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Further evidence for selective difficulty of upward eye pursuit in juvenile monkeys: effects of optokinetic stimulation, static roll tilt, and active head movements

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Abstract

The smooth-pursuit system moves the eyes in space accurately to track slowly moving objects of interest despite visual inputs from the moving background and/or vestibular inputs during head movements. Recently, our laboratory has shown that young primates exhibit asymmetric eye movements during vertical pursuit across a textured background; upward eye velocity gain is reduced. To further understand the nature of this asymmetry, we performed three series of experiments in young monkeys. In Experiment 1, we examined whether this asymmetry was due to an un-compensated downward optokinetic reflex induced by the textured background as it moves across the retina in the opposite direction of the pursuit eye movements. For this, we examined the monkeys' ability to fixate a stationary spot in space during movement of the textured background and compared it with vertical pursuit across the stationary textured background. We also examined gains of optokinetic eye movements induced by downward motion of the textured background during upward pursuit. In both task conditions, gains of downward eye velocity induced by the textured background were too small to explain reduced upward eye velocity gains. In Experiment 2, we examined whether the frame of reference for low-velocity, upward pursuit was orbital or earth vertical. To test this, we first applied static tilt in the roll plane until the animals were nearly positioned on their side in order to dissociate vertical or horizontal eye movements in the orbit from those in space. Deficits were observed for upward pursuit in the orbit but not in space. In Experiment 3, we tested whether asymmetry was observed during head-free pursuit that requires coordination between eye and head movements. Asymmetry in vertical eye velocity gains was still observed during head-free pursuit although it was not observed in vertical head velocity. These results, taken together, suggest that the asymmetric eye movements during vertical pursuit are specific for upward, primarily eye pursuit in the orbit.

Key Words: Smooth-pursuit, visual background, directional asymmetry, roll tilt, head-free pursuit

Introduction

The evolution of a high acuity fovea in primates requires maintaining target images on the foveae of both eyes in order to obtain accurate visual information. For small objects moving smoothly in fronto-parallel planes, the smooth-pursuit system is used to move the eyes in space while compensating for visual inputs from the moving background and/or vestibular inputs during head movements (see Leigh and Zee 1999 for a review). Recently, our laboratory has shown that young primates produce asymmetric eye movements during vertical pursuit across a textured background such that upward pursuit has low velocity and requires many catch-up saccades. This upward pursuit deficit was correlated with an inability to cancel the downward vestibulo-ocular reflex (VOR) during upward pitch rotation when the monkeys were required to fixate a target that moved with them (Takeichi et al. 2003).

To understand the neural substrates underlying this directional asymmetry, we need to further characterize this asymmetry. In this study we asked three questions. In Experiment 1 we asked whether this asymmetry was due to an un-compensated downward optokinetic reflex induced by the textured background as it moves across the retina in the opposite direction of the pursuit eye movements. To test this, we examined the monkeys' ability to fixate a stationary spot in space during movement of the textured background and compared it with vertical pursuit across the stationary textured background. We also examined gains of optokinetic eye movements induced by downward motion of the textured background during upward pursuit, because the gain of optokinetic responses could be different during fixation of a stationary spot on one hand and pursuit of a moving spot on the other (cf. Kawano and Miles 1986).

In Experiment 2 we asked whether the asymmetry was due to the control of eye movements in the orbit or eye movements in space. Although ineffective VOR cancellation during upward passive whole body rotation may suggest a deficit in the control of gaze (eye in space) movements (e.g.,

Lisberger and Fuchs 1978), it does not exclude the possibility that it is due to inability to generate appropriate upward eye movement signals to cancel the downward VOR induced by upward pitch rotation (see Leigh and Zee 1999 for a review). To examine this, we tested vertical pursuit while the animals were tilted in the roll plane nearly on their sides. Because it is well known that the gain of ocular counter-roll to static roll tilt is very low (~ 0.1 , see Leigh and Zee 1999 for a review), this method allowed us to dissociate vertical or horizontal eye movements in the orbit from those in space.

Because in head-free subjects smooth-pursuit is performed by coordination of eye and head movements (i.e., gaze-pursuit), in Experiment 3 we asked whether asymmetry was observed during head-free pursuit and whether head movements also revealed asymmetry. We show that the low-velocity, upward pursuit cannot be explained solely by an un-compensated downward optokinetic reflex and that the asymmetry is specific for upward, primarily eye, pursuit execution in the orbit.

Materials and Methods

Five male Japanese monkeys (K, M, B, H, Q, *Macaca fuscata*, 4.0-5.5 kg) were used. Three of them (K, M, H) were the same monkeys used in previous studies (Takeichi et al. 2003). As previously described, ages of monkeys (K, M, B, H) were determined by their dental ages defined by tooth eruption during initial training. Full eruption of all the permanent teeth occurs by 6.25 years old (Mouri 1994). Two monkeys (K, M) were approximately 5 years old for Experiment 1 and 2. Monkey H was approximately 6.5 years old during Experiment 1. Monkey Q whose birth month was known to us was 4 years old for Experiment 1. Monkeys (K, M) were 5 and 6 years old, respectively, for Experiment 3. Monkey B was also 6 years old during Experiment 3. Mouri (1994) reported that in Japanese macaques' adolescent growth, the male spurt seems to start far after the end of the female spurt. Thus, all the monkeys tested in this study seem to be juvenile. Our experimental protocols were approved by the Animal Care and Use Committee of Hokkaido University

School of Medicine.

Our methods for animal preparation and training, eye movement recording and data analysis were described in detail previously (Takeichi et al. 2003) except for those for motion of the textured background during pursuit, static whole body roll tilt and head-free pursuit. Briefly, each monkey was sedated with ketamine hydrochloride (5 mg/kg, i.m.), and then anesthetized with pentobarbital sodium (25 mg/kg, i.p.). Under aseptic conditions, head holders were installed to restrain the head firmly in the primate chair in the stereotaxic plane. Vertical and horizontal components of eye movements were recorded by the scleral search coil method (Fuchs and Robinson 1966). Analgesics and antibiotics were administered post-surgically to reduce pain and prevent infection. Following a week of recovery, the monkeys were rewarded with an apple juice for tracking a laser spot (0.2° in diameter) that was back-projected onto a vertical screen 75 cm in front of the animals' eyes that subtended 60° by 80° of visual angle. Two different types of backgrounds, homogeneous or textured, were presented on the vertical screen during target movements as described previously (Takeichi et al. 2003). For the homogeneous background, the screen was kept dim with the mean luminance of 0.1 cd/m^2 . The stationary textured background was a random dot pattern consisting of 100 dots. The mean luminance of the dark part of the textured background was 0.1 cd/m^2 and that of the bright part (dots) was 25 cd/m^2 . Dots were not presented along the target trajectories. The dot-free band was $\pm 1.5^\circ$. Smooth-pursuit was induced by spot motion at 0.5Hz ($\pm 10^\circ$) with or without the textured background. Reward circuits compared target position signals with the monkeys' gaze (eye in space) position signals. If the monkeys' gaze was within the error window of $\pm 1^\circ$ for 0.5-1 s, a drop of apple juice was automatically delivered to the monkeys (Fukushima et al. 2000).

In Experiment 1, the visual pattern was moved vertically at 0.5Hz ($\pm 10^\circ$) while the reward spot was maintained stationary in space in two head restrained monkeys (K, M). In two other monkeys (H, Q) the textured background was also moved at a constant velocity ($5^\circ/\text{s}$) while the reward spot was maintained stationary. In these monkeys, we also examined magnitudes of eye movement responses induced by motion

of the textured background during pursuit. For this, the pursuit target moved vertically at a constant velocity ($5^\circ/\text{s}$) between 10° down to 10° up of the straight-ahead position in a trapezoidal trajectory with the inter-trial interval of 1s while the textured background was stationary. When the target reached the straight-ahead position, the textured background was moved for 2 s at a constant velocity ranging from 3 to $15^\circ/\text{s}$ either upward or downward. Monkeys were required to continue pursuing the target moving at $5^\circ/\text{s}$. To induce optokinetic responses, the textured background was projected onto a mirror attached to a servomotor (General Scanning) and was moved by using a position signal derived from the computer. We also used a 22 inch computer monitor (120 Hz frame rate, Sony) for moving the reward spot and textured background. The textured background was a random dot pattern consisting of 100 dots of $1^\circ - 2^\circ$ diameter with the dot-free band of $\pm 1.5^\circ$. The mean luminance of the dark part of the textured background was 0.1 cd/m^2 and that of the bright part (dots) was 45 cd/m^2 .

In Experiment 2, we applied spot motion during static whole body roll tilt in the two monkeys (K, M) with their head stabilized by the head-holder. For this, a 14 inch computer monitor was used and a red spot (0.2° in diameter) was presented as a target for pursuit as used previously (Takeichi et al. 2003). The stationary textured background was a random dot pattern consisting of 100 dots of $1^\circ - 2^\circ$ diameter. Our laboratory has shown that the asymmetry for these monkeys was not affected by the use of the computer monitor instead of the vertical screen (Takeichi et al. 2003). The computer monitor together with the whole body and the coil frame for detection of eye movements was tilted in the roll plane to 80° from the earth vertical (either right ear down or left ear down). Target motion was applied in two conditions at 0.5Hz ($\pm 10^\circ$); in one, it was moved earth-vertically or earth-horizontally, and in the other it was moved monkey-vertically or horizontally either with or without the textured background.

In Experiment 3, we tested smooth-pursuit in a head-free condition in three monkeys (M, K, B), while they sat in the upright position facing the vertical screen 75 cm in front of the animals' eyes. The monkeys' body movement was restricted back and front by polystyrene foam so that they were unable to move their

trunk and sat in the primate chair with their back positioned near the earth vertical axis. All monkeys were trained to rotate their heads freely in this condition with minimal head translation. The estimated axis for horizontal head rotation was 1 cm behind the inter-aural midpoint of the animal's head. The estimated axis for vertical head rotation was close to the upper cervical spinal cord (C2-C3). Vertical and horizontal components of head movements were detected by a search coil that was attached to the head holder (i.e., head coil). The feeder for juice reward was attached to the head holder by a mechanical device so that the feeder moved together with the monkeys' head during pursuit in the horizontal and vertical direction at 0.5 Hz ($\pm 20^\circ$). Initially, this device weighed 500 g and head movements of all three monkeys were small. In later series of experiments, we revised the device and it weighed only 70 g. Because monkey M had been used for some other experiments before this new device was used, only two monkeys (K, B) were tested using the new device. Head movements were continuously monitored by an infrared camera.

All experiments were repeated on different days typically 5-7 times to calculate overall means for each monkey.

Data analysis

Eye-, target-, and head- position signals (in Experiment 3) were digitized at 500 Hz using a 16-bit A/D board (National Instruments) on a Macintosh Quadra computer. Signals from eye coils and head coils were differentiated by analogue circuits (DC-100 Hz, -12 dB/octave) to obtain velocity. During head-free pursuit, signals from the eye coils indicated gaze position (i.e., eye position in space). Our monkeys occasionally did not pursue the target. Such poor performance that was judged from the eye/gaze position traces was not considered and only those traces in which monkeys pursued the target were accepted for analysis. Eye position-in-orbit signals were obtained by subtracting head coil signals from the gaze position signals. Because the axes for head movements were shifted from the axis of eye rotation during head-free pursuit (see above), we compared eye movement signals using the values obtained by the simple subtraction described above and those calculated using the equation provided by Collewijn et al. (1982). For this, we

used values for the screen distance of 75 cm, inter-ocular distance of the monkeys of 20-21 mm, and the estimated distance between the axis of head rotation and the inter-ocular midpoint of 50 mm. The calculated values differed by only 5% for horizontal eye movements and 7% for vertical eye movements. Because these differences did not clearly affect our results, we used un-corrected values obtained by the simple subtraction.

Saccades were marked with a cursor on eye- and gaze- velocity traces and removed using the interactive computer program (Singh et al. 1981; Fukushima et al. 2000). More than 20 traces were aligned with stimulus velocity to obtain means and standard deviations (SD) for each session. To obtain gains for gaze-, eye- or head- velocity (re target velocity), a sine function was fitted to velocity traces using a least-squared error algorithm. The phase-shift of the peak of the fitted-function relative to stimulus velocity was calculated as a difference in degrees. Gain was calculated as the peak amplitude of the fundamental component divided by the peak amplitude of the fitted stimulus velocity. These values were further averaged to obtain overall means (\pm SD) for different sessions on different days for individual monkeys.

To examine eye movement responses induced by motion of the textured background during pursuit of a target moving at a constant velocity in Experiment 1, typically 50 traces were superimposed with respect to the stimulus onset. Traces in which saccades appeared within \sim 1s of the stimulus onset were omitted. Eye movement responses evoked by motion of the textured background using the mirror/galvanometer and the computer monitor were basically similar in their magnitudes with the tendency that latencies of optokinetic responses induced by the mirror/galvanometer were slightly shorter (85-100ms) compared to the latencies induced by the textured background motion on the computer monitor (90-105 ms). We therefore combined the data for comparing magnitudes of eye movement responses. As described below (Fig. 3A), optokinetic responses induced by the motion of the textured pattern had two components; the initial transient response and later steady-state response. We examined peak eye velocity for the initial response that occurred within 300 ms after onset of the background motion. For the steady state response, average eye velocity was calculated during 1-1.5 s after onset of the background motion.

Figure 1 near here

During head-free pursuit in Experiment 3, fast head movements may have contributed to calculation of head velocity gains. To examine this, we first detected fast head movements visually by comparing head position and velocity traces with target position and velocity, and measured peak velocities of individual fast head movements. Peak velocities ranged from 28 to 127°/s with the mean (\pm SD) of 67 (\pm 26)°/s for target pursuit at 0.5 Hz (\pm 20°, peak velocity 63°/s). We then compared head velocity gains with or without removing fast head movements manually. Figure 1 shows representative records for superimposed horizontal (A) and vertical (B) head position and velocity traces of monkey B before (Fig. 1A1, B1) and after removing fast head movements (Fig. 1A2, B2). As described below, head velocity did not exhibit a clear asymmetry for rightward and leftward or upward and downward movements. Therefore, to compare the effects of removing fast head movements, we calculated head velocity gains by fitting a sinusoid to averaged head velocity traces. As summarized in Fig. 1A3, B3, plotting head velocity gains without removing fast head velocity against those after removing fast head movements revealed regression slopes close to one in both horizontal (A3, 1.00) and vertical (B3, 0.88) directions. Because there were minimal differences, we used head velocity traces without removing fast head movements for further analysis.

As reported previously, vertical pursuit of young monkeys exhibited an asymmetry (Takeichi et al. 2003). For asymmetric eye- and gaze- (eye + head) velocity responses during sinusoidal vertical pursuit with or without accompanying head movements (see **Results**), we measured peak eye velocity for upward and downward components separately by manually positioning a horizontal cursor on the peak of the mean eye velocity trace on the computer monitor (e.g., Fig. 2A, mean \pm SD). Then, by dividing means of these values by peak stimulus velocity, mean gains for upward and downward eye velocity were calculated separately. Mean gains for upward and downward gaze velocity and head velocity were calculated similarly for consistency. Phase-shifts for upward and downward eye-, gaze-, and head- velocity were calculated manually by measuring the peak of their responses to stimulus velocity. Although head velocity traces did

not show an obvious asymmetry during vertical pursuit, upward and downward head velocity gains were calculated manually in the similar manner as described above to be consistent with the analysis for vertical gaze- and eye- velocity gains. Student *t* tests and ANOVA were used for statistical analysis on values collected on different days for each condition. We defined significant differences as a p-value <0.05.

Figures 2 and 3 near here

Results

Experiment 1: Effects of optokinetic stimulation

Fixation of a stationary spot

In two juvenile monkeys (K, M), we compared their ability to pursue vertically across a stationary, textured background and to fixate a stationary spot during movement of the textured background. As reported earlier (Takeichi et al. 2003), these monkeys had difficulty with upward pursuit when a stationary textured (but not a homogeneous) visual background was present (see **Materials and Methods**). Representative records are illustrated in Fig. 2. Although with the homogeneous background upward eye velocity gains tended to be smaller than downward eye velocity gains, the difference was not significant (means for two monkeys were 0.71 (± 0.16 SD) and 0.88 (± 0.10 SD), respectively (*t* test, $p > 0.1$). However, with the stationary textured background, upward peak eye velocity was reduced typically to one third of that with the homogeneous background (Fig. 2A and B, arrows). Moreover, as reported earlier (Takeichi et al. 2003), with the stationary textured background, upward and downward eye velocity gains were significantly different (0.31 ± 0.11 SD and 0.90 ± 0.08 SD, respectively; *t* test, $p < 0.05$, Fig. 2B).

When the textured visual background was moved at the same frequency while the reward spot remained stationary, both monkeys fixated the stationary spot. A representative record is shown in Fig. 2C (note expanded, 2x scale for vertical eye velocity calibration compared to gains for Fig. 2A and B; vertical eye position calibration is also expanded in Fig. 2C). Downward smooth eye

movements were induced only weakly and transiently during downward background movement (Fig. 2C, arrow). The induced peak downward eye velocity measured manually was $3.5^\circ/\text{s}$ ($\pm 1.2\text{SD}$, 3rd trace in Fig. 2C) which corresponded to the peak gain (re pattern velocity) of 0.12. The results were similar in the two monkeys tested (mean peak gain = 0.14). If the low-velocity, upward pursuit had been due to an un-suppressed optokinetic reflex induced by the movement of the textured background, the expected upward pursuit gains would have been 0.71 (upward pursuit gains across the homogeneous background) - 0.14 (downward optokinetic gains induced by textured background) = 0.57. However, the actual upward pursuit gain of these animals was about half of the expected gain (0.31).

Effects of optokinetic stimulation during pursuit

Gains of optokinetic responses could be different between fixation of a stationary spot and pursuit of a moving spot. In two monkeys (Q, H) we examined optokinetic responses that were induced by upward and downward motion of the textured background while the monkeys pursued the spot that moved upward or downward at a constant velocity ($5^\circ/\text{s}$, $\pm 10^\circ$, see Methods). Representative optokinetic responses are illustrated in Fig. 3A by superimposed mean \pm SD vertical eye velocity traces during upward pursuit. Initial eye velocities in the presence of the stationary textured background (i.e., zero pattern velocity in Fig. 3A) were reduced to nearly half of the eye velocity without the textured background. This is summarized in Fig. 3A (left); the presence of the textured background affected upward (open vs filled triangles) but not downward pursuit (open vs filled squares). When the background was moved abruptly upward (or downward) at $10^\circ/\text{s}$ during upward pursuit (indicated by pattern vel, Fig. 3A), optokinetic responses exhibited two components; the initial response followed by more or less steady-state response. The peak velocity of the initial upward eye velocity reached $8^\circ/\text{s}$ in response to $10^\circ/\text{s}$ upward background motion (Fig. 3A). Because the eyes were moving at $\sim 2^\circ/\text{s}$ at the onset of the background motion, actual upward retinal

slip was $\sim 8^\circ/\text{s}$ and the gain of this optokinetic response was $\sim 0.75 = (8-2)/(10-2)$. The mean steady-state eye velocity induced by upward motion of the background was $\sim 5.5^\circ/\text{s}$, and the gain of this response was $\sim 0.35 = (5.5-2)/(10-2)$, about half of the initial response gain. These gain values are plotted in Fig. 3B against the velocity of the background motion (pattern vel) at $10^\circ/\text{s}$ and the corresponding retinal slip velocity (pattern vel re eye).

However, if the textured background moved downward during upward pursuit, gains of optokinetic responses were weak. The initial peak eye velocity reduced to nearly zero (Fig. 3A). Because the eyes were moving upward at $\sim 2^\circ/\text{s}$ at the onset of $10^\circ/\text{s}$ downward motion of the background, actual downward retinal slip was $\sim 12^\circ/\text{s}$ and the gain of this optokinetic response was $\sim 0.17 = 2/(10+2)$. Similarly, the steady-state eye velocities after upward motion of the background were $\sim 1^\circ/\text{s}$, and the gain of this response was $\sim 0.08 = (2-1)/(10+2)$ (Fig. 3A, B). Thus, gains of optokinetic responses that were induced by downward motion of the textured background during upward pursuit were quite small. The results were similar in the two monkeys.

Figure 3C plots mean \pm SD amplitudes of the initial response against velocity of textured background motion (Pattern vel). Positive values in the abscissa indicate that the background and pursuit were in the same directions, whereas negative values indicate that their directions were opposite to each other. Open and filled circles indicate initial responses that were induced by background motion when it was applied during upward or downward pursuit for a target moving at $5^\circ/\text{s}$, respectively. To examine changes of magnitudes of optokinetic responses at different velocities of background motion, linear regressions were calculated for each condition. Initial optokinetic responses that were induced by background and spot motion in the same directions had the slopes of 0.32 and 0.37 for upward and downward directions, respectively (Fig. 3C, rightward). In contrast, if the pursuit directions were opposite to the directions of background motion (Fig. 3C, leftward), optokinetic responses were much weaker with nearly flat slopes of 0.07-0.10 for upward

and downward directions. Thus, the magnitudes of initial optokinetic responses induced by the background motion did not depend on the pursuit direction *per se*, but depended on the condition whether background motion and pursuit directions were the same or opposite.

Figure 3D plots mean \pm SD amplitudes of the steady-state response (open and filled circles) against velocity of textured background motion (Pattern vel). Similar to Fig. 3C, positive and negative values in the abscissa indicate that the background motion and pursuit were in the same and opposite directions, respectively. In all conditions, regression slopes were nearly flat (<0.1) if pursuit directions were opposite to background motion directions (Fig. 3D). Even if their directions were the same, the regression slopes were 0.13-0.16. Figure 3D also plots mean \pm SD eye velocities that were induced by motion of the textured background at different velocities during fixation of a stationary spot; optokinetic responses were weak with nearly flat slopes of 0.10-0.07 for down and up background motion, thus confirming the results obtained by sinusoidal motion of the textured background (Fig. 2).

These results indicate that optokinetic responses were consistently weak if background motion was applied in the directions opposite to pursuit directions (Fig. 3C, D), suggesting that optokinetic responses are not induced effectively even at higher stimulus velocities in such conditions.

Gains of initial and steady-state responses induced by upward and downward background motion during upward pursuit are summarized in Fig. 3B against velocities of background motion (pattern vel). Gains of both components were consistently higher if the textured background moved in the same directions as pursuit (Fig. 3B, rightward) compared to the conditions in which they were opposite to each other (Fig. 3B, leftward). In the former, gains were >1.0 at velocities of background motion $<5^\circ/s$, and decreased at higher velocities (Fig. 3B). However, in the latter condition, gains were 0.26-0.27 at background velocities of 3-5 $^\circ/s$ and decreased further at higher velocities. Gain curves of initial and steady-state optokinetic responses to background motion

during upward pursuit were basically similar, although the former tended to be larger than the latter (Fig. 3B).

During sinusoidal pursuit, both monkeys exhibited lower pursuit gains (0.4-0.5) during upward pursuit with the presence of the textured background compared to their gains (0.8-0.9) with the homogeneous background. These results indicate that the gain of optokinetic responses induced by downward motion of the textured background during upward pursuit was small, for example, less than 0.27 during downward retinal slip velocity of $5^\circ/\text{s}$ (Fig. 3B, pattern vel re eye), suggesting that the reduced eye velocity gains (by 50%) of upward pursuit in the presence of the textured background (Fig. 3A, open vs filled triangles) may not be explained solely by an un-suppressed optokinetic reflex induced by the textured background as it moves across the retina in the opposite direction of the pursuit eye movements (see Discussion).

Figure 4 near here

Experiment 2: Effects of whole body tilt in the roll plane

In two juvenile monkeys (K, M), we applied static 80° tilt in the roll plane in order to dissociate vertical or horizontal eye movements in the orbit from those in space. Effects of right ear down and left ear down were similar (see **Materials and Methods**) in the two monkeys. Both monkeys exhibited low-velocity vertical eye movements in the orbit but not in space. A representative record is shown in Fig. 4 during static 80° roll tilt (right ear down). Vertical pursuit in the orbit across the homogeneous background exhibited a minimal asymmetry for up and down pursuit (Fig. 4A, 2nd and 3rd traces). Mean eye velocity gains for upward and downward components were 0.73 ($\pm 0.11\text{SD}$) and 0.86 ($\pm 0.10\text{SD}$), respectively (t test, $p > 0.1$).

Across the stationary textured background, however, vertical pursuit in the orbit exhibited a clear asymmetry between upward and downward eye velocity (Fig. 4B, 2nd and 3rd traces); upward pursuit consisted mostly of saccades and upward eye velocity was reduced, typically to half of the

velocity of downward pursuit (Fig. 4B, arrow). Upward and downward eye velocity gains in the orbit in two monkeys were significantly different (means = $0.47 \pm 0.08SD$ and $0.84 \pm 0.10SD$, respectively; t test, $p < 0.05$). Horizontal pursuit in the orbit (which was close to vertical pursuit in space) across the stationary textured background did not show an obvious directional asymmetry (Fig. 4C, 2nd and 3rd traces). Mean horizontal eye velocity gain was $0.94 (\pm 0.08SD)$, and was similar for rightward and leftward pursuit.

Figures 5 and 6 near here

Experiment 3: Head-free pursuit

In daily life, smooth-pursuit is performed by coordination of eye and head movements (i.e., gaze-pursuit). To examine whether asymmetry was observed during head-free pursuit and whether head movements also revealed asymmetry, we compared gaze-, eye- and head- velocities during head-free tracking in the horizontal and vertical directions across the homogeneous and textured backgrounds. Figure 5 illustrates representative position records for horizontal and vertical head-free pursuit of monkey B across the two kinds of visual backgrounds. As shown by the gaze position records (Fig. 5, Gaze pos), our monkeys performed the task well, although individual eye- and head- position traces exhibited variability. In particular, corrective saccades were frequently observed during vertical pursuit (Fig. 5C, D, VE). Head movement contributions were small during horizontal pursuit but larger during vertical pursuit (Fig. 5A and B vs C and D, Head pos).

Representative velocity records (mean \pm SD) for horizontal and vertical pursuit are illustrated in Figs. 6 for monkey B with the homogeneous (Fig. 6A1, B1) and textured backgrounds (Fig. 6A2, B2). There were clear differences between horizontal and vertical eye velocity. During vertical pursuit across the textured background, a clear asymmetry was observed between upward and downward eye velocity (Fig. 6B2, \dot{V}_E). Moreover, even during vertical pursuit across the homogeneous background (Fig. 6A1, \dot{V}_E), a similar and slightly weaker asymmetry was also

observed. An asymmetry was not obvious during horizontal pursuit either between rightward and leftward pursuit or between the two visual backgrounds (Fig. 6A).

Figure 7 plots overall mean (\pm SD) gains for individual components of gaze pursuit for three monkeys for horizontal (A), upward (B) and downward (C) directions. There were differences in the performance of individual monkeys (see below), so we summarized mean (\pm SD) gains for individual monkeys for horizontal (Table 1), upward (Table 2A) and downward components (Table 2B) during head-fixed and head-free conditions with the two background conditions.

Tables 1, 2 and Figures 7, 8 near here
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Horizontal head-free pursuit

As illustrated in Fig. 7A, gains for gaze-, eye-, and head- velocity were similar for the two background conditions (open vs filled circles, N.S) during head-free pursuit. Gaze velocity gains were also similar during head-fixed pursuit across the two background conditions (Fig. 7A, Table 1), indicating that the presence of the textured background affected horizontal pursuit minimally. However, gaze velocity gains during head-free pursuit were smaller than gaze velocity gains during head-fixed pursuit (Fig. 7A, asterisks, $p < 0.05$). This difference was observed in monkeys B and M but not in K (Table 1).

Vertical head-free pursuit

Unlike horizontal pursuit (Fig. 6A, Table 1), vertical, especially upward, pursuit showed more variability (Fig. 6B). Therefore, in Fig. 8 we plotted gains for upward (A) and downward (B) components for the three monkeys for different task conditions and different recording sessions. Each point is a mean for one session. Comparison of upward gaze- and eye- velocity gains during head-free pursuit between the two backgrounds (Fig. 8A) indicates gains were consistently lower in monkey K and M for the textured background (also Table 2A). Such differences in gaze- and eye- velocity gains were not clearly seen in monkey B (circles Fig. 8A, Table 2A), although in the

head-fixed condition all monkeys exhibited a clear difference in upward gaze (=eye) velocity gains between the two backgrounds (Fig. 8A, Table 2A).

ANOVA analysis indicates that all the factors of direction (upward vs downward, $F_{(1,2)} = 223.098$, $p < 0.0001$), background (homogeneous vs textured, $F_{(1,2)} = 51.478$, $p < 0.0001$) and head condition (fixed vs free, $F_{(1,2)} = 14.503$, $p < 0.001$) showed significant differences in gaze velocity gains. Interaction effects were also significant between direction and head condition ($F_{(1,2)} = 6.094$, $p < 0.0149$) and between direction and background ($F_{(1,2)} = 22.117$, $p < 0.001$). Similar differences were also detected for eye velocity gains during head-free pursuit between direction (upward vs downward, $F_{(1,2)} = 130.2$, $p < 0.0001$) and background (homogeneous vs textured, $F_{(1,2)} = 14.5$, $p < 0.001$). However, a significant difference was not detected for head velocity gains during head-free pursuit between the two background conditions.

As summarized in Fig. 7(B, C), gains for upward gaze- and eye- velocity across the textured background were significantly smaller than those across the homogeneous background for all monkeys tested in head-fixed and head-free conditions (Fig. 7B, asterisks, *t* test, $p < 0.001$). Differences were not seen in downward gaze- and eye- velocity gains or upward- and downward-head velocity gains (Fig. 7B, C). Furthermore, upward gaze- and eye-velocity gains during head-free pursuit were clearly smaller than downward gaze- and eye-velocity gains during head-free pursuit not only across the textured background but also across the homogeneous background (Fig. 7B, C, *t* test, $p < 0.001$). These differences were observed in all three monkeys (Table 2A, B, *t* test, $p < 0.001$). Such differences were not observed in the head-velocity gains (Fig. 7B, C, Table 2A, B).

In addition, comparison of upward gaze velocity gains across the homogenous background between the head-free and head-fixed conditions (Fig. 8A) indicates that upward gaze velocity gains during head-free pursuit were smaller than those during head-fixed pursuit in all three monkeys tested (Figs. 7B, asterisks, $p < 0.003$, Fig. 8A, Table 2A). Similar comparison revealed significant

differences in upward gaze velocity gains between the two background conditions in monkey K and M but not in B (Fig. 8A, Table 2A), and gain comparison for all three monkeys revealed a significant difference (Fig. 7 B, asterisks, $p < 0.04$). Because these monkeys performed gaze pursuit well (Fig. 4), smaller gaze velocity gains during head-free upward pursuit suggest a larger contribution of eye position components during head-free pursuit compared to head-fixed pursuit (also Fig. 7A).

Downward gaze velocity gains did not reveal a difference between the two backgrounds or between the head-free and head-fixed conditions (Fig. 7C, N.S., Fig. 8B, Table 2B).

Discussion

Our results obtained in the three series of studies extend previous findings (Takeichi et al. 2003) by showing that the low-velocity, upward pursuit eye movements cannot be explained solely by the un-suppressed downward optokinetic reflex induced by the textured background as it moves across the retina in the opposite direction of the pursuit eye movements (Experiment 1, Figs. 2 and 3). It should be mentioned that optokinetic responses were clearly induced during upward and downward pursuit similarly if pursuit directions were the same as the direction of the background motion (Fig. 3A-C). The latencies (~ 100 ms) and gains that were induced by background motion at low velocities (Fig. 3B) are comparable to initial peak eye velocities induced by optokinetic stimulation in previous reports (e.g., Matsuo and Cohen 1984; see Leigh and Zee 1999 for a review), suggesting that optokinetic responses were appropriately tested in our task conditions. However, optokinetic responses were clearly weaker if motion of the textured background was applied in the directions opposite to the pursuit directions or during fixation of a stationary target (Figs. 2, 3). Notice that the effectiveness of inducing the optokinetic responses did not depend on the directions of the pursuit eye movements. These results suggest that, although the un-suppressed optokinetic reflex induced by motion of the textured background across the retina may contribute, it alone

cannot explain the low-velocity, specifically *upward* pursuit eye movements in our task conditions.

Our results in Experiment 2 show that the difference remains during static roll tilt (Fig. 4) so that the frame of reference for low-velocity, upward pursuit is orbital and not spatial. We did not measure torsional eye movements. However, it has been reported that the gain of ocular counter-roll to static roll tilt was ~ 0.1 (see Leigh and Zee 1999 for a review). Therefore, vertical components detected by our coil system during static roll tilt reflected mostly vertical eye movement in the orbit. Our results in Experiment 3 further show that asymmetry in vertical eye velocity gains was still observed during head-free pursuit that requires coordination between eye and head movements. However, we did not observe such an asymmetry in vertical head velocity (Figs. 7, 8, Table 2A, B), suggesting that the decrease of gaze velocity gains during upward head-free pursuit reflected mostly the decrease of upward eye velocity gains. Thus, our results taken together suggest that the deficit during the VOR cancellation task during passive upward whole body rotation (Takeichi et al. 2003) reflects primarily the inability to generate appropriate upward eye-pursuit commands to cancel the downward VOR induced by upward pitch (see Leigh and Zee 1999 for a review).

The presence of our textured background did not affect vertical pursuit of monkey B during head-free (but not head-fixed) pursuit in Experiment 3 (Fig. 8, Table 2A), although the exact reason is unknown. It should be noted that the asymmetry in upward and downward eye velocity was observed in our monkeys, including monkey B, even with the homogeneous background during head-free pursuit (Fig. 8, Table 2). Our previous study also showed that in young children, there is a directional asymmetry during vertical pursuit across a homogeneous background (Takeichi et al. 2003). These results suggest an existence of the directional asymmetry in vertical pursuit that manifests under demanding task conditions such as pursuit across a textured background and pursuit with active eye and head movements in our task conditions; in the latter condition accurate

tracking further requires the precise control of the VOR, the gain of which depends on the viewing distance (for a review, see Leigh and Zee 1999).

Possible neural correlates for the directional asymmetry in pursuit eye movements

The neural basis for asymmetric smooth-pursuit observed in this study is still unknown.

Pursuit-related neurons are found in the cerebral cortex including the medial superior temporal visual area, frontal and supplementary eye fields, and ventral intra-parietal area (Sakata et al. 1983; MacAvoy et al. 1991; Colby et al. 1993; Heinen and Liu 1997; Bremmer et al. 2002; Fukushima et al. 2004). Although upward and downward optic flows may be different in the natural environment, preferred directions for individual pursuit neurons in these cortical areas are distributed virtually evenly for all directions, making it difficult to explain the directional asymmetry observed in our study solely on the basis of cortical smooth-pursuit mechanisms (Takeichi et al. 2003). On the other hand, it is well known that vertical and horizontal smooth eye movements are executed by different brainstem and cerebellar mechanisms. Specifically, upward and downward eye movements are organized differently in the brainstem and cerebellum (for a review, see Leigh and Zee 1999; also Miles et al. 1980; Shidara and Kawano 1993; Kaneko and Fukushima 1998; Brettler and Baker 2003).

It is well known that preferred directions of majority of pursuit Purkinje cells in the simian floccular region are either ipsiversive or downward (Miles et al. 1980; Stone and Lisberger 1990; Shidara and Kawano 1993; Krauzlis and Lisberger 1996; Fukushima et al. 1999; also Shinmei et al. 2002 for dorsal vermis Purkinje cells). The floccular region consists of the flocculus and ventral paraflocculus, and the flocculus projects to the vestibular nuclei, particularly the medial and ventrolateral parts of the medial vestibular nucleus, superior vestibular nucleus and y group, whereas the ventral paraflocculus projects not only to the above vestibular nuclear regions but also

to the posterior interpositus and dentate nuclei (Nagao et al. 1997). A hint of the origin for the vertical pursuit asymmetry might be found in discharge characteristics of vertical pursuit Purkinje cells and in organization of vestibular responses modulated via the flocculus. It has been assumed that downward floccular Purkinje cells inhibit upward eye- and head- velocity neurons in the vestibular nuclei and y group (Chubb and Fuchs 1982; Scudder and Fuchs 1992; Zhang et al. 1995). In contrast, upward floccular Purkinje cells that presumably inhibit downward eye velocity neurons in the vestibular nuclei are reported to be scarce (Zhang et al. 1995). These observations suggest that floccular control of upward pursuit will be done not only by increased activity of upward Purkinje cells through inhibition of downward eye velocity neurons in the vestibular nuclei but, more importantly, by decreased activity of downward Purkinje cells through dis-inhibition of upward eye- and head- velocity neurons in the vestibular nuclei and y group (Zhang et al. 1995).

During on-direction pursuit, discharge rates of horizontal floccular Purkinje cells increase almost linearly with eye velocity, but during off-direction pursuit discharge rates do not decrease linearly (Stone and Lisberger 1990; Lisberger et al. 1994). It is possible that such non-linearity for off-direction pursuit also exists for downward Purkinje cells during upward pursuit. Moreover, recent studies (Fukushima et al. 2002; Akao et al. 2005) indicate that the majority of pursuit neurons in the caudal part of the frontal eye fields that are thought to contain pursuit command signals code pursuit eye movements not only in the frontal plane (i.e., smooth-pursuit) but also in depth (i.e., vergence eye movements). In fact, many floccular pursuit Purkinje cells discharge for vergence eye movements and the majority of them have vergence eye position sensitivity (Miles et al. 1980; Tsubuku et al. 2004). This suggests that off-direction target distance may further augment non-linearity in rate-velocity relationships of downward Purkinje cells by affecting their resting rates. Similar non-linearity in discharge modulation has also been observed in pursuit neurons in frontal eye fields (Fukushima et al. 2002). These factors may contribute to the selective,

low-velocity, upward pursuit in young primates.

It should be pointed out that downward eye velocity neurons in the vestibular nuclei are activated by inputs from the posterior semi-circular canal (see Leigh and Zee 1999 for a review). The difficulty to cancel the downward VOR during upward pitch rotation in young primates (Takeichi et al. 2003) may reflect the scarcity of upward floccular Purkinje cells that presumably inhibit downward eye velocity vestibular neurons as described above (Zhang et al. 1995). Similar mechanisms may also be involved in the directional asymmetry during head-free upward pursuit in this study (Table 2A). Asymmetry in floccular inhibition of VOR relay neurons is well known in rabbits and cats (Ito et al. 1977; Hirai and Uchino 1984; Sato and Kawasaki 1990). Asymmetry in low frequency responses of anterior and posterior canal vestibulo-ocular neurons in the vestibular nuclei was also reported in alert cats when the animals were rotated on their side (Brettler and Baker 2003).

It has been reported that vertical optokinetic nystagmus is asymmetric in monkeys when it is induced with animals lying on their sides in a 90° roll position (Matsuo and Cohen 1984). Optokinetic responses have direct and indirect components (Cohen et al. 1977). The direct component has properties similar to smooth-pursuit (Lisberger et al. 1981; Leigh and Zee 1999). They share cerebellar and brainstem pathways (Leigh and Zee 1999; Shidara and Kawano 1993). Common mechanisms may be involved in the asymmetric optokinetic nystagmus and smooth-pursuit, possibly including the above-mentioned vestibulo-ocular relay pathways (Brettler and Baker 2003).

A hint of the neural basis for the asymmetric vertical pursuit might also be found by examining how the asymmetry is compensated in adult monkeys. Our laboratory has reported that chemical inactivation of the supplementary eye fields (SEF) in adult monkeys reproduced the directional

asymmetry that had been compensated developmentally, suggesting that the SEF may be involved in the compensation (Fukushima et al. 2003). Although the exact neural mechanisms for the compensation and reappearance of the directional asymmetry induced by SEF inactivation are still unknown, preferred directions for individual SEF pursuit neurons are distributed virtually evenly for all directions (Heinen and Liu 1997; Fukushima et al. 2004). Therefore, it is difficult to explain the reproduced directional asymmetry solely by loss of SEF output signals. There is a possibility that the directional asymmetry may be reproduced by the loss of input signals to the SEF (Fukushima et al. 2003). Because the floccular region could furnish ascending pursuit signals through the deep cerebellar nuclei and vestibular nuclei, it may well be that the loss of eye-velocity-feedback signals from the floccular region to the SEF is responsible for the reappearance of the directional asymmetry induced by SEF inactivation. It is well known that eye-velocity-feedback is necessary for the gain control of accurate pursuit, although the neural basis for such feedback is still incompletely understood (see Leigh and Zee 1999 for a review; Fukushima 2003). We suggest the possibility that the selective, low-velocity, upward pursuit in young primates may be compensated in adult monkeys by gain increase of such feedback signals from the floccular region to the frontal oculomotor areas including the SEF and frontal eye fields (Fukushima et al. 2003; also Discussion of Akao et al. 2005).

Although further studies are needed to critically test the above-mentioned possibilities for the directional asymmetry observed in Japanese macaques, a similar asymmetry was also reported in a rhesus macaque during vertical pursuit across a dimly illuminated stationary background (Grasse and Lisberger 1992). This observation together with previous results showing an analogous asymmetry in human children (Takeichi et al. 2003) suggests that the directional asymmetry between upward and downward pursuit is observed widely in primates.

In summary, this directional asymmetry may reflect the difference in the floccular-vestibular

organization and the possible non-linearity in discharge rates of pursuit neurons in the related pathways including the frontal cortex (Fukushima et al. 2003).

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Legends for Figures and Tables

Fig. 1. Head movements during head-free pursuit. A and B, superimposed horizontal (A) and vertical (B) head position (pos) and velocity (vel) traces before (1) and after (2) removing fast head movements. All traces were aligned with target velocity (not shown). Some head velocities (Head vel) are clipped in A1 and B1. Horizontal straight lines indicate zero velocity. Thin curved lines in velocity traces (A1-2, B1-2) indicate fitted sinusoids. A3 and B3, head velocity gains without removing fast head movements (without) were plotted against head velocity gains after removing fast head movements (with) for 3 monkeys and different sessions. Linear regressions are fitted for horizontal and vertical head movements.

Fig. 2. Vertical pursuit and affects of optokinetic stimulation. A and B are vertical pursuit across the homogeneous and stationary textured background, respectively. C, affects of moving the textured background vertically while the monkey fixated a central stationary spot. VE and $\dot{V}\dot{E}$ indicate vertical eye position and vertical eye velocity, respectively. $\text{mean}\pm\text{SD}$ indicates de-saccaded $\text{mean}\pm\text{SD}$ vertical eye velocity. Vel indicates velocity. Saccade velocities are clipped in $\dot{V}\dot{E}$. Zero lines are indicated for velocity (but not position) traces.

Fig. 3. Optokinetic responses induced by motion of the textured background during vertical pursuit. A, left, symbols indicate $\text{mean}\pm\text{SD}$ eye velocities during pursuit for a target moving upward (open and filled triangles) and downward (open and filled squares) at $5^\circ/\text{s}$ with homogeneous (open symbols) and textured background (filled symbols). Representative eye movements traces indicate superimposed $\text{mean}\pm\text{SD}$ velocities in one session induced by upward and downward motion of the textured background (i.e., pattern) at $10^\circ/\text{s}$ during upward pursuit at $5^\circ/\text{s}$. Target moved upward at

time zero, and the pattern moved at 2s after target motion onset. B plots gains of optokinetic responses induced by background motion at different velocities during upward pursuit at 5°/s. Circles and triangles indicate initial and steady-state responses as indicated. C plots mean±SD initial optokinetic responses induced by background motion at different velocities (Pattern vel). D plots mean±SD steady-state responses induced by background motion at different velocities. Positive and negative values in the abscissa in C and D indicate that the background and pursuit were in the same and opposite directions, respectively. Open and filled circles in C and D indicate responses induced during upward and downward pursuit, respectively. D also plots mean±SD responses induced by background motion at different velocities during fixation of a stationary spot (X). For further explanation, see text.

Fig. 4. Comparison of vertical and horizontal eye movements in the orbit with those in space during whole body static roll tilt at 80°. A and B are vertical eye movements in the orbit across homogeneous and stationary textured background, respectively. C shows horizontal eye movements in the orbit across stationary textured background. HE and \dot{HE} are horizontal eye position and horizontal eye velocity, respectively. VE and \dot{VE} indicate vertical eye position and vertical eye velocity, respectively. mean±SD indicates de-saccaded mean±SD vertical eye velocity. Saccade velocities are clipped in \dot{VE} and \dot{HE} . Zero lines are indicated for velocity (but not position) traces.

Fig. 5. Horizontal and vertical head-free pursuit of monkey B across the two backgrounds. All traces show position (pos) traces for gaze, horizontal eye (HE), vertical eye (VE) and head movements across homogeneous (A, C) and textured background (B, D). All traces were aligned with target position.

Fig. 6. Pursuit of monkey B in the head-free condition. A, horizontal pursuit. B, vertical pursuit. All

traces show mean \pm SD velocity for target, gaze, eye ($\dot{H}\dot{E}$, $\dot{V}\dot{E}$) and head movement across homogeneous (A1, B1) and stationary textured background (A2, B2). Saccades were removed in gaze- and eye-velocity traces. Dashed lines indicate peak target velocity. Arrows in A1 and A2 indicate peak eye and head velocity for rightward (upward arrows) and leftward components (downward arrows). Arrows in B1 and B2 indicate peak eye and head velocity for upward (upward arrows) and downward components (downward arrows). Horizontal straight lines indicate zero velocity.

Fig. 7. Gain (re target velocity) plot for gaze-, eye- and head- velocity during pursuit in head-fixed and head-free conditions across the two backgrounds. A, B and C plots overall mean (\pm SD) gains for 3 monkeys for horizontal (A), upward (B) and downward (C) components. * indicates $p < 0.05$, t test for bracketed pair. N.S. indicates no significant difference between the two.

Fig. 8. Gain plots (re target velocity) for gaze-, eye- and head- velocity during vertical pursuit during head-fixed and head-free pursuit. Individual points indicate mean gains obtained on different days for different conditions for each monkey (key) during upward (A) and downward (B) pursuit.

Table 1. Mean gains (re target velocity) for gaze-, eye- and head- velocity during horizontal pursuit for each monkey and the two background conditions. During the head-fixed condition, eye velocity gains are identical to gaze velocity gains. Each value is the average of 5-7 different sessions for each monkey.

Table 2. Mean gains (re target velocity) for upward (A) and downward (B) gaze-, eye- and head- velocity during vertical pursuit for each monkey and the two background conditions. During the head-fixed condition, eye velocity gains are identical to gaze velocity gains. Each value is the average of 5-7 different sessions for each monkey.

Fig. 1

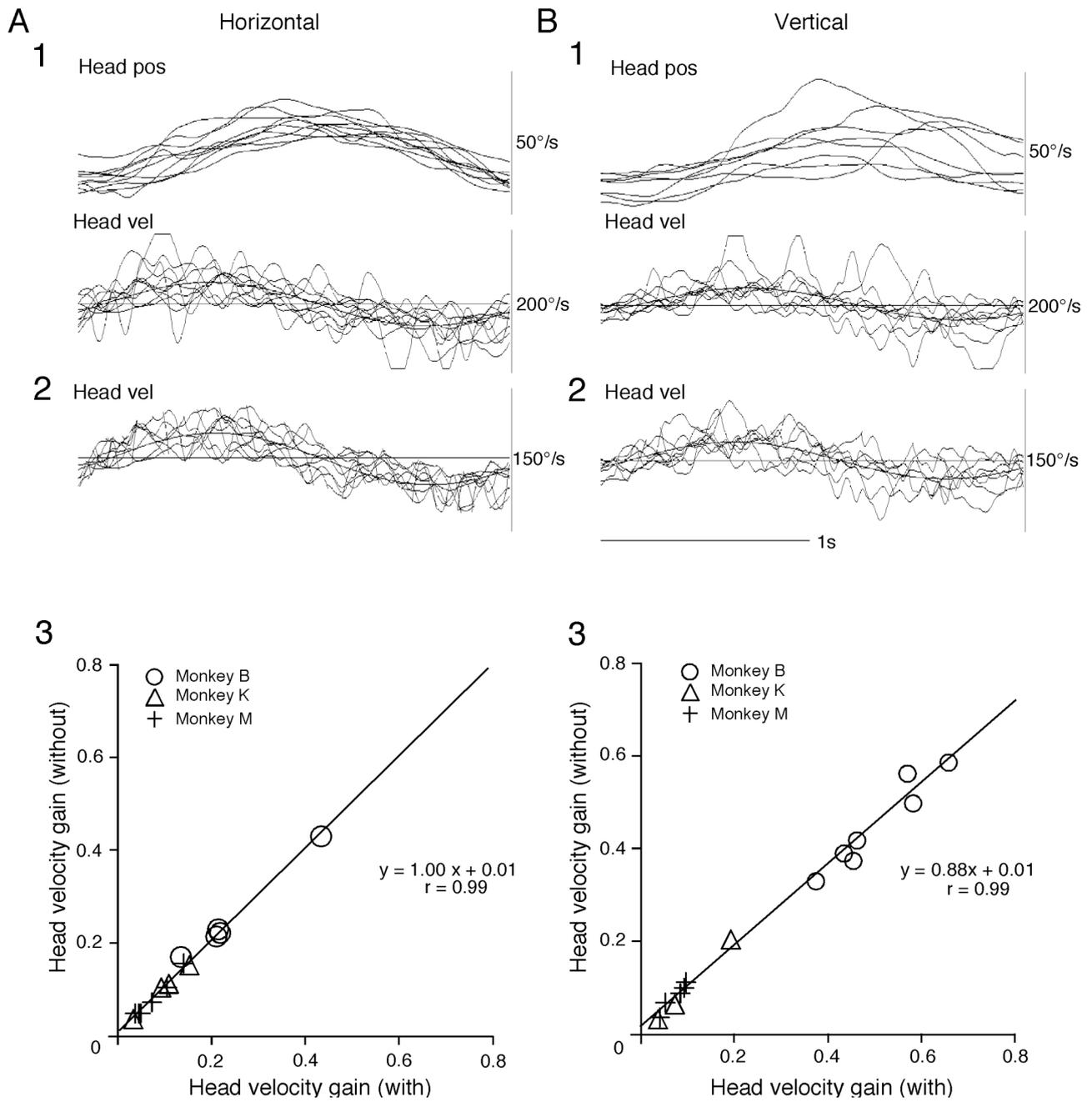


Fig. 2

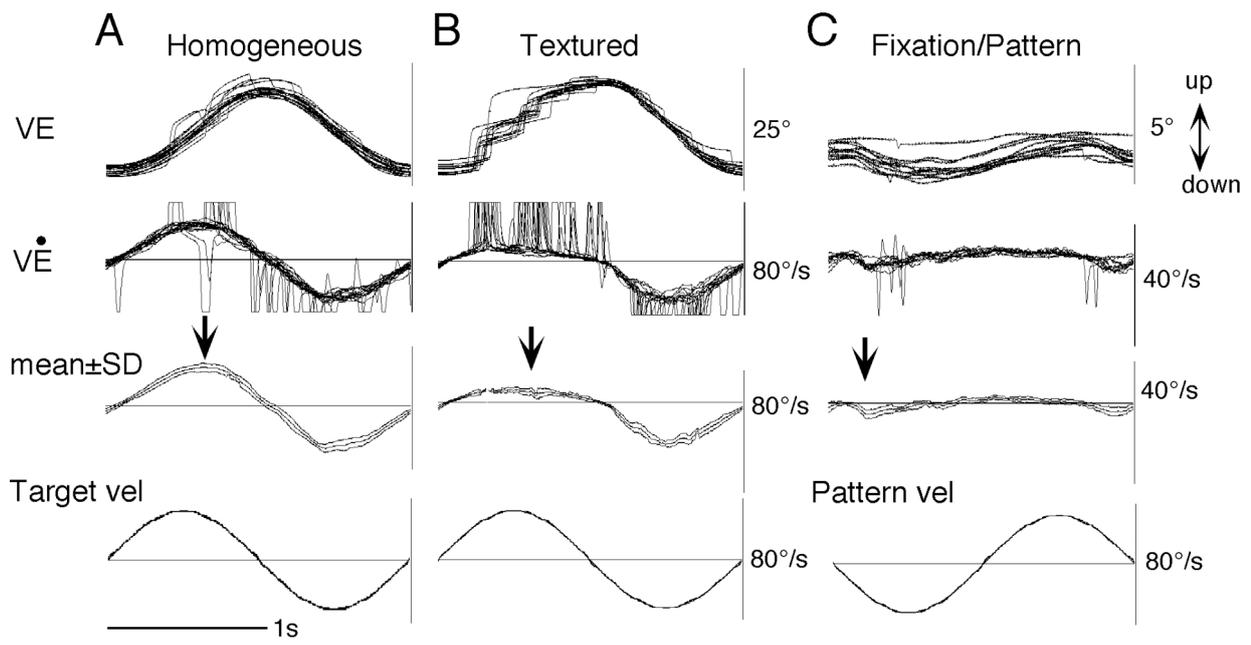


Fig. 3

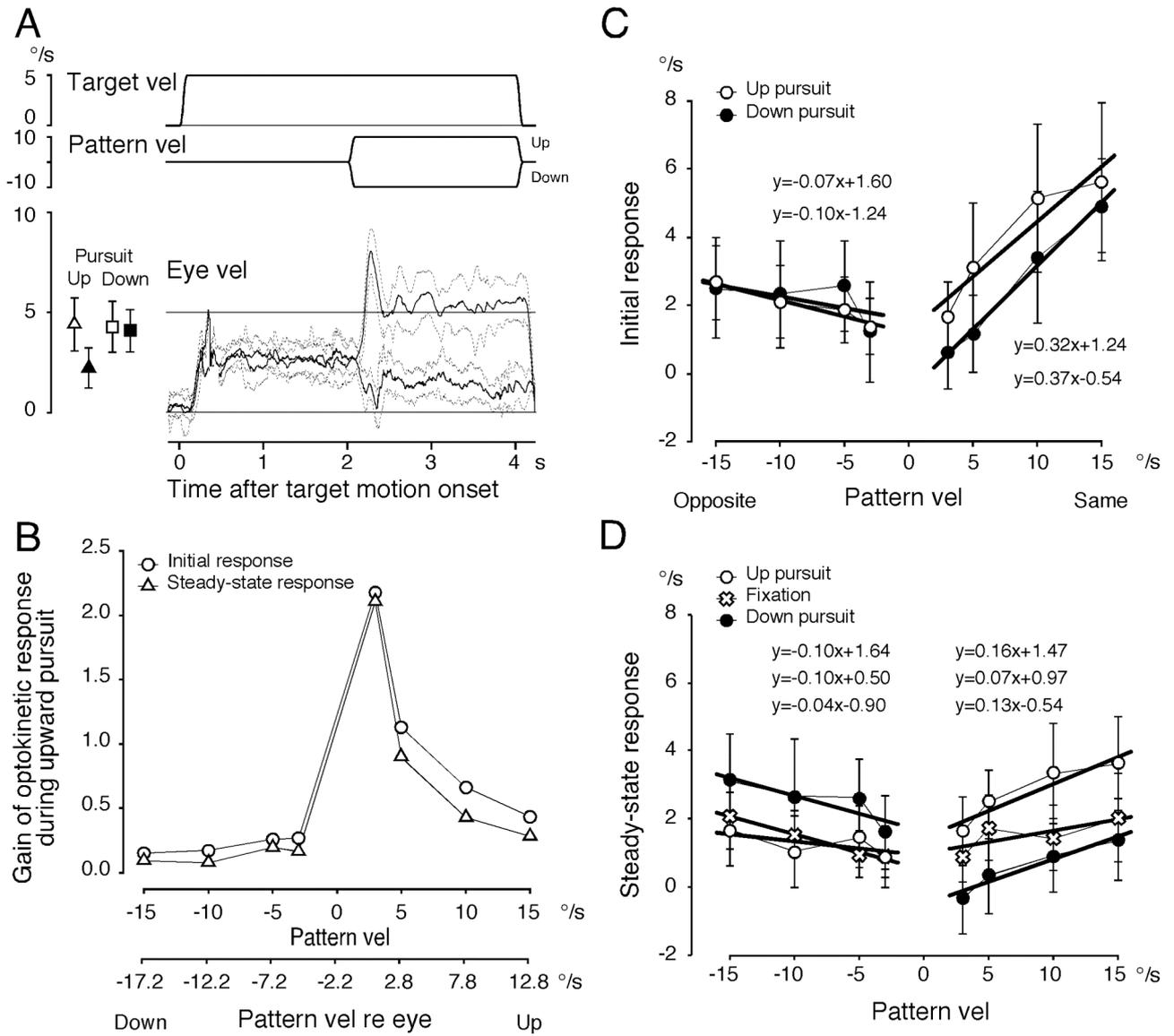


Fig. 4

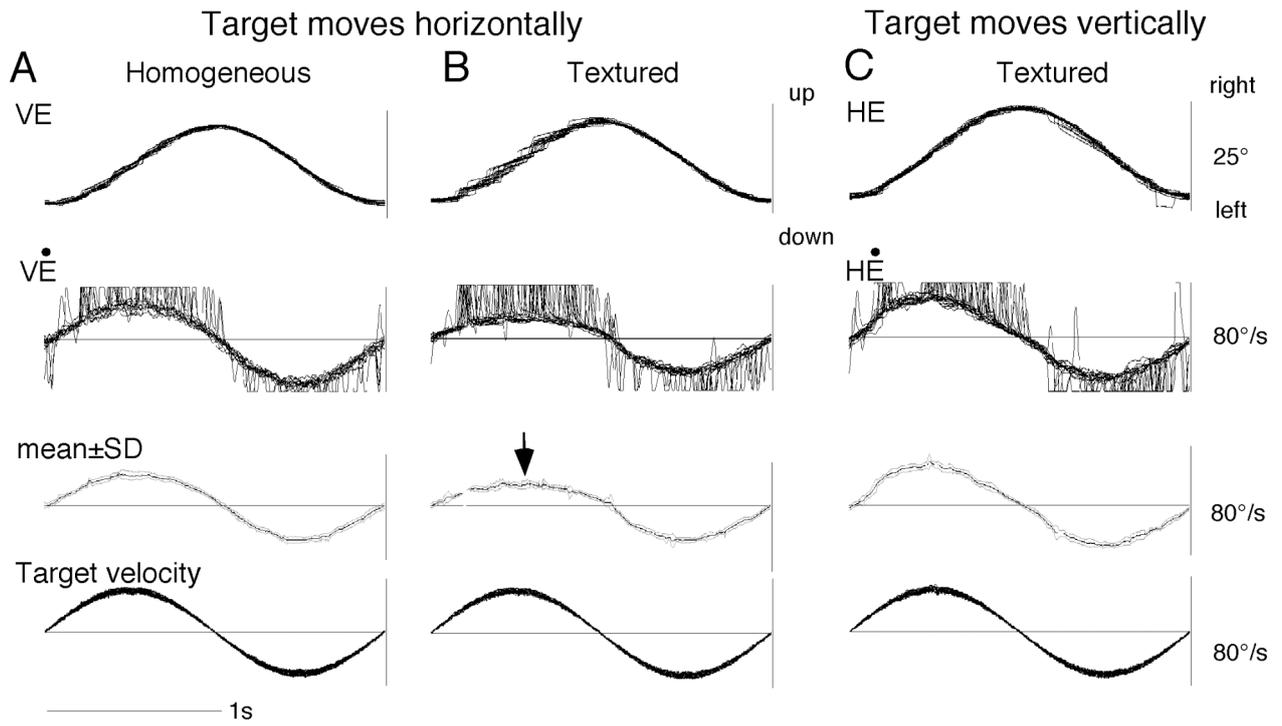


Fig. 5

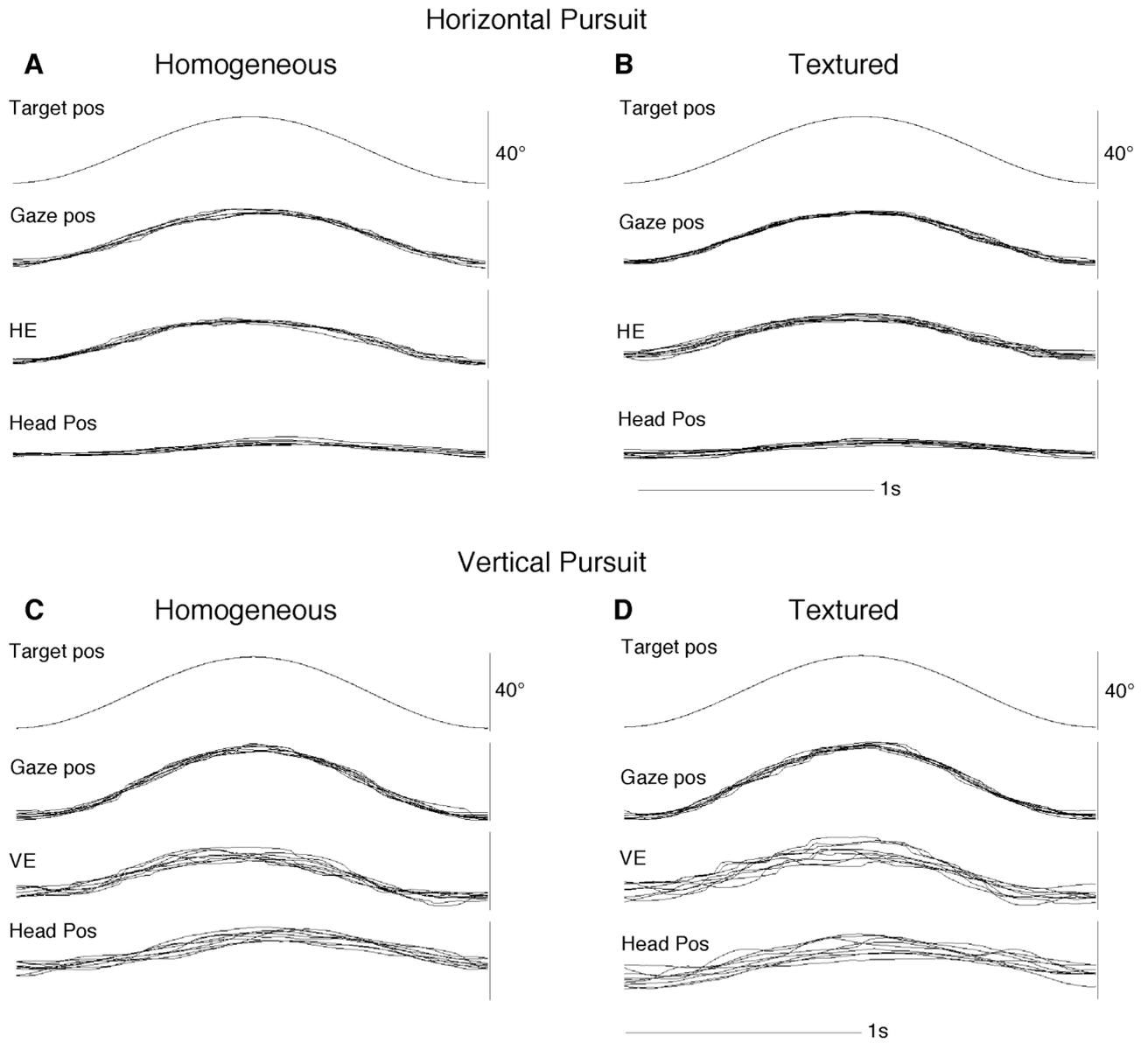


Fig.6

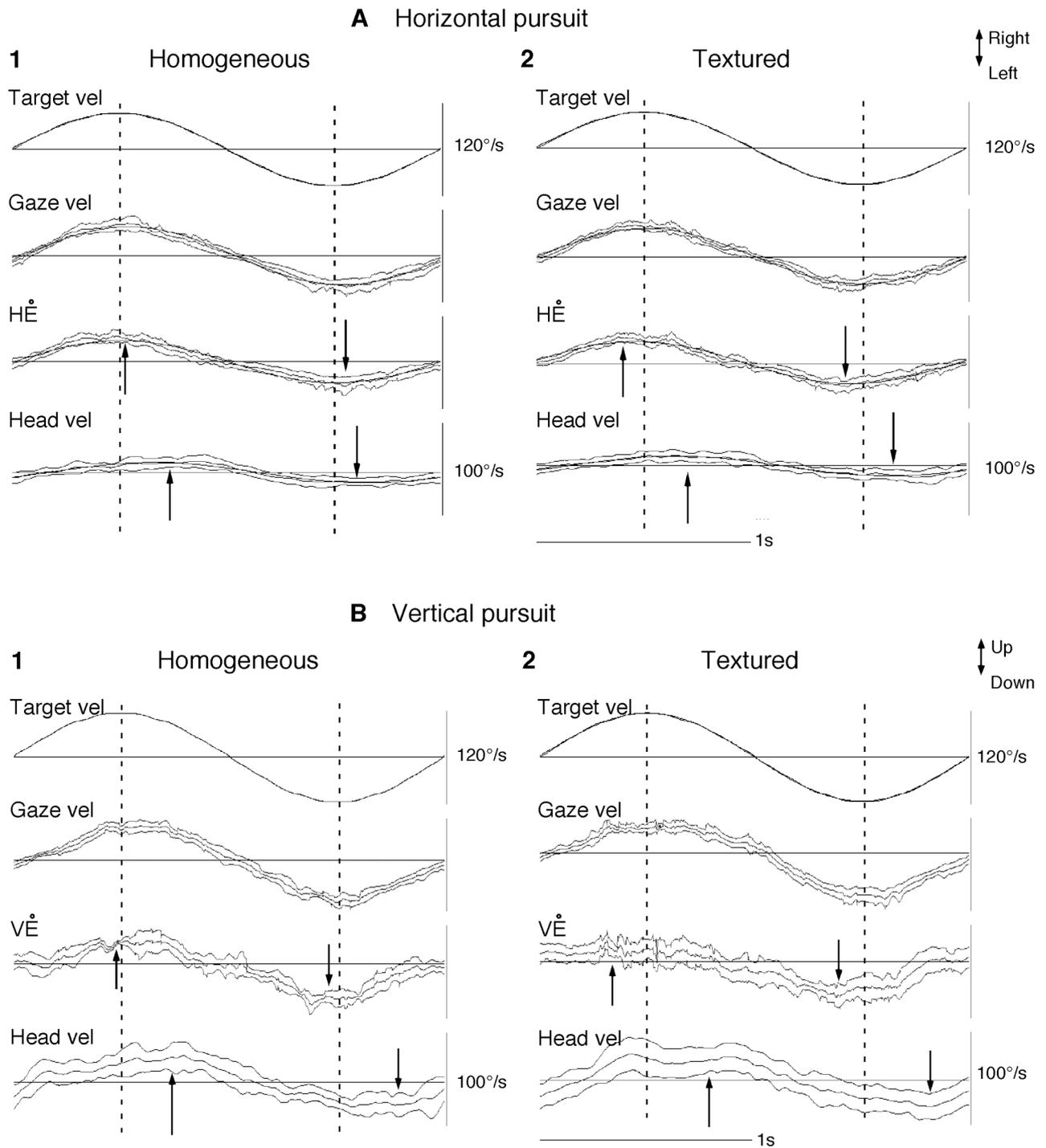


Fig. 7

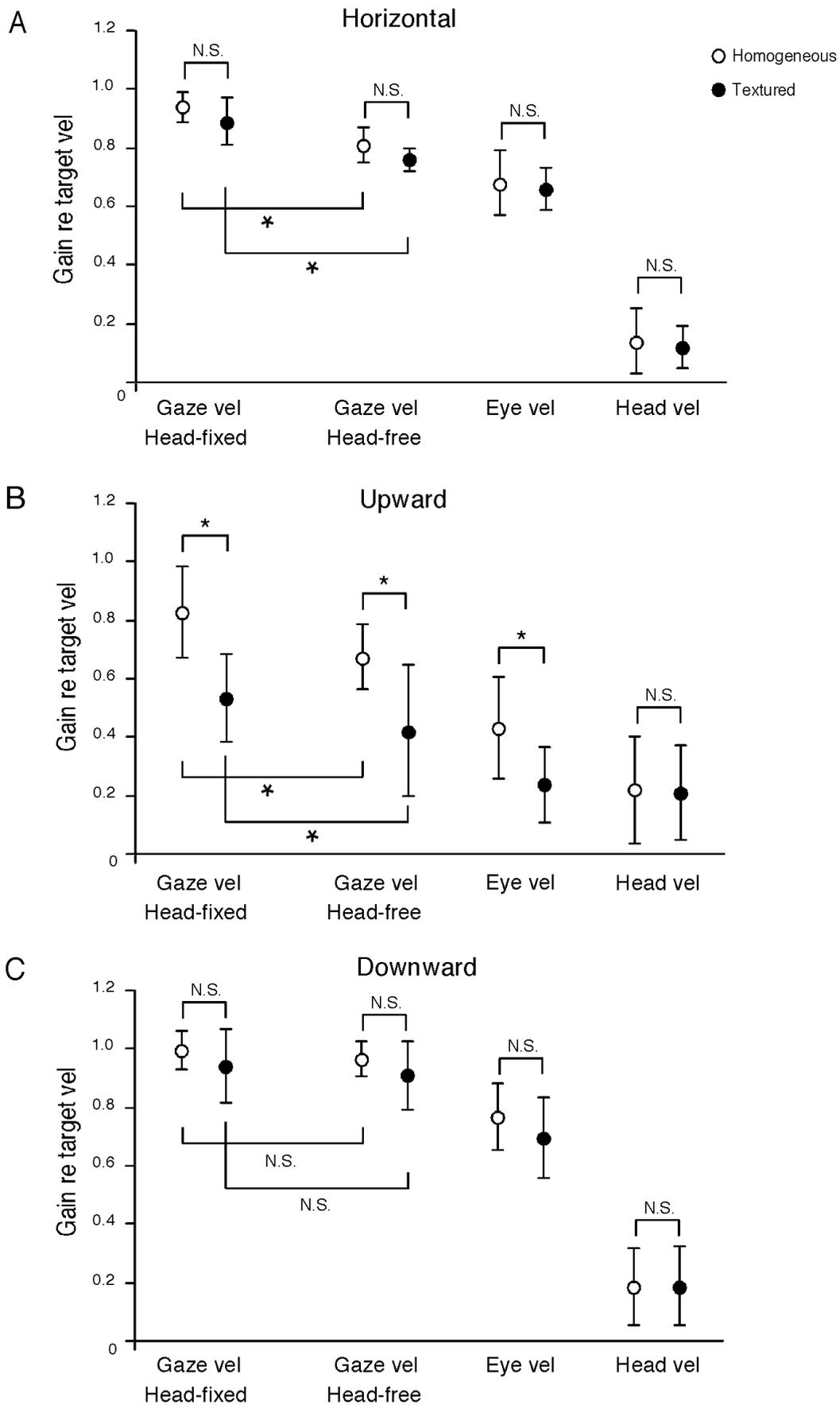


Fig. 8

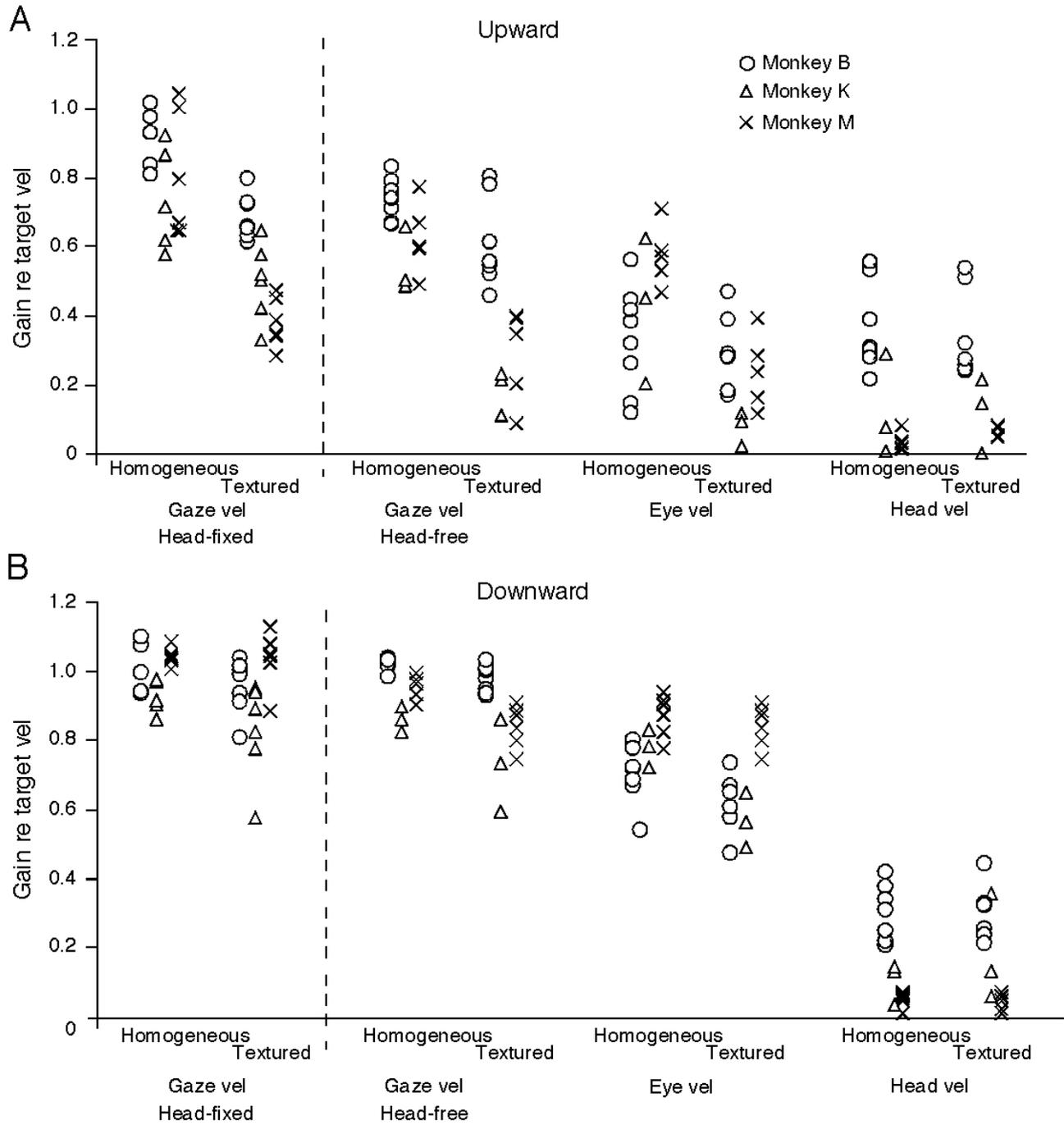


Table 1

Horizontal		Homogeneous				Textured			
		head-fixed		head-free		head-fixed		head-free	
Monkey		mean	SD	mean	SD	mean	SD	mean	SD
B	gaze vel	0.95	0.02	0.81	0.05	0.92	0.03	0.75	0.04
	eye vel			0.57	0.07			0.61	0.06
	head vel			0.24	0.12			0.18	0.05
K	gaze vel	0.84	0.02	0.81	0.10	0.77	0.06	0.74	0.03
	eye vel			0.72	0.12			0.60	0.08
	head vel			0.08	0.04			0.12	0.06
M	gaze vel	0.99	0.02	0.82	0.03	0.95	0.04	0.77	0.04
	eye vel			0.76	0.05			0.72	0.04
	head vel			0.07	0.04			0.07	0.02

Table 2

A. Upward		Homogeneous				Textured			
		head-fixed		head-free		head-fixed		head-free	
Monkey		mean	SD	mean	SD	mean	SD	mean	SD
B	gaze vel	0.93	0.08	0.75	0.06	0.69	0.07	0.62	0.13
	eye vel			0.34	0.15			0.30	0.11
	head vel			0.37	0.12			0.35	0.13
K	gaze vel	0.74	0.15	0.55	0.10	0.51	0.10	0.19	0.06
	eye vel			0.43	0.21			0.08	0.06
	head vel			0.13	0.15			0.12	0.11
M	gaze vel	0.80	0.18	0.63	0.11	0.38	0.07	0.29	0.14
	eye vel			0.58	0.09			0.24	0.11
	head vel			0.04	0.03			0.07	0.02

B. Downward		Homogeneous				Textured			
		head-fixed		head-free		head-fixed		head-free	
Monkey		mean	SD	mean	SD	mean	SD	mean	SD
B	gaze vel	1.01	0.07	1.01	0.02	0.96	0.08	0.98	0.04
	eye vel			0.69	0.10			0.62	0.08
	head vel			0.31	0.08			0.30	0.08
K	gaze vel	0.93	0.05	0.86	0.03	0.84	0.13	0.73	0.13
	eye vel			0.78	0.06			0.57	0.08
	head vel			0.11	0.06			0.19	0.15
M	gaze vel	1.04	0.03	0.96	0.03	1.03	0.08	0.92	0.07
	eye vel			0.87	0.06			0.84	0.06
	head vel			0.06	0.02			0.06	0.03