Eye Movements, Strabismus, Amblyopia, and Neuro-Ophthalmology

Conjugate Adaptation of Smooth Pursuit during Monocular Viewing in Strabismic Monkeys with Exotropia

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PURPOSE. Humans and monkeys are able to adapt their smooth pursuit output when challenged with consistent errors in foveal/parafoveal image motion during tracking. Visual motion information from the retina is known to be necessary for guiding smooth pursuit adaptation. The purpose of this study is to determine whether retinal motion signals delivered to one eye during smooth pursuit produce adaptation in the fellow eye. We tested smooth pursuit adaptation during monocular viewing in strabismic monkeys with exotropia.

METHODS. To induce smooth pursuit adaptation experimentally, we used a step-ramp tracking with two different velocities (adaptation paradigm), where the target begins moving at one speed ($25°/s$) for first 100 ms and then changes to a lower speed ($5°/s$) for the remainder of the trial. Typically, 100 to 200 trials were used to adapt the smooth pursuit response. Control trials employing single speed step-ramp target motion (ramp speed $= 25°/s$) were used before and after adaptation paradigm to estimate adaptation.

RESULTS. The magnitude of adaptation as calculated by percentage change was not significantly different ($P = 0.53$) for the viewing (mean, $40.3\% \pm 5.9\%$) and the nonviewing (mean, $39.7\% \pm 6.2\%$) eyes during monocular viewing conditions, even in cases with large angle ($18°–20°$) strabismus.

CONCLUSIONS. Our results indicate that animals with strabismus retain the ability to produce conjugate adaptation of smooth pursuit. Therefore, we suggest that a single central representation of retinal motion information in the viewing eye drives adaptation for both eyes equally. (*Invest Ophthalmol Vis Sci.* 2012;53:2038–2045) DOI:10.1167/iovs.11-9011

Visual (retinal) motion signals are essential for smooth pursuit eye movements, which maintain the image of a moving object on or near the fovea. The smooth pursuit system has the capability to adapt to changes associated with development and different environments. For example, adaptive changes of smooth pursuit gain occur using a step-ramp tracking with two different velocities (adaptation paradigm), where the target begins moving at one speed for the first 100 ms and then changes to either a higher or lower speed.[1–4] This adaptation paradigm is designed to provide larger retinal error signals than normal step-ramp tracking. These previous studies using an adaptation paradigm have demonstrated significant adaptive changes in initial smooth pursuit (first 100 ms) after 100 to 200 sequential trials. The first 100 ms of pursuit is defined as an open-loop response that occurs before the time of the visual feedback. It is known that adaptation of initial pursuit underlies plasticity mechanisms in the cerebellum.[4,5] These studies have shown that the cerebellum including flocular complex and oculomotor vermis plays a role in smooth pursuit adaptation. One hypothesis is that repeated coincident inputs of climbing fiber carrying error signals and mossy fiber in the cerebellum are essential for adaptation.[6] Especially for visually guided motor learning, retinal error information is necessary to modify incorrect responses during the cerebellar learning process.

Retinal error information is represented at a number of locations in central visual pathways. Neurons in the nucleus of the optic tract (NOT) are highly sensitive to the direction of visual motion during smooth pursuit, with a preference for motion toward the side of recording.[7–9] The visual motion information in the NOT is derived from contralateral retinal inputs[10] and ipsilateral striate and extrastriate visual cortical areas including the middle temporal cortex (MT).[11–13] Neurons in the NOT have appropriate connections to provide the flocular complex and oculomotor vermis of the cerebellum with retinal error signals through the ipsilateral dorsal cap of Kooy (dcK) and medial accessory (MAO) region of the inferior olive.[13–16] Recently, we have shown that electrical stimulation of the NOT is used to substitute for actual retinal error information to produce smooth pursuit adaptation.[17] Another study using coupled electrical stimulation of MT with smooth pursuit demonstrated that MT provides visual motion signals appropriate for visually guided motor learning during smooth pursuit.[18] Anatomical and functional connectivity studies have demonstrated that MT sends strong inputs to the NOT, which in turn project to the flocular complex of the cerebellum via climbing fiber.[12,19,20]

Although the nature and source of visual information have been demonstrated, it remains uncertain whether retinal error signals delivered to one eye during smooth pursuit produce adaptation in the fellow eye. The main goal of this study was to determine whether adaptation occurs in both viewing and nonviewing eyes during monocular viewing in the normal and strabismic monkeys. It is well known that disruption of coordinated binocular vision early in life leads to strabismus. Previous studies have described that the animals reared with strabismus induced by sensory dissociation evince large horizontal misalignments.[21–23] This is due, in part, to loss of functional connections in cortical–brainstem pathways for visual motion processing. Therefore, we attempted to determine whether directional retinal error information delivered to one eye induces smooth pursuit adaptation in animals with large horizontal misalignment.

MATERIALS AND METHODS

Surgical Procedures

Surgical procedures were performed in a dedicated facility using aseptic techniques under isoflurane anesthesia (1.25%–2.5%). Vital signs including blood pressure, heart rate, blood oxygenation, body temperature, and CO_2 in expired air were monitored with a Surgivet Instrument (Surgivet Inc, Waukesha, WI) and maintained in normal physiological limits. Postsurgical analgesia (buprenorphine, 0.01 mg/kg, intramuscular [IM] and anti-inflammatory (fluxinin meglumine, 1.0 mg/kg, IM) treatment were delivered every 6 hours for several days. We used stereotaxic methods to implant a titanium head stabilization post (Crist Instruments, Hagerstown, MD). In the same surgery, binocular scleral search coils for measuring eye movements[24] were implanted underneath the conjunctiva of both eyes.[25,26] All surgical procedures were performed in strict compliance with the NIH Guide for the Care and Use of Laboratory Animals and the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, and the protocols were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC).

We used one normal (N1) and two strabismic (S1 and S2) juvenile rhesus monkeys (*Macaca mulatta*) in this study. Monkeys with strabismus were reared using visual sensory deprivation methods designed to induce ocular misalignment (alternate monocular occlusion; AMO) for the first 4 to 6 months of life (Fig. 1A).[21–23] In the AMO rearing procedure, after birth (within the first 24 hours), an occluding patch (dark opaque contact lens) was placed in front of one eye for a period of 24 hours and then switched to the fellow eye for the next 24 hours. The patch was alternated daily for a period of 4 to 6 months. Two strabismic monkeys showed constant exotropia with angles of 20° (S1) and 18° (S2) on average when measured in primary position. (Please note that 20° angle of strabismus, which is measured by a coil-based eye position recording, is equivalent to 35.1 prism diopters.) Although visual acuity was not measured in these monkeys, AMO rearing is expected to induce minimal amblyopia. In fact, previous studies have shown that binocular visual acuity for the AMO animals, measured using preferential looking techniques with sinusoidal gratings (Teller Acuity Cards; Vistech Consultants, Dayton, OH), was close to the visual acuity of animals without strabismus.[23,27–29] It has also been reported that the AMO animals alternate fixation and saccade behavior during binocular viewing condition.[23]

Behavioral Paradigms

During all experiments, monkeys were seated in a primate chair (Crist Instruments) with their head stabilized in the horizontal stereotaxic plane. Visual stimuli were rear projected on a tangent screen 57 cm distant. All of our monkeys were extensively trained to perform a fixation task and track a small diameter (0.2°) target spot moving in sinusoidal or step-ramp trajectories. Eye position data (see below) were calibrated by requiring the monkey to fixate a small target spot at known horizontal and vertical eccentricities during monocular viewing. The monkey was rewarded with juice for fixating the target with the viewing eye during monocular viewing (within a ±3° window for duration of 0.5 seconds). Motion of the target spot was produced by a computer-controlled two-axis mirror galvanometer setup (General Scanning, Watertown, MA). The size of the step was adjusted, so that smooth pursuit was initiated without initial saccades.[30] Adaptive changes of horizontal smooth pursuit were produced by a step-ramp tracking with two different velocities (adaptation paradigm). In the adaptation paradigm, the target begins moving at 25°/s for first 100 ms and then changes to 5°/s for the remainder of the trial.[2,3] Smooth pursuit adaptation was evaluated during 100 to 200 trials for each adaptation paradigm. Control trials employing single-speed step-ramp tracking (ramp speed = 25°/s) were used before and after the adaptation paradigm. We conducted one set of adaptation trials in a given experimental session (separate days). Therefore, the three animals were each tested once with either the left or right eye viewing for leftward or rightward pursuit direction (see Table 1).

Data Collection and Analysis

Eye movements were detected using standard electromagnetic methods (Fuchs and Robinson)[24] and scleral search coil systems (CNC Electronics, Seattle, WA). Eye and target position feedback signals were processed with anti-aliasing filters at 200 Hz using 6-pole Bessel filters prior to digitization at 1 kHz with 16-bit precision using CED-Power1401 hardware (Cambridge Electronic Designs, Cambridge, UK). Eye velocity was generated by digital differentiation of the position arrays using a central difference algorithm in Matlab (Mathworks, Natick, MA). Saccades (velocity criterion > 50°/s) were marked with a cursor on eye velocity traces and were removed. After desaccading, the missing eye data were replaced with a linear fit connecting the pre- and post-saccadic regions of data using custom Matlab routines. Pursuit initiation during step-ramp tracking was taken as the time that average eye speed reached ≥3 SD above the pretrial values during fixation. To quantitatively estimate smooth pursuit adaptation, we calculated initial acceleration as the average eye acceleration in the first 100 ms of smooth pursuit.

RESULTS

Monocular Smooth Pursuit in Strabismic Monkey

Figure 1 illustrates representative horizontal smooth pursuit eye position and velocity during monocular viewing conditions in the exotropic monkey S1. The angle of the exotropia is measured by recording eye movements simultaneously from both eyes. During step-ramp tracking, the viewing eye (left eye) was on target, while the nonviewing eye (right eye) displayed an exotropia (angle = 19.6°; Fig. 1A). Furthermore, XY plots of viewing and nonviewing eyes (right panel) show a large horizontal misalignment, but a relatively small vertical misalignment (angle = 3.5°). Although the nonviewing eye was exotropic, eye velocity traces (Fig. 1B) document that both the viewing and nonviewing eyes moved conjugately during step-ramp tracking (target speed = 25°/s). For example, mean steady-state eye velocity for viewing eye (23.2°/s ± 2.3°/s) was similar to that for nonviewing eye (24.3°/s ± 2.8°/s, $P = 0.35$, unpaired *t*-test). Furthermore, initial pursuit acceleration (mean eye acceleration for first 100 ms of tracking), which was used to estimate smooth pursuit adaptation, also showed similar values between viewing and nonviewing eyes (125.3°/s^2 ± 11.7°/s^2 for viewing eye, 129.6°/s^2 ± 10.1°/s^2 for nonviewing eye, $P = 0.39$, unpaired *t*-test). Table 1 shows mean eye acceleration values in each testing condition (12 experimental sessions in total) including left or right eye viewing for leftward and rightward pursuit directions in one normal (N1) and two strabismic (S1, S2) monkeys. Initial eye acceleration of viewing eye (121.2°/s^2 ± 27.0°/s^2) and nonviewing eye (118.9°/s^2 ± 25.0°/s^2) were not significantly different ($P = 0.44$, paired *t*-test for the whole group) in all the conditions tested (Table 1, pre-adaptation).

Smooth Pursuit Adaptation during Monocular Viewing

Figure 2 shows a representative smooth pursuit adaptation experiment using the step-down adaptation paradigm (ramp speed = 25°/s to 5°/s) during monocular viewing condition (left eye viewing) in strabismic monkey S1. The adaptation paradigm is designed to decrease initial eye acceleration during smooth pursuit. To estimate smooth pursuit adaptation quantitatively, we calculated trial-by-trial initial acceleration as
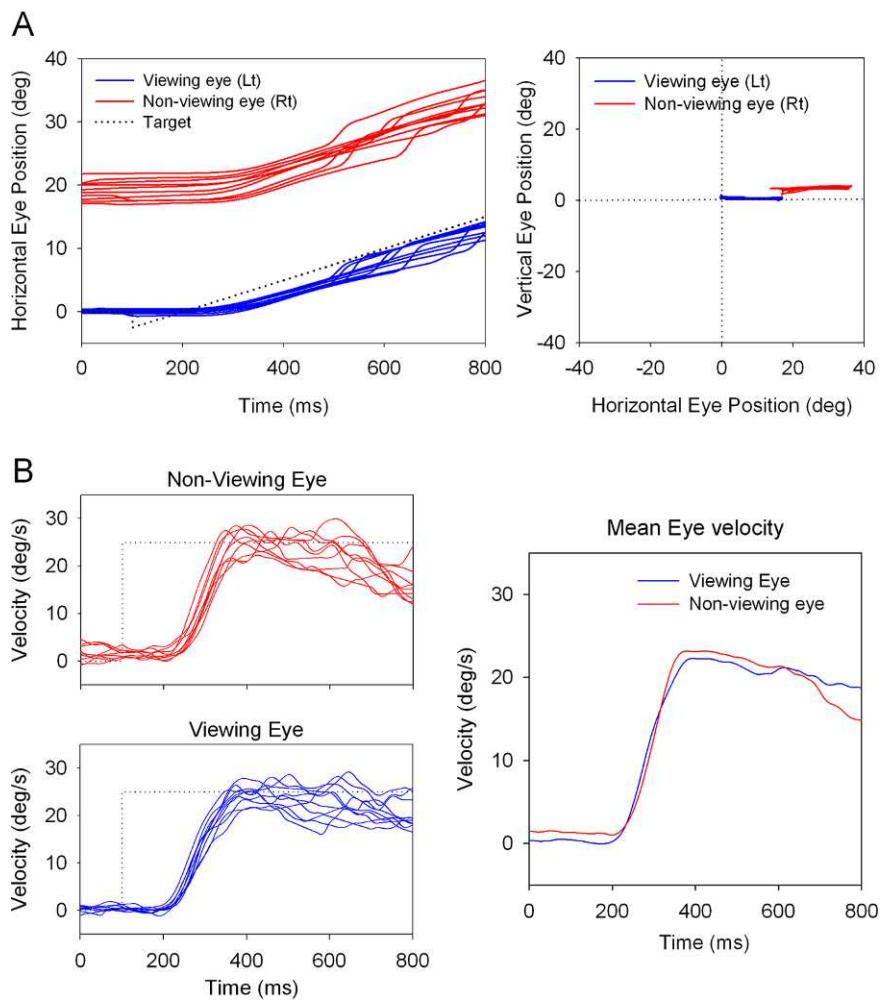
FIGURE 1. Horizontal smooth pursuit during monocular viewing (left eye viewing) in strabismic monkey S1. **(A)** Horizontal eye position traces of viewing eye (left eye, blue lines) and nonviewing eye (right eye, red lines) are shown as a function of time (*left panel*). XY plots of viewing eye (left eye) and nonviewing eye (right eye) during horizontal smooth pursuit (*right panel*). **(B)** Eye velocity traces of individual trials (*left panel*) and mean eye velocity traces (*right panel*) of viewing and nonviewing eyes are shown. Upward deflections show rightward eye motion.

TABLE 1. Initial Eye Acceleration of Viewing and Nonviewing Eyes during Smooth Pursuit

Exp. No.	Viewing Condition	Direction	Pre-Adaptation Eye Acceleration (°/s²)		Post-Adaptation Eye Acceleration (°/s²)		Adaptive Change (%)	
			VE	NVE	VE	NVE	VE	NVE
N1-1	LEV	Ltward	166.2 ± 15.7	159.8 ± 17.4	107.1 ± 18.5	101.8 ± 16.6	35.6	36.3
N1-2	LEV	Rtward	136.8 ± 18.6	122.6 ± 21.6	91.9 ± 21.7	84.6 ± 20.4	32.8	31.0
N1-3	REV	Ltward	165.7 ± 17.5	151.4 ± 18.7	110.5 ± 11.5	105.5 ± 14.9	33.3	30.3
N1-4	REV	Rtward	131.3 ± 15.2	132.2 ± 9.8	88.8 ± 12.5	85.0 ± 16.1	32.4	35.7
S1-1	LEV	Ltward	118.3 ± 10.1	120.6 ± 8.9	77.0 ± 11.9	76.1 ± 13.3	34.9	36.9
S1-2	LEV	Rtward	125.3 ± 11.7	129.7 ± 10.1	81.0 ± 11.2	83.2 ± 12.0	35.4	35.9
S1-3	REV	Ltward	94.3 ± 21.7	85.0 ± 12.3	63.2 ± 18.2	58.5 ± 19.4	33.0	31.2
S1-4	REV	Rtward	80.0 ± 11.5	74.9 ± 11.5	50.6 ± 19.9	49.9 ± 17.5	36.8	33.4
S2-1	LEV	Ltward	106.3 ± 17.5	126.8 ± 19.4	58.5 ± 15.3	73.6 ± 16.6	45.1	42.0
S2-2	LEV	Rtward	130.3 ± 23.8	121.6 ± 24.3	72.2 ± 17.4	64.1 ± 14.3	44.6	47.3
S2-3	REV	Ltward	98.2 ± 19.3	95.3 ± 15.6	51.2 ± 13.4	53.1 ± 11.9	47.9	44.3
S2-4	REV	Rtward	101.6 ± 21.8	107.7 ± 19.9	55.9 ± 12.4	56.9 ± 13.5	45.0	46.8

Exp., experiment; VE, viewing eye; NVE, nonviewing eye; Ltward, leftward; Rtward, rightward.
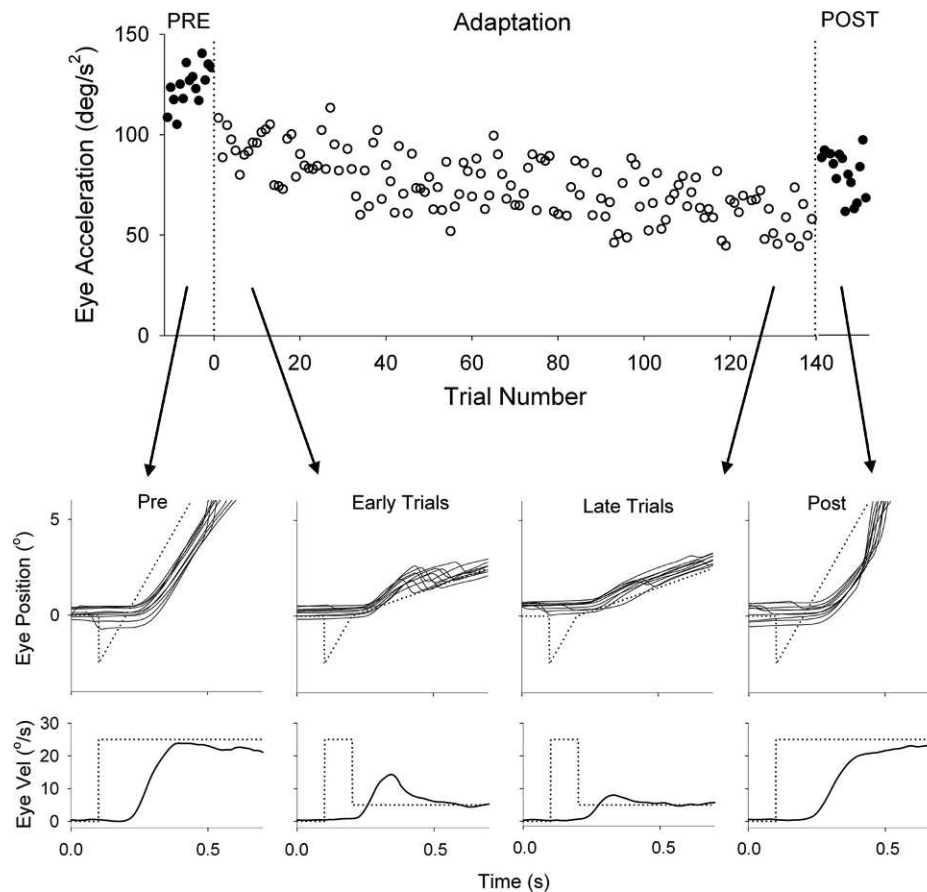
FIGURE 2. Smooth pursuit adaptation using adaptation (step-down) paradigm during monocular viewing in strabismic monkey S1. *Top panel*: initial acceleration (first 100 ms) of viewing eye during adaptation shown as a function of trial number (open circles). During adaptation, the target began moving at 25°/s for the first 100 ms and stepped down to 5°/s. Pre- and post-adaptation trials (control trials, ramp speed = 25°/s) are shown on the left and right, respectively (filled circles). *Bottom panel*: eye position and mean eye velocity traces are shown for pre- and post-adaptation, early and late in adaptation.

the average eye acceleration in the first 100 ms of smooth pursuit. Individual initial eye acceleration values during the step-down paradigm are plotted as a function of trial number (Fig. 2, top panel). The viewing eye showed significant adaptive changes of initial eye acceleration occurring continuously during adaptation trials (first 10 trials = $94.6°/s^2 \pm 8.1°/s^2$; last 10 trials = $54.9°/s^2 \pm 9.8 °/s^2$, $P < 0.001$, unpaired t-test). The time course of the adaptation comprised a gradually decreasing initial eye velocity over 100 trials. The bottom panels of Figure 2 illustrate eye position and velocity traces of the viewing eye, pre-adaptation, during the course of adaptation (early and late), and post-adaptation. In the early trials, eye motion overshoots the target after target speed decreases to 5°/s. In late adaptation, eye position nearly matches the second target speed, revealing an adapted initial smooth pursuit response. Eye velocity traces showed that a clear progression in smooth pursuit adaptation occurs from early to late trials.

Comparison between Viewing and Nonviewing Eyes during Adaptation

Figure 3 shows eye position traces of the viewing eye (A) and nonviewing eye (B) in exotropic monkey S1. During the adaptation paradigm, the viewing eye (left eye) is on target, while the nonviewing eye (right eye) is exotropic with a strabismus angle of 17° to 22°. Even though eye position of the

nonviewing eye showed much more variability (SD = 1.56°) than the viewing eye (SD = 0.24°), both eyes followed the same motion pattern. The nonviewing eye also overshot the target in early adaptation, while there were fewer overshoots in late adaptation trials. These adaptive changes are best illustrated using average eye velocity traces. Comparisons of pre- and post-adaptation eye velocity records are shown in Figure 4. Both the viewing and nonviewing eyes moved conjugately during adaptation, even in the presence of a large-angle strabismus. There is a clear adaptive change in both the viewing and nonviewing eyes post adaptation (Fig. 4, upper panels). Figure 5 shows quantitative estimates of smooth pursuit adaptation in the viewing and nonviewing eyes. We calculated initial acceleration as the average eye acceleration in the first 100 ms of smooth pursuit. Individual initial eye accelerations during adaptation across 100 trials were plotted. The normal monkey N1 (Fig. 5A) showed significant adaptive changes of initial eye acceleration in both the viewing eye ($166.2°/s^2 \pm 15.7°/s^2$, pre-adaptation; $107.1°/s^2 \pm 18.5°/s^2$, post-adaptation; $P < 0.001$, unpaired t-test) and nonviewing eye ($159.8°/s^2 \pm 17.5°/s^2$, pre-adaptation; $101.8°/s^2 \pm 16.6°/s^2$, post-adaptation; $P < 0.001$, unpaired t-test). The strabismic monkey S1 (Fig. 5B) also showed conjugate adaptation in initial eye acceleration for the viewing eye ($125.3°/s^2 \pm 11.7°/s^2$, pre-adaptation; $81.0°/s^2 \pm 11.2°/s^2$, post-adaptation; $P < 0.001$, unpaired t-test) and nonviewing eye ($129.7°/s^2 \pm 10.1 °/s^2$, pre-adaptation; $83.2 \pm 12.0 °/s^2$, post-adaptation; $P < 0.001$, unpaired t-test). All the conditions tested (Table 1) showed
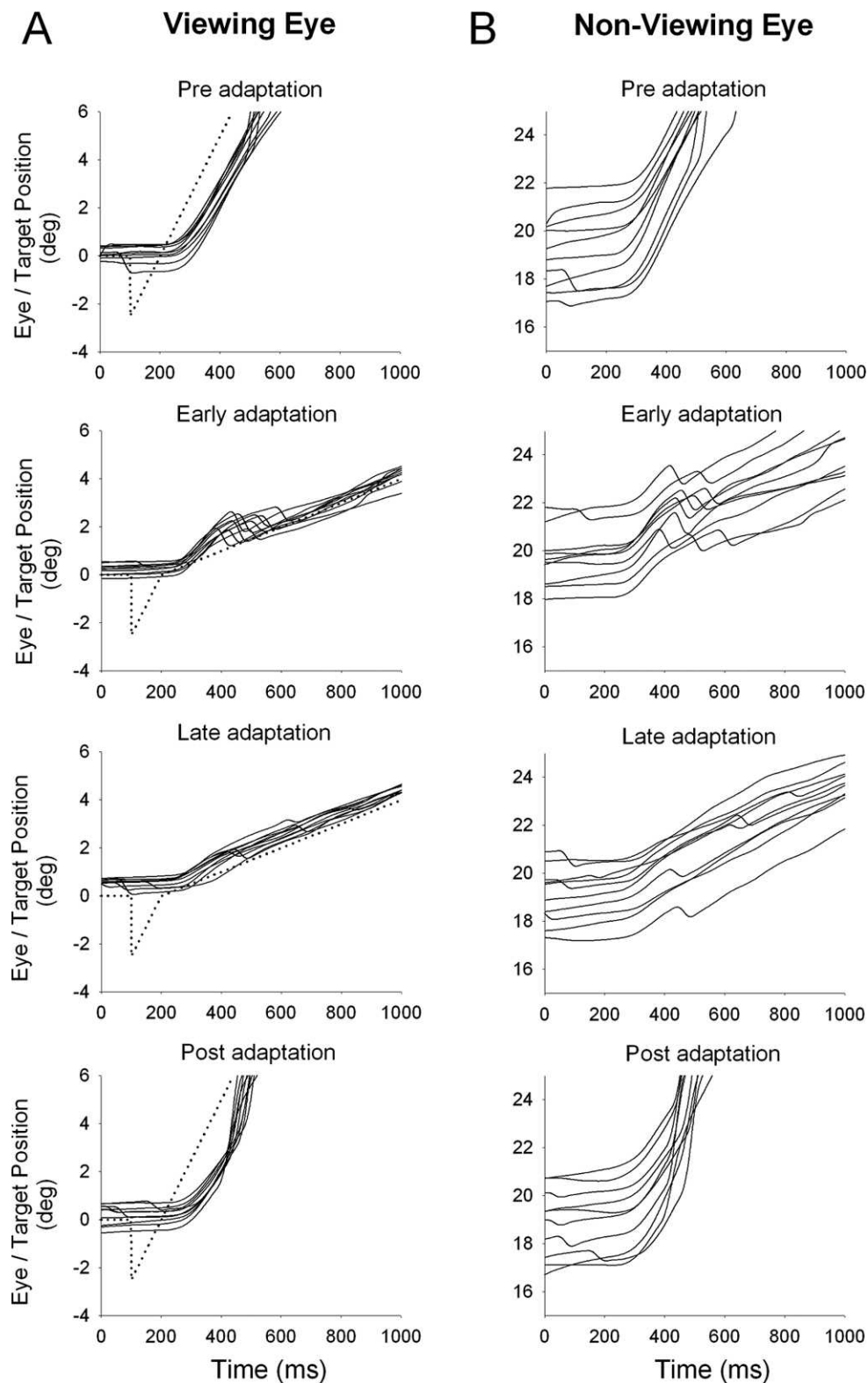
FIGURE 3. Representative eye and target position traces of viewing eye (**A**) and nonviewing eye (**B**) from strabismic monkey S1are shown as a function of time. From top to bottom, panels show pre-adaptation (control trials), early in adaptation (first 10 trials), late in adaptation (last 10 trials of adaptation), and post-adaptation trials.

significant adaptive changes in initial eye acceleration for both the viewing and nonviewing eyes ($P < 0.001$, paired *t*-test). Figure 6 shows comparisons of the percentage change in eye acceleration between pre- and post-adaptation for the viewing

and nonviewing eyes. Percentage change in eye acceleration ranged from 32.4% to 47.9% (mean, 38.0% ± 5.8%) in the viewing eye and from 30.3% to 47.3% (mean, 37.6% ± 6.1%) in the nonviewing eye. Mean values of percentage change in the
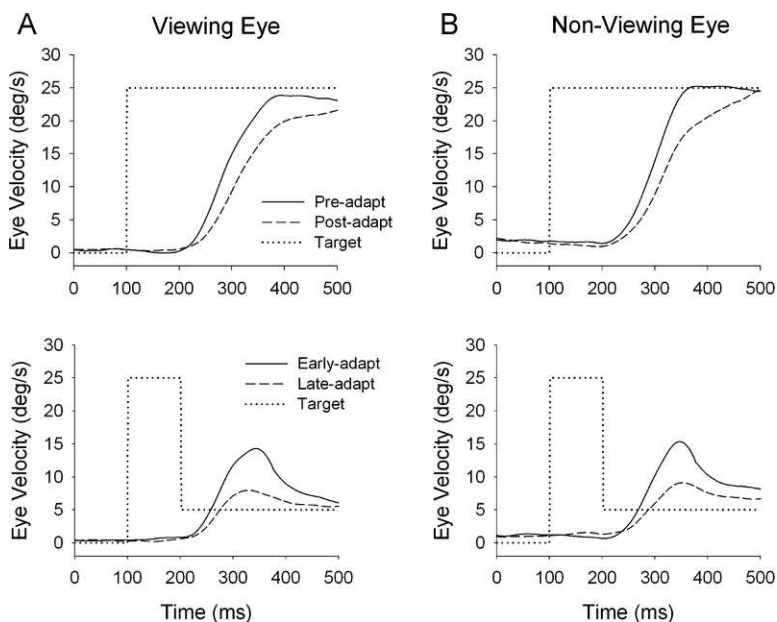
FIGURE 4. Representative eye and target velocity traces of viewing eye (**A**) and nonviewing eye (**B**) in strabismic monkey S1 are shown as a function of time. *Top panel*: traces from control trials pre- (solid lines) and post-adaptation (dashed lines). *Bottom panel*: traces from early (first 10 trials; solid lines) and late (last 10 trials; dashed lines) in adaptation. Eye velocity traces were de-saccaded. Dotted lines indicate target velocities. Adaptation occurs for both the viewing eye (**A**) and the nonviewing eye (**B**).
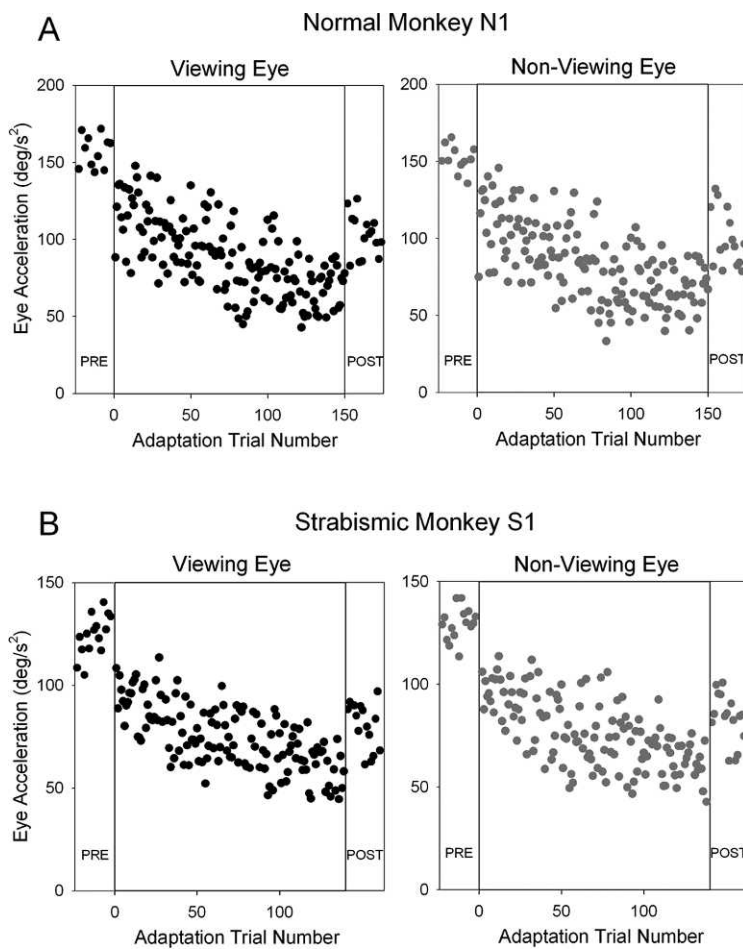

FIGURE 5. Initial eye acceleration (first 100 ms of tracking) of viewing eye (*left panel*) and nonviewing eye (*right panel*) in normal monkey N1 (**A**) and strabismic monkey S1 (**B**) shown as a function of trial number. Eye acceleration evinced significant adaptive change in both the viewing and nonviewing eyes. Plots also show that smooth pursuit adaptation is similar in normal and strabismic monkeys during monocular viewing.
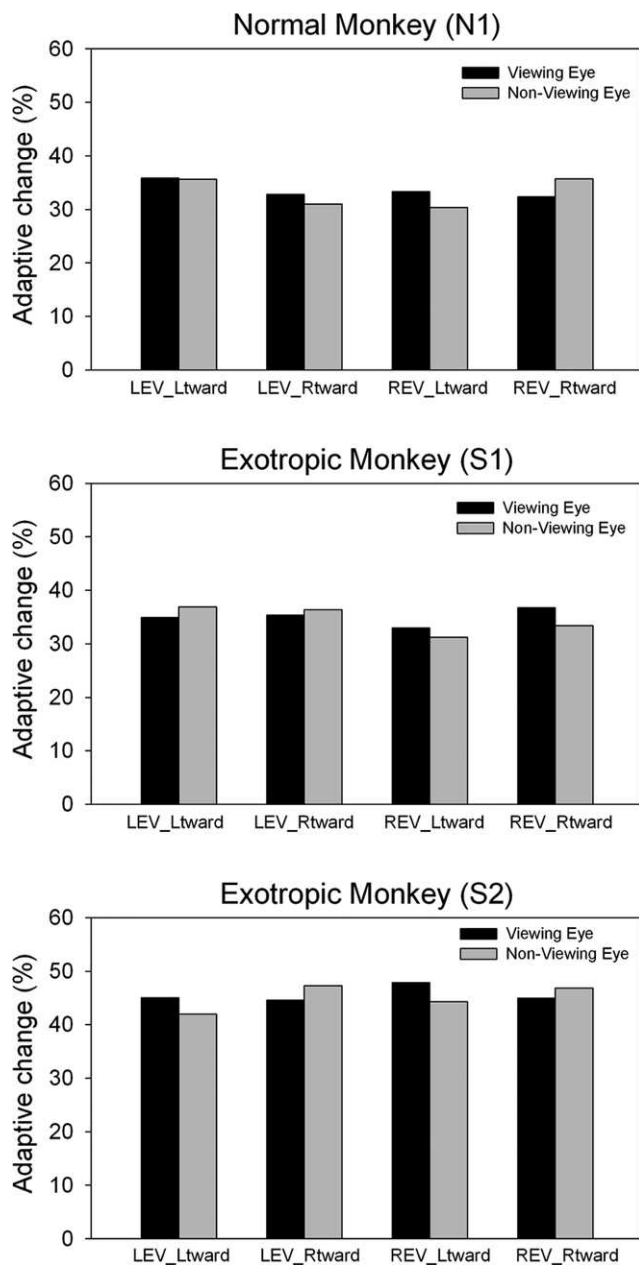
Normal Monkey (N1)

Exotropic Monkey (S1)

Exotropic Monkey (S2)

FIGURE 6. Percentages of adaptive change in normal monkey N1 and strabismic monkeys S1 and S2. Bar graphs show that percentages of adaptive change for viewing and nonviewing eyes are not significantly different, pre- and post-adaptation in left- (LEV) and right-eye viewing (REV) conditions.

viewing and nonviewing eyes were not significantly different (Table 1, $P = 0.54$, paired *t*-test for the whole group).

DISCUSSION

Our study was designed to examine the adaptive capability of horizontal smooth pursuit in normal and strabismic monkeys under monocular viewing conditions. The goal of this study was to determine whether monkeys with large-angle exotropic strabismus adapt both eyes equally. We found that strabismic monkeys showed conjugate adaptation of their initial smooth pursuit during the adaptation paradigm.

It has been demonstrated previously that daily alternating monocular viewing early in postnatal development produces a large-angle exotropia[21-23] and a small angle esotropia.[31,32] This form of early visual experience prevents binocular visual experience and could be associated with loss of functional binocular connections in cortical–brainstem pathways for visual-oculomotor control. Previous studies have demonstrated evidences for uniocular control of each eye in oculomotor circuits.[33,34] It has also been reported that strabismic monkeys displayed disconjugate saccade eye movements.[23] However, our results suggest that the pursuit adaptation system may involve a conjugate adaptive circuit mechanism even in animals with large misalignments and impoverished binocular sensitivity. In studies of saccade adaptation using an induced aniseikonia, Bucci and colleagues[35] found that strabismic subjects with residual binocular visual sensitivity could produce dysconjugate adaptation, but those with no measurable disparity sensitivity showed only conjugate adaptation. Our findings are also consistent with the results of previous studies, which demonstrated that transfer of saccade adaptation occurs between the viewing and the nonviewing eyes under monocular viewing conditions in normal humans[36] and strabismic monkeys.[37] Recent studies have suggested that sources of visual (retinal) error signals, which induce visually guided motor learning, are different between saccade[38] and smooth pursuit adaptation.[17] Therefore, we sought to determine whether directional retinal error information delivered to one eye induces conjugate smooth pursuit adaptation in animals with large horizontal misalignments.

We have shown that the pretectal NOT is a major source of error information that could provide instructive signals for visually guided motor learning during smooth pursuit.[17] The NOT provides the floccular complex and oculomotor vermis of the cerebellum with retinal error signals through the ipsilateral dorsal dcK and MAO region of the inferior olive.[13-16] The floccular complex and oculomotor vermis are known to play a role in smooth pursuit adaptation induced by the adaptation paradigm.[4,5] In fact, the visual sensitivity of units in the NOT is derived from contralateral retinal inputs[10] and ipsilateral striate and extrastriate visual cortical areas including the MT.[11-13] It has also been demonstrated that NOT neurons show binocular sensitivity in normal monkeys[39] and in monkeys reared with AMO.[40] Therefore, our results suggest that a single central representation of retinal error information in the viewing eye drives adaptation for both eyes equally. Conjugate smooth pursuit adaptation mechanisms could remain intact in animals with strabismus.

Furthermore, all of the smooth pursuit–related neurons in the NOT are sensitive to ipsiversive retinal image motion.[7-9] If NOT neurons in strabismic monkeys do not have binocular sensitivity, we would expect that the percentage of adaptive change could be different between left- and right-eye viewing conditions. However, our results showed that the percentage changes between different viewing conditions were not significantly different, even in cases with large-angle strabismus (see Fig. 6). Therefore, it is most likely that NOT or MT visual motion-related neurons, which could have binocular sensitivity, are important sources of instructive signals for guiding smooth pursuit adaptation during monocular viewing conditions.

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