Behavioral/Systems/Cognitive

Neural Correlates of Sensory Substitution in Vestibular Pathways following Complete Vestibular Loss

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Sensory substitution is the term typically used in reference to sensory prosthetic devices designed to replace input from one defective modality with input from another modality. Such devices allow an alternative encoding of sensory information that is no longer directly provided by the defective modality in a purposeful and goal-directed manner. The behavioral recovery that follows complete vestibular loss is impressive and has long been thought to take advantage of a natural form of sensory substitution in which head motion information is no longer provided by vestibular inputs, but instead by extravestibular inputs such as proprioceptive and motor efference copy signals. Here we examined the neuronal correlates of this behavioral recovery after complete vestibular loss in alert behaving monkeys (*Macaca mulatta*). We show for the first time that extravestibular inputs substitute for the vestibular inputs to stabilize gaze at the level of single neurons in the vestibulo-ocular reflex premotor circuitry. The summed weighting of neck proprioceptive and efference copy information was sufficient to explain simultaneously observed behavioral improvements in gaze stability. Furthermore, by altering correspondence between intended and actual head movement we revealed a fourfold increase in the weight of neck motor efference copy signals consistent with the enhanced behavioral recovery observed when head movements are voluntary versus unexpected. Thus, together our results provide direct evidence that the substitution by extravestibular inputs in vestibular pathways provides a neural correlate for the improvements in gaze stability that are observed following the total loss of vestibular inputs.

Introduction

Sensory substitution refers to the replacement of a defective or lost sensory modality with input from another functioning modality. When tactile stimulation is applied to replace, for example, visual (for review, see Bach-y-Rita and Kercel, 2003) or auditory (Schürmann et al., 2006) input in blind or deaf patients, a significant degree of functionality can be achieved. Understanding the changes that occur in the brain during such challenges, which require significant neural plasticity, remains a fundamental problem in neuroscience. Vestibular pathways are particularly well suited to establishing links between neurons, neural circuits, and motor performance, and the recovery that follows complete vestibular loss is impressive. Notably, immediately following bilateral loss, patients suffer from severe oscillopsia during head movements (Minor, 1998). However, within a month, subjects naturally regain much of their ability to control gaze, particularly when head movements are voluntary and predictable. In contrast, less predictable head movements remain relatively disabling (Maurer et al., 1998).

The neural mechanisms that underlie recovery of gaze control after complete vestibular loss are currently not understood. Behavioral studies suggest that humans and primates use analogous compensation strategies following bilateral vestibular damage that include: the enhancement of neck reflexes such as the cervico-ocular reflex (COR) and the preprogramming of compensatory eye movements based on an efference copy of the motor command to the head (Dichgans et al., 1973; Della Santina et al., 2002). COR gains are normally negligible to nonexistent in most species, including rhesus monkeys and humans (for review, see Cullen and Roy, 2004), but can be enhanced after vestibular loss (Schweigart et al., 1993). In addition, vestibular pathways receive direct inputs from structures that could carry an efference copy signal of active head motion including neurons within oculomotor/gaze control pathways (Sasaki and Shimazu, 1981), the vestibular cerebellum (Voogd et al., 1996), and the head/neck region of cortical areas 6pa, 6c, and 23cv (for review, see, Fukushima, 1997).

To date, the question of how extravestibular inputs replace vestibular inputs to control gaze remains unanswered. Normally the vestibulo-ocular reflex (VOR) produces compensatory eye movements to stabilize gaze for head movements produced during our daily activities. We hypothesized that, following complete vestibular loss, neck-related inputs substitute for vestibular inputs at the level of the simple three-neuron arc that mediates the most direct pathway of the VOR (Lorente de Nó, 1933). To test this, we recorded from the neurons that constitute the intermediate leg of the pathway. We found that, indeed, increasingly robust extravestibular neck inputs (i.e., proprioceptive as well as an efference copy signal) substitute for the vestibular inputs to

Received May 23, 2012; revised Aug. 10, 2012; accepted Aug. 27, 2012.

Author contributions: S.G.S., L.B.M., and K.E.C. designed research; S.G.S., L.B.M., and K.E.C. performed research; S.G.S. and K.E.C. analyzed data; S.G.S., L.B.M., and K.E.C. wrote the paper.

This work was supported by grants from the Canadian Institutes of Health Research and National Institutes of Health R01 DC02390. We thank Walter Kucharski and Steve Nuara for excellent technical assistance.

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DOI:10.1523/JNEUROSCI.2493-12.2012

 0270-6474/12/3214685-11$15.00/0

stabilize gaze at the level of single neurons in the VOR premotor circuitry. Furthermore, by altering the correspondence between intended and actual head movement we found that the sum of these inputs was sufficient to explain improvements in gaze stability during active self-motion. Thus, our results show that the substitution by extravestibular inputs in vestibular pathways provides a neural correlate for the improvement in gaze stability that is observed in the total absence of vestibular inputs.

Materials and Methods

Subjects and surgery. Two male rhesus macaque monkeys (*Macaca mulatta*) were chronically implanted with posts for head restraint, recording chambers for single unit recordings, and scleral search coils for high-resolution eye movement recordings as has been previously described (Sylvestre and Cullen, 1999). The analgesic buprenorphine (0.01 mg/kg, i.m.) and antibiotic cefazolin (Ancef; 25 mg/kg, i.m., 5 d) were given postoperatively. Using standard operant conditioning paradigms, animals were then trained to fixate visual targets for a juice reward. The present report presents the results of single-unit recordings made in the vestibular nuclei (VN) after complete (i.e., bilateral) vestibular loss. First, a unilateral labyrinthectomy was performed through the mastoid bone to remove the ampulla of the three semicircular canals, the utricle, and saccule, and the distal ends of the ampullary nerve branches (Sadeghi et al., 2006), and recordings were made in the contralateral VN. The findings of these experiments have been previously reported (Sadeghi et al., 2010, 2011). Here, in preparation for the present study, we identified the location of the VN ipsilateral to the first lesion in each animal. A second labyrinthectomy was then performed on each monkey's intact side to completely ablate vestibular inputs. To quantify the time course of the resultant changes in neuronal responses, our single unit recording experiments began the following day and continued over the next 2 months. 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.

Experimental design and data acquisition. Monkeys were initially head restrained during experiments. Yaw rotations about the earth's vertical axis were applied using a motion stimulator, located within a 1 m^3 magnetic field coil (CNC Engineering). A visual target (HeNe laser) was projected, via a system of two galvanometer controlled mirrors, onto a cylindrical screen located 60 cm away from the monkey's head. Monkeys were trained to follow the visual target and neuronal sensitivities to saccades, ocular fixation, and pursuit were characterized by having the monkey follow target motion that (1) stepped between horizontal positions over a range of ±30° and (2) moved sinusoidally (0.5 Hz, 40°/s peak velocity). Target and turntable motion were controlled by a UNIX-based real-time data acquisition system (REX; Hayes et al., 1982).

We used stimuli similar to those previously used following unilateral lesion (Sadeghi et al., 2010, 2011). Briefly, four stimulus conditions were used. First, to stimulate the vestibular system, monkeys were rotated about an earth vertical axis with their heads restrained (0.5 Hz, peak velocity of 40°/s) in the dark (whole-body rotation). Second, to stimulate neck proprioceptors the monkey's head was held stationary relative to the earth while its body was sinusoidally (0.5 Hz, 40°/s) rotated beneath. Third, combined stimulation of the vestibular system and neck proprioceptors was induced by passively rotating the monkey's head on its body using a torque motor (Kollmorgen) attached to the head (Huterer and Cullen, 2002; Sadeghi et al., 2010). The applied stimulation produced horizontal sinusoidal rotations of the head about the vertical axis, relative to the stationary body (0.5–1 Hz, 40°/s). Behavioral and neuronal responses were tested over a frequency range of 0.5–1 Hz to facilitate comparison with those measured following unilateral labyrinthectomy (Sadeghi et al., 2010). Finally, the monkey's head was slowly and carefully released so that it was free to make voluntary (i.e., active) horizontal head movements (i.e., horizontal rotations about the earth vertical axis) (Roy and Cullen, 2002). During these head-unrestrained periods, we randomly (<20% of head rotations) engaged a clutch just before the target presentation, to prevent head motion (Dichgans et al., 1973). The brake lasted for a period of 1–4 s, during which head and eye movements as well as the torque generated by the animal's attempt to move the head were measured.

Electrophysiology. Extracellular single-unit recordings were performed using enamel-insulated tungsten microelectrodes (7–10 MΩ impedance; Frederick-Haer) advanced into the brainstem through a transdural guidetube using a lightweight microdrive (Narishige). Single neurons were isolated using a conventional amplifier system and bandpass 8 pole filter (400 Hz–10 kHz). The abducens nucleus was first identified based on its stereotypical discharge patterns during eye movements (Cullen et al., 1993; Sylvestre and Cullen, 1999) and then used as a landmark to determine the location of the medial and lateral VN. In preparation for the present study, we identified the location of the VN ipsilateral to the first labyrinthectomy in each animal and confirmed that the position of the recording area was ~2–4 mm contralateral to the recording area following unilateral labyrinthectomy (i.e., contralateral VN) in previous studies (Sadeghi et al., 2010, 2011). In the present study we focused on understanding the information encoded by position-vestibular-pause (PVP) neurons. Since vestibular inputs were ablated and no vestibular responses were detected following bilateral labyrinthectomy, PVP neurons were identified solely on the basis of their responses to eye movements, signified by pauses during ipsilateral saccades and sensitivity to contralateral eye positions. Recordings were made in the VN contralesional to the second labyrinthectomy, to allow comparison with responses to those observed following unilateral lesion.

Gaze and head position were monitored using the magnetic search coil technique, and turntable velocity was measured using an angular velocity sensor (Watson). Single-unit responses, horizontal and vertical gaze and head positions, target position, and table velocity were recorded on a DAT tape for later playback. Action potentials were discriminated during playback using a windowing circuit (BAK) that was manually set to generate a pulse coincident with the rising phase of each action potential. In addition, gaze position, head position, target position, and table velocity signals were lowpass filtered at 250 Hz (8 pole Bessel filter) and sampled at 1 kHz.

Data analysis. Data were imported into the MATLAB (MathWorks) 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 filter with a Hamming window. Eye position was calculated from the difference between gaze and head position signals. Gaze, eye, and head position signals were digitally differentiated to produce velocity signals. Neuronal responses were represented using a spike density function in which a Gaussian was convolved with the spike train (SD = 10 ms for sinusoidal rotations and SD = 5 ms for gaze shifts) (Cullen and Guitton, 1996; Sylvestre and Cullen, 2006). Statistical significance was determined using Student's *t* tests.

Single-unit data were recorded starting from day 1 (i.e., 15–28 h) postlesion. Later recordings were made on a weekly basis up to 2 months postlesion. To quantify behavioral performance, COR- and VOR-like behavioral gains were calculated as the resultant slow phase (i.e., desaccaded) eye velocity divided by turntable and head velocities, respectively, after accounting for the difference in phase (Sadeghi et al., 2006, 2010, 2011). In addition, to compute the gain of VOR-like responses observed during active head movements (see Fig. 5*A*, arrowheads) eye movements were characterized during head motion that occurred in the 10–80 ms period that followed the end of the gaze shift (i.e., postgaze shift period) (Sadeghi et al., 2010, 2011).

To identify PVP cells, neuronal eye-position sensitivities were computed from periods of fixation using a multiple regression analysis (Roy and Cullen, 1998). Spike trains were also assessed to verify that neurons paused during saccades. As previously described (Sadeghi et al., 2010, 2011), a least-squared regression analysis was used to determine each unit's response to vestibular stimulation during passive whole-body rotations, to neck proprioceptive stimulation during passive rotation of the body under a stationary head, and to combined vestibular and proprioceptive stimulation evoked by passive sinusoidal head-on-body rotations. The general form of the equation used is as follows:

$$\hat{fr}(t) = b + S_v * \dot{X}(t) + S_a * \ddot{X}(t) + k * E(t), \quad (1)$$

where $\hat{fr}$ is the estimated firing rate, S_v and S_a are coefficients representing sensitivities to velocity and acceleration (of head or body), b is a bias term, and E is eye position, and $\dot{X}$ and $\ddot{X}$ are head or body velocity and acceleration, respectively. Only unit data from periods of slow-phase eye velocity that occurred between saccades were included in the analysis. The estimated coefficients S_v and S_a were then used to calculate each unit's modulation sensitivity [(spikes/s)/(°/s)] and phase shift (degree) relative to the velocity input (Sadeghi et al., 2009).

To investigate the possible presence of signals from higher brain areas (e.g., efference copy), we used two paradigms, which were described above. First, we measured both neuronal responses and VOR-like responses as monkeys made self-generated (active) head movements toward food targets. We used the following analysis during active head-on-body movements. We first hypothesized that sensory-driven modulation of a given PVP after bilateral loss should be described by the summation of its neck proprioceptive input and an additional signal arising from the motor command to produce the active rotation of the head relative to the body as follows:

$$FR = \mathrm{gNeck}_{\mathrm{proprio}}H + \mathrm{gNeck}_{\mathrm{motor}}H, \quad (2)$$

where FR is firing rate corrected for the neuron's resting discharge, $\mathrm{gNeck}_{\mathrm{proprio}}$ is the sensitivity to neck proprioceptor stimulation, $\mathrm{gNeck}_{\mathrm{motor}}$ is its sensitivity to the self-generated motion of the head relative to the body, and H is the phase-shifted head velocity. The sensitivity to neck proprioceptor stimulation, $\mathrm{gNeck}_{\mathrm{proprio}}$, can be calculated from each neuron's response during passive head-on-body rotation since there are no active head movements in this condition. Accordingly, during passive head-on-body rotation since $\mathrm{gNeck}_{\mathrm{motor}} = 0$, Equation 2 simplifies to the following:

$$FR = \mathrm{gNeck}_{\mathrm{proprio}}H. \quad (3)$$

So, it follows that we can obtain an estimate of a given neuron's modulation in response to neck proprioception ($\mathrm{gNeck}_{\mathrm{propri}}$) by measuring its modulation to passive head-on-body rotation and substitute this value into Equation 2. Then by rearranging terms we can obtain an estimate of the neuron's modulation in response to production of a neck motor command ($\mathrm{gNeck}_{\mathrm{motor}}$).

$$\mathrm{gNeck}_{\mathrm{motor}}H = FR - (\mathrm{gNeck}_{\mathrm{proprio}}H). \quad (4)$$

Second, in a small percentage of trials a clutch was engaged just before target presentation to brake active head movements in the head-unrestrained condition. During the brake period (1–4 s), we measured head and eye movements as well as the torque produced as a monkey attempted to move its head. Neuronal firing rates were measured and compared at different times after the lesion.

To quantify the ability of the linear regression analyses to model neuronal discharges during each paradigm, we computed the variance accounted for (VAF) provided by each regression equation (Cullen et al., 1996). The VAF was defined as $\{\mathrm{VAF} = 1 - [\mathrm{var}(\hat{fr} - fr)/\mathrm{var}(fr)]\}$, where $\hat{fr}$ represents the modeled firing rate (i.e., regression equation estimate) and fr represents the actual firing rate.

Results

To assess the contribution of vestibular and extravestibular signals to neuronal responses as well as any improvements in motor performance after bilateral vestibular loss, we recorded the activity of single neurons in the VN of two rhesus monkeys. In each animal, a unilateral labyrinthectomy was first performed and recordings were made in the contralateral VN (Sadeghi et al., 2010, 2011). For the present study, we then identified the location of the VN ipsilateral to the first labyrinthectomy and next performed a second labyrinthectomy on the contralateral side (see Materials and Methods). Because the second labyrinthectomy produced complete vestibular loss, we identified PVP neurons on the basis of their responses to eye movements: PVP neurons pause during ipsilateral saccades and show contralateral eye position sensitivity. We recorded from a total of 102 PVP neurons in the right VN of two rhesus monkeys with complete bilateral vestibular loss. Of these, 27 neurons were recorded on the first day (i.e., 15–28 h) postlesion, 37 neurons in the period of 7–21 d postlesion, and 38 neurons in the 1–2 months postlesion.

Response of neurons to vestibular and neck proprioceptive stimulation

We first characterized the response of neurons to vestibular inputs by applying passive whole-body rotations (0.5 Hz, 40°/s). On the first day after the lesion, we advanced the electrode to the area that we had identified as the VN before the second labyrinthectomy and recorded from neurons that were sensitive to eye position (Fig. 1*A*), and also paused during fast eye movements (i.e., saccades and quick phases). Confirming the complete lack of vestibular inputs following bilateral labyrinthectomy, neurons showed no modulation in firing rate during whole-body rotation (Fig. 1*B*). In contrast, when we passively stimulated neck proprioceptors by rotating the body under a stationary head, nearly one-half of the neurons showed robust modulation (Fig. 1*C*, compare left and right columns). Furthermore these "neck-sensitive" neurons showed modulation when combined vestibular and neck proprioceptive stimulation was applied by passively rotating the head on body (Fig. 1*D*). The predicted modulation (red dashed line) of the same two example PVP neurons based on the response to neck stimulation alone (Fig. 1*C*) is superimposed on each example neuron's response. For comparison, the average modulation of PVP neurons (based on average values from Sadeghi et al., 2010) in normal animals (blue) are also shown for each stimulus condition. Notably, one day after complete vestibular loss, the example neck-sensitive neuron responded during passive head-on-body but not whole-body rotation because the former condition provided neck proprioceptive as well as vestibular stimulation. In contrast, because neurons in normal animals responded to vestibular but not neck proprioceptive stimulation, their responses were comparable during passive whole-body and head-on-body rotations.

The changes observed for the example neurons were representative of the population of recorded neurons. Figure 2, *A* and *B*, shows the time course of the change in vestibular and neck sensitivities of the population of neurons on day 1 ($n = 27$), week 1 ($n = 20$), week 2–3 ($n = 17$), and >week 3 ($n = 38$) after bilateral labyrinthectomy. Immediately following complete vestibular loss (day 1), the average sensitivity of neurons to passive vestibular stimulation (0.5 Hz, 40°/s; Fig. 1*B*) was 0.04 ± 0.005 (spikes/s)/(°/s) for both neck-sensitive and neck-insensitive neurons, which was significantly lower ($p < 0.0001$) than control values on the contralateral side after the first (unilateral) labyrinthectomy (0.9 ± 0.15 and 0.5 ± 0.15 (spikes/s)/(°/s) for neck-sensitive and neck-insensitive neurons, respectively (Sadeghi et al., 2010). Over the following weeks, vestibular sensitivities did not show any improvement for either neck-sensitive or neck-insensitive neurons (average sensitivities: 0.04 ± 0.006, 0.03 ± 0.005, and 0.05 ± 0.007 (spikes/s)/(°/s) for week 1, weeks 2–3, and >week 3, respectively). Together, these results from bilateral labyrinthectomized animals prove the lack of any vestibular inputs to these neurons. Despite the absence of vestibular information, these neurons received eye motion-related signals and retained their connections to extraocular motoneurons as evidenced by their eye position sensitivity [0.95 ± 0.4 and 1.01 ± 0.3 (spikes/s)/° on day 1 and >week 3, respectively], which was similar to that observed under normal conditions ($p > 0.1$).

Next we quantified, for the population of neurons, the extent to which the extravestibular input provided by neck proprioceptive

tors substituted for the vestibular inputs after bilateral loss. Recordings were made from single neurons (20 on day 1, 15 for week 1, 15 for week 2–3, and 30 after week 3) after the lesion while we passively stimulated neck proprioceptors in isolation by sinusoidally rotating the monkey's body beneath its earth-stationary head (1 Hz, 40°/s; Fig. 1*C*). Neck proprioceptive inputs are unmasked on PVP neurons following unilateral labyrinthectomy in this condition (Sadeghi et al., 2010). Here, we found that following complete bilateral loss of vestibular inputs, PVP neurons continue to encode neck proprioceptive information but with two important differences. First, when the neck sensitivity of our population of neck-sensitive neurons was computed considering response direction as well as magnitude, the average sensitivity increased with time. In contrast, following unilateral labyrinthectomy this population of neurons showed minimal neck sensitivity acutely after the lesion as well as during the compensation process. Specifically, immediately following lesion (day 1), the average neck sensitivity was similar to that recorded previously following unilateral labyrinthectomy [0.06 ± 0.07 (spikes/s)/(°/s), $p > 0.1$]. Notably, however, the average neck sensitivity of these neurons significantly increased reaching values of 0.16 ± 0.02 and 0.14 ± 0.02 (spikes/s)/(°/s) ($p < 0.05$) on week 2 and >week 3, respectively. A second difference was that the percentage of neck-sensitive neurons decreased as a function of time (Fig. 2*B*, left inset). Thus these two findings are in contrast to the condition after a unilateral lesion where no change was observed in the percentage of neck-sensitive neurons after the first week postlesion, but neck sensitivities decreased over time with simultaneous improvement in vestibular sensitivities.

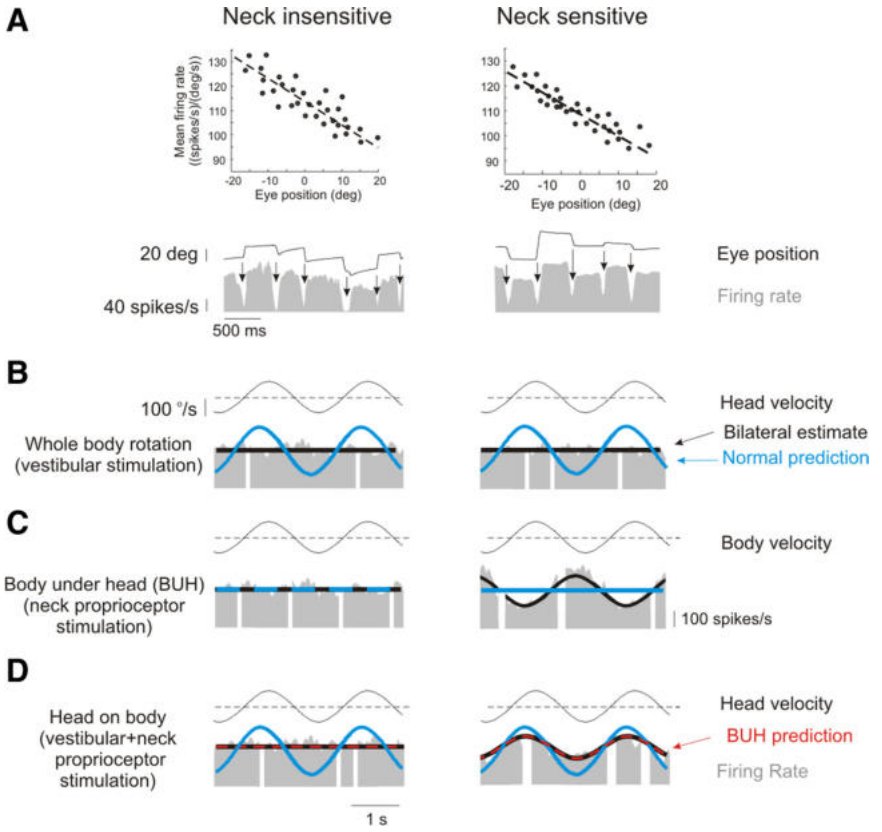

Figure 1. Examples of neuronal responses to different paradigms used in the present study. ***A***, Neurons were identified by their eye position sensitivity (top) and pauses during saccadic eye movements (arrows). ***B***, Responses of two example neurons to whole-body rotations. Following bilateral labyrinthectomy, no responses were observed. ***C***, Response to neck proprioceptor stimulation. Some of the neurons modulated during rotations of the body under a stationary head (i.e., neck proprioceptive stimulation), while others showed no response. ***D***, Response to passive head-on-body rotation. Neurons with neck sensitivity were similarly modulated during passive head-on-body and body-under-head (BUH) rotations (dashed red line). Predicted responses in normal animals (blue lines) are also shown for all panels (based on values from Sadeghi et al., 2010).

Finally, we quantified neuronal responses when neck proprioceptors were stimulated by passively rotating the head on body (0.5–1 Hz, 40°/s; Fig. 1*D*). Since neurons no longer received vestibular inputs, we hypothesized that their modulation should be identical to that measured during passive rotation of the body under head (Fig. 1*C*). Recordings were made from the majority of the same neurons studied above (15 on day 1, 12 on week 1, 11 on week 2–3, and 28 after week 3), and consistent with our prediction that each neuron's sensitivity to rotation was comparable in the two conditions (Fig. 2*B*, right inset). Thus, during head-on-body movements neck-sensitive PVP neurons encode a movement-related signal after bilateral labyrinthectomy. Moreover, while the encoded neck-related signal is smaller (~80%) than the vestibular signal encoded by PVP neurons in intact condition, it shows a significant increase within 2 weeks (relative to day 1) following bilateral labyrinthectomy ($p < 0.05$).

Do neck proprioceptive inputs affect the recovery in resting discharge?

A possible role for the observed enhancement of neck proprioceptive responses is that it reflects a homeostatic mechanism that functions to ensure the continued dynamic stimulation of individual vestibular neurons following vestibular loss. If this were the case, then we would expect that neck-sensitive neurons should show better and/or faster compensation compared with neck-insensitive neurons following lesion. Indeed, immediately following unilateral labyrinthectomy, the resting discharge rates of PVP neurons significantly decreased, and then recovered faster for neck-sensitive neurons compared with neck-insensitive neurons (Sadeghi et al., 2010). In contrast, following bilateral loss (i.e., immediately after the second labyrinthectomy), average resting discharge rates did not change compared with values measured after compensation to unilateral labyrinthectomy (Fig. 2*C*; 101 ± 5 and 110 ± 11 spikes/s for neck-sensitive and neck-insensitive neurons, respectively, $p > 0.05$ with regard to unilateral condition). In fact, the resting discharges of both neck-sensitive and neck-insensitive neurons significantly decreased over time, reaching values of 83 ± 9 and 85 ± 8 spikes/s, respectively, one month after the lesion. Moreover, at no time after the lesion did the resting discharges of the two groups of neurons differ ($p > 0.05$). Thus, the presence of neck-related inputs on VOR interneurons did not result in a parallel change to maintain the resting discharge of these neurons over time.

Does the enhancement of neck-driven ocular responses improve gaze stabilization?

PVP neurons constitute the intermediate leg of the direct VOR pathway (McCrea et al., 1987; Scudder and Fuchs, 1992; Cullen

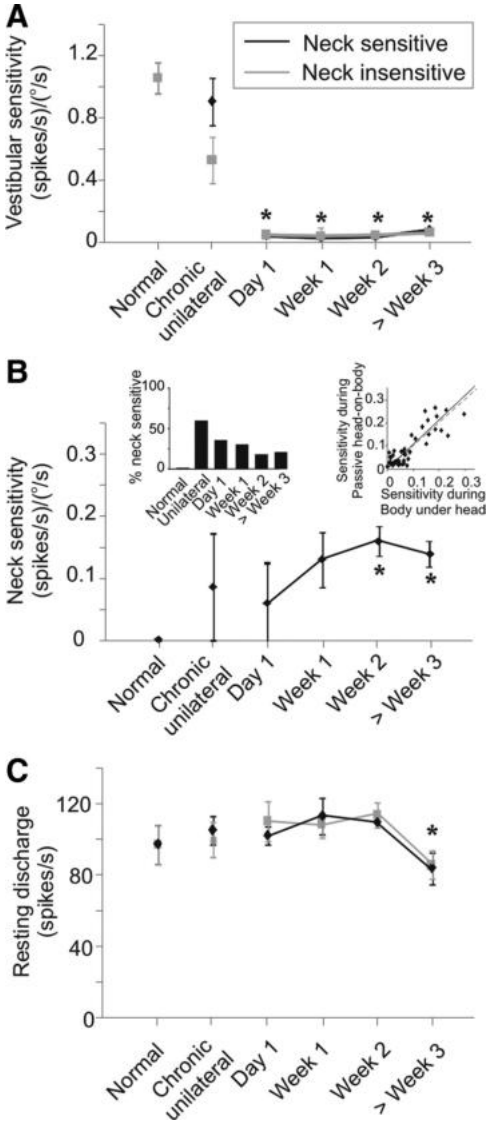

Figure 2. Changes in neuronal responses after bilateral labyrinthectomy. ***A***, Response of the population of PVP neurons to whole-body rotation. Vestibular sensitivities were absent after the second labyrinthectomy and did not recover at any time. Asterisks denote significant difference with regard to pre-lesion. ***B***, Response of neurons to stimulation of neck proprioceptors. For the population of neck-sensitive neurons [i.e., sensitivity $>$ 0.1 (spikes/s)/(°/s)]; average sensitivities increased over time after bilateral lesion. Note that the direction of neck sensitivities was accounted for in the calculation. Asterisks show significance with regard to day 1. Left inset, The proportion of neck-sensitive neurons decreased over time. Right inset, Individual neurons had comparable sensitivities during passive head-on-body and body-under-head rotations. ***C***, Changes in the resting discharge of PVP neurons after bilateral lesion. Resting discharges were similar to normal conditions and compensated chronic stage after unilateral labyrinthectomy for up to ~2 weeks after bilateral lesion and decreased afterward.

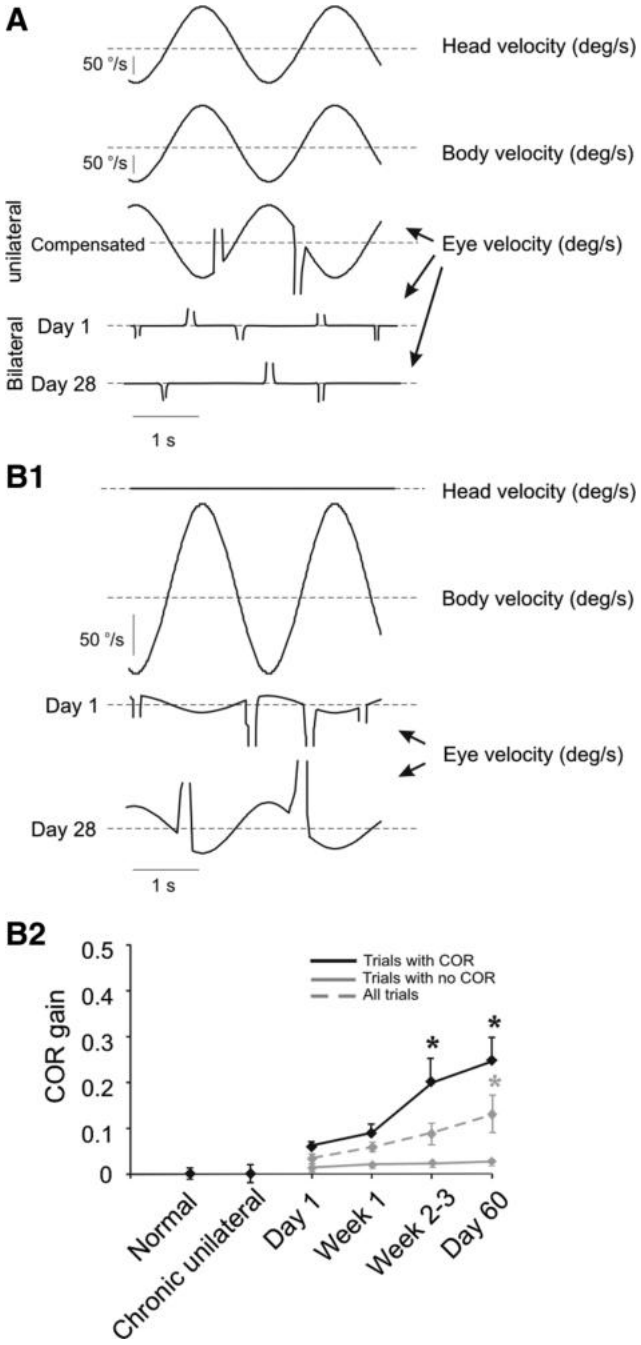

Figure 3. Development of the COR after bilateral labyrinthectomy in the absence of VOR. ***A***, Eye movements generated during whole-body rotations 2 months after unilateral labyrinthectomy (i.e., compensated VOR) (data from Sadeghi et al., 2010) and after bilateral labyrinthectomy. VOR responses are absent following bilateral lesion even after 4 weeks. ***B***, COR gain increased over time after bilateral labyrinthectomy. ***B1***, Example of COR responses after bilateral labyrinthectomy. ***B2***, At each time point after the lesion, the COR response was absent (i.e., gain $<$ 0.1) during some of the trials even in the same session (gray solid line). When all trials were considered together, the COR gain was significantly increased after ~1 month (dashed line). All stimuli had a frequency of 0.5 Hz. Asterisks signify significant differences compared with day 1.

and McCrea, 1993). After bilateral labyrinthectomy, consistent with their lack of vestibular modulation (Fig. 1*B*) we observed no significant VOR response in response to whole-body rotation either immediately following bilateral labyrinthectomy or after compensation (Fig. 3*A*; VOR gain $<$0.05 at all times) compared with compensated VOR 2 months after unilateral labyrinthectomy, which is similar to normal conditions. In contrast, in response to head-on-body rotations, PVP neurons did show enhanced modulation to the stimulation of neck proprioceptors over time. This suggests that that the reweighting of this extravestibular input plays a role in the behavioral recovery that follows complete vestibular loss.

To further investigate this possibility, we examined whether the increased weighting of neck proprioceptive input results in the enhancement of neck-driven ocular responses to improve gaze stabilization. The neck proprioceptive driven ocular response, produced by the COR, does not make significant contribution to gaze stabilization in normal subjects (Roy and Cullen,

2002) or following unilateral vestibular loss (Sadeghi et al., 2010). However, we hypothesized that the enhancement of neck reflexes would contribute to the improvement in gaze stability that is observed in the total absence of vestibular inputs. This prediction was validated by our quantification of the behavioral performance (i.e., the COR) measured during the same paradigms used to compute neuronal neck sensitivity above (Fig. 1*C*). Specifically, average behavioral gains were computed by measuring eye movements evoked by sinusoidal rotation of the monkey's body beneath its earth-stationary head. Figure 3*B1* shows typical data from measurements made on day 1 versus 28 after bilateral labyrinthectomy. Compensatory eye movements in the direction opposite to the motion of the neck (i.e., body) rotation were commonly observed at both intervals and compensatory eye velocity amplitude increased over time.

Figure 3*B2* shows the average behavioral performance measured in the two monkeys, before and at different times after complete vestibular loss. Neck proprioceptive-driven eye movements were negligible before the lesion in both the intact condition and after compensation for unilateral vestibular loss. However, immediately after bilateral loss significant COR gains (i.e., >0.1) were observed in only about half of the trials for both animals at each time tested. When only these trials were considered, COR gain increased over time reaching values of 0.25 ± 0.05 within 1 month following bilateral lesion (black trace, $p < 0.001$ with regard to control). Previous studies have reported comparable COR gains after bilateral labyrinthectomy (Dichgans et al., 1973) or plugging of all canals (Newlands et al., 1999) in monkeys. Furthermore, when all trials were averaged together, the gain of the COR still showed a significant, albeit smaller, increase over the same time period, reaching values of ~0.15 within 1 month (gray dashed trace; $p < 0.01$ with regard to control). Thus, together our findings show that neuronal sensitivities to extravestibular neck-related signals changed in parallel with improvements in motor performance (i.e., the COR), and reveal the neural mechanism by which neck-driven ocular responses improve gaze stabilization after complete vestibular loss.

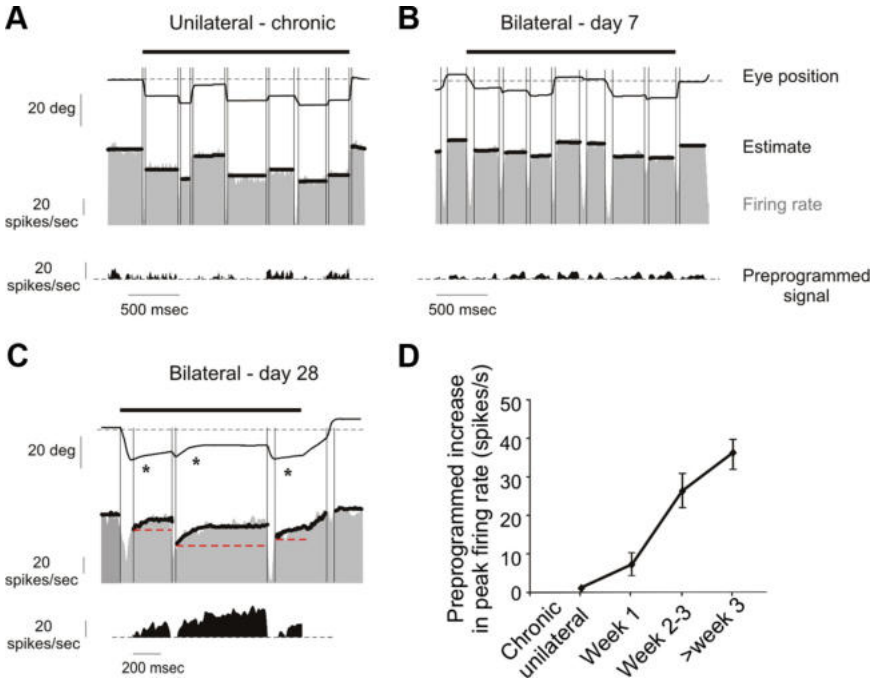

Figure 4. Evidence of a centrally programmed signal that mediates compensatory eye movements. ***A***, In animals fully compensated after unilateral labyrinthectomy, no compensatory eye movements were observed. Bottom trace shows the activity of neurons above the value at the beginning of eye fixation periods. ***B***, At the early stages after bilateral lesion (week 1) still no compensatory responses were observed. ***C***, Later in the course of compensation after bilateral lesion, compensatory eye movements were observed together with increases in the activity of PVP neurons (bottom trace). Trace labels are the same as ***A*** and ***B***. ***D***, For the population of neurons recorded, the centrally programmed signal increased significantly after the second week postlesion.

Evidence for the presence of motor efference copy signals

The results shown so far demonstrate a strong relationship between changes in the sensitivity of single neurons to neck proprioceptors and COR motor performance after bilateral labyrinthectomy. In a natural context head movements are often voluntarily generated and thus the brain has access to motor-related signals as well as proprioceptive and vestibular information. If neuronal sensitivities to head motion were further enhanced during actively generated versus passively applied head movements, then we could conclude that the substitution of motor efference copy signals at the first stage of central vestibular processing further contributes to improve gaze stability observed for active movements following a total loss of vestibular inputs.

First, to test whether an efference copy signal could potentially be used to improve gaze performance, we recorded from single neurons before and after bilateral lesion during a paradigm in which we unexpectedly applied a brake for 1–4 s to restrain the animal's head just as it prepared to orient to a target. In this way, we could study the influence of the presence of efference copy signals, in isolation from the generation of actual head motion, which would have produced concurrent stimulation of neck proprioceptors. We simultaneously measured neck torque to verify that the animal had intended to produce an active head movement, and in most trials, the head moved in the originally intended direction (i.e., toward the target) after releasing the brake.

Figure 4 shows the responses of three typical PVP neurons, one recorded before the second labyrinthectomy (Fig. 4*A*; compensated chronic unilateral condition) and the other two recorded 7 d (Fig. 4*B*) and 4 weeks after bilateral lesion (Fig. 4*C*). For each example neuron, the thick black line (top row) shows the duration of the application of the brake during which the monkey's planned head movement was prevented. Notably, during the brake interval, the animal's eyes remained stable and fixated between orienting saccadic eye movements when tested before the second labyrinthectomy and during the first week following complete bilateral lesion (Fig. 4*A*,*B*, respectively). Over time, however, we observed the emergence of slow eye movements during this same period of the brake application. These eye movements were in the direction opposite to the intended head movement (Fig. 4*C*, asterisks), and were effectively compensatory (i.e., "VOR-like") for the intended (but yet unrealized) head movement. Moreover, these eye movements were present in ~60% of trials, and were comparable to those previously described by Dichgans et al. (1973) who used a similar experimental design to study the behavioral effect of bilateral vestibular loss.

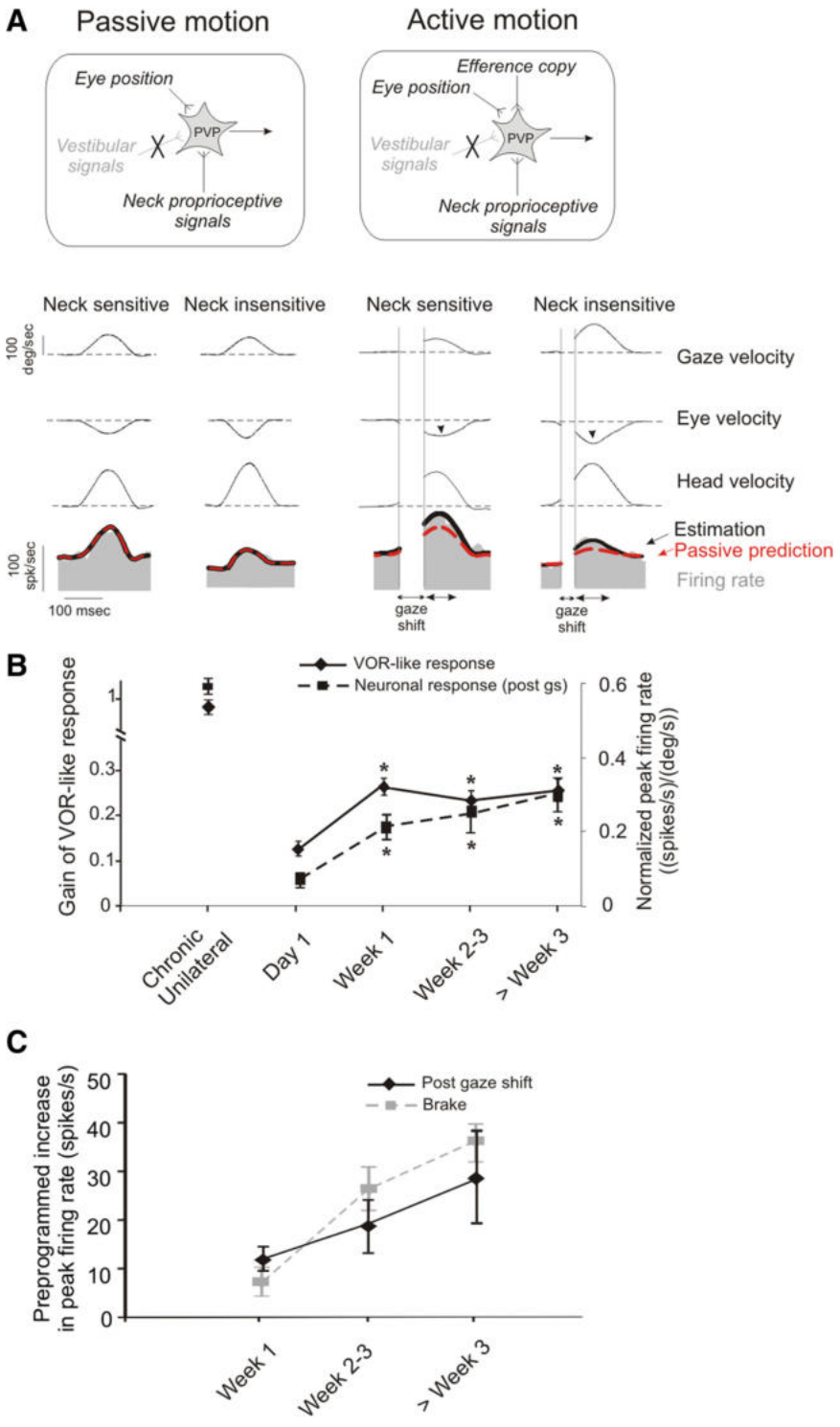

Figure 5. Comparison of average neuronal and behavioral responses during passive and active head-on-body rotations after bilateral labyrinthectomy. ***A***, The response of example neck-sensitive and neck-insensitive PVP neurons during passive and active head-on-body rotations 4 weeks after the lesion. The schematic illustrates an efference copy signal that is potentially available during active movements. Prediction (dashed red) based on passive movements underestimates neuronal responses during active movements (black line). ***B***, Population average of the gain of the VOR-like response and neuronal firing rates ($n = 12$ on day 1, 18 on week 1, 14 on week 2–3, and 21 after week 3) increased over time after the lesion. Asterisks signify significant differences compared with day 1. ***C***, The efference copy signal estimated during active head movements and brake paradigm were comparable. Note that this analysis was completed on neuronal responses to high-velocity active and passive head movements (~200°/s), that corresponded to the intended (but unrealized) movements during the brake paradigm.

Comparisons of neuronal firing rates and eye movements further revealed an excellent correspondence between the optimal fit to the neuron's response (black line) computed from the sum of the neuron's individual resting rate and eye position sensitivity. This was the case both before and after bilateral lesion. Before and 1 week following lesion, this model predicted the constant neuronal firing rates produced between saccades (Fig. 4*A*,*B*). In contrast, 1-month following lesion the same model predicted the scalloped neuronal firing rates produced between saccades (Fig. 4*C*). Note that for this latter example, the dashed red lines indicate the firing rate of the neuron which would have been expected if no VOR-like compensatory eye movement had been generated following each saccade. By calculating the difference between this value and the actual firing rate, we were able to obtain an estimate of the contribution of neck motor efference copy signals to shaping the neuronal firing rate during the brake period. The estimated contribution (labeled "preprogrammed signal") is plotted in the bottom row of each panel (Figs. 4*A–C*). Figure 4*D* summarizes the responses of 25 neurons recorded during brake application at different times after the lesion. Notably, a significant additional neuronal contribution was measured within ~2 weeks after bilateral lesion reaching values of ~40 spikes/s about 1 month after the lesion. Thus, our braking experiments provide evidence that, for active movements, the substitution of motor efference copy signals in the premotor VOR pathways contributes to the generation of compensatory eye movements following a total loss of vestibular inputs.

Neural correlates of motor efference copy signal during active head movements

Having established that two extravestibular inputs (i.e., neck proprioceptive as well as efference copy signals) can substitute for the vestibular inputs to stabilize gaze at the level of single neurons in the VOR premotor circuitry, we next asked how these two inputs combine during active head movements. During such movements, information about self-motion is available through an efference copy of the neck motor command as well as the vestibular and proprioceptive sensory signals (Fig. 5*A*, top). Here we tested whether these two sources of extravestibular information combine to support the behavioral improvement observed in the VOR-like response during active head movements following bi-

lateral peripheral vestibular lesion. Specifically, immediately following bilateral labyrinthectomy, both monkeys and patients systematically overshoot visual targets when making voluntary combined eye-head movements (i.e., gaze shifts; Dichgans et al., 1973; Newlands et al., 1999). An overshoot occurs because complete absence of vestibular inputs results in the loss of the VOR, which is normally required to counter rotate the eye at the end of the gaze shift. However, in the weeks that follow, gaze shifts become surprisingly accurate. In particular, eye movements are characterized by the emergence of a VOR-like counter rotation of the eye which again functions to stabile gaze at the end of voluntary movements. Before our study, the neural correlate for this extravestibular substitution was unknown.

Here, we specifically quantified the linkage between changes in neuronal response sensitivities and simultaneously measured passive and active head-on-body rotations with comparable trajectories (~300–400 ms long, with peak velocities of 200–400°/s). Figure 5*A* shows the response of a neck-sensitive and a neck-insensitive PVP neuron recorded 1 month after the lesion. During passive head-on-body rotations, there was excellent correspondence between both neurons' responses (black trace) and the prediction computed from the sum of the neuron's individual eye position and neck proprioceptive response sensitivities (dashed red trace). This, however, was not the case during active motion (right; black line). Following bilateral lesion, neuronal responses were underestimated by the neuron's sensitivities calculated for passive head-on-body rotations (Fig. 5*A*, right panels; dashed red lines). Accordingly, following labyrinthectomy neurons showed more robust modulation in response to active head than passive head movements. Note that because PVP neurons cease firing during gaze shifts (Roy and Cullen, 1998, 2002), fits were restricted to neural response associated with the active head motion produced before and after the monkey shifted its gaze.

Figure 5*B* summarizes the time course of the population response recorded following bilateral lesion during active movements. For each neuron, we computed the peak firing rate across active head movements and then normalized each value by the corresponding peak head velocity to obtain a measure of neuronal activity during active head movements. We then computed the average normalized peak firing rates for our PVP population. As can be seen in Figure 5*B*, response gains to active head movements increased during the first week after the lesion and reached values of >0.3 after a month (Fig. 5*B*, dashed line; $p < 0.05$ with regard to day 1). Furthermore, the analysis of the associated VOR-like behavioral response revealed that the gain of eye velocity relative to the velocity of active head movements similarly increased (Fig. 5*B*, solid black line) and reached values of ~0.25 after the first week postlesion. This latter finding is consistent with the results of previous behavioral studies of bilateral vestibular ablation (Dichgans et al., 1973; Newlands et al., 1999).

Thus, during active head-on-body head movements, both neuronal and associated behavioral responses showed a clear enhancement in modulation relative to comparable passive movements. Moreover, this enhancement increased, reaching stable levels, within the first month after total vestibular loss. These results suggest that the enhancement recorded during active versus passive head-on-body movements was the result of the motor command signals that were produced during the active movement. To pursue this argument further, we hypothesized that sensory-driven modulation of a given PVP after bilateral loss should be described by the summation of its neck proprioceptive input (measured during passive head-on-body rotation) and an additional signal arising from the motor command to produce the active rotation of the head relative to the body. As such, we can obtain an estimate of the neuron's modulation in response to production of a neck motor command by subtracting the response during passive head-on-body rotations from the measured firing rate during active movements (see Materials and Methods and Eqs. 2–4). This difference between the neuronal responses during active and passive head-on-body motion should also be predicted by a neuron's response to the production of motor efference copy measured above during the generation of planned (but unrealized) head movements in our braking experiments (Fig. 4). We verified that this was the case. Overall for our sample of neurons, the predicted (active head movements) and estimated (planned, but unrealized active head movements) response was comparable (Fig. 5*C*; $p = 0.1$). Moreover, responses in both conditions similarly increased after bilateral labyrinthectomy, reaching peak values of ~30 spikes/s by the third week. We therefore conclude that the summation of neck proprioceptive and motor efference copy signals substitutes for the lack of vestibular inputs to generate the VOR-like eye movements during active head movements.

Discussion

In the present study, we investigated how the substitution of extravestibular inputs in vestibular pathways provides a neural correlate for the improvement in gaze stability observed in the total absence of vestibular inputs. Primates use compensation strategies following bilateral vestibular damage that include the enhancement of neck reflexes (i.e., COR) (Bronstein et al., 1995; Maurer et al., 1998), the preprogramming of compensatory eye movements (Dichgans et al., 1973; Newlands et al., 1999; Della Santina et al., 2001), and the generation of multiple catch-up saccades (Gresty and Baker, 1976; Halmagyi and Henderson, 1988; Mesland et al., 1996). Here, we established the neural correlates of behavioral recovery after complete vestibular loss by recording from individual vestibular neurons in rhesus monkeys. We found that extravestibular inputs (i.e., neck proprioceptive and efference copy signals) substitute for vestibular signals at the level of single neurons that constitute the direct VOR pathway. First, approximately half of our neural population responded to passive stimulation of neck proprioceptors and an increase in this sensitivity over time correlated with a significant increase in the COR response. Additionally, enhanced modulation during active versus passive head movements was linked to VOR-like responses encoded when active head movements were planned but unrealized, suggesting efference copy signals further substitute for absent vestibular inputs. Notably, the summed weighting of neck proprioceptive and efference copy information was sufficient to explain simultaneously observed behavioral improvements in gaze stability. Thus, taken together our data show for the first time that the improvement in gaze stability observed following total vestibular loss is due to the substitution of extravestibular inputs at the level of the first-order vestibular sensory neurons that normally generate the VOR.

Substitution of extravestibular inputs: enhancement of the COR and efference copy signals

The COR is an ocular stabilization reflex that is evoked by stimulation of neck proprioceptors when the head is rotated relative to the body. While studies in reduced or anesthetized preparations have provided important insights into the functional circuitry underlying this reflex (Straka et al., 2005), the COR has a negligible role in normal humans and monkeys (Dichgans et al., 1973; Roy and Cullen, 2002; Schubert et al., 2004; Sadeghi et al.,

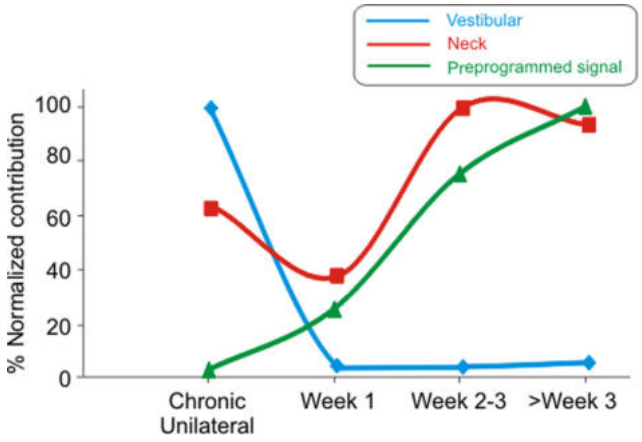

Figure 6. Time course of dynamic regulation of multimodal integration following bilateral labyrinthectomy. Responses are normalized relative to the maximum response to each of the three inputs: vestibular (blue, measured by whole-body rotation), neck proprioceptive (red, measured by body-under-head rotation), and preprogrammed/efference copy signal (green, measured by the brake paradigm and active head movements). Vestibular inputs are lost immediately after bilateral lesion. Over the weeks following the lesion, contribution of neck signals increased in about 2–3 weeks. Over the same time period, responses of PVP neurons were enhanced by a preprogrammed/efference copy signal from higher brain areas during actively generated movements.

2006) as well as following unilateral vestibular loss (Barnes and Forbat, 1979). In contrast, our findings suggest that COR plays an important role in stabilizing gaze when vestibular information is no longer available. Consistent with accumulating evidence from behavioral studies in human patients (Kasai and Zee, 1978; Bronstein et al., 1995; Maurer et al., 1998; Schubert et al., 2004), we found that following bilateral labyrinthectomy, COR gains increased over time reaching maximum values of 0.3 (Dichgans et al., 1973; Newlands et al., 1999). Moreover, our current findings show that individual premotor neurons of the direct VOR pathway that normally receive vestibular inputs and are insensitive to neck proprioceptive inputs, encode significant neck-related information after bilateral labyrinthectomy (Fig. 6, red line). Notably, this substitution of proprioception for vestibular inputs plays a functionally beneficial role evidenced by a significant increase in the efficacy of the COR.

After vestibular loss, motor efference copy signals can theoretically provide an additional source of head motion information for self-generated movements. Behavioral studies have shown that both monkeys and patients initially overshoot visual targets when making combined eye-head gaze shifts following bilateral labyrinthectomy (Dichgans et al., 1973; Newlands et al., 1999) due to absence of the VOR. However, over time, gaze shifts become surprisingly accurate as the result of the emergence of VOR-like counter rotations of eyes (Dichgans et al., 1973; Newlands et al., 1999). Additionally, when we altered the correspondence between intended and actual head movement such that active head movements were planned but unrealized, VOR-like eye movements that would have compensated for the intended head movement were observed within a comparable time window (Dichgans et al., 1973). Here, we provide strong evidence that motor-related extravestibular inputs (i.e., efference copy signals) contribute to these VOR-like movements by substituting for vestibular inputs at the level of single neurons in the VOR premotor circuitry. Importantly, this input was minimal acutely after bilateral labyrinthectomy and developed over time (Fig. 6, green line), and thus was not merely a remnant of the efference copy signal reported after unilateral (i.e., the first) labyrinthectomy in the same animals (Sadeghi et al., 2010).

Sensory substitution: common strategies and mechanisms

Following the loss of function in one sensory modality, patients can demonstrate enhanced sensitivity to the stimulation of other modalities. For instance, blind subjects have been reported to show heightened sensitivities to tactile and auditory stimulation (Ptito and Kupers, 2005; Ptito et al., 2005; Collignon et al., 2009) while deaf subjects can demonstrate increased sensitivities to visual stimulation (Finney et al., 2001; Lomber et al., 2010). It is commonly believed that this type of cross-modal plasticity is an important form of sensory substitution that functions to optimize performance during everyday activities. Recent studies addressing the mechanisms underlying cross-modal plasticity have not only demonstrated the expansion of cortical areas for the remaining intact modalities (Finney et al., 2001; Ptito and Kupers, 2005; Sanchez-Vives et al., 2006; Meredith et al., 2011) but have also provided evidence using transcranial magnetic stimulation for the rewiring of neural circuits through the unmasking/strengthening of existing neuronal connections (Kupers et al., 2007).

Homeostatic mechanisms likely play a vital role in this unmasking/reweighting of inputs from remaining modalities to restore network activity to a set point level after changes in sensory input. Experimentally induced changes in network activity (ranging from hours to days) have been shown to produce long-term changes in the excitability of synapses in auditory (Kotak et al., 2005) as well as visual (Maffei and Turrigiano, 2008) cortex. The plastic changes recently observed in barrel cortical neurons after the loss of olfaction suggest similar cellular mechanisms underlying the cross-modal sensory plasticity that upregulates tactile sensation (Ni et al., 2010).

To date, however, cross-modal plasticity has been primarily characterized in cortex using slice cultures (*in vitro*) or reduced preparations. Nevertheless, there is accumulating evidence that comparable mechanisms are likely recruited much earlier in sensory processing. For example, at the level of the VN, vestibular nerve damage induces changes in synaptic strength of remaining commissural and spinal inputs (Precht et al., 1966; Dieringer, 1995; Goto et al., 2000, 2001) as well as alterations in neuronal membrane properties (Beraneck et al., 2003, 2004). Such changes could mediate the reweighting of extravestibular inputs observed in the present study. Moreover, early auditory processing appears to recruit a striking similar compensatory mechanism. Notably, auditory nerve damage leads to the enhancement of extra-auditory (i.e., somatosensory) inputs at the first central stage of processing (i.e., cochlear nucleus) (Dehmel et al., 2008; Zheng et al., 2009). However, while the substitution of somatosensory inputs for auditory inputs can result in unwanted effects such as tinnitus (Shore et al., 2008), we found that the substitution of proprioceptive/efference copy inputs for vestibular inputs serves a functionally beneficial role.

Compensation after unilateral versus bilateral vestibular loss

It is noteworthy that the present study was done after sequential bilateral labyrinthectomies performed following an interval of >2 months. This approach evokes the Bechterew phenomenon, in which a subject compensated after the first unilateral labyrinthectomy initially shows lateralized symptoms when the remaining labyrinth is subsequently removed (Vibert et al., 1999; Straka et al., 2005). While inhibitory commissural inputs play a vital role in the initial recovery after unilateral lesion, the vestib-

ular symptoms in Bechterew's phenomenon are most likely due to disfacilitation of neurons contralesional to the second lesion (Bergquist et al., 2008). In the present study, we found that the resting activities of neurons were, unexpectedly, comparable to normal conditions as is the case following simultaneous bilateral labyrinthectomy (Ryu and McCabe, 1976; Ris and Godaux, 1998). However, it is possible that changes in commissural inputs after the first lesion altered the time course of the appearance of extravestibular inputs observed following the second lesion. Future studies using simultaneous bilateral labyrinthectomy will be required to address the influence of Bechterew's phenomenon on the time course of sensory substitution.

Conclusions and future directions

Sensory substitution has been the focus of recent rehabilitation programs for patients with vestibular deficiencies (Bach-y-Rita and Kercel, 2003; Lacour, 2006; Horak, 2010). These studies have focused on recruitment of extravestibular, such as visual and somatosensory (i.e., light touch, vibration), pathways. However, there is evidence for the role of proprioceptive inputs in recovery observed after vestibular lesions. For example, postural normalization is severely delayed in guinea pigs deprived of proprioceptive as well as somatosensory stimuli (Schaefer and Meyer, 1973; Jensen, 1979). Our findings suggest that the impressive behavioral recovery after complete vestibular loss takes advantage of a natural form of sensory substitution by proprioceptive and motor efference copy signals. These findings have important implications for designing goal-oriented rehabilitation programs in a timely manner. For example, proprioceptive stimulation is probably most effective early in the course of compensation, whereas exercises using active head movements can be beneficial even later.

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