Role of Arcuate Frontal Cortex of Monkeys in Smooth Pursuit Eye Movements. II. Relation to Vector Averaging Pursuit

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Abstract

When monkeys view two targets moving in different directions and are given no cues about which to track, the initiation of smooth pursuit is a vector average of the response evoked by each target singly. In the present experiments, double-target stimuli consisted of two identical targets moving in opposite directions along the preferred axis of pursuit for the neuron under study for 200 ms, followed by the continued motion for 800 ms of one target chosen randomly. Among the neurons that showed directional modulation during pursuit, recordings revealed three groups. The majority (32/60) showed responses that were intermediate to, and statistically different from, the responses to either target presented alone. Another large group (22/60) showed activity that was statistically indistinguishable from the response to the target moving in the preferred ($n = 15$) or opposite ($n = 7$) direction of the neuron under study. The minority (6/60) showed statistically higher firing during averaging pursuit than for either target presented singly. We conclude that many pursuit-related neurons in the frontal pursuit area (FPA) carry signals related to the motor output during averaging pursuit, while others encode the motion of one target or the other. Microstimulation with 200-ms trains of pulses at 50 μ A while monkeys performed the same double-target tasks biased the averaging eye velocity in the direction of evoked eye movements during fixation. The effect of stimulation was compared with the predictions of three different models that placed the site of vector averaging upstream from, at, or downstream from the sites where the FPA regulates the gain of pursuit. The data were most consistent with a site for pursuit averaging downstream from the gain control, both for double-target stimuli that presented motion in opposite directions and in orthogonal directions. Thus the recording and stimulation data suggest that the FPA is both downstream and upstream from the sites of vector averaging. We resolve this paradox by suggesting that the site of averaging is really downstream from the site of gain control, while feedback of the eye velocity command from the brain stem and/or cerebellum is responsible for the firing of FPA neurons in relation to the averaged eye velocity. We suggest that eye velocity feedback allows FPA neurons to continue firing during accurate tracking, when image motion is small, and that the persistent output from the FPA is necessary to keep the internal gain of pursuit high and permit accurate pursuit.

INTRODUCTION

Much recent evidence indicates that a region of the frontal cortex that we call the “frontal pursuit area” (FPA) plays several important roles in smooth pursuit eye movements. Lesions of this area cause a reduction of pursuit gain (Lynch 1987; Keating 1991; MacAvoy et al. 1991; Shi et al. 1998), recordings have identified neurons that discharge selectively for pursuit and not for saccades (Fukushima et al. 2000; Gottlieb et al. 1994; Tanaka and Fukushima 1998; Tanaka and Lisberger 2002b, companion paper), and stimulation has multiple effects on

pursuit (Gottlieb et al. 1993; Tanaka and Lisberger 2002a). Recording experiments presented in our companion paper help to cement the selective role of the FPA in pursuit. They imply that FPA is functionally distinct from the traditionally defined saccadic frontal eye fields (FEFs) and is not simply an extension of the FEF that represents retinal image positions just off the center of gaze.

One approach to analysis of the FPA is to ask whether it has a unique role in pursuit, and what that role is. In the INTRODUCTION to the companion paper, we outlined anatomical evidence that the FPA may have a unique role: it is part of a separate pursuit pathway that operates in parallel with the parietoponto-cerebellar pathways through the visual motion areas MT and MST. Our microstimulation data suggest one unique role: the output of the FPA seems to control the internal gain of pursuit. When activated by electrical stimulation, the gain control is nondirectional and has two effects that may be related to separate modulation of the gain of visual-motor transmission and the gain of eye velocity processing for pursuit (Tanaka and Lisberger 2001, 2002a).

A second approach is to ask how the FPA fits into the overall signal processing for pursuit. We have traditionally discussed the cortical circuits for pursuit in terms of signals that flow one way from the cortex to the cerebellum (e.g., Lisberger et al. 1987). However, the connections of cortical areas that are involved in somatic motor control involve extensive feedback from the cerebellum and the basal ganglia. The premotor cortex and the supplementary motor area are two areas that may be in the same conceptual position for somatic movement as is the FPA for pursuit eye movements. These two areas are part of feedback circuits that project to and receive abundant feedback from the cerebellum and the basal ganglia (for reviews see, Alexander et al. 1986; Leiner et al. 1986; Middleton and Strick 2000). With this parallel in mind, the present paper considers how the signals present in the FPA are formed, as well as how they might act to regulate the commands for smooth pursuit eye movements.

We have chosen a behavioral paradigm that allows us to discriminate signals related to the pursuit target from those related to the evoked eye movement. When equally salient visual stimuli are presented simultaneously without providing monkeys any cue about which to track, the presaccadic initiation of pursuit is a weighted vector-average of the responses evoked by each target presented singly (Lisberger and Ferrera 1997). This creates signals related to the motion of two targets in different directions, as well as those related to the averaging eye movement, which is different in amplitude and/or direction from either target motion. Available evidence indicates that vector averaging occurs somewhere between the output of visual area MT and the discharge of cerebellar Purkinje cells (Kahlon and Lisberger 1999). In the present paper, we analyze the role of the FPA in vector averaging eye movements using unit recording and microstimulation. Our goal was partly to understand the role of the FPA in vector averaging eye movements, but mainly to use vector averaging as a tool for understanding better the organization of the pursuit system.

Our data reveal that firing rate responses of many neurons in the FPA during vector averaging pursuit of double-target stimuli are intermediate between those evoked during pursuit of each target presented singly. These recording data imply that averaging pursuit is represented already at the level of the FPA. However, when we delivered trains of stimulation pulses and asked how the outputs of the FPA modulated averaging pursuit, our data supported a model in which vector averaging occurs downstream from the site where the FPA stimulation alters the internal gain of pursuit. These seemingly conflicting observations might be expected if the FPA is part of a recurrent cortico-cerebello-cortical pathway. We will suggest that the FPA receives eye velocity signals through ascending pathways from the brain stem and/or cerebellum, and regulates pursuit commands through descending pathways to the cerebellum.

METHODS

Data were collected from two rhesus monkeys that were used in the companion paper (Tanaka and Lisberger 2002b) and for the previous stimulation experiments (Tanaka and Lisberger 2001, 2002a). The general experimental procedures were identical to those described in the companion paper, so that only methods that were unique to the present paper are described here. As before, all experimental protocols were approved in advance by the Institutional Animal Care and Use Committee of the University of California, San Francisco.

Experimental paradigm

The experimental paradigm was similar to that used by Lisberger and Ferrera (1997). Target motions were presented in individual trials, and each block of trials consisted of two double-target motions and two to six single-target motions. Each trial began with the appearance of a central fixation target that was present for a random duration ranging from 1,000 to 1,500 ms. In the single-target paradigm (Fig. 1A), the target executed step-ramp motion either in the preferred direction of the neuron under study or in the opposite direction. The amplitude of target step was 1, 2, and 4° for target speeds of 5, 10, and 20°/s, respectively. The target always moved toward the position of initial fixation, and the monkeys usually did not make saccades during the initiation of pursuit. In the double-target paradigm (Fig. 1B), two identical targets (dashed and continuous traces) appeared simultaneously and, for recording experiments, moved in opposite directions along the cell's preferred axis. For microstimulation experiments, the targets moved either along the axis of the eye movements evoked by electrical stimulation during fixation, or along the orthogonal axis. In the double-target trials, one of the two targets disappeared 200 ms after target motion onset (dashed trace in Fig. 1B), and the other continued to move for an additional 800 ms. Fixation requirements were suspended until 600 ms after the onset of the double-target motion, so that the monkeys would have time to acquire the remaining target, which they were required to track to receive a water reward. Monkeys usually withheld saccades during the brief presentation of double-targets and made a saccade to the remaining target ~400 ms after the onset of target motion (upward arrow in Fig. 1B). As in previous behavioral studies (Gardner and Lisberger 2001; Lisberger and Ferrera 1997), the monkeys were not provided any cues about which target would disappear and which would become the tracking target. Different types of trials were interleaved randomly in each experimental block.

Physiological procedures

The initial half of this paper reports the activity of single pursuit neurons recorded from the FPA using procedures described in the companion paper (Tanaka and Lisberger 2002b). The second half of the paper examines the effects of electrical microstimulation on the eye movements evoked by single- and double-target stimuli. A train of cathodal pulses (0.2-ms width) was delivered through the electrode. The stimulation current was monitored by measuring the voltage drop across a 1-k Ω resistor in series with the electrode, and was maintained at 50 μ A. The sites of electrical stimulation were at or near the sites where pursuit-related neuronal activity was recorded, and where a 75-ms train of stimulation pulses at 333 Hz consistently evoked smooth eye movements during fixation as well as during the maintenance of pursuit (Tanaka and Lisberger 2002a). Once the site of stimulation was determined, we reduced the frequency of stimulation pulses to either 100 or 200 Hz to minimize the size of eye movements evoked by electrical stimulation, and used a stimulation train with a duration of 200 ms. Trials that delivered stimulation were interleaved randomly with equal number of trials presenting identical target motions in the absence of stimulation.

Data acquisition and analyses

The procedures for the data acquisition and analysis were the same as those used before (Tanaka and Lisberger 2002a) and are described only briefly here. Horizontal and vertical eye velocity were obtained by passing the eye position voltage through analog circuits that differentiated frequencies below 25 Hz and rejected higher frequencies (-20 db/decade). Action potentials were discriminated using commercial hardware (BAK model DDIS-2), and the resulting logic pulses were timed-stamped by the computer to the nearest 10 μ s. Analog data were sampled at 1 kHz on each channel and stored on a hard disk for analysis after the experiment on a UNIX workstation. Traces of eye position and eye velocity were reviewed on a video monitor using homemade software. The onset and offset of each saccade were detected visually in eye velocity traces and were marked by a mouse-controlled cursor. Subsequent analyses did not include the sections of data that had contained saccades and were performed using Matlab (Mathworks). For quantitative analyses, we counted spikes and measured eye velocity from individual trials for specified task intervals that were defined relative to the onset of target motion. The use of target motion onset as the time reference is common for unit recording studies of pursuit (e.g., Stone and Lisberger 1990). Further, the results would not be materially different if we had aligned data on the initiation of pursuit because the variation of pursuit latency is small (Lisberger and Westbrook 1985). Details are provided at the relevant places in RESULTS. To show examples of our results in figures, data were aligned on the onset of identical target motions, and the average of the responses in multiple trials was computed as a function of time. The time course of neuronal activity was estimated by convolving the spike train with a unit Gaussian with a SD of 10 ms (Richmond and Optican 1987).

RESULTS

Averaging eye movements

Figure 1, *A* and *B*, shows typical examples of the eye movements induced by the single- and double-target stimuli used for recording experiments. For the double-target stimulus, the two targets moved in opposite directions along the preferred axis of the neuron under study. In this example (Fig. 1*B*), the monkey initiated pursuit in the direction of motion of the target that would disappear (dashed target trace) at about the same latency as pursuit of single-target motions (Fig. 1*A*). To emphasize the similarity of the latency for single- and double-target stimuli, the two downward arrows in Fig. 1, *A* and *B*, have been placed at the same time, 110 ms after the onset of target motion.

For a given double-target motion, the direction and magnitude of the pursuit response varied considerably from trial-to-trial. We first quantified the variability by measuring horizontal and vertical eye velocity 250 ms after target motion onset for each target motion delivered during recording from each of our 64 neurons. Figure 2*A* shows an example of the data for target motions along the oblique axis for one recording session. The eye velocity evoked by single-target motions (black dots) grouped around $+10$ and $-10^\circ/\text{s}$, with no points plotting near zero velocity. The eye movement responses in the double-target trials (blue diamonds and red X's) lie along the regression line obtained for the responses to single-target trials, as would be expected if the pursuit response was a vector average of responses to the two target motions presented singly. However, the eye movement responses are not grouped tightly around zero, as would be expected if the monkey had delayed the initiation of pursuit for double-target stimuli. Since the monkeys received no cues about which of the targets would be extinguished after 200 ms, the double-target data were the same whether the animal ultimately was required to track the target moving in the preferred direction (red X's) or the opposite direction (blue diamonds). Note that the regression line for the responses to single-target stimuli (solid oblique line) has a slope that is less than one even though the horizontal and vertical speeds of the targets were the same. This common finding arises because the gain of the vertical component

is lower than that of the horizontal component for pursuit of target motion in oblique directions. With this observation in mind, we chose in the remainder of the paper to quantify the eye movement response by measuring the component eye velocity along the direction of eye movements evoked by single-target stimuli, rather than along the direction of target motion. When data pertain to neuronal responses, component eye velocity will be computed along the axis of the pursuit response for target motion in the preferred direction of the neuron under study. In subsequent figures and analyses, the positive values of component eye velocity denote eye movements in the preferred direction of the neuron under study.

The eye velocity evoked by double-target motions showed about the same breadth of distribution as did that for single-target motions. Figure 2*B* shows the normalized distribution of component eye velocity for the data shown in Fig. 2*A*. The distributions were normalized for each condition, filtered with a Gaussian function ($\sigma = 1^\circ$), and plotted with a resolution of $0.1^\circ/\text{s}$: each curve connects the points derived with this resolution. For the behavioral data summarized in Fig. 2*A*, the recorded neuron was active during pursuit to the left and down, which is indicated by the positive value of component eye velocity in Fig. 2*B*. The eye velocity evoked by double-target motions (red curve) distributed around zero eye velocity and had a mean that was centered between those evoked by each single target (thick black curves). However, the SDs of the distributions for the two single-target motions and the double-target motion were comparable and were different from that of eye velocity during fixation at the time of target motion onset (Fig. 2*B*, black dashed curve).

To quantify these findings, we plotted the SD of component eye velocity as a function of time. For the experiment shown in Fig. 2, *A* and *B*, the SD increased gradually after the initiation of pursuit (arrow in Fig. 2*C*) and followed the same values for single-target motions (black dashed trace) and double-target motions (red solid trace) out to almost 250 ms after the onset of target motion. At this time, the SD of the response to double-target motions becomes larger than that to single-target motions because one target or the other had already disappeared and the monkey began to generate eye acceleration alternately toward each of the two targets. Thus the variability of eye velocity shows similar time courses, although the magnitude of eye velocity was larger for the single-target motion and was minimal for the double-target motions. The same trend appeared in the averages of the time course of the SD of eye velocity for all 64 recording experiments (Fig. 2*D*). Again, the average value of the SDs followed the same trajectory for both single-target motions (black thick dashed trace) and double-target motions (red thick solid trace) for about 100 ms after the onset of pursuit.

The similar time course and amplitude of the SD of eye velocity in the single-target and double-target trials argues that the double-target trials activate the pursuit system but generate a small eye movement because of vector averaging. The data do not support the alternative view that activation of the pursuit system is delayed for double-target stimuli, since the SD of eye velocity is small when the pursuit system is inactive. The data from single trials in Fig. 2*A* emphasize the observation that averaging occurred in each individual trial and was not merely a property of average eye velocity. Thus our results were consistent with the previous studies showing that the eye movements during the initiation of pursuit for double-target motions without a cue are almost always averages of the responses to each component single-target motions (Ferrera 2000; Gardner and Lisberger 2001; Kahlon and Lisberger 1999; Lisberger and Ferrera 1997; Recanzone and Wurtz 1999).

Neuronal responses during averaging pursuit

The activity of 64 single neurons was examined in both single-target and double-target trials. Of these, 60 neurons showed statistically significant directional modulation during the initiation of pursuit, assessed by comparing the spike count during the interval from 90 to 250 ms after target motion onset for target motion in the preferred and opposite directions of the

neuron (2-tailed t -test, $P < 0.05$). Further analysis was performed on these 60 pursuit neurons that were grouped into 3 categories of neural responses based on the response magnitudes: averaging, winner-take-all, and summation.

Figure 3 illustrates three examples of the response profiles of pursuit neurons during averaging pursuit. For the neuron in Fig. 3A, the activity in the double-target trials was intermediate between the responses evoked by each target singly. The rasters for the single-target trials show that this neuron had a strong directional response, with early and strong firing during pursuit in its preferred direction and essentially no response during pursuit in the opposite direction. The spike density traces at the *bottom* of the *left column* show that the latency of the response to a single target in the preferred direction was about 100 ms, and that the responses in the preferred and opposite directions separated very early in the response (black traces). For the double-target trials, both the rasters and the spike density traces show that the activity was initially intermediate between the response to each target singly (red and blue traces). The initial responses to the two double-target stimuli are the same, as they should be since the visual stimulus and the oculomotor behavior were identical until one target disappeared after 200 ms of double-target motion (see Fig. 4). When the monkey began to track the remaining target, the neuronal activity either increased or decreased, depending on whether the remaining target moved in the preferred direction of the neuron (red trace) or the opposite direction (blue trace). Thus the response of the neuron illustrated in Fig. 3A showed averaging, as did the eye movements evoked by double-target stimuli.

For the neuron in Fig. 3B, the activity during the initial ~300 ms of double-target motion was similar to that evoked by a single-target moving in the preferred direction. This can be seen both by inspection of the rasters and in the spike density functions, where the responses for the double-target stimuli (red and blue traces) follow the same trajectory as that for single-target motion in the preferred direction (*top black trace*), as long as two targets are present. Other neurons showed a similar kind of response pattern during double-target stimuli, except that firing rate followed that evoked by a single-target in the direction opposite to the preferred direction. Again, after one target disappeared, firing rate increased or decreased to ultimately follow the trajectory of firing rate recording during tracking of the remaining target when it was presented in a single-target trial. For the neuron in Fig. 3C, the firing rate during averaging pursuit evoked by double-target stimuli was higher than that evoked by a single-target moving in either direction.

To quantify these data, we plotted the firing rate from individual trials in the interval from 90 to 250 ms after target motion onset as a function of component eye velocity measured at 250 ms after target motion onset. In Fig. 4A, for example, analysis of the neuron illustrated in Fig. 3A shows that both eye velocity and neuronal responses in the double-target trials (red and blue symbols) fell along the same relationship suggested by the responses evoked during tracking single-target motions at speeds of 5, 10, and 20°/s (small black symbols). Statistical analysis verified that the activity in the double-target trials was significantly different from that evoked by either of the component single-target motions in either direction (2-tailed t -test, $P < 0.0001$). Further, the activity in the double-target trials was higher than during fixation (horizontal dashed line) even when eye velocity was zero or in the direction opposite to the preferred direction of the neuron.

For the neuron illustrated in Fig. 3B, quantitative analysis showed that the activity during pursuit initiation in the double-target trials was not different from that in the single-target controls in the preferred direction (Fig. 4B, t -test, $P = 0.31$). Again, the responses in the individual double-target trials were consistently greater than the baseline firing (horizontal dashed line), even for the trials with zero eye velocity. Finally, for the neuron illustrated in Fig. 3C, quantitative analysis showed that the responses in the double-target trials were consistently

greater than those evoked by a single-target moving in the preferred direction (Fig. 4C, *t*-test, $P < 0.0001$).

To a first approximation, the responses in Fig. 4, A—C, could be characterized as vector averaging, winner-take-all, and vector summation, respectively. As quantitative criteria to assign each neuron to one of these three groups, we used a two-tailed *t*-test to compare the activity for the double-target trials with that for each of the component single-target trials. A slight majority of neurons (32 of 60, 53%) showed vector averaging: their responses were intermediate between those evoked by each target singly, and were statistically different from the responses to single-target motions in both the preferred and the opposite directions ($P < 0.05$). Twenty-two neurons (37%) were characterized as winner-take-all: 15 showed responses that were not statistically different from those to single-target motion in the preferred direction, while 7 had responses that were not different from those to single-target motions in the opposite direction. Finally, six neurons (10%) showed behavior characterized as vector-summation: their responses were significantly greater than those obtained from single-target trials in the preferred direction.

To summarize the data obtained from 60 pursuit neurons that were directional and were tested in these paradigms, we computed the weight of averaging in each individual double-target trial for both the component eye velocity along the preferred axis measured 250 ms after target motion onset and the neuronal responses measured from 90–250 ms after target motion onset. The weight of averaging was obtained by the equation

$$D_i = w_i \bar{S}_{\text{pref}} + (1 - w_i) \bar{S}_{\text{opp}} \quad (1)$$

where D_i represents data for the *i*th individual double-target trial, and $\bar{S}_{\text{pref}}$ and $\bar{S}_{\text{opp}}$ are the means of the responses to a single-target moving in the preferred and the opposite directions, respectively. If the response in a double-target trial were a weighted vector average of the responses to individual targets, then the weight w_i would be between 0 and 1, with perfect averaging represented when w_i was 0.5. If the response in a double-target trial were the same as or greater than the mean of the responses evoked by a single-target in the preferred direction, then w_i would be equal to or greater than 1. If the response in a double-target trial were the same as or less than the response evoked by a single-target in the opposite direction, then w_i would be equal to or less than 0.

We conducted both a trial-by-trial and a neuron-by-neuron analysis. In the trial-by-trial analysis, the response in each double-target trial for each neuron was plotted as a separate point (Fig. 5A). The weight of averaging for both the eye movements and the neuronal activity are plotted in Fig. 5A, which includes data from 1,656 double-target trials recorded in 60 neurons. On the eye movement axis, essentially all the trials plotted at weights between 0 and 1 and 93% plotted with $0.2 \leq w_i \leq 0.8$, an arbitrary criterion that we will use to define “averaging.” On the firing rate axis, 49% of the trials plotted within the range we considered to be averaging, 15% had weights less than 0.2 indicating winner-take-all behavior for target motion in the nonpreferred direction, 21% had weights between 0.8 and 1.2 indicating winner-take-all behavior for target motion in the preferred direction, and 16% had weights greater than 1.2 indicating vector summation. A small number of trials ($n = 46$, 4.8% of 1,702) were excluded because they would have plotted outside the range of the axes in Fig. 5A. Trials that had the same weight for both eye velocity and firing rate would have plotted along the dashed line connecting the large squares used to denote the responses in single-target trials: the filled and open squares indicate eye and neuronal responses to single target motion in the preferred and opposite directions, respectively.

The neuron-by-neuron analysis (Fig. 5B) obscured a lot of the variability inherent in the trial-by-trial analysis, but allowed us to compare the graphical analysis of weights with the systematic statistical evaluation of the nature of the neuronal responses reported above. To obtain the data plotted in Fig. 5B, we have combined the responses in double-target trials where each of the two different targets disappeared and computed the weights of eye velocity and firing rate across all trials. The neurons characterized by statistical analysis as showing vector-averaging behavior (filled circles) plot between the responses to each target alone (large squares). The neurons characterized by statistical analysis as showing winner-take-all behavior (open circles) plotted either with neuronal weights near one, indicating similarity with the neural responses to target motion in the preferred direction (filled large square) or with neuronal weights near zero, indicating similarity with the neural responses to target motion in the opposite direction (open large square). Finally, the six neurons characterized by statistical analysis as showing vector-summation behavior plotted with neuronal weights greater than one (filled triangles), indicating responses that were significantly greater than those obtained from single-target trials in the preferred direction. The data from one of the latter six neurons has been omitted since its neuronal weight fell outside the range plotted in Fig. 5B. The distribution of the weight of neuronal activity can be appreciated in the histogram shown in Fig. 5C, where the numbers of neurons were plotted as bars with different filling depending on whether the response in double-target trials was statistically different from that for both component single-target motions (filled bars), or was not different from the response to one of the single-target motions (open bars).

Alteration of averaging pursuit by electrical microstimulation in the FPA

We next examined how altering the output from FPA modulates averaging in the initiation of pursuit. We applied electrical microstimulation through recording electrodes while monkeys performed the same double-target tasks used above for the unit recording experiments. After a site had been located, we determined the direction of the smooth eye movements evoked by stimulation during fixation at 333 Hz for 75 ms. We then customized a set of trials to present target motion along this preferred axis, and sometimes along the orthogonal axis. A 200-ms duration train of stimulation pulses at either 100 Hz ($n = 12$ sites) or 200 Hz ($n = 32$ sites) was delivered starting at the onset of target motion in half of the trials, which were interleaved randomly with trials that presented identical target motion without stimulation.

Figure 6, A–D, illustrates the time course of eye velocity in single-target trials (A and C) and double-target trials (B and D) for targets that appeared 4° eccentric along the horizontal axis and moved toward the position of initial fixation at $20^\circ/\text{s}$. Stimulation at this site in the right FPA with the low-frequency pulse train evoked small rightward eye movements ($1.8^\circ/\text{s}$, arrows in Fig. 6, A and B) during fixation of a stationary target (dotted traces). The responses to single-target motions to the right and left were superimposed on the response to stimulation alone (Fig. 6A). For all further analysis, we isolated the responses to target motion from the direct effects of electrical stimulation by computing the millisecond-by-millisecond difference: eye velocity evoked by target motion in the presence of stimulation minus eye velocity evoked by stimulation during fixation. In single-target trials (Fig. 6C), comparison of the corrected eye velocity during stimulation (continuous traces) and the initiation of pursuit without stimulation (dashed traces) shows that stimulation enhanced the initiation of pursuit somewhat for target motion in the direction of stimulation-evoked eye movements during fixation (rightward), and less so for target motion in the opposite direction, in agreement with our previous study (Tanaka and Lisberger 2002a). The stimulation changed the latency of pursuit only slightly for single-target motions. We used the same analysis procedures in double-target trials (Fig. 6D), revealing that the eye velocity evoked by double-target motion during stimulation (continuous traces) appears to have a shorter latency relative to that evoked in the absence of stimulation

(dashed traces). However, the appearance of a shortening of latency probably results from the use of averaged traces in this figure, and not from a real shortening of latency (see discussion).

Figure 6, *E* and *F*, shows intertrial variation of the data in Fig. 6, *A–D*, plotting vertical and horizontal eye velocity from individual trials 180 ms after target motion onset. Since we used rightward and leftward target motions for experiments done in this site, the data lie nearly along the horizontal axis in Fig. 6*E*. For single-target trials (Fig. 6*E*), responses were enhanced by stimulation for target motion to the right (red X's) relative to those without stimulation (blue filled circles), but not for target motion to the left (red plus signs). For double-target trials (Fig. 6*F*), responses were shifted to the right during microstimulation (red X's) relative to those in the absence of stimulation (blue filled circles). For further analyses, we computed component eye velocity along the axis of eye movement responses to single-target motions, obtained by fitting a regression line to the data from single-target trials in the absence of stimulation (Fig. 6*E*, blue symbols).

We now use the responses to single- and double-target stimuli in the presence and absence of microstimulation to assess the relative locations of gain control and vector averaging. We use a modeling framework similar to that used previously to examine the relative locations of averaging and learning (Kahlon and Lisberger 1999). Figure 7 illustrates three alternative models we considered. *Model 1* predicts that vector averaging occurs downstream from gain control. *Model 2* predicts that the gain control is used to regulate the weight of averaging. *Model 3* places the site of vector averaging up-stream from that of gain control. The equations for the models and the analysis are described in detail in the APPENDIX. In other words, our approach was to take each combination of actual responses to the two single targets that composed a double-target motion, apply the equations for each model to those responses, and plot three predictions of the distributions of the responses to the double-target motion with electrical stimulation, one for each model.

For comparison with the predictions of the three models, we assembled the normalized distribution of component eye velocity for double-target and single-target motion with and without microstimulation, filtered each distribution by convolving with a Gaussian ($\sigma = 1^\circ/\text{s}$), and plotted it with a resolution of $0.1^\circ/\text{s}$. Inspection of the smooth distributions illustrated in Fig. 8, *A* and *B*, for trials without and with electrical stimulation confirms the impression given by the data in Fig. 6. Microstimulation caused a rightward shift in the distributions of the responses to rightward single-target motion (black curves on the *right* of Fig. 8, *A* and *B*) and to double-target motions (colored traces), while the responses to leftward single-target motion were little changed (black curves on the *left*). Comparison of the distribution of responses to double-target trials during microstimulation with those predicted by the three models revealed that *Model 1* predicted the data best for the stimulation site analyzed in Fig. 8. In Fig. 8*C*, the prediction of *Model 1* (bold, black curve) lies almost perfectly over the distribution computed from the data (red curve), while the predictions of *Models 2* and *3* are quite different. The error of each model's prediction was computed as the absolute area between the distribution from the data and that predicted by the model. In Fig. 8*C*, the prediction errors were 0.10, 0.24, and 0.48 for *Models 1–3*, respectively.

At 30 of the 34 sites we tested, microstimulation caused statistically significant changes ($P < 0.05$, 2-tailed *t*-test) in the eye velocity measured 180 ms after target motion onset in single-target trials. The data from the remaining four sites were excluded from further analysis. For the 30 sites we analyzed, Fig. 9*A* compares the prediction errors of the 3 models, based on measurements of eye velocity 180 ms after target motion onset. The distance of each data point from each model's side of the triangle corresponds to the size of the prediction error for that model. Thus points plot in the section of the graph corresponding to the model that best predicts the data from that site. Almost all of the sites plot in the section indicating that *Model 1* predicts

the data best. Statistical analysis excluded *Model 3*, in which the vector averaging occurs upstream from gain control. However, a post hoc comparison of the ANOVA failed to reveal a significant difference in the prediction errors of *Models 1* and 2 [Fisher's protected least significant difference (PLSD), $P = 0.053$].

We chose to analyze eye movement 180 ms after the onset of target motion because this represents the end of the "open-loop" interval, which is the period before eye movements begin to be altered by visual feedback subsequent to the initiation of pursuit. Analysis of the prediction errors in 5-ms bins in the interval from 120 to 250 ms after the onset of target motion (Fig. 9B) reveals, however, a similar picture. *Model 1* provides as good a prediction as the other models in all the bins, and a better prediction in most bins. *Models 1* and 2 provide comparable predictions late in the analysis interval, while *Model 3* predicts the actual data as well as *Model 1* only at the start and end of the analysis interval. Importantly, *Model 1* provides a better fit to the data than the other two models throughout the open-loop interval, which terminates at the vertical dashed line 180 ms after the onset of target motion.

We obtained an independent test of the three models by analyzing the effect of microstimulation in the FPA on the responses to double-target stimuli that presented motion in orthogonal directions. Plotting vertical eye velocity as a function of horizontal eye velocity for individual control trials without stimulation (Fig. 10A) reveals data that are consistent with previous studies (Ferrera 2000; Gardner and Lisberger 2001; Lisberger and Ferrera 1997). The responses to double-target stimuli (red symbols) plot between the responses to the component single-target stimuli (blue symbols), as expected if they arose from vector averaging of the responses to the two component target motions singly. The picture was similar in trials with stimulation at the onset of target motion (Fig. 10B): the basic phenomenon of vector averaging remained, but the amplitudes of the responses and the variability were increased. To show the alteration of the responses to target motions more clearly, Fig. 10C plots means of the responses in 16 conditions: 4 single-target trials (blue symbols) and 4 double-target trials with orthogonal motion (red symbols), each with (filled symbols) and without (open symbols) microstimulation. The stimulation applied in this site enhanced pursuit to the right, up, and left irrespective of number of targets presented.

To determine which model predicted the responses in double-target trials most closely, we used the equations described in the APPENDIX to predict the distributions of the double-target responses based on individual single-target responses. Then we computed the prediction error for each model as the distance between the mean of the prediction of the models and the mean of the actual data. Figure 10D plots the prediction errors for the site illustrated in Fig. 10, using different line weights to show the errors for each of the four double-target trials (dashed lines) and their means (filled symbols connected by continuous lines). *Model 1* predicted the data most accurately. For all 10 stimulation sites, the means $\pm$ SD of the prediction errors were 0.72 ± 0.16 , 1.65 ± 0.56 , and $1.20 \pm 0.39^\circ/\text{s}$ for *Models 1–3*, respectively. One-way factorial ANOVA and a post hoc comparison showed that the prediction errors for *Model 1* were statistically smaller than those from the other models [$F_{(2,27)} = 12.9$, $P < 0.001$, Fisher's PLSD, $P < 0.05$]. Thus stimulation of the FPA modulates the gain of pursuit at a site or sites that are upstream from vector averaging for double-target stimuli.

DISCUSSION

We have analyzed the responses of neurons in the FPA during the vector-averaging pursuit induced by double-target motions: many neurons discharge in relation to the averaged eye movement. Their responses suggest that many (but not all) of the neurons in the FPA are downstream from the site of vector averaging, so that the FPA either receives inputs from, or is, the site of averaging. We also have analyzed the effect of microstimulation in the FPA on

the eye movements evoked by double-target motions and concluded that the site of vector averaging is downstream from the site of gain control. Since the FPA itself seems to be upstream from the site of gain control (Tanaka and Lisberger 2001, 2002a), this raises the paradox that neuronal recordings place the FPA downstream from vector averaging, while microstimulation places the FPA upstream from vector averaging. In our discussion, we will propose a model of pursuit processing that can account for our data. We postulate that the FPA projects, possibly indirectly, to the site of vector averaging, but that it is part of a cerebrocerebellar feedback loop and receives feedback about the motor commands sent to the brain stem oculomotor system.

Vector averaging pursuit for targets moving in opposite directions

Much of our data are based on a double-target configuration that provides two targets moving in the opposite directions. Prior reports have left some uncertainty about whether this paradigm produces averaging pursuit with some examples where the averaging is perfect and eye velocity remains close to zero (Lisberger and Ferrera 1997; Recanzone and Wurtz 1999), or if it delays the initiation of pursuit in some or all trials (Ferrera and Lisberger 1995; Krauzlis et al. 1999; Recanzone and Wurtz 1999). Analysis of averages of eye velocity across multiple trials would not resolve this issue, because average eye velocity could be zero even if individual trials were nonzero but were balanced in terms of the direction and amplitude of eye velocity. For example, the use of averaged data in Fig. 6D of the present paper gives the possibly misleading impression that the latency is longer for double-target trials without microstimulation than for single-target trials. Ferrera (2000) has provided reason to believe a priori that our double-target paradigms would elicit averaging pursuit, rather than delaying the initiation of pursuit. His analysis suggests that delays do not occur in conditions like ours, where monkeys were not cued about which target to track and the early part of the trials did not provide any information about which target would remain as the rewarded tracking target.

Our paper adds four observations suggesting that vector averaging is responsible for the responses to our double-target stimuli, even though it produced zero eye velocity in some examples. First, microstimulation had similar effects on the eye movements evoked by double-target stimuli for conditions that provided either orthogonal or same-axis motions. We think that vector-averaging mechanisms apply to both target configurations, since previous experiments have demonstrated that orthogonal double-target stimuli causes vector-averaging pursuit without a change in pursuit latency (Ferrera 2000; Gardner and Lisberger 2001; Kahlon and Lisberger 1999; Lisberger and Ferrera 1997). Second, the initial eye velocity in the double-target paradigm with same-axis stimuli has SDs that are almost as large as those for single-target stimuli and that are considerably larger than those during fixation at the onset of target motion. This implies that the responses to double-target stimuli represent attempts at pursuit, and not fixation. Third, the distribution of responses to same-axis double-target stimuli was smooth. We think this makes it unlikely that the zero velocity responses represent delayed pursuit initiation, while the nonzero eye velocity responses were the consequences of unevenly weighted vector averaging of oppositely directed responses. Finally, the activity of FPA pursuit neurons during zero velocity trials was consistently higher than during fixation, indicating that the pursuit system is active in some sense during in these trials. We therefore conclude that the zero and nonzero eye velocity responses observed in individual trials resulted from averaging of pursuit signals evoked by individual moving targets, even in our double-target paradigms with motion in opposite directions.

Location of the FPA in the pursuit system

Figure 11 suggests a flow of signals that would be consistent with our data. The pursuit system contains separate pathways from the parietal and frontal cortex, respectively, to the brain stem and cerebellar oculomotor system. The diagram in Fig. 11 suggests that the parieto-ponto-cerebellar circuits transmit the visual drive for pursuit, which is averaged quite far down-stream

in the system, while the fronto-ponto-cerebellar circuits are used primarily for gain control. The hypothesis of a separation of function into visual-motor drive and gain control has been suggested by many of our recent behavioral experiments on pursuit eye movements (Churchland and Lisberger 2000; Goldreich et al. 1992; Grasse and Lisberger 1992; Schwartz and Lisberger 1994) and is broadly consistent with the finding that stimulation of the FPA enhances the gain of pursuit (Tanaka and Lisberger 2001, 2002a). The placement of vector averaging quite far downstream allows the model to be consistent with the microstimulation data in the present paper, which implies that vector averaging is downstream from the site of gain control. It is also consistent with earlier data equating pursuit learning with gain control and showing that averaging is downstream from learning (Kahlon and Lisberger 1996, 1999).

Our conclusions about the relative sites of vector averaging and other features of the pursuit system raise one question about the location(s) of vector averaging that cannot be answered definitively by available data. We are proposing that vector averaging for double-target stimuli occurs quite late in the sensory-motor processing for pursuit, possibly as deep into the system as the cerebellum. In an earlier report showing that vector averaging is downstream from the site of learning, Kahlon and Lisberger (1999) proposed that the brain creates two commands for the movements required to track each of the targets in a double-target stimuli, and that vector averaging is performed on those commands. The idea that the two individual target motions are represented in the pursuit system downstream from MT is supported by data in the present paper showing that the firing of some FPA neurons during averaging pursuit was indistinguishable from that during pursuit of one of the component single-target motions.

One might draw very different conclusions from experiments suggesting that a vector-averaging computation is used to decode local motion signals from the population responses in area MT (Churchland and Lisberger 2001; Groh et al. 1997). These studies have implied that vector averaging occurs at the immediate outputs from MT. To resolve the apparent discrepancy as to the location of vector averaging, we postulate that there are at least two sites of vector averaging in pursuit, as suggested previously (Kahlon and Lisberger 1999). One site would be at or near the output from MT and would convert the local population responses into signals related to the velocity of single targets. This “local vector averaging” would operate on a spatial scale that is small enough to create two separate commands for the two targets in a double-target stimulus used in this study. The other site would be downstream in the system, after the sites of gain control and learning, and possibly after the motor commands to track each of the individual targets have been created, as suggested by the present study and the earlier report (Kahlon and Lisberger 1999).

In keeping with the known anatomy of the circuit, the model in Fig. 11 includes connections between the frontal and parietal parts of the pursuit system. The presence of inputs from the parietal areas (MT and/or MST) to the FPA would provide a substrate for our finding of some neurons that show either winner-take-all or vector summation behavior during vector-averaging pursuit, since neurons in both MT and MST show winner-take-all behavior in double-target trials (Ferrera and Lisberger 1997). Finally, the model suggests that the frontal pursuit area receives feedback about the command for smooth eye velocity from a site that is downstream from vector averaging. Recurrent input to the FPA would allow the discharge of many neurons in the FPA to reflect the vector-averaging eye velocity, as we have found. Feedback signals encoding smooth eye velocity could be extended easily to vestibular signals to create a signal related to gaze velocity, which has been found in the FPA (Fukushima et al. 2000) as well as many other pursuit areas in the brain (Kawano et al. 1984; Lisberger and Fuchs 1978).

Parallel pursuit processing through the parietal and frontal cortices

Interpretation of our data in terms of the model in Fig. 11 relies on the hypothesis that the visual-motor drive occurs in the parieto-ponto-cerebellar circuits while gain control arises from the frontal cortex. For example, our interpretation of the effects of microstimulation of the FPA on vector-averaging pursuit is based on analysis of the three models in Fig. 7. If the separation into two parallel circuits with different functions is valid, then our three models represent all possibilities for the relative order of the sites of vector averaging and of gain control from the FPA. The anatomy of the cortical circuits for pursuit supports the existence of parallel pathways, since the parietal pursuit areas, MT and MST, project to the pons and cerebellum in parallel with the frontal pursuit area. Further, our earlier microstimulation reports (Tanaka and Lisberger 2001,2002a) imply that the output of the FPA has the special function of regulating the internal gain of pursuit, rather than serving simply as a relay for commands about the direction and speed of the desired smooth eye movement. The fact that the response to a brief perturbation of target motion is enhanced by concurrent stimulation of the FPA argues that the visual-motor processing occurs in a parallel pathway, since one might expect stimulation within the visual-motor pathway to suppress and supplant the concurrent visual signals rather than enhancing them. Indeed, microstimulation in MST seems to produce the latter result (Komatsu and Wurtz 1989).

The models in Fig. 7 cannot be used to interpret our microstimulation data if visual-motor processing occurs in a single stream that passes through the FPA. They do not deal effectively with this architecture because of the likelihood that there is feedback to the FPA from the cerebellar outputs. If the feedback operated with delays long enough so that our measurements effectively opened the feedback loop, then our models might be valid. However, our finding that vector averaging is represented in the responses of neurons in the FPA during the initiation of pursuit argues that feedback occurs very quickly. In a feedback circuit with short delays, it is probably incorrect to discuss signal flow in terms of “upstream” or “downstream,” since any one site would be both upstream and downstream of all other sites. Dynamic models would be required to assess this situation, but will require considerable additional information before reasonable simulations could be designed. For the time being, our conclusions are based on the seemingly valid assumption that the FPA is part of a frontal circuit that runs in parallel with the parieto-ponto-cerebellar circuit for visual-motor processing (e.g., Yamada et al. 1996), and that the output of the FPA converges with that of the visual-motor processing circuit at site(s) where the FPA controls the internal gain of pursuit.

Recurrent pathways through the frontal pursuit area

The inclusion of ascending pathways in Fig. 11 is not novel in terms of the anatomy of pursuit (Keller and Heinen 1991; Leigh and Zee 1991) and provides an element that draws attention to the similarities in the anatomy of the oculomotor systems and of somatic motor systems (Middleton and Strick 2000). For the pursuit system, recent evidence indicates a strong anatomical relationship between the FPA and subcortical structures. The FPA receives inputs from thalamic nuclei that relay signals from the basal ganglia and the cerebellum (Tian and Lynch 1997). The outputs from the FPA to the pons are present, but weaker than the outputs to the striatum (Cui et al. 2000), where increased regional blood flow has been observed during pursuit (O'Driscoll et al. 2000). In contrast, MT and MST have a strong anatomical relationship to the pons and appear to be part of the traditional cortico-ponto-cerebellar circuits. Thus the frontal and parietal components of the pursuit system may correspond to the separate cerebellar and basal ganglia circuits that also feature prominently in thinking about the operation of the somatic motor parts of the brain (for review, see Middleton and Strick 2000). Recurrent circuits have been known anatomically for many years, but their physiological functions remain unknown. The anatomical parallels between the two cortical components of the smooth pursuit system and the somatic motor system raises the hope that an understanding of the different

functions of the parietal and frontal cortex in pursuit may shed important light on the general issue of differences in the function of the recurrent cortical circuits through the cerebellum and basal ganglia.

Possible functions of eye velocity feedback through the FPA

Recurrent connections from the cortex through the cerebellum and/or basal ganglia and back to the cortex add a new element to models of the physiological function of pursuit, and they raise anew an old question: what is the function of the information transmitted through recurrent connections? A traditional answer arises from the widely accepted view that the pursuit system contains positive feedback circuitry that functions as “velocity memory” to maintain pursuit in the absence of image velocity (e.g., Goldreich et al. 1992; Krauzlis and Lisberger 1994; Robinson 1971). It has also been suggested that the gain control element of the pursuit system may be located at least partly within this feedback circuitry (Krauzlis and Lisberger 1994; Krauzlis and Miles 1996; Robinson et al. 1986; Tanaka and Lisberger 2002a). The neuronal circuit that mediates velocity memory seems likely to involve the cerebellum (Stone and Lisberger 1990), but the finding of eye velocity signals in the cerebral cortex (Gottlieb et al. 1994; Heinen 1995; Newsome et al. 1988; Sakata et al. 1983; Tanaka and Fukushima 1998) has raised the possibility that eye velocity memory is one function of recurrent connections between the cortex and the cerebellum and/or the basal ganglia (Tian and Lynch 1997). Our data neither confirm nor reject this possibility.

We propose a different view related to our findings that 1) control of its internal gain is an important feature of pursuit behavior and 2) the output of the FPA can control pursuit gain. We and others have suggested before that the visual-motor processing for pursuit has different states, and that the pursuit system is “off” during fixation and “on” to varying degrees during pursuit (Luebke and Robinson 1988), depending on the speed of target motion (Schwartz and Lisberger 1994). It seems plausible that the primary stimulus to increase the internal gain of pursuit would be retinal image motion. However, a system that relies entirely on retinal image motion would return to a low internal gain during accurate tracking of even a fast moving target because the velocity of target images is minimal during the maintenance of pursuit. Thus it would seem reasonable to use a combination of visual motion and eye motion inputs to control the internal gain of pursuit (e.g., Keating and Pierre 1996; Schwartz and Lisberger 1994). Since the output of the FPA controls pursuit gain, we propose that the recurrent eye velocity input keeps pursuit gain appropriate for the speed of target motion, even when image motion is small during accurate pursuit. The function we are suggesting is subtly different from that previously suggested for eye velocity feed-back through the cerebellum, but it has the same basic purpose, which is to maintain excellent tracking in the face of small retinal image motion.

Vector averaging, gain control, and target selection

Our experimental paradigms analyzed averaging pursuit that occurs before the pursuit system chooses a target. However, other research in our laboratory has suggested that gain control may be a component of target choice (Gardner and Lisberger 2001), and target choice should occur at the site of gain control, which we have suggested is upstream from vector averaging. This makes theoretical sense. Vector averaging for double-target motions should occur downstream from target choice, because target choice must have access to the information about each target; it would be impossible to reconstruct individual target motions from signals that are already averaged. Thus a consistent picture of the organization of the pursuit system is emerging from our research. The parieto-ponto-cerebellar pathways provide visual-motor drive for pursuit while the fronto-ponto-cerebellar pathways provide gain control and possibly target choice. Gain control, learning, and target choice seem to occur upstream of vector averaging for double-target motions. There are multiple recurrent circuits in the pursuit system,

and they use eye velocity feedback in different ways to maintain pursuit even when tracking is so accurate that image motion signals are small and unreliable.

APPENDIX

We compared the eye movement responses in the double-target trials in the presence of electrical microstimulation with the predictions derived from three different models described in Fig. 7, using similar equations employed by previous study that tested the relative locations of vector averaging and pursuit learning (Kahlon and Lisberger 1999). Predictions were based on the responses to target motion that have been isolated by subtracting the response to microstimulation during fixation (see RESULTS). The following sets of data are given: A_{cont} , responses to a single target moving in the direction A ; B_{cont} , responses to a single target moving in the direction B ; AB_{cont} , responses to two targets moving in the directions A and B ; A_{stim} , responses to a single target in the direction A in the presence of stimulation; B_{stim} , responses to a single target in the direction B in the presence of stimulation; and AB_{stim} , responses to two targets in the presence of stimulation.

For experiments that used two targets moving in opposite directions, the values of the A 's and B 's were component eye velocity along the axis of eye movements evoked by single-target motion in the absence of stimulation (Fig. 8 and Fig. 9). For experiments that used two targets moving in orthogonal directions, the values of the A 's and B 's were the horizontal and vertical components of eye velocity (Fig. 10). For each double-target stimulus in each experiment, we used the following equations to solve the weight of averaging in the nonstimulation control trials (w) and the gain changes caused by stimulation in single-target trials (g_A and g_B), given the mean values of eye velocity for both single- and double-target stimuli

$$\overline{AB}_{cont} = w\overline{A}_{cont} + (1 - w)\overline{B}_{cont} \quad (A1)$$

$$\overline{A}_{stim} = g_A \overline{A}_{cont} \quad (A2)$$

$$\overline{B}_{stim} = g_B \overline{B}_{cont} \quad (A3)$$

We then attempted to predict the distribution of AB_{stim} based on three models. To test the models, we used each combination of the sample distributions for each single-target motion to predict the response to the relevant double-target motion. Thus each equation attempts to predict the ij th response for the i th sample of one target motion and the j th sample of the other: if we obtained n and m trials of the two single-target motions, this yielded a predicted distribution based on $n \times m$ inputs to the model.

Model 1 placed vector averaging downstream from gain control

$$AB_{stim_{ij}} = wA_{stim_i} + (1 - w)B_{stim_j} \quad (A4)$$

Model 2 equates gain control with the weight used for vector averaging

$$AB_{stim_{ij}} = \frac{wA_{stim_i} + (1 - w) B_{stim_j}}{wg_A + (1 - w) g_B} \quad (A5)$$

Model 3 placed gain control downstream from vector averaging

$$AB_{stim} = g_A AB_{cont_A} \quad (A6)$$

where A represents the direction of the response, AB_{cont} is an interpolated estimate of what the control response to double-target motion would have been if the response had been in direction A , and g_A is an interpolated estimate of the effect stimulation of the FPA would have had on the single-target response if the response had been in direction A . We had to use estimates for intermediate directions because we did not measure the gain of pursuit in the intermediate direction between two orthogonal target motions. We interpolated under the assumption that the gain of the responses in the intermediate direction would be the weighted average of the gains in the orthogonal directions. To make predictions for *Model 3* for experiments that used double targets moving in orthogonal directions, we made our predictions by drawing samples from the distribution of averaging weights from the control responses to double-target stimuli. Thus the prediction of *Model 3* was

$$AB_{stim} = [u_i g_A + (1 - u_i) g_B] AB_{cont_i} \quad (A7)$$

where u_i indicates the weight of averaging calculated from i th trial of AB_{cont} .

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FIG. 1.

Time course of pursuit initiation for single-target motions (A) and in double-target motions (B). In each panel, the *top traces* show superimposed horizontal eye and target position, and the *bottom traces* show eye and target velocity. For the double-target motion shown in B, the trajectory of the target that disappeared after 200 ms is shown by dashed traces. The upward arrow in B indicates the occurrence of a catch-up saccade, observed commonly in the responses to double-target motions but rarely in those to single-target motions. The downward arrows in A and B are placed 110 ms after target motion onset to emphasize the similarity of pursuit latencies for single-target and double-target motions. Upward deflection of the traces indicate rightward motion.

FIG. 2.

Summary of the variability of eye velocity during single-target and double-target motions. **A:** each point plots data from a single trial according to the horizontal and vertical eye velocity measured 250 ms after target motion onset. Black symbols show data from single-target motions. The red and blue symbols indicate responses to double-target motion, with the final target motion in the preferred or opposite direction for the neuron under study, respectively. The oblique line was computed by linear regression on the data from single-target motions. **B:** smoothed histograms showing the normalized distribution of component eye velocity along the preferred axis of the neuron under study. Thick black curves show the normalized distributions of measurements made 250 ms after the onset of target motion for single-target motions and the red curve shows the distribution of the same measure for double-target motions. The black dashed curve shows the smoothed distribution of eye velocity measured at the onset of target motion for all trials. Each curve connects values derived in $0.1^\circ/\text{s}$ bins. **C:** the 2 traces show the time course of the SD of component eye velocity. Black dashed and red solid traces show data for single-target and double-target motions, respectively. The downward arrow indicates the time of the initiation of pursuit for single-target motions. **D:** bold traces show averages of the SD of component eye velocity across multiple experiments. Averages were aligned on the initiation of pursuit. Black dashed and red solid traces show data from single-target and double-target motions, respectively. The fine, dashed traces show the mean $\pm$ SD of the SDs, and indicate interexperimental variation.

FIG. 3.

Examples of the responses during double-target and single-target motions for neurons from the 3 major groups in our sample. *A*: vector-averaging neuron. *B*: winner-take-all neuron. *C*: vector-summation neuron. In each column, the rasters are sorted and grouped by 4 different target conditions. From *top* to *bottom* the groups show the following: double-target motion with the final tracking target motion in the preferred direction of the neuron under study; double target motion with the final tracking target motion in the opposite direction; single-target motion in the preferred direction; single target motion in the opposite direction. The curves at the *bottom of each column* plot the time course of spike density for each condition. The red and blue traces indicate responses to double-target motion, with the final target motion in the preferred or opposite direction for the neuron under study, respectively. The black traces summarize responses from single-target controls. The data are aligned on target motion onset, which is indicated by the vertical lines.

FIG. 4.

Quantitative analysis of the responses during double-target and single-target motions for neurons from the 3 major groups in our sample. *A*: vector-averaging neuron. *B*: winner-take-all neuron. *C*: vector-summation neuron. The time courses of the neuronal responses for these neurons are shown in Fig. 3. Each point plots data from one trial and shows firing rate as a function of component eye velocity along the preferred axis of the neuron under study, respectively. The neuronal responses were measured from 90–250 ms after target motion onset. Eye velocity was measured 250 ms after target motion onset. Black circles show responses to single-target motions at 5, 10, and 20°/s. Large open circles with error bars show the mean and SD of the responses to each target velocity. Colored symbols show data from double-target trials with both targets moving at 20°/s. Red and blue symbols show responses when the final tracking target moved in the preferred or the opposite direction for the neuron under study. The horizontal dashed line in each panel shows mean baseline firing rate measured in a 300-ms interval immediately before target motion onset.

FIG. 5.

Summary of the weights of neural and behavioral averaging for our sample of frontal pursuit area (FPA) neurons. *A* and *B*: scatter plots of the neuronal weight vs. eye movement weight. In *A*, each small point shows data from a single trial. In *B*, each small symbol shows averages from an individual FPA neuron. The filled symbols indicate the cells whose activity during double-target motions was statistically different from that during single-target control in both directions (t -test, $P < 0.05$). The open circles indicate neurons whose activity was the same during double-target motion as during 1 of the 2 component single-target motions. The filled triangles indicate neurons whose activity was statistically larger during double-target motion than during either of the 2 single-target motions. The large filled and open squares in *A* and *B* indicate the averaging weights of 1 and 0 that are the values for single-target motion in the cell's preferred or opposite direction. One outlier point ([0.69, 2.12]) has been omitted from *B*. *C*: distribution of the weight of averaging for neuronal activity. The histogram indicates the number of neurons with responses during double-target motions that were statistically different from those during both component single-target motions (filled bars), or were not different from the responses during at least 1 of the single-target motions (open bars). The bars with different fillings are stacked. The 2 horizontal arrows indicate the values of 1 and 0, which would obtain when the activity for double-target motions was same as for single-target motions.

FIG. 6.

Data from a single site showing the effect of microstimulation in the FPA on the responses to single-target (*A*, *C*, and *E*) and double-target (*B*, *D*, and *F*) motions. *A–D*: averages of eye velocity showing the time courses of pursuit initiation. *A* and *B* show the actual responses. Solid traces show the responses to target motion during electrical stimulation, and the dotted trace shows the response to electrical stimulation during fixation. The arrow indicates the small eye movement evoked by electrical stimulation. *C* and *D* show the corrected responses after subtraction of the response to stimulation during fixation. Continuous traces show the responses to target motion presented during stimulation, and the dashed traces show the responses to target motion in the absence of stimulation. The black bars on the horizontal scale show the time of electrical stimulation. *E* and *F*: each point shows measurements from a single trial and plots vertical vs. horizontal eye velocity measured 180 ms after target motion onset in single-target trials (*E*) and in double-target trials (*F*). The blue symbols show data from nonstimulation controls, and the red symbols show data from stimulation trials. The continuous, slightly oblique lines are the same in *E* and *F* and were obtained by linear regression on the blue points in *E*.

Model #1 *Model #2* *Model #3* **FIG. 7.**

Diagrams showing 3 models that represent the possible relative locations of vector-averaging and gain control. *Model 1* places the gain control upstream from averaging. In *Model 2*, the gain control is used to change the weight used for vector-averaging. *Model 3* places the gain control downstream from averaging. Note that each model situates the FPA within a pathway that runs in parallel to those that transform visual motion into eye velocity.

Normalized distribution

FIG. 8.

Quantitative comparison of the predictions of each model with the actual distribution of responses to double-target motions for one stimulation site. *A* and *B*: smoothed distributions of the responses to target motion in nonstimulation controls (*A*) and stimulation trials (*B*). Each curve shows the normalized distribution of eye velocity along the axis of eye movements evoked by target motion in the control trials. Each curve connects the values for the data grouped into $0.1^\circ/\text{s}$ bins. Black and colored curves show data from single-target and double-target trials. *C*: the red curve is identical to that in *D* and shows the distribution of eye velocity during averaging of pursuit with electrical stimulation. The 3 black curves show the normalized

distributions predicted by the 3 models. Continuous, dashed, and dotted curves were obtained from *Models 1, 2, and 3*, respectively.

FIG. 9.

Comparison of the prediction error for the 3 different models. *A*: errors from predictions based on measurements of eye velocity 180 ms after target motion onset. Each point shows data from one stimulation site and plots at a distance from each side of the triangle corresponding to the size of the prediction error for the model that corresponds to that side. Dashed lines indicate locations in the graph that correspond to equal prediction errors from 2 of the models, and the point of intersection of the 3 dashed lines indicates equal prediction error for all 3 models. *B*: each set of connected points plots the time course of prediction errors for one of the models, averaged across 30 stimulation sites. Filled squares, open circles, and filled circles show data

for *Models 1, 2, and 3*, respectively. The vertical dashed line indicates the time when the data plotted in *A* were measured. Error bars indicate ± 1 SE.

FIG. 10.

Effect of microstimulation at one site in the FPA on vector averaging for double-target motions in orthogonal directions. *A* and *B* plot horizontal and vertical eye velocity measured at 180 ms after target motion onset for nonstimulation control trials (*A*) and stimulation trials (*B*). The blue dots show the responses in single-target trials, and the red dots show those in double-target trials. Each target moved along horizontal or vertical meridian at $20^\circ/\text{s}$. The short line starting from the origin of *B* indicates the eye velocity evoked by electrical stimulation during fixation of a stationary target. *C*: means of the responses to target motion in 8 stimulation conditions (filled symbols) and 8 nonstimulation controls (open symbols). Responses during microstimulation were measured only after subtracting the eye velocity evoked during fixation from the responses measured in stimulation trials with target motion. The blue symbols plot data from single-target trials, and the red symbols plot data from double-target trials. Each pair of connected points shows the responses to a given target motion in the presence or absence of stimulation. *D*: prediction errors of the 3 models for this stimulation site. The dashed lines show the errors computed from 4 possible orthogonal double-target motions. The filled symbols connected with bold lines indicate means of the prediction errors across all 4 double-target motions. Error bars indicate ± 1 SD.

FIG. 11.

Summary diagram suggesting the location of the frontal pursuit area within the signal flow for pursuit eye movements. T_1 and T_2 indicate signals from 2 moving targets represented in the parieto-ponto-cerebellar pathways in the double-target trials. "FPA" indicates the location of the frontal pursuit area within a frontocerebellar feedback loop. Solid arrows indicate signal flow, while the outlined arrow emanating from the FPA indicates an output that provides control of internal pursuit gain. The 2 circles with X's in them indicate sites of gain control for the information about the motion of the 2 targets.