Multiplicative Computation in the Vestibulo-Ocular Reflex (VOR)

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Zhou W, Xu Y, Simpson I, Cai Y. Multiplicative computation in the vestibulo-ocular reflex (VOR). J Neurophysiol 97: 2780–2789, 2007. First published January 24, 2007; doi:10.1152/jn.00812.2006. Multiplicative computation is a basic operation that is crucial for neural information processing, but examples of multiplication by neural pathways that perform well-defined sensorimotor transformations are scarce. Here in behaving monkeys, we identified a multiplication of vestibular and eye position signals in the vestibulo-ocular reflex (VOR). Monkeys were trained to maintain fixation on visual targets at different horizontal locations and received brief unilateral acoustic clicks (1 ms, rarefaction, 85–110 dB NHL) that were delivered into one of their external ear canals. We found that both the click-evoked horizontal eye movement responses and the click-evoked neuronal responses of the abducens neurons exhibited linear dependencies on horizontal conjugate eye position, indicating that the interaction of vestibular and horizontal conjugate eye position was multiplicative. Latency analysis further indicated that the site of the multiplication was within the direct VOR pathways. Based on these results, we propose a novel neural mechanism that implements the VOR gain modulation by fixation distance and gaze eccentricity. In this mechanism, the vestibular signal from a single labyrinth interacts multiplicatively with the position signals of each eye (Principle of Multiplication). These effects, however, interact additively with the other labyrinth (Principle of Addition). Our analysis suggests that the new mechanism can implement the VOR gain modulation by fixation distance and gaze eccentricity within the direct VOR pathways.

INTRODUCTION

The vestibulo-ocular reflex (VOR) produces short-latency eye movement that compensates for rotational and translational head motion. It has been well documented, however, that the VOR does not generate the same eye movement in response to a given head motion. Rather, the VOR gain is modulated by behavioral contexts. One example of this is that the VOR gain depends on the distance a target is from the eyes. Previous behavioral and single unit recording studies suggest that the VOR gain modulation by fixation distance is implemented by a multiplicative interaction of the vestibular signal and the vergence eye position signal (i.e., the difference between the left and right eye positions) (Angelaki 2004; Chen-Huang and McCrea 1998, 1999a,b; Crane and Demer 1998; Crane et al. 2003; Hine and Thorn 1987; King et al. 2003; Lasker et al. 2002; Meng and Angelaki 2006; Meng et al. 2005; Paige and Tomko 1991; Ramat and Zee 2003; Schwarz et al. 1989; Snyder and King 1992; Viirre et al. 1986; Zhou et al. 2003). However, where and how the multiplication is implemented remains unknown.

To identify the neural substrates that mediate the VOR gain modulation by fixation distance, several studies used sinusoidal rotational and/or translational head motion to examine the effects of vergence on the vestibular-evoked responses in the VOR interneurons [burst-tonic (BT) neurons; eye-head (EH) neurons, and position-pause-vestibular (PVP) neurons] in the vestibular nuclei (Chen-Huang and McCrea 1998, 1999a,b; King et al. 2003; McConville et al. 1996; Meng and Angelaki 2006; Meng et al. 2005). These studies found that all of these VOR interneurons modulated their vestibular-evoked responses as a function of fixation distance. Given the extensive interconnections between the VOR premotor neurons, however, the analysis of steady-state responses cannot address whether the VOR interneurons are the sites that perform the fixation-distance related computation or the sites that transmit the outputs of the computation performed elsewhere, such as a bilateral network (Angelaki 2004; Green and Angelaki 2004) or the flocculus/ventral paraflocculus (Lisberger and Pavelko 1988; Lisberger et al. 1994; Partsalis et al. 1995a,b; Zhang et al. 1995a,b). To elucidate the neural substrates that perform the fixation-distance related multiplicative computation, we used unilateral short-duration acoustic clicks to evoke impulse responses in the abducens neurons while monkeys were trained to fixate on visual targets at different horizontal locations. We found that the interaction of vestibular and eye position signals was multiplicative in the abducens neurons. Based on the latency of the eye position effect, we further determined that the multiplication was implemented within the direct VOR pathways. Based on these results, we propose a novel neural mechanism that modulates the VOR gain with fixation distance within the direct VOR pathways.

METHODS

Four male rhesus monkeys were used in the experiments. The surgical and experimental procedures had been approved by the University of Mississippi Medical Center’s Institutional Animal Care and Use Committee.

Eye movement recording, acoustic stimulation and behavioral paradigms

The procedures for the surgery and the initial behavioral training were the same as those described previously (Zhou and King 1998; Zhou et al. 2003, 2004). Under general anesthesia and using sterile procedures, a search coil was implanted in each eye to monitor binocular eye position signals. In this study, acoustic clicks were used...
as a vestibular stimulus. Acoustic activation of the vestibular system has been well documented in humans and animals (Colebatch et al. 1994; in humans; Young et al. 1977; in squirrel monkeys; McCue and Guinan 1994; in cats; Murofushi et al. 1995; in guinea pig; Zhou et al. 2004 2005, in behaving monkeys; Carey et al. 2004; in chinchillas) and their potential value in the diagnosis of vestibular disorders has been widely recognized (for review, see Halmagyi et al. 2005). Acoustic clicks (1 ms, rarefaction, 85–110 db NHL) generated by a MA3 microphone amplifier (Tucker-Davis Technologies, Alachua, FL) were triggered by our behavioral control program. Unilateral acoustic clicks were delivered to a monkey’s external ear canal through an insert earphone (ER-3A), which reduced the bone conductance–induced stimulation of the contralateral labyrinth by >75 db. Because the highest intensity used in our study was 110 db, the stimulation of the contralateral labyrinth (<35 db) was lower than the threshold of 80 db at which clicks can evoke any observable behavioral and neuronal responses. Thus acoustic clicks offered the advantage of unilateral vestibular stimulation, which allowed us to study the eye position influences on the vestibular inputs from a single labyrinth (Carey et al. 2004).

During these experiments, the monkey was comfortably seated in a custom-designed chair, with its head upright and stabilized with respect to the electromagnetic field of the eye coil system by attaching a stainless steel rod to the monkey’s head holder. Each eye coil was calibrated at the start of each experimental day by requiring the monkey to fixate on horizontal or vertical target positions (±20°, every 5°). Monkeys were trained to fixate on visual targets for apple juice rewards. Visual targets were projected by lasers onto a far screen located ~275 cm from monkeys’ eyes. Acoustic clicks were delivered in individual trials that lasted ~2–4 s. Each trial started with the appearance of a visual target of randomly chosen ocular eccentricity (~20, −10, 10, 20°). The monkey was trained to fixate on the target with both eyes, i.e., maintaining eye position within a small window (1–4° in size) centered on the target’s position. After a successful fixation interval varying from 300 to 900 ms, six Clicks, 400 ms apart, were delivered to one of the monkey’s ears. The monkey was trained to maintain fixation through the trial. At the end of each successful trial, the monkey was rewarded with two drops of juice. To study the effect of eccentricity on the click-evoked neuronal responses, trials with different eccentricities were combined randomly and delivered in one single block. Each condition consisted of ~300 stimulations.

Single unit recording

Standard procedures were used to record single unit activity (for more details, see Zhou and King 1998; Zhou et al. 2001). Briefly, a stainless steel cylinder was implanted stereotaxically and a tungsten microelectrode was advanced through a 21-gauge guide cannula by a motorized microdrive. The abducens nucleus was identified by the characteristic tonal quality of the background activity as heard on the audio monitor (Fuchs et al. 1988; Robinson 1970). We included in our sample only neurons that were recorded concurrently with the characteristic background activity of the abducens nucleus. For each abducens neuron, we first recorded the neuron’s responses during pursuit of a sinusoidal target motion at 0.3 Hz and ±10° and fixation of the target in 5° steps from −20 to 20°. We recorded the abducens neuron’s responses to acoustic clicks (1 ms, rarefaction, 110 db NHL) delivered to each ear.

Data acquisition and data analysis

A PC running specialized software controlled the experiments, and a CED Power 1401 system (Cambridge Electronics Devices, Cambridge, UK) was used for data acquisition. Single unit responses were amplified and filtered (100–10,000 Hz) and a two-stage, time-amplitude window discriminator was used to discriminate single spikes (Bak Electronics, Mount Airy, MD). Signals of binocular horizontal and vertical eye position, target position, and the acceptance pulse for action potential (0.01-ms temporal resolution) were sampled at 2 kHz with 16-bit resolution and stored with the amplified extracellular voltage trace (sampled at 20 kHz) on a hard disk for off-line analyses.

Eye movement responses were analyzed using Spike2 (Cambridge Electronics Devices). Raw eye position data were filtered and differentiated with a band-pass of DC to 100 Hz to obtain eye velocity data. Trials in which monkeys made a saccade within 50 ms of the onset of the sound stimuli were rejected (approximately one-third trials rejected). Trials in the data stream were sorted, aligned on the onset of the sound stimulation, and averaged (~200 trials per condition) to obtain low-noise estimates of eye velocity as a function of time.

Single unit responses to acoustic clicks were analyzed using Spike2 and SigmaPlot. The amplitude of the click-evoked response was measured as the peak firing rate in the binned histogram with a bin size of 0.5 ms. We measured a neuron’s responses at three or four horizontal eccentricities and computed the slope and the intercept of the firing rate–eye position regression line in control (i.e., without click–stimulation) and (i.e., with clicks) conditions (Kevoked/Kcontrol, INTERCEPTevoked–INTERCEPTcontrol). To quantitatively assess the interaction of vestibular and eye position signals, we computed a multiplication index that was defined as the ratio of the slopes in stimulation and control conditions, i.e., Kevoked/Kcontrol. A multiplication index different from 1 indicates a multiplicative interaction of the two signals. We also computed an addition index that was defined as the ratio of the intercepts in stimulation and control conditions, i.e., INTERCEPTevoked/INTERCEPTcontrol. An addition index different from 1 indicates an additive interaction of the two signals. The interactions of vestibular and eye position signals were assessed for individual neurons and the population.

To assess the effect of eye position on click–evoked behavioral responses, we computed a scaling factor for an eye position E, which was defined as the percentage changes of click–evoked eye movement at the eye position E (AE) with respect to that at the center gaze (A0), i.e., (AE − A0)/A0. Because AE = A0 + K × E, the scaling factor is K × E/A0. Compared with the multiplicative index, the scaling factor is a better way to measure the amplitude of eye position effect on click–evoked responses because it takes the magnitude of the response at the center gaze into consideration. However, because the multiplicative index is the ratio of eye position sensitivities (K) in control and stimulation conditions, it is good to evaluate the nature of the interaction of vestibular and eye position signal in an abducens neuron. Thus in this study, we used the multiplicative index to assess the click–evoked neuronal responses in abducens neurons and used the scaling factor to assess the effect of eye position on click–evoked eye movements.

Results

Effects of eye position on vestibular-evoked responses in the abducens neurons

Figure 1, A and B, shows an example of the eye movement responses and an abducens neuron’s responses to acoustic clicks. Figure 1A shows the responses while the monkey was at the center gaze, and Fig. 1B shows the responses while the monkey fixated 20° right from the center. In this example, acoustic clicks were delivered to the left ear canal. They evoked contralateral eye movements (Fig. 1, A and B, top 2 traces) and increased the firing rates of the abducens neuron on the contralateral side (Fig. 1, A and B, middle and bottom traces). Note that the calibration bar is 1,000 spikes/s for histograms and 12°/s for eye velocity traces. The amplitudes of the click–evoked eye movements depended on eye position. In this example, the click–evoked eye movements had a peak eye velocity of 5.2 ± 0.3°/s at 20° to the right (Fig. 1B). This was
more than twice of that at the center gaze (2.4 ± 0.2°/s; Fig. 1A). The amplitudes of the click-evoked neuronal responses also depended on eye position. In this example, the click-evoked response of the abducens neuron was 1,000 spikes/s at 20° to the right (Fig. 1B). Again, this was more than twice of that at the center gaze (440 spikes/s; Fig. 1A).

To examine the interaction of the vestibular and eye position signals in the abducens neurons, we measured the firing rates of the abducens neurons at three or four gaze angles in control and stimulation conditions. As shown in Fig. 1C, the abducens neuron’s firing rates exhibited a linear relationship with eye position signal in both conditions, which was characterized by a slope and an intercept. The multiplication index (ratio of the slopes) and addition index (ratio of the intercepts) were computed to assess the interaction of vestibular and eye position signals in the abducens neurons. For the neuron shown in Fig. 1C, the multiplication index was larger than 1 (4.6 ± 0.4), and the addition index was close to 1 (1.06 ± 0.1). Figure 1D shows the average responses of a population of abducens neurons (n = 124) as a function of eye position in control and stimulation conditions. The population average response also had a multiplication index larger than 1 (3.5 ± 0.3) and an addition index close to 1 (0.8 ± 0.1).

In Fig. 2A, we plotted abducens neurons’ slopes to eye position in the stimulation condition (KEvoked) against that in the control condition (Kcontrol). The correlation between the two slopes were weak (Fig. 2A; R² = 0.02), indicating that abducens neurons’ slopes to eye position at the stimulation condition cannot be accounted for by their slopes in the control condition. Figure 2B shows the distribution of the multiplication indexes for the population of abducens neurons when the contralateral ear was stimulated. On average, the population had a multiplication index larger than 1 (4.49 ± 0.4, P < 0.001) and an addition index close to 1 (1.03 ± 0.05, P > 0.1), indicating a pure multiplicative interaction of vestibular and eye position signals in the VOR pathways.

We measured the responses in 34 abducens neurons when acoustic clicks were delivered into the ear canal ipsilateral to these neurons. We found that ipsilateral acoustic clicks evoked short latency excitatory responses. Because ipsilateral innervation from the semicircular canals is known to be inhibitory, we hypothesize that these excitatory responses are of otolith origin. We found that the effects of eye position were more diverse in the ipsilateral stimulation condition than that in the contralateral stimulation condition. The multiplication indexes of the ipsilateral stimulation ranged from -7.2 to 4.07 with a mean of 0.99 ± 2.0 (SE). Among the 34 neurons, the multiplication indexes were different from 1 in 33 neurons, indicating a multiplicative interaction of vestibular and eye position signals in these neurons. In particular, 8 of the 33 neurons had negative multiplication indexes, indicating that the click-evoked neuronal response decreases as the baseline firing rates increases.

Latency of the click-evoked peak responses in the abducens neurons

As shown in Fig. 1, the click-evoked peak responses of the abducens neurons exhibited linear dependencies on eye position. Thus the latencies of the peak responses were used to locate the sites of the multiplicative computation. Figure 3 shows the summary response of the population at the center gaze (Fig. 3A) and the distribution of the peak response latencies (Fig. 3B). We found that 87% of the abducens neurons exhibited their peak responses at the latency of 2.8 ms (Fig. 3B). The mean latency of the population was 2.78 ± 0.3 ms. Because the latency of the vestibular afferents to click stimulation was 0.82 ± 0.22 ms (Murofushi and Curthoys 1997), we estimated that the latency from the vestibular afferen-
ents to the abducens neurons was 1.96 ms, i.e., di-synaptic, suggesting that the multiplicative computation takes place within the direct VOR pathways.

Effects of eye position on vestibular-evoked eye movement responses

To examine whether there is a scaling effect of eye position signal on the vestibular-evoked eye movements, we measured the click-evoked eye movements at five horizontal eccentricities (−20, −10, 0, 10, 20) using clicks of six intensities (80–105 dB NHL). Figure 4A compares the stimulus-response curves at different eccentricities. In Fig. 4B, for each eccentricity, the click-evoked peak eye velocities were compared with that at the center gaze for all click intensities. Figure 4B shows that the data points from the same eccentricity fall on a single straight line, indicating a scaling effect of eye position on the click-evoked VOR responses. The scaling factor for an eye position was measured by the slope of the corresponding regression line in Fig. 4B, which was dependent on horizontal eccentricity but was independent of click intensity. Compared with the center gaze, the click-evoked VOR responses increased at eye positions that were more contralateral to the stimulated ear and decreased at eye positions that were more ipsilateral to the stimulated ear. Figure 4C summarizes the eye position-dependent scaling factors of the four monkeys. Within 20° from the center gaze, scaling factors exhibited approximately linear dependencies on eye position (ipsilateral eye: 2.05 ± 0.13%/°; contralateral eye: 1.65 ± 0.47%/°). While only peak responses are plotted in Fig. 4, regression analysis was performed on the whole response profile including rising, peaking, and falling phases, revealing that the same scaling effect of eye position signal were present through the frequency spectrum of the vestibular-evoked VOR responses. Because natural head movements reciprocally activate the two labyrinths with much lower frequency contents than the clicks, the interaction of vestibular and eye position signals during natural head movements may exhibit different characteristics and will be determined in future studies.
advantages to the electrical stimulation, but without the companion challenges of implanting, calibrating, and maintaining stimulating electrodes. Using this approach, we found that the interaction of vestibular and horizontal conjugate eye position signals in the abducens neurons was multiplicative, rather than additive as currently assumed. Latency analysis indicates that the multiplication takes place within the three-neuron-arc pathway of the VOR. Based on these results, we propose a neural model that uses the multiplicative interaction of vestibular and eye position signals to implement the VOR gain modulation by viewing distance and gaze eccentricity.

**Interaction of vestibular and eye position signals in putative abducens motoneurons and internuclear neurons**

In this study, we examined the interaction of vestibular and horizontal conjugate eye position signals in the abducens nucleus. It has been well established that the abducens nucleus has both motoneurons that innervate the ipsilateral rectus muscle and internuclear neurons that project to the contralateral medial rectus motoneurons and the flocculus of the cerebellum (Langer et al. 1985; Steiger and Buttner-Ennever 1978). Our population of abducens neurons was likely comprised of both motoneurons and internuclear neurons. We did not directly identify whether abducens neurons were motoneurons or internuclear neurons. However, we tried to identify indirectly whether abducens neurons were putative motoneurons or internuclear neurons using the criteria of Fuchs et al. (1988). In the earlier study, Fuchs et al. (1988) showed that the firing rates of both motoneurons and internuclear neurons were linearly associated with eye position and eye velocity. The firing rates associated with eye position can be described by the eye position sensitivity (K) and the eye position threshold (T). The firing rates associated with eye velocity can be described by the eye velocity sensitivity (R). Fuchs et al. (1988) showed that R increased with T for motoneurons but not for internuclear neurons. Based on this criteria, Broussard et al. (1995) categorized abducens neurons into putative motoneurons and internuclear neurons. We adopted the same approach in this study. For each abducens neuron, we computed its K, R, and T using the same methods of Fuchs et al. (1988). In Fig. 5B, R is plotted as a function of T, and the solid line is the regression line for identified motoneurons obtained by Fuchs et al. (1988) (R = 0.02 × T + 1.23). The dashed line in Fig. 5B divides motoneurons from internuclear neurons in the sample of Fuchs et al. (1988) (R = 0.044 × T + 2.2). Using the approach of Broussard et al. (1995), we identified abducens neurons that are plotted to the left and right of the dashed line in Fig. 5B as putative internuclear neurons and motoneurons, respectively.

The two populations exhibited similar characteristics as that described in Fuchs et al. (1988). The addition index and the latency to click are found to be similar between the two groups (P > 0.5). However, the putative internuclear neurons had larger multiplication index than the putative motoneurons (motoneuron: 6.92 ± 1.9, n = 11; internuclear neuron: 4.11 ± 0.5, n = 54; P < 0.05). This analysis indicates that the interaction of vestibular and eye position signals may be different in the two groups of abducens neurons. Nevertheless, because there is overlap between the two populations that cannot be separated using a single straight line, we suggest that more information should be obtained by analyzing identified motoneurons. This
The multiplication of vestibular and eye position signals may take place in the VOR interneurons in the vestibular nuclei, in the motoneurons in the abducens nuclei, or in both sites because these neurons receive separate vestibular signals (from vestibular afferents) and eye position signals (from neural integrators). Figure 6 shows a hypothetical convergence of vestibular and eye position signals in a VOR motoneuron or interneuron. Vestibular synapses are labeled as “contralateral (+)” or “ipsilateral (−)” to reflect that the VOR neuron receives monosynaptic (VOR interneurons: BT, EH, and PVP) or di-synaptic (VOR motoneurons) vestibular signals from the two labyrinths in a reciprocal fashion (Chubb et al. 1984; Fuchs and Kimm 1975; Keller and Daniels 1975; Keller and Kamath 1975; King et al. 1976; McFarland and Fuchs 1992; Miles 1974; Scudder and Fuchs 1992; Tomlinson and Robinson 1984). Eye position synapses are labeled as “left eye” or “right eye” to reflect that the VOR circuits encode monocular eye position signals (King et al. 1994; McConville et al. 1994; Sylvestre and Cullen 2002; Sylvestre et al. 2003; Zhou and King 1998). During fixation before click stimulation, the VOR neuron fires at a rate determined by eye position signals. After click stimulation, the click-evoked vestibular signals are first transmitted to the VOR interneurons (monosynaptic) and to the VOR motoneurons (di-synaptic).

There are two possible sites in a VOR neuron where eye position signal can modulate the vestibular-evoked response. The first site is in “the spike-generating mechanism” that converts the effective synaptic currents reaching the soma into action potentials. Eye position signal may contribute to the spike-generation nonlinearity by inducing changes in background excitation. However, the spike-generation nonlinearity alone may not produce the multiplication because a substantial amount of work has shown that it is not an easy task for a neuron to produce a response from its two inputs that approximates their multiplication (for review, see Salinas and Sejnowski 2001). The second site is in “the synaptic transmission mechanism” that converts presynaptic spike trains into postsynaptic currents. We hypothesize that the postsynaptic currents generated by synaptic inputs are dependent on both the characteristics of these inputs and the interactions between them. Two recent studies show that the spatial distributions of synaptic inputs can determine the modes of their interaction (Gasparini and Magee 2006; Poirazi et al. 2003; Prather et al. 2001). When synaptic inputs are distributed distantly in space,
input summation is additive. When synaptic inputs are clustered close in space, however, input summation is nonlinear and can be multiplicative. In the case of Fig. 6, the spatial separation of the vestibular inputs from the two labyrinths allows an additive interaction of their effects on the firing rates of the VOR neuron. For the same reason, the interaction of position signals from each eye is also additive. For the eye position and vestibular inputs that are clustered closely in space; however, their interactions are multiplicative. It will be important to determine the extent to which the two mechanisms contribute to the multiplicative computation reported here. This study, however, can not rule out the involvement of any mechanisms. Instead, it leaves an open question for future study.

Novel neural mechanism that implements the VOR gain modulation by fixation distance

The dependence of the translational VOR (TVOR) on target distance and gaze eccentricity has been well documented (Angelaki 2004; Crane and Demer 1998; Crane et al. 2003; Paige and Tomko 1991; Ramat and Zee 2003; Schwarz et al. 1989; Snyder and King 1992; Zhou et al. 2003). It is generally accepted that central signals proportional to fixation distance and eccentricity must exist to modulate otolith signals. The dependence of the angular VOR (AVOR) on target distance has been reported, but there has been controversy on whether semicircular canal signals are also modulated by fixation distance. Earlier studies (Snyder and King 1992; Viirre et al. 1986) documented the vergence effect on the gain of the AVOR, but the effect was attributed to the interaction of canal and otolith signals. These authors suggested that the canal-ocular reflex was not modulated by viewing-distance. Using head rotations with much higher frequency and acceleration, ocular reflex was not modulated by viewing-distance. Using and otolith signals. These authors suggested that the canal-ocular reflexes were modulated by viewing-distance. It is now believed that both canal and otolith signals are modulated by central signals proportional to fixation distance and eccentricity. Furthermore, the viewing distance effect was observed at the onset of both the TVOR and the AVOR, indicating that the VOR gain modulations are implemented not only by the indirect VOR pathways through the flocculus, but also by the direct VOR pathways in the brain stem (Angelaki 2004; Crane and Demer 1998; Crane et al. 2003; Lasker et al. 2002; Meng and Angelaki 2006; Meng et al. 2005; Paige and Tomko 1991; Ramat and Zee 2003; Schwarz et al. 1989; Snyder and King 1992; Zhou et al. 2003).

This study extends previous findings and further shows a multiplicative interaction of vestibular and horizontal conjugate eye position signals in the abducens neurons with disynaptic latency. Based on these results, we propose a novel neural mechanism that implements the VOR gain modulation by fixation distance and gaze eccentricity. The new mechanism consists of two principles that are derived from experimental data. The first principle is the Principle of Multiplication, which states that the effects of stimulating a single labyrinth interact multiplicatively with the position signals of each eye. The second principle is the Principle of Addition, which states that the effects of stimulating the two labyrinths interact additively. In the next section, we will show that the VOR gain modulation by fixation distance and gaze eccentricity can be implemented based on the two principles (Fig. 7).

Figure 7A shows that the effects of unilateral vestibular stimulation can be enhanced by vergence angle. The top panel of Fig. 7A schematically shows the Principle of Multiplication, i.e., the vestibular signals from a single labyrinth are multiplied by position signals of each eye before they are converted into motor commands that drive the movements of one eye. According to the Principle of Multiplication, the VOR gain (eye velocity/head velocity) of single labyrinth stimulation is linearly dependent on the position signals of each eye. Thus the
VOR gain of one eye (e.g., the right eye) to single labyrinth stimulation (e.g., the left labyrinth) can be described by the following equation

\[ G_{\text{LabyrinthL}} = G_{\text{LabyrinthL}} + G_{\text{Reye}} \times E_{\text{Reye}} + G_{\text{Reye}} \times E_{\text{Reye}} \]  \hspace{1em} (1.1)

where \( G_{\text{LabyrinthL}} \) is the VOR gain of the right eye when the left labyrinth is stimulated, \( G_{\text{LabyrinthL}} \) is the VOR gain when the left and right eyes are at the center gaze, respectively, \( E_{\text{Reye}} \) and \( E_{\text{Reye}} \) are the left and right eye positions, respectively, and \( K_{\text{Leye}} \) and \( K_{\text{Reye}} \) are the sensitivities of the VOR gain to eye position, respectively. In the bottom panel of Fig. 7A, the relationships of the VOR gain with the position signal of the right eye are represented by a straight line with a slope and an intercept that are corresponding to the \( K \) and \( G \) of that eye (e.g., \( K_{\text{Reye}} \) and \( G_{\text{Reye}} \)), respectively. When a subject fixates on a far target, the positions of the two eyes are equal \((E_{\text{Leye}} = E_{\text{Reye}})\). When the subject fixates on a near target that requires a 10° vergence angle, the left eye needs to rotate 10° more to the right than the right eye \((E_{\text{Leye}} = E_{\text{Reye}} + 10)\). The right eye at the center gaze is now accompanied by the left eye at the right 10°, i.e., the left eye line is shifted leftward by 10° and Eq. 1.1 becomes the following equation

\[ G_{\text{LabyrinthL}} = G_{\text{LabyrinthL}} + G_{\text{Reye}} \times E_{\text{Reye}} + G_{\text{Reye}} \times E_{\text{Reye}} \]  \hspace{1em} (1.2)

Equation 1.2 indicates that, compared with a far target, the VOR gain-eye position line for a near target has the same slope but a larger intercept \((G_{\text{Reye}} + G_{\text{Reye}} \times E_{\text{Reye}} + G_{\text{Reye}} \times E_{\text{Reye}})\), i.e., an upward shift of the black dotted line in the bottom panel of Fig. 7A. The new mechanism indicates that the VOR gain modulation by fixation distance can take place when only a single labyrinth is activated. This prediction is supported by data obtained in subjects with unilateral labyrinthectomy (Angelaki et al. 2000; Aw et al. 2003). However, there will be a potential problem if the Principle of Multiplication works alone. As indicated by the black lines in the bottom panel of Fig. 7A, the AVOR gain is dependent on gaze eccentricity, which is not appropriate because the AVOR gain should be independent of gaze eccentricity. We propose that the proper relationship of the VOR gain and gaze eccentricity can be achieved when the Principles of Multiplication and Addition work together.

Figure 7B shows how the VOR gain modulation by fixation distance and gaze eccentricity can be implemented by appropriate activations of the two labyrinths. The top panel of Fig. 7B schematically shows the Principle of Addition, i.e., the effects of the vestibular signals from the two labyrinths are linearly summed to drive the movements of one eye. According to the Principle of Addition, the VOR gain of one eye (e.g., the right eye) of a bilateral stimulation is the linear summation of the VOR gains of the two unilateral vestibular stimulations, which both are linearly dependent on eye position signals. These relationships can be described by the following equations

\[ G_{\text{LabyrinthL}} = G_{\text{LabyrinthL}} + G_{\text{LabyrinthR}} \]  \hspace{1em} (2.1)

\[ G_{\text{LabyrinthL}} = G_{\text{LabyrinthL}} + K_{\text{Liameter}} \times E_{\text{Reye}} \]  \hspace{1em} (2.1a)

\[ G_{\text{LabyrinthR}} = G_{\text{LabyrinthR}} + K_{\text{Liameter}} \times E_{\text{Reye}} \]  \hspace{1em} (2.1b)

where \( G_{\text{LabyrinthL}} \) is the VOR gain of the bilateral stimulation, \( G_{\text{LabyrinthL}} \) and \( G_{\text{LabyrinthR}} \) are the VOR gains of the left or the right labyrinth stimulation, respectively, \( G_{\text{LabyrinthL}} \) and \( G_{\text{LabyrinthR}} \) are the VOR gains of the left and right labyrinth stimulation, respectively, at the center gaze, and \( K_{\text{Liameter}} \) and \( K_{\text{Liameter}} \) are the sensitivities of the VOR gain to eye position when the left or the right labyrinth is stimulated, respectively. During a leftward head rotation or a leftward interaural head translation, the left labyrinth is excited (Fig. 7B bottom, blue line labeled L+) and the right labyrinth is inhibited (Fig. 7B bottom, red line labeled R–). When the two labyrinths are reciprocally stimulated, eye movements generated by the two labyrinths are in the same direction, but the slopes of the VOR gains to eye position have opposite signs \((K_{\text{Liameter}} = -K_{\text{Liameter}})\). Thus Eq. 2.1 is simplified as

\[ G_{\text{LabyrinthL}} = G_{\text{LabyrinthL}} + G_{\text{LabyrinthR}} \]  \hspace{1em} (2.2)

The solid black line in the bottom panel of Fig. 7B has slope 0, indicating that the VOR gain during the reciprocal activation of the two labyrinths is independent of eye position, as required by the geometrical constraints.

The new model can also account for the VOR gain modulation by gaze eccentricity during a nasal-occipital translation, which similarly activates the two labyrinths (Fig. 7B bottom, solid blue line, L+ and dotted red line, R–). In this situation, eye movements generated by the two labyrinths are in opposite directions, and the lines of the TVOR gain to eye position signal have the same slope but opposite intercepts \((K_{\text{Liameter}} = K_{\text{Liameter}}; G_{\text{LabyrinthL}} = -G_{\text{LabyrinthR}})\). Thus Eq. 2.1 is simplified as

\[ G_{\text{LabyrinthL}} = 2 \times K_{\text{Liameter}} \times E_{\text{Reye}} \]  \hspace{1em} (2.3)

The dotted black line \((L^+ + R^+)\) in the bottom panel of Fig. 7B shows that the nasal-occipital TVOR gain is proportionally dependent on gaze eccentricity as required by the geometric constraints (McHenry and Angelaki 2000; Paige and Tomko 1991). For example, as the head moves forward, the eyes must rotate rightward at a right gaze, leftward at a left gaze, and remain stationary at the center gaze.

For abducens motoneurons, this gaze eccentricity effect on the nasal-occipital translation VOR indicates that the neuronal responses caused by otolith activation should increase for a more lateral gaze. Because clicks activate the ipsilateral otolith-abducens pathways, the ipsilateral click-evoked abducens neurons’ responses should increase for either a more contralateral gaze or a more ipsilateral gaze. When the ipsilateral click-evoked responses increase for a more contralateral gaze, abducens neurons exhibit positive multiplicative indexes. When click-evoked responses increase for a more ipsilateral gaze, abducens neurons exhibit negative multiplicative indexes. Thus some abducens neurons mediating the nasal-occipital translational VOR are expected to exhibit negative multiplicative indexes. Indeed, when tested with ipsilateral clicks that activated the translational VOR pathways, a subgroup of abducens neurons (8 of the 34 neurons) had negative multiplication indexes. When tested with contralateral clicks that activated the angular VOR pathways, however, abducens neurons had positive multiplicative indexes. These results suggest that the interaction of vestibular and eye position signals in the AVOR pathways and the TVOR pathways may be implemented at different sites with different neural mechanisms.
Although the direct VOR pathways have the computational capacity to modulate the VOR gain by fixation distance, indirect VOR pathways have also been shown to contribute to the VOR gain modulation. For example, Snyder and King (1996) found that, during sudden off-axis head rotation, the responses of the gaze-velocity Purkinje cells in the cerebellar flocculus and ventral paraflocculus of rhesus monkeys was modulated by fixation distance. These indirect pathways may play an important role to account for the large differences in viewing distance effect for the TVOR and the AVOR. As shown in Fig. 8, the viewing distance effect is much larger for the TVOR than for the AVOR (Vierie et al. 1986). For example, when viewing distance is changed from 0.1 to 2 m, the AVOR gain is changed by a factor of 1.47, but the TVOR gain is changed by a factor of 20. Furthermore, earlier studies have shown TVOR gain changes in advance of (or even in the absence of) a change in eye position (Paige 1989; Schwarz and Miles 1991; Shelhamer et al. 1995; Skipper and Barnes 1989; Snyder et al. 1992), indicating that VOR gain changes could also be caused by other inputs to the direct or indirect pathways. We suggest that the appropriate parameters in the preceding equations for the direct and indirect TVOR and AVOR pathways need to be acquired through mechanisms of motor learning and neural plasticity.

The mechanism proposed here is consistent with a formal model by Khojasteh-Lakelayeh and Galiana (2006) that incorporated local nonlinearity to account for the VOR gain modulation by vergence. These results indicate that the VOR neurons should be treated as nonlinear summers of incoming activity with sensitivities that vary with the position signals of each eye. This local nonlinearity in the bilateral VOR network plays an important role in the VOR gain modulation by fixation distance and gaze eccentricity.

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REFERENCES

King WM, Lisberger SG, Fuchs AF. Responses of fibers in medial longitudinal fasciculus (MLF) of alert monkeys during horizontal and vertical


