RESEARCH ARTICLE

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Three-dimensional spatial characteristics of caloric nystagmus

Abstract We investigated the three-dimensional spatial characteristics of caloric nystagmus during excitation and inhibition of the lateral semicircular canal in five normal human subjects. Each subject was repositioned in 45° steps at 1-min intervals such that the right lateral semicircular canal plane was reoriented in pitch, from 135° backwards from the upright position to 135° forwards, while the right ear was continuously stimulated with air at 44°C. In orientations in which caloric stimulus resulted in excitation of the right lateral semicircular canal, the eye velocity axis was orthogonal to the average orientation of the right lateral semicircular canal plane. However, in orientations in which caloric stimulus resulted in inhibition of the right lateral semicircular canal, the eye velocity axis was orthogonal to the average orientation of the left and *not* the right lateral semicircular canal plane. These findings suggest that velocity and direction of caloric nystagmus depend not only on the absolute magnitude of vestibular activity on the stimulated side but also on the differences in activity between the left and right vestibular nuclei, most probably mediated centrally via brainstem commissural pathways.

Introduction

Heating or cooling one labyrinth in a healthy human subject via the external auditory canal produces nystagmus. In a supine position, which is commonly used for caloric testing, the nystagmus is predominantly horizontal.

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When the water or air-flow used for the irrigation is above body temperature (warm caloric stimulus), the horizontal nystagmus is directed away from the stimulated ear. Note that we use the direction of the *slow* phase of the nystagmus to characterize the direction of the eye movements. When water below body temperature is used, the nystagmus is directed towards the stimulated ear. In prone positions, the directions of the nystagmus are reversed (Bárány 1906). The proposed mechanism of the predominantly horizontal nystagmus in the supine and prone positions is convective ampullopetal or ampullofugal endolymph flow in the lateral semicircular canal, respectively (Bárány 1906; Gentine et al. 1990). We have previously shown that it is also possible to elicit nystagmus by thermal stimulation of vertical semicircular canals (Aw et al. 1998; Fetter et al. 1998). Similar to the eye movement responses from electrical stimulation of the ampullary nerve coming from semicircular canals (Cohen et al. 1964), this caloric nystagmus lies in the plane of the stimulated semicircular canal (SCC).

The exact direction about which the eye rotates during this nystagmus may provide insight into the central mechanisms that process the peripheral vestibular stimulus. We know that an excitatory caloric stimulus elicits a rotation of the eye along the plane of the stimulated semicircular canal (Cohen et al. 1964) about an axis orthogonal to the plane of the stimulated, excited canal. During inhibition of the same canal, the system could theoretically react in two different ways. If the caloric nystagmus is mediated only by the *ipsilateral* vestibular nucleus, the nystagmus produced by inhibition should be about the same axis as during excitation but in the opposite direction. But if the central nervous system responds to the *difference* in activity between the left and right vestibular nuclei, mediated through the vestibular commissural pathways, the eye should rotate about an axis perpendicular to the *contralateral* SCC, since during caloric inhibition the neural activity will be higher in the contralateral vestibular nucleus. Since in 90% of normal humans the two lateral SCCs do not lie in the same plane but have a different lateral tilt (in 70% they are both tilt-

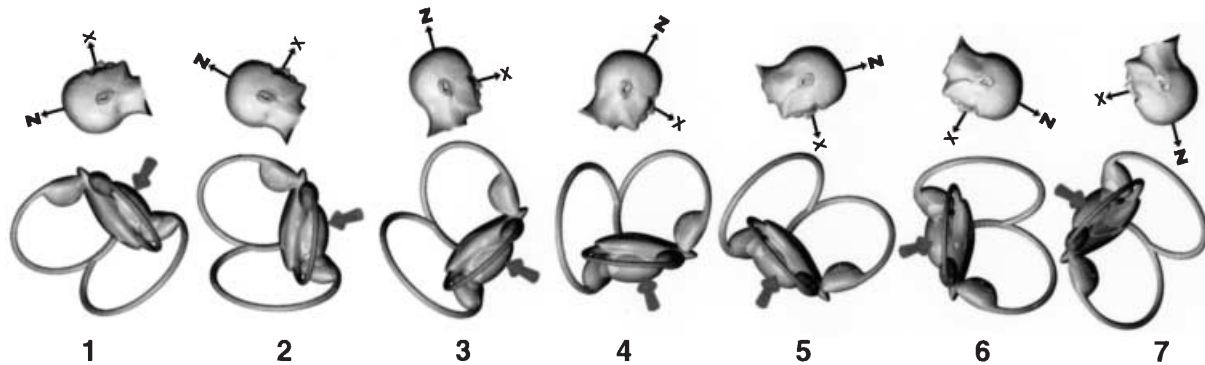# Pitch orientations of the lateral canal plane during caloric stimulation

Fig. 1 Pitch orientations of the subject's head and right lateral semicircular canal plane in space-referenced right-handed co-ordinates. The *right* labyrinth model was based on mean semicircular canal orientations (Blanks et al. 1975). The *arrow* shows the approximate position of the heat source from the external auditory meatus

ed downwards laterally, and in 20% they are both tilted upwards; Blanks et al. 1975), these two options lead to different predictions about the vertical eye movement component. In the first case, the vertical eye velocity should change its direction. In the second case, the vertical eye velocity should remain approximately constant.

A previous study by our group indicated that commissural interaction between the left and right vestibular nuclei may influence the eye velocity response to a caloric stimulus. In response to warm caloric stimulation, the eye velocity aligned with the plane of ipsilateral lateral canal, but during cold caloric stimulation the eye velocity aligned with the plane of the contralateral, and not the ipsilateral lateral SCC (Fetter et al. 1998). In the experiments presented below, we extend that study and systematically compare the three-dimensional spatial characteristics of eye movements elicited by excitation and inhibition of the lateral SCC.

Materials and methods

Subjects

We tested five normal subjects (mean age 32.6 years, range 28–39 years) with no history of vestibular disorder. The subjects had normal, symmetrical responses to the standard caloric test and showed no signs of positional nystagmus when tested clinically (Frenzel glasses, Dix-Hallpike method). All subjects gave informed consent according to the Declaration of Helsinki.

Recording system

Three-dimensional eye position was recorded with the dual search-coil technique, using the commonly employed Skalar search coils (Skalar, Delft, Netherlands). The coil signals were amplified and sampled at 100 Hz with 12-bit resolution. Technical details of the data acquisition are described by Bechert and Koenig (1996). The subject's head was positioned in different orientations by a three-dimensional (3-D) rotating chair with two perpendicular motorised axes and a manually adjustable innermost axis (Koenig et al. 1996). Head position was measured from the motorised outermost axis.

Experimental protocol

The subject was firmly secured to the rotating chair by seat belts, form-fitting vacuum cushions, a helmet and a bite-bar. The subject's head was positioned at the centre of rotations, with Reid's line (i.e. the line joining the infra-orbital margin and centre of the external auditory meatus) tilted 5° above earth horizontal. To calibrate the eye position recordings the subject was asked to fixate a laser spot straight-ahead at the beginning of the experiment. Then eye movements were recorded for one minute in darkness to check for spontaneous nystagmus.

Prior to caloric stimulation, the innermost frame of the 3-D chair was manually pitched 30° forwards to orient the subject's lateral SCC approximately earth horizontal. The subject was then pitched 135° backwards to *orientation 1*. Figure 1 shows the seven orientations of the right labyrinth during the experiment. The model of the labyrinth was constructed in Houdini (Side Effects Software) using mean SCC orientations (Blanks et al. 1975). The arrow in Fig. 1 shows the approximate position of the heat source with respect to the labyrinth (Swartz and Harnsberger 1992).

During the experiment, the subject's right ear was continuously stimulated with air at 44°C (Hortmann, Neuro-otometrie). Because of the access constraints in the experimental set-up, we chose air stimulation over the more effective water caloric stimulus. The subjects were in complete darkness during the recordings. At the start of the experiment, the ear was irrigated for 2 min in order to establish a temperature gradient across the labyrinth. Whilst being continuously stimulated, the subject was then repositioned at approximately 1-min intervals from –135° (orientation 1) to 135° (orientation 7), and then step-wise back to the initial position. Repositioning was done in 45° steps at 10°/s. Subjects stayed alert by performing mental arithmetic during the test.

Data analysis

Eye positions were determined from the search coil signals and expressed as quaternions. Eye movements to the left, down, and clockwise (as seen from the subject) are positive, respectively. The reference position was taken from the beginning or the end of the experimental session when the subject was looking straight ahead. From the eye position and its time derivative, three-dimensional eye velocity was calculated (Tweed et al. 1990). The eye velocity was desaccaded to obtain slow-phase eye velocity, which will be referred to only as "eye velocity" in the rest of the manuscript.

Eye velocity is characterized by its *magnitude* and its *direction*. Labelling torsional, vertical and horizontal components with x, y and z, respectively, we obtain:

$$\overrightarrow{eye\ velocity} = \vec{n} \cdot \omega$$

A. Three-dimensional caloric nystagmus in a normal subject
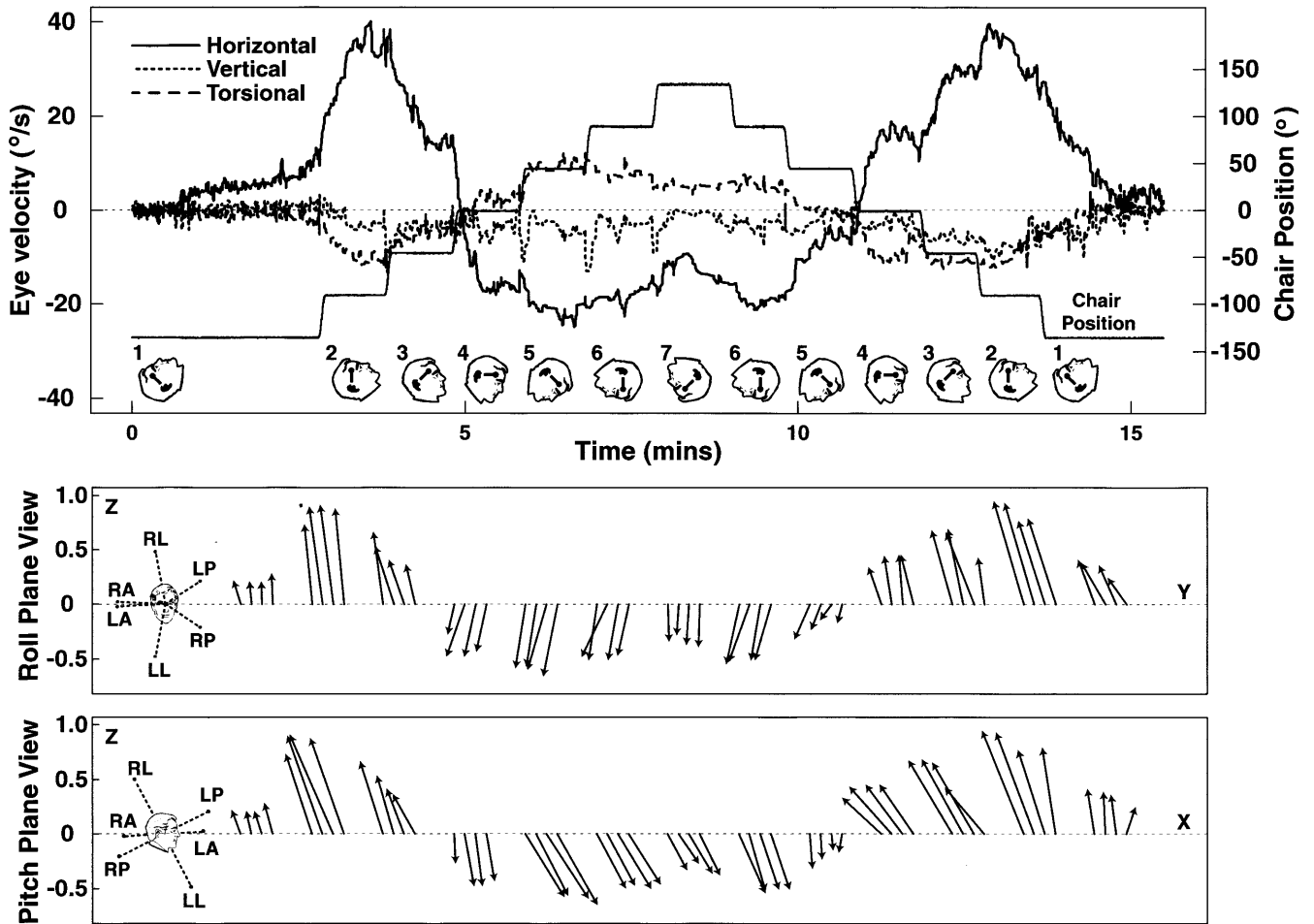
B. Caloric nystagmus in all subjects during lateral canal plane pitch orientations
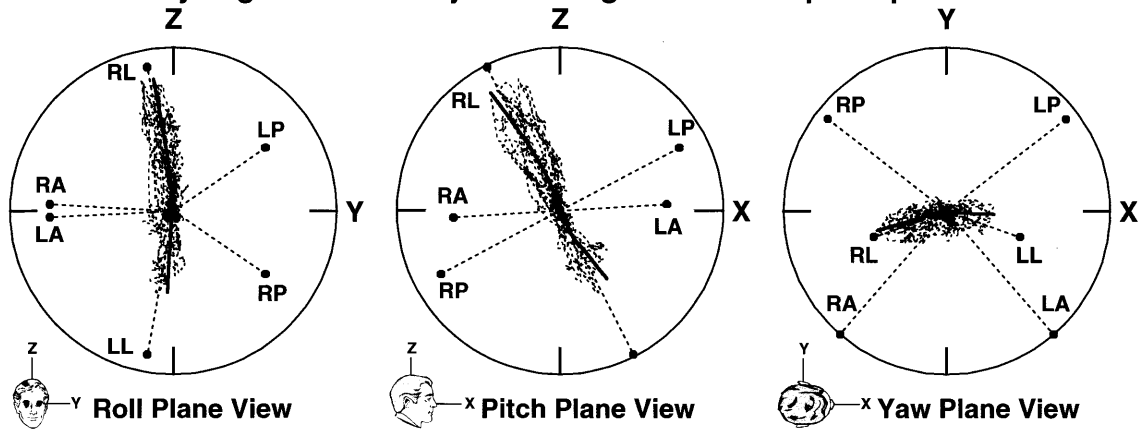

Roll Plane View Pitch Plane View Yaw Plane View

Fig. 2 A Three-dimensional eye velocity responses to continuous caloric stimulation of a normal subject's right ear at 44°C, while the lateral canal plane was pitched forward in 45° steps from orientation 1 to 7, and then stepwise back to the initial position (*first panel*). The *middle and bottom panels* display the roll and pitch plane views of the eye velocity direction, determined at 20 s, 30 s, 40 s, 50 s after each repositioning. The *cartoons on the left* show the on-directions of the semicircular canal vectors (Blanks et al.

1975): right lateral canal (*RL*), right anterior canal (*RA*), right posterior canal (*RP*), left lateral canal (*LL*), left anterior canal (*LA*), and left posterior canal (*LP*). **B** Eye velocity directions from all subjects during the caloric stimulation, displayed in roll-, pitch-, and yaw-plane views. The on-directions of the semicircular canal vectors (Blanks et al. 1975) are indicated by *dotted lines*. The *solid lines* show the mean eye velocity responses from all subjects

where $\omega = \sqrt{x^2 + y^2 + z^2}$ the *magnitude* of the eye velocity and $\vec{n} = \dfrac{\overrightarrow{eye\ velocity}}{\omega}$ the *direction*, i.e. the axis about which the eye rotates instantaneously. $\vec{n}$ is a vector of length 1, and is shown in Fig. 2A (second and third panels).

Results

Caloric nystagmus from continuous stimulation of one subject's right ear with air at 44°C is displayed in Fig. 2. The first panel shows the horizontal, vertical and torsional eye velocity components, and the second and third panels show the directions of eye velocity ($\vec{n}$) in roll and pitch plane views. The dashed lines in the cartoons on the left of Fig. 2A show the on-direction vectors of the SCCs (Blanks et al. 1975). The eye velocity directions were determined at 10 s intervals, 20 s after each repositioning.

In orientations 1–3, caloric stimulation results in excitation of the right lateral SCC (ampullopetal stimulation). The eye velocity was directed left, up and counterclockwise. In orientations 5–7, where warm caloric stimulation results in right lateral SCC inhibition (ampullofugal stimulation), the eye velocity was right, up, and clockwise. While the horizontal and torsional eye velocity components were modulated sinusoidally by the pitch tilt, the vertical component remained upwards in all orientations.

In roll plane view, the on-directions of the eye velocities in orientations 1–3 were tilted –11.2°±6.9° (mean ± SD) from the dorso-ventral yaw axis, and were thus aligned with the on-direction of the right lateral SCC vector (RL) at –10.50°. In orientations 5–7, the on-directions of the eye velocities were tilted 10.4°±7.2° from the yaw axis and were aligned with the on-direction of the left lateral SCC vector (LL) at 10.50°. During inhibition, the mean misalignment between the eye velocity direction and the left (contralateral) lateral SCC vector was 0.1°, but was 20.9° from the right (ipsilateral) lateral SCC vector.

In pitch plane view, the direction of eye velocity during excitation and inhibition was tilted –14.1°±9.1° and –17.6°±9.8° from the yaw axis, respectively. As these angles are smaller than the mean orientation of the right or left lateral SCC vector (both RL and LL at –27.0°), it suggests that the lateral SCC planes in this subject are oriented at a smaller roll angle than the usual 30° above horizontal in head-referenced co-ordinates.

In orientation 4, the right lateral SCC plane was approximately horizontal. In this position there was minimal caloric stimulation from thermal convection. But when the lateral SCC plane was repositioned from excitatory orientation 3 to orientation 4, where the right lateral SCC plane was approximately horizontal, the nystagmus did not vanish. Instead, we still recorded an eye velocity with a magnitude of 19.4°/s. The direction of eye velocity changed to 10.9°±2.8° with the yaw axis (roll plane view) and aligned closely with the on-direc-

tion of the left lateral SCC vector (LL). Similarly, when repositioned from inhibitory orientation 5 to the neutral orientation 4, the eye velocity magnitude was 22.0°/s and the direction of the eye velocity re-aligned closely with the RL (–9.1±4.9° with the yaw axis, roll plane view). In a control experiment, when this subject was only stimulated in orientation 4 for 2 min, the maximum eye velocity magnitude was only 4.3°/s.

These results were consistent across different subjects. The mean eye velocity magnitude in three subjects was only 3.5°/s when they were stimulated only in orientation 4 for 2 min. However, their mean eye velocity magnitude after repositioning from orientation 3 to 4 was 11.4°/s and after repositioning from orientation 5 to 4 was 13.6°/s. The mean eye velocity directions after repositioning from position 3 or 5 were similar to those of the subject shown in Fig. 2A.

Figure 2B shows the overall eye velocity directions for all subjects, projected onto the roll, pitch and yaw plane. The dotted lines show the on-direction vectors of the SCCs (Blanks et al. 1975). The responses during caloric stimulation were predominantly aligned with the on-directions of the RLs and LLs. In roll plane, the mean on-direction of the eye velocity vector was tilted 1.8° from RL and –6.4° from LL. In pitch plane it was –3.4° from RL and –7.4° from LL. In roll plane, the mean±95% confidence intervals of the on-direction of the eye velocity vector were –0.4±3.9° from RL in orientation 2 (maximum right lateral SCC excitation) and –1.2±4.6° from LL in orientation 6 (maximum right lateral SCC inhibition).

In all subjects, the eye velocity magnitude was larger during lateral SCC excitation than during inhibition. The ratio of the responses between maximum lateral SCC inhibition and excitation was 0.46±0.20 (mean ± SD).

Discussion

Our results confirm that the vestibulo-ocular reflex (VOR) in response to caloric excitation of the lateral SCC is aligned with the plane of the lateral SCC (Fetter et al. 1998). These results are also consistent with the observations of Cohen et al. (1964), who found that electrical stimulation of individual SCC nerves elicits eye movements that are approximately in the plane of the stimulated SCC.

Furthermore our findings suggest that the VOR from individual SCCs is generated by the difference in activity between the left and right vestibular nuclei, regardless of whether this difference is produced by excitation or inhibition. The spatial characteristics of this nystagmus are defined by the geometry of the SCC.

Blanks et al. (1975) showed that in most individuals the left and right lateral SCCs are not co-planar, but are approximately symmetrical mirror-images of each other about the mid-sagittal plane. They reported that, in 70% of the human skulls they measured, the lateral SCCs were tilted lower laterally than medially. This lateral tilt

of the SCCs allows us to reveal how the peripheral vestibular signals are interpreted by the central nervous system: while the eye velocity direction during caloric excitation aligns well with the on-direction of the stimulated lateral SCC, it changes its orientation during inhibition and re-aligns with the on-direction of the *contralateral* lateral SCC. This result corroborates our previous finding that, during cold caloric stimulation in the standard clinical caloric test position (i.e. supine, with head pitched 30° above earth horizontal), the eye velocity direction aligns with the plane of the contralateral lateral SCC (Fetter et al. 1998). It suggests that the central nervous system interprets the difference in activity between the two vestibular nuclei mediated via the brainstem commissural pathways and generates a nystagmus response that is spatially oriented in the plane of the SCC corresponding to the vestibular nucleus with the higher activity.

Since there is no established procedure to determine the stereotaxic orientation of the semicircular canals in vivo, we were not able to correlate the direction of eye velocity with lateral SCC orientation in each individual subject. Therefore, we have assumed that the symmetric shift of the direction of eye velocity on going from excitatory positions (orientations 1–3) to inhibitory positions (orientations 5–7) reflects the underlying geometry of the lateral SCCs. This assumption is supported by the agreement between the mean on-directions derived from the data of Blanks et al. (1975) and the averaged eye velocity directions measured in our experiments.

We can explain the responses to lateral SCC excitation by the increased primary vestibular afferent firing. According to Shimazu and Precht (1966), increase in the discharge rate of the type I neurons in the ipsilateral medial vestibular nucleus excites the contralateral type II neurons, which then in turn inhibit contralateral type I neurons. Consequently, higher activity from the ipsilateral vestibular nucleus results in VOR responses, which align with the plane of the stimulated lateral SCC (Cohen et al. 1964). Conversely, during lateral SCC inhibition, activity of the ipsilateral type I neurons is decreased or silenced. Excitation of contralateral type II neurons is also decreased, resulting in disinhibition of contralateral type I neurons. The activity in the contralateral medial vestibular nucleus becomes relatively higher than that in the ipsilateral vestibular nucleus and hence the VOR aligns with the plane of the contralateral lateral SCC. The resultant oculomotor responses are akin to the excitation of the contralateral lateral SCC. The spatial characteristics of the excitatory and inhibitory caloric responses further support the notion of the functional *push-pull* arrangement of the lateral SCC pair.

The caloric response magnitude produced by lateral SCC excitation in our experiment is more than twice that produced by inhibition. This finding is similar to the results of Coats and Smith (1967) and Böhmer et al. (1992). This asymmetry is at least partly due to an asymmetry in the peripheral vestibular activity: Goldberg and Fernandez (1971) showed such an asymmetry between excitatory and inhibitory responses from their single-unit recordings of peripheral SCC nerves in squirrel monkey during constant angular acceleration. They suggest that the reason for the asymmetry is that the resting discharge rate is in the lower half of the units' dynamic range, and therefore it is easier to silence the neurons than to drive it to its upper limit of their firing.

Suzuki et al. (1998) showed that warming the posterior SCC ampulla decreases the spontaneous discharge rate of the frog vestibular receptors, while cooling has the opposite effect. It is possible that the heating of the ampullary nerve endings by caloric stimulation could decrease the excitatory response and increase the inhibitory response. Therefore direct thermal effect on the SCC nerve endings is unlikely to contribute much to the difference in response magnitude during excitation and inhibition.

Murofushi and Mizuno (1994), Barnes (1995) and recently Formby and Robinson (2000) have demonstrated a horizontal post-caloric nystagmus that was opposite to that in the primary phase when the lateral SCC plane was repositioned from earth vertical to horizontal: they attributed this behaviour to vestibular adaptation. Similar spatial characteristics of the nystagmus were observed in our present experiment. When our subjects were in orientation 4, the lateral SCC plane was approximately earth horizontal, therefore the stimulus attributable to convection should have been near zero (Coats and Smith 1967). We have previously shown that, during warm caloric stimulation in this position, the eye movement response is close to zero (Aw et al. 1998; Fetter et al. 1998). However, when the lateral SCC plane was repositioned from orientation 3 to orientation 4, the eye velocity magnitude did not decrease towards zero. Instead the magnitude of the eye velocity vector increased and the direction changed and realigned with the plane of the contralateral lateral SCC. The opposite phenomenon was observed when the lateral SCC plane was repositioned from orientation 5 to orientation 4: the eye velocity changed direction and realigned from the contralateral to the ipsilateral lateral SCC plane (Fig. 2A, second and third panels).

Goldberg and Fernandez (1971) also showed that there was adaptation in some of the primary semicircular canal afferents during trapezoidal rotations. We propose that, during prolonged lateral SCC excitation, the activity of the ipsilateral medial vestibular nucleus was probably decreased due to adaptation. When the lateral SCC plane was repositioned to earth horizontal, the primary afferent input from the caloric stimulation was minimal. Consequently, the resulting imbalance in activity between the two vestibular nuclei could have generated the observed nystagmus responses in the opposite direction.

These results indicate that the oculomotor responses to caloric nystagmus reflect not only the unilateral vestibular activity but the difference in firing rates between the left and right vestibular nuclei. This finding may be important for clinical interpretation of the nystagmus responses to an inhibitor or cold caloric stimulus.

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