

# Memory of Learning Facilitates Saccadic Adaptation in the Monkey

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A motor learning mechanism called saccadic adaptation ensures accuracy of saccades throughout life despite growth, aging, and some pathologies of the oculomotor plant or nervous system. The present study investigates effects of preceding adaptation on the speed of subsequent adaptation during single experiments. Adaptive changes in gain (movement size divided by target eccentricity) were induced by intrasaccadic step (ISS) of the target. After the gain was altered (control block), we reversed the direction of ISS to bring the gain back to  $\sim 1.0$  (recovery). We then reversed ISS direction again to induce another adaptation (test block). Analyses revealed that the gain changed at a higher rate in the early part of test adaptation than in the corresponding part of control. After  $\sim 100$ – $300$  saccades in the test block, adaptation slowed down. The gain value at which adaptation slowed was correlated with the gain achieved in the control. We further examined effects of a 30 min intervention inserted between recovery and test blocks. When zero-visual-error trials ( $\sim 700$  saccades) were repeated during this period, the rate of test adaptation was similar to that of control. In contrast, when the animal was deprived of visual inputs during this period, test adaptation was still influenced by preceding learning. We conclude that a memory of previous learning remains during recovery to facilitate subsequent adaptation and that such a memory does not disappear merely with time but is erased actively by repeated zero-error movements. Our results, which cannot be explained by a single mechanism, suggest that the saccadic system is equipped with more than one plasticity process.

**Key words:** saccadic adaptation; memory; retention; erasure; facilitated learning; monkey

## Introduction

Saccades are rapid eye movements that shift the direction of gaze. They are so fast, and therefore brief, that visual feedback cannot be used to guide their trajectory. Therefore, without some error-correcting mechanism, alterations of mechanical properties of the oculomotor plant, for example, would inevitably lead to the generation of inaccurate saccades. In reality, saccades remain accurate throughout life despite growth, aging, and some pathologies of the plant or the nervous system. This is because the saccadic gain (saccade amplitude divided by target eccentricity) is constantly recalibrated by a learning mechanism called saccadic adaptation (for review, see Hopp and Fuchs, 2004). If saccades consistently overshoot the target, their amplitude gradually decreases. If they consistently fall short, their size gradually increases. There is good evidence that saccadic adaptation is a form of motor learning driven by visual error immediately after the end of saccades (Wallman and Fuchs, 1998; Shafer et al., 2000; Noto and Robinson, 2001).

Characteristics of saccadic adaptation in the monkey, as well

as in humans, have been studied extensively. Adaptation elicited by an intrasaccadic step (ISS) of the target (McLaughlin, 1967) has an approximately exponential course with a rate constant of 100–800 saccades (Straube et al., 1997; Scudder et al., 1998). The amount and rate of adaptation are highly variable across animals and also across experiments in the same animal (Fuchs et al., 1996; Straube et al., 1997). Adaptation is fairly specific to the amplitude and direction of adapted saccades and does not generalize fully to those with different vectors (Straube et al., 1997; Wallman and Fuchs, 1998; Noto et al., 1999; Watanabe et al., 2000). Finally, repeated exposures to the same paradigm over days (i.e., practice) do not cause faster or greater changes in saccade amplitude (Straube et al., 1997).

It is known that eye blink conditioning, another example of motor learning, exhibits a phenomenon called savings. Re-exposure to paired stimuli after extinction induces reacquisition that is much faster than original acquisition (Frey and Ross, 1968; Napier et al., 1992), indicating that a memory of learning is formed to facilitate subsequent learning. We wondered whether the saccadic system indeed lacks such a memory mechanism. One factor that might have masked possible effects of practice in saccadic adaptation is large day-to-day variability in its speed and magnitude (Fuchs et al., 1996; Straube et al., 1997). In the present study, we attempted to clarify whether repeated induction of adaptation within single experimental sessions affects the course of learning. We addressed this question by using the double reversal paradigm, a series of three alternating gain changes, which eliminates part of the complications related to the variability. Results

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show that saccadic adaptation occurs faster when repeated within single experiments, suggesting the storage of learning history. The present study also gives some insights into the erasure process of this memory of adaptation. Preliminary accounts of the present study have been reported previously (Kojima et al., 2002, 2003a,b).

## Materials and Methods

### Surgery

Two rhesus monkeys (*Macaca mulatta*, male; 4.5 and 6.8 kg) were prepared for eye movement recording by the magnetic search coil method (Fuchs and Robinson, 1966). Anesthesia was introduced with ketamine hydrochloride (15–20 mg/kg, i.m.) and maintained by inhalation of isoflurane. A coil of Teflon-coated stainless steel wire was implanted beneath the insertions of the four recti of one eye to measure eye movements. Stainless steel tubes were attached to the skull with bone screws and dental acrylic. During experiments, rigid metal rods were inserted into the tubes for painless immobilization of the animal's head. After surgery, antibiotics were given intramuscularly for 5 d to prevent infection. After recovery from the surgery, the monkeys were trained to follow a small jumping target (a red spot displayed on a video monitor) with their eye. All surgical and experimental protocols were approved by the University of Tsukuba Animal Care and Use Committee.

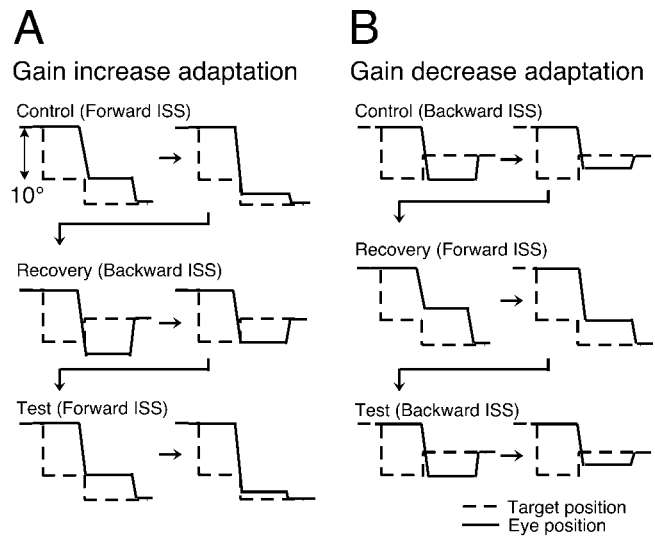
During recording sessions, the monkey sat in a primate chair in a darkened booth with its head restrained. The animal was required to make saccades toward a target spot ( $\sim 0.3^\circ$ ) presented on a monitor screen, which was 35.5 cm from its eyes. Whenever the monkey maintained its eye position within  $1.5^\circ$  of the target continuously for 0.8–1.0 sec, the target jumped to another position and the animal was rewarded with a small amount of apple juice. The animal followed the target spot reliably for several thousand trials in a single experiment, which lasted 1–1.5 hr.

### Behavioral paradigms

**Induction of saccadic amplitude adaptation.** Adaptive changes in saccade amplitude were induced by a conventional intrasaccadic target step paradigm (McLaughlin, 1967). The animal was exposed to a target that jumped along the horizontal meridian and then, during the saccade, stepped backward or forward by a fixed percentage of the initial step (ISS). This created a visual error at the end of the movement as if the saccade had been too large or too small, requiring the animal to make a corrective saccade to catch the target. This procedure, when repeated over several hundreds of movements, gradually decreased or increased the saccade amplitude. We adapted saccades that were elicited by horizontal  $10^\circ$  steps of the target. Only saccades in one direction (either left or right) were adapted in each experiment. The target stepped pseudorandomly in either direction within a movement range of  $40^\circ$  (within  $20^\circ$  of the straight ahead position).

**Double reversal paradigm.** In 30 experiments, we induced a series of three alternating gain changes by reversing the polarity of visual error twice during ongoing adaptation. After collecting 100–400 preadaptation saccades to horizontal steps of the target, we started the first block of adaptation session by subjecting the animal to 35% forward or backward ISS (control block). When the gain was altered by  $\sim 0.1$ – $0.2$  after 400–800 saccades, the direction of ISS was reversed to bring the gain back to the preadaptation value, i.e.,  $\sim 1.0$  (recovery block). We then reversed the ISS direction again and induced a gain change using the ISS of the same size as in the control block. This last block of the session (test block) contained a larger number of saccades than the control block. Figure 1 schematically illustrates these procedures for gain increase (A) and gain decrease (B) adaptation. These paradigms will be called the standard gain-increase or gain-decrease paradigms as opposed to their modifications described below.

**Modified paradigms.** In 44 experiments, we subjected the animal to one of five modified versions of the standard paradigm. In the “zero-error” paradigm, we discontinued the ISS of the target when the gain returned to  $\sim 1.0$  at the end of recovery block and required the animal to continue to track the target for 30 min. During this period, saccadic gain was kept at  $\sim 1.0$ , with the average end point error nearly zero. We then resumed



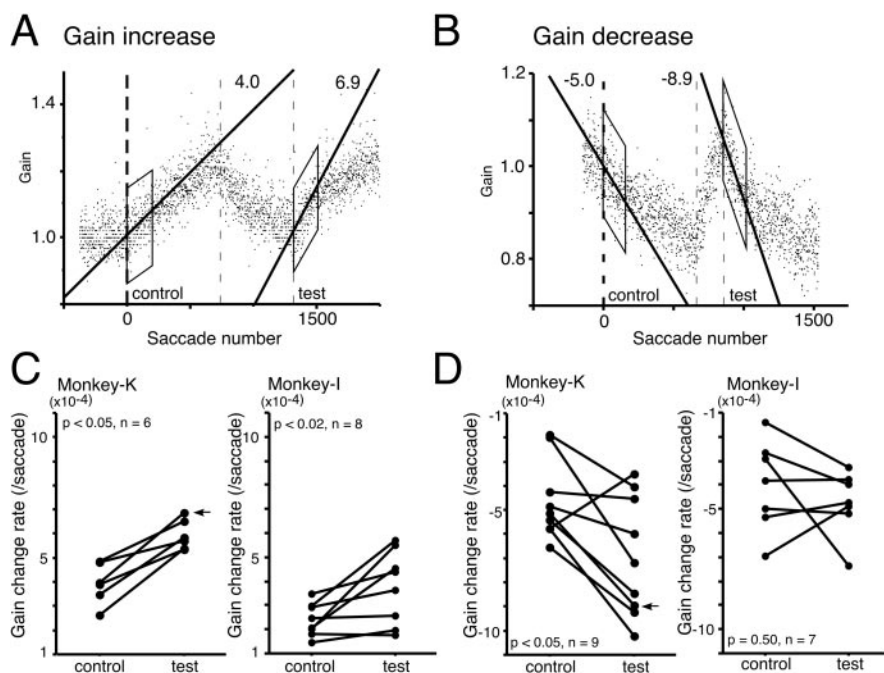
Type of experiment	Direction of intrasaccadic step					Number of experiments	
	Pre	Control	Recovery	Zero/Dark	Test	Monkey K	Monkey I
standard gain increase	no ISS	forward	backward	-	forward	6	8
standard gain decrease	no ISS	backward	forward	-	backward	9	7
zero-error gain increase	no ISS	forward	backward	no ISS	forward	4	4
zero-error gain decrease	no ISS	backward	forward	no ISS	backward	5	4
dark gain increase	no ISS	forward	backward	no target	forward	5	4
dark gain decrease	no ISS	backward	forward	no target	backward	9	4
dark No-ISS gain increase	no ISS	forward	backward	no target	no ISS	3	2

**Figure 1.** A, B, Illustration of standard double-reversal paradigm for gain-increase adaptation (A) and gain-decrease adaptation (B). First, adaptation was induced by 35% forward (A) or 35% backward (B) ISS (control block). The direction of ISS was reversed to bring the gain back to  $\sim 1.0$  (recovery block). We then reversed the ISS direction again and induced a gain change (test block) using the ISS of the same size and direction as in the control block. We adapted saccades elicited by horizontal  $10^\circ$  target steps in one direction. C, Summary of seven paradigms used in the present study.

the ISS with the same size and direction (test block) as in the control adaptation. In the dark paradigm, we placed the animal in the dark by gently covering its head and the top portion of the primate chair with a large piece of black cloth. We kept the animal alert by making noises or tapping the booth and continuously monitored the monkey's eye movements. After 30 min, we removed the cloth and subjected the monkey again to the ISS with the same size and direction as in the control adaptation. In five gain-increase experiments, we used the dark no-ISS paradigm, in which target steps were not followed by ISS during the test block. The seven paradigms used in the present study are summarized in Figure 1C.

### Analysis

Horizontal and vertical components of eye position and target position were digitized on-line at 1 kHz and stored on a disk with an interface (Micro1401; Cambridge Electronics Design, Cambridge, UK). Data were analyzed off-line on a computer (Power Macintosh G4; Apple Computers, Cupertino, CA) using homemade programs that ran on Spike2 software (Cambridge Electronics Design). Saccade onset and end were defined by an eye velocity threshold criterion of  $20^\circ/\text{sec}$ . Targeting saccades elicited by an initial (not intrasaccadic) target step were selected for analysis. The computer stored parameters of saccades and target steps (i.e., positions, timings, and peak eye velocities). These parameters were exported to statistics programs (StatView or JMP; SAS Institute, Cary, NC) to calculate other saccade characteristics. The target eccentricity is defined as the difference between the target and the eye positions at the saccade onset. The gain of a saccade is defined as the ratio of the horizontal saccade size to the horizontal target eccentricity. Saccades with laten-



**Figure 2.** *A*, Gain change profile of a gain-increase experiment with linear regression lines fitted for the first 150 saccades of control and test blocks. The slope of test adaptation was larger than that of control. *B*, Gain change profile of a gain-decrease experiment with similar regression lines. Note the steeper slope of test adaptation. *C*, *D*, Summaries of gain change rate for gain-increase experiments (*C*) and gain-decrease experiments (*D*). Test adaptation has a significantly higher rate than control adaptation except for gain-decrease experiments in monkey I. Data shown in *A* and *B* are indicated by small horizontal arrows in *C* and *D*, respectively.

cies <60 msec were regarded as anticipatory and removed. We also removed saccades with gains >2.0 or <0.35. The number of these eliminated saccades was ~20–30, <2% of the total number of saccades (>2500) in the relevant direction. For each experiment, we plotted the saccadic gain as a function of the accumulated number of saccades during which the target was stepped. The rate of adaptation in the control and test blocks was estimated by the slope of linear regression line fitted for 150 consecutive saccades.

## Results

Data were collected from a total of 74 experiments using two animals. In 30 experiments, we used standard double-reversal paradigms (see Materials and Methods) to compare the courses of control and test adaptations. The start gain difference had a mean of  $0.012 \pm 0.047$  ( $n = 30$ ), indicating that the two adaptations started with similar gains. In the remaining 44 experiments, we subjected the monkeys to either the zero-error paradigm or dark paradigm.

### Standard double-reversal paradigms

#### *Faster learning in the initial part of test adaptation*

In many experiments, the initial portion of test adaptation appeared to exhibit a faster gain change than that of control adaptation. Figure 2*A* shows the gain change profile of a standard gain-increase experiment, in which the gain was increased to ~1.2, decreased to ~1.0, and then increased again with 35% ISS. Note that gain changes faster in the initial part of the test block than in the initial part of the control block. We observed similar accelerated adaptation also in gain-decrease experiments, an example of which is shown in Figure 2*B*. Here, the gain was decreased to ~0.85, brought back to ~1.0, and decreased again with 35% ISS. The initial fall of the saccadic gain in the test is steeper than that in the control adaptation.

To test statistically whether there is a significant difference in the rate of adaptation between the test and control blocks, we chose the appropriate number of data points that could be used for all experiments and also was adequate for estimation of the adaptation rate. For this, we made a compromise. The faster gain change appeared to occur over the initial ~100–300 saccades in the test block. Therefore, to estimate the adaptation rate in this facilitated portion of test adaptation, it is desirable to take a small number of saccades. In contrast, because of saccade-to-saccade variability in gain, estimation would be more reliable for increasing number of saccades. We plotted the slope of the linear regression line as a function of the number of data points (20–300) for each experiment. In many experiments, variation in the slope increased markedly as the number of saccades decreased below ~100, suggesting that reliable estimation of the rate of adaptation requires more data points. Based on these considerations, we regarded the gain change rate obtained for the initial 150 saccades as a representative value for each block.

For estimation of the rate of adaptation, linear regression lines are fitted for the control and test blocks in Figure 2*A*.

Test adaptation shows a larger slope ( $6.9 \times 10^{-4}$ /saccade) than the control ( $4.0 \times 10^{-4}$ /saccade). Figure 2*C* shows gain change rates for all gain-increase experiments in monkey K ( $n = 6$ ) and monkey I ( $n = 8$ ). In both animals, the test adaptation had a significantly larger rate than the control adaptation (Wilcoxon signed rank test;  $p < 0.05$ ). The ratio of adaptation rate, the test rate divided by the control rate, had a mean of  $1.56 \pm 0.32$  and  $1.59 \pm 0.62$  for monkeys K and I, respectively. This is an average increase of ~60% over the control rate. An example of the fitted regression lines for gain-decrease experiments is shown in Figure 2*B*, the slope being  $-8.9 \times 10^{-4}$ /saccade and  $-5.0 \times 10^{-4}$ /saccade in the test and control, respectively. Figure 2*D* summarizes the results of gain-decrease experiments. In monkey K (Fig. 2*D*, left), the absolute value of the gain change rate in the test was significantly larger than that in the control adaptation (Wilcoxon signed rank test;  $p < 0.05$ ). The ratio of adaptation rate had a mean of  $1.68 \pm 0.85$  ( $n = 9$ ), indicating an average increase in adaptation rate of 70% over the control rate. In monkey I (Fig. 2*D*, right), there was no significant difference in gain change rate between the test and control ( $p = 0.50$ ). However, the ratio of adaptation rate exhibited a mean of  $1.42 \pm 0.73$  ( $n = 7$ ).

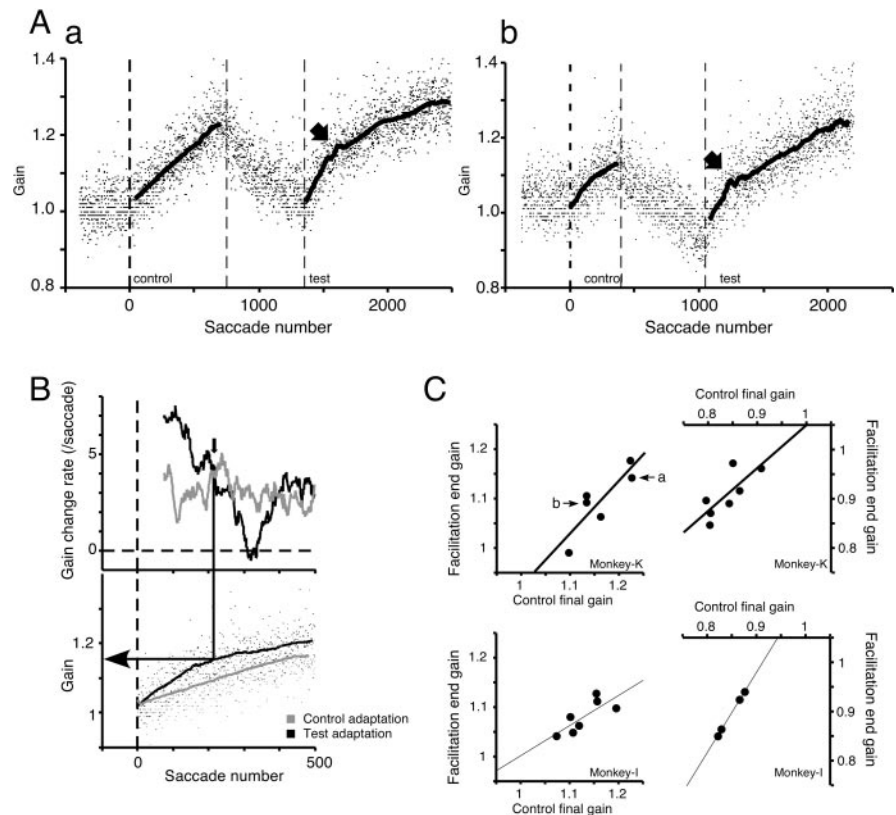
The size of the increase in adaptation rate was variable across experiments as seen in Figure 2*C* and *D*. The test-control difference in the absolute value of rate of adaptation ranged widely from  $-2.26$  to  $5.19$  ( $\times 10^{-4}$ /saccade) with a mean of  $1.62 \pm 1.81$  ( $\times 10^{-4}$ /saccade) ( $n = 30$ ; positive values indicate faster test adaptation). Test adaptation was faster than control adaptation in 25 experiments and slower in the remaining five experiments. The test-control ratio of adaptation rates ranged from 0.61 to 3.61 with a mean of  $1.57 \pm 0.66$  ( $n = 30$ ).

### Slowing of adaptation

The results described above indicate that adaptation occurs faster when repeated at a short interval. This increased adaptation rate was observed only over the initial ~100–300 saccades and did not continue throughout test adaptation. The saccade number at which this facilitation ended appeared to vary across experiments. We wondered what might determine or influence the end of the faster adaptation. To visualize the course of adaptation, we fit data points with a variable span smoother (Supersmoother in StatView, Cary, NC). In several experiments, the facilitated portion appeared to end so abruptly as to exhibit an inflection on the smoothed curve, as exemplified by two gain-increase experiments in Figure 3A (arrows). The control adaptation resulted in a higher gain in Figure 3Aa than in Ab. Correspondingly, the inflection in the test adaptation occurred at a higher gain in Figure 3Aa than it did in Ab. This suggested a possibility that the gain at the end of facilitation (facilitation end gain) was positively correlated to the gain at the end of control adaptation (control final gain).

To test this possibility, we had to define the control final gain and facilitation end gain. We calculated the control final gain as the average of gains of the last 50 saccades in the control block. To calculate the facilitation end gain, we used the following procedures. As a measure of “instantaneous” rate of adaptation, we set a window of 150 saccades and calculated the slope of the linear regression line for the window. We started with the first 150 saccades and assigned the slope of a line fit to these saccades to the seventy-fifth saccade. We then moved the window by one saccade, calculated the slope for the next 150 points (second to 151), and assigned it to the seventy-sixth saccade. This procedure was repeated until a slope value was assigned to the 300th saccade. We then compared such slope profiles of the control and test adaptations. Figure 3B (top) shows an example of slope profiles calculated for a gain-increase experiment. At the beginning of the block, the test adaptation (Fig. 3B, black line) has a larger slope than the control adaptation (gray line). The slope of the test adaptation then gradually decreases to cross the control profile between saccades 218 and 219. We regarded this crossing point, where the rate of test adaptation fell below that of control adaptation, as the facilitation end. The facilitation end gain for this particular experiment was then obtained as an average of gains of 50 consecutive saccades distributed equally before and after the facilitation end (i.e., 194–243). As shown in Figure 3B (bottom), the crossed trace method appears to pick a reasonable, if not unique, point that is not too deviated from the inflection on the smoothing curve (black line).

We performed a similar analysis for experiments in which the slope for the initial 150 saccades of the test block was steeper than that of the control block (Fig. 2C,D). In all such experiments (13 of 14 gain-increase and 11 of 16 gain-decrease), the slope profile



**Figure 3.** Slowing of adaptation. *A*, Gain change profiles for two gain-increase experiments, in which accelerated adaptation appears to end abruptly to produce inflections (arrows) on the fitted curves. Control adaptation in *Aa* exhibits a higher gain than that in *Ab*. Correspondingly, the gain at facilitation end in test adaptation in *Aa* is higher than in *Ab*. *B*, Estimation of facilitation end gain for the experiment in *Aa*. Profile of instantaneous rate of gain change, slopes of linear regression line for 150 saccade moving window plotted as a function of saccade number (top). Slope of test adaptation (black line) was initially larger but decreases beyond that of control adaptation (gray line). The crossing point was regarded as facilitation end. Facilitation end gain was calculated as the average gain of 50 saccades distributed about facilitation end (bottom). *C*, Relationship between facilitation end gain and control final gain. There was a significant positive correlation between the two parameters both in gain-increase adaptation (left) with  $p < 0.05$ ,  $r = 0.86$ , and  $n = 6$  for monkey K and  $p < 0.05$ ,  $r = 0.77$ , and  $n = 7$  for monkey I, and in gain-decrease adaptation (right) with  $p < 0.05$ ,  $r = 0.76$ , and  $n = 7$  for monkey K and  $p < 0.01$ ,  $r = 1.00$ , and  $n = 4$  for monkey I. Data shown in *Aa* and *Ab* are indicated by small horizontal arrows (labeled *a* and *b*, respectively) in *C*.

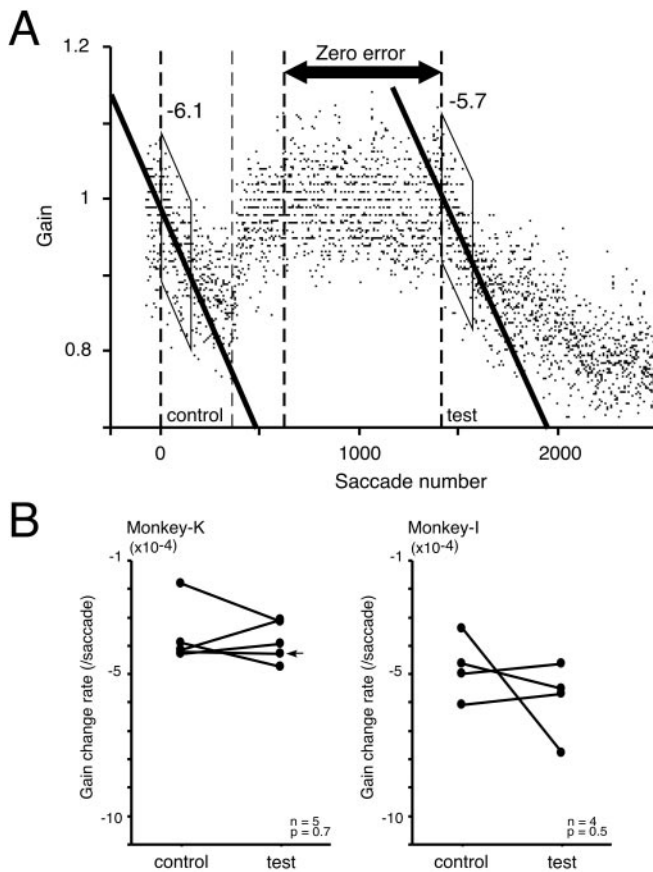
of test adaptation decreased below that of control adaptation. After its initial high rate, test adaptation proceeded at a rate lower than that of the control adaptation. The saccade number at which the two curves crossed ranged from 82 to 291 (mean,  $141.1 \pm 45.8$ ) in gain-increase experiments and 82–331 (mean,  $213.0 \pm 89.7$ ) in gain-decrease experiments. Finally, we plotted the facilitation end gain, calculated as described above, against control final gain (Fig. 3C). There was a significant positive correlation between the two parameters both for gain-increase and gain-decrease adaptations in each monkey ( $p < 0.05$ ).

### Modified double-reversal paradigms

To further characterize the facilitated learning described above, we investigated the course of adaptation in zero-error and dark paradigms (see Materials and Methods). For the ease of description, results obtained in gain-decrease experiments are presented first.

#### Gain-decrease experiments with zero-error paradigm

In nine gain-decrease experiments, we subjected the animal to  $10^\circ$  target steps not coupled with ISS when the saccadic gain returned to  $\sim 1.0$  by the recovery adaptation. Figure 4A shows the result of one experiment. The gain was first reduced to  $\sim 0.85$  by



**Figure 4.** *A*, Gain change profile of a zero-error gain-decrease experiment with linear regression lines fitted for the first 150 saccades of the control and test blocks. *B*, Summary of all experiments with this paradigm in two monkeys. There was no significant difference in gain change rate between the test and control. Data shown in *A* is indicated by a small horizontal arrow in *B* (monkey K).

backward ISS and brought back to  $\sim 1.0$  by forward ISS. We then discontinued the ISS and required the monkey to make normometric saccades in the adapted direction for 30 min ( $\sim 790$  saccades). After this zero-error block, the gain was again decreased by backward ISS. As shown by the regression lines in Figure 4*A*, their slopes were similar for the test and control ( $-5.7 \times 10^{-4}$ /saccade and  $-6.1 \times 10^{-4}$ /saccade, respectively). Figure 4*B* shows the results of all nine experiments for the two monkeys. The length of the zero-error block was fixed at 30 min across these experiments. The number of zero-error saccades made in the relevant direction during this block ranged from 574 to 877. There was no significant difference in gain change rate between the test and control for each animal as well as for the two animals combined (Wilcoxon signed rank test;  $p = 0.70$ ,  $n = 5$  in monkey K;  $p = 0.50$ ,  $n = 4$  in monkey I;  $p = 0.44$ ,  $n = 9$  in both animals). The results indicate that the test adaptation is not accelerated after hundreds of normometric saccades.

#### Gain-decrease experiments with dark paradigm

We then examined the effect of deprivation of visual inputs on the subsequent adaptation. Figure 5*A* shows the result of a gain-decrease experiment, in which the animal was placed in the dark for 30 min after the gain returned to  $\sim 1.0$  at the end of the recovery block. We continuously monitored the animal's eye movements during this dark block. The monkey was kept alert and made saccades of a variety of size and direction. However, the animal was unable to hold the eye at any location and showed

continuous drift of the eye (data not shown). We therefore assumed that during the dark block there were no visual targets to which the monkey could make saccades. After 30 min period in the dark, test adaptation still occurred at a higher rate than control adaptation (Fig. 5*A*). This was confirmed quantitatively by a steeper slope of the regression line for the test adaptation than that of the control adaptation ( $-7.2 \times 10^{-4}$ /saccade and  $-3.5 \times 10^{-4}$ /saccade, respectively). Figure 5*B* summarizes the results of 14 experiments conducted with the dark gain-decrease paradigm. In monkey K (Fig. 5*B*, left), the test block showed a significantly faster gain change than the control block ( $p < 0.01$ ;  $n = 9$ ), a similar result to that in the standard experiments (Fig. 2*D*, left). The ratio of adaptation rates had a mean of  $1.44 \pm 0.41$ , indicating an average increase by  $\sim 40\%$ . In monkey I, although the test-control difference did not reach a significant level ( $p = 0.07$ ), the test block exhibited faster adaptation in all four experiments (Fig. 5*B*, right). The ratio of the test rate to the control rate exhibited a mean of  $2.47 \pm 0.96$ , showing an average increase by  $\sim 150\%$ .

We examined whether, in this dark paradigm, the initial faster gain change was followed by slower gain change as in the standard paradigm. Figure 5*C* shows a smoothed function fitted to the same data in Figure 5*A*. It is clear that adaptation suddenly slowed down and resulted in an inflection on the smoothed curve (Fig. 5*C*, arrow). As in standard paradigms, we analyzed the course of the rate of adaptation for experiments in which the initial slope of the test block was steeper than that of the control block. Again, in all such experiments (seven and four for monkeys K and I, respectively), the slope profile of the test adaptation decreased to cross that of the control adaptation. The saccade number at the crossing point ranged from 103 to 281 (mean,  $179.4 \pm 65.2$ ;  $n = 11$ ). Figure 5*D* shows the relationship between the facilitation end gain and the control final gain. In monkey K, the two parameters were found to be significantly correlated in this dark gain-decrease paradigm (Fig. 5*D*, left) ( $p < 0.01$ ), as was the case with the standard paradigm. The data from monkey I were consistent with such a correlation but not significant (Fig. 5*D*, right) ( $p = 0.1$ ).

#### Gain-increase experiments with zero-error paradigm

The effect of zero-error saccades in gain-increase experiments was similar to that in gain-decrease experiments. Figure 6*A* illustrates the result of one experiment. After the gain returned to  $\sim 1.0$ , the animal was required to make saccades to target steps not followed by ISS for 30 min ( $\sim 780$  saccades in the relevant direction). The regression lines fitted for the initial 150 data points in the control and test blocks had similar slopes,  $4.4 \times 10^{-4}$  and  $4.2 \times 10^{-4}$ /saccade, respectively. Figure 6*B* summarizes the results of eight experiments. The number of zero-error saccades made in the relevant direction during the 30 min zero-error block ranged from 574 to 877. There was no significant difference in gain change rate between the test and control for each animal as well as for the two animals combined (Wilcoxon signed rank test;  $p = 0.50$ ,  $n = 4$  in monkey K;  $p = 0.50$ ,  $n = 4$  in monkey I;  $p = 0.99$ ,  $n = 8$  in both animals). The result indicates that the gain-increase adaptation is not accelerated after hundreds of normometric saccades, as was the case with gain-decrease adaptation (compare Fig. 4).

#### Gain-increase experiments with dark paradigm

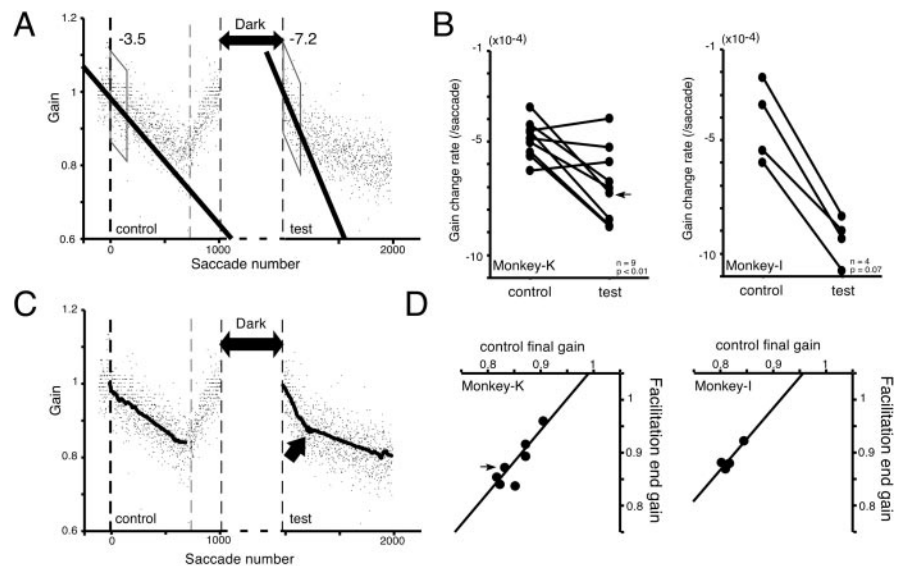
The result of this paradigm was not a simple mirror image of gain-decrease adaptation. Figure 7*Aa* shows a gain change profile for one experiment in monkey K. As indicated by a vertical open arrow, the test adaptation started with a gain that was clearly

higher than the gain at the end of the recovery block. The average gain of the initial 50 saccades in the test block was higher than that of the last 50 saccades in the recovery block by 0.08. Such discrepancies in gain, or apparent “jumps” in gain as we call them below, were more pronounced in the other animal. In one experiment in monkey I, the jump in gain was as large as 0.16 (Fig. 7*Ab*). However, similar jumps in gain might also be present in other paradigms. In fact, the standard gain-increase experiment shown in Figure 3*Ab*, for example, appears to exhibit some jump in gain at the beginning of test adaptation. We therefore tested quantitatively whether the jump in gain in the dark gain-increase paradigm is indeed larger than that in other paradigms. For standard and dark paradigms, the jump in gain was estimated by the same method as described above. For zero-error paradigms, we used the average gain of the last 50 saccades of the zero-error block for that of the recovery block. Figure 7*C* shows the jump in gain calculated for each paradigm. All paradigms showed positive jumps (i.e., changes in gain in the same direction as the ISS). The jump in gain in the dark gain-increase paradigm was significantly larger than that in any other paradigm in both animals (MANOVA Scheffé;  $p < 0.05$ ). There was no significant difference between any two of the remaining paradigms. The large, apparent gain jump at the beginning of the test adaptation was thus specific to the dark gain-increase paradigm.

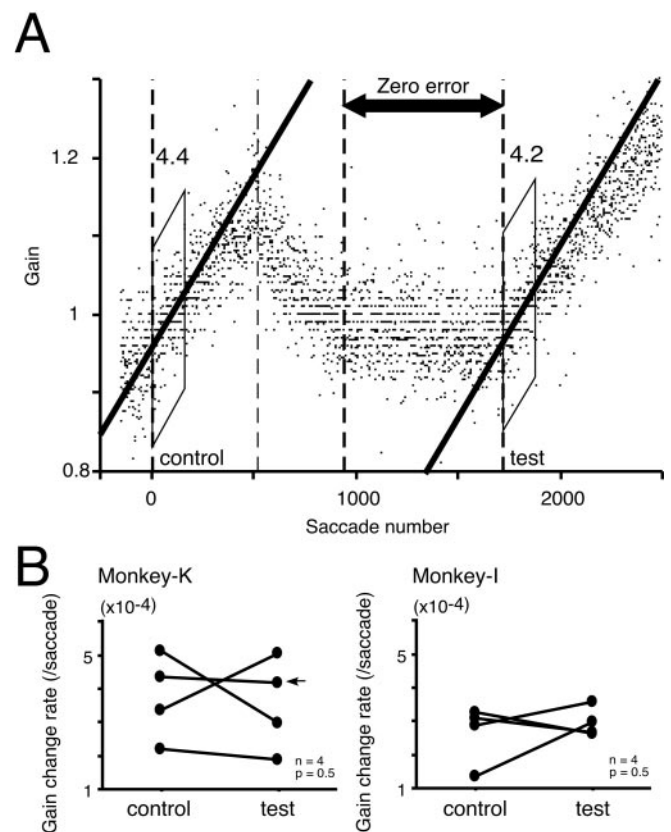
Observing this apparent increase in gain, one might suspect that the gain of the saccadic system gradually increased from  $\sim 1.0$  to a higher value during the dark block. To test this possibility, we required the animal in the test block to make saccades to target steps not followed by ISS. If the above explanation were true, we should observe an increased gain at the beginning and a subsequent recovery toward 1.0. However, this did not happen. The gain remained constant at  $\sim 1.0$  throughout this no-ISS test block as if the gain had been held constant during the dark block (Fig. 7*B*). The results of five dark no-ISS experiments confirmed the reproducibility of this phenomenon (Fig. 7*C*, double hatched bars). The jump in gain in the dark no-ISS paradigm was significantly smaller than that in the dark gain-increase paradigm (MANOVA Scheffé;  $p < 0.05$ ) and similar to those in other paradigms.

## Discussion

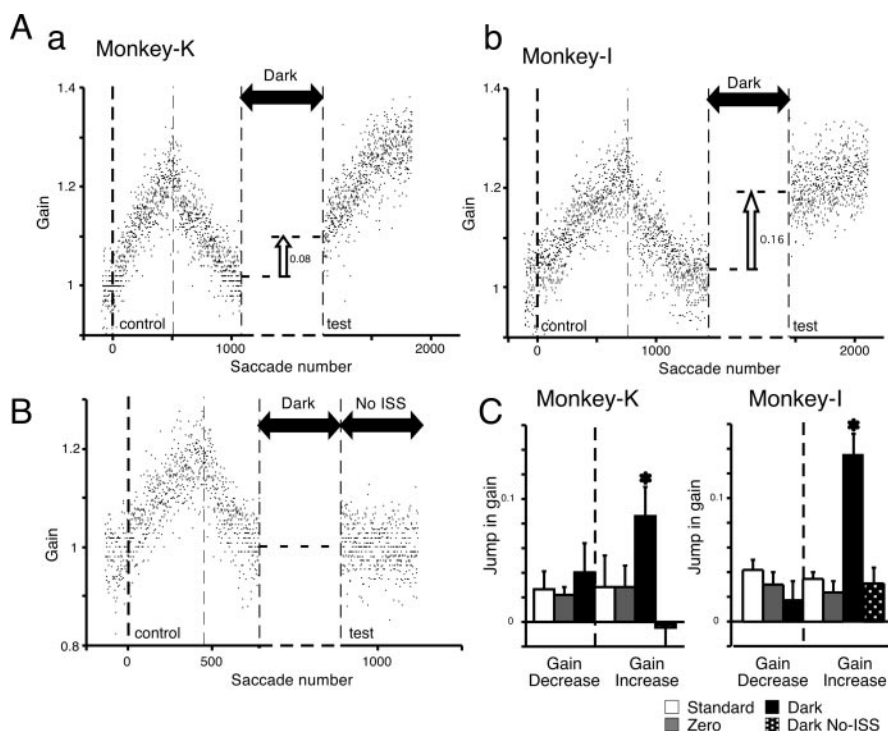
Our data provided evidence for the storage of learning history during saccadic amplitude adaptation. First, test adaptation occurred faster than control adaptation. In standard paradigms, the gain was brought back close to the preadaptation gain before test adaptation. If the saccadic system also had returned to the pre-learning state, test adaptation would have occurred in the same manner as control adaptation. Clearly, this was not the case. Furthermore, this accelerated learning did not continue throughout test adaptation but ended in relation to the final gain of control adaptation. Our results thus suggest that learning history is stored



**Figure 5.** *A*, Gain change profile of a dark gain-decrease experiment with linear regression lines fitted for the first 150 saccades of the control and test blocks. The slope of test adaptation is steeper than that of control. *B*, Summary of all experiments with this paradigm in two monkeys. Test adaptation has a significantly larger rate than control adaptation. Data shown in *A* are indicated by a small horizontal arrow in *B* (monkey K). *C*, Slowing of test adaptation seen as an inflection (arrow) on the fitting curve. *D*, Relationship between facilitation end gain and control final gain. The facilitation end gain was calculated by the same method as for standard paradigm data (Fig. 3*B*). There was a significant positive correlation between the two parameters in monkey K (left;  $p < 0.01$ ;  $r = 0.88$ ;  $n = 7$ ). The relationship did not reach a significant level in monkey I (right;  $p = 0.1$ ;  $r = 0.90$ ;  $n = 4$ ). Data shown in *C* are indicated by a small horizontal arrow in *D* (monkey K).



**Figure 6.** *A*, Gain change profile of a zero-error gain-increase experiment with linear regression lines fitted for the first 150 saccades of the control and test blocks. *B*, Summary of all experiments with this paradigm in two monkeys. There was no significant difference in gain change rate between the test and control. Data shown in *A* are indicated by a small horizontal arrow in *B* (monkey K).



**Figure 7.** *A*, Gain change profiles of dark gain-increase experiments in monkey K (*Aa*) and monkey I (*Ab*). Test adaptation starts with a gain that is higher than the gain at recovery end. Height of open arrows indicates this jump in gain, which is 0.08 and 0.16 for *Aa* and *Ab*, respectively. *B*, Gain change profile of a dark no-ISS experiment. In contrast to *A*, the no-ISS test block starts with a gain that is similar to the gain at recovery end. *C*, A jump in gain is shown as a bar chart with SD for each paradigm in the two monkeys. Positive values represent gain changes in the same direction as the ISS. The jump in the dark gain-increase paradigm (asterisk) was significantly larger than that in any other paradigm in both animals.

during adaptation and that this memory facilitates subsequent adaptation.

A previous study on the characteristics of saccadic adaptation has reported that repeated induction did not result in faster adaptation on different days (Straube et al., 1997). The gain change rate in control adaptation in our study also did not show any obvious increase over different experiments (our unpublished observation). Our study, however, showed a facilitatory effect of repetition within single experiments. If learning history is retained, as we concluded above, why does it not affect the next adaptation on a different day? The results of our zero-error paradigm may explain, at least in part, this apparent discrepancy. After making ~700 nearly normometric saccades, test adaptation was no longer faster. This suggests that the memory of adaptation lost its facilitatory action on subsequent learning, most likely because it was erased. Presumably, in our study as well as in the study by Straube et al. (1997), erasure of memory may have occurred after recovery, where saccades were accompanied by no consistent visual error.

The faster adaptation was followed by slowing (Fig. 3). Analysis of the rate of adaptation indicated that, after facilitation end, test adaptation was slower than control adaptation. These results, together with a linear relationship between facilitation end-gain and control final gain, suggest that the physiological function of the memory of adaptation may not be merely to increase the rate of learning. Rather, the memory might be regarded as a mechanism to bring the gain quickly to that achieved in preceding adaptation and hold the gain at that level.

### Erasure and retention of the memory of adaptation

The results of our modified paradigms provide clues to the nature of the process underlying the accelerated motor learning. In zero-error paradigms, the memory of learning clearly did not fade away merely with time, because gain-decrease adaptation was accelerated after the animal was placed in the dark. The memory thus appeared to be erased actively as the animal made normometric saccades. Exposures to visual errors with sizes that were approximately zero may have played a key role in this erasure process. Such visual stimuli could signal disappearance of the need for adaptation, resetting the saccadic system to the preadaptation state. Alternatively, maintaining the gain at a prelearning value (~1.0) for hundreds of saccades, rather than the exposure to zero visual error, might have been more important in promoting the erasure. If we could somehow maintain the gain at ~1.0 while exposing the animal to consistent visual error, the memory of adaptation might still be erased. Additional studies are required to discriminate between these possibilities.

The memory of previous adaptation did not remain after 30 min of zero-error block, during which the animal made several hundred saccades. It might seem surprising that only 30 min of zero-error saccades can erase previous learning. Note,

however, that only saccades to horizontal 10° target steps were adapted, recovered, and readapted in the present experiment. Previous studies have shown that adaptation is relatively specific to the size and direction of target eccentricity (Deubel et al., 1987; Semmlow et al., 1989; Frens and van Opstal, 1994; Straube et al., 1997; Noto et al., 1999; Watanabe et al., 2000). It has been demonstrated that adaptation progresses more slowly when the subject is exposed to adapting target steps of a variety of sizes and directions in humans (Miller et al., 1981) and monkeys (Scudder et al., 1998). As these authors pointed out, this is a direct consequence of the spatial specificity of adaptation. Saccades to a particular target eccentricity could be influenced only by saccades to similar target eccentricities. Thus, far more trials are needed to adapt movements to many different target eccentricities than those to a single fixed eccentricity. With the same logic, if the facilitation of adaptation also had similar specificity, the erasure of the memory of adaptation for target eccentricities of a variety of vectors, as may occur in physiological situations, would require a greater number of normometric saccades and therefore a longer time than in the present experiment.

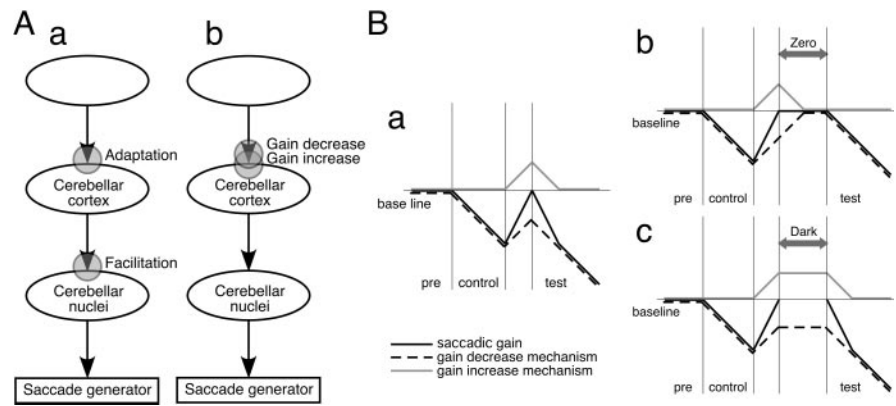
Our data suggest that the memory of forward adaptation was not merely retained but processed further during the dark block in gain-increase paradigm. Instead of accelerated adaptation, staying in the dark produced a jump-like increase in gain that was significantly larger than that in any other paradigm (Fig. 7C). Furthermore, the gain did not show such a large increase when tested with no ISS (Fig. 7B). Two explanations may be possible for this apparent increase in gain. The first assumes that the gain was held constant near 1.0 during darkness. Facilitatory effects of the

memory, nevertheless, were enhanced to such an extent during darkness that it produced in the test block an extremely fast adaptation that was completed within a very small number of saccades. To test this possibility, we calculated average gains of the first 5, 10, and 20 saccades. They were significantly higher than those of the same number of saccades at the recovery end (Wilcoxon signed rank test;  $p < 0.01$ ;  $n = 9$ ) by similar amounts, 0.089, 0.091, and 0.096, respectively. The average course of gain change (means across nine experiments) suggested that the gain did not change rapidly from  $\sim 1.0$  but jumped at the very start of the test block. These results make the first possibility unlikely. Alternatively, the saccadic system created a gain state of  $>1.0$  during the dark block while simultaneously retaining the gain state of 1.0. The system could then switch between the two states depending on visual errors it encountered at the beginning of the test block. Whatever the mechanism, it seems likely that consolidation-like processing of the memory takes place during darkness in a time-dependent manner. This contrasts with the erasure process discussed above, which appeared to depend on the number of trials rather than time. Finally, it should be noted that only gain-increase, not gain-decrease, adaptation exhibited the jump in gain, for which we currently do not have any plausible explanation.

#### Possible mechanisms of accelerated learning in saccades

We speculate below where and how saccadic adaptation might be facilitated on the basis of recent findings, including those on other forms of cerebellar-dependent motor learning. The oculomotor vermis and the fastigial oculomotor region (FOR) of the cerebellum have been shown to be key players in saccadic adaptation (Optican and Robinson, 1980; Takagi et al., 1998; Barash et al., 1999; Scudder, 2002; Inaba et al., 2003; Scudder and McGee, 2003). A recent study has further demonstrated that adaptation occurs upstream of the FOR (Robinson et al., 2002). We suggest here two general schemes for the accelerated learning in saccades. The first scheme is similar to that proposed for savings in eye blink conditioning. Medina et al. (2001) have suggested that plastic changes occur not only in the cerebellar cortex but also in the cerebellar nucleus during initial acquisition. The nuclear plasticity survives extinction and can later contribute to fast reacquisition. For saccadic adaptation, our first scheme assumes that a plasticity mechanism like long-term potentiation is activated gradually during control adaptation in the cerebellar nucleus, in addition to the one such as long-term depression (LTD) in the cortex (Fig. 8*Aa*). In the subsequent recovery block, the cortical plasticity decreases back to and possibly beyond the preadaptation level, as has been suggested for the extinction of eye blink conditioning (Medina et al., 2001), but the nuclear plasticity remains potentiated. Test adaptation then progresses faster because the effect of cortical plasticity is now augmented by the residual plasticity downstream in the nucleus.

The second scheme assumes oppositely directed plastic processes that could enhance each other. Blocking nitric oxide signaling in the goldfish cerebellum (Li et al., 1995) and use of a



**Figure 8.** Possible mechanisms for facilitated adaptation. *A*, Postulated sites of plasticity in two general schemes. *a*, A memory of learning forms in the cerebellar nucleus during control adaptation and remains during recovery. During test adaptation, this memory amplifies the effect of plasticity process occurring in the cerebellar cortex, resulting in accelerated adaptation. *b*, Increases and decreases in gain depend on separate plasticity mechanisms in the cerebellar cortex. *B*, Schematic illustrations of how the two oppositely directed mechanisms, assumed in *Ab*, might produce acceleration and subsequent slowing of adaptation observed in the present study. *a*, Standard gain-decrease paradigm. In the early phase of test adaptation, reactivation of gain-decrease process (broken line) combined with deactivation of gain increase process (gray solid line) produces accelerated gain change (black solid line). When gain increase process recovers fully to baseline, it stops being deactivated and can no longer contribute to overall gain change, resulting in slowing of adaptation (inflection on the gain curve). *b*, Zero-error paradigm. Erasure of memory is realized by simultaneous deactivation of the two mechanisms to baseline. *c*, Dark paradigm. Both mechanisms remain partially activated during the dark block, exhibiting acceleration and slowing in the test block.

novel behavioral paradigm in mice (Boyden and Raymond, 2003) have both suggested separate plasticity mechanisms for increases and decreases in vestibuloocular reflex gain. Similarly, the second scheme for saccadic adaptation assumes separate plasticity mechanisms in the cerebellar cortex for increases and decreases in gain (Fig. 8*Ab*). Figure 8*Ba*, taking our gain-decrease paradigm as an example, illustrates how such dual processes might combine to accelerate saccadic motor learning. In the control block, gain change (black solid line) is achieved only by activation of gain-decrease mechanism (broken line). During recovery, gain-increase mechanism (gray solid line) begins to be activated and, simultaneously, gain-decrease mechanism (broken line) now recovers toward the initial baseline level. At the beginning of test adaptation, the net gain change is zero because of equal contributions of two mechanisms. In the early part of the test block, reactivation of gain-decrease mechanism and recovery of gain-increase mechanism work together to accelerate gain decrease (facilitation). Because deactivation of gain-increase mechanism stops when it recovers to baseline, the slowing of adaptation will result, showing an inflection on the gain profile (black solid line). In this scenario, results of zero-error and dark paradigms also can be explained, respectively, by return of two mechanisms to baseline (Fig. 8*Bb*) and by retention of partial activation of both mechanisms at the end of the recovery block (Fig. 8*Bc*). The deactivation of plasticity mechanisms that does not progress beyond baseline that we postulate is not pure speculation. Recent results describe a previously unrecognized form of long-term potentiation in the cerebellar cortex (Lev-Ram et al., 2002) and a synaptic depotentiation in the hippocampus (Montgomery and Madison, 2002). Similar mechanisms could underlie the saccadic adaptation. Recently, a specific mechanism for acceleration and slowing of saccadic adaptation has been proposed in a theoretical model (Fujita, 2003a,b), which postulates a map of visual error in the cerebellar cortex. This can explain our results by LTD and its deactivation occurring simultaneously at different sites in the oculomotor vermis.

It should be noted that neither model explains the jump-like



increase in gain observed in the dark gain-increase experiment. Note also that the present study does not rule out other possibilities, including extracerebellar mechanisms. Nevertheless, our results strongly suggest that the saccadic adaptation system can recruit more than one plasticity process when the need arises, enabling previous learning to affect subsequent learning.

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