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Signals That Modulate Gain Control for Smooth Pursuit Eye Movements in Monkeys

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Abstract

The generation of primate smooth pursuit eye movements involves two processes. One process transforms the direction and speed of target motion into a motor command and the other regulates the strength, or “gain,” of the visual-motor transformation. We have conducted a behavioral analysis to identify the signals that modulate the internal gain of pursuit. To test whether the modulatory signals are related to eye velocity in the orbit or in the world (gaze velocity), we used brief perturbations of target motion to probe the gain of pursuit during tracking conditions that used head rotation to dissociate eye and gaze velocity. We found that the responses to perturbations varied primarily as a function of gaze velocity. To further understand the gaze velocity signals that control internal pursuit gain, we used adaptive modification of the gain of the vestibulo-ocular reflex (VOR) to dissociate physical gaze velocity from the component of gaze velocity that is driven by visual inputs. After VOR adaptation, perturbation responses were altered; the smallest perturbation responses now occurred during tracking conditions that required nonzero physical gaze velocity. However, perturbation responses during tracking conditions that mimicked the modified VOR were still enhanced relative to those obtained during fixation. We conclude that the signals that modulate the internal gain of pursuit are modified by VOR adaptation so that they are rendered intermediate between physical and visually driven gaze velocity. Similar changes in the gaze velocity signal have been reported in the cerebellar floccular complex following adaptive modification of the VOR and could be present in other brain areas that carry putative gaze velocity signals.

INTRODUCTION

Humans and other primates rely on smooth pursuit eye movements to track moving objects, thus keeping the objects' images relatively stable on the retina for high-acuity vision. Pursuit is normally excellent—for objects moving at constant speeds below 30° per second (deg/s), most individuals are able to nearly match eye speed to target speed, successfully achieving the goal of pursuit (Rashbass 1961; Robinson 1965). In other words, they are able to pursue with an *external* “gain” (eye velocity divided by target velocity) close to one.

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A number of recent experiments have demonstrated that pursuit involves two separate processes. The first process performs a visual-motor transformation that converts a representation of the direction and speed of object motion in the extrastriate visual cortex into commands for the direction and magnitude of smooth eye acceleration (Churchland and Lisberger 2001; Lisberger and Movshon 1999; Newsome et al. 1985). The second process, which we have called “gain control,” regulates the strength of this visual guidance of movement by controlling the *internal* gain of the pursuit system. The most direct evidence for gain control comes from experiments that delivered a brief perturbation of target motion under different initial conditions (Churchland and Lisberger 2002; Schwartz and Lisberger 1994). If a target is perturbed by the injection of a single cycle of a high-frequency sine wave during fixation, then eye velocity shows very little response to the perturbation. If the same perturbation (and the same image motion) is delivered during excellent pursuit of a target moving at a constant speed, then the eye velocity response is much larger and depends on the speed of ongoing target/eye motion. Thus the internal gain of pursuit depends on the ongoing behavior, and the amplitude of the response to a given image motion depends on the setting of the internal gain of the pursuit system.

How does the brain control the gain of the visual-motor transformation for pursuit? Two recent series of experiments have provided evidence that the site of gain control is downstream from the smooth eye movement region of the frontal eye fields, which we call the “frontal pursuit area” or FPA. If low-frequency electrical stimulation was delivered to the FPA at the same time that a brief perturbation of target motion occurred during fixation, then the eye velocity response to the perturbation was enhanced, as if the monkey were actually pursuing a target at 30 deg/s (Tanaka and Lisberger 2001). In addition, stimulation of both the FPA (Tanaka and Lisberger 2002) and the supplementary eye fields (Missal and Heinen 2001) caused enhancements of the eye velocity or eye acceleration induced by a given target motion at the initiation of pursuit.

A different and complementary approach to localizing the site of gain control is to use behavioral techniques to determine the nature of the neural signals that adjust the gain of the visual-motor transformation for pursuit. Prior studies of gain control have probed the setting of the internal gain of pursuit while monkeys and humans track a moving object by rotating the eyes within the orbit. When the head is stationary, the signals that control the internal gain of pursuit must be related to either smooth eye motion or target motion. However, primates can also track moving objects by turning the head smoothly while keeping the eyes stationary within the orbit by canceling or suppressing the vestibulo-ocular reflex (VOR). Head-fixed and head-moving pursuit can be accounted for by emphasizing that the goal of tracking is to program a “gaze velocity” that matches target velocity, where gaze velocity is defined as eye velocity with respect to the stationary world. Under conditions where the head can turn, gaze velocity can be composed of both eye motion in the orbit and head motion in the world.

In the present paper we have conducted behavioral experiments that ask two questions. First, are the signals that control the internal gain of pursuit related to gaze velocity or eye velocity? Our results indicate the former—the response to a brief perturbation of target velocity was enhanced whether tracking was instantiated by moving the eyes in the orbit or by keeping the eyes stationary in the orbit during head rotation. Second, what is the nature of the gaze velocity signals that control the internal gain of pursuit? During combined eye-head tracking, physical gaze velocity (eye velocity in the world) has two components, one driven by vestibular and one driven by visual inputs. In normal monkeys, the gain of the VOR is 1 so that the vestibular component of eye movement is equal and opposite to head movement and produces zero physical gaze velocity: any physical gaze motion is driven by visual inputs. In the present paper, we have dissociated physical gaze velocity from the

component of gaze velocity that is driven by vision, by using adaptive modification of the gain of the VOR to create a situation in which there is a substantial vestibular component of gaze velocity. Our results show that the internal gain of pursuit is controlled by gaze velocity signals that are altered by adaptive modification of the VOR and are intermediate between physical gaze velocity and the visually driven component of gaze velocity.

METHODS

General experimental procedure

All experimental procedures were approved in advance by the *Institutional Animal Care and Use Committee* of the University of California, San Francisco.

Two male rhesus monkeys (*Macaca mulatta*, 7-10 kg) served as subjects. Monkeys underwent initial behavioral training to sit in a primate chair and fixate a spot of light for a fluid reward. Following the initial training, surgical procedures were used to attach a head holder to the skull with 8-mm screws, orthopedic plates (Synthes-Stratec, Oberdorf, Switzerland; <http://www.synthes-stratec.com>), and dental acrylic. A few weeks after the first surgery, the monkeys underwent a second procedure to suture a fine coil of insulated wire to the sclera, beneath the conjunctiva and Tenon's capsule, for monitoring eye position. All surgical procedures were carried out using sterile procedure, with the monkey under isoflurane anesthesia. During recovery from all surgical procedures, animals were monitored carefully and given analgesic treatments. After full recovery, the monkeys were trained to pursue visual targets for a liquid reward. While they were involved in the study, the monkeys' water intake was restricted. To monitor their fluid status, the animals were weighed before each experimental session and their health was evaluated regularly by experimenters and UCSF veterinary staff.

Experiments were conducted approximately five times per week and lasted 2-4 h. During experiments, animals were removed from their home cages and transferred to the laboratory in a primate chair. The chair was placed on a servo-controlled turntable (Contraves-Goertz model 403, 20 foot-lb peak torque), and the implanted head holder was used to affix monkeys' heads to the ceiling of the chair. A bright, 0.5-deg diameter visual target was deflected by a pair of *x-y* mirror galvanometers (General Luminonics model CX660) and projected onto the back of a tangent screen 114 cm from the monkey. Except for the target, the room was completely dark. Darkness was especially critical for maintaining VOR gains throughout behavioral sessions involving monkeys that had undergone prior adaptive modification of the VOR.

Behavioral paradigms for head and target motion

Our experimental design was to compare the eye velocities evoked by a brief perturbation of target motion presented during a variety of ongoing tracking conditions. Stimuli were delivered in individual trials that were 2 to 4 s in duration, where each trial presented a single combination of head and/or target motion. Each trial began with the appearance of a stationary target that the monkey was required to fixate within 2°. After an initial fixation period of 400 to 1,000 ms, the target and/or turntable began to move toward the center of the screen at constant velocity, according to the tracking condition specified by the individual trial. Monkeys were rewarded if they kept their eye position within 2-3° of the target throughout the duration of the trial.

Accurate tracking always requires that gaze velocity, defined as eye velocity relative to the world (E_W), matches target velocity relative to the world. Gaze velocity is defined according to the equation

$$\dot{E}_w = \dot{E}_H + \dot{H}_w \quad (1)$$

where $\dot{E}_H$ and $\dot{H}_w$ correspond to eye velocity within the orbit and head velocity in the world. Eq. 1 emphasizes that a given gaze velocity can result from either head velocity or eye velocity, or a combination thereof, depending on the tracking condition. In our experiments, whenever the head was rotated, it was rotated at an angular velocity of 20 deg/s. We varied the speed and direction of target motion relative to head motion to create conditions consisting of varying amounts of eye and gaze velocity.

For tracking conditions that include head motion, we have adopted a terminology that specifies the ratio of eye to head velocity required for perfect tracking. Thus the traces in Fig. 1A illustrate three of the combinations of head and target velocity used in our experiments. During $\times 1$ -tracking, the target is kept stationary in the world while the head is rotated. In perfect $\times 1$ -tracking, gaze velocity is zero, but there is an eye movement of 20 deg/s that is equal in amplitude and opposite in direction to the head movement. In contrast, during $\times 0$ -tracking (also known as VOR cancellation), the head is rotated in the same direction and at the same speed as the target: perfect tracking requires zero eye velocity in the orbit to achieve a gaze velocity of 20 deg/s that is equal to head velocity. At the other extreme, in $\times 2$ -tracking, the head and target are moved at the same speed but in *opposite* directions. The overall gaze velocity required for accurate tracking is still 20 deg/s, which is accomplished by smooth rotation of the eye in the orbit at *twice* the head speed but in the opposite direction. These relationships are emphasized by the eye and gaze velocity records shown in each panel of Fig. 1A.

Trials were presented in pseudo-random order within blocks, each block comprising all types of trials for the day's experiment. A standard block consisted of 32 trials: four configurations of each of eight tracking conditions. Each tracking condition was configured in four different ways, to include trials with motion to the left and right, and trials with and without target perturbations. On a given day, monkeys were presented with one of two blocks of stimuli, including trials within the range of either $\times 0$ to $\times 1$ or $\times 1$ to $\times 2$ tracking. On a normal day with $\times 0$ to $\times 1$ stimuli, the tracking conditions consisted of fixation, $\times 1$ -, $\times 0.9$ -, $\times 0.67$ -, $\times 0.5$ -, $\times 0.33$ -, and $\times 0$ -tracking, and pursuit at 20 deg/s with the head stationary. For $\times 1$ to $\times 2$ stimuli, the tracking conditions consisted of fixation, $\times 1$ -, $\times 1.1$ -, $\times 1.33$ -, $\times 1.5$ -, $\times 1.67$ -, and $\times 2$ -tracking, and pursuit at 20 deg/s.

Because of the large number of stimulus conditions per block, and the necessity of averaging responses from many trials (see *Data Analysis*), we were unable to present the full range of $\times 0$ to $\times 2$ stimuli on individual days. These experiments were first conducted in Monkey Q, who worked for fewer trials a day than Monkey W. To ensure that we obtained enough repetitions of each stimulus, he was presented with six, rather than eight, tracking conditions per block (e.g., Fig. 4). Further, following adaptive modification to decrease or increase the gain of the VOR, we had three reasons to restrict trials to the $\times 0$ - to $\times 1$ -tracking or $\times 1$ - to $\times 2$ -tracking ranges, respectively. First, we predicted that VOR adaptation would affect the responses to perturbations most dramatically for the tracking conditions that mimicked the new VOR gain, and we wanted to maximize our ability to observe these changes. Second, given that trials similar to the ones we used as tracking conditions can induce acute changes in the gain of the VOR (Lisberger et al. 1984), it was important to avoid presenting the monkeys with trials that would tend to reverse the VOR adaptation induced by the spectacles. Third, the monkeys' performance on tracking conditions that differed greatly from the adapted VOR gain was extremely poor. Since we excluded all trials in which saccades occurred during the analysis window, the yield on these trials would have been impossibly low.

Target perturbations

The target perturbations used to probe the gain of pursuit consisted of single cycles of 10 Hz sine waves with peak-to-peak amplitudes of 10 deg/s. In all experiments reported here, we presented the perturbations in a peak first (onward) orientation, so that target velocity was increased above the ongoing level for the first half-cycle and then decreased. Previous studies (Churchland and Lisberger 2002; Schwartz and Lisberger 1994) have demonstrated the appropriateness of this stimulus for probing the internal gain of pursuit without altering it. Target perturbations, when present, occurred during steady-state tracking, 450 ms after the onset of target and/or head motion to allow sufficient time for the eye to capture the target before the presentation of the perturbation. To avoid possible effects of eye position on the amplitude of the eye movement response, we adjusted the initial position of the target and head in each trial so that the perturbations were delivered while the eyes were within 5° of the center of the orbit. Initial positioning of the target consisted of providing a step of target position at the same time as the onset of target motion, with the size and direction of the step contrived to achieve the desired eye position at the time of the perturbation. Initial positioning of the head often required lengthening the initial fixation interval so that the head could be moved at 20 deg/s to the desired initial position. Similarly, trials that included head motion were followed by an extended inter-trial interval to allow the head to be returned slowly to the home position.

VOR adaptation

Monkeys were fitted for magnifying ($\times 2.2$) and miniaturizing ($\times 0.25$) spectacles as previously described (Lisberger and Pavelko 1986; see http://keck.ucsf.edu/~sgl/top_goggles.htm). Briefly, optics were inserted into goggles that were fitted to a mold of each monkey's face, to allow the lenses to be close to the eyes while preventing contact between any part of the spectacles and the face. Spectacles were removed for each behavioral session, and on a daily basis for cleaning and inspection of proper fit. VOR gain (eye velocity divided by head velocity) was measured by imposing passive head rotations that consisted of trapezoids of angular head velocity at 20 deg/s in total darkness (Lisberger and Pavelko 1986). The VOR was tested at the beginning and again at the end of each experimental session, to ensure that the gain remained at adapted levels. There was a tendency for the VOR gain to drift toward 1 during an experimental session, especially following high-gain VOR adaptation. Experiments were conducted for 6 to 11 sessions after the VOR gain had reached asymptotic levels, within the interval from 3 days to 2 wk after the donning of the spectacles.

Data analysis

Only trials that were completed successfully by the monkey were included for analysis. In addition, trials were excluded if saccades were present during the perturbation or within the subsequent 200 ms. All other saccades were marked by hand and the portions of the eye velocity traces corresponding to saccades were treated as missing data. The perturbation responses are quite small and could not be measured reliably from individual trials. Therefore we averaged the eye velocity responses to each type of trial on each day (30–60 trials per average). We obtained nearly identical results whether we obtained the average perturbation response amplitudes by averaging amplitudes on individual days (as reported here) or by averaging all of the trials for individual conditions across days and then taking the amplitude of this averaged trace. We chose to report the data from the first method so that we could include error bars to give an estimate of day-to-day variability.

Figure 1*B* demonstrates our method of isolating perturbation responses for pursuit trials. We isolated the portion of the response for each tracking condition that resulted specifically from the target perturbation by subtracting the averaged eye velocity in trials *without*

perturbations from that in trials *with* perturbations to obtain a “difference eye velocity” trace. Subsequent analyses were performed on these averaged, isolated responses to the perturbations for each day. Statistical significance was assessed using an unpaired, two-tailed Student's *t*-test.

RESULTS

In the first part of the study, we present data from monkeys with normal VOR gains close to 1. We probed the gain of pursuit during tracking conditions that used passive head motion at 20 deg/s to dissociate eye and gaze velocity. The logic of our experiments is illustrated in Fig. 2, which plots the predicted responses to brief perturbations of target motion as a function of the tracking condition if pursuit gain were controlled by eye velocity in the orbit (fine diagonal line) or gaze velocity in the world (bold “V”). As the tracking condition changes from $\times 0$ - to $\times 2$ -tracking, the contribution of the eye becomes larger, and eye velocity during tracking increases from near 0 to 40 deg/s. If eye velocity signals control the internal gain of pursuit, then the response to our probe perturbations should be small for $\times 0$ -tracking and increase as the conditions move toward $\times 2$ -tracking. Over the same range of tracking conditions, in contrast, gaze velocity is 20 deg/s for $\times 0$ -tracking, decreases to zero during $\times 1$ -tracking, and increases again to 20 deg/s for $\times 2$ -tracking. If gaze velocity signals control the internal gain of pursuit, then perturbation responses should be equally large during $\times 0$ - and $\times 2$ -tracking and should be minimal during $\times 1$ -tracking.

Pursuit gain control: gaze velocity versus eye velocity

Figure 3 shows examples of the eye velocity responses to perturbations of target motion consisting of single cycles of a 10 Hz, ± 5 deg/s sine wave when the perturbations were presented during tracking involving different combinations of head and target motion. Eye velocity responses to target velocity perturbations were small when the perturbation was presented during fixation (Fig. 3, *thin traces*). In monkeys W and Q the evoked eye velocity responses had peak-to-peak amplitudes of 1.14 ± 0.15 and 2.0 ± 0.26 deg/s. During $\times 1$ -tracking, the responses to the target perturbation (*bold trace* in top set of Fig. 3) were not substantially enhanced relative to those elicited during fixation. In contrast, the response to the perturbation was enhanced substantially when it was presented during $\times 0$ - or $\times 2$ -tracking, and in each case reached levels close to those attained during pursuit with the head stationary (Fig. 3, *2nd through 4th set of traces*).

Figure 3 also illustrates our consistent finding that modulation of pursuit gain control affects the time course of the responses to perturbations. By comparison with the responses to perturbations delivered during fixation (*thin traces*), the larger responses during tracking conditions that increase the internal gain of pursuit (*bold traces*) start sooner, reach an earlier peak, and possess a large negative peak. In many examples, the increased gain of the response to the perturbation caused an oscillation of eye velocity that took two or more cycles to damp out.

To summarize the results obtained over the full set of tracking conditions, Fig. 4 plots the peak-to-peak amplitude of the perturbation responses as a function of the tracking condition, for comparison with the predictions in Fig. 2 for the competing “eye” and “gaze” velocity hypotheses. For both monkeys, the minimum response amplitude appears for conditions near $\times 1$ -tracking, when gaze velocity was minimal and eye velocity was large. As the tracking condition was altered to increase gaze velocity, the amplitude of the eye velocity response to the perturbation increased, nearly reaching the values measured during pursuit with the head stationary (horizontal dashed lines). Monkey W (Fig. 4A) exhibited a small increase in the peak-to-peak amplitude of the response to the perturbation from 1.14 ± 0.15 to 1.52 ± 0.24 deg/s between fixation and $\times 1$ -tracking, and large increases to 3.8 ± 0.4 and 5.2 ± 0.6 deg/s

for $\times 0$ - and $\times 2$ -tracking. Monkey Q showed a slight but nonsignificant decrease from 2.0 ± 0.26 to 1.96 ± 0.26 deg/s between fixation and $\times 1$ -tracking, and large increases to 4.56 ± 0.68 and 4.98 ± 0.8 deg/s for $\times 0$ - and $\times 2$ -tracking (Fig. 4B). During pursuit at 20 deg/s, Monkey W's perturbation response was 4.3 times its value for perturbations delivered during fixation, while Monkey Q's response was enhanced by a factor of 2.7.

At a qualitative level, the data fit the predictions made if the internal gain of pursuit was controlled by gaze rather than eye velocity. To provide a quantitative test of the two alternatives, we fitted the data with a linear model in which the amplitude of the perturbation response is a linear combination of components related to eye and gaze velocity

$$P = A_{E_w} \dot{E}_w + A_{E_h} \dot{E}_h \quad (2)$$

where P is the peak-to-peak amplitude of the response to the perturbation and A_{E_w} and A_{E_h} are the sensitivities of gain control to gaze and eye velocity. Monkey W's responses were best fit by a model with a gaze velocity sensitivity of 0.19 deg/s per deg/s and an eye velocity sensitivity of 0.047 deg/s per deg/s (*thin lines without symbols* in Fig. 4A). Thus Monkey W's pursuit gain exhibited a gaze velocity sensitivity approximately four times its eye velocity sensitivity. The data from Monkey Q were fit best by a model with a gaze velocity sensitivity of 0.22 deg/s per deg/s and a small *inhibitory* eye velocity sensitivity of -0.0025 deg/s per deg/s (Fig. 4B).

Note that the size of the sensitivities of pursuit gain to eye velocity are just right to account for the data observed during $\times 1$ -tracking. For monkey W, the linear model predicts that 20 deg/s of eye velocity with zero gaze velocity would result in a 0.4 deg/s increase in perturbation response over that observed during fixation, which is almost exactly what we observed (Fig. 4A). For monkey Q, the small negative sensitivity to eye velocity predicts that the response to the perturbation should be 0.05 deg/s smaller during $\times 1$ -tracking than during fixation, very similar to the observed decrease of 0.04 deg/s. To test the alternative explanation that some degree of enhancement would be expected if the VOR were being visually enhanced during $\times 1$ -tracking (Leigh et al. 1994), we measured the gain of the VOR in complete darkness in the two monkeys. In monkeys W and Q, the average VOR gains were 0.97 and 0.96. If the small enhancement of pursuit gain during $\times 1$ -tracking in Monkey W resulted from a visually enhanced VOR, then a similar enhancement would be expected but does not appear in Monkey Q.

Pursuit gain control: physical gaze velocity versus visually driven gaze velocity

In the second part of the study, we used long-term adaptation of the vestibulo-ocular reflex to further distinguish between two possible modulators of pursuit gain. The physical gaze velocity required by our tracking conditions is defined by the sum of head and target motion and is simply eye velocity with respect to the world, without regard for what drives eye velocity. However, physical gaze velocity can be thought of as having a vestibular and a visual component. The vestibular component is driven by the VOR is estimated as the gaze velocity recorded during the VOR in the dark. The visual component is the tracking eye movement, driven by visual inputs, that makes up for the difference between the gaze velocity caused by the VOR alone and the gaze velocity required by the target motion. Thus we define “visually driven gaze velocity” as physical gaze velocity minus the vestibular component of gaze velocity measured during the VOR in the dark. In monkeys with VOR gains near 1, physical gaze velocity and visually driven gaze velocity are nearly the same, differing only by the small amount that the gain of the VOR in darkness might differ from 1.

In the next set of experiments, we used spectacle-induced adaptive modification of the VOR to dissociate physical and visually driven gaze velocity signals. Figure 5 demonstrates how

changing the gain of the VOR would affect the response to perturbations of target velocity, depending on which signals control the internal gain of pursuit. If signals related to physical gaze velocity set the value of the pursuit gain control, then the results after VOR adaptation should be identical to those obtained with normal VOR gains of approximately 1 (bold “V-shaped” curve). However, during tracking conditions exactly mimicking the VOR gain, the target can be successfully tracked using only the component of gaze velocity that is driven by vestibular inputs. Therefore if visually driven gaze velocity signals control the internal gain of pursuit, then altering the gain of the VOR should shift the V-shaped predictions along the x -axis by the amount of VOR adaptation (thin V-shaped curves), and the tracking condition yielding the smallest perturbation response amplitude should be the one most closely mimicking the adapted VOR gain.

Reduction of the gain of the VOR to 0.4 ± 0.07 with miniaturizing spectacles had substantial effects on the perturbation response amplitudes during $\times 0$ to $\times 1$ -tracking for both monkeys (Fig. 6A). First, perturbation responses were now substantially larger during $\times 1$ -tracking than during fixation. In Monkey W, the perturbation response during $\times 1$ -tracking was enhanced by a factor of 2.7 above the response during fixation versus a factor of 1.33 before VOR adaptation. Monkey Q, who had a slight decrease in perturbation response during $\times 1$ -tracking when the VOR was normal, now exhibited an enhanced response equal to 2.3 times the fixation response. Second, the perturbation responses during $\times 0.33$ -tracking were now smaller than when the monkeys had normal VOR gains, but were still enhanced relative to responses during fixation. Monkey W's response during $\times 0.33$ -tracking decreased from 3.4 ± 0.34 to 2.66 ± 0.34 deg/s, while Monkey Q's response decreased from 4.9 ± 0.8 to 3.4 ± 0.35 deg/s. However, even with these decreases, Monkey W's and Q's responses during $\times 0.33$ tracking were still 2.2 and 1.9 times as large as those during fixation. Third, of the tracking conditions we tested following adaptive decreases in the gain of the VOR, the perturbations delivered during $\times 0.67$ -tracking elicited the smallest responses in both monkeys (Fig. 7).

Increases in the gain of the VOR to 1.5 ± 0.2 with magnifying spectacles had consistent, but more subtle, effects on the perturbation response amplitudes during $\times 1$ - to $\times 2$ -tracking for both monkeys (Fig. 6B). First, the responses to perturbations delivered during $\times 1$ -tracking were enhanced in both monkeys so that they were now 1.7 (Monkey W) and 1.3 (Monkey Q) times as large as the responses to perturbations delivered during fixation. Second, while perturbation responses decreased during tracking conditions similar to the new VOR gain, there was still substantial enhancement of the perturbation response, even during tracking conditions that almost exactly mimicked the adapted VOR gain. In Monkey W, the perturbation response during $\times 1.5$ -tracking was enhanced to 2.4 times the fixation response, compared with 3.4 times when the gain of the VOR was normal. Monkey Q's perturbation response during $\times 1.67$ -tracking was 2.0 times the fixation response compared with 2.4 times when the gain of the VOR was normal. Third, the tracking condition that yielded the smallest perturbation responses after high-gain VOR adaptation was $\times 1.1$ -tracking in both monkeys (Fig. 7).

A summary of our results in monkeys with adapted VOR gains is shown in Fig. 7, which plots the average amplitude of the response to perturbations as a function of the tracking conditions in which the perturbations were delivered. The data for decreases and increases in the gain of the VOR, plotted in the left and right halves of the graphs as open and filled symbols, follow separate functions and show clear differences for the one overlapping condition, $\times 1$ -tracking. The data are strikingly different from the results obtained when the VOR gain was normal (thin dashed lines) and are shifted along the x -axis in the direction predicted if the pursuit gain control were modulated by signals related to visually driven gaze velocity. However, shift of the data along the x -axis was incomplete; the persistence of perturbation response enhancement during tracking conditions mimicking the new VOR

gain is inconsistent with the hypothesis that visually driven gaze velocity alone controls the internal gain of pursuit.

Because the data shared features predicted if pursuit gain control were modulated by physical gaze velocity and visually driven gaze velocity, we tested two models that might predict the observed perturbation response amplitudes. The first model assumed that the V-shaped curve seen before VOR adaptation (Fig. 4) was shifted to the left or right, assuming a new reference point for “zero” gaze velocity. For Monkey W, the best fits to the data were obtained with a 47.5% shift toward the reduced VOR gain value of 0.4, and a 45% shift toward the increased VOR gain value of 1.5. The data for Monkey Q were asymmetric: the best fits to the data were obtained with a 78.7% shift toward the reduced VOR gain value of 0.4, and a 31.4% shift toward the increased VOR gain value of 1.7.

In a second model, we assumed that the pursuit system has access to both physical gaze velocity and visually driven gaze velocity and uses some linear combination of the two to modulate pursuit gain control. We fitted the data with the equation

$$P = A_{Gw} \dot{E}_W + A_{Gvis} \dot{E}_{vis} \quad (3)$$

where P is the peak-to-peak amplitude of the response to the perturbation and A_{Gw} and A_{Gvis} are the sensitivities to physical gaze velocity and visually driven gaze velocity, respectively. With this model, the best fits were obtained for Monkey W using 42% visually driven gaze velocity for both increases and decreases in VOR gain, Monkey Q using 59% visually driven gaze velocity for decreases, and 36% visually driven gaze velocity for increases in VOR gain.

While the two models yielded similar results in terms of the relative contributions of physical gaze velocity and visually driven gaze velocity, the first model, which simply shifted the V-shaped curve along the x-axis, provided much closer fits to the data for both monkeys (Monkey W: $\chi^2 = 0.2$ vs. 1.4; Monkey Q: $\chi^2 = 0.07$ vs. 0.5). The quality of the fits from the first model has been shown in Fig. 7 by plotting the values obtained with the model for the tracking conditions used in the data collection (thin solid lines without symbols). The curves are not V-shaped only because they have been sampled at the tracking conditions we used.

DISCUSSION

It has been known for a decade that the internal gain of pursuit eye movements is subject to modulation. Initially, the gain control was envisaged as a switch that was “off” during fixation and “on” during tracking, but it then became clear that it was more like a volume control because the internal gain of pursuit varied continuously as a function of ongoing eye/target velocity during pursuit with the head stationary (Churchland and Lisberger 2002; Schwartz and Lisberger 1994). The goal of the present paper was to use behavioral measurements to determine the nature of the signals that modulate pursuit gain.

If the head is stationary, then pursuit is achieved by moving the eye in the orbit. However, if the animal is allowed to turn its head, or the head is turned passively, then pursuit of the target motion can involve head motion, eye motion, or some combination. This leads to the concept of gaze velocity, which is eye velocity with respect to the world; many neurons in the brain discharge in relation to gaze velocity rather than simply in relation to eye velocity in the orbit. The first experiments in our paper asked whether the signals that control the internal gain of pursuit are related to eye velocity or to gaze velocity. We dissociated these two signals by moving the head during tracking and using a brief target perturbation to

probe the internal gain of pursuit during tracking that involved different combinations of head and target motion. The results revealed that gain control is modulated primarily by signals related to gaze velocity.

Next, we investigated the question of how the gaze velocity signals that control the internal gain of pursuit are represented in the brain. Are they related to physical gaze velocity, defined strictly as eye velocity with respect to the world, or are they related to the component of physical gaze velocity that is driven by visual inputs? We used spectacles to adaptively modify the gain of the VOR and thereby dissociate physical and visually driven gaze velocity. Our data indicate that the internal gain of pursuit is modulated by signals that are altered when the gain of the VOR is adapted and that the modulating signals are intermediate between physical gaze velocity and visually driven gaze velocity.

The effects reported here regarding modulation of pursuit gain control following VOR adaptation should not be confused with those reported by Lisberger (1994), where changing the gain of the VOR had only small effects on the initiation of pursuit. The earlier study was asking about the neural mechanisms of VOR adaptation by determining whether the signals that drive the initiation of pursuit eye movements are passed through the site of modification for the VOR. Our present results with the effects of adaptive modification of the VOR on the internal gain of pursuit do not address the mechanisms of VOR adaptation. Indeed, our data do not indicate that changes in the gain of the VOR alter the gain of pursuit, but rather the set-point for the lowest setting of the gain control. We were simply using adaptive modification of the VOR as a tool for understanding better the origin of the internal neural signals that are used to control smooth pursuit eye movements.

Constraints on the site and mechanism of pursuit gain control

Our data tell us two things about the neural signals that control the internal gain of pursuit and their locus in the brain. First, they indicate that the modulatory signals must represent gaze velocity. This does not constrain the origin of the modulatory signals very much, since gaze velocity signals are ubiquitous in the pursuit system. They have been observed in the cortex in the medial superior temporal area (MST) (Kawano et al. 1984; Shenoy et al. 1999; Thier and Erickson 1992) and frontal pursuit area (FPA) (Fukushima et al. 2000), and in the cerebellum in the vermis (Shinmei et al. 2002) and floccular complex (Fukushima et al. 1999; Lisberger and Fuchs 1978; Miles et al. 1980b).

Second, our data imply that the pursuit system's internal representation of zero gaze velocity undergoes a partial transformation when the gain of the VOR is modified, shifting toward the gain of the VOR in the dark. Changes in the gain of the VOR are accompanied by the same incomplete shift in the representation of gaze velocity in Purkinje cells in the floccular complex (Lisberger et al. 1994; Miles et al. 1980a). Thus the cerebellar floccular complex is a candidate source for the signals that control the internal gain of pursuit. However, the effect of adaptive modification of the VOR on gaze velocity signals needs to be studied in MST, the FPA, and the cerebellar vermis to know whether all gaze velocity representations are modified in the same way. Other experiments showing that stimulation of the FPA (Tanaka and Lisberger 2001, 2002) enhances the response to a perturbation of target velocity during fixation suggest that gain control occurs downstream from the FPA, possibly in the pontine nuclei or in the cerebellar vermis or floccular complex. More information will be needed to relate our behavioral findings to the signals that emerge from each of those areas.

When tracking a moving target during head turns, monkeys can control their gaze velocity either by using visual inputs to generate a smooth pursuit eye movement that is added to the VOR, or by parametrically adjusting the gain of the VOR to some degree (Cullen et al.

1991; Lisberger 1990). It seems unlikely, however, that parametric adjustment of the gain of the VOR is a major factor in our experiments, for three reasons. First, we used low-velocity head movements that invoke relatively little parametric modulation of VOR gain in rhesus monkeys (Lisberger 1990). Second, even if our monkeys were using some amount of parametric modulation of the gain of the VOR, it would be expected to reduce the magnitude of the visually driven gaze velocity uniformly across the tracking conditions, but not to alter the tracking condition that corresponded to the smallest perturbation response. Third, our findings suggest that the pursuit system does not have complete access to information about the state of the VOR. Therefore we would not expect modulation or suppression of the VOR during different kinds of tracking, including active head turns, to substantially affect our results.

Our results raise the intriguing possibility that some of the seeming redundancy in the representation of gaze velocity at several stages of processing in the pursuit system may be illusory. Some of these structures may be encoding visually driven gaze velocity, while others encode physical gaze velocity, as absolute eye velocity with respect to the world. Furthermore, some may be driving physical gaze velocity or visually driven gaze velocity, while others may be involved in modulation of the internal gain of pursuit. Investigation of the effects of adaptive modification of the VOR on the response properties of putative gaze-velocity encoding neurons throughout the brain could help resolve this issue.

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FIG. 1.

Tracking conditions used to identify signals controlling the internal gain of pursuit. *A*: the 3 columns of traces show examples of the stimuli used for "x0-tracking," "x1-tracking," and "x2-tracking." From top to bottom, the traces are superimposed target velocity and gaze velocity, head velocity and eye velocity. The arrows on the gaze velocity traces point to a small deflection of gaze velocity that results from the time delay of the VOR between the onset of head motion and eye motion. The horizontal dashed lines on the bottom traces indicate zero eye velocity. *B*: example data showing the enhancement of the response to perturbations delivered during pursuit versus during fixation. In the top row of traces the dashed and continuous lines indicate the target velocity and eye velocity response to a perturbation delivered during fixation. In the middle row of traces, the thin and bold traces show the eye velocity during pursuit of target motion at 20 deg/s without and with a perturbation of target velocity. The horizontal dashed line shows 0 eye velocity. In the bottom row of traces, the dashed trace shows the perturbation of target velocity; the bold trace shows the response to a perturbation delivered during pursuit at 20 deg/s, computed as difference between the eye velocity evoked by target motion with and without a perturbation, and the continuous fine trace shows the response to perturbations delivered during fixation.

FIG. 2.

Schematic diagram showing how the responses to brief perturbations of target velocity should vary as a function of tracking condition if the internal gain of pursuit was controlled by signals related to gaze velocity vs. eye velocity. The horizontal solid and dashed lines represent the perturbation responses during fixation and during pursuit at 20 deg/s. The thin diagonal line and the bold V-shaped curve show the responses expected if eye velocity or gaze velocity controls the internal gain of pursuit.

FIG. 3.

Effect of tracking condition on the responses to perturbations of target velocity. Examples of averaged eye velocity responses to perturbations of target velocity delivered under different initial conditions. From top to bottom, the bold traces show the responses to the perturbation during $\times 1$ -tracking, $\times 0$ -tracking, $\times 2$ -tracking, and pursuit with the head stationary. In each tracking condition, the responses to perturbations are shown as “difference eye velocity” records, obtained as described in Fig. 1B. The thin traces are the same for each row of superimposed traces and show the responses to target perturbations presented during fixation. The dashed trace in the top row shows the time course of the perturbation of target velocity itself. Data are from Monkey W.

FIG. 4.

Quantitative summary showing that pursuit gain is controlled by signals related to gaze velocity rather than eye velocity. Each graph plots the peak-to-peak amplitude of the response to perturbations as a function of the tracking condition during which the perturbation was delivered. *A*: Monkey W. *B*: Monkey Q. In each graph, the symbols connected by bold lines present data averaged across several experimental days and the finer lines without symbols show the best fit to the data, obtained from eq. 2. Because of the clear saturation at each extreme of the data, the points for $\times 0$ -tracking and $\times 2$ -tracking were not used when fitting eq. 2 to the data.

FIG. 5.

Predictions of the effect of changing the gain of the VOR on the dependence of the response to perturbations on tracking condition. The bold V-shaped function labeled “physical” shows the relationship that should pertain for all gains of the VOR if the internal gain of pursuit is controlled by signals related to physical gaze velocity (a.k.a. eye velocity in the world). The 2 thin V-shaped functions labeled “Visual (low)” and “Visual (high)” show the relationships predicted when the gain of the VOR is high or low if the internal gain of pursuit is controlled by signals related to visually driven gaze velocity. Vertical dashed lines indicate the mean VOR gains in our experiments in states of adaptation, from left to right, low, normal, and high VOR gains. The 2 shaded vertical columns indicate ± 1 SD of the VOR gains in our experiments with the gain of the VOR low and high.

FIG. 6.

Effect of tracking condition on the responses to perturbations after adaptive decreases (*A*) and increases (*B*) in VOR gain. Each panel shows examples of averaged eye velocity responses to perturbations of target velocity delivered under different initial conditions. In each tracking condition, the responses to perturbations are shown as “difference eye velocity” records, obtained as described in Fig. 1*B*. The thin traces are the same for each set of superimposed traces and show the responses to target perturbations presented during fixation. The dashed trace in the top row shows the perturbation of target velocity itself. Data are from Monkey W. *A*: from top to bottom, the bold traces show the averaged eye velocity responses to the perturbation during $\times 0.33$ -tracking, $\times 0.67$ -tracking, and $\times 1$ -tracking. *B*: from top to bottom, the bold traces show the responses to the perturbation during $\times 1.5$ -tracking, $\times 1.1$ -tracking, and $\times 1$ -tracking.

FIG. 7.

Quantitative summary showing that pursuit gain is controlled by gaze velocity signals that are modified in relation to changes in the gain of the VOR, becoming intermediate to physical and visually driven gaze velocity. Each graph plots the peak-to-peak amplitude of the eye velocity response to target velocity perturbations as a function of the tracking condition when the perturbation was delivered. *A*: Monkey W. *B*: Monkey Q. In each graph, the open and filled symbols connected by bold lines show data obtained after the gain of the VOR had been decreased to about 0.4 or increased to about 1.5. The finer lines without symbols show the best fit to the data, obtained by sliding the V-shaped “gaze velocity” function to the right or left. For comparison purposes, the fits obtained with a VOR gain of 1 are replotted from Fig. 4 (thin, dashed lines). Statistically significant differences were found between normal and adapted VOR gains for all conditions but $\times 0.9$ tracking in Monkey W and $\times 1.1$ tracking in Monkey Q (unpaired Student's *t*-test, $P < 0.01$). Because of the clear saturation at each extreme of the data, the points for $\times 0$ -tracking and $\times 2$ -tracking were not used when fitting the data. Error bars show one SD of the means from all experimental days.