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Context- and experience-dependent modulation of the sensorimotor transformation for smooth pursuit eye movements

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Context- and experience-dependent modulation of the sensorimotor transformation for smooth pursuit eye movements

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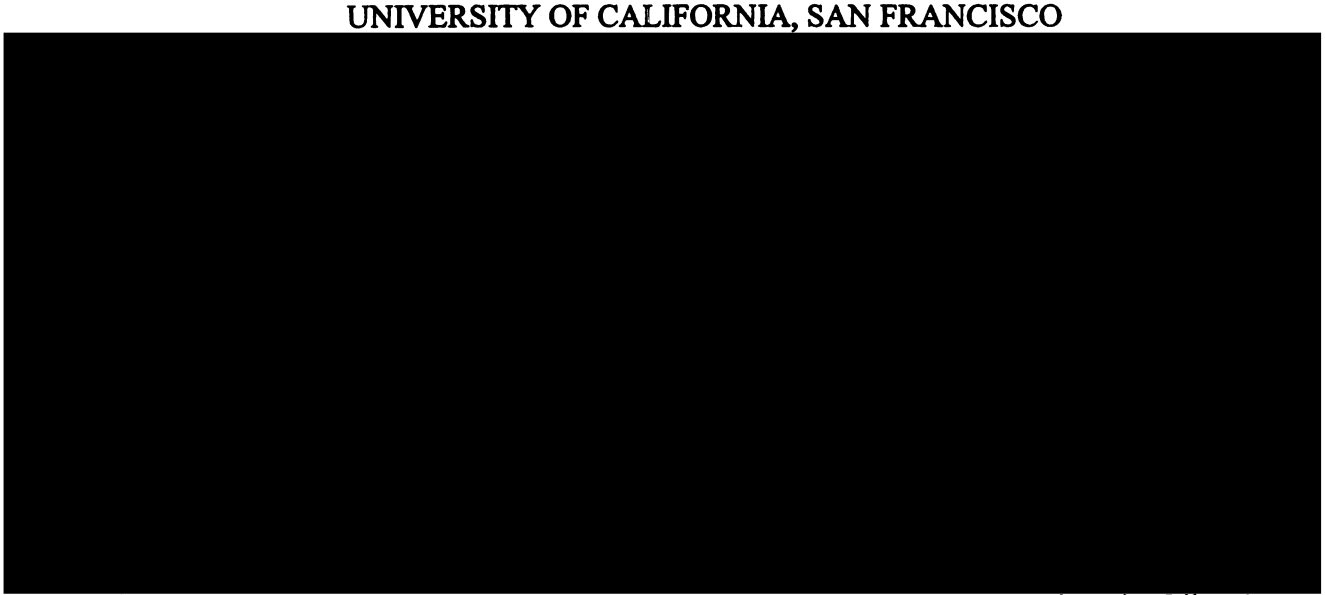

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In memory of my grandmother,

Catherine McDonald Carey

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Context- and experience-dependent modulation of the sensorimotor transformation for smooth pursuit eye movements

by Megan Rose Carey

Abstract

Smooth pursuit eye movements work in combination with other eye movement systems to ensure stable vision in a non-stationary world. Pursuit eye movements are tracking eye movements that allow primates to keep moving objects stable on the retina for improved visual processing. Although the basic task of the pursuit system is to perform a sensorimotor transformation that generates an eye velocity that matches target velocity, the relationship between target motion and subsequent eye movement is not fixed. This thesis investigates the neural signals that modulate the sensorimotor transformation for pursuit, based both on current context and on previous experience.

The amplitude of the pursuit response to a brief perturbation of target velocity is larger if the perturbation is presented during ongoing pursuit vs. during fixation. To understand the neural signals used by the pursuit system to control the gain of the response to target perturbations under different initial conditions and thereby constrain the possible sites and mechanisms of context-dependent pursuit modulation, I used passive whole body rotation to distinguish between eye velocity (eye in head) and gaze velocity (eye in world) signals. Adaptive modification of the vestibulo-ocular reflex allowed a further distinction between gaze velocity *per se* and the visually-driven component of gaze velocity. The results demonstrate that signals intermediate to gaze

velocity and visually-driven gaze velocity control context-dependent modulation of pursuit.

In a separate set of experiments, I investigated the signals that modulate the sensorimotor transformation for pursuit based on experience. Specifically, I used microstimulation in cortical area MT to test the hypothesis that visual motion signals represented there could provide instructive signals for pursuit learning. The results demonstrate that activity in MT, consistently associated with pursuit in a given direction, is sufficient to drive learning for pursuit. Additional experiments stabilizing the target on the retina and using motion of a visual background to mimic MT stimulation demonstrate that visual signals in general, including target motion relative to the eye, and activity in MT, are provide powerful instructive signals for pursuit learning under physiological conditions.

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Chapter 1

General Introduction

Smooth pursuit eye movements are voluntary eye movements that allow primates to track moving objects and keep them foveated for improved visual processing. Pursuit works in combination with other eye movement systems to ensure stable vision in a non-stationary world. Once a visual target of interest has been selected by the saccadic eye movement system, the vestibulo-ocular reflex protects our vision from contamination by self-generated motion, while pursuit protects our vision from contamination by the motion of the targets themselves.

The main task of the pursuit system is to perform a sensorimotor transformation that generates an eye movement in response to visual target motion. The pursuit system generally accomplishes its goal of keeping moving targets on the fovea by matching eye velocity to target velocity (Rashbass 1961, Robinson 1965). As shown in Figure 1.1, a step in target velocity results in an eye movement that begins after a short (~100 msec) delay, and eye velocity reaches target velocity within ~200 msec of target motion onset. Image motion, or motion of the target relative to the eye, is the visual signal that drives the initiation of pursuit. After the eye captures the target and they are both moving in the same direction at the same speed, however, pursuit is maintained in the absence of image motion.

At first glance, when presented with simple steps of target velocity, the pursuit system appears to perform a very basic and fixed sensorimotor transformation: match eye velocity to target velocity. In the real world, however, targets of interest rarely move in a straight line at a constant speed, and the 200 ms delay between the onset of visual motion and the generation of the matching eye movement presents a potential problem for the pursuit system. To maximize its usefulness, the pursuit system would ideally be able to

make intelligent predictions about changes in target trajectory based on both how the target is currently moving and previous experiences of tracking similar kinds of motion. This is exactly what it does.

The sensorimotor transformation for pursuit is not a simple, all-or-none transformation that always generates an eye movement at a velocity matching that of the target motion (Robinson, 1965, Luebke and Robinson 1988). It is modulated by behavioral context, and identical visual image motion signals can elicit drastically different pursuit responses under different conditions (Schwartz and Lisberger 1994, Churchland and Lisberger 2002). The pursuit system uses information about both current context and previous experience to modulate the relationship between incoming visual image motion signals and corresponding motor responses. By taking advantage of these contextual and experiential cues, the pursuit system is able to optimize its responses appropriately for different behavioral circumstances.

This thesis investigates the neural signals that control the modulation of the sensorimotor transformation for pursuit based on behavioral context (Chapter 2) and experience (Chapter 3). The shared philosophy behind both sets of experiments is that identifying the *signals* that modulate the sensorimotor transformation for pursuit provides powerful constraints on how and where *neurons* accomplish that modulation within the brain.

The basic pursuit circuit consists of canonical cortico-basal ganglia and cortico-ponto-cerebellar loops (Middleton and Strick 2000). Visual inputs to the pursuit system are provided by motion-sensitive cortical visual area MT; these signals are transformed by downstream areas including the frontal pursuit area, pontine nuclei, and cerebellum to

yield a motor output (for review, see Lisberger et al 1987). As shown in Figure 1.2, as the signals move through the brain, they are represented first in purely sensory, then in sensorimotor, and ultimately, at the level of motor neurons, in purely motor coordinate frames. It is because of these coordinate transformations between different stages of the pursuit circuit that identifying the specific nature of the sensory and/or motor signals that modulate the sensorimotor transformation for pursuit is a useful way to constrain the neural mechanisms of the modulation. Only once the modulatory signals have been described and the relevant neurons identified is it possible to ask how the patterns of activity that represent those signals are able to perform the modulation at a cellular level.

Context-dependent modulation of pursuit: Gain control

A given image motion of an object across the retina can result in different eye movements depending on when it is presented. In a phenomenon known as 'gain control', the gain of the pursuit response (defined as eye velocity divided by target velocity) to a brief perturbation of target velocity depends on the level of engagement of the pursuit system at the time of the presentation of the perturbation. Target perturbations presented during ongoing pursuit elicit higher-gain responses than identical perturbations presented while the target is otherwise stationary (eg Schwartz and Lisberger 1994). The enhancement of the response depends on the speed of ongoing pursuit, suggesting that feedback signals related to eye velocity could play a role in controlling the internal gain of the sensorimotor transformation for pursuit.

I took a behavioral approach to identifying the neural signal(s) that modulate the responses to brief target perturbations presented in different contexts. In particular, I

wanted to dissociate eye velocity (in the head) and gaze velocity (in the world, defined as eye velocity plus head velocity) signals as potential modulators of pursuit gain. Because different neurons within the pursuit circuit preferentially encode either gaze or eye velocity signals, determining which signal is primarily responsible for controlling the sensorimotor transformation for pursuit helps constrain the potential sites and mechanisms of gain control in the brain. However, during pursuit with the head stationary, gaze velocity signals are made up entirely of eye velocity signals and it is impossible to determine whether one or the other is responsible for controlling pursuit gain.

For the experiments presented in Chapter 2, I used passive whole body rotation to provide a vestibular stimulus that dissociated gaze velocity signals (eye in world) from eye velocity signals (eye in head). Comparing the amplitudes of pursuit responses to identical perturbations of target velocity presented during different ongoing behaviors revealed that pursuit responses vary as a function of gaze velocity, not eye velocity. Next, I used adaptation of the vestibulo-ocular reflex to further distinguish between the visually-driven component of gaze velocity and gaze velocity as traditionally defined as the physical motion of the eye in the world. The results demonstrate that pursuit gain is controlled by signals intermediate to visually-driven gaze velocity and gaze velocity *per se*.

Experience-dependent modulation of pursuit: Learning

Just as pursuit responses to a particular target motion depend on current context, they also depend on previous experience. Even once the basic pursuit behavior is

learned, pursuit eye movements continue to be updated based on experience. In the laboratory, pursuit learning can be demonstrated with tasks in which a consistent, repeated change in target speed or direction during pursuit in a given direction leads to changes in the pursuit eye movement elicited by target motion in that direction (Kahlon and Lisberger 1996, Medina et al. 2005, Boman and Hotson 1992). For example, a purely horizontally moving target normally elicits no vertical eye velocity. However, repeated presentation of "learning trials" in which a pursuit target moves horizontally and then consistently changes direction to move vertically at a fixed time after target motion onset leads to a learned, vertical eye movement on "probe trials" of purely horizontal target motion (Medina et al. 2005).

Chapter 3 investigates the source of the instructive signals for learning in pursuit. Identifying instructive signals for pursuit learning required a different approach from the analysis of the signals that modulated gain control. The gain control experiments in Chapter 2 focus on signals available to the pursuit system during ongoing pursuit at the time of the presentation of the visual probe stimulus, the target perturbation. However, the instructive signals that lead to *learned* changes in the sensorimotor transformation for pursuit must be present in learning trials, while the evidence of the altered sensorimotor transformation is observed on probe trials.

Following a long tradition of theories on the role of sensory signals in driving learned changes in behavior, I hypothesized that visual signals related to the change in target trajectory (image motion across the retina, retinal slip, or error) could serve as instructive signals for pursuit learning. Since visual cortical area MT is known to provide visual inputs to the pursuit system, I further reasoned that cortical area MT specifically

might be a source of visual instructive signals for learning in pursuit. To test this hypothesis, I asked whether microstimulation in MT could substitute for a real-world change in target direction and drive learning for pursuit. The experimental design was based on previous experiments using a change in target direction to drive pursuit learning (Medina et al. 2005). However, instead of a change in target direction at a fixed time after target motion onset, a cluster of MT neurons with a preferred direction roughly orthogonal to the direction of pursuit was stimulated through direct electrical microstimulation.

MT microstimulation learning experiments revealed two components of learning: one towards the preferred direction of the stimulated neurons, which is predicted if the microstimulation is effective at substituting for a change in target direction, and a second, later component in the opposite direction. The learning in the direciton *opposite* to the preferred direction of the stimulated neurons could be accounted for by retinal image motion signals related to target motion relative to the eye that resulted from a microstimulation-evoked eye movement on learning trials. Stabilizing the target on the retina on learning trials in order to eliminate target-related image motion signals resulting from the microstimulation-evoked eye movement eliminated the oppositely-directed learning. A parallel series of behavioral experiments in which a moving background of dots was substituted for microstimulation on learning trials yielded results strikingly similar to the MT microstimulation experiments. We conclude that visual image motion signals, including those from visual cortical area MT, provide powerful instructive signals for pursuit learning.

Figure 1.1

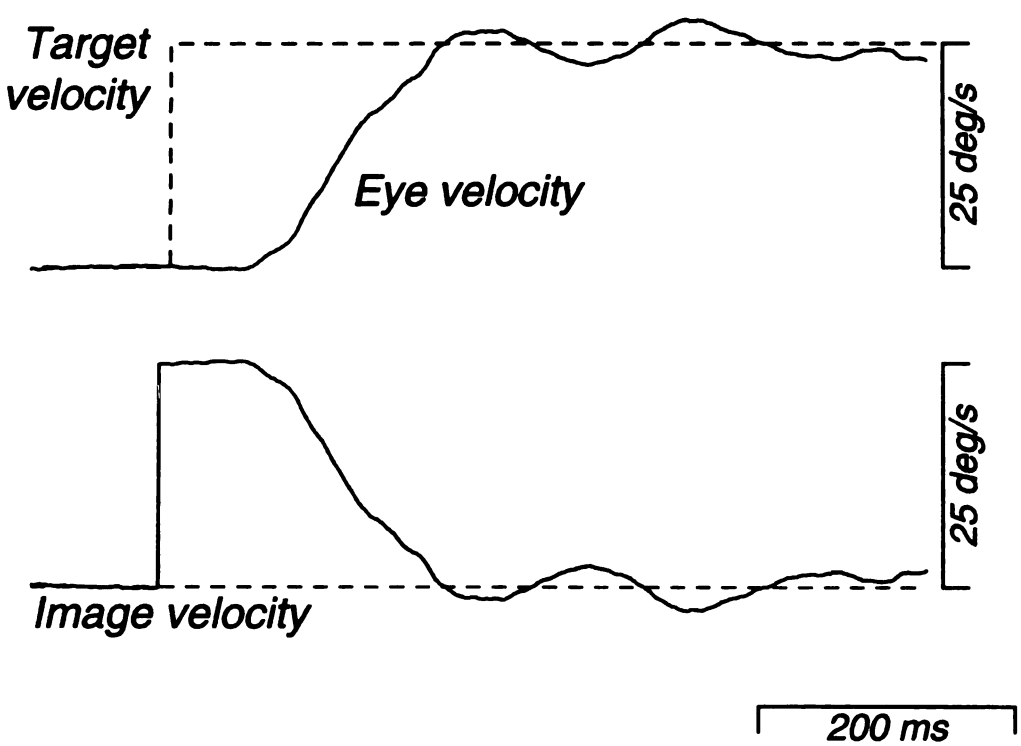
Target velocity
Eye velocity
25 deg/s
25 deg/s
Image velocity
200 ms

Figure 1.1

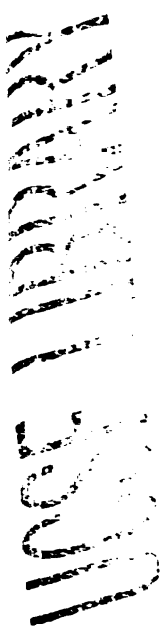

Illustration of target, eye, and image motion signals present during step-ramp smooth pursuit. Top set of traces plot target and eye velocity as a function of time. The step in target velocity (dashed line) is followed by a tracking eye movement (solid line) that begins about 100 msec after target motion onset, accelerates, and matches the speed of the target by approximately 200 msec after target motion onset. Image velocity, corresponds to target motion relative to the eye, is defined as target velocity minus eye velocity and is plotted in the bottom trace. Image velocity signals are at their maximum before pursuit onset and the maintenance of pursuit occurs in the absence of significant amounts of image motion.

Figure 1.2

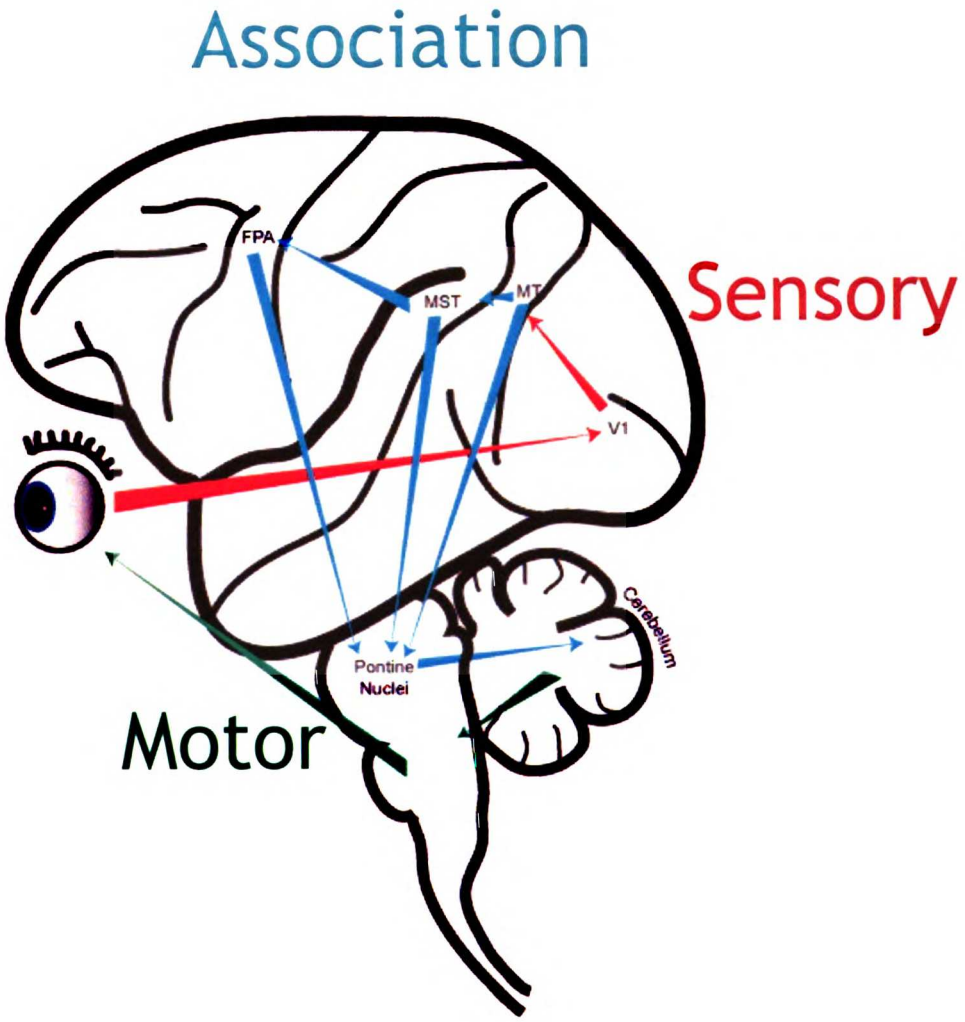

Figure 1.2

Illustration of the neural circuit for smooth pursuit eye movements. Visual inputs from the retina are processed in visual cortex. Target motion is represented in cortical area MT, which projects to cortical and subcortical association areas involved in generating pursuit eye movements. As signals pass through the pursuit circuit, they are transformed from sensory coordinates into motor coordinates, culminating in the output of brainstem ocular motor neurons.

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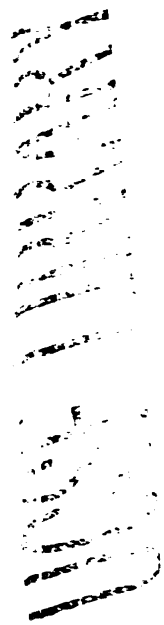
Chapter 2

Signals modulating gain control for smooth pursuit eye movements



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.

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 target velocity 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, electrical 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 when delivered 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.

Materials and 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 ($\dot{\mathbf{E}}_W$), matches target velocity relative to the world. Gaze velocity is defined according to the equation

$$\dot{E}_W = \dot{E}_H + \dot{H}_W \qquad (1)$$

where $\dot{\mathbf{E}}_H$ 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 Figure 2.1 illustrate three of the combinations of head and target velocity used in our experiments. During x1-tracking, the target is kept stationary in the world while the head is rotated. In perfect x1-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 x0-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 x2-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 Figure 2.1.

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 x0 to x1 or x1 to x2 tracking. On a normal day with x0 to x1 stimuli, the tracking conditions consisted of fixation, x1-, x0.9-, x0.67-, x0.5-, x0.33-, and x0-tracking, and pursuit at 20 deg/s with the head stationary. For x1 to x2 stimuli, the tracking conditions consisted of fixation, x1-, x1.1-, x1.33-, x1.5-, x1.67-, and x2-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 x0 to x2 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., Figure 2.5). Further, following adaptive modification to decrease or increase the gain of the VOR, we had three reasons to restrict trials to the x0- to x1-tracking or x1- to x2-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 (x2.2) and miniaturizing (x0.25) 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 2.2 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 Figure 2.3, 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 x0- to x2-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 x0-tracking and increase as the conditions move toward x2-tracking. Over the same range of tracking conditions, in contrast, gaze velocity is 20 deg/s for x0-tracking, decreases to zero during x1-tracking, and increases again to 20 deg/s for x2-tracking. If gaze velocity signals control the internal gain of pursuit, then perturbation responses should be equally large during x0- and x2-tracking and should be minimal during x1-tracking.

Figure 2.4 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 (Figure 2.4, *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 x1-tracking, the responses to the target perturbation (*bold trace* in top set of Figure 2.4) 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 x0- or x2-tracking, and in each case reached levels close to those attained during pursuit with the head stationary (Figure 2.4, *2nd through 4th set of traces*).

Figure 2.4 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, Figure 2.5 plots the peak-to-peak amplitude of the perturbation responses as a function of the tracking condition, for comparison with the predictions in Figure 2.3 for the competing "eye" and "gaze" velocity hypotheses. For both monkeys, the minimum response amplitude appears for conditions near x1-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 (Figure 2.5A) 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

x1-tracking, and large increases to 3.8 ± 0.4 and 5.2 ± 0.6 deg/s for x0- and x2-tracking. Monkey Q showed a slight but nonsignificant decrease from 2.0 ± 0.26 to 1.96 ± 0.26 deg/s between fixation and x1-tracking, and large increases to 4.56 ± 0.68 and 4.98 ± 0.8 deg/s for x0- and x2-tracking (Figure 2.5B). 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

$$P = A_{Ew}\dot{E}_W + A_{Eh}\dot{E}_H \qquad (2)$$

where P is the peak-to-peak amplitude of the response to the perturbation and A_{Ew} and A_{Eh} 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 Figure 2.5A). 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 (Figure 2.5B).

Note that the size of the sensitivities of pursuit gain to eye velocity are just right to account for the data observed during x1-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 (Figure 2.5A). 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 x1-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 x1-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 x1-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 2.6 deomonstrates the average change in VOR gain following spectacle-induced adaptation to high and low gains of 1.5 and 0.4, respectively.

Figure 2.7 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 x0 to x1-tracking for both monkeys (Figure 2.8). First, perturbation responses were now substantially larger

during x1-tracking than during fixation. In Monkey W, the perturbation response during x1-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 x1-tracking when the VOR was normal, now exhibited an enhanced response equal to 2.3 times the fixation response. Second, the perturbation responses during x0.33-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 x0.33-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 x0.33 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 x0.67-tracking elicited the smallest responses in both monkeys (Figure 2.9).

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 x1- to x2-tracking for both monkeys (Figure 2.8B). First, the responses to perturbations delivered during x1-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 x1.5-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 x1.67-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 x1.1-tracking in both monkeys (Figure 2.9).

A summary of our results in monkeys with adapted VOR gains is shown in Figure 2.9, 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, x1-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 (Figure 2.5) 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 Figure 2.9 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.

Modulation of pursuit gain alters pursuit latency and dynamics

Inspection of the eye velocity traces in Figures 2.2, 2.4, and 2.8 suggested to us that modulation of pursuit gain control was also affecting the time course of the responses to perturbations. To show this effect most clearly (Figure 2.10, traces labeled "Original eye velocity"), we averaged the responses during x0- and x2-tracking when the gain of the VOR was normal in both monkeys. By comparison with the responses to perturbations delivered during fixation (thin trace), the responses during tracking (bold trace) started sooner, reached an earlier peak, and possessed a large negative peak. Normalizing the two traces so that they have the same peak amplitude emphasizes the difference in latency (traces labeled "Normalized"). Finally, shifting the traces by 9 ms so that their rising phases overlap reveals a 7 ms difference in the time to peak response (traces labeled "Shifted"). Thus, the faster time course of the enhanced responses during tracking appears to be due to both a shorter response latency and altered response dynamics.

Figure 2.1

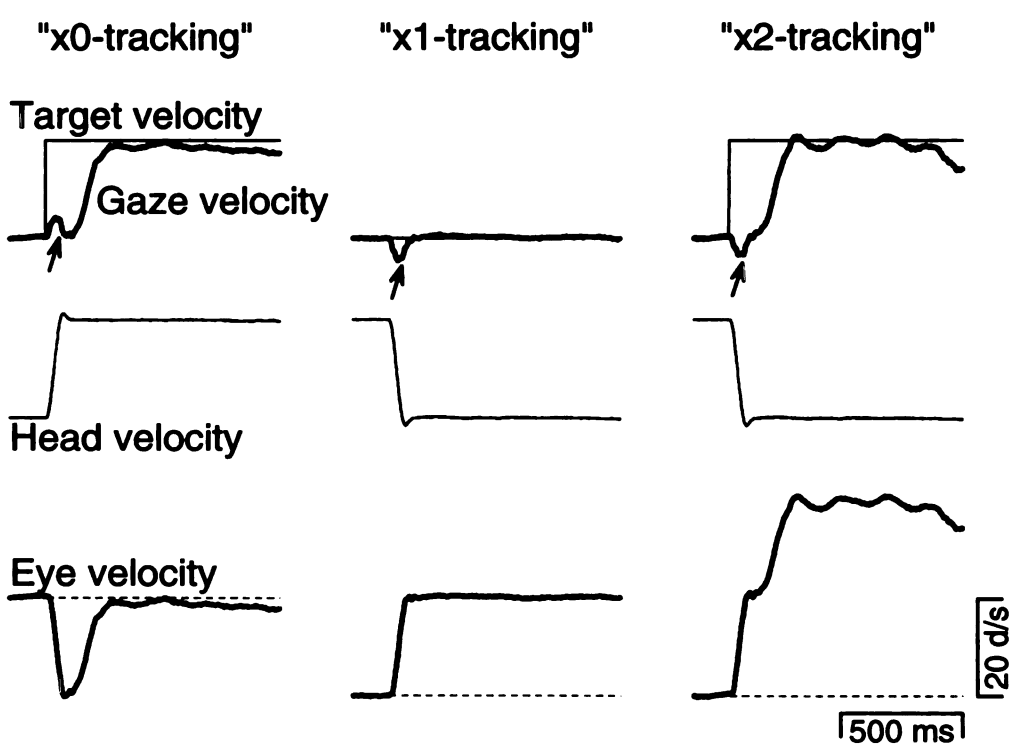
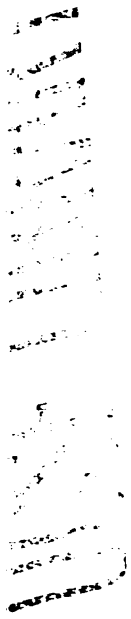

"x0-tracking"
"x1-tracking"
"x2-tracking"
Target velocity
Gaze velocity
Head velocity
Eye velocity
20 d/s
500 ms

Figure 2.1



Tracking conditions used to identify signals controlling the internal gain of pursuit. The three 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 (either 0 or 20 deg/s), 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.

Figure 2.2

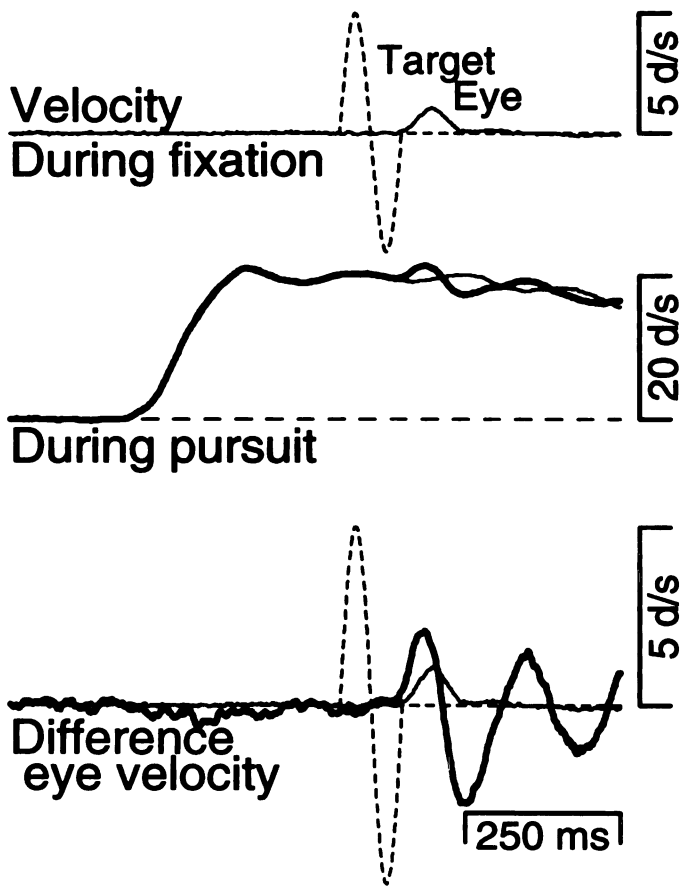

Target
Eye
Velocity
During fixation
5 d/s
20 d/s
During pursuit
5 d/s
Difference
eye velocity
250 ms

Figure 2.2

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 zero 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.

Figure 2.3

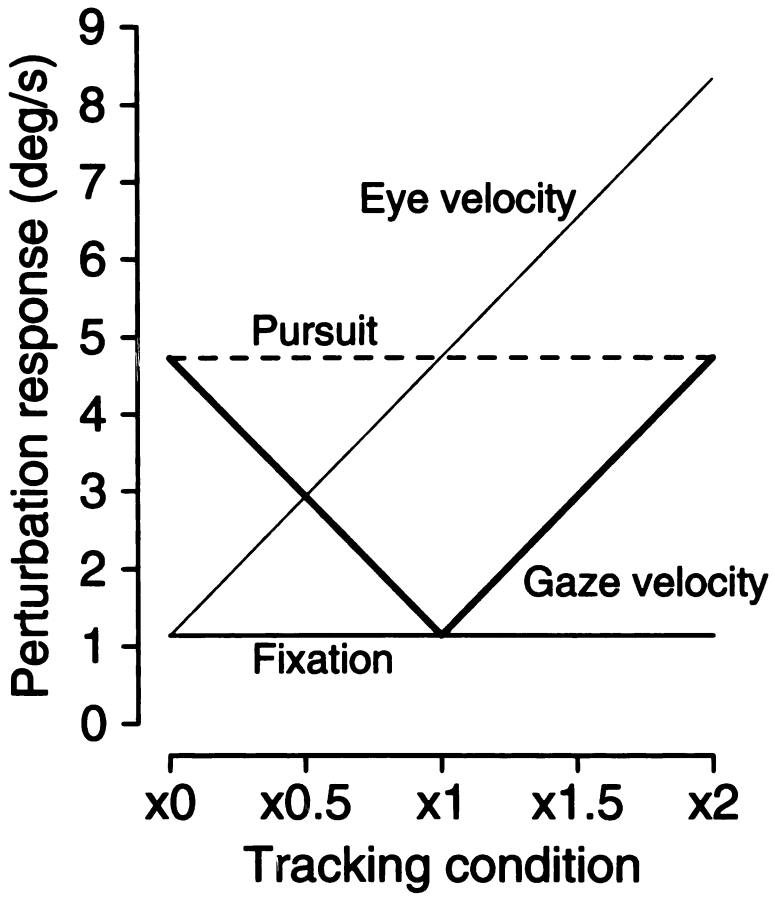

Perturbation response (deg/s)
9
8
7
6
5
4
3
2
1
0
Eye velocity
Pursuit
Gaze velocity
Fixation
x0
x0.5
x1
x1.5
x2
Tracking condition

Figure 2.3

Illustration of how the responses to brief perturbations of target velocity should vary as a function of tracking condition if internal pursuit gain is controlled by signals related to gaze velocity versus eye velocity. The horizontal solid and dashed lines represent the perturbation responses during fixation and during pursuit at 20 deg/s, respectively. 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.

Figure 2.4

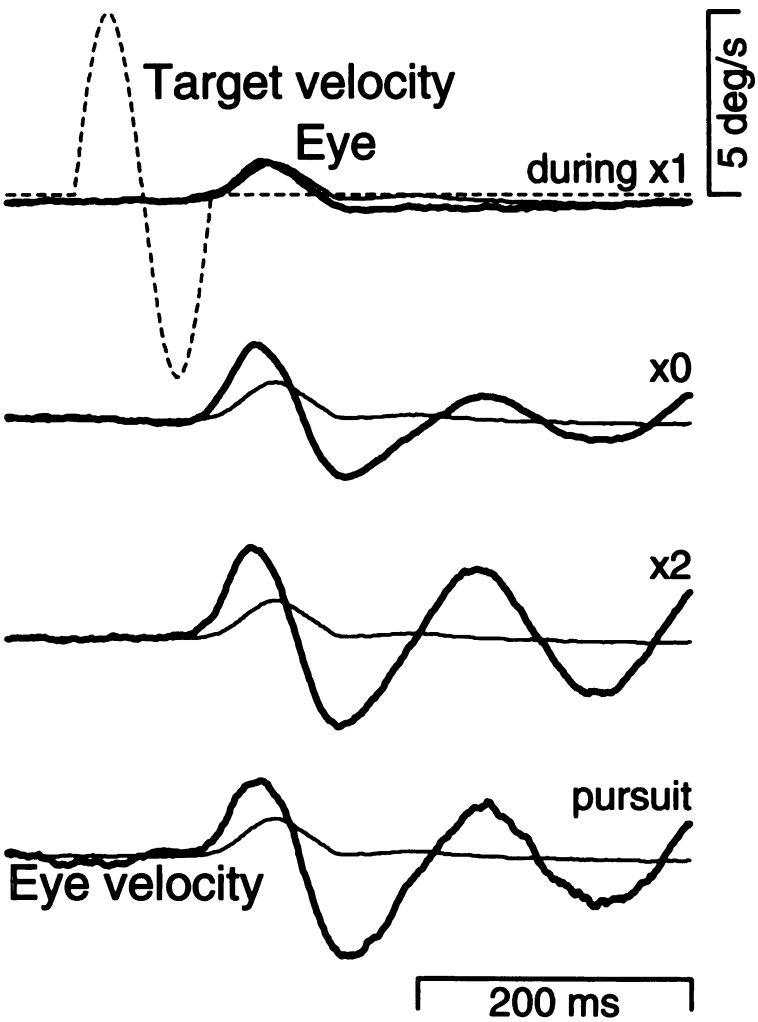

Target velocity
Eye
during x1
5 deg/s
x0
x2
pursuit
Eye velocity
200 ms

Figure 2.4

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 x1-tracking, x0-tracking, x2-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 Figure 2.2. 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.

Figure 2.5

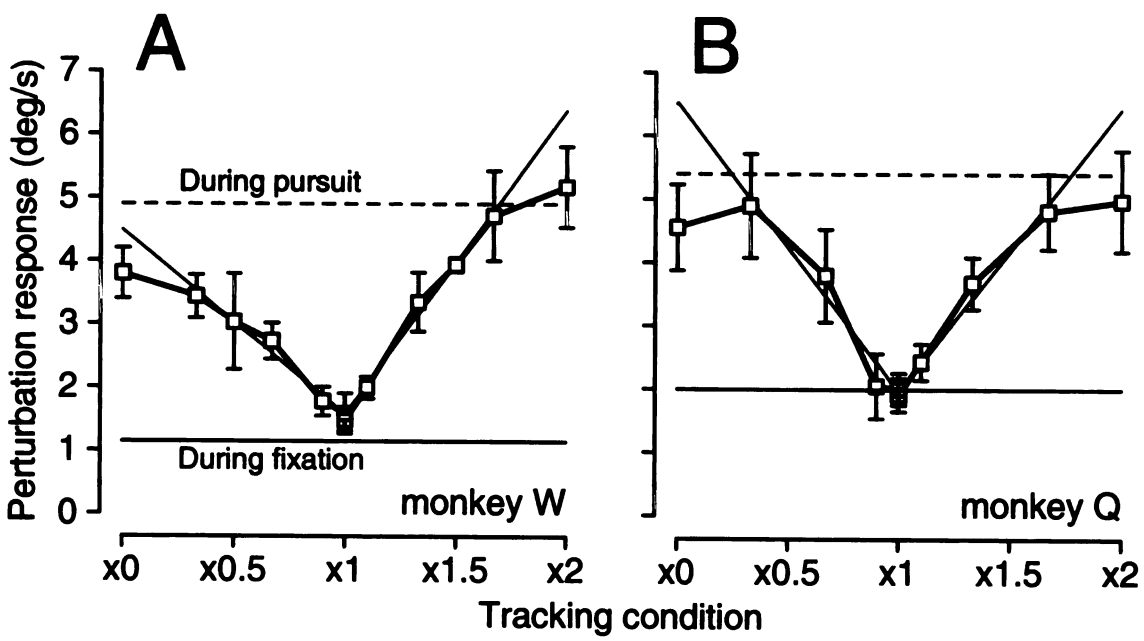

A
B
Perturbation response (deg/s)
7
6
5
4
3
2
1
0
During pursuit
During fixation
monkey W
monkey Q
x0
x0.5
x1
x1.5
x2
Tracking condition

Figure 2.5

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 equation 2. Because of the clear saturation at each extreme of the data, the points for x0-tracking and x2-tracking were not used when fitting equation 2 to the data.

Figure 2.6

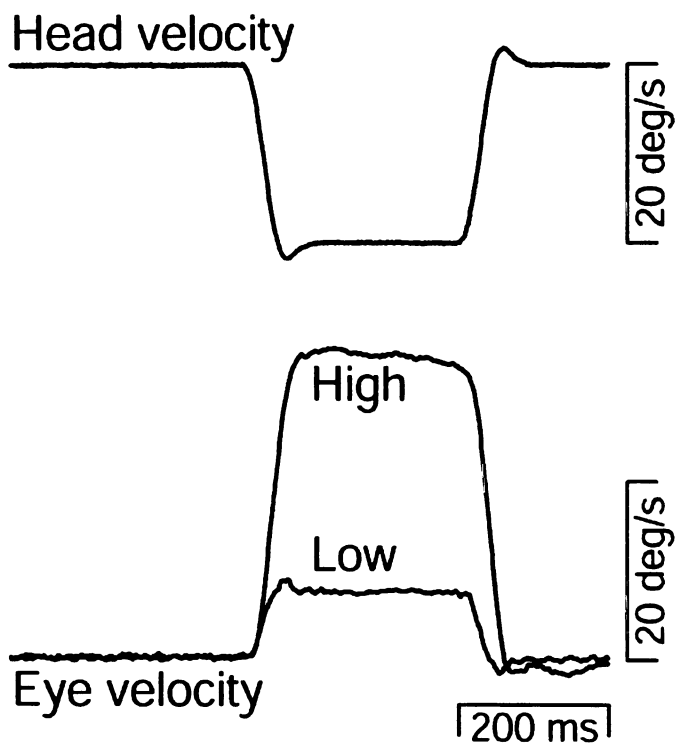


Figure 2.6

Example recordings of the VOR in the dark following adaptive modification of the VOR. The top trace shows head velocity and the superimposed bottom traces labeled "High" and "Low" show eye velocity evoked in darkness after adaptation with magnifying and miniaturizing spectacles.

Figure 2.7

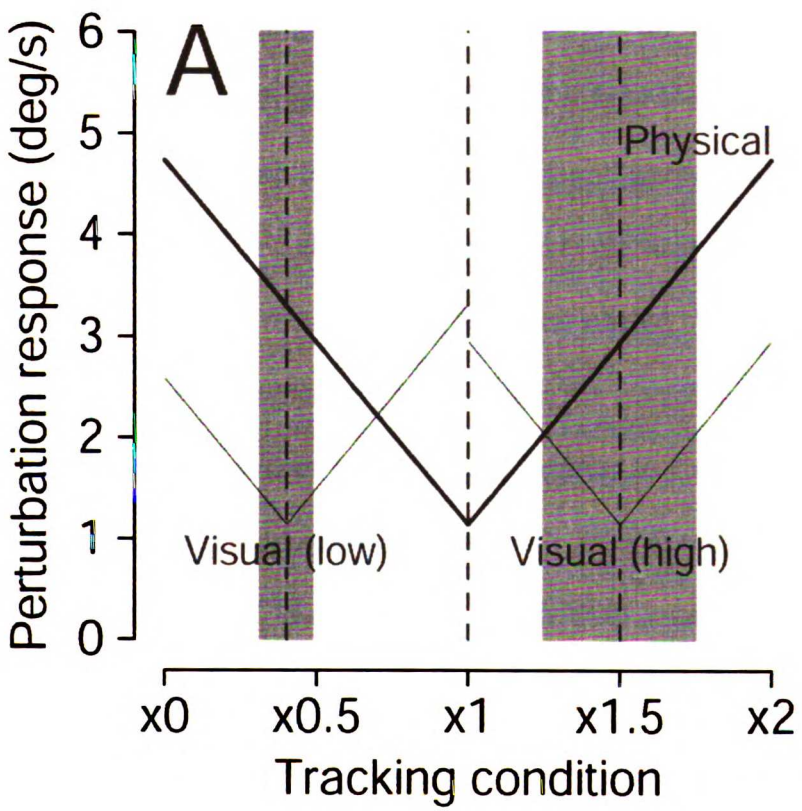


Figure 2.7

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 two 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 two shaded vertical columns indicate ± 1 standard deviation of the VOR gains in our experiments with the gain of the VOR low and high.

Figure 2.8

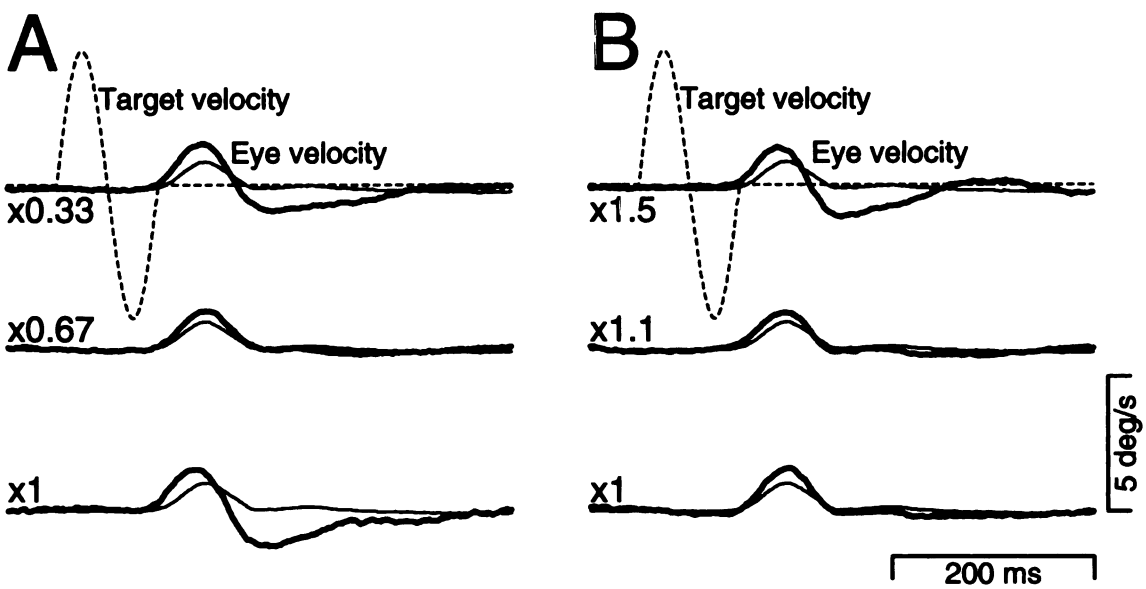

A
Target velocity
Eye velocity
x0.33
x0.67
x1
B
Target velocity
Eye velocity
x1.5
x1.1
x1
5 deg/s
200 ms

Figure 2.8

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 Figure 2.2. 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 x0.33-tracking, x0.67-tracking, and x1-tracking. B: From top to bottom, the bold traces show the responses to the perturbation during x1.5-tracking, x1.1-tracking, and x1-tracking.

Figure 2.9

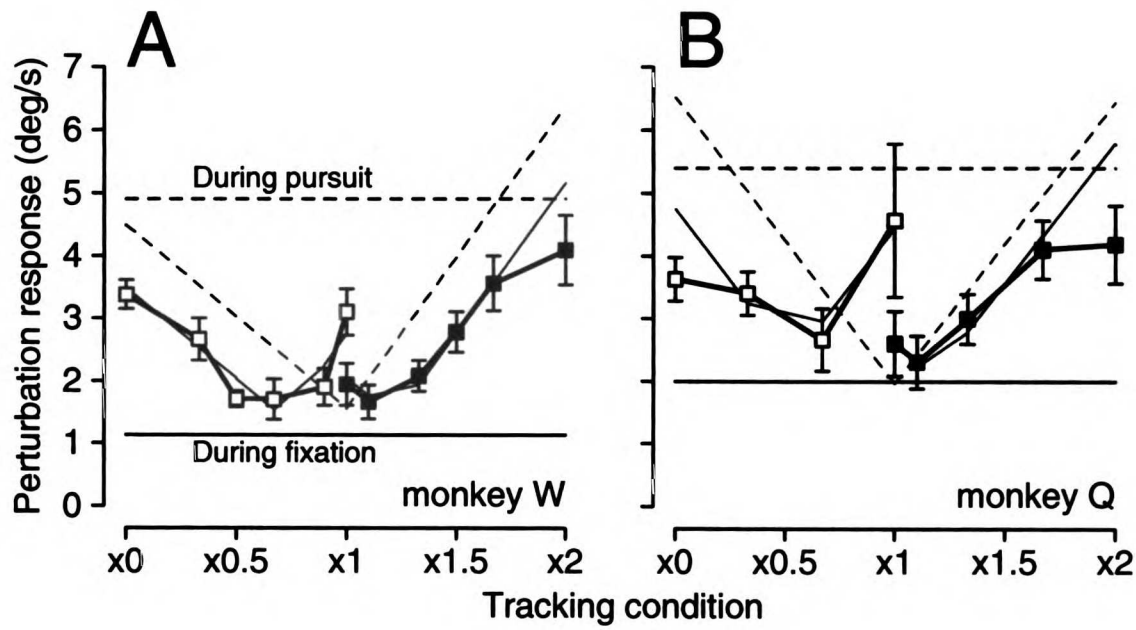

A
B
Perturbation response (deg/s)
0
1
2
3
4
5
6
7
During pursuit
During fixation
monkey W
monkey Q
x0
x0.5
x1
x1.5
x2
Tracking condition

Figure 2.9

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-guided 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 Figure 2.5 (thin, dashed lines). Asterisks indicate tracking conditions for which a statistically-significant difference was found between normal and adapted VOR gains (unpaired Students T-test, $p<0.01$). Because of the clear saturation at each extreme of the data, the points for x0-tracking and x2-tracking were not used when fitting the data. Error bars show one standard deviation of the means from all experimental days.

Figure 2.10

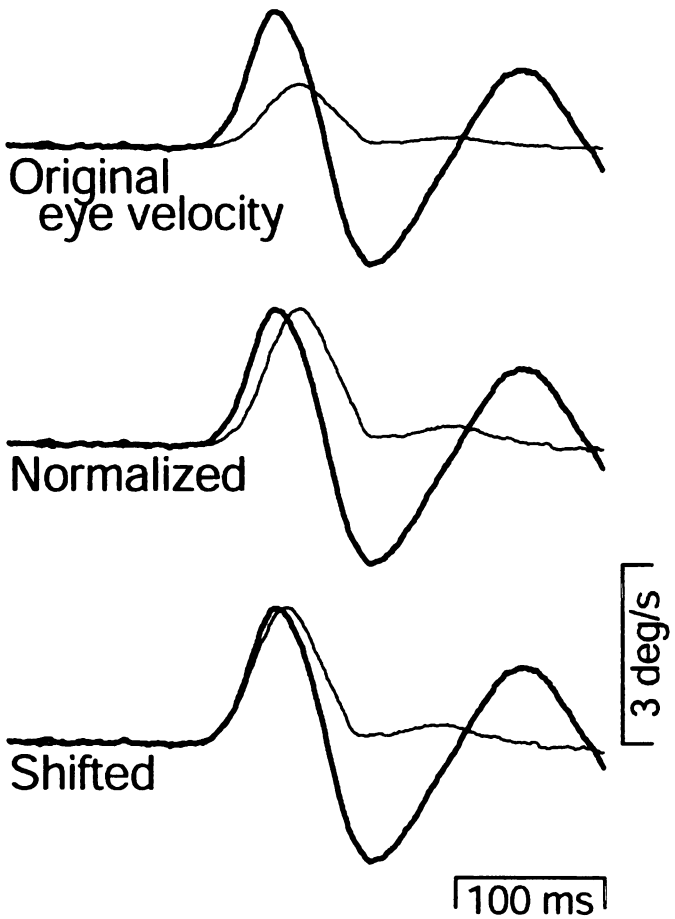


Figure 2.10

Effects of gain control on the time course of responses to perturbations. In each pair of superimposed traces, the bold trace shows the average of the responses to perturbations delivered during x0-tracking and x2-tracking when the gain of the VOR was normal, and the fine trace shows the average responses to perturbations delivered during fixation. In the top row of traces, the original averages are plotted. In the middle row, the response during fixation has been scaled so that it has the same peak amplitude as does the response during tracking. In the bottom row, the response during fixation has been shifted to the left by 9 ms so that the rising phases of the two responses are superimposed.

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.

In addition to determining how the gaze signals in different pursuit regions are affected by adaptive modification of the vestibulo-ocular reflex, it would also be interesting to know how neurons in different pursuit regions encode the visual stimulus

vs. the motor response to brief perturbations of target velocity. Primarily sensory neurons, for example, would be expected to respond identically to identical target motions. As the signals move through the pursuit circuit, through association to motor areas, however, neurons would be expected to begin to become more representative of the eye movement response. Specifically, there has been some controversy over the sensory vs. motor nature of responses of cerebellar Purkinje cells during the initiation of smooth pursuit (Stone and Lisberger 1990, Suh et al 2000). Recordings from cerebellar Purkinje cells in response to presentation of brief perturbations of target velocity during pursuit vs. fixation would provide a dissociation of image and eye velocity signals and might help resolve that issue.

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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Chapter 3

Visual cortical area MT provides an instructive signal for learning in smooth pursuit eye movements

Abstract

How do we learn from our mistakes? Sensory error signals have long been proposed to act as instructive signals to guide learning. Identifying how the brain encodes such sensory error signals and how and where they act to form the neural basis of learning is a fundamental goal in neuroscience. Here we use electrical microstimulation and a novel behavioral paradigm to demonstrate that visual signals from motion-sensitive cortical area MT provide an instructive signal for learning in smooth pursuit eye movements. We propose that sensory cortical areas in general could provide teaching signals for a wide range of cortically-mediated learned behaviors.

Introduction

We learn from our mistakes: incorrect movements are generally followed by sensory feedback indicating that an error has been made, and many learning theories (eg Schultz and Dickinson 2000, Rescorla and Wagner 1972, Ito 1972) propose that neural representations of sensory error signals act as teachers for motor learning. Yet exactly how the brain converts available sensory error signals into instructive signals, and how they act to induce behavioral learning is still poorly understood.

Here we investigated the source of the instructive signal for learning in smooth pursuit eye movements. The goal of pursuit is to track moving targets by matching eye velocity to target velocity (Rashbass 1961; Robinson 1965); in perfect pursuit, there is zero target motion relative to the eye. However, pursuit is a learned behavior, and the sensorimotor transformation for pursuit is modified by experience. In the laboratory, consistently associating pursuit in a given direction with a predictable change in the direction or speed of the target leads over time to a learned eye movement that occurs during pursuit in that direction even in the absence of the change in target trajectory (Kahlon and Lisberger 1996, Medina et al. 2005, Boman and Hotson 1992). In a previous paper (Medina et al. 2005), we demonstrated that for a directional learning task, the learned eye movements are timed appropriately for the expected change in target direction, and that the amplitude of the learned eye movements depends on the specific temporal interval between target motion onset and the change in target direction.

We hypothesized that visual retinal image motion signals could act as instructive signals for directional pursuit learning. Visual motion signals for pursuit are represented

in the Middle Temporal cortical area (MT) (Newsome et al 1985, Newsome et al 1988, Lisberger and Movshon 1999). MT neurons encode visual motion in retinal coordinates and are robustly tuned for direction and speed of motion as well as a variety of other features (Maunsell and Van Essen 1983, Albright 1984). Microstimulation in MT has been shown to have a directional effect on pursuit eye movements (Komatsu and Wurtz 1989, Groh et al 1997) as well as to bias monkeys' reports of direction of motion (Salzman et al 1992). Here we tested whether electrical microstimulation of clusters of MT neurons with shared direction preferences could substitute for a change in target direction to drive learning for pursuit.

Our results demonstrate that microstimulation in cortical area MT is sufficient to drive pursuit learning. We also develop a novel pursuit learning task and show that real visual motion signals drive pursuit learning in a manner highly consistent with an instructive signal coming from MT. We conclude that visual signals, including those from cortical area MT, are powerful instructive signals for the induction of learning in smooth pursuit eye movements. Our findings could have broad implications for a role of cortical sensory signals in guiding learning for a wide range of behaviors that share similar cortical and sub-cortical circuitry.

Materials and Methods

Animals

All experimental procedures were approved in advance by the *Institutional Animal Care and Use Committee* of the University of California, San Francisco and conformed to federal guidelines. Two male rhesus monkeys (Macaca mulatta, 7-12 kg) served as subjects. Surgical and training procedures to prepare the monkeys for the study have been described previously (Carey and Lisberger, 2004; Churchland and Lisberger 2001). Both monkeys were well-trained on pursuit tasks but naïve to pursuit learning experiments. Experiments were conducted approximately five times per week and lasted 2-5 hours.

Visual stimuli

Stimulus delivery. Visual stimuli were delivered with an analog oscilloscope (Hewlett Packard 1304A) with a refresh rate of 250 Hertz. The display was positioned at a distance of 30 cm from the monkey and subtended 41 deg horizontal x 34 deg vertical of visual angle. Target position and velocity were controlled through a DEC Alpha UNIX workstation, which provided the user interface, and a PC that controlled the oscilloscope through a digital-to-analog converter on a digital signal processing board. All experiments were conducted in a nearly dark room.

Pursuit targets. The pursuit target was a small bright spot. All pursuit trials were "step-ramp" pursuit, to minimize the occurrence of catch-up saccades during the first few hundred milliseconds of pursuit that were critical to our analyses. Each trial began with a

randomly determined 500-1000 ms fixation interval, after which the target stepped away from the fixation point by 2.5 deg (Monkey Q) or 3.0 deg (Monkey E) and simultaneously began to move at 20 deg/sec towards the fixation point.

Visual background. The 'visual background' stimulus consisted of randomly placed dots at an average density of 0.09 dots/deg^2. The dots were 1/16 as bright as the pursuit target. To avoid spatial overlap of the target and the background, dots were visible within two separate invisible apertures of 38 deg x 14 deg, one above and one below the horizontally-moving pursuit target. Thus, the pursuit target was centered vertically on a 6 degree tall horizontal stripe with no background dots. The stripe between the two apertures was only slightly taller than the average dot density, minimizing the interruption of the background pattern while preventing target/background overlap and any resulting ambiguity as to the task requirements. The placement of individual dots within the apertures in the background pattern was varied randomly on a trial-by-trial basis. Motion of the visual background consisted of 100% coherent vertical motion of the dots at 20 deg/s within the stationary apertures.

Target stabilization. In a subset of our experiments we used a target stabilization technique (Morris and Lisberger 1987) to eliminate retinal slip signals resulting from target motion relative to the eye on learning trials. Electronic feedback of eye position signals from the eye coil were sampled every millisecond and used to drive target motion in real time. Careful calibration of the eye coil at the start of each experimental day was critical for ensuring accurate image stabilization. We used the monkeys' eye movements in response to small position and velocity errors to verify the accuracy of the stabilization (Morris and Lisberger, 1987). Comparing eye movements on baseline pursuit trials with

and without target stabilization revealed no saccades or smooth eye accelerations that would have been predicted by systematic errors in stabilization. In a subset of our experiments we selectively stabilized the target in the learning axis only; learned eye movements were not affected by whether the target was stabilized in both the learning and pursuit axes or just the learning axis. Thus, while small stabilization errors are unavoidable, we do not believe that they were a major factor for the purposes of our experiments.

MT recording and microstimulation

Identifying MT. We recorded and stimulated in three MTs in two monkeys (left and right in Monkey Q, left only in Monkey E). In each case, area MT was identified as described previously (Churchland and Lisberger 2001) based on stereotaxic coordinates, previously described response properties of MT neurons and surrounding cortical areas, and retinotopic mapping. We took a vertical approach to MT, and a typical experiment involved passing through middle superior temporal area (MST) and the lumen of the superior temporal sulcus before arriving in MT. We focused our experiments on primarily foveal representations within MT.

Characterization of stimulation sites. Each experimental session involving microstimulation began with electrophysiological multiunit recordings to locate and characterize sites in MT with robustly shared direction preferences. Recording/stimulating electrodes were tungsten microelectrodes (Frederick Haer, Bowdointon, ME) with impedances from 800K to 1.2 MOhms measured at 1 kHz. Potential stimulation sites were identified first on the basis of their directional responses

to motion of dots (usually at 16 deg/s) within a 38 x 30 aperture in the visual hemisphere contralateral to the recording area. Only strongly direction selective sites with reasonably Gaussian direction tuning curves were selected for further experimentation. Once a potential stimulation site was identified we characterized its direction and speed preferences for motion of patches of dots as well as its spatial receptive field location and size, its responses to motion of pursuit targets and patches of dots, and the effects of microstimulation on eye movements during ongoing pursuit.

Stimulation parameters. Biphasic current pulses of ≤50 microamps and 0.2 ms in duration were delivered at a rate of 200 Hz in trains of 300 ms duration with a Grass S88 stimulator. Current amplitude was measured as the voltage drop across a 1 kOhm resistor configured in series with the stimulator and the monkey. Previous studies (Murasugi et al. 1993) have demonstrated that small changes in electrode position or current amplitude can have dramatic effects on the effectiveness of microstimulation in MT. We found that microstimulation at sites with weak or ambiguous direction tuning profiles consistently failed to elicit eye movements even during ongoing pursuit. In contrast, sites with strong responses and robust direction tuning nearly always evoked a directional eye movement at relatively low current levels (≤50 microamps). Thus, because we required the motion signal we were injecting through stimulation to be as pure and effective as possible to adequately test our hypothesis, the experiments in this study were all performed at sites that produced an eye movement when microstimulation was applied during ongoing pursuit. The stimulation-evoked eye movement also served the essential purpose of allowing us to monitor the continued effectiveness of the stimulation site during long

experiments in which there was not always an opportunity to monitor changes in the quality of the site with recording.

Learning paradigms

The learning experiments were similar in design to previous studies on pursuit learning (Kahlon and Lisberger 1996, Chou and Lisberger 2002, Medina et al. 2005) and consisted of two blocks of trials: a baseline block and a learning block. Each block consisted of one or more trial types presented in varying ratios in pseudorandom order. Pursuit target motion was identical on every kind of trial in every block; the axis in which the target moved was defined as the "pursuit axis". We measured learning by assessing changes in eye velocity in the "learning axis" which was always orthogonal to the pursuit axis (Medina et al. 2005). For experiments using a moving visual background the pursuit axis was always horizontal and the learning axis vertical. In microstimulation experiments, the learning axis was the cardinal axis closest to the preferred/null axis of the stimulation site, and the pursuit axis was either horizontal or vertical.

Figure 3.1 illustrates the basic experimental design. The first, 'baseline' block consisted primarily of 'baseline trials' in which the target moved at 20 deg/s in the pursuit axis without any additional experimental manipulations. To assess the effects of microstimulation at individual sites, up to 10% of the trials presented in the baseline block were microstimulation trials. Averaged eye velocities from baseline trials were subtracted from the eye velocities on microstimulation trials to isolate the stimulation-evoked eye movement. We confirmed the consistency of baseline eye velocities by making multiple averages from subsets of baseline trials before beginning learning

experiments. Occasionally, stable baselines could not be obtained and experiments were aborted to avoid the potential danger of contamination from random fluctuations.

The second, 'learning' block contained primarily 'learning trials.' The exact nature of the learning trials depended on the specific experiment, but they always consisted of pursuit target motion identical to that of baseline trials, with the addition of microstimulation or motion of a visual background for 300 ms beginning at a fixed interval (100-250 ms, usually 200 ms) after the onset of target motion. In experiments using target stabilization the target was only stabilized on learning trials, and only during the 300 ms segment involving microstimulation or motion of a visual background. 'Probe trials' made up ≤20% of trials in the learning block. Probe trials were identical to 'baseline trials' and were presented to assess learning. Learning was measured as the averaged eye velocity in the learning axis on 'probe trials' minus the averaged eye velocity in the learning axis on 'baseline trials'. Only data from probe trials presented after ~100 learning trials had been completed was included in the learned eye movement analyses presented here.

Fixation requirements. Monkeys were generally required to keep their eyes within a 3 deg window of the pursuit target in order to complete the trial and receive a fluid reward. Note that the changes in eye velocity we observed with learning would have been expected to cause deviations in eye position of less than one degree, and were therefore unlikely to affect the monkey's likelihood of successfully completing the trial. However, to be absolutely certain that learned eye movements did not result in the eyes exiting the fixation window, in the experiments presented here, we opened the fixation window to 5 deg **in the learning axis only** during the segment of the learning trials in

which microstimulation was applied or the visual background moved, and during the corresponding segments on baseline and probe trials. Opening the fixation window in this way had no effect on the eye movements made by our motivated and well-trained monkeys. However, in our attempts to eliminate potential confusion between the target and the dots in the visual background, we also conducted visual background motion experiments with the fixation window **in the learning axis only** narrowed to as little as 1 deg. Learning was unaffected by these changes in fixation requirements.

Data acquisition and analysis

Eye position signals recorded by the search coil were conditioned and differentiated by an analog circuit to obtain signals proportional to horizontal and vertical eye velocity. Frequency content above 25 Hz was filtered out with a rolloff of 20 db/decade. Eye position and velocity signals were digitized at 1 kHz. Extracellular potentials recorded by the microelectrode were amplified (Dagan) and bandpass filtered from 500 Hz to 8kHz. Multiunit activity was thresholded with a manually adjusted level detector, and individual events passing this threshold were recorded to the nearest 10 microsec.

Only trials that were completed successfully by the monkey were included for analysis. Saccades were marked by hand and the portions of the eye velocity traces corresponding to saccades were treated as missing data. Trials with saccades during the segment corresponding to microstimulation or visual background motion were excluded from analysis. The learned eye movements were 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. All analyses of eye velocity and statistics were performed using Matlab (The Mathworks Inc.) and consisted primarily of computing average eye velocity traces for responses to identical target motions, aligned on the onset of target motion or time of microstimulation/ visual background motion.

Results

Microstimulation in visual cortical area MT induces pursuit learning

To test the hypothesis that visual signals related to target image motion are responsible for driving pursuit learning, we asked whether microstimulation in area MT, when consistently associated with motion of a pursuit target, would be sufficient to drive directional learning of pursuit eye movements that is observed in response to a consistent change in target direction (Medina et al. 2005). A representative experiment is illustrated in Figure 3.1. We first centered our recording electrode in a cluster of cells with a given preferred direction of motion and recorded the receptive field characteristics at that site. For the experiment in Figure 3.1, the preferred direction of the neurons recorded at the stimulation site was up (Figure 3.1A).

The MT-stimulation pursuit learning paradigm is shown in Figure 3.1B. First, we presented "baseline trials" consisting of step ramp target motion at 20 deg/s in a cardinal axis close to orthogonal of the preferred/null axis of the MT neurons recorded at the stimulation site. In this case, the preferred direction of the site was close to upwards, and so the "pursuit axis" was horizontal, and we measured eye velocity in the vertical "learning axis". "Learning trials" consisted of step ramp target motion identical to baseline trials, but after 200 ms of target motion, electrical microstimulation (20-50 microamps, 200 Hz) was applied for 300 ms. After 100 or more repetitions of "learning trials", learning was assessed by measuring eye velocity on infrequent "probe trials" that were identical to baseline trials. Learning was defined as the eye velocity in the learning

axis on probe trials minus eye velocity in the learning axis on baseline trials before learning.

As shown in Figure 3.1C, microstimulation elicited a small eye movement towards the preferred direction of the stimulation site (Komatsu and Wurtz 1989, Groh et al. 1997). Repeated microstimulation at this site during rightwards pursuit, 200 ms after the onset of target motion, led to learned changes in the vertical eye movement observed on probe trials. The learned eye movement had two components (Figure 3.1C). First, there is a learned eye movement towards the preferred direction of the stimulation site that peaks at approximately 200 ms after the onset of target motion. It is followed by an eye movement in the opposite direction from the preferred direction of the stimulation site. The oppositely-directed component of learning was not observed in previous experiments in which learning was induced with a change in target direction (Medina et al 2005), and will be discussed further below.

We performed similar MT stimulation learning experiments at 42 sites in three cylinders of two monkeys. Figure 3.2 summarizes the data from all 42 experiments, aligned on the time of stimulation on learning trials, for Monkeys Q and E. All preferred directions have been rotated to up, and baseline eye velocities have been subtracted off. The top panels of Figure 3.2 show the average effect of microstimulation in MT on the learning axis eye velocities across experimental days. Microstimulation-evoked eye velocities were recorded in the first few learning trials, before repeated pairing of stimulation with pursuit target motion. As shown in the top panels of Figure 3.2, microstimulation consistently evoked an eye movement towards the preferred direction of of the stimulated neurons. The temporal profiles of the stimulation-induced eye

movement were slightly different in the two monkeys, and the amplitude was consistently larger in Monkey Q.

The bottom panels of Figure 3.2 plot the averages +/- variance of the learned eye velocities, across all experimental days. The two thick lines for Monkey E represent experiments in which microstimulation began 200 ms (blue) and 250 ms (black) after target motion onset (differences are discussed below). As shown in the example experiment in Figure 3.1, on average there were generally two components of learning, one towards the preferred direction of the stimulated neurons, and a later component in the opposite direction.

Figure 3.3 summarizes the data from individual experiments by plotting the amplitudes of the maximum and minimum learned eye velocity values from each experiment as a function of time. All data are aligned on the time corresponding to the onset of stimulation on learning trials (time 0). Each individual experiment is plotted as a line between the maximum learned eye velocity value (and the time at which it occurred, relative to the onset of stimulation on learning trials) and the minimum learned eye velocity value (and the time at which it occurred, relative to the onset of stimulation on learning trials). While there is some variability, the slope of all of the lines is negative, indicating that the peak in the component of learning in the same direction as the preferred direction of the site of stimulation occurred before the peak in the opposite direction. The average from all days is plotted with a thick line. On average, the peak in the same direction occurred around the time of the onset of stimulation, whereas the oppositely-directed peaks occurred later – during the 300ms that would have been the stimulation period had these been learning trials. The remarkably consistent slopes of the

lines for each experiment represent a narrow range of eye accelerations, and are probably partly due to intrinsic dynamics of pursuit.

A potential explanation for the biphasic nature of the eye velocity on probe trials could be that it is due to online corrections for visual feedback resulting from the first component of the learned response on probe trials. The data so far present three arguments against this interpretation (more will be presented below). First, such biphasic responses are not observed in experiments where learning is induced by a change in target trajectory (Medina et al. 2005), even though the probe trials are identical in the two cases. Second, the second component of learning is often larger than the first, which would not be predicted if correcting for visual feedback from the first component were driving the second component. Third, as demonstrated in Figure 3.4, the amplitude of the second component of learning does not depend on the amplitude of the first component of learning for individual experiments.

Site-to-site variation in the learning induced by MT microstimulation

Because pursuit keeps the target on the fovea and we were looking at the effects of MT microstimulation during the maintenance phase of pursuit, we were unable to cater individual experiments to the spatial receptive field of each site, as had been done in most previous MT stimulation studies (Salzman et al. 1992, Groh et al. 1997, Born et al. 2000). Therefore we expected that some (particularly more foveal) sites might be more effective at mimicking target motion and driving learning towards the direction of the neurons being stimulated, while others (with more eccentric receptive fields) might only result in target motion-related learning in the opposite direction. That is not what we found.

Although we observed a substantial amount of variability in the amount of learning in the two directions induced by stimulation at specific sites (Figure 3.3), we did not identify any features of the stimulation sites (including spatial receptive field size (Figure 3.5), spatial receptive field location/ distance from fovea (Figure 3.6), relative strengths of responses to target vs. background during pursuit (Figure 3.7), preferred speed (Figure 3.8), strength of direction tuning (Figure 3.9), or size of the stimulation-evoked eye movement (Figure 3.10)) that correlated with amplitude of the learning observed towards the preferred direction of the neurons recorded at the stimulation site.

Target stabilization selects for the first component of learning

The relative timing (Medina et al. 2005) and directions of the two components of learning suggested to us that the earlier component of learning was driven by image motion signals resulting directly from MT stimulation, while the later, oppositely directed component might be a consequence of target-related image motion signals present on learning trials. Since MT stimulation causes an eye movement towards the preferred direction of the stimulated neurons, there is a retinal slip signal corresponding to target motion relative to the eye on learning trials that is in the direction **opposite** to the direction of the stimulation-evoked eye movement. Target image motion signals would be expected to be delayed relative to the onset of microstimulation because of the latency between stimulation and the evoked eye movement and visual system processing delays. The temporal offset between the visual motion signals resulting directly from MT stimulation and those that are a visual response to target motion resulting from the

microstimulation-evoked eye movement would predict just such oppositely directed, temporally segregated components of learning.

To test the hypothesis that visual signals related to electrical microstimulation of MT and target image motion relative to the eye were responsible for driving the two oppositely directed components of learning observed in Figures 3.1 and 3.2, we used a technique called "target stabilization". An electronic circuit monitored changes in eye position and used them to drive target motion in real time, virtually eliminating target motion relative to the eye in the learning axis. Figure 3.11 shows the results of learning experiments based on those in Figure 3.2, with the addition of target stabilization during the microstimulation segment of learning trials. The **eye movements** in response to microstimulation were similar to non-stabilized microstimulation trials (Figures 3.2 and 3.11). However, the **learning** we observed was qualitatively different when the target was stabilized on the retina on learning trials. As shown in Figure 3.11, target stabilization selected for the component of learning towards the preferred direction of the stimulation site and eliminated the oppositely-directed component of learning.

The learning induced by MT microstimulation with target stabilization did not provide consistent peak eye velocities away from the preferred direction of the stimulated neurons, and so we have not plotted the data for the stabilization experiment on the peak vs. time plots shown in Figure 3.3. Instead, to give an idea of the variability of the results obtained following pairing of MT stimulation with pursuit with target stabilization, Figure 3.12 compares learned eye velocity data from the MT microstimulation experiments with (B) and without (A) target stabilization on learning trials. The data for each millisecond have been sorted so that the largest learned eye velocities away from the

preferred direction of the stimulated neurons are plotted in blue at the top of each graph, and the largest learned eye velocities toward the preferred direction of the stimulated neurons are plotted in red at the bottom. Plotting the data in this way demonstrates that the learning towards the preferred direction of the stimulated neurons consistently occurs before or around the time corresponding to the onset of stimulation for both experiments. However, stabilizing the target during MT microstimulation on learning trials eliminates the temporally-specific learned eye velocities away from the preferred direction of the stimulated neurons. Thus, stabilizing the target on the retina consistently eliminated the second, oppositely-directed component of learning while selectively maintaining the learned eye movement towards the preferred direction of the stimulated neurons.

The results of this experiment provide additional evidence that the biphasic nature of the learned eye movement observed in Figures 3.1-3.3 was not a result of online visual feedback on probe trials. If the second component of the learned response was simply compensation for the first component of the learned response, and was not itself learned, then any experiments with identical testing conditions that elicited the first learned component would be expected to elicit biphasic responses. However, biphasic responses are not observed when learning is induced with a change in target trajectory (Medina et al. 2005) and they are not observed when the target is stabilized on learning trials when learning is induced with MT microstimulation. The differences in learned eye movements observed on identical probe trials must therefore be due to the different conditions on learning trials.

In both sets of experiments (with and without target stabilization), microstimulation evoked an eye movement towards the preferred direction of the

stimulated neurons. For Monkey E, the microstimulation-evoked eye movements on learning trials were nearly identical regardless of whether or not the target was stabilized on the retina (Figure 3.2, top right, and Figure 3.11, top right). For Monkey Q, stabilization slightly enhanced and prolonged the eye movement response to stimulation. However, in both the stabilized and non-stabilized cases for both monkeys, the eyes consistently move towards the preferred direction of the stimulated neurons. The learned eye movements, however, are both towards and away from the preferred direction in the non-stabilized case. Thus, these results provide an important dissociation between the direction of the eye movement on learning trials and the direction of learning that suggest that the direction of learning cannot be accounted for by the direction of the eye movement evoked on learning trials. Instead, the results of the stabilization experiment strongly suggest that visual signals resulting from both MT stimulation and from target motion relative to the eye are sufficient to drive directional pursuit learning.

Visual background motion induces learning

To further examine the role of visual signals in driving learning for pursuit, and to compare the effects of MT microstimulation with real world visual motion, we developed a novel pursuit learning task that used motion of a visual background, rather than a change in target trajectory or electrical stimulation, to drive learning. The experimental design is depicted in Figure 3.13. As in the experiments presented so far, the pursuit target was presented on an otherwise blank screen. Once the monkey fixated the target, a visual background stimulus consisting of a random array of stationary dots 16 times dimmer than the target came on. On learning trials, the visual background remained

stationary for the first 200 ms of pursuit target motion, and then the dots moved at 20 deg/s, orthogonally to the direction of ongoing pursuit, for 300 msec. Motion of the visual background elicited an eye movement towards the direction of the background motion (Kodaka et al. 2004, Figure 3.13, top panels).

Presentation of infrequent probe trials in which the background remained stationary revealed that motion of a visual background consistently associated with pursuit target motion induced learned eye movements similar to those we had observed after pairing MT stimulation with pursuit (Figure 3.13, bottom panels). There was an early learned eye movement on probe trials towards the direction of background motion, followed by a later learned eye movement in the opposite direction. Once again, the timing was such that the oppositely-directed component of learning was aligned temporally with the eye movement response to the background on learning trials (Figure 3.5).

Next, we repeated the background learning experiments using target stabilization to eliminate target motion relative to the eye (Figure 3.14). As in the MT microstimulation experiments, target stabilization did not have a major effect on the response to the motion of the visual background (top), but the shape of the learned eye movement changed markedly (bottom). Target stabilization selectively maintained the earlier component of learning towards the direction of background motion, and eliminated the later, oppositely-directed component of learning. We conclude that visual signals related to the target as well as more global motion are capable of driving pursuit learning, and that microstimulation in MT is effective at mimicking the role of these visual signals in pursuit learning.

One difference that we observed between the background motion and MT microstimulation learning experiments was in the robustness of the first component of learning. Although target stabilization appeared to unmask a consistent, "same-direction" learned eye movement, in non-stabilization experiments, the learning towards the direction of background motion in the behavioral experiments was more consistent than the learning towards the preferred direction of the stimulated neurons in the microstimulation experiments (compare Figures 3.3 and 3.16). A possible explanation for the discrepancy was variation in the efficacy of microstimulation at various sites. Although we had failed to correlate the amplitude of learning with our measures of receptive field location and/or size at individual microstimulation sites, it is possible that the influence of receptive field properties at individual sites was obscured by other factors, such as imprecision in our measurements of receptive field location and size, differences between the properties of neurons recorded vs. activated by stimulation at individual sites, or the noisiness of the learned eye movements observed following MT microstimulation. Therefore we wondered whether varying the size and/or location of visual background motion might influence learning. Varying the size and/or location of visual background motion would be expected to activate a smaller number of MT neurons than would a large-field stimulus, and might therefore yield some insight as to whether the total number of neurons activated by microstimulation (a quantity which we could not measure directly) might affect the amplitude of learning.

To address some of these issues, we conducted behavioral learning experiments like those described in figures 3.13 and 3.14, but this time with a smaller (8 deg) patch of dots, located 10 deg from the fovea. The results are shown in Figure 3.15, for

experiments with and without target stabilization. Compared to large-field visual background motion, the smaller patch of dots induced learning with a smaller component towards the direction of dot motion, more similar to some of the less effective MT microstimulation sites. However, target stabilization unmasked the potential of even quite extrafoveal visual motion to drive learning for pursuit.

Comparing MT stimulation-induced and visual motion-induced learning

We previously demonstrated (Medina et al. 2005) that learned eye movements in a directional pursuit learning task are timed appropriately for an expected change in target trajectory and that the magnitude of learning varies as a function of the interval between target motion onset and the change in trajectory. In the present study, we observed interesting temporal differences between the learning induced by MT microstimulation and motion of a visual background, even when the two experimental manipulations both began 200 msec after the onset of target motion. Aligning the peaks of the learned eye movements from the behavioral and stimulation experiments on the onsets of visual background motion or MT stimulation, as shown in Figure 3.16, reveals that the learned eye movement induced by MT stimulation (red lines) occurs earlier relative to the experimental manipulation than does the learned eye movement induced by motion of the visual background (black lines).

While the learning towards the preferred direction of the stimulated neurons peaks just before the time corresponding to the onset of microstimulation on learning trials (Figure 3.3), in the visual background experiments, the learning towards the preferred

direction of the stimulated neurons peaks well after the time when the visual background started moving on learning trials.

The temporal offset between microstimulation-induced and moving background-induced learned eye movements illustrated in Figure 3.16 suggested to us that we could use temporal features of the learning to estimate the relative times at which instructive signals were acting during learning trials in the two cases. If visual signals from MT were serving as the instructive signal in both forms of learning, then the learned eye movements in the two cases should be offset by a time corresponding to the latency of MT neuronal responses to visual stimuli. To address this question, we investigated the effects of varying the temporal interval between pursuit target motion and background motion in both monkeys, and the interval between pursuit target motion and microstimulation in Monkey E.

Figure 3.17 plots the learned eye movements for experiments in which the background moved and/or microstimulation occurred at various intervals from pursuit target motion onset. All data are aligned on the onset of pursuit target motion. Changing the temporal intervals by 50 ms had significant effects on the shape and timing of learning in both moving background experiments and microstimulation experiments. In each case, lengthening the interval resulted in a longer latency to the peak of the learned eye movement towards the preferred direction of the stimulation site, consistent with our previous findings (Medina et al 2005) on the temporal specificity of learned eye movements. In addition, as the duration of the interval increased, the magnitude of this component of learning also increased, consistent with our previous finding of an "eligibility trace" for pursuit learning (ie, the finding that the amplitude of the learned eye

movements depends on the specific temporal interval between target motion onset and the change in target direction).

Note that the dependence of the temporal features of the learned eye movement on the temporal interval between target motion onset and MT microstimulation/ visual background motion provides additional evidence that the biphasic nature of the learned response cannot be due to online corrections for visual feedback resulting from the first component of the learned response on probe trials.

However, as suggested by Figure 3.16, Figure 3.17B confirms that the shape of the microstimulation-induced learning did not correspond to the shape of visual background-induced learning at the same temporal interval. For monkey Q, the learning in 200 ms interval MT stimulation experiments falls between the learning observed in visual background experiments with an interval of 100-150 ms. The relationship of an approximately 75 ms discrepancy between learned eye movements from MT stimulation and moving visual background experiments held true for both monkeys and for both 200 and 250 ms microstimulation intervals in Monkey E. Thus, we conclude that the signals that drive learning in the visual background experiments are activated with a 75 ms delay relative to the onset of MT microstimulation experiments.

Figure 3.1

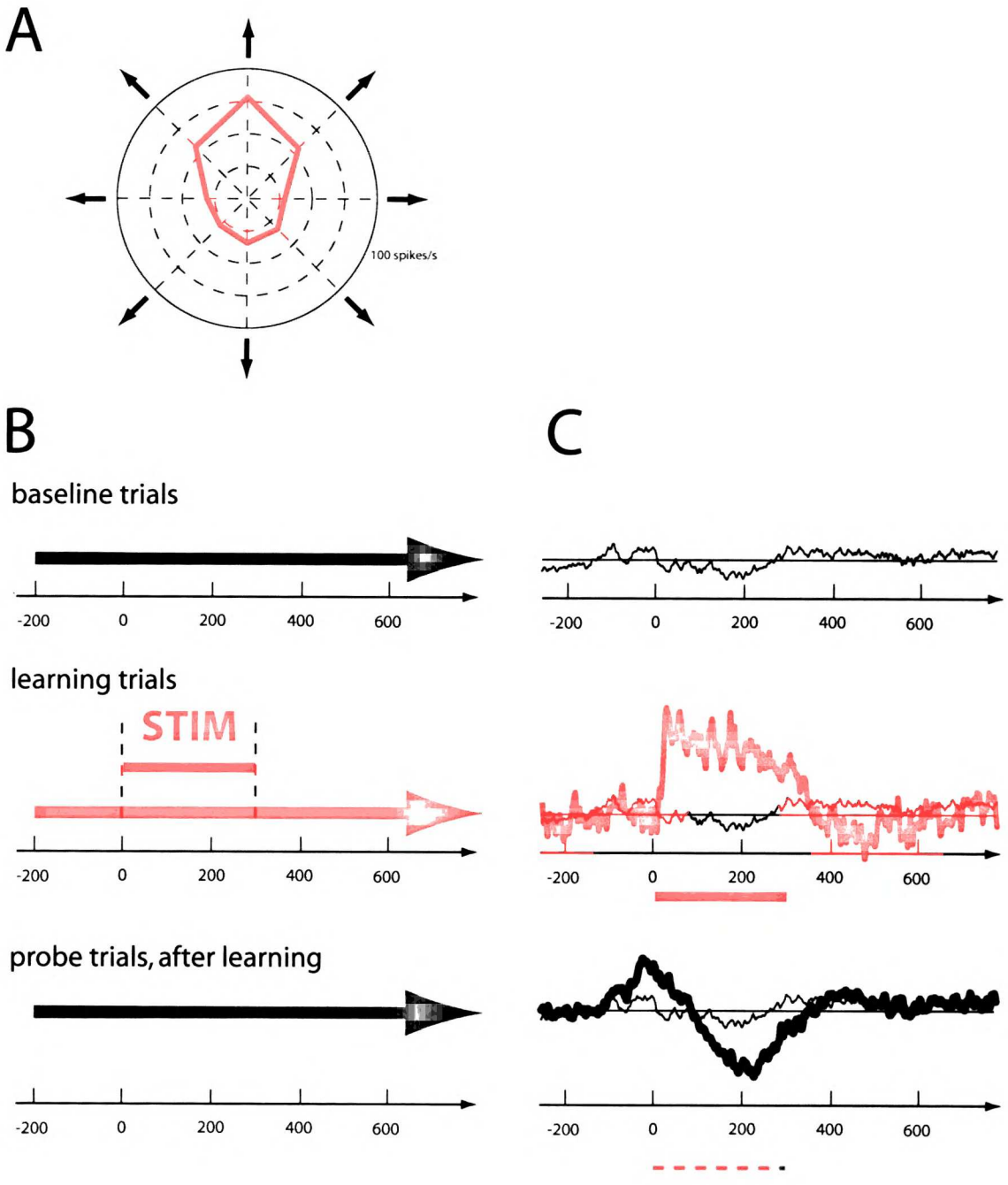
A
100 spikes/s
B
C
baseline trials
-200
0
200
400
600
learning trials
STIM
probe trials, after learning

Figure 3.1

An example of an experiment using MT microstimulation to induce learning.

A: Polar plot of multiunit responses recorded in response to motion of a patch of dots at 16 deg/s in eight directions at one stimulation site. The preferred direction at this site was up; the pursuit axis was horizontal and the learning axis vertical. B: Schematic of the experimental design for an MT microstimulation-learning experiment. First, vertical (learning axis) eye velocities were measured during horizontal (rightwards) pursuit at 20 deg/s. The pursuit target began moving at -200 msec. During the learning phase of the experiment, microstimulation was applied for 300 msec, beginning 200 msec after the onset of pursuit target motion (time 0). Infrequent probe trials identical to baseline trials were presented after repeated pairing of stimulation with ongoing pursuit. C: Learning axis eye velocities were measured in each of the three trial types. Averaged baseline eye velocity (thin blue lines) was subtracted from eye velocity on early learning trials (thick red line) to determine the stimulation-evoked eye velocity before learning. The learned eye movement (thick blue lines) was computed as averaged eye velocity on probe trials minus baseline eye velocity.

Figure 3.2

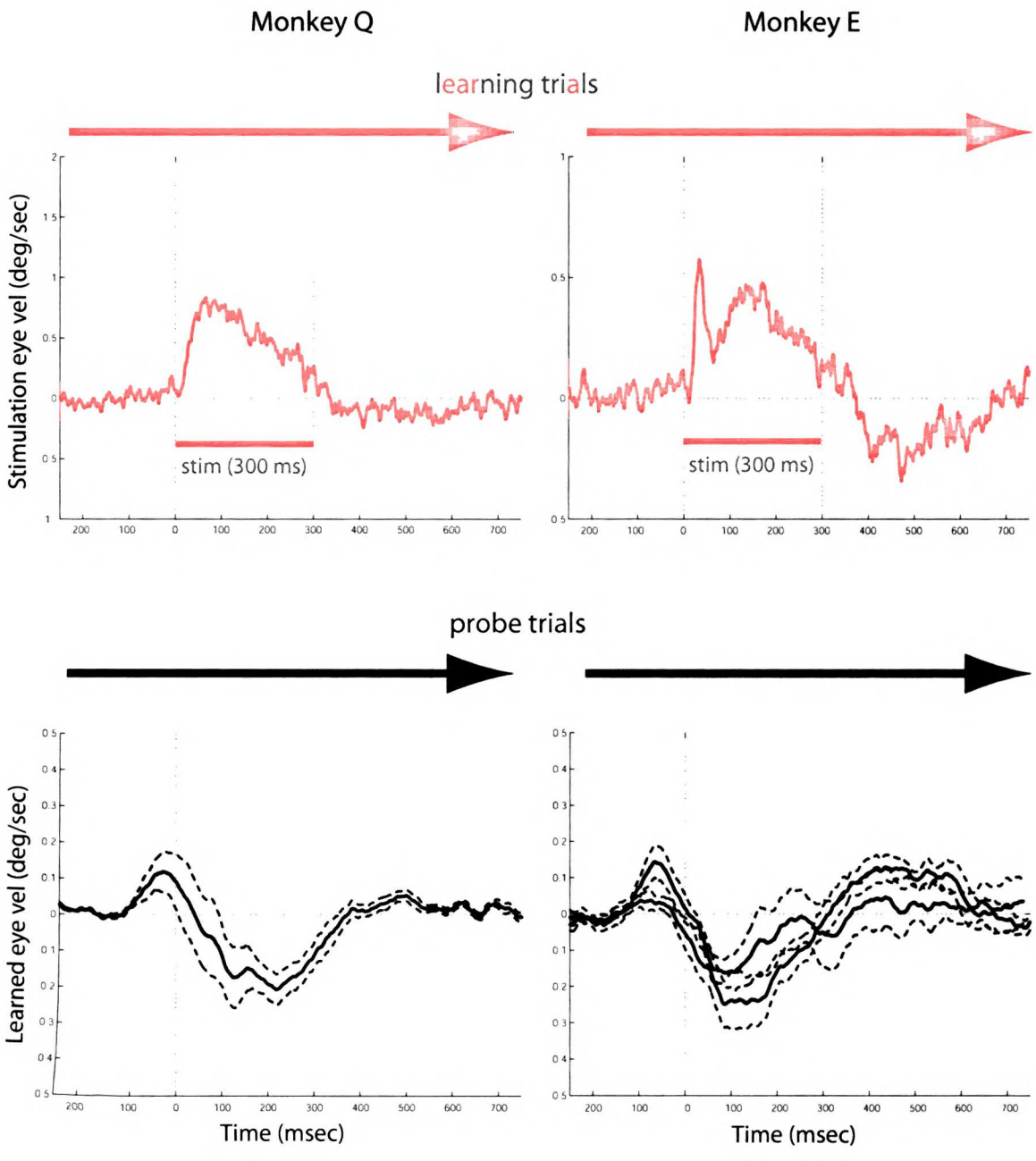
Monkey Q
Monkey E
learning trials
Stimulation eye vel (deg/sec)
stim (300 ms)
stim (300 ms)
probe trials
Learned eye vel (deg/sec)
Time (msec)
Time (msec)

Figure 3.2

Averages from all microstimulation learning experiments.

Top panels plot averaged eye velocity responses during MT microstimulation, measured as the eye velocity in the learning axis on learning trials in which microstimulation was applied minus the averaged eye velocity in the learning axis on baseline trials in which no microstimulation was applied. Data are averages across experimental days and are plotted as a function of time from onset of microstimulation (time 0). Microstimulation was applied for 300 msec. Learning trial eye velocities are taken from the first few presentations, before learning.

Bottom panels plot the learned eye movements in the learning axis, measured as the change in learning axis eye velocity on infrequent probe trials consisting of pursuit without microstimulation following repeated presentation of learning trials. Data are plotted as mean +/- variance as a function of time from microstimulation onset on learning trials. For all plots, Left: Monkey Q, Right: Monkey E. Microstimulation was applied beginning 200 msec after target motion for all experiments except for those plotted in black for Monkey E, in which microstimulation was applied from 250 msec after target motion onset.

Figure 3.3

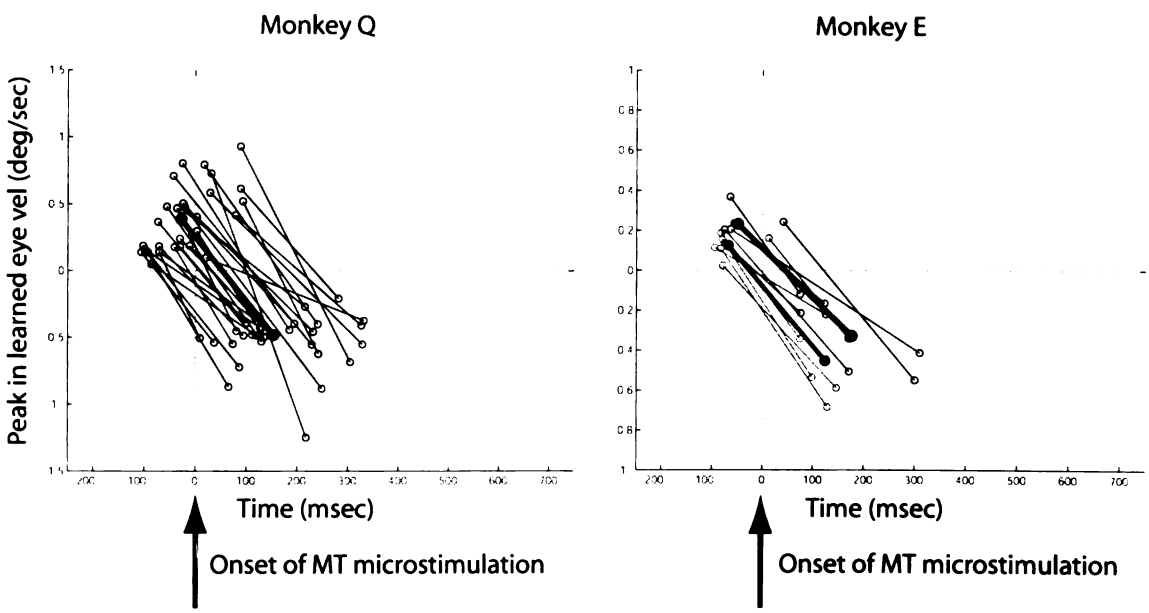
Monkey Q
Monkey E
Peak in learned eye vel (deg/sec)
Time (msec)
Onset of MT microstimulation
Time (msec)
Onset of MT microstimulation

Figure 3.3

Summary of all MT microstimulation experiments.

For each individual experimental day, learned eye velocity data from probe trials are plotted as a thin lines connecting the maximum and minimum eye velocities and the times, relative to the onset of microstimulation on learning trials, at which they occurred (circles). Averages across experimental days are indicated with thick lines and circles. Data from experiments in which microstimulation was applied 200 msec after target motion onset for Monkey E are plotted in red.

Figure 3.4

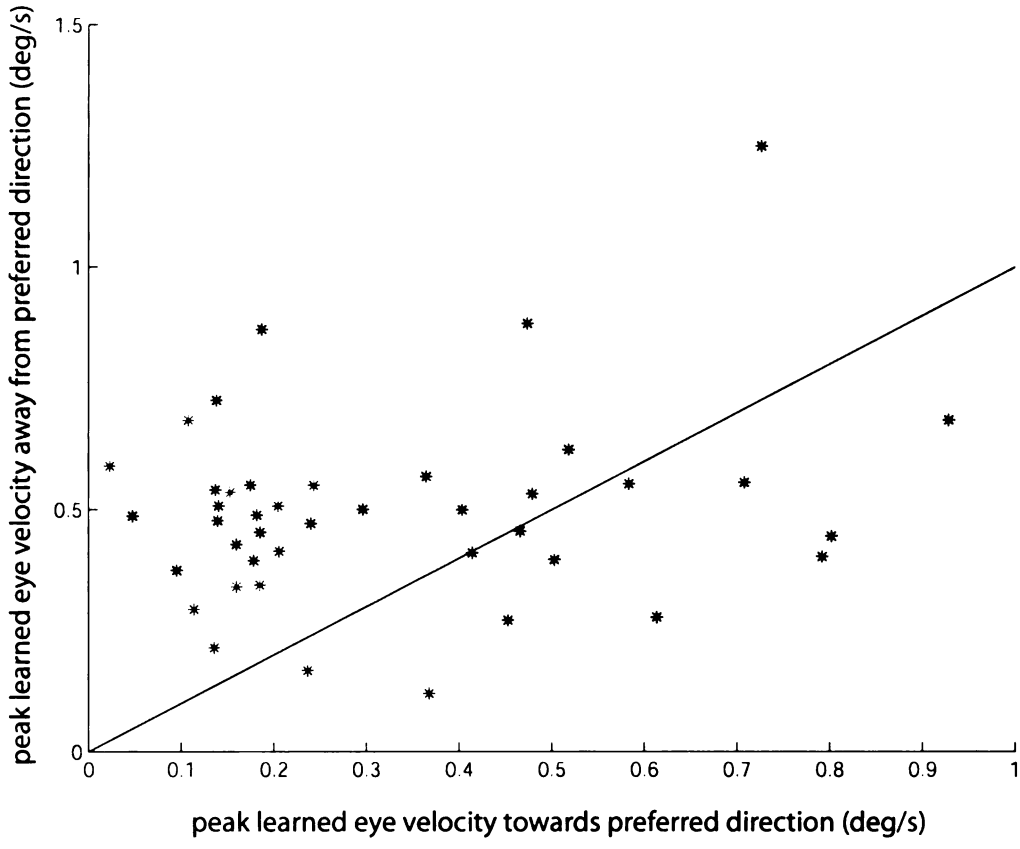
peak learned eye velocity away from preferred direction (deg/s)
1.5
1
0.5
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
peak learned eye velocity towards preferred direction (deg/s)

Figure 3.4

Amplitudes of the two oppositely-directed components of learning are independent. Peaks of averaged learned eye velocities away from preferred direction of stimulated neurons on individual days are plotted as a function of the peaks in the learned eye velocities towards the preferred direction of the stimulated neurons on those same days. Each point represents one experiment. Diagonal line indicates equal amplitudes of the two components of learning; points above the line indicate larger amplitudes of learning away from the preferred direction of the stimulated neurons than towards the preferred direction. Blue: Monkey Q; magenta: Monkey E, 200 msec interval; red: Monkey E, 250 ms interval.

Figure 3.5

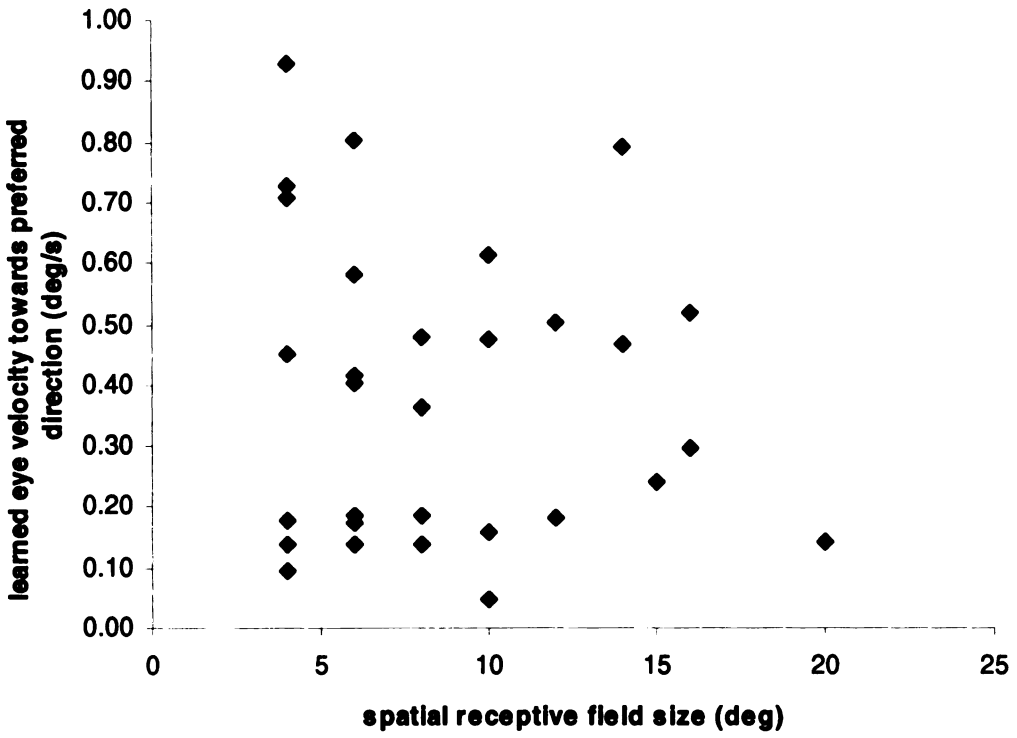
learned eye velocity towards preferred direction (deg/s)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
5
10
15
20
25
spatial receptive field size (deg)

Figure 3.5

Spatial receptive field size does not predict amplitude of learned eye velocity towards the preferred direction of the stimulated neurons. Amplitude of learned eye movement towards the preferred direction of the stimulated neurons is plotted as a function of the size of the spatial receptive field recorded at the stimulation site. Each data point represents one experiment. All data are from Monkey Q. The smallest patch of dots used to measure the spatial extent of the receptive field was 4 deg.

Figure 3.6

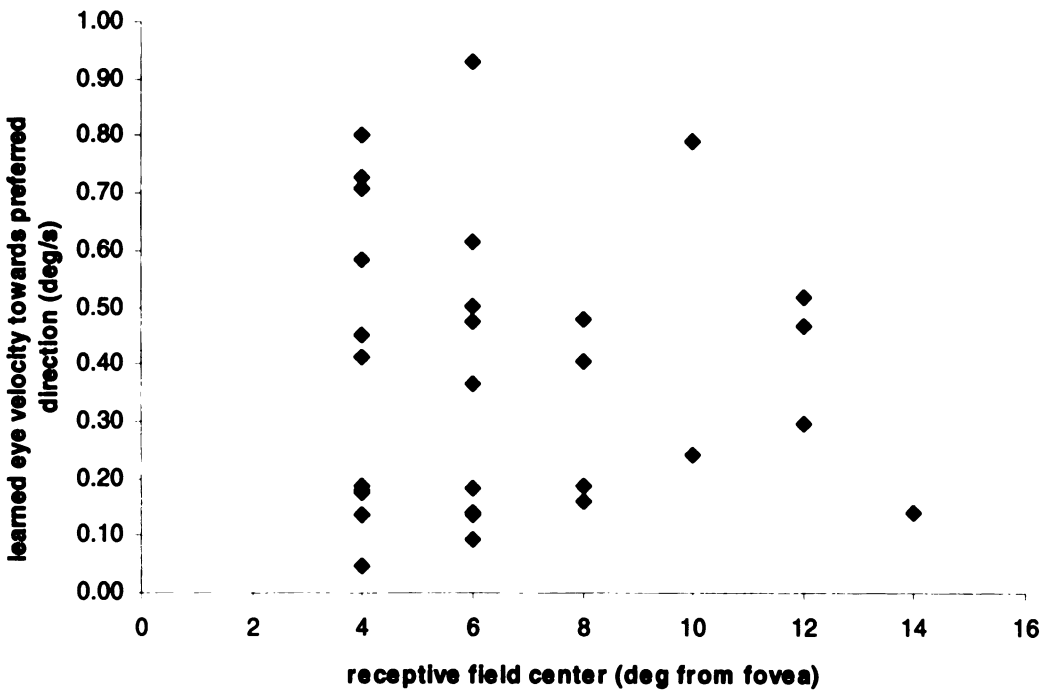
learned eye velocity towards preferred direction (deg/s)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
2
4
6
8
10
12
14
16
receptive field center (deg from fovea)

Figure 3.6

Spatial receptive field location does not predict amplitude of learned eye velocity towards the preferred direction of the stimulated neurons. Amplitude of learned eye movement towards the preferred direction of the stimulated neurons is plotted as a function of the approximate distance of the center of the spatial receptive field from the fovea. Each data point represents one experiment. All data are from Monkey Q. Receptive field locations within the central 0-4 deg have been binned and are plotted as 4 deg from the fovea.

Figure 3.7

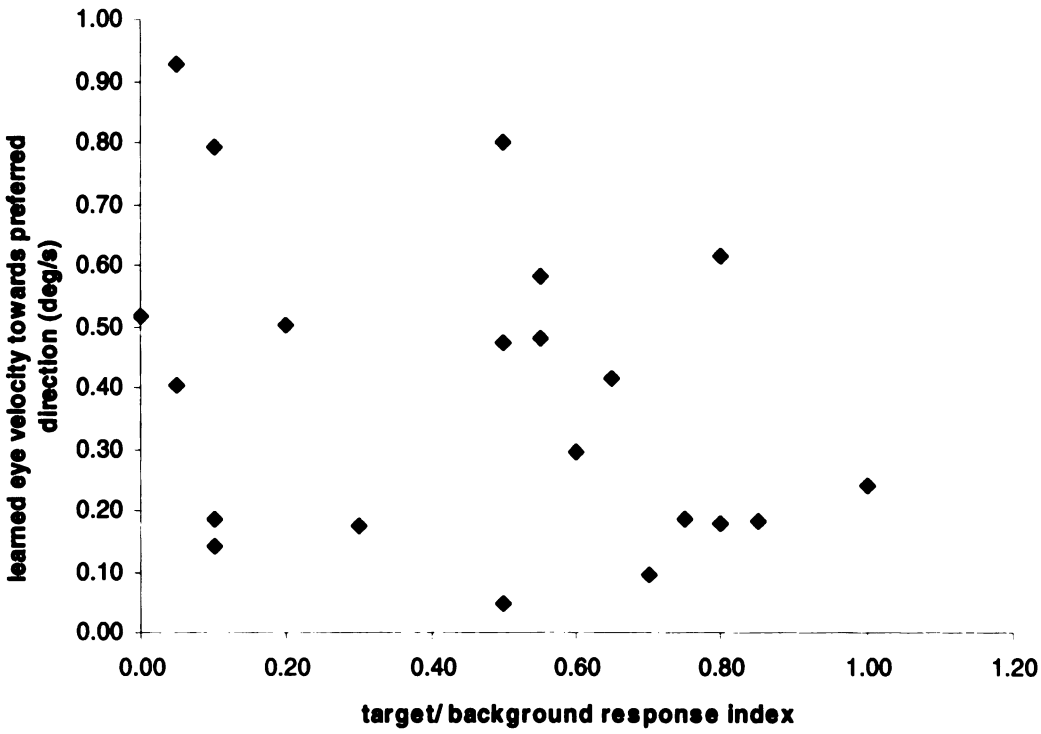
learned eye velocity towards preferred direction (deg/s)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.00
0.20
0.40
0.60
0.80
1.00
1.20
target/ background response index

Figure 3.7

Relative strength of response to target vs. background motion during pursuit does not predict amplitude of learned eye velocity towards the preferred direction of the stimulated neurons. Amplitude of learned eye movement towards the preferred direction of the stimulated neurons is plotted as a function of target/background response index. Response index was calculated as the number of spikes in response to the motion of the target during the initiation of pursuit divided by the sum of the response to the target and the response during pursuit maintenance in the opposite direction (response to the visual background during pursuit). Each data point represents one experiment. All data are from Monkey Q.

Figure 3.8

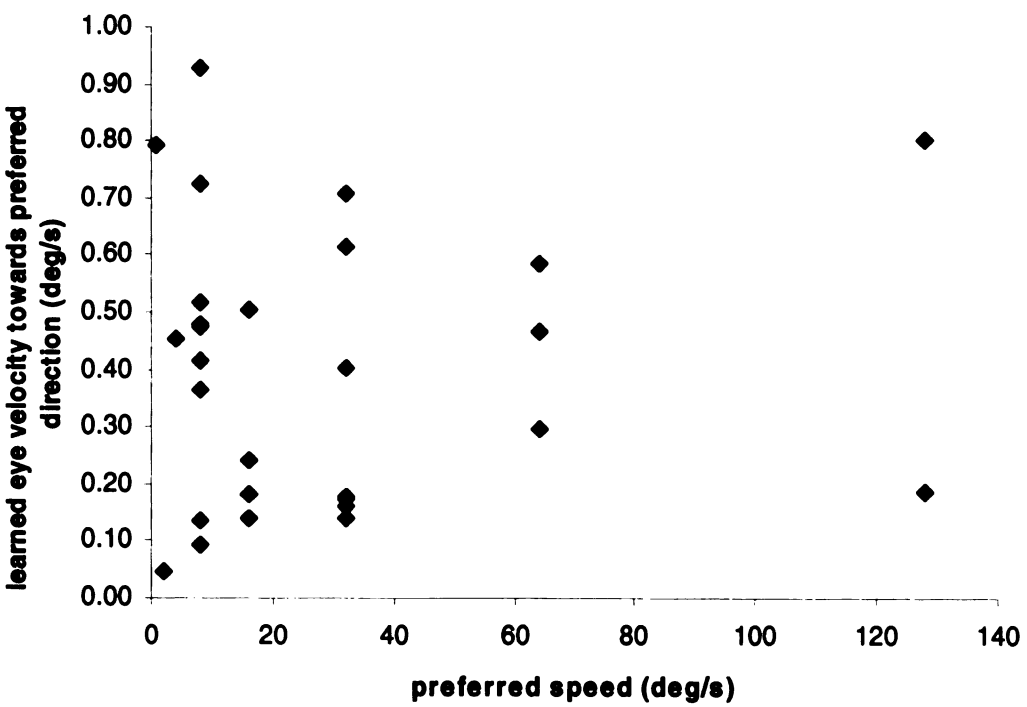
learned eye velocity towards preferred direction (deg/s)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
20
40
60
80
100
120
140
preferred speed (deg/s)

Figure 3.8

Preferred speed does not predict amplitude of learned eye velocity towards the preferred direction of the stimulated neurons. Amplitude of learned eye movement towards the preferred direction of the stimulated neurons is plotted as a function of preferred speed recorded at the stimulation site. Each data point represents one experiment. All data are from Monkey Q.

Figure 3.9

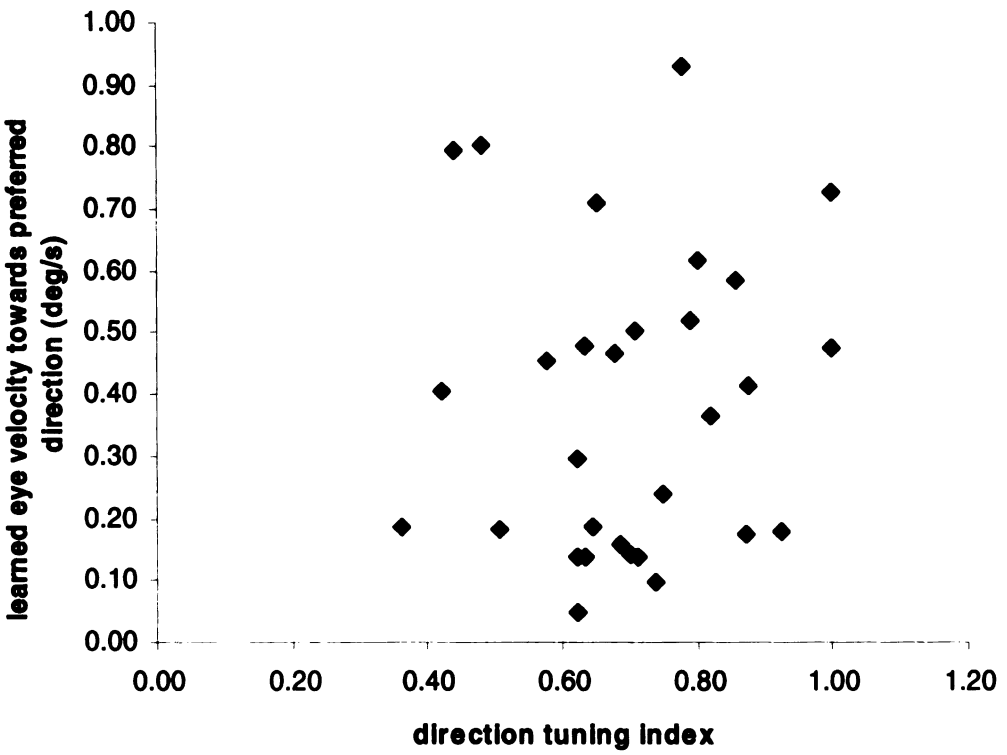
learned eye velocity towards preferred direction (deg/s)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.00
0.20
0.40
0.60
0.80
1.00
1.20
direction tuning index

Figure 3.9

Strength of direction tuning does not predict amplitude of learned eye velocity towards the preferred direction of the stimulated neurons. Amplitude of learned eye movement towards the preferred direction of the stimulated neurons is plotted as a function of direction tuning index. Direction tuning index was calculated as the difference between the number of spikes in the preferred vs. null direction divided by the sum of the number of spikes in the preferred and null directions. Each data point represents one experiment. All data are from Monkey Q.

Figure 3.10

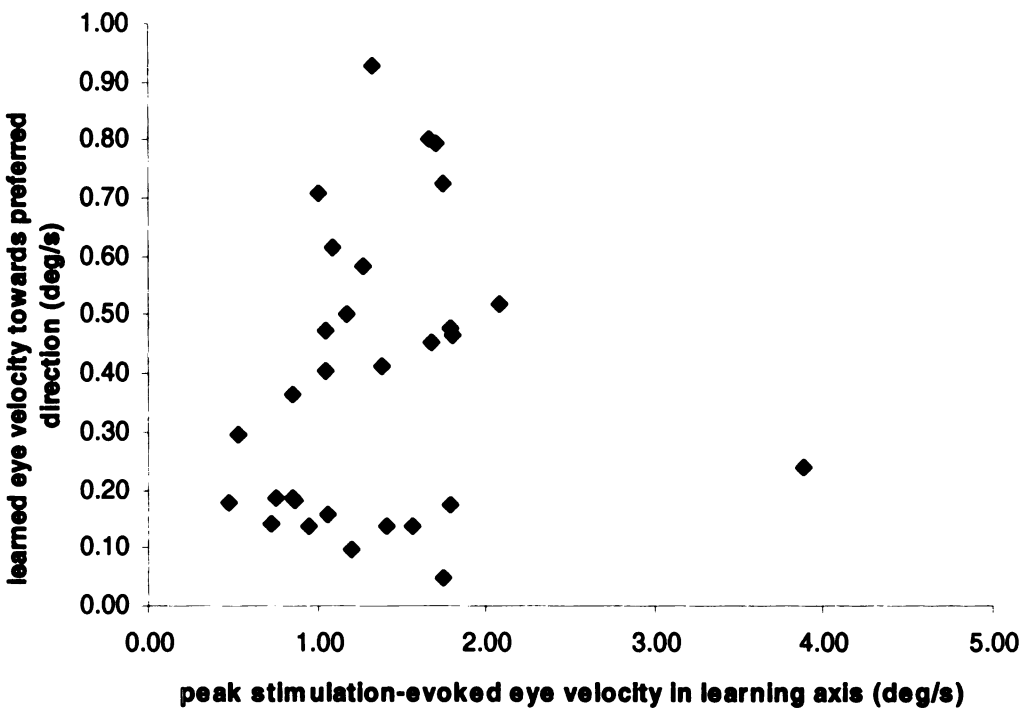
learned eye velocity towards preferred direction (deg/s)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.00
1.00
2.00
3.00
4.00
5.00
peak stimulation-evoked eye velocity in learning axis (deg/s)

Figure 3.10

Amplitude of stimulation-evoked eye movement does not predict amplitude of learned eye velocity towards the preferred direction of the stimulated neurons.

Amplitude of learned eye movement towards the preferred direction of the stimulated neurons is plotted as a function the of the amplitude of the eye movement in that direction evoked by microstimulation. Each data point represents one experiment. All data are from Monkey Q.

Figure 3.11

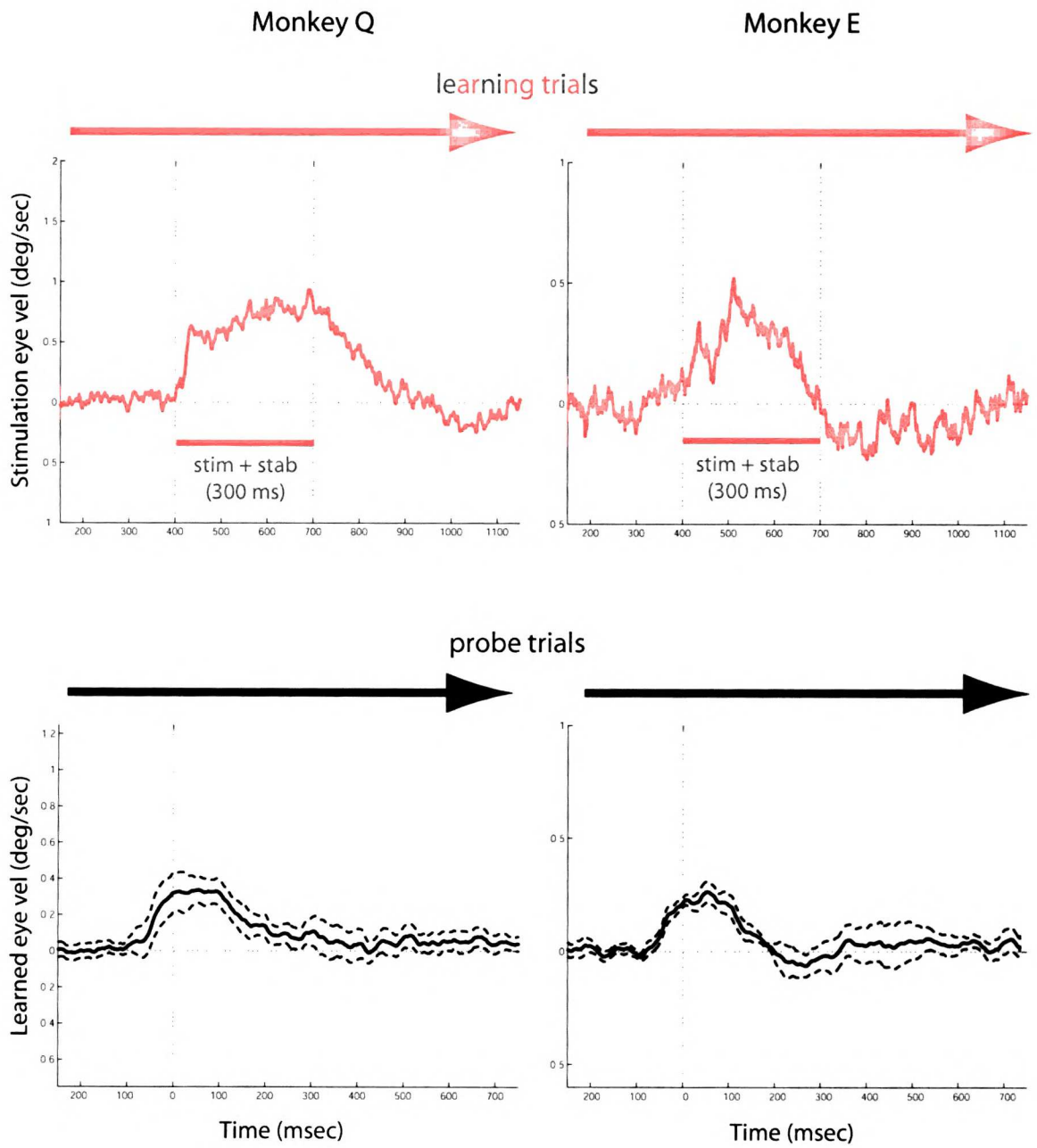
Monkey Q
Monkey E
learning trials
Stimulation eye vel (deg/sec)
stim + stab
(300 ms)
stim + stab
(300 ms)
probe trials
Learned eye vel (deg/sec)
Time (msec)
Time (msec)

Figure 3.11

Effects of stabilizing the target on the retina during microstimulation on learning trials.

Top panels plot averaged eye velocity responses during MT microstimulation with target stabilization, measured as the eye velocity in the learning axis on learning trials in which microstimulation and stabilization were applied minus the averaged eye velocity in the learning axis on baseline trials in which no microstimulation was applied. Data are averages across experimental days and are plotted as a function of time from onset of microstimulation (time 0). Microstimulation and stabilization were simultaneously applied for a duration of 300 msec. Learning trial eye velocities are taken from the first few presentations, before learning.

Bottom panels plot the learned eye movements in the learning axis, measured as the change in learning axis eye velocity on probe trials consisting of pursuit without microstimulation or stabilization following repeated presentation of learning trials. Data are plotted as mean +/- variance as a function of the time that microstimulation began on learning trials. For all plots, Left: Monkey Q, Right: Monkey E. Microstimulation was applied beginning 200 msec after target motion for all experiments.

Figure 3.12

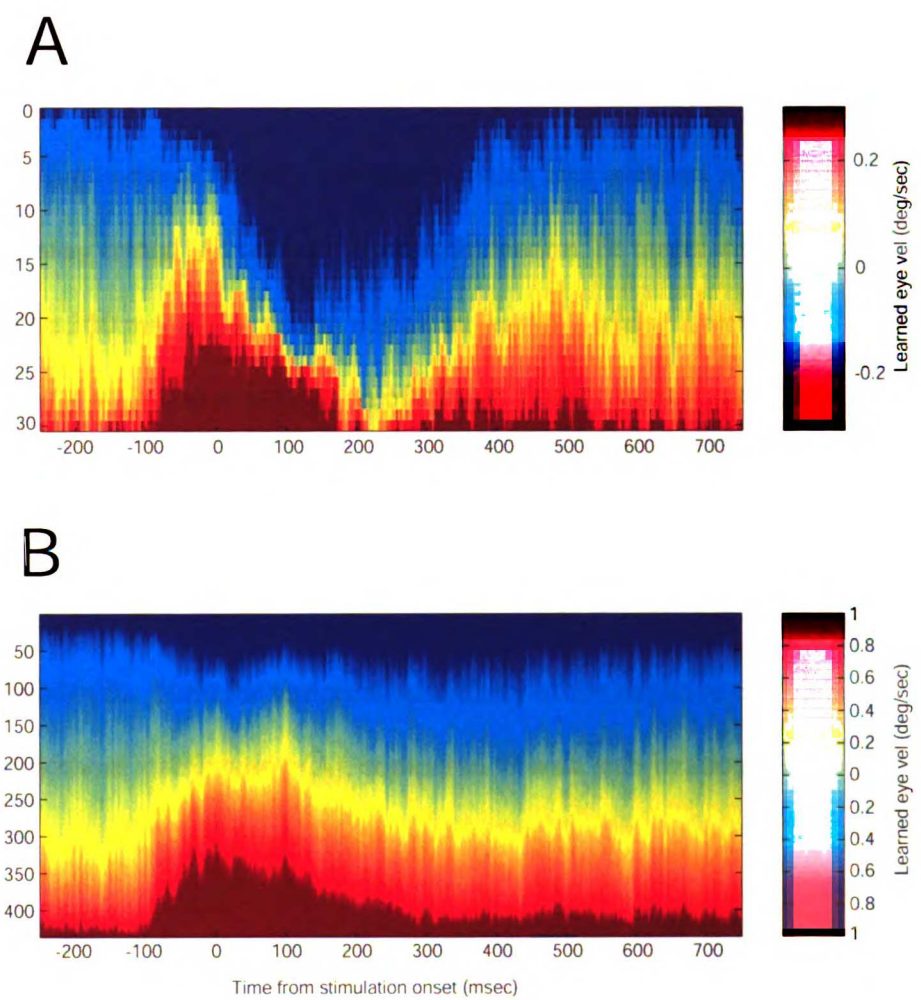
A
0
5
10
15
20
25
30
-200
-100
0
100
200
300
400
500
600
700
0.2
0
-0.2
Learned eye vel (deg/sec)
B
50
100
150
200
250
300
350
400
-200
-100
0
100
200
300
400
500
600
700
Time from stimulation onset (msec)
1
0.8
0.6
0.4
0.2
0
0.2
0.4
0.6
0.8
1
Learned eye vel (deg/sec)

Figure 3.12

Comparison of learning induced by MT stimulation with and without target stabilization on learning trials. A: without target stabilization. B: target was stabilized on the retina during the 300 msec stimulation period on learning trials. Learning axis eye velocities on probe trials is plotted as a function of time from MT microstimulation onset on learning trials. For each millisecond, the data from all experiments (A) or trials (B) have been sorted from highest to lowest (top, blue) to highest (bottom, red) eye velocity values for that millisecond. The number of rows corresponds to the number of experiments (A) or trials (B). Note the temporal specificity of the negative eye velocity data points obtained without stabilization (A), compared to with stabilization (B).

Figure 3.13

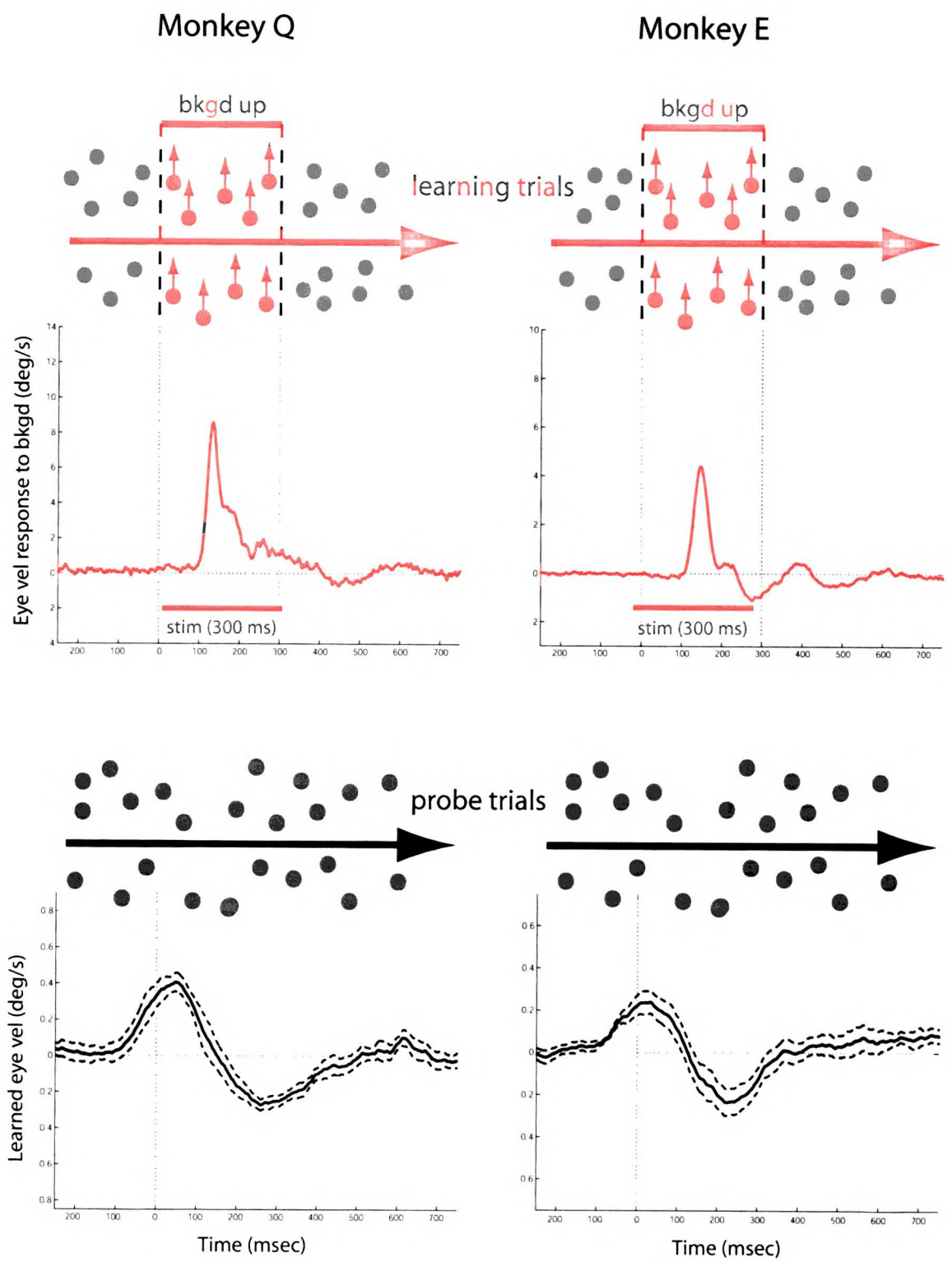
Monkey Q
Monkey E
bkgd up
bkgd up
learning trials
Eye vel response to bkgd (deg/s)
stim (300 ms)
stim (300 ms)
probe trials
Learned eye vel (deg/s)
Time (msec)
Time (msec)

Figure 3.13

Learning induced by motion of a visual background.

Top panels plot averaged eye velocity responses during visual background motion, measured as the eye velocity in the learning axis on learning trials in which the background moved minus the averaged eye velocity in the learning axis on baseline trials in which the background remained stationary. Data are averages across experimental days and are plotted as a function of time from onset of visual background motion (time 0). Visual background motion was orthogonal to the direction of pursuit, began 200msec after target motion onset, and lasted for a duration of 300 msec. Learning trial eye velocities are taken from the first few presentations, before learning.

Bottom panels plot the learned eye movements in the learning axis, measured as the change in learning axis eye velocity on probe trials consisting of pursuit across a stationary background following repeated presentation of learning trials. Data are plotted as mean +/- variance as a function of the time that visual background motion began on learning trials. For all plots, Left: Monkey Q, Right: Monkey E.

Figure 3.14

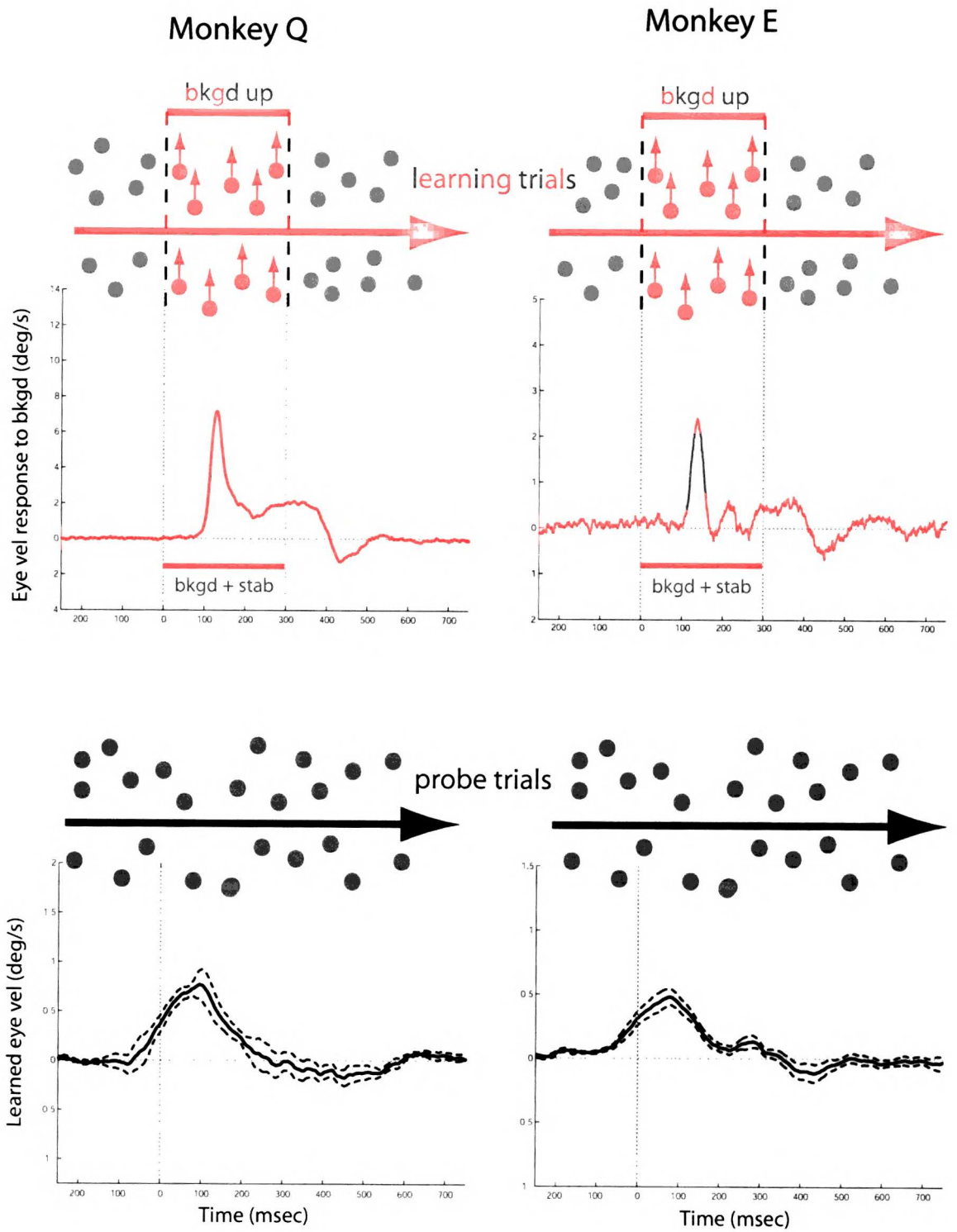
Monkey Q
Monkey E
bkgd up
bkgd up
learning trials
Eye vel response to bkgd (deg/s)
bkgd + stab
bkgd + stab
probe trials
Learned eye vel (deg/s)
Time (msec)
Time (msec)

Figure 3.14

Effects of target stabilization on learning induced by motion of a visual background. Top panels plot averaged eye velocity responses during visual background motion with target stabilization. Responses were measured as the eye velocity in the learning axis on learning trials in which the background moved and the target was stabilized minus the averaged eye velocity in the learning axis on baseline trials in which the background remained stationary. Data are averages across experimental days and are plotted as a function of time from onset of visual background motion and target stabilization (time 0). Visual background motion and target stabilization were simultaneously applied for a duration of 300 msec, beginning 200 msec after target motion onset. Visual background motion was orthogonal to the direction of pursuit. Learning trial eye velocities are taken from the first few presentations, before learning.

Bottom panels plot the learned eye movements in the learning axis, measured as the change in learning axis eye velocity on probe trials consisting of pursuit across a stationary background following repeated presentation of learning trials. Data are plotted as mean +/- variance as a function of the time that visual background motion and target stabilization began on learning trials. For all plots, Left: Monkey Q, Right: Monkey E.

Figure 3.15

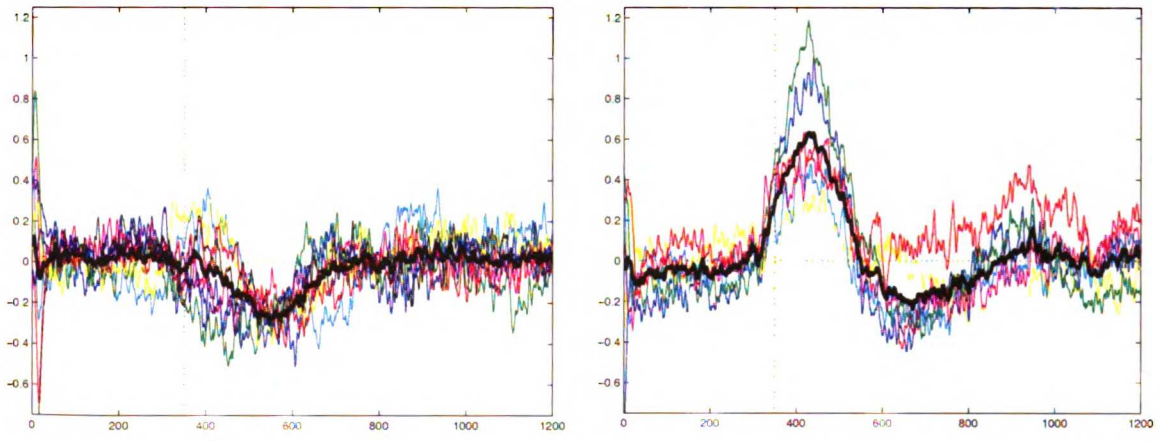

Figure 3.15

Learning induced by motion of an extrafoveal, 8x8 degree patch of dots.

Learned eye velocity averages for individual experiments (different colors) are plotted as a function of time from target motion onset (time 0). Averages across experimental days are plotted with a thick, black line. Left, without target stabilization. Right, with target stabilization during the period of background dot motion on learning trials. The motion of the patch of dots was orthogonal to the direction of pursuit, began 150msec after target motion onset (dotted vertical line), and had a duration of 300 msec. All data are from Monkey Q.

Figure 3.16

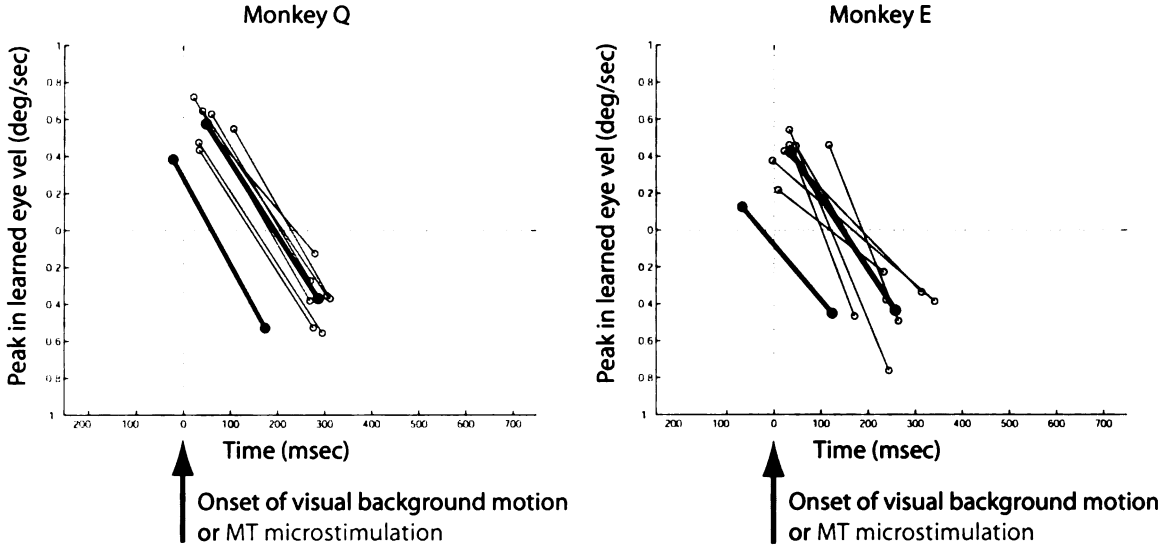
Monkey Q
Peak in learned eye vel (deg/sec)
Time (msec)
Onset of visual background motion
or MT microstimulation
Monkey E
Peak in learned eye vel (deg/sec)
Time (msec)
Onset of visual background motion
or MT microstimulation

Figure 3.16

Temporal relationship between MT microstimulation-induced learning and visual background motion-induced learning.

For each individual experimental day, learned eye velocity data from probe trials are plotted as a line connecting the maximum and minimum eye velocities and the times, relative to the onset of visual background motion or microstimulation on learning trials, at which they occurred. Black lines indicate experiments in which learning was induced with motion of a visual background. Thick red lines are averages across experimental days for learning induced with microstimulation in MT. All data are aligned on the onset of the experimental manipulation (visual background motion or MT microstimulation) on learning trials. For all experiments, microstimulation was applied 200 msec after target motion onset.

Figure 3.17

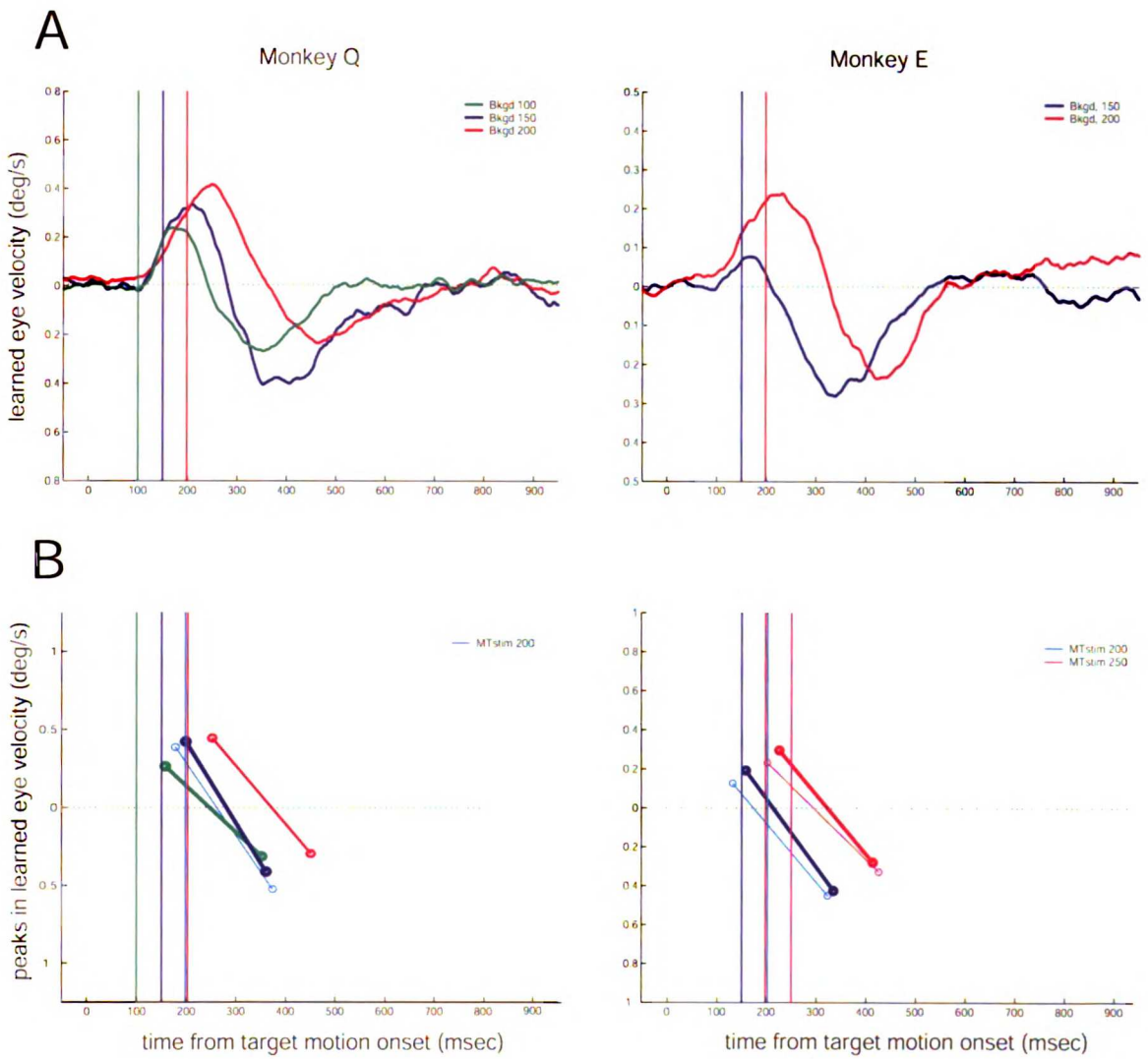
A
Monkey Q
Monkey E
learned eye velocity (deg/s)
Bkgd 100
Bkgd 150
Bkgd 200
Bkgd, 150
Bkgd, 200
B
peaks in learned eye velocity (deg/s)
MTstim 200
MTstim 250
time from target motion onset (msec)
time from target motion onset (msec)

Figure 3.17

Learning induced by motion of a visual background, aligned at target motion onset.

A. Averaged learned eye velocity traces across experimental days for experiments pairing visual background motion with target motion onset at intervals from 100-200 msec. All traces are aligned on onset of pursuit target motion (time 0). Green: 100 msec interval between target motion onset and onset of visual background motion, blue: 150 msec interval, red: 200 msec interval. Vertical lines indicate time of visual background motion for each experiment.

B. Comparison of visual background-induced learning with MT stimulation-induced learning at different intervals. Peaks in learned eye velocities are plotted as a function of time from target motion onset (time 0). Thick lines: learning induced by motion of a visual background. Thin lines: learning induced by MT stimulation.

Figure 3.18

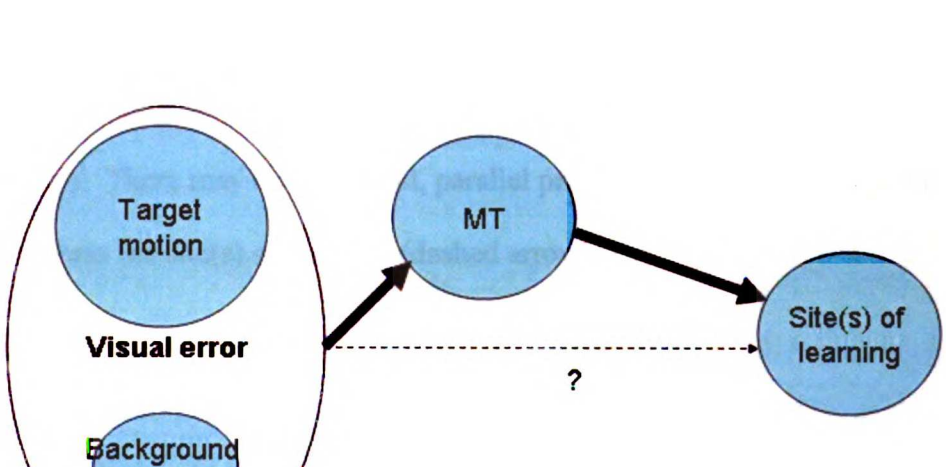
Target motion
Visual error
Background motion
MT
Site(s) of learning
?

Figure 3.18

Schematic of signals driving learning for pursuit.

Visual signals, including target-related retinal image motion and more global motion signals drive learning. Cortical area MT responds to each of these visual motion signals (bold arrow). Here, we have demonstrated that activation of MT drives learning (second bold arrow). There may be additional, parallel pathways through which visual motion signals access the site(s) of learning (dashed arrow).

Discussion

An instructive signal for pursuit learning

We have shown that electrical microstimulation in area MT is sufficient to drive learning for smooth pursuit eye movements. We also demonstrated that visual signals related to target motion relative to the eye and global visual motion drive learning. Our findings suggest a paradigm for understanding pursuit learning as illustrated in Figure 3.18. According to this schematic, visual motion signals pertaining to the target and/or more global motion provide major instructive signals for pursuit learning. Such motion signals are known to be represented in cortical area MT (bold arrow). While visual motion signals that drive learning may also be represented in other brain regions, here we show that MT has access to the sites of learning and that activation of MT is sufficient to drive learning (bold arrow). Furthermore, the learning induced by MT stimulation closely matches learning induced by real visual motion when a ~75 ms latency is taken into account. We conclude that visual signals from area MT provide a powerful instructive signal to drive pursuit learning.

Because MT microstimulation caused an eye movement, we cannot rule out the possibility that the visual signals from MT that drive learning have been partially converted into motor coordinates before they reach the site of learning. We used suprathreshold stimulation because we were concerned about the lengthy nature of our learning experiments and wanted a continual readout of the purity, effectiveness, and consistency of the signal we were injecting with stimulation. Subthreshold stimulation might help resolve the issue of whether the outputs from MT have been converted to

motor coordinates before they reach the site of learning. However, given that the effects of visual stimuli (eg Schwartz and Lisberger 1994, Carey and Lisberger 2004) and MT activation (Komatsu and Wurtz 1989) on inducing eye movements are gated based on ongoing pursuit, we think that the effects of MT activation on inducing learning are also likely to be gated. Such gating, as well as issues relating to the number of neurons activated and the small size of learning observed even with suprathreshold stimulation, would make negative results from experiments using subthreshold stimulation both very likely and difficult to interpret.

We think that the instructive signals for pursuit learning are primarily visual in nature for three reasons. First, the response properties of MT neurons are purely visual (Albright 1984, Maunsell and Van Essen 1983, Newsome et al 1988), and therefore MT stimulation should inject a purely visual signal. Second, we found that when learning trials are configured so that eye movements and target motion relative to the eye are in opposite directions, learning goes in the direction predicted by the target motion, not the eye movement (Figures 3.1, 3.2, 3.13). Third, the timing of the learning in the stimulation vs. background conditions is consistent with an instructive signal time-locked to MT activation (Figure 3.17).

Sensory error signals

Sensory error signals have been widely hypothesized to act as instructive signals to drive behavioral learning, and yet there are relatively few examples of behaviors for which activation of a specific class of sensory neurons has been demonstrated to be sufficient to drive learned changes in behavior. Behavioral, lesion, and

electrophysiological studies have suggested candidate loci for instructive signals for a variety of behaviors (Lanuza et al 2004, Nagao 1983, Lisberger et al 1984, Robinson 1976), but establishing causality has been more elusive. Electrical microstimulation has been used successfully for a few behaviors, including eyelid conditioning (Mauk et al. 1986), tone recognition (McLin et al 2002), and sensory discrimination (Talwar and Gerstein 2001).

To our knowledge, the current study represents the first time that activation of a cortical sensory area has been shown to be sufficient to drive behavioral learning. We took advantage of the established role of visual motion processing in cortical area MT in pursuit and the fact that MT neurons respond robustly and in a directionally specific way to image motion in retinal coordinates – exactly the visual signal that is present during directional pursuit learning tasks (Medina et al 2005). Learning induced with MT stimulation corresponds remarkably well in both size and shape with the learning we observed in experiments using motion of a visual background as an instructive signal. We developed the moving-background learning paradigm to mimic the effects of MT stimulation because it provided a non-spatially specific visual motion stimulus and also induced an eye movement that moved the eyes off the target. The striking similarity in the shape of the learned eye movement in the two cases is probably partly due to intrinsic dynamics of pursuit, but the shared dependence on the timing of the instructive signal strongly argues that MT stimulation is tapping into natural mechanisms of pursuit learning.

Our failure to correlate the relative amplitudes of the two components of learning with features of the multiunit recordings at each site could reflect biases in our selection

of stimulation sites (ie we were within the foveal 8 deg most of the time, mostly used a large patch of dots moving at 16 deg/s as a search stimulus and did not position our electrode optimally for shared speed tuning) or could simply indicate that something more general, like the number of neurons being stimulated or exact location of the stimulating electrode, that we could not detect with recording, played an important role. In retrospect, the finding that motion of a large-field visual motion stimulus like our background induced learning towards the direction of background motion also argues against our initial hypothesis that stimulation at the most foveal sites would be required to drive learning effectively.

Although we were not able to use features of the activity recorded at individual stimulation sites to predict the relative amplitudes of the two components of learning induced by microstimulation at individual sites within MT, we would predict that microstimulation in other brain areas might allow for dissociation of the two components of learning. For example, microstimulation in areas with more motor response properties than the sensory visual cortical area MT, such as the frontal pursuit area or cerebellum, might be relatively ineffective at inducing learning towards the preferred direction of the stimulated neurons. In fact, they might be downstream of the site of learning. However, stimulation in those areas would still be predicted to induce learning in the direction opposite the preferred direction of the stimulated neurons, as it would not interfere with the target image motion relative to the eye that we believe is driving that component of learning.

Implications for site(s) of learning

Pursuit shares fundamental aspects of its circuitry with a variety of sensory-guided behaviors – from reaching movements to speech – that are mediated by canonical sensorimotor loops between cortex, the basal ganglia, and the cerebellum (Middleton and Strick, 2000). Many researchers (Doya 2000, Hikosaka et al. 2002, Jueptner et al 1997) have proposed that the basal ganglia and the cerebellum could act together to provide reward and error-related instructive signals, respectively, for a wide range of learned behaviors.

Our experiments do not speak directly to the site of learning for pursuit, other than to indicate that the site of learning must receive major inputs from MT. However, we believe that our results are consistent with a possible role of the cerebellum in pursuit learning (Kahlon and Lisberger 1996, Chou and Lisberger 2004, Medina et al. 2005), for several reasons. Area MT is a major source of visual motion signals to the cerebellar flocculus and vermis in primates, providing inputs to both classes of cerebellar afferents, mossy fibers and climbing fibers, via the dorsolateral pontine nucleus and the nucleus of the optic tract (Distler et al 2002, Alley et al 1975, Brodal 1979). Moreover, visual cortical lesion studies (Fetter et al 1988) have suggested that cortical visual processing plays an important role in adaptation of the monkey vestibulo-ocular reflex, a cerebellar-mediated learned behavior.

Pursuit learning is a form of associative motor learning in which a particular target motion is consistently associated with an instructive signal that changes the relationship between that target motion and the motor response. A general problem for learning theories that propose sensory error feedback as an instructive signal is that the

feedback is delayed relative to the time of the incorrect movement itself. In the brain, this means that plasticity mechanisms at sites of learning must affect movement-related inputs that are active before the instructive signals arrive to ensure properly-timed learned responses. Our experiments indicate that the pursuit system compensates for the temporal delay in the instructive signal from MT – learned eye movements clearly begin, and even peak before the time when stimulation occurred on learning trials. Thus, plasticity mechanisms underlying pursuit learning would be expected to have asymmetrical temporal requirements as has been proposed for other cerebellar-based learned behaviors (Raymond and Lisberger 1998, Medina et al. 2000) and demonstrated for some forms of cerebellar plasticity (Wang et al 2000, Chen and Thompson 1995).

The precise locus of learning for pursuit and other cortically-mediated behaviors is still an open question for future experiments. Here, we have demonstrated that visual signals are a powerful instructive signal for pursuit learning and that the site of learning must receive significant inputs from area MT. In conclusion, we propose that cortical sensory cortex may provide instructive signals for learning in a wide range of behaviors, from reaching movements to language.

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Chapter 4

General conclusions and future directions

This thesis has characterized neural signals that modulate the sensorimotor transformation for pursuit based on context and experience. By using passive whole body rotation and adaptation of the vestibulo-ocular reflex, we demonstrated that signals intermediate to gaze velocity *per se* and the visually-driven component of gaze velocity, but not eye velocity signals, are responsible for gain control, the modulation of the sensorimotor transformation for pursuit based on context. Microstimulation in cortical area MT and manipulations of visual pursuit targets and moving visual backgrounds demonstrated that visual signals, including target-related visual signals and signals from cortical area MT, are capable of driving changes in the sensorimotor transformation for pursuit that are learned based on previous experience.

Identifying the neural signals responsible for modulating the sensorimotor transformation for pursuit, as we have done here, is an important first step in elucidating the neural basis of the more complex aspects of the pursuit behavior. It allows us to understand the behavioral conditions under which modulation of pursuit occurs, which constrains the spatial and temporal patterns of activity that trigger the modulation, and ultimately yields valuable insight into the potential sites and mechanisms of pursuit modulation.

Taken together, the work in this thesis suggests a possible framework for pursuit in which image motion, when associated with visually driven gaze velocity, is gated in such a way that it both evokes enhanced eye movement responses and drives learning. It has been previously shown that stimulation in area MT evokes eye movements whose amplitude depends on the speed of ongoing pursuit (Komatsu and Wurtz, 1989), in a manner consistent with the dependence of the response to visual target perturbations on

the speed of ongoing pursuit (Schwartz and Lisberger 1994). What gates the output of MT neurons during fixation vs during ongoing pursuit? Chapter 2 demonstrated that the enhancement of responses to visual target perturbations is triggered by gaze velocity signals. Based on our findings in Chapter 2, a reasonable hypothesis is that the output from area MT is gated by ongoing gaze velocity signals. If so, then in order to effectively evoke an eye movement, the activation of MT would have to occur concurrently with ongoing gaze velocity signals.

Does the gating of MT outputs during ongoing pursuit also determine their effectiveness at inducing learning? While Chapter 3 demonstrates that visual motion signals consistently associated with motion of a target in a given direction leads to learned eye movements, it does not address the question of what signals present during the ongoing motion of the target are being associated with the instructive visual motion signals. The results of Chapter 2 suggest that ongoing gaze velocity signals are a reasonable candidate. Indeed, based on the known gating of the outputs from MT, and the behaviorally-demonstrated associative nature of pursuit learning (Kahlon and Lisberger 1996, Chou and Lisberger 2002), it seems plausible that an association between ongoing gaze velocity signals and the output from area MT might form the basis for the associative nature of pursuit learning.

The hypothesis that the association between the output of area MT and ongoing gaze velocity signals are sufficient to drive pursuit learning suggests a number of possible future experiments. First, in this thesis we only performed experiments pairing MT microstimulation with ongoing pursuit. What would happen if microstimulation in MT were consistently associated with a non-motion cue, such as the appearance of a pursuit

target? During fixation, both visual stimuli and the output of MT are gated in such a way that both evoke smaller pursuit responses than they do during ongoing pursuit. Are they also gated in such a way that they would be less effective at inducing learning? If the gating of the outputs from MT is shared for both gain control and learning, then MT microstimulation paired with a cue that does not carry gaze velocity signals would not be predicted to support learning. Experiments pairing microstimulation in MT with non-motion cues might also help clarify the similarities and differences between pursuit learning, which we studied here, and the phenomenon of predictive pursuit, which is not strictly an associative form of learning and is believed to have a cognitive basis (Barnes and Asselman 1991, Kowler 1989).

A related question concerns the ability of visual signals from area MT to drive adaptation of the vestibulo-ocular reflex. Behaviorally, image motion paired with head turns leads to VOR adaptation (duLac et al. 1995). Lesions studies (Fetter et al. 1988) have implicated a role for visual cortex in VOR adaptation. Are visual signals from MT capable of adapting the gain of the VOR, even if they are presented during the VOR, which does not provide ongoing gaze velocity signals? Again, the answer to this question depends on whether gaze velocity signals gate the absolute output from area MT. Some theories of VOR adaptation argue that gaze velocity signals are a necessary component of VOR adaptation, while others focus primarily on visual signals. Stimulating in MT during the VOR vs. during VOR cancellation (in which there is a non-zero gaze velocity) and comparing the effects on adaptation of the vestibulo-ocular reflex might help address this ongoing debate. However, due to the fact that VOR adaptation is a change in gain (both directions) while pursuit learning is a change in one direction, these experiments

would require an ability to rotate the monkey in more than one dimension, and also the ability to either repeatedly turn the monkey in the same direction or to alternately excite and inhibit MT neurons, in order to avoid extinguishing learning when turning the monkey in the opposite direction.

It would be useful to have a better understanding of the gating of MT output and its role in gain control and in learning. To that end, there is almost no end to conceivable two-electrode experiments involving microstimulation in MT while recording in downstream pursuit regions under different behavioral conditions. Comparing responses in different brain areas during pursuit and fixation, for example, would help us understand the gating of visual inputs during gain control. Similarly, comparing responses under conditions that do and do not support learning would not only indicate whether the gating of MT output is shared for gain control and learning, but would help identify the patterns of neural activity that lead to long term changes in behavior. Finally, comparing results from different brain areas for different behavioral conditions would improve our understanding of the contribution of different regions to different aspects of the pursuit behavior.

Although this thesis considered the modulation of the sensorimotor transformation for pursuit based on context and experience as two separate phenomena, one could speculate that they may not be as unrelated as they might seem (Chou and Lisberger 2004). Pursuit is a learned behavior. What is it that is learned? Perhaps it is the ability to maintain pursuit in the maintenance phase of pursuit, after the transient image motion that drives the initiation of pursuit. Essentially, repeated presentation of continuous motion would teach the pursuit system – through image motion instructive

signals – that once objects start moving, they are likely to continue moving. Given Newton's first law of motion, maintaining pursuit at a constant velocity is generally an effective way to keep the eyes on the target. Furthermore, the pursuit system could also learn that once pursuit is engaged – that is, while there is a non-zero gaze velocity signal that is at least partly visually-driven – the target is more likely to undergo a change in direction or speed than is a target at rest, which tends to stay at rest. Such learning could form the basis for gain control.

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