Rapid Motor Learning in the Translational Vestibulo-Ocular Reflex

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Motor learning was induced in the translational vestibulo-ocular reflex (TVOR) when monkeys were repeatedly subjected to a brief (0.5 sec) head translation while they tried to maintain binocular fixation on a visual target for juice rewards. If the target was world-fixed, the initial eye speed of the TVOR gradually increased; if the target was head-fixed, the initial eye speed of the TVOR gradually decreased. The rate of learning acquisition was very rapid, with a time constant of ~ 100 trials, which was equivalent to <1 min of accumulated stimulation. These learned changes were consolidated over ≥ 1 d without any reinforcement, indicating induction of long-term synaptic plasticity. Although the learning generalized to targets with different viewing distances and to head translations with different accelerations, it was highly specific for the particular combination of head motion and evoked eye movement associated with the training. For example, it was specific to the modality of the stimulus (translation vs rotation) and the direction of the evoked eye movement in the training. Furthermore, when one eye was aligned with the heading direction so that it remained motionless during training, learning was not expressed in this eye, but only in the other nonaligned eye. These specificities show that the learning sites are neither in the sensory nor the motor limb of the reflex but in the sensory-motor transformation stage of the reflex. The dependence of the learning on both head motion and evoked eye movement suggests that Hebbian learning may be one of the underlying cellular mechanisms.

Key words: motor learning; VOR; monkey; sensory-motor transformation; synaptic plasticity; Hebbian learning; otolith

Introduction

The vestibulo-ocular reflex (VOR) generates compensatory eye movements during head movements to stabilize fixation on visual targets. Because the VOR functions as an open-loop control system, an adaptive process or “motor learning” is required to keep the VOR appropriately calibrated. Because of its machine-like operation and its well studied neural circuitry, the VOR has proven to be an excellent model system for studying neural mechanisms related to learning and memory in the CNS (for review, see Miles and Lisberger, 1981; Ito, 1982; du Lac et al., 1995; Lisberger, 1996; Partsalis and Highstein, 1996; Peterson et al., 1996).

According to the sensory stimulus, two VORs may be distinguished: the angular VOR (AVOR), activated by angular accelerations that are detected by the semicircular canals, and the linear VOR, activated by linear accelerations detected by the otolith organs. Both VORs are required to stabilize foveal images during natural head movements that routinely include complex combinations of angular and linear motion. In the past several decades, motor learning of the AVOR has been emphasized, primarily because the AVOR output can be reliably adapted to lessen the magnitude of retinal slip induced by experimental manipulations

using lenses (Miles and Fuller, 1974), Dove prisms (Gonshor and Melvill-Jones, 1976a; Robinson, 1976), mirrors (Gonshor and Melvill-Jones, 1976b), or synchronized visual/vestibular stimuli (Schultheis and Robinson, 1981). Similar experimental manipulations, however, have failed to consistently induce motor learning in the translational VOR (TVOR). On the one hand, Crane and Demer (2000) showed that human subjects wearing lenses expressed significant adaptive changes in their AVOR but few, if any, adaptive changes in their TVOR. On the other hand, motor learning in the TVOR has been demonstrated using prisms (Seidman et al., 1999) or visual–vestibular interactions (Hegemann et al., 2000; Shelhamer et al., 2000; Wei and Angelaki, 2001). Nevertheless, these TVOR adaptations were much less robust than those induced in the AVOR.

Because the TVOR depends on viewing distance and heading direction, a motor-learning paradigm that induces robust adaptation of the TVOR could offer novel possibilities in the study of neural mechanisms related to sensorimotor adaptation. To develop such a behavioral paradigm, however, one must first identify a learning signal that can effectively initiate motor learning in the TVOR. Retinal slip per se is not an effective learning signal for the TVOR (Crane and Demer, 2000; F. A. Miles, personal communication) because the TVOR normally tolerates the presence of retinal slip in much of the visual field that is outside the binocular fixation plane. In a seminal study, Jones et al. (1984) suggested that a spatial context cue, i.e., whether a target is head-fixed or world-fixed during head rotations, could be a powerful learning signal to modify the AVOR. This novel approach was recently extended to the TVOR in monkeys (Zhou et al., 2002). In this study, our goal is to identify specific conditions that lead to

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TVOR adaptation to localize potential adaptation sites and to elucidate the underlying neural mechanisms.

Materials and Methods

Experiments and surgical procedures were performed in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* and were approved by the University of Mississippi Medical Center's Institutional Animal Care and Use Committee.

Animal preparation for eye movement recordings. Data reported here were collected from six monkeys (*Macaca mulatta*) that were prepared for chronic recording of binocular eye movements in multiple staged surgical procedures. First, a stainless steel receptacle was implanted on the animal's skull so that the animal's head could be stabilized with respect to the vestibular stimulator and the electromagnetic field of the eye coil system. An eye coil was implanted on one eye during the surgery (Robinson, 1963; Judge et al., 1980). During a second surgery, performed after the animal was trained to fixate visual targets, a second coil was implanted on the other eye for binocular recording of eye movements and to control vergence eye position. After recovery from surgery, the monkeys were brought to the laboratory for training or experiments. In the laboratory, the monkey was comfortably seated in a custom-fabricated monkey box mounted on the vestibular stimulator. The field coils and the monkey's head were stabilized relative to the main axis of the vestibular stimulator. The head was stabilized by attaching a stainless steel rod to the post implanted on the monkey's head. The stainless steel rod did not introduce any appreciable distortion of the magnetic field used by the search coil system. The eye coil was calibrated by placing targets at known positions ($\pm 20^\circ$, every 5°) and requiring the monkey to fixate these positions with its head fixed. An eye coil calibration was performed at the start of each experimental day.

Monkeys were trained to fixate and track visual targets in exchange for fruit juice rewards. To receive a reward, the monkey was required to fixate a small visible target projected by a laser onto a far screen (located ~ 2.75 m from the monkey's eyes) or onto a near screen located in a horizontal plane extending 8–50 cm from the animal's nose. The monkey was rewarded if eye position was maintained for several hundred milliseconds within a computed window ($1\text{--}4^\circ$ in size) centered on the position of the target. Monkeys were trained to fixate and track in dim illumination or darkness with and without vestibular stimulation. In addition to the laser target controlled by mirror galvanometers, additional LED lasers were mounted on the eye coil frame to provide head-fixed targets for suppression of the VOR.

Vestibular stimulation. Rotational and translational motion stimuli were delivered by a vestibular stimulator (Acutronic USA, Inc.) with three axes of motion: a manually controlled horizontal axis ($\pm 30^\circ$) used to tilt the monkey, a servo-controlled vertical axis for yaw rotation (maximum acceleration, $500^\circ/\text{sec}^2$), and a servo-controlled horizontal linear axis (maximum acceleration, 0.8 g). Because the rotary axis allowed one to position the monkey's head at any angle relative to the linear axis, linear accelerations could be delivered in any direction in an earth-fixed horizontal plane. The sled and turntable were controlled by an Acutronics 2000 digital controller, slaved to our data acquisition personal computer (PC) via an IEEE interface. Each axis could be independently controlled, and linear and angular accelerations could be delivered to the monkey in any combination. The monkey box, CNC search coil system (CNC Engineering, Seattle, WA), and head holder apparatus were modified especially for this device with the goal of creating a mechanically stiff system so that accelerations of the sled or turntable were faithfully delivered to the monkey's head. The mechanical characteristics of the system were validated using a miniature accelerometer (mounted on the monkey's head) to tune the acceleration profiles delivered to the animal and to measure linear accelerations delivered to the monkey's head during experiments.

Behavioral paradigms. Visual targets were presented by either projecting a laser onto a tilted screen or a tangent screen in front of the monkey (Zhou and King, 1998). Target positions were chosen over a range of ocular eccentricities and vergence angles, and the monkey was required to fixate them binocularly. After a fixation interval between 300 and 900 msec, monkeys were subjected to abrupt steps of linear acceleration

(peaks of 0.1, 0.2, or 0.3 g), angular acceleration ($500^\circ/\text{sec}^2$), or visual image motion (step-ramp smooth pursuit, 5 or $15^\circ/\text{sec}$) to evoke transient eye movement responses. At the end of each trial, monkeys were rewarded with a drop of apple juice for fixation of the target. The head acceleration phase had a duration of ~ 200 msec and was followed by a slower deceleration phase resulting in linear displacements of ~ 7.5 cm or rotations of 10° . Information about whether the target was head-fixed or world-fixed was provided to the subject in two ways. In one condition, the target was kept on during head movement (target-on condition). In the second condition, the target was turned off before the onset of motion and subsequently turned on after all motion ceased (target-off condition). These two conditions differed in the visual cues that were available during head movement and the VOR. In the experiment that estimated the latency of visual feedback on the VOR, i.e., defining its open-loop interval, the two conditions were randomly intermixed. In the other experiments reported in this study, however, only the target-on condition was used. The direction of linear motion with respect to gaze direction could be varied from 0° (nasal-occipital condition) to 90° inter-aural condition). Linear steps were also delivered while the subject's body and head were tilted to the left or the right. Steps in different directions and for different tilt angles were used to study motor learning specificity and to constrain possible neural mechanisms of otolith adaptation. To ensure the observed changes were caused by neural plasticity rather than the result of a general cognitive strategy, testing trials were made unpredictable with respect to timing, direction, and context. During training, monkeys could be presented with blocks of similar trials to induce learning in a single condition (see Figs. 2, 3, 4, 6, 7, 8) or with two trial types randomly interleaved to induce differential learning in the two conditions (see Fig. 5, Table 4). Each trial lasted ~ 3 sec with an intertrial interval of 1 sec. The experiment room was light-tight. Thus, trials could be presented in complete darkness (preventing retinal slip) or with a visible target (retinal slip condition). During intertrial intervals, photographic safe lights were turned on to limit dark adaptation.

Experiments were designed to induce learning that either increased or decreased the amplitude of TVOR compensatory eye movements evoked by steps of linear acceleration. To increase TVOR amplitude, monkeys were presented repeated trials with a world-fixed target (TVOR trials). To decrease the TVOR, monkeys were presented repeated trials with a head-fixed target (TVORC trials). "Generalization trials" consisted of head motions that were in other directions, of other amplitudes, were of another modality (i.e., rotation), or were delivered when monkeys viewed targets at other locations. Each generalization experiment consisted of three blocks of trials. During the prelearning stage, we either randomly intermixed at least two types of generalization trials (~ 30) or randomly intermixed them with learning trials. In the learning stage, $\sim 600\text{--}1400$ VOR or TVORC learning trials were presented. A postlearning block of trials (~ 30) was similar to the first block.

Data acquisition and analysis. An IBM-compatible PC was used to control experiments and the slave computers (ACUTROL, CED Power 1401). The CED system (Cambridge Electronics Devices, Cambridge, UK) was used for data acquisition. A master PC controlled the experiments using specialized software. Experimental conditions were formulated as temporal sequences of instructions to operate devices (start or stop data acquisition, activate vestibular stimulator, etc.). Instructions were also used to randomize timing, direction, and intensity of the vestibular stimulation. Signals representing eye movement, target position, and rotary or linear motion were sampled at 2 kHz with 16 bits resolution and stored on a hard disk for off-line analyses. Eye movement responses were analyzed using Spike2 (CED; Cambridge Electronics Devices) and Matlab (Mathworks, Natick, MA) software. Raw position data were filtered and differentiated with a bandpass of DC to 90 Hz to obtain eye velocity data. Any trials in which the monkey broke fixation or made a saccade within the first 100 msec of the onset of the head movement were rejected. Different trial types mixed in the data stream were sorted and selected for further analysis. To obtain low-noise estimates of eye velocity as a function of time, traces were aligned on the onset of the head motion and averaged over multiple trials ($\sim 15\text{--}100$). We have elected to analyze only the first 80 msec of the TVOR, because during this interval (the "open loop interval"), the TVOR is uncontaminated by effects of external visual feedback. This approach has been validated by several previous

Figure 1. Single trial responses of the TVOR in different adaptation states. *A*, The three traces are head position, velocity, and acceleration, respectively. *B*, Unadapted state. This trial, with a world-fixed target, was obtained before TVOR training. Black and gray traces are eye position and velocity of the left and right eyes, respectively. *C*, High-gain state. This trial, with a world-fixed target, was obtained after several days of TVOR training. *D*, TVORC Training. To initiate low gain adaptation, the target was head-fixed. The trial shown was the fifth trial of TVORC training. *E*, Low-gain state. This trial occurred on the ninth day of low gain training. For eye position traces, the calibration bar (unlabelled) is 30° in *B–D* and 15° in *E*. For eye velocity traces, the calibration bar (unlabelled) is 150°/sec in *B*, *D*, 90°/sec in *C*, and 30°/sec in *E*.

studies in paradigms that studied visual-motor transformations in the pursuit system (Lisberger and Westbrook, 1985; Krauzlis and Lisberger, 1994) and by our own control experiments (see below). The effect of motor learning was evaluated by a ratio [learning ratio (LR)] of eye velocity before and after training (averaged over 75–85 msec from the onset of head motion). A learning ratio with a value equal to 1, >1, or <1, indicates the absence of learning, gain increase learning, or gain decrease learning, respectively.

Results

Open loop interval of the TVOR

Figure 1 shows single trial responses to brief rightward translations (Fig. 1*A*) when the TVOR was in different states. In an unadapted state (Fig. 1*B*), the compensatory eye movement was not adequate, and a catch up saccade (arrow) was required to bring the eyes onto the world-fixed target after the cessation of translation. In an adapted high gain state (Fig. 1*C*), however, the compensatory eye movement was nearly perfect, and there was no corrective saccade. When the monkey viewed a head-fixed target, its compensatory eye movements took the eyes away from the target, and a corrective saccade was required to re-fixate the target (Fig. 1*D*). Further training with repeated TVORC trials

nearly suppressed the compensatory eye movements (low gain state) (Fig. 1*E*).

Because a visual target was present during head translations, the observed responses were not entirely driven by vestibular stimuli (Lisberger and Westbrook, 1985; Miles et al., 1986). To determine the effect and latency of any possible visual feedback in this paradigm, monkeys were subjected to TVOR trials with continuous target visibility randomly mixed with TVOR trials during which the target was turned off before head movement and not turned back on until 200 msec after cessation of head movement. The “open loop” interval of the TVOR was estimated by measuring the latency of the divergence between the eye velocity traces obtained in the two conditions, which was 97.9, 125.6, and 113.5 msec for monkeys 3, 4, and 5, respectively. Thus, any effect of visual feedback was excluded in our analysis of TVOR motor learning by its focus on the initial 80 msec of compensatory eye movement (“initial eye speed”).

TVOR learning: time course, retention, latency, and dynamics

Figure 2 illustrates changes in initial compensatory eye speed induced by gain-decrease or gain-increase training over a period of several days. Initially, monkeys were given TVOR trials to maximize their compensatory response (high-gain state). Control data, obtained in this state, are plotted as open circles in the top left panel of Figure 2 (see arrow). After the control trials, monkeys were given repeated TVORC trials to initiate a gain-decrease process (Fig. 2, top panel, day 1, filled circles for TVORC trials). In the first 20 TVORC trials, there was a rapid decrease in initial eye speed evoked by head translation (from ~60 to 38.2°/sec). This response decrement at the beginning of the adaptation process reflected a parametric adjustment that may have resulted from the animal's recognition of the altered context. An additional adaptive learning process was activated as the monkey completed more TVORC trials. Initial eye speed continued to decrease, following an exponential time course, with a time constant of 152 trials. The learning ratio was 0.46, indicating a 54% reduction in initial eye speed as a result of TVORC training on day 1. The learning process was also very rapid, with a time constant that was equivalent to <1.5 min of accumulated vestibular stimulation. Between test days, monkeys were allowed to move freely in their home cages in normal lighting conditions. When tested on day 2, the decrement in initial eye velocity achieved at the end of day 1 was 90% retained. After day 3 of training, the monkey was left in its home cage for 4 d. When tested on day 7, the reduced gain had been retained without the need of any further reinforcement (day 3: $13.0 \pm 3^\circ/\text{sec}$ vs day 7: $13.4 \pm 4^\circ/\text{sec}$). When two more days (days 8 and 9, data not shown) of TVORC training confirmed that the TVOR reached the low gain state, the monkey was given TVOR trials to initiate a gain-increase process. In day 1 of the TVOR training, an initial set of control TVORC trials (Fig. 2, bottom panel, filled circles, see arrow) were obtained first followed by a block of TVOR trials (open symbols). Within the first few TVOR trials, there was a rapid increase of initial eye velocity (from 5.8 to 16.7°/sec) that we believe was parametric. Further increases in eye velocity followed an exponential time course with a time constant of 345 trials, which was much longer than that observed during TVORC motor learning. On day 2 of the TVOR trials, the enhanced eye speed attained the previous day was 93% retained. Furthermore, the high-gain state achieved after day 2 was retained for 3 d without training (day 2: $41.4 \pm 3^\circ/\text{sec}$ vs day 5: $43.1 \pm 3^\circ/\text{sec}$). Table 1 lists learning ratios ($\text{VEL}_{\text{after}}/\text{VEL}_{\text{before}}$) for gain decrease and gain increase training for six monkeys, demonstrating the effectiveness of the behavioral paradigm in

Figure 2. Consolidation of context-dependent adaptation of the TVOR. Eye speed measured at 80 msec after the onset of head translation is plotted against trial number. Filled symbols are from the TVORC trials, and open symbols are from the TVOR trials. The top panels show the time course of TVOR low gain adaptation over several training days. The bottom panels show the time course of TVOR high gain adaptation. Note that before the onset of the training trials, the monkey was given 50 control trials (see arrows) to demonstrate the initial gain state before the onset of the training trials.

Table 1. Summary of LRs of day 1 training from six monkeys

Monkey	LR (gain decrease)	LR (gain increase)
1	0.54 ± 0.02	1.47 ± 0.1
2	0.45 ± 0.02	2.05 ± 0.3
3	0.46 ± 0.03	2.15 ± 0.3
4	0.54 ± 0.04	1.73 ± 0.1
5	0.35 ± 0.06	2.54 ± 0.2
6	0.22 ± 0.05	1.66 ± 0.2

LR = VEL_{after}/VEL_{before}

inducing adaptation of the TVOR. Table 2 lists the retention rates for three monkeys 24 hr after adaptation, demonstrating that the rapidly acquired changes in the TVOR were consolidated over time.

The rate of acquisition of the low gain state during TVORC training and the degree of adaptation finally achieved were relatively independent of any previous experience the monkey may have had with the training paradigm. Figure 3 shows the time course of changes in initial eye speed when monkeys were exposed to a block of TVORC trials on three separate occasions when they were initially in the high gain state. Exponential curves were fitted to the data from each training session, and their time

Table 2. Learning retention after 24 hr

	VEL (before) (deg/sec)	VEL (after) (deg/sec)	VEL (after 24 hr) (deg/sec)	Retention (%)
Monkey 3				
Decrease	31.8 ± 2	17.4 ± 4	18.8 ± 4	90
Increase	16.7 ± 2	34.3 ± 5	33.1 ± 3	93
Monkey 4				
Decrease	42.1 ± 7	18.5 ± 5	24.6 ± 6	74
Increase	15.1 ± 4	28.9 ± 4	26.2 ± 4	80
Monkey 5				
Decrease	33.7 ± 6	13.6 ± 3	14.4 ± 6	96
Increase	15.5 ± 4	37.1 ± 5	30.7 ± 5	70

constants and learning ratios are summarized in Table 3. It is evident from these data that there was no progressive increase in the degree of adaptation and no consistent change in the rate of acquisition.

To quantify changes in eye velocity dynamics associated with the adaptive changes during the open-loop period of the TVOR, eye speed was averaged over 100 trials in either the high-gain or low-gain states (Fig. 4, solid gray traces from high-gain state, solid black traces from low-gain state). The latency of the TVOR was

Figure 3. Time course of TVORC motor learning is independent of previous experience to the training paradigm. The initial eye speed from each of the 3 d was plotted as a function of trial number for monkeys 3 (A), 4 (B), and 5 (C). Time constants and learning ratios are listed in Table 3.

Table 3. TVOR learning associated with repeated exposure to TVORC trials

	Monkey 3		Monkey 4		Monkey 5	
	LR	TC	LR	TC	LR	TC
First	0.46 ± 0.03	162 ± 9	0.54 ± 0.04	54 ± 4	0.35 ± 0.06	80 ± 5
Second	0.43 ± 0.03	112 ± 5	0.49 ± 0.03	68 ± 5	0.38 ± 0.03	53 ± 3
Third	0.49 ± 0.03	82 ± 5	0.56 ± 0.03	94 ± 8	0.39 ± 0.03	86 ± 8

LR, Learning ratio; TC, time constant.

10, 7, and 13 msec for monkeys 3, 4, and 5, respectively. There was a zero-latency anti-compensatory eye movement in the initial eye velocity of monkey 5, which may have resulted from the mechanical compression of the eyeball by linear acceleration (Collewijn and Smeets, 2000). To estimate its latency, we compared the averaged eye velocity traces evoked by the same head translation while the monkey viewed a near (16.5 cm) or a far target (275 cm). The two traces diverged at 13 msec from the onset of head translation, which was taken as an upper estimate of the TVOR latency for monkey 5. Averages were also obtained of the first 20 trials (short dashed traces) and the last 100 trials (long dashed traces) of the gain decrease training on day 1 (Fig. 2, top panel, filled symbols). Comparison of the eye velocity trajectories revealed that there were at least two sequential temporal components during the open-loop interval of the TVOR. The late component (Fig. 4, black arrows) was more labile because it was parametrically modified after only a few trials of a new context (compare solid gray and short dashed traces in Fig. 4). The latency of the late component was 35, 34, and 55 msec for monkeys 3, 4, and 5, respectively (Fig. 4, black arrows). The late compo-

nent was further adapted by additional training trials presented during the same day. In all three monkeys, the amplitude of the late component was minimized after the low gain states were achieved (solid black traces). In contrast to the lability of the late component, the early component of initial eye velocity appeared to be uninfluenced by changes in task context. When given additional training trials, however, part of the early component (Fig. 4, gray arrows) was systematically modified. This interval was ~20–35 msec for monkey 3, ~26–33 msec for monkey 4, and ~32–55 msec for monkey 5. Because of technical limitations and safety concerns, we limited peak acceleration to <0.3 g. It is possible that an earlier expression of motor learning might be detected if higher accelerations were used (Clendaniel et al., 2001). The initial eye velocity of the TVOR exhibited different dynamics in high gain (solid gray traces) or low gain state (solid black traces). In the high gain state, linear regression analysis revealed that the initial eye velocity resembled head velocity with a regression coefficient (r^2) of 0.99, 0.98, and 0.98 for monkeys 3, 4, and 5, respectively. In the low gain state, however, the regression coefficients were reduced to 0.27, 0.52, and 0.01 for monkeys

Figure 4. Motor learning modifies the dynamics of the TVOR. Averaged eye speeds from different training stages of three monkeys are overlaid to compare the time course of adapted TVOR responses.

Figure 5. Directional specificity of the TVOR motor learning. *A*, Motor learning induced in a trained direction (left panel, filled symbols; right panel, black bars) did not transfer to an untrained direction (left panel, open symbols; right panel, open bars). *B*, Differential learning. In a single training session, gain decrease learning was induced in one direction (left panel, filled symbols; right panel, black bars), and gain increase learning was induced simultaneously in the other direction (left panel, open symbols; right panel, open bars). The asterisk above the bars indicates statistical significance (t test, $p < 0.001$).

3, 4, and 5, respectively. Furthermore, eye velocity in the low gain state quantitatively resembled head acceleration, with a regression coefficient of 0.67, 0.70, and 0.29 for monkeys 3, 4, and 5, respectively.

Specificity of TVOR motor learning

Directional specificity

Figure 5A shows a block of TVORC trials that induced motor learning in the monkey's right TVOR without modification of its left TVOR. The histograms in the right panel of Figure 5A show learning ratios in both directions from five monkeys. It is evident that motor learning significantly reduced initial eye speed in the trained direction (black bars), but not in the untrained direction (open bars). In an additional experiment, we maximized the TVOR in one direction while minimizing it in the other direction (Fig. 5B, left panel) during the same training session. To accomplish this differential adaptation, monkeys were given a block of trials consisting of a random mix of 50% TVORC trials in one direction and 50% TVOR trials in the other direction. In all five monkeys tested, the initial eye velocity during the open loop interval was increased in the direction of the TVOR trials (Fig. 5B, right panel, open bars) but was decreased in the opposite direction (Fig. 5B, right panel, black bars).

Table 4. Modality specificity in TVOR adaptation

Learning in the rightward TVOR without learning in the rightward AVOR	LR (TVOR)	LR (AVOR)
Monkey 1	0.17 ± 0.02*	1.00 ± 0.05
Monkey 2	0.46 ± 0.06*	1.00 ± 0.06
Monkey 5	0.55 ± 0.05*	0.96 ± 0.04
Gain decrease learning in the rightward TVOR and gain increase learning in the rightward AVOR in the same training session		
Monkey 3	0.48 ± 0.03*	1.56 ± 0.07*
Monkey 4	0.79 ± 0.05*	1.17 ± 0.04*
Gain increase training in the right TVOR but no training of rightward smooth pursuit	LR (TVOR)	LR (smooth pursuit)
Monkey 3	1.43 ± 0.1*	1.05 ± 0.1
Monkey 5	2.34 ± 0.2*	1.15 ± 0.1

LR (TVOR, AVOR) = $\text{VEL}_{\text{after}}/\text{VEL}_{\text{before}}$; LR (pursuit) = $\text{ACC}_{\text{after}}/\text{ACC}_{\text{before}}$.

* $p < 0.001$.

Modality specificity

To determine whether motor learning is specific to the sensory modality used in training, we analyzed eye velocity elicited by the AVOR and smooth pursuit before and after motor learning was induced in the TVOR. Learning ratios listed in Table 4 show that there were no changes in initial eye speed of the right AVOR, despite a significant reduction in the initial eye speed in the rightward TVOR. Furthermore, we demonstrated that the TVOR and the AVOR could be adapted independently, even when the reflexive eye movements were in the same direction. Two monkeys were given a block of trials consisting of a random mix of 50% TVORC trials in one direction and 50% AVOR trials in the same direction. Both monkeys decreased their eye movement responses to the head translation but increased their responses to the head rotation in the same training session (Table 4). Finally, we examined whether TVOR motor learning could transfer to smooth pursuit. Two monkeys were presented a block of leftward TVOR trials each day for two consecutive days to increase their initial eye velocity. At the beginning of each day, smooth pursuit eye acceleration, elicited by step-ramp (15°/sec) target motions (Rashbass, 1961), was also measured. Learning ratios listed in Table 4 show that there was no change in the open-loop eye acceleration elicited by step-ramps despite a significant change in eye velocity evoked by translation. These results suggested that learning was restricted to neural pathways specific for the TVOR.

TVOR motor learning is specific to combinations of the head motion and evoked eye response.

In the first experiment, we used TVORC trials to induce reductions in initial eye speed at a heading of 30° to the right, which evoked leftward compensatory eye movements (Fig. 6A, black arrow). Before and after training, we measured initial eye speeds at a heading of 30° to the left (Fig. 6A, white arrow), which evoked rightward compensatory eye movements. In the trained direction, the learning ratio was 0.49 for monkey 4 and 0.48 for monkey 6, indicating a significant reduction in eye velocity resulted from training. However, the learning ratio in the test direction was 0.96 for monkey 4 and 1.01 for monkey 6 ($p > 0.05$), indicating that motor learning did not transfer from the training direction to the test direction, although the two directions were similar in a vestibular coordinate frame. Thus, adaptation sites are unlikely to be in the sensory limb of the reflex (peripheral end organs and primary afferents), which transforms linear accelerations into neuronal signals and then transmits them into the vestibular nuclei.

In the second experiment, we examined whether adaptation sites are in the motor limb of the reflex (motoneurons and extraocular muscles), which converts the neuronal signals into con-

Figure 6. Motor learning is localized within the sensorimotor transformation stage of the reflex. *A*, Motor learning is not in vestibular coordinates. Motor learning induced in one heading direction (black arrow) did not transfer to a similar heading direction that evoked compensatory eye movement in a different direction (white arrow). *B*, Motor learning is not in an oculomotor coordinate frame. Motor learning induced in upward vertical eye movement by leftward translation with 20° head tilt to the right (black arrow) did not transfer to the upward vertical eye movement evoked by rightward translation with 20° head tilt to the left (white arrow). The asterisks above the bars indicate statistical significance (t test, $p < 0.001$).

tractions of extraocular muscles. To achieve this, we took advantage of the fact that the vertical TVOR depends not only on heading direction, but also on the orientation of the head with respect to earth. For example, if a monkey's head is tilted to the left and the animal is translated to the right, the TVOR generates oblique eye movements with upward components (Fig. 6B). Alternatively, if the head is tilted to the right, leftward translation generates oblique eye movements that are also accompanied by upward components (Fig. 6B). If the learning site were located in the motor limb of the reflex, then adaptation should be expressed

Figure 7. Ocular specificity of motor learning. *A*, Motor learning was induced in a naso-occipital TVOR with a target aligned with the left eye. *B*, Motor learning induced in the training condition was expressed in the right (non-aligned), but not in the left (aligned) eye.

whenever eye movements are generated in the trained direction, although the heading directions might be different. Two monkeys were trained using TVORC trials with their heads and bodies tilted 20° to the right with leftward translation (Fig. 6*B*, black arrow). Learning ratios in the vertical eye movements were 0.64 for monkey 3 and 0.65 for monkey 6, indicating a significant adaptation (Fig. 6*B*, right panel black bars). After training, monkeys were tilted 20° to the left, and initial eye velocity was measured during rightward translations (Fig. 6*B*, white arrow). In this direction, the evoked compensatory eye movements had the same upward components, as did the trained eye movements. However, learning ratios in vertical eye movements were 0.94 for monkey 3 and 1.02 for monkey 6, indicating that learning did not transfer to the test condition. These data suggest that adaptation does not occur at the motor limb of the reflex. Similar results have been reported in AVOR adaptation in cats (Baker et al., 1987).

In the third experiment, we examined whether motor learning could be induced in an eye that remains motionless during training (Fig. 7). The monkey was required to fixate a near target (10° vergence angle) that was aligned with the left eye while subjected to backward head translations in the nasal-occipital direction. The compensatory eye movements of the right eye (i.e., the converged eye) were rightward (Fig. 7*A*, middle panel, thick black trace). However, the same head translations evoked much smaller horizontal compensatory eye movements in the left eye (i.e., the aligned eye) (Fig. 7*A*, bottom panel). The monkey was given a block of TVORC trials that resulted in smaller compensatory eye movements of the right eye (Fig. 7*A*, middle panel, dotted trace). The effect of training on the left eye was examined

by comparing its initial eye speed in a test condition before and after training. In the test condition, the target was placed at the same initial distance from the monkey, but displaced to the left of the training target (Fig. 7*B*). In this condition, the same head translation used in the trained condition (Fig. 7*A*) evoked rightward compensatory eye movements in both eyes (Fig. 7*B*, middle and bottom panels, thick black traces). The dashed traces in Figure 7*B* shows that learned changes were present in the response of the right eye (middle panel) but not in the response of the left eye (bottom panel), suggesting that the TVOR motor learning is sensitive to the combination of head translation and evoked eye movement used in the training.

TVOR motor learning is not specific for translation acceleration and target distance

The slope of eye velocity versus head acceleration was measured before (Fig. 8*A*, filled circles in the left panel and black bars in the right panel) and after training using an acceleration of 0.2 *g* (Fig. 8*A*, open circles in the left panel and white bars in the right panel). Figure 8*A* shows that the initial eye speed and translation acceleration were still linearly related but with a reduced slope in the three monkeys tested, suggesting that motor learning transferred to other accelerations.

The initial eye speed of the TVOR is inversely proportional to viewing distance (Schwarz et al., 1989; Snyder and King, 1992). The slope of initial eye velocity versus viewing distance was measured before and after training using a target with a viewing distance of 22 cm. Figure 8*B* shows that initial eye speeds and inverse viewing distance were still linearly related after training but with a reduced slope in five monkeys tested, suggesting that learning transferred to other viewing distances.

Discussion

In this study, we developed a new behavior paradigm to elicit rapid and robust motor learning in the TVOR (Fig. 2). Four features of this paradigm distinguish it from previous behavior paradigms used to induce motor learning in the AVOR. First, as showed in a separate study, TVOR motor learning does not require retinal slip (Zhou et al., 2002). Instead, the direction of motor learning is determined by a behavioral context, i.e., whether to suppress (TVORC condition) or optimize the evoked ocular response (TVOR condition). Second, instead of using self-generated or sinusoidal head motions such as have been used in AVOR adaptation (for review, see du Lac et al., 1995), we used computer-controlled transient head motions to induce motor learning in the TVOR. Using this paradigm, we were able to systematically manipulate the vestibular stimulus and eye movement response during its open-loop interval to reveal the specificity of the learning process and obtain insights into potential learning sites and learning mechanisms. Third, motor learning in the TVOR is very rapid and efficient. Unlike previous AVOR adaptation to altered visual conditions that takes from hours to days, TVOR motor learning has a time constant of ~100 trials, which is equivalent to ~1 min of accumulated stimulation. Fourth, instead of measuring the default VOR in darkness which is ill-defined for the TVOR, we evaluated motor learning by measuring initial compensatory eye speed while the monkey was engaged in a behavioral task, i.e., maintaining binocular fixation on a visual target to obtain juice rewards. These unique features of the TVOR motor learning paradigm make it an excellent model for studying the neural mechanisms underlying motor learning and memory in behaving nonhuman primates.

TVOR adaptation involves neural plasticity

Several pieces of evidence support the idea that the observed changes in the TVOR after training are attributable to neural plasticity rather than simply to strategy-specific parametric adjustments. First, the training induced changes in initial compensatory eye velocity that followed an exponential time course (Fig. 2). Second, the effects of training were retained between training sessions without reinforcement (Fig. 2), even during several days of normal visual-vestibular experience in the home cage, suggesting that the learned changes were specific to the stimuli experienced during the training. Third, the rate of acquisition and the degree of motor learning finally achieved were independent of previous exposures to the training condition (Fig. 3). Fourth, motor learning was specific to the direction and modality of head motion and was only expressed in conditions that had the combined head motion and evoked eye movements experienced during training (Figs. 5–7). These characteristics of TVOR motor learning argue against the hypothesis that the observed motor learning is simply the result of a general cognitive strategy that presets the reflex's amplitude to a higher or lower value.

Motor learning modifies dynamics of the initial compensatory eye speed of the TVOR

In the open-loop interval of the TVOR, we identified at least two temporally distinct components. The later component began ~34–55 msec after the onset of head motion and was labile. Its amplitude not only could be changed immediately after a new context, but also could be suppressed completely by additional training trials (Figs. 2, 4). It is also evident that there is a substantial difference in the dynamics of the open-loop responses. The profiles of initial eye velocity resembled the profile of head velocity in the high gain state, but resembled the profile of head acceleration in the low gain state. These data suggest that motor learning may target the integration process that converts head acceleration signals into eye velocity signals. In contrast to the late component, the early component apparently is not subject to parametric adjustment and may be only partially modified by additional training trials. Because the measured latency of learning expression is dependent on the intensity of vestibular stimuli in both TVOR (N. Lin, W. Zhou, and W. M. King, unpublished results) and AVOR adaptation studies (Khater et al., 1993; Clendaniel et al., 2001) and our accelerations were limited to 0.3 g, we cannot rule out the possibility that TVOR motor learning may occur within the shortest pathway that generates the TVOR.

Unlike the well established three-neuron arc pathway identified with the AVOR (Lorente De No, 1933; Fernandez and Goldberg, 1971; Scudder and Fuchs, 1992), the neural pathways involved in the TVOR have just begun to be studied (Fernandez and Goldberg, 1976; Uchino et al., 1994, 1996; Angelaki et al., 2001; Chen Huang and McCrea, 1999). Snyder and King (1992) hypothesized that different neural pathways may contribute to the temporal re-

Figure 8. Motor learning is not specific for translation acceleration magnitude or viewing distance. *A*, The initial eye speed was linearly related to acceleration before (left panel, filled symbols) and after (left panel, open symbols) motor learning. *B*, The initial eye speed of the TVOR was proportional to viewing distance before (left panel, filled symbols) and after (left panel, open symbols) motor learning. The asterisks above the bars indicate statistical significance (*t* test, *p* < 0.001).

sponse components of the TVOR. The earliest component of the open loop eye velocity might involve brainstem circuits that include central vestibular and oculomotor neurons via the direct utricle-abducens pathway and the utricle-vestibulo-oculomotor pathways (Uchino et al., 1994, 1996). In contrast, the latency of the latest component of the open loop eye velocity interval is long enough to involve the vestibulo-cerebellum and even cerebrovestibular pathways. Lisberger et al. (1994a,b,c) and Lisberger and Pavelko (1988) showed that gaze-velocity Purkinje cells project monosynaptically to the vestibular nuclei and inhibit neurons involved in the AVOR. Single-unit recordings by Snyder and King (1996) showed that this cell type also encodes a signal related to translational acceleration, suggesting a similar role for the cerebellum in the modulation of the TVOR. Furthermore, the parametric modulation of the late component after a change of context may involve a cerebrovestibular or cerebrocerebellar vestibular pathway wherein a cortical signal reflecting the animal's intention modifies or interacts with afferent vestibular signals. Several studies demonstrate that neurons in the frontal and parietal eye fields encode attention/intention signals associated with task context (for review, see Colby and Goldberg, 1999; Schall and Thompson, 1999) and project monosynaptically to the brainstem VOR pathways (for review, see Guldin and Grusser 1998), suggesting that they could be involved in parametric adjustment of the TVOR.

Sites of neural plasticity

Figure 9 provides a conceptual framework to understand potential neural mechanisms underlying TVOR learning. Linear acceleration may generate compensatory eye movements in any direction and of any amplitude depending on heading, gaze direction,

Figure 9. Hebbian model of the TVOR motor learning. Three potential neural learning sites are shown: 1, sensory limb of the reflex; 2, sensory-motor transformation; 3, motor limb of the reflex. At the sensory-motor transformation stage, the TVOR, the AVOR, and smooth pursuit systems may share the same group of neurons located in the vestibular nucleus and/or the nuclei prepositus hypoglossi. However, each system has its own synaptic contacts with target neurons so that motor learning can be induced independently in each subsystem. Four types of signals are proposed to modulate otolith sensory inflow to oculomotor neurons through presynaptic or postsynaptic inhibition. One signal gates otolith sensory signals according to head orientation so that eye movements can be generated in the correct direction depending on head orientation in space (i.e., θ_H). The second signal is hypothesized to modulate the otolith sensory inflow according to a behavioral context (i.e., VORC condition). The third signal modulates the amplitude of the TVOR according to viewing distance. The fourth signal carries the feedback of its own output.

head orientation, and viewing distance (Paige and Tomko, 1991a,b). Thus, otolith afferent signals must be selectively routed to appropriate premotor circuits to generate the correct eye movement response. Figure 9 schematically illustrates a possible mechanism to transform otolith inflow into upward or downward eye movements depending on head orientation. We assume that eye movement direction is selected or gated by signals that are related to head orientation. This assumption is supported by recent morphological evidence for abundant axo-axonic synapses within the medial vestibular nucleus (Holstein et al., 1999). When the head is tilted to the left, transmission of otolith signals related to rightward translation is blocked by inhibition ($-\theta_H$) from reaching the downward eye movement pathways. However, otolith signals to the upward eye movement pathways are facilitated by disinhibition. Thus, signals related to head acceleration can be channeled into particular premotor eye movement pathways. A goal of this study was to determine whether learning sites could be localized within the sensory limb, the motor limb, or the central sensory-motor transformation stage (vestibular nuclei, cerebellum, and cortex) of the reflex. Our data suggest that learning sites cannot be located at synapse 1 (Fig. 9); otherwise learned changes should be expressed for translations that are similar to the trained direction regardless of the direction of the elicited eye movements (Figs. 6A, 7). The learning sites cannot be at synapse 3 (Fig. 9); otherwise learned changes would be expressed in the eye movement that was in the trained direction but evoked by untrained stimuli (Fig. 6B, Table 4). By exclusion, we conclude that the learning sites are centrally located, presumably in the brainstem and cerebellum. A novel feature of the model illustrated in Figure 9 is that the learning sites are hypothesized to be synapses located on the dendrites of the postsynaptic neuron (site 2). According to this arrangement, only synapses of the neuron that receive inputs from otolith afferents will be modified during

TVOR motor learning. Other synapses of the neuron that receive signals from canal afferents or the smooth pursuit system, remain unchanged. Thus, this model allows for the modification of the response of a neuron to a subset of its inputs, a feature essential to implement modality specificity. Furthermore, Figure 7 shows that otolith activation alone was not adequate to induce motor learning in the TVOR pathway because learning did not take place in the eye without evoked eye movements during training. These data suggest that induction of learning may require the activation of both a vestibular input (presynaptic) and an oculomotor output (postsynaptic), which is characteristic of Hebbian associative learning (for review, see Brown et al., 1990). These characteristics are also shared by rapid saccade adaptation (Fuchs et al., 1996) and smooth pursuit adaptation (Kahlon and Lisberger, 1996, 1999; Chou and Lisberger, 2002). The similarities suggest that motor learning underlying these phenomena may use similar neural mechanisms and that these mechanisms may be widely used by the CNS.

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