Interaural Translational VOR: Suppression, Enhancement, and Cognitive Control

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Ramat, Stefano, Dominik Straumann, and David S. Zee. Interaural translational VOR: suppression, enhancement, and cognitive control. *J Neurophysiol* 94: 2391–2402, 2005. First published May 18, 2005; doi:10.1152/jn.01328.2004. We investigated the influence of cognitive factors on the early response of the interaural translational vestibuloocular reflex (tVOR) in six normal subjects. Variables were prior knowledge of direction of head motion and the position of the fixation target relative to the head [head-fixed (HF) or space-fixed (SF)]. A manually driven device provided a step-like head translation (~35 mm distance, peak acceleration, 0.6–1.3 *g*). Subjects looked at the SF or HF target located 15 cm in front of their heads in otherwise complete darkness. The testing paradigms were: *random* interleaving of SF and HF targets with *unknown* direction of head movement, *known* target location with *random* head direction (SFR or HFR), and *known* target location with *known* head direction (SFP or HFP). Timing was always unpredictable. A "gain" of the slow phase was calculated with respect to ideal performance (maintained fixation of the SF target, recorded/ideal eye velocity computed at time of peak head velocity). At such times, there were no significant differences in gain between HF and SF trials in the random condition; the average gain was ~36% of ideal. On the other hand, responses in the SFR and HFR conditions differed as early as 20 ms after the head began moving. Average gain was higher (0.43 ± 0.11 vs. 0.34 ± 0.14; means ± SD, *P* < 0.05) for each subject in the SFR than the HFR condition. For SFP and HFP, the responses differed from the onset of head motion. Average slow-phase gain was higher (0.49 ± 0.12 vs. 0.31 ± 0.12, *P* < 0.02) for each subject in SFP than in HFP. The timing of corrective saccades during the tVOR was also influenced by cognitive factors. Visual error signals seemed to be more important for triggering saccades in HF trials, whereas preprogramming, probably based on labyrinthine information, seemed to be more important in SF trials. Simulations showed that the changes in slow-phase gain with cognition could be reproduced with simple parametric adjustments of the gain of activity from otolith afferents and suggest that higher-level cognitive control of the VOR could occur as early as the synapse of peripheral afferents on neurons in the vestibular nuclei, either directly from higher level centers or via the cerebellum. In sum, the tVOR—both in its slow-phase response and the saccadic corrections—is subject to "higher-level" cognitive influences including knowledge of where the line of sight must point during head motion and the impending direction of head motion.

INTRODUCTION

Eye movements assure best vision by pointing the fovea at a target of interest and keeping its image stable there, whether the head is moving or still. To compensate for perturbations of the head, angular motion is detected by the semicircular canals and translational motion by the otolith organs, producing the rotational and the translational vestibuloocular reflex (rVOR and tVOR), respectively. Although the anatomical and physiological organization of the rVOR have been extensively studied, including its response to both predictable and unpredictable stimuli, much less is known about the tVOR. Here we focus on the tVOR response to interaural head translations.

Compensating for translation of the head requires a broad range of behaviors because the amplitude and even the direction of the response depend on the distance and the eccentricity of the target (Angelaki 2002; Busettini et al. 1994; Crane and Demer 1998; Moore et al. 1999; Paige 1991; Ramat and Zee 2003; Schwarz et al. 1989). The tVOR response is considerably undercompensatory, which may be related to the fact that the correct response of the tVOR to an identical pattern of head translation differs considerably depending on where the line of sight must be directed (Ramat and Zee 2003). Hence choice, salience, and other cognitive factors including knowledge of the impending direction of head motion and of the behavior of the fixation target might be expected to influence the tVOR.

The ability to suppress and enhance the rVOR has been investigated previously in both human and non-human primates. A rotational perturbation of the head during steady-state tracking was used to investigate short-latency suppression and enhancement of the rVOR in monkeys (Lisberger 1990). The ability to suppress and enhance the rVOR depending on the location of the target of interest relative to the head also has been investigated extensively in humans (Crane and Demer 1999; Furst et al. 1987; Gauthier and Vercher 1990; Huebner et al. 1992; Johnston and Sharpe 1994; McKinley and Peterson 1985; Vercher and Gauthier 1990). These studies show that the gain of the rVOR can be enhanced in trials when the target is space-fixed and diminished in trials when the target is head-fixed, but exactly how this occurs is uncertain. Johnston and Sharpe (1994) and Crane and Demer (1999) found that the rVOR gain was modifiable within the first 80 ms of the response, whereas Gauthier and Vercher (1990) found no differences between responses to head- and space-fixed targets within the first 150 ms. The timing of VOR modulation is key to understanding which mechanisms might be used by the brain to modify the response. Latencies for modifying the response that are >90–100 ms are compatible with a visual tracking mechanism, e.g., the smooth pursuit system, which could be triggered by the actual (or imagined) movement of a target. On the other hand, a lower latency of the modified (suppressed or

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enhanced) response would exclude a mechanism that is solely based on visual feedback and would suggest parametric changes in the central neural pathways that mediate the reflex.

It has been previously shown that during sinusoidal oscillations with fixation of real or of imagined head-fixed targets, the tVOR can be modified by nonvisual mechanisms but only at relatively low frequencies (<4 Hz) (Paige et al. 1998). The ability of the brain to adaptively enhance or suppress the response of the tVOR was investigated by Gianna et al. (1997) using large-field visible targets (space- and head-fixed) and transient accelerations (0.17 and 0.08 *g*). They found that the response to head-fixed targets differed from space-fixed targets within times that were only slightly longer than the latency of the response itself. They concluded that the attenuation of the response to head-fixed targets "was observed from the earliest stages of the response." It has also been hypothesized (Gianna et al. 1997; Ramat and Zee 2003) that the gain of the tVOR can be preset to a value depending on contextual information (e.g., the initial position of the target relative to the head and the initial position of the eye in the orbit). More recently, using higher frequency and acceleration stimuli, Crane et al. (2003) reported that cancellation effects were seen at latencies of 33–87 ms after stimulus onset, with a decrease in latency as the target became closer to the subject until the closest distance (15 cm) when the latency of the cancellation effect began to increase again.

Because of the limited information about the modulation of the tVOR by visual and cognitive factors, we reexamined the ability of the brain to enhance or suppress the tVOR response using a space- or head-fixed target, respectively. Here we sought to clarify the issues relative to the timing of such modulation and how it is affected by prior knowledge of the direction of head motion and the location of the target of interest relative to the motion of the head. To see the effects more clearly, we opted for high transient accelerations and close targets, which lead to a relatively robust slow-phase response (e.g., Ramat and Zee 2003).

METHODS

Normal subjects

Six normal subjects (ages between 19 and 56, 1 woman and 5 men) with normal vestibular function and no eye-movement abnormalities participated in this study. All subjects gave informed consent before participating in the experiment. The protocol was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins University School of Medicine. Four subjects (*S1, S2, S5,* and *S6*) were naïve to the protocol and to the goals of the study. Subjects who used corrective spectacles did not wear them during recording of eye movements but were able to see the fixation targets clearly.

Recording of eye and head movements

The movements of both eyes and the head were recorded around all three axes of rotation (horizontal, vertical, and torsional) using the magnetic field search coil method with dual coil annuli. The output signals of the coils were filtered with a single pole RC analog filter with a bandwidth of 0–90 Hz, and then sampled at 1 kHz with 12-bit resolution. Head rotations were sensed with a search coil embedded in the bite bar. The head search coil was calibrated in vitro as for the eye annuli. System noise was limited to 0.1°. Data were stored on disc for later off-line analysis using Matlab (Mathworks). The details of the calibration and eye-movement recording procedures have been described previously (Bergamin et al. 2001; Ramat and Zee 2003).

Head movements were also recorded with a 6 dof miniBIRD device (bandwidth of 144 Hz, manufactured by Ascension Technology) that determines the position and orientation of a receiver with respect to a transmitter. The receiver was embedded in the bite bar worn by the subject (as was the head rotation search coil), while the transmitter was fixed in space at a distance of ~35 cm from the subject. The bite bar prevented any concurrent rotation of the head around the yaw axis that might have lead to a confounding, compensatory slow phase for angular motion. The resolution of the miniBIRD device was 0.5-mm RMS for position and 0.1° RMS for orientation, at 30 cm from the transmitter (manufacturer's specification). Static position accuracy was 1.8-mm RMS averaged over a range of ±75 cm in any direction. Head translation was also measured with a linear accelerometer attached to the bite bar; the resulting signal was sampled at 1 kHz and then recorded. The accelerometer signal was integrated, and the resulting head velocity was used to detect the onset of head motion as well as to confirm the accuracy of the translational signal recorded by the miniBIRD device. The accelerometer signal was also used on-line to turn off one of the two targets during the RND paradigm (see *Experimental paradigms*).

The scleral coils were placed on each eye after application of a topical anesthetic (proparacaine HCL 0.5%, Alcaine). The head of the subject was centered in the field coils precisely, using two space-fixed, horizontally and vertically oriented laser beams emanating from the location of the zero-position light-emitting diode (LED) so that the center of the interpupillary line coincided with the center of the field coils and the interpupillary line was parallel to the earth horizontal. The position recorded by the miniBird device when the subject was centered in the fields was considered as the reference position for measures of both rotational and linear head movement.

To deliver quasi-reproducible translational stimuli along the interaural axis, we used a "head sled" device (Ramat et al. 2001), which has the advantage of a low inertia compared with whole body sleds. The head sled device consists of two Plexiglas plates that can be connected together and tightened on the sides of the head of the subject. Padding material is inserted between the ears of the subject and the Plexiglas plates for comfort. Two square section rods are rigidly attached to the external sides of the two plates providing the guide rail for the motion of the device, which can slide en bloc along the subject's interaural axis. A detailed description of the characteristics and repeatability of the stimuli and of the reliability of the measurement of the motion of the head was reported previously (Ramat and Zee 2003).

Experimental paradigms

Subjects were asked to fix on a laser spot target just before and as their head was being translated along the interaural axis. Visual targets were projected as a red laser dot (3 mm diam) onto a translucent screen. The target remained illuminated throughout the trial. The room was in otherwise complete darkness. Trials were performed at a single viewing distance with the target at 15 cm in front of the eyes of the subject. Prior to each head movement, we verified that the subjects were binocularly fixating the target by computing the intersection of the line of sight of the two eyes. Each trial began with the laser target aligned with the midsagittal plane of the subject. To prevent anticipation stimuli were delivered with random timing.

We used five different paradigms involving different degrees of predictability of the position of the target relative to the translation of the head and the direction of translation: RND: random head movement direction and target unpredictably head-fixed (RndHF) or space-fixed (RndSF); HFR: random head movement direction with a head-fixed target; HFP, predictable head movement direction with a head-fixed target; SFR: random head movement direction with a

space-fixed target; and SFP: predictable head movement direction, with a space-fixed target.

To provide a compelling stimulus for the RND paradigm in which the subject could not predict the behavior of the target, we used two lasers: one attached to the head sled structure and the other to the structure holding the chair on which the subjects were seated. The lasers were arranged so that when the head of the subject was in the starting position (monitored through a computer driven display), the two lasers projected superimposed dots on the translucent screen. The computer turned on the two lasers only when the head of the subject was held still in the starting position for a minimum of 0.5 s. Using a threshold based on the accelerometer signal, the computer randomly switched off one of the two lasers as the head of the subject was translated in one direction or the other. None of the subjects was consciously able to perceive the existence of two targets.

In the rest of the paradigms only one laser, either head-fixed or space-fixed, was on.

Analytical techniques

CALCULATION OF EYE MOTION. Using the maximum field values from the in vitro calibration of the eye and head coils, rotation matrices were generated and then transformed into rotation vector coordinates (Bergamin et al. 2001). The angular positions of each eye coil (relative to spatial coordinates) were calculated from the rotation vectors. To calculate the angular velocity trajectories, a fifth-order 100-Hz low-pass finite impulse response (FIR) filter was first applied to the rotation matrices. The resulting data were differentiated using a fifth-order REMEZ (Matlab) FIR filter, designed to differentiate the data ≤40 Hz and to low-pass filter the data >100 Hz. The differentiated data were then used with the undifferentiated, filtered data to calculate angular velocity (Hepp 1990). To calculate angular acceleration, the angular velocity data were differentiated with the same fifth-order REMEZ combination differentiator and low-pass filter. All the eye-movement responses refer to the displacement of the cyclopean eye, computed as the average of the right and left eye, from its position at the beginning of the head movement.

CALCULATION OF HEAD MOTION. To calculate the motion of the head, we used six coordinates describing the position and the orientation of the head of the subject: three angles from the bite bar coils, describing head orientation with respect to the magnetic fields, and three linear coordinates from the miniBIRD receiver in the bite bar, describing the position of the subject with respect to the space-fixed coordinate system originating from the transmitter. Using the instantaneous position of the head in space and of the visual target, we were able to compute the instantaneous ideal eye position of the eyes in the orbit needed to maintain perfect fixation of the visual target, following the technique detailed in Ramat et al. (2001).

Analysis of responses

The ideal movement of the eye in the orbit in response to head translation was compared with the recorded position of the eye in each trial. Because the head-sled stimulus moves the head from the center of the magnetic fields, it could produce a spurious change in the eye position signals (Ramat and Zee 2003). The error in our gain measurements introduced by artifacts related to head movement in the magnetic fields was at most 2% (0.15° at the time of the gain measurements). This factor was therefore disregarded in the subsequent analysis.

Using the procedure described in the preceding text, we computed the ideal behavior of the tVOR and evaluated its performance as the ratio of recorded eye (angular) velocity/ideal eye (angular) velocity over a 20-ms interval centered at the time of peak head (linear) velocity. Trials containing a saccade occurring prior to the time of measurement of gain were excluded from the analysis for all gain

measures, although they were considered in other aspects of the analysis. The detection of the onset of movement of the head, which was used to align data for the computation of the mean trial trace, was based on fitting the head position data with a piecewise polynomial waveform composed of a constant value followed by a quadratic function. The switching between the two functions was constrained to correspond to the vertex of the parabola and was chosen as the onset of the head movement (Ramat and Zee 2003).

We computed the onset of the eye movement based on the mean response to the mean stimulus: we averaged the responses to those head movements that were within 1 SD from the mean head trace and then used a 3-SD technique to determine the latency of the mean eye-movement response (Ramat and Zee 2003). This procedure allowed us to compute mean eye-movement traces based on a subset of the head movements that were most alike (a minimum of 7 trials were used for this calculation and in most cases (90%) more than 7).

Saccades were detected by an automatic procedure based on velocity thresholds, and their beginning and end were interactively validated by the experimenter. In all of the slow-phase gain analysis, we considered only trials in which corrective saccades occurred after the time of measurement of gain. On average, in <6% of trials was a saccade triggered before the time of peak head velocity. In reporting the latencies and amplitudes of saccadic corrections, only the first saccade in each trial was considered. Saccade latencies were computed with respect to the onset of the head movement.

Statistical significance was assessed using ANOVA or the Wilcoxon rank-sum tests depending on whether or not the distribution of observations was Gaussian. Unless otherwise indicated, results were considered to be significant at $P < 0.05$.

RESULTS

We will first describe the characteristics of the stimulus, then the morphology and general characteristics of the response in each experimental condition. We will consider both the slow-phase response and the first corrective saccade produced in each trial. Finally we will compare the responses across conditions within each subject.

Combining all subjects in all conditions and both directions, head displacement averaged 3.5 ± 0.4 cm and peak head velocity averaged 36 ± 4 cm/s. Peak head acceleration averaged 0.90 ± 0.19 g and ranged (90% confidence interval) between 0.56 and 1.27 g. Head movements lasted on average 220 ± 30 ms and reached peak velocity 90 ± 14 ms after their onset.

Random (RND) paradigm

During the random paradigm for each subject, ≥40 head movements were applied in each direction. The timing, direction, and whether the target was head- or space-fixed were not predictable.

Figure 1 shows a typical response in the RND paradigm. The ideal and recorded eye positions—normalized with respect to ideal eye position—are shown for *subject S5*. Traces corresponding to trials in which the fixation target was space-fixed are recognized easily by a forward corrective saccade because the slow-phase response was undercompensatory. Conversely, trials in which the fixation target was head-fixed are recognized by a backward corrective saccade.

The response to both target configurations was similar. There was an initial slow-phase eye movement in the orbit in the direction opposite to that of the head. This was followed by a corrective saccade, usually in the appropriate direction to
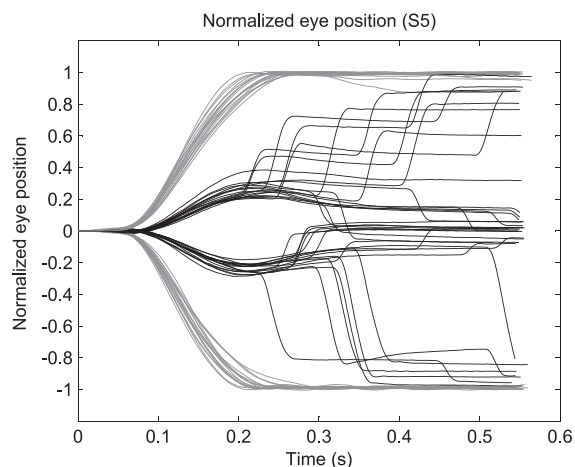
Normalized eye position (S5)

FIG. 1. Representative set of responses in 1 subject (*S5*) to the random (RND) paradigm. Responses are normalized with respect to the maximum deviation of the ideal eye movement allowing fixation of a stationary target. Gray traces: ideal eye movements. Black traces: recorded eye movements. Responses to space-fixed targets can be recognized by a corrective saccade in the direction of the undercompensatory slow phase. Responses to head-fixed targets, by a corrective saccade directed back toward the center position of the eye in the orbit.

allow target refixation. For this subject, peak head velocity was reached at 87 ms after movement onset.

Medians and 25th and 75th percentiles of slow-phase gains in response to the RND paradigm are shown in Fig. 2 for each subject. The slow-phase gain was 0.36 ± 0.12 during space-fixed and 0.36 ± 0.09 during head-fixed trials. There were no significant differences in gain between head- and space-fixed trials for any subject ($P > 0.3$). When pooling data from all subjects, saccadic corrections occurred significantly sooner ($P < 0.01$) during space- than head-fixed trials (250 ± 80 and 292 ± 84 ms after the onset of the head movement, respectively). On a subject-by-subject basis, saccadic latencies were significantly lower ($P < 0.03$) during space-fixed than head-fixed trials in three (*S1–S3*) of the six subjects.

Space-fixed target, unpredictable head motion (SFR)

The responses to the SFR paradigm were qualitatively similar to the responses during those trials in the RND paradigm in which the target was space-fixed with corrective saccades still

being present for almost all trials. The mean response to the SFR condition is shown for each subject in Fig. 3 (red traces). The overall mean slow-phase gain was 0.43 ± 0.11 averaged over all subjects. The latency of the slow phases averaged 22 ms and ranged between 12 and 32 ms. Considering all subjects, average saccade latency was 186 ± 52 ms. The mean amplitudes of corrective saccades averaged $4.0 \pm 1.3°$ (Fig. 4).

Space-fixed target, predictable head motion (SFP)

The mean response to the SFP paradigm is shown in Fig. 3 by the light blue trace. This paradigm differed from the SFR paradigm because the subjects knew beforehand in which direction the head would be translated. Head movements were delivered at random times in two sets of 15 stimuli having the same direction with a slower return to the starting position between each trial. Although morphologically similar to the responses to the SFR condition, the initial slow-phase response in the SFP paradigm increased its velocity and diverged from the response in the SFR paradigm as early as 50 ms after the head began moving (Fig. 3). The onset of the overall response had a mean latency of 16 ms and ranged from 8 to 26 ms. Combining data from all subjects the overall mean slow-phase gain was 0.49 ± 0.12. Corrective saccades were still present in >95% of the trials. Mean latencies ranged between 145 and 201 ms with the mean across subjects being 177 ± 51 ms. The mean amplitude of corrective saccades over all subjects was $3.9 \pm 1.5°$.

Head-fixed target, unpredictable head motion (HFR)

The ideal response in the head-fixed paradigm, of course, would be no response at all: a total suppression of the tVOR. Nevertheless, all subjects showed a tVOR response to head movement, which moved the fovea away from the fixation target. The mean response in the HFR paradigm is shown for each subject in Fig. 3 (dark blue traces). The initial response was morphologically similar to the response in the SFR paradigm. In fact, three subjects (*S3–S5*) also showed occasional (<5%) saccades in the direction normally compensatory for head motion (as if they were preprogrammed), thus impairing fixation of the head-fixed target even more.

Using the mean value for all trials for each subject, latencies averaged 26 ms and ranged between 22 and 35 ms. Across all
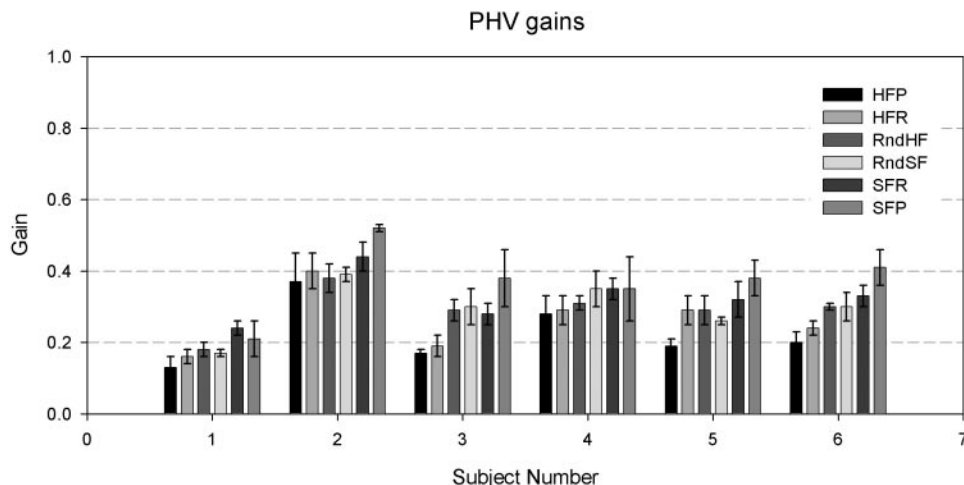
PHV gains

FIG. 2. Histograms of slow-phase gains for each subject in the different experimental conditions. The height of each bar shows the median of the represented data, while error bar extends between the 25th and 75th percentiles. Each group of columns represents data from one subject. For each subject the graph shows (left to right) head-fixed target, predictable head motion (HFP); head-fixed target, random head motion (HFR); head-fixed target trials during the random condition (RndHF); space-fixed trials during the random condition (RndSF); space-fixed target, random head motion (SFR); space-fixed target, predictable head motion (SFP) conditions.
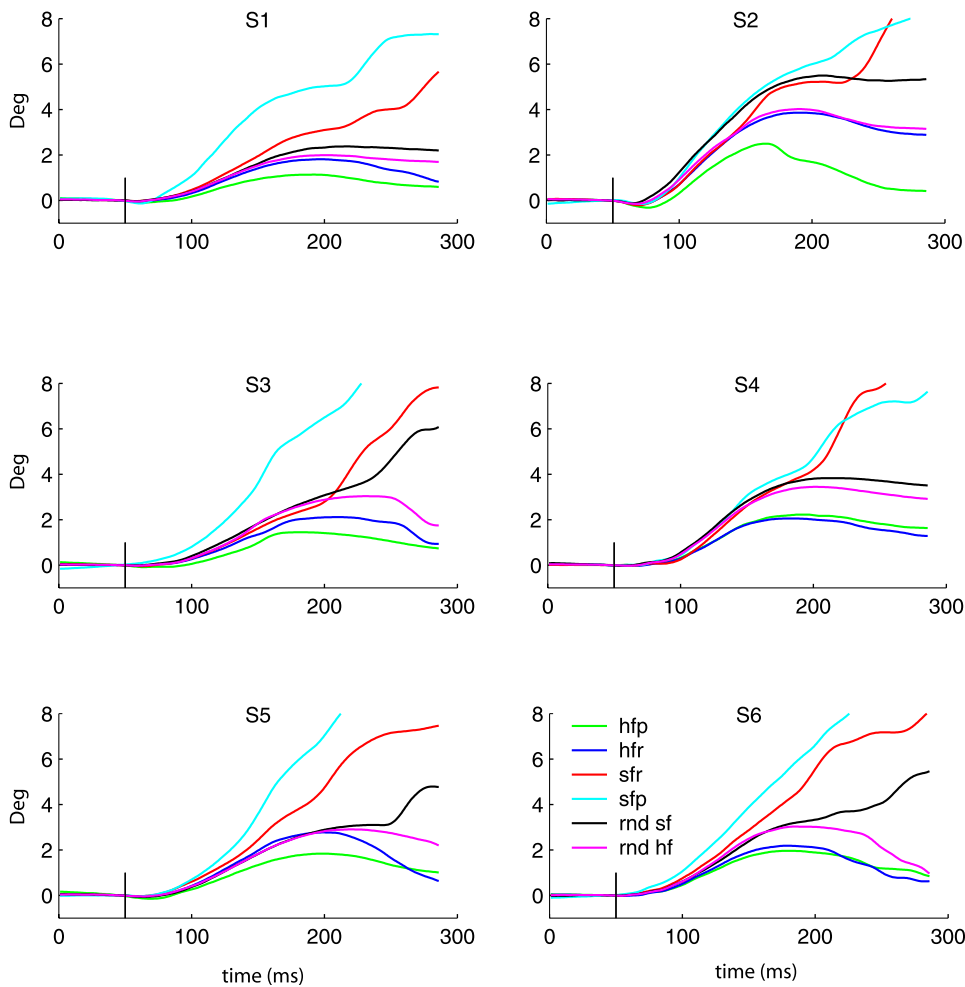
FIG. 3. Mean traces of the responses to each experimental condition. Each panel represents 1 subject. HFR, HF target, random head direction; SFR, SF target, random head direction. Two traces are shown for the RND condition representing the mean of the trials in which the target was HF (magenta trace, RndHF) and the mean of the trials in which the target was SF (black trace, RndSF).

subjects, the overall mean gain was 0.34 ± 0.14. Corrective saccades occurred in 83% of all trials and were usually in the anticompensatory direction for head motion, thus in the direction appropriate for target refixation. Over all subjects, the average saccade latency was 270 ± 81 ms. The mean amplitude of corrective saccades over all subjects was 1.3 ± 0.8°, excluding the occasional saccades made in the wrong direction.

Three subjects (*S1, S2,* and *S4*) showed a progressive reduction of the slow-phase gain of the response in at least one direction of head movement, implying a form of motor learning. A representative example, from *subject S5* is shown in Fig. *5A.* The correlation coefficient of a linear regression of the gain with the repetition number in these three subjects ranged between 0.4 and 0.6.

Head-fixed target, predictable head motion (HFP)

The mean response to the HFP paradigm is shown in Fig. 3 with the green traces. During the HFP trials, subjects were aware of the direction of head movement beforehand, and trials were delivered in sets of 15 head movements in the same direction with a slower return to the starting position between each trial. Knowledge of both target location and head-movement direction was not sufficient to suppress completely an initial slow-phase response in the direction that is usually compensatory for head motion. Across subjects, the latency of the compensatory slow phase averaged 42 ms and ranged

between 25 and 51 ms. The mean slow-phase gain across all subjects was 0.31 ± 0.12.

The initial slow phase was followed by a saccade in the (correct) anticompensatory direction in ~67% of the trials, pooling all data from all subjects. Mean saccade latencies ranged between 218 and 396 ms with an overall mean of 281 ± 92 ms over all subjects. Mean saccade amplitude over all subjects was 0.7 ± 0.6°.

Four of the six subjects (all but *S1* and *S4*) showed a progressive reduction of the gain of the response with the repetition of the stimulus over the course of the trials imposed in each of the two directions (Fig. *5B*), implying a form of short-term motor learning. Linear regression analysis of gain values versus stimulus number yielded correlation coefficient (r^2) values ranging from 0.5 to 0.7.

Comparison among paradigms

The mean responses to head and space-fixed trials recorded during the RND paradigm are also shown in Fig. 3 (magenta and black traces respectively). Only *subject S2* showed an appreciable difference between the responses to the two conditions within 100 ms of the onset of the head movement (see also Fig. 3). For each subject, responses to the experimental paradigms that provided a priori information on the required eye movement—using knowledge of either the direction of head movement or the location of the target with respect to the
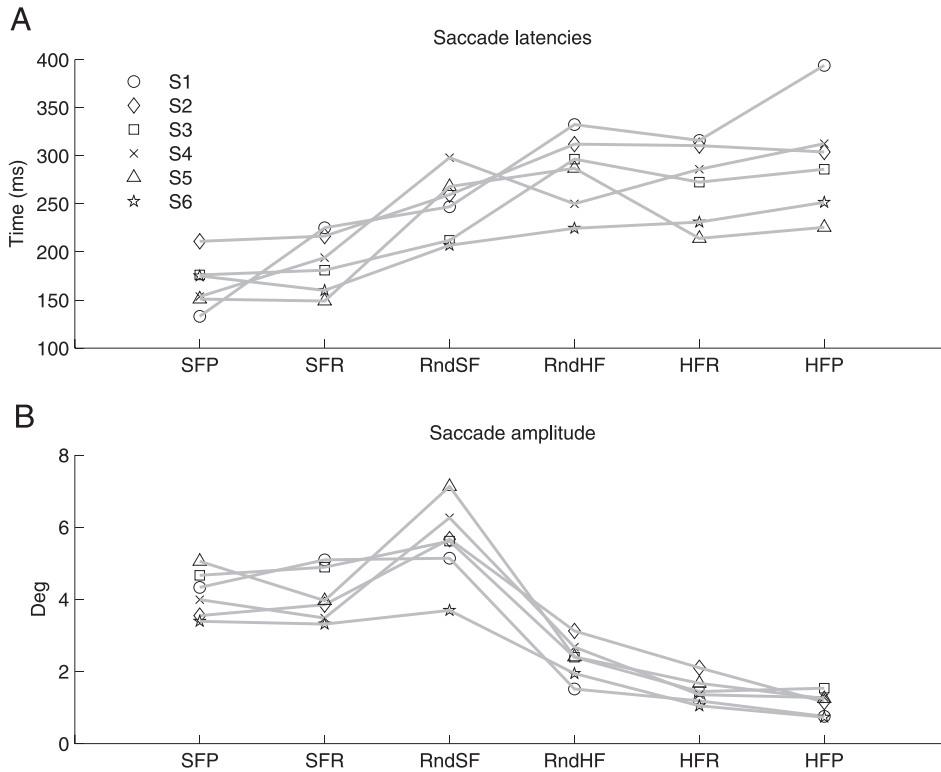
A

B

FIG. 4. Corrective saccades. *A*: latency of corrective saccades during responses to each experimental condition. *B*: amplitude of corrective saccades. Each different symbol represents data from a different subject. In abscissa (left to right) are SFP, SFR, RndSF, RndHF, HFR, and HFP experimental conditions.

head movement—were markedly different among conditions. The overall picture of slow-phase gains for each subject in each experimental condition is shown in Fig. 2. The height of the bars represents the median gain value and the extremes of the black line show its 25th and 75th percentiles. Gains were not significantly larger in the subset of space fixed trials with respect to the head fixed trials during the RND paradigm (RndSF and RndHF, respectively). Figure 2 shows that in all subjects the gain was lowest in response to the HFP paradigm followed, in increasing value of gain, by the HFR, SFR, and SFP paradigms. On a subject-by-subject basis, slow-phase gains were significantly higher during SFP than SFR trials in 4/6
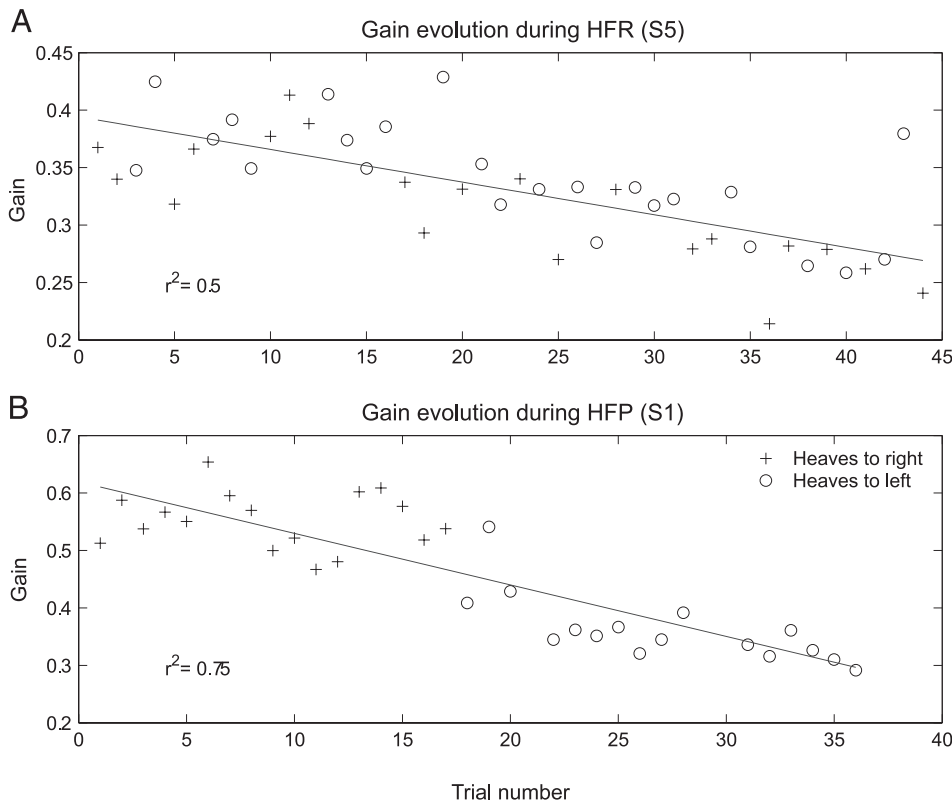
A

B

FIG. 5. Short-term learning in translational vestibuloocular reflex (tVOR) responses, examples from 2 subjects. *A*: temporal evolution of slow-phase gain in *subject S5* during HFR paradigm. *B*: temporal evolution of slow-phase gain in *subject S2* during HFP paradigm. $+$ and $\bigcirc$, gains of responses to head movements to the right and to the left, respectively. Continuous line: linear regression. r^2: correlation coefficient of the regression shown. Note that in HFR paradigm right- and leftward head movements are mixed, whereas in HFP paradigm, a set of leftward stimuli follows a set of rightward ones.

subjects (all but S1 and S4); SFR gains were significantly higher than HFR for all subjects, and HFR gains were significantly higher than HFP gains in 4/6 subjects (all but *S2* and *S4*).

The latency of the initial compensatory slow phase was the largest in the HFP paradigm (mean: 42 ms) and the smallest in the SFP paradigm (mean: 16 ms) for all subjects but *S4,* who showed no significant differences across the different paradigms.

The latency of the corrective saccades was significantly greater during responses in the two paradigms calling for suppression (HFP and HFR) than during the paradigms in which the target was fixed in space (SFR and SFP). The mean latency of the corrective saccade is shown for each subject in each experimental condition in Fig. 4*A*, whereas *B* shows the same for saccade amplitudes. In both panels, each different symbol represents a different subject. The latency of corrective saccades during the RND paradigm was significantly larger in RndHF compared with RndSF for three of six subjects. Likewise, the latency of corrective saccades in response to RndHF was significantly larger than that during the SFR paradigm in five of the six subjects (all but *S4*).

Figure 4*B* shows that all subjects produced significantly smaller saccades during head-fixed trials (HFP, HFR, and RndHF) than during space-fixed trials (SFP, SFR, and RndSF). During space fixed trials, only one subject (*S5*) showed significantly different (larger) saccades in response to the SFP than to SFR, whereas corrective saccades in the RndSF paradigm were significantly larger than during the SFR paradigm in four of the six subjects (all but *S1* and *S3*). All subjects showed significantly larger saccades during the RndSF than the RndHF paradigm, whereas during the RndHF paradigm, saccades were larger than during the HFR paradigm in three subjects. Corrective saccades in the HFP paradigm were smaller than in the HFR paradigm in four of the six subjects.

In four subjects, the latency of the first corrective saccade significantly decreased as the trial number increased during the SFR paradigm, again suggesting a form of short-term motor learning. No significant correlation with time, however, was found for saccade amplitude.

DISCUSSION

Here we investigated the ability of the brain to enhance and suppress the tVOR response to brief (~220 ms), high-acceleration (0.56–1.27 *g*) interaural head translations while viewing a near (15 cm) target. Previous reports (Crane et al. 2003; Gianna et al. 2000) have shown the ability to attenuate the response of the tVOR at different viewing distances using relatively low (0.08 and 0.17 *g*) or somewhat higher (0.47 *g*) interaural accelerations and compared responses to sets of head- and of space-fixed targets. Our study extended those experiments to considerably higher accelerations in addition to investigating the effects of expectation in the modulation of the tVOR. We compared trials in which subjects had no information about target location or the direction of head motion (RND) with trials in which subjects knew the location of the target relative to the head but not the direction of head motion (HFR and SFR), and, finally, with trials in which subjects knew both the location of the target and the direction of head motion (HFP and SFP). The main finding is that the pattern of both the initial slow-phase response and subsequent corrective saccades

was influenced by the expectation of where the target would be located during head translation and the predictability of the direction of head motion.

When the subject knew the position of the target relative to the head, the brain was able to modulate the tVOR slow-phase response by attenuating the response in head-fixed and enhancing the response in space-fixed target conditions. This was true even when the tVOR was evoked with the higher accelerations and closer stimuli used in our experiments. Just as previous results on suppression of the rotational VOR, we have shown that the tVOR response can be both *enhanced and suppressed* by cognitive factors.

We have also shown that only when the subjects had a priori information about the position of the target and/or direction of the movement of the head was the modulation of tVOR within times that are shorter than the latency that would be necessary for visual information to produce pursuit (~90–100 ms) eye movements that might modify the response. In other words, the latency of the divergence between HF and SF trials was lower than the presumed visual latency in all conditions but RND, during which the slow-phase responses were not significantly different between the head- and space-fixed target trials over the first 100 ms (5/6 subjects). The mean eye-movement responses of the head- and of the space-fixed trials during the RND trials are grouped as shown in Fig. 3 (magenta and black traces respectively). Only one subject (*S2*) showed an appreciable difference between the two conditions within the first 100 ms of the response. The slow-phase responses in the RND paradigm usually fell between those in the HFR and SFR condition (in 4/6 subjects, Fig. 3).

On the other hand, changes in the gain of the tVOR were significantly different in all subjects when they knew where the target would be located or knew both the target location and the direction in which the head was going to move. Furthermore, when subjects knew where the target was going to be, responses were significantly larger during SFR than during HFR trials within the first few milliseconds of the response. The lowest gains were measured in responses to HFP trials, in which the additional knowledge of the direction of the head movement allowed subjects to further reduce their responses. Most subjects (4/6) were also able to significantly increase the gain of the slow-phase response during SFP compared with SFR trials, although all responses were still undercompensatory.

Mathematical model

We next asked where within the neural circuitry of the tVOR cognitive influences could affect the early slow-phase response. To explore possible mechanisms, we investigated the relationship between the input signal to the tVOR, head acceleration and its output signal, eye position using a mathematical model of the tVOR. The model does not include a saccadic mechanism, and we did not attempt to explain the modulation of saccadic corrections by cognitive factors. We did ask, however, if the modulation of the tVOR by intent could be explained simply by parametric control of a gain factor either modulating the transmission of primary otolith afferent activity to more central structures, or, for comparison, in the central neural integrator that has been considered as part of the tVOR circuitry (Angelaki et al. 2001). Previous studies of adaptation

of the tVOR have suggested that the neural integrator might be involved (Hegemann et al. 2000). The details of our model and the simulations are presented in the APPENDIX.

The main conclusion of these simulations is that the gain of the transmission of primary otolith signals from the labyrinth to the brain stem is a plausible site for the modulation of the tVOR by cognitive factors. A similar mechanism has been suggested for modulation of afferent activity from the semicircular canals to adjust the gain of the angular VOR for viewing distance (Chen-Huang and McCrea 1999) and for active versus passive head motion (Cullen and Roy 2004). While this does not establish the anatomical structures in which the modulation takes place, it suggests that the higher level cerebral cortical mechanisms that mediate anticipation and prediction might have access to low-level VOR circuits, either directly at the vestibular nuclei or through cerebellar pathways that modulate activity in the vestibular nuclei. Indeed, there is considerable anatomical evidence for projections from the cerebral cortex to the vestibular nuclei (Akbarian et al. 1994; Fukushima 1997), and of course, to the cerebellum.

tVOR learning

Our results in the HFP paradigms also support the hypothesis that, provided the required response is known, the brain can progressively reduce the response of the tVOR slow-phase through a short-term learning process that takes place in as few as 10–15 trials. In a paradigm designed specifically to elicit motor learning, Zhou et al. (2003) showed that monkeys undergo relatively rapid tVOR learning and that the locus may be in the sensorimotor transformation stage of the tVOR. In our experiments because there was no difference in the gain of the slow phases between the head- and space-fixed trials during the RND paradigm, it is unlikely that the progressively altered tVOR response was related to rapid immediate processing of visual information to modify the first 100 ms of the tVOR response. Rather some type of motor learning, akin to what Zhou et al. reported, seems likely. We also observed a gradual decrease in the latency of the corrective saccades in the RndSF paradigm implying that the saccadic system, too, can undergo an adaptive change in latency that improves gaze stability during head translation. Similar changes in saccade latency during short-term saccade adaptation have been shown in monkeys with dorsal vermis cerebellar lesions (Takagi et al. 1998). In our experiments, we cannot exclude that subjects adopted a cognitive strategy to change their tVOR response rather than undergoing motor learning based on neural plasticity in the more traditional sense. Clearly, additional experiments specifically designed to test motor learning in the tVOR are needed to address the role of cognitive factors in the adaptive control of the tVOR.

Corrective saccades and cognitive control of the tVOR

As previously demonstrated by ourselves and by others (Ramat and Zee 2003; Ramat et al. 2001; Tian et al. 2002), corrective saccades are a fundamental part of the response to translations during near target viewing. In our previous work, we showed that such saccadic corrections were symbiotic to the tVOR slow phase; their amplitude varied with varying viewing distances and roughly compensated for the same fraction of the required eye movement. The results presented here show that such a symbiosis is preserved in the response to experimental conditions in which the magnitude of the tVOR response is modified by cognitive factors.

We found that five of six subjects showed smaller latencies (and larger amplitudes in 4 of 6) for the first corrective saccade in the SFR paradigm compared with the RndSF trials of the RND paradigm. This finding argues for a component of pre-programming of corrective saccades in the SFR paradigm as their timing appears to be influenced by the knowledge of the position of the target relative to the head. Conversely the large difference in saccadic amplitudes between the head- and space-fixed conditions during the random trials (i.e., RndSF vs. RndHF) argues for visual information being rapidly available to influence the timing and the direction of the corrective saccade.

It is important to note that the standard paradigm for assessing tVOR function in previous reports is equivalent to our SFR paradigm. Our results show a significant effect of the predictability of the stimulus in reducing the latency of the first corrective saccade. Thus in prior experiments in which the target was always space-fixed, it is conceivable that the timing of the first corrective saccade had been underestimated, from its "true" value in the unpredictable RND paradigm.

We also examined the effect of the retinal position error on the saccade correction mechanism, computing the absolute value of the difference between the ideal and the recorded eye position at saccade onset. Figure 6A shows the mean values of these errors for each subject in each experimental condition. The errors at the onset of the saccade corrections are larger in the three target space-fixed than in the three target head-fixed conditions. This result was similar to the relationship between the different paradigms and saccadic amplitudes (Fig. 4B). We thus computed the regression coefficients of saccadic amplitudes versus the error at the onset of the saccade for each experimental condition, pooling the data for all subjects (Fig. 6B, □). The correlation was relatively low for the SFP and SFR trials (~0.25 and 0.33, respectively) but increased up to ~0.75 for the RndSF trials, 0.7 for the RndHF trials, and ~0.6 for both HFR and HFP. These findings, with the generally longer latency for the known head-fixed conditions (Fig. 4A, HFR and HFP) suggest that the brain uses different strategies for programming saccade corrections in the space-fixed trials (the most common situation in real life conditions) than in the head-fixed trials. One interpretation is that saccadic corrections during the space-fixed trials may be largely driven by the vestibular signals [the VCUS, vestibular catch-up saccades, previously reported in the literature for both angular (Halmagyi et al. 1990; Peng et al. 2004; Tian et al. 2000) and linear (Tian et al. 2002, 2003) vestibular stimuli] while saccadic corrections during the head-fixed paradigms may be largely visually driven. During the random paradigms, there may be some combination, depending on how early information is received from the visual system. This hypothesis is supported by a second set of correlation coefficients for the relationship between the gain of the vestibular slow phase and the amplitude of the corrective saccades. The negative correlation coefficient for the SFP condition indicates that part of the saccade programming in these conditions takes into account a low tVOR gain and so produces larger saccades. The figure also shows that during HF trials larger tVOR gains produced instead
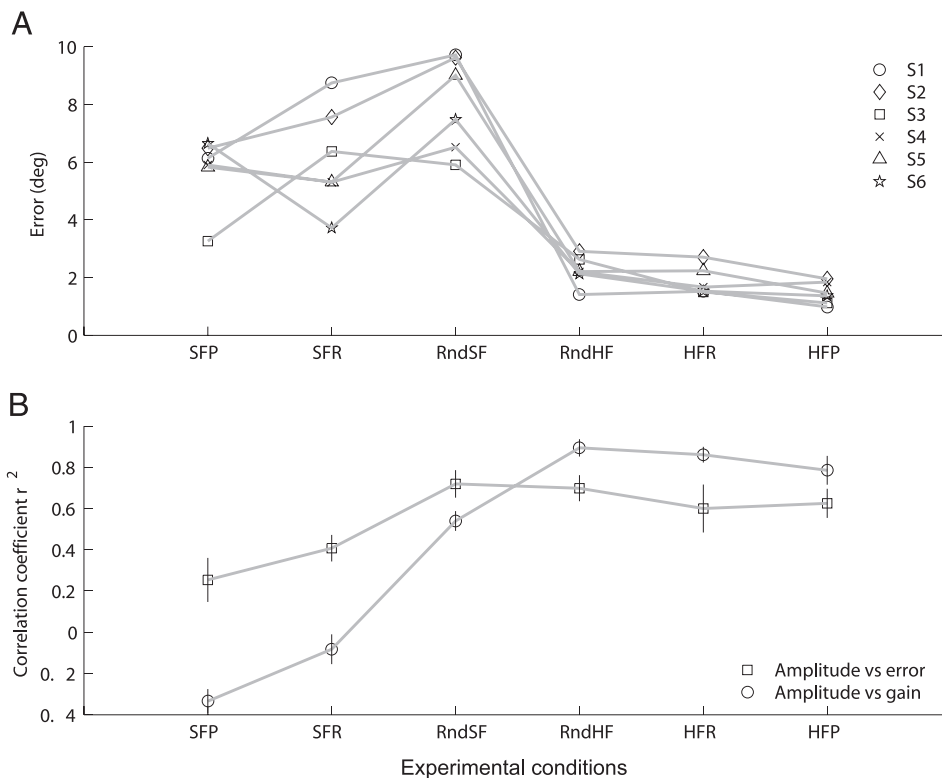
FIG. 6. *A*: average retinal error computed at the beginning of the 1st corrective saccade for each subject in each paradigm. *B*: correlation coefficients for the linear regression of saccade amplitude vs. retinal error (□) and of saccade amplitude vs. tVOR gain (○). Vertical lines at each symbol indicate ± SE.

appropriately larger saccades (in the anticompensatory direction since higher gain corresponded to larger eye deviations), which, considering their long latencies, were most likely visually driven. The results are shown as ○ in Fig. 6*B*. The large saccade amplitudes (Fig. 4*B* and r^2 value in Fig. 6*B*) and the relatively shorter latencies in the RndSF trials compared with the RndHF trials, indicate that vestibularly driven, preprogrammed saccade corrections may also occur during the RndSF trials, while the corrections in the RndHF trials appear visually driven as with the other head-fixed conditions.

The finding, in three subjects, of saccades that were inappropriately directed in the direction compensatory for head motion during RndHF and HFR trials, provides even more evidence for preprogramming of corrective catch-up saccades tailored to the space-fixed target condition in which the slow-phase response is typically undercompensatory. This also implies that in the RndHF trials the tVOR saccade mechanism can cancel (at least most of the time) any preprogrammed augmenting saccades and then generate visually driven saccades in the other direction to reacquire the head fixed target.

What determines which of the two corrective saccade strategies—vestibularly driven or visually driven—is invoked during the random paradigm because these two conditions (RndHF and RndSF) are unpredictably interspersed? One possibility is that the brain uses retinal-slip information acquired during the first few tens of milliseconds of head motion to determine the condition to which the subject is exposed. In an analogous situation, the size of the corrective saccade during pursuit tracking of a target moving in a step-ramp fashion (the Rashbass stimulus) can be modified (Carl and Gellman 1987; Rashbass 1961), probably based on retinal slip information acquired early during smooth pursuit tracking. In the case of the tVOR, if the estimates of head velocity and of retinal slip velocity have opposite signs, then the brain can infer that the

subject is tracking the space-fixed target and a vestibularly driven saccadic correction (the size of which might also be based on vestibular information) is automatically produced as per past experience. If instead the two velocities have the same signs, then the brain can opt to wait for more precise visual information to become available before producing a saccade, possibly because the head-fixed condition during the tVOR is a condition less frequently encountered in everyday life, and there has been no previous learning to optimize corrective saccades. Nevertheless, some everyday life situations do require suppression of the tVOR, for example, while viewing a target that is translating in the same direction as the head, but the amount of required tVOR suppression varies depending on the relative velocity of the target. In such conditions, the brain may attenuate the tVOR response and wait for a reliable estimate of relative motion provided by visual information. If there is no visual information, i.e., the tVOR is elicited in complete darkness, then the default preprogramming strategy occurs and the corrective saccade is still made (Tian et al. 2000).

In sum, the tVOR—both in its slow phase response and the necessary subsequent saccadic corrections—is subject to a number of "higher-level" cognitive influences including knowledge of where the line of sight must point during head motion and an expectation of the impending direction of head motion.

APPENDIX

To investigate the early slow-phase response of the tVOR, we implemented a mathematical model of the otolith-ocular reflex (Fig. A1) based on the "eye plant" hypothesis (Angelaki et al. 2001; Green and Galiana 1998; Musallam and Tomlinson 1999) using Simulink (Mathworks). In this model, head acceleration is sensed by the otolith
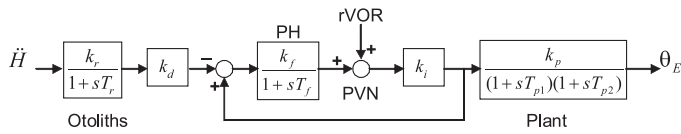
FIG. A1. Mathematical model of the tVOR derived from Green and Galiana (1998). The input to the model is head linear acceleration, which is converted into a neural signal by the block representing the otolith afferent transfer function ("Otoliths"). This signal is then scaled by the inverse of the viewing distance (k_d), reaches the vestibular nuclei and is fed to the nucleus prepositus hypoglossus, (PH) where it enters a positive feedback loop providing an integration of the signal. The integrated signal then proceeds toward the oculomotor plant, producing its output as eye position in the orbit. The input from the semicircular canals enters the loop at the level of the premotor vestibular nuclei (PVN). Parameters used in the simulation: $T_r = 0.03$ s; $k_d = 1/0.15$; $k_f = 1$; $T_f = T_{p1} = 0.22$ s; $T_{p2} = 0.012$ s; $k_i \approx 0.99$.

organs (block "Otoliths" in Fig. 7) and is sent to the vestibular nuclei (VN) and then to the nucleus prepositus hypoglossi (PH) where it combines with signals from the semicircular canals. Before reaching the PH the signal transduced by the otoliths is scaled by the inverse of viewing distance ($k_d = 1/\text{viewing distance}$). A reciprocal inhibition between the PH and the preoculomotor VN generates a positive feedback loop that can act as a distributed neural integrator (Chun and Robinson 1978). The different sites at which the canal and otolith afferents enter the positive feedback loop account for the different ways the two signals are processed (Green and Galiana 1998). For the signals originating in the semicircular canals (SCC), the PVN-PH feedback loop introduces a lead-lag element with a zero that compensates for the pole in the eye plant. The otolith afferent signals, however, enter the feedback loop at the level of the PH, which contains an internal model of the eye plant. No zero is created by the loop so that the pole in the plant is not compensated and thus the pole in the plant provides an additional integration of frequencies above ~0.6 Hz (see *Eq. A1* in the following text).

The otolith system is modeled as a low-pass filter for head acceleration with a cut-off frequency ~5 Hz. Such a value was estimated

by fitting our slow-phase eye-movement data and is lower than the 10-Hz cutoff value previously reported for the monkey (Angelaki et al. 2001). The PVN-PH positive feedback loop consist of a first-order internal model of the ocular motor plant in the forward pathway and a gain (k_i), as derived from Green and Galiana (1998), in the feedback loop. The plant is represented as a second order system (Keller 1973).

Thus the overall transfer function between head linear acceleration and eye position in the orbit is given by

$$\frac{\theta_E}{\ddot{H}} = -\frac{k_r}{1 + sT_r} k_d \frac{1}{1 - k_i k_f} \frac{k_i k_f}{1 + s\frac{T_f}{1 - k_i k_f}} \frac{1}{(1 + sT_{p1})(1 + sT_{p2})} \quad (A1)$$

where $T_r = 0.03$ s; $k_d = 1/0.15$; $k_f = 1$; $T_f = T_{p1} = 0.22$ s; $T_{p2} = 0.012$ s; $k_i \approx 0.99$; $k_r = 2$.

With these values, the integrator time constant is 22 s. Any parametric adjustment within the positive feedback loop changes the time constant of the common neural integrator and thus affects the rVOR as well as other types of conjugate eye movements and eccentric gaze-holding. Previous studies on the adaptation of the phase of the tVOR response (Hegemann et al. 1999, 2000) found changes in eccentric gaze-holding in adapted subjects, suggesting that the adaptation of the phase of the tVOR was accompanied and possibly mediated by changes in the neural integrator time constant.

Thus we explored two hypotheses to explain the cognitive changes observed in the tVOR responses. First, we asked whether our experimental findings could be explained simply by varying the *gain* of otolith information reaching the VN. Considering k_d as a fixed parameter for a given viewing distance, we tried to fit the data by adjusting the gain of otolith afferents (k_r).

Second, we considered whether our experimental findings could be explained by changes in the gain of the internal model of the plant (k_f), which would affect both the gain [$k_f/(1 - k_i k_f)$] and the time constant [$T_f/(1 - k_i k_f)$] of the leaky integrator. For both approaches, we only adjusted one parameter to simulate the data.
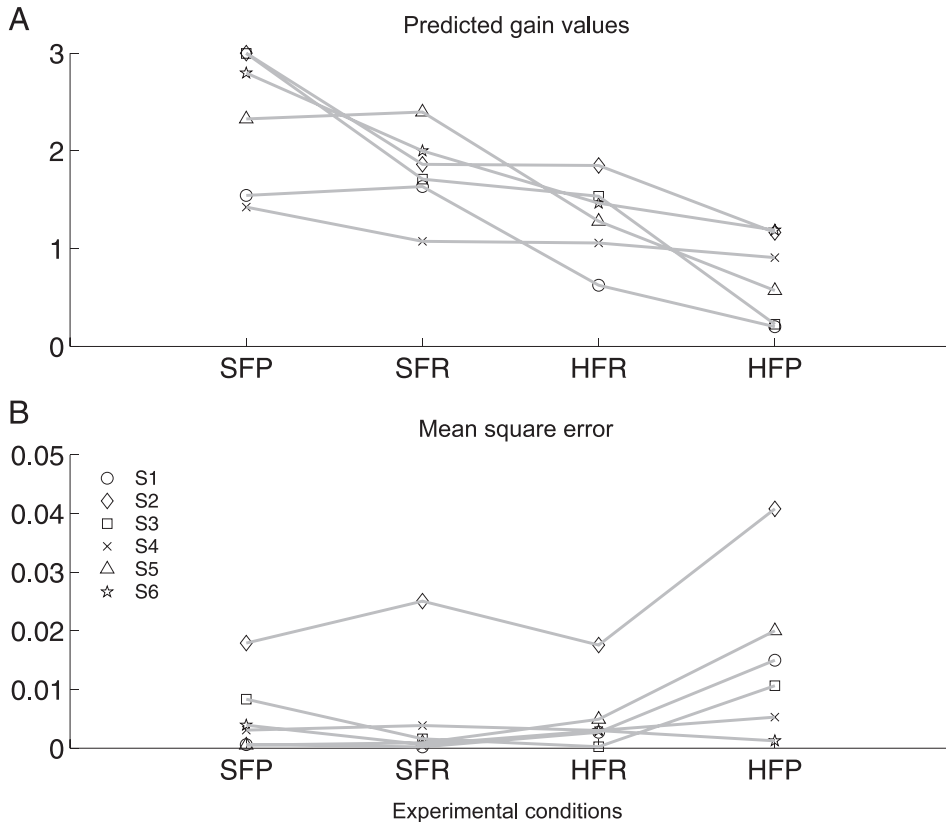

FIG. A2. Simulation of parametric changes in the otolith afferents. *A*: k_r values derived from the optimization procedure that minimized the error between the output of the model and the average trial of each subject in each experimental condition. *B*: mean squared error values for the simulations performed with optimized k_r gains.

We simulated the first 100 ms after the onset of head movement for both the individual and the averaged responses for each subject and in each condition. The input to the model was the linear acceleration of the head (based on the output of the linear accelerometer attached to the bite bar). The output of the model was eye position in orbit, which we then compared with the actual eye-movement data. The gain parameter of interest was estimated using the Matlab implementation of the Levenberg-Marquardt optimization algorithm, aimed at minimizing the sum of squares error between the simulated and recorded eye movements.

We first simulated our data simply by changing the gain (k_r) of the otolith afferents; mean squared error values between the data and the simulated eye movement were <0.05. Figure A2 shows the values for k_r used to simulate the mean response in each experimental condition for each subject (*top*) and the corresponding mean squared error values (*bottom*). As expected from the experimental findings, for the model to simulate our data the gain had to decrease progressively from SFP to SFR to HFR to HFP. The model performed well across the first three conditions in all subjects though in four of the six subjects, the model did not do quite as well for the HFP condition. This may be related to the fact that fixation in which the eyes are simply held still is a somewhat special case of visual tracking (Luebke and Robinson 1988; Shelhamer et al. 1994).

We next altered the k_f parameter, representing the internal model of the plant but with k_r fixed at 2.0. Again we found that our data could be simulated with comparable mean squared error measures. The k_f parameter, however, had to be varied from 1 (in SFP for *subject S3*) to 0.5 (in HFP for *subjects S1* and *S3*). Such a change in the k_f parameter would cause the time constant of the neural integrator (shared with the rVOR and the other oculomotor subsystems) to vary from 22 to ~0.5 s in the HFP condition. If such a low value of the integrator time constant persisted beyond the end of the translation, the ability of the subject to hold eccentric gaze would be markedly impaired immediately after the head movement. We saw no such change in gaze-holding ability between the SFP and HFP conditions, thus excluding this interpretation though we cannot exclude the idea that the parameter k_f was transiently and selectively modulated only during the head movement itself.

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