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Unidirectional rotations produce asymmetric changes in horizontal VOR gain before and after unilateral labyrinthectomy in macaques

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Abstract

Unilateral vestibular lesions cause marked asymmetry in the horizontal vestibulo-ocular reflex (VOR) during rapid head rotations, with VOR gain being lower for head rotations toward the lesion than for rotations in the opposite direction. Reducing this gain asymmetry by enhancing ipsilesional responses would be an important step toward improving gaze stability following vestibular lesions. To that end, there were two goals to this study. First, we wanted to determine whether we could selectively increase VOR gain in only one rotational direction in normal monkeys by exposing them to a training session comprised of a 3 hr series of rotations in only one direction ($1000^\circ/\text{s}^2$ acceleration to a plateau of $150^\circ/\text{s}$ for 1 s) while they wore 1.7x magnifying spectacles. Second, in monkeys with unilateral vestibular lesions, we designed a paradigm intended to reduce the gain asymmetry by rotating the monkeys toward the side of the lesion in the same way as above but without spectacles. There were three main findings: 1) unidirectional rotations with magnifying spectacles result in gain asymmetry in normal monkeys, 2) gain asymmetry is reduced when animals are rotated towards the side of the labyrinthectomy via the ipsilesional rotation paradigm, 3) repeated training causes lasting reduction in VOR gain asymmetry.

Introduction

Permanent loss of function in one labyrinth can occur for a variety of reasons, including vestibular neuritis (Nadol 1995; Palla et al. 2004), vestibular schwannoma resection (Minor et al. 1999a), and intratympanic gentamicin delivery for treatment of intractable Meniere's disease (Carey et al. 2002). Individuals with reduced or absent function in one labyrinth transiently suffer vestibular symptoms including spontaneous nystagmus, head tilt and postural dysfunction due to the imbalance in tonic input to the brainstem vestibular nuclei (Baloh et al. 1984; Paige 1989). The brain compensates well to these static imbalances in that the majority of these symptoms and signs disappear over time (Fetter and Zee 1988). The response of the angular vestibulo-ocular reflex (VOR) to rotations of low-frequency and velocity also returns toward normal after unilateral vestibular lesions through process of vestibular compensation. However, a marked asymmetry in the response to high-frequency, high-acceleration rotations persists (Halmagyi and Curthoys 1988; Halmagyi et al. 1990; Aw et al. 1996; Cremer et al. 1998; Carey et al. 2007). VOR gain is markedly reduced when

the head moves in the direction towards the lesion (ipsilesional) but is closer to normal when the head moves away from the lesion (contralesional). This asymmetry in gain causes oscillopsia, decreased visual acuity and a feeling of imbalance during ipsilesional head rotation.

Interestingly, evidence suggests that animals with stable asymmetric VOR gain deficits after unilateral labyrinthectomy (UL) retain sufficient “adaptive reserve” to raise the gain of the VOR if they are exposed to a training regimen comprising repeated whole body rotations in both directions while viewing a patterned background (Maioli and Precht 1985) or while wearing magnifying spectacles (Clendaniel et al. 2003). This raises a question: If VOR gain for ipsilesional rotations can be increased through selective adaptation training, then why does this not occur spontaneously through recovery processes? One reason could be that during normal visual conditions and natural head movements typical of daily life, VOR gain adaptation predominantly acts on semicircular canal inputs *after* a difference signal between the two labyrinths has been computed, so that gain increases that would bring the deficient ipsilesional VOR up toward normal do not occur because they would be accompanied by retinal slip in the opposite direction causing an undesirable change in contralesional VOR gain to *above* normal. If this is the case, then a training session that introduces retinal slip only for ipsilesional head rotations and never for contralesional head rotations might decouple ipsilesional and contralesional VOR gain adaptation sufficiently to allow selective enhancement of ipsilesional VOR gain.

Constrained learning paradigms have been successfully employed to overcome other asymmetric motor deficits, such as when a healthy appendage is constrained from use so that selective use of the unhealthy side facilitates compensation (Taub et al. 1993; Taub et al. 1994; Wittenberg and Schaechter 2009; Helveston 2010). Because the VOR shows a robust capacity to adapt to optically-induced changes (Gonshor and Melvill Jones 1976; Clendaniel et al. 2001; Clendaniel et al. 2002; Schubert et al. 2008) we hypothesized that an analogous asymmetric VOR training paradigm might selectively increase the ipsilesional gain of the VOR. We first tested this hypothesis by rotating monkeys in only one direction ($1000^{\circ}/s^2$ leftward acceleration to a plateau of $150^{\circ}/s$ for 1 s, repeated for 3 hrs) while they wore 1.7x magnifying spectacles. This was to determine whether normal monkeys exposed to this training regimen could increase VOR gain asymmetrically. Second, we tested an analogous paradigm in monkeys with stable asymmetric VOR gains after unilateral labyrinthine lesions, by rotating the monkeys towards the side of the lesion in the same way as above but without spectacles.

Methods

Surgical preparation

All animal procedures were performed in accordance with a protocol approved by the Johns Hopkins University School of Medicine Animal Care and Use Committee. Surgery was done under sterile conditions in three rhesus monkeys (*1 Macaca mulatta* and *2 M. fascicularis*) anesthetized with inhalation of halothane/nitrous oxide/oxygen. A head bolt was cemented to the skull at a position such that the animal was pitched 15° nose-down relative to the horizontal stereotaxic plane when in the upright position. The horizontal semicircular canals are approximately in the earth-horizontal plane when the head is in this position (Blanks et al. 1985; Minor and Goldberg 1990; Minor et al. 1999b). A prefabricated search coil was implanted in the frontal plane about the limbus of each eye (Minor and Goldberg 1991; Paige and Tomko 1991; Lasker et al. 1999), and the leads were soldered to plugs cemented to the skull. Labyrinthectomy was performed on the left side in each animal by making a postauricular incision and removing the mastoid bone with an otologic drill and curettes to expose the horizontal and posterior semicircular canals. The petrous bone was

removed further anteriorly and superiorly to visualize the superior canal near its union with the common crus. Each of the semicircular canals then was obliterated with removal of the ampulla. The vestibule was entered, and the utriculus and sacculus were removed. The internal auditory canal was opened next, and the distal ends of the ampullary nerve branches were removed. The space created by the labyrinthectomy was packed with muscle and fascia and the postauricular incision was closed (Lasker et al. 2000).

Eye movement recording and rotational testing

Each animal was seated in a plastic chair with its head restrained by securing the implanted bolt to a chair-mounted clamp. The chair was connected to a superstructure that was mounted to the top surface of a servo-controlled rotation table capable of generating a peak torque of 375 N-m (Acutronic, Pittsburgh, PA). The horizontal angular vestibulo-ocular reflex (VOR) was tested with the animal seated in the upright position in the superstructure and aligned such that the horizontal canals were approximately in the earth-horizontal plane of rotation. The VOR was measured in darkness before and after adaptation by using a step stimulus consisting of $1,000^{\circ}/s^2$ accelerations to a peak velocity of $150^{\circ}/s$ followed by a plateau of head velocity lasting 0.45 s and then deceleration at $1,000^{\circ}/s^2$ to rest (Fig. 1). Eye movement trials were removed if the animal blinked or made a saccade during the initial head acceleration. In order to keep the animals alert during the testing sessions, D-amphetamine (0.2-0.3 mg/kg) was given orally 15 min before the beginning of a session (Raphan et al. 1979, Minor et al. 1999b)

Adaptation paradigms

We have three training paradigms each of which was made up of multiple sessions. The first training paradigm was performed in 3 monkeys before vestibular lesions. The second and third training paradigms were performed in monkeys who have had a unilateral labyrinthectomy on the left side.

Paradigm 1 - Training in normal animals

Before each training session each animal was rotated in the dark with the step stimuli randomly in the leftward (n=30) and rightward (n=30) directions (Fig. 1). To induce adaptation, monkeys were first fit with magnifying (1.7X) spectacles that were attached to their acrylic skullcap. Each session for each animal consisted of a series of steps in the leftward direction (described above) for 3 hours. Animals were kept stationary for 1.1 s between each rotation, to allow for the horizontal semicircular canal cupulae to go back to their resting position. This minimized development of left-beating nystagmus due to velocity storage (Raphan et al. 1979). Because each step stimulus took a total of 2 seconds, each animal was rotated 5400 times during the 3 hour adaptation session. After the training session was completed each animal was rotated in the dark with the step stimuli in the leftward (n =30) and rightward (n = 30) directions (Fig. 1). In normal animals this training session was repeated 1 week later in the rightward direction.

Training after Unilateral Labyrinthectomy

Paradigm 2 (Ipsilesional training)—All three monkeys underwent the following procedure. First a unilateral labyrinthectomy was performed on the left side of each animal as described above. Sadeghi et al. (2006) have shown that VOR gain reaches a steady-state level within 25 days after the lesion; therefore, we allowed animals to recover for 4-5 weeks in normal diurnal lighting conditions without exposure to any training sessions. The VOR was tested 3-4 times in the dark during this time to obtain baseline data before the training sessions were started. During the second month after the labyrinthectomy the animals began the ipsilesional direction training paradigm. The ipsilesional direction training paradigm

consisted of a series (3 or 4) of training sessions over the next month that were similar to the training sessions described for normal animals.

Before each training session each animal was rotated in the dark with the step stimuli randomly in the leftward ($n = 30$) and rightward ($n = 30$) directions (Fig. 2) in order to determine the gain of the VOR. In the training sessions after labyrinthectomy, animals were not fitted with magnifying spectacles but instead were rotated without spectacles in the ipsilesional direction. The gain was already low in this direction and we wanted to determine the effects of adaptation without additional magnification. Each session for each animal consisted of a series of steps in the ipsilesional direction for 3 hours. A total of 5400 ipsilesional rotations were performed on each animal during each adaptation session. The VOR was then tested in each animal in the dark to determine the acute changes in gain after the adaptation session. Each animal was tested in the dark again 3 days later (returning to their normal cages and lighting conditions in the interim) to determine whether changes persisted. A training session was not performed at this point, just the testing of the VOR. Four days later, animals were then exposed to another identical training session. This procedure was repeated in each monkey 2-3 additional times.

Paradigm 3 - Bidirectional training—After Experiment 2 was concluded, animals were tested with a bidirectional training session. Before each training session each animal was rotated in the dark with the step stimuli randomly in the leftward ($n = 30$) and rightward ($n = 30$) directions in order to determine the gain of the VOR. In the training sessions after labyrinthectomy, animals were not fitted with magnifying spectacles but instead were rotated without spectacles. Each session for each animal consisted of a series of steps randomly in the ipsilesional and contralesional directions for 3 hours. A total of 5400 rotations (2700 contralesional and 2700 ipsilesional) were performed on each animal during each adaptation session. The VOR was then tested in each animal in the dark to determine the acute changes in gain after the adaptation session. Animals were then exposed to a final training session approximately 2 weeks later for a total of 2 sessions in each animal

Data Analysis

Gains were measured during the $1000^\circ/\text{s}^2$ to $150^\circ/\text{s}$ steps by the mean ratio of eye velocity divided by head velocity during the constant-acceleration portion of the stimulus (G_A) and during the constant-velocity plateau of the step (G_V) (Fig. 1). G_A was measured during the initial 20 – 120 msec after the start of the stimulus and G_V was measured during 500-700 msec after the start of the stimulus. Fast phases were removed prior to the measuring of gains. We quantified gain asymmetry for G_A (SG_A) and G_V (SG_V) by computing the ratio between the contra- vs ipsilesional difference in gain and the average gain, $SG_x = 200 * (G_{x\text{contra}} - G_{x\text{ipsi}}) / (G_{x\text{contra}} + G_{x\text{ipsi}})$.

Results were described as means \pm SD. Data from two groups were compared with an unpaired t -test. ANOVA was used to compare data from more than two groups.

Results

Normal animals (Before and after magnifying spectacles)

Fig. 1 shows the individual responses in monkey 1 before and after spectacle-induced adaptation for steps of yaw head velocity in the rightward and leftward directions. All VOR training and testing was done with this stimulus. Three monkeys were tested before and after 1.7 X spectacle-induced adaptation. The average change in G_A , G_V and the values for SG_A and SG_V are shown in Table 1. On average G_A increased by $21 \pm 5\%$ (mean \pm SD, $p < 0.001$, $n = 6$) and G_V increased by $18 \pm 5\%$ ($p < 0.001$, $n = 6$) when pooling together all

rotations in the direction of the adapting stimulus compared to no change for rotations in the opposite direction. When gain was measured one week after the first training session there was no difference from pre-adaptation values from a week before ($p > 0.35$).

Responses after labyrinthectomy

Unilateral labyrinthectomy resulted in an enduring asymmetry in VOR gain during step rotations that persisted throughout the testing. Figure 2 shows an example of an increase in the ipsilesional gain and a reduction of asymmetry after performing the ipsilesional adaptation paradigm.

Before ipsilesional training—After the labyrinthectomy there was a significant asymmetry with SG_A measuring 0.62 ± 0.09 and SG_V measured 0.54 ± 0.01 , 1 week after the labyrinthectomy. By 4-5 weeks after labyrinthectomy (and prior to any training), SG_A had remained diminished (0.50 ± 0.05 , $p > 0.1$) but SG_V had decreased to 0.28 ± 0.01 ($p < 0.015$). These findings agree with the general trend that the high-frequency asymmetry (SG_A) does not recover after unilateral vestibular loss whereas the low-frequency asymmetry (SG_V) shows significant recovery.

Acute effects of ipsilesional and bidirectional training paradigms—In order to study the specific effects of training for each individual monkey, we show the changes in SG_A and SG_V before and after each ipsilesional training paradigm in Figure 3. In monkeys 1 and 2 a reduction in SG_A and SG_V was evident after each training session. In monkey 3 a reduction in SG_A was only evident after the third training session, and a reduction of SG_V only occurred after the first and second training sessions ($p < 0.05$). For the first training session in monkeys 1 and 2, the reduction in SG_A was due to a decrease in contralesional gain with no change in ipsilesional gain ($p < 0.05$ for $G_{A\text{contra}}$, $p > 0.05$ for $G_{A\text{ipsi}}$). In contrast, the reduction of SG_A in the subsequent sessions in monkeys 1 and 2 was due to an increase in the ipsilesional gain ($p < 0.05$ for $G_{A\text{ipsi}}$, $p > 0.05$ for $G_{A\text{contra}}$). For each of the training sessions, reduction in SG_V was due to an increase in ipsilesional gain ($p < 0.05$ for $G_{A\text{ipsi}}$, $p > 0.05$ for $G_{A\text{contra}}$). Monkey 3 showed no increase in ipsilesional gain after each ipsilesional training session for either G_A or G_V ($p > 0.05$). We pooled all of the training sessions from each monkey before and after ipsilesional training (Table 2). After the ipsilesional training paradigm, SG_A decreased an average of $15 \pm 10\%$ ($p < 0.013$) and SG_V decreased an average of $11 \pm 5\%$ ($p < 0.018$).

After the bidirectional training paradigm (Figure 4), SG_A and SG_V decreased in only 1 of the 6 training sessions (monkey 1, training session 2). When we pooled the bidirectional training sessions we found no significant change in gain or asymmetry in SG_A ($p > 0.38$) or SG_V ($p > 0.97$).

Long-term changes after ipsilesional training—Figure 5 shows the average contra and ipsilesional gain at four specific time points during the first 2 months after unilateral labyrinthectomy before and after the ipsilesional training sessions. After the last ipsilesional training session, SG_A was 0.18 ± 0.11 [$p < 0.01$ when compared to SG_A (0.50 ± 0.05) from 1 month prior] and SG_V decreased to 0.08 ± 0.04 [$p < 0.04$ when compared to SG_V (0.28 ± 0.01) from 1 month prior]. After waiting 3 days after the last ipsilesional learning paradigm the value for SG_A was 0.26 ± 0.05 ($p < 0.01$, compared to SG_A from 1 month prior). SG_V was unchanged at 0.13 ± 0.05 ($p > 0.07$ compared to SG_V from 1 month prior).

Discussion

Normal animals (Before and after magnifying spectacles)

Prior studies that have varied the gain of the VOR through asymmetrical adaptation paradigms have involved low-frequency sinusoidal rotations paired with asymmetric optokinetic stimulation such that the gain would increase in one direction and not change and/or decrease in the other (Aoki et al. 1998; Hirata et al. 2002; Maruyama et al. 2004; Marti et al. 2006). In the present study, we showed that we could increase VOR gain for one direction of rotation by placing magnifying spectacles on monkeys during high acceleration head rotations. This is important because fast head rotations have dramatically reduced gains in the ipsilesional direction (Halmagyi and Curthoys 1988; Halmagyi et al. 1990; Lasker et al. 1999; Lasker et al. 2000; Carey et al. 2007; Sadeghi et al. 2007; Minor and Lasker 2010). In normal animals, gains increased by about 20 % after three hours of continuous unidirectional adaptation with 1.7 X spectacles. Although a significant increase, 20% seems small considering that the animals were adapting for 3 hours and similar short-term adaptation experiments using bidirectional stimulation paired with gain enhancing adaptation paradigms in monkeys have yielded increases of 40 % or more (Raymond and Lisberger 1996; Ushio et al. 2009). There are at least two possible reasons for these findings. First, the animals were not trained or rewarded in our experiments. Second, Hirata et al. (2002) showed that vertical gain change during conflicting visual optokinetic stimulation (X0 in one direction and X2 in the opposite direction) changed with an overall lower magnitude than in monkeys that had the same visual command in both head directions. We hypothesize that while it is possible to alter the gain of the VOR differentially, depending on head direction, the lower efficacy may result from an incomplete dissociation between the error signal driving the change and the direction of the head motion.

Acute effects of ipsilesional and bidirectional training paradigms

Previous studies have attributed the reduced gain in the ipsilesional direction to an inherent asymmetry in the neurons that supply the signals to the VOR. One hypothesis is that high acceleration rotations almost solely stimulate the excitatory side of the vestibular end organ because the neurons on the inhibitory side go rapidly in to cutoff (negative saturation). It has been suggested, that rapid head rotations are a form of unilateral stimulation (Halmagyi et al. 1990). If that is the case then adaptation paradigms seeking to increase the gain of the VOR in the ipsilesional direction should be ineffective due to this inhibitory cutoff. We were, however, able to increase the gain of the VOR in the ipsilesional direction after the ipsilesional adaptation paradigm.

There are at least two reasons that could account for the average increase in ipsilesional gain being relatively modest (~10%). First, the improvement in ipsilesional gain may have persisted from one adaptation session to the next. Such persistence in the adapted change could reduce increases resulting from subsequent training sessions. Results presented in Figure 5 show that reductions in gain asymmetry did persist for at least three days after the final training paradigm. Another possible reason for the modest increase in ipsilesional gain is that one animal (monkey 3), showed little improvement in its ipsilesional gains. We do not have an explanation for the reduced adaptation in this animal. It does not appear to be species related as monkey 1 and monkey 3 were the cynomolgus monkeys and monkey 1 showed the largest amount of adaptation. It is interesting to note that this monkey also had the smallest change in gain when using magnifying lenses before the labyrinthectomy and so may not have been as susceptible to adaptation-induced changes in VOR gain. These differences in the absolute magnitude of changes in gain lead us to conclude that asymmetry is more useful as a measure than is the magnitude of the gain.

The fundamental finding from this study is that the asymmetry in G_A after unilateral labyrinthectomy did not improve until we had the monkeys undergo the ipsilesional adaptation paradigm. This is in contrast to G_V , which showed marked improvement during the first month after the labyrinthectomy (Figure 3). There are two reasons that may account for this finding. There is some evidence that patients who suffer from vestibular dysfunction may change their movement strategies such that they move less (Herdman 1998; Cromwell et al. 2004; Kvale et al. 2008). One possibility is that the monkeys are moving less toward the side of the lesion, which prevents an increase in gain due to the scarcity of retinal slip error in that direction. Clendaniel et al. (2002) showed that adaptation of gain during rapid head rotations could only occur if the retinal slip error signal was paired with head rotations that were of similar frequency and velocity to the test stimuli. It may be that these animals are not moving their heads rapidly enough during everyday activity to induce the necessary gain increases in the ipsilesional direction. Another possible reason underlying the lack of improvement in ipsilesional gain is that the animals are using non-vestibular compensatory mechanisms to supplement the VOR, such as compensatory saccades. (Peng et al. 2005; Tian et al. 2007). Although we do not see evidence of these types of eye movements, it is important to remember we are using passive whole-body rotations. Other mechanisms of compensation might be evident for head-on-body or active head rotations.

Another possible explanation for improvement in the ipsilesional gain during the ipsilesional adaptation paradigm but not during everyday activity is that gain adaptation during rapid head rotations is partially constrained such that the retinal error signal causes a change in gain to occur for both leftward and rightward directions (Hirata et al. 2002). This could occur, for instance, if the gain changing circuitry is downstream of neurons that compute the difference between inputs from the two labyrinths. Because in everyday activity the animal moves its head in both directions and never repeatedly in one direction, there may be a conflict in the error signal induced by motion in the contralesional and ipsilesional directions. This error signal could result because the gain is normal for rotations in the contralesional direction. Therefore, an increase in gain would cause an error signal opposite to the error signal resulting from the low gain in the ipsilesional direction. Rotating the animal exclusively in one direction overcomes this limitation because the animal receives only an error signal to increase the gain. The fact that the asymmetry reduced only after the ipsilesional adaptation paradigm but did not reduce after the bidirectional adaptation paradigm supports this theory.

If plasticity remains in the ipsilesional direction why does such a large asymmetry in gain between the ipsi- and contralesional directions occur after a unilateral lesion? One explanation comes from our two pathway model of the VOR (Minor et al. 1999b; Lasker et al. 1999; Lasker et al. 2000; Clendaniel et al. 2001; Lasker et al. 2002; Migliaccio et al. 2004, Minor and Lasker 2010). In this model, one component has phasic dynamics which primarily encode head acceleration and velocity. The second component has tonic dynamics which encode head velocity over a broad range of frequencies and velocities. In the model inhibitory cutoff is mainly occurring in the phasic pathway and is the main cause of the reduced responses to ipsilesional head rotation. The tonic pathway provides linear encoding of head velocity with little susceptibility to inhibitory cutoff. VOR adaptation occurs when the lesioned animal is allowed to see and receive retinal slip error. Initially, the gain increases dramatically in the phasic pathway and is what is responsible for the initial x2 increase in the contralesional gain immediately after the lesion. Because the neurons in the phasic pathway are highly asymmetric (i.e. susceptible to inhibitory cutoff) the gain in the ipsilesional direction does not increase very much.

We hypothesize, therefore, that the gain adaptation occurs in the phasic pathway much more rapidly than adaptation in the tonic pathway. Once the contralesional gain recovers to

normal further adaptation is prevented because of conflicting error signal between ipsilesional and contralesional head movements. Repeated ipsilesional training may increase the gain in those neurons that are still performing in their linear operating range, the majority of which probably reside in the tonic pathway. Interestingly, in squirrel monkeys (Clendaniel et al. 2001) and rhesus monkeys (Ushio et al. 2008), G_A increased substantially more than G_V after adaptation with magnification spectacles. This preferential increase of G_A over G_V was thought to be due to adaptation in the phasic pathway. However, in this study following the ipsilesional adaptation paradigm, unlesioned animals with magnifying spectacles had both G_A and G_V increased by the same amount (~20 %). Identical increases of G_A and G_V lends further support to the hypothesis that unidirectional stimulation preferentially increased the gain of the tonic pathway in comparison to the phasic pathway.

Long-term changes after unidirectional training

In normal animals, G_A and G_V exhibited no retention in adaptation-induced changes when tested 1 week after the unidirectional training paradigm. It is not surprising that a maladaptive gain asymmetry does not persist during normal activity. Retinal slip error would presumably return the adapted gain to normal once the lenses were removed. There was a significant change in SG_A and SG_V immediately following the last ipsilesional adaptation paradigm in animals after unilateral labyrinthectomy; however, the change persisted in SG_A but not in SG_V when tested 3 days after the last paradigm (Figure 5). One possible reason for this finding is that there is an optimal gain based on both visual and vestibular information. Because optokinetic and pursuit signals can contribute to the gain of the VOR during low-frequency head movements (G_V), it may be that these visual signals make up for the deficiency of VOR gain in the ipsilesional direction rather than vestibular signals. The reduced role of visual following mechanisms in responses to rapid head movements may account for the retention of changes in SG_A compared to SG_V . These results show that repeated ipsilesional training may be a potential rehabilitative technique for increasing the gain of the VOR during rapid head movements in the ipsilesional direction for patients that have unilateral hypofunction.

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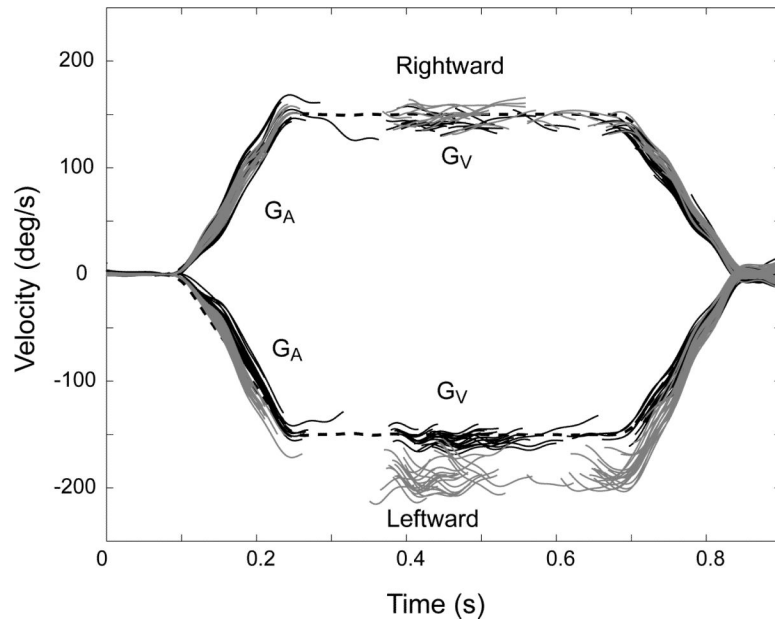


Figure 1. Responses to rightward (positive) and leftward (negative) yaw head rotations (dashed, black) ($1000^{\circ}/s^2$ to a peak head velocity of $150^{\circ}/s$). Eye responses are shown with the fast phases removed. Eye responses in the dark before training are in black. Monkey was then fitted with 1.7 X magnifying spectacles and trained with the unidirectional training paradigm in the counterclockwise direction. Post training eye responses are shown in gray.

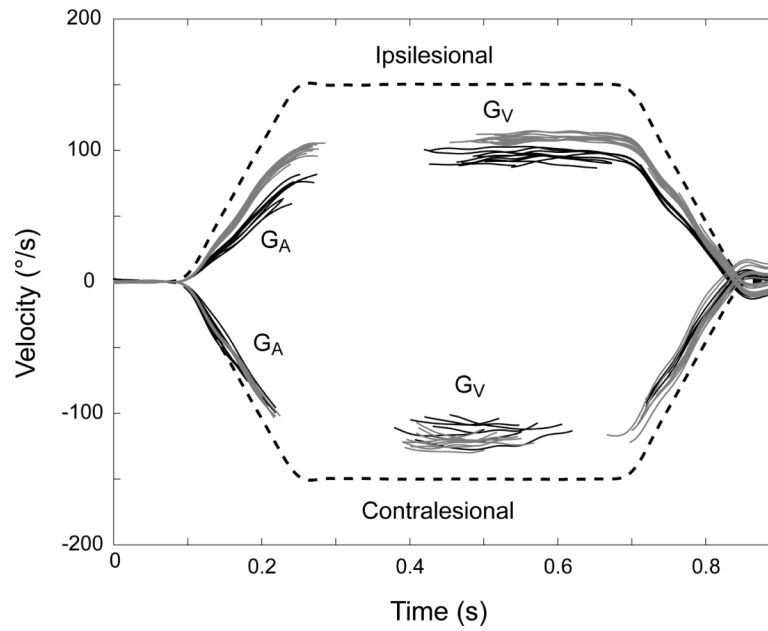


Figure 2. Responses to ipsilesional (positive) and contralesional (negative) yaw head rotations (dashed, black) ($1000^{\circ}/\text{sec}^2$ to a peak head velocity of $150^{\circ}/\text{sec}$). Eye responses are shown with the fast phases removed. Eye responses in the dark before the ipsilesional training paradigm are in black. Monkey 1 was trained with the ipsilesional training paradigm in the ipsilesional direction (training paradigm 2). Post training eye responses are shown in gray.

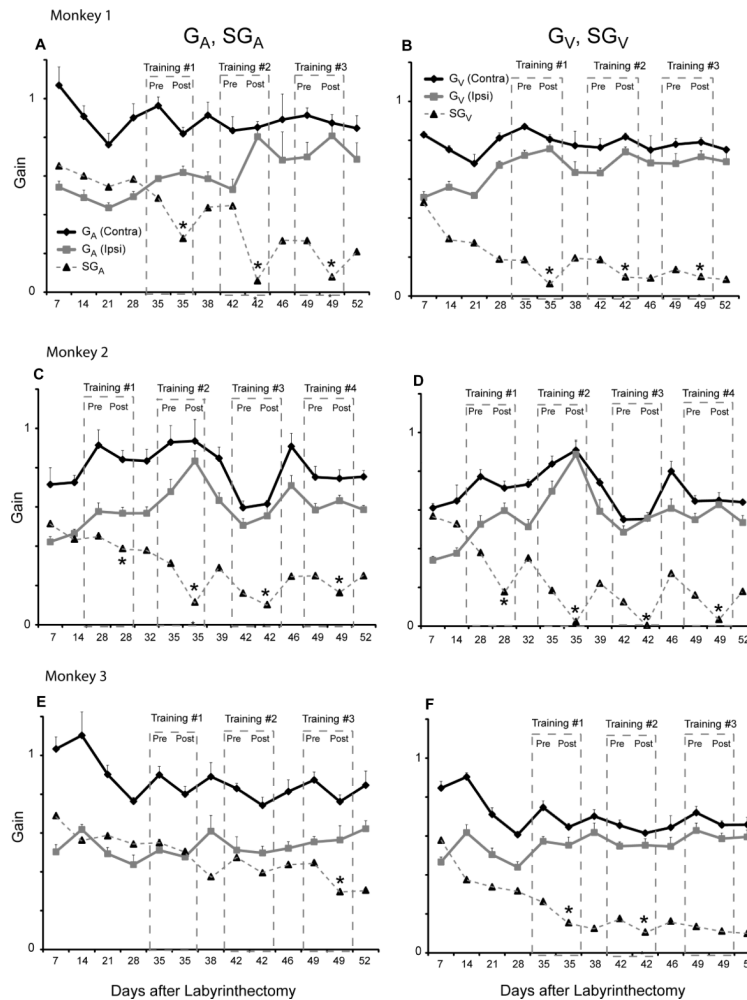


Figure 3.

Data after the labyrinthectomy from each of the 3 animals before and after ipsilesional training. A (monkey 1), C (monkey 2) and E (monkey 3) show the contralesional G_A , ipsilesional G_A and S_{G_A} for each monkey over the first 2 months after the labyrinthectomy. B (monkey 1), D (monkey 2) and F (monkey 3) show the contralesional G_V , ipsilesional G_V and S_{G_V} for each monkey. Contralesional gain is denoted in black and ipsilesional gain is denoted in gray. S_{G_A} and S_{G_V} are shown with a dashed line. Dashed boxes denote the gains tested immediately before and after each ipsilesional training session. Pre refers to the gain tested before the ipsilesional training session and post refers to the gain values tested immediately after the ipsilesional training session. In every training session animals were trained by rotating them in the ipsilesional direction without magnifying spectacles. An asterisk denotes if there was a reduction in asymmetry after each ipsilesional training session ($p < 0.05$). In all animals there is was a general decline in the asymmetry over time.

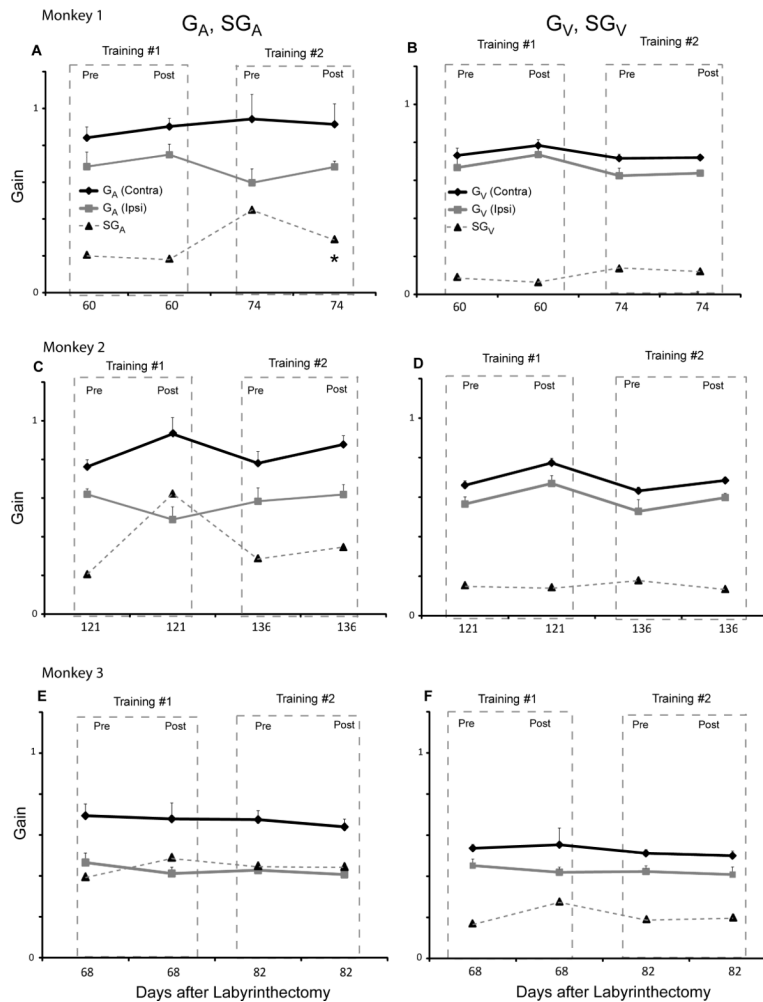


Figure 4. Responses before and after the bidirectional training for each monkey. A (monkey 1), C (monkey 2) and E (monkey 3) show the contralesional G_A , ipsilesional G_A and SG_A for each monkey during the 3rd month after the labyrinthectomy. B (monkey 1), D (monkey 2) and F (monkey 3) show the contralesional G_V , ipsilesional G_V and SG_V for each monkey. Contralesional gain is denoted in black and ipsilesional gain is denoted in gray. SG_A and SG_V are shown with a dashed line. Dashed boxes denote the gains tested immediately before and after each bidirectional training session. Pre refers to the gain tested before the bidirectional training session and post refers to the gain values tested immediately after the bidirectional training session. In every training session animals were trained by rotating them randomly in the ipsilesional and contralesional directions without magnifying spectacles. An asterisk denotes if there was a reduction in asymmetry after each bidirectional training session ($p < 0.05$).

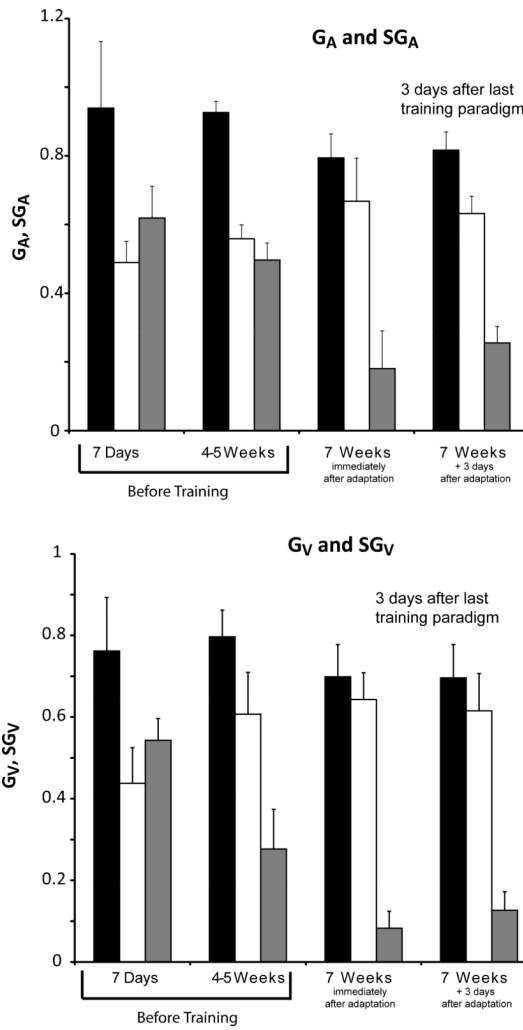


Figure 5.

Average long-term change in G_A (A) and G_V (B) for each labyrinthectomized monkey after the ipsilesional adaptation paradigm. Bars in black represent the gains in the contralesional direction. White bars represent the gain in the ipsilesional direction. Gray bars represent SG_A in A and SG_V in B. Before ipsilesional training there is a marked asymmetry in SG_A 7 days after the lesion. This asymmetry is still evident 4-5 weeks after the lesion ($p > 0.1$). At 7 weeks after the lesion, after 3-4 ipsilesional adaptation sessions, there is a marked reduction in SG_A ($p < 0.01$). This reduction in SG_A persists when tested 3 days later ($p < 0.01$). Before ipsilesional training there is a marked asymmetry in SG_V 7 days after the lesion. This asymmetry is still evident but markedly reduced 4-5 weeks after the lesion ($p < 0.015$). At 7 weeks after the lesion, after 3-4 ipsilesional adaptation sessions, there is a reduction in SG_V ($p < 0.01$). This reduction in SG_V , however, is not different from SG_V before the ipsilesional training sessions when tested 3 days later ($p > 0.07$).

Table 1

Mean \pm SD percentage change in gain from before to after the unidirectional training paradigm using 1.7 X magnifying lenses in normal monkeys. A negative change in asymmetry SG_A denotes a change in the rightward direction. SG_A and SG_V refer to the total asymmetry of the response.

| Training Paradigm | Change in G_A | | SG_A | Change in G_V | | SG_V |
|-------------------|------------------|------------------|-------------------------------|------------------|------------------|-------------------------------|
| | CW | CCW | | CW | CCW | |
| Rightward | 0.24 \pm 0.07 | -0.02 \pm 0.06 | -0.23 \pm 0.07 ^a | 0.17 \pm 0.05 | -0.02 \pm 0.09 | -0.18 \pm 0.07 ^a |
| Leftward | -0.04 \pm 0.04 | 0.19 \pm 0.03 | 0.21 \pm 0.03 ^a | -0.03 \pm 0.04 | 0.19 \pm 0.06 | 0.20 \pm 0.03 ^a |

^a $p < 0.008$

Table 2

The Mean \pm SD percentage change in gain from before and after all of the ipsilesional and bidirectional training sessions in the unilateral labyrinthectomized monkeys. We refer to the % change in SG_A and SG_V with a negative change in asymmetry denoting a decrease in the asymmetry of the response and positive value denoting an increase in the asymmetry. Ipsilesional training sessions caused a decrease in the average asymmetry while bidirectional rotations caused no change in the asymmetry.

| Training Paradigm | Change in G _A and SG _A | | | Change in G _V and SG _V | | |
|-------------------|--|------------------|-------------------------------|--|-----------------|-------------------------------|
| | Ipsi | Contra | SG _A | Ipsi | Contra | SG _V |
| Ipsilesional | 0.10 \pm 0.16 | -0.06 \pm 0.07 | -0.15 \pm 0.10 ^a | 0.09 \pm 0.10 | 0.01 \pm 0.06 | -0.11 \pm 0.05 ^a |
| Bidirectional | -0.01 \pm 0.14 | 0.05 \pm 0.11 | 0.06 \pm 0.19 ^b | 0.06 \pm 0.10 | 0.06 \pm 0.07 | 0.00 \pm 0.05 ^b |

The p values for the comparisons indicated by superscripts are as follows:

^a p < 0.018

^b p > 0.38