

Response of Vestibular-Nerve Afferents to Active and Passive Rotations Under Normal Conditions and After Unilateral Labyrinthectomy

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Sadeghi SG, Minor LB, Cullen KE. Response of vestibular-nerve afferents to active and passive rotations under normal conditions and after unilateral labyrinthectomy. *J Neurophysiol* 97: 1503–1514, 2007. First published November 22, 2006; doi:10.1152/jn.00829.2006. We investigated the possible contribution of signals carried by vestibular-nerve afferents to long-term processes of vestibular compensation after unilateral labyrinthectomy. Semicircular canal afferents were recorded from the contralesional nerve in three macaque monkeys before [horizontal (HC) = 67, anterior (AC) = 66, posterior (PC) = 50] and 1–12 mo after (HC = 192, AC = 86, PC = 57) lesion. Vestibular responses were evaluated using passive sinusoidal rotations with frequencies of 0.5–15 Hz (20–80°/s) and fast whole-body rotations reaching velocities of 500°/s. Sensitivities to nonvestibular inputs were tested by: 1) comparing responses during active and passive head movements, 2) rotating the body with the head held stationary to activate neck proprioceptors, and 3) encouraging head-restrained animals to attempt to make head movements that resulted in the production of neck torques of ≤ 2 Nm. Mean resting discharge rate before and after the lesion did not differ for the regular, D (dimorphic)-irregular, or C (calyx)-irregular afferents. In response to passive rotations, afferents showed no change in sensitivity and phase, inhibitory cutoff, and excitatory saturation after unilateral labyrinthectomy. Moreover, head sensitivities were similar during voluntary and passive head rotations and responses were not altered by neck proprioceptive or efference copy signals before or after the lesion. The only significant change was an increase in the proportion of C-irregular units postlesion, accompanied by a decrease in the proportion of regular afferents. Taken together, our findings show that changes in response properties of the vestibular afferent population are not likely to play a major role in the long-term changes associated with compensation after unilateral labyrinthectomy.

INTRODUCTION

In normal animals, the vestibuloocular reflex (VOR) effectively stabilizes gaze for head velocities and frequencies in the range of natural head movements (Huterer and Cullen 2002; Minor et al. 1999; Ramachandran and Lisberger 2005). Moreover, the VOR is capable of remarkable adjustments in response to environmental challenges including the use of magnifying or minimizing optical lenses as well as lesions of the vestibular system. For example, immediately after unilateral labyrinthectomy, there is a marked asymmetry in gain characterized by diminished responses to rotations that would be excitatory for the lesioned side. Within a month, however, the VOR shows nearly complete functional recovery for head rotations at lower frequencies, velocities, and/or accelerations, in primates (human: Allum et al. 1988; Curthoys and Halmagyi

1995; squirrel monkey: Lasker et al. 2000; Paige 1983b; macaque: Fetter and Zee 1988).

A simple three-neuron arc (vestibular afferents, to neurons in the vestibular nuclei, to extraocular motoneurons) mediates the most direct pathway of the VOR (Lorente De No' 1933). Previous investigations used in vivo and in vitro approaches in a variety of species to characterize the mechanisms that underlie compensation after labyrinthectomy within this pathway at the level of single-neuron responses and intrinsic cellular properties (reviewed in Curthoys and Halmagyi 1995; Straka et al. 2005). These studies focused on changes at the level of the neurons of the vestibular nuclei that constitute the middle leg of the direct VOR pathway. There is general agreement across studies that neuronal resting rates initially show significant changes and then return to prelesion values within 30 days (Newlands and Perachio 1990a,b; Ris and Godaux 1998; Ris et al. 1995; Smith and Curthoys 1989). In addition, neuronal response gains decrease in both the ipsilesional and contralesional vestibular nuclei immediately after lesions and remain attenuated after compensation (Newlands and Perachio 1990a,b; Ris and Godaux 1998; Ris et al. 1995; Smith and Curthoys 1989). The compensatory decrease in the sensitivity of neurons on the contralesional side prevents inhibitory cutoff and excitatory saturation in responses, thereby increasing the linear response range.

Although many studies have considered the central changes that occur after vestibular lesions, it remains to be determined whether corresponding changes at the level of vestibular nerve afferents might also contribute to the vestibular compensation process. Vestibular hair cells and afferent fibers receive bilateral inputs from the vestibular efferent system, which consists of a group of neurons located in the brain stem neighboring the abducens nucleus (Gacek and Lyon 1974; Goldberg and Fernandez 1980; Rasmussen and Gacek 1958). The results of previous investigations are consistent with the hypothesis that the vestibular efferent system could be used to extend the dynamic range of the input that is available from the intact side after vestibular damage (see Cullen and Minor 2002). Electrical activation of the vestibular efferent pathway results in an increase in resting discharge and a decrease in sensitivity of vestibular afferents in toad fish and squirrel monkey (Goldberg and Fernandez 1980; Highstein and Baker 1985; Marlinski et al. 2004). Support for the idea that activation of the efferent system can induce long-term changes in afferent physiology is provided by studies of the sensory periphery of the auditory

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system (Lieberman 1990; Walsh et al. 1998). Because the vestibular and auditory systems have a common phylogenetic origin (reviewed in Fritzsche 1992), it is possible that the vestibular efferent system plays an analogous role in shaping vestibular afferent responses.

The functional role of the vestibular efferent system in primates is not well understood. The findings of prior investigations in the frog led to the proposal that extravestibular inputs (e.g., somatosensory, proprioceptive, and motor efference copy signals) transmitted through efferent neurons can be used to change the background discharge and sensitivity of vestibular afferents under specific behavioral conditions (Bricout-Berthout et al. 1984; Caston and Bricout-Berthout 1984; Precht et al. 1971; Schmidt 1963). In toadfish, efferent innervation alters the background discharge and sensitivity to motion of vestibular-nerve afferents as a component of the escape reaction (Boyle and Highstein 1990; Highstein and Baker 1985). Such nonvestibular signals could be functionally useful. For example, after vestibular lesions they could in part substitute the missing vestibular information, which could provide an explanation for the enhanced VOR gains for active as compared with passive head-on-body rotations (Della Santina et al. 2001; Dichgans et al. 1973; Newlands et al. 2001).

The principal goal of the present study was to test whether the vestibular efferent system plays a role in the long-term changes associated with compensation after unilateral labyrinthectomy over the range of natural head movements. To address this, afferents innervating the semicircular canals were recorded in alert macaques before labyrinthectomy and then on the contralesional side in response to head movements over the frequency range where compensation is the most complete (i.e., <4 Hz), as well as during more challenging stimulation designed to probe the full range of physiologically relevant head movements (Sadeghi et al. 2006). We also assessed whether extravestibular inputs including inputs from neck proprioceptors and/or motor efference signals resulting from motor commands to the neck altered afferent responses after unilateral labyrinthectomy. First, recordings were made from the same afferents during passively applied head rotations and active head movements. Additionally, two supplementary paradigms were used in which we selectively activated neck proprioceptors or induced the production of motor commands to the neck in the absence of vestibular stimulation.

METHODS

Surgical preparation

Three macaque monkeys (*Macaca fascicularis*) were prepared for chronic behavioral experiments under aseptic conditions. All procedures were approved by the McGill University Animal Care Committee and Johns Hopkins University Animal Care and Use Committee and were in compliance with the guidelines of the Canadian Council on Animal Care and the National Institutes of Health.

The surgical preparation was previously described elsewhere (Sylvestre and Cullen 1999). Briefly, using aseptic techniques and isoflurane anesthesia (2–3%, to effect), we implanted several stainless steel screws into the skull and attached a stainless steel recording chamber and a post for head restraint to these screws with dental cement. 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 each eye beneath the conjunctiva (Fuchs and Robinson 1966). After the surgery, the animals were administered buprenor-

phine [0.01 mg/kg, administered intramuscularly (im)] for postoperative analgesia and the antibiotic cephazolin (Ancef; 25 mg/kg im, for 5 days). Animals were given at least 2 wk to recover from the surgery before experiments began.

Labyrinthectomy was performed as previously described (Lasker et al. 2000). A postauricular incision was made and the mastoid bone was removed with an otologic drill and curettes to expose the horizontal and posterior semicircular canals. The petrous bone was removed further anteriorly and superiorly to visualize the superior canal near its union with the common crus. Each of the semicircular canals was then obliterated with removal of the ampulla. The vestibule was entered and the utricle and saccule were removed. The internal auditory canal was opened next and the distal ends of the ampullary nerve branches were removed. The space created by the labyrinthectomy was packed with muscle and fascia and the postauricular incision was closed.

Data acquisition

The experimental setup, apparatus, and methods of data acquisition were similar to those described before (Cullen and Minor 2002; Huterer and Cullen 2002). We monitored gaze and head position using the magnetic search coil technique (1-m field coil system; CNC Engineering). Single-unit extracellular recordings were made using glass electrodes with impedances of about 25 M Ω . Once a unit was isolated, the semicircular canal innervated by that fiber was determined based on the responses of the afferent to rotations delivered while the head was restrained (see Cullen and Minor 2002). Gaze and head positions, target position, and table velocity were recorded on DAT tape with unit activity for later playback. During playback head and gaze position signals were low-pass filtered at 250 Hz by an eight-pole Bessel filter and sampled at 1 kHz.

Experimental design

Afferents were recorded in each animal before labyrinthectomy to obtain prelesion data. A labyrinthectomy was then performed on the side in which the recording had been done and postlesion data were collected from the contralesional nerve. At the end of all experiments and after sacrificing the animal, the location of the microelectrode within the vestibular nerve was confirmed by histology. Vestibular stimulation and data acquisition were controlled by a QNX-based real-time data-acquisition system (REX) (Hayes et al. 1982).

RECORDINGS MADE DURING PASSIVE HEAD ROTATIONS. Neuronal sensitivities to head velocity were measured using whole-body rotations (WBRs) applied at 0.5, 1, 2, and 4 Hz (peak velocity ± 20 , ± 50 , and $\pm 80^\circ/s$). For some afferents, responses to more dynamic stimuli were also characterized. Their responses were recorded during 1) higher frequency (5, 10, and 15 Hz at ± 20 , ± 50 , or $\pm 80^\circ/s$) horizontal head-on-body rotations that were applied by a torque motor (Animatics) securely coupled to the post implanted on the monkey's head (Huterer and Cullen 2002) and/or 2) rapid position steps (about 600 ms) with displacements of 20–100° and peak velocities of 50–500°/s.

RECORDINGS MADE DURING VOLUNTARY HEAD ROTATIONS. 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). If the neuron remained well isolated, its activity was then recorded during voluntary combined eye–head movements made to orient to laser and food targets.

RECORDINGS MADE TO DETERMINE THE INFLUENCE OF MOTOR COMMAND SIGNALS AND/OR NECK PROPRIOCEPTION ON NEURONAL ACTIVITY. We recorded from afferents during large saccades (>30°) to test whether the production of neck motor command alters their

responses (see Roy and Cullen 2004). The concurrent neck torque produced against the head restraint (reaction torque transducer, Sensotec) was recorded and ≥ 10 intervals where torques reached high levels (>1 Nm) were analyzed. In addition, the influence of passive activation of the neck proprioceptors was assessed by passively rotating the animal's body under its stationary head (BUH paradigm) at frequencies of 0.5, 1.0, and 2.0 Hz (± 20 or $\pm 50^\circ/s$).

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 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. A normalized coefficient of variation (CV*) was calculated using the method described by Goldberg et al. (1984). Afferents with a CV* >0.2 and sensitivity at 2-Hz stimulation of <1.5 (spikes/s)/($^\circ/s$) were assigned to the C (calyx)-irregular group as suggested by the morphophysiological results of Baird et al. (1988) in the chinchilla. Regular afferents were identified as having a CV* <0.1 . All other afferents were identified as D (dimorphic)-irregular units (Hullar et al. 2005). It should be noted that similar to previous studies (Haque et al. 2004; Hullar et al. 2005; Marlinski et al. 2004; Ramachandran and Lisberger 2006), we did not examine the morphology of the afferent endings directly, but instead used this functional classification.

A least-squares regression analysis was used to determine the phase shift of each unit relative to head velocity, resting discharge (bias, spikes/s), and head velocity sensitivity [(spikes/s)/($^\circ/s$)] (see Roy and Cullen 2001; Sylvestre and Cullen 1999), using ≥ 10 cycles of the stimulus. Neuronal responses to body-under-head rotations (BUH paradigm) and active head rotations were similarly characterized. Afferents were typically driven into the nonlinear range (inhibitory cutoff) for large-velocity head movements in their off direction. Accordingly, fits to the passive and active rotations were made based on responses that were >10 spikes/s. To compare the model's ability to predict the firing rate, the variance-accounted-for (VAF) value was determined (Cullen et al. 1996). Because the head rotations for the vertical canal afferents were not in the plane of the canal, trigonometric corrections were made based on the canal planes in this species (Reisine et al. 1988) for the sensitivities of the units as described previously (Cullen and Minor 2002). A neuron's response to fast rotations was described by least-squares optimization of a sigmoidal function.

Statistical analysis

Data are described as means \pm SE. A Student's *t*-test was used to determine whether the average of two measured parameters differed significantly from each other. We used a *z*-test to compare changes in population percentages of regular and irregular afferents pre- and postlabyrinthectomy.

RESULTS

We recorded from 639 vestibular nerve fibers in three animals. Of these, 241 (67 horizontal canal, 66 superior canal, 50 posterior canal, and 58 otolith) were recorded in normal animals. The remaining 398 afferents (192 horizontal canal, 86 superior canal, 57 posterior canal, and 63 otolith) were recorded from the contralesional nerve 1–12 mo after unilateral

labyrinthectomy. The following results are confined to those afferents that innervate the three semicircular canals. For purposes of this study, we combined the vertical and horizontal canal afferents in the data analysis of resting rates and sinusoidal WBRs ≤ 4 Hz because they encoded similar signals.

In one animal, recordings were also made from the ipsilesional nerve under direct visualization 12 mo after the lesion and immediately before sacrificing the animal. From nine microelectrode passes along the nerve, only three units were recorded. Two units had sporadic activity and one had a resting discharge that varied between 50 and 80 spikes/s. This appreciable reduction in activity in the ipsilesional vestibular nerve is consistent with the evidence that resting discharge activity is dependent on transmitter release from hair cells (Guth et al. 1998).

Resting discharge and regularity before and after lesion

Figure 1A shows the distribution of the resting rate and CV* of the entire population of canal afferents recorded in this study, before (gray histograms) and after (black histograms) unilateral labyrinthectomy. Resting discharge distributions (Fig. 1A, left) were similar in both conditions (population averages: 107.4 ± 2.6 vs. 101.1 ± 2.0 spikes/s, before vs. after labyrinthectomy, respectively, $P = 0.07$). Moreover, both pre- and postlesion distributions were comparable to those reported in previous studies of normal macaque monkeys (Bronte-Stewart and Lisberger 1994; Lisberger and Pavelko 1986).

Before lesion, the distribution of CV* was bimodal (Fig. 1A, right, gray histograms) as previously described (e.g., Baird et al. 1988). Although the distributions appeared qualitatively similar before and after labyrinthectomy, there was an overall increase in the percentage of irregular afferents (CV* >0.1) in our postlesion sample compared with our prelesion sample (62 vs. 55%). This difference was statistically significant (*z* statistics, $P < 0.001$) and was the result of a specific increase in the percentage of irregular afferents that had CV* values >0.2 (26 vs. 39% in our pre- vs. postlesion samples, respectively). This change was accompanied by a relative decrease in the proportion of afferents with $0.1 < CV^* < 0.2$ postlesion (29 vs. 23%). The potential mechanisms mediating these changes and implications of these findings are further addressed under DISCUSSION.

Categorization of afferents: responses at 2 Hz before and after lesion

Afferents were further divided into three groups (regular, D-irregular, C-irregular) based on their CV* and sensitivities to 2-Hz rotations (Table 1 and Fig. 1B; see METHODS). The mean resting rate for each of the three groups of afferents was comparable before and after labyrinthectomy ($P > 0.3$). Resting discharges of regular and C-irregular afferents were comparable, whereas those of the D-irregular afferents were significantly higher in both conditions ($P < 0.001$). Furthermore, response sensitivities and phases of each of the three groups of afferents were comparable before (Fig. 1B, gray symbols) and after (Fig. 1B, black symbols) labyrinthectomy ($P > 0.4$). Thus the dynamic range of the input available from the intact nerve after unilateral labyrinthectomy is not extended by changes in afferent resting discharge and/or sensitivity in response to 2-Hz sinusoidal rotations.

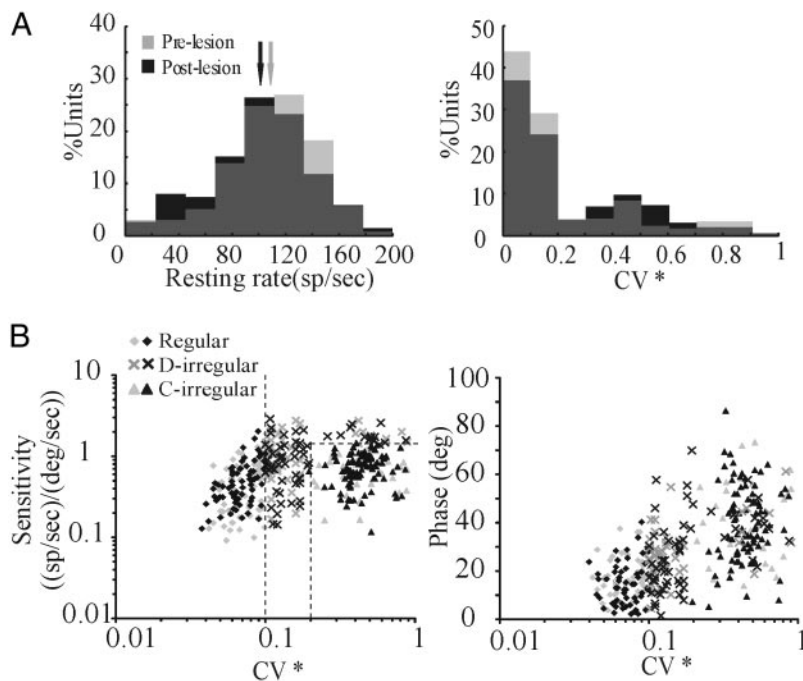


FIG. 1. *A*: comparison of the distribution of resting discharge and normalized coefficient of variation (CV^*) of resting rate of afferents innervating the horizontal and vertical semicircular canals, before (gray) and after (black) unilateral labyrinthectomy. Postlesion values in all figures are from the contralesional side. Arrows represent the mean resting discharge prelesion (gray) and postlesion (black). *B*: sensitivity and phase lead of horizontal and vertical canals in response to 2-Hz sinusoidal rotation ($50^\circ/s$) as a function of CV^* , before (gray symbols) and after (black symbols) unilateral labyrinthectomy. Dashed lines in *B* mark the borders between the regular (diamonds), D (dimorphic)-irregular (crosses), and C (calyx)-irregular (triangles) afferents.

Comparison of the distributions of each afferent class established that the increase in the percentage of irregular afferents observed after labyrinthectomy (see previous section) corresponded more specifically to an increase in the proportion of C-irregular afferents (22 vs. 34%, $P < 0.001$, z statistics). In contrast, the decrease in the number of D-irregular afferents recorded after the lesion was not significant (28 vs. 33%, $P > 0.05$, z statistics). Furthermore, these changes were comparable in individual animals. The proportion of C-irregular units increased by 11–16% ($P < 0.001$) in each of the three animals. The proportion of regular afferents decreased by 6–12% ($P < 0.01$) in each of the three animals, whereas the change in the proportion of D-irregular afferents was not significant. Thus although resting rates as well as rotational sensitivities and phases at 2 Hz were comparable pre- and postlesion for regular, D-irregular, and C-irregular afferents, there was an increase in the proportion of C-irregular units and a decrease in the proportion of regular units after labyrinthectomy.

Afferent responses as a function of frequency of rotation

Figure 2A shows examples of the responses of a regular and a D-irregular afferent on the contralesional side, at different frequencies of sinusoidal rotation. Plots quantifying response gain and phase as a function of frequency are shown in Fig. 2B for each class of afferents. Before labyrinthectomy, response

gains of all afferent classes increased as a function of rotation frequency (Fig. 2B, solid lines). This can be seen in Fig. 2A for the two example afferents; response modulation became larger as stimulus frequency was increased from 0.5 to 15 Hz, although peak head velocity was held constant at $50^\circ/s$. D-irregular units had the highest gains in response to stimulation ≤ 10 Hz. At 15 Hz, however, the response gains of C-irregular units reached values comparable to those of D-irregular units (1.5 ± 0.5 vs. 1.3 ± 0.4 , $P > 0.1$). The phase leads of all afferent classes also increased as a function of rotation frequency. In both conditions, C-irregular units had the highest phase lead over the range of frequencies tested (i.e., ≤ 15 Hz). Taken together, these findings show that the response dynamics of all three afferent classes in normal macaques are similar to those of previous studies in normal chinchillas (Hullar and Minor 1999; Hullar et al. 2005) and macaques (Ramachandran and Lisberger 2006) for rotations with frequencies of ≤ 15 Hz.

Response gains and phase leads also increased as a function of rotation frequency after labyrinthectomy (Fig. 2B, dashed lines) and there was no significant difference in the frequency response of any of the three afferent classes before versus after the lesion ($P > 0.4$). Thus the relationship between CV^* and response properties was preserved after unilateral labyrinthectomy. One potential limitation of this analysis is that dividing units based on CV^* could have eliminated the ability to detect

TABLE 1. Resting rate (rr), CV^* , and the number (percentage) of canal afferents recorded before and after unilateral labyrinthectomy in each of the three groups of afferents

Group	Prelesion			Postlesion		
	rr	CV^*	n	rr	CV^*	n
Regular	106.2 ± 3.0	0.08 ± 0.01	83 (45%)	101.9 ± 2.5	0.07 ± 0.001	127 (38%)
D-irregular	123.0 ± 4.2	0.19 ± 0.02	60 (33%)	118.6 ± 3.6	0.19 ± 0.15	93 (28%)
C-irregular	95.6 ± 7.5	0.50 ± 0.03	40 (22%)	85.9 ± 3.8	0.47 ± 0.15	115 (34%)

Values are means \pm SE.

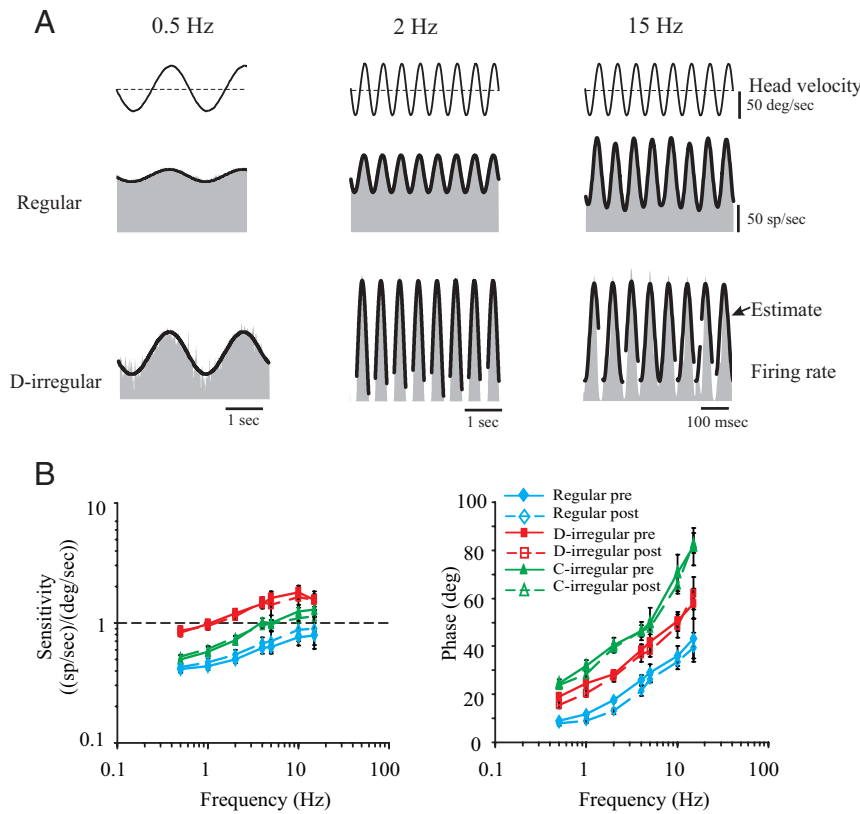


FIG. 2. Response of afferents as a function of frequency. *A*: example of the response of a regular ($CV^* = 0.05$) and a D-irregular ($CV^* = 0.5$) horizontal canal afferent to sinusoidal rotations with frequencies of 0.5, 2, and 15 Hz (50°/s). *B*: sensitivity and phase lead of responses of the population of canal afferents to sinusoidal rotations with frequencies of 0.5 to 15 Hz (50°/s) before (continuous lines, filled symbols) and after (dashed lines, empty symbols) labyrinthectomy. Vertical canals were included only in frequencies of 0.5–4 Hz. Responses were similar before and after the lesion.

more global changes in the population of afferents as a whole. Thus we also compared mean response gains and phase leads of all recorded afferents before and after lesion and found that both were comparable at each frequency of stimulation (P values ranging from 0.07 to 0.5).

Thus the response dynamics of each group of afferents (regular, D-irregular, C-irregular) were comparable before and after labyrinthectomy not only in response to stimuli within the frequency range, where compensation is more robust (i.e., <4 Hz), but also for more challenging stimuli for which compensation is not sufficient to restore VOR performance to normal levels.

Afferent responses as a function of velocity of rotation

In normal monkeys irregular units can be easily driven into inhibitory cutoff or excitatory saturation for head velocities within the physiologically relevant range of about 300°/s (Goldberg and Fernandez 1971; Hullar et al. 2005). After labyrinthectomy, an increase in the linear range of afferents on the intact side can be accomplished through an increase in resting rate or a decrease in the sensitivities of these afferents. However, as described earlier neither afferent resting rates (Fig. 1 and Table 1) nor response gains (Fig. 2; 0.5–15 Hz, 50°/s peak velocity) were different before and after lesion.

To address whether instead there might be a systematic change in the linear range of afferents, we next characterized afferent responses as a function of velocity before and after labyrinthectomy using two methods. First, afferent responses to sinusoidal rotations at 0.5 Hz with peak velocities of 20, 50, and 80°/s were characterized. Figure 3*A* shows responses of an example regular and D-irregular afferent after unilateral laby-

rinthectomy, where the superimposed thick black lines show the best estimate of the firing rate at each velocity based on the head velocity stimulus (see METHODS). In addition, predictions of each afferent's response to 50 and 80°/s rotations are superimposed (Fig. 3*A*, dashed white lines). This prediction is simply a linearly scaled estimate of each afferent's modulation at 20°/s. Overall, the VAF provided by the predictions and the best estimates differed by <1%, indicating that responses were linear over this velocity range. Estimated head velocity sensitivities are plotted as a function of velocity in Fig. 3*B* (left) for each of the three groups of afferents. As expected, based on our prediction analysis, head velocity sensitivity did not change with increasing velocity either before (solid gray lines) or after the lesion (dashed black lines) ($P > 0.1$). Similarly, the phase leads (Fig. 3*B*, right) remained constant with increasing velocities and were not different before versus after the lesion ($P > 0.3$).

To further address whether there might be a systematic change in the linear range of afferents after labyrinthectomy, we characterized afferent responses using a second stimulus that probed a more extended range of velocities. Rapid position steps with peak velocities of $\leq 500^\circ/s$ (see METHODS) were chosen because this stimulus was sufficient to drive almost all irregular units (>90%) and some regular units (<25%) into excitatory saturation and inhibitory cutoff. Figure 4 shows the responses of regular ($CV^* < 0.1$) and irregular ($CV^* > 0.1$) horizontal canal units, before (Fig. 4*A*) and after (Fig. 4*B*) unilateral labyrinthectomy. The linear response range was generally between +80 and -80°/s for irregular units and between +120 and -120°/s for the regular units, both before (solid curves, $n = 29$ with 11 regulars, nine D-irregulars, and nine C-irregulars) and after (broken curves, $n = 27$ with 10 regulars, four D-irregulars, and 13 C-irregulars) lesion

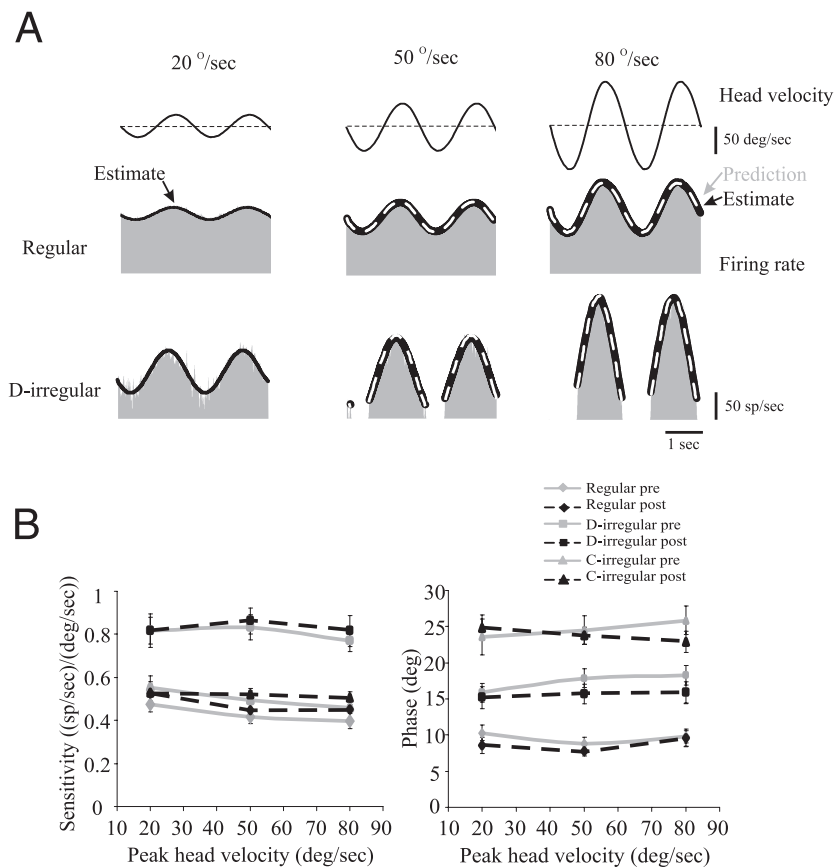


FIG. 3. Response of afferents as a function of velocity. *A*: examples of the response of same units as in Fig. 2*A* to 0.5-Hz sinusoidal rotations with peak velocities of 20, 50, and 80°/s. Black lines on top of the firing rate represent estimates based on head velocity. White broken lines represent predictions based on values estimated for 20°/s stimulation. *B*: sensitivity and phase of the response of the population of canal afferents to 0.5-Hz sinusoidal rotations with peak velocities of 20, 50, and 80°/s before and after unilateral labyrinthectomy. Head velocity sensitivity did not change with increasing velocity, indicating that responses were linear over this range of velocities before the lesion (solid gray lines) and remained linear after the lesion (dashed black lines). Furthermore, the phase lead of the response did not change as a function of velocity for either group of afferents before (solid gray lines) and after the lesion (dashed black lines).

(Fig. 4*C*). At higher velocities, the responses of most of the irregular units could be driven into cutoff during contralateral rotations and saturated during ipsilateral rotations. In contrast, we could drive only a minority of the regular units into complete cutoff or saturation. The average slopes of each curve (i.e., the response sensitivity to head velocity) were not different either before or after the lesion for regular (0.77 ± 0.13 vs. 0.73 ± 0.12 , $P > 0.8$) or irregular (1.35 ± 0.20 vs. 1.31 ± 0.15 , $P > 0.8$) units. These findings extend the results shown in Fig. 3 and confirm that there is no systematic change in the linear range of contralateral afferents after unilateral labyrinthectomy.

Afferent responses during active versus passive movements

To assess whether extr vestibular inputs (e.g., the activation of neck proprioceptors or the production of motor commands to the neck) might influence afferent responses after unilateral labyrinthectomy, we recorded from the same afferents during passively applied head rotations and active head movements. The responses of 43 afferents (ten regular, nine D-irregular, and 24 C-irregular) were recorded in two monkeys after lesion. We selected intervals of head rotation that were of comparable frequency and velocity during passive and active head movements (see METHODS). Figure 5*A1* shows examples of response of a regular and an irregular unit to active head movements. We predicted each neuron's response to active rotations using the coefficients of the fit to passive head movements. The VAF of predictions using the passive model (Fig. 5*A1*, red lines) to fit the data from active rotation were comparable to the VAF provided by the best fit to the active condition (Fig. 5*A1*, black lines). Overall, a maximum difference of 3% was observed. We also

recorded the responses of 27 horizontal semicircular canal afferents (ten regular, nine D-irregular, eight C-irregular units) in the same monkeys before labyrinthectomy. In agreement with the results of a previous study (Cullen and Minor 2002), we found no difference between the sensitivity of afferents to active and passive head movements before the lesion.

Figure 5*A2* presents a comparison of the bias discharge rate (*top*) and rotational sensitivity (*bottom*) for the fits to responses of neurons recorded before (gray symbols) and after (black symbols) lesion during active and passive rotations. Neither bias nor head velocity sensitivities differed significantly in the two conditions (paired *t*-test, $P > 0.8$; see Table 2). Thus the afferent response dynamics did not differ for active and passive head movements even after unilateral labyrinthectomy.

Does selective activation of neck afferents influence afferent responses?

We directly confirmed that neither the activation of neck proprioceptors nor the generation of a neck motor command during active head movements influences afferent responses, by recording from afferents during two additional paradigms. First, we recorded from 10 afferents before (four regulars, two D-irregulars, four C-irregulars) and 10 afferents after (four regulars, two D-irregulars, four C-irregulars) lesion during BUH paradigm (see METHODS) to test whether passive activation of neck proprioceptors influences afferent firing. Figure 5, *B1* and *B2* shows the mean firing rate of each afferent during ipsilateral (black symbols) and contralateral (gray symbols) rotations for ≥ 10 half-cycles of rotation, before and after lesion, respectively. There was no significant difference be-

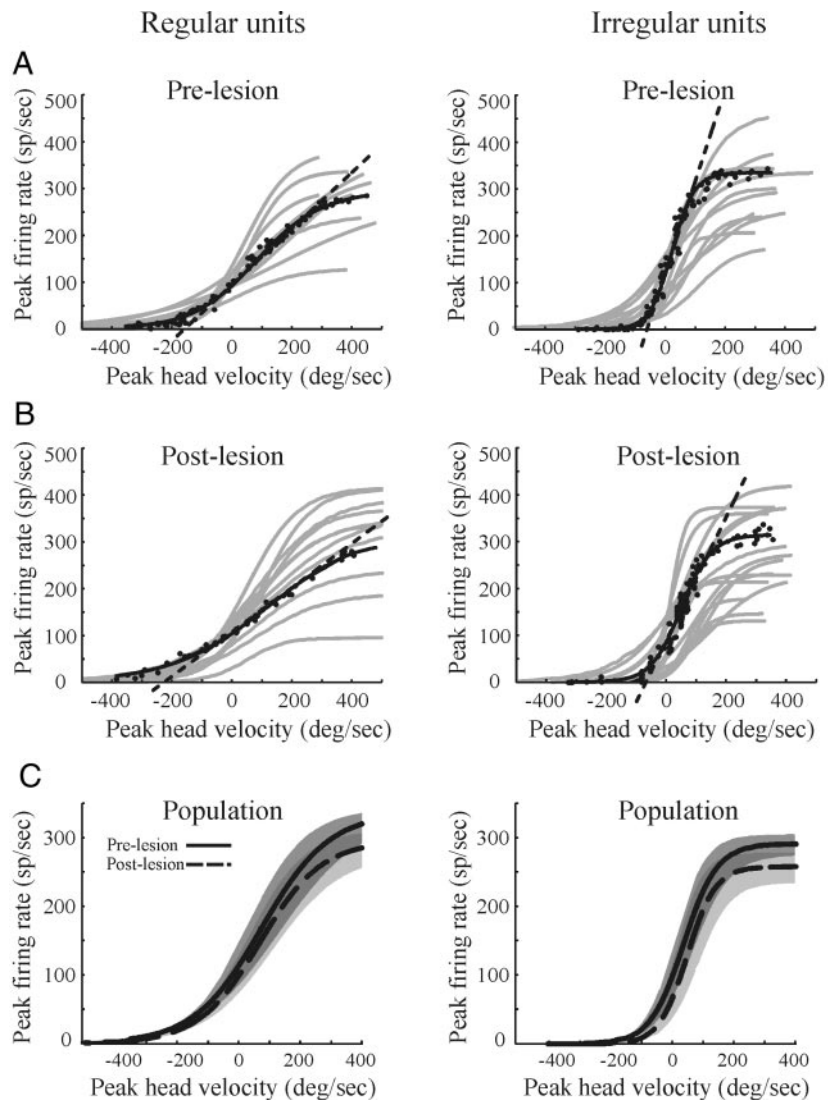


FIG. 4. Response of horizontal canal vestibular afferents to rotations with velocities of $\leq 500^\circ/\text{s}$. **A:** response of regular and irregular afferents in normal animals. Data points are shown for one example regular ($CV^* = 0.06$) and irregular ($CV^* = 0.4$) afferent. Sigmoidal functions fit to the data for the example afferents (black sigmoid curves), as well as the other afferents that were recorded in each condition, are superimposed (gray curves) and provided variance-accounted-for values (VAFs) of $>97\%$. Dashed lines denote the linear portion of the example afferents' responses. **B:** response of regular and irregular afferents on the contralesional side after unilateral labyrinthectomy. Data points are shown for one example regular ($CV^* = 0.05$) and irregular ($CV^* = 0.35$) afferent. Dashed and gray lines are the same as in **A**. **C:** mean of the sigmoid fit to the responses of the population of irregular and regular afferents before (solid lines) and after lesion (dashed lines). Gray areas represent the SE of the responses before (dark gray) and after (light gray) lesion. Differences in each group were not significant under the 2 conditions.

tween resting discharge and neuronal firing rate in the two conditions (paired *t*-test, $P > 0.5$, see Table 2 and insets of Fig. 5, *B1* and *B2*). Thus passive stimulation of neck proprioceptors in the absence of vestibular stimulation had no effect on the resting discharge of the irregular or regular afferents, either before or after labyrinthectomy.

We then tested whether neck efference copy signals might influence the responses of vestibular afferents by specifically characterizing their response during large-amplitude saccades (see METHODS). Previous studies showed that large saccades in monkeys (Bizzi et al. 1971; Lestienne et al. 1984; Roy and Cullen 2004; Vidal et al. 1982) and humans (Andre-Deshays et al. 1991) are normally accompanied by the production of significant neck torque even if the subject is head-restrained. In Fig. 6A, head velocity and neck torque trajectories are illustrated for example regular and irregular afferents postlesion. Neither of the example afferents showed any modulation in response to generation of neck torque when responses were aligned on torque (*left*) or saccade (*right*) onset. We recorded from 18 (eight regulars, three D-irregulars, seven C-irregulars) and 13 (six regulars, two D-irregulars, five C-irregulars) units during this paradigm before and after labyrinthectomy, respec-

tively. For analysis purposes, we compared resting rates (i.e., zero torque generation or eye positions in the range of $\pm 5^\circ$) to cell discharge during saccades $>25^\circ$ for which torques of 1–3 Nm were produced. There was no difference between resting discharge and neuronal firing rate during individual large saccades accompanied by torque before or after labyrinthectomy (paired *t*-test, $P > 0.5$; see Table 2 and insets of Fig. 6, *B1* and *B2*). Taken together, these findings confirm the proposal that neither the activation of neck proprioceptors nor the generation of a neck motor command during active head movements influences afferent responses either before or after unilateral labyrinthectomy.

DISCUSSION

On the basis of our comparisons of populations of vestibular-nerve afferents before to the contralesional side after labyrinthectomy, we conclude that there is no change in resting rate or sensitivity and phase of the response of vestibular nerve afferents to sinusoidal rotations with frequencies in the range of natural head movements. Furthermore, we found that the vestibular-nerve afferents are driven into inhibitory cutoff or

Active and passive head movements

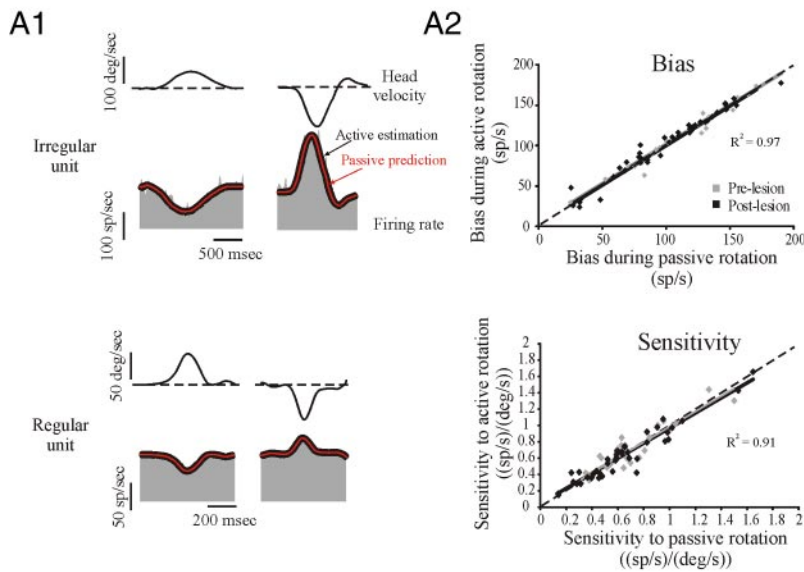
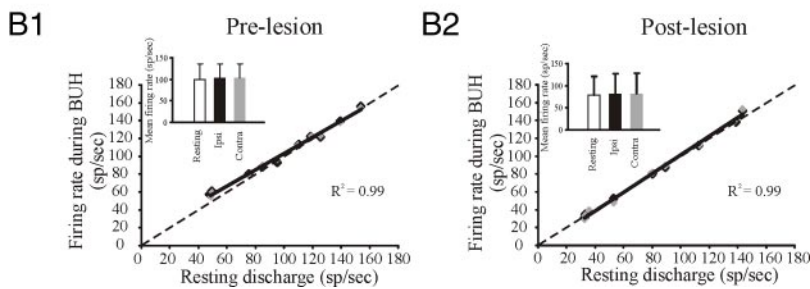


FIG. 5. Response of horizontal canal afferents to active head movements or sinusoidal rotation of the body under stationary head (BUH paradigm at 1 Hz, 50°/s). *A1*: example of the response of a regular ($CV^* = 0.07$) and an irregular ($CV^* = 0.6$) afferent on the contralesional side after unilateral labyrinthectomy to active head movements. Thick black line shows the best fit to the firing rate; red line shows the firing rate predicted based on passive head movements. Note that the red and black lines are superimposed. *A2*: bias (*top*) and sensitivity (*bottom*) of the population of regular and irregular afferents during active and passive head movements, before (gray) and after (black) lesion. Dashed lines have a slope of one (y-intercept = 0). *B1*: mean firing rate in response to ipsilateral (black symbols) or contralateral (gray symbols) rotation of body during BUH paradigm plotted as a function of resting rate, in normal animals. Dashed line has a slope of one. *Inset*: comparison between mean of the resting discharge (white column) of these afferents and their mean discharge during BUH rotation in ipsilateral (*black column*) or contralateral (*gray column*) directions. *B2*: mean firing rate in response to BUH paradigm as a function of resting rate after unilateral labyrinthectomy. Symbols and lines of the figure and inset are the same as in *B1*. Firing rates were similar during BUH paradigms with contra- or ipsilateral rotations and were not different from the mean resting rate, before and after the lesion.

Body under head movements



excitatory saturation at similar velocities before and after lesion. Our findings also show that extravestibular inputs do not affect the response of afferents on the intact side after unilateral labyrinthectomy. We did, however, observe a change in the overall distribution of afferent types after labyrinthectomy. In the following sections, we discuss the implications of each of these four findings.

Response dynamics of vestibular-nerve afferents before and after unilateral labyrinthectomy

Afferent response dynamics were compared over the full range of physiologically relevant head movements [i.e., frequencies ≤ 15 Hz (Armand and Minor 2001; Grossman et al. 1988; Huterer and Cullen 2002) and velocities $\leq 500^\circ/s$ (Armand and Minor 2001; Roy and Cullen 2003; Roy et al. 2003)]. Previous studies showed that the VOR is compensatory for even the most challenging of these rotational stimuli in normal monkeys (Fetter and

Zee 1988; Huterer and Cullen 2002; Minor et al. 1999; Paige 1983a; Ramachandran and Lisberger 2005), but after unilateral labyrinthectomy compensation is most robust for frequencies of rotation < 4 Hz and velocities $< 50^\circ/s$ (Fetter and Zee 1988; Lasker et al. 2000; Sadeghi et al. 2006).

At the level of the periphery, prior studies in normal primates showed that the response gains of regular and irregular afferents both increase as a function of rotational frequency ≤ 4 Hz. The relative increase in gain, however, is considerably larger for irregular afferents than for regular afferents (Fernandez and Goldberg 1971; Goldberg 2000; Haque et al. 2004). Results obtained in chinchillas (Hullar and Minor 1999; Hullar et al. 2005) and macaques (Ramachandran and Lisberger 2006) suggest that this difference is further enhanced for higher frequencies. Consistent with these previous studies, the sensitivities of C-irregular afferents in the present study were between those of regular and D-irregular units at lower frequencies, but showed a steeper rise as

TABLE 2. Comparison between responses of afferents to extravestibular inputs before and after unilateral labyrinthectomy

	Passive		Active		BUH			Torque		
	Bias	Gain	Bias	Gain	rr	Ipsi	Contra	rr	Ipsi	Contra
Prelesion	112 \pm 34	0.64 \pm 0.31	112 \pm 37	0.64 \pm 0.32	100 \pm 35.7	102 \pm 33.7	101 \pm 33.4	107 \pm 35	108 \pm 34	107 \pm 34
Postlesion	110 \pm 45	0.67 \pm 0.30	109 \pm 43	0.66 \pm 0.29	78 \pm 42.5	81 \pm 46.1	81 \pm 44.9	83 \pm 33	84 \pm 31	84 \pm 32

Values are means \pm SE. BUH, body-under-head paradigm; Ipsi, ipsilesional response (sp/sec); Contra, contralesional response (sp/sec); rr, resting rate (sp/sec).

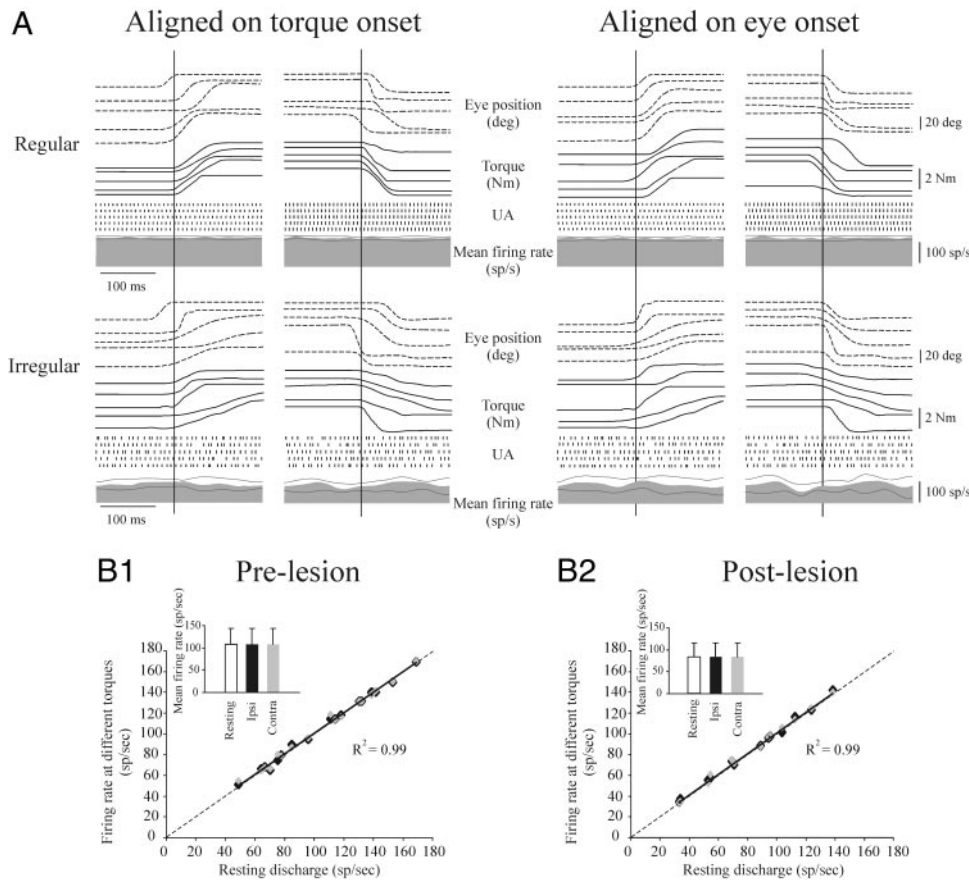


FIG. 6. Effect of the generation of neck motor command on afferent discharges. **A**: examples of the responses of a regular ($CV^* = 0.05$) and an irregular ($CV^* = 0.36$) afferent recorded from the contralesional side after unilateral labyrinthectomy, in a head-restrained monkey during attempted gaze shifts in the ipsi- (left) and contralateral (right) directions. Measured torques were >1 Nm. Traces are aligned on torque (left) or saccade (right) onset. Individual action potentials are represented by tick marks [unit activity (UA)]. Mean firing rate (\pm SD) for 10 trials in each direction is shown in the last trace in each panel. Afferent responses were not modulated when characterized using either analysis. **B1** and **B2**: mean firing rate of the regular and irregular afferents plotted as a function of resting rate, in normal animals (**B1**) and after unilateral labyrinthectomy (**B2**). Insets: comparison between mean of the resting discharge (white column) of these afferents and their mean discharge during attempted gaze shifts to ipsi- (black column) or contralateral (gray column) directions. Slopes of the regression lines (solid lines) were not different from unity (dashed lines) either before ($P > 0.1$) or after ($P > 0.7$) unilateral labyrinthectomy.

a function of frequency, such that they reached values similar to those of D-irregular afferents at 15 Hz (Fig. 2B, solid lines). C-irregular units also showed the highest phase leads over the range of frequencies tested.

The vestibular efferent system preferentially innervates type I hair cells and the terminals of irregular afferents (Goldberg 2000). As a result it follows that efferent-mediated effects should be more apparent in the responses of irregular than regular afferents. Our findings indicate that the responses of both regular and irregular afferents were similar after versus before labyrinthectomy. Thus our conclusion that the head velocity sensitivity of afferents does not change after vestibular compensation complements that of Miles and Braitman (1980) for spectacle-induced motor learning in the VOR. Notably, in this latter study afferent responses were studied only during 0.5 Hz rotations. Our present findings further show that changes in vestibular afferent sensitivity are not likely to contribute to VOR compensation (or by extension to spectacle-induced motor learning) even at higher frequency rotations where the relative gain of responses for the efferent-recipient irregular afferents is enhanced.

Functional range of vestibular-nerve afferent responses before and after unilateral labyrinthectomy

The head movements produced during normal daily activities such as running and gaze shifts can reach velocities ≤ 400 – $500^\circ/s$ in monkeys (Armand and Minor 2001; Roy et al. 2003). Because the VOR responses produced by passive whole body rotations after unilateral labyrinthectomy depend solely

on the inputs from afferents on the contralesional side, the velocity at which afferent responses show saturation and cutoff will limit the compensation that can occur in response to ipsilesional and contralesional rotations, respectively. In the present study we show that afferents were similarly driven into complete cutoff or saturation at velocities of about 400 and $200^\circ/s$ for regular and irregular units, respectively (Fig. 4) in both conditions. These results show that the vestibular efferent system is not used to extend the dynamic range of the input available from the intact side after vestibular damage. This finding is consistent with results that show that the gain of the VOR is subnormal even at rotational velocities as low as about $100^\circ/s$ after unilateral labyrinthectomy (squirrel monkeys: Lasker et al. 2000; Paige 1983b; macaque monkey: Fetter and Zee 1988; Sadeghi et al. 2006; and humans: Galiana et al. 2001; Paige 1989).

Influence of extr vestibular inputs before and after unilateral labyrinthectomy

Previous behavioral studies in humans and monkeys provided evidence that nonvestibular inputs are used to supplement vestibular signals during compensation (Gresty and Baker 1976; Halmagyi and Henderson 1988; Mesland et al. 1996). The idea that nonvestibular mechanisms can substitute for missing vestibular information is further supported by the finding that VOR gains are enhanced for active compared with passive head-on-body rotations (Della Santina et al. 2001; Dichgans et al. 1973; Newlands et al. 2001). Analogous strategies are used by monkeys after bilateral

vestibular damage. Immediately after bilateral labyrinthectomy, resulting from loss of VOR, monkeys systematically overshoot visual targets when making voluntary combined eye–head movements (i.e., gaze shifts; Dichgans et al. 1973; Newlands et al. 1999, 2001). In the weeks that follow, gaze shifts become more accurate as nonvestibular information is used to produce the required compensatory eye movement. The neural mechanisms underlying these effects are not known in primates, but studies in frogs have suggested that changes in the synaptic efficacy of extravestibular inputs to central vestibular neurons substitutes for the loss of vestibular input (reviewed in Dieringer and Straka 1998).

Because extravestibular signals can substitute for missing vestibular information after lesions of the labyrinth, it was important to establish whether these nonvestibular sources compensate for deficits at the level of the vestibular afferents. As reviewed above, one possible pathway through which signals reach vestibular pathways is by the vestibular efferent system. To explicitly test this proposal we first compared the responses of vestibular afferents during active head movements and passive whole body rotations. We saw no difference between the activity of afferents during passive and active head movements either before or after lesion. This confirms previous results in normal animals (Cullen and Minor 2002) and extends our conclusion to afferent responses after compensation. We also found that neither activation of neck proprioceptors (Fig. 5B) nor generation of a neck motor command (Fig. 6)—both without concomitant vestibular stimulation—influenced afferent resting discharges in normal or labyrinthectomized monkeys.

Changes in the proportion of regular and irregular vestibular afferents in the contralesional nerve

The principal change noted in our study in the distribution of afferents post- versus pre-labyrinthectomy was an increase in the proportion of C-irregular afferents (from 22% prelesion to 34% postlesion) and a decrease in the proportion of regular afferents (from 45 to 38%). We did not observe a significant change in D-irregular afferents postlesion. Thus although the proportion of D-irregular afferents was somewhat larger than that of the prior study in primates that explicitly characterized these cells, this proportion remained constant pre- and postlesion. Small differences in resting rate or a species difference (i.e., squirrel monkey vs. macaque) could account for the variance in the relative proportion of regular and D-irregular afferents between a previous study (Lysakowski et al. 1995) and our data. The distinction between regular and C-irregular afferents is more robust and less dependent on resting rate. Although we cannot completely exclude effects of sampling bias pre- and postlesion, our findings suggest that the change in afferent distribution is representative of a population change that is worthy of consideration and further follow-up. With these caveats in mind, we will discuss the potential mechanisms by which such a change in afferent distribution could occur and how this change might be useful from a functional perspective.

Possible mechanisms for an increase in the proportion of irregular units

Previous studies showed that the three groups of afferents (i.e., regular, D-irregular, and C-irregular) are not only different in their discharge properties and dynamic responses, but also have specific patterns of termination within the sensory epithelia of the labyrinth (Goldberg 2000). Afferents with dimorphic terminations can be regularly or irregularly discharging depending on their location within the sensory epithelium of the cristae. In contrast, C-irregular afferents terminate as calyx endings exclusively onto type I hair cells in the central zone. There are at least two possible mechanisms that could account for the change that we observed in the proportion of C-irregular afferents after labyrinthectomy: 1) an increase in the number of type I hair cells and calyx-only (C-irregular) afferents or 2) a change in the response dynamics of regular afferents with dimorphic endings that then results in these afferents having properties that resemble C-irregular afferents.

In support of the first possibility, there is evidence from studies of hair cell regeneration after ototoxic injury in chicks that type I hair cells develop from further differentiation of type II hair cells (Weisleder et al. 1995; Zakir and Dickman 2006). Although the mechanisms responsible for this differentiation process have not yet been identified, the change in the distribution of hair cells could perhaps be mediated through the efferent signals. These mechanisms of differentiation from one hair cell group to another involve alterations in hair cell and afferent morphology and physiology. It seems unlikely, although not yet directly tested by experimental methods, that such processes would occur in an established sensory epithelium as is found in the contralesional labyrinth after labyrinthectomy.

The second proposed mechanism is supported by recent studies showing that the discharge regularity of afferents in toad fish depends on the activation of γ -aminobutyric acid type B (GABA_B) receptors (Holstein et al. 2004a,b). Previous studies in mammals also showed that GABA receptors are predominantly expressed in the efferent nerve endings surrounding type I hair cells (rat: Kitahara et al. 1994; Kong et al. 1998b; squirrel monkey: Usami et al. 1987; human: Kong et al. 1998a). Thus one possibility is that efferent activity might influence discharge regularity through postsynaptic effects. Accordingly, this mechanism could potentially account for the changes we observed in the relative distribution of regular and C-irregular afferents on the contralesional side after labyrinthectomy.

Possible functional role for an increase in the proportion of irregular units

Our findings confirm those of previous studies (Fernandez and Goldberg 1971; Haque et al. 2004; Hullar and Minor 1999; Hullar et al. 2005; Ramachandran and Lisberger 2006), indicating that irregular afferents show more phasic properties, with a wider range of sensitivities during rotation. An increase in the phasic component of the VOR evoked by contralesional rotations was shown to contribute to the recovery of these responses after labyrinthectomy (Fetter and Zee 1988; Lasker et al. 2000; Sadeghi et al. 2006). The changes in afferent

distribution that we observed after labyrinthectomy would lead to an increase in the phasic signal from the intact labyrinth. Earlier studies of cellular mechanisms of vestibular compensation showed an increase in the proportion of cells with phasic properties (i.e., type B cells) in the contralesional vestibular nuclei after unilateral lesions (Beraneck et al. 2004). Our findings could thus provide a plausible mechanism to explain the change in the physiology of central vestibular neurons that would also be consistent with previous modeling results (Lasker et al. 2000). Accordingly, such an increase in irregular afferent inputs to neurons in the vestibular nuclei provides a possible signal for restoring the properties of these central neurons. However, we note that our findings do not exclude other compensatory mechanisms such as changes in the synaptic strength of afferents or changes in intrinsic membrane properties of central vestibular neurons (reviewed in Straka et al. 2005). The latter could be the result of homeostatic plasticity and/or changes in ionic conductances of vestibular neuron membranes. Under these conditions, modifications at the level of vestibular nuclei could influence the proportion of irregular vestibular nerve afferent fibers, either by means of the efferent vestibular system (see above) or by retrograde signaling (e.g., see Zweifel et al. 2005).

Conclusion

In conclusion, our findings indicate that afferents from the semicircular canals of the contralesional labyrinth show no change in resting rate, head-velocity sensitivity, inhibitory cutoff, excitatory saturation, and/or sensitivity to nonvestibular inputs after unilateral labyrinthectomy. Our experiments were performed 1–12 mo after the lesion so acute changes that then reverted to baseline physiological properties cannot be excluded based on the data reported here. These results show that mechanisms of compensation proposed on theoretical grounds—such as an increase in the resting discharge rate and decrease in sensitivity of afferents on the intact side—do not occur.

We did observe a statistically significant increase in the proportion of C-irregular afferents and decrease in regular afferents in our recordings postlabyrinthectomy. Although artifacts based on sample bias cannot be excluded with certainty, this change in afferent distribution may provide a mechanism for adjustments in the VOR and in central vestibular neurons reported postlabyrinthectomy in other studies. Further investigations that explore potential morphological or cellular changes in the contralesional labyrinth are needed to clarify these issues.

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