Cerebellar Flocculus and Ventral Paraflocculus Purkinje Cell Activity During Predictive and Visually Driven Pursuit in Monkey

M. SUH,1 H.-C. LEUNG,2 AND R. E. KETTNER3

1Department of Biomedical Engineering, Northwestern University, Evanston, Illinois 60208; 2Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut 06520; and 3Department of Physiology and Neuroscience Institute, Northwestern University Medical School, Chicago, Illinois 60611

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Suh, M., H.-C. Leung, and R. E. Kettner. Cerebellar flocculus and ventral paraflocculus Purkinje cell activity during predictive and visually driven pursuit in monkey. J Neurophysiol 84: 1835–1850, 2000. Purkinje cells in the flocculus and ventral paraflocculus were studied in tasks designed to distinguish predictive versus visually guided mechanisms of smooth pursuit. A sum-of-sines task allowed studies of complex predictive pursuit. A perturbation task examined visually driven pursuit during unpredictable right-angle changes in target direction. A gap task examined pursuit that was maintained when the target was turned off. Neural activity patterns were quantified using multi-linear models with sensitivities to eye position, velocity, and acceleration of both motor output (eye motion) and visual input (retinal slip). During the sum-of-sines task, neural responses led eye motion by an average of 12 ms, a value larger than the 9-ms transmission delay between flocculus stimulation and eye motion. This suggests that flocculus/paraflocculus neurons drove pursuit along predictable sum-of-sines trajectories. In contrast, neural responses led eye motion by an average of only 2 ms during the perturbation task and by 6 ms during the gap task. These values suggest a follow-up role during tasks more heavily dependent on visual processing. Activity in all three tasks was explained primarily by sensitivities to eye position and velocity. Eye acceleration played a minor role during ongoing pursuit, although its influence on firing rate increased during the high accelerations following unexpected changes in target motion. Retinal slip had a relatively small influence on responses during pursuit. This was particularly true for the sum-of-sines and gap tasks where predictive control eliminated any consistent retinal-slip signals that might have been used to drive the eye. Surprisingly, the influence of retinal slip did not increase appreciably during unpredictable perturbations in target direction that generated large amounts of retinal slip. Thus although visual control signals are needed in varying amounts during the three pursuit tasks, they have been converted to motor control signals by the time they leave the flocculus/paraflocculus system. Individual neurons showed a remarkable constancy in eye-sensitivity direction across tasks that indicated direct links to oculomotor neurons. However, some neurons showed changes in sensitivity magnitude that suggested changes in control strategy for different tasks. Magnitude differences were largest for the perturbation task. We conclude that the flocculus/paraflocculus system plays a major role in driving predictive pursuit. It also processes visually driven control signals that originate in other brain regions after a slight delay.

INTRODUCTION

During smooth pursuit of an unpredictable target motion, the oculomotor system uses visual input to guide the eye. However, pursuit accuracy improves dramatically for predictable target trajectories. The eye can pursue targets moving along ramp (Rashbass 1961), triangle-wave (Bahill and McDonald 1983), square-wave (Barnes and Asselman 1991; Kowler and Steinman 1979), sinusoidal (Lisberger et al. 1981; Stark et al. 1962; Westheimer 1954), and circular (Collewijn and Tamminga 1984) trajectories with very small lags. Our own experiments indicate that the eye lags the target by less than 20 ms during simple sinusoidal motions as well as more complex circular and sum-of-sines motions (Leung and Kettner 1997). This short-delay pursuit cannot rely exclusively on visual inputs that are processed with delays of ~90 ms (Fuchs 1967; Leung and Kettner 1997; Lisberger and Westbrook 1985; Rashbass 1961). In fact, the eye sometimes leads the target during low-frequency components of sum-of-sines motions (Barnes et al. 1987; Collewijn and Tamminga 1984; Dallos and Jones 1963; Kettner et al. 1996; Yasui and Young 1984). Additional evidence for predictive processing comes from observed continuations of pursuit when the target is extinguished (Barnes and Asselman 1992; Becker and Fuchs 1985) or stabilized on the retina (Morris and Lisberger 1987; van den Berg 1988). In both cases, pursuit is maintained in the absence of visual input. It is not known how or where these predictive signals are generated by the brain. In fact, it is likely that several brain regions are involved in the various types of predictive control that are observed based on visual, motor, and even cognitive inputs (Barnes 1993; Kowler 1989, 1990).

The flocculus/paraflocculus system plays a well-established role in generating smooth eye movements (Fukushima et al. 1999; Gomi et al. 1998; Kobayashi et al. 1998; Lisberger and Fuchs 1978a,b; Miles et al. 1980; Noda and Suzuki 1979; Noda and Warabi 1982, 1987; Zee et al. 1981). However, its specific role in the pursuit of small targets has been unclear. Although Purkinje cell firing is correlated with pursuit in step-ramp paradigms, these responses tend to lag eye motion during the initiation of pursuit (Stone and Lisberger 1990). Its mossy-fiber inputs (Lisberger and Fuchs 1978b; Miles et al. 1980; Noda 1986; Noda and Warabi 1987) are influenced primarily by eye motion (~80%), less strongly by head motion (~30%), and only weakly by visual motion (~10%). These input patterns reflect strong anatomic feedback from brain stem premotor...
nuclei (Langer et al. 1985b) and weak projections from pontine nuclei that provide visual inputs related to small-target motion (Glickstein et al. 1994; Nagao et al. 1997). Thus the flocculus/paraflocculus system may be more involved in the maintenance and refinement of ongoing pursuit rather than the initiation of pursuit in response to visual target motion.

We have recently demonstrated how predictive control could be generated by the flocculus/paraflocculus system using biologically realistic neural-network models of this system (Ketten and Suh 1998; Kettnner et al. 1997). These models incorporate the known anatomy and physiology of this cerebellar system including mossy fiber tuning functions, realistic numbers of granule cells, and appropriate processing delays. Importantly, the model continues to generate predictive control using only eye-motion input after visual mossy-fiber input is eliminated (Kettner and Suh 1998). Others have proposed pursuit models that suggest how motor feedback might improve step-ramp pursuit (Robinson et al. 1986; Young et al. 1968) or pursuit during image stabilization (Krauzlis and Lisberger 1989, 1994b; Lisberger et al. 1987; Stone and Lisberger 1990). Strong inputs derived from efference copies of oculo-motor output make the flocculus/paraflocculus system a strong candidate for these types of nonvisual control during pursuit.

Purkinje cell responses were examined during three pursuit tasks that required various types and combinations of predictive and visual control. A sum-of-sines task presented repeated waveforms that offered the greatest opportunity for predictive control. A perturbation task required visual control because abrupt changes in target direction were presented randomly and could not be predicted. A gap task was used to study the neural mechanisms of predictive control when the target was extinguished briefly while predictive circular pursuit was maintained. All of these tasks were designed to study ongoing pursuit well after pursuit had been initiated.

METHODS

The techniques used to record single-neuron activity during pursuit behavior have been presented elsewhere (Leung et al. 2000). Only those techniques specific to this report are explained in detail.

Animals, surgery, and death

Adult male rhesus monkeys (Macaca mulatta; 4–8 kg) were cared for and housed by the Northwestern University Center for Experimental Animal Resources (CEAR) according to Principles of Laboratory Animal Care (National Institutes of Health Publication No. 86-23, revised 1985). The monkeys were checked daily by a certified veterinarian, and care was provided if necessary. Standard techniques were used to surgically implant an eye coil, a head-fixation post, and an eye coil with a head-fixation post. This was done under sterile conditions with deep anesthesia induced by sodium thiopental (20 mg/kg iv) and maintained with halothane (1%) administered via an endotracheal tube. After surgery, daily doses of cephalothin (15 mg/kg iv) and a topical antibiotic were used to prevent infection. Analgesia was maintained for 4 days by injections of buprenorphine HCl (0.01 mg/kg im) and later with topical applications of lidocaine until the incisions had healed.

On each day of recording, the head was solidly attached to the primate chair. The use of a microdrive in conjunction with a grid system (Crist et al. 1988) allowed accurate three-dimensional (3D) placement of glass-coated platinum-iridium electrodes (1- to 2-μm tip diam, 1–2 MΩ impedance) delivered through a guide tube. At the completion of experiments, each monkey was sedated with ketamine hydrochloride (10 mg/kg im), killed by an overdose of pentobarbital sodium (100 mg/kg iv), and perfused transcardially with normal saline followed by paraformaldehyde (10%). The brain was cut into 50-μm sections that were mounted on slides, stained with thionin, and scanned using a high-resolution computer scanner. A custom computer program allowed alignment of 3D maps of recording sites with brain scans based on marking lesions (30-μA direct positive current for 30 s) that bracketed the recording sites of interest.

Behavioral paradigms

Eye position was monitored by a magnetic search coil system. The target was a laser spot back-projected on a tangent screen 40 cm from the monkey controlled by servo-controlled mirror galvanometers. A custom computer program generated eye and target position waveforms and delivered juice rewards. Calibrations were performed before each session.

SUM-OF-SINES TASK. Responses were recorded during four sum-of-sines and four component-sinusoid trajectories (see RESULTS). Trials began when the monkey fixated a stationary target light for 1,000 ms. The monkey was then required to track the target with an error smaller than ±2° for five complete repetitions of a trajectory. If his performance was accurate, he received a liquid reward on each repetition of the trajectory. When an error occurred, the monkey did not receive a reward on that repetition, and the trajectory was repeated until correctly executed. Trajectories were selected randomly until all were presented in a block. A second block of data was then obtained under identical conditions to ensure the reliability of the results. Eighty (8 trajectories, 5 repetitions, 2 blocks) trajectories were presented for each neuron.

CIRCLES-AND-SINUSOIDS TASK. Neural responses were recorded during six trajectories: a clockwise (CW) circle, a counterclockwise (CCW) circle, and sinusoids along four axes (0°/180°, 45°/225°, 90°/270°, 135°/315°). All trajectories had amplitude 5° and frequency 0.6 Hz. Sixty trajectories (6 trajectories, 5 repetitions, 2 blocks) were presented randomly as described for the sum-of-sines task.

GAP TASK. Neural responses were recorded during CW and CCW circular trajectories (5°, 0.6 Hz) while the target light was turned off for 100 ms at four points beginning at 0, 90, 180, and 270°. Forty trajectories (2 trajectories, 10 repetitions, 2 blocks) were presented randomly as described for the sum-of-sines task.

PERTURBATION TASK. Neural responses were recorded during four trajectories with perturbations in the up, down, right, or left directions. Each trajectory consisted of four cycles: two cycles of CCW circular pursuit (5°, 0.6 Hz), one cycle when the target was perturbed from CCW circular pursuit along a circle meridian, and a final cycle of CCW circular pursuit. Accurate tracking within a error window of ±2° was required during the two cycles of circular pursuit preceding perturbation onset. If an error occurred, the entire trajectory was repeated. Forty trajectories (4 trajectories, 1 repetition, 10 blocks) were presented randomly as described for the sum-of-sines task.

Data collection and analysis

A separate computer system was used to collect horizontal and vertical eye position, horizontal and vertical target position, laser intensity, and reward pulses. It also stored the time of individual neural events. Periods containing saccades were deleted by computer when the eye and target differed by >2° in position, 20°/s in velocity, or 200°/s² in acceleration along horizontal or vertical axes. Visual inspection of analyzed data records indicated that all saccades had been deleted as well as periods when the monkey showed poor tracking. In all analyses, left-hemisphere data were converted to right-hemisphere format so that spatial angles of 0, 90, 180, and 270°...
indicate ipsi-versive, upward, contra-versive, and downward directions, respectively.

Eye-motion leads during the perturbation task were determined using the technique described by Leung and Kettner (1997). Briefly, latencies were based on difference waveforms created by subtracting the previous cycle of circular pursuit from the perturbed cycle. Baseline changes in firing rate were defined by a regression line fit to activity during a 25-ms period around perturbation onset. The onset of smooth pursuit corrections was defined as the first deviation from this baseline after perturbation onset. This deviation had to be maintained for 100 ms to reduce the chance that an initiation time was due to random fluctuations in baseline firing.

Eye-motion leads during the sum-of-sines task were determined for both position and velocity by time shifting eye and target records until an optimal fit was obtained. The position lead, \( \tau_{\text{pos}} \), was the value that minimized the position error, \( E_{\text{pos}}(\tau) \), defined by

\[
E_{\text{pos}}(\tau) = \sum |P_{\text{eye}}(t) - P_{\text{target}}(t + \tau)|
\]

Here, the sum is taken over all times, \( P_{\text{eye}} \) and \( P_{\text{target}} \) define the two-dimensional position of the eye and target, and \( \tau \) is the distance between eye and target positions. The average position error between eye and target was defined as \( E_{\text{pos}}(\tau_{\text{ave}}) \). The velocity lead, \( \tau_{\text{vel}} \), and the average velocity error, \( E_{\text{vel}}(\tau_{\text{ave}}) \), were defined similarly.

Model fits were computed with custom computer programs that implemented standard multi-linear regression techniques (Draper and Smith 1981) using matrix-inversion algorithms (Press et al. 1992). Regressions were based on nonaveraged data from individual cycles of pursuit. This eliminated the possibility that local variations in eye motion and retinal slip were obscured in average records and allowed tests of lack-of-fit based on repeated cycles. This practice produced lower total \( R^2 \) values than were obtained for analyses of the same data averaged across cycles. Neural response leads relative to eye motion were estimated separately for each neuron and each task. The eye-motion lead, \( \tau \), was defined by the lead that produced the highest total \( R^2 \) value for the eye-motion model (Eq. 2) based on separate regressions in which \( \tau \) was changed from \( \pm 50 \) ms in 1-ms steps. These leads were also used for the eye-PV and combination models (see RESULTS). The retinal-slip lead, \( \tau_r \), was always set to \( -88 \) ms for model analyses because retinal-slip terms were too small to allow reliable estimates. This was the average lead obtained using the retinal-slip model for the perturbation task (see RESULTS).

RESULTS

Pursuit behavior during the sum-of-sines task

The sum-of-sines task was designed to study neural responses during a complex, but predictable, target motion. This task required the monkey to track four sum-of-sines trajectories (H2H3, V2V3, H2V3, and V2H3), as well as the horizontal (H2, H3) and vertical (V2, V3) sinusoids used to create them. Here numbers identify low (5.0°, 0.6 Hz)- and high (3.3°, 0.9 Hz)-frequency components that were two and three times the sum-of-sines waveform frequency (0.3 Hz). Two-dimensional displays of eye and target motion during the H3V2 trajectory are shown in Fig. 1. The horizontal and vertical components of this trajectory are shown in Fig. 2 as well as the other seven trajectories. The monkey tracked each trajectory with high precision that indicated predictive control. For position traces, the average position error was 0.6 ± 0.1° (mean ± SD) and the average lag between eye and target motion was 10 ± 4 ms for the four sum-of-sines trajectories. In terms of phase, this 10-ms lag corresponds to a 3° phase lag at 0.9 Hz, the highest frequency used in this study. For velocity traces, the average lag was 13 ± 2 ms and the average velocity error was 2.1 ± 0.1°/s. These small lags indicate the presence of predictive control because they were much smaller than the 94-ms average delay associated with visual processing during the perturbation task (see following text).

Neural responses during the sum-of-sines task

Figure 2 also shows typical responses during the sum-of-sines task for a neuron that was strongly correlated with horizontal eye motion and only weakly correlated with vertical eye motion. Tests of component additivity were performed to determine whether multi-linear models could be used to quantify responses. That is, would the neural modulation during sum-of-sines motion equal the sum of the neural modulations along the two component sinusoids used to create the sum-of-sines motion. For example, the horizontal sum-of-sines motion H2H3 was created by adding horizontal sinusoidal components H2 and H3. Component additivity suggests that \( M_{H2H3}(t) = M_{H2}(t) + M_{H3}(t) \) where \( M \) is the modulation in firing rate at time \( t \). Quantitative tests of component additivity were performed for the 21 neurons studied during the sum-of-sines task. These analyses were based on the \( \chi^2 \) test to determine whether there was a difference in the response pattern for composite versus summed-component modulations. Component additivity was supported for 80% of comparisons (\( n = 84 \)) by a nonsignificant \( \chi^2 \) test (\( P > 0.05 \)). The remaining 20% of comparisons showed no strong or systematic pattern of deviation that would have suggested the use of nonlinear models.

Models describing the influence of eye motion and retinal slip on neural firing rate

The “eye-motion model” model was defined by

\[
R(t) = \beta + \rho \cdot P(t + \tau) + \nu \cdot V(t + \tau) + \alpha \cdot A(t + \tau)
\]

Here, \( R(t) \) is the firing rate at time \( t \), \( \beta \) is the baseline firing rate, and \( \rho \), \( \nu \), and \( \alpha \) are two-dimensional (2D) vector sensitivities that operate on 2D position, velocity, and acceleration vectors \( P(t) \), \( V(t) \), and \( A(t) \) to generate firing rates via the dot product. For example, the position sensitivity vector \( \rho = (\rho_h, \rho_v) \) operates on the position vector \( P(t) = [P_h(t), P_v(t)] \) via the dot product \( \rho \cdot P(t) = \rho_h \cdot P_h(t) + \rho_v \cdot P_v(t) \) to create the firing rate
due to eye position at a given time. The lead, \( \tau \), between neural firing and eye motion is positive when firing rate leads eye motion and is negative for lags.

Two alternate models were also used to evaluate the influence of retinal slip on firing rate. The “retinal-slip model” defined the firing rate in terms of retinal slip (target minus eye motion) by

\[
R(t) = \beta + \mathbf{P}(t + \tau) + \mathbf{V}(t + \tau) + \mathbf{A}(t + \tau)
\]

This equation is identical to the eye-motion model except that terms relating to eye motion have been replaced by terms for retinal slip identified by the subscript “s”.

"Combination model" defined the firing rate due to both eye and retinal-slip motion by

\[
R(t) = \beta + \mathbf{P}(t + \tau) + \mathbf{V}(t + \tau) + \mathbf{A}(t + \tau) + \mathbf{P}_s(t + \tau) + \mathbf{V}_s(t + \tau) + \mathbf{A}_s(t + \tau)
\]  

It will be shown in the following text that the eye-motion model provided the best description of the data. This conclusion was based on comparisons between the three models. Initially we had expected that the combination model would provide the best fits with its larger number of variables and parameters. However, almost identical fits were obtained using the eye-motion model. This allowed us to make the stronger conclusion that retinal-slip played essentially no role in explaining firing patterns during pursuit.
Model fits for the sum-of-sines task

Correspondences between model fits and histograms of the average modulation in neural firing rate (shaded areas) are shown at the top of each panel in Fig. 3 for the sum-of-sines responses displayed in Fig. 2. Both the combination model (thick lines) and the eye-motion model (thin lines) provided excellent fits of the data that are generally difficult to distinguish in Fig. 3. Therefore the simpler eye-motion model provided the best description of the data. In contrast, traces obtained for the retinal-slip model (dotted lines) were nearly flat in appearance and poorly related to firing rate.

Six graphs, below each set of model fits, in Fig. 3 show averaged eye-motion and retinal-slip signals. Visual inspection of these curves indicates that eye motion (solid lines) was most highly correlated with the neural firing pattern, while retinal slip (dotted lines) was small and poorly correlated with average firing rates. This finding can be explained by an increased emphasis on predictive control and a decreased emphasis on visual control during sum-of-sines pursuit that produced highly accurate performance without retinal slip. It appears that visual input did not have a strong average influence on either behavioral or neural responses during the sum-of-sines task. Since regression analyses were based on data from individual cycles, this lack of correlation between retinal slip and eye motion does not result from data averaging.

Figure 4 shows computer simulations that explain how eye-velocity and -position influences combine to produce responses during 2D pursuit. The area of each small circle in this display...
represents the firing rate at a point along a 2D sum-of-sines trajectory. Responses from the neuron in Fig. 4A were produced by approximately equal eye-position and -velocity sensitivity vectors that pointed in the contralateral direction. Notice that responses at the bottom-left corner of the H2V3 trajectory still increased after the target had changed its movement direction because of the strong contralateral eye-position influence. Responses from the neuron in Fig. 4B had an even more complex firing pattern due to a misalignment in preferred directions for eye-velocity and -position sensitivity vectors. The influence of eye velocity produced maximal firing in the downward direction. In contrast, the influence of eye position created maximal firing at ipsilateral locations for both trajectories. These two influences summed to create the patterns of activity that were observed. In both instances, quantitative knowledge of sensitivity vectors for both eye position and velocity were required for the accurate reconstruction of observed variations in firing rate along complex 2D trajectories.

Pursuit behavior during circular tracking with and without target gaps

The gap task was used to study behavioral and neural responses in the absence of a target while eye motion was maintained. We first demonstrate that pursuit behavior with gaps was very similar to behavior observed during circular pursuit without gaps. In the gap task, the target was turned off briefly for 100 ms at four points along CW and CCW circular trajectories (5°, 0.6 Hz). These results were compared with non-gap performance along the same circular trajectories in the circles-and-sinusoids task. The monkey tracked each trajectory with high precision. Two-dimensional plots of eye motion during both tasks (Fig. 5) suggest that both gap and non-gap trajectories were tracked similarly. Horizontal and vertical components for gap-task traces (Fig. 6) indicate a lack of interruption following gap onset. Similar results were obtained for all 13 neurons studied during the gap task.

This observation was supported by quantitative analyses. Average leads between eye and target traces were not statistically different for gap and non-gap conditions ($P > 0.05$). During CW pursuit, gap and non-gap leads were $13 \pm 9$ and $8 \pm 10$ ms for eye position and $12 \pm 7$ and $12 \pm 8$ ms for eye velocity. Interestingly, small lags were observed for the other rotation direction. These differences in CCW versus CW latency were statistically significant ($P < 0.005$) except for position latencies during circular pursuit without gaps. During CCW pursuit, gap and non-gap leads were $-6 \pm 10$ and $-3 \pm 18$ ms for eye position and $-5 \pm 5$ and $-5 \pm 5$ ms for eye velocity. All of these values indicate predictive control because they are much smaller than visual processing delays during pursuit of $\approx 94$ ms (see following text). Average position and velocity errors were also not significantly different for gap and non-gap pursuit ($P > 0.05$). For CW pursuit, gap and non-gap errors were $0.9 \pm 0.8$ and $0.6 \pm 0.2^\circ$ for eye position and $2.4 \pm 1.2$ and $1.7 \pm 0.4^\circ/\text{s}$ for eye velocity. Similar errors were observed during gap and non-gap CCW pursuit; errors were $0.6 \pm 0.3$ and $0.6 \pm 0.2^\circ$ for eye position and $1.9 \pm 0.5$ and $1.9 \pm 0.3^\circ/\text{s}$ for eye velocity. The pursuit system was able to fill in the gaps and to predict the appropriate course of action without visual input.
Neural responses during the gap task

The gap paradigm was used to study the effects of abrupt changes in visual input on firing patterns without the confounding influence of changes in eye motion. Figure 6 shows raster and histogram displays for a typical neuron. There were no disruptions in the smooth firing pattern of this neuron or the other neurons studied in the gap task. This suggests that flocculus and paraflocculus neurons drive pursuit during both gap and non-gap performance. Two alternative hypotheses were not confirmed. An increase in firing during gaps would have suggested the existence of control signals specifically designed to compensate for reduced visual input during gaps. A decrease in firing would have suggested the converse, that compensatory signals were generated elsewhere.

Correspondences between model fits and average firing rate are shown in Fig. 7, top, for the responses shown in Fig. 6. As for the sum-of-sines task, it is apparent that both the eye-motion model (thin lines) and the combination model (thick lines) provided excellent and nearly identical fits, and the retinal-slip model (dotted lines) failed. This result can again be explained by eye-motion traces that were highly correlated with neural firing patterns, while retinal-slip signals were weak and not correlated with neural firing patterns.

Behavioral responses during the perturbation task

The perturbation task was designed to study neural responses during nonpredictable perturbations from a CCW circular target motion. Because changes in target direction were unpredictable, visual input played a dominant role in guiding the eyes after each right-angle change in target direction. Displays of 2D eye and target motion during the task are shown in Fig. 8. Each trial began with pursuit during 2 to 2.75 cycles of a circular trajectory. The direction of target motion was then perturbed at right angles along a circle meridian in either the up, down, right (ipsilateral), or left (contralateral) direction. The eye overshot each unexpected perturbation and continued along the expected circular target motion until smooth corrections moved the eye in the new target direction. On average, smooth horizontal and vertical corrections appeared 94 ± 6 and 93 ± 10 ms after perturbations. These smooth correction latencies are similar to those of our previous study (Leung and Kettner 1997).

Neural responses during the perturbation task

Responses during the perturbation task from a typical neuron are shown in Fig. 9. This neuron fired primarily in relation to horizontal target motion. There were clear disruptions in the neural firing pattern during perturbations in the up and down direction because these perturbations disrupted horizontal motion for one half cycle while vertical motion was maintained. Perturbations in the right and left directions had little effect on this cell’s firing pattern because these perturbations only affected vertical motion.

Model fits were based on the “perturbed cycle” defined as the cycle period (1,667 ms) centered on perturbation onset to emphasize influences during perturbed pursuit. Expanded views of responses during the perturbed cycle and the cycle immediately preceding it are illustrated in Fig. 10 along with corresponding eye-motion and retinal-slip inputs. It is apparent that both the eye-motion model (thin lines) and the combina-
tion model (thick lines) provided excellent fits. Although model fits were based on only the perturbed cycle, the model also produced good fits for the cycle proceeding the perturbed cycle. The retinal-slip model (dotted lines) provided much poorer fits. This result cannot be explained by a lack of retinal slip input because there were consistent periods of retinal slip after each perturbation.

Statistical evaluation of model fits

Detailed statistical analyses of the entire population of neurons supported the conclusion that the eye-motion model provided the best fit of the data in all three tasks. This finding was based on separate regression analyses of the combination (Eq. 4), eye-motion (Eq. 2), and retinal-slip (Eq. 3) models described in the preceding text. In addition, an eye-PV (position-velocity) model was evaluated to see how well a model based solely on eye position and eye velocity would fare; this model was the same as the eye-motion model minus its acceleration term. Table 1 lists the average total \( R^2 \) for each model fit for the sum-of-sines, gap, and perturbation tasks. In each case, the eye-motion and combination models provided similar good fits of the data with the eye-PV model doing almost as well. For each task, these three models provided statistically significant fits \((P < 0.001)\) without significant \((P > 0.05)\) lack of fit for each neuron. In contrast, the retinal-slip model did a much poorer job and produced significant lack of fit \((P > 0.05)\) for all neurons.

![FIG. 9. Behavioral and neural responses during the perturbation task. Top: horizontal and vertical traces for eye position show clear overshoots when target direction is unexpectedly changed. Below: raster displays show a consistent firing pattern for repeated presentations of the same perturbation. At the bottom of each panel, histograms show the average neural response for each perturbation direction. See Fig. 2 for additional detail.](image)

![FIG. 10. Model analyses of the perturbation task. Top: model fits for the combination (heavy lines), eye-motion (thin lines), and retinal-slip (dotted lines) models are compared with average firing rates (histograms) for the neuron shown in Fig. 9. Below: corresponding eye (thin lines) and retinal-slip (dotted lines) components are shown. Each panel shows an expanded view of the responses shown in Fig. 9 including the cycle immediately preceding the perturbation and the cycle centered about the transition from circular to straight-line motion. See Fig. 3 for additional detail.](image)

<table>
<thead>
<tr>
<th>Model</th>
<th>SS</th>
<th>Gap</th>
<th>Pert</th>
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</thead>
<tbody>
<tr>
<td>Combination</td>
<td>34 ± 15</td>
<td>48 ± 16</td>
<td>45 ± 17</td>
</tr>
<tr>
<td>Eye motion</td>
<td>33 ± 15</td>
<td>47 ± 16</td>
<td>44 ± 18</td>
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<tr>
<td>Eye PV</td>
<td>30 ± 16</td>
<td>46 ± 17</td>
<td>42 ± 18</td>
</tr>
<tr>
<td>Retinal slip</td>
<td>8 ± 4</td>
<td>12 ± 6</td>
<td>15 ± 5</td>
</tr>
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Values are expressed as means ± SD in percentages. \( n = 21, 13, \) and 26 for sum-of-sines (SS), gap, and perturbation (Pert) tasks, respectively.
Comparisons among total $R^2$ values for individual neurons are shown in Fig. 11. In each comparison, results from the combination model are plotted on the horizontal axis, and results from the other three models are plotted on the vertical axis. Total $R^2$ values for the eye-motion model ($\bigcirc$) were generally close to the diagonal line that indicated no difference between it and the combination model. The combination model with its larger number of variables and parameters provided a marginally better fit for only a few neurons and only during the perturbation task. Values obtained from fits of the eye-PV model ($\triangle$) were also close to the diagonal but showed consistent drops in performance compared with the eye-motion and combination models particularly for the perturbation task. This suggests that the eye-motion model with its acceleration term improved the fit obtained for many neurons. For every neuron studied, there was a strong drop in performance to low levels for the retinal-slip model ($\bigcirc$). Thus the eye-motion model provided the most parsimonious account of the data for the neural population.

The relative influence of the three eye-motion terms and the three retinal-slip terms in the combination model are shown in Fig. 12. In the top 3 panels, each line shows partial $R^2$ values for an individual neuron based on responses in a particular task. Although there was some variability in the relative influence of eye position and velocity across neurons, the strong influence of these two inputs is clear. All neurons showed much weaker influences from eye acceleration and retinal-slip position, velocity and acceleration. Figure 12D shows average values (normalized by partial $R^2$ values for eye velocity) that confirm these results and demonstrate their consistency across tasks. The only exception was a small, albeit significant ($P < 0.01$), relative increase for retinal-slip velocity during the perturbation task. These results indicate why the eye-motion model did as good a job as the combination model in accounting for most of the data.

Variations in model parameters across tasks

Model parameters computed separately for the perturbation, sum-of-sines, and gap tasks were compared with see if individual neurons played similar or different roles in the three tasks. These comparisons were based on the baseline rate, eye-position sensitivity, and eye-velocity sensitivity parameters that accounted for most of the firing rate for all three tasks. Baseline level, eye-position direction (Fig. 13A), and eye-velocity direction (Fig. 13B) were highly correlated ($r > 0.94$) and not significantly different ($P > 0.05$) for each task comparison. This supports the stability of baseline levels and the generality of the model in identifying a consistent set of preferred directions for different tasks. It suggests that Purkinje cells activate the extra-ocular muscles in equal ratios independent of task. Eye-position magnitude (Fig. 13C) and eye-velocity magnitude (Fig. 13D) were also not significantly different ($P > 0.05$) but showed more variation from task to task. Magnitudes were similar across tasks for some neurons but for

FIG. 11. Comparisons between total $R^2$ values for various regression models. The horizontal axis indicates values obtained with the combination model. The vertical axis shows corresponding values obtained with the eye-motion model ($\bigcirc$), the retinal-slip model ($\bigcirc$), and the eye-PV model ($\triangle$). Panels show results for the sum-of-sines task (A), the gap task (B), and the perturbation task (C).

FIG. 12. Partial $R^2$ values for eye position, velocity, and acceleration as well as retinal-slip position, velocity, and acceleration based on the combination model (Eq. 4). Each line in the top 3 panels shows results for an individual neuron for the sum-of-sines task (A), the gap task (B), and the perturbation task (C). D: comparisons among average values for each of the 3 tasks. To facilitate comparisons, these values have been normalized relative to the average partial $R^2$ value for eye velocity in each task.
other neurons magnitudes doubled or tripled when task conditions changed. Correlations in magnitude for position and velocity were weakest for perturbation/gap comparisons \((r = 0.44, 0.37)\), stronger for sum-of-sines/perturbation comparisons \((r = 0.69, 0.71)\), and largest for sum-of-sines/gap comparisons \((r = 0.86, 0.89)\). Thus magnitude variability was greatest for comparisons involving the perturbation task.

**Distributions of sensitivity vectors for the three tasks**

A neuron’s position-sensitivity vector, \(p\), points in its preferred direction for position with length equal to its position sensitivity in that direction. Similarly, a neuron’s velocity-sensitivity vector, \(v\), defines the magnitude and direction of its velocity sensitivity. For directions away from the preferred direction, sensitivity declines with the cosine of the angle between actual and preferred directions (Leung et al. 2000). Figure 14 shows eye-position (left) and eye-velocity (middle) sensitivity vectors for the sum-of-sines, gap, and perturbation tasks. These vectors are distributed over a wide range of directions in all quadrants. Scatter plots (right) compare the preferred direction of eye-position and -velocity sensitivities. Several points are near the diagonal that indicates no difference in preferred direction, while other points indicate neurons with clear differences in preferred direction. Overall, 57, 54, and 62% of neurons had eye-position and -velocity sensitivity vectors that differed by \(45^\circ\) for the sum-of-sines, gap, and perturbation tasks, respectively.

**The timing of neural responses**

Figure 15, top, shows \(R^2\)-versus-lead curves for each neuron analyzed in the three tasks. Each curve shows the change in total \(R^2\) relative to the optimal \(R^2\) value obtained for a neuron at different leads. Below each of these panels are corresponding scatter plots of optimal lead versus peak \(R^2\) value. The perturbation task was designed to produce the sharpest changes in behavioral and neural responses. Therefore it is not surprising that this task produced the most sharply peaked lead-versus-\(R^2\) curves and the most reliable lead estimates. On average, neural activity led eye motion by 2 ± 6 ms during the perturbation task and by 6 ± 15 ms for the gap task. These values were not statistically different \((t = 0.8, P > 0.05)\). In contrast, the average lead of 12 ± 13 ms during the sum-of-sines task was statistically larger than leads for both the perturbation \((t = 3.6, P < 0.003)\) and gap \((t = 2.1, P < 0.03)\) tasks. These trends were confirmed for neurons studied in more than one task (Fig. 16): there is a clear tendency for neurons to show smaller leads during the perturbation task. The perturbation-task lead was significantly smaller \((t = 7.1, P < 0.001)\) than the 9-ms lead expected from stimulation studies (see DISCUSSION); leads for the other two tasks were not \((|t| < 1.0, P > 0.16)\).

Leads between neural responses and retinal-slip motion were difficult to define because the influence of retinal slip was weak during each of the three tasks. For all three tasks, analyses based on the retinal-slip model produced lead-versus-\(R^2\) curves that were flatter and more variable than those obtained for the eye-motion model. Only the perturbation task produced curves that were sufficiently peaked to allow consistent estimates of maximum values. The results of this analysis are shown in the rightmost panel of Fig. 15. Although there was a good deal of variability, the average delay was 88 ± 15 ms, a value similar

![Image](http://jn.physiology.org/)

**FIG. 13.** Comparisons between the direction and magnitude of eye-position and -velocity sensitivity vectors for neurons studied in more than 1 task. Different symbols indicate comparisons between sum-of-sines and perturbation tasks (●), perturbation and gap tasks (○), and sum-of-sines and gap tasks (●). Data from each pair are plotted on horizontal and vertical axes, respectively.

**FIG. 14.** Distributions of eye-position (left) and eye-velocity (center) sensitivity vectors as well as comparisons between eye-position and -velocity sensitivity directions (right). Panels show results for the sum-of-sines task (A), the gap task (B), and the perturbation task (C). Sensitivity magnitudes were multiplied by the amplitude \((5^\circ)\) and velocity \((18.8^\circ/s)\) of circular pursuit \((A = 5^\circ, f = 0.6 Hz)\) so that vector lengths represent firing rates.
to the average behavioral delay of 94 ± 9 ms in the perturbation task.

Anatomical location of recorded neurons

The anatomical locations of the 35 neurons studied in the sum-of-sines, gap, and perturbation tasks are shown in Fig. 17. Most of the neurons were localized to the flocculus and the ventral paraflocculus with a smaller number found within the base of the lobulus petrosus adjacent to the ventral paraflocculus and within the dorsal paraflocculus. Different symbols distinguish neurons with different leads. They indicate no obvious correspondence between anatomical location and the optimal lead of a neuron.

Model simulations of responses during step-ramp pursuit

Although neural responses were not obtained during step-ramp performance, simulated responses were obtained to determine whether a more complex model of eye-motion sensitivities could account for the onset responses that have been reported (see DISCUSSION). Simulations were based on the eye-motion model using sensitivity parameters measured for the sum-of-sines and circles-and-sinusoids tasks. Horizontal eye-position and -velocity traces during step-ramp performance were obtained from published results (Fig. 7A in Stone and Lisberger 1990), and an eye-acceleration trace was obtained by differentiation. Figure 18 shows the range of responses that were obtained. A neuron (Cell 1) with eye-position and eye-velocity sensitivities in similar directions showed a strong initial increase in firing rate that slowly leveled off. Another neuron (Cell 2) with oppositely directed eye-velocity and eye-position sensitivities produced simulated responses with an initial rapid increase followed by a slow decline in activity. A neuron (Cell 3) with a relatively high sensitivity to eye acceleration exhibited an onset burst.

DISCUSSION

Influence of eye motion on flocculus and paraflocculus firing patterns

An eye-motion model based on sensitivities to eye position, velocity, and acceleration provided good fits for the temporal firing patterns of all neurons without significant lack of fit. Eye-position and -velocity sensitivities accounted for most of the firing rate profile. However, eye-acceleration sensitivities were also required for neurons that showed bursts in firing rate.
during the high eye accelerations that occurred after target perturbations. These results are compatible with previous studies that have shown strong variations in response phase during sinusoidal pursuit. Distributions of phase for populations of flocculus and paraflocculus neurons tend to peak near eye velocity. However, individual neurons have phases that deviate from this peak by as much as ±90° (Lisberger and Fuchs 1978a; Lisberger et al. 1994; Miles et al. 1980; Stone and Lisberger 1990). These responses reflect the combined influence of eye position, velocity, and acceleration.

A striking constancy in preferred direction was observed when eye-position- and velocity sensitivity vectors were computed separately for the three tasks. This supports the robustness of the eye-motion model in accounting for firing rate patterns under a variety of pursuit conditions. Constancy in preferred direction indicates the relatively direct control of oculomotor output by flocculus and paraflocculus Purkinje cells. It suggests that Purkinje cells activate horizontal and vertical eye muscles in set ratios. This idea is supported by anatomical experiments that show direct projections from the flocculus and paraflocculus to the vestibular nuclei that in turn project to the oculomotor nuclei (e.g., Langer et al. 1985a). Interestingly, more than half the neurons had positions and velocity sensitivity vectors that differed by 45°. These differences in sensitivity direction were required for the accurate generation of complex one-dimensional and 2D sum-of-sines trajectories.

More variability was observed for sensitivity magnitudes. Although sensitivities for some neurons were similar during the execution of different tasks, other neurons showed two- or threefold changes in sensitivity when task conditions changed. The most striking changes were observed for the perturbation task. These changes in magnitude may reflect the presence of externally generated visual control signals that act in combination with flocculus/paraflocculus signals to move the eye. The influence of external visual signals would tend to be strongest during the perturbation task during unpredictable changes in target direction. They would have a weaker influence during predictive pursuit in the sum-of-sines task where visual input was reduced.

**Influence of retinal slip on flocculus and paraflocculus firing patterns**

Retinal slip did not influence firing rates for the highly predictable motions of the sum-of-sines and gap tasks. Analyses based on the combination model that included terms related to both eye motion and retinal slip produced no improvement in performance over the eye-motion model. This finding was explained in part by the near absence of retinal slip during predictive tracking. In addition, periods of retinal slip on individual cycles of a trajectory did not show a consistent relationship to eye motion that would have been detected by our regression analyses based on individual waveform cycles. Related results were obtained by Stone and Lisberger (1990). They saw no change in flocculus and paraflocculus firing rate when retinal-slip input was eliminated by stabilizing the target image on the retina after pursuit initiation.

We were surprised that retinal slip also had a minimal influence in shaping responses during the perturbation task. Here unexpected perturbations from ongoing pursuit led to consistent periods of retinal slip. For most neurons, however, the eye model again generated very good estimates of responses both before and after unexpected perturbations. The combination model did a somewhat better job for only a few neurons. This absence of correlation between firing rate and retinal slip does not imply the absence of visual control. Rather it suggests that visual signals have been transformed into motor coordinates by the time they leave the flocculus/paraflocculus system. This is expected for a region tightly linked to oculomotor output.
Role of flocculus and paraflocculus neurons during unexpected perturbations

Neurons in the flocculus and paraflocculus process signals involved in the visual control of pursuit. The high quality of these signals was indicated by the strong correlation between neural firing patterns and eye motion during the perturbation task. However, neural responses led eye motion by an average of only 2 ms during this task, a value considerably smaller than the 9-ms lead expected from stimulation studies (Lisberger and Pavelko 1988; Shidara and Kawano 1993). Although a brain region could control eye motion using neurons with various lead times, an average lead of only 2 ms during this task, a value considerably smaller than estimated transmission delays (Stone and Lisberger 1990). It was concluded that other brain systems supplied the earliest control signals during pursuit initiation.

That said, Stone and Lisberger (1990) also argued that visually driven control signals passed through the flocculus (albeit at a short delay) and that these signals had a different neural substrate than the signals that produced ongoing pursuit. They argued that onset responses must be driven by visual inputs because they were unable to derive onset responses from sensitivities to eye velocity during ongoing pursuit. Our results are also compatible with the existence of visual control signals. However, computer simulations based on the eye-motion model indicate that sensitivities derived from ongoing pursuit do produce onset responses for some neurons. For example, a sensitivity to eye acceleration produces an onset response during the acceleration burst at pursuit onset. This is compatible with the idea (see preceding text) that visual control signals are coded in motor coordinates. Nevertheless, our results suggest that other neurons in our population would have shown responses during pursuit initiation that were not derivable from ongoing responses. These neurons showed changes in sensitivity magnitude for the perturbation versus the sum-of-sines tasks.

Possible sources for the earliest visual signals that drive pursuit include the frontal cortex (Gottlieb et al. 1994; Heinen 1995; Heinen and Liu 1997; Keating 1991, 1993; MacAvoy et al. 1991; Schnyder et al. 1985; Stanton et al. 1988; Tian and Lynch 1996), the parietal cortex (Kawano et al. 1994; Lisberger and Movshon 1999; Newcombe et al. 1988; Tusa and Ungerleider 1988; Ungerleider et al. 1984), and the cerebellar vermis (Kase et al. 1979; Suzuki and Keller 1988a,b; Suzuki et al. 1981). In addition, one should not rule out a role for the dorsal paraflocculus (Noda and Mikami 1986), which receives stronger visual input from the dorsolateral pontine nuclei (Kawano et al. 1992; Mustari et al. 1988; Suzuki et al. 1990; Their et al. 1988) than either the flocculus or the ventral paraflocculus (Glickstein et al. 1994) and was not sampled extensively in the present study. Each of these regions projects (via one or more synapses) to oculomotor nuclei along anatomical pathways that both bypass and include the flocculus and paraflocculus (see review by Keller and Heinen 1991). This would explain how these areas might provide the earliest influences on oculomotor behavior while still using the flocculus/paraflocculus system to refine visually driven pursuit at a short delay. A related possibility is that these signals are supplied by the vestibular nuclei and the nucleus prepositus hypoglossi that both have strong projections to the flocculus/paraflocculus and are involved in oculomotor control (Fuchs and Luschei 1970; McFarland and Fuchs 1992; Scudder and Fuchs 1992; Stahl and Simpson 1995a,b; Tomlinson and Robinson 1984; Zhang et al. 1995a,b).

Role of flocculus and paraflocculus neurons during target gaps

Neural and behavioral responses during the gap task were not affected by gaps and were highly correlated with eye
motion. This suggests the involvement of these neurons in the control of pursuit even when the target is off. However, the average response lead of 6 ms for the gap task was more similar to the 2-ms lead for the perturbation task than the 12-ms lead for the sum-of-sines task. This could reflect a dependence on input from parietal cortex neurons that continue firing when the target light is extinguished (Newsome et al. 1988). As in the perturbation task, these neocortical signals could provide the earliest drive during target gaps. Influences from flocculus/paraflocculus neurons based on either direct or indirect neocortical input would then influence eye motion after a small delay.

Another intriguing possibility is that short neural leads in the gap task reflect a reduced overall dependence on predictive control during CCW circular pursuit. This idea is suggested by the 12-ms lead associated with CW circular pursuit in contrast to the 5-ms lag observed for CCW pursuit. This asymmetry could have resulted from the consistent presentation of unpredictable trajectories during CCW pursuit in the perturbation task, and the absence of unpredictable trajectories during CW pursuit. The idea that alterations in the predictability of the same target motion can influence response leads should be explored in future experiments. Would leads have been larger for the gap task if the monkey had not performed in the perturbation task? Conversely, would leads have been smaller for less-predictable sum-of-sines trajectories with longer repeat periods?

Role of flocculus and paraflocculus neurons during predictive sum-of-sines pursuit

The flocculus/paraflocculus system does generate predictive control during ongoing pursuit. Neural responses were highly correlated with eye motion during the sum-of-sines task. In addition, the average response lead of 12 ms exceeded the 9-ms estimate of flocculus-to-eye transmission delays (Lisberger and Pavelko 1988; Shidara and Kawano 1993). Thus it appears that the flocculus/paraflocculus system can add a predictive signal based on eye-motion information to other incoming control signals. This improves pursuit accuracy by reducing the system’s reliance on visual control signals that are processed too slowly (100-ms delay) to produce the short latency (<20-ms delay) pursuit observed during predictable target trajectories (e.g., Leung and Kettner 1997; review by Barnes 1993). We imagine that this processing is accomplished using computational strategies similar to those used in our network model of the flocculus/paraflocculus system that is able to generate predictive control (Kettner and Suh 1998; Kettner et al. 1997). During constant-velocity pursuit along a straight line, the system provides a predictive signal that maintains eye motion at constant velocity using mossy-fiber inputs related to eye motion. This accounts for the maintenance of responses when visual input is removed during image stabilization (Stone and Lisberger 1990). During complex target motions that are predictable, the system provides a more complex set of predictive signals derived from an ever-changing stream of efference-copy input. Visually driven smooth and saccadic corrections are only required when the eye moves away from the target. Thus the flocculus/paraflocculus system provides a predictive signal that is the system’s best estimate of upcoming target motion. This signal is added to signals based on visual feed-back and other types of predictive control that are generated outside of the flocculus/paraflocculus system. In combination, these control signals produce the highly accurate pursuit that is observed behaviorally.

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