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RESEARCH NOTE

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# Dependence of adaptation of the human vertical angular vestibulo-ocular reflex on gravity

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**Abstract** We determined the spatial dependence of adaptive gain changes of the vertical angular vestibulo-ocular reflex (aVOR) on gravity in five human subjects. The gain was decreased for 1 h by sinusoidal oscillation in pitch about a spatial vertical axis in a subject-stationary surround with the head oriented left-side down. Gains were tested by sinusoidal oscillation about a spatial vertical axis while subjects were tilted in 15° increments from left- to right-side down positions through the upright. Changes in gain of the vertical component of the induced eye movements were expressed as a percentage of the preadapted values for the final analysis. Vertical aVOR gain changes were maximal in the position in which the gain had been adapted and declined progressively as subjects were moved from this position. Gain changes were plotted as a function of head orientation and fit with a sine function. The bias level of the fitted sines, i.e., the gravity-independent gain change, was −29±10% (SD). The gains varied around this bias as a function of head position by ±18±6%, which were the gravity-dependent gain changes. The gravity-dependent gain changes induced by only 1 h of adaptation persisted, gradually declining over several days. We conclude that there is a component of the vertical aVOR gain change in humans that is dependent on the head orientation in which the gain was adapted, and that this dependence can persist for substantial periods.

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## Introduction

The angular VOR (aVOR) maintains stable orientation of gaze (eye-in-head position + head position) in space by generating compensatory eye velocity. The accuracy of the aVOR is defined by its gain (eye velocity/head velocity), which can vary considerably under different experimental conditions and in different species. In humans, the gain is about 0.6–0.75 in darkness, but is close to unity when imagining distant visual targets or when subjects are tested in light (Ferman et al. 1987; Crawford and Vilis 1991; Demer et al. 1993; Tweed et al. 1994; Aw et al. 1996; Crane and Demer 1997; Cremer et al. 1998; Clarke et al. 2000). If counterrotation of the eyes in response to head movement is inadequate to stabilize gaze over a prolonged period, the induced retinal slip drives aVOR gain modification. Some gain changes can be seen as early as 5–15 min after the beginning of adaptation (Gonshor and Melvill Jones 1976b; Collewijn et al. 1981, 1983; Demer et al. 1989), but at least 40 min is necessary to obtain most of the gain changes (Gonshor and Melvill Jones 1976a, 1976b; Collewijn et al. 1983).

It has been demonstrated recently that one component of the adapted gain of the vertical aVOR in the monkey depends on head orientation re gravity (Yakushin et al. 2000, 2003). When the vertical aVOR gains were adapted in a side-down orientation, gain changes were maximal in that position relative to preadapted values and were minimal or absent with the other side down. The gain changes were fitted with sine functions. The bias level was considered to be gravity independent. Around this bias the gains varied as a function of head position with regard to gravity, which was considered to be the gravity-dependent component.

A similar gravity-dependent modification of the aVOR gain has been observed in humans. With the head tilted 45° forward or 45° left-ear down, the gain changes were greater when the subject was tested in the head orientation used for adaptation, then when the head was tilted 45° in the opposite direction (Tan et al. 1992; Tiliket et al. 1993). Since in these experiments different canals were stimulated in the different head orientations, it is possible that the observed gain changes could have been either in the context of the head position with regard to gravity or related to the different sets of canals that were stimulated.

In this paper, we studied the effects of gravity on the gain of the vertical aVOR in humans. The intent was to determine whether the dependence of the vertical aVOR gain adaptation on gravity, previously observed in the monkey, was also present in humans.

## Methods

Experiments were performed in a three-axis, motorized vestibular stimulator (Acutronic, Jona, Switzerland) on five subjects (three men and two women; average age 37±6 years, range 28 to 44 years). During the experiments, the subject sat comfortably in the rotational chair, secured with safety belts and evacuation pillows. The head was immobilized by a special mask, made of a thermoplastic material (Posicast). The plastic was molded to the contour of the head after warming, in the position in which the crossing of the interaural axis of the head and longitudinal axis of the body was at the center of rotation (see Bockisch and Haslwanter 2001, for details). The experiments complied with the 1964 Declaration of Helsinki for research involving human subjects and were approved by a local ethical committee at Zurich University Hospital.

Eye position was recorded with dual search coils (Skalar Medical, Delft). The head was surrounded by 0.5-m-square field coils that generated three frequencies (80, 96, and 120 kHz) in orthogonal directions (Primelec, Regensdorf, Switzerland). A high-performance digital signal processor computed a fast Fourier transform in real time on the digitized search coil signal to determine the voltage induced in the coil by each magnetic field. The eye coils were precalibrated using a small gimbal system that was placed in the center of the field coils, close to the location of the measured eye (Straumann et al. 1995). At the beginning of each experiment, the straight-ahead eye position was recorded while visually fixating a central target (size 0.5°) on a flat screen placed in front of the subject. The direction of eye movements was defined by the right-hand rule, with clockwise, downward, and leftward eye movements from the subject's point of view being positive. Eye-position signals were digitized at 1 kHz with 12-bit precision. Stimulator control and data collection programs were written in LabView. In the data analysis, eye positions were expressed as rotation vectors (Haustein 1989), with three-dimensional eye velocities expressed as angular velocity vectors (Hepp 1990).

### Adaptation and testing procedures

To adapt the gain of the vertical aVOR, subjects were positioned 90° left-side down (LSD) facing a flat 0.57×0.57 m screen. Adaptation was performed in light by oscillating subject and screen sinusoidally together at 0.2 Hz for 1 h about an earth-vertical axis, with a peak velocity of 25°/s. The screen, which had subject-horizontal, black and white stripes of ≈2° width, was located 0.6 m away and covered 50°×50° of the visual field. The sides of the screen were blocked with white paper to occlude lateral portions of the visual field, so that subjects saw only a subject-fixed visual surround.

The dependence of the vertical aVOR gain on orientation re gravity was tested by oscillating the subjects with the same amplitude and frequency about a spatial vertical axis again, at 0.2 Hz in darkness, with a peak velocity of 25°/s, while varying the head–body orientation with regard to the axis of rotation. Using this approach, the recorded vertical aVOR gains varied as a sine function of head tilt, which was maximal when subjects were in on-side position. We considered the "true" or spatial gain of the vertical aVOR to be the peak value of the sinusoid that was fit through these data (Yakushin et al. 2003). This test has proven to be an effective measure of gravity-dependent gain changes in monkeys after on-side adaptation (Yakushin et al. 2003).

During testing, subjects were instructed to imagine and fixate a faraway visual target. Tests started with the subject LSD (–90°) in darkness. After 10 cycles of oscillation, the head position was moved through the upright toward RSD (90°) in 15° increments. The screen was illuminated for 2–5 s before each 10 cycles of rotation began to suppress any possible spontaneous nystagmus. Drowsiness was identified on-line by an associated drop in eye velocity. When this occurred, subjects were instructed to stay alert.

At the beginning of the experiment, a coil was placed on one eye 2–3 min after several drops of local anesthetic (oxybrucaine 0.4%) had been applied to reduce discomfort. The primary (straight ahead) eye position was calibrated and preadaptation data were collected as described above. Subjects were then returned to the upright position, and the search coil was removed. They were then positioned LSD and adapted for 1 h. At the end of adaptation, a coil was remounted on the same or the other eye. The straight-ahead reference eye position was recorded again, and postadaptation data were collected in darkness. Four of the five subjects were tested at least two more times over the next 3 days. Subjects did not restrict their daily activity after adaptation.

### Measuring aVOR gain

The gain of the aVOR (eye velocity/head velocity) for each head orientation was calculated by comparing the desaccaded pitch eye velocity component, i.e., the component along the body-vertical, with the maximum head velocity along the spatial vertical, which was the axis of rotation. The stimulus was invariant in all head orientations, but the evoked pitch eye velocities were largest with the subjects on their side and smallest when subjects were upright. Gains were assumed to be negative when the evoked eye velocity was in phase with stimulus velocity and positive when they were out of phase (Fig. 1B). Gain changes were expressed as a percentage of the preadapted level and plotted as a function of head orientation re gravity (residual gain). Since gain measurements obtained about the upright were close to zero, small variations in gain before and after adaptation could lead to large changes in percentages that were not meaningful. Therefore, we did not calculate gain changes for data within ±15° of the upright position.

Similar to the study performed in the monkey (Yakushin et al. 2003), we assumed that there are two components to the adaptive gain changes that occurred simultaneously. One is independent of gravity and can be observed with any head orientation, while the other is specific to the head position in which adaptation occurred. Since our hypotheses were that otolith signals can serve as a context for gain adaptation and that activation of the otolith receptors varied as a continuous sine function of head orientation, we fitted individual values of gain changes as a function of head orientation (Fig. 1C) with the function $y=A\times\sin(x+B)+C$, where $A$ is the variation of gain as a function of head orientation re gravity or the gravity-dependent change, $B$ is the phase of head orientation where maximal changes occurred, and $C$ is the bias level of the sinusoidal fit, which represents the gravity-independent change.

Significance of the sine fit through the data was verified with an $F$-statistic (Yakushin et al. 1995). Sine fits through the residual gains, which were plotted as a function of head orientation, were compared with a horizontal line at the level of the average gain to test the significance of the gravity-dependent gain changes ($H_o$: no gain modulation occurs at $P<0.05$).

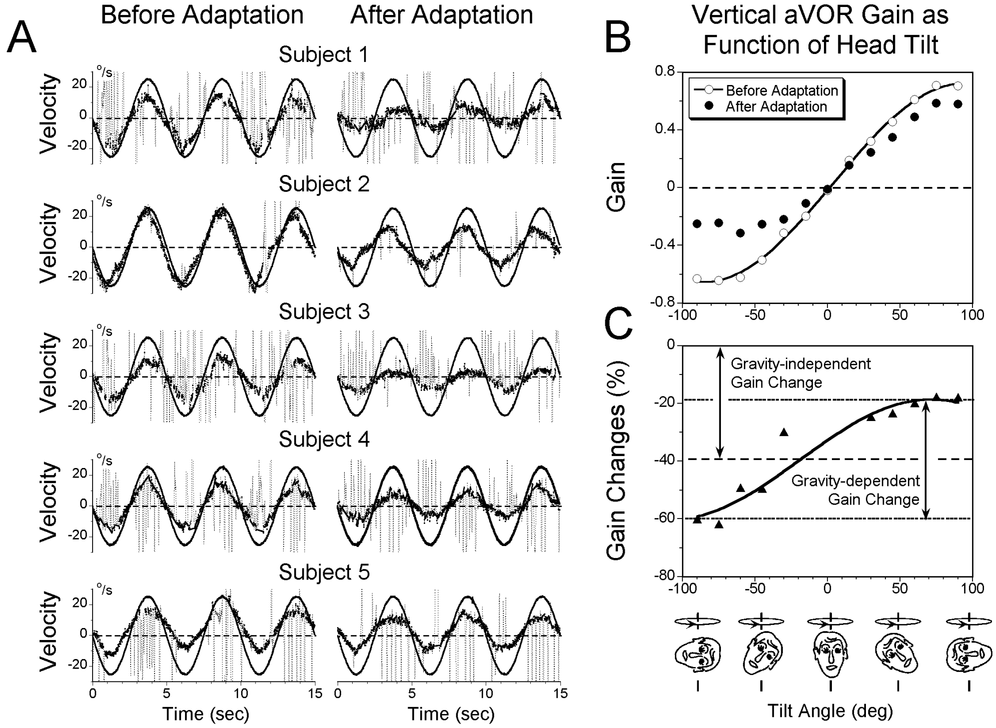

**Fig. 1A-C** Vertical angular vestibulo-ocular reflex (*aVOR*) gain changes after 1 h of gain decrease in left-side down (LSD) position. **A** Vertical (pitch) eye velocities induced in five subjects in LSD head orientation before (*left column*) and after (*right column*) gain decrease. **B** Gain of the vertical aVOR of one subject (shown in **A**, *top row*) before (*open circles*) and after (*filled circles*) adaptation plotted as a function of head orientation re gravity (*abscissa*). **C** Percentage changes in gain (shown in **B**) with regard to preadapted level, plotted as a function of head orientation re gravity. Data were fitted with a sine function (*solid curve*), whose amplitude and phase represents gravity-dependent vertical aVOR gain changes. The *dashed line* shows the bias, i.e., gravity-independent gain change. The *inserts* under **C** indicate representative head orientations re gravity during oscillation about spatial vertical axis used to test the vertical aVOR gains

## Results

Individual eye velocities evoked by sinusoidal oscillation about a pitch axis in the left side down (LSD) head orientation are shown in Fig. 1A (left traces). When the vertical aVOR gain was tested in various head orientations relative to the axis of rotation, the vertical gain was maximal when subjects were on their sides (Fig. 1B, open symbols) and decreased as subjects were reoriented toward the upright because of the decreasing stimulus to the vertical canals. The vertical aVOR gains as a function of head orientation were fitted with a sine function, whose amplitude is a measure of the spatial gain (Yakushin et al. 1995). The average spatial vertical aVOR gain was 0.57±0.16 (±SD) among subjects, varying from 0.43 to 0.79. This was similar to the vertical aVOR gains observed by others (Baloh et al. 1985, 1986; Clement et al. 1999).

After 1 h of gain adaptation in the left-side-down position, there was substantial reduction in vertical eye velocity when subjects were tested on the left side (Fig. 1A, right traces). When the vertical aVOR gains were plotted as a function of head orientation (Fig. 1B, filled circles), the gain reduction was greater with the left-side then with right-side down ($P<0.05$). The average reduction in gain on the side of adaptation was 47±13% (range 30–59%). On the opposite side (RSD), the reduction in gain was 14±5% (range 9–20%; *t*-test, $P<0.0003$). Thus, the gain reduction was greatest when the subjects were in the position in which the gain had been adapted.

Since vertical aVOR gain varied among subjects, the residual gain changes were expressed in percentages, plotted as a function of head orientation and fit with a sine function (Fig. 1C). After the aVOR gain was decreased in LSD (−90°), the gravity-dependent gain changes (*A*) varied from 12.9 to 28.2%, with a mean amplitude of 18.0±6.0%. The peak-to-peak effect of gravity on the vertical VOR gain was therefore 36%. The gravity-independent changes (*C*) were −29.0±10.0%, varying from −12.3 to −39.1%. The average phase of the gravity-dependent changes (*B*) was −116±35°, which was close to the head orientation in which the gain was adapted.

Four of the five subjects were retested within 3 days after adaptation. In one of the subjects, the gravity-dependent gain change was 28.2% just after adaptation (Fig. 2A, $P<0.01$). Adaptation persisted for longer than 24 hours and was 23.6% (Fig. 2B; $P<0.01$) and 6.5% (Fig. 2C, $P<0.025$) 1 and 3 days later. The gravity-independent changes were −30.7% in the day of adapta-

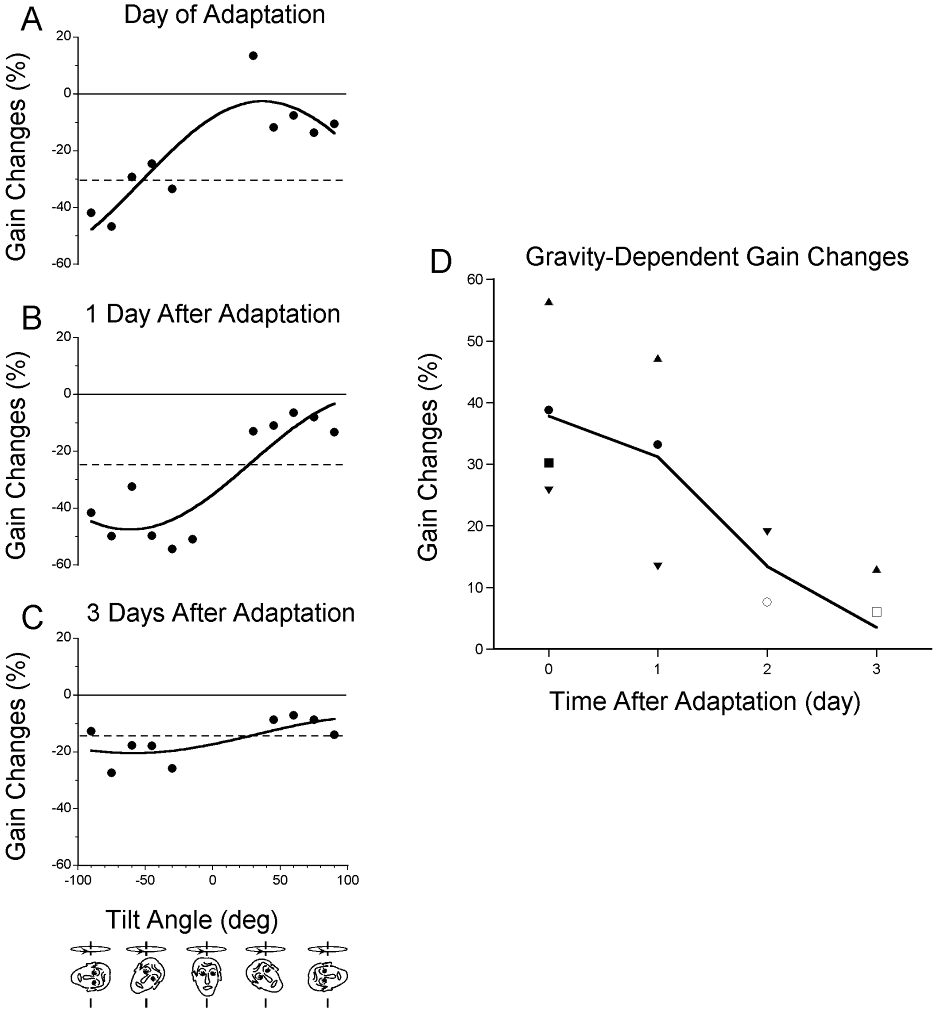

**Fig. 2A–D** Gain changes obtained in one subject within the 1st h (**A**) as well as 1 day (**B**) and 3 days (**C**) after the vertical aVOR gain was decreased in the left-side down position. The *solid line* is a sine fit through the data and the *dotted horizontal line* indicates the bias of the sine fit. **D** Gravity-dependent gain changes of the vertical aVOR at various times after adaptation. *Filled symbols* represent significant values

tion, decreasing to –23.8% and –13.9%, respectively, in the 1st and 3rd days after adaptation.

Changes in gain were significant in all three subjects when tested 1 day after adaptation ($P<0.05$; Fig. 2D). Two subjects were tested 2 days after adaptation, and two other subjects were tested 3 days later. Of this group, one of the subjects had significant changes on the 2nd and one on the 3rd day. Thus, gain changes that were produced by only 1 h of adaptation in a side-down position were maintained in all subjects for 1 day and sometimes longer, despite the fact that the subjects were free to move about in any orientation during this time.

## Discussion

We have demonstrated that a substantial portion of the adaptive change in the gain of the vertical aVOR in humans is dependent on the head orientation in which adaptive changes are induced. The gain changes are largest in this orientation and became progressively smaller as the head was moved away from this position. These data demonstrate that adaptation of the VOR is more complex than has previously been assumed, since the otolith system plays an important role in what has previously been assumed to be a pure semicircular canal-dependent function. The finding that the adapted VOR gain in any position is composed of both gravity-dependent and gravity-independent components suggests that there was probably a substantial gravity-dependent component in the gain changes observed in previous studies in which the subjects were tested in the same orientation re gravity as during adaptation.

The gain changes were well approximated with a sine function. We called the peak-to-peak amplitude of the sine fit the "*gravity-dependent gain change*," and the bias the "*gravity-independent gain change*." This formulation implies that a constant level of gain change is achieved by the nervous system in response to an adapting stimulus and that this level is then modulated by activity related to head position re gravity, probably largely derived from otolith activation. The average peak-to-peak gravity-dependent gain changes were about 36% in this study, which is higher than the 20–24% observed in the monkey (Yakushin et al. 2003). Despite this difference in amplitude, it seems clear that gravity-specific gain changes are a cross-species phenomenon.

The fact that alterations in gain were present starting from the first cycle of oscillation when subjects were brought into a new head position suggests that the gain changes relative to gravity had been stored. The site for the storage of the gravity-dependent gain changes is not known, but is probably located in the vestibular nuclei, since canal and otolith information converge on neurons, which are likely to be a part of the direct aVOR pathway (Kubo et al. 1977; Wilson et al. 1990; Angelaki et al. 1993; Bush et al. 1993; Endo et al. 1995; Kushiro et al. 2000; Ono et al. 2000; Sato et al. 2000; Uchino et al. 2000; Zakir et al. 2000). The vestibulocerebellum is also likely to be involved.

The finding that the adapted gain changes were preserved well beyond the time of the adaptation period, despite the fact that the subjects were free to move into any position in light or in darkness, has not been described before to our knowledge. In previous studies, the aVOR gain normalized within an hour after the subjects were brought back to their normal in-light condition even after several hours of adaptation (Istl-Lenz et al. 1985; Paige and Sargent 1991). A similar prolongation of adaptive changes has been shown for monkeys only if the head is kept immobilized. In this case, the changes in the gain can be observed for at least a week (Miles and Eighmy 1980). In the present study, however, there were significant gain changes over the 2 days after only 1 h of adaptation.

There are several possible explanations for the long-lasting adaptive changes of the vertical aVOR gain that were specific to the LSD head position. In daily life, the body is generally oriented upright, in a position where gravity-specific changes are minor. Data from the monkey support this idea, since, when the vertical aVOR gain was decreased in one side-down head orientation and increased with the other side down, gravity-dependent changes in gain in one head position had no effect on the gain changes in the other position (Yakushin et al. 2003). Since retinal slip drives adaptation, subjects may have made little or no head movement in light in the side-down position in which the gain changes were induced. This body orientation is usually assumed in bed where there is relatively little head movement or retinal slip that would require gain modification. This implies that similar long-lasting changes would not have been observed if the vertical aVOR gain had been adapted in the upright position. In future studies it would be of interest to adapt the vertical aVOR gain in upright position and see if the gain changes are similarly maintained.

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