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Multimodal Integration After Unilateral Labyrinthine Lesion: Single Vestibular Nuclei Neuron Responses and Implications for Postural Compensation

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Sadeghi SG, Minor LB, Cullen KE. Multimodal integration after unilateral labyrinthine lesion: single vestibular nuclei neuron responses and implications for postural compensation. *J Neurophysiol* 105: 661–673, 2011. First published December 8, 2010; doi:10.1152/jn.00788.2010. Plasticity in neuronal responses is necessary for compensation following brain lesions and adaptation to new conditions and motor learning. In a previous study, we showed that compensatory changes in the vestibuloocular reflex (VOR) following unilateral vestibular loss were characterized by dynamic reweighting of inputs from vestibular and extravestibular modalities at the level of single neurons that constitute the first central stage of VOR signal processing. Here, we studied another class of neurons, i.e., the vestibular-only neurons, in the vestibular nuclei that mediate vestibulospinal reflexes and provide information for higher brain areas. We investigated changes in the relative contribution of vestibular, neck proprioceptive, and efference copy signals in the response of these neurons during compensation after contralateral vestibular loss in *Macaca mulata* monkeys. We show that the time course of recovery of vestibular sensitivity of neurons corresponds with that of lower extremity muscle and tendon reflexes reported in previous studies. More important, we found that information from neck proprioceptors, which did not influence neuronal responses before the lesion, were unmasked after lesion. Such inputs influenced the early stages of the compensation process evidenced by faster and more substantial recovery of the resting discharge in proprioceptive-sensitive neurons. Interestingly, unlike our previous study of VOR interneurons, the improvement in the sensitivity of the two groups of neurons did not show any difference in the early or late stages after lesion. Finally, neuronal responses during active head movements were not different before and after lesion and were attenuated relative to passive movements over the course of recovery, similar to that observed in control conditions. Comparison of compensatory changes observed in the vestibuloocular and vestibulospinal pathways provides evidence for similarities and differences between the two classes of neurons that mediate these pathways at the functional and cellular levels.

INTRODUCTION

Within the vestibular nuclei is a class of second-order neurons, which had been classically termed vestibular-only (VO) neurons on the basis of their lack of eye-movement–related responses in head-restrained animals (Chubb et al. 1984; Cullen et al. 1993; Fuchs and Kimm 1975; Keller and Daniels 1975; Scudder and Fuchs 1992; Tomlinson and Robinson 1984). However, given that they reliably encode passively applied head velocity but are far less sensitive to active head motion, this nomenclature has been deceptive. This group of neurons is thought to play a vital role in the generation of vestibulospinal reflexes via direct projections to the spinal cord (Boyle 1993; Boyle et al. 1996; Gdowski and McCrea 1999; Wilson et al. 1990). In addition, VO neurons are reciprocally interconnected with the fastigial nucleus (Batton 3rd et al. 1977; Carleton and Carpenter 1983; Shimazu and Smith 1971) and nodulus/uvula (Walberg and Dietrichs 1988; Xiong and Matsushita 2000a,b) of the cerebellum, suggesting that they are essential for the computation of spatial orientation as well as for the regulation of gait and posture. Finally, these neurons also send ascending projections to the thalamocortical system via their projections to the ventral posterior and ventral lateral vestibular thalamus (Marlinski and McCrea 2008a,b; Meng et al. 2007).

The results of recent in vitro (reviewed in Straka et al. 2005) and in vivo (Sadeghi et al. 2010) experiments have provided important insights into the cellular and neural mechanisms that mediate the vestibuloocular reflex (VOR) and its adaptive capabilities in response to environmental requirements. In contrast, the neural mechanisms that underlie the recovery of postural control and spatial orientation remain unclear. Notably, the loss of vestibular function from one labyrinth results in significant head tilt in the roll plane toward the lesion (Fetter and Zee 1988; Smith and Curthoys 1989). Additionally, immediately following unilateral labyrinthectomy subjects show hypoexcitability of ipsilesional and hyperexcitability of contralesional spinal reflexes in the limbs as well as a tendency to deviate toward the lesioned side when walking (reviewed in Curthoys and Halmagyi 1995). Furthermore, the ability of subjects to accurately estimate subjective spatial orientation is compromised following vestibular loss and the subjective visual vertical becomes biased toward the lesioned side immediately after unilateral labyrinthectomy (Bergenius et al. 1996). Fortunately, however, these symptoms generally reside within a few weeks, such that the head tilt and extension and flexion of the extremities observed immediately following lesion largely disappear and the ability to accurately estimate spatial orientation recovers to control levels (reviewed in Smith and Curthoys 1989).

Here, we made in vivo recordings from individual neurons at the first central stage of processing (the vestibular nucleus) in alert, behaving rhesus monkeys before and at different time points after labyrinthectomy to understand the neuronal mechanisms that underlie the significant improvement in postural control and spatial orientation that occurs in the first 2 mo.

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Notably, we focused on VO neurons, which are thought to be involved in the computation of spatial orientation as well as the regulation of gait and posture (reviewed in Cullen and Roy 2004). We simultaneously measured the status of the vestibulocollic reflex (VCR) as a behavioral indicator of the recovery of vestibulospinal reflexes. In particular, we addressed how three critical inputs, *1*) vestibular information, *2*) neck proprioceptive information, and *3*) a neck motor efference copy signal representing the motor command to the neck musculature, are integrated at the level of the vestibular nuclei to ensure behavioral compensation. We show that, immediately following contralateral labyrinthectomy, neuronal modulation in response to vestibular stimulation dramatically decreased. Consistent with our recent findings regarding the neural mechanisms underlying VOR improvement observed following lesion (Sadeghi et al. 2010), we further show that, during this same time window, powerful inputs from neck proprioceptors are unmasked. As such, although VO neurons are normally insensitive to neck stimulation they show strong modulation in response to neck stimulation immediately after lesion that remain so even 2 mo after lesion. Finally, we show that following lesion, neuronal responses are suppressed during active movement in a manner similar to that observed in control conditions. We conclude that although similar homeostatic mechanisms can explain reweighting/unsilencing of vestibular and extravestibular inputs in position–vestibular–pause (PVP) and VO neurons, the differences in the course of compensation are most likely due to differences in membrane properties between the two classes of neurons.

METHODS

Subjects and surgery

Experiments were performed on two male rhesus macaque (*Macaca mulata*) monkeys (~8 kg) implanted with a post for head restraint, recording chamber, and scleral search coils for eye-movement recording as described previously (Sadeghi et al. 2007b). Following the surgery, the animals were administered buprenorphine (0.01 mg/kg, administered intramuscularly [im]) for postoperative analgesia and the antibiotic cephazolin (Ancef; 25 mg/kg im, for 5 days). We recorded from single units directly after standard operant conditioning to fixate visual targets for a juice reward, as well as following unilateral labyrinthectomy. Labyrinthectomy was performed as described previously (Sadeghi et al. 2006) to remove the ampulla of the three semicircular canals, the utricle, and saccule, and the distal ends of the ampullary nerve branches. 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 head restrained initially and rotated about the earth-vertical axis by a motion stimulator, located within a 1-m^3 magnetic field coil (CNC Engineering). A visual target (HeNe laser) was projected onto a cylindrical screen located 60 cm away from the monkey's head. Neuronal sensitivities to saccades, ocular fixation, and pursuit were characterized by having the monkey follow a target that stepped between horizontal positions (±30°) and then 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).

The experimental design consisted of five stimuli as described in a previous study (Sadeghi et al. 2010). First, vestibular stimulation was applied by rotating monkeys about an earth-vertical axis with their heads restrained (0.5 Hz, peak velocity of ±40°/s) both in darkness (whole-body rotation) and while suppressing VOR by fixating a visual target that moved with the vestibular turntable (VOR cancellation). Second, neck proprioceptor stimulation was applied by holding the monkey's head stationary (re: Earth) while its body was sinusoidally (0.5 Hz, ±40 or ±80°/s) rotated beneath (i.e., no vestibular stimulation). Third, vestibular plus neck proprioceptor stimulation 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. 2006, 2007a,b, 2009). Sinusoidal (1 Hz, ±40°/s) as well as passive head-on-body rotations with trajectories comparable to those produced during actively generated head movements were applied. Fourth, to study the VCR, the monkey's head was slowly and carefully released and we used whole-body rotation (0.5 Hz, ±40°/s) to stimulate the vestibular system. The main reason for choosing the 0.5- to 1-Hz frequency range is because previous studies have shown almost complete behavioral recovery in this range of frequencies within 1 mo after lesion. We then measured the movement of the head relative to body and quantified the degree of head stabilization. Finally, with the head unrestrained the monkey produced voluntary (i.e., active) head rotations about the earth-vertical axis to orient its gaze to a visual target (Roy and Cullen 2002).

Electrophysiology

Extracellular single-unit recordings were performed using enamel-insulated tungsten microelectrodes (7–10 MΩ impedance; FHC) advanced through a guide tube using a microdrive (Narishige). Single neurons were isolated using a conventional amplifier system and band-pass filtered (400 Hz to 10 kHz). We first identified the abducens nucleus based on the typical discharge pattern of its neurons during eye movements (Cullen et al. 1993; Sylvestre and Cullen 1999) and then moved more lateral and posterior to locate the medial and lateral vestibular nuclei. In the present study, we recorded from vestibular-only (VO) neurons, which were identified as neurons that responded to rotation but were not sensitive to eye movements (Roy and Cullen 2001b, 2004). These were typically located slightly lateral relative to the PVP neurons (Scudder and Fuchs 1992) recorded in our previous study (Sadeghi et al. 2010). Following unilateral labyrinthectomy we recorded from the contralesional vestibular nuclei since results of prior in vitro studies had suggested greater improvement compared with the lesioned side (reviewed in Straka et al. 2005). We focused only on neurons that receive inputs mainly from the horizontal canals, which were further divided into two groups: type I and type II neurons (Duensing and Schaefer 1958). Notably, whereas type I neurons receive excitatory inputs from the ipsilateral horizontal canal, type II neurons receive excitatory input from contralateral type I neurons and constitute part of the inhibitory input to type I neurons on the same side (Malinvaud et al. 2010; Shimazu and Precht 1966). Note, neurons that receive excitatory inputs from the vertical canals (i.e., mainly respond to pitch or roll rotation) on the ipsilateral side and behave like type II neurons during horizontal rotations (Precht and Shimazu 1965) were discarded in the present study.

Gaze and head position were measured using the magnetic search coil technique and turntable velocity was measured by an angular velocity sensor (Watson). All signals 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 low-pass filtered at 250 Hz (8-pole Bessel filter) and sampled at 1 kHz.

Data were collected from each animal before (control condition) and after labyrinthectomy from contralesional vestibular nuclei, start-

ing from day 1 (i.e., 15–28 h) postlesion. Later recordings were made on a weekly basis ≤2 mo postlesion.

Data analysis

For analysis, data were imported into the Matlab (The MathWorks, Natick, MA) programming environment. 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. Eye position was calculated from the difference between gaze and head position signals. Velocities of gaze, eye, and head movements were produced by digitally differentiating the position signals. We convolved a Gaussian (SD = 10 ms for sinusoidal rotations and SD = 5 ms for gaze shifts) with the spike train to represent the neuronal responses (Cullen et al. 1996; Sylvestre and Cullen 2006). Statistical significance was determined using paired or unpaired Student's *t*-tests.

To quantify behavioral performance, we calculated the gain of the VCR as the velocity of the head relative to the turntable after accounting for the phase difference. Thus the gain would vary between zero and one, with a gain of one representing a perfect VCR and zero showing no VCR (Guitton et al. 1986).

A least-squares regression analysis was used to determine each neuron's response to vestibular stimulation during passive whole-body rotations

$$\hat{fr}\,(t) = b + Sv_{vest}\,\dot{H}\,(t) + Sa_{vest}\,\ddot{H}\,(t) \qquad (1)$$

where $\hat{fr}$ is the estimated firing rate, Sv_{vest} and Sa_{vest} are coefficients representing sensitivities to head velocity and acceleration, b is a bias term, and H and $\ddot{H}$ are head velocity and head acceleration, respectively. The estimated coefficients Sv_{vest} and Sa_{vest} were then used to calculate each unit's modulation sensitivity [(spikes/s)/(°/s)] and phase shift (deg) relative to head velocity (Sadeghi et al. 2009, 2010). Note that because VO neurons are insensitive to eye movements, no eye-movement term was included in the regression model.

To quantify each unit's response to neck proprioceptive stimulation during passive rotation of the body under a stationary head (i.e., no vestibular stimulation) we determined the best estimate of each neuron's sensitivity to neck rotation using the equation

$$\hat{fr}\,(t) = b + Sv_{neck}\,\dot{B}\,(t) + Sa_{neck}\,\ddot{B}\,(t) \qquad (2)$$

where Sv_{neck} and Sa_{neck} are coefficients representing sensitivities to neck (= body or, equivalently, the vestibular turntable) velocity and acceleration, and $\dot{B}$ and $\ddot{B}$ are body velocity and acceleration, respectively. Because neuronal responses typically led rather than lagged body velocity, our formalization of the model included velocity and acceleration terms. Similar to vestibular sensitivities, the estimated coefficients were then used to calculate each unit's modulation sensitivity [(spikes/s)/(°/s)] and phase shift (deg) relative to velocity of body rotation (Sadeghi et al. 2009). Similar to previous studies (e.g., Wilson and Schor 1999), we used a sensitivity threshold of 0.1 (spike/s)/(°/s) to divide neurons into responsive and unresponsive to neck proprioceptor stimulation.

Finally, during combined vestibular and proprioceptive stimulation evoked by passive sinusoidal head-on-body rotations (i.e., the combined condition) or active head-on-body movements, neuronal responses were estimated as

$$\hat{fr}\,(t) = b + Sv_{hob}\;\dot{HB}\,(t) + Sa_{hob}\;\ddot{HB}\,(t) \qquad (3)$$

where Sv_{hob} and Sa_{hob} are coefficients representing sensitivities to head-on-body velocity and acceleration, $\dot{HB}$ and $\ddot{HB}$ are head-on-body velocity and acceleration, respectively. Estimated sensitivities were then compared with those predicted based on the linear summation of the vestibular and proprioceptive sensitivities estimated for the same neuron during whole-body rotations (*Eq. 1*) and body-under-head rotations (*Eq. 2*).

The ability of the linear regression models described in *Eqs. 1–3* to reproduce neuronal discharges during each paradigm was quantified by computing the variance accounted for (VAF) (Cullen et al. 1996), defined as $\{VAF = 1 - [var(\hat{fr} - fr)/var(fr)]\}$, where $\hat{fr}$ represents the modeled firing rate (i.e., regression equation estimate) and fr represents the actual firing rate.

RESULTS

To assess neuronal sensitivities to vestibular and extravestibular inputs, we recorded the activity of single neurons in the vestibular nuclei of two rhesus monkeys. We focused on a class of cells termed vestibular-only (VO) neurons, which project to the spinal cord (Boyle 1993; Boyle et al. 1996; Gdowski and McCrea 1999; Wilson et al. 1990) as well as to higher centers such as thalamus and cortex (Marlinski and McCrea 2008a,b; Meng et al. 2007). We recorded from type I neurons that receive inputs from the ipsilateral horizontal canal, as well as type II neurons, which constitute part of the inhibitory commissural pathway. Type I and type II VO neurons were identified by their lack of sensitivity to eye movements and an increase in discharge rate as a function of ipsilateral or contralateral head velocities, respectively. We recorded from 183 VO neurons in the left vestibular nuclei of two rhesus monkeys before ($n = 39$) and after ($n = 144$) right labyrinthectomy. The variability of neuronal firing was quantified by computing the coefficient of variation (CV = SD/mean of interspike intervals) before and at different time points after lesion. CV values were comparable across all time points (*t*-test, $P > 0.2$) with a value of about 0.4, suggesting that lesion did not alter the response variability of VO neurons. Following the lesion, 72 neurons were recorded on the first day (i.e., 15–28 h) postlesion, 44 neurons in the period of 7–21 days postlesion, and 28 neurons in the 1–2 mo postlesion. All neurons responded to rotations in the horizontal plane, but showed very little or no response to pitch rotations or translational movements.

Vestibular inputs

We first characterized the response of 95 type I and 88 type II neurons to passive whole-body rotation (0.5 Hz, 40°/s). Figure 1*A* (*left column*, *middle* and *bottom rows*) shows responses of example type I and type II VO neurons, respectively, recorded before lesion. VO neurons in this condition responded to head rotations and were insensitive to eye movements, as described previously (Roy and Cullen 2001a, 2004). Immediately after contralateral labyrinthectomy (Fig. 1*A*, *middle column*), the sensitivity of both type I and type II neurons decreased dramatically. For type I neurons, this diminished response recovered in the following days and, as shown in Fig. 1*A* (*right column*, *middle row*) for an example type I neuron, on day 28 after lesion the responses were similar to those obtained before lesion. In contrast, type II neurons did not recover their normal responses, as shown for a typical neuron in Fig. 1*A* (*right column*, *bottom row*).

The changes observed for the example neurons were representative of the population of type I and type II VO neurons recorded. Figure 1*B* shows the time course of the change in vestibular sensitivity of the population of neurons before and

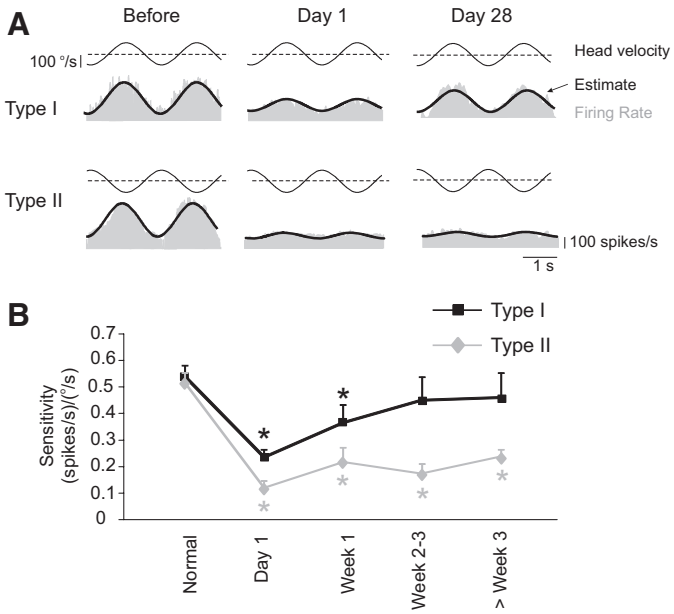

FIG. 1. Changes in responses of vestibular-only (VO) neurons after unilateral labyrinthectomy. *A*: examples of type I and type II position–vestibular–pause (PVP) responses before and at different time points after contralateral labyrinthectomy. Response of both cell types decreased significantly immediately after lesion (day 1). Whereas the sensitivity of type I neurons (n = 21, 25, 14, 22, and 13 cells for control, day 1, week 1, week 2–3, and >week 3, respectively) improved over time, reaching normal values by day 28, that of type II neurons (n = 18, 14, 19, 20, 17 cells for control, day 1, week 1, week 2–3, and >week 3, respectively) did not show significant improvement. *B*: summary of the change in sensitivity of the population of VO neurons recorded under control conditions (n = 39) and after lesion (n = 144) at different time points. The asterisk (*) represents significant difference with regard to control (i.e., before lesion), $P < 0.05$. Error bars indicate SE.

on different days after lesion. The average sensitivity of type I and type II VO neurons recorded in control animals was 0.53 ± 0.05 and 0.51 ± 0.03 (spike/s)/(°/s) (VAF = 0.69 ± 0.05 and 0.61 ± 0.06), respectively. Following contralateral labyrinthectomy, the sensitivity of both type I and type II neurons decreased significantly ($P < 0.0001$), reaching values of 0.28 ± 0.03 and 0.17 ± 0.03 (spike/s)/(°/s) (VAF = 0.41 ± 0.07 and 0.38 ± 0.03), respectively, on day 1 postlesion. In the following weeks, the responses of type I neurons improved, so that their vestibular sensitivity reached normal values by week 2 to week 3 postlesion [0.45 ± 0.07 (spike/s)/(°/s), $P > 0.05$, VAF = 0.65 ± 0.04]. Although type II neurons showed a slight improvement in their responses, their sensitivities never reached normal values, even 60 days after lesion [0.22 ± 0.03 (spike/s)/(°/s), $P < 0.001$, VAF = 0.51 ± 0.09]. Note that the VAFs initially decreased after lesion, returning to control values over time. This was expected since whereas CV values remained constant over time, vestibular sensitivities were reduced by roughly 50% after lesion and thus the modulation for the same input reduced by half. In addition, the finding that type II neurons show little recovery was expected since they had lost their main input, received indirectly from the contralateral lesioned nerve. In contrast, the main source of excitatory input to type I neurons remained intact (i.e., direct input from the contralesional vestibular nerve). These findings are qualitatively similar to those recently reported for another group of neurons in the vestibular nuclei, which mediate the VOR, i.e., PVP neurons (Sadeghi et al. 2010).

Extravestibular inputs

Under natural conditions, vestibular receptors are commonly stimulated by head-on-body movements, during which neck proprioceptors are also stimulated. Neck proprioceptive information is conveyed to the vestibular nuclei using a disynaptic pathway (Sato et al. 1997). In addition, during self-generated head movements, a copy of the neck motor command (i.e., an efference copy) can provide additional information to the vestibular nuclei neurons. Such multimodal sensory convergence in the vestibular nuclei can have important implications in the observed behavioral recovery. Indeed, we have previously shown an unmasking of such inputs on PVP neurons after unilateral loss of vestibular inputs (Sadeghi et al. 2010). In the following sections we describe the results observed for VO neurons with paradigms similar to those used in our previous study on PVP neurons and highlight the differences between these two groups of vestibular nuclei neurons.

Neck proprioceptive input

To directly assess whether passive activation of neck proprioceptor signals modulates the activity of VO neurons in the vestibular nuclei following unilateral labyrinthectomy, we recorded from these neurons during neck proprioceptor stimulation by sinusoidally rotating the body under a stationary head (see METHODS). Figure 2*A* illustrates the responses recorded from three typical type I VO neurons during this paradigm at different time points relative to labyrinthectomy. Consistent with previous studies in rhesus monkeys (Roy and Cullen 2001b, 2004), VO neurons did not respond to stimulation of neck proprioceptors under control conditions. In contrast, the example VO neuron shows a clear modulation in response to contralateral body rotations on day 1 after lesion. Moreover, neurons remained sensitive to passive stimulation of the neck proprioceptors 4 wk after lesion. Taken together, these findings were similar to those observed for PVP neurons in our previous study (Sadeghi et al. 2010).

Overall, following lesion, the majority (>50%) of recorded type I and type II VO neurons were sensitive to stimulation of neck proprioceptors [week 1: 0.27 ± 0.05 (spike/s)/(°/s), VAF = 0.37 ± 0.04 and 0.21 ± 0.06 (spike/s)/(°/s), VAF = 0.34 ± 0.07, respectively] and over time, the values [after week 3: 0.26 ± 0.03 (spike/s)/(°/s), VAF = 0.39 ± 0.04 and 0.24 ± 0.06 (spike/s)/(°/s), VAF = 0.37 ± 0.07, respectively] and percentages showed little change (Fig. 2*B*). Note that VAFs were comparable for all time points after lesion. This was expected since both CV values and neck sensitivities (measured in the absence of vestibular stimulation) of VO neurons remained constant over time. Neck sensitivities that were nonexistent in control animals peaked just following lesion and remained elevated (tested ≤2 mo after lesion) (Fig. 2*C*; note that population values are the averages of the absolute values of response sensitivities). When the ratio of neck/vestibular sensitivities was computed at different time points, neck signals showed the greatest contribution immediately after the lesion and the ratio decreased over time (Fig. 2*D*). Although qualitatively similar, the decrease in the ratio for VO neurons from week 1 to week 3 and later was smaller (24 and 53% decrease for type I and type II, respectively) than that observed for PVP neurons (81 and 83% decrease for type I and type II, respec-

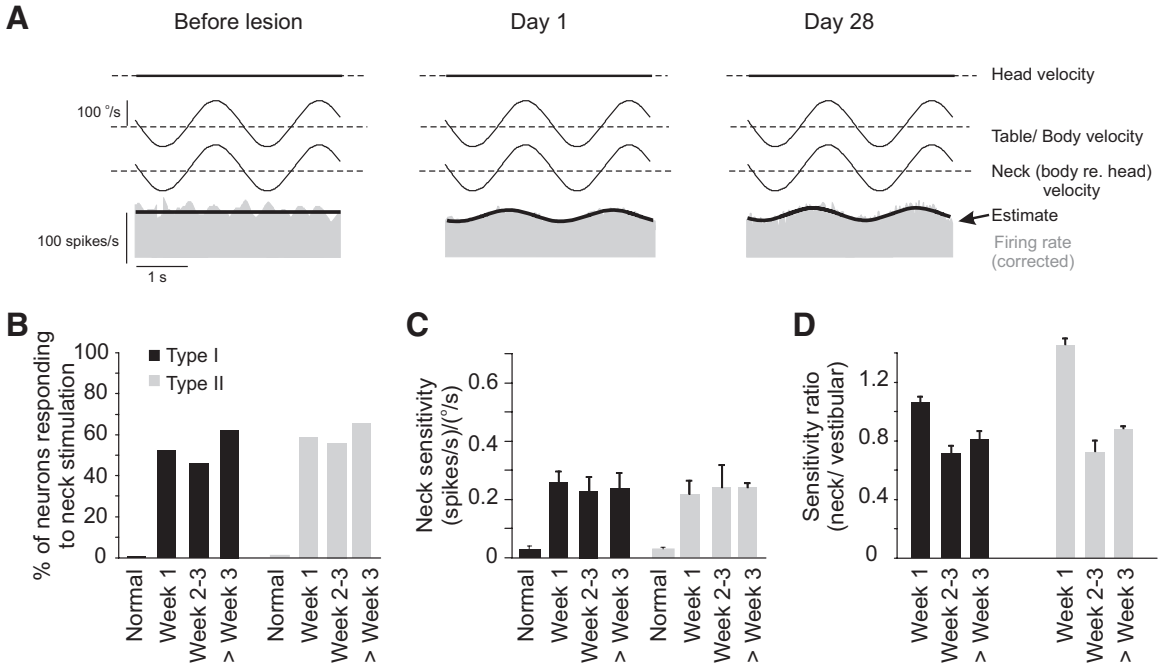

FIG. 2. Following unilateral labyrinthectomy, the majority of contralateral VO neurons respond to stimulation of neck proprioceptors. *A*: examples of type I neuronal responses during stimulation of neck proprioceptors. In intact animals, neurons are not sensitive to stimulation. In contrast, the example neuron shown on day 1 after the lesion responded robustly to neck stimulation. The neuron shown on day 28 also responded to neck stimulation, but with a lower sensitivity. *B*: the percentage of type I (n = 19, 36, 22, and 11 cells for normal, week 1, week 2–3, and >week 3, respectively) and type II (n = 17, 32, 20, and 17 cells for normal, week 1, week 2–3, and >week 3, respectively) neurons with neck sensitivity remained constant (50–70%) from week 1 to week 8 after lesion. *C*: the average of the absolute values of neck sensitivities of neck sensitive type I (n = 18, 11, and 8 cells on week 1, week 2–3, and >week 3, respectively) and type II (n = 19, 11, and 11 cells on week 1, week 2–3, and >week 3, respectively) neurons did not change over the course of recovery ≤2 mo after lesion. *D*: the ratio of neck and vestibular sensitivities shows that neck sensitivities of type I and type II neurons were most robust the first week after lesion and decreased over time, which is mainly due to the increase in vestibular sensitivities after week 1 (see Fig. 1). Same neurons as in *C*. Error bars indicate SE.

tively) reported in a previous study (Sadeghi et al. 2010). Note that the larger change for PVPs reflects not only a greater change in neck sensitivities, but also better improvement in their vestibular sensitivities. These differences point to a relatively greater contribution of neck signals at later stages of compensation in VO neurons and are further addressed in the DISCUSSION.

To test the interaction between vestibular and neck proprioceptor inputs, we next quantified neuronal responses during passive head-on-body movements (Fig. 3*A*, *top*). The response of an example neuron is shown in Fig. 3*A* during a 0.5-Hz passive head-on-body rotation and the neuron's sensitivity was estimated (black line) using *Eq. 3* (see METHODS). Notably, the neuron's response was well predicted (dashed red line) by adding the vestibular and neck coefficients (calculated during whole-body and body-under-head rotations, respectively). The VAFs of predictions were comparable to the VAF provided by the best fit to the neuron's actual response in this condition (0.69 vs. 0.71, respectively). The population data are summarized for type I and type II neurons in Fig. 3*B*. There was an excellent correspondence between the optimal fit to neurons' responses and the predictions computed from the sum of the individual vestibular and proprioceptive response sensitivities at different times after lesion. The slope of the line fitted to the data (solid line) was 0.88, which was not statistically different from 1 (dashed line) (n = 42, P > 0.4). The figure *inset* illustrates the average response sensitivities and phases of the type I and type II neuronal populations after lesion. Again, both quantities were well predicted by the average of the linear sum of the individual vestibular and proprioceptive response sensitivities; estimated (black arrow) and predicted (red arrow) sensitivities for type I VO neurons were 0.52 and 0.56 (spike/s)/(°/s), with phase leads of 34 and 30°. For type II neurons, the estimated (gray arrow) and predicted (light red arrow) values were 0.25 and 0.23 (spike/s)/(°/s) and phase leads of 40 and 30° during passive head-on-body rotations.

To better understand the functional significance of the neck-related inputs that were unmasked after lesion, we compared the average sensitivities of our populations of type I and type II VO neurons to head-on-body and whole-body rotations. Figure 3*C* shows the average sensitivities to vestibular only (i.e., whole-body rotation, black line) and combined vestibular and neck (i.e., head-on-body, gray line) stimulation. Responses were comparable in both conditions and followed a similar time course. The similarity in responses measured during conditions in which the neck did and did not move might be surprising, considering that individual VO neurons showed robust responses to neck stimulation after lesion. However, this finding was consistent with the directional sensitivity of the neck-driven response calculated across the population of neurons. Specifically, neck-related and vestibular responses were agonistic or antagonistic for individual VO neurons. For example, a type I neuron (in the left vestibular nucleus) with antagonistic responses will have excitatory vestibular responses during whole-body rotation to the left and excitatory responses to neck proprioceptor stimulation during body-under-head rotation also to the left. Such a cell will be less responsive during head-on-body rotation to the left, since the

vestibular and neck sensitivities would effectively cancel each other. In contrast, the response of a VO neuron with agonistic vestibular and neck sensitivities will be enhanced during head-on-body rotation. Thus when response direction as well as magnitude were considered, the average effect of neck sensitivity was minimal at the population level (Fig. 3*C*; body-under-head rotation, dashed gray line), resulting in comparable neuronal sensitivities during whole-body and head-on-body rotations ($P > 0.1$).

To further study the functional role of the neck proprioceptive signals that were unmasked after lesion, we next addressed the possibility that this signal might influence vestibularly driven reflexes during compensation. Specifically, VO neurons send direct descending projections to the cervical segments of the spinal cord (Boyle 1993; Gdowski and McCrea 1999) and are thus thought to contribute to generation of the VCR. To test whether the VCR was altered after lesion, we stimulated the vestibular system using whole-body rotations while the monkey's head was unrestrained. The gain of the VCR response was then calculated to provide a measure of head stabilization (see METHODS). As such, a gain of 1 would indicate perfect head stabilization (i.e., stabilization of the head relative to space), whereas a gain of 0 would indicate a lack of head stabilization (i.e., the head moves with the body). As can be seen in Fig. 4*A*, whereas the VOR was present during whole-body (dashed black line) and head-on-body (gray line) rotations (Sadeghi et al. 2010), VCR gains (black solid line) were negligible at all times before and after unilateral labyrinthectomy. This was consistent with the small average value of neck sensitivities calculated across the population of neurons that was described earlier (i.e., Fig. 3*C*). Moreover, computed neck sensitivities were even smaller when both the phases and the polarity of each neuron's individual response vector were taken into account (Fig. 4*B*). This observation held true during the first week after lesion, as well as during the weeks that followed.

Finally, we explored the possibility that the unmasking of neck proprioceptive inputs supports a homeostatic mechanism that ensures continued dynamic stimulation of individual neurons after lesion. In particular, we asked whether neck-sensitive VO neurons demonstrated better and/or faster compensation after lesion. Results of this analysis (shown in Fig. 4, *C* and *D*) compare the vestibular sensitivities and resting discharges of neck-sensitive and neck-insensitive VO neurons (black and gray bars, respectively) as well as the population of all neurons (white bars), acutely (i.e., week 1), and >2 wk after lesion. Although VO neurons showed a significant increase in vestibular sensitivity after the first week, no significant differ-

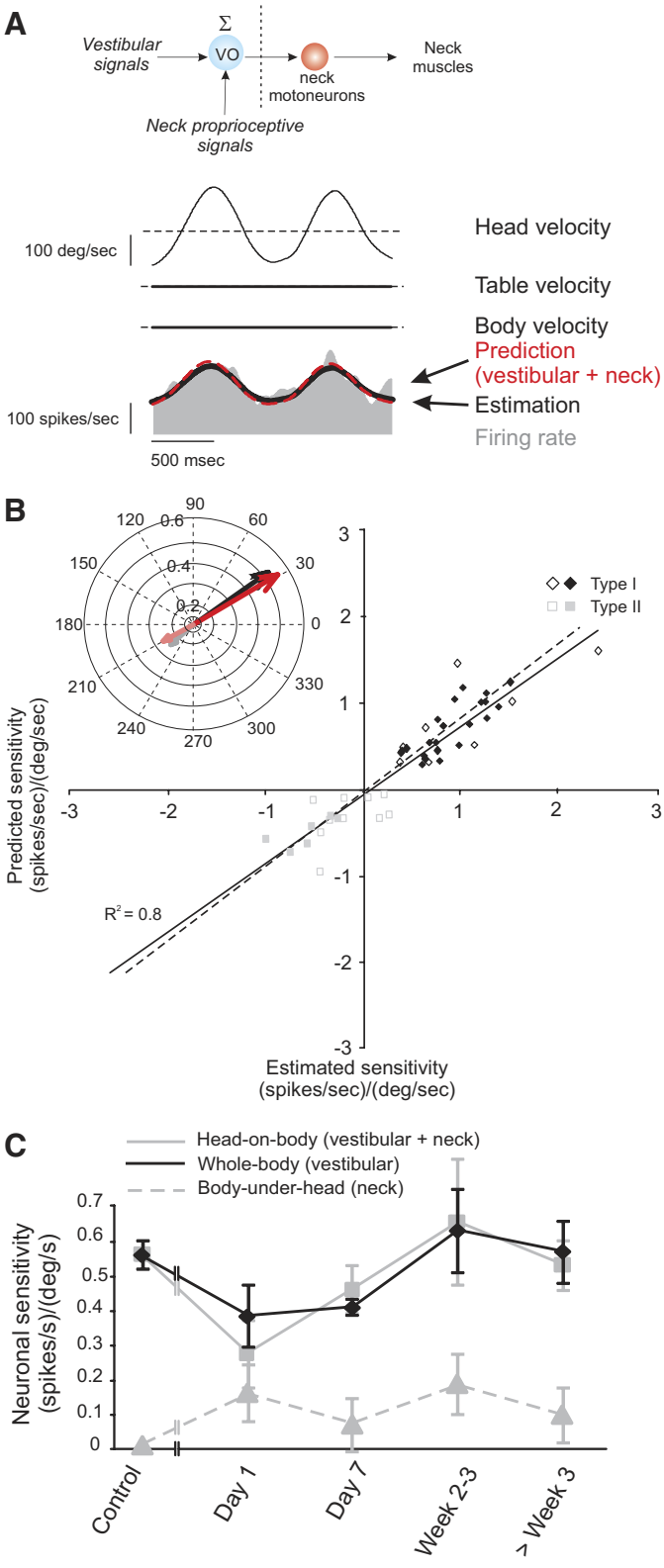

FIG. 3. Response of VO neurons to simultaneous passive stimulation of vestibular and neck proprioceptive receptors. *A*: example of the response of a type I VO neuron to passive head-on-body rotation. A prediction (red dashed line) based on linear summation (schematic) of passive sensitivities to neck and vestibular stimuli were similar to the response estimation from the head-on-body movement (thick black line). *B*: comparison of the estimated and predicted sensitivities during passive head-on-body rotations for the population of type I (black) and type II (gray) VO neurons recorded from day 1 to day 60 after lesion. Empty symbols represent neurons that have antagonistic neck and vestibular sensitivities (note that the abstract value of neck sensitivity is used for predictions). *Inset* shows vector plots for the average predicted (dark and light red for type I and type II neurons, respectively) and estimated (black and gray for type I and type II neurons, respectively) responses of neurons (day 1–day 60 postlesion) during passive head-on-body rotation. *C*: average neuronal sensitivities computed for the population of type I neurons (n = 17, 9, 9, 10, and 8 cells for Control, day 1, week 1, week 2–3, and >week 3, respectively) recorded during the 3 different rotational paradigms that stimulate the vestibular (whole-body), neck proprioceptive (body-under-head), or both (passive head-on-body) receptors. Note that the direction of neck sensitivities was accounted for in the calculation (i.e., sensitivities to rightward vs. leftward stimulation were considered as positive and negative values, respectively).

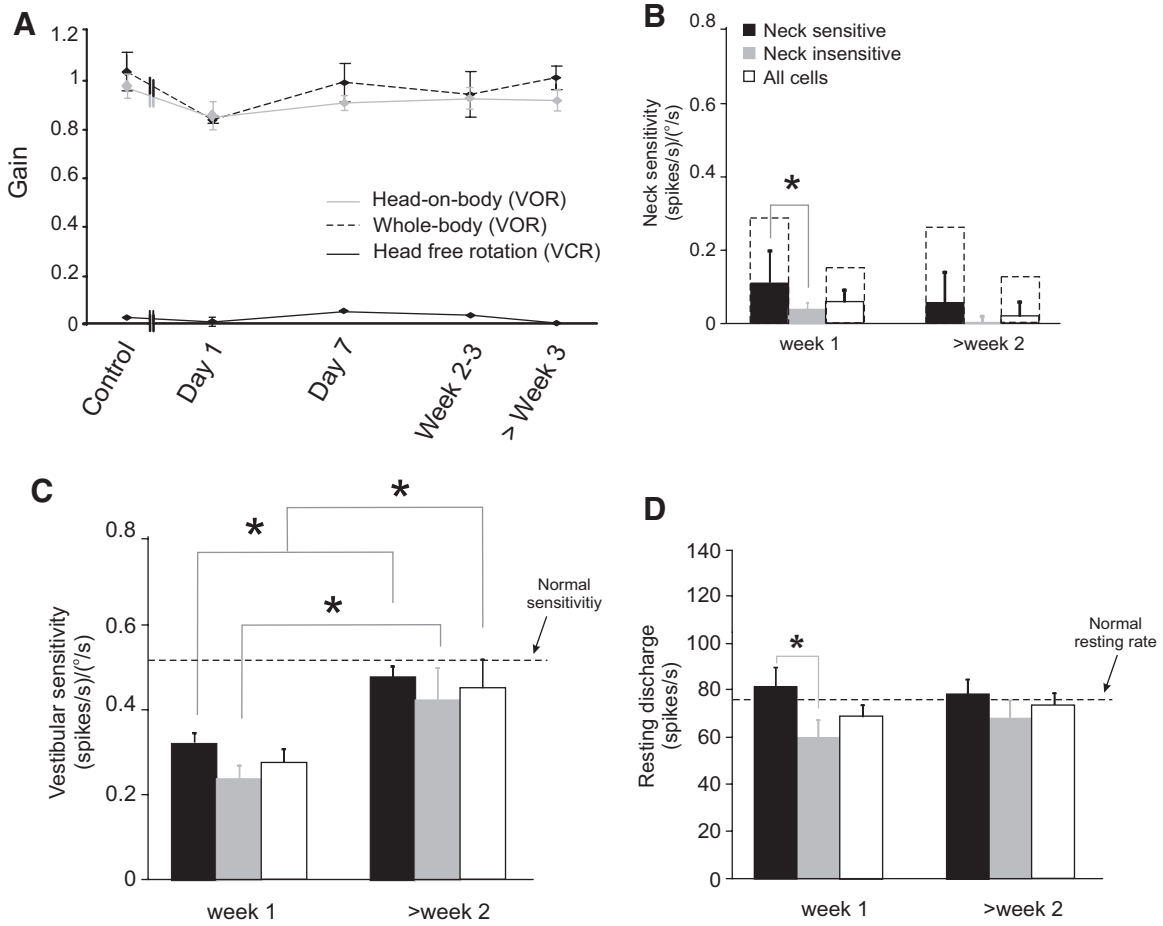

FIG. 4. The role of neck inputs in improvement of vestibular responses of VO neurons. *A*: the presence of neck proprioceptive responses on type I neurons did not enhance the vestibulocollic reflex (VCR, black line). Vestibuloocular reflex (VOR) responses are also shown for comparison (data from Sadeghi et al. 2010). *B*: average neck sensitivity for neck sensitive, neck insensitive, and the population of VO neurons. Note that the directions of the neck sensitivities are considered in the calculations. For comparison, the averages of absolute values of neck sensitivity are shown by the dashed line. *C*: there was no difference in the recovery of the vestibular sensitivity between neck-sensitive and neck-insensitive type I neurons. Dashed line represents the value for sensitivity in control condition. *D*: initially, the resting discharge of neck-sensitive type I neurons has better recovery compared with that of neck-insensitive neurons. Dashed line represents the resting discharge rate in control condition. *B*, *C*, and *D* include $n = 18$ and 19 neurons with neck sensitivity and $n = 15$ and 17 neck-insensitive neurons, during week 1 and >week 2, respectively. Asterisks (*) show significant differences (*t*-test) at $P < 0.05$. Error bars indicate SE.

ences were observed between the two groups. Notably, this contrasts with the findings of a previous study of PVP neurons, in which vestibular sensitivities of neck-sensitive neurons showed greater long-term improvement (Sadeghi et al. 2010). In contrast, the resting discharge of neurons with and without neck sensitivity differed during the first week after lesion with higher values for neck-sensitive VO neurons. By week 2 postlesion, both groups of neurons demonstrated comparable improvement. This latter result is similar to that previously reported for resting discharge of PVP neurons with neck sensitivity in the same time window (Sadeghi et al. 2010). Comparable findings were also observed for type II neurons (not shown).

Motor efference copy input

In everyday life, head movements can be self-generated as well as passively experienced. During the production of self-generated head movements, information about self-motion is available both from the motor command produced by the brain and from the resultant stimulation of vestibular and proprioceptive inputs. Thus we next asked whether during active head-on-body movements the production of a motor command might also play a role in compensation. Although it has been suggested that such extravestibular information could support the improvement observed in the VOR after peripheral vestibular lesion (Della Santina et al. 2001; Dichgans et al. 1973; Newlands et al. 2001), the only evidence for this proposal at the level of single neurons comes from our previous study of the VOR, in which we found that production of an efference copy signal was accompanied by relative enhancement in PVP neuron response that mirrored an increase in VOR gain during active versus passive head movements (Sadeghi et al. 2010).

To explicitly address the question with respect to VO neurons and postural recovery, we recorded their activity during passive and active head-on-body rotations with comparable trajectories. The duration of these head movements was typically about 300–400 ms, reaching peak velocities of 200–400°/s. Figure 5 shows the responses of example type I VO neurons recorded before, 1 day after, and 4 wk after contralateral labyrinthectomy. During passive rotations a good estimation of the response could be obtained using *Eq. 3*, which

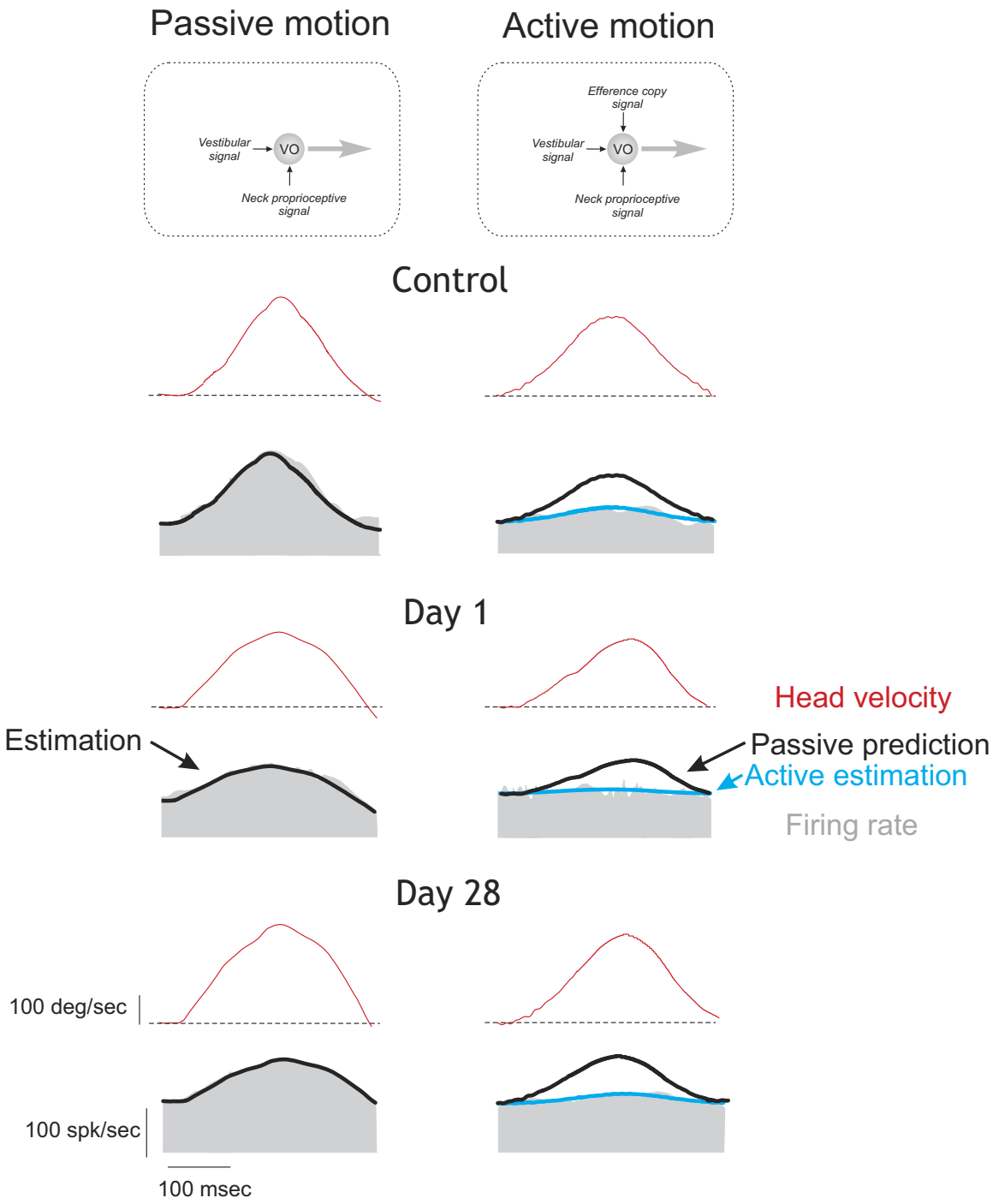

FIG. 5. Responses of example type I VO neurons during passive vs. active head-on-body rotations before and after contralateral labyrinthectomy. During active head movements, an efference copy signal sums with the vestibular signal and attenuates the response of VO neurons in control conditions (Roy and Cullen 2001b, 2004). We found similar results under control conditions with attenuation of the response during active head movements (blue, estimation) compared with passive conditions (black, prediction). Interestingly, following short-term (day 1) and long-term (day 28) compensation after unilateral labyrinthectomy, responses were still attenuated during active head movements.

accounted for a given neuron's sensitivity to both vestibular and neck inputs. In addition, as expected based on previous characterizations of these cells in control conditions (Roy and Cullen 2001b, 2004), neuronal responses were greatly attenuated during the whole period of active head movement.

Overall for the population of VO neurons recorded, neuronal responses continued to show marked attenuation in response to active (relative to passive) head movements at different time points after lesion ($n = 86$). For example, the average sensitivity of our subpopulation of type I VO neurons to passive motion was 0.3 and 0.5 on the first week and after the second week, respectively (Fig. 6*A*, gray curve). For comparison, the average sensitivity of the same neurons to active head motion was about 0.1 (spike/s)/(°/s) during both periods (Fig. 6*A*, black curve). As such, the percentage of attenuation during active movement decreased on the first week and then in-

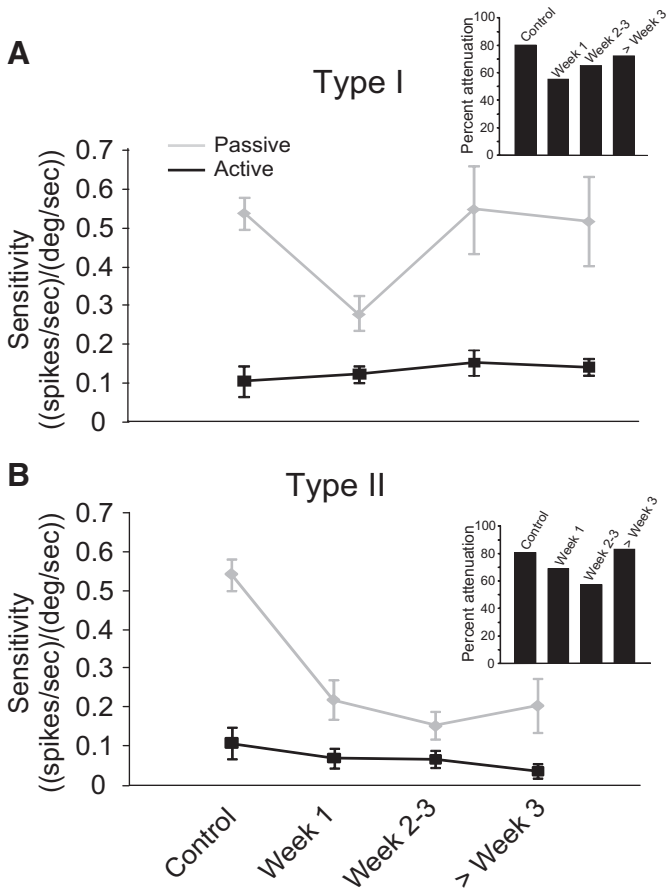

FIG. 6. Comparison of average responses of VO neurons during passive and active head-on-body rotations. *A*: average sensitivities of the population of type I neurons ($n = 56$) during passive (gray) and active (black) movements before ($n = 11$) and after ($n = 45$) contralateral labyrinthectomy. There was no significant difference between the sensitivity of type I neurons during active movements at any time point (paired *t*-test, $P > 0.1$). *Inset* shows the percentage attenuation in sensitivity during active vs. passive movements, which was more prominent 1 wk after lesion. Note that neurons showed very small sensitivities (<0.1) during active movements at all times. *B*: average sensitivities of the population of type II neurons ($n = 51$) during passive (gray) and active (black) movements before ($n = 10$) and after ($n = 41$) contralateral labyrinthectomy. There was no significant difference between the sensitivity of type II neurons during active movements at any time point (paired *t*-test, $P > 0.08$). *Inset* shows the percentage attenuation in sensitivity during active vs. passive movements. Similar to type I neurons, sensitivities were very small (<0.1) during active movements and neurons showed greater attenuation early after lesion. Error bars indicate SE.

creased to control values (Fig. 6*A*, *inset*). The attenuated responses measured after lesion were similar in magnitude to those observed during active head movements made in normal conditions ($n = 21$). A similar reduction in sensitivity during active head movements was also observed for type II VO neurons before and after labyrinthectomy (Fig. 6*B*). These findings contrast with our previous finding in PVP neurons after lesion (Sadeghi et al. 2010) and will be further addressed in the following section.

DISCUSSION

The present study provides evidence that compensatory changes observed in a specific group of vestibular nuclei neurons after unilateral labyrinthectomy are mediated by the relative reweighting of inputs from different modalities (i.e., vestibular and extravestibular). In particular, neck proprioceptive signals, not present prior to the lesion, play an important role early in the course of the vestibular compensation, as evidenced by the faster recovery in the resting discharge of the group of neurons that carry neck-related signals. In the following sections, the significance of these findings is addressed in relation to the suggested roles for VO neurons in mediating vestibulospinal reflexes and their projections to higher brain centers. We will also compare the findings of the present study in VO neurons to the compensation observed in another group of vestibular nuclei neurons, position–vestibular–pause (PVP) neurons, which mediate the VOR. Our findings suggest that, although similar homeostatic mechanisms can explain the unmasking of extravestibular signals at the level of VO and PVP neurons during the compensation process, there are certain differences at the cellular level between these two groups of vestibular nuclei neurons.

Recovery in vestibular responses

The vestibular sensitivities of type I VO neurons in the present study acutely decreased by >50% relative to control values following lesion, but over the next month increased such that responses to contralesionally directed rotations fully recovered. This is similar to what we have previously shown for another group of vestibular nuclei neurons (Fig. 7, *A* and *B*; compare blue lines) that mediate the VOR response (Sadeghi et al. 2010). Previous studies of central vestibular neurons, performed in anesthetized animals, have reported less robust

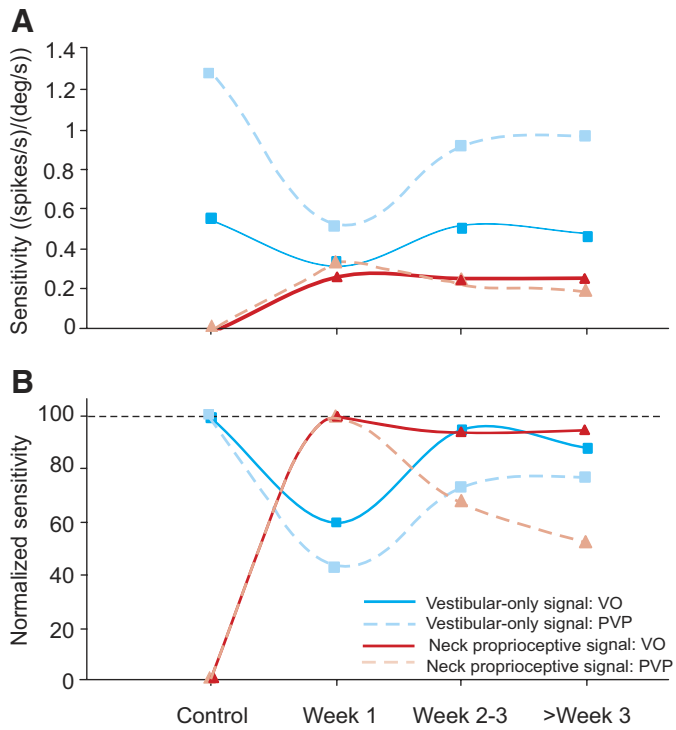

FIG. 7. Comparison of the time course of dynamic regulation of multimodal integration in type I PVP (data from Sadeghi et al. 2010) and VO neurons after contralateral labyrinthectomy for the actual (*A*) and normalized values relative to the maximum response (*B*) to vestibular (blue; measured by whole-body rotation) and neck proprioceptive (red; measured by body-under-head rotation) inputs.

recovery (Newlands and Perachio 1990a,b; Ris and Godaux 1998; Smith and Curthoys 1988), although it is likely that synaptic inputs were suppressed as a result of the anesthesia. Although the only other study in alert animals reported less recovery (Ris and Godaux 1998) recordings were made only ≤1 wk after lesion, a period when we also saw little recovery in neuronal sensitivities. In addition, we show that type II VO neurons in the contralesional vestibular nucleus show less recovery, likely related to their main vestibular input being from the lesioned nerve. Nevertheless, the improvement in their vestibular sensitivities supports the recovery of type I neurons through disinhibition. To date few studies have investigated the recovery of vestibulospinal reflexes over time. Electromyography and behavioral experiments have measured acute decreases in the responses of soleus, tibialis anterior, and triceps muscles to stimulation, as well as decreased tendon and righting reflexes, which recover in 2–3 wk after the lesion (Dutia 1985; Igarashi and Guitierrez 1983; Lacour et al. 1979; Lindsay and Rosenberg 1977). This reported behavioral recovery corresponds well with our observed recovery in vestibular sensitivity of VO neurons 2–3 wk after lesion (Fig. 7, *A* and *B*, blue solid line). However, following unilateral labyrinthectomy in rhesus monkeys, the recovery in VO neurons' sensitivity is not accompanied by the presence of a behavioral VCR response (see also Boyle et al. 1996; Guitton et al. 1986; Vidal et al. 1982; Wilson and Schor 1999).

Unmasking of neck proprioceptive signals

Here we have shown that VO neurons, which do not respond to neck proprioceptive stimulation in normal animals (Roy and Cullen 2001b, 2004; present study), became sensitive to such stimuli following lesion. As such, VO neurons are similar to VOR interneurons (i.e., PVP neurons) in that neck inputs are unmasked only after lesion (Sadeghi et al. 2010). Interestingly, in both studies, the percentage of neck-sensitive neurons observed after lesion (~50%) was comparable to that observed in normal conditions in other species (Gdowski et al. 2001; Kasper et al. 1988; Sadeghi et al. 2009). We suggest that the acute appearance of neck proprioceptive signals in the vestibular nuclei neurons of rhesus monkeys after lesion reveals neck-vestibular connections that are present before lesion, but make silent synapses on vestibular nuclei neurons that become active only when vestibular inputs are decreased. This idea is supported by previous in vitro studies showing an increase in the strength of projections from the spinal cord to the vestibular nuclei neurons following unilateral peripheral lesion (Dieringer et al. 1984; Straka and Dieringer 1995; Vibert et al. 1999). An alternative, but not mutually exclusive, explanation is that neck proprioceptive inputs are unmasked due to the modification of the gating mechanism that normally suppresses their input (also see Sadeghi et al. 2010). In the present study, we also observed a number of differences between the dynamic changes in the neck-related responses of VO neurons compared with PVP neurons (Sadeghi et al. 2010). Notably, the neck sensitivity of PVP neurons decreased as the vestibular responses recovered over time, whereas that of VO neurons remained constant (Fig. 7, compare red lines). For both cell types, however, neck sensitivities decreased to reach a similar minimum value [~0.2 (spike/s)/(°/s)] after week 3. On average, under normal conditions VO neurons are half as sensitive to head rotations (i.e., change in firing rate per increment of head rotation speed) as are PVP neurons (Roy and Cullen 2001b, 2002, 2004; Sadeghi et al. 2010; Scudder and Fuchs 1992). It is possible that the differences in their sensitivity to sensory inputs arises as a result of differences in membrane properties (see Beraneck et al. 2007; Straka et al. 2004) and/or differences in synaptic input strength.

Functional role for unmasking of neck proprioceptive signals

In the present study, we directly measured the functional implications of a reweighting of spinal inputs to vestibular nuclei neurons. Neck signals added linearly to the vestibular input such that neuronal responses during passive head-on-body rotations could be predicted by addition of a given neuron's vestibular and neck sensitivities. On average, however, population responses were similar during whole-body and head-on-body rotations. This is because the directionality of the neck sensitivity was highly variable and the magnitude of the population vector was negligible. In this way, VO neurons and PVP neurons in rhesus monkeys are comparable after lesion (compare with Sadeghi et al. 2010). Similar findings have been reported in studies performed in the vestibular nuclei of normal cats (Kasper et al. 1988), squirrel monkeys (Gdowski et al. 2001), and cynomolgus monkeys (Sadeghi et al. 2009).

To further explore the functional implications of a reweighting of spinal inputs to vestibular nuclei neurons, we next combined neuronal and behavioral measurements and showed that the increased efficacy of spinal inputs to VO neurons is not linked to compensatory changes in the status of the vestibulocollic reflex: VCR gains were negligible before and after unilateral labyrinthectomy. We attribute this finding to the fact that, despite the presence of substantial neck sensitivity in single neurons, the average magnitude of neck sensitivity of the population of neurons was small [<0.1 (spike/s)/(°/s)]. Similarly, we have previously shown that, although roughly 50% of PVP neurons in rhesus monkeys with unilateral labyrinthectomy (Sadeghi et al. 2010) and about 50% of both VO and PVP neurons in intact cynomolgus monkeys (Sadeghi et al. 2009) are neck sensitive, neck-related reflexes (i.e., cervicoocular reflex and VCR) are negligible in all cases. One limitation of the present experiments is that we did not measure the cervicocollic reflex, which functions to stabilize the head in response to activation of the neck proprioceptors. However, it is unlikely that this reflex played a significant role in the changes measured in the present study because its contribution to head stabilization is negligible in primates (Reynolds et al. 2008) compared with that in other species (e.g., Peterson et al. 1985). Thus our finding that the spinal reflexes remain negligible following lesion is in agreement with the proposal that the reorganization of synaptic inputs to the vestibular nuclei neurons is probably more beneficial at the cellular than at the network level (Rohregger and Dieringer 2003). Notably, VO neurons also send their projections to higher brain centers such as thalamus and vestibular cortical areas (Marlinski and McCrea 2008a,b), as well as to the spinal cord. The neck inputs that are unmasked after lesion could potentially contribute to the improvement in spatial orientation reported in patients during combined vestibular/neck proprioceptive stimulation (Schweigart et al. 1993).

Finally, we explored an alternate possible role for the unmasked neck proprioceptive inputs by comparing the rate of recovery of neurons that were neck-sensitive and neck-insensitive, to test whether the former group showed faster recovery. Indeed, we found that the resting discharges of type I neck-sensitive VO neurons were normal by the first day after lesion, whereas the resting discharge of neck-insensitive neurons reached normal values only after 2 wk, similar to PVP neurons (Sadeghi et al. 2010). However, whereas neck-sensitive PVP neurons demonstrated better recovery of vestibular sensitivity, neck-sensitive and neck-insensitive VO neurons showed comparable vestibular recovery over time. One possible explanation for this difference is that the smaller neck-related modulation of VO neurons was not strong enough to drive compensatory changes.

Cancellation of vestibular signals during active head rotations

The VO neurons in the present study responded similarly to active head motion, before and after labyrinthectomy. This is in contrast to our previous finding showing PVP responses to active motion are enhanced following lesion (Sadeghi et al. 2010). The modulation of VO neurons in intact rhesus monkeys is significantly suppressed during active movements (Roy and Cullen 2001b, 2004). In the present study, the modulation of VO neurons during active movements remained suppressed following lesion, where the relative suppression (i.e., vs. passive movements) was acutely smaller and then increased over time after lesion with the concurrent increase in passive vestibular sensitivity. The change in suppression could be the result of a relative change in amplitude of the cancellation signal that suppresses the canal-derived input to these neurons (see Roy and Cullen 2004) and/or cellular changes at the level of the VO neurons themselves. Although testing these possibilities is beyond the scope of the present study, based on our data, it is clear that the contribution of these neurons to vestibulospinal reflexes following lesion remains suppressed during active movements. As mentioned previously, VO neurons send projections to higher brain areas (Marlinski and McCrea 2008a,b; Meng et al. 2007) and thus are also likely to contribute cues required for the estimation of spatial orientation and self-motion. Our results suggest that the resulting sensation of balance would be less affected during daily activities, since they are largely comprised of active movements. Indeed, this proposal is consistent with the reported lack of correlation between the subjective sensation of dizziness (i.e., presumably derived in part from the modulation of VO neurons) and the VOR gain asymmetry measured by caloric test and passive head impulse test (i.e., mediated by PVP neurons that continue to help stabilize gaze during active head motion) in patients with unilateral vestibular loss (Hirvonen et al. 2008).

What mechanisms underlie the compensation at the cellular level?

In a previous study, we suggested several mechanisms for the observed improvement in responses of vestibular nuclei neurons mediating the VOR response (Sadeghi et al. 2010). The observed similarities between the compensatory changes observed in VO neurons imply that similar mechanisms could govern recovery in these neurons. Briefly, in addition to long-term potentiation and long-term depression (Caria et al. 1996, 2001; Grassi and Pettorossi 2001), homeostatic mechanisms that promote network stability can be simultaneously recruited to regulate the excitability of neurons in response to changing network activity (reviewed in Feldman 2009). The latter mechanism functions over a longer timescale (i.e., hours to days) and includes activity-dependent synaptic scaling (Kotak et al. 2005; Maffei and Turrigiano 2008a,b).

We propose that vestibular nuclei neurons homeostatically adjust their synaptic strengths in response to changes in their own firing during the first weeks following the loss of peripheral vestibular inputs, offsetting it by an increase in weighting of neck-related inputs through activation of previously silent neck proprioceptive synapses. Furthermore, since head movement propensity is reduced in unilateral vestibular lesion patients (Brandt et al. 1997), the resulting reduction in neck activity could also potentially provide a trigger to homeostatic mechanisms in this pathway (at the level of proprioceptors or further along the pathway). Based on the studies in other systems, such a mechanism could be mediated via a homeostatic increase in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (King et al. 2002) that activates (Kerchner and Nicoll 2008) the *N*-methyl-D-aspartate (NMDA) receptors that mediate the neck proprioceptive inputs (Smith et al. 1991; Straka and Dieringer 2004). Another possible explanation is that neck proprioceptive inputs are normally gated out by additional inhibitory inputs, which are modified after vestibular lesion (see DISCUSSION in Sadeghi et al. 2010).

Conclusion

Our results show that both neck proprioceptive and motor command information play a critical role in vestibular compensation. We further show that there are similarities and differences between the recovery processes in different neuronal classes in the vestibular nuclei. Neck proprioceptive inputs play a more enduring role in compensatory changes of VO neurons, whereas the role of these inputs after labyrinthectomy for PVP neurons is most prominent in the early stages of compensation and diminishes as the vestibular sensitivity of these neurons increases. Importantly, for both groups of neurons these processes involve reweighting of synapses from vestibular inputs as well as unmasking of inputs from other modalities. Our findings provide information that may be useful in the development of novel rehabilitation methods that take advantage of the convergence of sensory inputs and motor signals contributing to the early and late stages of compensation. For example, there is evidence for (Herdman et al. 1995) and against (Cohen and Kimball 2002; Mruzek et al. 1995) the use of rehabilitation exercises that are specifically focused on neck movements, and therefore involve the activation of neck proprioceptors, in the acute stage after injuries. We showed that during vestibular compensation changes in convergent multiple sensory inputs and different signals occur at the early and late stages of compensation. For example, stimulation of neck proprioceptors in the early stages is essential for better vestibular compensation. At later stages, extravestibular inputs might be useful for better VOR recovery, but probably do not affect the vestibulospinal reflexes. These findings led us to

hypothesize that more effective compensation could be obtained by tailoring different rehabilitation exercises for the acute and chronic stages. For example, selective activation of neck proprioceptors with neck movement or with vibratory stimuli applied to the neck in those patients in whom neck movements are difficult may accelerate the early stages of compensation. Finally, our findings point out that in future studies on vestibular compensation and other forms of motor learning, it is important to consider different groups of neurons based on their physiological responses to vestibular stimuli (i.e., PVP vs. VO) as well as their neck sensitivity.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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