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Distinct Short-Term and Long-Term Adaptation to Reduce Saccade Size in Monkey

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Robinson, Farrel R., Robijanto Soetedjo, and Christopher Noto. Distinct short-term and long-term adaptation to reduce saccade size in monkey. *J Neurophysiol* 96: 1030–1041, 2006. First published May 3, 2006; doi:10.1152/jn.01151.2005. In monkeys, saccades that repeatedly overshoot their targets adapt to become smaller by the time the monkey has made 1,000–2,000 saccades. In life, adaptation must keep movements accurate for long periods of time. Previous work describes only saccade adaptation that occurs within a few hours. Here we describe long-term saccade adaptation elicited in three monkeys by 19 days of training. Each day a monkey made saccades to track 16° leftward and rightward target movements. During saccades, the target stepped back toward its starting position 6.4° (40%) in two monkeys or 8° (50%) in the third. After each day's adaptation, we blindfolded the monkey with goggles and returned it to its cage overnight. We found that adapting saccades for 19 days elicited significantly larger, long-lasting reduction in saccade size than did adapting for only 1 day. Further, after 19 days of adaptation we could elicit additional, apparently normal, short-term reduction in saccade size by increasing the size of the intra-saccade target movement. In contrast, we could elicit only small additional size reduction after only 1 day of adaptation. A simple model using separate short- and long-term adaptation mechanisms can reproduce many of the features of saccade gain exhibited by monkeys during a 19-day adaptation. We conclude that there is a long-term saccade-adaptation mechanism that is distinct from the well-characterized short-term system and that this newly recognized system is responsible for long-term maintenance of saccade accuracy.

INTRODUCTION

When a monkey's saccades repeatedly overshoot their targets, they become smaller, and thus more accurate, within 1,000–2,000 saccades (Straube et al. 1997). We and others study this reduction in saccade size because it is a tractable example of motor learning, or adaptation, in a voluntary movement.

Saccades adapt to remain accurate when the oculomotor system changes during development and aging or after damage (e.g., Abel et al. 1978; Kommerell et al. 1976). The effects of saccade adaptation need to persist for months or years if they are to be useful. Despite this need, the adaptation that occurs within 1,000–2,000 saccades can fade quickly. For example, size-reducing adaptation can decay when a monkey is in the dark as briefly as ~20 min (Seeberger et al. 2002).

How do the effects of saccade adaptation persist for months when they can diminish significantly after only 20 min in the dark? One possibility is that there is a separate, long-term, saccade adaptation mechanism that makes enduring changes in saccades. Long-term adaptation of nonsaccade movements

produces more persistent changes than does shorter exposure. For example, training the vestibuloocular reflex (VOR) in squirrel monkeys for 3 mo causes larger and longer-lasting changes in the VOR than does training them for only 2–3 h (Kuki et al. 2004). Training for as briefly as several days can cause adaptive changes that are distinct from those caused by training for a single day. Adapting a monkey's VOR to linear whole-body movement with daily training sessions for 3 days causes bigger, more enduring adaptation than does training for just 1 day (Zhou et al. 2003). Likewise, adapting the optokinetic response (OKR) in mice for 4 days produces changes that are larger and more persistent than those after adapting for only 1 day (Shutoh and Nagao 2003).

The work described here tests whether or not a long-term saccade adaptation system exists in monkeys. We found that long-term training elicits saccade adaptation that is significantly slower and longer lasting than the adaptation that occurs within 2,000 saccades. Further, this long-term saccade adaptation (LTSA) does not interfere with short-term adaptation. This indicates that LTSA uses a brain mechanism that is functionally separate from that of short-term saccade adaptation (STSA). We have published a preliminary report on these findings (Robinson et al. 2004).

METHODS

Subjects and animal preparation

The subjects in these experiments were three juvenile male rhesus monkeys (*Macaca mulatta*), monkeys 1–3, that were 4–6 kg. In a sterile surgical procedure, we secured plastic stabilization hardware to a monkey's skull with titanium screws and dental acrylic as well as a mount for blindfolding goggles. We also implanted a three-turn coil of Teflon-coated wire in one eye and connected the wire's ends to a plug attached to the top of the monkey's skull. During surgery, we anesthetized the monkeys with Isoflurane inhalation anesthesia, warmed them, and monitored their vital signs. Monkeys recovered overnight in a heated, padded cage and then remained in their home cage for a week before training started.

Animal training

We used the search coil technique (Fuchs and Robinson 1966; Robinson 1963) to measure horizontal and vertical eye position. We trained monkeys to use saccades to track a small (0.3°) red laser spot projected onto a screen 57 cm in front of them. A computer determined the position of the spot by controlling two mirror galvanome-

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ters. The monkey and screen were in a light-tight sound-attenuating booth that was dark except for the target spot.

During training and data collection a monkey fixated on the target spot for a random time 1–2 s. After that, the spot made a rapid, brief (<10 ms) movement to a new location. If the monkey made a saccade that ended within 2° of the target within 500 ms, then it received a dollop of applesauce from a feeding tube near its mouth. The target moved again after 1–2 s.

Eliciting short-term saccade adaptation (STSA)

To adapt a monkey's saccades, we used the now common technique, first used by McLaughlin (1967), of moving saccade targets during each movement. As monkeys tracked brief 16° horizontal target movements, we detected each saccade with dedicated electronics (eye velocity: >70°/s). The occurrence of a saccade triggered a brief target movement back toward the starting position of the saccade. Intra-saccade target movements made saccades seem to end beyond their targets so that monkeys made a corrective saccade after the normal reaction time of 120–250 ms. We used these backward intra-saccade target movements that were either 40% (6.4°) or 50% (8°) of the size of the initial 16° target movement. We adapted saccades to both leftward and rightward target movements. Adapting saccades in one direction does not influence saccades in the opposite direction (Albano 1996; Deubel et al. 1986; Frens and van Opstal 1997; Miller et al. 1981; Straube et al. 1997; Weisfeld 1972), so we treated saccades in each direction as parts of two independent adaptations.

Eliciting long-term saccade adaptation (LTSA)

The monkeys adapted during one session per day. During each session, they made ~1,000–3,000 saccades to 16° horizontal target movements that were each followed by backward intra-saccade target movements. After each day's adaptation, we blindfolded the monkey. We used opaque goggles formed to fit the monkey's face. Monkeys tolerated the goggles very well. They exhibited no signs of distress, fed themselves, climbed easily into and out of their cages, and moved around their home cages without difficulty.

Before the next day's adaptation we placed the monkey in the experimental booth and removed its goggles immediately before closing the door. Thus nearly all of the monkey's visually guided saccades were to targets that moved backward during the movement. The only exceptions were the saccades that the monkey made at the beginning and end of each adaptation session between the time we removed the goggles and closed the booth door. This represented a total of <2 min/session.

After a monkey had adapted for 19 days, we used the next few days to make several measurements, including a test of short-term adaptation after long-term adaptation. During this test, we attempted to elicit an additional 40% reduction in saccade size in *monkeys 1* and *2* and an additional 50% reduction in *monkey 3*. These tests were complete on day 22 in *monkeys 1* and *2* and on day 23 in *monkey 3*. We then began presenting normal 16° target movements, i.e., those not followed by intra-saccade movements, during each day's session in the booth. We continued this for the number of days necessary for the size of the monkey's saccades to recover to normal.

During the first 14 days of LTSA, we trained a monkey 7 day/wk. After that we trained it 6 day/wk leaving it blindfolded in its cage 1 day/wk. Because these 1-day interruptions occurred late in the long-term adaptation, they had only a very small effect on saccade gain, i.e., gain was nearly identical to immediately before and after the interruption.

Data collection and analysis

We digitized horizontal and vertical eye and target position at 1 kHz and recorded them on a computer hard drive with a CED Power

1401 laboratory interface. Eye and target position records were digitized voltages produced by the search coil system and galvanometer feedback, respectively. We used a custom-made program written in Spike 2 (Cambridge Electronic Design) to search the eye position record in the period between 100 and 700 ms after a target movement. When the program detected an eye velocity >70°/s, it examined the eye record before and after that point and identified the points in the record where eye velocity had increased and decreased to 20°/s. These points were the beginning and end of the saccade. The program used these points to measure saccade size and duration. We stored the saccade measurements and exported them to commercial programs (e.g., Matlab and Excel) for statistical comparisons and making illustrations.

We expressed saccade size as gain, i.e., the size of the saccade divided by the target movement size, and assessed each day's percent gain reduction with two measures. We calculated relative percent gain reduction using the mean gain of the first 50 and last 50 saccades each day with the following equation (Eq. 1)

Percent gain change = $100 \times (\text{Mean gain of the first 50 saccades}$

– Mean gain of the last 50 saccades)/Mean gain of the first 50 saccades (1)

This measure slightly underestimated the size of the gain change in the early days of LTSA. At the start of these days saccade gain fell rapidly within the first 50 saccades. Therefore the mean gain of the first 50 saccades was lower than that of the first few saccades of the day.

We assessed absolute gain change by first fitting a decaying exponential curve to the relationship between saccade gain and sequential trial number. For this we used a commercial program (Matlab, Mathworks) that minimized the sum-squared error. The equation for that curve is (Eq. 2)

$$\text{Gain} = \text{bias} + A * \exp(-\# \text{ of saccade}/\tau) \quad (2)$$

Parameter *A* in Eq. 2 is the absolute gain change, i.e., the difference between the first point of the curve and the asymptotic value. To fit the increasing saccade gains that occurred during recovery, we modified Eq. 2 slightly to represent increasing, not decreasing gains (Eq. 3)

$$\text{Gain} = \text{bias} - A * \exp(-\# \text{ of saccade}/\tau) \quad (3)$$

We used two-tailed Student's *t*-test and considered $P < 0.05$ to be significant.

All surgical and behavioral training procedures were approved by the Animal Care and Use Committee at the University of Washington. The animals were cared for by the veterinary staff of the Regional Primate Research Center. They were housed under conditions that comply with National Institutes of Health standards as stated in the *Guide for the Care and Use of Laboratory Animals* (DHEW Publication NIH85-23 1985) and with recommendations from the Institute of Laboratory Animal Resources and the American Association for Accreditation of Laboratory Animal Care.

RESULTS

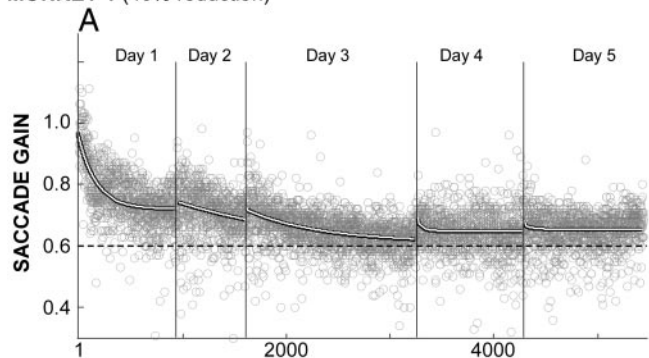
We adapted the saccades of *monkeys 1* and *2* to 16° leftward and rightward target movements by presenting 40% (6.4°) backward intra-saccade target movements. We adapted *monkey 3*'s saccades to these targets with 50% (8°) backward movements. We used larger intra-saccade target movements for *monkey 3* because, unlike most monkeys whose saccades we have adapted in our laboratory (e.g., Robinson et al. 2003; Seeberger et al. 2002; Straube et al. 1997), *monkey 3* adapted effectively to 50% backward intra-saccade target movements. As we explain in the following text, it was important to

produce gain reductions that were as large as possible during 1 day of adaptation.

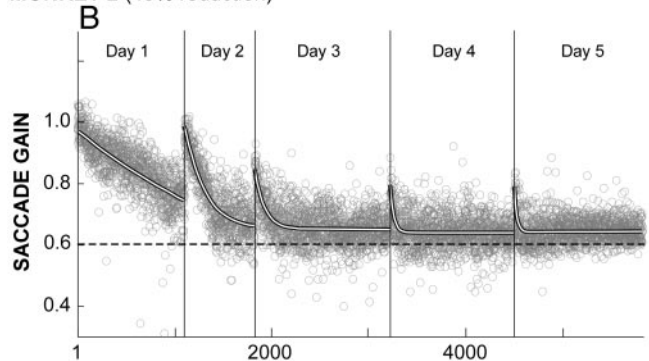
Gain change during long-term saccade adaptation and long-term recovery

LONG-TERM ADAPTATION. Figure 1 shows the gain of leftward saccades for all three monkeys during the first 5 days of a 19-day adaptation. The gain reductions of left- and rightward saccades were similar although not identical. For brevity, we show the gains of only leftward saccades here and in the other figures. Table 1 summarizes saccade gain changes during the first 2 days of adaptation and recovery.

MONKEY 1 (40% reduction)



MONKEY 2 (40% reduction)



MONKEY 3 (50% reduction)

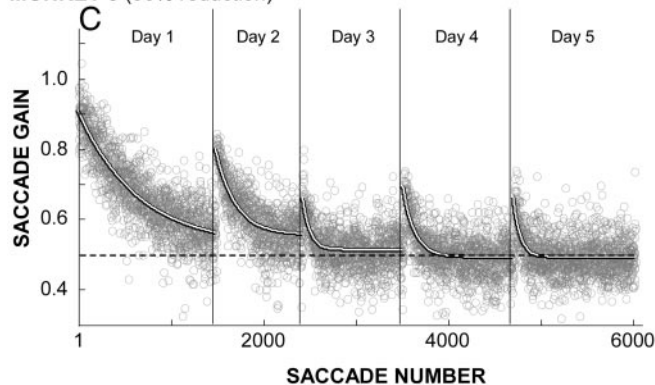


FIG. 1. Saccade gain reduction during the 1st 5 days of a 19-day adaptation for monkey 1 (A), monkey 2 (B), and (C) monkey 3. Monkeys 1 and 2 adapted to 40% backward intra-saccade target movements. Monkey 3 adapted to 50% backward intra-saccade target movements. Thus complete adaptation would produce a gain of 0.6 in A and B and 0.5 in C (marked by a ---). Fit curves are exponential decay functions (Eq. 2).

TABLE 1. Day 1 and Day 2 of Long-Term Adaptation

Elicited Change	Monkey 1 (40% Smaller)				Monkey 2 (40% Smaller)				Monkey 3 (50% Smaller)			
	Adapt left (Fig. 1A)	Adapt right (Not shown)	Recover left (Fig. 2A)	Recover right (Not shown)	Adapt left (Fig. 1B)	Adapt right (Not shown)	Recover left (Fig. 2B)	Recover right (Not shown)	Adapt left (Fig. 1C)	Adapt right (Not shown)	Recover left (Fig. 2C)	Recover right (Not shown)
Day 1												
Number	941	1558	1388	1648	1115	1127	973	985	1487	1481	1528	1611
Initial gain	0.95 ± 0.08	0.94 ± 0.07	0.71 ± 0.08	0.67 ± 0.03	0.99 ± 0.04	0.94 ± 0.04	0.68 ± 0.03	0.63 ± 0.04	0.89 ± 0.06	0.84 ± 0.08	0.53 ± 0.06	0.49 ± 0.07
End gain	0.71 ± 0.07	0.82 ± 0.05	0.86 ± 0.06	0.87 ± 0.04	0.77 ± 0.07	0.67 ± 0.07	0.96 ± 0.05	0.79 ± 0.04	0.56 ± 0.06	0.56 ± 0.06	0.89 ± 0.07	0.85 ± 0.11
Relative change, %	25.3	12.8	21.1	29.9	22.2	29.0	39.9	26.0	37.1	33.3	67.9	73.5
Absolute change	0.25	0.39	0.46	0.47	0.65	0.36	0.65	0.31	0.39	0.29	0.31	0.41
Rate constant	172	3017	2688	2871	2523	881	1707	1042	652	471	525	729
Day 2												
Number	672	874	1435	1250	734	716	539	540	943	951	2036	2010
Initial gain	0.74 ± 0.11	0.87 ± 0.05	0.78 ± 0.06	0.74 ± 0.04	0.94 ± 0.04	0.82 ± 0.07	0.90 ± 0.03	0.76 ± 0.05	0.78 ± 0.03	0.75 ± 0.06	0.70 ± 0.05	0.69 ± 0.06
End gain	0.69 ± 0.06	0.79 ± 0.03	0.93 ± 0.06	0.94 ± 0.04	0.66 ± 0.05	0.63 ± 0.05	0.98 ± 0.04	0.86 ± 0.05	0.58 ± 0.09	0.60 ± 0.07	0.90 ± 0.07	0.92 ± 0.08
Relative change, %	6.8	9.2	19.2	27.0	30.4	23.2	7.9	13.2	25.6	20.0	28.6	25.0
Absolute change	0.01	0.25	0.19	0.21	0.34	0.25	0.1	0.35	0.25	0.22	0.21	0.21
Rate constant	732	1904	583	550	218	110	195	1428	213	156	266	290

Values are means ± SD.

During the first several days of adaptation, the mean gain of saccades in all three monkeys was smaller at the beginning of each day than it was at the beginning of the previous day. In *monkey 1* (Fig. 1A), the gain of leftward saccades decreased on day 1 from 0.95 ± 0.08 to 0.71 ± 0.07 (means \pm SD). This represents a 25.3% relative gain reduction and 0.25 absolute reduction as determined by the fit exponential curve. At the start of day 2, leftward saccade gain had recovered slightly to 0.74 ± 0.11 . This overnight increase in gain is the well-described decay of STSA that occurs when, after a single adaptation session, a monkey does not make visually guided saccades for many hours (Straube et al. 1997). By the end of day 2, saccade gain had decreased to a mean value of 0.69 ± 0.06 (Table 1, *monkey 1*, day 2).

At the start of day 3, saccade gain had again increased overnight. By the end of day 3, it had decreased to a mean of

0.63 ± 0.05 , lower than that at the end of day 2. Days 4 and 5 produced very little additional gain reduction.

Saccade gains for *monkeys 2* and *3* (Fig. 2C) showed the same general pattern as those for *monkey 1* but with more overnight gain recovery. The gain of *monkey 2*'s leftward saccades fell from 0.99 ± 0.04 to 0.77 ± 0.07 on day 1 but had recovered to 0.94 ± 0.04 at the start of day 2. Similarly, *monkey 3*'s leftward saccade gain decreased from 0.89 ± 0.06 to 0.56 ± 0.06 on day 1 but recovered to 0.78 ± 0.03 at the start of day 2.

By the end of 19 days of adaptation, two changes occurred in the gains of all three monkeys' saccades. First, gains had fallen to values near those representing complete adaptation (Table 2, end gain). These gains were significantly smaller than at the end of day 1 (each $P < 0.05$). Thus long-term training produced larger gain changes than short-term training produced.

Second, the size of the overnight recovery of saccade gain had become very small. For example, the mean gain of *monkey 1*'s last 50 leftward saccades on day 18 was 0.58 ± 0.04 and that of the first 50 saccades on day 19 was 0.59 ± 0.06 . The corresponding values for *monkey 2* were 0.63 ± 0.04 and 0.62 ± 0.04 . Those for *monkey 3* were 0.48 ± 0.05 and 0.48 ± 0.04 . None of these differences was significant (each $P > 0.07$).

LONG-TERM RECOVERY. Figure 2 shows the gains of leftward saccades in all three monkeys during recovery from the long-term saccade adaptation illustrated in Fig. 1. On the first day of recovery, saccade gain increased quickly. Overnight, however, this gain increase decayed so that gains at the start of the second day of recovery were lower than at the end of the first day. This pattern was the same for all monkeys and repeated each day with gain increasing toward normal during recovery but decreasing overnight. In general, the size of the overnight decay decreased with increasing days of recovery.

By the end of recovery, mean saccade gain had returned to near normal. Saccade gain at the end of recovery was higher than at the start of adaptation. This was true for all three monkeys and for leftward and rightward saccades with one exception (*monkey 2*, rightward saccades). This is probably because our measurement of gain at the start of adaptation i.e., the mean of the first 50 saccades of adaptation was below normal gain. Gain decreased quickly during those 50 saccades.

Rates of long-term saccade adaptation and recovery

Figure 3 graphs the relationship between absolute gain change and day of adaptation (*left*) and recovery (*right*). During adaptation, the size of absolute gain change decreased in *monkeys 1–3* with rate constants of 1.0, 1.87, and 4.83 days. Multiplying these rate constants by the mean number of saccades/day during each monkey's adaptation shows they represent $\sim 1,100$, 2,400, and 6,500 saccades, respectively. During recovery, the size of absolute gain change decreased with rate constants of 0.89, 0.47, and 1.69 days or $\sim 1,400$, 1,900, and 2,200 saccades in *monkeys 1–3*, respectively. These estimated rate constants for LTSA are much longer than typical rate constants for STSA of 400–500 saccades (Straube et al. 1997).

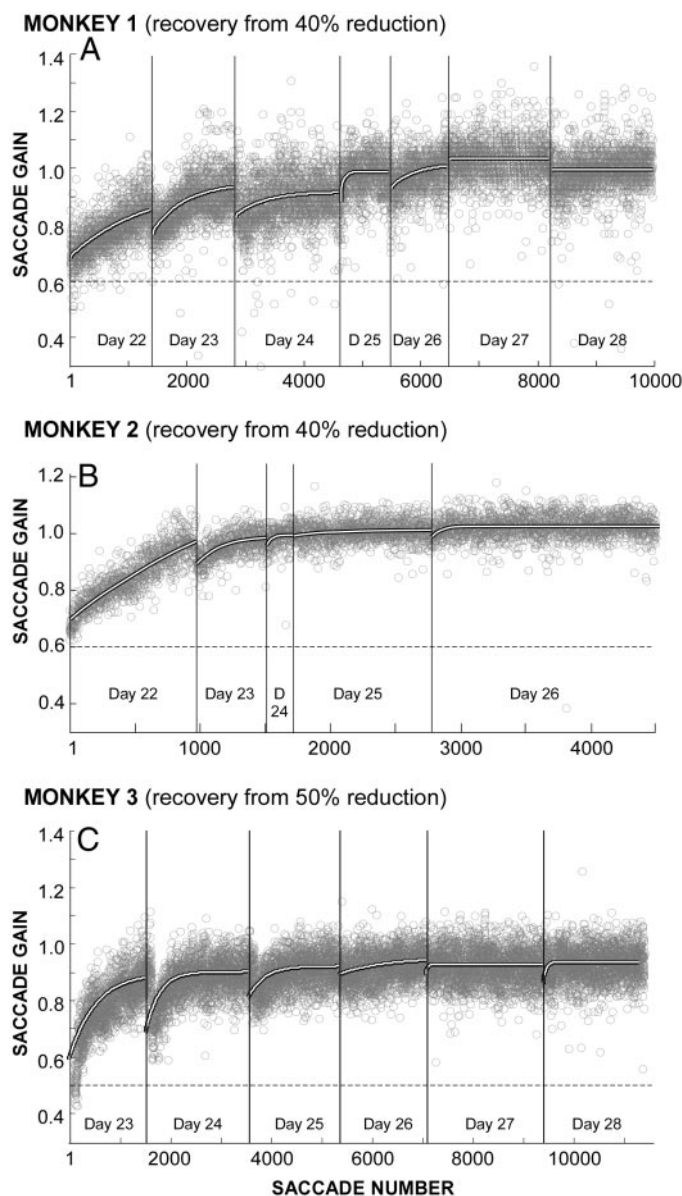


FIG. 2. Saccade gain increase during the recovery from the 19-day adaptation shown in Fig. 1 for *monkeys 1* (A), *2* (B), and *3* (C). ---, gains representing complete adaptation. Fit curves are exponential decay functions (Eq. 3).

TABLE 2. Whole long-term adaptation or recovery

Elicited Change	Monkey 1 (40% Smaller)				Monkey 2 (40% Smaller)				Monkey 3 (50% Smaller)			
	Adapt left (Fig. 1A)	Adapt right (Not shown)	Recover left (Fig. 2A)	Recover right (Not shown)	Adapt left (Fig. 1B)	Adapt right (Not shown)	Recover left (Fig. 2B)	Recover right (Not shown)	Adapt left (Fig. 1C)	Adapt right (Not shown)	Recover left (Fig. 2C)	Recover right (Not shown)
Number	20575	23098	9957	11273	24178	24113	4493	4491	25589	25675	11312	11360
Initial gain	0.95 ± 0.08	0.94 ± 0.07	0.71 ± 0.08	0.67 ± 0.03	0.99 ± 0.04	0.94 ± 0.04	0.68 ± 0.03	0.63 ± 0.04	0.88 ± 0.06	0.84 ± 0.08	0.53 ± 0.08	0.49 ± 0.07
End gain	0.61 ± 0.05	0.66 ± 0.03	1.01 ± 0.06	1.00 ± 0.04	0.62 ± 0.03	0.62 ± 0.04	1.01 ± 0.04	0.99 ± 0.05	0.50 ± 0.04	0.50 ± 0.06	0.93 ± 0.08	0.96 ± 0.08
Absolute change	0.2	0.36	0.32	0.37	0.35	0.31	0.34	0.42	0.34	0.26	0.25	0.36
Relative change, %	35.8	29.8	*	*	37.4	34.0	*	*	43.8	40.5	*	*
Absolute change rate constant, day	1.00	1.44	0.89	1.22	1.87	2.64	0.47	2.23	4.83	5.62	1.69	1.13

Bold font indicates relative percent gain change (Eq. 1) for LTSA in each monkey. Asterisks (*) mark recovery from LTSA for which we did not calculate relative percent gain change. LTSA, long-term saccade adaptation.

LTSA does not interfere with STSA

Our finding that LTSA causes larger, longer-lasting gain reductions than STSA does is consistent with the idea that LTSA is distinct from STSA. If so, then producing gain reductions with LTSA will not prevent further reduction by STSA. To test this possibility, we measured the gain reduction caused by STSA immediately after two different previous adaptations, one with a duration of 1 day and the other with a duration of 19 days.

The top half of Table 3 shows measurements of the first and second adaptation that occurred on a single day for each monkey. Each monkey started in an unadapted state and adapted its saccades tracking 16° horizontal target movements with backward intra-saccade movements of 40% for *monkeys 1* and 2 and 50% for *monkey 3*.

During the first adaptation, in which we presented 40% backward intra-saccade target movements, *monkey 1*'s gain decreased from 0.91 ± 0.09 to 0.73 ± 0.06 (from a mean saccade size of 14.5 – 11.7°). This is a 19.8% relative reduction and 0.17 absolute gain change (Fig. 4A, left). Increasing the size of the intra-saccade target movement another 40% decreased gain further to 0.70 ± 0.06 (to a mean saccade size of 11.2°). This represents a 4.1% relative reduction and a 0.06 absolute gain reduction; (Fig. 4A, right).

In *monkey 2*'s first adaptation, which we elicited with 40% backward intra-saccade target movements, its gain decreased from 0.95 ± 0.04 to 0.65 ± 0.05 (from a mean saccade size of 15.2 to 10.4° ; Fig. 4D, left). Increasing the size of the intra-saccade target movement another 40% decreased gain further to 0.51 ± 0.07 (to a mean saccade size of 8.2°). This is a 20.3% relative reduction and a 0.53 absolute reduction (Fig. 4D, right).

During *monkey 3*'s first adaptation, which we elicited with 50% backward intra-saccade target movements, the gain of *monkey 3*'s saccades decreased from 0.84 ± 0.06 to 0.61 ± 0.07 (from a mean saccade size of 13.4 to 9.8°). This is a 27.4% relative reduction and 0.32 absolute gain change (Fig. 4G, left). Increasing the size of the intra-saccade target movement another 50% decreased gain again to 0.55 ± 0.06 (to a saccade size of 8.8°). This is an 11.3% relative reduction and a 0.06 absolute gain reduction (Fig. 4G, right).

Note that in *monkey 3* saccade size increased briefly by a small amount immediately after we increased the size of the intra-saccade target movement. During previous short-term saccade adaptation, we have occasionally observed similar small, brief gain increases immediately after we change something about the adapting stimulus. We currently do not know why these small, transient gain increases occur.

Much larger gain reductions occurred when we increased the size of the intra-saccade target movement after a long-term adaptation. After 19 days of training, the gains of leftward saccades in *monkeys 1* and 2, which we had adapted with 40% backward intra-saccade target movements had stabilized near 0.6, and those of *monkey 3*, adapted backward 50%, were near 0.5 (Fig. 4, B, E, and H, left). We then increased the size of intra-saccade target movements another 40% in *monkeys 1* and 2 and another 50% in *monkey 3*. On day 20, *monkey 1*'s gain decreased from 0.59 ± 0.05 to 0.46 ± 0.06 (from a mean size of 9.4 to 7.4°), a 22% relative reduction and 0.14 absolute gain change (Fig. 4B, right). *Monkey 2*'s gain decreased from

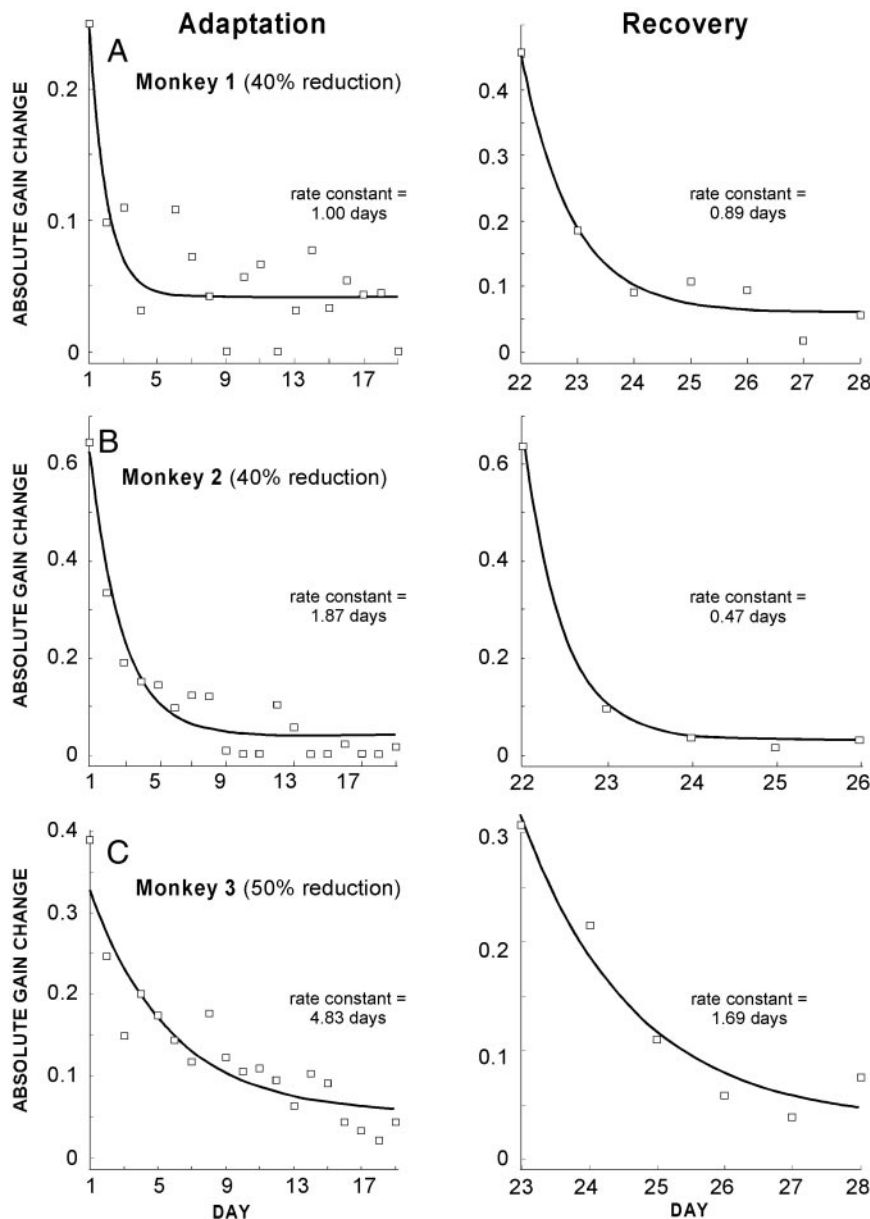


FIG. 3. Graph of absolute gain change (parameter A in Eqs. 2 and 3) as a function of the number of days that monkeys 1 (A), 2 (B), and 3 (C) adapted (left) or recovered (right). The fit curve is a decaying exponential. The rate constant of this curve is the absolute rate constant in Table 2.

0.62 ± 0.06 to 0.4 ± 0.03 , (from a mean size of 9.9 to 6.4°), a 35.5% relative reduction and a 0.25 absolute gain change (Fig. 4E, right). Monkey 3's gain decreased from 0.45 ± 0.05 to 0.31 ± 0.06 (from a mean size of 7.2 to 5°), a 31.1% relative reduction and 0.32 absolute gain change (Fig. 4H, right).

The additional adaptation that the monkeys produced on day 20 is similar to normal STSA in size and rate. We characterized normal STSA by adapting monkeys from an unadapted state with the same postsaccade visual stimulus that they saw on day 20. Specifically, monkeys 1 and 2 tracked 9.6° target movements with a 40% backward intra-saccade target movement that put the target 5.8° from its initial position. Monkey 3 tracked 8° target movements with 50% back-steps that brought the target to 4° from its starting position.

In Monkey 1, 40% backward intra-saccade target movements caused saccade gain to decrease from 1.00 ± 0.06 to 0.83 ± 0.07 (from a mean size of 9.6 to 8°), a 17% relative reduction and 0.18 absolute gain change (Fig. 4C). This is a smaller

relative gain change (17 vs. 22%) but larger absolute gain change (0.18 vs. 0.14) than monkey 1 exhibited on day 20. In monkey 2, 40% backward intra-saccade target movements caused saccade gain to decrease from 0.95 ± 0.04 to 0.74 ± 0.07 (from a mean size of 9.1 to 7.1°), a 22.1% relative reduction and a 0.28 absolute gain change (Fig. 4F). As with monkey 1, monkey 2 exhibited a smaller relative gain change (22.1 vs. 35.5%) but a larger absolute gain change (0.28 vs. 0.25) during normal STSA than it did on day 20. In monkey 3, 50% backward intra-saccade target movements caused saccade gain to decrease from 0.89 ± 0.07 to 0.62 ± 0.08 (8.5 – 6.0°), a 30.3% relative reduction and 0.34 absolute gain change (Fig. 4I). Again this represents a smaller relative gain change (30.3 vs. 31.1%) but a larger absolute gain change (0.34 vs. 0.32) than monkey 3 exhibited during its adaptation on day 20.

We also compared the rate constant of each monkey's day-20 adaptation to that of its normal adaptation. The rate constants of monkey 1's day 20 and normal adaptations were

TABLE 3. STSA after previous adaptation

	Monkey 1		Monkey 2		Monkey 3	
	Adapt left (40% smaller)	Adapt right (40% smaller)	Adapt left (40% smaller)	Adapt right (40% smaller)	Adapt left (50% smaller)	Adapt right (50% smaller)
1-Day						
First adaptation	(Fig. 4A, left)	(Not shown)	(Fig. 4D, left)	(Not shown)	(Fig. 4G, left)	(Not shown)
number	1349	1841	1065	806	1064	1058
init gain	0.91 ± 0.09	0.96 ± 0.04	0.95 ± 0.04	0.90 ± 0.04	0.84 ± 0.06	0.81 ± 0.06
end gain	0.73 ± 0.06	0.80 ± 0.04	0.65 ± 0.05	0.67 ± 0.04	0.61 ± 0.07	0.60 ± 0.07
relative change, %	-19.8	-16.7	-31.6	-25.6	-27.4	-25.9
absolute change	0.17	0.19	0.35	0.28	0.32	0.25
rate constant	329	988	630	273	592	312
Second adaptation	(Fig. 4A, right)	(Not shown)	(Fig. 4D, right)	(Not shown)	(Fig. 4G, right)	(Not shown)
number	1014	1221	862	873	710	721
init gain	0.73 ± 0.09	0.81 ± 0.05	0.64 ± 0.05	0.61 ± 0.04	0.62 ± 0.07	0.61 ± 0.06
end gain	0.70 ± 0.06	0.77 ± 0.03	0.51 ± 0.07	0.50 ± 0.04	0.55 ± 0.06	0.52 ± 0.07
relative change, %	-4.1	-4.9	-20.3	-18.0	-11.3	-14.8
absolute change	0.06	0.05	0.53	0.21	0.10	0.13
rate constant	416	97	3184	1107	70	51
19-day	(Fig. 4B, right)	(Not shown)	(Fig. 4E, right)	(Not Shown)	(Fig. 4H, right)	(Not shown)
Second adapt						
number	1010	1011	1494	1463	1576	1590
init gain	0.59 ± 0.05	0.63 ± 0.03	0.62 ± 0.03	0.56 ± 0.03	0.45 ± 0.05	0.46 ± 0.05
end gain	0.46 ± 0.06	0.49 ± 0.03	0.40 ± 0.03	0.38 ± 0.03	0.31 ± 0.06	0.31 ± 0.05
relative change, %	-22.0	-22.2	-35.5	-32.1	-31.1	-32.6
absolute change	0.14	0.18	0.25	0.18	0.32	0.16
rate constant	377	731	613	469	268	274
Normal (like 19-DAY 2nd)	(Fig. 4C)	(Not shown)	(Fig. 4F)	(Not shown)	(Fig. 4I)	(Not shown)
number	1521	1455	1407	1404	1570	1527
init gain	1.0 ± 0.06	0.98 ± 0.06	0.95 ± 0.04	0.94 ± 0.05	0.89 ± 0.07	0.83 ± 0.10
end gain	0.83 ± 0.07	0.89 ± 0.13	0.74 ± 0.07	0.68 ± 0.05	0.62 ± 0.08	0.57 ± 0.10
relative change, %	-17.0	-9.2	-22.1	-27.7	-30.3	-31.3
absolute change	0.18	0.10	0.28	0.30	0.34	0.27
rate constant	597	456	642	557	760	320

STSA, short-term saccade adaptation.

377 and 597, respectively. For monkey 2, those rate constants were 613 and 642, and for monkey 3 they were 268 and 760.

The two rate constants for each monkey were not identical. For example, monkey 3's normal adaptation took ~2.8 times longer than its day-20 adaptation. Still, we cannot conclude that these monkeys' normal adaptations were consistently slower than their day-20 adaptation. Monkeys can exhibit large day-to-day variations in STSA rate constants. Straube et al. (1997) note, for instance, that on four repeated adaptations the rate constants of their monkey R ranged over a factor of ~4.6 times (146 vs. 669 saccades).

DISCUSSION

The main finding of the work described here is that 19 days of training produces an adaptive reduction in saccade size that is distinct from that caused by only 1 day of training. The reductions in saccade size caused by 19 days of training are significantly larger and longer lasting than those caused by 1 day of training. In addition, long-term training does not interfere with short-term training.

Proposal for distinct short- and long-term adaptation mechanisms

We propose that there are distinct short- and long-term saccade adaptation mechanisms. The short-term mechanism is labile. It adapts saccades rapidly but its effects decay rapidly.

The long-term mechanism is more sluggish. It adapts saccades slowly and its effects decay slowly. The operation of distinct short- and long-term saccade adaptation mechanisms can account for the fact that LTSA does not interfere with STSA and also for the pattern of saccade gain changes that all three monkeys exhibited during LTSA and recovery from LTSA.

LTSA DOES NOT INTERFERE WITH STSA. Previous work shows that even very effective short-term training in monkeys reduces saccade size to ~40–60% of normal (Robinson et al. 2003). Therefore a 1-day adaptation that changed saccade size by about this amount depletes much of the adaptive capacity of the short-term mechanism. We assert that this is what happened during the first part of the 1-day adaptations illustrated in the left panel of Fig. 4, A, D, and G, and the top of Table 3. This large initial adaptation depleted much of the adaptive capacity of the short-term saccade adaptation mechanism. The small remaining capacity allowed only a relatively small further gain reduction when we increased the size of the intra-saccade target movement.

In our view, after 19 days of training the long-term mechanism maintained adapted saccade gain. The short-term mechanism does not need to participate and has returned to its unadapted state. From this state, it can produce normal short-term adaptation even though saccade gain is already strongly adapted and very low. This is why all three monkeys produced an apparently normal additional gain reduction when we increased the size of the intra-saccade target movement.

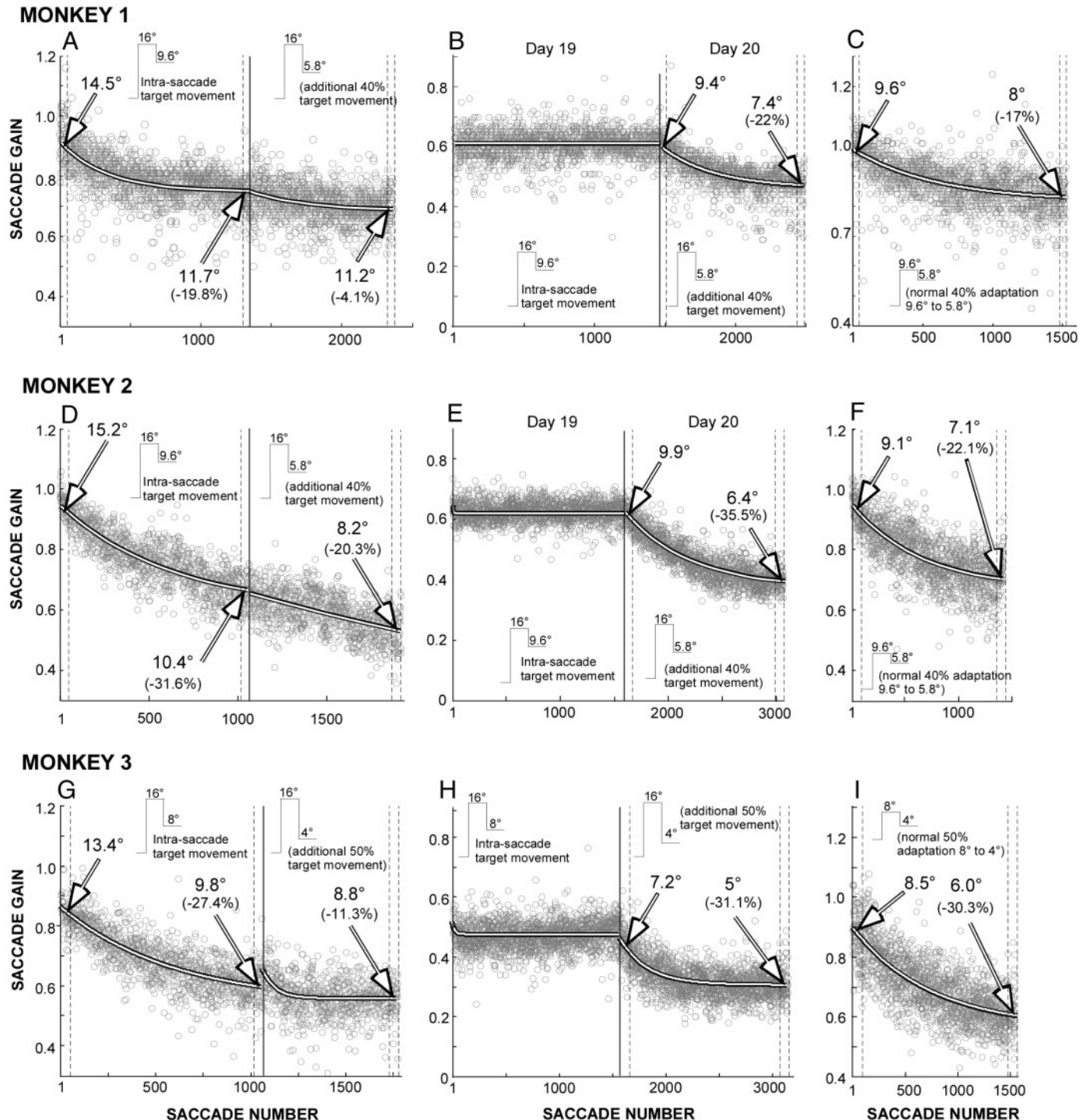


FIG. 4. Short-term adaptation of leftward saccades after previous adaptation for 1 day (A, monkey 1; D, monkey 2; G, monkey 3) or 19 days (B, monkey 1; E, monkey 2; H, monkey 3). C, F, and I: normal short-term adaptations in monkeys 1–3 from an unadapted state beginning at the same saccade size as the short-term adaptation after the 19-day adaptation. Vertical dashed lines mark approximate borders of the region that contains the 50 saccades the mean gain of which we used to calculate relative gain change. Numbers by the arrow for each region give the mean size of the 50 saccades in this region.

PATTERN OF GAIN CHANGES DURING LTSA AND RECOVERY FROM LTSA. On day 1 of a 19-day adaptation in all three monkeys, the short-term mechanism reduced saccade gain substantially, but some of this change decayed overnight. We assert that this overnight decay of adaptation moved saccade gain toward the gain set by the long-term mechanism. Near the start of the long-term adaptation experiments the gain set by the long-term

mechanism was nearly normal (1.0). The long-term mechanism adapted slowly and had reduced saccade gain only a small amount by the start of day 2. As the number of days of adaptation increased, the gain set by the long-term mechanism slowly decreased. This decrease caused the size of overnight gain decay to decrease as gain decayed toward a lower and lower value. Little or no overnight decay occurred late in

adaptation because by then, the short-term mechanism contributed little or nothing to the adapted gains.

On day 1 of recovery, the short-term mechanism increased saccade gain rapidly. Some of this gain increase decayed overnight so that gain moved back toward the low value set by the long-term mechanism during the preceding long-term adaptation. As the number of days of recovery increased, the gain set by the long-term mechanism increased. As the gain set by the short-term mechanism decayed toward this increasing value, the size of the overnight gain change decreased.

Brain areas implicated in STSA and LTSA

STSA. STSA depends critically on the posterior-medial region of the cerebellum. This region includes the oculomotor vermis (OMV) (Noda and Fujikado 1987) and the area in the caudal part of the fastigial cerebellar nucleus that receives a large projection from the OMV (Yamada and Noda 1987). We call this nuclear area the caudal fastigial nucleus (CFN). The axons of CFN neurons project to elements of the saccade burst generator in the brain stem (Noda et al. 1990; Scudder et al. 2000). Thus CFN neurons relay saccade-related signals out of the cerebellum to the oculomotor system.

Recording and lesion data implicate both the OMV and CFN in STSA. The saccade-related signals that the cerebellum sends to the oculomotor system via CFN neurons change roughly in parallel with changes in saccade size during developing STSA (Inaba et al. 2003; Scudder and McGee 2003). Lesions of the OMV (Barash et al. 1999; Optican and Robinson 1980; Takagi et al. 1998) abolish STSA. Inactivation of the CFN with direct injections of muscimol also blocks changes in saccade size while the CFN is inactivated. After the muscimol dissipates and, presumably, CFN activity returns to normal, the adaptation of saccades is revealed (Robinson et al. 2002).

We interpret this to mean that adaptation occurs upstream from the CFN, perhaps in the OMV. Activity in the CFN relays the adapted signals that formed upstream to the oculomotor system. Supporting this interpretation are our preliminary findings that inactivating the OMV blocks saccade adaptation and erases the effect of previous adaptation (Robinson and Noto 2005).

LTSA. To date there are no data indicating what brain areas support LTSA. Still the situation for saccade adaptation may be similar to that for VOR adaptation. Short-term adaptation of the VOR relies on the cerebellar cortex just as we propose that STSA relies on the OMV. Longer-term VOR adaptation does not rely on the cerebellar cortex. Specifically, Kassardjian et al. (2005) measured VOR gain in cats after inactivating the flocculus bilaterally. Before inactivation they adapted the cat's VOR for either 60 min or 3 days. Inactivating the flocculus after only 60 min of training erased the effects of VOR adaptation. This indicates that activity in the flocculus is critical to the expression of short-term VOR adaptation. In contrast, inactivating the flocculus after training the VOR for 3 days diminished the learned gain change only slightly. This indicates that activity in the flocculus is not necessary for the expression of most of the longer-term VOR adaptation.

Assuming that we can generalize these findings to saccade adaptation and other motor learning, we can ask what structures outside the cerebellar cortex could support long-term

adaptation? The necessary structure(s) could be within the cerebellum. Raymond et al. (1996) propose that motor adaptation occurs first in the cerebellar cortex and then in the cerebellar nuclei. It is possible that activity in the cerebellar nuclei supports long-term adaptation because these nuclei exhibit a variety of adaptive mechanisms (Hansel et al. 2001).

Structures outside the cerebellum may also support long-term adaptation. For example, during long-term adaptation of rat limb movements, the synapses made in the thalamus by axons of neurons in the cerebellar nuclei become stronger and more numerous (Aumann and Horne 1999). In short, until we have more information about the neural mechanisms underlying LTSA, the only basis we have for speculation is the analogy to the VOR indicating that LTSA may not rely on the OMV.

Simple model of short- and long-term adaptation

Despite not knowing what brain areas support LTSA, we implemented a simple computational model to determine if we could use a combination of fast and slow adaptation mechanisms to reproduce the characteristic pattern of saccade gain that monkeys exhibit during LTSA. Consistent with our proposal, our model used two distinct adaptation mechanisms, one with a relatively short time constant and one with a long time constant. Figure 5A shows a schematic representation of the model. We propose that the short-term mechanism is in the OMV. We do not know the location of the long-term mechanism. It may be distributed within several structures and employ several different learning mechanisms.

The model produced saccade gains during a 19-day 50% backward adaptation like the adaptation task that we presented to *monkey 3*. Below is a summary of the model's operation.

At 1 in Fig. 5A, a target appears 16° to the right or left of current eye position. This elicits a command at 2, to the saccade system. This command consists of the drive to the 16° target and a reduction in that command the size of which is set by the state of the long-term adaptation system. At 3, this command is reduced again by an amount set by the state of the short-term adaptation system. At point 4, we add noise to the twice-reduced saccade command. This noise mimics the variability that we and others observe in saccade gain both normally and during adaptation. At 5, the reduced and noisy command moves the eye with a saccade. We calculate the gain (saccade size/target distance) of each saccade at 6. Point 7 displays saccade gain.

During each saccade the target moves 50% of the distance back toward the eye's initial position so that the eye seems to have overshot its goal that is now located only 8° from the initial eye position. We set the final position of the target at 8. At 9, the model calculates the size of the postsaccade visual error as the difference between eye position and target position. Error size integrators for STSA and LTSA are at 10 and 11, respectively. The occurrence of a postsaccade error increases the values held in both the STSA and LTSA integrators, but it increases the value in the STSA integrator much more. Integrator output determines how much STSA and LTSA systems reduce the command for the next saccade. At 12 and 13, the model adds output of the STSA and LTSA integrators, respectively, to the states of these systems at the start of adaptation, a value that we set at 14 to zero.

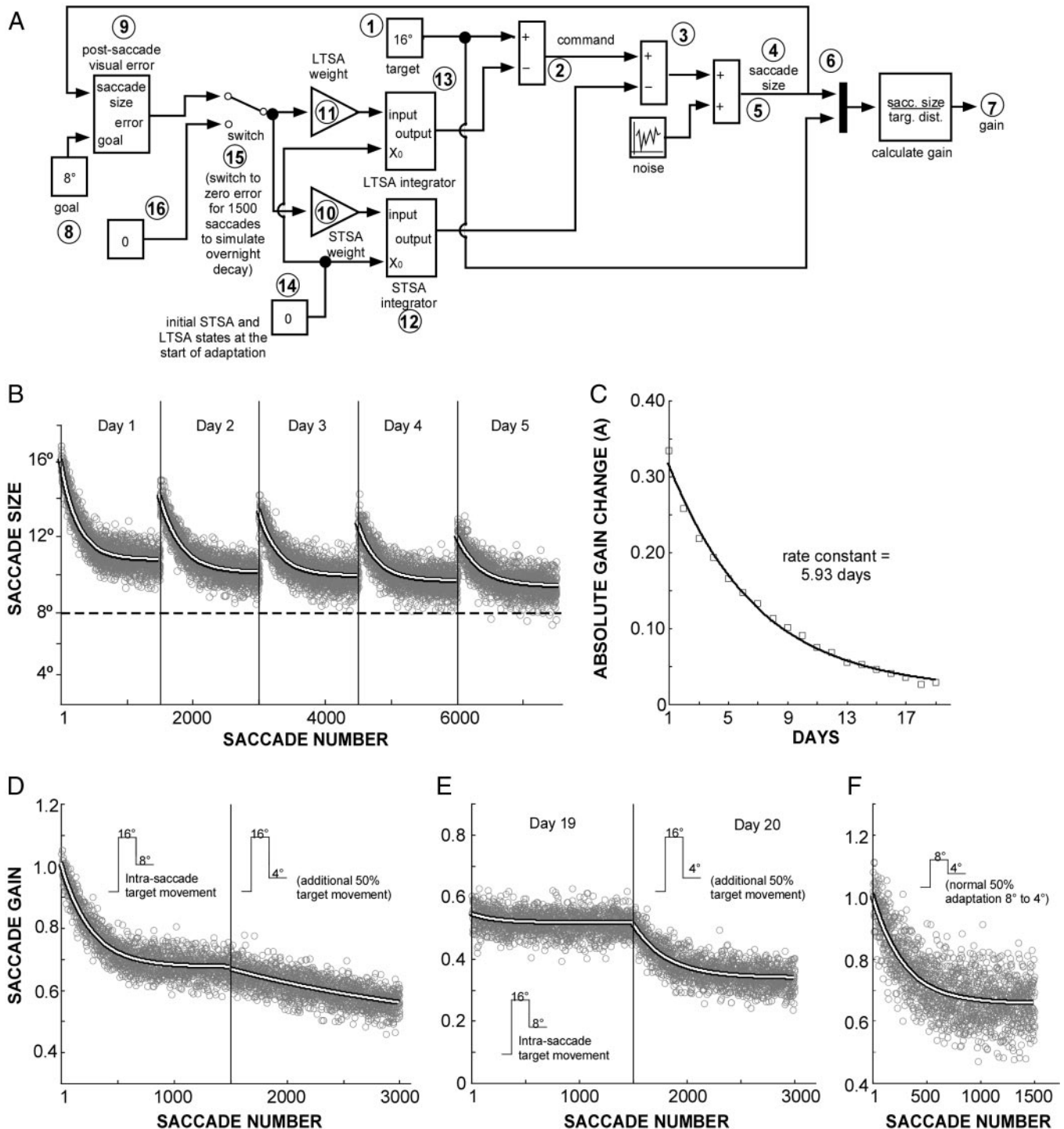


FIG. 5. A simple model of separate short- and long-term adaptation mechanisms operating in parallel. **A**: a schematic representation of the model. Text contains a step-by-step summary of its operation, referenced to the points in the model identified by circled numbers. **B**: simulated saccade gains during the first 5 days of a 19-day adaptation of 16° saccades with 50% (8°) backward intra-saccade target movements. The horizontal dashed line marks the gain representing complete adaptation. This is similar to the adaptation of *monkey 3* in Fig. 1C. **C**: graph of absolute gain change (parameter A in Eq. 2) as a function of the number of days that the model adapted. The fit curve is a decaying exponential with a rate constant of 5.93 days. Compare with Fig. 3C, left, showing the same measurements of *monkey 3*'s adaptation. **D**: STSA after a previous 1-day adaptation. Compare with Fig. 4G showing the same data for *monkey 3*'s adaptation. **E**: STSA after a previous 19-day adaptation. Compare with Fig. 4H. **F**: model's performance on a normal short-term adaptation from an unadapted state beginning at the same saccade size as the short-term adaptation after the 19-day adaptation. Compare with Fig. 4I.

Two features of this model are particularly important in creating the characteristics of its output. First, the integrator for the short-term system, at 10, is leaky. The signal that it accumulates decays exponentially with a rate constant of 500 saccades. Second, larger visual errors produce larger input signals to both integrators. Thus as adaptation progresses and error size decreases, the model reaches a point at which the signal in the short-term integrator is saturated and does not increase further. The signal in the long-term integrator continues to grow. As error size continues to decrease, the influence of the leakage from the short-term integrator becomes larger than the influence of the error. Therefore the value accumulated in the short-term integrator starts to decay while that in the long-term integrator continues to grow. The average gain at which the model reaches this point, after 1,500 saccade, is ~ 0.75 on day 1. The gain at which the model reaches this point falls slowly with increasing days of adaptation because the output of the LTSA integrator increases as it slowly accumulates the small effect of many postsaccade error signals.

To simulate overnight STSA decay, this model makes 1,500 saccades with zero postsaccade error after every day of adaptation. We toggle the switch at 15 so at the end of every day's adaptation the error size is 0, a value that we set at 16.

Many, but not all, features of the saccade gains produced by this model resemble those produced by *monkey 3* (Fig. 1B) and its tests of STSA after previous adaptation (Fig. 4, G–I). Figure 5B shows simulated saccade gains during the first 5 days of adaptation. As in *monkey 3*'s 50% backward adaptation, simulated saccade gains decrease rapidly on day 1 and decay, i.e., increase overnight. The size of the overnight increase falls on each succeeding day of adaptation. Gain at the end of each day is slightly lower than at the end of the previous day. The model's first day of adaptation does not decrease gain as far as the first day of *monkey 3*'s adaptation and does not reach a gain of ~ 0.5 as quickly.

Figure 5C shows the decrease in absolute gain change in the model's simulated saccades with increasing days of adaptation. The model's decrease is, of course, less variable than *monkey 3*'s (Fig. 3C) but has a similar size (difference between the highest point and asymptote, i.e., term A in Eq. 1, is 0.298 for the model vs. 0.270 for *monkey 3*) and rate constant (5.93 days for the model vs. 4.83 for *monkey 3*).

Figure 5, D–F, shows the model's performance during adaptation preceded by either short-term (Fig. 5D) or long-term (E) training. As in *monkey 3*'s adaptations under the same conditions (Fig. 4, G and H), an initial short-term adaptation precludes a second normal short-term adaptation. Unlike *monkey 3*'s gains, however, those produced by the model continue to decrease slowly during the second adaptation. By day 19, saccade gains have fallen nearly, but not quite to, 0.5 (Fig. 5E, left). On day 20, apparently normal short-term adaptation occurs. The similarity of the model's and *monkeys 3*'s performances indicate that distinct short- and long-term adaptation mechanisms can account for the pattern of saccade gains that we observed in our monkeys during LTSA.

Size-decreasing and -increasing saccade adaptation

In the preceding text, we show evidence that size-decreasing LTSA exists. It is important to remember that this evidence tells us little about size-increasing LTSA. Although it seems

likely that size-increasing LTSA plays some role in recovery from size-decreasing LTSA, it is premature to infer anything about it from recovery data alone. Size-increasing LTSA may exhibit characteristics different from those of size-decreasing LTSA. This is plausible because size-increasing STSA is different from size-decreasing STSA, i.e., it is slower and smaller (Robinson et al. 2003; Straube et al. 1997). Further, there is now evidence from both VOR adaptation (Boyden and Raymond 2003) and saccade adaptation (Kojima et al. 2004) that size-increasing and -decreasing adaptation use separate mechanisms.

Advantages of distinct short- and long-term adaptation mechanisms

An adaptation system employing separate short- and long-term mechanisms is more capable than a system relying on either mechanism alone. When a movement is repeatedly inaccurate, the short-term component will provide rapid adaptation to improve movement accuracy. When the need for adaptation persists, the long-term component will produce enduring changes to keep movements accurate over the months and years after the need for adaptation first arose. In this view, the short-term mechanism that we currently associate with the cerebellum does not provide permanent repair of movements. Instead it supplies rapid first-aid to make errant movements more accurate until the long-term mechanism can make enduring repairs.

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