Distinct Patterns of Stimulus Generalization of Increases and Decreases in VOR Gain

Rhea R. Kimpo,* Edward S. Boyden,* Akira Katoh, Michael C. Ke, and Jennifer L. Raymond
Department of Neurobiology, Stanford University School of Medicine, Stanford, California

Kimpo, Rhea R., Edward S. Boyden, Akira Katoh, Michael C. Ke, and Jennifer L. Raymond. Distinct patterns of stimulus generalization of increases and decreases in VOR gain. *J Neurophysiol* 94: 3092–3100, 2005. First published July 20, 2005; doi:10.1152/jn.00048.2005. Motor learning must be capable of increasing or decreasing the amplitude of movements to meet the demands of the environment. One way to implement such opposite learned changes would be to store them with bidirectional plasticity mechanisms (i.e., long-term potentiation and depression at the same synapses). At the behavioral level, this scheme should result in similar patterns of stimulus generalization of increases and decreases in movement amplitude because the same synapses would be modified but in opposite directions. To test this idea, we quantitatively compared the stimulus generalization of learned increases and decreases in the gain (amplitude) of the vestibuloocular reflex (VOR) in mice and in monkeys. When examined across different sinusoidal frequencies of head rotation, decreases in VOR gain generalized more than increases in gain. This difference was apparent not only in the gain, but also the phase (timing) of the VOR. Furthermore, this difference held when animals were trained with high-frequency rotational stimuli, a manipulation that enhances frequency generalization. Our results suggest that increases and decreases in VOR gain are not exact inverses at the circuit level. At one or more sites, the plasticity mechanisms supporting decreases in VOR gain must be less synapse-specific, or affect neurons more broadly tuned for head rotation frequency, than the mechanisms supporting increases in gain.

INTRODUCTION

Cerebellum-dependent motor learning is essential for improving and maintaining the accuracy of movement throughout life. Over time, both adaptive increases and decreases in movement amplitude may be required as the organism, its environment, or both, change. A longstanding model of motor learning assumes that both increases and decreases in movement amplitude are implemented by a single plasticity mechanism, applied to synapses carrying different sensory or motor signals (Albus 1971; Ito 1982; Marr 1969). However, a recent behavioral analysis of the reversal of motor learning suggests a new hypothesis: opposite learned changes in movement amplitude may engage long-term potentiation (LTP) and long-term depression (LTD) at the very same synapses (Boyden and Raymond 2003). Bidirectional plasticity has been discovered at sites throughout the cerebellar circuit (Aizenman et al. 1998; Caria et al. 2001; Coesmans et al. 2004; Jorntell and Ekerot 2002; Lev-Ram et al. 2002, 2003; Rancillac and Crepel 2004), and there is evidence that plasticity mechanisms at more than

one site contribute to cerebellum-dependent motor learning (reviewed in Boyden et al. 2004). This raises an important question: do increases and decreases in movement amplitude alter the same set of synapses, but in opposite directions, at all sites of plasticity in the circuit—i.e., are they exact inverses at the circuit level?

One way to assess whether learned increases and decreases in movement amplitude are exact inverses is to examine their patterns of generalization to contexts different from those used to induce learning. If, at all sites of plasticity in the circuit, the same synapses are altered for increases and decreases in movement amplitude but in opposite directions, then the behavioral changes in both directions should have similar patterns of generalization. On the other hand, if different sets of synapses are modified during increases and decreases in movement amplitude, then these synapses may be tuned differently for the contexts in which the behavior is produced, and therefore the learned behavioral changes may exhibit different patterns of generalization.

Here, we analyze a simple eye movement, the vestibuloocular reflex (VOR), the amplitude (gain) of which can be adaptively increased or decreased by cerebellum-dependent learning. In particular, we examine the patterns of stimulus generalization to evaluate whether opposite learned changes in the amplitude of this movement are exact inverses of each other at the circuit level. The VOR stabilizes images on the retina during head movement by producing eye movement in the direction opposite to the head. If the VOR is poorly calibrated, head movements cause image motion on the retina. In such conditions, motor learning can adaptively adjust the gain of the VOR to improve image stability. In the laboratory, one can induce motor learning in the VOR by exposing animals to paired visual and vestibular stimuli. The acquisition of both adaptive increases and decreases in VOR gain depends on the cerebellum as evidenced by lesion and inactivation studies in many species (Ito et al. 1974; Koekkoek et al. 1997; McElligott et al. 1998; Michnovicz and Bennett 1987; Rambold et al. 2002; Robinson 1976). Despite this common requirement for the cerebellum, there are behavioral differences between increases and decreases in VOR gain consistent with the reliance of these two closely related motor learning tasks on different plasticity mechanisms (Boyden and Raymond 2003; Cohen et al. 2004; Eggers et al. 2003; Kuki et al. 2004; Miles and Eighmy 1980). Furthermore, a few studies have provided evidence for their reliance on different molecular mechanisms (Boyden et al. 2003; Carter and McElligott 1995; Li et al. 1995). Thus

---

increases and decreases in VOR gain appear to rely on different neural mechanisms. However, it is not known whether these different mechanisms are inverses of one another at all sites of plasticity in the circuit.

In this study, we compared the stimulus generalization of increases and decreases in VOR gain across head-rotation frequency. Previous studies have demonstrated that learning is best expressed at the sinusoidal frequency of head rotation used for training, and less so at different test frequencies (De Zeeuw et al. 1998; Feil et al. 2003; Iwashita et al. 2001; Lisberger et al. 1983; Raymond and Lisberger 1996; Wallman et al. 1982). However, the generalization of increases in VOR gain across stimulus frequency had not been explicitly compared with the generalization of decreases in VOR gain. We quantitatively compared the two and found that decreases in VOR gain generalized across head-rotation frequency more than increases in gain. This suggests that increases and decreases in gain are not exact inverses at the circuit level.

METHODS

Mouse experimental setup

All animal protocols were approved by the Stanford University Administrative Panel for Laboratory Animal Care. Experiments were performed on 33 adult ($\geq$8 wk old) B6129PF2/J male mice with black eyes (Jackson Lab, Bar Harbor, ME).

B6129PF2/J mice are F2 hybrids of C57BL/6 and 129 inbred strains. For these mice, the pretraining VOR gain (defined as the ratio of peak eye velocity to peak head velocity and measured as described in *Data analysis*) was 0.18 $\pm$ 0.02 at 0.5 Hz (mean $\pm$ SD; $\pm$10°/s peak head velocity), and 0.27 $\pm$ 0.02 at 2 Hz. These values were similar to those reported in previous studies using B6 strain mice and measuring the VOR gain with eye coils (De Zeeuw et al. 1998; Koekkoek et al. 1997). These values were slightly lower than those reported for C57 mice, measured using eye coils (Boyden and Raymond 2003; Coesmans et al. 2003; Harrod and Baker 2003; van Alphen et al. 2001). Studies of the VOR using video methods have reported higher VOR gains (Katoh et al. 1998; Stahl et al. 2000), and one study of eye movements in the light has suggested that an eye coil or the associated surgical implantation technique can load the eye or otherwise reduce eye-movement gains (Stahl et al. 2000). On the other hand, the accuracy of the video method is limited by several factors including changes in the size of the pupil, which can vary during and between experiments and affect the measurement of eye position. Furthermore, video methods preclude the measurement of VOR gain immediately before a visual-vestibular training session because it requires pupil-constricting drugs to measure the VOR in the dark, and these drugs compromise vision in lighted conditions appropriate for training. Eye-coil methods were therefore preferred because the goal in this study was the measurement of learning-related *changes* in the VOR by comparison of the VOR in the dark immediately before and after visual-vestibular training.

Surgical methods were identical to those described previously (Boyden and Raymond 2003). Briefly, while the mouse was under anesthesia, a head post was attached to the top of the skull using anchor screws and dental acrylic, and a scleral search coil (IET, Marly, Switzerland) weighing ~50 mg was implanted on the temporal side of the right eye just underneath the conjunctiva. The search coil leads were run subcutaneously to a two-pin connector. Mice were allowed to recover from surgery for 5–7 days. Mice with eye scarring after surgery were excluded from the study (5/38 mice).

For experiments, the head of the mouse was immobilized by attaching the implanted head post to a restrainer. The restrainer was attached to a turntable (Carco IGTS, Pittsburgh, PA), which delivered a vestibular stimulus by rotating the mouse about an earth vertical axis. The restrained mouse was positioned in the center of a magnetic field generated by a set of 18-in magnetic coils (CNC Engineering, Seattle, WA), which was fixed to the turntable. The magnetic coils generated signals in the scleral search coil that were related to the eye position. An analog differentiator and filter with a 300-Hz corner frequency were used to obtain eye velocity from eye position. All signals were digitized at a sampling frequency of 500 Hz. The raw velocity traces used only for illustration purposes in Fig. 1 were obtained by averaging both eye and head velocity within a sliding window of 50 ms. Visual motion was delivered by a moving optokinetic drum made of a white translucent plastic half-dome with black vertical stripes, each of which subtended 7.5° of visual angle. The optokinetic drum was back-lit by two 60-W lamps. A silvered acrylic plate attached to the turntable helped to ensure that the motion of the drum filled most of the mouse's field of view (~600° of solid angle).

Mouse behavioral testing

After recovery from surgery and prior to any behavioral experiments, each mouse was acclimatized to the experimental set-up for 15–40 min. During this period, the eye coil was calibrated by rotating the magnetic coils around the stationary mouse in a sinusoidal manner at 0.5 and 2 Hz, $\pm$10°/s peak velocity.

One to 2 days after acclimatization, we began experiments on motor learning in the VOR. Before and after training, we measured the VOR in the dark in response to vestibular stimuli with sinusoidal velocity
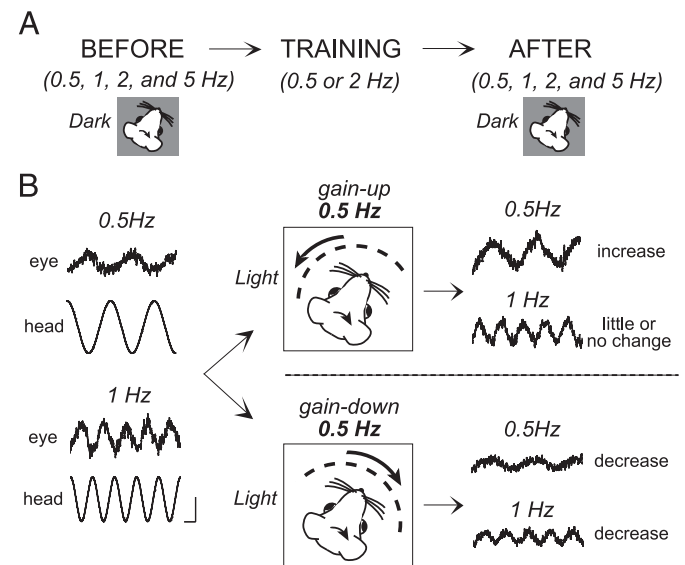

FIG. 1. Schematic of the experimental paradigm. *A*: before and after training, vestibuloocular reflex (VOR) performance was measured by rotating the head and body of the mouse in total darkness at 0.5, 1, 2, and 5 Hz. Changes in VOR performance were induced by pairing head rotations with a moving visual stimulus at a training frequency of 0.5 or 2 Hz. *B*: representative raw eye- velocity and head-velocity traces. Traces are from 1 mouse obtained before training (*left*), and after gain-up (*top right*) or gain-down (*bottom right*) training at a frequency of 0.5 Hz. For gain-up training, the head and the visual stimulus (dashed semicircular line) were moved in opposite directions (see arrows) and for gain-down training, in the same direction. For clarity of illustration, eye- and head-velocity traces are shown only for the 0.5- and 1-Hz test frequencies and only 1 set of before-training traces. After gain-up training at 0.5 Hz, the gain of the VOR at 0.5 Hz increased, whereas there was little or no change at 1 Hz. After gain-down training at 0.5 Hz, the VOR gain at 0.5 and 1 Hz both decreased. Horizontal calibration bar represents 500 ms; vertical calibration bar, 5°/s for eye velocity traces and 10°/s for head velocity traces.

profiles at 0.5-, 1-, 2-, and 5-Hz test frequencies with $\pm 10°/s$ peak velocity (Fig. 1A). At least 8 s before taking a data file, a bright light was flashed to keep the animal alert. Gain increases were induced by presenting sinusoidal visual and vestibular stimuli that were at the same speed and 180° out of phase (gain-up training; Fig. 1B). Gain decreases were induced by presenting sinusoidal visual and vestibular stimuli that were at the same speed and exactly in phase (gain-down training). The training frequency was either 0.5 or 2 Hz with peak velocity of $\pm 10°/s$. The training stimuli were presented in two 15-min blocks, and the VOR in the dark at the training frequency was measured between blocks (90–105 s).

Between experiments, the VOR gain was allowed to return to baseline by permitting mice to experience a normal visual-vestibular environment for at least 2 days after gain-up training or 3 days after gain-down training before the next experiment. A longer recovery period was used after gain-down training because previous reports have shown that decreases in VOR gain decay more slowly than increases in gain (Boyden and Raymond 2003; Miles and Eighmy 1980), especially with extended gain-down training. However, with a single 30-min training session, as used in the present experiments, recovery is fairly rapid. Within 2 days after gain-up training, the VOR gain was not different from the original gain ($P > 0.23$, paired t-test), and within 3 days after gain-down training, the VOR gain was not different from the original gain ($P > 0.71$). In general, gain-up and gain-down training sessions were alternated. To determine whether learning in naïve mice is the same as that in previously trained mice, we compared the percent change in VOR gain of both groups of mice, and found no difference ($P > 0.05$, unpaired t-tests). The recovery period of 2–3 days after 30 min of training is therefore sufficient to restore not only the VOR gain but also the capacity of the VOR circuit for learning.

Mouse data analysis

Custom software was used to analyze eye- and head-velocity traces. Eye-velocity traces were visually inspected for any deviations, such as saccades and movement artifacts. Such deviations were marked, and the whole sinusoidal cycle containing the deviation was excluded from the analysis. Eye- and head-velocity cycles were averaged and subjected to Fourier analysis. Harmonic distortion (defined as the ratio of the amplitude of the 2nd harmonic to the amplitude of the 1st harmonic) was fairly small and did not change with learning (pretraining: 15% at 0.5 Hz, 6% at 2 Hz, $n = 6$ representative mice; after gain-up: 11% at 0.5 Hz, 6% at 2 Hz; after gain-down: 18% at 0.5 Hz, 5% at 2 Hz). Therefore the amplitude and timing of the fundamental frequency component was used to calculate the averaged VOR gains and phases. The VOR gain was defined as the ratio of eye- over head-velocity amplitudes. The VOR phase was defined as the difference between eye-velocity phase and head-velocity phase, with phase equal to zero when the peak eye velocity occurred at the same time as the peak head velocity in the opposite direction. Positive VOR phase values indicate a phase lead of eye relative to head velocity and negative values, a phase lag. Plots illustrating learned changes in mouse VOR gain and phase show data that are normalized to the pretraining value. All raw gains and phases, before and after training, are provided in Tables 1 and 3. We analyzed the amplitude and timing separately to determine how learning affected each of these aspects of eye movement.

The following criteria were applied to determine which experiments would be considered for further analysis. Experiments where less than a total of 10 cycles per test frequency remained for calculating the VOR gain before and after learning were excluded (9/106 experiments). Experiments where we were unable to obtain a reliable measurement of the VOR gain before training were also excluded. More specifically: if the variance of the VOR gain from 5 to 10 18-s data files taken prior to training was more than half of the average VOR gain across these files, then the measurement was deemed unreliable (4/106 experiments from 4 mice). Because generalization of learning to a test condition is only meaningful if a change is observed in the training condition, we excluded data from experiments in which the mouse did not exhibit changes in VOR gain in the adaptive direction at the training frequency (18/106 experiments; 17 gain-up, 1 gain-down). The criterion for rejection was the final gain at the end of the half hour had changed in the maladaptive direction relative to baseline. Data that met all of our criteria (75/106 experiments) were weighted equally across mice by averaging the changes in gains and phases for replications in each mouse before averaging across mice. For 2-Hz experiments, one replication of each training condition was included in the analysis: $n = 18$ mice for gain-up, $n = 16$ mice for gain-down. One mouse did not have posttraining 1-Hz data after gain-down training at 2 Hz and was excluded from the analysis of the generalization index (see following text). For 0.5-Hz experiments, one to two replications of a given training condition per mouse were included in the data analysis: for gain-up, one replication from $n = 7/14$ mice, two from $n = 7/14$ mice, and for gain-down, one replication from $n = 18/19$ mice, two from $n = 1/19$ mice.

To compare the overall pattern of generalization of increases and decreases in VOR gain, we defined a generalization index as the fraction of learning at the training frequency that is expressed, on average, at test frequencies other than the training frequency, calculated as

$$\text{Generalization index} = \frac{\frac{1}{j}\left(\sum_i \Delta\text{gain}_i\right)}{\Delta\text{gain}_{\text{train}}}, \text{ where } i \neq \text{train}$$

Δgain_i represents the percent change in VOR gain measured at one of the j head rotation frequencies other than the training frequency (e.g., for 2-Hz training, $i = 0.5$, 1, and 5 Hz, $j = 3$) and $\Delta\text{gain}_{\text{train}}$, the percent change in gain at the training frequency of 0.5 or 2 Hz. Increasing values of the generalization index indicate increasing extents of generalization. When the average change in gain at non-training frequencies is equal to $\Delta\text{gain}_{\text{train}}$, the index is 1, indicating broad generalization. When the average change in gain at the test frequencies other than the training frequency is 0, the index is 0, indicating specificity. When the average change in gain at nontraining frequencies is larger than the change at the training frequency, the index is >1, and when the average change in gain at nontraining frequencies is maladaptive, the index is <0.

Statistical analysis was performed using StatView (SAS Inst., Cary, NC). To determine whether changes in the VOR gain and phase were significantly different from zero, we performed a one-sample t-test with Bonferroni correction for multiple comparisons. A one-factor ANOVA was performed to determine whether VOR gain changes varied significantly with frequency of head rotation. In cases where changes in gain did vary significantly with frequency, we determined whether the changes at the test frequencies were significantly different from the change at the training frequency using Dunnett's post hoc test. Dunnett's test allows comparisons of the mean from each group to the mean of a "control" group (Dunnett 1955). To determine the overall magnitude of the effect of learning on phase changes at nontraining frequencies, the weighted average of the absolute phase change across all nontraining frequencies was calculated for each training condition and compared. A Mann-Whitney test was used for comparing absolute phase and generalization index values between training conditions.

Primate protocols

Rhesus macaque surgical preparation, calibration, behavioral experimentation, and data analysis were performed as described in Raymond and Lisberger (1996) except that learning was induced with 2 h of visual-vestibular training, and changes in VOR gain were assayed at five frequencies (0.2, 0.5, 1, 2, and 5 Hz). All frequencies

TABLE 1. *VOR gain at each test frequency before and after training*

Test Frequency	Training Condition							
	Gain-Up at 0.5 Hz		Gain-Down at 0.5 Hz		Gain-Up at 2 Hz		Gain-Down at 2 Hz	
	Before	After	Before	After	Before	After	Before	After
0.5 Hz	0.14 ± .02	0.18 ± .03	0.16 ± .02	0.10 ± .01	0.20 ± .02	0.19 ± .02	0.19 ± .02	0.15 ± .02
1 Hz	0.22 ± .03	0.21 ± .04	0.23 ± .03	0.14 ± .02	0.24 ± .03	0.26 ± .03	0.25 ± .03	0.17 ± .02*
2 Hz	0.25 ± .04	0.24 ± .05	0.26 ± .03	0.19 ± .02	0.29 ± .03	0.38 ± .05	0.30 ± .03	0.20 ± .02
5 Hz	0.25 ± .04	0.24 ± .04	0.27 ± .03	0.21 ± .03	0.30 ± .03	0.34 ± .04	0.31 ± .03	0.24 ± .03

Values are means ± SE for *n* mice. *n* = 14, 19, 18, and 16 for gain-up at 0.5 Hz, gain-down at 0.5 Hz, gain-up at 2 Hz, and gain-down at 2 Hz, respectively. **n* = 15; in 1 mouse, 1-Hz data was not collected after training.

tested were used in the calculation of the generalization index. In the current study, monkeys underwent gain-up and gain-down training at 0.5 Hz (*n* = 2 monkeys) and 5 Hz (*n* = 1). For the data extracted from Raymond and Lisberger (1996), monkeys underwent gain-up and gain-down training at 0.5 Hz (*n* = 3 monkeys), 2 Hz (*n* = 2), 5 Hz (*n* = 3), 8 Hz (*n* = 2), and 10 Hz (*n* = 2). Data from one monkey for the 10-Hz training frequency were excluded from the analysis of generalization index because there was no change in gain at the 10-Hz training frequency, yielding an invalid generalization index value (i.e., dividing by 0). We analyzed the data with Mann-Whitney tests.

RESULTS

Learned decreases in VOR gain generalize more than increases in VOR gain

Motor learning in the VOR was induced in mice by pairing horizontal head rotations with a moving visual stimulus to either increase (gain-up training) or decrease (gain-down training) the gain (amplitude) of the VOR (Fig. 1). In all experiments, the movements of the head and visual stimulus had sinusoidal velocity profiles, and the frequency of head and visual stimulus rotation used to induce learning (training frequency) was either 0.5 or 2 Hz. Before and after training, the gain of the VOR was measured in the dark across a range of test frequencies: 0.5, 1, 2, and 5 Hz (Table 1).

The central finding was that increases in the gain of the VOR were expressed primarily at the training frequency, whereas decreases in gain were expressed more broadly across test frequency. After gain-up training at 0.5 Hz, a significant increase in gain was observed only at 0.5 Hz, indicating that the learned change was specific to the training frequency (Figs. 1*B* and 2*A*; *n* = 14 mice, *P* < 0.01, one-sample *t*-test with Bonferroni correction for multiple comparisons). After gain-down training at 0.5 Hz, significant decreases in the gain of the VOR were evident across all frequencies tested (*n* = 19 mice, *P* < 0.01). The decrease at the 0.5-Hz training frequency was not significantly different from the decrease at the 1-Hz test frequency *F*(3,72) = 4.45, *P* < 0.01, one-factor ANOVA; *P* > 0.05, post hoc Dunnett's test. The generalization, however, was not complete because the gain decrease at 0.5 Hz was significantly larger than the gain decrease at the 2- and 5-Hz test frequencies. Yet even though the generalization of gain decreases was incomplete, these learned decreases generalized more than the increases in VOR gain induced with the same 0.5-Hz stimulus frequency.

Previous work has suggested that different plasticity mechanisms are engaged by high- and low-frequency training (Boyden et al. 2003; Raymond and Lisberger 1996, 1998). In

addition, it has been shown that training at higher stimulus frequencies leads to more generalization of VOR motor learning (Raymond and Lisberger 1996). Therefore, we determined whether the greater generalization of gain decreases relative to gain increases was still observed for learning induced with a higher training frequency. We trained mice at a higher head-rotation frequency of 2 Hz and found that learned decreases in the gain of the VOR still generalized more than increases in gain (Fig. 2*B*). After gain-up training, a significant gain increase was observed only at the training frequency of 2 Hz (*n* = 18 mice, *P* < 0.01, one-sample *t*-test with Bonferroni correction for multiple comparisons). In contrast, after gain-down training at a frequency of 2 Hz, significant learned
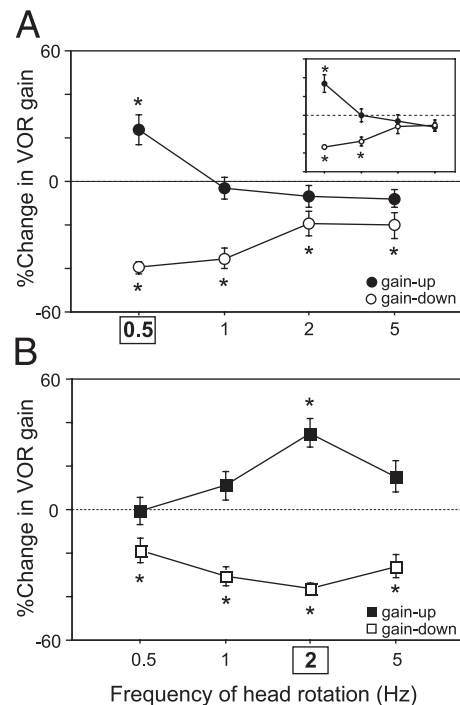

FIG. 2. Decreases in VOR gain generalize across test frequency more than increases in gain. Mean percent change in the gain of the VOR, measured with head rotation at several frequencies. *A*: changes in VOR gain induced by a training stimulus frequency of 0.5 Hz (*n* = 14 mice for gain-up, *n* = 19 for gain-down). *Inset*: a similar plot for a subset of the data (*n* = 9 for gain-up, *n* = 13 for gain-down) for which the mean percent change in VOR gain at the training frequency is similar. *B*: changes in VOR gain induced by a training stimulus frequency of 2 Hz (for gain-up: *n* = 18, for gain-down: *n* = 16 except *n* = 15 for 1 Hz). Error bars indicate SE. * indicates a significant increase or decrease in VOR gain (**P* < 0.01, one-sample *t*-test with Bonferroni correction).

decreases in gain were expressed across all frequencies tested ($n = 16$, except $n = 15$ for 1 Hz, $P < 0.01$). In addition, the percent decreases at each frequency were not significantly different from each other $F(3,59) = 2.58$, $P > 0.05$, one-factor ANOVA). Thus even at the higher training frequency of 2 Hz, more generalization was observed for decreases in VOR gain, suggesting that the difference in generalization between increases and decreases in gain is common to the potentially different sets of plasticity mechanisms mediating the effects of training at high and low frequencies.

To quantify the overall pattern of generalization, we calculated a generalization index that reflects the fraction of learning at the training frequency that is expressed, on average, at test frequencies other than the training frequency (described in METHODS). Higher index values represent more generalization. When the changes in gain across all frequencies are equal, the index is 1. When the changes in gain at test frequencies other than the training frequency are zero, the index is 0. For both lower (0.5 Hz) and higher (2 Hz) training frequencies, decreases in VOR gain were associated with significantly higher generalization index values than increases in gain (Fig. 3, *A* and *B*; $P < 0.05$, Mann-Whitney test). Thus when the overall pattern of generalization was quantified, the generalization of gain decreases was more extensive than that of gain increases regardless of the training frequency.

To confirm whether learning induced with a higher stimulus frequency does indeed generalize more than learning induced with a lower stimulus frequency, as previous work in monkeys suggested (Raymond and Lisberger 1996), we compared generalization indice x values of mice trained with a lower (0.5

Hz) and a higher (2 Hz) stimulus frequency for each direction of learning (Fig. 3, *A* and *B*). The learned increases in VOR gain induced with a 2-Hz stimulus were associated with significantly higher generalization index values than the increases induced with a 0.5-Hz stimulus ($P < 0.05$, Mann-Whitney test). In contrast, learned decreases in VOR gain induced with 0.5- and 2-Hz training stimuli resulted in comparable high levels of generalization, perhaps reflecting a ceiling effect.

In rhesus monkey, previous papers have examined the generalization of motor learning in the VOR across stimulus frequency (Lisberger et al. 1983; Raymond and Lisberger 1996). However, no direct statistical comparison of the generalization of increases and decreases in gain was performed. We calculated generalization indice x values for data published in our earlier study on rhesus macaques (originally plotted in Raymond and Lisberger 1996; Fig. 7) to determine whether our generalization index could resolve differences between increases and decreases in gain in those earlier data. We also ran generalization experiments on two additional monkeys. For four of five training frequencies tested, the generalization index for a learned decrease in VOR gain was higher than for an increase in gain (Table 2). These differences were not significant at any individual training frequency ($P > 0.12$, Mann-Whitney test). However, when experiments with the five different training frequencies were pooled, monkeys exhibited a significantly higher generalization index for decreases in gain than for increases in gain (Fig. 3*C*; $P < 0.05$). Therefore the greater generalization of learned decreases than increases in VOR gain is present across species.
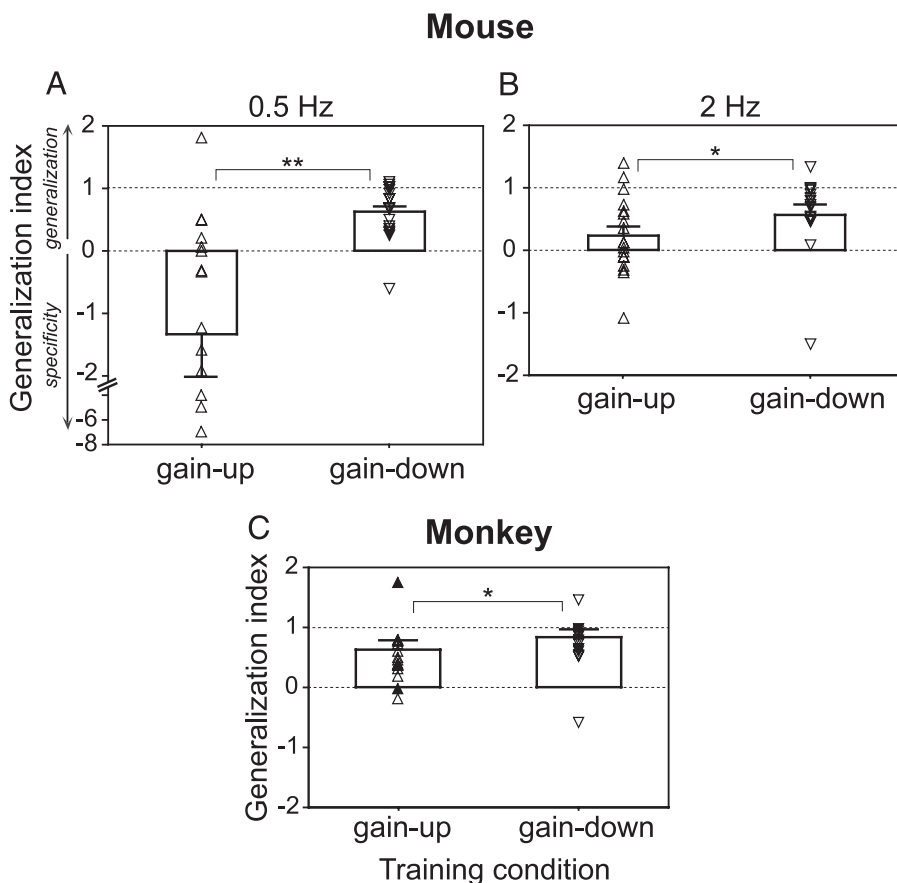

FIG. 3. Generalization produced by gain-up and gain-down training. Generalization indice x values for mice trained at 0.5 Hz (*A*) or 2 Hz (*B*). Bars indicate the mean generalization index (see METHODS) for each training condition, and error bars, SE. Individual points indicate the generalization index for individual mice. *C*: generalization indice x values for 5 rhesus macaques trained across a broad range of frequencies. Each point represents data from 1 experiment in one monkey. △ and ▽, generalization indice x values from 3 different monkeys, taken from the raw data in Raymond and Lisberger (1996), (Fig. 7) ($n = 12$ experiments for gain-up, $n = 11$ for gain-down). Data from 2 additional monkeys (▲ and ▼, $n = 3$ experiments for gain-up, $n = 3$ for gain-down) were collected for the current study. *, indicates significantly higher generalization indice x values associated with gain-down training than gain-up training (*$P < 0.05$, **$P < 0.01$, Mann-Whitney test).

TABLE 2. *Generalization indice x values for monkey experiments*

Training Frequency	n	Gain-Up	Gain-Down	P
0.5 Hz	5	0.27 ± 0.08	0.40 ± 0.27	0.12
2 Hz	2	0.62 ± 0.14	0.68 ± 0.15	0.44
5 Hz	4	1.00 ± 0.25	0.88 ± 0.19	0.56
8 Hz	2	0.37 ± 0.20	0.75 ± 0.03	0.12
10 Hz	2	0.12 ± 0.32	0.91*	0.22
Total		0.51 ± 0.12	0.66 ± 0.12	0.04

Values are means ± SE for n monkeys. P values are for Mann-Whitney tests. *$n = 1$.

The different amounts of generalization of increases and decreases in gain could not be explained by different amounts of learning in the two directions. In mice, with training at 2 Hz, decreases in gain generalized more than increases in gain even though the percent changes in gain at the training frequency were similar for the two directions (Fig. 2B, Table 1). When the training frequency was 0.5 Hz, however, the percent decrease in the VOR gain at 0.5 Hz was larger than the percent increase in VOR gain. Nevertheless, we did not find any significant correlation between the amount of learning and the amount of generalization in individual mice ($R = 0.39$ for gain-up, $R = -0.12$ for gain-down, $P > 0.18$). Furthermore, when the analysis was restricted to only those experiments with learned increases and decreases in gain of similar amplitudes at the training frequency, the result was the same. Experiments with a training frequency of 0.5 Hz were ranked by percent change in gain at the training frequency, and experiments with the largest decreases in gain and the smallest increases in gain were discarded until the mean amplitude of the percent change in gain at the training frequency was similar for both training paradigms (mean ± SE for gain-up: 34 ± 9%, $n = 9$; gain-down: $-34 ± 2$%, $n = 13$; $P > 0.05$ Mann-Whitney test; Fig. 2A, inset). Even when the percent changes in gain in the two directions were thus matched, gain decreases were still associated with a significantly higher generalization index (0.53 ± 0.13) than gain increases (-0.30 ± 0.27; $P < 0.01$, Mann-Whitney test). Thus the greater generalization of decreases in VOR gain is not the result of more learning.

Gain decreases influence VOR phase more than gain increases

Consistent with our observations regarding changes in VOR gain, changes in the timing of the VOR (as reflected by the phase) were more pronounced across test frequency after
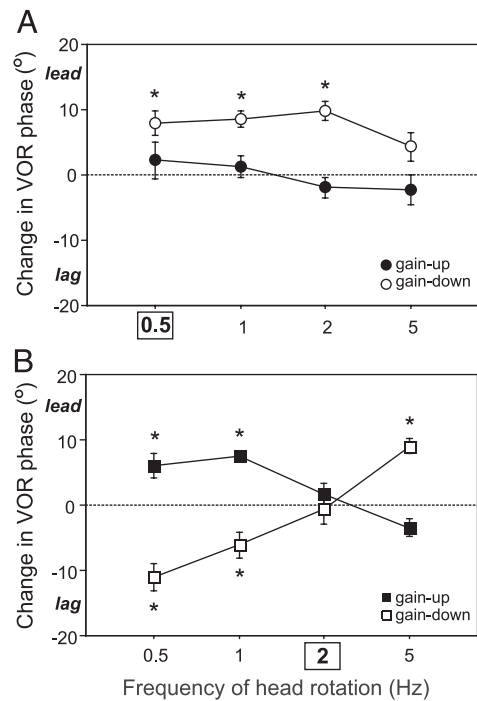

FIG. 4. Gain-down training induces larger changes in the phase of the VOR than gain-up training. Shown are the mean changes in VOR phase measured at different head rotation frequencies, after training at a frequency of 0.5 Hz (A) or 2 Hz (B). Positive values indicate an increase in phase lead of eye velocity relative to head velocity; negative values, a decrease in phase lead. Error bars indicate SE. * indicates significant changes in VOR phase ($P < 0.01$, one sample t-test with Bonferroni correction).

gain-down training than after gain-up training. Before and after training, the phase of the VOR was measured at each test frequency (Table 3). When motor learning was induced with a 0.5-Hz training stimulus, there were no significant changes in VOR phase at 0.5 Hz or any of the other test frequencies after gain-up training (Fig. 4A; $P > 0.0125$ one sample t-test with Bonferroni correction for multiple comparisons). After gain-down training, however, significant increases in phase lead were found at test frequencies of 0.5, 1, and 2 Hz. Thus gain-down training produces larger phase changes across frequency of head rotation than gain-up training.

Both gain-up and gain-down training at 2 Hz induced substantial changes in phase only at head rotation frequencies other than the training frequency. Learned changes in phase were in opposite directions for test frequencies above versus below the training frequency (Fig. 4B; $P < 0.01$). This "phase-change cross-over" has been noted in previous reports

TABLE 3. *VOR phase at each test frequency before and after training*

Test Frequency	Training Condition							
	Gain-Up at 0.5 Hz		Gain-Down at 0.5 Hz		Gain-Up at 2 Hz		Gain-Down at 2 Hz	
	Before	After	Before	After	Before	After	Before	After
0.5 Hz	27 ± 5	29 ± 5	30 ± 3	38 ± 3	28 ± 2	34 ± 3	31 ± 3	20 ± 2
1 Hz	18 ± 4	19 ± 4	23 ± 2	32 ± 2	20 ± 1	27 ± 2	22 ± 2	16 ± 3†
2 Hz	6 ± 2	4 ± 2	4 ± 2	13 ± 2	9 ± 2	10 ± 1	10 ± 2	9 ± 3
5 Hz	−13 ± 3	−15 ± 3	−8 ± 9	−4 ± 8	−13 ± 2	−17 ± 2	−13 ± 2	−4 ± 1

Values are mean VOR phase in degrees ± SE for n mice. A positive value indicates a phase lead of eye velocity relative to head velocity. $n = 14$ for gain-up at 0.5 Hz, 19 for gain-down at 0.5 Hz, 18 for gain-up at 2 Hz, 16 for gain down at 2 Hz. †$n = 15$, as in Table 1.

(Iwashita et al. 2001; Lisberger et al. 1983; Raymond and Lisberger 1996). In addition, we found that gain-down training affected the changes in phase at the nontraining frequencies more than gain-up training. After gain-down training, more test frequencies exhibited significant changes in phase than after gain-up training. Furthermore, the mean amplitude of the change in phase after gain-down training (mean absolute value = 9.4 ± 0.92°) across all test frequencies other than the training frequency was significantly larger compared with the mean after gain increases (6.8 ± 0.67°; $P < 0.05$, Mann-Whitney test). Thus for both 0.5- and 2-Hz training frequencies, the greater generalization of gain-down training across head rotation frequency is manifested not only in terms of more widely expressed changes in gain but also in terms of more widely expressed changes in phase.

DISCUSSION

We quantitatively compared the generalization of learned increases and decreases in VOR gain and found that gain decreases generalized more across head-rotation frequency than gain increases. Our data support the idea that opposite learned changes in the VOR are not exact inverses at the circuit level. If increases and decreases in VOR gain altered the same set of synapses in opposite directions, then changes in gain in both directions should generalize across frequency to a similar extent contrary to what we found. Our data thus refine the idea that opposite learned behavioral changes could be stored using bidirectional plasticity mechanisms in the cerebellum, such as LTP and LTD (Aizenman et al. 1998; Boyden and Raymond 2003; Caria et al. 2001; Coesmans et al. 2004; Jorntell and Ekerot 2002; Lev-Ram et al. 2002, 2003; Rancillac and Crepel 2004). Increases and decreases in VOR gain may be stored using bidirectional plasticity mechanisms at some sites of plasticity—indeed, modeling and behavioral studies of the cerebellum suggest that opposite behavioral changes are at least partial inverses at the circuit level (Boyden and Raymond 2003; Mauk and Ohyama 2004). However, they must violate this relationship at one or more sites of plasticity in the circuit.

Our study is the first to provide a direct, statistical comparison of the generalization of increases and decreases in the gain of the VOR, although previously published data provided some suggestion of a difference (Iwashita et al. 2001; Lisberger et al. 1983; Raymond and Lisberger 1996). The re-analysis of our earlier rhesus monkey data, combined with new rhesus experiments, revealed significantly greater generalization of decreases than increases in VOR gain, and, in mice, these differences could be resolved for individual training frequencies. The difference between increases and decreases in gain was observed whether training was done with low- or high-frequency stimuli. Thus, although different combinations of plasticity mechanisms may mediate the effects of training at low and high frequencies (Boyden et al. 2003; Raymond and Lisberger 1996, 1998), the mechanisms that underlie the greater generalization of gain decreases are common to both. Furthermore, this difference in generalization was apparent in the changes in VOR phase after gain-up and gain-down training. Gain-down, but not gain-up, training at 0.5 Hz resulted in a significant phase change across all test frequencies, and gain-down training at 2 Hz resulted in significantly larger changes in phase at nontraining frequencies than gain-up train-

ing. At the higher training frequency of 2 Hz, we observed a phase change cross-over, which had been previously hypothesized to result from the existence of multiple, independently modifiable frequency channels in the VOR circuit (Lisberger et al. 1983). In this scheme, phase changes at a given test frequency would result from the modification of frequency channels tuned for the training frequency but with broad enough tuning to also contribute to VOR performance at the test frequency. Our results suggest an extension of this model, namely that there would need to be broader tuning in the frequency channels modified by gain-down training than in the channels modified by gain-up training.

Neurons in the circuit for the VOR have been found to have different tuning properties, supporting the possibility that gain-up and gain-down training could affect differently tuned neurons. Synaptic plasticity in neurons tightly tuned for head rotation frequency may contribute selectively to gain increases, whereas changes in broadly tuned neurons may contribute selectively to gain decreases. In the vestibular nucleus, neurons exhibit a range of tuning to head-rotation frequency: some neurons show frequency selectivity, but others respond to a wide range of frequencies (Broussard et al. 2004; Dickman and Angelaki 2004). In the cerebellar cortex, the large number of cerebellar granule cells may permit each neuron to be tightly tuned for a particular context in which a movement is made (Albus 1971; Marr 1969). Therefore, one influential hypothesis has been that learning expressed in response to a narrow range of stimuli would be mediated by plasticity in the cerebellar cortex, whereas learning that generalizes broadly would be mediated by plasticity at a downstream site such as the deep cerebellar nuclei/vestibular nuclei (DCN/VN) (Thach et al. 1992). Interpreted in this framework, our current data would suggest that increases in VOR gain are more dependent on plasticity in the cerebellar cortex, whereas decreases in VOR gain are more dependent on plasticity in the vestibular nucleus. However, this "cortex-nucleus" model is at odds with several studies of cerebellum-dependent learning. Post-training lesions of the cerebellum resulted in similar effects on both learned increases and decreases in VOR gain even across studies that found different degrees of impairment (Luebke and Robinson 1994; McElligott et al. 1998; Michnovicz and Bennett 1987; Partsalis et al. 1995; Pastor et al. 1994). Furthermore, in another form cerebellum-dependent learning, eye-blink conditioning, disconnecting the cerebellar cortical input to the DCN did not degrade the specificity of learned eye blinks for the tone used in conditioning, suggesting that plasticity in the DCN/VN can support stimulus-specific learning (Ohyama et al. 2003). Thus it is unlikely that increases and decreases in VOR gain rely on entirely separate sites in the VOR circuit.

Another way in which gain-up and gain-down training may affect different sets of synapses is that gain-down training could engage plasticity mechanisms that affect signaling through synapses not activated during training, whereas gain-up training could engage plasticity mechanisms that affect only synapses activated during training. In the cerebellum, there is evidence for both synaptic and nonsynaptic plasticity that affects information processing at synapses that were not activated during the plasticity-inducing event. These include both passive spread of plasticity from activated synapses to nearby nonactivated synapses (Jacoby et al. 2001; Reynolds

and Hartell 2000; Wang et al. 2000) and changes in intrinsic excitability, which would affect the neuronal spiking response to any synaptic input (Aizenman and Linden 2000; Nelson et al. 2003; Smith and Otis 2003). Our results suggest that the plasticity mechanisms contributing to decreases in VOR gain may be less synapse-specific than those contributing to increases in gain.

The idea that changes at different synapses may contribute to oppositely directed motor learning in the VOR is consistent with a number of previous findings. Across multiple stimulus dimensions, there is a consistent pattern of greater generalization of learning for decreases versus increases in VOR gain. Studies have shown that gain decreases generalize more than gain increases when tested at head tilts different from those used during training (Yakushin et al. 2000, 2003). In addition, gain decreases induced by visual stimuli delivered to a single eye are expressed in the movements of the untrained eye, whereas gain increases do not generalize to the other eye (McElligott and Wilson 2001). Furthermore, the concept that opposite learned changes in behavior are stored with distributed changes that are not exact inverses at the circuit level is consistent with studies of other cerebellum-dependent learning tasks, such as extinction and savings of eye-blink conditioning (Mauk and Ohyama 2004; Perrett et al. 1993), and saccadic adaptation, in which learned increases and decreases in movement amplitude possess different behavioral properties (for review, see Hopp and Fuchs 2004). Further studies of these differences between opposite learned behavioral changes should yield insights into the neural mechanisms that iteratively refine learned movements over time.

REFERENCES

Aizenman CD and Linden DJ. Rapid, synaptically driven increases in the intrinsic excitability of cerebellar deep nuclear neurons. Nat Neurosci 3: 109–111, 2000.

Aizenman CD, Manis PB, and Linden DJ. Polarity of long-term synaptic gain change is related to postsynaptic spike firing at a cerebellar inhibitory synapse. Neuron 21: 827–835, 1998.

Albus J. A theory of cerebellar function. Math Biosci 10: 25–61, 1971.

Boyden ES, Chatila T, and Raymond JL. Motor memories in the vestibulo-ocular reflex of CaMKIV knockout mice. Soc Neurosci Abstr 73.18, 2003.

Boyden ES, Katoh A, and Raymond JL. Cerebellum-dependent learning: the role of multiple plasticity mechanisms. Annu Rev Neurosci 27: 581–609, 2004.

Boyden ES and Raymond JL. Active reversal of motor memories reveals rules governing memory encoding. Neuron 39: 1031–1042, 2003.

Broussard DM, Priesol AJ, and Tan Y-F. Asymmetric responses to rotation at high frequencies in central vestibular neurons of the alert cat. Brain Res 1005: 137–153, 2004.

Caria MA, Melis F, Solinas A, Tavera C, and Mameli O. Frequency-dependent LTP/LTD in guinea pig Deiters' nucleus. Neuroreport 12: 2353–2358, 2001.

Carter TL and McElligott JG. Cerebellar NMDA receptor antagonism by AP5 blocks vestibulo-ocular reflex adaptation in the goldfish. Soc Neurosci Abstr 21: 271, 1995.

Coesmans M, Smitt PA, Linden DJ, Shigemoto R, Hirano T, Yamakawa Y, van Alphen AM, Luo C, van der Geest JN, Kros JM, Gaillard CA, Frens MA, and de Zeeuw CI. Mechanisms underlying cerebellar motor deficits due to mGluR1-autoantibodies. Ann Neurol 53: 325–336, 2003.

Coesmans M, Weber JT, De Zeeuw CI, and Hansel C. Bidirectional parallel fiber plasticity in the cerebellum under climbing fiber control. Neuron 44: 691–700, 2004.

Cohen MR, Meissner GW, Schafer RJ, and Raymond JL. Reversal of motor learning in the vestibulo-ocular reflex in the absence of visual input. Learn Mem 11: 559–565, 2004.

De Zeeuw CI, Hansel C, Bian F, Koekkoek SK, van Alphen AM, Linden DJ, and Oberdick J. Expression of a protein kinase C inhibitor in Purkinje cells blocks cerebellar LTD and adaptation of the vestibulo-ocular reflex. Neuron 20: 495–508, 1998.

Dickman JD and Angelaki DE. Dynamics of vestibular neurons during rotational motion in alert rhesus monkeys. Exp Brain Res 155: 91–101, 2004.

Dunnett CW. A multiple comparison procedure for comparing several treatments with a control. J Am Statist Assoc 50: 1096–1121, 1955.

Eggers SD, De Pennington N, Walker MF, Shelhamer M, and Zee DS. Short-term adaptation of the VOR: non-retinal-slip error signals and saccade substitution. Ann NY Acad Sci 1004: 94–110, 2003.

Feil R, Hartmann J, Luo C, Wolfsgruber W, Schilling K, Feil S, Barski JJ, Meyer M, Konnerth A, De Zeeuw CI, and Hofmann F. Impairment of LTD and cerebellar learning by Purkinje cell-specific ablation of cGMP-dependent protein kinase I. J Cell Biol 163: 295–302, 2003.

Harrod CG and Baker JF. The vestibulo ocular reflex (VOR) in otoconia deficient head tilt (het) mutant mice versus wild type C57BL/6 mice. Brain Res 972: 75–83, 2003.

Hopp JJ and Fuchs AF. The characteristics and neuronal substrate of saccadic eye movement plasticity. Prog Neurobiol 72: 27–53, 2004.

Ito M. Cerebellar control of the vestibulo-ocular reflex–around the flocculus hypothesis. Annu Rev Neurosci 5: 275–296, 1982.

Ito M, Shiida T, Yagi N, and Yamamoto M. The cerebellar modification of rabbit's horizontal vestibulo-ocular reflex induced by sustained head rotation combined with visual stimulation. Proc Jpn Acad 50: 85–89, 1974.

Iwashita M, Kanai R, Funabiki K, Matsuda K, and Hirano T. Dynamic properties, interactions and adaptive modifications of vestibulo-ocular reflex and optokinetic response in mice. Neurosci Res 39: 299–311, 2001.

Jacoby S, Sims RE, and Hartell NA. Nitric oxide is required for the induction and heterosynaptic spread of long-term potentiation in rat cerebellar slices. J Physiol 535: 825–839, 2001.

Jorntell H and Ekerot CF. Reciprocal bidirectional plasticity of parallel fiber receptive fields in cerebellar Purkinje cells and their afferent interneurons. Neuron 34: 797–806, 2002.

Katoh A, Kitazawa H, Itohara S, and Nagao S. Dynamic characteristics and adaptability of mouse vestibulo-ocular and optokinetic response eye movements and the role of the flocculo-olivary system revealed by chemical lesions. Proc Natl Acad Sci USA 95: 7705–7710, 1998.

Koekkoek SK, van Alphen AM, van den Burg J, Grosveld F, Galjart N, and De Zeeuw CI. Gain adaptation and phase dynamics of compensatory eye movements in mice. Genes Funct 1: 175–190, 1997.

Kuki Y, Hirata Y, Blazquez PM, Heiney SA, and Highstein SM. Memory retention of vestibuloocular reflex motor learning in squirrel monkeys. Neuroreport 15: 1007–1011, 2004.

Lev-Ram V, Mehta SB, Kleinfeld D, and Tsien RY. Reversing cerebellar long-term depression. Proc Natl Acad Sci USA 100: 15989–15993, 2003.

Lev-Ram V, Wong ST, Storm DR, and Tsien RY. A new form of cerebellar long-term potentiation is postsynaptic and depends on nitric oxide but not cAMP. Proc Natl Acad Sci USA 99: 8389–8393, 2002.

Li J, Smith SS, and McElligott JG. Cerebellar nitric oxide is necessary for vestibulo-ocular reflex adaptation, a sensorimotor model of learning. J Neurophysiol 74: 489–494, 1995.

Lisberger SG, Miles FA, and Optican LM. Frequency-selective adaptation: evidence for channels in the vestibulo-ocular reflex? J Neurosci 3: 1234–1244, 1983.

Luebke AE and Robinson DA. Gain changes of the cat's vestibulo-ocular reflex after flocculus deactivation. Exp Brain Res 98: 379–390, 1994.

Marr D. A theory of cerebellar cortex. J Physiol 202: 437–470, 1969.

Mauk MD and Ohyama T. Extinction as new learning versus unlearning: considerations from a computer simulation of the cerebellum. *Learn Mem* 11: 566–571, 2004.

McElligott JG, Beeton P, and Polk J. Effect of cerebellar inactivation by lidocaine microdialysis on the vestibuloocular reflex in goldfish. *J Neurophysiol* 79: 1286–1294, 1998.

McElligott JG and Wilson A. Monocular vestibulo-ocular reflex (VOR) adaptation in the goldfish. *Soc Neurosci Abstr* 403.1, 2001.

Michnovicz JJ and Bennett MV. Effects of rapid cerebellectomy on adaptive gain control of the vestibulo-ocular reflex in alert goldfish. *Exp Brain Res* 66: 287–294, 1987.

Miles FA and Eighmy BB. Long-term adaptive changes in primate vestibuloocular reflex. I. Behavioral observations. *J Neurophysiol* 43: 1406–1425, 1980.

Nelson AB, Krispel CM, Sekirnjak C, and du Lac S. Long-lasting increases in intrinsic excitability triggered by inhibition. *Neuron* 40: 609–620, 2003.

Ohyama T, Nores WL, and Mauk MD. Stimulus generalization of conditioned eyelid responses produced without cerebellar cortex: implications for plasticity in the cerebellar nuclei. *Learn Mem* 10: 346–354, 2003.

Partsalis AM, Zhang Y, and Highstein SM. Dorsal Y group in the squirrel monkey. II. Contribution of the cerebellar flocculus to neuronal responses in normal and adapted animals. *J Neurophysiol* 73: 632–650, 1995.

Pastor AM, de la Cruz RR, and Baker R. Cerebellar role in adaptation of the goldfish vestibuloocular reflex. *J Neurophysiol* 72: 1383–1394, 1994.

Perrett SP, Ruiz BP, and Mauk MD. Cerebellar cortex lesions disrupt learning-dependent timing of conditioned eyelid responses. *J Neurosci* 13: 1708–1718, 1993.

Rambold H, Churchland A, Selig Y, Jasmin L, and Lisberger SG. Partial ablations of the flocculus and ventral paraflocculus in monkeys cause linked deficits in smooth pursuit eye movements and adaptive modification of the VOR. *J Neurophysiol* 87: 912–924, 2002.

Rancillac A and Crepel F. Synapses between parallel fibres and stellate cells express long-term changes in synaptic efficacy in rat cerebellum. *J Physiol* 554: 707–720, 2004.

Raymond JL and Lisberger SG. Behavioral analysis of signals that guide learned changes in the amplitude and dynamics of the vestibulo-ocular reflex. *J Neurosci* 16: 7791–7802, 1996.

Raymond JL and Lisberger SG. Neural learning rules for the vestibulo-ocular reflex. *J Neurosci* 18: 9112–9129, 1998.

Reynolds T and Hartell NA. An evaluation of the synapse specificity of long-term depression induced in rat cerebellar slices. *J Physiol* 527 Pt 3: 563–577, 2000.

Robinson DA. Adaptive gain control of vestibuloocular reflex by the cerebellum. *J Neurophysiol* 39: 954–969, 1976.

Smith SL and Otis TS. Persistent changes in spontaneous firing of purkinje neurons triggered by the nitric oxide signaling cascade. *J Neurosci* 23: 367–372, 2003.

Stahl JS, van Alphen AM, and De Zeeuw CI. A comparison of video and magnetic search coil recordings of mouse eye movements. *J Neurosci Methods* 99: 101–110, 2000.

Thach WT, Goodkin HP, and Keating JG. The cerebellum and the adaptive coordination of movement. *Annu Rev Neurosci* 15: 403–442, 1992.

van Alphen AM, Stahl JS, and De Zeeuw CI. The dynamic characteristics of the mouse horizontal vestibulo-ocular and optokinetic response. *Brain Res* 890: 296–305, 2001.

Wallman J, Velez J, Weinstein B, and Green AE. Avian vestibuloocular reflex: adaptive plasticity and developmental changes. *J Neurophysiol* 48: 952–967, 1982.

Wang SS, Khiroug L, and Augustine GJ. Quantification of spread of cerebellar long-term depression with chemical two-photon uncaging of glutamate. *Proc Natl Acad Sci USA* 97: 8635–8640, 2000.

Yakushin SB, Raphan T, and Cohen B. Context-specific adaptation of the vertical vestibuloocular reflex with regard to gravity. *J Neurophysiol* 84: 3067–3071, 2000.

Yakushin SB, Raphan T, and Cohen B. Gravity-specific adaptation of the angular vestibuloocular reflex: dependence on head orientation with regard to gravity. *J Neurophysiol* 89: 571–586, 2003.