Exp Brain Res (1998) 123:242–254

RESEARCH ARTICLE

Darrin P. D. Gilchrist · Ian S. Curthoys
Andrew D. Cartwright · Ann M. Burgess
Ann N. Topple · Michael Halmagyi

High acceleration impulsive rotations reveal severe long-term deficits of the horizontal vestibulo-ocular reflex in the guinea pig

Received: 11 March 1998 / Accepted: 2 June 1998

Abstract While there is agreement that unilateral vestibular deafferentation (UVD) invariably produces an immediate severe horizontal vestibulo-ocular reflex (HVOR) deficit, there is disagreement about whether or not this deficit recovers and, if so, whether it recovers fully or only partly. We suspected that this disagreement might mainly be due to experimental factors, such as the species studied, the means chosen to carry out the UVD, or the nature of the test stimulus used. Our aim was to sort out some of these factors. To do this, we studied the HVOR of alert guinea pigs in response to low and high acceleration sinusoidal and high acceleration impulses after UVD by either labyrinthectomy or by vestibular neurectomy. The HVOR in response to high acceleration impulsive yaw rotations was measured before, and at various times after, either unilateral labyrinthectomy or superior vestibular neurectomy. Following UVD, there was a severe impairment of the HVOR for ipsilesional rotations and a slight impairment for contralesional rotations, after either operation. This asymmetrical HVOR deficit in the guinea pig parallels the deficit observed in humans. Between the first measurement, which was made 1 week after UVD, and the last, which was made 3 months after UVD, there was no change in the HVOR. This lack of recovery was the same after labyrinthectomy as after vestibular neurectomy. The HVOR to low and high acceleration sinusoidal yaw rotations were measured after UVD, and the results were compared with those in response to impulsive rotations. For low acceleration sinusoidal rotations (250°/s^2), the gain was symmetrical, although reduced bilaterally. As the peak head acceleration increased, the HVOR became increasingly asymmetric. The HVOR asymmetry for sinusoidal rotations was significantly less than for impulsive rotations that had the same high peak head acceleration (2500°/s^2). Our results show that the HVOR deficit after UVD is the same in guinea pigs as in humans; that it is the same after vestibular neurectomy as after labyrinthectomy; that it is lasting and severe in response to high acceleration rotations; and, that it is more obvious in response to impulses than to sinusoids.

Key words Vestibular · Deafferentation · Vestibular compensation · Horizontal vestibulo-ocular reflex · Impulse · Guinea pig

D.P.D. Gilchrist (✉) · I.S. Curthoys · A.D. Cartwright
A.M. Burgess · A.N. Topple
Department of Psychology, University of Sydney, Sydney, NSW 2006, Australia
e-mail: darring@psych.usyd.edu.au,
Tel.: +61-2-9351-5953, Fax: +61-2-9351-2603

M. Halmagyi
Eye and Ear Research Unit, Neuro-otology Department, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Introduction

In response to a yaw head rotation, the horizontal vestibular ocular reflex (HVOR) generates equal and opposite eye rotations and thereby maintains a stable image on the retina. There is general agreement that immediately after unilateral vestibular deafferentation (UVD) there is a severe deficit of the HVOR in animals and humans (see Curthoys and Halmagyi 1995 for review). There is, however, no agreement about whether the HVOR recovers and, if so, whether it recovers partially or fully. The truth about the recovery of the HVOR after UVD is not only of scientific interest but also of some clinical importance.

Testing the HVOR after UVD using only low acceleration sinusoidal rotations shows that the HVOR largely recovers, in humans (Baloh et al. 1984; Takahashi et al. 1984; Allum et al. 1988; Paige 1989; Fetter and Dichgans 1990), and in monkeys (Takahashi et al. 1977; Wolfe and Kos 1977; Fetter and Zee 1988), whereas recovery may be less complete in rabbits (Baarsma and Collewijn 1975), cats (Maioli et al. 1983) and guinea pigs (Vibert et al. 1993). However, in response to high acceleration impulsive rotations, the HVOR deficit clearly remains even 1 year after UVD (Halmagyi et al. 1990; Tabak et al. 1997b). So far, this type of stimulus has only been used in human studies of HVOR recovery.

Our aim here was to discover the extent to which these differences in the data on the long-term recovery of the HVOR after UVD could be due to the type of stimulus used to test the HVOR, rather than to the species used or the type of UVD performed. To do this, we studied the guinea pig HVOR in response to high acceleration impulsive yaw rotations before and after unilateral labyrinthectomy or superior vestibular neurectomy, and in response to low and high acceleration sinusoidal yaw rotations after labyrinthectomy.

Search coils were used to measure the HVOR in guinea pigs that had undergone either a unilateral surgical vestibular labyrinthectomy, or a selective superior vestibular neurectomy, excision of the superior portion of Scarpa's ganglion in addition to labyrinthectomy. Neurons in Scarpa's ganglion survive labyrinthectomy (Richter 1981; Schuknecht 1982; Jensen 1983; Sirkin et al. 1984; Fermin et al. 1989; Kevetter and Perachio 1994; Li et al. 1995; Naito et al. 1995). It is possible that these surviving ganglion cells affect the activity of ipsilesional vestibular nucleus neurons and modify the HVOR. Therefore, HVOR recovery might be greater following labyrinthectomy than after neurectomy, a surgical approach that also deafferents the ganglion cells. For example, Cass and Goshgarian (1991) using low acceleration sinusoidal rotations in cats found a larger HVOR asymmetry after unilateral vestibular neurectomy than after unilateral labyrinthectomy.

The magnitude of the head rotation stimulus could influence the HVOR deficit measured after UVD. For example, after unilateral labyrinthectomy in guinea pigs, Vibert et al. (1993) found only a slight asymmetrical HVOR gain response to low acceleration sinusoidal rotations, whereas the HVOR was severely impaired and asymmetrical in response to high acceleration velocity steps (0–300 °/s^2 at 1000 °/s^2). In this study, we not only compare directly the HVOR of guinea pigs in response to low and high acceleration sinusoidal rotations, but also in response to high acceleration impulses that are identical to those previously used in the study of human HVOR after UVD (Halmagyi et al. 1990; Tabak et al. 1997a, b).

Materials and methods

Subjects

Twenty-two normal healthy pigmented guinea pigs weighing between 600 g and 1000 g were tested. Seven animals underwent surgery for unilateral superior vestibular neurectomy and 11 animals underwent surgery for labyrinthectomy. Four animals remained bilaterally intact. The Animal Care and Ethics Committee of the University of Sydney, NSW, Australia approved all procedures used.

Surgical procedures

Head holder

Each guinea pig was anaesthetised with intramuscular injections of Ketamil (ketamine hydrochloride, 100 mg/kg, Troy Laboratories) and Xylase Injection (xylazine, 4 mg/kg, Parnell Laboratories). Once anaesthetised, the dorsal surface of the skull was exposed and four small stainless steel screws (0–80 UNF × 1/8") were implanted to anchor a plastic rod of square cross-section 20-mm long and 3.3 mm on a side, embedded in dental acrylic. A plastic rod was used because it is lightweight, non-ferrous and can be mated to a larger-diameter plastic tube of square cross-section (6.4×6.4 mm OD) that was attached to the restraining box. The plastic rod was orientated parallel to the animal's interaural axis whilst the animal was positioned in a guinea-pig nose bar (40° pitched nose down). The square-rod system provided a secure means by which to fix the guinea pig in the test apparatus and prevent head movement in yaw, pitch or roll. The orientation of the rod also allowed a quick and effective way to position the guinea pig so that the horizontal semicircular canals were approximately earth horizontal (40° pitched nose down; Curthoys et al. 1977). Following implantation of the head holder, the wound was sutured and a subcutaneous injection of Marcaine (Astra Pharmaceuticals) was injected around wound margins for management of post-operative pain. The animal was allowed to recover for at least 1 week following the surgery.

Unilateral labyrinthectomy

A right unilateral labyrinthectomy was performed. Each guinea pig was anaesthetised with intramuscular injections of Ketamil and Xylase, as above. Following subcutaneous injection of xylocaine (Astra Pharmaceuticals) to all wound margins, a midline incision was made and the skin and tissue were retracted by blunt dissection to expose the right temporal bone. A small hole was drilled into the temporal bone to expose the junction of the horizontal and anterior semicircular canals. Using a fine dental burr, the horizontal and anterior semicircular canal ampullae were opened and the contents aspirated. The hole in the canals was then enlarged to allow removal of the otolith maculae by fine probing and aspiration. Upon completion of the labyrinthectomy, the hole was sealed with dental acrylic and the wound sutured. Animals recovered from the anaesthesia under a heat lamp, in a fully-lit room.

Unilateral superior vestibular neurectomy

The same procedure as for a labyrinthectomy was employed. In addition, the point at which the superior vestibular nerve left the vestibule was identified and a hole drilled at that point to visually expose the ganglion of the superior vestibular nerve. Using a fine probe with a sharpened end and a fine-tipped aspirator, the ganglion was excised. Particular care was taken not to damage the brainstem or cerebellum.

Measurement of the static symptoms of vestibular compensation

Following UVD (labyrinthectomy or neurectomy), visual measurement of spontaneous ocular nystagmus (SN), roll head tilt (RHT) and yaw head tilt (YHT) were carried out every 10 h for the first 50 h. For SN, the number of quick phase beats of nystagmus in a 15-s interval was counted by visual observation. Five measurements of SN were made for each animal at each measurement time and the mean calculated. Measurements were made in light and were obtained without any restraint or physical contact with the animal. Measurements were only made when the animal remained completely still for the entire 15-s duration. Using a protractor, measurements of YHT and RHT were made, as previously described (Curthoys et al. 1988). A 2-factor analysis of variance (ANOVA) with repeated measures on time was used to compare the results from the labyrinthectomy group to the neurectomy group. Note that because the severity of the static symptoms that follow UVD should diminish as a function of time, factor B (time) for the ANOVA is always significant and, therefore, not reported in the results section.

Measurement of the dynamic response before and after UVD

The recording system

Three-dimensional head and eye position were obtained using the search coil technique (Robinson 1963), with the guinea pig's eye positioned at the centre of a 40-cm^3 transmitter field that had a linear region of approximately ±30°. The Remmel system used a non-resonant transmitter so that the detector signal was not substantially affected by metal in or near the transmitter field (Remmel 1984). A combination coil consisting of two small detector coils approximately 2 mm in diameter each, with ten turns of 20-µm wire and a combined weight of less than 10 mg, was positioned on the locally anaesthetised cornea (Amethocaine Hydrochloride sterile ophthalmic drops, Smith & Nephew, Ltd) with a drop of cyanoacrylate adhesive (Pronto CA8, 3 M) (Hess & Dieringer 1991).

The detector coils were hand wound from broken human search coils, glued together with a small amount of epoxy (Araldite, Selleys) and positioned orthogonally to one another. The leads from the detector coil were tightly twisted to avoid artefacts generated by the movement of loops in the lead wire during the head impulse. The wire was fine and soft, even after twisting, so the lead to the eye was not stiff enough to drag on the eye itself. A second similar combination detector coil was fixed to the head holder rod to measure head displacement.

With three transmission magnetic fields and two detection coils each for head and eye, 12 anti-aliased output voltages were sampled with 12-bit or 16-bit resolution at 1000 Hz. The raw signals were acquired and displayed by an IBM-compatible PC running LabVIEW 3.01 (National Instruments) from within Windows 3.1.

Calibration of the recording system

An in vitro calibration of both the head and eye coils was performed at the beginning of each recording day. The head and eye coils were placed on a Fick gimbal at the centre of the transmission fields, and a calibration was performed by moving the gimbal between ±20° in 10° steps for yaw, pitch and roll. To approximate the exact position of the guinea pig during the testing session, the calibration was performed using a guinea-pig skull with artificial eyes. According to the right-hand rule, the calibration procedure produced a positive voltage for yaw movements to the left, pitch movements downwards and roll movements counter clockwise. Many control calibrations were conducted without an animal to ensure that artefacts did not contribute to the measured data. On a number of testing occasions, the Fick gimbal was moved to various known angles to assess the accuracy of the measurement system. In addition, actual high acceleration angular rotations were also performed using the guinea-pig skull to replicate the actual test. It should be noted that because we only measure the ocular response during the first 100 ms, the maximum displacement of the head and the point at which peak head velocity is achieved occur during the first 8° of the angular rotation. This is well within the linearity range of our recording system.

Experimental protocol

Measurement of dynamic eye movement response

After at least 1 week of recovery time following surgical implantation of the head holder, guinea pigs were trained to sit quietly whilst being firmly restrained by Velcro straps in a canvas bag that was placed in a specially designed Perspex guinea-pig holding box. The body of the guinea pig was further restrained by encasing the animal with foam rubber. Guinea pigs accept this mild restraint well and will sit in such a bag for periods up to 1 h without showing any sign of discomfort or distress. If the animal did show any signs of distress, the testing session was terminated. The box was positioned so that the midpoint between the two vestibular labyrinths of the animal was located over the centre of the axis of rotation, whilst the eye was at the centre of the field. The guinea pig's head was restrained by sliding a larger spring-loaded square plastic tube over each end of the smaller head holder rod. The spring-loaded mechanism allowed a quick release should the guinea pig struggle or show signs of discomfort. Once the guinea pig was comfortable with the restraining apparatus, a test session consisted of placing the detector coils onto the anaesthetised eye, restraining the guinea pig as above and delivering either unpredictable, high-acceleration head rotations in light or sinusoidal stimuli in darkness.

When placing the coil on the guinea pig eye, care was taken to place the coil over the centre of the pupil and to use the minimum amount of glue. To minimise error in coil placement, a flashlight was used to view the eye during the placement, highlighting the centre of the pupil. To determine the position at which each impulse began, the guinea pig was rotated and on-line voltages monitored to ensure the optic axis was parallel to the field. This procedure served to optimise the signal from the detector coils and maximise their range of linearity within the angular limits set by the Remmel system.

An IBM-compatible PC running LabVIEW (National Instruments) was used to drive a velocity servomotor (ASR Servatron) that delivered each impulse. Although we refer to this test as a head impulse, unlike for the human equivalent of this test, the guinea pigs are rotated *en bloc*. In order to ensure that each impulse was unpredictable, the program randomly assigned the direction of the impulse and the delay to onset. For the measurement of the VOR response to impulses over time, each test impulse consisted of a total angular displacement of 18° with a peak head velocity of 230°/s and a peak head acceleration of 3100°/s^2. For each animal, eye movement measurements were made prior to, 1 week following, 8 weeks following and 12 weeks following UVD. All sinusoidal tests were performed in darkness. To directly compare the symmetry of the HVOR in response to sinusoidal stimulation and high-acceleration impulses, five compensated guinea pigs (at least 12 weeks post-labyrinthectomy) and four normal guinea pigs experienced five sets of sinusoidal stimuli (five cycles each, all at 2 Hz) with an increasing amplitude. These different stimuli were presented within the one testing session.

Data analysis of eye movement

Once the eye movement responses were obtained, data was transferred to a DEC Alpha station for off-line processing. For the data acquired from the calibration procedure, a least-squares fit was made to a sine wave for each channel of the form:

$$V = V_0 + G\sin(\theta + \theta_0), \quad (1)$$

where V is the measured signal in volts, V_0 is the offset, G is the gain, θ is the angle the jig has moved from the starting position, and $\theta+\theta_0$ is the angle between the detection coil and the transmission coil for that channel. The angle θ_0, corresponding to the initial offset of the coil, was not used in calculation because it could be found by other means.

The data were processed using a code written in the programming language C and New S (Becker et al. 1988). Data for each coil were calibrated by first subtracting V_0 and then dividing by G for each channel, to give values of the form $sin(\theta+\theta_0)$. Using Gram-Schmidt orthogonalisation (e.g. Anton 1984), each set of six data points was converted to a rotation matrix. The data for the first ten samples were averaged, and a reference rotation matrix calculated from them. Rotation matrices for each point were then divided by this reference matrix, so that all positions were given with respect to the position at the start of the first test. Rotation vectors were calculated from the rotation matrices according to the Cayley formulae (Eq. 23 of Haslwanter 1995). Rotation vectors for eye-in-head were calculated from those for gaze and head by composition of rotation vectors (Eq. 24 of Haslwanter 1995).

The time derivatives of the rotation vectors for gaze, head and eye-in-head were estimated by differentiating 21-point fits of qua-

dratic polynomials calculated using the method of Savitsky and Golay (1964). Angular velocities were calculated from the differentiated rotation vectors using Eq. 29 of Haslwanter (1995).

For analysis of eye movement data obtained in response to head impulse stimuli, the following procedures were used. For each impulse, head and eye coil position was acquired for 1000 ms. To prevent contamination of eye movement responses with non-vestibularly driven input, the analysis was restricted to the first 100 ms after the onset of the rotation (Halmagyi et al. 1990; Aw et al. 1996 a, b; Tabak et al. 1997 a, b). To determine the point of onset for each rotation, the moment at which peak head velocity occurred was identified, and the program counted back from this value until it reached the moment when the head velocity exceeded the arbitrary threshold of 1.5°/s. The end of the impulse was defined as either the moment of the peak head velocity or 100 ms after the onset of the head impulse, whichever came first. The results during the window defined by these criteria were used to produce eye velocity/head velocity plots and for the calculation of HVOR gain. If a response was contaminated by a saccade, only the data up until the peak slow phase eye velocity were used. Any impulses deemed unacceptable (e.g. due to blinks) were excluded from the final data analysis. The data for all acceptable impulses were plotted as time series of eye and head position and velocity.

For each animal, eye velocity was plotted as a function of head velocity for each trial. The data points for all ten impulses for a test were combined and a single lowess curve fitted to all these data points to represent the animal's overall HVOR performance for that test. The lowess procedure is a robust locally weighted regression method used to smooth scatterplots (Becker et al. 1988; Cleveland 1979). A spline fit was performed to interpolate the smoothed lowessed data to even intervals of 0.5°/s. Average vectors obtained in this way for each animal were superimposed and the mean and 95% confidence intervals for all animals were then calculated.

In previous studies, we have assessed HVOR gain by measuring eye velocity/head velocity at an arbitrary high head velocity. Such a single gain value does not deal with a considerable amount of data. In order to provide a more complete representation, we have used a linear regression fit to the eye velocity/head velocity vectors for ipsilesional and contralesional rotations separately. The slope of the line of best fit is a gain measure over a large range of head velocities. The diagonal of these plots represents constant HVOR gain of 1.0 at all head velocities.

For analysis of eye movement data obtained in response to sinusoidal rotations, the following procedures were used. Sinusoidal data were desaccaded manually. Because saccades took up a large percentage of each cycle, saccade data were removed completely rather than being replaced with data interpolated from the slow phases. To compare sinusoids to impulses and to quantify the responses to sinusoids at all accelerations tested, the various components of each phase of the sinusoid were separated. To determine the gain, least-squares fits of straight line were made to eye-in-head velocity versus head velocity for each phase of the cycle for which the absolute value of the velocity was increasing. These fits were done only for data occupying 1/12 of a period on either side of zero velocity, i.e. the portion of the sinusoidal waveform that is approximately linear. In doing this, we were able to obtain gain values for sinusoidal rotation that were directly comparable to the impulse data.

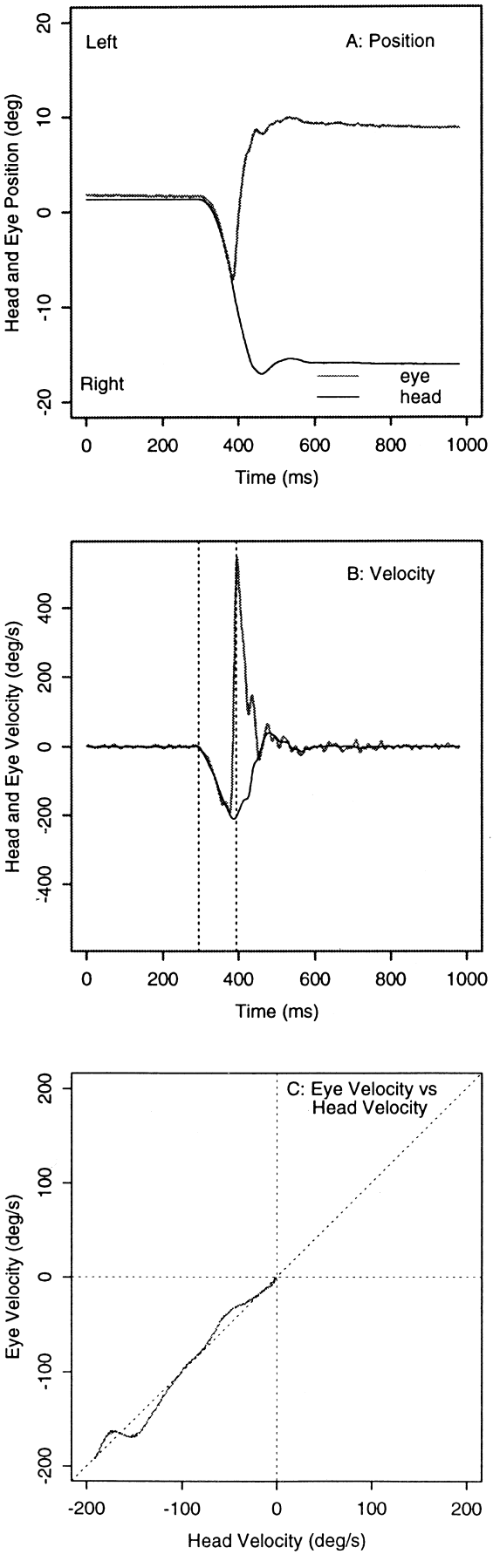

Fig. 1 A–C Examples of the head rotation stimulus and the eye movement response during a single rightward impulse in a naive guinea pig (first testing occasion). The eye position and eye velocity records have been inverted for ease of comparison. During the initial segment of the head impulse, eye position and eye velocity closely match head position and head velocity. **A** Position time series. **B** The corresponding velocity time series. **C** Eye velocity vs head velocity (velocity gain plot) for this impulse. A best-fitting (lowest) line is superimposed on the raw data

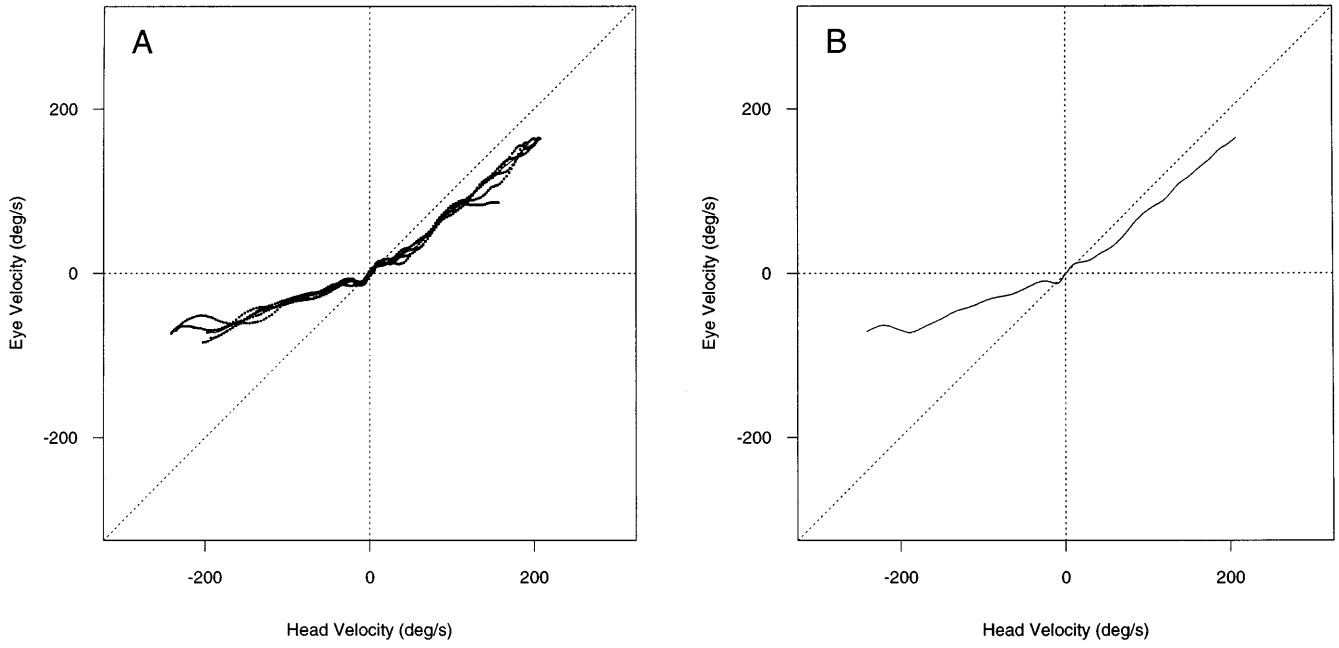

Fig. 2. A An example of ten individual impulses, five in each direction delivered to an animal post-unilateral vestibular deafferentation (UVD). Note the repeatability of the response. **B** The single best-fitting lowess line to all the individual impulses

Results

Resolution of static symptoms; labyrinthectomy versus neurectomy

Following UVD, all animals exhibited typical static oculomotor and postural deficits with symptoms directed toward the lesioned side. Ten hours after UVD, all guinea pigs had close to 20 beats/15 s of SN in the light. Within 50 h following the lesion, SN had decreased to approximately 2–3 beats/15 s. This is consistent with other reports in the literature for the disappearance of SN in guinea pig (e.g. Schaefer and Meyer 1973; Smith et al. 1986). There was, however, no difference between guinea pigs that had undergone a neurectomy and those that had undergone a labyrinthectomy, either in the frequency of SN [$F(1, 40)=2.43$, $P=0.15$] or in the rate at which SN diminished [$F(4, 40)=2.47$, $P=0.06$].

In the roll plane, all guinea pigs exhibited a head tilt (roll head tilt, RHT) that was directed toward the side of UVD. Although the measured RHT was higher at all measurement times after UVD for the animals that had a neurectomy, the large variation between animals rendered any difference between the labyrinthectomy and neurectomy groups non-significant [$F(1, 40)=4.44$, $P=0.06$]. At 50 h post-UVD, all animals had a residual RHT of between 5° and 20°, which remained throughout the course of the experiment (3 months for each animal). The rate at which RHT disappeared did not depend on the surgical procedure used to produce the UVD [$F(4, 40)=0.40$, $P=0.81$].

In the yaw plane, all guinea pigs exhibited a head deviation (yaw head tilt, YHT) that was directed toward the lesioned side. YHT gradually declined over 50 h for all animals. There was no difference in YHT between the animals that had undergone neurectomy or labyrinthectomy [$F(1, 40)=0.81$, $P=0.40$]. There was no difference in the rate at which YHT decreased between labyrinthectomy and neurectomy animals [$F(4, 40) =0.43$, $P=0.79$].

Recovery of the HVOR; labyrinthectomy versus neurectomy

During the first 100 ms of each impulse in a normal guinea pig, the position and velocity of the compensatory horizontal eye rotation closely matches position and velocity of the head rotation (Fig. 1). Figure 1 shows a typical response to a single rightward head rotation, with position (Fig. 1A), velocity as a function of time (Fig. 1B), and eye velocity as a function of head velocity (Fig. 1C). The line through the points in Fig. 1C is an example of the lowess line that was fitted to each eye velocity/head velocity record. This line we call a velocity gain vector – a response lying along the diagonal would have a gain of 1.0.

For comparison with previous work in human (Halmagyi et al. 1990), the head velocity at 122.5°/s was compared with eye velocity at 122.5°/s to obtain a gain measure for 22 normal guinea pigs. The particular head velocity chosen for HVOR gain calculations is fast enough and late enough that any effects of VOR latency and eyeball inertia are minimal. The HVOR gain for rightward rotations was 0.89±0.09 (all gain values throughout the report refer to gain±1 standard deviation of the mean) and 0.90±0.07 for leftward rotations. The velocity gains for rotations in the two directions were not significantly different from each other [$T(21)=1.44$;

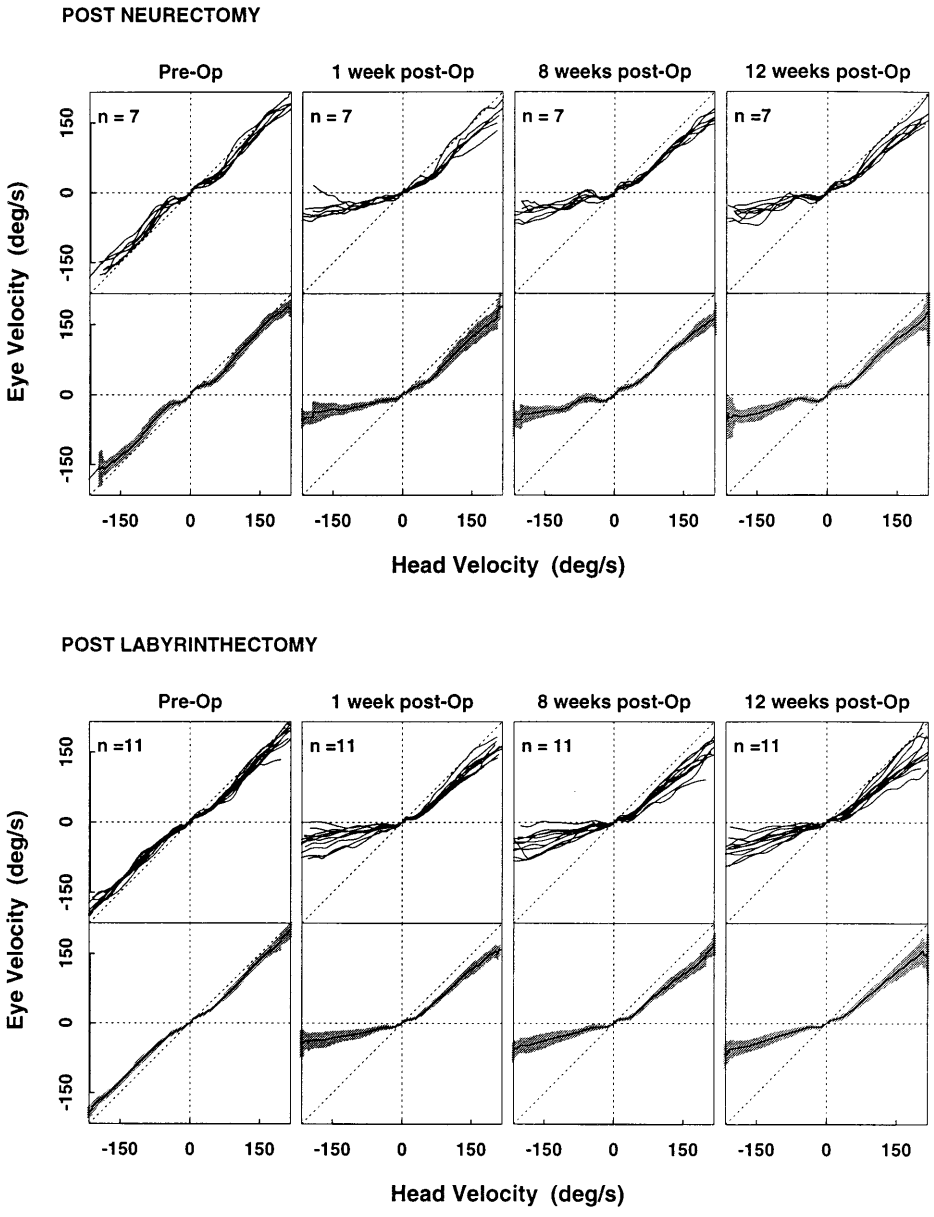

Fig. 3 Changes in horizontal vestibulo-ocular reflex (HVOR) over time after unilateral vestibular deafferentation (UVD). The single best-fitting lowess line for each animal at each measurement time is presented in the *upper panels* and the corresponding two-tailed 95% confidence intervals in the *lower panels*. The *top two rows* present the HVOR response to head impulse stimuli for animals that had received a right surgical superior vestibular neurectomy (n=7). The *bottom two rows* present the HVOR response to head impulse stimuli for animals that had received a right surgical labyrinthectomy (n=11)

P=0.166]. The HVOR gain for guinea pig was slightly lower than that we reported for human (0.95±0.08 for rotations toward the right and 0.93±0.08 for rotations toward the left) (Halmagyi et al. 1990).

The pre-operative data obtained for the 18 animals that subsequently underwent surgery for UVD is presented in the first column of the top and bottom panels of Fig. 3. The top row of each panel in Fig. 3 represents the individual data for each animal and the bottom row represents the mean and two-tailed confidence intervals of the velocity gain vectors. Note that for all normal animals, the data fall within a tight band and the 95% confidence intervals for the velocity gain plot for the two directions of yaw rotation are therefore narrow and symmetrical for the two directions of head rotation. It is important to note that during the initial part of the response there appears to be a near perfect VOR gain of 1 – both before and after a lesion. We attribute this part of the response to coil inertia. By systematically increasing the weight of the coil during a high acceleration impulse test with a guinea pig, the initial artefact was enhanced. However, even with an eye coil up to ten times heavier than a typical coil, the gain values calculated were affected only minimally. This inertia does, however, obscure the onset of the VOR and so prevents accurate measurement of the exact onset of the VOR; for that reason, we have not attempted to calculate VOR latency.

Animals were tested at 1, 8 and 12 weeks post-UVD to assess the recovery of the HVOR over time. The data are expressed either in terms of a velocity gain or directional deficit – a measure of HVOR asymmetry ([contralesional HVOR gain – ipsilesional HVOR gain)]/[contralesional HVOR gain + ipsilesional HVOR gain]). The accuracy of this measure is dependent both on the good-

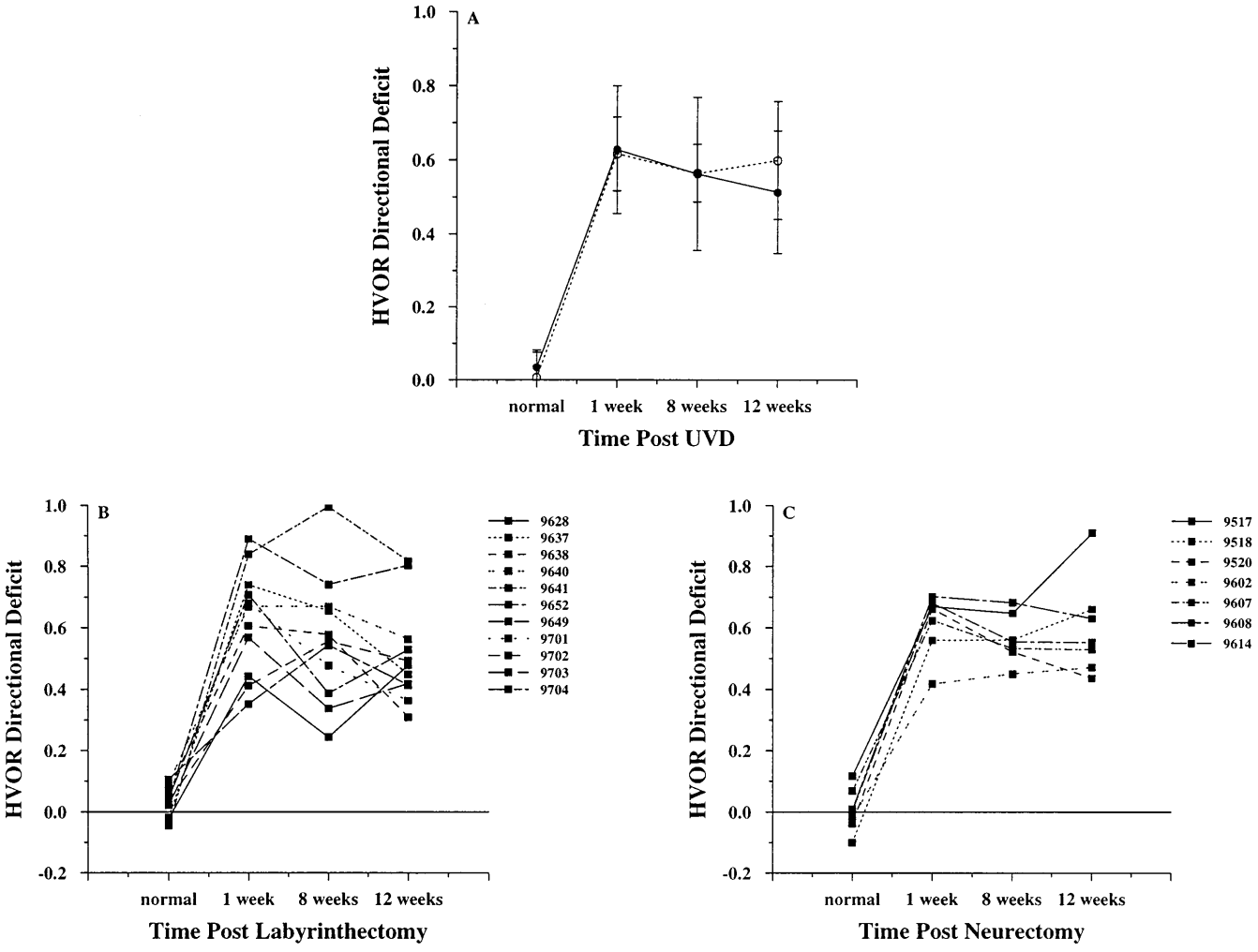

Fig. 4. A, B Changes in the asymmetry of the horizontal vestibulo-ocular reflex (HVOR) over time (as defined by directional deficit). **A** Directional deficit over time for animals before, and at various times after, either a unilateral labyrinthectomy (−●−) or a superior vestibular neurectomy (--○--). **B** Directional deficit over time for each individual animal before, and at various times after, a unilateral labyrinthectomy. **C** Directional deficit over time for each individual animal before and at various times after a superior vestibular neurectomy. Note that a score of 0 represents a perfectly symmetrical response and a score of 1 represents maximal asymmetry

ness-of-fit of a straight line to the velocity gain plot and on the repeatability of the response (see Fig. 2). Figure 2A shows superimposed plots of lowess lines from ten impulses for a UVD animal during a single test session (five impulses in each direction). Given that the stimulus is motor driven and therefore highly repeatable, it is clear that the eye movement responses for rotations in each direction were also highly consistent (see Fig. 2A). As Fig. 2B demonstrates, the single average lowess fit to the ten individual impulses was representative of all the impulses.

Figure 3 depicts the gain velocity plots over time for guinea pigs that either had a unilateral vestibular neurectomy (top two panels) or a unilateral vestibular labyrinthectomy (bottom two panels). The top panel for each set shows the individual raw data for each animal (averaged over ten impulses) and the bottom panel shows the average data with 95% confidence intervals. After UVD, there is a large decrease of HVOR gain for ipsilesional rotations. That is, the compensatory eye movement is of much lower velocity than head velocity. For contralesional rotations, there was a small decrease in HVOR gain compared with normal in both the labyrinthectomy and neurectomy animals. The HVOR gain for both groups of animals remains impaired up to 3 months post-UVD (see also Table 1).

To appreciate the degree of asymmetry over time, the directional deficit scores for each group were plotted as a function of time (see Fig. 4A). There was no difference in asymmetry between animals that received a labyrinthectomy and those that received a neurectomy [$F(1, 32)=0.146$, $P=0.15$] nor was there a change in asymmetry over time [$F(2, 32)=2.8$, $P=0.07$]. There was no significant difference between the two groups as a function of time [$F(2, 32)=1.13$, $P=0.34$].

A plot of the individual data clearly demonstrates the variability of the asymmetry over time, both between and within animals, particularly for the labyrinthectomy group (see Fig. 4B, C). It should be noted that, following

Table 1 Mean gain (± 1 standard deviation) for guinea pig in response to impulse stimuli post-UVD

Time post-UVD	Neurectomy		Labyrinthectomy	
	Ipsilesional gain	Contralesional gain	Ipsilesional gain	Contralesional gain
1 week	0.21±0.07	0.86±0.12	0.20±0.13	0.80±0.11
8 weeks	0.22±0.06	0.79±0.05	0.29±0.14	0.76±0.12
12 weeks	0.22±0.11	0.83±0.12	0.27±0.13	0.78±0.13

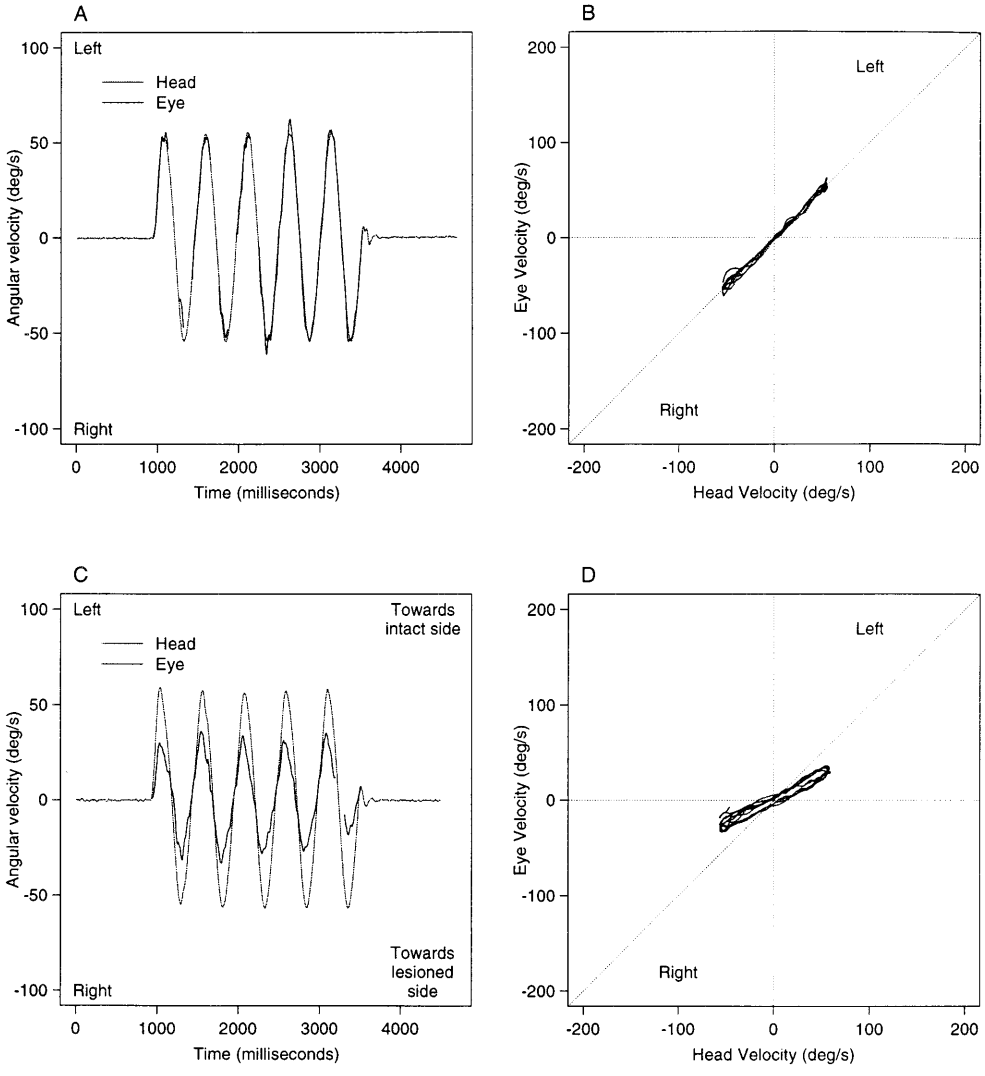

Fig. 5A–D The guinea pig horizontal vestibulo-ocular reflex (HVOR) response to sinusoidal rotations at a frequency of 2 Hz with a peak head velocity of 60°/s and a corresponding peak angular head acceleration of 750°/s^2. **A** and **C** are time-domain plots, whereas **B** and **D** are gain plots (eye velocity versus head velocity). Figures **A** and **B** are the eye movement responses measured from a normal guinea pig: Figures **C** and **D** are the eye movement responses measured from a compensated labyrinthectomised guinea pig

labyrinthectomy and neurectomy, some animals show a change over time. However, even in animals that do show a change, the difference in overall response to the two sides is still largely asymmetric. It is clear that there is virtually no change in gain over time for rotations in either direction for either group (Table 1).

HVOR to sinusoidal rotations versus HVOR to impulses

Figure 5 shows the velocity of the eye movement response to a sinusoidal stimulus of 2 Hz with a peak head velocity of 60°/s and a corresponding peak angular head acceleration of 750°/s^2 for a normal animal (Fig. 5A) and a UVD animal (Fig. 5C). For comparison to the way in which the impulse data is expressed, the sinusoidal data is also expressed as an instantaneous time–domain plot. That is, eye velocity is compared to head velocity on a point-by-point basis (Figs. 5B, D).

For the normal animal, the head and eye traces essentially lie over the top of one another and, as a result, for the gain plot, the trace lies on the diagonal indicative of a gain re-velocity of 1. When applying the formula described in the methods section to obtain a gain value for each direction of rotation, the gain for rotations to the right was 1.01 and the gain for rotations toward the left was 1.10. For the UVD animal, the amplitude of the response is impaired as can be seen in Fig. 5C. In terms of

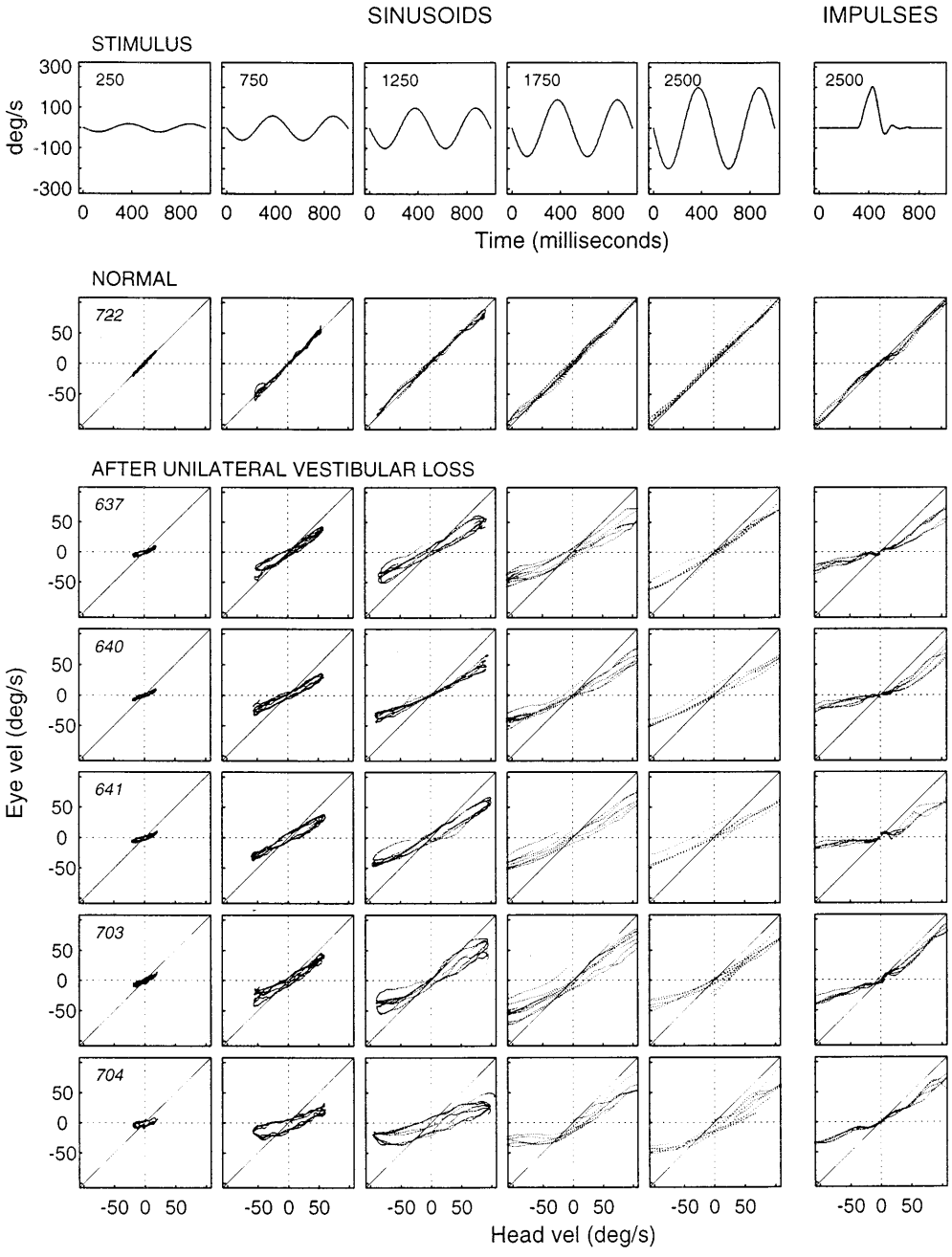

Fig. 6 Summary of the guinea pig horizontal vestibulo-ocular reflex (HVOR) to rotations at various stimulus intensities. The first row describes the stimulus. Note that for sinusoidal rotation, the frequency was held constant at 2 Hz and only the amplitude of the stimulus changed, producing a change in peak head acceleration. The corresponding peak head acceleration is at the *top left* of each box in *row 1*. Each row below the first row corresponds to the HVOR to the various stimuli for a single animal during the same testing session. *Row 2* presents the HVOR to the various stimuli for a normal animal. All remaining rows present the HVOR to the various stimuli for animals that had received a right surgical labyrinthectomy (the animal's number is italicised at the *top left* of each box in *column 1*). To directly compare impulse stimuli to sinusoidal rotation, the last column is the HVOR response to a "head impulse" for each animal. The peak angular head acceleration for the impulse ($2500°/s^2$) was matched to the peak head acceleration for the largest amplitude sinusoidal rotation

the gain plot, although the gain at this acceleration appears symmetrical, the trace is rotated slightly away from the diagonal, indicating that the gain re-velocity is decreased for the rotation in both directions. The calculated gain value for ipsilesional rotations in this animal was 0.58 and 0.53 for contralesional rotations (Fig. 5D). The shape of the gain plot also tends towards an ellipse for the UVD animal, indicating that the eye movement response is lagging behind the head movement. Also note that, for the time–domain eye traces, part of the response is missing, because all eye traces have been manually desaccaded.

To summarise all of the sinusoid data, the response for each animal that had a unilateral labyrinthectomy has been compared with a typical example of a normal animal (Fig. 6). In Fig. 6, each row represents an individual animal's response to sinusoidal stimuli of different values of peak angular head acceleration (as indicated by the stimuli description in the top row). To compare sinusoids to impulses and to quantify the response to sinusoids at all accelerations tested, the various components of each phase of the sinusoid were separated and a straight-line fitted to each phase of the cycle for which the absolute value of the velocity was increasing.

The straight-line fit was restricted to the portion of the sinusoid that was mostly linear (see Methods). Because the beginning of the sinusoid stimuli is effectively

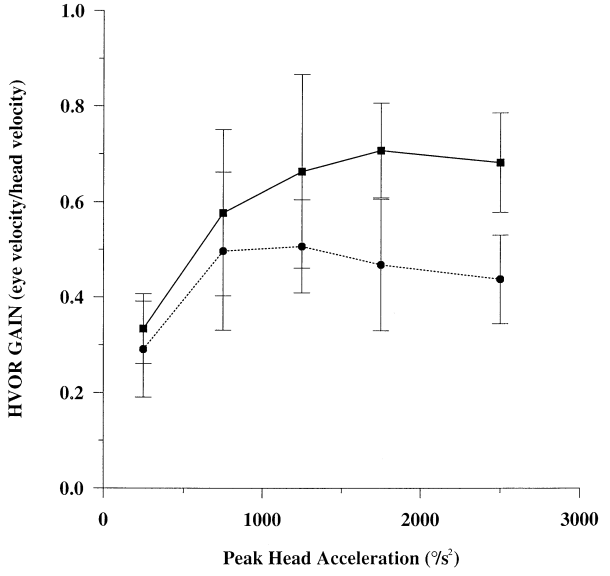

Fig. 7 The gain of the horizontal vestibulo-ocular reflex (HVOR) toward the side of the lesion (--●--) or toward the intact side (–■–) to sinusoidal rotations of increasing peak head acceleration

an impulse, the first quarter cycle of the sinusoid was not included in the analysis. For the normal animal the velocity gain of the HVOR was always very close to 1 (see Fig. 6). Following unilateral labyrinthectomy, the eye movement response for all animals was impaired, although there was a fair amount of variation between animals. At lower accelerations, the response appeared symmetrical, although the gain for rotations in both directions was lower than for the normal animal. For the sinusoidal rotation with the lowest value of peak head acceleration (250°/s^2), the average HVOR gain for contralesional rotations was 0.33±0.07 and 0.29±0.10 for ipsilesional rotations (Fig. 7).

As the value of the head acceleration increased, the eye movement response became increasingly asymmetrical for UVD animals. For the sinusoidal rotation with the highest peak head acceleration (2500°/s^2), the average HVOR gain for contralesional rotations was 0.68±0.10 and 0.44±0.07 for ipsilesional rotations. It is also important to note that all stimuli were delivered at 2 Hz, so even at the lowest acceleration it was unlikely that any eye movement responses were due to prediction.

To compare the change in gain over the different sinusoidal stimuli, a within-subjects repeated measures ANOVA was calculated for the sinusoid data for five UVD animals (note that one animal did not complete all trials within the same testing session and was therefore omitted from the multiple comparison). As acceleration increased, there was a significant increase in average gain [$F(4,16)=13.09$, $P=0.001$] and a significant change in gain for rotations to either side [$F(1,4)=10.03$, $P=0.034$]. There was a significant interaction between direction of the rotation and acceleration [$F(4,16)=3.69$, $P=0.026$]. That is, the response became increasingly asymmetrical as acceleration increased (see Fig. 7).

To directly compare the HVOR to a sinusoidal rotation and to a head impulse at a comparable high peak head acceleration (2500°/s^2), six UVD guinea pigs were subject to both stimuli (note that the sixth additional animal, not included in the above multiple comparison, did complete both stimuli with the comparable peak head acceleration). A directional deficit value was calculated for each guinea pig for both types of stimuli. Interestingly, at this value of peak head acceleration, the directional deficit for the sinusoidal stimuli (0.21±0.15) was significantly less asymmetric than the impulse of the same peak head acceleration (0.42±0.08) [$T(5)= 3.07$, $P=0.03$]. Most of this improvement in directional deficit for a response to a sinusoid versus an impulse can be attributed to an improvement in gain for rotations toward the side of UVD.

Discussion

Our aim was to resolve the differences that exist in the literature concerning the recovery of the HVOR after UVD. We suspected that most of the reported differences could be attributed to the type of the stimulus used to test the HVOR, rather than to the species used or the type of UVD performed.

Static vestibular compensation: labyrinthectomy versus neurectomy

The disappearance of the static symptoms that follow UVD has often been used as an index of vestibular compensation. In guinea pig, the static symptoms that follow UVD disappear within the first 52 h (Smith et al. 1986; de Waele et al. 1989). In the present study, the rate at which the static symptoms diminished were similar to that previously reported for guinea pig (Smith et al. 1986; de Waele et al. 1989). We can therefore assume that our measures of dynamic vestibular function, the HVOR, are also indicative of a typical guinea pig response after UVD. In addition, the rate at which the static symptoms diminished did not depend on the type of surgery used to produce UVD (labyrinthectomy or neurectomy). Cass and Goshgarian (1991) also report no difference in cat in the pattern of SN after unilateral vestibular neurectomy or labyrinthectomy. Although Li et al. (1995) found the postural deficits in rat to be more severe after neurectomy than after a labyrinthectomy, the disappearance of the postural symptoms can be highly variable (Sirkin et al. 1984; de Waele et al. 1993). In the present study, there was also large variability between animals in the compensation of the postural symptoms, particularly in the compensation of RHT.

The HVOR to high acceleration stimuli

The HVOR in response to high acceleration head rotations, before and after UVD, behaves the same way in

the guinea pig as in human (Halmagyi et al. 1990; Aw et al. 1996 a, b; Tabak et al. 1997 a, b). The guinea pig HVOR is severely impaired for ipsilesional rotations and only slightly impaired for contralesional rotations. While this agrees with the results we obtained in humans (Halmagyi et al. 1990), Tabak et al. (1997b) report less of a deficit for ipsilesional rotations and no deficit for contralesional rotations. They attribute the difference between the two studies to their use of a reactive torque helmet that can deliver a constant acceleration. Although the present study is not exactly comparable with these two human studies, since the guinea pig is rotated en bloc, we also used a constant acceleration. The results obtained in guinea pig more closely resembled the deficit observed in our human data (Halmagyi et al. 1990) than the deficit observed by Tabak et al. (1997b). We do note that our measure of eye velocity is contaminated initially by coil inertia at the onset of the head rotation. This prevents an accurate measure of latency of the VOR response and could have a small effect on the absolute value of our gain measure (Tabak et al. 1997 a, b); however, the most important thing to note is that the asymmetry of the VOR response post-UVD is still profound.

Irrespective of small differences in the gain of the response following UVD in humans between Halmagyi et al. (1990) and Tabak et al. (1997b), both studies report a severe HVOR deficit that is still present long after UVD. Similarly, in the present study, the guinea pig HVOR deficit shows no recovery in the 3 months post-UVD and it is likely, therefore, that the deficit in guinea pig is also permanent. Although Vibert et al. (1993) used a lower acceleration stimulus (1000°/s^2), they too report that the guinea pig HVOR remained severely impaired in response to brief accelerations. In fact, Vibert et al. (1993) justified the pooling of the results of 12 guinea pigs, 35–160 days post-UVD, into a single long-term group on the grounds that there was no statistical difference between animals at the various test times. That is, after 1 month post-UVD, there was no further recovery of the HVOR.

We cannot exclude the possibility that there was some recovery of dynamic function in the first week post-UVD, as noted by Fetter and Zee (1988) for monkey. In the present study, the first measure of the HVOR to impulse stimuli was not made until the end of the first week post-UVD. Based on neural data obtained from guinea pig (Smith and Curthoys 1988 a, b; Ris et al. 1995, 1997), we could expect a small improvement in gain for contralesional rotations to have already taken place before our first measure. The most important thing to note is that there would still be a large asymmetry of the HVOR when comparing rotations in either direction.

As with the recovery of the static vestibular function, there was no difference in the recovery of dynamic vestibular function (i.e. in the HVOR) between animals that had a labyrinthectomy and animals that had a neurectomy. Therefore, in response to high acceleration impulse stimuli, there is no recovery of the HVOR after 1 week post-UVD and the type of UVD performed had no effect on the HVOR deficit. In contrast, in response to low acceleration sinusoidal stimuli, Cass and Goshgarian (1991) report a greater HVOR asymmetry in cats after labyrinthectomy than after neurectomy and Vibert et al. (1993) observed some recovery of HVOR function in guinea pig. The results obtained from different studies appear to depend on the type of stimulus used to test the HVOR.

The HVOR to sinusoidal rotation: a comparison with high acceleration impulse stimuli

Several studies have concluded that there is almost complete recovery of the HVOR to low angular acceleration (see details in Introduction). We have previously argued that any changes or improvements in dynamic function that occur in response to low frequency stimulation may be contaminated by other non-vestibular components (Curthoys and Halmagyi 1992, 1995). By using high acceleration stimuli and analysing the eye movement response during the first 100 ms, it is argued that the response is of purely vestibular origin.

We sought to compare directly the HVOR responses to sinusoidal and impulse stimuli. It is important to note that, for this part of the study, we did not seek to evaluate whether there would be a difference between a neurectomised or labyrinthectomised animal in response to a sinusoid, nor whether the response to sinusoidal stimuli changed over time. For sinusoidal stimuli, frequency was held constant at 2 Hz – a frequency high enough to prevent prediction. Vibert et al. (1993) have demonstrated that following UVD in guinea pig, there is only a slight HVOR gain asymmetry in response to low frequency sinusoids, whereas the HVOR to higher acceleration velocity steps is severely asymmetrical. Using a sinusoidal stimulus and increasing the value of peak angular acceleration, we have attempted to determine at what values of peak head acceleration the transition from symmetry to asymmetry occurs.

For a normal animal, the gain for sinusoidal rotation for all values of peak head acceleration was close to 1 (Fig. 6). As can be seen in Figs. 6 and 7, there was variability between animals; however, it is clear from Fig. 6 and statistical analysis, that the HVOR response to low acceleration sinusoidal stimuli was far more symmetric than for high acceleration sinusoidal stimuli. In agreement with Vibert et al. (1993), for low acceleration sinusoidal stimuli, the gain re-velocity was bilaterally depressed. At the second lowest value of peak head acceleration, the gain for rotation toward both sides dramatically increases (Fig. 7). For the following three highest values of peak head acceleration, the gain for rotations toward the contralesional side shows a slight improvement, whereas the gain for rotations toward the ipsilesional side shows a slight decrease. For the largest amplitude sinusoid the difference between the gain for rotations in either direction was maximal.

It has been suggested that for low-acceleration, low-frequency stimuli, the apparent symmetry of response

may occur as a result of factors such as the predictive nature of the stimuli (see Curthoys and Halmagyi 1995, for review). At high frequencies, sinusoidal stimuli will also reveal an asymmetry between the two sides following UVD (Istl et al. 1983; Hyden et al. 1988; Tabak et al. 1997b). We aimed to test directly whether the HVOR to a sinusoidal rotation would, in fact, produce the same degree of asymmetry when both stimuli were matched for the value of peak head acceleration. Whilst we acknowledge that in comparing sinusoids with impulses we are comparing two very different stimuli, we have used the novel approach of presenting and analysing both types of stimuli in the time domain.

It is of interest that, even when the value of peak head acceleration is the same for both stimulus waveforms, the response to sinusoidal stimuli is significantly more symmetric. It is not the peak head acceleration itself, per se, that determines the HVOR, but the way in which peak head acceleration is achieved. Most of the improvement of the directional deficit measured for the sinusoid compared with the impulse can be attributed to an increase in gain for rotations toward the ipsilesional side. The validity of using a sinusoidal stimulus to measure HVOR function following UVD in the clinic has recently been questioned. As in the present study, Tabak et al. (1997a, b) tested human subjects with both sinusoidal oscillations and high acceleration impulse stimuli. Although they did not analyse the symmetry of the eye rotation to sinusoidal stimuli the same way we have, they too report that assessment of the HVOR following UVD is limited when using even high frequency sinusoidal oscillations. Foster et al. (1997) came to a similar conclusion, also recommending the use of high acceleration impulse testing instead of using traditional sinusoidal rotations to quantify the HVOR following UVD.

In summary, following UVD, the HVOR in response to high acceleration impulse stimuli was severely impaired in guinea pig. The HVOR deficit did not show any recovery in the 3 months following UVD. We have shown that the HVOR deficit is a direct result of the UVD, irrespective of how the lesion was performed and irrespective of the species. Assessment of the extent to which recovery of HVOR function occurs can also depend on the choice of test. At very low values of peak head acceleration using sinusoidal stimuli, the HVOR was symmetrical. As the value of peak head acceleration increased, the HVOR deficit became more noticeable. However, the response to a head impulse test is significantly more asymmetric than the HVOR to a sinusoidal rotation, even when the value of peak head acceleration is matched and the frequency is sufficient to prevent prediction. From a clinical perspective, to fully evaluate HVOR function following disease or deafferentation, it is necessary to use tests that deliver natural stimuli in the high dynamic range (Halmagyi et al. 1990; Foster et al. 1997; Tabak et al. 1997b). Interestingly, vestibular compensation is often cited as a useful model of CNS plasticity. While it is well known that the static symptoms diminish rapidly following UVD, to refer to changes in dynamic vestibular function following UVD as a form of CNS plasticity may be misleading. It would seem that if there is any significant recovery of the HVOR, it is specific for low-frequency stimulation.

Acknowledgements This research was supported by a project grant from the National Health and Medical Research Council of Australia. The authors wish to thank Mr. Warren Davies and Mr. Hamish MacDougall for their excellent technical assistance.

References

Allum JHJ, Yamane M, Pfaltz CR (1988) Long-term modifications of vertical and horizontal vestibulo-ocular reflex dynamics in man. Acta Otolaryngol (Stockh) 105:328–337

Anton H (1984) Elementary linear algebra. Wiley, New York

Aw ST, Halmagyi GM, Haslwanter T, Curthoys IS, Yavor RA Todd MJ (1996a) Three-dimensional vector analysis of the human vestibuloocular reflex in response to high-acceleration head rotations II. Responses in subjects with unilateral vestibular loss and selective semicircular canal occlusion. J Neurophysiol 76:4021–4030

Aw ST, Haslwanter T, Halmagyi GM, Curthoys IS, Yavor RA, Todd MJ (1996b) Three-dimensional vector analysis of the human vestibuloocular reflex in response to high-acceleration head rotations. I. Responses in normal subjects. J Neurophysiol 76:4009–4020

Baarsma EA, Collewijn, H (1975) Changes in compensatory eye movements after unilateral labyrinthectomy in the rabbit. Arch Otorhinolaryngol 211:211–230

Baloh RW, Honrubia V, Yee RD, Hess K (1984) Changes in human vestibulo-ocular reflex after loss of peripheral sensitivity. Ann Neurol 16:222–228

Becker RA, Chambers JM, Wilks AR (1988) The new S language: a programming environment for data analysis and graphics. Wadsworth & Brooks, California

Cass SD, Goshgarian HG (1991) Vestibular compensation after labyrinthectomy and vestibular neurectomy in cats. Otolaryngol Head Neck Surg 104:1–10

Cleveland WS (1979) Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 74:829–836

Curthoys IS, Halmagyi GM (1992) Brainstem neuronal correlates and mechanisms of vestibular compensation. In: Shimazu H, Shinoda Y (eds) Vestibular and brain stem control of eye, head and body movements. Japan Scientific Press, Tokyo / Karger, Basel, pp 417–426

Curthoys IS, Halmagyi GM (1995) Vestibular compensation: a review of the oculomotor, neural and clinical consequences of unilateral vestibular loss. J Vestib Res 5:67–107

Curthoys IS, Curthoys EJ, Blanks RKI, Markham CH (1977) The orientation of the semicircular canals in the guinea pig. Acta Otolaryngol 80:197–205

Curthoys IS, Smith PF, Darlington CL (1988) Postural compensation in the guinea pig following unilateral labyrinthectomy. Prog Brain Res 76:375–384

Fermin CD, Igarashi M, Martin GK Jenkins HA (1989) Ultrastructural evidence of repair and neuronal survival after labyrinthectomy in the squirrel monkey. Acta Anat 135:62–70

Fetter M, Dichgans J (1990) Adaptive mechanisms of VOR compensation after unilateral peripheral lesions in human. J Vestib Res 1:9–22

Fetter M, Zee DS (1988) Recovery from unilateral labyrinthectomy in rhesus monkey. J Neurophysiol 59:370–393

Foster CA, Demer JL, Morrow MJ, Baloh RW (1997) Deficits of gaze stability in multiple axes following unilateral vestibular lesions. Exp Brain Res 116:501–509

Halmagyi GM, Curthoys IS, Cremer PD, Henderson CJ, Todd MJ, Staples MJ, D'Cruz DM (1990) The human horizontal vestibulo-ocular reflex in response to high-acceleration stimulation

before and after unilateral vestibular neurectomy. Exp Brain Res 81:479–490
Haslwanter T (1995) Mathematics of three-dimensional eye rotations. Vision Res 35 1727–1739
Hess BJM, Dieringer N (1991) Spatial organization of linear vestibuloocular reflexes of the rat: responses during horizontal and vertical linear acceleration. J Neurophysiol 6:1805–1818
Hyden D, Larsby B, Odkvist LM (1988) Broad-frequency rotatory testing. Acta Otolaryngol Suppl (Stockh) 455:48–52
Istl YE, Hyden, D, Schwarz DW (1983) Quantification and localisation of vestibular loss in unilaterally labyrinthectomised patients using a precise rotatory test. Acta Otolaryngol Suppl (Stockh) 96:437–445
Jensen DW (1983) Survival of function in the deafferented vestibular nerve. Brain Res 273:175–178
Kevetter GA, Perachio AA (1994) Cytochrome oxidase histochemistry in Scarpa's ganglion after hemilabyrinthectomy. Neurosci Lett 175:141–144
Li H, Godfrey DA, Rubin AM (1995) Comparison of surgeries for removal of primary vestibular inputs: a combined anatomical and behavioural study in rats. Laryngoscope 105:417–424
Maioli C, Precht W, Ried S (1983) Short- and long-term modifications of vestibulo-ocular response dynamics following unilateral vestibular nerve lesions in the cat. Exp Brain Res 50: 259–274
Naito Y, Naito E, Honjo I, Newman A, Honrubia (1995) Effect of nerve section on cytochrome oxidase activity in the vestibular ganglion cells of the squirrel monkey. Hearing Res 90:72–78
Paige GD (1989) Nonlinearity and asymmetry in the human vestibulo-ocular reflex. Acta Otolaryngol (Stockh) 108:1–8
Remmel RS (1984) An inexpensive eye movement monitor using the scleral search coil technique. IEEE Trans Biomed Eng 31: 388–390
Richter E (1981) Scarpa's ganglion in the cat one year after labyrinthectomy. Arch Otorhinolaryngol 230:251–255
Ris L, de Waele C, Serafin M, Vidal PP, Godaux E (1995) Neuronal activity in the ipsilateral vestibular nucleus following unilateral labyrinthectomy in the alert guinea pig. J Neurophysiol 74:2087–2099
Ris L, Capron B, de Waele C, Vidal P-P, Godaux E (1997) Dissociation between behavioural recovery and restoration of vestibular activity in the unilabyrinthectomised guinea-pig. J Physiol (Lond) 500:509–522
Robinson DA (1963) A method of measuring eye movement using a scleral search coil in a magnetic field. IEEE Trans Biomed Eng 10:137–145
Savitsky A, Golay MJE (1964) Smoothing and differentiation of data by simplified least squares procedures. Anal Chem 36: 1627–1639
Schaefer KP, Meyer DL (1973) Compensatory mechanisms following labyrinthine lesions in the guinea pig. In: Zippel JP (ed) Memory and transfer of information. Plenum Press, New York, pp 203–232
Schuknecht HF (1982) Behaviour of the vestibular nerve following labyrinthectomy. Ann Otolrhinolaryngol 97:16–32
Sirkin DW, Precht W, Courjon JH (1984) Initial, rapid phase of recovery from unilateral vestibular lesions in rat not dependent on survival of central portion of vestibular nerve. Brain Res 302:245–256
Smith PF, Curthoys IS (1988a) Neuronal activity in the contralateral medial vestibular nucleus of the guinea pig following unilateral labyrinthectomy. Brain Res 444:295–307
Smith PF, Curthoys IS (1988b) Neuronal activity in the ipsilateral medial vestibular nucleus of the guinea pig following unilateral labyrinthectomy. Brain Res 444:308–319
Smith PF, Darlington CL, Curthoys IS (1986) The effect of visual deprivation on vestibular compensation in the guinea pig. Brain Res 364:195–198
Tabak S, Collewijn H, Boumans LJJM, Van der Steen (1997a) Gain and delay of human vestibulo-ocular reflexes to oscillation and steps of the head by a reactive torque helmet I. Normal subjects. Acta Otolaryngol 117:785–795
Tabak S, Collewijn H, Boumans LJJM, Van der Steen (1997b) Gain and delay of human vestibulo-ocular reflexes to oscillation and steps of the head by a reactive torque helmet. II. Vestibular-deficient subjects. Acta Otolaryngol 117:796–809
Takahashi M, Igarashi M, Wright W (1977) Damped pendular rotation nystagmus after unilateral labyrinthectomy or unilateral semicircular canal block in squirrel monkeys. J Otolaryngol 6: 157–165
Takahashi M, Uemura T, Fujishiro T (1984) Recovery of vestibulo-ocular reflex and gaze disturbances in patients with unilateral loss of labyrinthine function. Ann Otorhinolaryngol 93: 170–175
Vibert N, de Waele C, Escudero M, Vidal PP (1993) The horizontal vestibulo-ocular reflex in the hemilabyrinthectomised guinea-pig. Exp Brain Res 97:263–273
de Waele C, Graf W, Josset P, Vidal PP (1989) A radiological analysis of the postural syndromes following hemilabyrinthectomy and selective canal and otolith lesions in the guinea pig. Exp Brain Res 77:166–182
Wolfe JW, Kos CM (1977) Nystagmic responses of the rhesus monkey to rotational stimulation following unilateral labyrinthectomy: final report. Trans Am Acad Ophthalmol Otolaryngol 84:38–45