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Complementary gain modifications of the cervico-ocular (COR) and angular vestibulo-ocular (aVOR) reflexes after canal plugging

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Abstract

To determine whether the COR compensates for the loss of aVOR gain, independent of species, we studied cynomolgus and rhesus monkeys in which all six semicircular canals were plugged. Gains and phases of the aVOR and COR were determined at frequencies ranging from 0.02 to 6 Hz and fit with model-based transfer functions. Following canal plugging in a rhesus monkey, the acute stage aVOR gain was small and there were absent responses to thrusts of yaw rotation. In the chronic state, aVOR behavior was characterized by a cupula/endolymph time constant of ≈ 0.07 s, responding only to high frequencies of head rotation. COR gains were ≈ 0 before surgery but increased to ≈ 0.15 at low frequencies just after surgery; the COR gains increased to ≈ 0.4 over the next 12 weeks. Nine weeks after surgery, the summated aVOR + COR responses compensated for

head velocity in space in the 0.5–3 Hz frequency range. The gains and phases continued to improve until the 35th week, where the combined aVOR + COR stabilized with gains of ≈ 0.5 –0.6 and the phases were compensatory over all frequencies. Two cynomolgus monkeys operated 3–12 years earlier had similar frequency characteristics of the aVOR and COR. The combined aVOR + COR gains were ≈ 0.4 –0.8 with compensatory phases. To achieve gains close to 1.0, other mechanisms may contribute to gaze compensation, especially with the head free. Thus, while there are individual variations in the time of adaptation of the gain and phase parameters, the essential functional organization of the adaption to vestibular lesions is uniform across these species.

Keywords

Cervico-ocular reflex; Semicircular canal plugging; Rhesus monkey; Cynomolgus monkey; Adaptation; Angular VOR; COR

Introduction

The angular vestibulo-ocular reflex (aVOR) generates slow-phase eye velocity that counter-rotates the eyes to stabilize gaze in space during angular head motion. The performance of the aVOR can be characterized by its gain (eye velocity/head velocity) and phase. When the head is rotated on the body, neck joints and muscle proprioceptors are also activated through the cervico-ocular reflex (COR), but how the COR contributes to gaze stabilization is not clear. Normally, the action of the aVOR is sufficient to maintain stability of gaze in space during head rotation, and the gain of the horizontal component of the aVOR is close to unity in monkey over a wide range of frequencies (Robinson 1963; Keller 1978; Crawford and Vilis 1991; Minor et al. 1999). If the COR complements the aVOR to stabilize gaze in space, then its gain should be close to zero under normal circumstances, a finding confirmed in a number of studies in humans (Takemori and Suzuki 1971; Barnes and Forbat 1979; Barlow and Freedman 1980; Thoden and Mergner 1988; Jurgens and Mergner 1989; Sawyer et al. 1994; Schubert et al. 2004), monkeys (Dichgans et al. 1973; Böhmer et al. 1982; Böhmer and Henn 1983a, b; Roy and Cullen 2002) and cats (Gresty and Baker 1976; Baker et al. 1982). Some investigators have found that when the body is rotated with the head held stationary in space, eye velocities induced by the COR are in phase with body rotation (Suzuki 1972; Baker et al. 1982; Böhmer et al. 1982; Böhmer and Henn 1983a). This is opposite to the direction of relative head-re-body rotation and would add a compensatory component when combined with the response of the aVOR. Other studies found the COR action to be anticomensatory (Barlow and Freedman 1980; Fuller 1980; Leopold et al. 1982; Chambers et al. 1985; Jurgens and Mergner 1989). This variation in phase could be due to the low COR gain in normal subjects, which has little effect on combined COR/aVOR responses in the normal state.

After bilateral semicircular canal plugging, however, the COR velocity gain increases (Baker et al. 1982; Böhmer et al. 1982; Böhmer and Henn 1983a). We recently demonstrated that the COR, following canal plugging, has a significantly increased gain and a compensatory phase for head velocity at frequencies where there is a loss of aVOR function (Yakushin et al. 2009). At higher frequencies, there is a substantial aVOR gain, and the COR gain progressively decreases to zero. The hypotheses that the COR acts to complement aVOR loss (Meiry 1971; Suzuki 1972; Dichgans et al. 1973; Hikosaka and Maeda 1973) is also supported by a study, which shows that the human COR gain increases with age as the aVOR gains declines, presumably due to hair cell loss (Bronstein et al. 1991). Thus, while other mechanisms may contribute to aiding gaze compensation following vestibular loss (Halmagyi and Curthoys 1988; JC 1952), the COR is well suited to play an important role in this gaze compensation.

The complementary function of the aVOR and the COR is reflected in vestibular and neck afferent inputs to central vestibular neurons. The activity of second-order vestibular-only (VO) neurons is significantly modulated by cervical input in normal squirrel and cynomolgus monkeys (Gdowski and McCrea 2000; Gdowski et al. 2001), but has not been found in rhesus monkeys (Sadeghi et al. 2009d). This presumed lack of cervical input to VO neurons has been inferred as an indication of an interspecies difference, leading to the conclusion that cervical inputs are not important for gaze stabilization in rhesus monkeys or by extrapolation, to humans either (Sadeghi et al. 2009d). This finding might also imply that there is different coupling of cervical inputs to central vestibular neurons in different nonhuman primate species and humans. Alternatively, the action of the cervical input via the COR may be equally important in every species when there is adaptation to a vestibular deficit. The purpose of this study was to compare the compensatory COR response in normal and canal-plugged rhesus and cynomolgus monkeys to study this question.

Methods

Experiments, which were performed on a rhesus monkey (*Macaca mulatta*) and four cynomolgus monkeys (*Macaca fascicularis*), conformed to the Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of Mount Sinai School of Medicine. Under anesthesia and sterile surgical conditions, a head mount was implanted on the skull of the animals to provide painless head fixation in stereotaxic coordinates during testing (Yakushin et al. 2000). Two weeks later, two coils were implanted on the left eye to measure horizontal, vertical, and torsional eye position (Judge et al. 1980; Dai et al. 1994). Later, all six semicircular canals were plugged in one rhesus (M3002) and two cynomolgus (M9357, M17115) monkeys by opening each bony canal via the mastoid cavity and packing the canal with fascia and bone chips (Suzuki et al. 1991; Cohen et al. 1983; Raphan et al. 1983; Yakushin et al. 1995, 1998). Specifically, the canal plugging involved “blue-lining” a 2–3 mm thin segment of each SCC, a gentle insertion of fascia sufficient to compress the membranous labyrinth and displace all endolymph and perilymph from the packed region, and finally an insertion of bone chips with sufficient force to ensure complete occlusion of the membranous labyrinth via compaction against the inner curvature of the osseous SCC.

Testing protocol

The rhesus monkey was tested before plugging and weekly after surgery, starting in the first week after canal plugging and continuing for 12 weeks. Tests were also repeated at 35–40 weeks after plugging. Cynomolgus monkeys were tested for five consecutive days, 3 (M17115) and 12 (M9357) years after canal plugging (long after they recovered from the surgery). There were no differences in the data obtained for the individual experiments, so they were combined. Data from one of these experimental days have been reported elsewhere (Yakushin et al. 2009).

Testing and recording paradigm

A manual two-axis rotator was designed for these experiments. It allowed rotation of the body in yaw under the head, which was fixed in space in the horizontal stereotaxic plane (Yakushin et al. 2009). The body was fixed to the back wall of the primate chair with harness. Yaw, pitch, and roll components of eye movement were recorded by a phase detection system mounted on the head (Ogorodnikov et al. 2006). Leftward yaw, downward pitch, and clockwise roll from the animal's point of view were positive. Eye movements were calibrated off-line based on induced eye velocities during rotation at 30°/s in light. We assumed that yaw and pitch aVOR gains of the canal-plugged monkeys were 1.0, and roll gain was 0.6 (Robinson 1963; Crawford and Vilis 1991; Henn et al. 1992; Dai et al. 1994;

Yue et al. 1994; Telford et al. 1996). Chair yaw and pitch positions and the three components of eye position were stored with a resolution of 16 bits at 1 kHz for off-line analysis. Body rotation relative to the spatially stationary head was inverted to represent relative head-re-body position. Only yaw eye movements were analyzed in this study. Differentiation for determining velocity was done by a linear fit to 11 data points of position. Saccades were identified using a maximum likelihood ratio criterion (Singh et al. 1981) and removed from the data stream.

aVOR gains were determined by sinusoidal oscillation of the animal with the head fixed in darkness at frequencies ranging from 0.05 to 6 Hz. The aVOR was also tested with manual thrusts of acceleration, which reached $\approx 5000^\circ/\text{s}^2$ and peak head velocities of $\approx 300^\circ/\text{s}$ (Curthoys and Halmagyi 1995; Halmagyi et al. 2001, 2008). COR gain was determined by rotating the body sinusoidally from 0.05 to 6 Hz with the head fixed in space (Yakushin et al. 2009). Because of technical limitations, oscillation was manual for frequencies above 1 Hz. There was some variability in frequency when manually oscillating from cycle to cycle. Because of this, the data were fit with a sinusoid at the average frequency of oscillation. COR and aVOR gains were defined as (amplitude of the sine fit through eye velocity)/(amplitude of the sine fit through head velocity at the same frequency). Positive phase shifts indicate that eye velocity led head velocity. We define the 180° out-of-phase relationship of eye and head velocity as 0° phase shift, since they were compensatory from the standpoint of the aVOR.

Data analysis

Responses of the aVOR were fit by a complex function derived from the model that represents the aVOR as a combination of a first-order model of the semicircular canal cascaded with velocity storage and a direct pathway around it. The model had been previously developed by Raphan et al. 1979 (see Raphan and Cohen 2002 for review). According to this model, the gains and phases of the aVOR were fit using the complex gain function, written in Laplace form as follows:

$$\text{aVOR_gain}(s) = \left(\frac{sT_c}{1+sT_c} \right) \cdot \left(g_0 \frac{T_o}{1+sT_o} + g_1 \right) \quad (1)$$

where T_c is the time constant of the cupula/endolymph canal eighth nerve response

- g_1 is the direct pathway gain
- g_0 is the canal coupling to the integrator
- T_o is the time constant of the velocity storage integrator.

The COR can also be modeled as first-order low-pass filter (leaky integrator) with a direct pathway gain from the neck to the oculomotor system:

$$\text{COR_gain}(s) = \left(\frac{g_{0\text{COR}}}{1+sT_{\text{COR}}} + g_{1\text{COR}} \right) \quad (2)$$

where

- $g_{1\text{COR}}$ is the direct pathway gain for the COR
- $g_{0\text{COR}}$ is the coupling to the COR integrator
- T_{COR} is the time constant of the COR integrator

Our previous studies showed that the direct pathway gain of the COR was negligible (Yakushin et al. 2009). Therefore, for fitting purposes, g_{1COR} was set to zero. The remaining model parameters (gains and time constants) for both the aVOR and COR were obtained by converting the sinusoidal gain and phase data to points in the complex plane in uniform units. The sum of distances between experimental points and model predictions was the error function that was minimized, using a modification of the gradient descent algorithm (Kivinen and Warmuth 1997). Local minima were avoided by reducing the parameter variation steps as the fit converged. Each parameter and associated variation step could be separately constrained and set manually at the start of the minimization procedure. The combined aVOR-COR response was obtained from separate aVOR and COR fits and summing the complex gains. Gain and phase plots were then derived from Eqs. 1 and 2 and their sum.

A coefficient of determination, R^2 , was used to determine goodness of the model fit to the data (Daniel 1995). This coefficient is given by:

$$R^2 = 1 - \frac{SS_{\text{err}}}{SS_{\text{Tot}}} \quad (3)$$

where SS_{err} is the sum of the squared errors between the data and model, given by Eq. 1 or 2, and SS_{Tot} is the total sum of squares, proportional to sample variance (Eq. 3). As the sum of squared errors between model and data approaches that of the sample variance of the data, the coefficient of determination approaches zero. Coefficients of determination were computed separately for aVOR and COR model fits based on data presented in uniform units in the complex plane (see Table 1). They went toward smaller values with time after plugging and the model fit to the data improved.

Results

Gain of aVOR and COR in normal animals

The gain of the aVOR of the rhesus monkey (M3002) was about 0.95, and the phase was compensatory across all frequencies (Fig. 1a, black symbols; Note that zero degrees, 0° , is out-of-phase with head velocity). The COR gain was negligible at frequencies above 1 Hz in this animal (Fig. 1a, gray symbols). The COR gains increased slightly to 0.1–0.2 as the stimulus frequency was decreased to 0.02 Hz. The phases of the COR were close to compensatory at low and medium frequencies, but were more scattered at higher frequencies (Fig. 1b, gray symbols).

Similar results were obtained from a normal cynomolgus monkey (M0216, Fig. 1c, d). That is, while the aVOR had an average gain of 0.86 (Fig. 1c, d, black symbols), the COR gain was above zero only at frequencies below 1 Hz (Fig. 1c, gray symbols). The dependence of the COR gain on frequency of oscillation was the same in a second cynomolgus (M17092, compare gray symbols in Fig. 1e), but the phase of the COR was not compensatory across frequencies (significantly different from 0° , $p < 0.05$) (Fig. 1f). The average gain of the aVOR in this animal was 0.86.

Thus, whether rhesus or cynomolgus, the normal monkeys had aVOR's that accurately compensated for head velocity with gains close to 1.0, and the COR gains were negligible. The COR gain was somewhat greater at low frequencies, but the phases were irregular, being compensatory or anticomensatory. This was not important, however, because of the negligible gains.

Gain of the aVOR and COR in a canal-plugged rhesus

aVOR—In the acute phase, 1 week after the canals were plugged in the rhesus monkey, the aVOR gain was less than 0.1 in response to sinusoidal rotation at 1 Hz, and the phase was advanced by about 180° relative to the compensatory response (Fig. 2a, 1 week After). At 5–35 weeks (Fig. 2b–d), the aVOR gain had increased, and the phase advance approached ≈90°. The gain and phase at 35 weeks were consistent with results previously obtained in six-canal-plugged cynomolgus monkeys (Yakushin et al. 1998) and a rhesus monkey (Hess et al. 2000). The aVOR gains were <0.1 in the acute phase for frequencies up to 6 Hz (Fig. 2f). The phases declined to ≈90° as the stimulus frequency approached 6 Hz. The characteristics of the gain and phase curves were also different in the chronic stage (Fig. 2f, g, blue traces) compared to the acute stage (Fig. 2f, g, red traces). When the animal was given head thrusts, no slow-phase eye velocity was induced 2 weeks after plugging (Fig. 2h, i). This was in contrast to the strong response to head thrusts in the chronic stage (Fig. 2j, k). Thus, the response of the aVOR was compromised at all frequencies in the acute state, but it adapted to a steady state level in the chronic state, where the high-frequency response was to a large extent preserved. The different time courses of the aVOR gain changes following canal plugging that were previously reported for cynomolgus (Yakushin et al. 1998) and rhesus (Angelaki and Hess 1996) monkeys indicates that the time course of the adaptation depends on the individual monkey rather than on the species.

COR—One week after plugging, the small COR gains were approximately the same as before surgery at frequencies above 3 Hz. There was, however, a significant increase in the COR gains at lower frequencies (Fig. 3a, compare gray and red symbols). The phase of the COR was compensatory relative to head velocity at frequencies below 2 Hz and lagged the compensatory response at higher frequencies (Fig. 3b, red symbols). Thirty-five weeks after plugging, the COR gains were above 0.1 at frequencies above 2 Hz (Fig. 3a, blue symbols). At lower frequencies, the COR gain gradually increased to 0.4–0.6 and the phase was compensatory and lagged the stimulus by ≈90° as the frequencies approached 6 Hz (Fig. 3b, blue symbols). Thus, after recovery from the effects of surgery, the COR gain was substantially larger. It was compensatory for head velocity at lower frequencies, but was anticomensatory at higher frequencies.

Complementary functions of aVOR and COR in a canal-plugged rhesus—In the first two weeks after plugging, the aVOR gain was negligible at all frequencies (Fig. 4a, red and gray traces), but it gradually increased over time, reaching ≈0.5, thirty-five weeks after surgery. The phase of the aVOR led the compensatory response by more than 200° at low frequencies during the first 5 weeks after surgery (Fig. 4b, red, gray and black lines) and was ≈90° at higher frequencies. By 9 weeks, the phase lead was ≈90° at low frequencies and approached 50° at higher frequencies. Later, the phase lead declined at high frequencies from ≈50° to 10° (Fig. 4b, dark blue). This animal was also tested 38, 39, and 40 weeks after surgery; the data were virtually the same as at 35 weeks (not shown). Thus, the acute stage of recovery lasted for ≈5 weeks in this animal and subsequently entered a chronic phase.

The COR gains and phases complemented the deficiencies in aVOR in both the acute and chronic states (Fig. 4c, d). The COR gain increased at low frequencies 2–5 weeks after surgery (Fig. 4c, gray and black lined), and at 9 weeks after surgery, the increase in the COR gain was substantial at all frequencies (Fig. 4c, light blue). The COR gain also remained high at 12 and 35 weeks (Fig. 4c, blue lines). The phase of the COR was compensatory at low frequency, but lagged by 80°–90° at higher frequencies. Such phase behavior remained the same in the chronic phase (Fig. 4d). Thus, the COR had a frequency response characteristic of a simple integrator and adapted its gain over time after plugging so that it

complemented the aVOR in the rhesus monkeys as in cynomolgus monkeys (Yakushin et al. 2009).

The summated aVOR + COR responses were not compensatory in the acute state following plugging (Fig. 4e–f, red, gray and black traces) particularly for frequencies from 1 to 3 Hz. In the chronic state, (ninth week after surgery), however, the gain of the summated response was above 0.3 with a phase that was close to compensatory. The summated gains stabilized 35th weeks after the surgery.

Gain of the aVOR and COR in a canal-plugged cynomolgus

A cynomolgus monkey (M9357) was retested several times 12 years after all six canals were plugged (Fig. 5). The aVOR gain was negligible at low frequencies (Fig. 5a), leading the compensatory response by $\approx 90^\circ$ (Fig. 5b). As the frequency was increased to 4 Hz, the phase lead decreased to $\approx 25^\circ$. This animal had the highest COR gain at the lowest frequencies (Fig. 5c) and the COR gain remained above 0.1 at all frequencies below 3 Hz. The phase of the response was compensatory (0°) at the lowest frequencies and gradually lagged the compensatory response by $\approx 90^\circ$ as the stimulus frequency reached 2–3 Hz (Fig. 5d). When the COR and aVOR were summed as vectors, the summated gain was above 0.4–0.5 for most of the tested frequencies (Fig. 5e), while the phases of the summated responses were close to compensatory at all times (Fig. 5f).

Model-based analyses of the data

To fit the data with the model described in Eq. 1–3, we assumed that $g_{0COR} = 0$. Four parameters determined by the fitting algorithm were g_{1COR} , T_{COR} , g_1 , and g_0 . The time constants T_o were set to 20 s, corresponding to the central velocity storage time constants of normal and canal-plugged monkeys (Raphan et al. 1979; Yakushin et al. 1998). The time constants T_c were set to 4 s and 0.07 s, corresponding to the canal time constants of normal and canal-plugged animals, respectively (Goldberg and Fernandez 1971; Büttner and Waespe 1981; Correia et al. 1992; Yakushin et al. 1998).

The time constant obtained for the COR was small at all times, being on average 0.104 ± 0.03 s. The gain of the direct pathway of the COR (g_{1COR}) was ≈ 0.2 and aVOR (g_1) was close to zero one week after surgery. Both parameters then gradually increase to ≈ 0.4 and ≈ 0.6 , respectively, within 12 weeks after the surgery. After that time, gains of both direct pathways remained unchanged (Fig. 6a).

Increases in the direct pathway gains over time were linear ($R > 0.9$, $n = 7$, $p \leq 0.01$). The slope of the fitted line was higher for aVOR gain (0.046) than for the COR gain (0.02), indicating that canal-related input played a dominant role in the compensation process. The coupling to the velocity storage integrator was relatively small ($-5 < g_0 \leq 5$) during the first several weeks after surgery, but became larger ($g_0 \geq 12$) for long period after surgery (12, 35 weeks). The phase of the aVOR in the acute state just after plugging was $\approx 180^\circ$, not the expected $\approx 90^\circ$ phase lead at low frequencies that is found in the chronic state (Yakushin et al. 1998). The model-based analysis indicated that there was a small negative coupling to velocity storage in the acute stage that gave rise to this inversion. The physiological reason for this is not clear, but because of the small gain of the response, this phase inversion was not significant.

Parameters of the model were also determined for the cynomolgus monkey M9357 and tested 12 years after the surgery. On average, T_{COR} was 0.223 s, the direct pathway gains for the COR and aVOR were 0.460 and 0.658, respectively. The coupling to the velocity storage integrator g_0 was 10.3. Similar results were obtained in the chronic state in the other cynomolgus monkey (M17115) 3 years after canal plugging (Table 2).

Thus, our results indicate that except for minor parameter variations, there was no substantive species difference between cynomolgus and rhesus monkeys, either in the properties of the aVOR or the complementary COR, following plugging. Our conclusions therefore indicate that there are convergent inputs from the neck and the vestibular periphery to central vestibular neurons in both species. There may be differences in the coupling of the parameters in the normal state between rhesus and cynomolgus, but after plugging the reflexes reorganize in a fundamentally similar fashion.

Discussion

This study demonstrates that the COR adapts over time to compensate for peripheral vestibular deficits. In the normal state, the canals function adequately to stabilize gaze via the aVOR, and the COR has a reduced function with negligible gain. When the canals are plugged, there is diminished function of the aVOR. Consequently, the COR in time takes over some of the aVOR functionality to stabilize gaze during head turns. The diminished canal function had both the acute and chronic states. In the acute state, the aVOR gain was negligible and did not respond to high acceleration head thrusts. While there was a response to sinusoidal stimulation, it appeared to be due to an inverted activation of velocity storage, but the coupling gains were small. The reason for inverted coupling is not clear. The aVOR gain and phase were adapted so that in the chronic state it was compensatory at higher frequencies, but at low frequencies the gain and phase remained compromised (Cohen et al. 1983; Raphan et al. 1983; Yakushin et al. 1995, 1998). The COR changes occurred during the acute state and stabilized approximately 9 weeks after plugging, while the aVOR was still altering its gain characteristics up to 35 weeks. This study also shows that these complementary changes in the aVOR and COR occurred in the same way in both the rhesus and cynomolgus monkeys and there were no interspecies differences in aVOR + COR reorganization after canal plugging.

There is universal agreement that in the normal state, there are essentially no compensatory slow eye movements induced by the COR (Takemori and Suzuki 1971; Dichgans et al. 1973; Gresty and Baker 1976; Barnes and Forbat 1979; Barlow and Freedman 1980; Baker et al. 1982; Böhmer et al. 1982; Böhmer and Henn 1983a, b; Thoden and Mergner 1988; Jurgens and Mergner 1989; Sawyer et al. 1994; Roy and Cullen 2002; Schubert et al. 2004), due to the complete compensatory behavior of the aVOR over a wide frequency range (Keller 1978; Büttner et al. 1981; Jäger and Henn 1981; Baloh 1989; Minor et al. 1999). There has been considerable controversy, however, whether there is adaptation of the COR following peripheral vestibular damage that compromises aVOR function (Atkin and Bender 1968; Gresty et al. 1977; Kasai and Zee 1978; Barnes and Forbat 1979; Baker et al. 1982; Böhmer et al. 1982; Leopold et al. 1982; Böhmer and Henn 1983a; Leopold et al. 1983; Chambers et al. 1985; Pettorossi et al. 1987; Rioult-Pedotti and Dieringer 1988; Bronstein et al. 1991, 1995; Heimbrand et al. 1996; Schubert et al. 2004; Sadeghi et al. 2006; Yakushin et al. 2009). A recent study of the COR in the rhesus monkey after unilateral neurectomy indicates that there was no increase in COR gain (Sadeghi et al. 2008, 2009a, c). This is to some extent consistent with the report on humans, when after unilateral vestibular lesions, some patients had no increase in the COR gain (Schubert et al. 2004). However, some patients had substantial increases in gain (Schubert et al. 2004), which may be related to differences in the lesions or to the rehabilitation protocol. Our finding that plugging generated substantial changes in the COR further indicates that there are differences in how the COR adapts following neurectomy. Our hypothesis is that bilateral canal nerve section abolishes spontaneous activity of vestibular neurons both peripherally and centrally (Yakushin et al. 2005), while plugging maintains central integrity (Goldberg and Fernandes 1975; Sadeghi et al. 2009b) that allows the neck afferents to access vestibulo-ocular neurons to implement the adaptive changes.

We have identified two states of adaptation following canal plugging: acute and chronic. The aVOR gain in a single rhesus in our study was negligible at low frequencies immediately after plugging, and it gradually increased to 0.6 at 6 Hz at 35 weeks after surgery. Further testing of the aVOR with thrusts of velocity supported the idea that there was no canal activation in the acute stage of recovery. Our conclusion is also supported by a study in guinea pigs that demonstrated that canal-plugged animals had no responses to thrusts of velocity within two–three months after surgery, although aVOR pathways could be activated with electrical stimulation of the labyrinth (Gilchrist et al. 2000). One reason for this acute deficit after canal plugging could be cupular detachment from the roof of the ampulla as a result of the plugging (Rabbitt et al. 1999). Over time, however, the cupula reattaches, giving rise to the chronic stage.

In the chronic stage following canal plugging, the phase of the aVOR response led the compensatory response by 90°. At higher frequencies, however, the phase of the aVOR was close to compensatory (0°). This is consistent with our previous finding that such changes in aVOR gains are the result of a reduction of the dominant time constant of the plugged canal from 4 s to 0.07 s (Yakushin et al. 1998). It is also consistent with primary afferent activity recorded after canal plugging in different species (Rabbitt et al. 1999; Sadeghi et al. 2010). As a result, the gain of the aVOR in the chronic state after plugging becomes deficient at low frequencies and the phase is advanced by 90° (Yakushin et al. 1995; Angelaki et al. 1996; Yakushin et al. 1998; Lasker et al. 1999; Rabbitt et al. 1999; Hess et al. 2000). At higher frequencies, however, function of the aVOR approaches normalcy.

In our previous studies, we found that cynomolgus monkeys reached a chronic state of aVOR adaptation within a week or two following plugging (Yakushin et al. 1998). In the present study, the acute stage in the rhesus lasted about 35 weeks, similar to gradual changes in gain following canal plugging in rhesus monkeys reported by others (Angelaki and Hess 1996; Angelaki et al. 1996). The first changes in the COR gain were observed a week after canal plugging, and the changes became maximal (gain $\approx$ 0.4) over the next 9 weeks; then stabilizing over 10 months after the surgery. Thus, adaptation of the COR is probably related to the relative time that aVOR adaptation remains in the acute state and stabilizes gaze, while aVOR gain adaptation enters the chronic state. Our study further indicates that all species examined have potential COR functionality, but the adaptation of the parameters that define the COR and the time course of adaptation is dependent on individual variability, not on species. Our previous study reported larger changes in COR gain at least in one cynomolgus monkey (Yakushin et al. 2009). This animal (M98078) also had an aVOR gain much lower than would be expected from an animal with plugged canals. Gains were very small even when tested with the thrusts of velocities in canal planes (unpublished data). Thus, the reported differences in COR gain for some cynomolgus monkeys show that adapted parameters of aVOR and COR gains are interrelated. Greater aVOR loss is accompanied by greater COR gains (Yakushin et al. 2009).

A question that arose was why the COR gain only increased to 0.4–0.8 even at the lowest frequency even though data from the same animals indicate that COR gains can be forced to adapt to higher values (Kolesnikova et al. 2009; Yakushin et al. 2010). One possible explanation is that there are two types of cervically induced, oculomotor responses during passive body oscillation relative to the head: a slow phase of eye rotation and eye position changes due to saccades that occur in the same direction as the slow COR phase (Schlagfeldverlagerung) (Frenzel 1928; Leopold et al. 1982). Normal subjects utilize one or another behavior to a different extent. Barnes and Forbat (Barnes and Forbat 1979) demonstrate that if only the slow component is considered for analysis, then the COR gain of all normal human subjects was about 0.05. When changes in eye position due to saccades were considered together with slow eye movements, the gain was $\approx$ 0.3 in the subjects that

utilized saccadic behavior ($\approx 40\%$ of subjects). Thus, a more complete understanding of the aVOR + COR will come from a model-based analysis that includes saccades as well as the slow compensatory behavior, which is beyond the scope of this work.

Our study did allow us to put the function of the COR in a contextual frame. Although the normal aVOR stabilizes gaze at frequencies up to 20 Hz (Minor et al. 1999), COR adaptation after lesions only resulted in measurable responses for stimuli below about 2–3 Hz. The COR is therefore essentially a low-frequency system, like visual following mechanisms i.e., smooth pursuit and optokinetic responses, and the COR's normally negligible gain suggests that it is merely redundant with those systems. However, our data indicate that the frequency range over which cervical proprioceptive inputs provide useful information about head rotation bridges the zone where neither visual following systems (which are low-pass) nor the aVOR (which is high-pass) can stabilize gaze alone. Even though the velocity storage mechanism extends the aVOR's frequency response down to partly overlap with that of visual following systems (Raphan et al. 1979), gaze stabilization in this range evidently requires a combination of systems, with each acting near its limits of performance. In addition to their role in driving a COR that is unmasked after labyrinthine injury, perhaps neck proprioceptive inputs normally play a corroborative role during activities for which no one sensory system provides a definitive signal to drive gaze stabilization.

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Fig. 1.
a, b, aVOR gains (*black symbols*) and COR gains (*gray symbols*) from a normal rhesus monkey (M3002). **c–f,** aVOR and COR gains and phases for normal cynomolgus monkeys (M0216, and M17092). The *horizontal dashed lines* represent unity gains and zero phases. The responses were tested for frequencies up to 6 Hz

Fig. 2.

a–e, Yaw eye velocities induced at different times after canal plugging in rhesus monkey M3002 by head oscillations at 1 Hz. Note that the scale on the ordinates represent different velocities. The *dashed vertical line* shows the peak head velocity, and the *gray vertical line* represents the peak eye velocities in each test. The *down arrow* in **e** represents a 90° phase advance. **f, g,** aVOR gains and phases tested in M3002 one week (*red symbols*) and 35 weeks (*blue symbols*) after canal plugging. Curves are model-based fits through the data (see Eqs. 1–3). **h–k,** Responses to head thrusts two weeks (*red, on left*) and 35 weeks (*blue, on right*) after canal plugging for rotation in clockwise (*top traces*) and counter-clockwise directions (*bottom traces*). The head velocities (*gray traces*) in all panels of this figure were inverted to facilitate comparison with eye velocity

Fig. 3. COR gains (a) and phases (b) from rhesus monkey M3002 one week (red symbols) and 35 weeks (blue symbols) after canal plugging. Lines are model-based least mean square fits through the data (Eqs. 1–3)

Fig. 4.

a, b, aVOR gains and phases, **c, d,** COR gains and phase, **e, f,** and summated aVOR + COR gains and phases from rhesus monkey M3002. Each curve is a model fit of the actual data. The *individual colors* represent data obtained on different days after plugging, as shown by the insets in **d**. The *horizontal dashed lines* in **d** and **f** represent 0° phases

Fig. 5.

a, b, aVOR gains and phases, **c, d,** COR gains and phase, **e, f,** and summated aVOR + COR gains and phases from cynomolgus monkey M9357. Each curve is a model fit of the actual data. The *horizontal dashed lines* in **b, d** and **f** represent 0° phases

Fig. 6.
a Model-based direct pathway gains of the COR (g_0 COR, gray) and aVOR (g_1 aVOR, black). **b** Coupling to velocity storage integrator (g_0 COR). The symbols in (a) and (b) represent parameters taken from fits through actual data obtained in single experiments. Lines are linear fits through the model parameters were from data taken in the first twelve weeks after surgery

Table 1

R^2 of the model fits to the data as a function time after canal plugging

Time after canal plugging (weeks)	COR	aVOR
1	0.75	0.90
2	0.68	0.94
3	0.54	0.36
5	0.81	0.57
9	0.59	0.27
12	0.62	0.25
35	0.23	0.14

Table 2

Experimentally determined model parameters

Monkey	Time after surgery	T_{COR}	$g_{1\text{COR}}$	g_0	g_1
M3002	35 weeks	0.104	0.416	12.4	0.548
M9357	12 years	0.223	0.460	10.3	0.658
M17115	3 years	0.271	0.494	12.4	0.676