Evidence indicates that the COR in normal humans usually causes eye deviations in the opposite direction of the body twist, thus 180 degrees out of phase with the VOR (Takemori and Suzuki 1971; Barnes and Forbat 1979; Barlow and Freedman 1980; Chambers et al. 1985) and is best elicited during low frequency stimulation (Barlow and Freedman 1980), eye closure (Takemori and Suzuki 1971; Barlow and Freedman 1980), active instead of passive head movements (Dichgans et

al. 1973; Doerr et al. 1981) and instructions to imagine head motion (Thoden et al. 1983).

Theoretically, the compensatory eye movements induced by the head rotations in our LD subjects could be due to enhancement of the cervico-ocular reflex. Several authors (Gresty et al. 1977; Kasai and Zee 1978; Bles et al. 1984; Huygen et al. 1991) elicited the COR by low frequency (< 1 Hz) trunk-on-head rotation and found a COR enhancement in asymptomatic, LD subjects. Huygen et al. (1991) observed in 30 LD subjects a clear COR with a mean gain of about 0.7 (SD 0.3) at 0.1 Hz, decreasing to about 0.4 (SD 0.2) at 0.4 Hz. Chambers et al. (1985), using a pseudorandom oscillatory stimulus with a frequency bandwidth of 0 to 5 Hz in three asymptomatic LD subjects, observed low-gain, compensatory COR-responses with a phase shift of 180 degrees over the full range of tested frequencies (COR-gain strongly fluctuated in the three LD subjects between 0.5-0.16; 0.25-0.14 and 0.25-0.10 respectively). There was no clear frequency-dependence of the COR-gain in these LD subjects, but the compensatory phase shift of about 180 degrees at 0.5 Hz decreased to about 90 degrees at 5 Hz in two of these LD subjects. No documentation on the COR at higher frequencies (> 5 Hz) can be found in the literature, but it seems very unlikely that such a reflex, involving a multisynaptic pathway with a delay of 100 ms (Leopold et al. 1982), could operate at frequencies of 10-20 Hz. In the literature a large variability in COR-gains is reported among normal subjects, but also among LD subjects. Therefore it is hard to evaluate the role of the COR in compensating for loss of the VOR in our three tested LD subjects. In any case, with a delay of 100 ms the COR cannot contribute to the short-latency responses to the step stimuli found in normals; the late responses in the LD subject shown in Fig. 6 could, however, represent a COR.

For the range from 2 to 14 Hz, our three LD subjects showed results that were quite different from normal, healthy subjects. Especially the responses to the position steps were replicable and very informative in the three tested LD subjects. We already mentioned that 'LD' subject 3 according to our results does not belong to the same category as subject 1 and 2, but has probably a predominantly unilateral vestibular loss on the right side. Goebel and Rowdon (1992) reported that in a group of 34 subjects with bilaterally reduced caloric responses, only roughly one third of these LD subjects showed an abnormally low gain for either active headshaking and passive whole-body rotation (both 0.5 Hz). The data of Goebel and Rowdon (1992) and our present results suggest that a bilateral reduction or absence of caloric-induced nystagmus does not necessarily imply a complete loss of compensatory eye movements. Because of the

long delays (> 70 ms), the compensatory responses seen in our LD subjects 1 and 2 probably originate from the visual system or the COR. The absence of a response to caloric stimulation in these two subjects agrees with the severely delayed and reduced responses to step displacements of the head. However, the response observed in these two LD subjects to high frequency sinusoidal head oscillations in these two subjects, although strikingly lower than normal, does suggest some rest function of the labyrinths, despite the negative caloric tests. Unfortunately we do not have information on the caloric test in 'LD' subject 3.

In conclusion, the method described here of imposing head rotation with a helmet, driven by a reactive torque, seems a useful and flexible technique for investigating compensatory eye movements at relatively high frequencies. The method appears to have a potentially wide use, ranging from clinical evaluation to basic research of the VOR.

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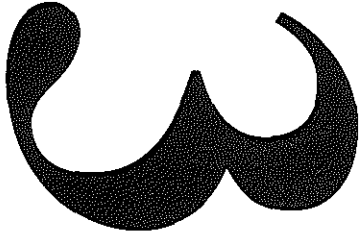


Gain and delay of human vestibulo-ocular responses to oscillation and steps of the head in normal and pathological conditions

3.1 Abstract

We evaluated vestibulo-ocular responses (VOR) as an index of functionality of the vestibular system in normal humans and in groups of subjects whose vestibular function was compromised to various degrees. A reactive-torque helmet (Tabak and Collewijn, 1994a, b) imposed high-frequency oscillation (2-20 Hz) or step displacements of the head in the horizontal plane. For comparison, we also applied manually controlled head-steps as have been described in the literature. Eye and head movements were recorded with magnetic search coils. Non-vestibular effects were avoided by suitable choice of frequencies and time-windows. Helmet-imposed steps caused a virtually constant head acceleration (770 deg/s^2 at average) in the first 90 ms. This results in a linear relation between eye and head velocities; we show that the gain and delay of the VOR can be calculated independently from the slope and offset of this relation. Such estimates appear more reliable than those obtained with conventional techniques. Normal subjects had a VOR gain of about 0.9 and a delay of about 5 ms. Characteristically, gain was lowered in one or both directions after, respectively, unilateral or bilateral vestibular lesions; the magnitude of the gain reduction correlated, in general, well with the degree of complaints and disability. Surprisingly, delay was systematically prolonged (up to several tens of ms) in all groups of subjects with manifest vestibular pathology. These results suggest that the determination of delay, in addition to gain of the VOR, is feasible and important in the evaluation of vestibular function. The results of head oscillation generally support the results for steps, but are somewhat less specific. The responses to manually generated head steps roughly agree with those to helmet-induced steps, but due to the non-uniform acceleration they allow a less exact analysis of VOR function.

3.2 Introduction

The vestibulo-ocular reflex (VOR) maintains a constant direction of gaze during rotational perturbations of the head. The visual consequences of loss of vestibular function become apparent from reports of patients who have to live without a 'balancing mechanism' (Ford and Walsh 1936; J.C 1952). Most of these patients have impaired vision and oscillopsia, especially during walking (Grossman and Leigh 1990). This is not surprising, since in daily life the head undergoes rotations of up to 5 Hz during walking and even higher during running (Grossman et al. 1988, Pozzo et al.

1990, Leigh et al. 1992); such frequencies are beyond the range of purely visual compensation (see e.g. Martins et al., 1985). On the other hand, the peak velocity of these head movements generally does not exceed 150 deg/sec and, during walking, is usually less than 30 deg/sec, which is well within the range of operation of the VOR (Pulaski et al. 1981).

Of the vestibular tests that are routinely used in many clinics, the torsion swing and caloric stimulation, only the first one gives direct information about the physiological performance of the system. However, the rotational stimuli applied in most reported studies of the VOR had a much lower frequency than those occurring during locomotion. The use of these low frequencies in rotatory testing appears to be inadequate since the performance of the vestibulo-ocular system is far from optimal in this frequency range (Meiry 1971, Baarsma and Collewijn 1974, Barr et al. 1976). The limitation to low frequencies, which is essentially determined by the limited torque of the driving systems, also causes difficulties in isolating, during data analysis, the VOR from non-vestibular factors that contribute to compensatory eye movements (Schwarz and Tomlinson 1979).

Visual contributions to gaze stabilization (Barnes et al. 1978, Benson and Barnes 1978, Tomlinson et al. 1980, Koenig et al. 1986) as such can be easily eliminated, but even in total darkness the results are strongly influenced by visual imagery and the mental state of the subject (attention, instructions etc.), as described originally by Barr et al. (1976) in normal subjects, and confirmed in labyrinth defective (LD) subjects (Möller and Ödkvist 1989). Thus, the elimination of light does not guarantee that the VOR can be examined in isolation. Especially low-velocity rotatory tests with periodic stimulation are of doubtful value in VOR quantification because compensatory eye movements are improved by predictive motor programs in healthy individuals (Schwarz and Tomlinson 1979, Hydén et al. 1982) as well as in vestibularly impaired humans (Dichgans et al. 1973, Kasai and Zee 1978, Hydén et al. 1983) and monkeys (Dichgans et al. 1974, Larsby et al. 1982). For this reason, most previous studies have shown only a slight asymmetry (Baloh et al. 1977, Istl-Lenz et al. 1983, Jenkins 1985, Allum et al. 1988, Segal and Katsarkas 1988, Paige 1989) in humans with only one single intact labyrinth. However, only low-frequency, low-acceleration, predictable sinusoidal rotations were used in these studies.

Isolation of the vestibular contribution to compensatory eye movements appears to be possible, provided that the rotatory acceleration exceeds the dynamic range of visual

tracking. Such high accelerations have been produced by applying active head movements (Tomlinson et al. 1980, Fineberg et al. 1987, Grossman and Leigh 1990, O'Leary and Davis 1990, O'Leary et al. 1991) or high-frequency (>2 Hz), passive, horizontal head rotations (Skavenski et al. 1979, Hydén et al. 1982, 1983, Istl-Lenz et al. 1983, Gauthier et al. 1984, Stott 1984, Paige 1989, Kasteel van Linge 1990, Tabak and Collewijn 1994, 1995). A more recently introduced approach measures the VOR in response to passive step rotations of the head that are manually administered by the experimenter. Such head movements, which contain, in principle, high frequencies, have been applied very successfully in normals and vestibular patients (Cremer et al. 1988, Halmagyi et al. 1990, 1991a, b, 1992).

In our previous work (Tabak and Collewijn 1994, 1995) we developed a helmet containing a motor-driven mass, which exerted a reactive torque on the head, without any rigid attachment to other structures. In combination with search-coil recording techniques, we could reliably measure the horizontal VOR for sinusoidal, horizontal oscillations in the frequency range of 2-20 Hz and for horizontal steps. In the present work we applied these techniques to large groups of normal subjects and of patients with clinically diagnosed total or partial unilateral or bilateral vestibular areflexia.

3.3 Materials and methods

3.3.1 Stimulation technique

Passive, horizontal head rotations were generated by a helmet (Tabak and Collewijn, 1994, 1995), placed on the subject's head, with on top a torque motor (GEC Alsthom/Parvex; Code: RS240B; 150 Watt) which rotated a fly-wheel. The weight of the helmet was balanced by suspending it with a spring from the ceiling; this left the subjects free to translate and rotate their heads. The torque motor was powered by a driver (Soprel/Milano Transdriver (I) DB 425 W/R), which received a sinusoidally or stepwise changing voltage as the control signal. Control signals were generated by a DEC PDP 11/73 computer in conjunction with the data-acquisition protocol. The torque motor could produce horizontal head oscillations at frequencies up till at least 20 Hz. The amplitude of the control signal was kept constant throughout this frequency range to obtain an approximately constant, maximum torque.

In addition, sudden, unpredictable step displacements of the head were generated by applying voltage steps to the helmet driver. Such steps typically had amplitudes of 10-20 deg, peak velocities of 80-150 deg/s and accelerations of 700-1500 deg/s^2 (for more details see Tabak and Collewijn 1994, 1995). For comparison with the earlier work by Halmagyi and colleagues step-wise head rotations were also applied manually; standing behind the subject, we held the head of the subject (who kept wearing the helmet with torque-motor) and delivered a rapid, horizontal head rotation. These manual steps had amplitudes of 20-40 deg, peak velocities of 200-400 deg/s and peak accelerations of 2000-6000 deg/s^2.

3.3.2 Recording technique

Horizontal rotations of the left eye were recorded with the scleral coil technique according to the amplitude detection principle of Robinson (1963), relative to a large, earth-fixed, homogeneous magnetic field (Collewijn, 1977) to ensure that the recordings reflected only rotations and were invariant for translation. To record the head movements, a second sensor coil was firmly attached to a biteboard with a customized impression of the teeth in dental impression material to ensure a firm connection between the skull and the head coil.

The sensor coils were connected to high quality lock-in amplifiers (Princeton Applied Research, model 5210) to obtain the horizontal positions. The sensitivity of the eye and head coils was calibrated prior to every experimental session with a protractor. The system's resolution was better than 1 min arc.

3.3.3 Visual targets

Measurements were made in two conditions: 1) an imagined stationary target in total *darkness*; 2) a stationary *visual target* (LED), positioned at optical infinity by placing it in the focal plane of a Fresnel lens (size 94 x 70 cm; focal length 118 cm). Infinity of the target was implemented to avoid changes in target angle due to head translations. We verified that there was invariance of the recorded gaze, eye and head angles for head translation and invariance of the viewed angular direction of the target for head translation.

3.3.4 Protocol

The subject was seated in the magnetic field, viewing the target binocularly and with the head in what was felt as the 'natural central position'. All experiments were conducted in complete darkness, except for the point target. Each of 5 sinusoidal head rotation frequencies (2, 4, 8, 14 and 20 Hz) were applied four times, in random order, with the visual target present and in darkness. Consequently, there were 40 trials (5x4x2), each lasting 8 s. The visual target conditions were alternated in a fixed sequence.

Helmet-generated step displacements were applied in 4 trials of 80 seconds, in each of which 20 head displacements in each direction (left and right) were generated. To reduce predictability, the interval between the head impulses was varied randomly between 1.3 and 2.3 s. In addition, we manually delivered unpredictable, rapid, stepwise head rotations in the horizontal plane in 2-3 measurements (each lasting 80 s and containing 25-35 steps).

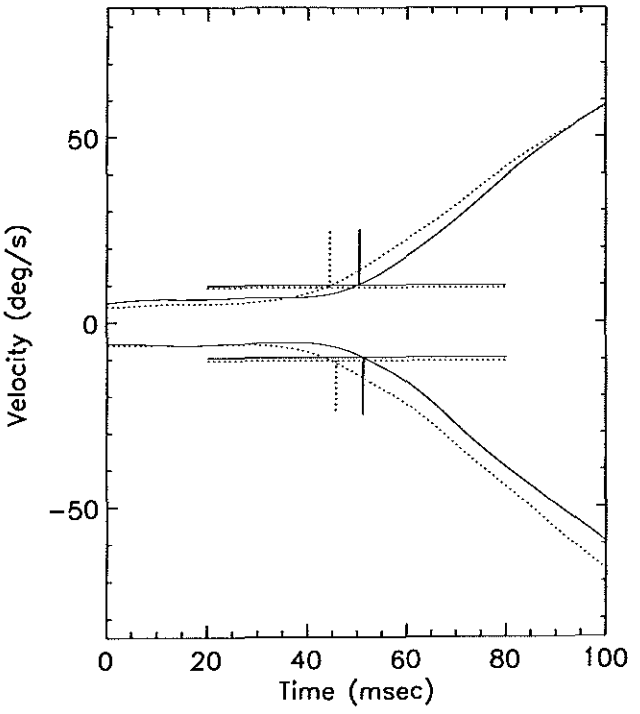
3.3.5 Data processing of responses to sinusoidal head oscillations

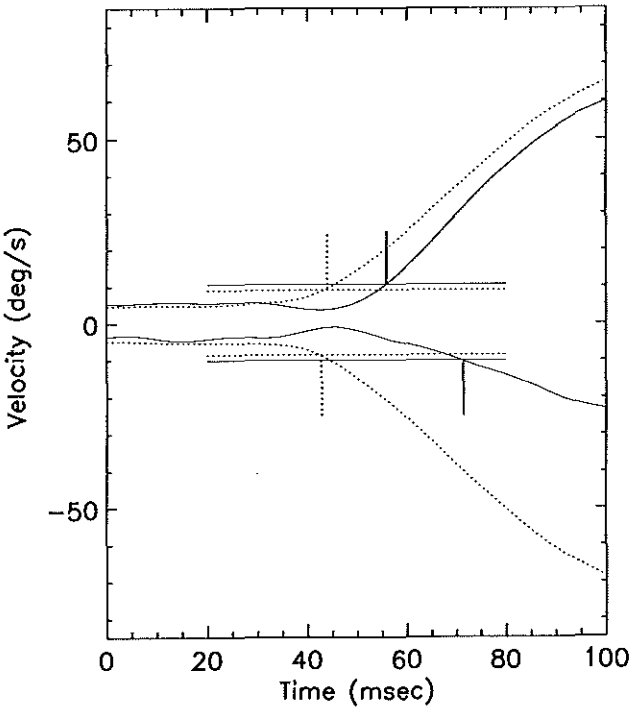
After anti-alias low-pass filtering at 125 Hz each signal was digitized at 500 samples/s and stored on disk by a DEC PDP 11/73 computer. For the off-line analysis data were transferred to a UNIX system (Silicon Graphics Indigo), on which the data were processed by a set of routines developed under PV-Wave (Precision Visuals, Inc.). First, the saccades were removed from the gaze signal and a cumulative smooth eye movement signal was constructed. Saccade detection was based upon minimum velocity, acceleration and amplitude, as well as minimum and maximum duration criteria. In most subjects these values were respectively 25-30 deg/s, 2000 deg/s^2, 0.1 deg, 5 ms and 500 ms. The correctness of the saccade detection procedure was always graphically verified. Eye-in-head position was computed by subtraction of the head signal from the smooth gaze signal. The *trend* of this signal was calculated as the cumulative displacement of the eye, across a trial, in a particular direction. Such trend (in deg/s) was one measure of a left-right asymmetry of the VOR. Prior to analysis in the frequency domain by transformation in a FFT routine, any trend and offset were removed. Using a Hanning window, we computed gain and phase from the cross- and auto- spectral densities of the FFT signals.

3.3.6 Data processing of responses to step displacements of the head

These signals were digitized at 250 samples/s and stored in the same way as described above. For off-line analysis we used the same tools. However, we restricted the analysis to a time window of 90 ms, beginning at the onset of head rotation. In this way we isolated the 'pure' VOR without contamination by visually controlled responses or the cervico-ocular reflex. Because virtually no saccades occurred in the first 90 ms after onset of head movement, we did not need to de-saccade the gaze signal. For identification of the onset of each head movement, the program identified the peak head velocity in the direction of the delivered head acceleration. Subsequently, the program identified the point before the peak head velocity where head velocity exceeded 10 deg/s. The program contained a number of protections against the intrusion of spurious head movements in the data. Head and eye-in-head velocities were obtained by differentiation of the position signals using a two-point central difference digital differentiation method. For each 80 seconds trial, the computer calculated and plotted the averaged velocities ± 1 SD of all detected head movements with the corresponding compensatory eye movements, for a time window extending from 50 ms before until 90 ms after onset of each head movement. A conventional estimate of gain was obtained by taking the ratio's of instantaneous (simultaneous) eye and head movements at specified head velocities. We shall show later that this estimate is inaccurate due to the neglect of delay.

The delay between *mean* head and compensatory eye movements was, at first, calculated with a conventional approach, based on velocity criteria. The program calculated, for the period between 50 and 10 ms before the detected onset of head and eye-in-head movements, two lines (Fig. 1) that represented, respectively, the levels of the mean *head* and *eye-in-head* velocity, each augmented by the sum: (2 deg/s + 8 times the standard deviation of the resting velocity). This was a fairly conservative criterion, that avoided false, noise-related detections of induced movements. Subsequently, these two lines were extrapolated into the period after head movement onset and the program computed the moments when mean head and compensatory eye velocity crossed these threshold-lines. The difference between these two moments for head and eye-in-head signals was considered as a measure of the delay of the VOR. The upper panel of Fig. 1 shows this mean delay calculation in a healthy subject; the lower panel for a subject with a total rightsided vestibular loss.


50
0
−50
Velocity (deg/s)
0
20
40
60
80
100
Time (msec)


50
0
−50
Velocity (deg/s)
0
20
40
60
80
100
Time (msec)

Because of the sample frequency of 250 Hz in the trials with the step stimuli, temporal resolution of the calculated delays is not better than 4 ms for individual trials. However, the random distribution of the sampling times with respect to the measured events (head and eye movements) considerably reduces this limitation for the mean of a number of samples, by a factor (n-1). As n is about 80 in our case, the resolution of the mean is about $4/\sqrt{79}$ = 0.45 ms. More important disadvantages of this threshold-technique are 1) the inherent confusion between a reduced gain and a genuinely increased delay, and 2) the dependence of the computed delays on the choice of the threshold criteria.

In an other graphic analysis the computer plotted the weighted velocity averages (in 10 deg/s bins) of all compensatory eye movements, as a function of the corresponding, simultaneous head velocities. In this way, the VOR performance for both directions of movement could be visualized and quantified. As we shall show, these eye velocity / head velocity relationships also allow independent, correct estimates of gain and delay of the VOR step-response, which do not suffer from the ambiguities mentioned above.

3.3.7 Subjects

Approval of the local ethical committee and informed consent from the subjects was obtained for all experiments. We recorded 24 healthy subjects who had no known ocular or vestibular pathologies. The tested labyrinthine defective *(LD)* patients consisted of several groups:

A) Patients (n=7) with *clinically bilateral strong vestibular hyporeflexia* (according to routine testing: torsion swing and bithermal caloric stimulation) and severe,

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←—— *Fig. 1 Averaged head velocity (dotted line) and inverted eye-in-head velocity (solid line). Upward direction reflects a head movement to the left. The horizontal dotted and solid lines represent respectively averaged head and eye-in-head velocities, augmented by 8 x SD + 2 deg/s, calculated in the period preceding the detected start of head movement. The intersections of these lines with the head and eye traces are marked by vertical lines. Delay of the response is defined as the difference in time between the intersections of the dotted and solid vertical lines. The upper panel shows the mean delay calculation in a healthy subject for 21 leftward and 16 rightward head movements, the lower panel shows the result for a patient with a total vestibular loss on the right side.*

sustained, invalidating vestibular symptoms in daily life such as oscillopsia or severe unsteadiness during walking, necessitating the use of a wheelchair or walking frame. The case histories of four of these patients mentioned the administration of gentamicine/streptomycine for meningitis (n=3) or osteomyelitis (n=1). Of the remaining patients, one patient probably suffered a large cerebrovascular accident. Another patient had undergone ear surgery during which the left labyrinth was damaged; her right labyrinth also showed a severe hyporeflexia on routine clinical testing. For the last patient the underlying pathology was unknown. Obviously, this group was not homogeneous.

B) Patients with *clinically total unilateral vestibular loss* (n=40). Most of these patients (n=35) had undergone unilateral vestibular neurectomy during surgery for an acoustic neuroma some years before (mean 4.5 years ± 3.2, SD). The other patients (n=5) had an acoustic neuroma that had not yet been operated but had a clinically similar, total, unilateral, vestibular loss. Most of the patients in this group hardly had vestibular symptoms; i.e. they did not feel disoriented or dizzy except after rapid head or body movements.

C) Patients with *clinically bilateral vestibular hyporeflexia* (n=14) without severe, sustained, invalidating, vestibular symptoms. Many of these patients had, however, intermittent periods with attacks of rotatory dizziness with or without nausea and feelings of disorientation or dizziness after rapid head movements. Additionally, most of them (n=11) showed, according to routine clinical testing, some degree of asymmetry in their vestibular responses. For 9 patients in group C these routine clinical tests had been done recently (less than 6 months ago; mean 1.9 months ± 0.9 SD). Six patients of group C had bilateral Ménière's disease. In the other patients the various occurring diagnoses were: Cogan syndrome (n=1), Usher syndrome (n=1), congenital deafness without established cause (n=2) and other types of intractable vertigo (n=4). None of these patients, notably those with Ménière's disease, had an acute exacerbation of vestibular complaints during the period of routine clinical tests or our measurements. Only 3 patients of this group (aged 70-74 years) used a walking stick because of mild unsteadiness.

D) Patients with *transient clinical phenomena*. This group consisted of 3 patients who were originally classified in group C, but whose vestibular symptoms had totally disappeared in the period between the routine clinical test and our measurement.

E) Patients with *clinically partial unilateral vestibular loss* (n=11). Six of these patients had an acoustic neuroma but had not been operated yet; none of these had severe vestibular symptoms. Three other patients had unknown causes for their attacks of vertigo in the past, but they had very few vestibular complaints at the time of our measurements. The two remaining patients still had mild vestibular symptoms.

3.4 Results

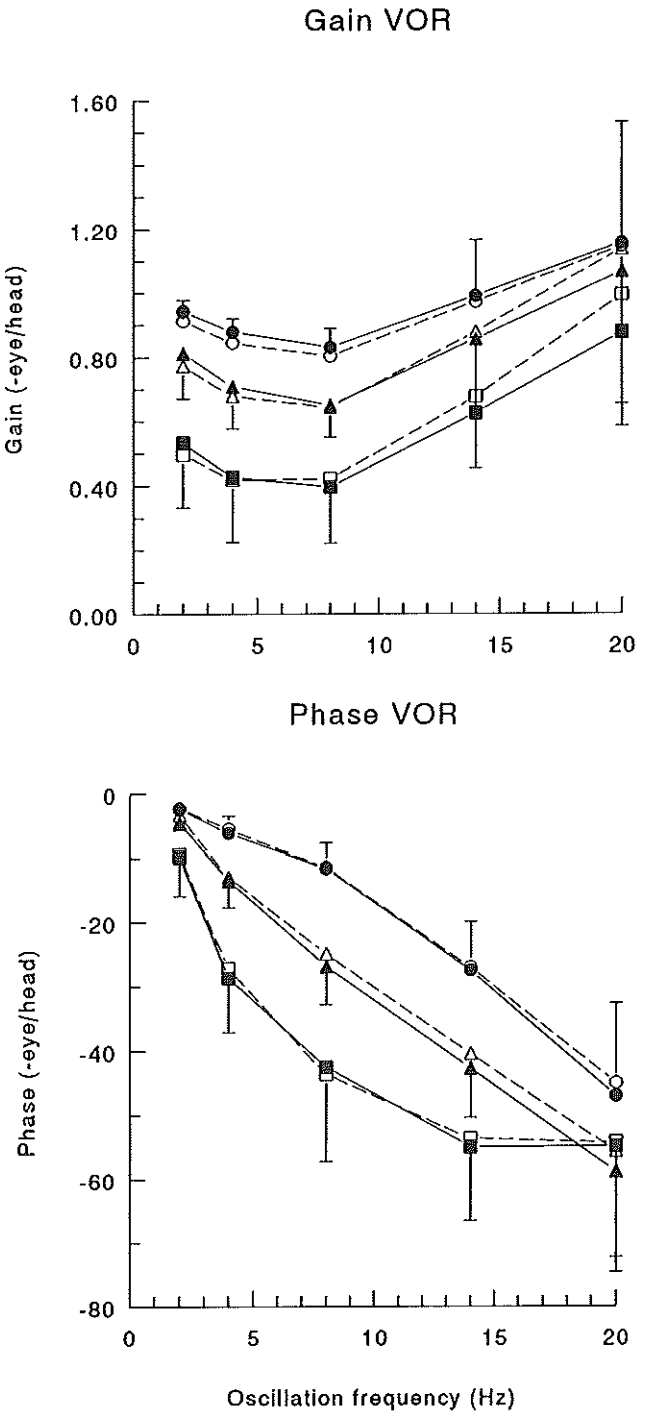
3.4.1 Frequency dependence of the oscillatory stimulus

The maximum torque of the motor, in combination with the inertial moment of the helmet and the head resulted in more or less constant peak-accelerations of the head on the order of 1000 deg/s^2. Accordingly, average maximum head amplitudes decreased with increasing head frequency, from a maximum of about 7 deg (zero-to-peak) at 2 Hz to about 0.08 deg at 20 Hz (see also Tabak and Collewijn, 1994a). Average peak velocities of the head decreased from about 38 deg/s at 2 Hz to about 10 deg/s at 20 Hz. Due to individual differences in head and neck mechanics, the actual values in different subjects varied somewhat about these averages.

3.4.2 Normal responses to sinusoidal head oscillations

Fig. 2 shows the mean VOR gain and phase as a function of frequency for the 24 healthy subjects, in the conditions 'visual target' (continuous lines, filled circles) and 'darkness' (dashed lines, open circles). The bars represent the variability (1 SD) between these subjects for the condition 'darkness'.

Variability for the other condition (visual target) was comparable. There was no significant difference between the VOR gains for the two measurement conditions, except for the lowest frequency of 2 Hz ($P < 0.05$), at which VOR gain was 0.94 ± 0.04 with a visual target and 0.91 ± 0.06 in darkness. At frequencies above 2 Hz, VOR gain initially decreased slightly, but this decline reversed beyond 8 Hz, where gain increased again to about 1.15 ± 0.35 at 20 Hz. The phase graphs show a lag, increasing with frequency from a mean value of 2.4 deg at 2 Hz to 47 deg at 20 Hz. Expressed in time, the lag was 3.3 ms at 2 Hz, 4.2 ms at 4 and 8 Hz, 5.4 ms at 14 Hz, and 6.5 ms at 20 Hz.


Gain VOR
Gain (-eye/head)
1.60
1.20
0.80
0.40
0.00
0
5
10
15
20
Phase VOR
Phase (-eye/head)
0
-20
-40
-60
-80
0
5
10
15
20
Oscillation frequency (Hz)

There were no significant differences in phase lag for the two different measurement conditions at any frequency. The present results are in perfect agreement with the results in 15 normal subjects in our previous work (Tabak and Collewijn 1994a, b), and confirm that the influence of a visual target is negligible above 2 Hz. Variability is small in the range 2-8 Hz (Fig. 2), but increases at 14 and especially 20 Hz.

The mean *trends* for the same group of normal subjects are shown in Fig. 3 (left panels, black bars). In all cases, we plotted the value obtained from the trial with the highest value of trend for each applied frequency and each condition. It is clear from Fig. 3 that trend was virtually absent in the normal subjects (black bars).

3.4.3 Step displacements of the head: shape of the stimulus

In the interpretation of the responses to steps it is important to know the course of head acceleration, velocity and position as a function of time. Simplicity of these functions (at least during the first 90 ms) will facilitate the interpretation of the stimulus-response relations. For this purpose, we measured the time elapsed until certain head velocities were reached in our step paradigms. For helmet-induced steps, head velocities of 15 deg/s, 25 deg/s, 50 deg/s and 65 deg/s were reached in the control group, at the average (± 1 SD), after 11.5 ms ± 1.6, 23.7 ms ± 4.6, 57 ms ± 16.4 and 76.6 ms ± 14.7, respectively. These values have been plotted in Fig. 4, upper panel.

A linear regression of the form

$$Vhead_t = a*t + b \qquad [1]$$

(with t measured in seconds) fitted these values perfectly ($r^2 = 0.9998$). This means that the helmet imposed, in the initial phase of the movement, a constant head acceleration a with a mean value of 770 deg/s^2 and a range (± 1 SD) between 619 and 978 deg/s^2. The value of b was 6.4 deg/s; this represents the head velocity at the time of detection

←—— Fig. 2 Mean VOR gain and phase lag during sinusoidal head oscillations of the 24 normal subjects (circles), 7 patients with bilateral vestibular areflexia (group A, squares) and 40 patients with total unilateral vestibular loss (group B, triangles). Darkness: open symbols, dashed lines; visual target: closed symbols, continuous lines. For clarity, we plotted 1 SD (vertical bars) only for the condition darkness, as the values obtained with the visual target were similar.

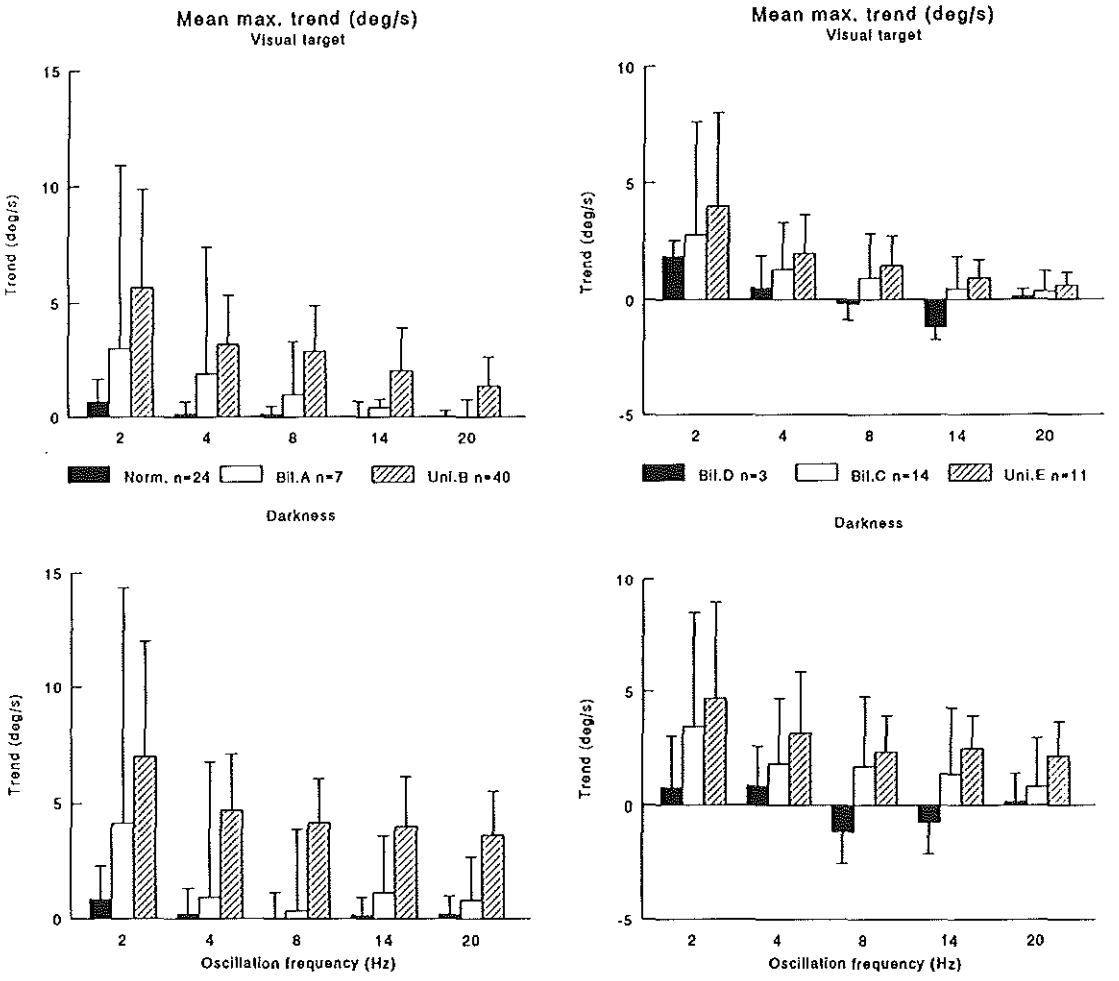


Fig. 3 Mean maximum trend in deg/s at the different head oscillation frequencies with a visual target (upper panels) and in darkness (lower panels). The two left panels show the results of the control group (black bars, n=24), patient group A (open bars, bilateral vestibular areflexia, n=7) and patient group B (dashed bars, unilateral vestibular loss, n=40). The two right panels show the results of patient group C (open bars, bilateral vestibular hyporeflexia with mild vestibular symptoms, n=14), patient group D (black bars, transient bilateral vestibular hyporeflexia, n=3), and patient group E (dashed bars, unilateral vestibular hyporeflexia, n=11). Polarity: for normals and bilateral LD: leftward is plotted upward; for unilateral LD: trend in the direction of the dysfunctioning labyrinth is plotted upward.

of the head movement, $t = 0$ (the difference with the nominal detection criterion of 10 deg/s corresponds to the velocity build-up during 1 sampling interval).

For the manually induced head-steps, the velocity build-up was not uniform. The manually induced steps reached eventually higher velocities and accelerations than the helmet-induced steps, but initial head acceleration was lower. Head velocities of 15 deg/s, 25 deg/s, 50 deg/s and 65 deg/s were reached after respectively 15.6 ms ± 5.2, 26.9 ms ± 7, 48.7 ms ± 10.7 and 58 ms ± 11.5 in the normal group. This build-up of head velocity is shown in Fig. 4, lower panel. For the lowest (15 deg/s) and the highest head velocity (65 deg/s) there was a significant difference in the timing ($P < 0.005$) between the manually and helmet-generated step movements of the head. Clearly, the build-up of head velocity during manually administered steps was not a linear function of time. Acceleration was not constant, but gradually increasing. The average velocity build-up in the early phase of the movement was fitted (Fig. 4, lower panel) well ($r^2 = 0.999$) by a second order function of the form:

$$Vhead_t = p + q^*t + rt^2 \qquad [2]$$

This non-linear function is probably a result of the activation pattern and force build-up in the experimenter's arms, which does not have the abruptness of the activation of a torque motor.

3.4.4 Normal responses to helmet-induced step displacements of the head

First, we show in Fig. 5 (left panels) a representative example from a single healthy subject of the average responses (first 90 ms) to helmet-generated step displacements of the head (condition: darkness).

In the lower left panel in Fig. 5, mean head (solid lines) and compensatory eye movements (inverted; dotted lines) lie close to each other. Their ranges (± 1 SD; grey areas; dark: head, light: eye) are narrow, except later in the response. This situation corresponds to a VOR with a very short delay and a gain near unity, and low variability among consecutive responses. A high gain is also shown by the graph in the upper left panel in Fig. 5, in which some instantaneous eye velocities are plotted as a function of simultaneous head velocities.

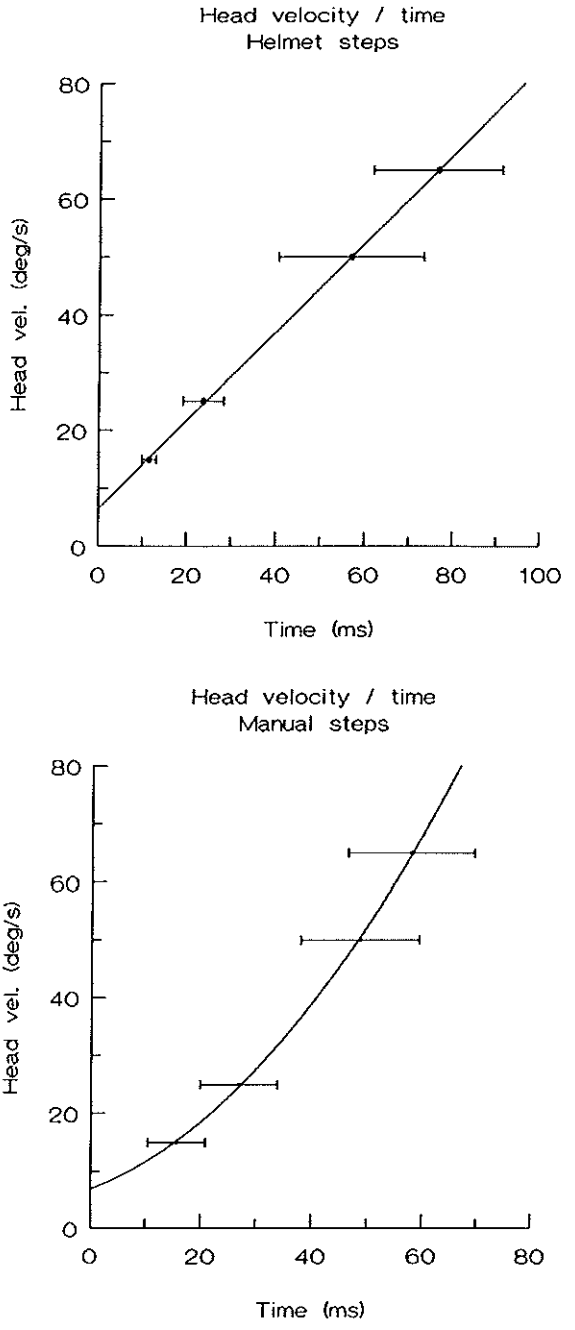


Fig. 4 Mean times (± 1 SD) after which head velocities of 15, 25, 50 and 65 deg/s were reached for passive steps induced by the helmet (upper panel) or manually by the experimenter (lower panel).

The VOR gain, computed as the quotient between eye velocity and simultaneous head velocity is, however, an inaccurate estimate of the true VOR gain in this early period, because of the delay of the ocular response to a continuously increasing head velocity; this point will be worked out below. The delays in this subject, determined with the method shown in Fig. 1, for rightward and leftward head movements, were 5.7 ms and 8.6 ms.

Mean results for helmet-induced steps in the whole group of normals, measured in darkness, are plotted in Fig. 6 (upper panel), which shows the mean velocities of the compensatory eye movements as a function of the corresponding mean head velocities (both pooled in 10 deg/s bins). We shall show below that this relation is very useful in the analysis of VOR responses. Consistently with the range of the head acceleration (see above), not all of the 24 subjects reached the higher velocities in the first 90 ms of the response; velocities of 15-25 deg/s, 50 deg/s and 65 deg/s were reached by 23, 14 and 9 subjects, respectively. To avoid any bias by small numbers of data, we discarded all averaged head velocities and corresponding averaged response velocities that were based on less than 3 values. In total, 982 head movements to the left and 958 to the right were collected for this measurement condition in 23 healthy subjects.

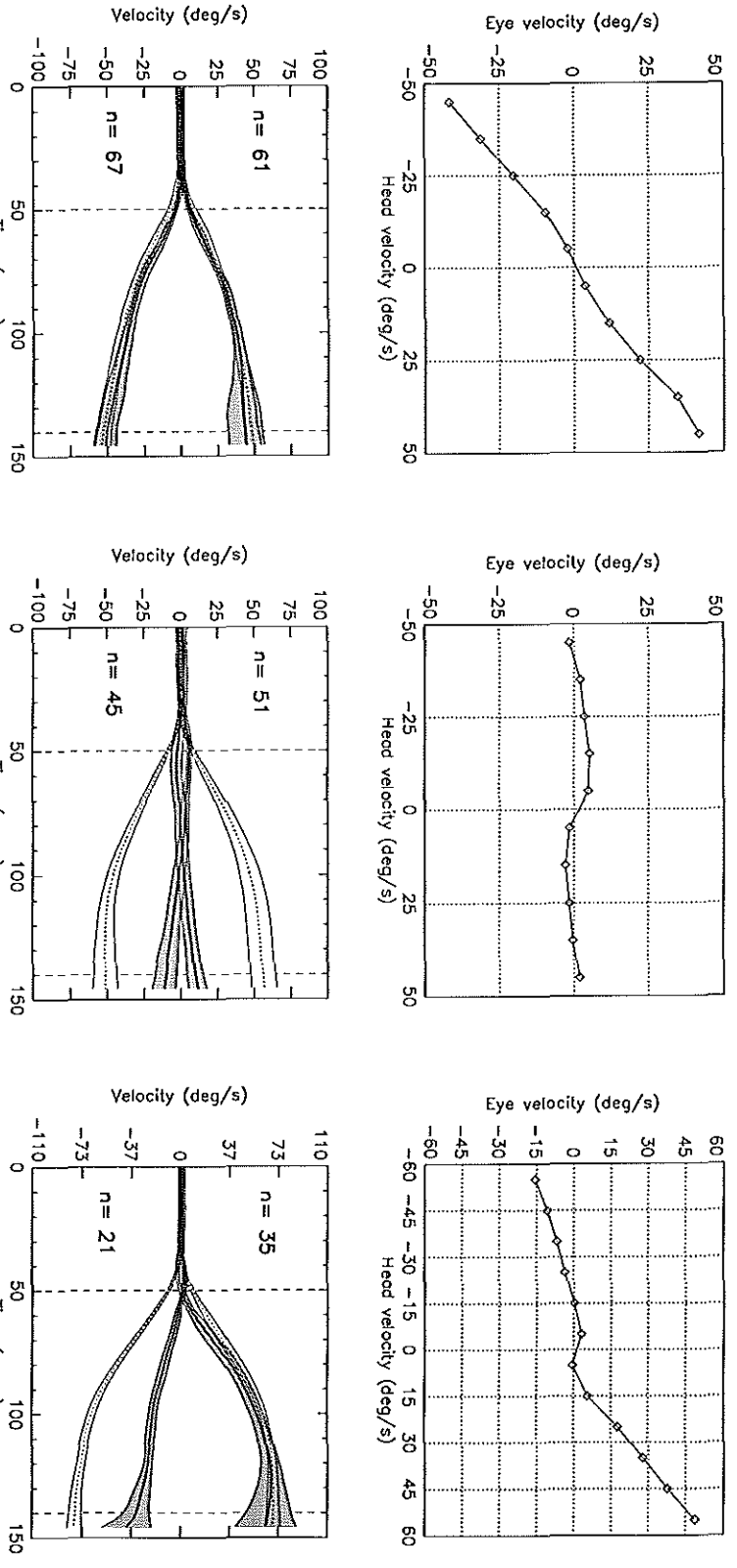
Mean delays in this normal group, determined with the conventional method shown in Fig. 1, were 6.6 ms ± 4.3 for leftward movements and 9.1 ms ± 5.1 for rightward movements. These values are not significantly different ($P > 0.05$) from each other. Therefore directions may be pooled; the overall mean delay was 7.8 ms ± 4.8 (SD).

3.4.5 Theoretical analysis of the eye velocity / head velocity relation

The diagonal, dashed line through the origin in Fig. 6 represents a unity ratio (slope 1.0) between compensatory eye movements and head movements without delay. If the responses followed this theoretical relation, compensation would be perfect. The real responses deviate from this ideal in two ways: 1) gain *(g)* is smaller than unity; 2) the response has a delay *(d)*.

As a consequence, the relation between eye velocity *(Veye)* and head velocity *(Vhead)* will have the following form:

$$-Veye_t = g * Vhead_{(t-d)} \qquad [3]$$


Eye velocity (deg/s)
Head velocity (deg/s)
Velocity (deg/s)
Time (msec)
n= 61
n= 67
n= 51
n= 45
n= 35
n= 21

In the case of a constant head acceleration, as we have found for the helmet-induced steps, *Vhead* will rise uniformly as a function of time:

$$Vhead_t = a*t \qquad [4]$$

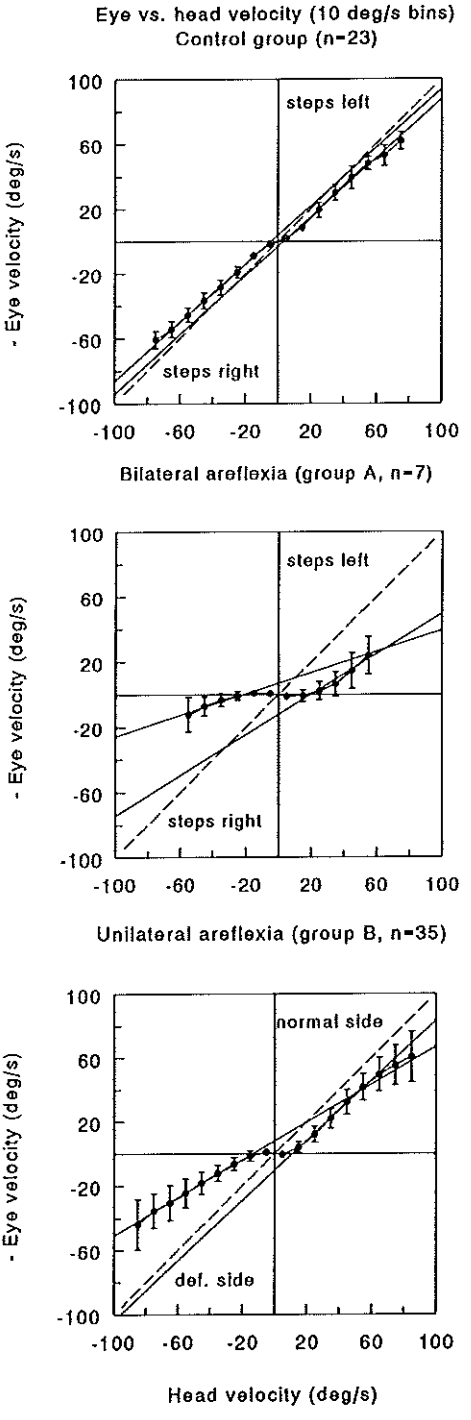
By substitution of [4] in [3] we obtain:

$$-Veye = g*a*t - g*a*d = g * Vhead_t - g*a*d \qquad [5]$$

Limiting conditions are that *Vhead* = 0 for $t < 0$ and that *Veye* = 0 for $t < d$. Assuming that g and d, like a, do not vary as a function of time, *-Veye* will thus be a linear function of *Vhead* with slope g. Theoretical *eye velocity / head velocity* relations can be calculated on the basis of this relation. An example is shown in Fig. 7 (with eye velocity plotted inverted, as in Fig. 6).

For clarity, pathological values have been assumed here. The right upper quadrant shows theoretical responses with a (normal) gain of 0.94 and a (prolonged) delay of 14 ms; the left lower quadrant shows responses with a (subnormal) gain of 0.59 and a (very prolonged) delay of 20 ms. Head acceleration *(a)* was set to the mean value in the control group, 770 deg/s^2. Constant gain values are reflected in the constant *slopes* of the parts of the relations for which eye velocity is not zero. Delays are reflected in the intersection of these straight parts with the *Vhead* axis: *Veye* does not deviate from zero until the delay d has elapsed. During this delay, head velocity has increased to a value $Vhead_d = a * d$.

← *Fig. 5 Left, middle and right panels represent the response of respectively one healthy subject, one subject with total bilateral vestibular loss (group A) and one subject with total unilateral vestibular loss (group B) to step displacements of the head, generated by the helmet. Measurement condition: darkness. The lower panels show a time window of 140 ms, starting 50 ms before detected start of head movements. The first dashed vertical line indicates the detected start of head movements, the second vertical dashed line the end of the time window. Mean head velocity ± 1 SD is represented by the dark grey areas, mean eye-in-head velocity ± 1 SD by the light grey areas (n: number of measurements). Upward direction reflects a head movement to the left. For clarity, we have inverted the eye-in-head signal. The upper panels represent the mean head velocity and corresponding eye-in-head velocities found in the 90 ms after the detected start of the head movement.*


Eye vs. head velocity (10 deg/s bins)
Control group (n=23)
steps left
steps right
- Eye velocity (deg/s)
100
60
20
-20
-60
-100
-100 -60 -20 20 60 100
Bilateral areflexia (group A, n=7)
steps left
steps right
- Eye velocity (deg/s)
Unilateral areflexia (group B, n=35)
normal side
def. side
- Eye velocity (deg/s)
Head velocity (deg/s)

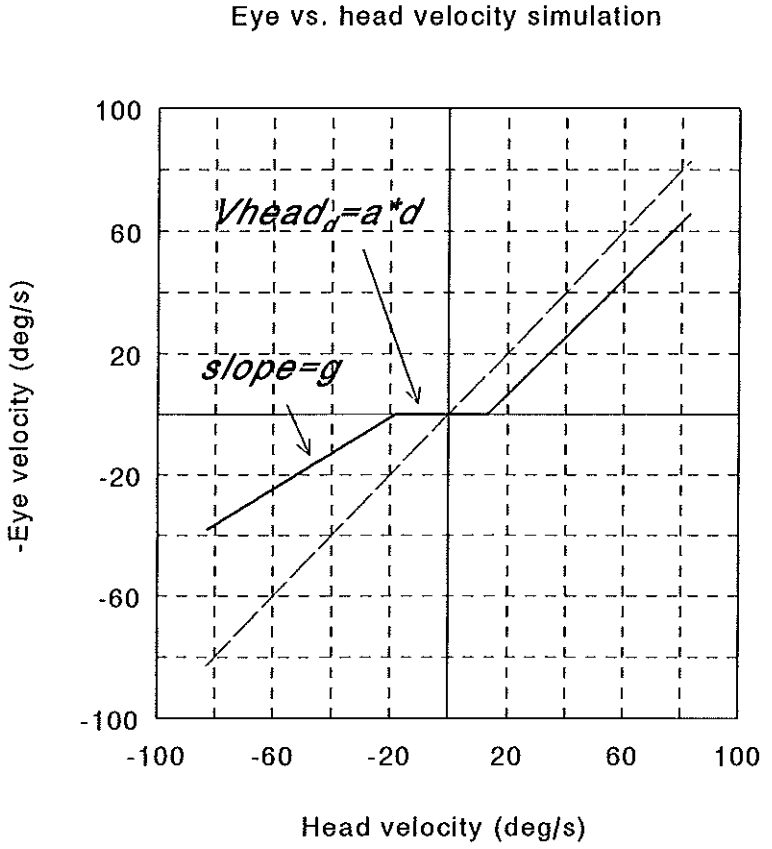


Fig. 7 Theoretical relationships between instantaneous eye and head velocities for VOR responses to a step in head acceleration with a constant delay and gain; see text for further details.

← *Fig. 6 Upper, middle and lower panel are group averages of the responses of respectively 23 control subjects, all patients of group A (n=7, total bilateral vestibular loss) and 35 patients of group B (total unilateral vestibular loss) to step displacements of the head, generated by the helmet. Measurement condition: darkness. The bars (± 1 SD) represent the variability between the subjects. The diagonal dashed line through the origin represents a perfect 1:1 relation between compensatory eye movements and head movements without delay. The two solid lines represent the regression lines to two parts of the head velocity / eye velocity graph; i.e. for the data points between 15 and 65 (or 55) deg/s head velocity and for data points between -15 and -65 (or -55) deg/s head velocity.*

Therefore, the delay can be estimated from the intersection, $Vhead_d$, of the straight parts of the *Veye/Vhead* relation with the *Vhead* axis:

$$d = Vhead_d / a \qquad [6]$$

Thus, the constancy of a in our helmet-induced steps allows, theoretically, independent estimation of gain and delay from the relations between $Veye_t$ and $Vhead_t$.

It can be shown that for a non-uniform acceleration of the head, such as seen in the manually applied steps (Fig. 4, lower panel), the relations are more complex. Quadratic and higher terms will make the slope of *Veye / Vhead* time-dependent and thus not straight. Therefore, estimates of gain and delay from manual steps with a similar procedure as described above will be less reliable than for constant acceleration steps.

3.4.6 Normal Veye / Vhead diagrams

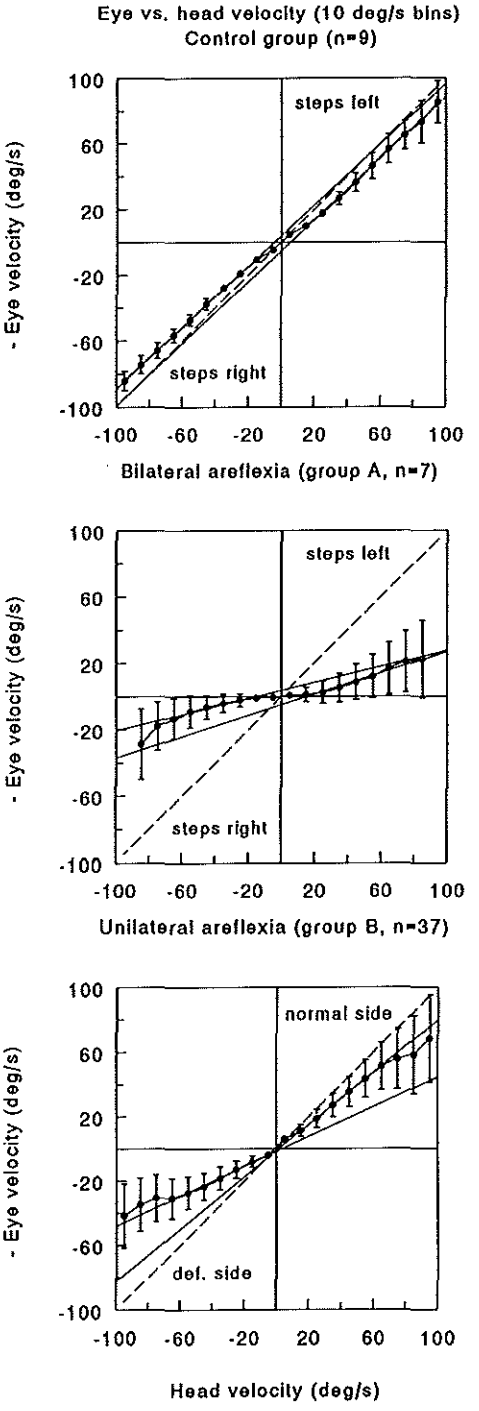
We return now to the data for normals in Fig. 6, upper panel. It is clear that the data follow indeed linear relations, that intersect with the *Vhead* axis. We calculated two linear regression lines on the eye velocity / head velocity data for the head velocity ranges between 15 and 65 deg/s and between -15 and -65 deg/s, respectively. The expected, high gains are expressed in the slopes of both regression lines: 0.899 ± 0.015 (Standard Error, S.E.) for movements to the right and 0.908 ± 0.052 (S.E.) for movements to the left. The responses in the two directions were, as expected, symmetrical; there was no significant difference ($P > 0.05$) in gain between the two movement directions. The delays, calculated from the intersections $Vhead_d$, were found to be 5.5 ms for rightward steps and 4.1 ms for leftward steps; at average, delay would thus be about 4.8 ms. Notice that this value is lower than the 7.8 ms estimated on the basis of velocity thresholds and in better agreement with the lag times estimated from phase delays of responses to oscillation (see above). For the condition with the visual target (883 movements to the right and 912 movements to the left), the responses were virtually identical to those obtained in darkness. Slopes of linear regressions were respectively 0.99 and 0.96 (not shown in Fig. 6). Although these values were marginally higher than in darkness, the differences were not significant at any of the head velocities. The same was the case for the mean delay values, calculated according to the method in Fig. 1 (8.5 ms ± 3.4 to the right and 7.7 ms ± 3.8 to the left).

3.4.7 Responses to manual steps in normals

Fig. 8, upper panel, shows the mean responses of the control group to manually applied step displacements of the head in darkness. In total, 224 head movements to the left and 240 to the right were collected for this condition in 9 of the healthy subjects. The use of manual stimuli for generating the step displacements of the head resulted in roughly comparable responses as the use of the helmet, but with some important differences, related to the shape of the stimulus. Compared to Fig. 6, Fig. 8 does not show such a marked flattening of the *Veye / Vhead* relations at low head velocities, corresponding to the beginning of the movement. This may be due to the less abrupt start of the head movement. The latter also made the determination of the delays with the conventional threshold method (Fig. 1) less reliable than for the helmet-generated movements: 7.3 ms ± 5.0 for leftward head movements and 3.8 ms ± 2.5 for rightward head movements. These values were not significantly different ($P > 0.05$) and therefore delays may be pooled for directions, with as a result a mean value of 5.5 ± 4.4 ms. The second, intersection based method was not applied to the manual steps, because acceleration was not constant. Linear regression lines could, however be fitted for the speed ranges 15-65 deg/s; their slopes for rightward and leftward movements were 0.927 ± 0.011 (S.E.) and 0.94 ± 0.023 (S.E.), respectively. These values are close to the values determined for the helmet-induced steps, but also this gain estimate is less reliable for manual steps due to the non-constant acceleration, and the larger variability of manually controlled movements.

The responses to manual steps with the visual target present were statistically identical to the responses in darkness. To avoid iteration, we like to state at this point that the presence of a visual target did not affect the responses to steps, as evaluated here, in a significant way in any of the subject groups (normal or patient). Therefore we shall no longer separately discuss the responses to steps with the visual target present in the following descriptions of patient groups.

*Summary of results in normals:*The various tests of the VOR in normals led to essentially concordant results. Analysis of oscillation, for the frequency range with the most reproducible results (2-8 Hz), led to estimates of a mean gain of 0.86 and a mean delay (derived from phase) of 4 ms. Helmet-induced steps, analyzed with the eye velocity / head velocity relations, yielded a gain of 0.9 and a delay of 5 ms. Manual steps led to a (conventionally) estimated mean delay of 6 ms and a gain of 0.94. All responses were essentially symmetrical in the two movement directions.


Eye vs. head velocity (10 deg/s bins)
Control group (n=9)
steps left
steps right
- Eye velocity (deg/s)
100
60
20
-20
-60
-100
-100 -60 -20 20 60 100
Bilateral areflexia (group A, n=7)
steps left
steps right
- Eye velocity (deg/s)
Unilateral areflexia (group B, n=37)
normal side
def. side
- Eye velocity (deg/s)
Head velocity (deg/s)

3.4.8 Responses of clinically total, bilateral LD patients (group A)

Oscillation. Fig. 2 shows mean VOR gain and phase of patients with clinically bilateral vestibular areflexia (n=7, group A), in the conditions 'visual target' (continuous lines, filled squares) and 'darkness' (dashed lines, open squares). The bars (-1 SD) represent intersubject variability for the condition darkness; the larger variability compared to the normal group reflects the inhomogeneity of group A. Variability for the other condition (visual target) was comparable. There was no statistical difference between the results with a target and in darkness. VOR gain and phase values for this patient group (A) were significantly lower ($P < 0.001$) than in the control group, except at the highest frequency (20 Hz).

Fig. 3 (left panels, open bars) shows the mean maximum trends for this group. Although there was a tendency for trends to be higher than in normals, the differences were not significant for any of the frequencies in either measurement condition ($P > 0.05$), due to the large variability in this patient group.

Helmet-induced steps. Fig. 5, middle panels (condition darkness) show an example of one severely afflicted patient from group A. This patient (a woman, aged 74) had received gentamicin in the treatment for meningitis. She showed severe unsteadiness during walking and complained of oscillopsia, especially in the vertical direction. Responses to step movements of the head were extremely poor and had very long delays (83 ms and 89 ms for leftward and rightward movements). The presence of a visual target did not improve the responses.

Fig. 6 (middle panel) gives the mean results of all patients of group A (n=7) for the helmet-applied steps in darkness. The collected head movements (206 to the right and 222 to the left) covered a range of head velocities up to only ±55 deg/s. Clearly, the corresponding eye-in-head velocities were very much lower than in the normal subjects; the differences were highly significant ($P < 0.001$) for all velocities.

← *Fig. 8 As Fig. 6, but for manually applied head steps: averages of the responses of 9 subjects of the control group, all patients of group A (n=7, total bilateral vestibular loss) and 37 patients of group B (total unilateral vestibular loss).*

We plotted two regression lines on the eye velocity / head velocity data for head velocities between ±55 deg/s and ±15 deg/s. The slopes for these two lines were 0.326 ± 0.040 (S.E.) for movements to the right and 0.62 ± 0.084 (S.E.) for movements to the left. Due to the large variance, this difference between the directions was not significant at any head velocity. For the same reason, the unexpectedly high gain based on the slope of the *Veye/Vhead* relation for steps to the left may be not entirely realistic. The problem of large variability is exacerbated by the, coincidental, fact that the head velocities reached within 90 ms were lower than usual in this group. Averaged over directions, gain would be estimated at 0.47.

Mean delays in this group of patients, estimated with the conventional technique (Fig. 1) were 62 ms ± 29 and 52 ms ± 30 for the responses to rightward and leftward movements. These delays were significantly higher ($P < 0.001$) than the mean delay found, with the same method, in the control group. However, especially in this group, the conventional technique for estimating delay appears to be very prone to contamination by low gain values; therefore, these very high values are untrustworthy. Our alternative method, based on the intersection of the fitted linear relations with the *Vhead* axis, led to delay estimates of 27 ms for steps to the right and 25 ms for steps to the left. These values, which we propose as more realistic, are still very considerably higher than those found for normals.

Fig. 8, middle panel, shows the mean responses of the bilateral areflexia group to manually applied steps. In this case there was, as expected, a very low response in both directions. In total, 158 head movements to the left and 167 to the right were collected for this measurement condition in 7 patients; a range up to ± 85 deg/s was covered. The slopes for the two regression lines were 0.241 ± 0.024 (S.E.) for rightward movements and 0.318 ± 0.027 (S.E.) for leftward movements. Again, this asymmetry was not statistically significant. Similarly as for the helmet-generated step displacements of the head, the velocities of the compensatory eye movements were significantly different ($P < 0.001$) from the control group (Fig. 8, upper panel) for all tested velocities. Conventionally estimated (thus almost certainly over-estimated) delays for rightward and leftward movements were 64 ms ± 28 and 55 ms ± 26; these values were also significantly different ($P < 0.001$) from the control group.

Summary of bilateral patients: Firstly it is clear that, as a group, these patients were not homogeneous, and that vestibular functions were, at average, only partially lost. Again, the various methods led to essentially concordant results. For oscillation (range

2-8 Hz) mean gain was about 0.45 and delay (derived from phase lag) about 16 ms. For helmet-induced steps, gain was at average about 0.48 and delay (intersection method) 26 ms. Manual steps lead to gain-estimates of about 0.28 at average. Conventional (threshold) estimates of delay from step responses (50-60 ms) were clearly inflated due to confusion by low gain. In view of the differences among subjects, such mean results should not be considered as representative for individual patients, but they do show consistently that gain was severely lowered and delay was markedly prolonged in this group with clinically bilateral areflexia.

3.4.9 Responses of clinically total, unilateral LD patients (group B)

Oscillation. Fig. 2 (triangles) shows mean VOR gain and phase curves of patients with total unilateral vestibular loss (n=40, group B), in the conditions 'visual target' (continuous lines, filled triangles) and 'darkness' (dashed lines, open triangles). Bars (-1 SD) represent intersubject variability for the condition darkness, but were comparable for the condition visual target. Once again, there was no statistical difference between the two conditions. In the frequency range 2-14 Hz there was a significant difference in VOR gain for both measurement conditions ($P < 0.001$ for 2-8 Hz; $P < 0.05$ for 14 Hz) in comparison to the control group. At the highest frequency (20 Hz) both P-values were >0.05. For the VOR phase curves there were significant differences at all frequencies and both measurement conditions, except at 2 Hz in darkness.

Fig. 3 (left panels, hatched bars) shows the mean maximum trends for this group. For each frequency and measurement condition there was a highly significant difference ($P < 0.001$) with the control group. Examples of recordings of the raw head and gaze signals (before elimination of saccades) for two patients after surgery for an acoustic neuroma, respectively on the left side and right side, are plotted in Fig. 9. The systematically asymmetrical responses to the rightward and leftward components of the oscillation and the cumulation of trend are very conspicuous.

Helmet-induced steps. Fig. 5 (right panels, condition darkness) show an example of a patient (aged 56 years), 7 years after surgery for an acoustic neuroma on the right side. As expected, there was a much better response to leftward head movements. This asymmetry is also expressed in the delays calculated, in the conventional way, for this subject, which were 11.4 ms for the response to leftward head movements and 22.8 ms for rightward movements. The result with the visual target was comparable.

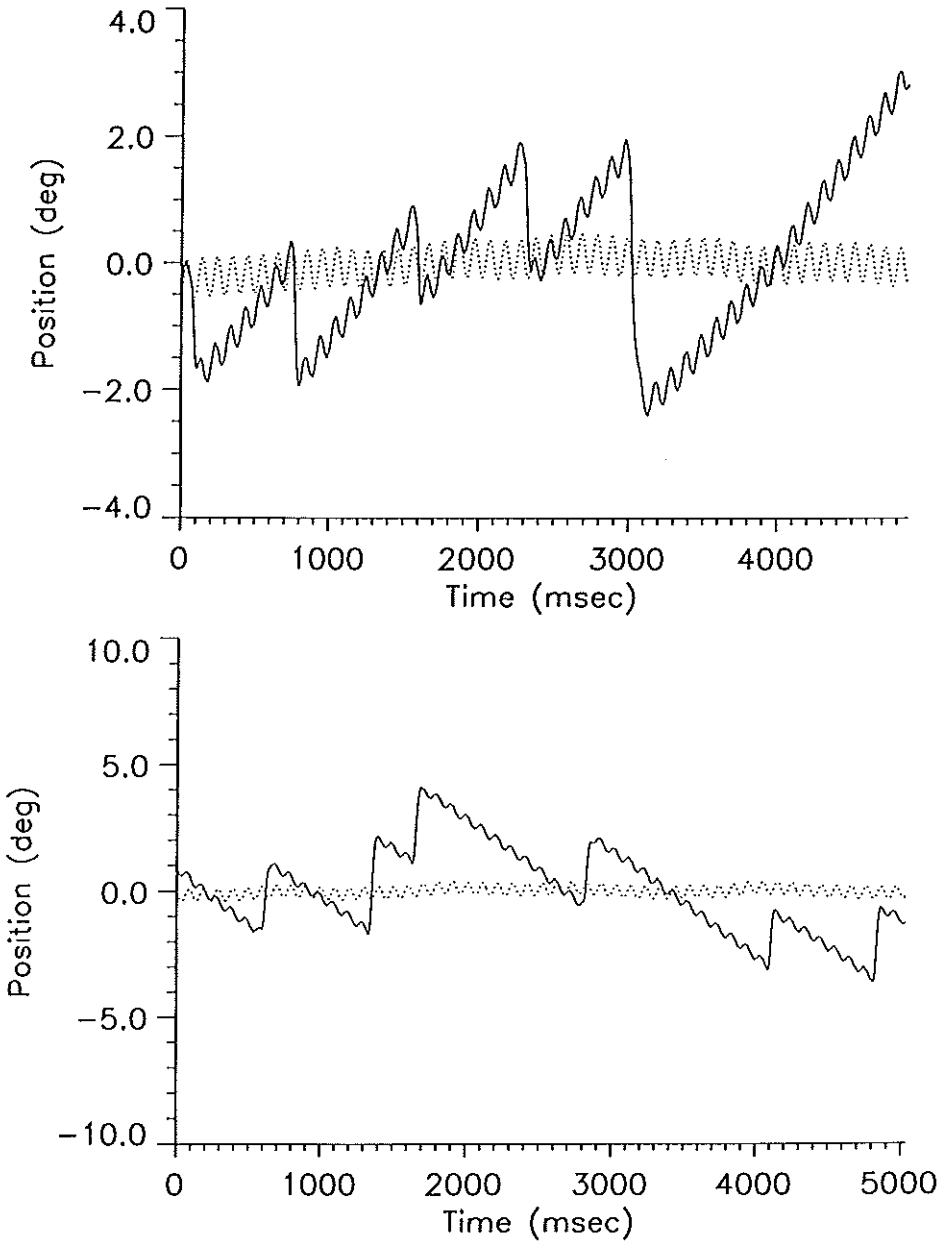
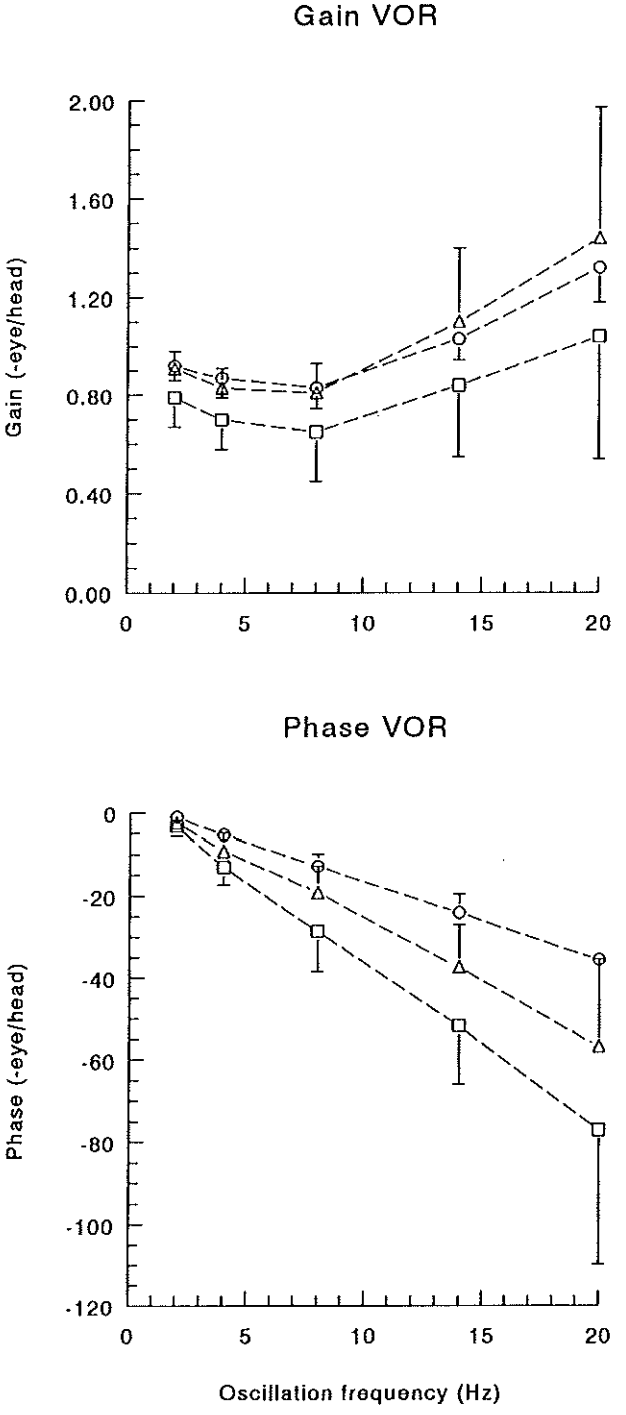


Fig. 9 Examples of head (dotted lines) and gaze (solid lines, without saccade removal) recordings during sinusoidal head oscillations in two patients, operated for an acoustic neuroma (group B) on the left side (upper panel) and on the right side (lower panel). Upward direction reflects a head or eye movement to the left.

Fig. 6 (lower panel, condition darkness, 911 head movements to the defective side and 960 to the normal side) shows the mean response of 35 patients of group B. The directions have been normalized to place all responses to the healthy side in the right upper quadrant. There is a clear asymmetry in this mean response; the responses to head movements to the normal side were much better than to the defective side. The slopes of the regression lines were 0.588 ± 0.011 (S.E.) for movements to the defective side and 0.936 ± 0.018 (S.E.) for movements to the normal side. At all head velocities between ± 5 deg/s and ± 85 deg/s there was a highly significant difference ($P < 0.001$) between the responses in the two movement directions. In addition, for all head velocities to the *defective* side, the corresponding velocities of the compensatory eye movements were highly significantly lower ($P < 0.001$) than the responses at corresponding head velocities in the control group. For head velocities <65 deg/s to the *normal* side, corresponding eye-in-head velocities were also highly significantly lower than in the control group. This result, however, is probably spurious, because it is based on the comparison of simultaneously occurring eye and head velocities. This approach neglects the effects of delay. Typically, the slope of the regression line for movements to the normal side (0.94) was similar to the slopes for movements to the left and right in normal subjects but the regression line was offset further from the 'ideal' diagonal (compare Fig. 6 lower and upper panels). This was apparently the result of an increased delay.

Calculated in the conventional way (Fig. 1, lower panel), mean delay was 14.8 ms ± 5.7 for steps toward the normal side and 20.7 ms ± 8.6 for steps to the side of the lesion. There was not only a significant difference ($P < 0.05$) between these mean delay values for both movement directions, but mean delay for the response to head movements to the normal side was also significantly higher ($P < 0.001$) than for rightward and leftward movements in the control group. We also applied the intersection method to determine the delays in these unilateral patients; the resulting values were 17.8 ms to the defective side and 14.4 ms to the healthy side. These values are only marginally lower than the conventionally determined ones but they are essentially more reliable. Notice that the simulation in Fig. 7 was based on the values found for our unilateral group (Fig. 6).

Manual steps. Fig. 8 (lower panel) shows mean responses of the unilateral group to manually applied steps in darkness. Once again there was, as expected, a better response to movements to the normal side. In total, 668 head movements to the normal side (mean 'conventional' delay 13.4 ms ± 9.8, slope 0.81) and 707 to the defective side


Gain VOR
Gain (-eye/head)
2.00
1.60
1.20
0.80
0.40
0.00
0
5
10
15
20
Phase VOR
Phase (-eye/head)
0
-20
-40
-60
-80
-100
-120
0
5
10
15
20
Oscillation frequency (Hz)

(mean 'conventional' delay 19.2 ms ± 12, slope 0.46) were collected for this measurement condition in 37 patients. There was a significant difference ($P < 0.05$) between these two mean delay values and they were also significantly different from the corresponding delay in the control group ($P < 0.025$). The compensatory eye velocities for movement to the defective side were at all head velocities up till 85 deg/s significantly lower ($P < 0.001$) than compensatory eye velocities for movement to the normal side. The responses to movements to the normal side were not significantly different from the control group.

We conclude that the asymmetry between VOR responses to head movements to the normal and defective side was not more pronounced for manually delivered than for helmet-generated step displacements of the head. This lack of a difference, despite a higher peak velocity of the manual movement, was probably due to the markedly lower acceleration in the first 90 ms of the manual movement compared to the helmet (see Fig. 4, lower panel).

Summary of clinically total, unilateral patients: The distinctive feature of this group is the consistent asymmetry of the VOR. Responses to steps to the healthy side have a virtually normal gain, whereas gain is on the order of 0.5 for steps in the de-afferented direction. Remarkably, the delay seems to be prolonged in both directions; all methods lead to estimations of about 14 ms in the healthy direction and about 18 ms in the de-afferented direction. Responses to oscillation (in the range 2-8 Hz) show a gain of about 0.69 and a delay of about 8 ms; these values are in between those for normal and bilaterally deficient subjects. Asymmetry is reflected in the responses to oscillation as a consistent trend (Figs. 3 and 9).

3.4.10 Responses of clinically partial, bilateral LD patients (group C)

Oscillation. Fig. 10 (squares) shows mean VOR gain and phase in darkness of patients with clinically bilateral vestibular hyporeflexia (n=14, group C), who did have only

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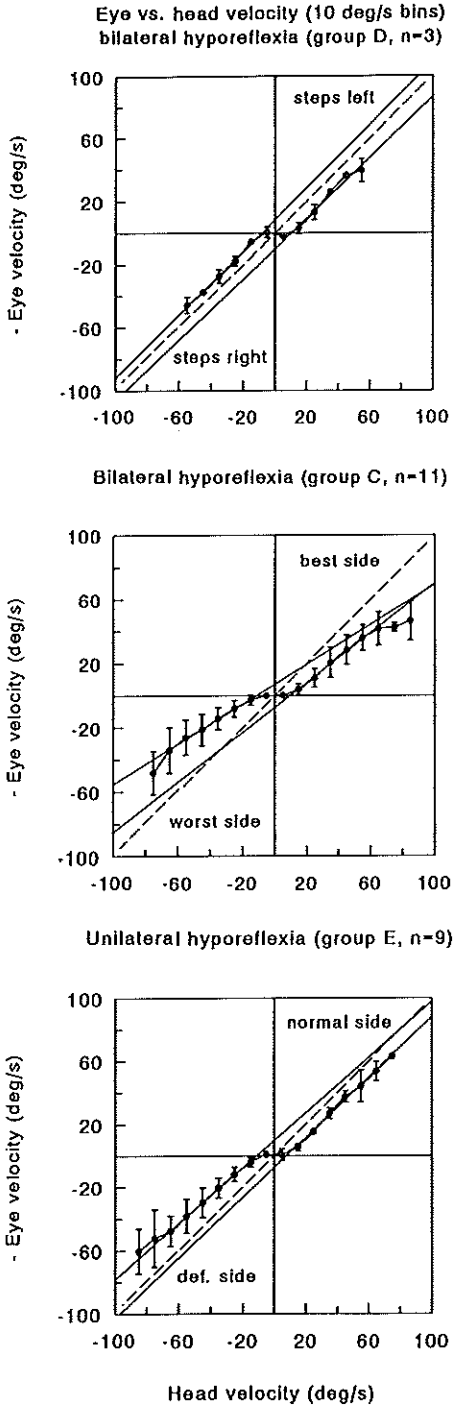
←—— ***Fig. 10** Mean VOR gain and phase lag values during sinusoidal head oscillations (vertical bars representing + 1 SD or - 1 SD) of the 3 subjects of group D with bilateral vestibular hyporeflexia without symptoms (circles), 14 patients of group C with symptoms (squares) and 11 patients of group E with unilateral vestibular hyporeflexia (triangles). For clarity we plotted only the results for the condition darkness, as the values obtained with the visual target were similar.*


Eye vs. head velocity (10 deg/s bins)
bilateral hyporeflexia (group D, n=3)
steps left
steps right
- Eye velocity (deg/s)
100
60
20
-20
-60
-100
-100 -60 -20 20 60 100
Bilateral hyporeflexia (group C, n=11)
best side
worst side
- Eye velocity (deg/s)
Unilateral hyporeflexia (group E, n=9)
normal side
def. side
- Eye velocity (deg/s)
Head velocity (deg/s)

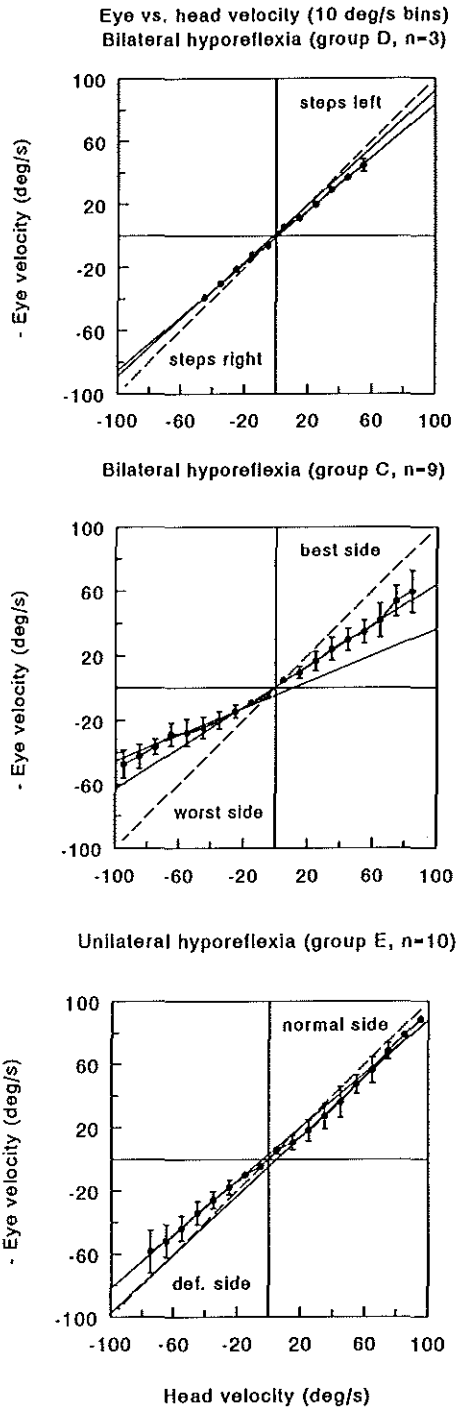
moderate, non-invalidating vestibular symptoms in daily life. In addition, eleven of these patients had some degree of asymmetry in vestibular function according to routine clinical testing. The bars (-1 SD) represent intersubject variability for the condition darkness. VOR gain, phase and variability for the other condition (visual target) were comparable. VOR gain in the frequency range 2-8 Hz was significantly lower ($P < 0.005$) than in the control group. At the highest frequencies (14-20 Hz) there was no significant difference ($P > 0.05$). VOR phase for this patient group lagged significantly more ($P < 0.001$) than in the control group in the frequency range 4-20 Hz. For the other condition (visual target) there was also a significant difference at 2 Hz ($P < 0.005$).

In comparison to the clinically total bilateral LD patients (group A), VOR gain in group C was higher ($P < 0.025$) and VOR phase showed a smaller lag ($P < 0.01$) in the frequency range 2-8 Hz. This smaller deficiency in objectively measured VOR function agrees well with the fact that group A patients had clinically total areflexia and much worse vestibular symptoms in daily life.

Fig. 3 (right panels, open bars) shows the mean maximum trends for this group. In the frequency range 2-14 Hz there was a significantly ($P < 0.025$) higher trend, to the most defective side, than in the control group.

Steps. Fig. 11 (middle panel, condition darkness, 210 head movements to the less defective side and 250 to the most defective side) shows the mean response to helmet-induced steps of 11 patients of group C. The directions have been normalized to place all responses to the less defective side in the right upper quadrant.

←—— *Fig. 11 Upper, middle and lower panel are group averages of the responses of respectively 3 patients of group D (previous bilateral vestibular hypofunction but with no remaining vestibular complaints in daily life), 11 patients of group C (bilateral vestibular hyporeflexia and mild vestibular complaints in daily life) and 9 patients of group E (partial unilateral vestibular loss) to step displacements of the head, generated by the helmet. Measurement condition: darkness. The bars (± 1 SD) represent the variability between the subjects. The diagonal dashed line through the origin represents a perfect 1:1 relation between compensatory eye movements and head movements without delay. The two solid lines represent the regression lines to two parts of the head velocity / eye velocity graph; i.e. for the data points between 15 and 65 (or 55) deg/s head velocity and for data points between -15 and -65 (or -55) deg/s head velocity.*


Eye vs. head velocity (10 deg/s bins)
Bilateral hyporeflexia (group D, n=3)
steps left
steps right
- Eye velocity (deg/s)
100
60
20
-20
-60
-100
-100 -60 -20 20 60 100
Bilateral hyporeflexia (group C, n=9)
best side
worst side
- Eye velocity (deg/s)
100
60
20
-20
-60
-100
-100 -60 -20 20 60 100
Unilateral hyporeflexia (group E, n=10)
normal side
def. side
- Eye velocity (deg/s)
100
60
20
-20
-60
-100
-100 -60 -20 20 60 100
Head velocity (deg/s)

There was an asymmetry in this mean response; i.e. mean response to head movements to the less defective side (slope 0.78) was better than the mean response to movements to the most defective side (slope 0.62). However, this difference was not significant at any of the head velocities. At all head velocities between ±15 and ±55 deg/s, corresponding velocities of the compensatory eye movements were significantly lower ($P < 0.001$) than the responses at corresponding head velocities in the control group. Comparing the response of this group C (Fig. 11, middle panel) with the response of group A (Fig. 6, middle panel) we see a better response in group C for head velocities between ±25 and ±45 deg/s ($P < 0.025$).

Mean delays, measured in the conventional way (Fig. 1), were 15.8 ms ± 6.2 for the response to movements to the less defective side and 21 ms ± 8.3 for the response to the most defective side. There was no significant difference ($P > 0.05$) between these mean delay values for both movement directions, but mean delays for the response to head movements to both sides were significantly ($P < 0.001$) higher than the mean delays (determined in the same way) in the control group. With the intersection method, delays were estimated (Fig. 11, middle panel) as 13 ms for steps to the less defective side and 15 ms for steps to the more defective side. These delays are clearly longer than in normals, but not as long as in group (A) with the more severe bilateral defects.

Fig. 12, middle panel (condition darkness) shows mean responses to the manually applied step displacements. In total, 160 head movements to the less defective side and 154 to the most defective side were collected for this measurement condition in 9 patients of this group. The slopes indicate gains of 0.64 and 0.41 in the best and worst direction. The asymmetry in the response to both movement directions was not significant at any of the head velocities. There was also no significant difference between the two mean, conventionally determined, delays (17.7 ± 7.7 and 18.7 ±9 ms), but these were significantly different from the corresponding delay value in the control group ($P < 0.001$). Head movements to the most defective side with velocities between 25-95 deg/s revealed a clearly lower response ($P < 0.001$) than in the control group. Contrary to the helmet-generated head movements (Fig. 11, middle panel), the manual

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←—— *Fig. 12 As Fig. 11, but for manually applied head steps: averages of the responses of all patients of group D (n=3), 9 patients of group C and 10 patients of group E (partial unilateral vestibular loss).*

head movements to the less defective side showed a significantly lower response (P <0.025) only at head velocities of 55 and 65 deg/s. Comparison of the response to manual head movements of this group C (Fig. 12, middle panel) with the response in group A, the severely bilaterally affected patients (Fig. 8, middle panel), reveals a significantly (P <0.025) better response in group C at all head velocities between ±75 deg/s.

Notice that, once again, delays of responses to manual steps were calculated only with the conventional threshold technique (Fig. 1). Comparison of Figs. 11 and 12, middle panels, shows another clear example that the *Veye/Vhead* relation shown in Fig. 7, allowing independent estimates of gain and delay, emerges typically only for the constant acceleration steps, induced by the helmet technique.

3.4.11 Responses of clinically transient, bilateral LD patients (group D)

Oscillation. Fig. 10 (circles) shows mean VOR gain and phase in darkness of the three patients with clinically bilateral vestibular hyporeflexia, whose vestibular symptoms had disappeared almost totally in the period between the routine clinical vestibular test and our measurement. The bars (-1 SD) represent intersubject variability for the condition darkness. VOR gain, phase and variability for the other condition (visual target) were comparable. VOR gain and VOR phase for this patient group were not significantly different (P >0.05) from those in the control group at any frequency.

Fig. 3 (right panels, black bars) shows the mean maximum trend for this group. There was no significant difference in mean maximum trend between this group and the control group.

Steps. Fig. 11 (upper panel, condition darkness, 72 head movements to the left side and 67 to the right side) shows the mean response of 3 patients of group D to helmet-induced steps. There was a symmetrical response, expressed in two almost similar slopes of the regression lines (0.97 for leftward and 1.00 for rightward steps) for both movement directions. In comparison with the control group, there was no significant difference in response at any of the head velocities. Conventionally determined mean delays for movements to the leftward and rightward head movements were respectively 8.6 ± 4 and 11.4 ± 4 ms. These values were also not significantly different from the delay in the control group. These results would seem to suggest completely normal

vestibular function. The only abnormality suggested by a comparison between Fig. 11 and Fig. 6, upper panels, is a larger offset *($Vhead_d$)* for group D. Indeed, the mean delays calculated with the intersection method for group D were abnormally long at 14 and 11 ms for leftward and rightward steps. Fig. 12 (upper panel, condition darkness) shows mean responses to the manually applied step displacements. In total, 71 head movements to the left (mean delay 12.4 ms ± 11.5, slope 0.87) and 79 to the right side (mean delay 8.5 ms ± 5.7, slope 0.93) were detected for this measurement condition in all patients (n=3) of this group. As we expected, there was no significant difference with the control group at any of the head velocities. Mean (conventionally determined) delays for either direction were also not significantly different from the control group.

3.4.12 Responses of clinically partial, unilateral LD patients (group E)

Oscillation. Fig. 10 (triangles) shows mean VOR gain and phase curves of patients with partial, unilateral vestibular loss (n=11, group E), in the condition darkness. Bars (1 SD) represent intersubject variability for the condition darkness. VOR gain, phase and variability were comparable for the condition visual target. In the frequency range from 4-14 Hz there was, for both measurements conditions, a significant difference ($P < 0.005$) in VOR phase in comparison to the control group. VOR gain, however, was not significantly different from the control group at any frequency in either of the measurement conditions.

Comparing the result of this group E with the patient group with total unilateral vestibular loss (group B), we found in darkness a significant difference in VOR gain in the frequency range from 2-14 Hz ($P < 0.025$). With a visual target there was also a significant difference at 20 Hz ($P < 0.025$). VOR phase was for both conditions only different from group B at 4 and 8 Hz ($P < 0.05$).

Fig. 3 (right panels, hatched bars) shows the mean maximum trends for this group. In the frequency range 2-20 Hz there was a highly significant difference ($P < 0.005$) with the control group. Again we compared the mean maximum trend of this group with group B. Only in darkness there appeared to be a significant difference at 8-20 Hz ($P < 0.05$).

Steps. Fig. 11 (lower panel, condition darkness, 201 head movements to the defective side and 201 to the normal side) shows the mean response to helmet-induced steps of 9

patients of group E. The directions have been normalized to place all responses to the healthy side in the right upper quadrant. Slopes for both regression lines were respectively 0.88 for movements to the defective side and 0.96 for movements to the normal side. However, a significant difference between the response to both movement directions was found only at ±35 deg/s ($P < 0.025$) and ±45 deg/s ($P < 0.05$).

For movements to the defective side, the difference with the control group (upper panel, Fig. 6) was highly significant ($P < 0.001$) between 5-35 deg/s and significant ($P < 0.025$) at 45 deg/s. For movements to the normal side there was a significant difference with the control group only at 15 deg/s ($P < 0.025$) and at 25 deg/s ($P < 0.05$). Conventionally determined mean delay was 11.7 ms ± 3.6 for movements to the normal side and 12.7 ms ± 6.6 for movements to the defective side. There was no significant difference between these two delays; both were significantly higher ($P < 0.05$) than the mean delay in the control group. Delays determined with the intersection method were 10 ms to the normal side and 14 ms to the defective side. When we compared the response in patient group E with the response of patient group B (lower panel, Fig. 6), there appeared to be in group E a better response to movements to the defective side ($P < 0.05$ at 15 deg/s and $P < 0.001$ at 25-65 deg/s). For movements to the normal side there was no significant difference at any velocity. Additionally, there appeared to be a significantly ($P < 0.025$) shorter delay for the response to the defective side in group E than in group B.

Fig. 12 (lower panel, condition darkness) shows mean responses to the manually applied step displacements. In total, 190 head movements to the normal side (mean delay 9 ms, SD 11.3, slope 0.93) and 243 to the defective side (mean delay 16.3 ms, SD 19.7, slope 0.85) were collected for this measurement condition in 10 patients.

There was no significant difference between the two mean delays values and the corresponding delay of the control group. The compensatory eye velocities for the defective side were not significantly different from the compensatory eye velocities for the normal side at any of the head velocities. Additionally, there was no significant difference from the control group at any of the head velocities in either movement direction (Fig. 8, upper panel). Comparison of group E with patient group B revealed in group E significantly higher ($P < 0.025$ at 25 deg/s and $P < 0.005$ at 35-75 deg/s) responses to movements to the defective side than the corresponding responses in group B. The responses to movements to the normal side were in group E and B statistically the same.

3.5 Discussion

Our previous work (Tabak and Collewijn 1994a, b) indicated that precise measurements of compensatory eye movements induced by the reactive-torque helmet could reliably quantify the VOR without contamination of non-vestibular mechanisms like the visual system. In the present paper we show that this method can be successfully and safely applied in the evaluation of vestibular pathology. The accelerations of the head are strictly rotatory and limited by the power of the device to values on the order of 1000°/s^2. As head accelerations over 2000°/s^2 have been mentioned for natural activities such as running (Maas et al., 1989), our device operates in a safe range and, in fact, our subjects did not find the imposed head torques stressful in any way.

3.5.1 Responses to head oscillation

In our conditions, peak acceleration remained relatively constant at about 1000 deg/s^2; accordingly, amplitudes and peak velocities of head oscillations decreased with increasing frequency. A small drawback of this situation may be that VOR gains for the different head frequencies were measured at different amplitudes and peak velocities, but in the absence of overt non-linearities of the VOR this seems of little consequence. Some reservation may be in order, though, in interpreting the data at 20 Hz. Firstly, amplitudes at this frequency were very small and therefore prone to error (standard deviations were high). Furthermore, the elevation of VOR gain at this high frequency could possibly be related to a purely mechanical contribution by the inertia of the eyeball. Although, as we have argued before (Tabak and Collewijn, 1994a), such a contribution is unlikely on the basis of orbital mechanics, it is difficult to exclude, particularly as we had no opportunity to investigate subjects with proven complete bilateral vestibular de-afferentiation. The patient material that we have does suggest, however, some convergence between normals and LD subjects at 20 Hz (Fig. 2) for gain and phase. This would be compatible with a non-vestibular component of the responses at the highest frequency used.

The value of the traditional vestibular tests with low-frequency oscillation is known to be dubious. For example, Jenkins et al. (1982) concluded that low-frequency rotations were not consistently effective in separating patients from normal subjects, due to the large variance of the test results in the patient group with total unilateral vestibular loss.

Their results also indicated that any asymmetry of VOR gain was most pronounced in acute vestibular lesions and often disappeared as compensation occurred (see also Allum et al. 1988, Takahashi 1981, Takahashi et al. 1984, Baloh et al. 1982, 1984, Wolfe et al. 1982, Li 1992, Vibert et al. 1993). Other authors also concluded that the low-frequency rotatory test failed to reveal any additional clinically useful information (especially in cases of unilateral vestibular loss) that the routine caloric test was not already providing (Aschan 1966, Stahle 1958, Baloh et al. 1979, Mizukoshi et al. 1984). The caloric test is at best qualitative and has no definable input/output relation. Its only advantage is that it permits comparisons of one side with the other, while during rotatory testing both labyrinths are stimulated. Even in normal subjects the results of caloric testing are highly variable due to anatomical factors. Caloric stimulation may be considered as an ultra-low frequency stimulus and in fact, the responses to the bi-thermal caloric test correlate with responses to very low frequency sinusoidal rotation but not with responses to 'high frequency' rotations (Baloh et al. 1984, Honrubia et al.1985, Goebel and Rowdon 1992). Thus, a total bilateral absence of the caloric response does not necessarily imply a complete loss of compensatory eye movements. On the other hand, high frequency testing alone could miss a significant loss of VOR sensitivity that would be identified with caloric testing or low frequency rotational testing. Finally, both low (0.0125-0.2 Hz) and 'high' (0.4-1.5 Hz) frequency rotational tests were insensitive in identifying unilateral loss of the caloric response (Baloh et al. 1984).

Few studies of the performance of the human VOR at stimulus frequencies above 8 Hz have been made. Gauthier et al. (1984) found that, for subjects fixating an earth-stationary target, VOR gain fell to 0.6 around 8 Hz but increased to values greater than 1.0 above 15 Hz. They reported a phase lag of 50 deg at 10 Hz; this would correspond to a pure delay of about 14 ms. Our VOR gain curve showed, although with somewhat higher values, a similar course; i.e. a slight decrease in VOR gain from about 0.90 at 2 Hz to about 0.8 at 8 Hz, followed by an increase in gain above 8 Hz to values above unity at 20 Hz. Skavenski et al. (1979) measured the VOR in two subjects at 10 Hz and found a gain of 0.7 in both subjects. They reported a phase shift that was, over the range 8-15 Hz, proportional to a pure delay of 5 ms in one subject and 9 ms in the other. Maas et al. (1989) studied the horizontal VOR during transient, high-acceleration head rotations (1900-7100 deg/s^2, with significant spectral power in the range 9-12 Hz) in four human subjects. Median VOR gain ranged from 0.61-0.83 and the delay of the VOR ranged from 6 to 15 ms. The results from normal subjects in our present study are generally in agreement with these three previous reports. As expected there was

virtually no systematic deviation (trend) of the compensatory eye movements to a particular side in normal subjects (see Fig. 3, left panels, black bars).

To our knowledge no previous studies were carried out with patients with unilateral or bilateral vestibular deficits across the frequency range applied in our present paper. Therefore, comparisons with other studies have to be restricted to the lower, overlapping frequencies in our experiments (about 2-5 Hz). Looking first at our bilateral LD patients (group A) who had almost no response to caloric irrigation, it is interesting to note that they still showed some compensatory eye movements at all frequencies (see Fig. 2). Gains and phase lags were highly significantly lower and larger, respectively, than in the control group, except at 20 Hz, as discussed above. As expected there was no significant difference between measurements with and without a visual target. These results suggest that our head oscillation test is more sensitive than the caloric procedure and that a total bilateral absence of the caloric response does not necessarily imply a total loss of compensatory eye movements in the higher frequency range. Somewhat similar conclusions were reached by Baloh et al. (1984), Honrubia et al. (1985) and Goebel and Rowdon (1992). For this reason we have to conclude that none of our seven 'total, bilateral LD' patients had actually a total bilateral vestibular loss. This is plausible because none of them underwent surgical section of both vestibular nerves, the only case with a proven total bilateral vestibular loss. Unfortunately, we had no opportunity to include such a patient in our study.

Potentially, compensatory mechanisms for vestibular deficiency could be an alternative source of the residual eye movements. Dichgans et al. (1973) and Kasai and Zee (1978) found, respectively in monkeys and in men, that three different mechanisms can be utilized to stabilize gaze in compensation for a VOR-deficit. Firstly, the cervico-ocular reflex (COR) may be potentiated. This mechanism is controversial in the literature and unlikely to function at frequencies as high as we used. Recent evaluations and reviews of the COR were provided by Huygen et al. (1991) and Bronstein (1992). For the frequency range 0.1 - 0.4 Hz they found a compensatory COR with a gain on the order of 0.1 and lower in normals, but substantially higher in LD-subjects (about 0.7 at 0.1 Hz and about 0.4 at 0.4 Hz). The COR showed low-pass behavior, with gain decreasing and phase-lag increasing as a function of frequency. At 0.4 Hz, phase lag was 20-30 deg (Huygen et al., 1991); this would correspond to a delay of 140 ms. These findings make it unlikely that the COR would contribute significantly to our responses to high-frequency oscillation or to the early responses to head-steps.

Secondly, pre-programming of compensatory eye movements may play a role in voluntary head movements; this mechanism would also not apply to our high-frequency, passive head motions. Thirdly, increased saccadic activity may substitute for incomplete slow eye movements. Indications for this third mechanism could be found in our study: several patients in group A showed irregular eye movements contaminated with saccades, the amplitude of which decreased markedly at higher frequencies. As we evaluated VOR performance after removing saccades, also this third mechanism cannot account for the remaining compensatory eye movements and we conclude that these do reflect residual vestibular function.

Hydén et al. (1983) tested 7 patients with bilateral vestibular impairment, defined by the criterion that the total 'sum of responses' to bithermal caloric stimulation (maximum slow phase velocity [SPV] R44° + R30° + L44° + L30°) was less than 40 deg/sec. These patients were tested with oscillations across a frequency range of 0.5 - 3.5 Hz and eye movements were recorded with EOG. VOR gains and phases were in agreement with our results for the overlapping frequencies. All patients showed lower gains and longer phase lag values than the normal range, even in the lower frequency area. Hydén et al. (1983) found, like we did, rather large variability in gains and phases between the different patients. The high variability in VOR gains and phase lags in our patient group A is probably due to the variability in etiology of the vestibular impairment. Typically, the lowest VOR gains and largest phase lags were found in our patients with the severest vestibular symptoms in daily life.

Möller and Ödkvist (1989) measured 3 patients with bilateral vestibular loss (unknown diagnoses, no caloric response on ice-water) in the range of 0.25-3.25 Hz (peak velocity 65 deg/sec), using EOG. At 2 Hz they found a VOR gain of less than 0.2 in darkness and of about 0.5 with a stationary target. The same authors found a phase lead at 0.16 Hz in patients with a bilateral vestibular loss; this phase lead was much higher than in normal subjects. Such a phase lead, often described in patients with vestibular dysfunction, is considered to be a quantitative measure of vestibular loss. Möller and Ödkvist (1989) suggested, however, that this phase lead could instead be a reflection of non-vestibular mechanisms interacting with a vestibular deficiency, to compensate for gain losses. The fact that the frequencies used in our paper were probably too high for these non-vestibular mechanisms might be the reason that we did not find a phase lead in our patients with strong bilateral vestibular hyporeflexia.

Etiology (acoustic neuroma) was much more homogeneous in our group B (n=40).

Averaged gains of all patients in this group were significantly lower than in the normal control group, except at 20 Hz. In addition, phase lags were significantly higher than in normals at all frequencies. When we only consider the most reproducible VOR gains for the lower frequencies (2, 4 and 8 Hz) in the individual patient, merely 6 patients did not exhibit lower gains than the normal range, defined as the mean ± 1 SD, of the control group. The results are even clearer when we consider also the other parameters, phase and trend. Half of these 6 patients had larger trends and phase lags; the other 3 had only a clearly larger trend. As expected, de-saccaded eye movement records revealed deviation of the compensatory eye movements towards the side of the vestibular sensory loss. The averaged trend values were highly significantly larger for all frequencies than in the control group. Although very high frequencies (>2 Hz) are out of the functional range of the visual system, the presence of a fixation light did significantly lower the mean trend values in this group at the higher frequencies (4-20 Hz). This is probably caused by the fact that this drift, although caused by high-frequency oscillation, is actually a slow phenomenon that is visually corrigible.

Istl-Lenz et al. (1983) measured the VOR of unilaterally labyrinthectomized patients during passive whole body rotation using sinusoidal (0.5-3 Hz) oscillation. With a stationary visual target, they found at 2 Hz significantly lower gains than in a normal population. There was quite some variation in VOR gains at 3 Hz. Only 50% of their patients (n=8) exhibited a marked gain loss. Nevertheless, statistical analysis of the normal and patient populations revealed a significant difference between the two groups. These authors concluded that the response variabilities at 3 Hz could neither be attributed to the postoperative time period (correlation coefficient =-0.39) nor to patient age (correlation coefficient=0.04). The frequency above which eye movement asymmetry appeared varied among their patients, but all patients exhibited asymmetrical VOR responses at and above 2 Hz. Unfortunately, no information about VOR phase was given in their article.

Averaged VOR gains for patients with a partial unilateral vestibular loss (group E, n=11) did not differ from the control group but mean VOR phase lag was significantly larger than in normal subjects for the frequency range 4-14 Hz. In total, 4 individual patients of this group did show lower VOR gains in combination with larger phase lags (n=4) and larger trend values (n=3) than the normal range (mean ± 1 SD) of the control group. Among the patients with normal VOR gains (n=7), three did have clearly higher trend values and one also showed larger phase lags.

As expected, patients from group C (bilateral vestibular hyporeflexia without severe invalidating symptoms, n=14) had clearly lower VOR gains and larger phase lags (2-8 Hz) than the control group, but performed better than group A patients. Eleven of these patients were known to have some degree of asymmetry in their vestibular responses during the ENG test; accordingly, we found higher trends than in normal subjects.

The three patients from group D (with completely resolved vestibular symptoms) did not differ clearly from our normal subjects with respect to their VOR gain, phase and trend values. This corresponds well with the symptom-free daily life of these patients at the moment of our measurements.

3.5.2 Responses to head-steps

Passive step-rotations of the head have been successfully introduced as a VOR test by Halmagyi and his colleagues (Cremer et al. 1988; Halmagyi et al. 1990, 1991a, b, 1992; Aw et al. 1994, 1995). Halmagyi et al. (1990, 1991a, b, 1992), using manually generated head-steps, calculated in unilaterally vestibular de-afferented patients the VOR gain at an arbitrarily selected head velocity of 122.5 deg/s and found that the mean gain for steps toward the deficient side (0.21 ± 0.20, n=12) was significantly lower than in normal subjects at 122.5 deg/sec (0.94 ± 0.08, n=29). This deficit was permanent (no improvement between 1 week and 1 year after de-afferentation). However, the mean VOR gain for steps toward the healthy side (0.83 ± 0.13, n=10) was also significantly lower than the mean gain of the horizontal VOR gain in normal subjects (O.94 ± 0.08, n=29).

We confirm the great potential of this technique, but propose a number of refinements. Our helmet-technique appears to be superior compared to manually delivered steps because the helmet provides a constant torque, resulting in a constant acceleration (Fig. 4), whereas the acceleration of manually delivered steps, in our hands, increased as a function of time. Also, manual steps will be intrinsically more variable across time, experimenters and subjects. The constant acceleration offers the special advantage that gain and delay may be estimated independently from *eye velocity / head velocity* relationships (Fig. 7), as described in the Results.

Delay is important in two respects. Firstly, a reliable, independent estimate of VOR delay yields a potentially significant parameter of vestibular functionality. Secondly,

neglect of delay may distort estimates of VOR gain.

Conventional estimates of delay are based on estimates of the times at which head and eye start moving; usually some form of velocity criterion is used and attempts are made to exclude the basic noise that is usually present in velocity signals. Our variant of this technique is shown in Fig. 1. Intrinsic disadvantages of this method are that results are determined by one threshold crossing per response (i.e., a very small part of the response) and, even worse, that low gains will masquerade as long delays. Most attempts to estimate VOR delay accurately with such methods have been made in animal experiments (e.g. Lisberger, 1984, monkey; about 14 ms). Human data, based on high-acceleration stimuli, were given by Maas et al. (1989; 6-15 ms). Our estimate for normals, with the same method, was about 8 ms. Using the intersection of linear fits to the eye velocity / head velocity relations, however, and thus using essentially all data points, we found a lower mean delay of about 5 ms. More interestingly, we found that the delay, estimated in this way, was markedly prolonged in all cases of vestibular pathology, including steps toward the healthy side after unilateral de-afferentation. We believe that these results may be a basis for more systematic measurements of delay in vestibular pathology. We should make it clear that our present delay estimates were based on group averages; verification in individual cases (with data sampling at a higher frequency) will be needed in the future.

The second aspect of delay is, that it should be considered in the calculation of VOR gain from step-responses. Typically (e.g. Halmagyi et al. 1990) the ratio of *instantaneous* eye and head velocities is taken as the VOR gain. However, it is easy to show that this apparent gain, g_{app} will underestimate the real gain, g. From our previously derived equations:

$$-Veye_t = g * Vhead_{(t-d)} \qquad [3]$$

and, for constant head acceleration,

$$Vhead_t = a*t \qquad [4]$$

we can derive that

$$g_{app} = -Veye_t / Vhead_t = g * (1 - d/t) \qquad [7]$$

Two examples will show that this is an important effect. First, assume that t = 100 ms (the accepted limit for evaluation of step responses), g = 0.94, and d = 5 ms. These (normal) numbers yield g_{app} = 0.89; a moderate underestimate of g. As a second case, assume t = 100 ms, g = 0.94 and d = 14 ms (our values for the healthy side in unilaterally de-afferented subjects). In this case, we find that g_{app} = 0.81; a serious underestimate of g, which might make all the difference between a lowered or a normal gain for steps toward the normal side. The effects of d on t will become even stronger when t is taken shorter, that is, when instantaneous eye and head velocities are compared earlier in the response. In conclusion, the helmet-induced steps, analyzed in the proper way, appear to allow more specific conclusions than manually induced steps.

Finally, the possibility of purely mechanical components in our step-responses should be discussed. Zero-latency eye movement responses to acceleration pulses with 10 ms duration and 4000 deg/s$_2$ magnitude have been described by Khater et al. (1993) in cats. Such responses survived bilateral labyrinthectomy and were apparently a purely inertial, orbital phenomenon. Our accelerations were considerably lower and we never observed zero-latency compensatory eye movements in either normals or patients, as shown in Figs. 1 and 5 and as evident from the systematic effects of pathology on our measured delays. We conclude, therefore, that mechanical components were negligible in our step responses.

3.5.3 General conclusions

Our present results indicate that the reactive-torque helmet technique, in combination with precise recording of head and eye movements, has considerable potential in evaluating vestibular function as expressed in the VOR. The most specific results were obtained with constant acceleration head steps, proper analysis of which allowed independent estimates of gain and delay in both directions. Both of these parameters were systematically affected by vestibular pathology and the magnitude of changes from the normal values correlated well with the subjective level of vestibular dysfunction. The results obtained with head oscillation in the 2-8 Hz range generally supported the results with steps, showing similar changes in gain and delay (expressed in phase-lag). We conclude that not only gain, but also delay is an important parameter of the VOR. Both appear to be open to reliable, objective measurement and should be considered in future assessments of vestibular function.

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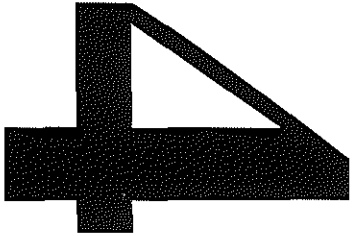

Deviation of the subjective vertical in longstanding unilateral vestibular loss

4.1 Abstract

We evaluated changes in the subjectively perceived gravitational vertical, as an index of unbalance in the function of the right and left otolith organs. In addition to normal subjects (n=25), we measured patients with a longstanding (mean 4.5 year ±3.2 S.D.; range 0.5-11.5 years) unilateral vestibular loss after surgery for acoustic neuroma (n=32), patients with partial unilateral vestibular loss (n=7) and patients with bilateral vestibular hyporeflexia (n=8). Normal subjects could accurately align a vertical luminous bar to the gravitational vertical in an otherwise completely dark room (mean setting -0.14°±1.11 S.D.). Patients with leftsided (complete; n=13) or rightsided (complete; n=19 and partial; n=7) unilateral vestibular loss made mean angular settings at 2.55°±1.57 (S.D.) leftward and 2.22° (±1.96 S.D.) rightward, respectively. These means differed highly significantly from the normal mean (p<0.00001). In the time interval investigated (0.5-11.5 years) the magnitude of the tilt angle showed no correlation with the time elapsed since the operation. The mean setting by patients with clinically bilateral vestibular loss (-1.17°±1.96 S.D.; n=8) did not significantly differ from the control group. The systematic tilts of the subjective vertical in patients with a unilateral vestibular impairment were correlated with their unbalance in canal-ocular reflexes, as reflected by drift during head-oscillation at 2 Hz (r^2=0.44) and asymmetries in VOR-gain for head-steps (r^2=0.48-0.67). These correlations were largely determined by the *signs* of the asymmetries; correlation between the absolute values of the VOR gain asymmetries and subjective vertical angles proved to be virtually absent. We conclude that the setting of the subjective vertical is a very sensitive tool in detecting a left-right unbalance in otolith-function, and that small but significant deviations towards the defective side may persist during many years (probably permanently) after unilateral lesions of the labyrinth or the vestibular nerve.

4.2 Introduction

The perception and control of the orientation of the head relative to the direction of gravity is vital in maintaining a normal posture and equilibrium. Obviously, the otolith organs provide an important sensory input to these functions. The evaluation of otholith function has, however, been, until recently, complicated and often unreliable. Historically, a link between the otoliths and the torsional position of the eyes has been demonstrated early on, and for many decades it has been attempted to assess otolith

function from the magnitude of ocular counterrolling (OCR). Diamond & Markham (1) reviewed this work and concluded that this approach is unfruitful in diagnosing unilateral deficits in otolith function. Attempts to correlate the side of the reduced OCR or asymmetry with the side of injury produced contradictory results, and a significant number of cases of known unilateral vestibular nerve section showed neither asymmetry nor reduced magnitude of the OCR. As a refinement, Diamond & Markham (1) recorded OCR continuously during ongoing roll at a constant, low velocity. Even under these conditions the asymmetry of the binocular OCR profiles in patients with unilateral vestibular nerve section appeared to be inconsistent, although the binocular OCR profiles of these patients were abnormal, compared to the normal subjects, when consistency, conjugacy, smoothness, and symmetry were examined. Such tests of the OCR probe the modulation of ocular torsional position in relation to changes in the relative orientation between head and gravity; they do not address changes in the basic torsional orientation of the eye. In other words, they probe gain, not offset of otolith-ocular reflexes. As the gain of OCR is very low (about 0.1) even in normal conditions, this probe is indeed likely to be not very sensitive.

In recent years it has become clear, however, that a primary effect of unilateral labyrinth lesions consists in a substantial change (offset) of the basic torsional angle of the eyes, with rotation of the upper poles of the eyes towards the lesioned side; this ocular tilt is accompanied by a similarly directed tilt of the subjective vertical. Early observations of changes in the subjective vertical due to peripheral and central vestibular lesions were reported by Friedmann (2). Halmagyi, Gresty & Gibson (3) described a case of transient abnormalities of posture after acute destruction of the left labyrinth, consisting of leftward ocular torsion (25°, as assessed by fundus photography), leftward head tilting (10°), and a right-over-left skew deviation (7°). The above described symptomatology is known as the 'ocular tilt reaction': a head-eye postural synkinesis including ocular torsion, head tilt, and changes in visual perception of the vertical, all directed to the side of the lesion. Dai, Curthoys & Halmagyi (4) tested the ability to perceive roll tilt in 33 patients before and from 1 week to 6 months after unilateral vestibular neurectomy, by rotating the subjects on a fixed-chair centrifuge in a complete dark room and having them set a small, illuminated bar to the perceived gravitational horizontal. (Both the subjective vertical and horizontal are being used in this type of experiments, with identical results). Normal subjects (n=31) accurately aligned the bar with respect to the gravito-inertial resultant vector. In contrast, patients had asymmetrical perceptions of resultant vectors to the right and to the left one week after the unilateral vestibular loss. Even at rest there was an

asymmetry in the baseline settings; i.e. in order to see the bar as gravitationally horizontal, they set the bar down to the side of the lesion. A progressive decrease in perceptual asymmetry followed, rapidly in the first 3 weeks and more slowly in the next 6 months. These findings were further amplified by Curthoys, Dai & Halmagyi (5), who established with fundus photography that in 23 patients, measured one week after unilateral vestibular neurectomy, both eyes were torted towards the side of the operation (average 9.5°). There was a significant reduction of this torsion in the 16 weeks following the operation, after which time residual torsion was on the order of 2.8°. The change in torsion was paralleled by a change in the orientation of the subjective gravitational horizontal: a high correlation (r=0.95) was found between the direction and magnitude of the change in torsional eye position and the direction and magnitude of the change in the perceived visual horizontal one week after the operation, with the change in perception being roughly similar to (and statistically even slightly larger than) the change in torsion.

Thus, it is apparent that absolute changes in the orientation of eye torsion and subjective vertical are a much more sensitive and specific index of unbalance in otolith signals than asymmetries in the OCR responses to tilt stimuli. The robust correspondence between the rotations of the subjective vertical and of the eye (5) suggests that they are either controlled by a same, common factor or that the subjective vertical is predominantly retinotopically determined. Whichever of these may be the case, determination of the subjective vertical seems much more practical as a test of otolith unbalance than fundus photography. Normal subjects can align a luminous rod in a dark room with the objective vertical or horizontal with an accuracy better than 2° (4,6). Thus, this test, which requires only simple equipment, has an absolute reference. In contrast, fundus photography requires special equipment and expertise, while small torsional deviations may remain undetected because of the anatomical variability in retinal landmarks.

In our previous work (7,8 and in preparation) we measured three dynamic vestibular responses to high frequency, passive head movements: (1) VOR gain; (2) VOR phase lag and (3) directional trend of gaze during head oscillation, in normals and vestibular patients. These tests addressed semicircular canal functions. In the present article we describe the changes in the subjective vertical for a number of these patients, as a probe of the static vestibular otolith functions. The result of our study extend the results of the authors cited above; while the latter concentrated on the effects occurring within months after acute lesions, our patients were measured years after the lesion. The mean

settings in our patient group with unilateral vestibular loss were systematically biased towards the side of the lesion. Patients with bilateral vestibular hyporeflexia did not significantly differ from the control group.

4.3 Material and methods

4.3.1 Protocol

To evaluate changes in the subjective vertical, subjects were seated on a chair in complete darkness and rested their head on chin and forehead rests in an upright position, to the best estimate of the experimenter. A dim luminous bar (length 81 cm, width 1 cm) was back-projected on a large translucent screen, 145 cm in front of the subject. This was the only visible object. The tilt of the line could be adjusted by the subject by rotating a disk, connected to a potentiometer, to a subjectively vertical position. The voltage emerging from the potentiometer reflected the objective tilt of the line and was recorded when the subject had finished his setting. The initial orientation of the line was randomized before each of 16 successive trials. Mean and S.D. of the 16 settings were determined for each subject. The true vertical orientation will be denoted as 0°; leftward and rightward tilts will be represented by negative and positive angles.

4.3.2 Subjects

Approval by the local ethical committee and informed consent from the subjects were obtained for all experiments. We recorded 25 healthy subjects who had no known ocular or vestibular pathologies. Absence of vestibular pathology was confirmed by testing them with our reactive torque helmet (7, 8), using steps and high-frequency oscillation. Subjects were instructed to abstain from alcohol and any drugs in the 24 hours preceding the measurements. The labyrinthine defective (LD) patients consisted of several groups:

A) Patients with, according to routine clinical testing (torsion swing and bithermal caloric stimulation) and surgical history, *total unilateral vestibular loss* (n=32; 13 leftsided, 19 rightsided). All of these patients had undergone surgery for an acoustic neuroma (vestibular Schwannoma) several years ago (mean 4.5 years, ±3.2 S.D.; range 0.5-11.5 years). The size of their tumors was known for 27

patients: <2 cm (n=15); 2-4 cm (n=8); >4 cm (n=4). All surgeries were, in principle, radical; only 1 patient showed a recurrence. Patients in this group had only few vestibular symptoms; i.e. they had feelings of disorientation or dizziness only after rapid head or body movements. Postoperative evaluation of eye movements (ENG) was done in 27 of these patients; only 3 of them showed mild deficits of smooth pursuit, optokinetic nystagmus or saccades.

B) Patients with, according to routine clinical testing, *partial unilateral vestibular loss* (n=7). The vestibular loss happened to be in all of these patients on the right side; 5 of these patients had an acoustic neuroma but had not been operated yet. The case histories of the 2 other patients were a traumatic fall on the mastoid bone and lesion of the labyrinth after stapedectomy. None of them were on any medication.

C) Patients with, according to routine clinical testing, *bilateral strong vestibular hyporeflexia* (n=8). Three of these patients had severe, sustained, invalidating vestibular symptoms in daily life such as oscillopsia or severe unsteadiness during walking, necessitating the use of a wheelchair or walking frame. One of these 3 patients got gentamicine in the past for a meningitis; the second had undergone, in the past, middle ear surgery during which the left labyrinth was damaged (the right labyrinth also showed a severe hyporeflexia on routine clinical testing); the third had a bilateral hyporeflexia with unknown etiology. The diagnosis of the remaining, not severely invalidated, 5 patients was in most cases bilateral Ménière; these patients were not on any medication at the time of the measurements. None of the patients of this group had a labyrinth predominance of more than 8%.

4.4 Results

The normal subjects were quite accurate in aligning the luminous bar correctly with the true vertical. The frequency distribution (in 1° bins) of the mean settings of each subject is shown in Fig. 1; the inter-subject means and S.D.'s are shown in Fig. 2. The overall mean of all normals was -0.14°±1.11 S.D. The majority of the normal subjects was accurate within ±1°, and all were accurate within ±2°, in agreement with previous literature (see Introduction). It is important to note that the intra-subject S.D.'s for the means of 16 successive settings of individual normals were much smaller (mean 0.20°) than the inter-subject S.D. of the means. Thus, successive settings by normals were

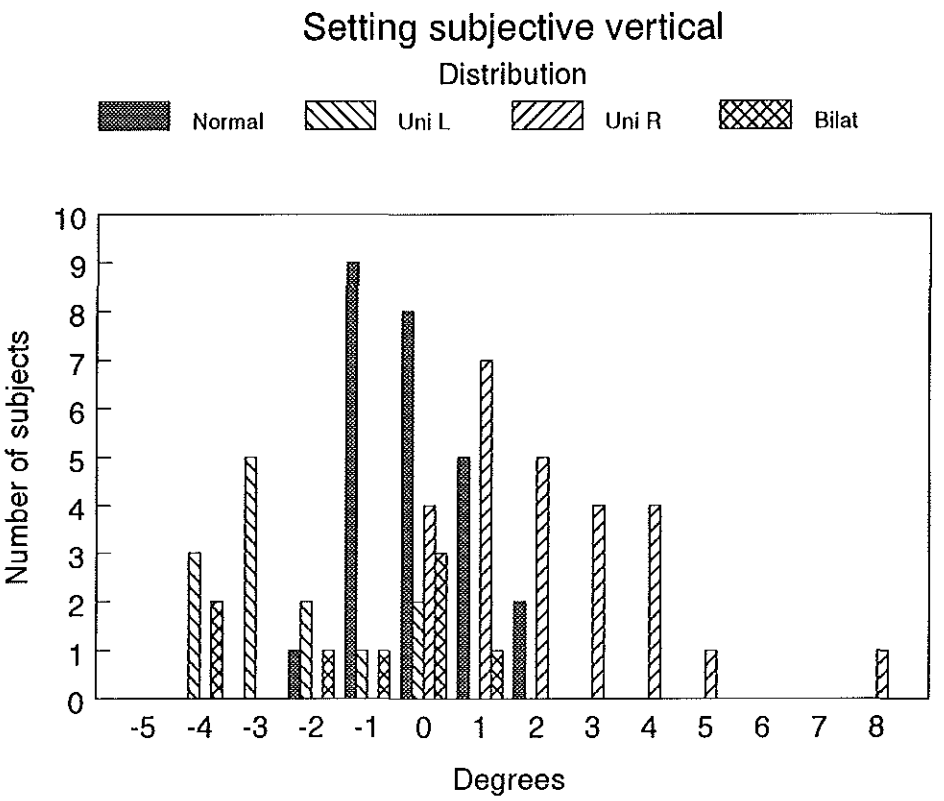

Fig. 1 Frequency distribution of mean settings of subjective vertical for normals, patients with unilateral leftsided (Uni L) or rightsided (Uni R), or bilateral (Bilat) vestibular lesions. Binwidth: 1°.

quite reproducible, reflecting a high degree of confidence of the individual means, while the inter-subject distribution of the mean settings probably reflects small, but consistent individual biases.

The settings by the subjects with long-standing unilateral vestibular lesions differed very systematically from the normals. The results for the 'partial' lesions followed the same pattern and were statistically indistinguishable from the 'total' group. Therefore, both groups were pooled in Figs. 1 and 2 so that these represent 13 leftsided and 26 rightsided unilateral lesions. For the leftsided lesions the mean setting was -2.55°±1.57 (S.D.); for the rightsided lesions the mean was 2.22°±1.96 (S.D.). Both means differed

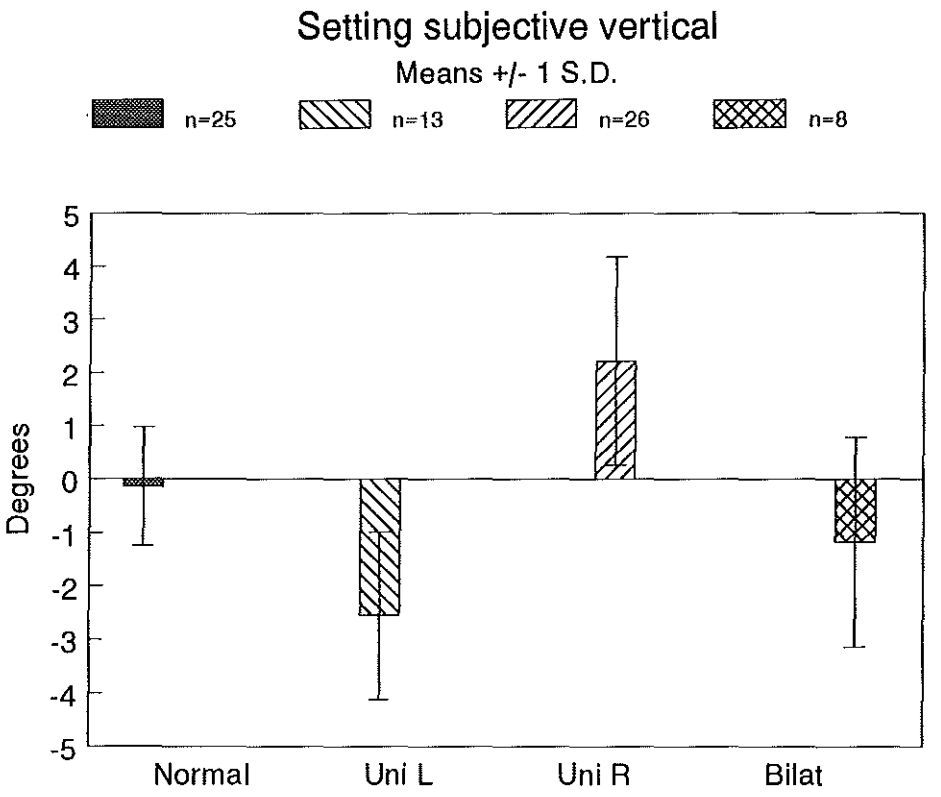

Fig. 2 Means and standard deviations of mean settings in the various subject groups, shown in Fig. 1.

highly significantly from the normal mean (p<0.00001; two-tailed t-test). Thus, the subjective vertical was tilted systematically towards the lesioned side. As shown in Fig. 1, there were overlaps between the 'normal' and 'unilateral lesion' distributions. However, 8 out of the 13 leftsided lesions and 10 out of the 26 rightsided lesions showed tilts of the subjective vertical exceeding 2°, the maximum value for normals. The unilateral groups showed a larger inter-subject variability than the normals; this may reflect different degrees of long-term adaptation to the defect, with part of the patients reaching the normal range. Also the intra-subject S.D. of the settings was somewhat larger than in normals: 0.33 vs. 0.20°. Thus, reproducibility of successive settings was somewhat lower in the unilateral patients than in the normals.

To test whether the deviation of the subjective vertical still diminished systematically

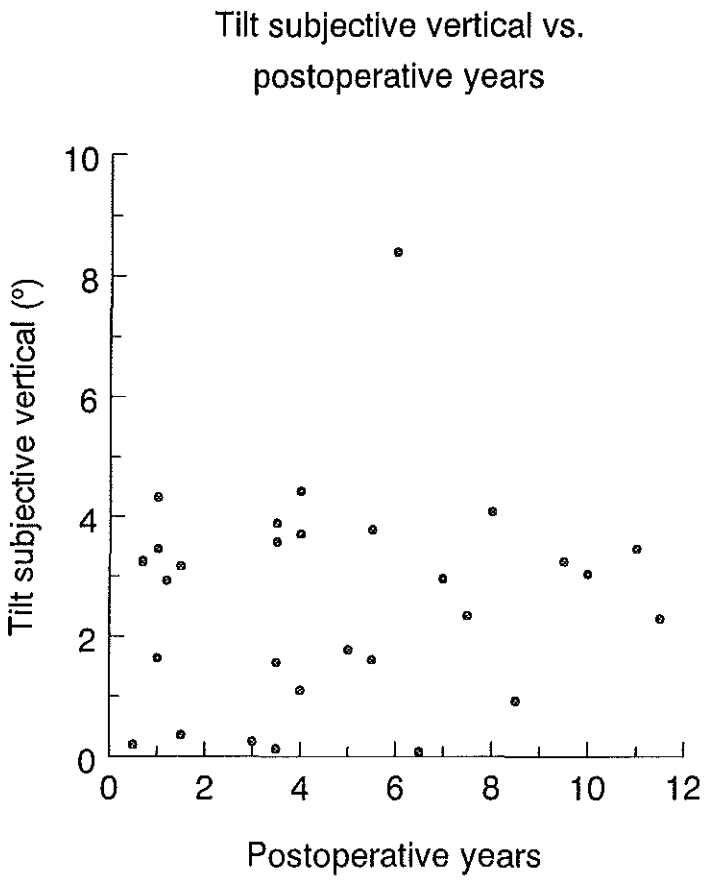

Fig. 3 Tilt (° absolute value) of the subjective vertical, plotted as a function of the number of post-operative years in 30 patients operated for a unilateral acoustic neuroma. The graph demonstrates the absence of any correlation.

as a function of time in the period starting half a year after the operation, we plotted the tilt of the subjective vertical (degrees absolute value) against the number of post-operative years for 30 subjects that had undergone unilateral surgery for an acoustic neuroma at least half a year previously. As shown in Fig. 3, and verified by regression calculation, there was no correlation whatsoever between the residual tilt of the subjective vertical and postoperative time for the range 0.5 to 11.5 years.

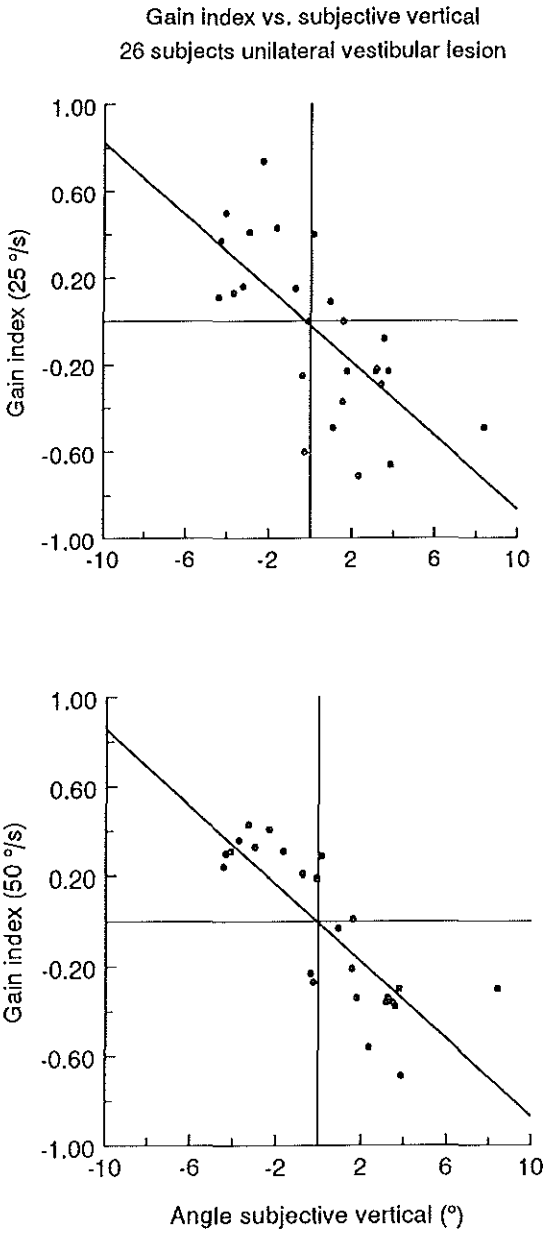

Fig. 4 Asymmetry of the canal-ocular VOR to head-steps, plotted as the gain-index (see text for definition), in relation to the angle of the subjective vertical, as measured in 26 subjects with a unilateral vestibular lesion. The gain-index was determined for the moments at which head velocity reached 25°/s (upper panel) and 50°/s (lower panel). The oblique lines show the calculated linear regressions (see text).

In the group of 8 bilaterally deficient subjects, the mean setting was -1.17°±1.96 (S.D.). This mean did not differ significantly from the normal distribution (p=0.19; two-tailed t-test). The lack of a systematic deviation is also evident from Fig. 1, which shows that 6 out of the 8 bilaterally deficient subjects had means within the normal 0±2° range, and two were outliers at -4°. The mean intra-subject S.D. of successive settings in the 'bilateral' group was 0.64°, which is twice as high as in the unilateral group. Thus, there was a clear trend for successive settings by a subject to be less reproducible as the overall vestibular functionality was lower.

As the unilaterally operated group formed an essentially homogeneous group, which was deficient for both otolith and canal function, it was meaningful to search for correlations between the present findings on the subjective vertical, and two parameters relating to asymmetries of canal-function, determined for the same subjects in separate studies using an inertial torque helmet (7,8). Unilateral vestibular lesion cause an asymmetry in the vestibulo-ocular response to head rotations: gain is much lower for rotation of the head towards the lesioned side than for rotation towards the intact side.

Firstly, this asymmetry is very evident when brief acceleration pulses are applied to the head, as has been first described by Halmagyi and colleagues (9). Such acceleration impulses (on the order of 1000°/s^2) induce head velocities exceeding 50°/s within 100 ms, a period short enough to preclude other than pure vestibular effects. We determined VOR-gain as *-eye velocity/head velocity* at the moments at which head velocity reached 25 and 50°/s for rightward (G_R) and leftward (G_L) pulses. These velocities were reached about 25 and 50 ms after the onset of head movement; effects of latency were disregarded for the present purpose. To compare gain in the two directions, we define the *gain index* as: $(G_R - G_L)/(G_R + G_L)$.

This index has a range between 1 (for G_L=0 and G_R=1) and -1 (for the opposite gain values). This index is plotted in Fig. 4 as a function of the angle of the subjective vertical, for head velocities of 25°/s (upper panel) and 50°/s (lower panel). Both graphs show a reasonable correlation between the two parameters of vestibular asymmetry. The oblique lines show linear regressions of the type $y = a + bx$, calculated separately for each graph. In both cases, a (the intercept) was not significantly different from zero, and b (the slope; gain index / angle of subjective vertical) equalled about 0.085 (0.084 for 25°/s and 0.086 for 50°/s). The coefficients of determination (r^2) were 0.48 for 25°/s and 0.67 for 50°/s.

Secondly, VOR-gain asymmetry is evident as a cumulative drift of the eye towards the lesioned side during continuous, sinusoidal oscillation of the head. Using our torque-helmet (7,8), we determined the maximum ocular drift velocity, *trend*, (in°/s) during head oscillation at 2 Hz. In Fig. 5, trend has been plotted as a function of the angle of the subjective vertical for 30 unilaterally deficient subjects. Again, a positive correlation was present; the oblique line shows the calculated linear regression with a slope (trend / angle of subjective vertical) of 1.92 and intercept not significantly different from zero; r^2 was 0.44. These comparisons show that deviations of the subjective vertical, reflecting imbalance in otolith functions, are significantly, although not very tightly, correlated with parameters reflecting imbalance in canal function.

4.5 Discussion

Our results confirm and extend recent investigations (3-5) that addressed the effect of unilateral vestibular loss on torsional eye position and the concomitant changes in the subjective vertical and horizontal. Normal healthy subjects are able to set a visible LED bar to the visually perceived gravitational horizontal (in°) with great accuracy and precision. Our values (mean setting -0.14°±1.11) agree very well with those of Dai et al.(2) who found -0.2°±1.0. Curthoys et al. (5) reported that patients who underwent a vestibular neurectomy showed very large deviations of the subjective horizontal towards the side of the lesion, one week after the operation (mean tilt toward the lesioned side 11.7°±5.6 S.D. n=23, p<0.001). These authors found also a high and statistically significant correlation (r=0.95) between ocular torsion and perceived horizontal. In addition, there appeared to be a significant decrease in the tilt of the perceived horizontal from one week after operation (11.8°±8.1, n=8) to 16 weeks after the operation (3.8°±3.6, n=8), but the perceived horizontal at 16 weeks was still significantly different from these patients own pre-operative measures. This reduction in static ocular torsion and its accompanying decrease in the slope of the perceived horizontal seemed to be a manifestation of vestibular compensation.

Our present data show that such compensation may remain incomplete at times much longer after unilateral vestibular neurectomy. The lack of any correlation (Fig. 3) between tilt of the subjective vertical and postoperative time in the range 0.5-11.5 years suggests that compensation essentially reaches an asymptotic value within the first half year. Roughly about half of our unilateral patients fell outside the maximum normal range (0±2°) even many years after the operation. As only 3 out of 25 normal subjects

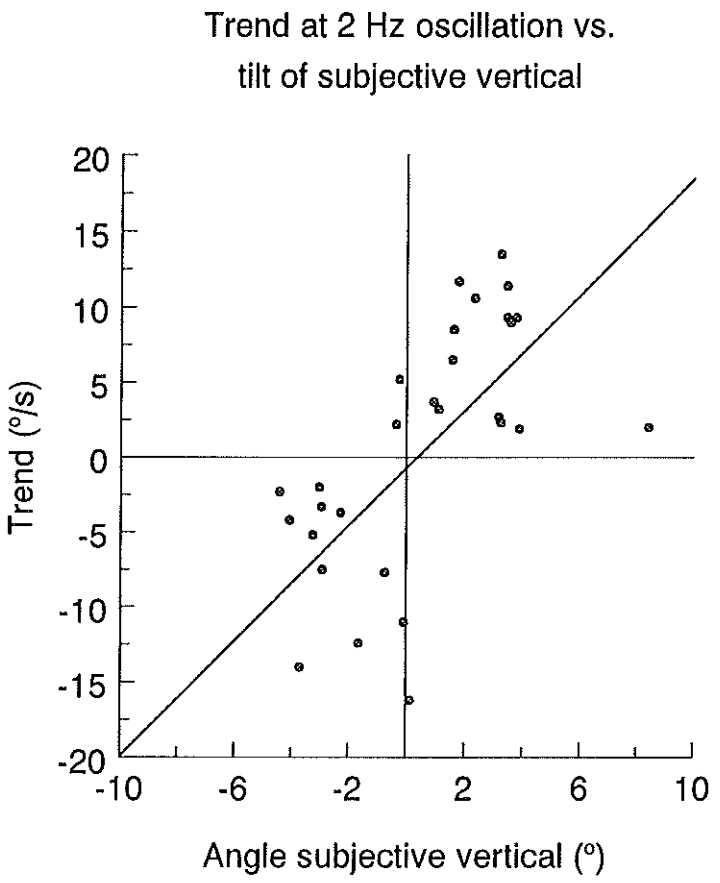

Fig. 5 Asymmetry of the canal-ocular VOR to 2 Hz head oscillation, plotted as the trend (see text for definition), in relation to the angle of the subjective vertical, as measured in 30 subjects with a unilateral vestibular lesion. The oblique line shows the calculated linear regression (see text).

exceeded the 0±1° range (Fig. 1), the 2° criterion is actually quite strict and any values of the subjective vertical exceeding ±1° should be considered as suspect for a vestibular asymmetry, while 2° and more may be considered as definitely abnormal. Fig. 1 also shows that none of the unilateral cases showed a tilt of the subjective vertical towards the wrong (healthy) side. Thus, the side-specificity of the test appears to be excellent. Finally, there is a tendency for the reproducibility of successive settings to be lower in subjects that lack the function of one, and especially two labyrinths, compared to normals. This may be expected, as subjects receiving less information are likely to increase the variable error in their settings.

In view of the fact that both the deviation of the subjective vertical and asymmetry in the gain of canal-ocular reflexes are highly side-specific, substantial correlations between these parameters are almost unavoidable in our unilateral patients, whose vestibular lesion was massive and indiscriminate for canals or otoliths. Figs. 4 and 5 suggest that much of this correlation was indeed due to this sign-correlation; virtually all data points were located in the lower left and upper right quadrants. Apart from this sign effect, the numeric correlation between the magnitudes of both deviations was very weak. In fact, correlations between *absolute values* of VOR gain asymmetries and subjective vertical angles proved to be virtually absent. This suggests that, while the sign of vestibular asymmetries is specific for the side of the lesion, the magnitude of the canal- and otolith-related asymmetries varies independently, indicating separate compensation processes for canal and otolith subsystems.

We conclude that the measurement of the subjective vertical, which requires little time, effort and equipment, is a highly sensitive and specific test in assessing asymmetries in otolith function.

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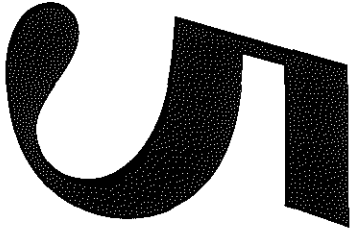


The modulation of the human vestibulo-ocular reflex during saccades: probing by high-frequency oscillation and torque-pulses of the head

5.1 Abstract

We probed the gain and phase of the vestibulo-ocular reflex (VOR) during the execution of voluntary gaze saccades, with continuous oscillation or acceleration-pulses, applied through a torque-helmet. Small amplitude (<1 deg), high frequency (10-14 Hz) head oscillations in the horizontal or vertical plane were superimposed upon ongoing, horizontal gaze saccades (40-100 deg). Torque pulses to the head ('with' or 'against' gaze) were superimposed upon 40 deg horizontal saccades. Eye and head movements were precisely measured with sensor coils in magnetic fields. Techniques were developed to separate the oscillatory (horizontal or vertical) component from the gaze shift and obtain VOR gain and phase with Fourier techniques from the relation between eye-in-head and head oscillations. These involved either subtraction of exactly matching saccades with and without oscillation (drawback: low yield) or time-shifting of successive trials to synchronize the oscillations (drawback: slight time-blurring of saccades). The results of these matching and synchronization methods were essentially identical and consistent. Presaccadic gain values of the horizontal VOR (typically about unity) were reduced by, at average, about 20 and 50% during horizontal saccades of 40 and 100 deg, respectively. Although these percentages may be slightly truncated due to methodological limitations, our results do not support a complete saccadic VOR suppression. Qualitatively similar changes were found when the vertical VOR was probed during 100 deg horizontal saccades. Concomitant with the reductions in gain, VOR phase was advanced by about 20 deg during the saccade. In the wake of gaze saccades, VOR-gain was consistently elevated (to about 1.0) above the pre-saccadic level (about 0.9). We submit that this mechanism ensures stable fixation of the newly acquired target at a time when the head is still moving substantially. Although the responses to head torque pulses showed idiosyncratic asymmetries, analysis of the *differences* in eye and head movements for pulses 'with' and 'against' consistently showed a sharp fall of VOR gain at saccadic onset, following an approximately exponential course with a time constant of about 50 ms. This decay may be assumed to reflect VOR gain for a period of about 50 ms, after which secondary gaze control mechanisms become dominant.The time course of the gain-decay and phase shift of the VOR suggest that suppression of the 'integrative (position) loop' of the VOR circuit was more complete than suppression of the direct, 'velocity' pathway.

5.2 Introduction

Natural shifts of gaze between different objects are often effected by combined eye and head movements. A frequently debated question is whether and how the vestibulo-ocular reflex (VOR) is modified during such gaze saccades. As long as the gaze remains aimed at the same object, the VOR is known to automatically turn the eye in the head in the direction opposite to any head movement, at nearly the same velocity, in order to hold gaze stationary. If the VOR continued to work during gaze saccades accompanied by an active head movement, it would slow the saccade in the head by the velocity of the head and, consequently, make eye movement in space independent of head movements. This latter type of behavior of the VOR was advocated in the early seventies by Bizzi and colleagues (Bizzi et al. 1971; Morasso et al. 1973; Dichgans et al. 1973), who basically argued that eye movements in the head were programmed as an independent activity and that whatever the head did was irrelevant because all the head movements were compensated by the VOR. Under this 'linear summation hypothesis' (a term introduced by Laurutis and Robinson 1986) the velocities, amplitudes and durations of gaze saccades should be unaffected by head movements, while eye-in-head velocities would be strongly affected. On the other hand, absence of such linear summation would permit the head movement to speed up gaze velocity, with faster acquisition of the target by combined eye and head movements as a useful result. Obviously, mechanisms other than the VOR would then be required to commensurately reduce the duration of the gaze movement and maintain saccadic accuracy.

Since the seventies, continued work, especially on primates, has gradually eroded support for straightforward 'linear summation', in favor of a (total or partial) suppression of the VOR during the saccadic, fast part of gaze-shifts. The early work (Bizzi et al. 1971; Dichgans et al. 1973) concentrated on the later part of the gaze movement, when gaze is already on target but the head is still moving. The vestibular origin of the compensatory eye movements in this phase remains undisputed but generalization of the linear summation hypothesis to the early part of the gaze shift has been shown to be untenable. Initially, Morasso et al. (1973) supported continuous linear summation in monkeys by showing that peak velocity and duration of gaze-shifts were unaffected by the head being free or restrained, but only gaze-shifts up to 40 deg were studied. The linear summation hypothesis could not logically account in any case for the dynamics of large gaze saccades that exceed the oculomotor range of

the eye in the head, because head movements contribute to such large gaze shifts by definition. Already Jürgens et al. (1981) showed only a partial (about 70%) summation of VOR and eye saccades in humans during passive head rotations at peak velocities of 125 deg/s. Tomlinson and Bahra (1986), using short, passive head-perturbations in monkeys, found that the VOR was functional during saccades smaller than 20 deg but absent for saccades larger than about 40 deg. Absence of linear summation, except may be for saccades smaller than 30 deg, was also supported by a variety of experimental evidence by Laurutis and Robinson (1986). Related experiments by other authors have also indicated that the VOR is operational during small saccades, but progressively turned off with increasing saccadic amplitude (Pélisson et al. 1988; Tomlinson 1990). Considerable idiosyncratic differences among human subjects in the degree of suppression, however, were demonstrated by Guitton and Volle (1987). Furthermore, the time course of the VOR-suppression remains unclear. Laurutis and Robinson (1986) assumed an immediate switching between 'on' and 'off' conditions; Guitton and Volle (1987) proposed a more gradual VOR restoration; Pélisson et al. (1988) proposed an exponential VOR variation law and, finally, Lefèvre et al. (1992) came up with a result arguing for a restoration of VOR gain from zero to unity in the last 40 ms of the gaze saccade.

A problem with many of the experiments discussed above is that they interfered with the ongoing gaze motion by considerable alteration of the natural head movement; in this way, the object of the measurement (the gaze signal) was often disturbed in a rather crude way. In fact, it has been difficult to demonstrate suppression of the VOR during natural gaze movements, when subjects were not forced to move their head very fast (Pélisson et al. 1988; Becker and Jürgens 1992; Van der Steen 1992; Smeets et al. 1996). A recent experiment with occasional, passive head perturbations during a sequence of natural gaze-shifts (Epelboim et al., 1995) confirmed the maintenance of accuracy under such perturbations, but suggested considerable trial-to-trial variability in the contribution of VOR and non-VOR mechanisms to this accuracy.

In this study, we probed the VOR during gaze-shifts using a helmet with torque-motor (Tabak and Collewijn 1994, 1995) that enabled us to apply to the head either high-frequency (10-14 Hz), low amplitude (<1 deg) oscillations or torque-pulses, superimposed upon gaze saccades. The ocular response to oscillation, which did not affect the gaze or head movements in a systematic way, could be extracted as an

independent probe of the VOR. In this way it was, in principle, possible to evaluate the gain and phase of the VOR as continuous functions of time in relation to saccades, with minimum activation of non-VOR mechanisms correcting gaze-accuracy. Analysis of the oscillations showed that VOR gain was indeed reduced during saccades. In contrast, VOR gain was enhanced in the wake of saccades. Furthermore, systematic advances in the phase of the VOR occurred along with the changes in gain. Changes in the VOR extended to the vertical VOR during horizontal saccades, and thus were not plane-specific. The phase-advances indicated, in addition to a decrease in gain, a change in the VOR-dynamics, possibly due to a deficit in the integration of vestibular signals. To further explore this point we administered, in complementary experiments, torque-pulses to the head in conjunction with 40 deg gaze-saccades. The *difference* in the responses of the eye to perturbations of the head in opposite directions (with or against the saccade) was similar for all subjects, although the responses themselves showed idiosyncratic asymmetries. The initial part of this difference could be approximated by an exponential decline of VOR gain, starting at saccadic onset, with a time-constant of about 50 ms.

5.3 Methods

5.3.1 Subjects and stimulation technique

Eleven healthy subjects, who had no known ocular or vestibular pathologies, served in the experiments. Three of them wore spectacles (for mild refraction errors) but did not need these during the experiments. Passive, horizontal high frequency head rotations were generated by a helmet, placed on the subject's head, with on top a torque motor (GEC Alsthom/Parvex; 120 Watt). The torque motor rotated a freely rotating fly-wheel. Acceleration of the fly-wheel caused a reactive torque of the helmet, which was transferred to the head. For a complete description of this method we refer to Tabak and Collewijn (1994, 1995). Vertical high frequency head rotations were generated with another helmet, which had two similar but smaller torque-motors (each 70 Watt) mounted coaxially and symmetrically on the right and left side. The spindles of these torque-motors were suspended in an aluminum U-shaped frame by means of two small ball-bearings, such that their common rotational axis coincided approximately with a transverse axis through the center of the head. Each of the torque-motors rotated a fly-wheel in identical directions about the transverse

axis. The gravitational load of the helmet devices on the head was balanced by suspending them from the ceiling by a suitable spring. This suspension also left the subjects free to translate and rotate their head in all directions. The springs balanced the weight of the helmets but did, of course, not neutralize the extra mass attached to the head, which caused an additional inertial load on the head-neck motor system. Moments of inertia (around the vertical axis) for the horizontal and vertical helmets were respectively 0.03 $kg.m^2$ and 0.45 $kg.m^2$, while the moment of inertia of the head is approximately 0.2 $kg.m^2$. The large inertia of the 'vertical' helmet, caused by the two eccentrically placed torque-motors with attachments, noticeably limited the subject's ability in making fast and large horizontal head movements.

All torque motors were powered by a driver (Soprel/Milano Transdriver (I) DB 425 W/R), which received a sinusoidally changing voltage as the control signal. For safety, control signals were high-pass filtered so that they returned exponentially to zero in about 1 s; this prevented the build-up of high spinning velocities of the fly-wheels.

5.3.2 Recording technique

Eye and head movements were recorded with the scleral coil technique (Robinson, 1963; Collewijn et al. 1975), relative to an earth-fixed, homogeneous magnetic field. The recordings should reflect only rotations and be invariant for any translations. To achieve this, the magnetic fields were made homogeneous in strength and direction over a space including any possible head position (see Collewijn, 1977 for details on coil construction). An ocular sensor coil (Skalar, Delft) was attached to one eye. To record the head movements, a second sensor coil was firmly attached to an individually fitted dental-impression biteboard.

The sensor coils were connected to high quality lock-in amplifiers (Princeton Applied Research, model 5210) to obtain their horizontal and vertical positions by amplitude detection. The sensitivity of the eye and head coils was calibrated prior to every experimental session with a protractor. The system's resolution was better than one minute of arc. Each signal was digitized at 500 samples per second after anti-alias low-pass filtering at 125 Hz and stored into a DEC PDP 11/73. Eye-in-head orientation was computed by subtraction of head orientation from gaze orientation.

5.3.3 Visual conditions

To obtain invariance for head translation of the gaze and head signals and of the angular viewing direction of the target, we placed the visual targets (two LEDs) at optical infinity in the focal plane of a Fresnel lens (size 94 x 70 cm; focal length 118 cm). Unfortunately, the Fresnel lens was too small to cover the largest gaze saccades (100 degrees). For this experimental condition the LEDs were place at an distance of about 200 cm. This did not influence VOR gain, because this is not affected by optical infinity of the visual target in the frequency range from 2 to 20 Hz (Tabak and Collewijn 1994), but it did probably increase the variability of the size of our largest saccades somewhat. In both types of experiment the subjects were seated in the magnetic field, viewing the targets binocularly with the head unrestrained. All experiments were conducted in complete darkness, except for the two point targets.

5.3.4 Procedures in oscillation experiments

A first series of measurements concerned horizontal gaze shifts of various sizes with superimposed, high-frequency, horizontal head oscillations; i.e. combined eye-head movements (gaze saccades) of 100 and 80 deg and saccades of 40 deg without active head movement. For the largest gaze saccades, subjects (n=11) shifted their gaze from the visual target 50 deg to the left to the one 50 deg to the right. In the next trial they made a gaze saccade from the right target back to the left target, and so on. Each trial lasted 4 seconds. The subjects were cued by an auditory signal to make the gaze saccades at the appropriate time. In addition we imposed (in alternating fashion) a passive, horizontal head oscillation with a frequency between 9.0-10.5 Hz (6 Hz on one occasion) during 50% of the pairs of gaze saccades. We asked the subjects to make head movements in a natural way, with velocities that felt like normal, i.e., not at maximum attainable velocities. Subjects made between 30-40 gaze saccades in each direction, with and without head oscillation. Because of the shorter duration of the 80 deg gaze saccades and 40 deg saccades (without head movement) we had to apply higher oscillation frequencies (12 and 14 Hz) to accommodate a sufficient number of oscillation periods for analysis within the duration of the saccade. Head oscillation amplitudes (peak-to-peak) decreased when the frequency was increased, from about 0.5 deg at 10 Hz to about 0.3 deg at 14 Hz (Tabak and Collewijn, 1994).

In a second series of measurements the subjects (n=9) made horizontal gaze saccades of 100 degrees but the head oscillation (frequency 5.8-6.8 Hz) was vertical, i.e. orthogonal to the plane of the gaze saccade. Each trial in this experiment lasted twice as long (8 s instead of 4 s), therefore, subjects made fewer gaze saccades (between 20 and 35 to the right and left, with and without oscillation). Unfortunately, in this experiment the subjects found it very difficult to reach the normal head velocities associated with 100 deg saccades, because of the substantial increase in the moment of inertia by the helmet.

5.3.5 Procedures in torque-pulse experiments

Subjects made saccades between the two continuously visible LEDs separated by 40 deg. Each trial started with a warning-tone, followed after 4 s by a second tone, which was the signal for the subjects to make one saccade. In part of the trials, the torque-motor started to rotate the fly-wheel just before the expected start of the saccade. The resulting head movements started about 100-150 ms before the saccade. The purpose of starting the head-movement before the saccade was to obtain a substantial head velocity during the saccade. A disadvantage of this technique was that the relative timing between saccade and head movement was rather variable. As the head perturbation started more than 100 ms before the saccade it is, furthermore, possible that subjects used information about the perturbation when they generated the saccadic command.

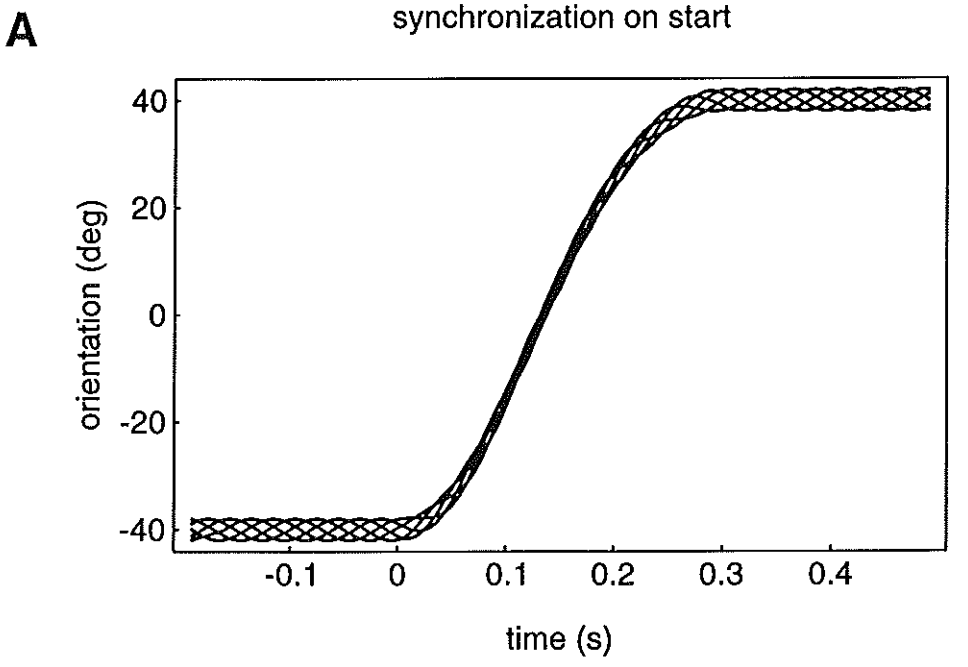
Three conditions of head movements were used in the experiment. In one condition (head static), the head did not move; in the other two the head was moved, either in the same direction as the saccade (head with), or in the opposite direction (head against). As the response of the head to the torque differed between conditions (see results), we used a different timing of the torque relative to the go-signal for the two perturbed conditions: pulses 'with' were given 50 ms earlier than pulses 'against'. In this way, we ensured that the moment of maximum velocity of the head was near saccadic onset. Subjects made saccades in 4-8 blocks of 20 trials. In each block, all saccades were in one direction; the head-movement condition for each trial was unpredictable for the subject.

5.3.6 Data analysis of oscillation experiments

To analyze VOR gain it was necessary to separate the components in the head, eye and gaze signals associated with the imposed head oscillation from the components related to the gaze saccade. For this purpose, we developed two methods, both yielding equivalent results. The first method (matching method) is conceptually simple, but can only be used to analyze a few saccades. The second method (phase-synchronization) is more complex, but able to analyze all trials. Both methods started by synchronizing the recordings of all trials so that the start of the gaze-shift (according to a velocity criterion of 50 deg/s) corresponded to t=0.

The matching method treated the trials in which no perturbations (oscillations) were applied as reference saccades. For each perturbed trial, the set of unperturbed trials was searched for the single trial of which the gaze-related components best resembled the perturbed trial, assuming that the perturbation did not affect the dynamics of the saccade (this assumption is supported by the data). In a few initial experiments, this search for matching saccades was done manually by overlying plots of saccades with and without oscillation. Later on, the search was computerized and done by summing the squared difference between the signals (for both head and gaze) of a pair of trials from 50 ms before till 500 ms after the start of the saccade. For the best-corresponding pair, the unperturbed signals were subtracted from the perturbed ones, and these difference signals were regarded as the perturbation (head) and the response to it (eye-in-head).

The phase-synchronization method used only the trials in which oscillations were applied to the head but used all of those. The phase of the oscillation of the head at t=0 was random (see Fig. 1A). To enable the averaging of the perturbations, the signals were re-synchronized on the phase of the head-oscillation (determined by fitting a sine-function to the head-signal preceding the gaze-shift). For trials with a phase between 0 and 180 deg, all signals were shifted backwards in time so that the phase of the head oscillation at t=0 became zero. For trials with a phase between 180 and 360 deg, all signals were shifted backwards in time so that the phase of the head oscillation at t=0 became 180 deg. This yielded two groups of trials, one with phase 0, and one with phase 180 deg (see Fig. 1B). For both groups, the gaze-shift (for a 10 Hz oscillation) started somewhere between t=-50 and t=0 ms (on average: t=-25 ms). After calculating the average signals for both groups, we could easily determine the average saccade and the perturbation. Because the perturbations have opposite signs


A
synchronization on start
40
20
0
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orientation (deg)
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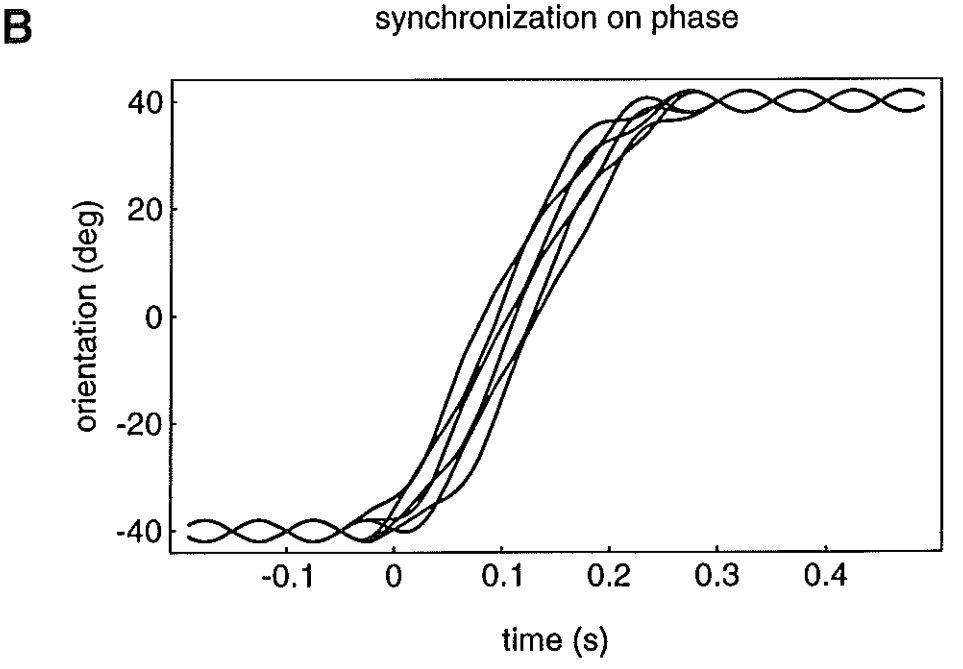
time (s)


B
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time (s)

in both groups, summing of the averages of both groups (and dividing by two) removed all perturbations and isolated the saccadic components. On the other hand, taking the difference between the two groups, divided by two, removed the saccade and isolated the perturbation (head signal) and the response to it (eye in-head-signal). In this way, the perturbation and the response could be determined very accurately, in exchange for a decrease in the temporal resolution of the saccade (from 2 ms in individual trials to 25 ms in the phase-synchronized signals). In the experiment with vertical oscillation and horizontal saccades the separation was, in principle, much simpler because of the orthogonality of the signals. Nevertheless, we applied the same procedures in this case to ensure that the results of the analysis were comparable for all conditions.

After separating the perturbation from the saccade by one of the methods mentioned above, VOR gain was determined as a function of time. For each instant, a Fourier-transformation of the signals of head perturbation and eye-in-head response was calculated, using data windowed by a Parzen window-function ranging from 256 ms before until 256 ms after that instant. From the power and phase of the signals at the perturbation frequency, the gain and phase-lag of the VOR was determined as a function of time. The rather long window was needed to be able to limit the analysis to a 2 Hz band around the perturbation frequency.

The two techniques we need to obtain the average response of all subjects (the phase synchronisation and the Fourier transform) both blur the signal.To illustrate this artifact, we constructed artificial experimental data. One set of data was constructed using a VOR-gain which was equal to 0.9 until the onset of the saccade, zero during the saccade and restored immediately to 0.9 after the saccade (Fig. 2A). This would represent the maximum possible degree of intra-saccadic VOR suppression. A second set of data simulated a symmetrical, triangular decline and recovery of VOR gain, with a minimum (but not sustained) value of zero (Fig. 2B). This case represents the minimum degree of VOR suppression in which complete suppression

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←—— *Fig. 1 Principles of the phase-synchronization method. (A) In a first step, starts of gaze displacements of all trials with head oscillation in a session are aligned at t=0. (B) In a second step, phase of the superimposed oscillation is re-aligned to 0 or 180 deg at t=0 (whichever is closest), by time-shifting of the individual gaze records. In this way, phase is synchronized, at the expense of some time-blurring of the gaze movement.*

is reached at least at one moment; a conservative model. A zero phase-lag between eye and head movement was used. The time-course of phase and gain obtained after averaging the artificial trials and Fourier analysis are plotted in Fig. 2 A and B for a simulated saccadic duration of 300 ms (about the duration of a 100 deg saccade). The time-course of the VOR gain is blurred: instead of an immediate reduction to zero at 0 ms, the gain reduces gradually before the saccade, reaching its minimum (0.17) at 124 ms, whereafter the gain restores slowly to its original value. One important artifact of the analysis technique is thus that a sudden change in VOR-gain is blurred to a smooth change, which means that it is impossible to determine accurately the timing of the VOR suppression. In addidition, the phase-synchronization technique shifts the time of maximum suppression 25 ms forward (Fig. 2A). A further effect of our data-analysis techniques is underestimation of the maximum amount of VOR-suppression. The magnitude of this underestimation depends both on the duration of the suppression and on the shape of the suppression profile. For a simulated 'square' profile of suppression to zero gain, the minimum gain values yielded by the analysis for 400, 300 and 150 ms duration were 6.2%, 18.7% and 51%, instead of zero percent, of the pre-saccadic gain value. For a triangular profile, the corresponding values were 38%, 47.1% and 65.8%, respectively. These numbers show the limitations of the estimates of time course and minimum value of VOR gain as obtainable with the techinque in its present version. It should be emphasized that, in contrast, distortions of phase were negligible (Fig. 2 A, B).

5.3.7 Data analysis of torque-pulse experiments

As the perturbations of the head could cause changes in the movements of the gaze, we had to determine the onset of the saccades carefully. As the acceleration of the head was low near saccadic onset, we used a gaze-acceleration criterion of 5000 deg/s^2 to define saccadic onset and offset. This onset criterion was used in aligning gaze-saccades in averages such as shown in Figs. 9 and 10. Saccades with amplitudes less than 30 deg were excluded from further analysis. Trials without perturbation in which the head moved by more than 2 deg during the trial were also excluded. For the perturbed trials, we had to check whether the perturbation during the saccade was sufficiently large. We used only trials in which the head moved more than 1.5 deg during the saccade with a velocity of more than 10 deg/sec at saccade onset in further analysis. A total of 1085 trials (75%) passed these criteria.

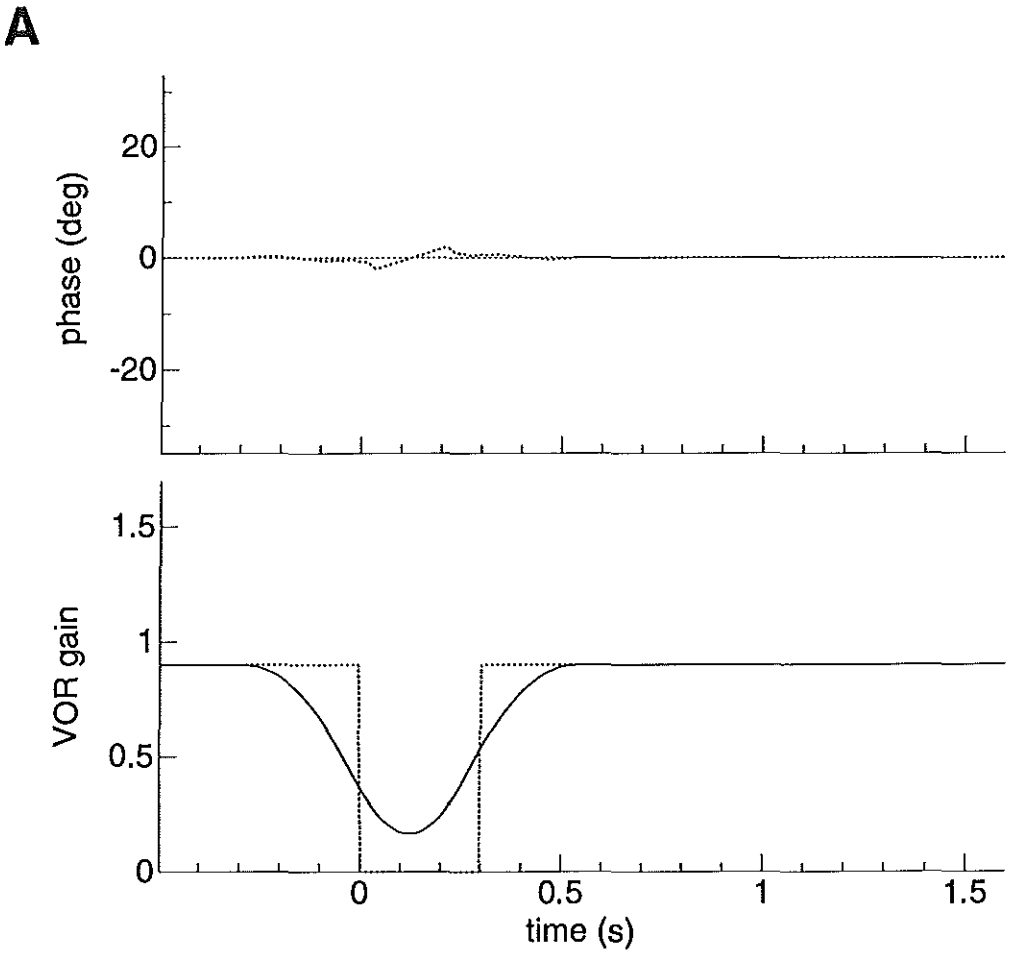


Fig. 2A Simulation of blurring effects of phase-synchronisation and window used in Fourier transform on the time-course of phase and gain of the VOR. Dashed curves: time courses for the (artificial) data. Solid curves: the relations obtained by analysing these data using the techniques described in the methods section. Simulation of abrupt decline and recovery of VOR gain at saccadic onset and offset, with total suppression in between ('sqare' profile of suppression).

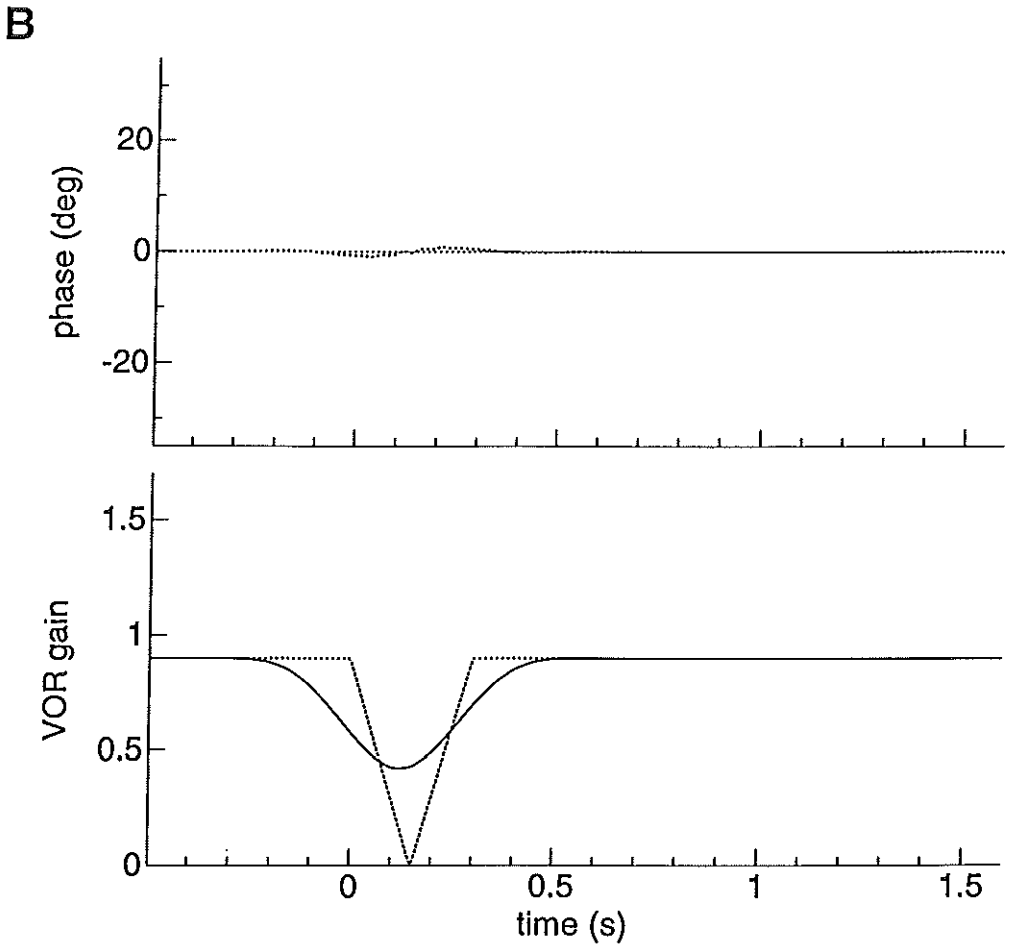


Fig. 2B Simulation of blurring effects of phase-synchronisation and window used in Fourier transform on the time-course of phase and gain of the VOR. Dashed curves: time courses for the (artificial) data. Solid curves: the relations obtained by analysing these data using the techniques described in the methods section. Simulation of linear decline and recovery of VOR gain, reaching total suppression only for a brief instant ('triangular' profile of suppression).

For the quantification of the effect of the head-perturbation on the dynamics of the saccade, we calculate the instantaneous VOR-gain, *G(t)*. This gain is an estimate of the effect of head movement on eye-in-head velocity during the saccade. It is calculated by dividing the difference in eye-in-head-velocity between two head-movement conditions ('with' and 'against') by the difference in head-velocity between these conditions occurring 6 ms earlier:

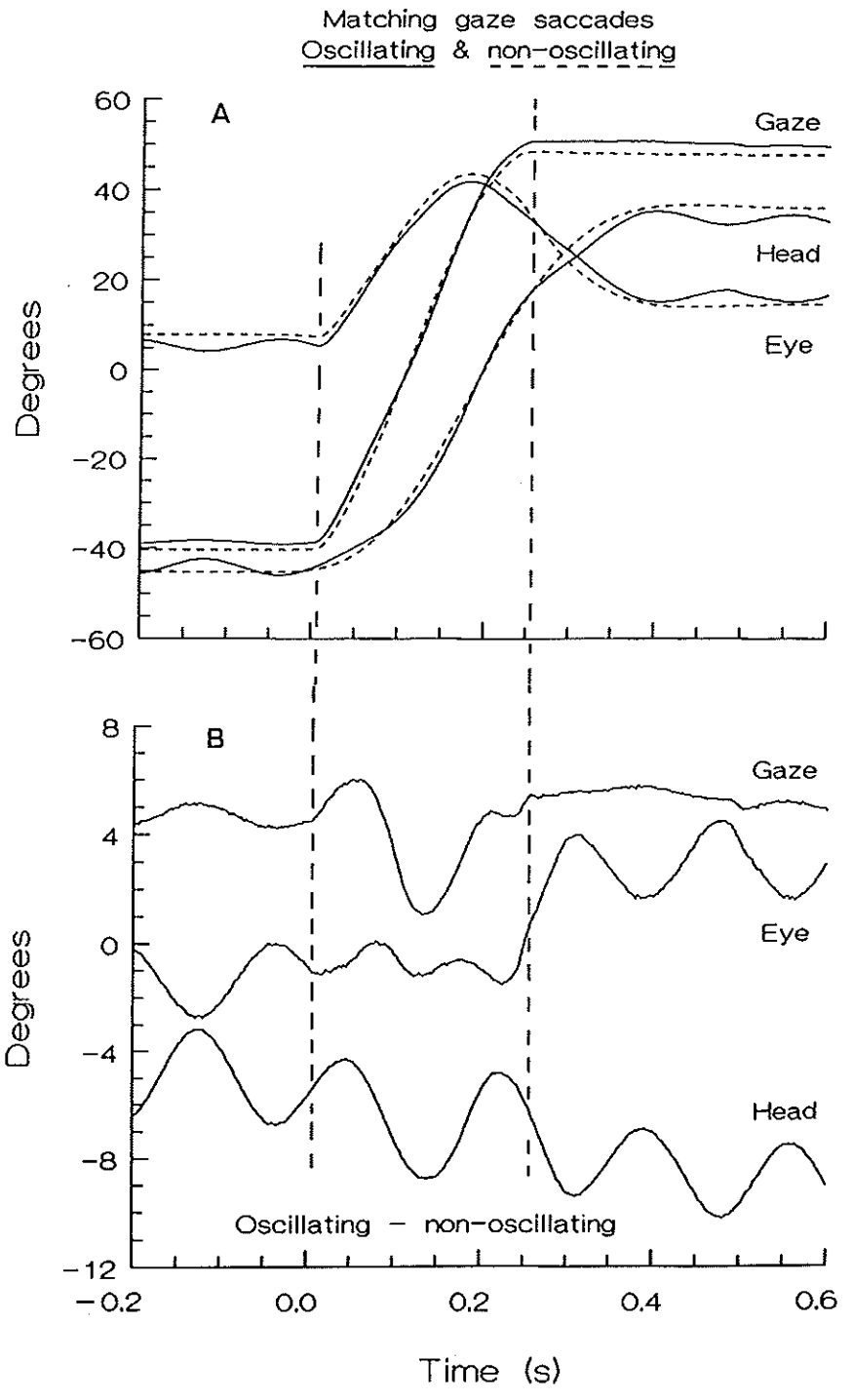
$$G(t) = DV_{eye}(t)/DV_{head}(t-6)$$

Velocities were calculated as the position difference between two successive samples, divided by the sample interval (0.002 s); subsequently, this signal was low-pass filtered (effective cut-off 100 Hz) in both forward and reversed direction to prevent phase-shift (Ackroyd, 1973). The 6 ms time-difference is our estimate for the delay of the human VOR. This delay is considerably shorter than the 14 ms determined by Lisberger (1984) in the monkey; our shorter estimate is based on our direct measurements of latency with helmet-induced torque pulses in humans (Tabak et al., 1996, submitted) and is in agreement with the few published data for humans (Maas et al. 1989). The total response of the head to the torque perturbation was measured by its orientation 200 ms after the onset of the saccade. For values that are averaged across subjects, the inter-subject variability is indicated by the inter-subject standard deviation.

5.4 Results

5.4.1 Probing the VOR with horizontal oscillation during horizontal gaze saccades

The basic result, obtained by the 'matching' technique from a manually selected pair of saccades without and with head oscillation (in this particular case at 6 Hz) is illustrated in Fig. 3. Panel A shows the gaze, eye and head displacements, all of which matched exceptionally well in this pair, except for the oscillations. Therefore, subtraction of the 'non-oscillation' from the 'oscillation' records resulted in an almost perfect isolation of the oscillatory components (Fig. 3B). These difference signals show marked, characteristic changes during the saccade. The head-difference signal shows that head oscillation continued with little change during the saccade. The gaze-difference signal shows that before the gaze saccade (which started at t=0) there


Matching gaze saccades
Oscillating & non-oscillating
A
Gaze
Head
Eye
Degrees
60
40
20
0
-20
-40
-60
B
Gaze
Eye
Head
Oscillating - non-oscillating
Degrees
8
4
0
-4
-8
-12
-0.2
0.0
0.2
0.4
0.6
Time (s)

was some modulation of gaze in phase with the applied head oscillation, indicating that the VOR was working at a gain below unity. Subsequently, during the fast displacement of gaze, there was a large increase in the amplitude of oscillation in the gaze signal, which now resembled the oscillation of the head. Simultaneously, there was a complementary decrease in the eye-in-head signal. This change indicates a marked reduction in VOR gain. The oscillatory modulation of the gaze signal was much reduced again around the time of the landing of gaze on target, and in the last phase of the gaze saccade, when gaze had landed but the head and eye continued to move in opposite directions, gaze showed even less oscillation and thus, was more stable than just prior to the gaze saccade (again with complementary changes in the eye-in-head signal), indicating that the VOR functioned at a higher gain (closer to unity) after the gaze shift than before it.

These basic, but somewhat qualitative findings (confirmed by a number of other manual matchings) were quantified by computerized matching and Fourier analysis of the oscillatory eye and head signals to determine gain and phase of the VOR. Fig. 4A shows an example of such an analysis for a *single* pair of matched saccades (amplitude about 100 deg; oscillation at 9.6 Hz with an amplitude of about 1.0 deg peak-to-peak).

The Fourier analysis shows that VOR gain was reduced, from a pre-saccadic value of about 0.9, to slightly below 0.5 during the saccade, with a subsequent recovery to initially about 1.0 after the saccade, followed by a gradual reduction to the presaccadic level. Remarkably, these changes in gain were accompanied by a temporary advancing of the phase by about 20 deg.

Thus, the 'matching' technique clearly demonstrates the existence of intrasaccadic changes in gain and phase of the VOR and suggests a characteristic time course for these phenomena. A limitation of these results is that matching pairs are rare and that

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←—— *Fig. 3 The principle of the matching method. A pair of gaze saccades from one session was selected (one with and one without head oscillation) in which gaze, eye and head movements matched as well as possible, except for the oscillations. Panel A shows a good match. Subtraction of the non-oscillated from the oscillated trial isolated the oscillatory components (panel B). The modulations of the oscillation as a function of time show the changes in the VOR. (In this example the oscillation had an uncharacteristically low frequency of 6 Hz).*

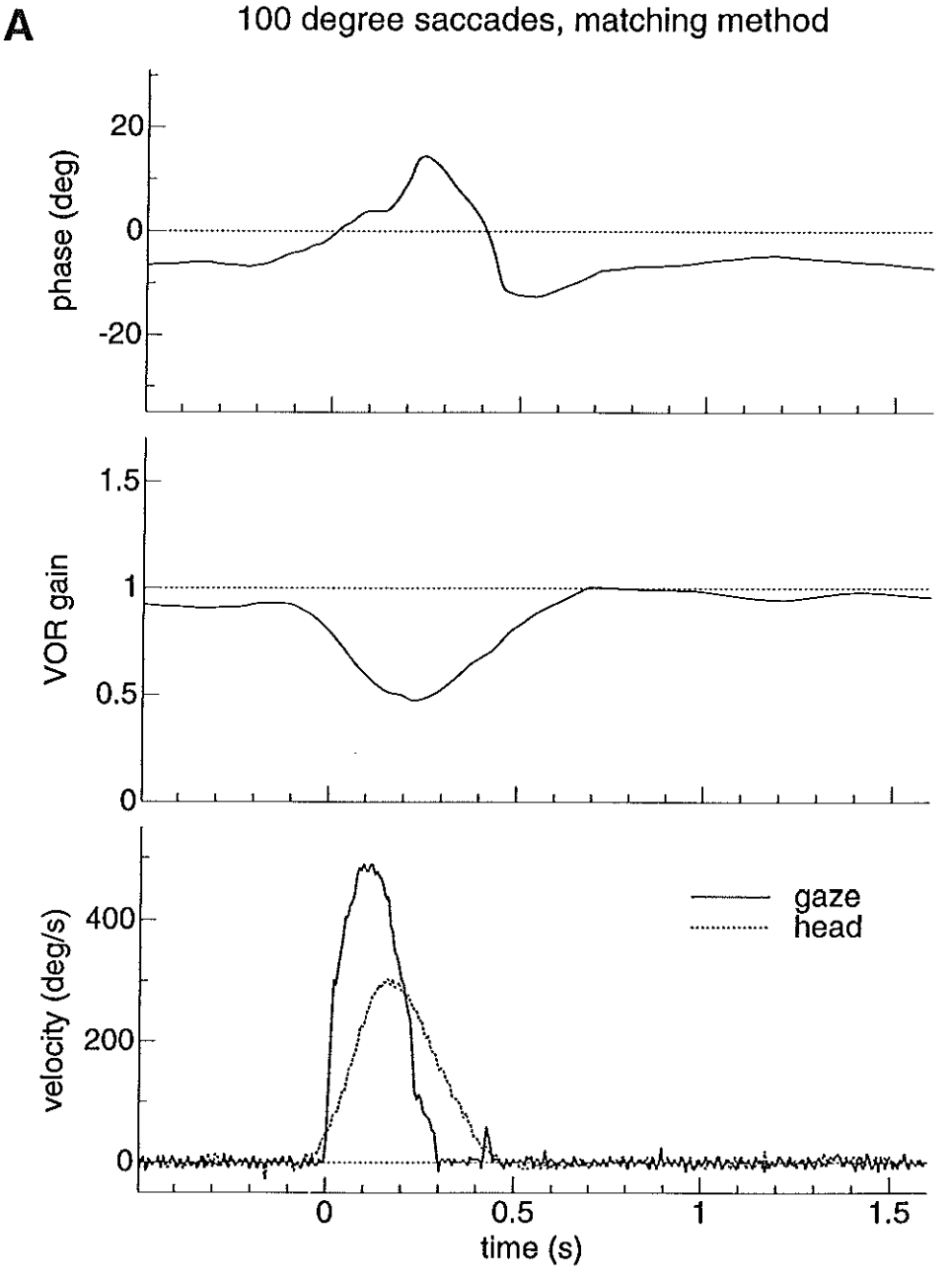


Fig. 3 (A) Example of the results of Fourier analysis, applied to a single matching pair of 100 deg saccades. The lower panel shows the saccadic components (as velocity profiles) of the gaze movements; the upper two panels show the phase and gain of the VOR, estimated from the oscillatory component (which is not shown here).

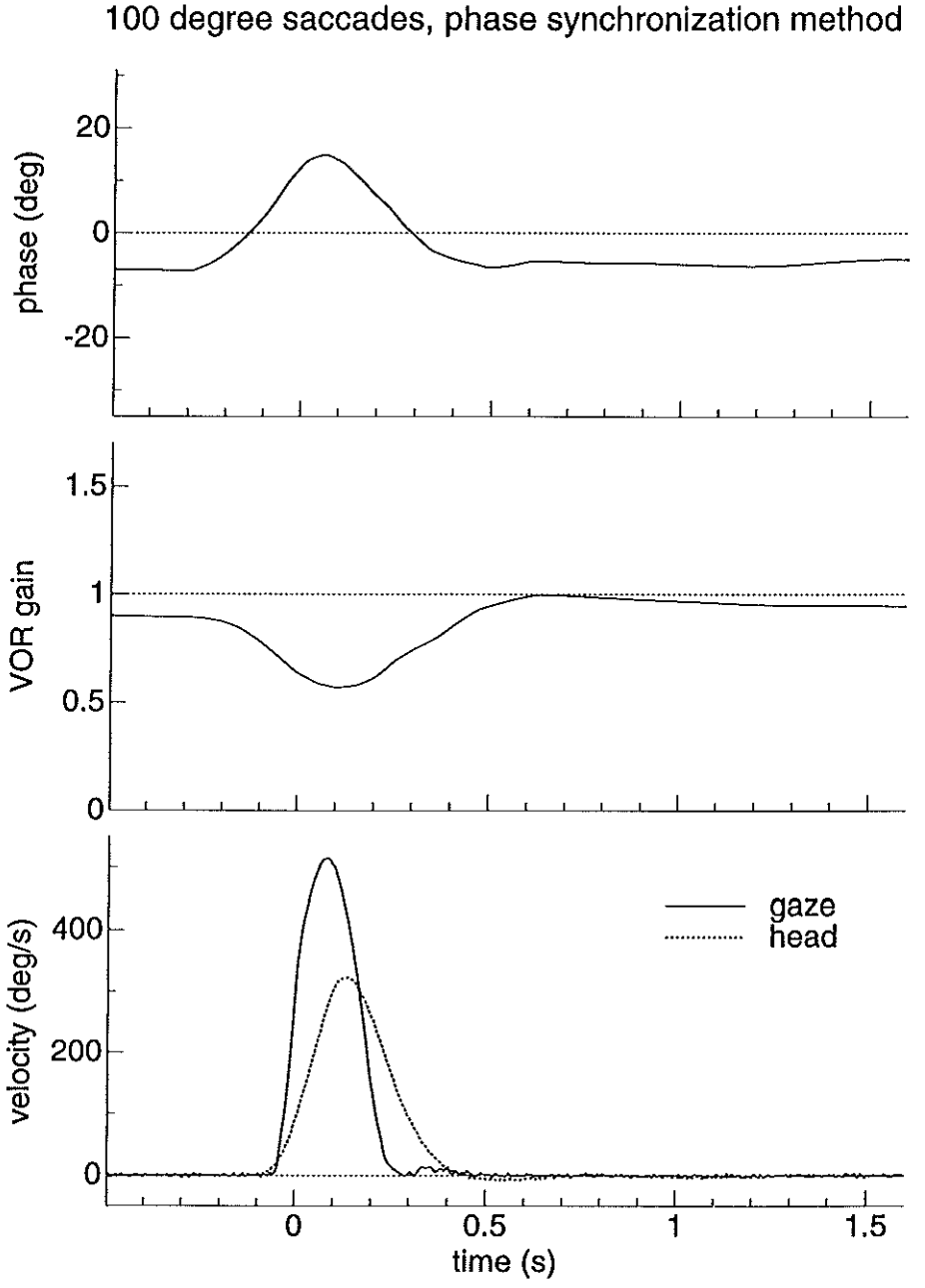


Fig. 3 (B) Results of Fourier analysis after applying the phase-synchronization technique to all oscillated trials in the same session from which the single matching pair in panel A was derived. Notice the overall similarity between the results in panels A and B.

the analysis is therefore based on few saccades. Fortunately, our second method of analysis, the phase-synchronisation technique, which uses all (oscillated) saccades, corroborated and refined the results of the matching method. Fig. 4B shows the result of this analysis for all oscillation trials in the same session from which the single matching pair of saccades in Fig. 4A was derived. The graphs in Fig. 4B confirm that the VOR before the gaze saccades was working at a gain of 0.90. During the gaze saccades the VOR was partially suppressed, with an apparent minimum gain of 0.56, which is 62% of the presaccadic value. At the mean saccadic duration of about 400 ms, total suppression with a square or triangular profile (see Methods, Fig. 2 A, B) would yield in our analysis apparent minima of 7.2% and 38% of presaccadic VOR gain, i.e. 0.07 and 0.34. Thus, for the subject illustrated in Fig. 4B, the limitations of our technique allow the conclusion that VOR suppression during 100 deg saccades was incomplete: the minimum gain of 0.56 was very much higher than the prediction of 0.07 for a complete suprression during the whole saccade, and also clearly higher than the predicted 0.34 for a triangular suppression profile with only momentary complete suppression (the most conservative assumption for suppression reaching 100% at any time during the saccade).

Strikingly, immediately after gaze landed on target the VOR was working at a *supranormal* gain (1.0). This supranormal VOR gain gradually returned to its normal, presaccadic value.

Finally, there was a significant intrasaccadic change in VOR phase. Before the start of the gaze saccades this subject showed a phase lag between compensatory eye movements and head oscillation movement of about 7 deg. This value progressively turned into a phase lead of 14 deg during the gaze saccade, and slowly returned to its original phase lag value. The lower graph of Fig. 4B shows the dynamics of the gaze and head movement velocities.

Fig. 5A, B and C show the means (and ± 1 SD) of the gain and phase relationship of the VOR as a function of time (obtained by the phase-synchronisation method) of all trials in all 11 subjects for the 100 deg, 80 deg and 40 deg saccades, respectively. Mean VOR gains and phase lags preceding the gaze saccades were in agreement with the values of VOR gain and phase previously described for the applied frequencies (Tabak and Collewijn, 1994). Specifically, VOR gain has been found to increase progressively for frequencies increasing above 8 Hz, up to values exceeding unity.

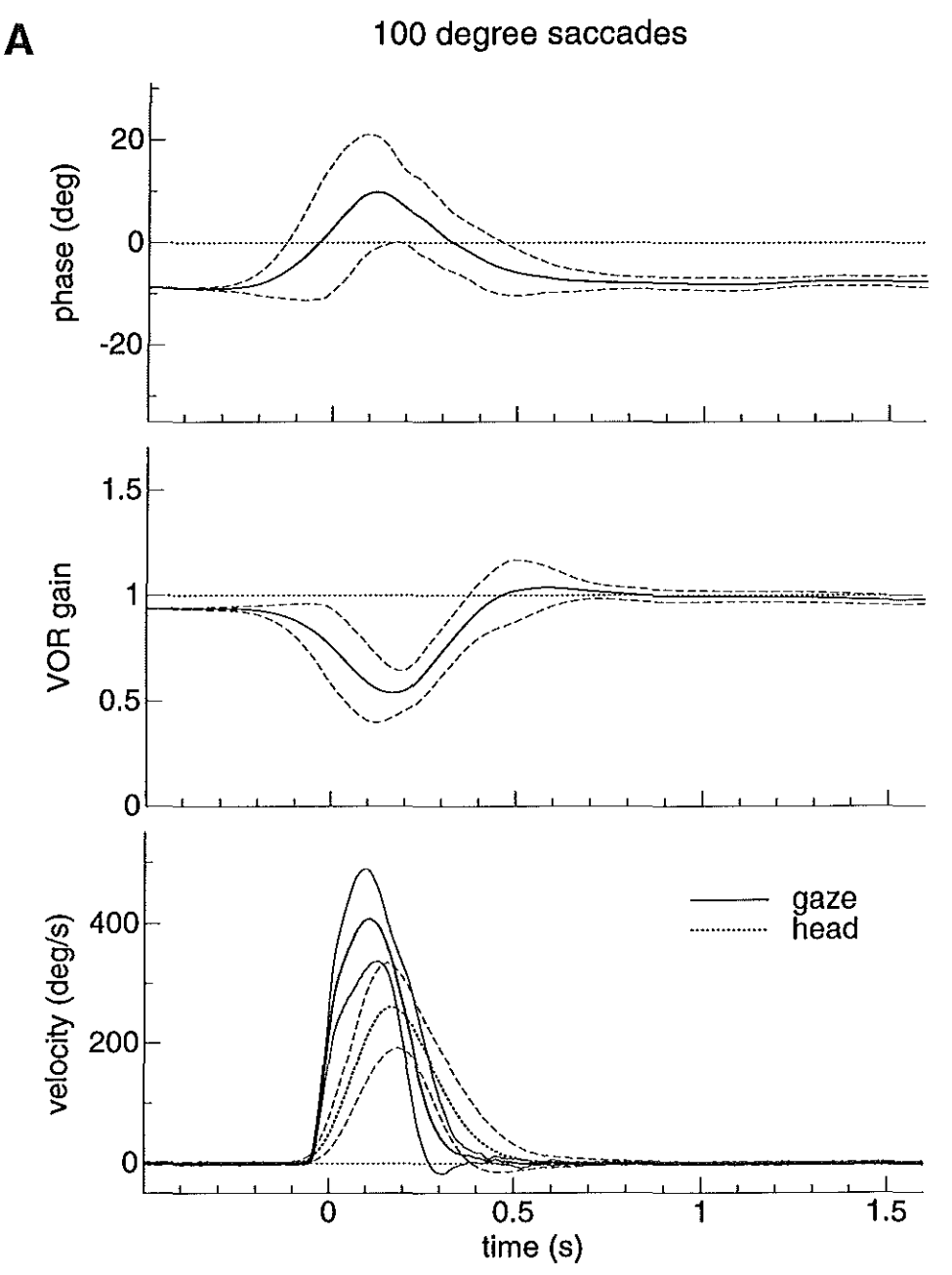


Fig. 5 Mean results of the phase-synchronization method and Fourier analysis; pooled results for all horizontal 100 deg saccades (with oscillation superimposed) in all subjects. Fine dashed lines demarcate ± 1 SD (inter-subject variability).

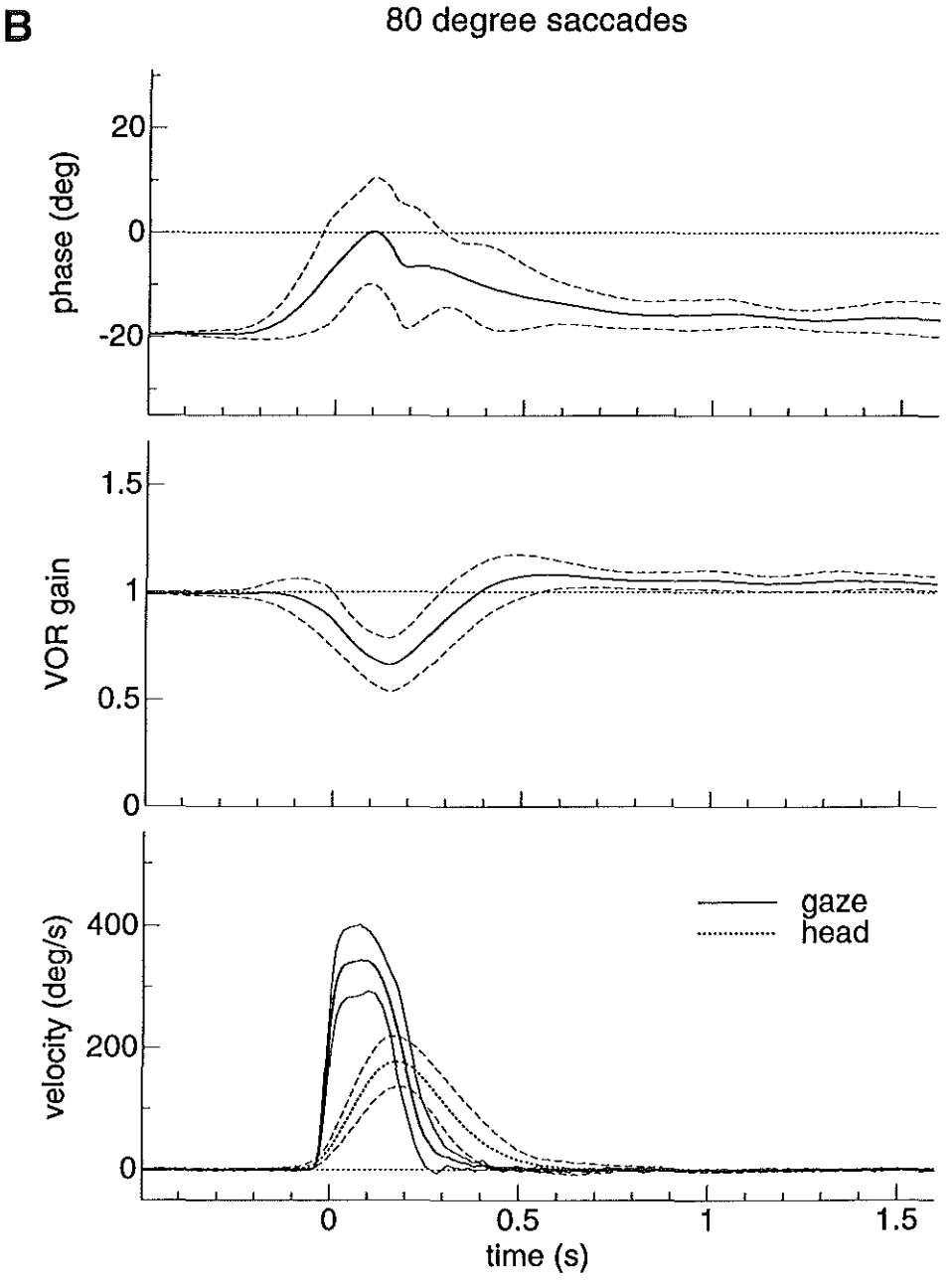


Fig. 5 Mean results of the phase-synchronization method and Fourier analysis; pooled results for all horizontal 80 deg saccades (with oscillation superimposed) in all subjects. Fine dashed lines demarcate ± 1 SD (inter-subject variability).

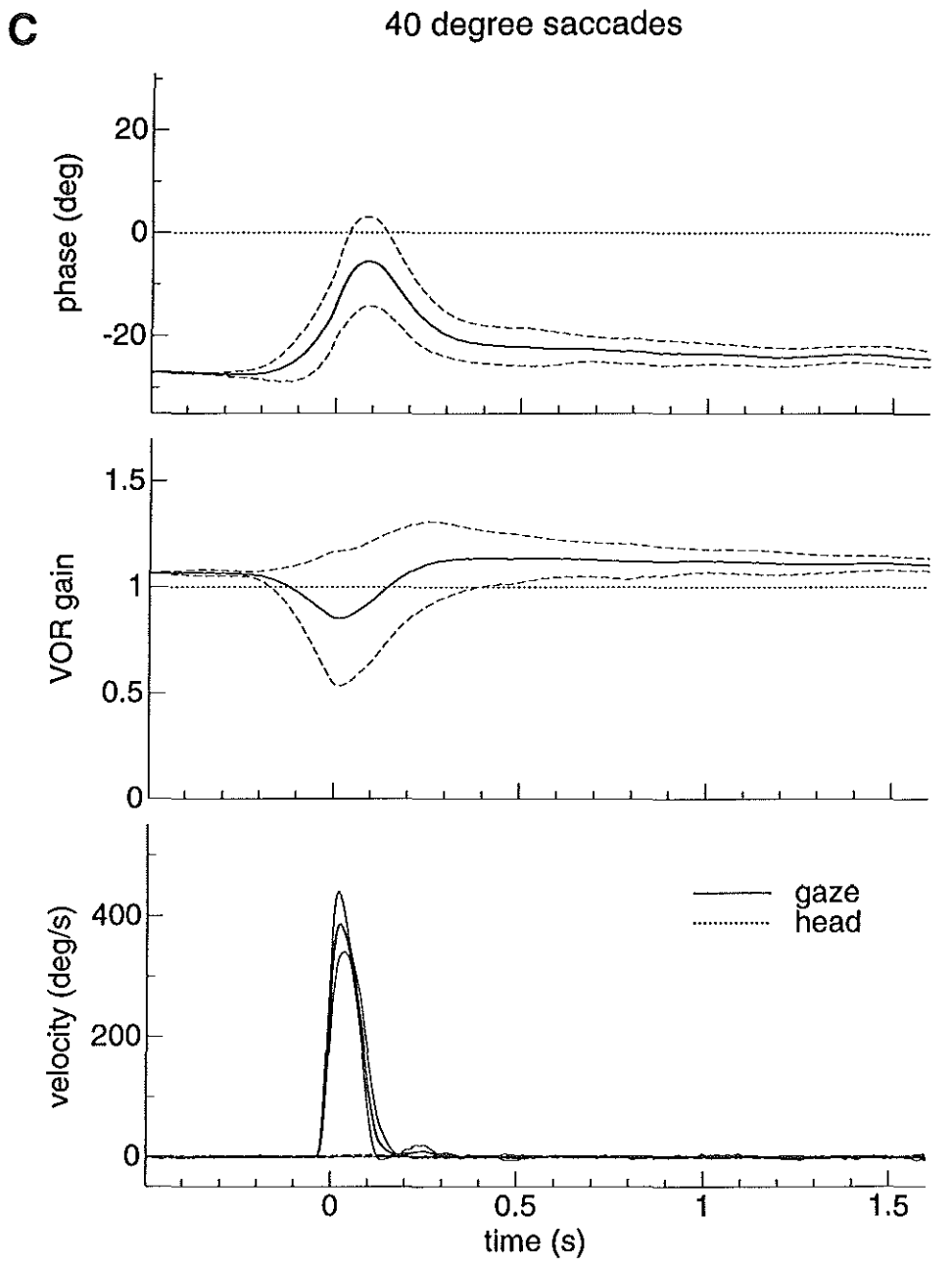


Fig. 5 Mean results of the phase-synchronization method and Fourier analysis; pooled results for all horizontal 40 deg saccades (with oscillation superimposed) in all subjects. Fine dashed lines demarcate ± 1 SD (inter-subject variability).

The average results for the 100 deg gaze saccades (Fig. 5A) strongly resemble the result of the single subject shown in Fig. 4. The mean VOR gain before the gaze saccade was about 0.94 with a phase lag of about 9 deg. During the gaze saccade, mean VOR gain reached a minimum of about 0.51 ± 0.13 (SD; n=11), i.e. a VOR suppression by 47% ± 13% from the pre-saccadic level, see Fig. 6A). The total range of the percentage of suppression for 100 deg saccades was between 22% and 75% for individual subjects. Once again, the average and even the whole range across subjects seems incompatible with a total VOR suppression during the whole saccade (predicted suppression shown by our technique 93.8%; see Methods). On the other hand, for a part of the subjects, the data would not exclude a triangular (or may be trapezoid) suppression profile reaching complete suppression for a brief fraction of the duration of 100 deg saccades.

Around the time when gaze landed on target, mean VOR gain became about 1.1, followed by a slow return to the pre-saccadic level. The averaged phase lag of about 9 deg before the gaze saccade changed into a phase lead of about 11 deg during the gaze saccade (phase shift of about 21 deg, see panel B in Fig. 6), which also gradually returned to the original phase lag existing prior to the gaze saccade. Notice that the maximum VOR-inhibition coincided with peak head velocity.

Saccades of 80 and 40 deg (Fig. 5 B and C) showed basically a similar course of VOR gain and phase as seen for 100 deg saccades, except for a less profound VOR suppression. Suppression amounted to 36% ± 11% (mean ± SD; n=7) for 80 deg gaze saccades. Once again, this value is incompatible with a 100%, 'square' suppression, which should yield a suppression by 81.3% in our analysis at the mean duration of 300 ms for 80 deg saccades. Even the theoretical, apparent reduction by 52.9% for 'triangular' suppression reaching momentarily 100% was not reached, suggesting that complete VOR suppression, even momentarily, was only exceptionally reached in our experiments.

For 40 deg saccades, VOR gain reduction, as calculated in our analysis, was 19% ± 19% (SD; n=7). One difference with the larger saccades was that there was no head movement during the 40 deg saccades (Fig. 5C, lower panel). Another difference was the higher inter-subject variability in VOR suppression for 40 deg saccades (see middle panel in Fig. 5C and Fig. 6A). Two subjects showed a suppression of less than 1%, three subjects between 8 and 16% and two subjects still had a substantial suppression of about 45%. At the mean duration for 40 deg saccades of about 150

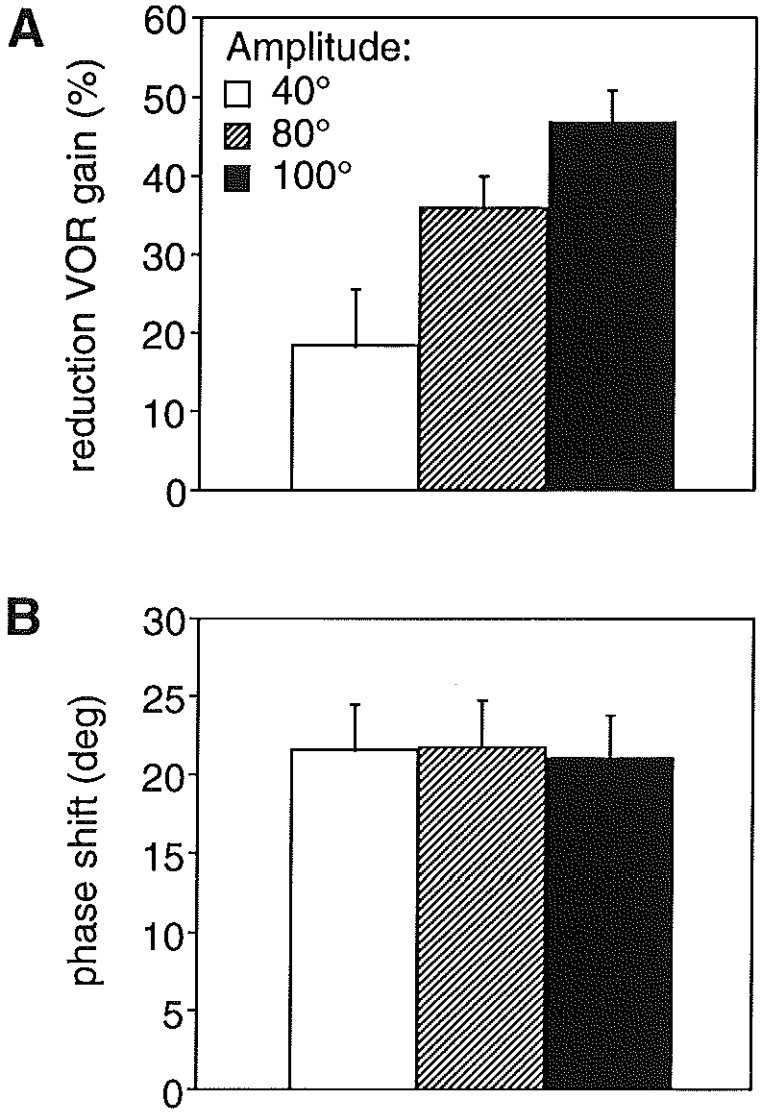
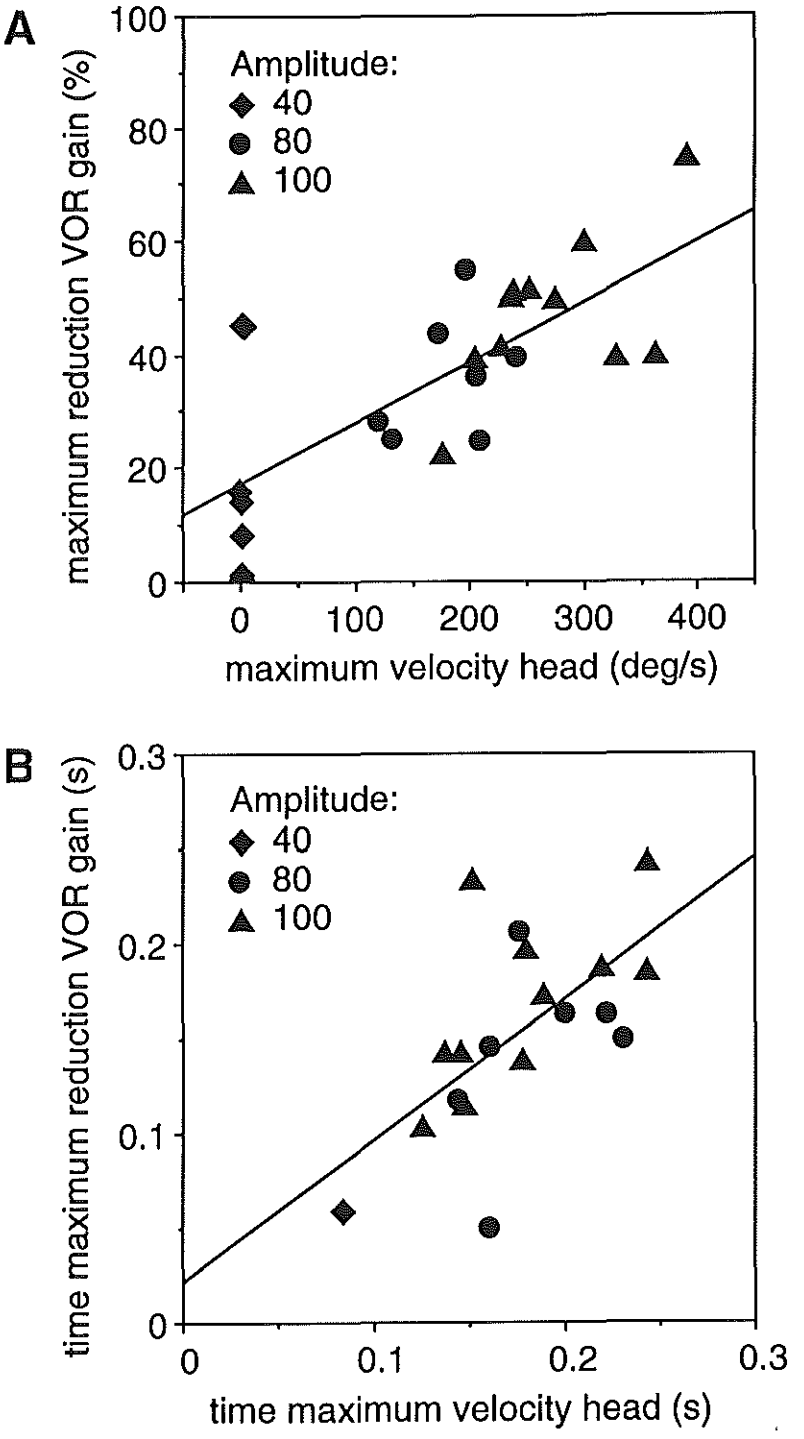


Fig. 6 Diagrams summarizing the mean changes (compared to pre-saccadic values) in gain (A) and phase (B) of the VOR during 40, 80 and 100 deg horizontal saccades for all subjects (± 1 SD of intersubject variability).

ms, the theoretical outcome of our analysis would be an apparent gain reduction by 49% and 34% for a square and triangular profile reaching a maximum of 100%


A
100
80
60
40
20
0
maximum reduction VOR gain (%)
Amplitude:
40
80
100
0
100
200
300
400
maximum velocity head (deg/s)
B
0.3
0.2
0.1
0
time maximum reduction VOR gain (s)
Amplitude:
40
80
100
0
0.1
0.2
0.3
time maximum velocity head (s)

suppression (see Methods). Once again, our mean results are not compatible with either of these cases; only the 2 (out of 7) subjects with about 45% gain reduction during 40 deg saccades may have had a completely suppressed VOR at some time during the saccade.

The maximum phase shift of the VOR response during 40 and 80 deg gaze saccades amounted again to an advance of about 21 deg and was similar in magnitude for all subjects.

A summary of the maximum saccadic reduction in gain and phase shift of the VOR (means and 1 SD of all subjects) is shown in Fig. 6 for the various saccadic sizes. Fig. 6B shows a constant phase shift for all gaze amplitudes. Because we did not use the same head oscillation frequencies for the different gaze shift amplitudes, this constant phase shift does not imply a constant change in delay. Fig. 6A shows that the reduction in VOR gain, as calculated with the Fourier technique, increases as a function of saccadic size. Given the filtering effects of this technique, as evaluated in our simulation experiments (see Methods), part of this trend could be a calculation artifact (short-lasting suppressions being truncated more than long-lasting suppressions). To test this possibility, we did a linear regression of calculated gain reduction on the duration of gaze-shift (means for all subjects and saccadic sizes). Surprisingly, a correlation between the magnitude of gain reduction and gaze-shift duration proved to be absent ($r^2 = 0.019$; $P > 0.5$). Therefore, the possibility that the increase in gain reduction as a function of saccadic size, as shown in Fig. 6, is only an artifact, can be rejected.

The relations between *head movements* and *VOR gain changes* were analyzed quantitatively in Fig. 7, which shows scattergrams of mean values per subject and per gaze amplitude. In Fig. 7A we plotted the relation between the magnitudes of maximum VOR-suppression and maximum head velocity, with a linear regression fitted through the data points. With a r^2 value of 0.514, this relationship was

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← *Fig. 7 Scattergrams, showing results for all subjects. Each symbol represents the average result for horizontal saccades of one amplitude in one subject. The lines show linear regressions. (A): relation between maximum reduction in VOR gain and maximum head velocity. (B): relation between times of occurrence of maximum VOR suppression and maximum head velocity. Both correlations are significant; see text.*

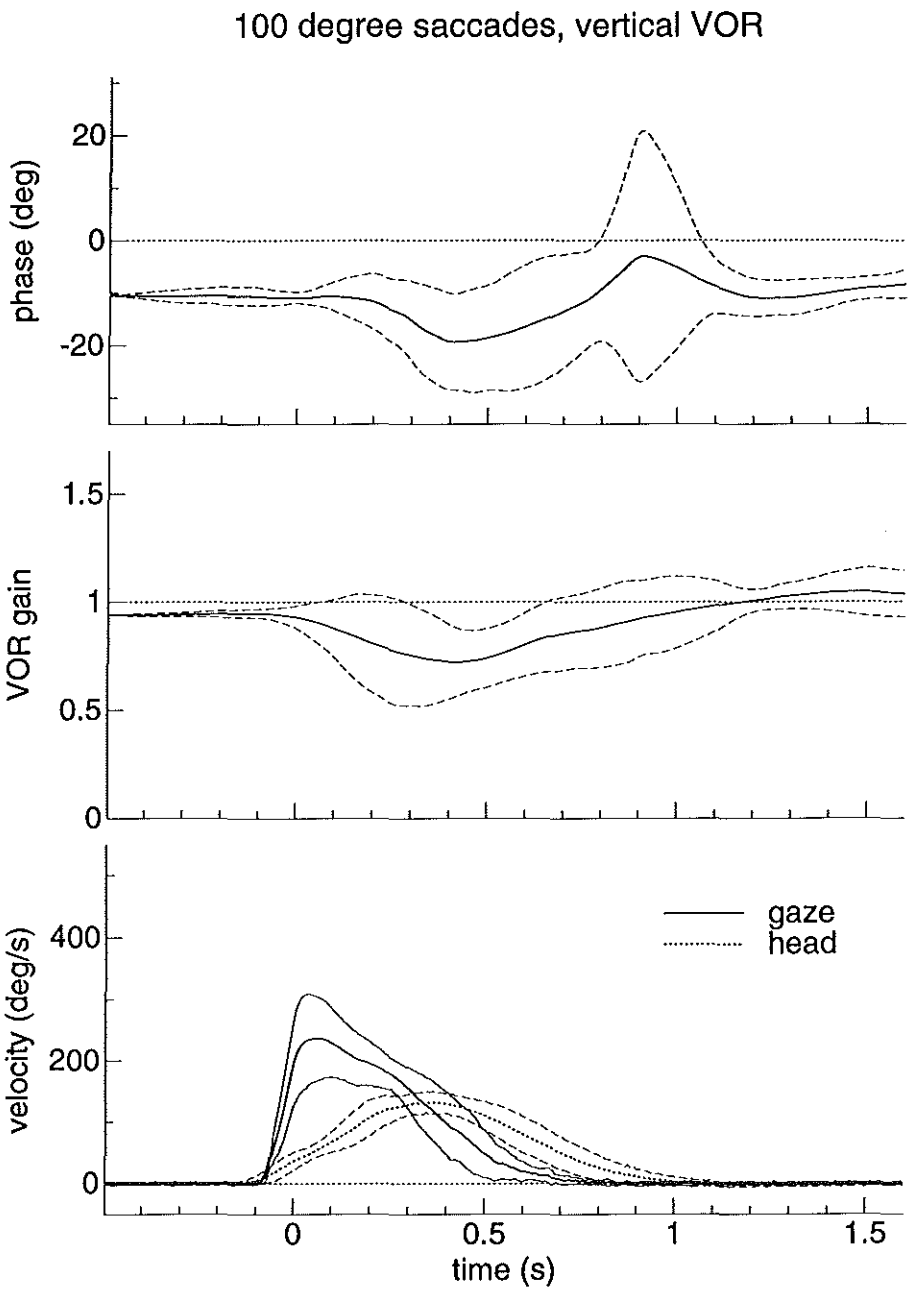
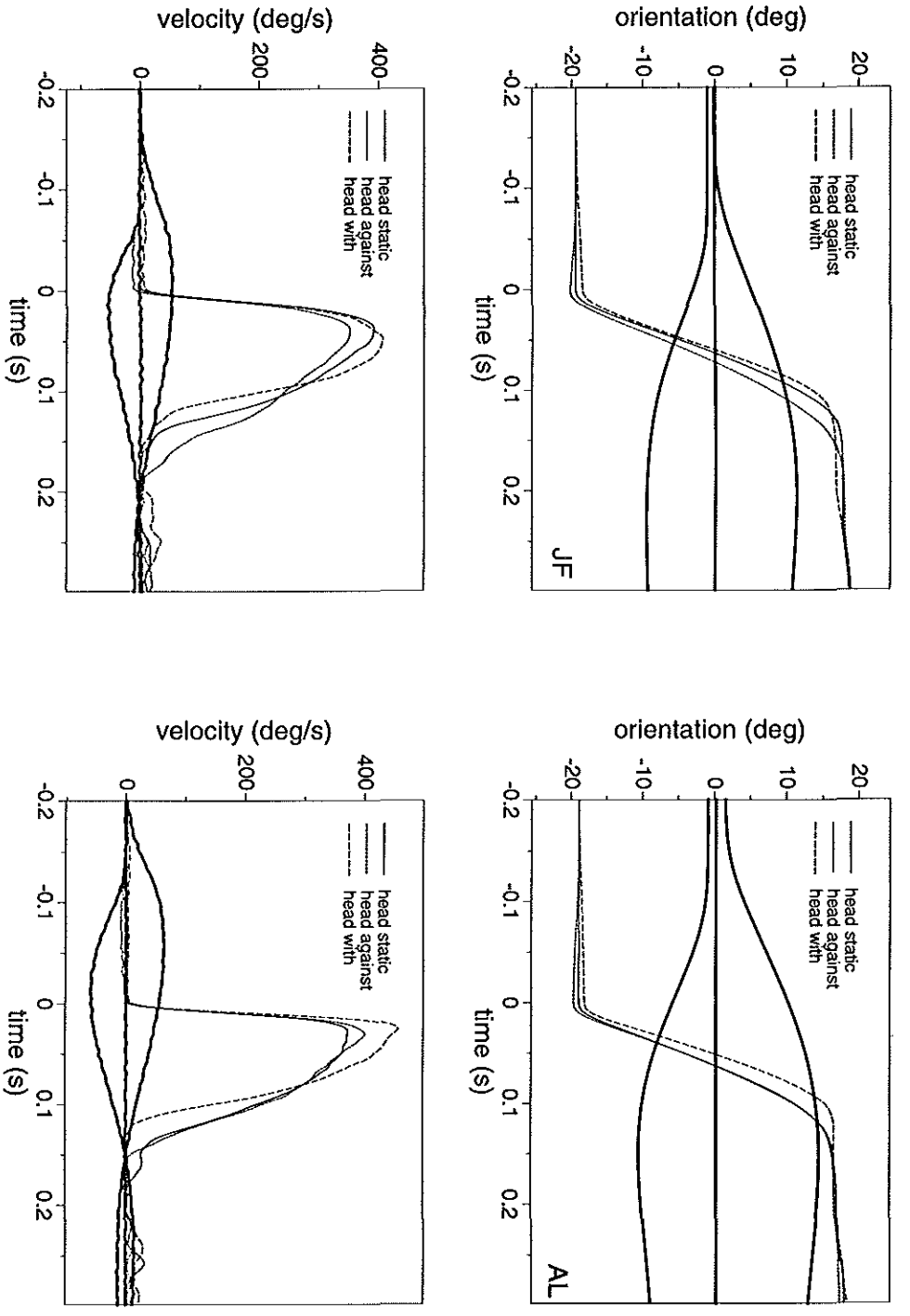


Fig. 8 Changes in the vertical VOR gain and phase during horizontal 100 deg horizontal saccades. Means (± 1 SD) of all participating subjects. Notice the slowness of the saccades, caused by the large inertia of the helmet providing the vertical head oscillation.

significant (P <0.0001). We also plotted the relation between the time until maximum VOR-suppression and the time until maximum head velocity after the start of the saccade (Fig. 7B). The diamond in Fig. 7B represents the only subject whose head velocity exceeded the minimum threshold of 5 deg/s during the 40 deg saccades. The linear regression in Fig. 7B had a r^2 value of 0.392 and was also significant (P=0.0041). In the same way as described for the head movement, we also quantified the relation between magnitude and timing of VOR suppression and the *gaze movement* as well as the *eye-in-head movement*. Multiple regressions between the parameters of the VOR suppression and movement parameters of head and eye again showed that only the variations in head movement contributed significantly (P <0.05) to the variations in VOR suppression.

5.4.2 Probing the VOR with vertical oscillations during horizontal gaze saccades

Fig. 8 shows the averaged mean time-course of vertical VOR gain and phase relationship of all subjects. During this experiment subjects had a higher head rotational inertia because of the large eccentric mass of the helmet used in this experiment. For this reason, subjects found it very difficult to make natural movements of the head. This is manifest in the low peak head velocity and the longer duration of the gaze saccade (see lower panel in Fig. 8). Both the head velocity and the suppression were significantly (P<0.05) smaller than for the 100 deg saccades obtained with the horizontally oscillating helmet. Despite this effect, which has been described before (Gauthier et al., 1986), there was a very consistent pattern of VOR gain reduction among the different subjects. Mean VOR suppression was about 37% at a maximum head velocity of 142 deg/s. The most striking dissimilarity between Fig. 8 and Fig. 5A, B and C is the difference in mean phase behavior, with higher variability during the gaze saccades with vertical oscillation. Mean maximum phase shift in comparison with the phase lag value just prior to the gaze saccade was only about 10 deg. The variability in phase behavior of the vertical VOR was, however, so high that this phase shift differed not significantly from zero deg, nor from 21 deg (the mean phase shift in the horizontal VOR).


orientation (deg)
velocity (deg/s)
time (s)
head static
head against
head with
JF
AL

5.4.3 Probing the VOR with horizontal torque pulses during horizontal saccades

In Fig. 9 we show the average result for two subjects; for these averages the individual records fulfilling the criteria were aligned on the onset of gaze movement (see Methods). Head (thick lines) and gaze (thin lines) positions and velocities during a 40 deg gaze-shift are shown for the unperturbed head and for head-torque pulses 'with' and 'against' the gaze shift. Without perturbation, the head moved slightly (on average 0.3 deg) in the direction of the saccade. The responses of the head to the torque-perturbations varied strongly between subjects: the total magnitude of the resulting head movement was on average 12 deg (range: 3-22 deg); about half of this occurred during the saccade. For all subjects, the amplitude of the head movement was larger when the perturbation was in the same direction as the saccade (13.3±4.5 deg), than when the perturbation was in the direction opposite to that of the saccade (8.7±4.4 deg). To compensate for these differences in response, the moment of onset of the head-perturbation was made direction-dependent (see Methods). In this way, the part of the head movement which occurred *during* the saccades was made less dependent on the direction of the saccade: the head movements during saccades were 5.9 deg (head with) and 4.9 deg (head against) on average.

The head movement before the start of the saccade, (8.2±5.3 deg) caused a drift of the gaze of 0.7±0.5 deg in the direction of the perturbation, which corresponds to a VOR-gain of about 0.9. The response to the perturbation during the saccades varied strongly between subjects, as illustrated for two subjects in Fig. 9. For both subjects, the sign of the initial effect of the perturbation was independent of the perturbation direction: initial gaze-velocity increased for AL, and decreased for JF, compared to undisturbed saccades. Despite this great variability in response, the *difference in the responses* to the perturbations in the two directions, with and against gaze, and thus

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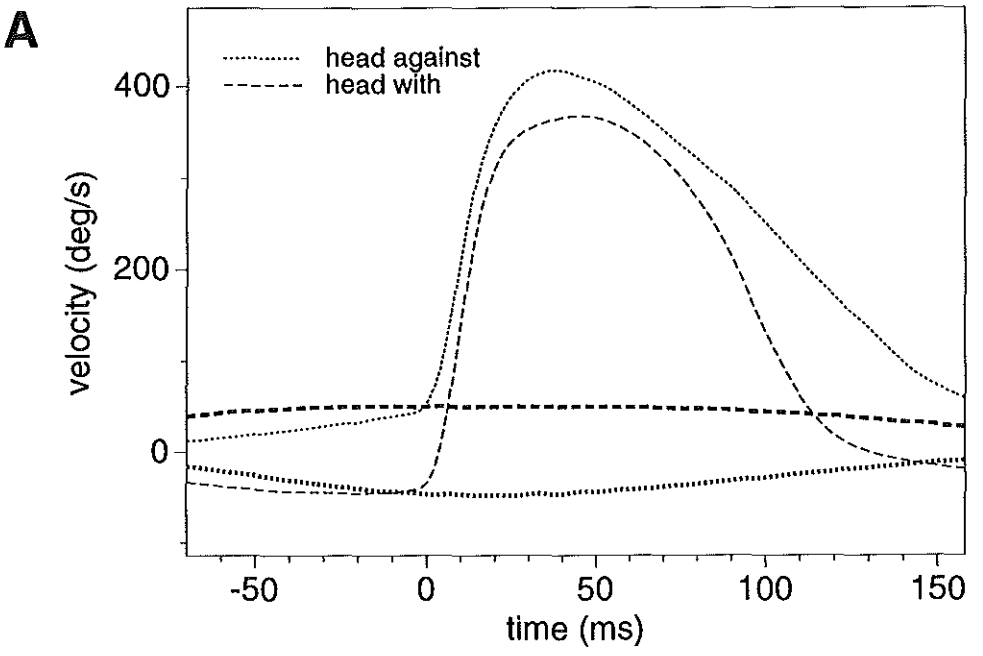
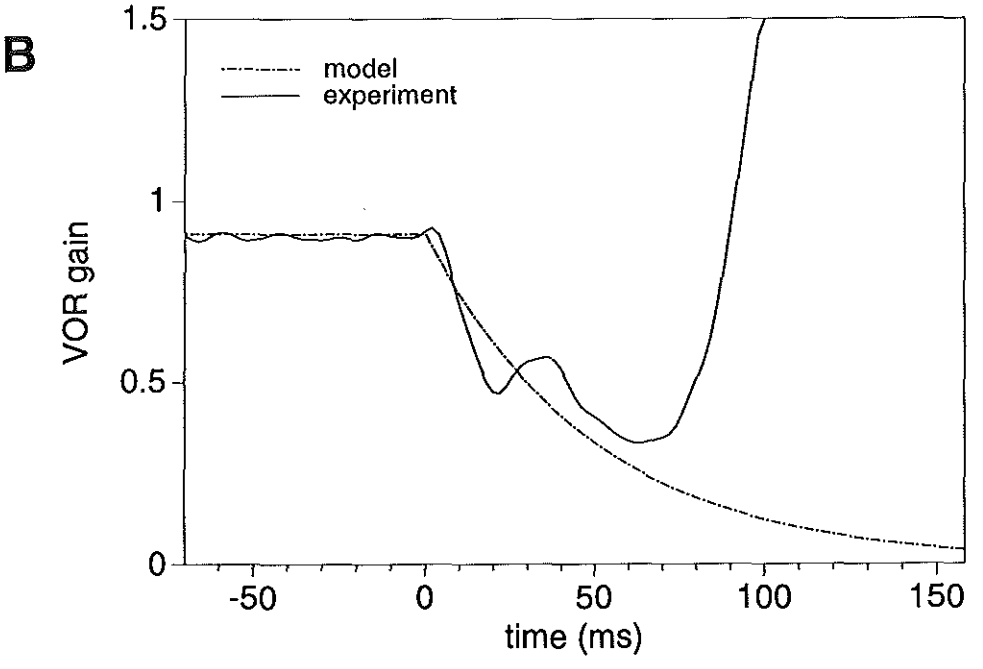
←—— *Fig. 9 The average movements of the gaze (thin lines) and head (thick lines) during saccades in three conditions of head perturbation (no perturbation, torque pulse in direction opposite to saccade, torque pulse in direction of saccade). For each condition, the average of all saccades to the left and to the right is plotted for two subjects (AL and JF). For one subject (AL), head-perturbation increased gaze velocity during the initial 50 ms whereas for the other subject (JF), head-perturbation decreased gaze velocity during the initial 50 ms.*


A
head against
head with
400
200
0
velocity (deg/s)
-50
0
50
100
150
time (ms)


B
model
experiment
1.5
1
0.5
0
VOR gain
-50
0
50
100
150
time (ms)

the VOR, was the same for all subjects. Saccades had a higher speed and shorter duration in trials in which the gaze moved in the same direction as the perturbation than in trials with a perturbation in the opposite direction.

The duration of the gaze saccades was on average 137 ms. The duration varied between subjects (range 119-168 ms) and head movement direction (head with: 122 ms; head against: 150 ms). One would expect longer durations for saccades with larger eye-in-head amplitudes; this hypothesis was tested using a linear regression analysis. For each subject, the duration of the (gaze-)saccade correlated as expected with the eye-in-head amplitude, with a regression coefficient of 3.0±0.5 ms/deg (averaged over the 12 experiments, r^2 = 0.53). For all subjects, the difference between the duration of the saccades with the two different perturbations was 28±6 ms. For some subjects, mainly head-movements opposite to the saccade induced a clear change (increase) in duration, whereas for other subjects, the duration was mainly changed (decreased) when the head moved with the saccade.

The perturbations of the head changed the maximum velocity of the eye-in-head movements. A perturbation in the direction of the saccade (head velocity 52 deg/s) decreased the maximum velocity from 402 deg/s to 391 deg/s; a perturbation opposite to the saccade (head velocity 45 deg/s) increased it to 431 deg/s. These changes in eye-in-head velocity were not enough to compensate for the head movements: the maximum speed of gaze increased from 403 deg/s to 444 deg/s when the head moved with the saccade, and decreased to 387 deg/s when the head moved against the saccade. For all subjects, a perturbation in the direction of the saccade resulted in higher gaze-velocities and shorter durations than a perturbation in the opposite direction. As the average magnitude of this difference in the responses to the two perturbations did not differ very much between subjects, we averaged the response over all subjects (Fig. 10). The gain of the VOR (calculated on the basis of the difference in the responses to the two perturbations) was about 0.95 before the saccade. When the saccade started, VOR gain dropped very quickly and stayed low

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←—— ***Fig. 10** The average movements of the head and eye for all subjects. Note the difference in time-scale with Figure 1. A: The average velocity-response of eye-in-head (thin lines) and head (thick lines) to the two types of perturbation of the head. B: The VOR gain calculated from the difference in the responses to the two types of perturbations (continuous line). The dashed-dotted line indicates an exponential decay of the VOR, with a time-constant of 50 ms.*

till about 70 ms after saccadic onset. As shown in Fig. 10, this decrease in gain can be approximately described as an exponential decay with a time constant of 50 ms. Thereafter, the gain of the VOR appeared to increase very fast but actually could not be further evaluated from the torque-pulses, as non-VOR compensatory mechanisms clearly dominated at this stage.

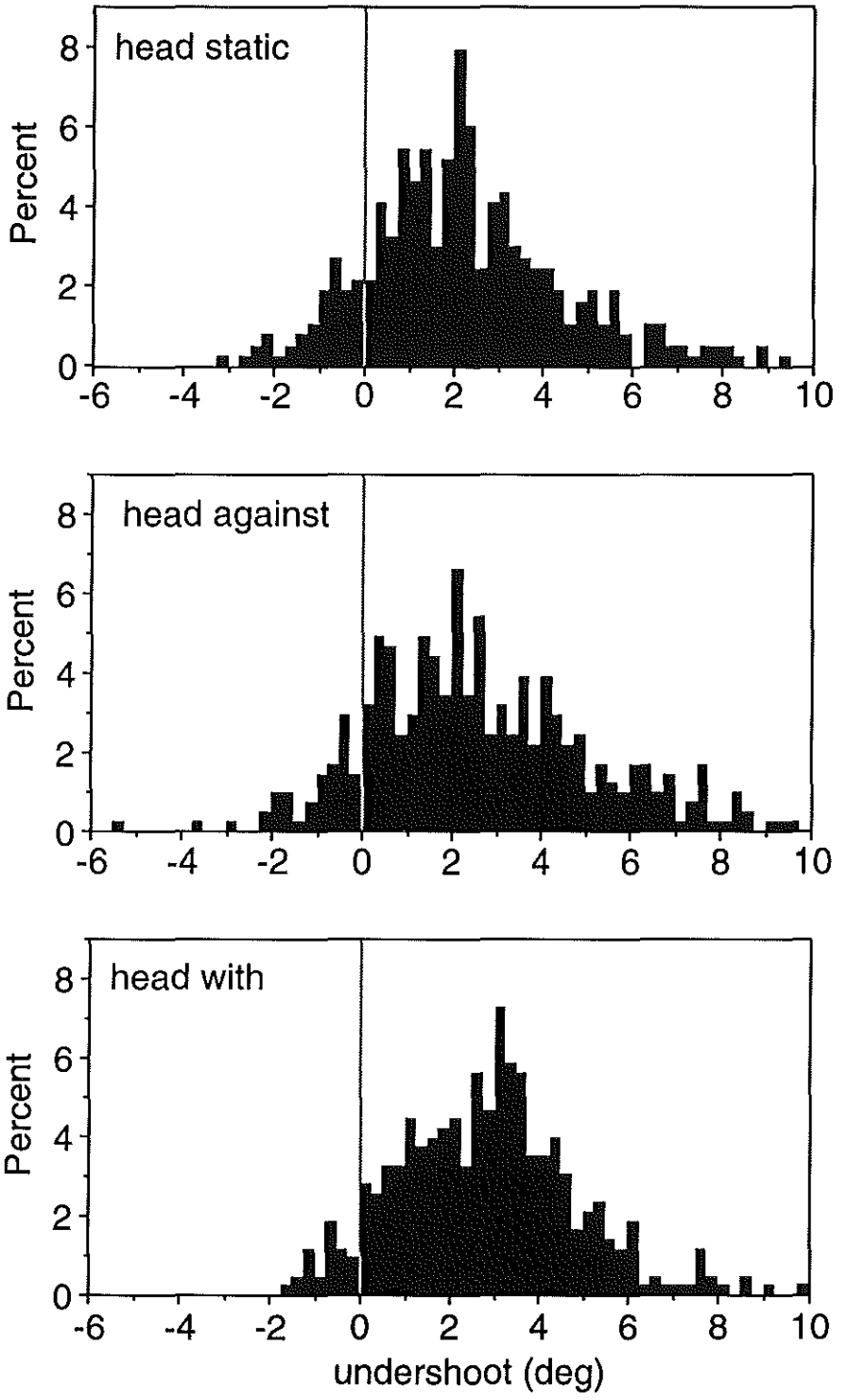
Although the effect of the perturbations on saccadic dynamics differed between subjects, the gaze accuracy remained fairly constant for all subjects. Fig. 11 shows the accuracy of the saccades with and without perturbations of the head. For unperturbed saccades, the saccade undershot the target by 2.3 deg (median value). Perturbations of the head increased the undershoot significantly (paired *t*-test, $p<0.05$) to 2.9 deg (head with) or 3.3 deg (head against). The sign of the change in gaze-amplitude was thus independent of the direction of the head movement. The standard deviation of the undershoot was 1.9±0.2 deg, independently of the perturbation. For all conditions, the undershoot of the first saccade was corrected to a large amount during the first 200 ms after the saccade.

5.5 Discussion

5.5.1 Saccadic VOR-changes revealed by head oscillation

Our previously (Tabak and Collewijn, 1994,1995) developed method of 'high-frequency' head oscillation was successfully applied to probing the VOR during gaze saccades. Distinct advantages of the method in this application are: 1) the probing signal adds only a 'dither' to the ongoing movements and does not systematically interfere with the gaze movement; 2) the probe is easily applied and allows the continuous measurement of VOR gain and phase as a function of time, within limits imposed by unavoidable windowing-techiques; 3) the high frequencies effectively exclude any high-level modulation of the VOR by visual or visually related effects such as smooth pursuit, VOR-cancellation and mental set (imagined targets and frames of reference).

Analysis requires the separation of the oscillatory component from the (very much larger) gaze-shift component. Our first, and most intuitive approach to this separation was to find matching pairs of gaze saccades among two subpopulations of similar gaze shifts with and without head oscillation. Simple subtraction of such pairs leaves


head static
head against
head with
Percent
0
2
4
6
8
-6
-4
-2
0
2
4
6
8
10
undershoot (deg)

only the oscillatory component. Unfortunately, the yield of this 'matching' method is low: because the amplitude of the oscillation is only on the order of 1% of that of the gaze saccade, even the minor normal variability in the dynamics of successive gaze saccades is sufficient to restrict acceptable matches to a small fraction of the collected data. Successful matches do show the phenomenon of intrasaccadic VOR suppression in a convincing but qualitative manner (Figs. 3, 4A), and a quantitative analysis technique using all the data is obviously preferable. A working solution was found in the phase-synchronization method, in which all signals were slightly shifted in time around the moment of saccadic onset, to reset the phase of the oscillatory component of the head movement to 0 or 180 deg (whichever was closest). Subtraction and addition of the two synchronized groups isolated the oscillatory and saccadic motions, respectively, at the price of some blurring in time. Subsequent to the isolation of the oscillatory component by any of the two methods, gain and phase of the VOR as a function of time could be determined as a continuous function of time by Fourier techniques, using a sliding window.

The consistent results obtained with both separation methods, for all subjects, corroborate the validity of the analysis, although the maximum suppression values found were truncated due to the blurring of time inherent to both the synchronization and the sliding-window techniques. Similarly, this time-blurring leads to some uncertainty in the exact timing of the changes in the VOR. The Parzen window extended over ± 256 ms (± 128 samples); this length is dictated by the frequency range of our oscillations (1 period having a duration on the order of 0.1 s). In this way, the obtained results are not contaminated by low-frequency components (drift) in the signals. Although the use of this window does not systematically shift events forward or backward, it smears events out in time so that it blurs the actual time course of gain and phase. Simulations with artificial signals (Fig. 2 A, B) showed that this blurring could shift the start and end of an instantaneous offset and onset up to 256 ms forward and backward, respectively. In this respect, the apparent start of VOR suppression *ahead* of the saccade, as visible in Figs. 5 A-C, is probably an (unavoidable) artifact of the Fourier technique. The timing of the minima and maxima of VOR gain should be correctly assessed by our technique, although sharp

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←—— *Fig. 11 Histograms of the error at the end of the primary saccade for the three conditions. Negative values indicate undershoot, positive overshoot. All trials which passed the criteria mentioned in the introduction of all subjects are used. Bin-width 0.25 deg.*

peaks in these values could be filtered out by the synchronization and windowing procedures. The amount of underestimation of the obtained peak values of suppression depends on the duration and the profile of the suppression. To assess the distortion of gains by the time-blurring of our technique we simulated the results for two theoretical profiles of saccadic VOR gain reduction that represent more or less extreme cases: 1) total suppression during the entire saccadic duration ('square' profile); and 2) gradual reduction and recovery ('triangular' profile) of VOR gain, with suppression reaching 100% only for a brief instant. As shown in detail in the Results, the outcome of our measurements, interpreted in the framework of these simulations, excludes the 'square' profile of suppression in all cases, and suggests that even total suppression for a brief fraction of saccadic duration is the exception, rather than the rule.

The suppression found with the oscillation technique is in general agreement with the conclusions from earlier work on saccadic VOR suppression, but adds further detail. The tendency for the depth of VOR suppression to gradually increase along with saccadic amplitude confirms earlier reports by several groups (Pélisson et al. 1988, Tomlinson, 1990). The magnitude of the suppression has been variously estimated, probably depending on the methods used. Laurutis and Robinson (1986) concluded to a virtually complete suppression for saccadic amplitudes above 40 deg; Tomlinson (1990) reported an equally profound suppression in monkeys; Pélisson et al. (1988) found a slightly less strong suppression, while Guitton and Volle (1987) emphasized the variation of depth and time course of suppression among subjects. We confirm the existence of subject variability, especially for saccades of intermediate size, but in general we find a less complete suppression than previous authors. A recent study by Epelboim et al. (1995), in which gaze movements of human subjects between close targets were occasionally perturbed by 'pushes', also provided evidence for saccadic VOR suppression that was only partial and, moreover, variable among trials.

A new finding, which could only be obtained with the oscillation technique, is that VOR phase is advanced, concomitantly with the reduction in VOR gain. This phase advance suggests possible mechanisms that could underlie the VOR-suppression, as will be discussed later.

Another new and highly consistent finding in the oscillation experiments is the existence of a period of supra-normal VOR gain after the saccadic gaze shift has

ended. In the period when head and eye are still moving and even in the ensuing period when the gaze movements have been completed, VOR gain was higher than in the period preceding the saccade (Figs. 3-5). As the purpose of a gaze shift is to fixate a new object of interest, it is important to carry gaze to the new object and then hold it very steady for some time. Gaze lands on target often long before the head reaches a steady position; thus, perfect function of the VOR in the wake of the gaze-shift is of considerable functional importance. We submit that, therefore, VOR gain in this period is tuned closer to unity to assist in the stability of fixation of the new target. In this respect, it is important to emphasize that VOR gain is frequency dependent: we previously assessed (Tabak and Collewijn 1994) with the oscillated helmet that the horizontal VOR gain in normal humans is about 0.9 in the 2-4 Hz range, but rises to unity and higher in the 12-20 Hz range. This tendency is clearly reflected in Figs. 5 A-C, in which progressively higher probing frequencies were used for smaller saccades. Natural horizontal head movements (including such behaviors as running and vigorous head rotation) contain no energy above 5 Hz (Grossman et al. 1988). Therefore, it seems fair to conclude that for natural behavior the VOR has a baseline gain slightly below unity, so that the post-saccadic enhancement will bring VOR gain indeed closer to unity in the physiological frequency range.

Our experiments with vertical oscillation during horizontal saccades show the existence of VOR suppression in a plane orthogonal to the saccades. Thus, VOR-suppression was not entirely plane specific. This finding is somewhat at variance with the results of Tomlinson and Bahra (1986) who found, using horizontal head perturbations, that during small (<10 deg) and large (30-40 deg) vertical saccades the horizontal VOR was 'on' in monkeys. During large horizontal gaze shifts (>30-40 deg) they found that the horizontal VOR was completely switched off. Our findings are compatible with some degree of plane-specificity; suppression of the vertical VOR was certainly smaller than of the horizontal VOR (Figs. 5A and 9). However, the slowing of the head velocities by the larger inertial mass of the 'vertical' helmet may significantly contribute to this difference. Statistical analysis (Fig. 7) suggests that VOR suppression is most tightly correlated with head velocity: the magnitude of suppression correlated best with the maximum head velocity, and the timing of the VOR gain minimum also correlated best with the time of maximum head velocity. This suggests that the amount of VOR gain reduction depends more on head velocity parameters than on saccadic size as such. Head movement was, however, not absolutely necessary to get VOR-suppression, as shown by some subjects for our 40

deg saccades (diamonds in Fig. 7A).

5.5.2 Gaze control in relation to head-torque pulses

In contrast to the oscillations, torque-pulses biased the head position systematically in one direction and needed to be corrected, somehow, for gaze saccades to remain accurate. We investigated the effect of torque-pulses for 40 deg saccades that hardly involved any voluntary head rotation. We found that such perturbations of the head reduced the amplitude of saccades slightly, independently of the direction of the perturbing head-movement. This amplitude-change, combined with the asymmetries found in the changes in speed and duration, supports the hypothesis that the saccadic command is changed by the perturbation. The accuracy of the unperturbed saccades in our experiment corresponds to the accuracy of saccades to stationary targets (in dark surroundings) as reported by Lemij & Collewijn (1989). The average undershoot of the saccades increased slightly in our experiment when the head was moved (independent of its direction), without an increase of its standard deviation. Pélisson et al. (1988) did also find a slight increase of the undershoot of saccades due to head-perturbations, but in their experiments variability increased as well. The increase in undershoot that we found for head-perturbations may have a parallel in the increase in undershoot found when targets are not continuously visible (Lemij & Collewijn, 1989): both changes might reflect that, in uncertain situations, the programming of saccades is changed in a conservative direction to have a larger safety-margin.

A striking result in our experiments was the asymmetry in the effects on saccadic dynamics. While one would expect that, given the presence of saccadic VOR suppression, gaze saccades would speed up for torque-pulses 'with' gaze and slow down for torque-pulses 'against' gaze, compared to the unperturbed condition, such a symmetric response was not obtained in many subjects (see Fig. 9). Pélisson and Prablanc (1986) also reported an asymmetric response for some of their subjects in response to head-perturbation during 30 and 40 deg saccades: complete compensation for perturbations against the saccade, and almost no compensation for perturbations in the other direction. Tomlinson & Bahra (1986), studying VOR-saccade interaction in monkeys, reported an asymmetry in the opposite direction for responses to head-perturbations during 20 deg saccades. The various asymmetries the we found are thus not a peculiarity of our experiment, but were present as well

(although not emphasized) in other experiments.

Subject-dependent asymmetries in the VOR could be accounted for in two ways. A first explanation would be that the VOR is really suppressed asymmetrically in a subject-dependent way. Suppression, however, cannot lead to an increase in gaze-velocity when the head moves against the saccade (as for example in Fig. 9, right panels). Therefore, asymmetric suppression of the VOR cannot explain the asymmetries we found. A second explanation is that the head-perturbation changed the speed of the saccade. Such subject-dependent general changes in saccadic speed profiles have been also reported in other conditions. For instance, Collewijn et al. (1992) investigated the effect of fixing the head to a bite-board on saccadic velocity profiles. The effect of this fixation on these profiles was quite different for the two subjects they studied, and not directly related to the actual head movements they made when the head was free. In a similar way, one could imagine that a head-perturbation changes the saccade generation in a subject-dependent way.

A second asymmetry that we found was that the response of the head to the torque-perturbation was direction-dependent: perturbations opposite to the saccade were counteracted more effectively than perturbations in the direction of the saccade. A similar asymmetry was found by Tomlinson (1990) in monkeys for the response to torque perturbations during active head-movements. Our result suggests that, even though our subjects did not move their head voluntarily, the motor-output to eyes and head was coordinated. Possibly, this coordination involved a saccade-direction dependent setting of the gain of the stretch-reflex of the neck muscles. A similar coordinated change in reflex gain of muscles that are not causing movements themselves has been reported for muscles around the shoulder during elbow flexion movements (Smeets et al., 1995).

5.5.3 Saccadic VOR-changes revealed by head-torque pulses

The difference in the response to perturbations in opposite directions showed a time-dependent effect of head movements on eye-in-head velocity, which supports the hypothesis that the VOR is partially suppressed during saccades. The essential result (Fig. 10) is that VOR gain falls sharply at the beginning of the saccade and continues to do so at a lower rate till about 70 ms after saccadic onset. At that time (long before the saccades ends), the VOR becomes uninterpretable in this type of experiment, due

to the interference of other mechanisms, as will be discussed later. As this technique of estimating VOR gain is not corrupted by time-blurring (which could not be avoided in the oscillation experiments), it probably provides the best estimate of the course of VOR gain around saccadic onset. In particular, it does not suggest any alteration of VOR gain preceding saccadic onset, a conclusion which is further supported by the raw results of the 'matching' technique such as shown in Fig. 3 (not subjected to Fourier analysis).

We confirm that, despite of this VOR suppression, gaze saccades remain approximately accurate. When no saccades are made, VOR gain is in general slightly lower than unity in the physiological range of frequencies (Tabak & Collewijn, 1994). If the compensation for head movements would be based on the VOR, a head movement would introduce a gaze-error in the same direction as and proportional to the head-amplitude. So, one would expect a larger gaze-error (overshoot for head-with, undershoot for head-against) at the end of the saccade than at saccade onset. In our experiments, however, the gaze-error introduced by the perturbation was *smaller* at the end of the saccade than just before the start of the saccade. Moreover, the direction of the error was independent of the direction of the head movement. The accuracy of the saccade was, thus, even better than could be expected on the basis of a working VOR alone.

In our experiment, in agreement with previous literature, head movements changed both the amplitude and the duration of the eye-in-head saccade. The variation in duration is actually one of the key arguments in favour of saccadic VOR suppression because if the VOR would compensate for head movements, the duration of the saccade would be independent of the head movement. Actually, the changes in duration of the saccades with head-perturbation appear to obey the classical duration-amplitude relation. Collewijn et al. (1988) reported, for head-fixed saccades up to 50 deg, a linear relation between the amplitude and duration with a slope of 2.7 ms/deg. We found a virtually similar relation between eye-in-head amplitude and duration: 3.0±0.5 ms/deg. Our data on the accuracy and duration of the saccades corroborate the conclusion of many other authors (see Introduction) that it is not possible to model eye-head coordination during saccades as the linear summation of a VOR and an unchanged saccade. In the next section we shall discuss the possible mechanisms responsible for the behavior of the VOR as probed with the two types of perturbation.

5.5.4 *Mechanisms*

Several authors (Laurutis & Robinson, 1986; Pélisson et al., 1988; Tomlinson, 1990; Guitton, 1992) have proposed variations on the local feedback model (Robinson, 1975) of saccade generation to account for the interaction between saccades and head movements. In these models, the inputs to the burst neurones and to the neural integrator are in gaze-coordinates, instead of eye-in-head coordinates as in the original model. Without head movements, the models behave just as the Robinson (1975) model. If the head moves during the saccade, the effect of the head movement on the saccade will develop as follows. As the initial activation of the eye-muscles is only based on the gaze-error at the start of the saccade, the initial part of the saccade will be independent of head movements and the VOR during the saccade. If the VOR functions at unity gain during the saccade, the error in gaze will be equal to the error in eye-in-head, so the gaze-saccade will be the same as without head movements. If the VOR is (partially) suppressed during the saccade, the burst-activity will gradually change on the basis of the larger (head against) or smaller (head with) motor-error. This will change the saccadic dynamics, but the saccade will reach the target as accurately as without head movements.

According to these models, the response to a head movement during saccades consists of two components: one mediated by a 'short' path (the actual VOR, which is supposed to be suppressed to a certain amount), and one mediated by a 'long' path through the saccade-generating circuitry. Importantly, the processing of vestibular signals through the long, 'saccadic' path is supposed to take much longer than that in the 'short' VOR. The difference in delay between these two paths has been estimated as about 50 ms (Laurutis & Robinson, 1986). If this is correct, then the first 50 ms of the saccade would still show the changes in the response of the true, 'short path' VOR to a torque-pulse. As a consequence, Fig. 10 would be correct in showing that during this period the VOR gain decreases roughly exponentially towards zero, with a time-constant of about 50 ms, leaving VOR gain at about 0.3-0.4 at 50 ms after saccadic onset.

The VOR pathway is assumed to contain two components. The shortest connection of the afferents from the semicircular canals to the oculomotor neurons is a disynaptic, three-neuron arc, the middle neuron being a secondary vestibular neuron in the vestibular nuclei. The VOR-related canal-afferents are mostly in phase with head velocity for frequencies above 0.1 Hz (see e.g. Highstein, 1988). Most of the

involved vestibular neurons are of the PVP (position-vestibular-pause)-type, i.e., they carry signals related to head velocity and eye position, and pause during saccades. The velocity signals on these neurons provide the appropriate velocity input to the oculomotor neurons but to account for the input-output relations of the VOR throughout the frequency range, the VOR pathway must also carry an eye position control signal, which is created by integration of the velocity signals (Skavenski and Robinson, 1973). This 'neural integrator' function appears to be distributed among several parts of the brainstem, including the nucleus prepositus hypoglossi and the vestibular nuclei themselves (Cannon and Robinson, 1987; for review see Keller, 1991). Part of the integrated signal is also carried by the PVP-cells, although probably not with a high enough gain to provide the oculomotor neurons with sufficient position information during the VOR (Tomlinson and Robinson, 1984). A crucial role of the saccadic 'pause' of vestibular neurons in mediating the VOR suppression during saccades in a graded manner has been postulated (see e.g. Berthoz et al., 1989). Saccadic suppression of vestibular neurons is likely to affect the stream of both velocity- and position-related signals to the oculomotor neurons, possibly to different extents. Therefore, a residual (partly suppressed) VOR during a saccade might have dynamic properties that differ from the normal VOR. Our finding that VOR-phase is advanced by about 20 deg during saccades would be consistent with a complete suppression of the integrated signal, in addition to a graded reduction of the velocity signal. Thus, saccadic suppression of the VOR can not be described as a pure reduction in gain.

5.5.5 Conclusions

Our experiments show, in agreement with earlier work, that the VOR is suppressed during gaze saccades. VOR gain appears to fall sharply at saccadic onset, following approximately an exponential course with a time constant of about 50 ms. Our work strongly suggests, however, that this suppression is never complete, even for very large saccades. The transient reduction in gain is accompanied by a transient advance in VOR phase, suggesting that the 'neural integrator' is suppressed more completely than the direct velocity pathway. At the end of the saccade, VOR gain is restored to a level (about 1.0) that is consistently higher than presaccadic VOR-gain (about 0.9); a result that would strongly favour stable fixation of the newly acquired target.

5.6 References

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Summary / samenvatting

Summary

From the literature it is known that the 'pure' vestibulo-ocular reflex, without contamination by other systems such as the visual system, can only be measured in the higher frequency range. Because of the costs and technical limitations of high-frequency rotation chairs, only few studies on the human VOR in this higher frequency range have been done until now. This was the reason for us to develop a convenient, inexpensive and safe method, enabling us to assess the human VOR in this higher frequency range. The final result was a helmet with a torque motor, oscillating a mass, producing a reactive torque of the head.

This thesis reports on a series of experiments done with this new technique. Using this, we could generate high-frequency, sinusoidal head oscillations in the 2-20 Hz frequency range, but also rapid, unpredictable step displacements of the head. In combination with a very accurate eye movement recording technique (magnetic sensor coils) we could measure the compensatory eye movements, known as the vestibulo-ocular reflex (VOR), for these passively elicited head movements.

Chapter 2 starts with more detailed information about the new stimulation technique (helmet with torque motor) in combination with the used accurate recording technique for the head and eye movements (magnetic sensor coils). The helm provided rotatory head-accelerations in the order of 1000 °/s^2.

The results from a group of normal, healthy subjects were consistent for the sinusoidal rotations up to the frequency range of 14 Hz. We found, as expected, hardly any differences in VOR gain values between the three different visual conditions that were tested: darkness, earth-fixed target or head-fixed target. The responses to horizontal step displacements of the head were symmetrical, with VOR gains near unity.

This chapter also shows some preliminary results of three bilaterally labyrinth-defective subjects. For the range from 2 to 14 Hz these three subjects showed responses that were much reduced in magnitude and increased in phase-lag, compared to those in the control group. Defects in the VOR were even more obvious in the lack of an early response to high-acceleration head steps.

We concluded that the new technique seemed to be a useful and flexible method for

investigating compensatory eye movements at relatively high frequencies. The method appeared to have a potentially wide use, ranging from clinical evaluation to basic research of the VOR.

Continuing the work described in chapter 2, chapter 3 reports on a larger control group, and several different patient groups. The most important groups of patients investigated were patients with total unilateral vestibular loss after surgical extirpation of an acoustic neuroma and a much more heterogeneous group of patients with strong bilateral vestibular hyporeflexia.

The helmet-imposed steps caused a virtually constant head acceleration in the first 90 ms. This resulted in a linear relation between eye and head velocities; we showed that the gain and delay of the VOR can be estimated independently from the slope and offset of this relation. Such estimates appear more reliable than those obtained with conventional techniques.

The various tests of the VOR in normals led to essentially concordant results. Analysis of oscillation showed the most reproducible results in the 2-8 Hz frequency range. Estimates of VOR gain in this range yielded a (high) mean VOR gain of 0.86 and a mean delay (derived from phase) of 4 ms. Step displacements, analyzed with the eye velocity / head velocity relations, yielded a comparable gain and delay. In the control group all responses were symmetrical in the two horizontal directions.

In the patients, the most specific results were obtained with constant acceleration head steps, proper analysis of which allowed independent estimates of gain and delay in both directions. Both of these parameters were systematically affected by vestibular pathology and the magnitude of changes from the normal values correlated well with the subjective level of vestibular dysfunction. A distinctive feature of the patient group with unilateral vestibular loss was a consistent asymmetry of the VOR. Responses to steps to the healthy side in patients with unilateral vestibular loss had a virtually normal gain, whereas gain was on the order of 0.5 for steps in the de-afferented direction. This asymmetry was also reflected, as a consistent trend of the eye position, in the responses to oscillation. Surprisingly, VOR-delay was systematically prolonged in all patients with manifest vestibular pathology. The results obtained with head oscillation in the 2-8 Hz range generally supported the results with steps, showing similar changes in gain and delay (expressed in phase lag).
We concluded that not only gain, but also delay is an important parameter of the VOR.

Both appear to be open to reliable, objective measurement and should be considered in future assessments of vestibular function.

In chapters 2 and 3, we measured three dynamic vestibular responses to high frequency, passive head movements: (1) VOR gain; (2) VOR phase lag and (3) directional trend of gaze during head oscillations, in normals and vestibular patients. These tests addressed semicircular canal functions. In chapter 4 we describe the changes in the subjective vertical for a number of these patients, as a probe of the static vestibular otolith functions.

Normal subjects could accurately align a vertical luminous bar to the gravitational vertical in an otherwise completely dark room. The mean settings in the patient group with a longstanding unilateral vestibular loss were systematically biased towards the side of the lesion. However, patients with bilateral vestibular loss did not significantly differ from the control group.

We conclude that the setting of the subjective vertical is a very sensitive tool in detecting a left-right unbalance in otolith-function, and that small but significant deviations towards the defective side persist during many years after unilateral lesions of the labyrinth or the vestibular nerve.

The purpose of gaze shifts (combined eye and head movements) or saccades is to move gaze to a new point of interest, not to stabilise it. A fully functional VOR seems therefore not very useful during saccades or combined eye head movements.

Chapter 5 deals with changes in the functionality of the VOR during gaze shifts or saccades. For this purpose we probed the gain and phase of the VOR during ongoing voluntary gaze saccades by superimposing high frequency head oscillations in the horizontal or vertical plane or horizontal acceleration-pulses ('with' or 'against'), applied through the torque-helmet.

Important findings were that presaccadic gain values of the horizontal VOR were only partially reduced (by 20 to 50%, compared to pre-saccadic values) during horizontal saccades of 40 and 100 degrees, respectively, but elevated above presaccadic levels in the wake of the saccades. Concomitant with the reductions in gain, VOR phase was advanced by about 20 degrees during saccades. Qualitatively similar changes were found when the vertical VOR was probed during 100 degrees horizontal saccades.

In contrast to the oscillations, torque-pulses during 40 degrees horizontal saccades biased the head position systematically in one direction. The responses to these head torque pulses showed subject-dependent asymmetries in their effects on saccadic dynamics. Analysis of the differences in eye and head movements for pulses 'with' and 'against' showed that VOR gain appeared to fall sharply at saccadic onset, following an approximately exponential course with a time constant of about 50 ms.

We concluded that VOR suppression is never complete, even for very large saccades. The 'supra-normal' VOR gain at the end of the saccade strongly favours stable fixation of the newly acquired target. The time course of the gain-decay and phase shift of the VOR suggest that suppression of the 'neural integrator' of the VOR circuit was more complete than suppression of the direct velocity pathway.

Samenvatting

Het is uit de literatuur bekend dat de 'zuivere' vestibulo-oculaire reflex, zonder invloed van andere neurale systemen, zoals het visuele systeem, alleen kan worden gemeten in het hogere frequentie gebied. Vanwege de hoge kosten en technische beperkingen van draaistoelen waarmee 'hoge' frequenties kunnen worden bereikt, zijn slechts enkele studies verricht naar de humane VOR in deze frequentie range. Dit was voor ons de reden om een praktische, niet kostbare en veilige methode te ontwikkelen waarmee de humane VOR in het hogere frequentie gebied kan worden bepaald. Dit resulteerde uiteindelijk in de ontwikkeling van een torque-helm. De torque-motor genereert oscillaties van een massa waardoor er draaimomenten op het hoofd ontstaan.

Dit proefschrift beschrijft een serie experimenten, die zijn verricht met behulp van deze nieuwe techniek. Met deze nieuwe methode werd het mogelijk hoogfrequente, sinusvormige hoofdoscillaties te genereren in het frequentiebereik van 2 tot 20 Hz. Tevens konden we snelle, 'onvoorspelbare' stapvormige hoofdbewegingen opwekken. In combinatie met een zeer nauwkeurig meetsysteem voor oogbewegingen (magnetische sensor spoeltjes) konden we de compensatoire oogbewegingen, ook bekend als de vestibulo-oculaire reflex (VOR), voor deze passief gegenereerde hoofdbewegingen meten.

Hoofdstuk 2 geeft een gedetailleerde beschrijving van de nieuwe stimulatie techniek (helm met torque-motor) in combinatie met het gebruikte nauwkeurige meetsysteem voor oog- en hoofdbewegingen (magnetische sensor spoeltjes). De helm met torque motor produceert rotatoire hoofdversnelling van ongeveer 1000 $^{o}/s^{2}$.

De resultaten voor een groep gezonde proefpersonen waren consistent voor sinusvormige hoofdrotaties met frequenties tot en met 14 Hz. Zoals verwacht, werden vrijwel geen verschillen aangetoond in VOR gain waarden tussen de drie verschillende test condities: 1) duisternis, 2) vast fixatiepunt in de ruimte of 3) een fixatiepunt gekoppeld aan het hoofd. De respons op horizontale stapvormige hoofdbewegingen was symmetrisch met vrijwel perfecte VOR gains.

Dit hoofdstuk toont tevens de resultaten van de eerste drie gemeten patiënten met bilaterale vestibulaire uitval. De waarden van de VOR-gain van deze drie patiënten waren in vergelijking met de controlegroep in het 2-14 Hz frequentie gebied duidelijk verlaagd met een grotere faseachterstand. Vermindering van de VOR was vooral

duidelijk door het ontbreken van een vroege respons op stapvormige hoofdbewegingen met hoge versnellingen.

We constateerden dat deze nieuwe techniek een bruikbare en flexibele methode is voor het onderzoeken van compensatoire oogbewegingen bij relatief hoge frequenties. De methode bleek ook brede toepassingsmogelijkheden te hebben, variërend van klinisch tot basaal wetenschappelijk onderzoek.

Voortbordurend op het werk in hoofdstuk 2, rapporteert hoofdstuk 3 over een grotere controle groep en verschillende groepen van onderzochte patiënten. De meest belangrijke groep bestond uit patiënten met unilaterale vestibulaire uitval na chirurgisch extirpatie van een acousticus neurinoom. Een andere belangrijke, maar meer heterogene groep, waren patiënten met sterke bilaterale vestibulaire uitval.

De door de torque-helm gegenereerde stapvormige hoofdbewegingen vertoonden in de eerste 90 ms een constante acceleratie. Dit resulteerde in een lineaire relatie tussen oog- en hoofdsnelheden. Uit de grafiek van genoemde relatie konden we met behulp van de helling en het snijpunt met de x-as de gain en latentie van de VOR schatten. Deze schatting bleek betrouwbaarder te zijn dan de conventionele berekeningen.

De verschillende metingen van de VOR in normale proefpersonen leverden overeenstemmende resultaten. Analyse van de oscillaties toonde de meest reproduceerbare resultaten in het frequentie gebied van 2 tot 8 Hz. Schattingen van de VOR gain in dit gebied toonde een (hoge) gemiddelde VOR gain van 0.86 en een gemiddelde latentie (afgeleid van de fase) van 4 ms. Stapvormige bewegingen, geanalyseerd met de lineaire relatie tussen oog- en hoofdsnelheden, leverden vergelijkbare waarden voor gain en latentie. In de controlegroep was de VOR respons symmetrisch voor beide richtingen van de horizontale hoofdbewegingen.

De beste resultaten in de patiëntengroepen werden verkregen met stapvormige hoofdbewegingen met constante versnellingen. Een goede analyse van de respons op deze hoofdbewegingen maakte onafhankelijke schattingen van de VOR gain en latentie voor beide bewegingsrichtingen mogelijk. Beide parameters werden systematisch beïnvloed door vestibulaire pathologie. De ernst van verandering in de gain en latentie van de VOR ten opzichte van de normale waarden stemden overeen met de subjectieve vestibulaire symptomen. Een consistente asymmetrie in de VOR was typerend voor de patiëntengroep met unilaterale vestibulaire uitval. Tijdens stapvormige hoofdbewe-

gingen naar het gezonde labyrinth hadden deze patiënten een normale VOR gain, terwijl de VOR gain 50% lager was tijdens hoofdbewegingen naar het aangedane labyrinth. Deze asymmetrie kwam ook tot uiting als een consequente trend in het oogpositie signaal tijdens hoofdoscillaties. Verrassend genoeg was de VOR-latentie systematisch verhoogd voor alle patiënten met manifeste vestibulaire pathologie. De resultaten met hoofdoscillaties in het frequentiegebied van 2 tot 8 Hz kwamen grotendeels overeen met de resultaten verkregen met stapvormige hoofdbewegingen.

Wij concludeerden dat niet alleen de gain, maar ook de latentie een belangrijke parameter van de VOR is. Beide bleken betrouwbaar te zijn voor objectieve bepaling in toekomstige metingen naar de vestibulaire functie.

In hoofdstuk 2 en 3 werden verschillende dynamische vestibulaire responsies gemeten op hoogfrequente, passieve hoofdbewegingen. Voor zowel gezonde proefpersonen als patiënten werd (1) de VOR gain, (2) VOR faseachterstand en (3) de richting van de trend van de blikrichting tijdens hoofdoscillaties gemeten. Deze metingen zeggen iets over de functie van de vestibulaire, halfcirkelvormige kanalen. In hoofdstuk 4 beschrijven we de veranderingen in de subjectieve verticaal voor een aantal van deze patiënten als een aanduiding van de meer statische vestibulaire functie van de otolieten. In een overigens donkere kamer werd een lichte lijn gepresenteerd, waarvan proefpersonen de helling in het frontale vlak konden instellen. Gevraagd werd om deze helling in overeenstemming te brengen met de verticaal (richting van de zwaartekracht).

Bij gezonde proefpersonen bleek deze subjectieve instelling nauwkeurig overeen te komen met de objectieve verticaal. De gemiddelde instellingen van de subjectieve verticaal waren in de groep patiënten met langdurige unilaterale vestibulaire uitval scheef naar de kant van de vestibulaire uitval. Patiënten met bilaterale vestibulaire uitval verschilden echter niet significant van de controlegroep.

We kwamen tot de conclusie dat de instelling van de subjectieve verticaal een zeer gevoelige methode was om een links-rechts asymmetrie van de otholiet functie te detecteren. Tevens bleek dat kleine, maar significante afwijkingen naar de kant van de laesie vele jaren aanwezig blijven na het ontstaan van unilaterale uitval van het labyrint of de nervus vestibularis.

Het doel van saccades of gecombineerde oog- en hoofdbewegingen is niet het

stabiliseren van de blikrichting, maar het verplaatsen van de blikrichting naar een nieuw fixatiepunt. Om deze reden zou een volledig functionele VOR tijdens dit soort bewegingen niet erg nuttig zijn.

Hoofdstuk 5 behandelt veranderingen in het functioneren van de VOR tijdens verplaatsingen van de blikrichting. Om deze te onderzoeken hebben we de VOR gain en fase getest tijdens vrijwillige verplaatsingen van de blikrichting. Dit werd met de torque-helm bereikt door het opleggen van hoogfrequente hoofdoscillaties, in het horizontale en verticale vlak, of door versnellingsimpulsen in dezelfde of tegenovergestelde richting van de actieve hoofdbeweging.

Een belangrijke bevinding was dat de horizontale VOR tijdens horizontale saccades van 40 en 100 graden slechts gedeeltelijk werd onderdrukt (respectievelijk 20% en 50%). Direct na de saccade was de VOR gain echter hoger dan de presaccadische waarde. Samenvallend met de afname in VOR gain tijdens de saccade vond er een vermindering in VOR faseachterstand plaats van circa 20 graden. Kwantitatief vergelijkbare veranderingen werden gevonden in de VOR bij de analyse van de verticale oscillaties tijdens horizontale saccades van 100 graden.

In tegenstelling tot oscillaties, verdraaien stapvormige hoofdbewegingen, veroorzaakt door de torque-motor gedurende horizontale saccades van 40 graden, de hoofdstand systematisch in één richting. De responsies op deze stapvormige hoofdverplaatsingen, in dezelfde richting of tegenovergestelde richting van de saccade, vertoonden asymmetrische effecten op de dynamiek van de saccaden die van persoon tot persoon konden variëren. Analyse van de verschillen in hoofd- en oogbewegingen voor hoofdimpulsen in de richting van de hoofdbeweging (of tegenovergestelde richting) lieten een scherpe daling van de VOR gain zien bij de start van de saccade. De daaropvolgende daling van de VOR verliep vrijwel exponentieel met een tijdconstante van 50 ms.

Uiteindelijk moesten we concluderen dat de VOR-suppressie nooit compleet is, zelfs niet tijdens grote saccades. De hogere VOR gain direct na het einde van de saccade komt stabiele fixatie van het nieuw verworven fixatiedoel ten goede. Het tijdsverloop van de VOR gain afname en de VOR fase verschuiving suggereert dat de suppressie van de 'neurale integrator' van het VOR-circuit meer compleet was dan de suppressie van de meest 'directe' vestibulo-oculumotorische baan, die op zich zelf vooral een snelheidssignaal geleidt.

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Poortugaal, oktober 1996

Curriculum Vitae

De schrijfster van dit proefschrift werd geboren op 9 augustus 1965 te Rotterdam. Het eindexamen VWO werd in 1983 behaald aan de Christelijke Scholengemeenschap Maarten Luther te Rotterdam. In 1984 werden twee VWO deelcertificaten voor natuur- en wiskunde behaald, waarna zij in 1985 kon aanvangen met de studie Geneeskunde aan de Erasmus Universiteit Rotterdam. In april 1991 behaalde zij haar arts-examen.

Vanaf april 1991 tot en met oktober 1991 was zij werkzaam als AGNIO op de afdeling longziekten in het Medisch Centrum De Klokkenberg te Breda. Het onderzoek en het schrijven van dit proefschrift werd verricht vanaf november 1991 tot en met februari 1995 onder leiding van Prof. H. Collewijn bij de vakgroep Fysiologie van de Faculteit Geneeskunde en Gezondsheidswetenschappen van de Erasmus Universtiteit Rotterdam.

In maart 1995 werd zij aangesteld als AGNIO in het Oogziekenhuis Rotterdam, waar zij in december 1995 in opleiding kwam tot oogarts (opleider Drs. S Baarsma).