The interaural translational VOR: suppression, enhancement and cognitive control

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Abstract

We investigated the influence of cognitive factors on the early response of the interaural translational vestibulo-ocular reflex (tVOR) in six normal subjects. Variables were 1) prior knowledge of direction of head motion and 2) 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, 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 while 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 upon 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 vestibulo-ocular reflex (rVOR) and the translational vestibulo-ocular reflex (tVOR), respectively. While 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 since the amplitude and even the direction of the response depend on the distance and the eccentricity of the target (2; 5; 10; 29; 31; 34; 37). 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 upon where the line of sight must be directed (34). 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 nonhuman 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 (26). The ability to suppress and enhance the rVOR depending upon the location of the target of interest relative to the head also has been investigated extensively in humans (9; 14; 15; 23; 24; 28; 43). 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 msec of the response, while Gauthier and Vercher (1990) found no differences between responses to head-fixed 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 above 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 enhanced) response would exclude a mechanism that is solely based upon 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 non-visual mechanisms but only at relatively low frequencies (below 4Hz) (32). The ability of the brain to adaptively enhance or suppress the response of the tVOR was investigated by Gianna et al. (17) 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 (16; 34) 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. (11) 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 (15cm) 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-fixed 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).

 Materials and methods

 Normal subjects

 Six normal subjects (ages between 19 and 56, one woman and five 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, Inc). The details of the calibration and eye movement recording procedures have been described previously (4; 34).

Head movements were also recorded with a six-degrees-of-freedom miniBIRD device (bandwidth of 144Hz, manufactured by Ascension Technology Corp.) 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 about 35 cm from the subject. The bite bar prevented any concurrent rotation of the head around the yaw axis which 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 the Experimental paradigms section).

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 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.

In order to deliver quasi-reproducible translational stimuli along the interaural axis we used
a 'head sled' device (35), which has the advantage of a low inertia compared to 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 (34).

**Experimental paradigms**

Subjects were asked to fix upon 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
diameter) 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:

1- RND: Random head movement direction and target unpredictably head-fixed (RndHF) or space-fixed (RndSF).

2- HFR: Random head movement direction with a head-fixed target.

3- HFP: Predictable head movement direction with a head-fixed target.

4- SFR: Random head movement direction with a space-fixed target.

5- SFP: Predictable head movement direction, with a space-fixed target

In order 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 0.5s. Using a threshold based upon 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 (4). The angular positions of each eye coil (relative to spatial coordinates) were calculated from the rotation vectors. To calculate the angular velocity trajectories, a 5th order 100Hz low pass finite impulse response (FIR) filter was first applied to the rotation matrices. The resulting data were differentiated using a 5th order REMEZ (Matlab) FIR filter, designed to differentiate the data up to 40Hz and to low-pass filter the data above 100Hz. The differentiated data were then used with the undifferentiated, filtered data to calculate angular velocity (22). To calculate angular acceleration, the angular velocity data were differentiated with the same 5th 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 (35).

**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. Since 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 (34). 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 above, 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, though 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 (34).

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 one standard deviation from the mean head trace and then used a three standard deviations technique to determine the latency of
the mean eye movement response (34). 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 seven trials were used for this calculation and in most cases (90%) more than seven).

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 less than 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 the analysis of variances test (ANOVA) or the Wilcoxon rank sum test 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 \( 3.5\pm0.4 \) cm and peak head velocity averaged \( 36\pm4 \) cm/s. Peak head acceleration averaged \( 0.90\pm0.19 \) 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.

**Fig 1 near here**

*Random (RND) paradigm*

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

Fig 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 since 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 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-fixed than head-fixed trials (250±80 ms 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.

**Fig 2 near here**

**Fig 3 near here**

*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±1.3 deg (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 since the subjects knew beforehand in which direction the head would be translated. Head movements were delivered at random times in two sets of fifteen 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 over 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±1.5 deg.

**Fig 4 near here**

**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 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 (±SD) was 270±81 ms. The mean amplitude of corrective saccades over all subjects was 1.3±0.8 deg, 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 fifteen 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 about 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 deg.

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. 5, panel B), implying a form of short-term motor learning. Linear regression analysis of gain values vs. stimulus number yielded correlation coefficient ($r^2$) values ranging from 0.5 to 0.7.

**Fig 5 near here**

**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. 2A). 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 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). Fig 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 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 Figure 4, panel A, while panel 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 to 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).

Panel 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, while 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, while 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 (about 220 ms), high acceleration (0.56 to 1.27g) interaural head translations while viewing a near (15 cm) target. Previous reports (11; 17) 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-fixed 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 (~90-100ms) 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 Figure 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 ms 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 to 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 (3). Previous studies of adaptation of the tVOR have suggested that the neural integrator might be involved (20). 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 brainstem 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 (7) or for active versus passive head motion (12). 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 (1; 13), 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 ten to fifteen trials. In a paradigm, designed specifically to elicit motor learning Zhou et al (44) 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, since there was no difference in the gain of the slow phases between the head-fixed 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 (39). In our experiments, we can not exclude that subjects adopted a cognitive strategy to change their tVOR response rather than undergoing motor learning based upon 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 (34; 35; 42), 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 four of six) for the first corrective saccade in the SFR paradigm compared to 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 fixed 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.

**Fig 6 near here**

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 (Figure 4, panel B). We thus computed the regression coefficients of saccadic amplitudes vs. the error at the onset of the saccade for each experimental condition, pooling the data for all subjects (Figure 6B (squares)). The correlation was relatively low for the SFP and SFR trials (about 0.25 and 0.33, respectively) but increased up to about 0.75 for the RndSF trials, 0.7 for the RndHF trials, and around 0.6 for both HFR and HFP. These findings, with the generally longer latency for the known head-fixed conditions (Figure 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 (19; 33; 40) and linear (41; 42) 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 upon 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 appropriately larger saccades (in the anticompaensatory direction since higher gain corresponded to larger eye deviations), which, considering their long latencies, were most likely visually driven. The results are shown as open circles in Figure 6B. The large saccade amplitudes (Figure 4B and r² value in Figure 6B) and the relatively shorter latencies in the RndSF trials compared to 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 of 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 since 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 (6; 36), probably based upon 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 (41).
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.

**Fig 7 near here**

**APPENDIX**

To investigate the early slow-phase response of the tVOR, we implemented a mathematical model of the otolith-ocular reflex (Fig. 7) based on the ‘eye plant’ hypothesis (3; 18; 30) using Simulink® (Mathworks Inc.). In this model head acceleration is sensed by the otolith 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 ($k_d=1/$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 (8). 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 (18). 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 about 0.6 Hz (see Eq. 1 below).
The otolith system is modeled as a low-pass filter for head acceleration with a cut-off frequency around 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 (3). 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 (25).

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

$$\frac{\theta_e}{H} = \frac{k_f k_d}{1 + s T_r} \cdot \frac{1}{1 - k_f k_d} \cdot \frac{k_f}{1 + s T_f} \cdot \frac{1}{1 - k_f k_d}$$

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

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 (20; 21) 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 ($k_e$).

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 ($k_f/(1-k_f k_d)$) and the
time constant \((T_f/(1-k_f k_f))\) of the leaky integrator. For both approaches, we only adjusted one parameter to simulate the data.

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 upon 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 less than 0.05. Figure 8 shows the values for \(k_r\) used to simulate the mean response in each experimental condition for each subject (top panel) and the corresponding mean squared error values (bottom panel). 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 (27; 38).

**Fig 8 near here**

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 about 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 can not exclude the idea that the parameter $k_f$ was transiently and selectively modulated only during the head movement itself.

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Figure 1. Representative set of responses in one subject (S5) to the RND paradigm. Responses are normalized with respect to the maximum deviation of the ideal eye movement allowing fixation of a stationary target. Grey 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.

Figure 2. Histograms of 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 25\textsuperscript{th} and 75\textsuperscript{th} percentiles. slow-phase gains computed for each subject in all conditions. Each group of columns represents data from one subject. For each subject the graph shows (left to right) HFP, HF, RndHF, RndSF, SF and SFP conditions where RndSF are space fixed trials during the random condition and RndHF are head fixed trials during the random condition.

Figure 3. Mean traces of the responses to each experimental condition. Each panel represents one subject. HFP: head fixed target, predictable head direction. HFR: head fixed target, random head direction. SFR: space fixed target, random head direction. SFP: space fixed target, predictable 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).

Figure 4. Corrective saccades. Panel A: Latency of corrective saccades during responses to each experimental condition. Panel 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. RndSF: space fixed trials during the random condition; RndHF: head fixed trials during the random condition.

Figure 5. Short-term learning in tVOR responses, examples from two subjects. Panel A: temporal evolution of slow-phase gain in subject S5 during HFR paradigm. Panel B: temporal evolution of slow-phase gain in subject S2 during HFP paradigm. ‘+’ and ‘o’ signs represent 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 rightward and leftward head movements are mixed, while in HFP paradigm a set of leftward stimuli follows a set of rightward ones.

Figure 6 Panel A. Average retinal error computed at the beginning of the first corrective saccade for each subject in each paradigm. Panel B. Correlation coefficients for the linear regression of saccade amplitude vs. retinal error (squares) and of saccade amplitude vs. tVOR gain (circles). Vertical lines at each symbol indicate ± the standard error of the mean.

Figure 7. 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 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; \( k_i=0.99 \);
Figure 8. Simulation of parametric changes in the otolith afferents. Panel 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. Panel B: mean squared error values for the simulations performed with optimized $k_r$ gains. HFP: head fixed target, predictable head direction. HFR: head fixed target, random head direction. SFR: space fixed target, random head direction. SFP: space fixed target, predictable head direction.


Figure 1
Figure 2
Figure 4

(A) Saccade latencies

(B) Saccade amplitude
Figure 5

A

Gain evolution during HFR (S5)

$\text{Gain} = 0.5$

B

Gain evolution during HFP (S1)

$\text{Gain} = 0.75$

Heaves to right

Heaves to left
Figure 6
Figure 7
Figure 8