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RESEARCH ARTICLE

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Off-center yaw rotation: effect of naso-occipital linear acceleration on the nystagmus response of normal human subjects and patients after unilateral vestibular loss

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Abstract Dual search coils were used to record horizontal, vertical and torsional eye movement components of one eye during nystagmus caused by off-center yaw rotation (yaw centrifugation). Both normal healthy human subjects (n=7) and patients with only one functioning labyrinth (n=12) were studied in order to clarify how the concomitant linear acceleration affected the nystagmus response. Each subject was seated with head erect on the arm of a fixed-chair human centrifuge, 1 m away from the center of the rotation, and positioned to be facing along a radius; either towards (facing-in) or away from (facing-out) the center of rotation. Both yaw right and yaw left angular accelerations of 10°s^{-2} from 0 to 200°/s were studied. During rotation a centripetal linear acceleration (increasing from 0 to 1.24×g units) was directed along the subject's naso-occipital axis resulting in a shift of the resultant angle of the gravitoinertial acceleration (GIA) of 51° in the subject's pitch plane and an increase in the total GIA magnitude from 1.0 to 1.59×g. In normal subjects during the angular acceleration off-center there were, in addition to the horizontal eye velocity components, torsional and vertical eye velocities present. The magnitude of these additional components, although small, was larger than observed during similar experiments with on-center angular acceleration (Haslwanter et al. 1996), and the change in these components is attributed to the additional effect of the linear acceleration stimulation. In the pitch plane the average size of the shift of the axis of eye velocity (AEV) during the acceleration was about 8° for a 51° shift of the GIA (around 16% of the GIA shift) so that the AEV-GIA alignment was inadequate. There was a very marked difference in the size of the AEV shift depending on whether the person was facing-in [AEV shift forward (i.e. non-compensatory) of about 4°] or facing-out [AEV shift forward (i.e. compensatory) of around 12°]. The linear acceleration decreased the time constant of decay of the horizontal component of the post-rotatory nystagmus: from an average of 24.8°/s facing-in to an average of 11.3°/s facing-out. The linear acceleration dumps torsional eye velocity in an manner analogous to, but independent of, the dumping of horizontal eye velocity. Patients with UVD had dramatically reduced torsional eye velocities for both facing-in and facing-out headings, and there was little if any shift of the AEV in UVD patients. The relatively small effects of linear acceleration on human canal-induced nystagmus found here confirms other recent studies in humans (Fetter et al. 1996) in contrast to evidence from monkeys and emphasizes the large and important differences between humans and monkeys in otolith-canal interaction. Our results confirm the vestibular control of the axis of eye velocity of humans is essentially head-referenced whereas in monkeys that control is essentially space-referenced.

Key words Linear acceleration · Otoliths · Utricular macula · Nystagmus · Labyrinth vestibular · Vestibulo-ocular · Vestibulo-ocular response · Vestibular commissures · Vestibular compensation · Labyrinthectomy

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Introduction

Normal head movements are complex three-dimensional rotations and translations which stimulate both the canals and the otoliths. The eye movement responses elicited by the stimuli are correspondingly complex with horizontal, vertical and torsional components. Understanding the in-

teraction of angular and linear accelerations in determining the operation of the vestibulo-ocular response (VOR) requires a way of presenting the stimuli reproducibly and a way of measuring the response accurately. Rotation on a fixed-chair human centrifuge generates a reproducible combination of linear and angular acceleration stimuli (Lansberg et al. 1965) and dual scleral search coils are a means of measuring the three-dimensional components of the eye movement response accurately.

In an earlier study we used three-dimensional search coils to measure the relative magnitudes of horizontal, vertical and torsional eye velocities of subjects receiving long duration steps of yaw angular acceleration ($20°s^{-2}$ from 0° to 200°/s) in darkness with head erect and precisely centered over the axis of chair rotation (Haslwanter et al. 1996). During on-center yaw rotation some subjects showed small vertical and torsional eye velocities which appeared to be dependent partly on the projection of the vertical canals into the yaw plane of rotation and partly on the subject's Listing's plane. In that study we tested patients with only one functioning labyrinth (UVDs) with the same stimulus parameters and showed that the vertical and torsional eye velocities were larger than in healthy subjects. It was argued that the increase was due to the fact that in UVD patients the vertical and torsional eye velocities generated by the stimulation of the single remaining labyrinth were not opposed or cancelled by oppositely directed eye velocity components from the other ear.

That earlier study was the control condition for the present off-center study which sought to identify how concurrent naso-occipital linear acceleration modifies the nystagmus due to yaw angular acceleration. We studied this by testing subjects and patients with stimulus parameters similar to those used in our on-center study, but in the present study the subjects were located 1 m from the axis of rotation so that during the rotation there was a centripetal linear acceleration directed along a naso-occipital axis either towards the nose in some trials or towards the occiput in others. In the present study the angular acceleration was reduced to $10°s^{-2}$ from 0° to 200°/s because most subjects found the higher accelerations unacceptable during off-center rotation.

During on-center yaw angular acceleration of a subject with head erect, the horizontal semicircular canals are predominantly stimulated and each otolith receives a centripetal linear acceleration and a small tangential linear acceleration. It is usually assumed that during on-center rotation of healthy subjects, these small otolith signals are equal and symmetrical so that their effects cancel out. However, when a subject is moved off-center by 1 m on a fixed-chair centrifuge and given the same angular acceleration up to the same constant velocity, the angular acceleration remains the same, but a concomitant linear acceleration now stimulates both labyrinths during and after the angular acceleration. The predominant component of this linear acceleration is a centripetal linear acceleration, whose direction *re* head depends on the orientation of the subject's head with respect to the axis of yaw rotation and whose magnitude depends on the final centrifuge constant velocity (see Fig. 1).

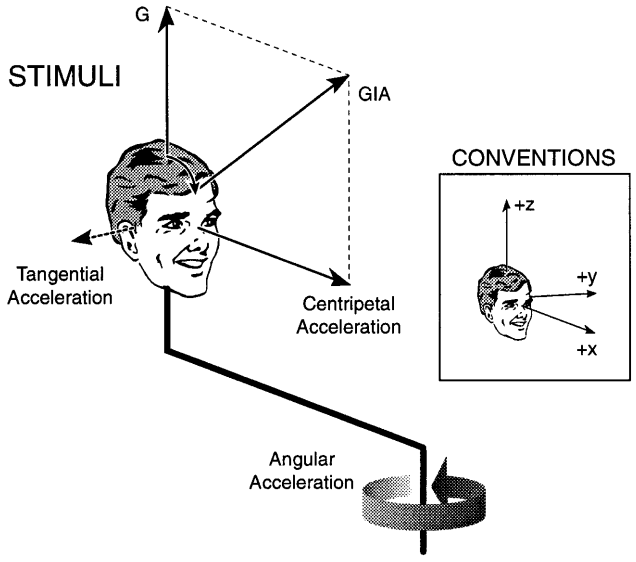

Fig. 1 A schematic illustration to show the orientation of the subjects during off-center rotation 1 m from axis and to show the resultant (GIA) of gravity (*G*) and the centripetal linear acceleration which act in this situation. The angular acceleration is yaw left which activates predominantly the left semicircular canal. During the angular acceleration a very small tangential linear acceleration acts along the subject's interaural axis. *Inset* The standard Hixson et al. conventions that we used

During off-center rotation the small tangential linear acceleration (which is present only during the angular acceleration) is increased relative to the centered condition by the distance from the subject to the center of rotation (1.0 m in our case) and is in the same direction for both ears. In the present study we measured the three-dimensional eye movements of human subjects when the subjects were off-center in a facing-in or facing-out configuration so that the centripetal linear acceleration was directed along the subject's naso-occipital axis, and the small tangential linear acceleration was directed along the subject's interaural axis. There have been previous reports that such off-center rotation changes the magnitudes of the components of nystagmus in human subjects (Lansberg et al. 1965; Gresty and Bronstein 1986; Gresty et al. 1987; Crane et al. 1997). None of these studies used three-dimensional search coils. The original Lansberg et al. study used EOG to record eye movements, so torsional eye movement components could not be measured. In the present study three-dimensional search coils were used to provide measures of the horizontal, vertical and torsional components of the eye movement response.

Other evidence shows otolithic modulation of semicircular canal induced nystagmus in primates (Sargent and Paige 1991; Merfeld and Young 1992, 1995; Merfeld et al. 1991; Wearne et al. 1996). In particular the Merfeld and Wearne studies have found large vertical and torsional eye velocities in primates during off-center rotation facing-in or facing-out using stimulus parame-

ters which closely approximate the values used here. One principle which appears to emerge from that work is that for monkeys the axis of eye velocity (AEV) moves towards alignment with the direction of the resultant gravitoinertial acceleration (GIA). The location of the AEV is defined by the relative magnitudes of the horizontal, vertical and torsional eye velocity components of the nystagmus. Merfeld found that the AEV of the squirrel monkey moved towards alignment with the GIA both for tangential headings of the monkeys (facing-motion and back-to-motion) and for radial headings (facing-in and facing-out). He showed that for monkeys this AEV shift was symmetrical for facing-in and facing-out trials. The results of experiments on humans (Wearne 1993) suggest that the shift of the AEV in humans in comparable stimulus conditions is much less.

Various theoretical approaches have been taken in these studies (Merfeld et al. 1993a,b; Merfeld 1995; Angelaki and Hess 1994, 1996; Raphan et al. 1996; Raphan and Sturm 1991; Wearne et al. 1996). We consider that such theorizing is premature for the human data since the human results appear to differ so substantially from the monkey results (Fetter et al. 1996). Here we report the results using a sufficiently large sample of normals and UVDs so that the results are unambiguous and can form the basis for theorizing about human otolith-canal interaction during centrifugation.

By analysing the separate *H*, *V* and *T* eye velocities ($\dot{H}$, $\dot{V}$, $\dot{T}$) we sought to identify how the AEV shift comes about – whether the concurrent linear acceleration stimulation alters the maximum magnitude or the time constant of decay of the separate eye velocity components (or both). In addition, we sought to measure the size and direction of the AEV shift in patients with only one functioning labyrinth in order to identify whether the shifts of the AEV could show the side of the UVD. The major questions addressed were:

- What is the direction and magnitude of the shift in human AEV for linear accelerations directed along a naso-occipital axis? Does the AEV move towards alignment with the GIA?
- Is the shift in the human AEV symmetrical for facing-in and facing-out stimuli?
- How do the individual eye movement components result in the AEV shift and are these comparable to those found in monkeys?
- How does the loss of one labyrinth affect the location and shift of the AEV?

Methods

The methods have been described in detail (Haslwanter et al. 1996), and here we only present a brief description of major and novel features of the methods. Seven normal healthy subjects aged between 21 and 54 years were tested. No subject reported any history of vestibular or auditory dysfunction. In addition, there were 12 patients tested who had undergone unilateral surgical vestibular deafferentation (UVD) for therapeutic treatment of acoustic neuroma or Ménière's disease at least 1 year prior to testing: 6 LUVDs and 6 RUVDs. All patients had recovered well after the operation in that they had returned to their usual lifestyle and did not complain of vestibular symptoms. All procedures were in accordance with the Declaration of Helsinki and were approved by the Human Ethics Committees of the Royal Prince Alfred Hospital and the University of Sydney. Subjects and patients were fully informed as to the procedures and given a "practice run" on the centrifuge before testing began and signed a consent form before the start of the experiment and were free to withdraw at any time during the experiment. None did.

The centrifuge

Testing was conducted using a Servo-Med fixed-chair human centrifuge. Subjects were seated upright with the center of their head 1.0 m from the axis of rotation and positioned so that they were facing along a radius either towards (facing in) or away from (facing out) the center of rotation (Fig. 1). During constant velocity rotation in this orientation the centripetal linear acceleration was directed along the subject's naso-occipital (x) axis. For each subject the head was held in a standard position pitched nose up so that Reid's line (between the upper margin of the external auditory meatus and the inferior bony margin of the orbit) was 7° nose up *re* earth horizontal. In this head position the average plane of the horizontal semicircular canals was around 30° pitched nose up (Blanks et al. 1975) above earth horizontal (and thus 30° above the earth horizontal plane of rotation of the centrifuge). In this position there is a significant projection of the posterior canals onto the plane of rotation (see "Discussion"). The "average plane" of the utricular macula in this head orientation is close to the plane of the horizontal canals and so would be pitched around 30° nose up. Subjects were firmly but comfortably held in place by means of head, trunk and hip supports, as well as by four seat belts.

In total darkness subjects were given stimuli each of which consisted of baseline recording at 0°/s for 10 s; a step of angular acceleration of $10°s^{-2}$ from 0°/s to 200°/s; constant velocity at 200°/s for 60 s; a step of angular deceleration at $10°s^{-2}$ from 200°/s to 0°/s; constant velocity at 0°/s for 60 s. A trial was defined with respect to angular acceleration as: pre-acceleration (baseline recording for 10 s), acceleration (20 s), post-acceleration (recording for 60 s). When rotated off-center, the centripetal linear acceleration was directed along the subject's naso-occipital (x) axis and increased from 0 to $1.24\times g$ tilting the resultant GIA through an angle of 51°.2 in the pitch plane around the subject's y-axis. Depending on the subject's heading (either facing-in or facing-out) the centripetal linear acceleration was directed either towards the nose or towards the occiput. The tangential acceleration was $0.018\times g$.

Three-dimensional eye position was recorded using a chair-mounted coil system based on a non-resonant circuit (Remmel 1984). For each subject the position of the magnetic field transmitter coils (a cube 51 cm on a side) was adjusted such that the measured eye was exactly in the center of the coil-frame. Dual scleral search coils (Collewijn et al. 1985; Skalar, Delft, The Netherlands) were used to measure horizontal, vertical and torsional eye position of one eye. The output voltages of the on-chair amplifiers were conducted over slip rings to low-pass anti-aliasing filters with a 100 Hz cut-off in the acquisition computer in the control room (Wearne 1993; Haslwanter et al. 1996). Data were sampled at 500 Hz with 12-bit A/D resolution by a PDP-11/73 mini-computer, and later transformed to rotation vectors, digitally differentiated and desaccaded. Desaccaded time series of the slow phase eye velocities of all subjects were combined to generate a mean time series together with a standard error of the mean for horizontal, vertical and torsional components of the eye velocity responses separately. Examples of the desaccaded raw eye velocity data for normal subjects are shown in Fig. 2. Some UVD subjects showed a small (2–4°/s) spontaneous nystagmus in complete darkness, and this was calculated from their pre-acceleration eye velocity records and subtracted from their time series of eye velocity.

Attached to the rotating chair was an eye position calibration bar consisting of orthogonal rows of horizontal and vertical light

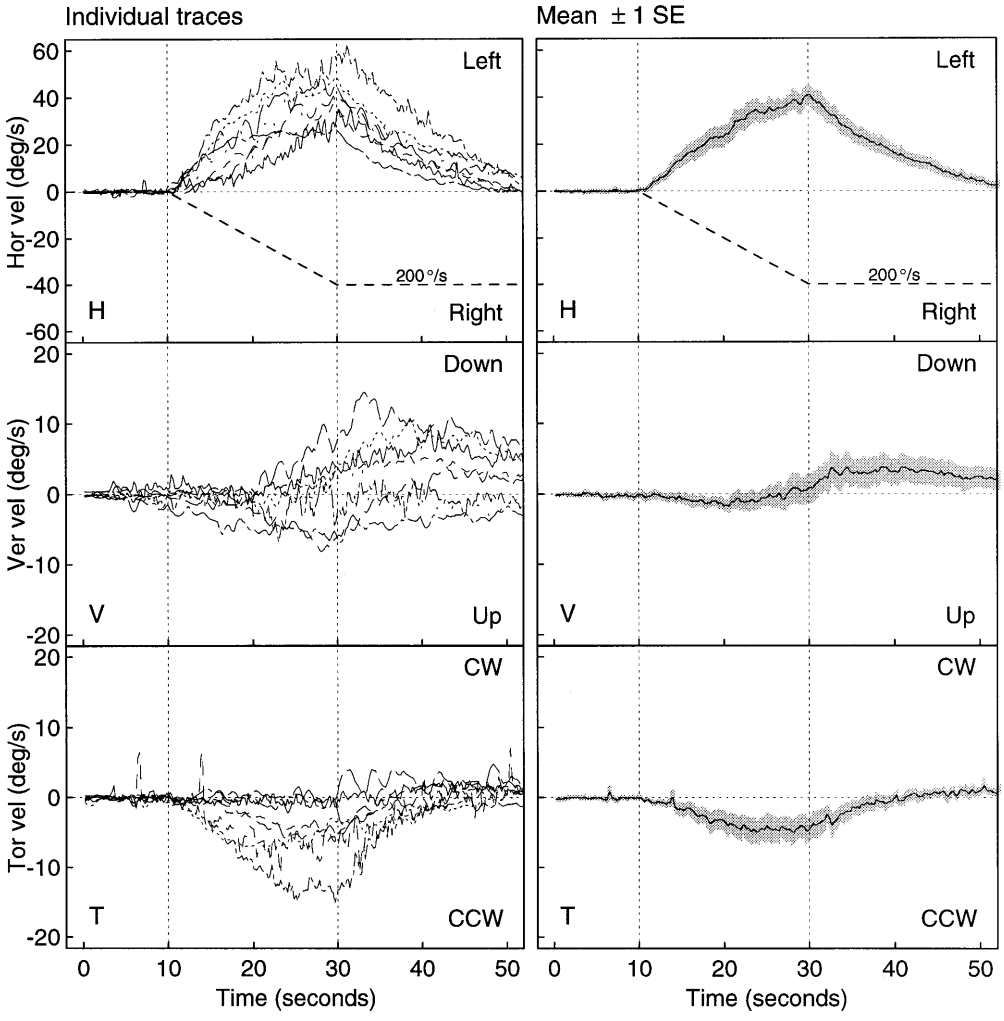

Fig. 2 Slow-phase eye velocities: normals facing in, CW acceleration, showing the variability amongst normal subjects and how the standard error bands relate to the raw data traces. *Left* Eye velocity traces for the seven normal subjects for yaw right chair accelerations while facing-in. *Dashed line* (at 200°/s) Chair angular velocity, which is plotted on a different scale from the eye velocities. *Right* Mean eye velocity for the traces plotted on the left *(solid line*); *broad grey trace* range of ±1 SE

emitting diodes (LEDs). When centrally placed at 60 cm from the subject's eye, the bar subtended an angular range of ±20° horizontally and vertically, with LEDs at 10° angular separations. Prior to testing, each detector coil was calibrated in vitro using a plexiglas calibration jig which held the detector coil and allowed it to be rotated through known angles in yaw, pitch and roll so that the voltages corresponding to known angles could be recorded. The height of the calibration jig was adjusted using a carpenter's level to ensure that the central gimbal axis of the calibration jig and the central calibration light were at the same level. When seated for the test, the subject was aligned by fixating the central calibration LED through an "alignment sight" with the coiled eye. This ensured that the spatial location of the coiled eye coincided exactly with the position of the gimbal at which the detector coil had been calibrated. Fixation distance was set at 60 cm (eye to LED), and the head was positioned and maintained at this distance by the head restraint for the duration of the test. Reid's line (the line between the upper margin of the external auditory meatus and the lower edge of the bony orbit) was set at 7° open anterior (nose pitched up) by using a plumb-bob and protractor and this head position was maintained by the use of a neck brace during testing. After the subject had been positioned the four offset voltages were not re-zeroed again. In the evaluation of the coil-signals, we made the assumption that gains and offsets were the same during the in vivo tests (i.e. with the coil on the eye) and the in vitro calibration. We conducted tests which showed that this was a reasonable assumption (see Haslwanter et al. 1996). Trials in which there was more than 3° of slippage in torsion position were discarded and the subject re-tested.

Data analysis

At the beginning of each acceleration trial and at the end of each deceleration trial, a fixation light mounted straight in front of the recorded eye was turned on, and the subject was asked to fixate on this light and then push a button which triggered a 1 s recording by the computer. This eye position was taken as the reference position for the ensuing trial, and the search coil voltages with the eye in this reference position were used to determine the orientation of the coil on the eye and whether the coil had slipped. Three-dimensional eye position was calculated using an algorithm developed by Merfeld and Young (1992), and expressed as rotation vectors (Haustein 1989; Haslwanter 1995). Figure 2 shows examples of superimposed desaccaded eye velocity plots and the means ±1 SE for these.

From the eye position data, three-dimensional angular eye velocity was determined (Hepp 1990). The eye velocity traces were desaccaded (Holden et al. 1992), and the desaccading checked by visual inspection of the data traces. VOR time constants were calculated using a modified Levenberg-Marquardt algorithm (Press et al. 1988; Wearne 1993) to fit double exponential curves with a DC-offset to the individual desaccaded velocity records (Bates and Watts 1988). All fits were inspected visually, and only good fits included in the data analysis. [Only the value of the first exponent (the dominant time constant) is reported below.] Data were pooled as follows. Recordings were grouped into data obtained from normals, data obtained from patients during angular acceleration towards the intact labyrinth (termed ipsilabyrinthine rotations), and patient data obtained during angular acceleration away from the

intact labyrinth (termed contralabyrinthine rotations). For each patient before the angular acceleration the amount of spontaneous nystagmus in darkness was determined for the horizontal, vertical, and torsional eye velocity components, and subtracted from the data before pooling. Within each data group the mean time series of eye velocity and the corresponding standard errors were calculated. For the purposes of this study we used the convention from Haslwanter et al. (1996) for the directions of eye movements. For horizontal data, eye movements are called *compensatory* if they were away from the direction of chair angular acceleration. For torsional data, *towards* and *away from rotation* refer to the movement of the upper pole of the eye and the direction of chair angular acceleration (rather than of chair angular velocity). For example, a roll of the upper pole of the eye towards the left is referred to as "away from rotation" for a yaw right chair acceleration. The statistical analysis and the generation of graphs were done using programs written in Splus (Becker et al. 1988), C and Matlab on a DEC 5000/240 workstation running under UNIX.

The tilt of the AEV in the pitch plane is determined by the arctan of the ratio of the torsional to the horizontal eye velocity components, and the tilt of the AEV in the roll plane by the arctan of the ratio of the vertical to the horizontal components. Since the measure of AEV location is erratic during very small eye velocities, we have calculated AEV only for eye velocities where the total eye speed was larger than 8°/s.

The coiled eye was illuminated by an infra-red light source, and continuously monitored by a small chair-mounted closed-circuit television camera. In this way we could detect artefacts during the test (such as the coil being dislodged) and ensure that the head position of the subject remained constant, and that the subject was awake and alert. For each trial the eye reference position was first determined, and eye position recording then started. The subject was asked to continue looking straight ahead at the location of the chair-fixed target throughout the trial, even after the light had gone out.

Results

We commence by reporting the time series of the shift of the AEV of normals and UVDs, followed by the *H*, *V* and $\dot{T}$ slow phase eye velocity results (i.e., time series of $\dot{H}$, $\dot{V}$, $\dot{T}$; peak velocities; time constants of decay) and finally the time series of *H*, *V* and *T* eye position.

For normal subjects, where there were no statistically significant differences between absolute magnitudes of the responses for yaw left and yaw right angular accelerations, the results for the two directions were combined for statistical tests and the numbers below are the averages of the parameters for the two directions of rotation. After checking the LUVD and RUVD patient data to ensure that some sidedness difference had not been obscured, we combined data for LUVDs and RUVDs. Data for left UVDs have been combined with those of right UVDs (with the opposite chair velocity) so that the directions of the angular accelerations were referred to the single remaining labyrinth.

The data from decelerations were not combined with the data from accelerations because the linear acceleration stimuli (and the results) are so different in the two cases: during acceleration the centripetal linear acceleration starts from zero and increases nonlinearly, whereas during deceleration the centripetal linear acceleration starts from its maximum value and decreases (see dashed lines Fig. 3).

Shifts of the AEV

Pitch plane

During the angular acceleration the GIA magnitude increases from 1.0 to 1.59×*g* and the resultant angle of the GIA deviates from being directly vertical *re* head to a maximum of 51°.2 pitched forward or back *re* head vertical, depending on whether the subject was facing-in or facing-out. During acceleration, the upper pole of the AEV of normal subjects initially shows a small, constant tilt backward for both facing-in and facing-out (Fig. 3) just as occurs during on-center rotation (Haslwanter et al. 1996). (Throughout the following the AEV tilts refer to the tilt of the upper pole of the AEV.) For facing-in this AEV tilt backwards is in the opposite direction to the increasing tilt of the GIA forwards and the AEV stays in this "non-compensatory" backwards tilted position during the acceleration as the GIA pitches forward by 51°.2 (Fig. 3A). After the end of the acceleration the AEV gradually moves forward *re* head as the eye velocity components decay at different rates, until the AEV eventually shows a very small pitch forward (Fig. 3). In contrast, facing-out there is also initially a sustained backward tilt of the AEV during the angular acceleration which is now in the direction of the GIA ("compensatory"), and this backward pitch tilt of the AEV increases even further after the end of the acceleration. In sum, during the acceleration the GIA is oppositely directed for facing-in and facing-out, but the AEV is located in the same direction (backwards *re* head) in both. Any movement of the AEV towards alignment with the GIA occurs after the end of the angular acceleration when the eye velocities are very small and subject to error (shown by the increasing size of the error bars at that time in Fig. 3). After UVD the shift of the AEV in the pitch plane is almost completely abolished for both facing-in and facing-out (Fig. 3C,D).

Roll plane

For normals during off-center rotation there are small but consistent vertical eye velocity components which start to appear once the centrifuge velocity increases above about 100°/s. The direction of these vertical components changes with changes in the GIA direction. These vertical components act to cause the AEV to shift in roll towards alignment with the roll-component of the GIA (Fig. 3A, roll plane) but that shift of the AEV occurs after the GIA roll-tilt has returned to zero. (The stimulus shift is so small (only 1°.04) that it is shown 10 times enlarged on Fig. 3). The AEV tilts in the roll plane are approximately symmetrical for facing-in and facing-out. However, they become statistically significant only after the end of the angular acceleration, increasing to values far larger (around 20°) than the GIA roll-tilt had been (1°.04). At constant velocity there is no roll-tilt component of the GIA since the tangential linear acceleration is

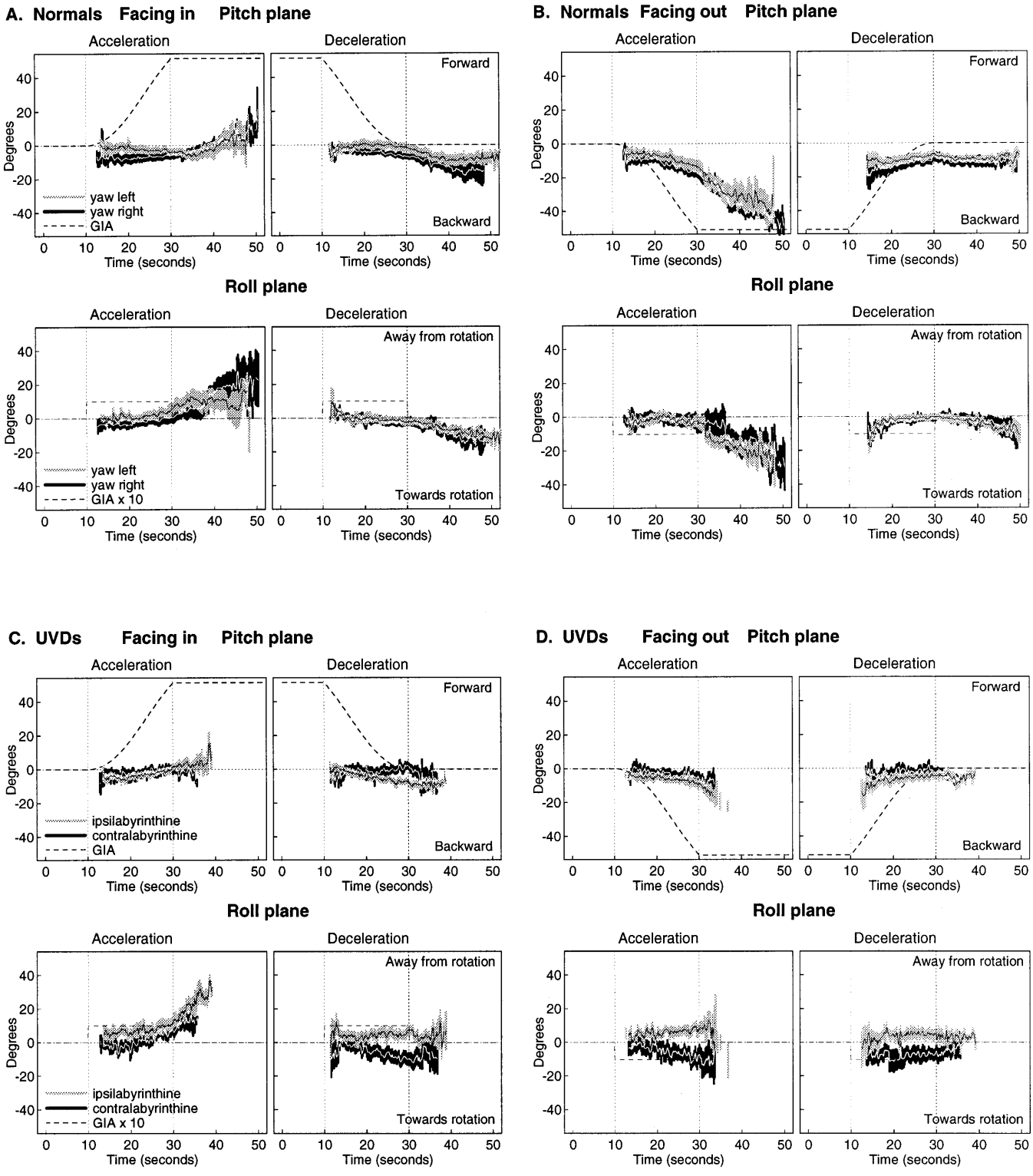

Fig. 3A–D Means and standard errors for the time series of angles of tilt from the vertical of the upper pole of the axis of eye velocity in the pitch and roll planes. The angle of tilt of the GIA vector in the same plane is shown by the *dashed line*. The roll plane axis shift and the pitch plane shift are shown separately as are acceleration and deceleration. *Vertical dotted lines* (at 10, 30 s), the start and the end of the $10°s^{-2}$ angular acceleration. Other figures follow these same conventions. A roll tilt "away from the rotation" indicates a tilt of the upper pole of the AEV to the right for yaw left chair accelerations, and to the left for yaw right chair accelerations. **A** Tilt of the axis of eye velocity in the pitch plane (*top*) and roll plane (*bottom*) for normal subjects facing-in. **B** Data for the same subjects facing-out. **C** UVD subjects facing-in. **D** Data for the same subjects facing-out. Data for chair accelerations are shown *to the left of each panel*, and for decelerations *to the right*. *Light and dark grey bands* (for normal subjects), data for yaw left and yaw right chair accelerations, respectively. *Yaw r.* Either a yaw right acceleration from rest, or deceleration to rest from a yaw left velocity. *Light and dark grey bands* (for UVDs), ipsilabyrinthine and contralabyrinthine chair accelerations, respectively. An ipsilabyrinthine-

Table 1 Means ± SD of the maximum slow phase eye velocity (degrees per second) for facing-in and facing-out, for both acceleration and deceleration. The maximum velocity is determined from the whole recorded eye velocity response, and not taken just at the end of the acceleration. Since the sign of the horizontal and the vertical eye velocities depends on the direction of the rotation, only the absolute value is given

	Acceleration		Deceleration	
	Facing-in	Facing-out	Facing-in	Facing-out
Horizontal				
Normals	41.2±12.4	37.7±14.0	43.1±17.1	38.7±12.0
Ipsilabyrinthine	23.5±9.5	21.7±8.7	19.5±7.7	17.1±6.5
Contralabyrinthine	18.3±7.2	13.6±4.9	27.2±12.0	26.6±16.2
Vertical				
Normals	8.6±2.5	7.5±2.8	5.2±2.0	4.8±1.3
Ipsilabyrinthine	7.5±3.6	5.9±2.8	5.3±2.1	4.8±1.6
Contralabyrinthine	5.9±1.7	4.5±2.3	6.7±2.8	5.9±2.2
Torsional				
Normals	6.1±3.8	12.2±7.4	5.2±3.0	8.3±4.6
Ipsilabyrinthine	3.4±1.2	4.7±3.0	3.7±2.4	3.2±0.8
Contralabyrinthine	3.7±1.7	3.3±1.8	5.0±2.2	4.4±3.1

Table 2 Mean and standard deviations of the dominant (first) time constant of decay of the double exponential fits to the decay of horizontal and torsional slow phase eye velocity at the end of the angular acceleration

	Acceleration		Deceleration	
	Facing-in	Facing-out	Facing-in	Facing-out
Horizontal				
Normals	23.2±10.7 (7)	11.3±2.4 (7)	17.7±4.8 (8)	19.3±5.1 (8)
Ipsilabyrinthine	8.9±3.5 (12)	6.6±4.9 (11)	8.3±3.8 (11)	8.0±2.8 (13)
Contralabyrinthine	9.3±3.2 (11)	9.0±4.5 (9)	8.6±3.5 (12)	8.4±3.0 (9)
Torsional				
Normals	10.5±3.7 (6)	27.7±8.1 (5)	20.4±8.3 (5)	23.3±5.6 (7)
Ipsilabyrinthine	9.2 (1)	10.2±3.3 (4)	10.2±5.4 (5)	15.6±5.4 (5)
Contralabyrinthine	11.8±4.8 (3)	21.5±0.3 (2)	17.5±16.7 (2)	26.0±7.4 (2)

only present during the angular acceleration. Yet at constant velocity there is a relatively large roll-tilt of the AEV which continues to increase after the removal of the tangential component. The shift of the AEV in the roll plane of UVDs is small and inconsistent (Fig. 3). During deceleration the AEV remains almost vertical in both pitch and roll planes for both normals and UVDs.

Eye velocity

Horizontal eye velocity

The peak horizontal eye velocities are similar for both directions of rotation: facing-in mean 41.2±12.4°/s (here and later this ± value is the sample standard deviation) and facing-out mean 37.7±14.0°/s (Fig. 4, Table 1). However, the concomitant linear acceleration during off-center rotation results in a significant change in the time constant of $\dot{H}$ decay once constant velocity has been reached. The average horizontal decay time constant facing-in is 24.8±12.7 s whereas for facing-out it is 11.3 ±2.4 s (see Table 2). Despite the large variability of the decay time constant for the facing-in data these values are significantly different from one another (t=2.76, P<0.05). For comparison, the time constant of decay of horizontal eye velocity for normal subjects centered was 14.0±2.9 s (Haslwanter et al. 1996). The naso-occipital linear acceleration prolongs the decay time constant for facing-out but shortens it for facing-in. (There are small discrepancies between the tabled averaged peak velocities and the figures because to obtain the best fitting double exponentials the peak value just after the end of the acceleration was occasionally used.)

For unilabyrinthine subjects the horizontal eye velocities and the time constants of decay are both significantly reduced in comparison to normals, with rotations towards the affected side giving the smaller response.

Vertical eye velocity

Off-center rotation causes small vertical eye velocity components, slow phase down during facing-in, and slow phase up during facing-out (see Fig. 4). These vertical components had an average peak velocity of 8.6 ±2.5°/s facing-in and 7.5±2.8°/s facing-out. Since these vertical

◀ rotation denotes either a chair acceleration from rest towards the intact labyrinth, or a deceleration to rest from a chair velocity away from the intact labyrinth. The angle of tilt of the GIA vector in the relevant plane (pitch or roll respectively) for the given chair acceleration is plotted on each graph. For the sake of visibility, the traces for GIA in the roll plane have been multiplied by 10; the full roll-tilt of the GIA is only 1°.04

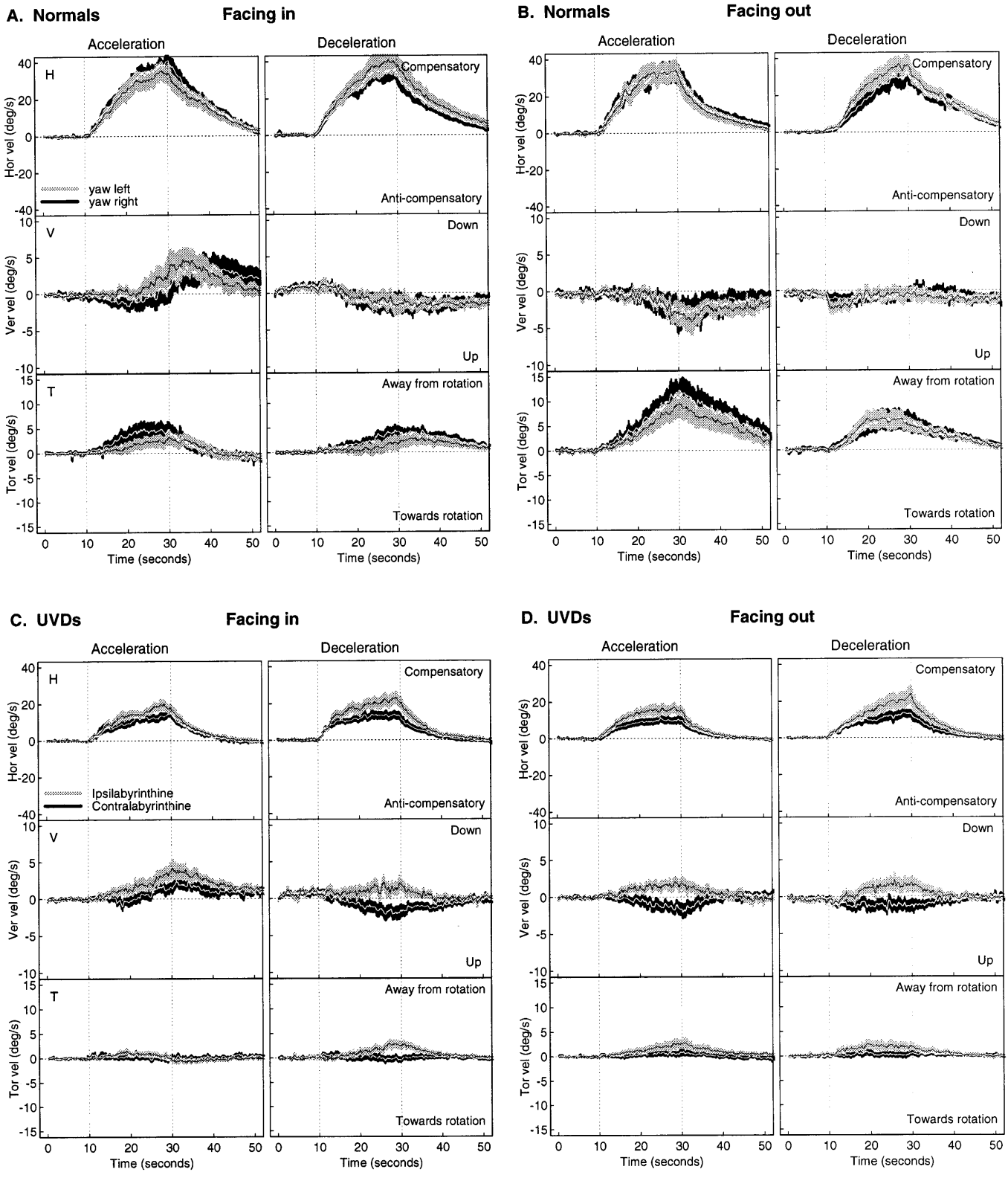

Fig. 4A–D Means (±1 SE) of the time series of slow phase eye velocity for normals and unilabyrinthine subjects for yaw-right and yaw-left rotation about the yaw axis. The rows show horizontal, vertical, and torsional components of eye velocity (top to bottom). Note that the scales for vertical and torsional eye velocity have been expanded. Here (and Fig. 5) a compensatory horizontal eye movement denotes a movement in the direction away from the chair acceleration. A torsional eye movement "away from the rotation" denotes that the upper pole of the eye moves in the direction away from the chair's angular acceleration: for example, a clockwise eye movement from the subject's point of view is "away from the rotation" for yaw left chair accelerations and for decelerations to rest from yaw right chair velocities. For yaw right rotation of normal subjects the torsional eye velocity is away from rotation whether the linear acceleration is directed forward or backward (bottom row). **A** Horizontal, vertical and torsional eye velocities

components are the same for both directions of angular acceleration but reverse when the direction of the centripetal linear acceleration is reversed, we attribute them to otolithic modulation of the canal response. Note that these vertical components only become detectable about midway through the angular acceleration (where the velocity exceeds about 100°/s). Also these vertical components continue once constant velocity has been reached unlike the horizontal and torsional components (see Fig. 4). There is a small but persisting vertical eye velocity present during the whole constant velocity segment. Interestingly this same small vertical component appears even in unilabyrinthine patients where ipsilabyrinthine rotations produce this same maintained eye velocity (Fig. 4C). The persisting vertical eye velocity was eliminated by the fixation light presented before the deceleration.

Torsional eye velocity

During yaw right and yaw left angular accelerations of normal subjects, the torsional eye velocity is positive (i.e. the upper pole of the subject's eye rolls towards that shoulder of the subject's away from which the chair is accelerating) for both facing-in and facing-out configurations. Although the linear acceleration does not change the direction of the slow phase torsional eye velocity it does affect both the peak velocity and the time constant of decay.

The torsional eye velocities increase during the acceleration to peak values which are significantly greater facing-out 12.2±7.4°/s than facing-in: 6.1±3.8°/s (see Fig. 4). For comparison the peak torsional eye velocities centered were 8.3±4.7°/s (Haslwanter et al. 1996).

In addition to this modulation of the peak torsional eye velocity, it seems that a forward directed linear acceleration acts to dump the torsional eye velocity integrator (see Fig. 4): compare the decay of normals facing-in accelerating (Fig. 4A) with normals facing-out (Fig. 4B). Facing-in there is a rapid decay (mean time constant=10.5±3.7 s), whereas facing-out has a significantly slower decay (mean time constant=27.7±8.1 s; t=4.76, P<0.01). For comparison the torsional time constant centered was 18.9±8.7 s (Haslwanter et al. 1996). During deceleration the decay time constants for both facing-in and facing-out are similar to those found centered.

For three reasons we consider the torsional eye velocity components to be canal components. (a) They start at the very onset of the angular acceleration whereas during off-center rotation the magnitudes of the centripetal linear acceleration stimulus increases slowly and reaches a "threshold" value by around 100°/s. (b) The torsional eye velocities do not reverse with opposite linear accelerations. (c) They are present in subjects centered.

◀ for normal subjects facing-in. **B** Data for the same subjects facing-out. **C** UVD subjects facing-in. **D** Data for the same subjects facing-out. As in Fig. 3, data for left UVDs have been combined with those of right UVDs with the opposite chair velocity

In UVD patients consistent torsional eye velocity responses were very small. During acceleration, the value of the time constant during ipsilabyrinthine rotations facing-out (10.2±3.3 s, n=4) was similar to the one during contralabyrinthine rotations facing-in (11.8±4.8 s, n=3). During ipsilabyrinthine decelerations, the time constants did not strongly depend on orientation (facing-in: 10.2 ±5.4 s, n=5; facing-out: 15.6±5.4 s, n=5). Little weight can, however, be attached to these since the numbers were so small and variable.

Eye position

Horizontal eye position

Figure 5 shows the mean value±1 SE of the time series of H V and T eye position of normals, LUVDs, and RUVDs during the acceleration trials. The sign conventions are the same as for the eye velocities. In this figure the ordinates show both rotation vectors and degrees. For each component of the rotation vector, the value shown in degrees is given by twice the arc-tangent of that component: this is equivalent to the angle of rotation we would obtain if the other two rotation-vector components were set to zero. During the angular acceleration phase, the horizontal eye position in normals shows the well known shift of the mean eye position, in the direction of the quick phase (the "Schlagfeld shift"; see Evanoff and Lackner 1986) which slowly declines and then reverses after the end of the acceleration. This shift in eye position is similar for both facing-in and facing-out.

During yaw right angular acceleration the mean eye position shifts about 8° to the right, and during yaw left angular acceleration, the mean position shifts about the same amount to the left. In UVD patients, the Schlagfeld shift is not clear during the acceleration. However, after the end of the acceleration the reversal of the shift in the mean eye position appears to show approximately the same characteristics as in normals.

Vertical eye position

There were no systematic changes in vertical eye position during centrifugation; however, the data are very variable.

Torsional eye position

The bottom row of Fig. 5A,B shows the effects of off-center rotation on ocular torsion position. In normal subjects yaw right angular acceleration facing-in induces a small systematic torsion of 2°.8 away from the rotation, and yaw left rotation induces a torsion of 2°.3 away from the rotation. In both cases this change in torsion position reaches a maximum at the end of the angular acceleration and then decays slowly during constant velocity,

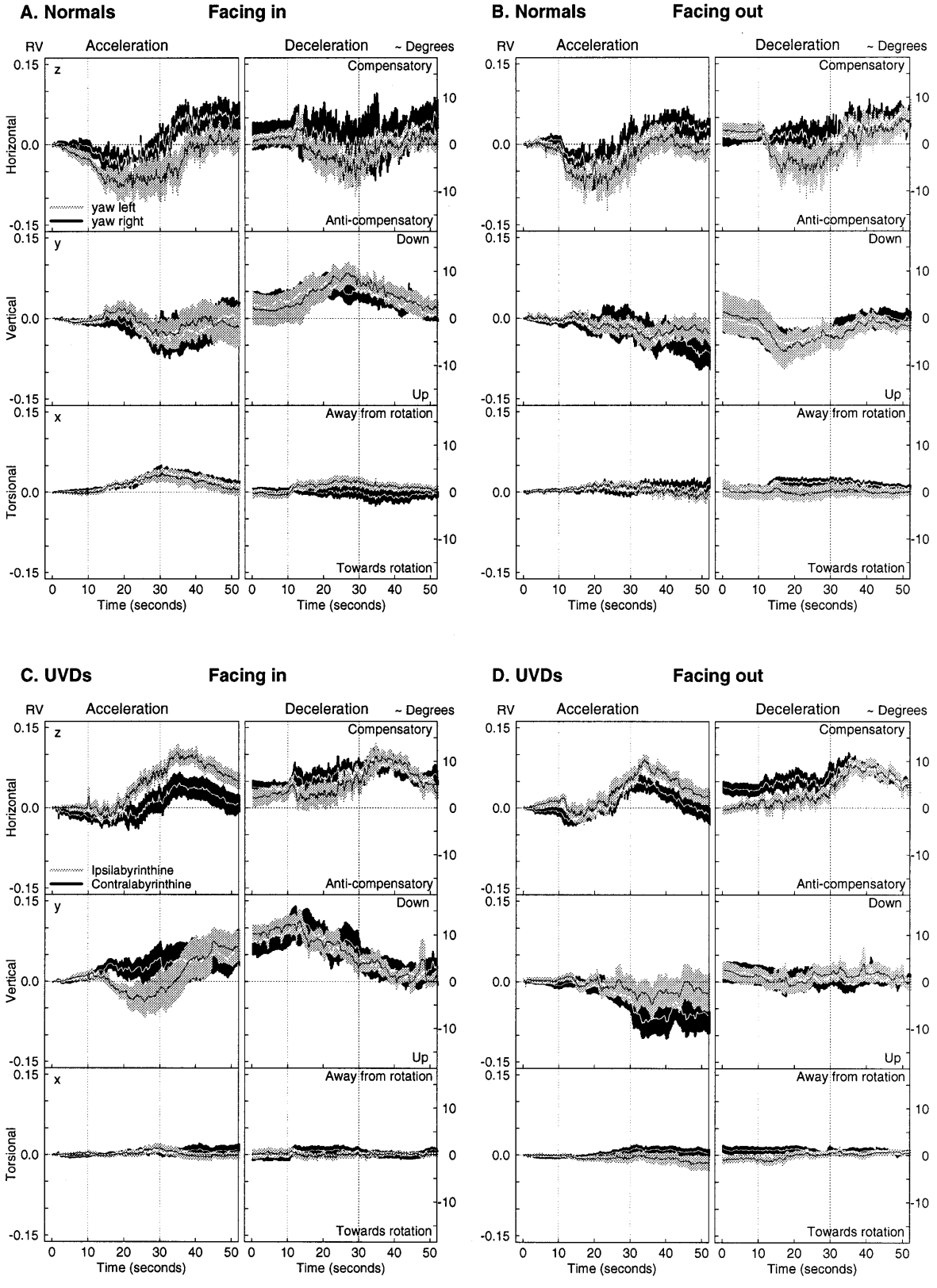

Fig. 5A–D Means (±1 SE) of the time series of eye position for normals and unilabyrinthine subjects for yaw right and yaw left rotation about the yaw axis. The rows show horizontal, vertical, and torsional components of rotation vectors (*top to bottom*). These eye position traces have not been desaccaded; they are the averages of all the eye position data including quick phases. Eye positions are given as rotation vectors, with the approximate values in degrees marked on the right of the plot. **A** Horizontal, vertical and torsional eye positions for normal subjects facing-in. **B** Data for the same subjects facing-out. **C** UVD subjects facing-in. **D** Data for the same subjects facing-out. As in Fig. 3, data for left UVDs have been combined with those of right UVDs with the opposite chair velocity

even though the centripetal linear acceleration is maintained. For facing-out the size of the torsional change is considerably smaller (Fig. 5B). It is not clear from this figure but there were more quick phases facing-out than facing-in.

Discussion

We have shown that the combination of angular and linear accelerations generated during off-center rotation on a human centrifuge produces complex three-dimensional oculomotor responses, confirming and extending the major previous study of off-center rotation on human subjects (Lansberg et al. 1965). In this situation there are a number of concurrent oculomotor changes produced by the linear acceleration: changes in ocular torsional position; changes in the time constant of horizontal and torsional eye velocity; generation of vertical eye velocity components. The two major outcomes of the study are: (a) that there is an asymmetry in otolith-dependent eye movement response facing-in as opposed to facing-out; (b) results which question whether the principle that the AEV moves towards alignment with the GIA is appropriate for human subjects.

Individual differences

Although we took care to ensure that the head position of all subjects was comparable, there were large individual differences between normal healthy subjects (as Fig. 2 shows). We attribute part of that variability to differences in labyrinth orientation in the head (Blanks et al. 1975; Curthoys et al. 1977; Curthoys et al. 1982). In the original data from the human bony canals the pitch angle of the posterior canal was an average of 68° (open anterior) *re* Reid's line, but there were large differences between individuals, and the standard deviation of this angle was around 8° (Curthoys et al. 1977) so that the range of pitch angles of the posterior canals was from 54° to 82° (from original raw data). The proportion of posterior canal stimulation for such a range varies from 0.59 to 0.14. Using our standard testing position the horizontal canals are pitched back by about 28° *re* an earth-horizontal plane and the pitch angle of the posterior canals becomes around 61°. Consequently the posterior canals have a large projection onto the horizontal (stimulus) plane and so will be substantially stimulated during the yaw angular acceleration we applied here. Our previous study showed a consistent torsional velocity (Haslwanter et al. 1996). With the head in this position there is very little projection of the anterior canal into the stimulus plane. Changing the pitch angle of the head changes the projection of these vertical canals. The increasing otolith signal interacts with this complex canal stimulation pattern which varies considerably between individuals.

Tilt-dumping

At the end of the acceleration the decay profile of the slow phase eye velocity is complementary for the $\dot{H}$ and $\dot{T}$ components; so that when $\dot{T}$ decays slowly (facing-out), $\dot{H}$ decays quickly and when $\dot{H}$ decays slowly (facing-in) $\dot{T}$ decays quickly. The direction of the linear acceleration modulates this decay: where the linear acceleration is directed backwards *re* head, the time constant of decay is much shorter than during centered rotation; when the linear acceleration is directed forward, the time constant is much longer. These complementary effects show that this "dumping" is not just some non-specific reduction in nystagmus but is a specific and independent modulation of the horizontal and torsional eye velocity components by the linear acceleration. These data show that tilt-dumping occurs for human torsional eye velocity just as it does for horizontal eye velocity, but the oppositely directed effects show that these processes are independent.

During off-center rotation the linear acceleration is not applied as a single step, as it is during most studies of the tilt-dumping of horizontal nystagmus (Guedry 1965a; 1965b; Schrader et al. 1985; Fetter et al. 1992, 1996). Instead the centripetal linear acceleration increases in a parabolic fashion during the angular acceleration (see Fig. 4, dashed lines). This difference may partly account for the difference between our results and other studies of tilt-dumping of horizontal nystagmus. Both subjectively and objectively, the effects of the increasing linear acceleration do not become apparent until a velocity of around 80–100°/s has been reached, (i.e. about halfway through the angular acceleration stimulus (see Figs. 3, 4) where the centripetal linear acceleration is about $0.3 \times g$, and the resultant GIA angle is around 17°).

Other experimental investigations of tilt-dumping of horizontal nystagmus have revealed that the processing of a combination of canal and otolith signals in humans is quite different from the case in monkeys. In monkeys after the rapid change in head position the AEV aligns with gravity (Angelaki and Hess 1996; Merfeld 1990, 1995; Merfeld and Young 1992) whereas in humans the AEV remains head vertical (Fetter et al. 1996). Our results with the slowly increasing linear acceleration confirm the previous conclusion from tilt-dumping – that the human AEV is predominantly head-referenced rather than gravity-referenced as occurs with monkeys.

Torsion position change

This small torsion position change during the angular acceleration confirms previous studies which have shown an angular-acceleration dependent change in ocular torsion position. This was originally found during on-center rotation using search coils (Wearne 1993) and subsequently confirmed using a slip-free video recording of eye position (Smith et al. 1995). Interestingly the direction of the linear acceleration seems to modify this tor-

sion since it is smaller facing-out where the nystagmus is much more vigorous, suggesting that quick phases may act to discharge the integrator which is responsible for this torsional position change. Other experiments in progress in our laboratory show that quick phases of horizontal nystagmus dump this torsion velocity to position integrator.

Vertical eye velocity

For unilabyrinthine subjects the vertical eye velocities are surprisingly similar to those in normals – "surprisingly" since it is usually presumed that the UVD abolishes or disables the mechanism presumed to mediate the shift of the AEV, the velocity storage integrator (Raphan et al. 1977, 1996). In both normals and UVDs the small vertical component continues during the constant velocity rotation. Here the GIA is stationary and yet the average eye velocity remains significantly non-zero (slow phase down). The vertical component remains during the constant velocity suggesting that it is produced by the centripetal linear acceleration acting directly on the otoliths, since the tangential linear acceleration returns to zero at the end of the angular acceleration. However, is it the increased magnitude or the increased GIA angle which causes the vertical eye velocity components? One answer comes from studies of off-center rotations with subjects facing along a tangent: where there is also a small maintained vertical eye velocity component which persists during the constant velocity (Wearne 1993), suggesting that it is increased magnitude of the GIA which is responsible for the constant vertical eye velocity.

Axis shift

Our previous study with on-center angular acceleration (Haslwanter et al. 1996) showed that the AEV is not exactly vertical during on-center rotation. In normal healthy subjects small torsional components are present so that the AEV is pitched back by about 5° *re* head vertical in the pitch plane. That result is confirmed again here (see Fig. 3) at the early phase of the angular acceleration. The imposed linear acceleration changes this AEV location. How does the linear acceleration cause the AEV shift? Angular acceleration of healthy subjects exactly centered yields large compensatory horizontal slow phase eye velocity together with small positive (away from rotation) torsional eye velocity (Haslwanter et al. 1996). It appears that the torsional eye velocity is due to canal stimulation since it reverses when the direction of yaw angular acceleration is reversed. This is the baseline against which any effects of concomitant linear acceleration must be measured.

The effect of the linear acceleration during the facing-in condition is not sufficient to cancel or reverse the torsional eye velocity component as should happen if the AEV were to shift towards aligning with the GIA. The shift of the AEV is so small that the AEV is still pointing in an inappropriate direction (backwards) when the GIA was pointing 51°.2 forwards at the end of the angular acceleration.

Two changes seem to be responsible for the AEV shift during naso-occipital linear acceleration: a decrease in the time constant for $\dot{H}$ facing-out as compared to facing-in, and the concomitant increase in the time constant of $\dot{T}$ decay. This means that for facing-out, after the end of the acceleration there is a small $\dot{H}$ and a large $\dot{T}$ resulting in a large shift of the AEV in the direction of the GIA. This AEV shift is substantially larger than the case for the symmetrical stimulus facing-in where the AEV remains almost upright without any shift during the acceleration and afterwards.

A simplifying principle which has emerged from similar studies of squirrel and rhesus monkeys is that the AEV moves towards alignment with the GIA. In experiments on squirrel monkeys where almost the same stimulus parameters were used, this AEV shift can be so fast that it appears to move towards and even to track the GIA (Merfeld 1990, 1995, 1996), so that the AEV of monkeys moves towards remaining space vertical. In contrast, the shift of the AEV of humans is slow and small. Inspection of the raw data traces and the small error bars in Fig. 3 shows that this result is consistent across subjects. In our opinion, this idea of the AEV moving to align with GIA is not an adequate description for human eye velocity results. Our results confirm previous human research (Fetter et al. 1996; Wearne 1993) which has shown that the AEV tends to remain head vertical instead of space vertical.

Recent evidence may resolve this large discrepancy between species. Wearne et al. (1997) showed that in monkeys the AEV shifts are mediated by the velocity storage mechanism: disabling that mechanism by sectioning the commissures abolishes the AEV shifts. Given that humans have very poor velocity storage (Lafortune et al. 1986) it would appear that the reason for the small AEV shifts found here may be the poor velocity storage in humans.

The AEV must be treated with caution since an axis location can be calculated from data in which the eye velocity components are small and subject to error. Calculation of the AEV from such data requires dividing by small values and such divisions can be potentially erroneous generating an apparent AEV shift which can appear to be very large. We have tried to minimize this error by calculating our AEV only where the total eye speed (the square root of the sum of the squares of $\dot{H}$, $\dot{V}$ and $\dot{T}$) was greater than 8°/s but even with this cut-off, relatively small eye velocities can produce AEV measures which appear equivalent to the much more robust AEV locations found with higher eye velocities. Because the eye velocities are relatively small after the end of the angular acceleration the AEV deviations after the end of the acceleration must be regarded with caution and are not interpreted further here.

Asymmetry of the axis shift

There was a very substantial difference in the shift of the AEV for symmetrically opposite stimuli; trials facing-in gave very different results from accelerations facing-out. Such an asymmetry is not apparent in the squirrel monkey data under similar conditions (Merfeld 1990, 1996). This asymmetry in the human response may be due to (a) the fact that there is a "front-back" asymmetry in the structure and sensitivity of the otoliths, or (b) differential sensitivity of the lateral regions of the otoliths to the two directions of (tangential) accelerations – (that sweeping the stimulus vector one way may give very different results from sweeping it the opposite direction), or (c) the different regions of the saccule are being stimulated.

Otolith-ocular responses

These results show both pure otolith-induced nystagmus (the vertical eye velocity which is maintained at constant velocity rotation long after the decay of any canal induced eye velocity component) and the effect of otolith stimulation on the canal-induced nystagmus. For example, Blanks et al. (1978) showed convergence of otolith input onto vertical eye muscle motoneurons in cat and such could be the means by which the torsional eye velocity is modulated by otolith stimulation. Similarly, Curthoys and Markham have shown otolith-horizontal canal convergence at the level of the vestibular nucleus (1971). In monkeys the nodulus seems to be one means by which otolith stimulation may control canal-induced signals in the vestibular nuclei (Wearne et al. 1996).

Recently a model has been proposed for accounting for off-center rotation results where the subject is facing along a tangent (instead of along a radius as here; Wearne et al. 1996; Raphan et al. 1996). In that work the results of rhesus monkeys and of humans facing-motion and back-to-motion are very different; humans show smaller horizontal peak eye velocity back-to-motion as opposed to facing-motion whereas monkeys have the reverse pattern. Their new model uses time constant modulation by the linear acceleration to account for the AEV shift but the model had to invoke a new "centering mechanism" in human subjects to account for the very different results between species.

UVDs

The results from UVDs showed, with one exception, very little effect of the linear acceleration. Most patient data showed the effects expected on the basis of past results – a reduced horizontal slow phase eye velocity for rotations towards the affected ear (contralabyrinthine) and very short time constants for both directions of rotation. It seems that the unilateral vestibular loss disables the velocity storage integrator which is presumed to be the mechanism by which the linear acceleration modulates the canal-induced nystagmus (Raphan et al. 1977, 1996; Wearne et al. 1996). The sole exception appears to be the torsional eye velocities facing-out. For UVDs only the rotations which excite the remaining horizontal canal show torsional eye velocities (grey bands in Fig. 4), suggesting that excitation of the horizontal canal is necessary for the generation of the torsional eye velocity component.

Patients are affected in two ways: not only do these patients lack the input from the labyrinth on one side but the UVD has also severely impaired their velocity storage mechanism which is held to be the means by which the linear acceleration causes the AEV shift. We suggest that studies of simpler stimuli, the three-dimensional eye movement components to stimuli consisting of pure linear accelerations, are needed in order to understand the complex results which derive from combined linear and angular accelerations.

Conclusion

The answers to the questions posed in the Introduction are:

- The AEV shifts by a relatively small amount to align with the GIA facing-out but not facing-in where the shift is opposite to the GIA tilt.
- There is a larger shift of the AEV for facing-out than for facing-in.
- The loss of one labyrinth effectively eliminates this AEV shift in the pitch plane.

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