Effects of Canal Plugging on the Vestibuloocular Reflex and Vestibular Nerve Discharge During Passive and Active Head Rotations

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[1]*Department of Physiology, McGill University, Montreal, Quebec, Canada;* [2]*Department of Neurobiology, Pharmacology, and Physiology, University of Chicago, Chicago, Illinois; and* [3]*Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland*

Sadeghi SG, Goldberg JM, Minor LB, Cullen KE. Effects of canal plugging on the vestibuloocular reflex and vestibular nerve discharge during passive and active head rotations. *J Neurophysiol* 102: 2693–2703, 2009. First published September 2, 2009; doi:10.1152/jn.00710.2009. Mechanical occlusion (plugging) of the slender ducts of semicircular canals has been used in the clinic as well as in basic vestibular research. Here, we investigated the effect of canal plugging in two macaque monkeys on the horizontal vestibuloocular reflex (VOR) and the responses of vestibular-nerve afferents during passive head rotations. Afferent responses to active head movements were also studied. The horizontal VOR gain decreased after plugging to <0.1 for frequencies <2 Hz but rose to about 0.6 as frequency was increased to 15 Hz. Afferents innervating plugged horizontal canals had response sensitivities that increased with the frequency of passive rotations from <0.01 (spikes/s)/(°/s) at 0.5 Hz to values of about 0.2 and 0.5 (spikes/s)/(°/s) at 8 Hz for regular and irregular afferents, respectively (<50% of responses in controls). An increase in phase lead was also noted following plugging in afferent discharge, but not in the VOR. Because the phase discrepancy between the VOR and afferent discharge is much larger than that seen in control animals, this suggests that central adaptation shapes VOR dynamics following plugging. The effect of canal plugging on afferent responses can be modeled as an increase in stiffness and a reduction in the dominant time constant and gain in the transfer function describing canal dynamics. Responses were also evident during active head rotations, consistent with the frequency content of these movements. We conclude that canal plugging in macaques is effective only at frequencies <2 Hz. At higher frequencies, afferents show significant responses, with a nearly 90° phase lead, such that they encode near-rotational acceleration. Our results demonstrate that afferents innervating plugged canals respond robustly during voluntary movements, a finding that has implications for understanding the effects of canal plugging in clinical practice.

INTRODUCTION

Occlusion (plugging) of the slender duct of a semicircular canal has been used clinically for the treatment of vestibular disorders, including benign paroxysmal positional vertigo that is not alleviated by repositioning maneuvers (Parnes and McClure 1990) or surgical treatment of the superior canal dehiscence syndrome (Minor et al. 1998). The procedure was originally introduced by Ewald in the late 1800s (Ewald 1892) and reintroduced by Money and Scott (1962) to study the function of semicircular canals. As a result of this intervention, the movement of endolymph within a semicircular canal is greatly reduced, leading to minimal stimulation of hair cells during angular motion. Notably, studies of the

vestibuloocular reflex (VOR) have demonstrated that plugging produces a selective reduction in function of the operated canal while preserving relatively normal function in the other canals (Carey et al. 2007; Cremer et al. 1998). Furthermore, plugging an individual canal or combination of canals has long been a preferred method for studying the consequences of vestibular loss since the spontaneous discharge of afferents innervating the plugged canals is preserved (Goldberg and Fernandez 1975; Rabbitt et al. 1999). In contrast, labyrinthectomy—a method also commonly used in studies of vestibular compensation—eliminates the resting discharge of vestibular-nerve afferents (Guth et al. 1998; Sadeghi et al. 2007). Finally, afferent recordings (Goldberg and Fernandez 1975) and behavioral studies (Arai et al. 2002; Lasker et al. 1999) show that otolith function is preserved after canal plugging. For these reasons, the method has become an important tool in basic research studies of the responses of individual canals and canal–otolith interactions.

It had been thought that plugging rendered a canal insensitive to head rotations (Goldberg and Fernandez 1975; Money and Scott 1962). VOR studies, however, have shown that canal plugging does not result in a complete loss of function. In rhesus monkeys (Angelaki and Hess 1996; Angelaki et al. 1996; Hess et al. 2000), squirrel monkeys (Lasker et al. 1999), and cynomolgus monkeys (Yakushin et al. 1998) canal plugging effectively reduces VOR responses at rotational frequencies <0.5 Hz. At higher rotational frequencies, however, the gain of the VOR response after plugging reaches up to about 50% of values obtained in studies of normal animals (Huterer and Cullen 2002; Minor et al. 1999; Paige 1983; Sadeghi et al. 2006). Consistent with these VOR results in monkeys, vestibular-nerve recordings in the toadfish have shown that plugging is effective in reducing the responses of canal afferents by 10- to 100-fold during low-frequency (0.2 Hz) rotations, but has a much smaller effect as frequency is raised toward 10 Hz, where the gain was reduced by a factor of only about 2 (Rabbitt et al. 1999, 2001). Rabbitt and colleagues developed a three-dimensional model to explain the influence of surgical plugging on semicircular canal mechanics. In the model, localized distensions and contractions of the membranous canal duct, which are negligible under normal circumstances, are exacerbated after canal plugging and can lead to displacements of the cupula and endolymph. The hypothesized deformations depend on the stiffness of the membranous canal duct and surrounding perilymphatic space and are postulated to vary across species.

Here our first goal was to characterize the response dynamics of afferents innervating plugged canals in macaque monkeys. Although the results in toadfish provide a convincing

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qualitative explanation for the VOR results in monkeys, there were two reasons that prompted our study. First, the response dynamics of afferents from plugged canals in monkey versus those reported in the toadfish study are likely to differ. Notably, plugging in the toadfish was done in acute preparations and was accomplished by a small-caliber indenter narrowly occluding a widely exposed canal duct. In monkeys, the procedure is done chronically and involves only restricted exposure of the canal duct, which is closed with bone dust and fascia (Lasker et al. 1999). Given the procedural differences, canal plugging in the monkey would likely result in a greater increase in stiffness and thus a greater decrease in rotational sensitivity. Second, previous studies in monkeys (Lasker et al. 1999; Yakushin et al. 1998) have assumed that changes in the VOR that result from canal plugging faithfully parallel alterations in canal biomechanics. To investigate this assumption, we also compared the VOR with afferent discharge in the same animals. We found that afferents innervating plugged horizontal canals had response sensitivities that increased with the frequency of rotations, such that plugging in macaques was effective only at frequencies <2 Hz. An increase in phase lead was also noted following plugging in afferent discharge, but not in the VOR.

A second goal of our study was to characterize afferent responses that innervate plugged canals during active head movements. The aforementioned studies were done in head-restrained monkeys. Previous studies (Armand and Minor 2001; Huterer and Cullen 2002) have shown that orienting head-on-body movements have significant power for frequencies up to about 20 Hz. Considering the residual response of these afferents to passive high-frequency (i.e., >2 Hz) rotations, we predicted that afferents innervating plugged canals should be responsive during the voluntary head movements made in everyday life. To address this question, recordings were made from afferents while head-unrestrained monkeys made voluntary head-on-body movements during orienting gaze shifts. Our results demonstrate that the afferents innervating plugged canals respond robustly during voluntary movements—a finding that has important implications for understanding the effects of canal plugging, an intervention used to treat specific vestibular pathologies.

METHODS

Surgical preparation

Two macaque monkeys (*Macaca fascicularis*) were prepared for chronic recordings from the vestibular nerve. All procedures were approved by the McGill University Animal Care Committee and were in compliance with the guidelines of the Canadian Council on Animal Care and the National Institutes of Health.

The surgical preparation has been previously described (Sadeghi et al. 2007). Briefly, using aseptic techniques and isoflurane anesthesia (2–3%, to effect), a dental acrylic implant was fastened to each animal's skull using stainless steel screws. In addition, a stainless steel post, which was used to restrain the animal's head in the standard stereotaxic position, and a stainless steel recording chamber, which was positioned to provide access to the vestibular nerve (posterior angle of 30°), were attached to the implant. In the same procedure, a 17- to 18-mm-diameter eye coil, consisting of three loops of Teflon-coated stainless steel wire, was implanted in one eye beneath the conjunctiva (Fuchs and Robinson 1966). Following the surgery, animals were administered buprenorphine (0.01 mg/kg, administered intramuscularly [im]) for postoperative analgesia, and the antibiotic cephazolin (Ancef; 25 mg/kg im, for 5 days).

After >1 mo, a labyrinthectomy contralateral to the recording side was performed on the animals, as previously described (Sadeghi et al. 2007). About 2 mo later, a final surgery was performed in which we plugged the horizontal (HC) and posterior (PC) semicircular canals on the previously intact side with bone dust and fascia, as described previously (Carey et al. 2007; Lasker et al. 1999). Because of the contralateral labyrinthectomy, VOR responses were the result of activation of ipsilateral canals. We did not histologically verify our canal plugs. Rather, we relied on a physiological criterion. As shown, by Rabbitt et al. (1999), appreciable low-frequency responses would result even if a small fraction of the canal duct would remain patent. Such responses were not seen.

Data acquisition

The experimental setup, apparatus, and methods for data acquisition were similar to those previously described (Sadeghi et al. 2007). Gaze and head position were monitored using the magnetic search coil technique: a search coil was implanted around the monkey's eye to measure gaze position (see earlier text) and another coil was fixed to the monkey's head during the experiments to measure head position. Vestibular stimulation and data acquisition were controlled by a real-time data-acquisition system (REX) (Hayes et al. 1982). Gaze and head positions and vestibular turntable velocity were recorded on digital audio tape with unit activity for later playback off-line. During playback head and gaze position as well as table velocity signals were low-pass filtered at 250 Hz by an eight-pole Bessel filter and sampled at 1 kHz.

Vestibular nerve recording procedures

Single-unit extracellular recordings from vestibular nerve afferents were made using glass micropipettes during a period of 2 wk to 2 mo after canal plugging. Micropipettes were filled with 3 M NaCl and had impedances of 20–25 MΩ. Throughout the experiments, the head was held fixed in the normal stereotaxic position (i.e., HC angled ~22° upward from the plane of horizontal rotation). To minimize linear forces, the ear on the recording side was centered over the axis of rotation. Once an afferent was isolated, a series of manual rotations and tilts were applied to identify its organ of origin (Goldberg and Fernandez 1975). Notably, after plugging the HC and PC, units were identified as superior canal (SC) afferents if they responded to contralateral yaw and nose-down pitch rotations (~0.5 Hz, 50°/s) and as a non-SC (HC or PC) unit if they did not respond to 0.5-Hz yaw or pitch rotations or tilts. Although we could not stimulate the plugged canals with rotations at low frequencies, afferents innervating the HC or PC could be distinguished by their response to higher frequencies. Afferents innervating the HC showed excitatory responses to ipsilateral rotations, whereas those innervating the PC were excited during contralateral rotations. On most punctures, SC units with nearly normal responses indicated that the recording microelectrode was in the vestibular nerve.

Experimental paradigms

VESTIBULOOCULAR REFLEX. Whole-body sinusoidal yaw axis rotations were applied at frequencies of 0.5, 1, 2, 4, 8, 10, and 15 Hz to test the vestibuloocular reflex (VOR). Rotations at frequencies <8 Hz reached peak velocities of 50°/s, whereas rotations at 8, 10, and 15 Hz were limited to peak velocities of 40°/s. VOR testing was first done in the stereotaxic plane. To test whether the SC contributed to observed responses, the VOR was also tested with the animal's head aligned in the HC's plane of maximum activation (22° nose down), such that inputs from the SC were eliminated. The gain of the VOR in this nose-down position increased by only about 10% relative to that in the stereotaxic position and the response phase was unaffected.

VESTIBULAR-NERVE AFFERENTS. The responses of afferents inner-vating the plugged horizontal canals were characterized by applying whole-body sinusoidal rotations at frequencies of 0.5, 1, 2, 4, and 8 Hz in the stereotaxic plane. Rotations at frequencies <8 Hz reached peak velocities of 50°/s. For rotations at 8 Hz, peak velocities were limited to 40°/s to maintain single-unit isolation. Only data from afferents that were recorded for at least three frequencies were analyzed.

Once the neuron's sensitivity to head velocity during passive rotations was characterized, the monkey's head was carefully released to allow freedom of motion about the yaw (horizontal) axis (Roy and Cullen 2001; Sadeghi et al. 2007). The activities of neurons were then recorded during voluntary combined eye-head gaze shifts (>50°) made to orient to food targets. Such gaze shifts typically result in head velocities of ≤400°/s and a frequency content of ≤20 Hz (Huterer and Cullen 2000; Fig. 3).

Data analysis

Data were imported into the Matlab (The MathWorks, Natick, MA) programming environment for analysis. Recorded gaze and head position signals were digitally filtered with zero phase at 125 Hz using a 51st-order finite-impulse-response (FIR) filter with a Hamming window. Position signals were then differentiated to produce velocity signals. The neural discharge was represented using a spike density function in which a Gaussian function was convolved with the spike train (Cullen et al. 1996).

The resting discharge of each unit and coefficient of variation (CV) of the interspike interval were determined from about 10 s of resting discharge that was collected while the animal was stationary in the standard stereotaxic position. A normalized coefficient of variation (CV*) was calculated, as in Sadeghi et al. (2007), using the method described by Goldberg et al. (1984). Afferents with a CV* > 0.1 were considered as irregular and regular afferents were identified as having a CV* < 0.1. A least-squared regression analysis was used to describe each unit's response

$$fr = bias + (g_v \times hhv) + (g_a \times hha) \qquad (1)$$

where fr is the firing rate, hhv is the horizontal head velocity, hha is the horizontal head acceleration, bias is the resting discharge, and g_v

and g_a are coefficients. To compare a model's ability to predict an afferent's firing rate, the fractional variance-accounted-for (VAF) was computed: VAF = 1 − [var (mod − fr)/var (fr)], where mod represents the modeled firing rate and fr represents the actual firing rate, and a VAF of 1 indicates a perfect fit to the data (Cullen et al. 1996). Note that the VAF in linear models is equivalent to the square of the correlation coefficient (R^2). The coefficients in *Eq. 1* were then used to determine each afferent's head velocity sensitivity (spikes/s)/(°/s) and phase with respect to head velocity (deg) using the following equations (Sadeghi et al. 2007, 2009b)

$$S = \sqrt{[g_v^2 + (2 \times pi \times f \times g_a)^2]}$$

$$\varphi = atan [2 \times pi \times f \times (g_a/g_v)] \times (180/pi)$$

Sensitivities and phases were calculated for sinusoidal rotations at each frequency tested (Sadeghi et al. 2007).

Unless otherwise stated, values are means ± SD.

RESULTS

We first describe the VOR evoked by passive sinusoidal head rotations ≤15 Hz following contralateral labyrinthectomy and ipsilateral plugging of horizontal (HC) and posterior (PC) canals. We then describe the corresponding afferent response dynamics during passive sinusoidal head rotations, as well as the responses of these neurons to active head movements.

VOR responses to passive sinusoidal rotations in the horizontal plane

To characterize response dynamics of the VOR evoked by stimulation of the plugged HC, we applied whole-body rotations over a large frequency range (0.5–15 Hz). In both animals, the VOR response was negligible at lower frequencies (<2 Hz). However, as shown in Fig. 1A, a small response was observed at 2 Hz and response amplitude increased as frequency was raised. This point is emphasized in the *right panels* of Fig. 1A, where robust VOR responses were elicited by
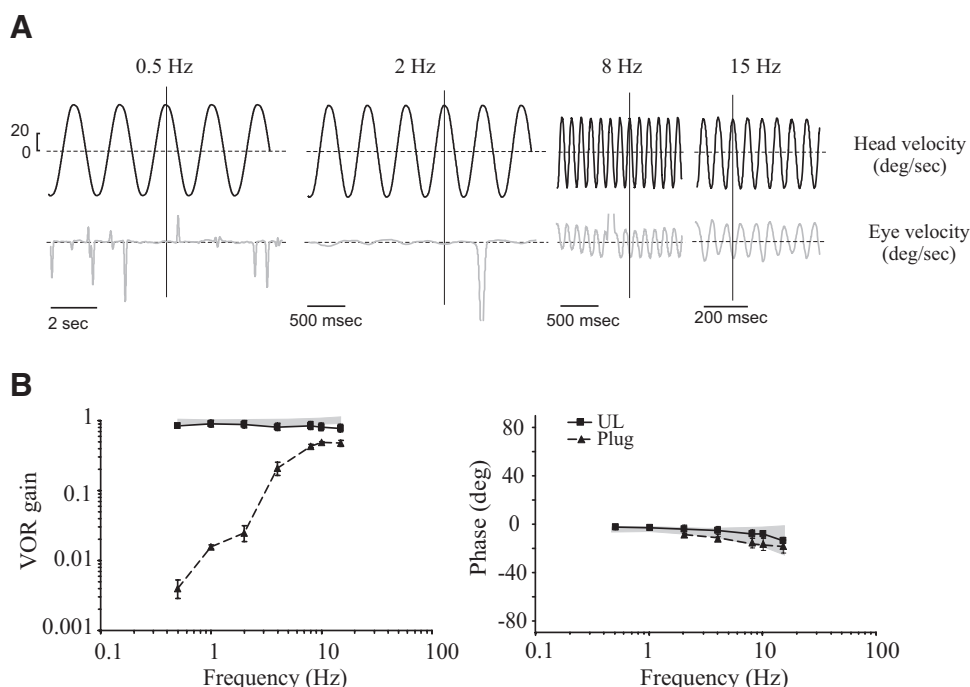

FIG. 1. Vestibuloocular reflex (VOR) response to sinusoidal whole-body rotations. *A*: VOR responses in one animal at different rotation frequencies after unilateral labyrinthectomy (UL) and plugging (PL) of the horizontal and posterior canals on the opposite side. The response is negligible at 0.5 Hz, but the gain increases as frequency increases to 8 and 15 Hz. Note the different timescales. *B*: Bode plot averaged for 2 animals after UL + PL. The gain of the response (*left plot*, dashed line) increases with increasing frequency, reaching values close to those observed following unilateral labyrinthectomy (solid line; from Sadeghi et al. 2007) and control animals (gray shaded area; from Huterer and Cullen 2002) at the highest frequency tested. The phase of the response (*right*, dashed line) was similar to that of the response following unilateral labyrinthectomy (UL, solid line; from Sadeghi et al. 2007) or in control animals (gray area; from Huterer and Cullen 2002).

rotation at 8 and 15 Hz. A Bode plot, averaged for the two animals after canal plugging, is shown in Fig. 1B. Notably, the gain of evoked eye movements was negligible (<0.1) for frequencies <2 Hz (Fig. 1B, left). Response gain then increased as a function of frequency between 2 and 10 Hz and plateaued after this such that it reached a maximum of about 0.6 at 15 Hz.

Average control responses in intact animals (gray area; Sadeghi et al. 2007) as well as after unilateral labyrinthectomy (UL) but before plugging for the two animals are included in Fig. 1B and compared with plugged data for the same two animals. Similar to a previous study (Sadeghi et al. 2006), the gain of the response for the two animals decreased by roughly 50% immediately following unilateral labyrinthectomy at all frequencies of rotation and recovered to values of 0.89 ± 0.02 (mean $\pm$ SE) to 0.71 ± 0.01 for rotations at 0.5 to 15 Hz 1 wk after lesion and stayed at this level 1 mo after lesion. Response gains after plugging never quite reached the levels observed in either control or UL conditions. Moreover, similar to our previous results, the phase of the VOR response after UL (Fig. 1B, right) was in the range observed in control conditions for both animals. Notably, our results in fascicularis monkeys also resemble those of previous studies in cynomolgus (Yakushin et al. 1998) and squirrel monkeys (Lasker et al. 1999) in that gains, which are relatively constant in control animals, were lower than normal at low frequencies (0.5–2 Hz) and increased with frequency of rotation after canal plugging. In the other monkey species, canal plugging resulted in appreciable phase leads that were, nevertheless, smaller than predicted theoretically (Rabbitt et al. 1999) or observed in our vestibular-nerve recordings (see following text).

Responses of afferents innervating the plugged HC to passive sinusoidal rotations in the horizontal plane

We recorded from 92 vestibular nerve fibers after contralateral labyrinthectomy and ipsilateral plugging of the horizontal and posterior canals. On the basis of their responses to low- and high-frequency passive sinusoidal rotations 44, 22, and 26 of these afferents were identified as innervating the HC, PC, and SC, respectively. In the present study, we focused on the responses of HC afferents since we were able to apply high-frequency rotations along their axis of maximal sensitivity. When classified based on regularity of discharge, there were 20 regularly discharging (CV* = 0.04 ± 0.01) and 24 irregularly discharging (CV* = 0.3 ± 0.15) HC afferents, with mean resting discharges of 81.4 ± 8.0 and 80.5 ± 41.2 spikes/s, respectively. Although the mean resting rate values were lower for both afferent classes (t-test, $P < 0.000$ and $P = 0.03$) than those reported in our previous studies after unilateral labyrinthectomy [Sadeghi et al. 2007; 101.9 ± 28.6 and 100.5 ± 41.3 spikes/s for regular ($n = 127$) and irregular ($n = 208$) afferents, respectively], the difference most likely reflects a sampling bias. This assumption is supported by the observation that the apparent differences decrease when afferents innervating plugged PC units (9 regular, 13 irregular) were added to the population of afferents in the present study (regular units: 89.1 ± 13.9 spikes/s, t-test, $P = 0.001$; irregular units: 89.2 ± 33.2 spikes/s, t-test, $P = 0.07$).

Of the 44 HC units, 19 (11 regular, 8 irregular) afferents were tested at three or more frequencies in the range of 0.5–8 Hz. Figure 2A shows examples of the responses of two units, one regular and the other irregular, each innervating a plugged HC. The afferents were typical in that both showed minimal responses at ≥ 0.5 Hz and larger responses as frequency was increased, reaching values of 0.2 and 0.5 (spike/s)/(°/s) at 8 Hz, for the regular and irregular units, respectively. Similar results were seen across our population of afferents (Fig. 2B, left); response sensitivities were negligible (<0.03) at the lowest frequencies of rotation, but increased as a function of frequency >2 Hz. Average sensitivities of irregular and regular afferents innervating intact canals (gray area: top and bottom traces, respectively; Sadeghi et al. 2007) are superimposed for comparison. Even at the highest frequency tested the mean sensitivities of either regular or irregular units were smaller after canal plugging. Figure 2B (right) compares the mean phase lead of irregular and regular afferents innervating plugged canals (black and gray lines) and intact canals (gray shaded area). Both irregular and regular afferents innervating plugged canals showed phase leads of 70–90° relative to velocity over the 2 to 8 Hz frequency range (Fig. 2B, right). In contrast, the phase leads for afferents innervating intact canals increased as a function of rotation frequency, but remained smaller than those for plugged canals by an average of 40° (regular units) and of 20° (irregular units).

Responses of afferents innervating the plugged HC to active head-on-body rotations in the horizontal plane

We next recorded from afferents in head-unrestrained monkeys to establish whether an afferent innervating a plugged canal would respond to voluntary head movements made during everyday activities. Figure 3 illustrates the responses of an irregular (Fig. 3A) and a regular (Fig. 3B) afferent innervating the plugged HC during active head movements. The top panels show head velocities and accelerations for two typical active head movements produced in association with large (~60°) eye–head gaze shifts. Like the vast majority (>80%) of large head movements, these examples were typical in that they reached velocities of >300°/s and accelerations of >4,000°/s^2. Moreover, consistent with previous studies (Armand and Minor 2001; Huterer and Cullen 2002), these orienting head-on-body movements had significant power for frequencies up to about 20 Hz (top panels, insets).

Given that 1) orienting head movements have significant high-frequency content and 2) afferents innervating plugged canals are responsive to head rotations in this frequency range, we predicted that HC afferents in plugged animals would be responsive during active orienting head movements. To test this prediction, we recorded from the afferents that innervated plugged canals during voluntary horizontal head movements. Of the 30 fibers innervating the plugged HC and tested during active head movements, we were able to test 21 afferents during both low- and high-frequency passive sinusoidal rotation. Of these, 9 units had regular (CV* = 0.05 ± 0.03) and 12 units had irregular (CV* = 0.32 ± 0.17) resting discharges. Figure 3 (bottom) shows the corresponding responses of an irregular and a regular afferent during large active, self-generated head movements.
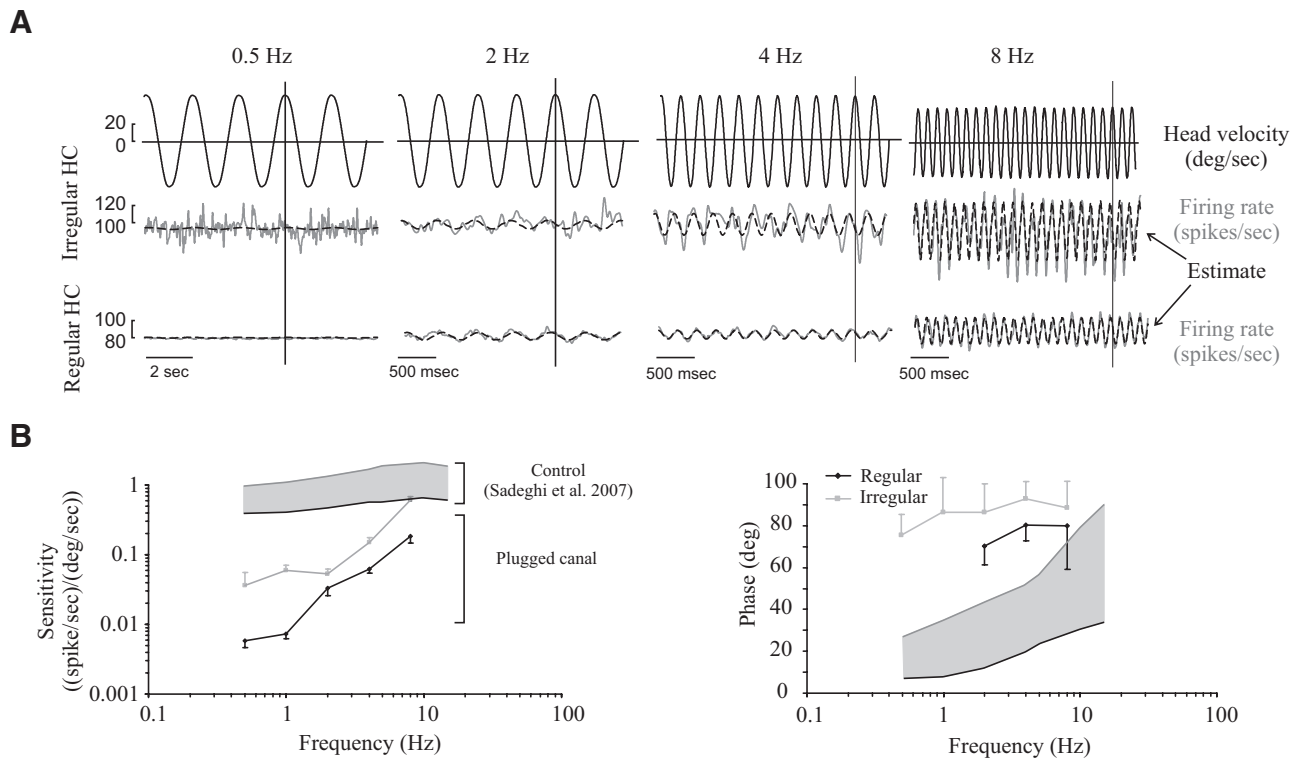
FIG. 2. Response of vestibular-nerve afferents innervating the horizontal canal, during passive whole-body rotations in the horizontal plane. *A*: response of 2 afferents innervating the plugged horizontal canal to sinusoidal rotations at different frequencies; one unit is irregular and the other is regular. For both units, response is negligible at 0.5 Hz and increases with increasing rotation frequency. Note the different timescales. *B*: Bode plots of the afferent responses averaged for 2 animals with plugged canals. The sensitivity (*left*) increased with increasing rotation frequency for both irregular (gray line) and regular (black line) afferents. The gray shaded area shows the range of responses for regular and irregular afferents, after contralateral labyrinthectomy (UL) (data from Sadeghi et al. 2007). For regular afferents, the phase of the response (*right*) was not measured for rotations with frequencies <2 Hz, where the sensitivities were too small. The response showed a phase lead of about 90 and 70° for irregular and regular afferents, respectively. Control values (gray shaded area) are from Sadeghi et al. (2007).

Each afferent's response was estimated as a weighted sum of the velocity and acceleration of the particular head movement (see *Eq. 1*). For the irregular afferent, the response was estimated with good approximation (thick black line; VAF = 0.69), using bias = 86 spikes/s, g_v = 0.05 (spike/s)/(°/s), and g_a = 0.03 (spike/s)/(°/s^2). For the population of irregular afferents, the mean estimated parameters (±SE) were: bias = 88 ± 8 spikes/s, g_v = 0.05 ± 0.01 (spike/s)/(°/s), g_a = 0.006 ± 0.002 (spike/s)/(°/s^2), and VAF = 0.5 ± 0.04. Interestingly, a good estimation could also be obtained when *Eq. 1* was simplified such that it had only an acceleration term and a bias term (Fig. 3*A*, *bottom*, dashed red line). Thus the response of irregular units is dominated by the acceleration component [Fig. 3*A*, *bottom*; compare acceleration-plus-velocity (black) and acceleration only (red) with velocity only (blue) fits].

In contrast to irregular afferents, regular afferents showed far less robust responses during active head movements. The response of the regular unit (Fig. 3*B*) was well estimated by *Eq. 1*: bias = 81 spikes/s, g_v = 0.1 (spike/s)/(°/s), g_a = 0.007 (spike/s)/(°/s^2), and VAF = 0.7. For the population of regular afferents, the mean estimated parameters were: bias = 108 ± 4 spikes/s, g_v = 0.02 ± 0.01 (spike/s)/(°/s), g_a = 0.001 ± 0.0002 (spike/s)/(°/s^2), and VAF = 0.3 ± 0.08. Note that because the numerical values of the accelerations were roughly tenfold larger than those of the velocities of rotations, a small g_a makes a relatively large contribution to the estimated response of the afferent. Since the amplitude of

the response was less for regular than that for irregular afferents, VAFs provided by the optimal fit of *Eq. 1* for regular afferent responses were smaller. Moreover, when the response was estimated using a model that included only an acceleration term, the VAF further decreased (on average a 69% decrease for the population) compared with that obtained with *Eq. 1*.

Taken together, these findings show that the dynamics of afferents innervating plugged canals shift such that they are, on average, more in phase with head acceleration than with velocity. This contrasts sharply with the dynamics of afferents innervating normal canals. To illustrate this, we predicted the responses of afferents to a similar head movement under normal conditions (Fig. 3*B*, control firing rate) based on parameters obtained for average responses of regular and irregular afferents in a previous study (Sadeghi et al. 2007). The responses of both regular and irregular afferents are more in phase with head velocity in the control condition compared with the responses after plugging [peak responses (arrow) with respect to peak head velocity (vertical line)]. The significance of these findings is further addressed in the DISCUSSION.

Simulation of responses of afferents innervating plugged HC

To characterize the response dynamics of afferent responses following plugging, we used a transfer function of the form

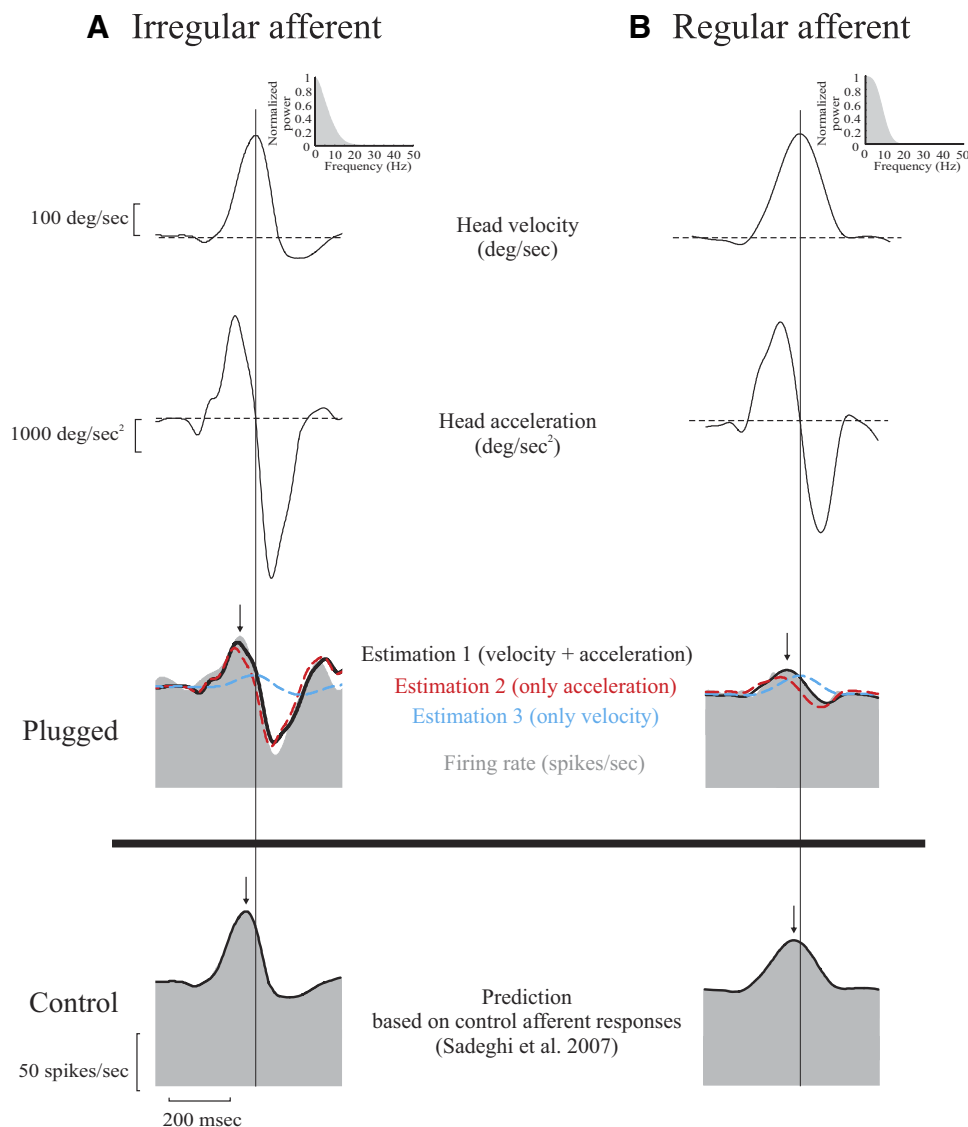## A Irregular afferent

B Regular afferent

FIG. 3. Example of the response of irregular (*A*) and regular (*B*) vestibular-nerve afferents innervating a plugged horizontal semicircular canal during active head-on-body movements. Head velocity during these movements reached >300°/s (*top row*) and had enough power for frequencies of up to about 15 Hz (*top row, insets*). Peak acceleration reached >4,000°/s² (*2nd row*). Irregular afferents responded more strongly than regular afferents and were estimated well with combination of velocity and acceleration terms (black line over firing rate). Similarly, an acceleration-based (dashed red lines) model provided a better fit of the responses compared with a velocity-based (dashed blue line) model for irregular vs. regular afferents. Lead times of 48 and 38 ms were measured for the example irregular and regular afferents, respectively, when peak firing rate (arrow) was compared with peak velocity (vertical line). The same head velocity was then used to predict the responses of afferents under control conditions (*bottom traces*) using *Eq. 1* and coefficients from a previous study (Sadeghi et al. 2007). The lead times under control conditions for the predicted responses for irregular and regular afferents were 30 and 17 ms, respectively.

that was originally shown to describe the canal afferent response dynamics in normal squirrel monkeys (Fernandez and Goldberg 1971; Hullar et al. 2005)

$$\frac{sT_c\,(1\,+\,sT_1)}{(1\,+\,sT_c)\,(1\,+\,sT_2)}$$

where T_c and T_2 are the long and short time constants of the torsion–pendulum model of canal biomechanics and T_1 is proportional to the ratio of acceleration to velocity sensitivity of the afferent response. Similar models have more recently been shown to provide an accurate description of canal afferent responses in monkeys (Haque et al. 2004; Minor and Goldberg 1991) up to about 20 Hz (Ramachandran and Lisberger 2006), in chinchillas (Hullar and Minor 1999; Hullar et al. 2005), and in mice (Lasker et al. 2008). For the normal condition we used time constants of: $T_1 = 0.015$ s, $T_2 = 0.003$ s, and $T_c = 5.7$ s (Fernandez and Goldberg 1971). These values reproduced responses similar to those of regular afferents. To simulate responses of irregular units, we kept T_c and T_2 at the same values, but increased T_1 to 0.05 s. Because canal plugging increases the effective stiffness of the canals, it should result in

a decrease in T_c, resulting in a lowered gain and response dynamics approaching that of an acceleration transducer. Consistent with this prediction, decreasing T_c to 0.03 s resulted in model gains that increased in proportion to frequency and phases approaching 90° (Fig. 4*A*). Although qualitatively appropriate, the model underestimated the gain reductions by a factor of approximately 3 and, to provide a good match between the experimental and simulated values, the model gains were multiplied by a factor of 0.3 in Fig. 4. No change was made in the model phases. Consistent with the analysis of Rabbitt et al. (1999), the treatment assumes that plugging affects canal biomechanics, but not later stages in transduction. The shortcomings of each modeling approach are further addressed in the DISCUSSION.

Figure 4*A* shows the afferent responses predicted by our simulation for sinusoidal rotations at different frequencies. Similar to our experimental findings (Fig. 2*A*), the responses of simulated irregular and regular afferents were negligible at 0.5 Hz but became more robust at higher frequencies. Bode plots for experimental and simulated data (Fig. 4*A*) are in reasonable agreement in both their gains and their phases. The same regular and irregular
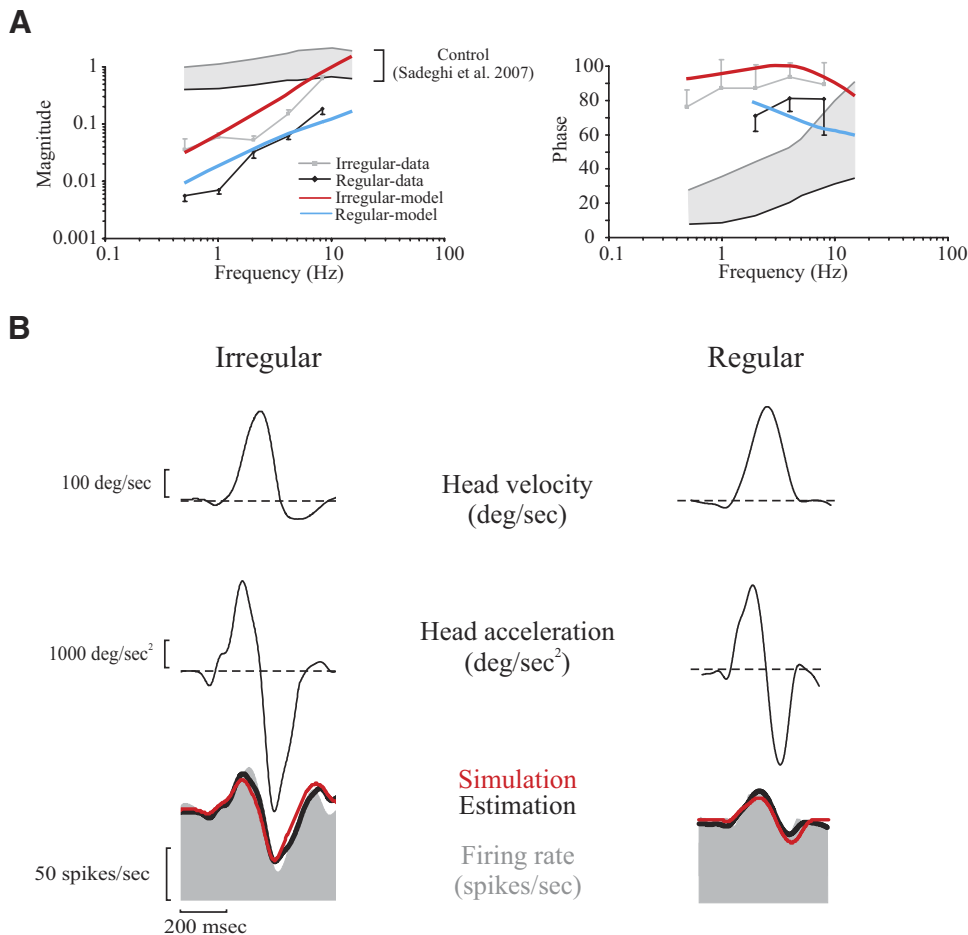
A

B

FIG. 4. Simulation of the response of vestibular-nerve afferents innervating plugged canals. *A*: Bode plots of the output of the irregular (red) and regular (blue) models during sinusoidal rotations. Both the sensitivities (*left*) and phases (*right*) of the responses were in the range obtained from single-unit recordings (gray and black lines for irregular and regular units, respectively). Note that at 20 Hz, the responses of plugged canal models are close to those obtained under normal conditions (gray shaded area). *B*: responses to the active head movements shown in Fig. 3 predicted by our model (see text) of regular vs. irregular afferents innervating plugged canals. Predicted responses (red line) superimposed well on the actual response (gray shaded area) of the afferents. For comparison, the fit to the response using *Eq. 1* (black line) is also shown.

models were next used to predict responses during active movements. Figure 4*B* shows the predictions using the head movements shown in Fig. 3. The models provide good predictions for responses of the irregular (*left column*) and regular (*right column*) afferents during active head rotations. Note that the model prediction (red line) superimposes well on the neuron's response (black line shows response fit using head velocity and head acceleration—i.e., *Eq. 1*).

DISCUSSION

We examined the response dynamics of the horizontal VOR and canal afferents following canal plugging in macaque monkey. Single-unit recordings made from afferents innervating plugged horizontal canals over a frequency range similar to that of natural head movements showed that response gains were minimal at lower frequencies of stimulation (<2 Hz), but showed a frequency-dependent increase at higher frequencies. Furthermore, evaluation of the VOR gain also revealed a comparable frequency response. In addition, afferents showed a relatively constant phase lead of 70–90°, which was markedly higher than phase lead of afferents in control animals, particularly for lower frequencies of stimulation. The VOR did not show such phase leads. Rather, eye movements remained compensatory for head movements, much as in control animals.

Notably, canal afferents also showed significant modulation during active head rotations, consistent with the frequency content of these movements. Taken together, our results sug-

gest that canal plugging is completely effective only at frequencies <2 Hz in macaques. These findings have practical implications, since canal plugging is used both in the clinic, to treat patients with intractable vestibular pathologies, and in the laboratory, to investigate basic properties of the vestibular system including canal–otolith interactions.

Afferents innervating plugged HC respond to high-frequency rotations

Our recordings in macaque monkeys show that single afferents innervating plugged canals respond to rotations >2 Hz and that modulation increases as a function of frequency, so that sensitivities nearly approach normal values at 8 Hz (Ramachandran and Lisberger 2006; Sadeghi et al. 2007). In addition, we found that the modulation of both regular and irregular afferents over this frequency range consistently led rotational velocity by about 70–90°. This finding contrasts with responses of afferents in normal macaques, which show an increasing lead of about 10–30° (regular afferents) and 30–70° (irregular afferents) over the same frequency range (Ramachandran and Lisberger 2006; Sadeghi et al. 2007).

To date, only one prior report has studied the responses of afferents innervating plugged canals. Rabbitt and colleagues (1999) recorded from the afferents innervating the canals of toadfish. The responses of toadfish afferents following plugging were qualitatively similar to our findings. Nevertheless, different methods were used in the two studies, which probably

led to quantitatively dissimilar results. First, the toadfish recordings were made immediately after plugging, while we waited ≥2 wk. Second, the canal duct remained broadly exposed in the toadfish experiments. Finally, plugging in the toadfish was effected with a glass rod, rather than by plugging the canal duct with bone dust and fascia. As discussed by Rabbitt et al. (1999), all three differences would be expected to increase the stiffness in our experiments and thus might be expected to result in a larger gain reduction. This is what was actually observed (Fig. 5*A*). On the other hand, a larger phase difference might be expected in the monkey studies and this was not seen (Fig. 5*B*).

The goal of the model approach used in the present study was somewhat different from that used previously (Rabbitt et al. 1999). Rabbitt et al. developed a detailed biomechanical model based on a thorough anatomical reconstruction of the relevant labyrinthine structures. The torsion–pendulum model used in the present study is a simple, descriptive model. One drawback of the Rabbitt model is that it depends on multiple parameters, many of which are difficult to measure. In contrast, the torsion–pendulum model uses a single parameter (T_C), the effective stiffness of the canals, to explain the effects of canal plugging. Although having the merits of simplicity, the torsion–pendulum model is not quantitatively accurate in predicting a gain reduction that was threefold smaller than was actually observed. Moreover, both models assume that plugging affects only canal biomechanics, not later stages in transduction. A strong prediction is that the gain reductions and phase leads should be identical for all units. In our study, gain reductions were similar for regular and irregular units, but phase leads were not identical.

Finally, it should be noted that differences in canal size and membranous labyrinth properties between different species can also affect the efficiency of plugging. A prediction of the model by Rabbit et al. (1999) is that canal plugging should be relatively more effective in a species with smaller and stiffer labyrinths such as the monkey. To compare our findings (Fig. 5*B*, black lines) with those of Rabbitt et al. (1999) (gray lines), we pooled the results for all (i.e., regular and irregular) afferents. Importantly, our results in macaque best matched the predictions for human afferents, as would be expected based on the similarity of canal sizes (humans: Curthoys and Oman 1987; Spoor and Zonneveld 1998; macaques: Jones and Spells 1963).

Responses of afferents innervating the plugged horizontal canal are similar for active and passive head movements

In the present study, we also for the first time describe the response of afferents innervating plugged canals during *active* head movements. Previous studies have shown that in normal animals, as well as in animals with unilateral lesion, vestibular-nerve afferents respond to active head movements and passively applied movements with similar dynamics (Cullen and Minor 2002; Sadeghi et al. 2007). Here, we expected that afferents innervating plugged canals would respond to active head movements generated during orienting gaze shifts, given that these movements have a high-frequency content (≤20 Hz), high peak velocities (400°/s), and high accelerations (4,000°/s^2) (Armand and Minor 2001; Huterer and Cullen 2002). Indeed, our results demonstrate that the afferents inner-
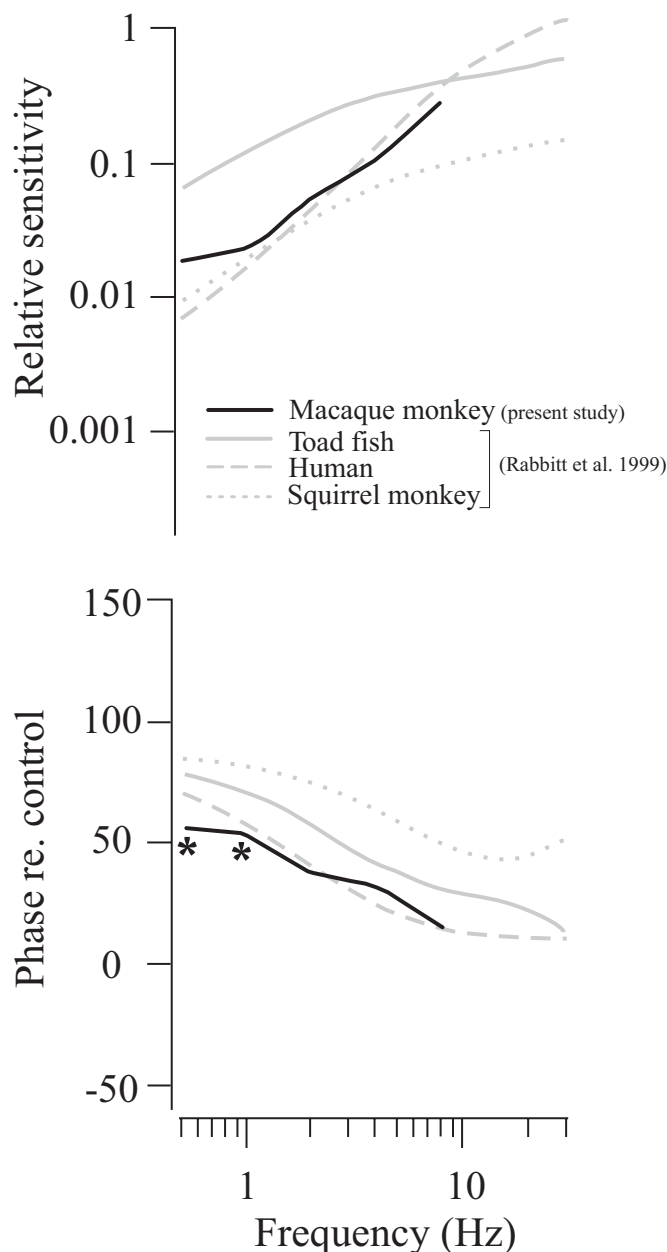

FIG. 5. Comparison of the response of vestibular-nerve afferents following plugging in different animals. Attenuation is shown as the relative sensitivity (plugged/control) and phase advance (difference of plugged and control values). Predictions of responses based on the biomechanical model of Rabbitt et al. (1999) are presented by gray lines for toadfish (solid line), squirrel monkeys (dotted line), and humans (dashed line). Results from the present study in macaque monkeys are presented by the solid black line. The attenuation in sensitivity and the phase advance of afferent responses in macaques are closer to those predicted for humans. Note that phases for responses at 0.5 and 1 Hz (stars) are calculated for irregular afferents since the responses were too small for regular afferents.

vating plugged canals respond robustly during voluntary movements.

There are two obvious possible explanations for why afferents respond during active head movements after canal plugging. One possibility is that responses to active head movements result, at least in part, from extravestibular signals that are transmitted through the efferent vestibular system to the periphery. However, although the efferent

vestibular system is active in alert macaques (Sadeghi et al. 2009a), there is no evidence that it carries any extravestibular signals either in normal conditions or following unilateral labyrinthectomy (Cullen and Minor 2002; Sadeghi et al. 2007). A more likely possibility is that afferents respond during active head movements as a result of residual endolymph movement comparable to that observed during passive rotations. Indeed, afferents innervating plugged canals showed comparable decreases in sensitivity during passive and active rotations. Moreover, our model simulations show that the same simple transfer function can be used to simulate afferent discharges during both passive and active head movements following plugging.

VOR responses to high-frequency rotations

We applied passive whole-body rotations in the horizontal plane that spanned a frequency range of 0.5–15 Hz to characterize the response dynamics of the horizontal VOR in macaque monkeys, which had undergone a labyrinthectomy on one side and plugging of the horizontal and posterior semicircular canals on the other side. Accordingly, the VOR responses were the result of activation of a single HC. Similar to previous studies in monkeys, in which the HCs were bilaterally plugged (Angelaki et al. 1996; Lasker et al. 1999; Yakushin et al. 1998) or all six canals were plugged (Hess et al. 2000; Lasker et al. 1999; Yakushin et al. 1998), we found a marked decrease in the gain of the VOR following canal plugging, particularly for lower frequencies of rotation. Notably, we found that the response gain of the VOR at frequencies <2 Hz was <0.1, consistent with the values reported for this same frequency range in a previous study in cynomolgus monkeys (Yakushin et al. 1998). Similar, albeit slightly higher values (gain <0.3) have also been reported for rhesus monkeys over this same range (Hess et al. 2000).

As rotation frequency increased from 2 to 4 Hz, we observed significant but still significantly reduced responses, in agreement with results reported in cynomolgus monkeys, where the gain was half normal (Yakushin et al. 1998). Although lower gains (<0.1) have been reported for squirrel monkeys over this same frequency range (Lasker et al. 1999), the same general trend of increasing gain as a function of frequency was observed. It is likely that differences in canal size (and, in turn, afferent responses) underlie the larger VOR gains in macaques (Angelaki and Hess 1996; Angelaki et al. 1996; Hess et al. 2000; Yakushin et al. 1998; present study) compared with those in squirrel monkeys (Lasker et al. 1999). Specifically, the relatively smaller and stiffer canal sizes of squirrel monkeys predict responses (Fig. 5, dotted line) that have the highest attenuation and phase advance relative to patent canals.

Interestingly, following plugging, despite the 90° phase lead in afferent responses at lower frequencies, the phase lag of the VOR remained normal. This compensation is most likely mediated by visually driven compensatory changes in central pathways. Support for this idea comes from the observation that compensation is impaired following plugging or unilateral labyrinthectomy when the animals were kept in darkness compared with when they were kept in the light (Lasker et al. 1999, 2000). This is consistent with the established fact that both the gain and phase of the VOR response can be modified by

wearing ocular prisms (reviewed in Cullen 2008). We propose that, similar to changes observed during prism-induced adaptation, vestibular pathways that engage the cerebellum (Ito et al. 1977; Lisberger et al. 1994) likely underlie the compensation observed in the present study. Additional studies are required to verify this hypothesis. What our results make clear is that changes in the VOR need not parallel peripheral dynamics. To cite a specific example, Yakushin et al. (1988) fit the response dynamics of the VOR in cynomolgus monkeys after canal plugging with a torsion–pendulum model in which the time constant (T_c) was changed from a normal value of 4 to 0.07 s. The change was attributed to peripheral dynamics. The Yakushin model is similar to the one we used to describe the changes in afferent discharge in our fascicularis monkeys. Without vestibular-nerve recordings, however, it is unclear whether the VOR dynamics in the Yakushin study merely reflects changes in canal dynamics or, as in our case, changes in both peripheral and central dynamics.

Finally, in the present study, we further extended the findings of previous studies and tested frequencies of ≤15 Hz, to more completely probe the range of frequencies that are experienced during normal everyday activities (Armand and Minor 2001; Grossman et al. 1988; Huterer and Cullen 2002). Notably, at the highest frequencies tested, VOR gains reached values approaching 60% of those seen in control animals and around 75% of values recorded after only unilateral labyrinthectomy (Sadeghi et al. 2006).

Conclusions and clinical implications

Our experimental and modeling results directly demonstrate that canal plugging is completely effective only at lower frequencies of rotation (<2 Hz) in macaque monkeys. Furthermore, we show that afferents produce robust responses during active head rotations, consistent with the frequency content of these movements. Responses during both passive and active rotations could be predicted based on the biomechanical model of Rabbit et al. (1999) and were similar to those predicted for human afferents.

The present findings also have practical implications that provide insights into the use of canal plugging both as a clinical intervention and as a technique for investigating basic properties of the vestibular system. The surgical procedure of canal plugging was originally used to provide a method for studying the contribution of individual canals to vestibular reflexes (Ewald 1892). More recently, this technique has been used for treatment of vestibular disorders, including intractable vertigo caused by benign paroxysmal positional vertigo (Parnes and McClure 1990) and surgical treatment of the superior canal dehiscence syndrome (Minor et al. 1998). In most clinical cases only one superior canal is plugged and this selective plugging leads to no more than a 40–50% reduction in responses to rapid head rotations delivered in the plane excitatory for the plugged superior canal (Carey et al. 2007). Thus the VOR responses attributable to a plugged canal in patients are consistent with the findings of the present study. In contrast, the VOR responses evoked by rapid ipsilesional head movements following unilateral labyrinthectomy show a 70–80% reduction (e.g., Aw et al. 1994; Carey et al. 2002; Cremer et al. 1998; Halmagyi et al. 1990; Lasker et al. 2000; Sadeghi et al.

2006). We conclude that the observed responses from plugged afferents to higher-frequency rotations have important physiological consequences, since they will be significantly activated by head movements made and experienced during everyday life.

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