

Activation and Inactivation of Rostral Superior Colliculus Neurons During Smooth-Pursuit Eye Movements in Monkeys

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Activation and inactivation of rostral superior colliculus neurons during smooth-pursuit eye movements in monkeys. *J Neurophysiol* 84: 892–908, 2000. Neurons in the intermediate and deep layers of the rostral superior colliculus (SC) of monkeys are active during attentive fixation, small saccades, and smooth-pursuit eye movements. Alterations of SC activity have been shown to alter saccades and fixation, but similar manipulations have not been shown to influence smooth-pursuit eye movements. Therefore we both activated (electrical stimulation) and inactivated (reversible chemical injection) rostral SC neurons to establish a causal role for the activity of these neurons in smooth pursuit. First, we stimulated the rostral SC during pursuit initiation as well as pursuit maintenance. For pursuit initiation, stimulation of the rostral SC suppressed pursuit to ipsiversive moving targets primarily and had modest effects on contraversive pursuit. The effect of stimulation on pursuit varied with the location of the stimulation with the most rostral sites producing the most effective inhibition of ipsiversive pursuit. Stimulation was more effective on higher pursuit speeds than on lower and did not evoke smooth-pursuit eye movements during fixation. As with the effects on pursuit initiation, ipsiversive maintained pursuit was suppressed, whereas contraversive pursuit was less affected. The stimulation effect on smooth pursuit did not result from a generalized inhibition because the suppression of smooth pursuit was greater than the suppression of smooth eye movements evoked by head rotations (vestibular-ocular reflex). Nor was the stimulation effect due to the activation of superficial layer visual neurons rather than the intermediate layers of the SC because stimulation of the superficial layers produced effects opposite to those found with intermediate layer stimulation. Second, we inactivated the rostral SC with muscimol and found that contraversive pursuit initiation was reduced and ipsiversive pursuit was increased slightly, changes that were opposite to those resulting from stimulation. The results of both the stimulation and the muscimol injection experiments on pursuit are consistent with the effects of these activation and inactivation experiments on saccades, and the effects on pursuit are consistent with the hypothesis that the SC provides a position signal that is used by the smooth-pursuit eye-movement system.

INTRODUCTION

In the previous paper, we described how rostral superior colliculus (SC) neurons change their activity as the position of a parafoveal target changes. By stepping a visual target to locations around the fovea out to an eccentricity of 5°, we showed that rostral SC neurons increase their activity with target locations in the contralateral hemifield. Like neurons

further caudal in the SC, rostral neurons are tuned for particular locations—showing peaks of activity between 0.2 and 3° eccentricity. Moreover these neurons cease to discharge if the target steps into the ipsilateral hemifield. Rostral neurons have two additional properties. First, they behave similarly whether monkeys remain fixating after the target steps or if they make a saccade to the eccentric target. Second, rostral SC neurons are active in a similar manner during smooth-pursuit eye movements. For example, if a visual target moves smoothly into the contralateral hemifield and monkeys are required to pursue the target, these neurons increase their discharge rates. Moving a target slightly into the ipsilateral hemifield results in decreased discharge rates of these neurons. Thus rather than representing a static command to keep the eyes still, we suggest that these neurons reflect a position-error signal for movements of the eyes close to the fovea, including pursuit (Krauzlis et al. 1997, 2000). According to this hypothesis, a signal reflecting the difference between eye and target position—an error signal—would be shared by these oculomotor subsystems, saccades, fixation, and pursuit.

These single neuron experiments, however, only correlate the neuronal activity to smooth-pursuit behavior and do not show that the activity contributes to the production of pursuit. For example, one way in which the neuronal activity might change with pursuit without contributing to pursuit generation would be for it to change in relation to preparation of a saccade that is ultimately not produced. Since the direction of the impending pursuit and the impending saccade would both be related to the activity of the same SC neurons, it would not be possible to separate activity into that related to the impending pursuit and that related to the impending saccade. Therefore to test directly the contribution of these rostral SC neurons to pursuit, we altered their activity and measured the effects on smooth-pursuit eye movements independent of saccades.

We performed two sets of experiments. First, we used electrical stimulation of the rostral SC during pursuit initiation and maintenance to determine if activation of these neurons influences smooth-pursuit eye movements. Second, we inactivated the neurons using the GABA agonist muscimol to determine whether a reduction of the activity of these neurons also influences pursuit eye movements. The results of these experiments show that changing the activity of rostral SC neurons influences smooth-pursuit eye movements. Additionally, the

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results of our experiments are consistent with the hypothesis that the SC may provide a position signal for the smooth-pursuit system.

Brief reports of some of these experiments have been made previously (Basso et al. 1997, 1998; Krauzlis et al. 1997b).

METHODS

Two monkeys were prepared for chronic electrophysiological recording of single neurons, electrical stimulation, and reversible lesions of the SC and recording of eye movements. The surgical procedures were described in previous reports on experiments in which the same monkeys were used (Basso and Wurtz 1998; Krauzlis et al. 1997a–c). All protocols were approved by the Institute Animal Care and Use Committee and complied with the Public Health Service Policy on the humane care and use of laboratory animals.

Behavioral paradigms

The general behavioral paradigms and storage of data were identical to that described in the preceding paper (Krauzlis et al. 2000).

Monkeys performed visually guided saccade and pursuit tasks. For the saccade tasks, monkeys fixated a centrally located light-emitting diode (LED) for a duration of 500 ms, after which time the fixation point stepped to a peripheral location of 15° in either hemifield on the horizontal meridian. Monkeys were required to make a saccadic eye movement to the target quickly and accurately. Trials were aborted if the monkeys failed to acquire the target within 500 ms or were not accurate within 2° as measured by an electronic window. For pursuit trials, monkeys fixated a centrally located LED for a variable duration of 1,000–1,500 ms and with an accuracy of at least 2°. After this time, the target either started to move away from the fovea at a constant velocity (ramp trials) or stepped horizontally to a slightly eccentric position and then moved back toward the fovea (step-ramp trials). The amplitude of the step was adjusted to minimize the occurrence of catch-up saccades (Rashbass 1961). Monkeys were required to track the target with an accuracy of 3°. If the monkeys failed to track the target, the trial was aborted by extinguishing the target and delaying the onset of the next trial by 2 s.

During correct performance of trials in all experiments, monkeys were rewarded with a drop of fruit juice or water. Monkeys worked daily until satiated and were given supplemental fluid as required. The monkeys' weight was monitored daily and they remained under the supervision of the Institute veterinarian.

Electrical stimulation

Electrical stimulation was applied through tungsten microelectrodes (Frederick Haer) with impedances between 0.3 and 1.0 M Ω measured at 1 kHz. Electrodes were aimed toward the SC through stainless steel guide tubes held in place by a plastic grid that was secured to the recording chamber (Crist et al. 1988). Electrical stimulation was applied as biphasic pulses. The parameters of stimulation were adjusted on-line to produce the maximum effects on saccades following the parameters used by Munoz and Wurtz (1993b) and Paré and Guitton (1994) for the fixation zone. The minimum pulse width was 100 μ s and did not exceed 250 μ s. The minimum frequency was 100 Hz and did not exceed 250 Hz. These parameters are also consistent with producing a sustained activity similar to that seen in buildup neurons rather than the high-frequency bursting (>600 spikes/s) of the saccade related burst neurons. Current intensity ranged between 9 and 35 μ A. The duration of stimulus train differed depending on the behavioral paradigm as described in the following text.

During stimulation trials, saccades frequently were suppressed for the duration of the presentation of the electrical stimulation train. During these trials, the size of the windows was adjusted to avoid deterring task performance. The electrical stimulation parameters

were adjusted at this time to maximize the effects on saccades. We also interleaved trials in which electrical stimulation occurred while monkeys attentively fixated at primary position without a visual stimulus present to determine the amplitude of any evoked saccades, thereby identifying the location of the stimulating electrode on the SC map (Robinson 1972).

After the stimulation parameters were set for a given site, tests of the effects of stimulation on pursuit commenced. Two basic experimental manipulations were used, namely, stimulation during pursuit initiation and stimulation during maintained pursuit (Fig. 1). We applied stimulation during pursuit initiation simultaneously with the onset of the target motion (15°/s) in the ramp trials and continued for 400 ms (Fig. 1, initiation). For a number of sites, we varied the relative timing of the stimulus train and the onset of the target motion in ramp trials. In these experiments, two conditions were used. First, the stimulation occurred simultaneously with the onset of the target motion (0 ms). In the second condition, stimulation occurred 100 ms before the onset of target motion (100 ms). In both conditions, the speed of target motion was 15°/s. In another set of experiments, we varied the speed of the target motion in step-ramp trials. The speeds tested were 2, 5, 10, and 15°/s. For these experiments, we started the stimulation simultaneously with the onset of target motion. Finally, for the experiments testing the effects of SC stimulation on maintained pursuit (Fig. 1, maintained), a stimulus train of 300 ms occurred during maintained pursuit in step-ramp trials, defined as 600 ms after the onset of target motion. This period was typically well after any catch-up saccades if they occurred and after pursuit had maintained a constant speed approximating that of the target (either 5 or 15°/s).

We also tested the effects of SC stimulation on smooth eye movements evoked by vestibular stimulation and compared these effects to those obtained during visually driven smooth eye movements. To evoke vestibular eye movements, monkeys experienced whole body passive rotation achieved by mounting the primate chair on a rotating platform. The monkeys were rotated sinusoidally at 0.4 Hz and a peak-to-peak amplitude of 20° about a vertical axis that intersected the interaural line, producing movement along the horizontal meridian. Monkeys were required to maintain eye position at a central location while they were rotated in complete darkness with no visible fixation stimulus present. In one monkey, we were unable to control completely for eye position, but the effects of the stimulation did not differ dramatically between the two monkeys. SC stimulation began during the phase of the sinusoidal motion in which eye velocity was maximal for each direction, ipsiversive or contraversive, and was maintained for 400 ms. For a direct comparison with visually driven smooth eye movements, the monkeys remained stationary and a visual target moved along the horizontal meridian sinusoidally with a frequency of 0.4 Hz and a peak to peak amplitude of 20°. Identical to the vestibular condition, SC stimulation began during the phase of the sinusoid in which the eye velocity was maximal for each direction and was maintained for 400 ms. For all experimental conditions, the stimulation and no-stimulation trials were presented in an interleaved fashion except for the vestibular and sinusoidal pursuit trials, which were presented in separate, interleaved blocks.

Muscimol injections

We injected muscimol (Sigma) dissolved in saline in the SC of two monkeys. The injection technique we used was originally described by Dias and Segreaves (1997). Briefly, a closed pressure system was used to inject small volumes of muscimol into the SC. This system allows for precise control and measurement of the injected volumes. The micropipette system was adapted for use with the grid and guide-tube system described by Crist et al. (1988). Moreover, a fine wire inserted within the pipette allowed us to electrically stimulate or record the neuronal activity prior to making the injection. Once the location of a site was identified by stimulation or by mapping the movement field, brief pulses of air pressure of fixed intensity (30–80

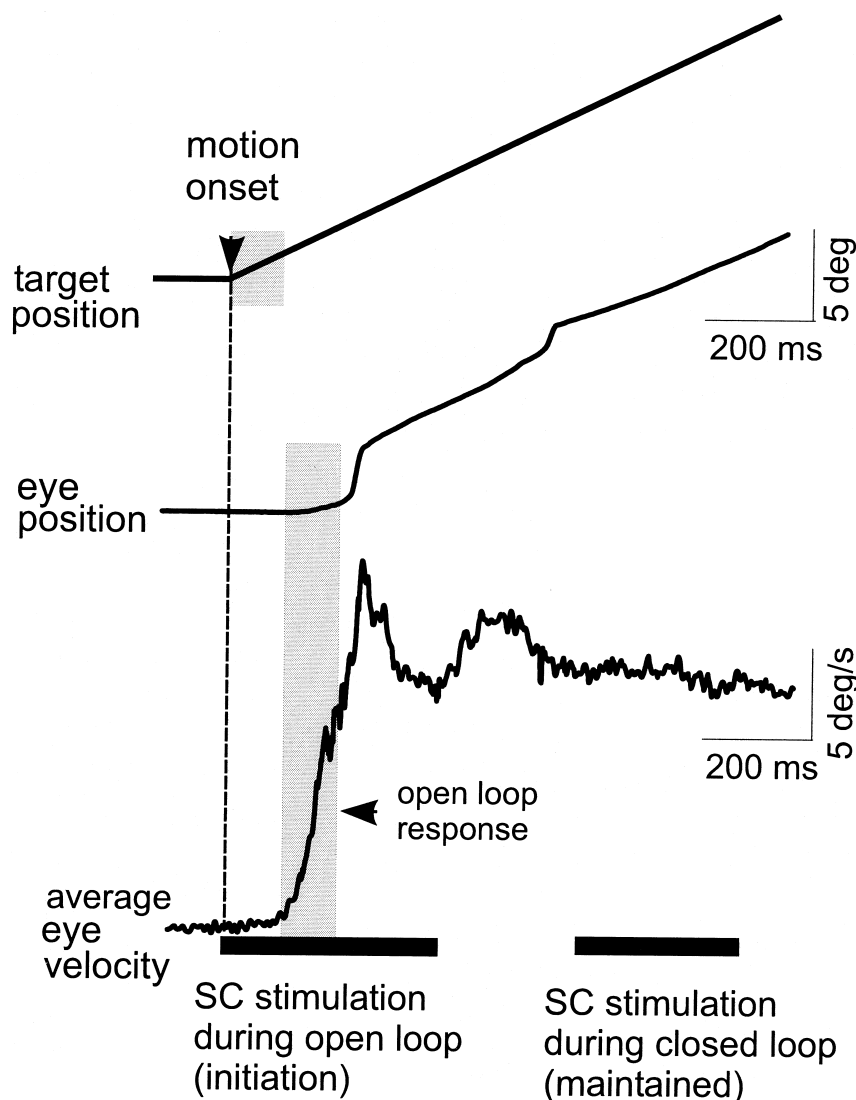


FIG. 1. Timing of superior colliculus (SC) stimulation during pursuit initiation and during maintained pursuit. *Top*: the position of the target as a function of time. *Middle*: a representative eye-position signal recorded in response to rightward motion of a target at 15°/s. Up is right and down is left. *Bottom*: an average of 10 differentiated eye-position traces. In the eye-velocity traces, high-velocity saccades have been removed. Traces are aligned on the onset of the target motion. The black bars indicate the onset and duration of the train of electrical stimulation pulses applied to the SC. The shaded regions on the eye-velocity and eye-position traces indicate the open-loop period of the pursuit response. The shaded region on the target position trace indicates the visual input period driving the open-loop pursuit response. For the pursuit-initiation experiments, a 400 ms duration, 150 Hz, 100 μ s pulse width, biphasic stimulation train occurred simultaneous with the onset of target motion. In the maintained pursuit experiments, the same stimulus train for 300 ms duration occurred 600 ms after target motion onset.

psi) and duration (4–20 ms) were applied by a picopump (World Precision Instruments) to release the muscimol contained within the pipette. The injected volumes for each site in the two monkeys are listed in Table 1. We collected preinjection and postinjection data on interleaved saccade and pursuit trials. Recovery data were collected 24 h after the injections. Monkeys were required to perform saccades along the horizontal meridian of 2, 5, 10, and 20° amplitude (8 trial conditions). Pursuit trials consisted of ramps and step ramps of constant velocity targets moving at 15°/s along the horizontal meridian in either direction. The location of the step varied between 2 and 5° along the horizontal meridian in either hemifield. Thus for pursuit trials, there were 10 possible conditions. A step location either at 2 or 5° in the contralateral hemifield and a subsequent ipsiversive or contraversive target motion (4 conditions), or a step location of 2 or 5° in the ipsilateral hemifield and a subsequent contraversive or ipsiversive direction of target motion (4). Finally, ramp trials were those in which the target motion originated at primary position and moved at a constant speed either ipsiversively or contraversively (2).

Data analysis

Voltage signals proportional to the horizontal and vertical components of eye position were filtered (6 pole Bessel, -3 dB at 240 Hz) and then digitized at a resolution of 16 bits and sampled at 1 kHz. The data were saved on disk for subsequent off-line analysis. An interactive computer program was then used to filter, display, and measure

eye-position and eye-velocity signals. A signal encoding horizontal eye velocity was obtained by applying a 29-point finite impulse response filter (-3 dB at 96 Hz) to the eye-position signal. The high frequency was used to insure detection of small saccades (compare Abel et al. 1979; Bahill et al. 1975; Breznen and Gnadt 1997). Also to maximize detection of small saccades, we used stringent velocity (20°/s) and acceleration (500–800°/s²) criteria. For the pursuit-initiation measurements, data after the occurrence of detected saccades were excluded from analysis as well as the saccades themselves. Once individual eye-velocity records were obtained, the computer program calculated average smooth eye velocity by aligning the traces with respect to target motion onset and calculating the mean and SD of the

TABLE 1. SC injection sites, volumes, and concentrations

Injection	Site in SC, °	μ g/ μ l	μ l	μ g
1	1.0	3	0.5	1.5
2	2.4	3	0.3	0.9
3	0.2	1	1.0	1.0
4	1.0	5	0.4	2.0
5	1.2	5	0.2	1.0
6	2.0	1	0.2	0.2
7	3.4	1	0.2	0.2
8	8.8	1	0.2	0.2

SC, superior colliculus.

eye velocity for each millisecond of data. Measurements of the data resulting from experiments manipulating pursuit speed or pursuit maintenance, or during the muscimol experiments, were made on the velocity traces in which each millisecond of the trace marked as a saccadic velocity was excluded from the calculation of the average smooth eye-velocity traces. These traces were defined as desaccaded eye-velocity traces. For data passing normality tests run by *SigmaStat*, we used Student's *t*-test for statistical analysis; otherwise, we used the Mann-Whitney rank sum test.

RESULTS

Electrical activation of the rostral SC

SACCADES AND PURSUIT INITIATION. In two monkeys, we electrically stimulated the SC at rostral sites within the central 5°

of the visual field. To verify that we were stimulating at the rostral SC locations that have previously been shown to alter saccades, we first determined the effect on saccadic eye movements made to large target steps (10–15°). Ipsiversive saccades were suppressed completely and typically for the duration of the stimulus train (Fig. 2A). Contraversive saccades (Fig. 2E) were also suppressed somewhat, and frequently small contralateral saccades intruded during the stimulation. As the stimulation site in the SC was moved further from the foveal representation, stimulation was less effective in suppressing large saccades, even large ipsilateral saccades and more frequently evoked small contralateral saccades (not shown). These results are consistent with those reported previously (e.g., Munoz and Wurtz 1993) and serve to confirm the loca-

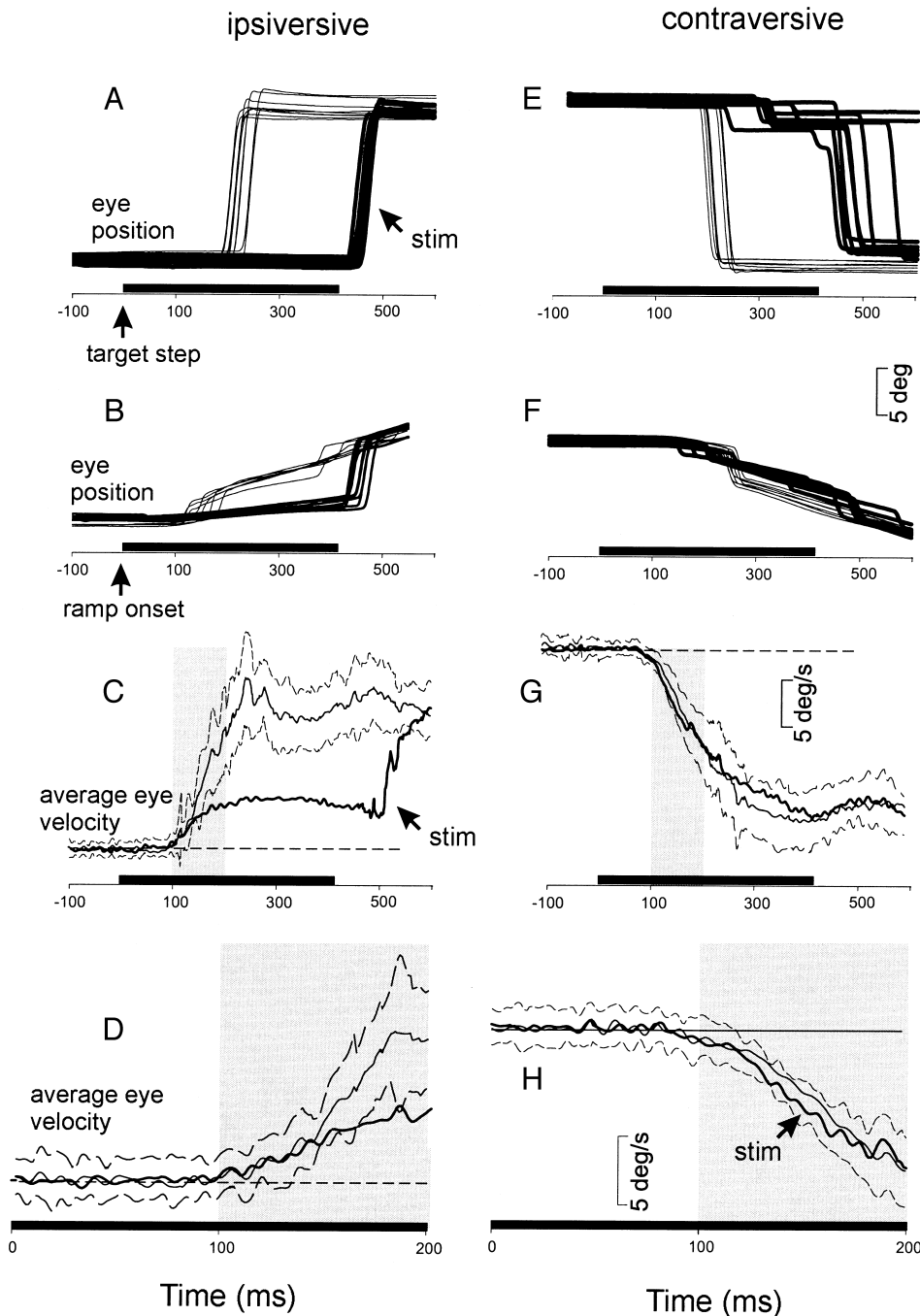


FIG. 2. Rostral SC stimulation affects saccades and pursuit. All traces are aligned on the onset of the target step or ramp (up arrow). Monkeys made saccades to the target steps and a combination of saccades and pursuit to the target ramps. The black bar indicates the onset and duration of the electrical stimulation and the thick lines are traces with stimulation. Dashed traces in C, D, G, and H are SD of the control trials. *Left*: trials during pursuit or saccades in the hemifield ipsilateral to the site of the stimulated SC. *Right*: traces from contraversive trials. A: eye-position traces in response to target steps of 15°. B: eye-position traces in response to target ramps of 15°/s. C: average eye-velocity traces from a subset of the trials with saccades removed (see METHODS). D: traces in C are expanded to show the 1st 200 ms of data beginning at the time of the onset of the target motion and the electrical stimulation. The traces have been truncated at the time of the first saccade. Horizontal dashed lines indicate 0°/s. Arrow in H identified the trace obtained with electrical stimulation of the SC. The stimulation site was the same for saccades and pursuit.

tion of our stimulating electrode within the rostral pole of the SC map.

During pursuit initiation, when the target ramped away from the fovea and the monkeys were required to track the target with a combination of smooth-pursuit and saccadic eye movements, electrical stimulation of the rostral SC dramatically reduced the smooth-pursuit response. As in the case of saccades, the reduction was strongest when pursuit was directed into the ipsilateral hemifield (Fig. 2*B*). During contraversive pursuit, the stimulation had little effect on pursuit but frequently evoked small, contraversive, catch-up saccades (Fig. 2*F*).

To reveal the dynamics of the pursuit response, we examined pursuit eye-velocity traces (Fig. 2, *C–H*). Ipsiversive initial pursuit velocity and ipsiversive maintained pursuit velocity were both reduced with stimulation (Fig. 2*C*). One factor that might explain the reduction of ipsiversive pursuit velocity during stimulation is the suppression of the usual catch-up saccades, resulting in pursuit of an eccentric target, which has been shown to be slower than pursuit of centrally located targets (Lisberger and Westbrook 1985). To eliminate this confounding factor, we restricted our analysis of pursuit velocity to the initial 100 ms of the pursuit response because pursuit is not influenced by feedback during the 100 ms period before the eye starts to move. Therefore no visual feedback signals or catch-up saccades can contribute to this 100 ms open loop period of the pursuit response (see Figure 1 Lisberger et al. 1987). For ipsiversive pursuit during the open loop period (Fig. 2*D*, shaded region), eye velocity was reduced, ruling out an interpretation based on suppression of catch-up saccades and parafoveal pursuit. Contraversive velocity records also revealed a small but consistent effect on eye velocity (Fig. 2*G* and expanded traces in *H*). The SC stimulation slightly increased the initial velocity (Fig. 2*H*, shaded region) prior to the initiation of the first saccade.

Thus in general, smooth-pursuit eye movements to targets

moving in the ipsilateral hemifield are suppressed with electrical stimulation of the rostral SC, whereas smooth-pursuit eye movements to targets moving in the contralateral hemifield show little effect.

We performed a number of experiments that individually demonstrate a contribution of SC neuronal activity to smooth-pursuit eye movements and collectively suggest that the signal produced by the SC and used by the pursuit system is a position signal. In Fig. 3, we present a schematic diagram that represents a framework for describing the relation of the site of stimulation within the SC to the effect on the direction of pursuit. For example, if electrical stimulation is applied to the SC at a site representing a position of 1.5° , as measured by the evoked saccade amplitude, we would expect that when the motion signal (from the target) and the SC position signal (from the stimulation) are in the same direction, pursuit eye velocity should either be unaffected or it should be enhanced (Fig. 3, rightward eye-velocity traces). In contrast, when the SC stimulation and the target motion signal are opposite, pursuit eye velocity should be reduced (Fig. 3, leftward eye-velocity traces). Two points are important to note. First, the effects should be asymmetric—position steps in the direction of motion do not facilitate pursuit as much as position steps in the opposite direction reduce it (Carl and Gellman 1987; Morris and Lisberger 1987). Second, the magnitude of the reduction and facilitation will depend on the magnitude of the position signal that is imposed—within limits, larger steps produce greater changes in pursuit (Carl and Gellman 1987; Morris and Lisberger 1987). Therefore in the following experiments we compare the effects of stimulation of the SC at different locations in the SC map while monkeys make smooth-pursuit eye movements in both directions. We also manipulate stimulation timing and target speed as well as examine the effects of SC stimulation during maintained pursuit.

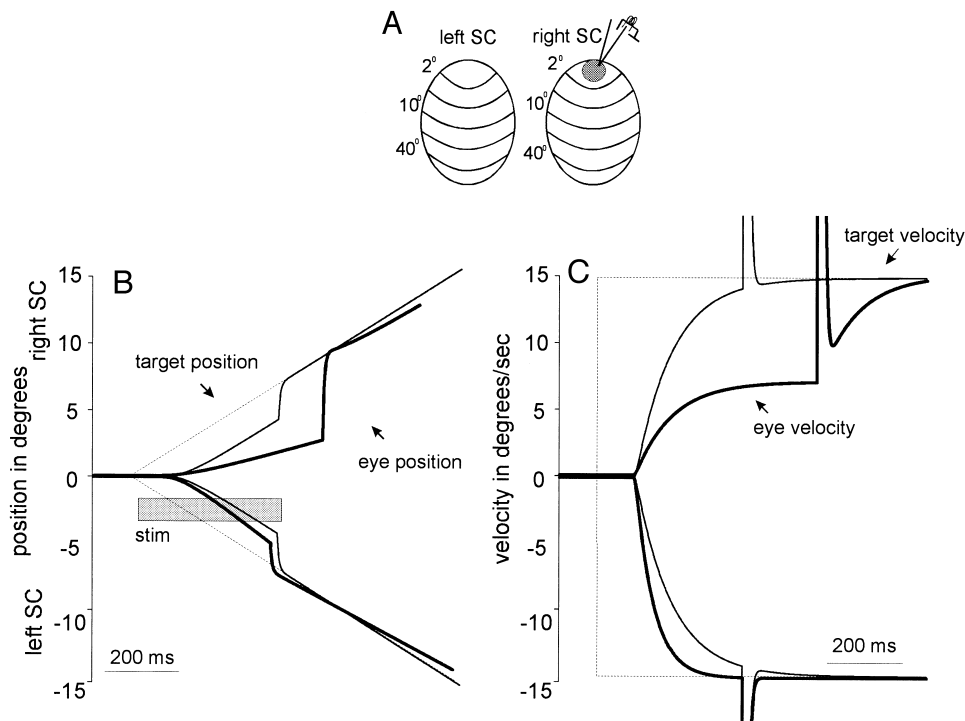


FIG. 3. A schematic representation of what might be expected if the SC stimulation generates a position signal that interacts with the visual motion stimulus to drive the pursuit response. In *A*, the ovals represent the SC map showing an example electrical stimulation site of the right SC evoking a 2.0° leftward saccade. In *B*, the vertical line indicates degrees of visual angle with negative values indicating leftward positions represented in the right SC. The gray bar indicates the onset and duration of the SC stimulation and is plotted to represent the SC location. The effects on pursuit are represented by the position traces with the thick lines indicating stimulated trials and thin lines indicating control trials. Upward traces are rightward eye movements. With a visual target moving $20^\circ/\text{s}$ leftward (dotted line beginning at "target onset") and stimulation of a 2.0° leftward site in the SC, we would expect to modestly speed up leftward pursuit. In contrast, rightward pursuit would be expected to slow down (see RESULTS). In *C*, the same example is provided but plotted in the velocity domain. Conventions are the same as in *B*.

EFFECTS OF STIMULATION AT DIFFERENT SC LOCATIONS. Comparing the eye-velocity responses with and without electrical stimulation at different sites within the SC revealed a dependence on the SC site stimulated (Fig. 4). For a site at the very rostral end of the SC, which virtually never evoked saccades, pursuit eye velocity was slightly reduced during ipsiversive pursuit and unaffected during contraversive pursuit (Fig. 4, *A* and *E*). For a stimulation site slightly more caudal (Fig. 4, *B* and *F*), ipsiversive pursuit velocity was reduced more dramatically, whereas contraversive pursuit velocity was not. For a stimulating electrode even more caudal (Fig. 4, *C* and *G*) that evoked very small saccades during fixation, there was a reduction of ipsiversive pursuit eye velocity and a modest increase in contraversive pursuit. A site further caudal, which evoked on average a 4° saccade, produced no pursuit effect in either direction (Fig. 4, *D* and *H*).

As is suggested by Figs. 2 and 4, the stimulation effects

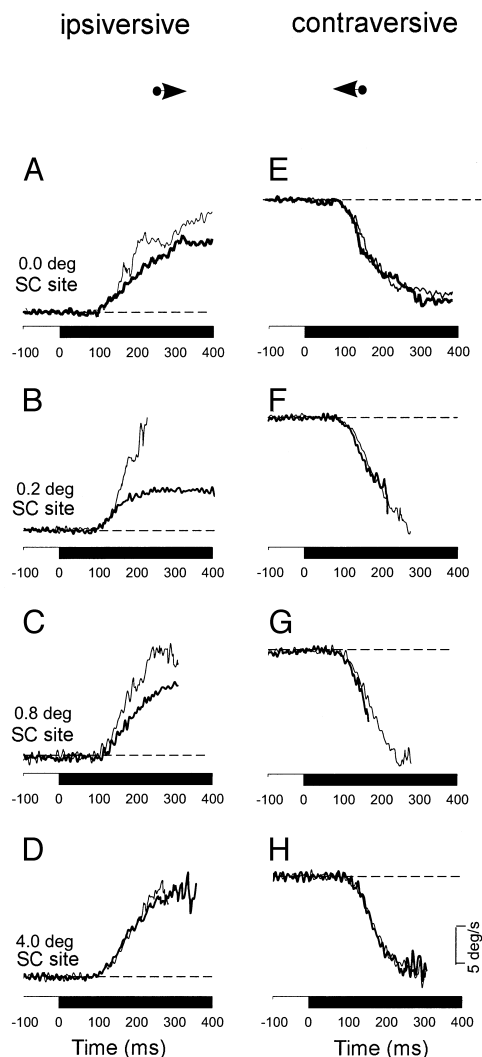


FIG. 4. Stimulation of different locations in the SC affects pursuit initiation differently. Average eye velocity in response to target motion ramping away from the fovea at 15°/s is plotted as a function of time. All trials have been truncated at the time of the 1st saccade. Thick lines, traces from stimulation trials; thin lines, traces from trials without stimulation. *Left*: pursuit responses ipsiversive to the SC stimulation site. *Right*: contraversive. Horizontal dashed lines indicate 0%.

appeared to occur later in the initial open-loop period of the eye-velocity responses. Therefore to quantify the data across our sample of stimulation sites, we divided the first 100 ms of pursuit eye velocity into two separate intervals, a first and second 50 ms. We plotted the difference in the average eye speed of the stimulation and no-stimulation trials as a function of SC stimulation site (Fig. 5). Negative values indicate a reduction of eye velocity with stimulation. We did this for both intervals as well as for both directions of pursuit. The SC site was determined by the average saccade amplitude evoked by stimulation while the monkey fixated straight ahead with no visual stimulus present. In general, stimulation reduced ipsiversive pursuit velocity for most sites tested. The number of statistically significant points was higher in the second 50-ms interval of the pursuit response (compare Fig. 5, *A* and *C*). For contraversive pursuit, by about 1° in amplitude, velocity was unaffected although for a couple of cases beyond the 1° site, pursuit velocity was increased (Fig. 5, *B* and *D*). Similar to ipsiversive pursuit, the number of statistically significant points occurred more frequently in the second 50 ms interval of the contraversive pursuit response.

Note in Fig. 5 that for a few sites close to the fovea ipsiversive pursuit velocity increased with stimulation as indicated by the points above the line in Fig. 5*C* (and see example in Fig. 6*A*). One possibility for this result is that the signal generated by the stimulation reflects the tuning of the underlying neurons within the rostral SC that had unusual properties; some neurons increase their discharge rates for in response to targets located slightly ipsilateral to the fovea (Krauzlis et al. 1997c, 2000). Preferential activation of these ipsilateral neurons can explain the modest increases in ipsiversive velocity seen occasionally. Stimulation of these sites close to the foveal representation also frequently suppressed contraversive pursuit eye velocity across the sample of sites (Fig. 5*D*).

To confirm quantitatively the dependence of the stimulation effects on SC site, we performed a two-way ANOVA comparing SC stimulation and no-stimulation conditions with the location of the stimulating electrode on the SC map. For this analysis, we were only interested in the interaction term, namely, the comparison of eye velocity with and without SC stimulation across SC location. We did one ANOVA for each direction of pursuit. For ipsiversive pursuit there was a significant interaction between the stimulation condition and the location on the SC map [$f(1,14) = 7.65$; $P < 0.001$]. For contraversive pursuit, the differences failed to reach significance [$f(1,14) = 1.27$; $P = 0.22$].

Thus the effect of SC stimulation on pursuit varied with the location of the stimulation within the SC with more rostral sites producing more effective inhibition of ipsiversive pursuit.

EFFECTS OF SC STIMULATION TIMING ON PURSUIT. As just described, the effects on pursuit frequently differed depending on *when* in the initial 100 ms of open loop pursuit the eye speed was measured. Specifically, the effect was largely restricted to the later 50 ms of the open loop period (compare Fig. 5, *A* and *C* and *B* and *D*).

This difference in the stimulation effect between the two intervals of pursuit initiation may reflect the known differences in early and late phases of pursuit initiation (e.g., Lisberger and Westbrook 1985). Alternatively the differences may reflect the timing delays for the SC stimulation to reach the smooth-pursuit pathways. To distinguish between these two possibili-

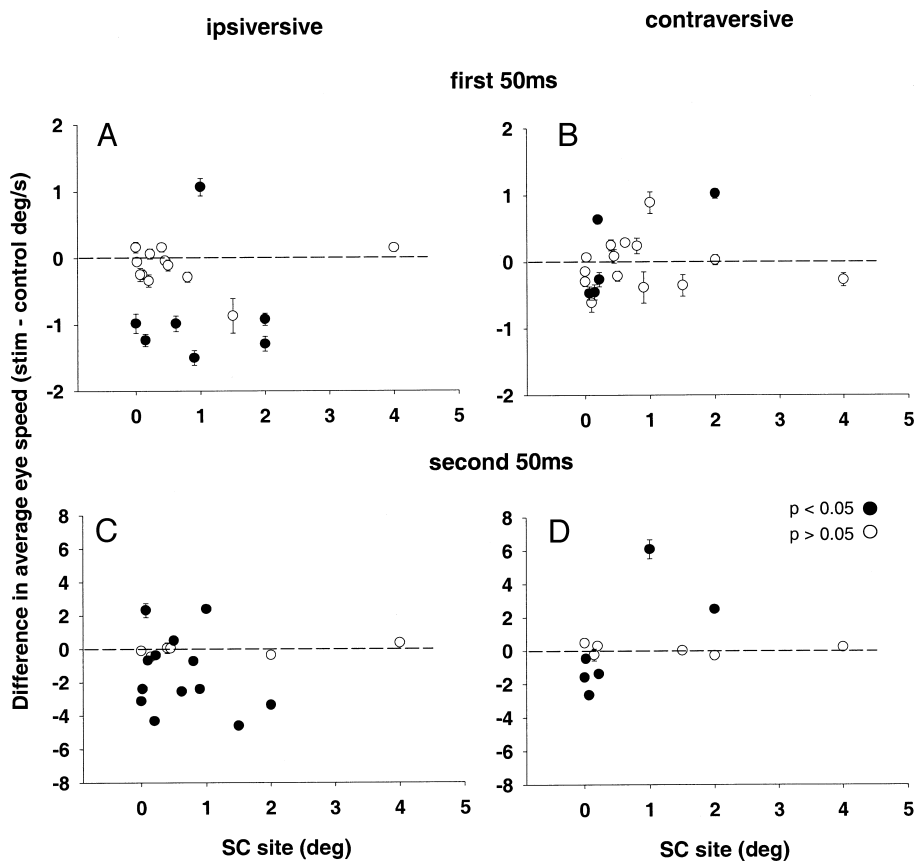


FIG. 5. Effects of rostral SC stimulation across the sample of stimulation sites. The difference in eye speed between the stimulated and unstimulated trials ($^{\circ}/s$) is plotted as a function of the site of stimulation for the sample of 19 stimulation sites. The data are taken from pursuit ramp trials with any portion of the eye velocity containing saccades omitted by truncating the trace at the time of the 1st saccade. The 1st 100 ms of the stimulation trace during presaccadic pursuit—the open-loop period—was subtracted millisecond by millisecond from the same time period of the no-stimulation trace. We then took the average difference for 2 intervals; a 1st 50-ms interval after the onset of target motion (A and B) and a 2nd 50-ms interval (C and D). Closed symbols indicate statistically significant differences between stimulation and no-stimulation trials (see METHODS). Missing symbols result from components of the pursuit response that are missing such as would occur during a saccade. *Left*: the difference in eye velocity between the stimulation and no-stimulation trials is plotted for ramps ipsiversive to the site of SC stimulation (A and C). *Right*: the difference in eye velocity between stimulation and no-stimulation trials is plotted for ramps contraversive to the site of SC stimulation (B and D). Points falling along the dashed line indicate no difference between the stimulation and no-stimulation conditions. Negative values indicate pursuit eye speed was suppressed and positive values indicate eye speed was increased by the stimulation.

ties, we manipulated the interval between the onset of the SC stimulation and the onset of the target motion. In one condition, we presented the 400 ms train of SC stimulation simultaneous with the onset of target motion, examples of which we have already presented. In the second condition, we presented the onset of the SC stimulation train 100 ms before the onset of the target motion. In both conditions, we compared only the ipsiversive eye velocity with and without stimulation at different SC sites because of the larger and more reliable effects on ipsiversive pursuit eye velocity (Fig. 6). When stimulation preceded target motion onset, the pursuit effects were evident immediately when the pursuit response was initiated (Fig. 6, *left*). When the stimulation occurred simultaneously with the onset of target motion, the effects were delayed, as already demonstrated (Fig. 6, *right*). This difference was particularly evident at a site representing about 0.8° amplitude (compare Fig. 6, C and G).

This effect was evident across our sample of 14 sites. We measured the latency of the stimulation effect by first taking the mean and standard deviation of the first 100 ms of ipsiversive pursuit eye velocity in the stimulation condition and then subtracting, millisecond by millisecond, the no-stimulation velocity trace for each site. We considered the onset of the stimulation effect as the time when the difference trace changed from the mean eye-velocity trace in the no-stimulation condition by two standard deviations for at least 5 ms. When the stimulation onset preceded the onset of the target motion by 100 ms, the median latency of pursuit onset was 36 ms. In the simultaneous stimulation and target motion condition, the median latency of the effect of SC stimulation was 61 ms. These

differences were statistically significant across the sample of 14 sites ($P < 0.017$).

Thus the effects of SC stimulation on pursuit initiation are not restricted to the later 50-ms phase of pursuit initiation, demonstrating that the effects of stimulation are not a result of the known differences in the early and late phases of pursuit initiation phases (e.g., Lisberger and Westbrook 1985) but more likely result from the time it takes for the stimulation effects to enter the smooth-pursuit pathways. Moreover the results demonstrate that the signal generated by the SC has access to the initial portion of pursuit.

STIMULATION OF SC AT DIFFERENT PURSUIT SPEEDS. Up to this point, we have presented the results of SC stimulation on pursuit eye movements of a single speed ($15^{\circ}/s$). Past experiments demonstrate that the pursuit system responds differently to target perturbations depending on the speed of pursuit. For example, by imposing small changes in the speed of a moving target that monkeys were required to track, Schwartz and Lisberger (1991) demonstrated that the pursuit response to the speed perturbations increased as the target speed increased. Perturbations had a dramatically smaller effect during fixation than during pursuit. Similarly, Komatsu and Wurtz (1989) demonstrated that the effect of electrical stimulation of middle temporal/medial superior temporal (MT/MST) depended on the speed of pursuit and was not influential during fixation. Both sets of results were interpreted as acting on the visual input to the pursuit system, which, in the case of the stimulation, was subsequently combined with the information obtained from the speed of the moving visual target. We tested whether the effects of SC stimulation also depended on pursuit

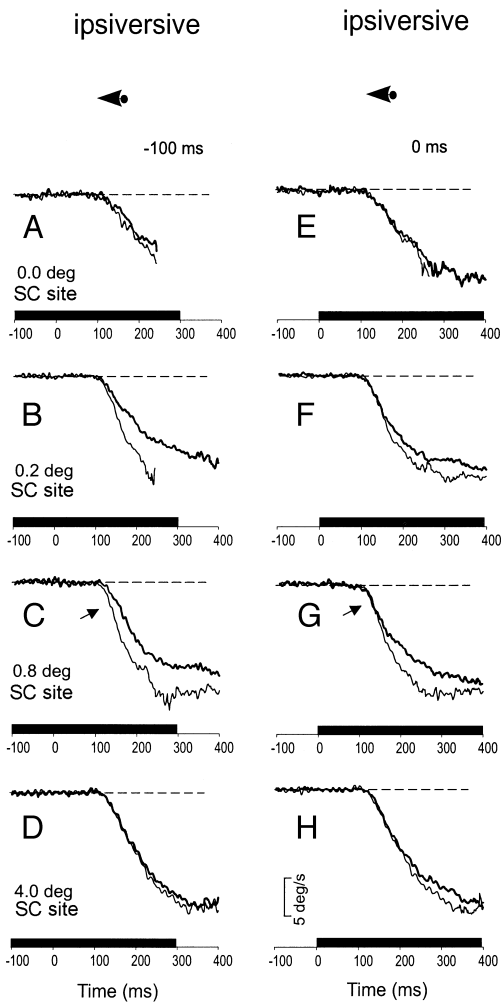


FIG. 6. Effects of SC stimulation are evident in the early phase of pursuit initiation. A–D: representative examples of pursuit eye velocity with (thick lined traces) and without (thin lined traces) rostral SC stimulation beginning 100 ms before the onset of target motion. All target motions are directed ipsiversively. E–H: trials when the stimulation and target motion onset occurred simultaneously. All trials have been truncated at the time of the 1st saccade. Thick lines, traces from stimulation trials; thin lines, traces from trials without stimulation. Horizontal dashed lines indicate 0°/s.

speed to determine whether the SC signal could be combined with the visual input to the pursuit system.

At 15 stimulation sites, we varied the target speed among 2, 5, 10, and 15°/s and measured the effects of SC stimulation on the pursuit responses. To determine the influence of pursuit speed, we plotted the difference in eye speed during the stimulation and no-stimulation conditions against target speed for each of the 15 stimulation sites (Fig. 7). The eye speed used for the calculation was the second 50 ms of the open-loop pursuit response. During this period of the pursuit response, the effect of SC stimulation depended on pursuit eye speed for many of the sites tested. Across the sample of stimulation sites, indicated by different symbols in Fig. 7, the difference in eye speed becomes increasingly negative as the speed increases, indicating that the suppression of pursuit eye speed was greater for faster speeds. Across the sample, there were significant differences between the eye speeds in the stimulation and no-stimulation conditions for ipsiversive pursuit [Kruskal-Wallis; $H = 7.829(3)$; $P = 0.050$]. The pairwise comparisons (Dunn's) indicated that the statistical significance resulted from the

differences between the 2 and 15°/s conditions. The differences for contraversive pursuit across the sample of sites failed to reach significance [Kruskal-Wallis; $H = 7.308(3)$; $P = 0.063$] for any of the speeds despite the tendency for the stimulation to have a greater effect on faster pursuit speeds. This finding is consistent with both behavioral and stimulation experiments in that greater effects are seen for faster speeds, indicating that the SC stimulation interacts with the visual inputs for pursuit eye movements.

The dependence of the stimulation effects on speed varied with the site of the stimulation of the SC map. For example, a stimulation site close to the fovea tended to have greater effects on faster speeds than slower speeds. The effects at this site also tended to occur sooner for the faster speeds of target motion [Fig. 8A; $t(19) = 15.93$; $P < 0.001$]. Similarly, this site reliably, albeit very modestly, increased contraversive pursuit at the slowest speed ($P =$ not significant) and reduced ipsiversive pursuit at the highest speed but only at a later pursuit period [Fig. 8E; $t(36) = -2.098$; $P = 0.04$]. Additionally, the effects of stimulation at sites further from the fovea differed. A site evoking a saccade amplitude of 0.2° suppressed pursuit maximally for both directions of pursuit at the fastest speed [ipsilateral $t(84) = 3.73$; $P < 0.001$ and contralateral $t(96) = -4.023$; $P < 0.001$] and was slightly better at suppressing the slower speed than the 0° site (Fig. 8B). Finally, a stimulation site of 4.0° had a negligible effect on pursuit except for a

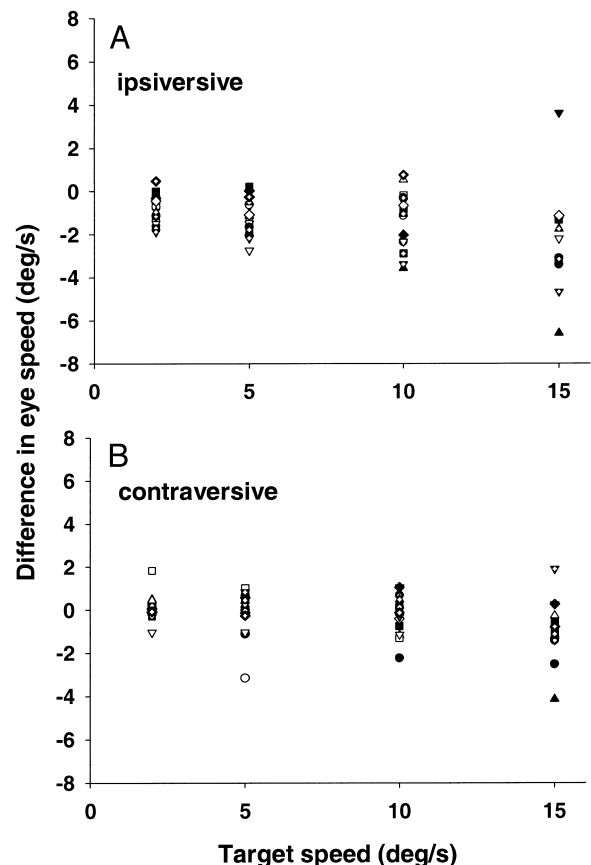


FIG. 7. SC stimulation effects are dependent on target speed. The difference in eye speed between the stimulation and no-stimulation trials for the 2nd 50 ms of the open-loop pursuit period is plotted as a function of target speed for each site of stimulation. Negative values indicate that pursuit speed was reduced in the stimulation trials compared with the no-stimulation trials.

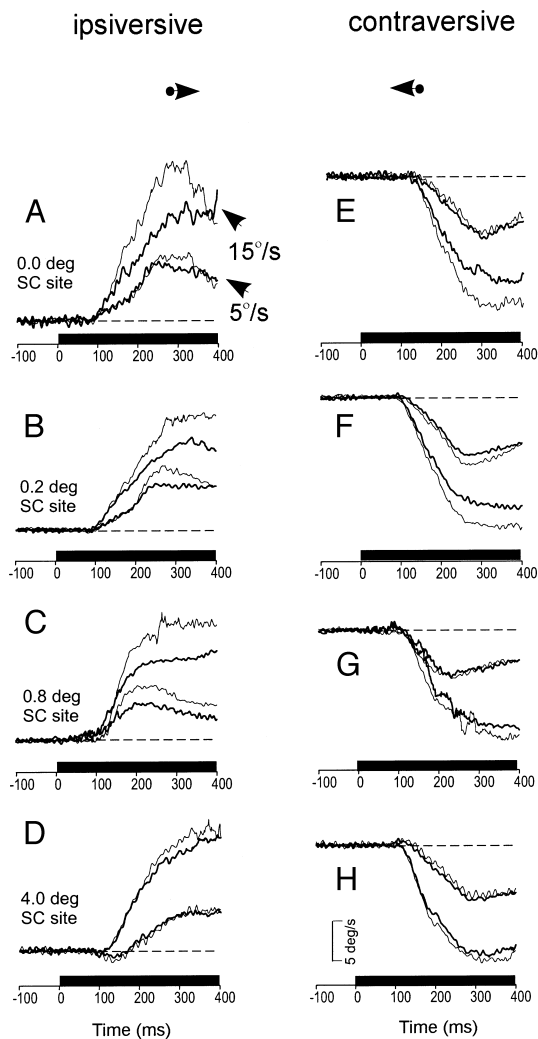


FIG. 8. Stimulation of the SC affects pursuit at different speeds. Two speeds, 5 and 15°/s, with and without SC stimulation are superimposed. Portions of the eye-velocity traces containing saccades have been removed (see METHODS). Thick lines are traces from stimulation trials and thin lines are traces from trials without stimulation. *Left*: pursuit responses ipsiversive to the SC stimulation site. *Right*: contraversive. Horizontal dashed lines indicate 0°/s. Note that the same stimulation site and parameters had different effects on pursuit depending on the speed of target motion.

modest effect on the later phase of the 15°/s ipsiversive pursuit (ipsilateral and contralateral, $P =$ not significant).

Finally, as a correlate to the behavioral experiments where speed perturbations were imposed during both pursuit and fixation, we tried to stimulate the SC during fixation to see if we could evoke smooth-pursuit eye movements under similar conditions. At sites where stimulation affected both saccades and pursuit, presentation of electrical stimulation during fixation never evoked a smooth-pursuit response, even at currents exceeding threshold for producing effects on saccades (not shown).

In summary, the effects of SC stimulation depend on the speed of pursuit, consistent with the SC stimulation affecting the visual processing stages of smooth pursuit rather than later stages of the pursuit pathway. The effects are not exclusively motor either since electrical stimulation of the SC did not evoke smooth-pursuit eye movements during fixation such as is seen in the frontal eye field smooth-pursuit region (Gottlieb et al. 1993). Additionally, as seen with a single target speed, the

effects of stimulation depended on the location of the stimulation on the SC map with maximal effects seen at locations representing target positions just slightly off the fovea. Taken together, these results support the hypothesis that the SC provides a signal that can influence smooth-pursuit eye movements.

SC STIMULATION AND PURSUIT MAINTENANCE. Stimulation of the rostral SC affected the monkeys' ability to maintain smooth-pursuit eye movements as well as to initiate them (Fig. 2C). Therefore we specifically tested the effects of rostral SC stimulation on maintained pursuit by presenting 300 ms trains of stimulation at 600 ms after the onset of target motion. By 600 ms, the initial catch up saccades, if any, had already occurred, and in most cases, pursuit attained a constant velocity approaching that of the target (as illustrated in Fig. 1). The effects on maintained pursuit with rostral SC stimulation mirrored the effects seen for pursuit initiation. For example, at a site close to the fovea, stimulation of the SC resulted in suppression of maintained pursuit at 15°/s ipsiversively (Fig. 9A). For this site, contraversive pursuit was suppressed also (Fig. 9B). We tested the effects of SC stimulation on pursuit eye velocity maintained at 5°/s as well and found that for most cases the trend was similar (not shown).

To quantify the effects of the SC stimulation across our sample of 15 sites, we calculated the difference in eye speed between the stimulation and the no-stimulation conditions for a 200 ms interval beginning 100 ms after the onset of the SC stimulus train. We then plotted this difference for ipsiversive and contraversive pursuit directions at two speeds, 5 and 15°/s, as a function of SC stimulation site (Fig. 10). Most of these sites were within 1° of the foveal representation, and many suppressed maintained pursuit in both directions. Some sites resulted in a slight facilitation of contraversive pursuit (Fig. 10B, filled circles above dashed line). However, the predominant effect was a reduction in the average pursuit eye speed.

In sum, like the effects on pursuit initiation, maintained pursuit was reduced in both directions and was greater for faster pursuit speeds when the stimulation site in the SC represented small locations ipsilateral to the pursuit target position, very close to the fovea. Indeed, there were occasional increases in contralateral pursuit as well.

SC STIMULATION AND THE VOR. We next tested whether rostral SC stimulation affected smooth eye movements simply because the stimulation affected all smooth eye movements or because the effects of stimulation were specific for smooth-

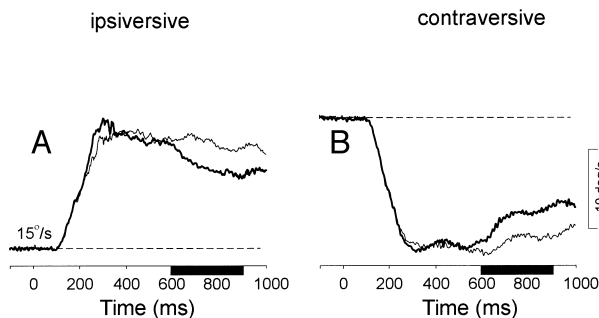


FIG. 9. Stimulation of the SC influences maintained smooth pursuit. Average eye-velocity traces are shown for stimulation and no-stimulation trials for ipsiversive (A) and contraversive (B) directions of pursuit. Portions of the eye-velocity traces containing saccades have been removed (see METHODS). The black bars indicate the onset and duration of the SC stimulation. Horizontal dashed lines indicate 0°/s. Thick lined traces, with stimulation; thin lined traces, without stimulation.

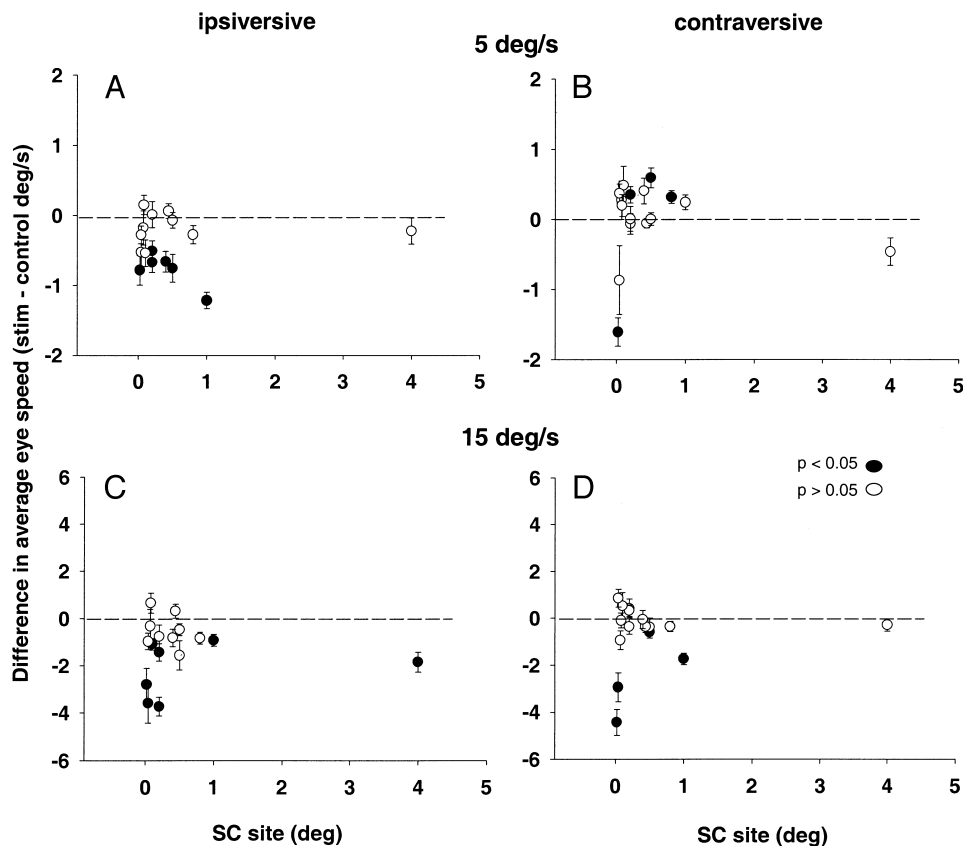


FIG. 10. Effects of stimulation on maintained pursuit for all sites. The difference in average eye speed with and without stimulation is plotted for 16 sites of SC stimulation site in 2 monkeys. The arrangement of this figure is the same as in Fig. 4. Points falling along the dashed line indicate no difference between the 2 conditions. Points falling below the line indicate suppression and points falling above the line indicate facilitation of maintained pursuit. We quantified the maintained pursuit effects by calculating the difference between the stimulation and the no-stimulation eye-velocity traces millisecond by millisecond for a 20 ms interval beginning 100 ms after the onset of the SC stimulus train. The duration of the SC stimulation was 300 ms. We then calculated the average difference between the 2 traces. This was done for both speeds of pursuit, 5 and 15°/s, as well as both directions of pursuit. We then plotted the difference in the average eye speed as a function of the location of the site of stimulation within the SC.

pursuit eye movements. We did this by comparing the effects of stimulation during smooth eye movements evoked by head rotations—the vestibular-ocular reflex (VOR)—to the effects of stimulation obtained during smooth-pursuit eye movements. For pursuit in these experiments, we presented monkeys with a target moving sinusoidally at 0.4 Hz and a peak-to-peak amplitude of 20°. To generate the VOR, monkeys fixated straight ahead in the dark while the chair was rotated sinusoidally at 0.4 Hz with a peak-to-peak amplitude of 20°. On interleaved trials, SC stimulation was introduced for 400 ms beginning during the phase in which the ipsiversive and contraversive eye velocity was maximal. Stimulation within the SC during sinusoidal pursuit when the peak eye velocity was maximal in the direction ipsilateral to the stimulation suppressed smooth-pursuit eye velocity (Fig. 11A; note that when the velocity trace begins to turn downward, this reflects the time when the eye velocity peaks and then declines indicating the turn around of the sinusoidal movement). At the same SC site and stimulation conditions but during the VOR, there was only a modest effect on smooth eye velocity (Fig. 11B). There were no effects on contraversive pursuit or VOR at this site (not shown). Across our sample of seven sites, six showed significantly different effects of stimulation in the ipsiversive sinusoidal pursuit and VOR conditions (Fig. 11C). Thus the effects of electrical stimulation differ for pursuit and VOR eye movements and argue against the possibility that the SC stimulation is a generic inhibitory signal that affects all smooth eye movements similarly.

STIMULATION OF SUPERFICIAL SC LAYERS. Since our sites of stimulation in the SC were at locations where low-threshold stimuli evoked saccades, it seems likely that the pursuit effects resulted from activation of the premotor neuronal elements

within the intermediate and deep layers. Despite this, it is possible that the effects on pursuit resulted from activation of the overlying visual neurons within the superficial layers of the SC as well. The significance of stimulating the superficial rather than the intermediate layers is particularly important because it is known that cortical areas encoding visual motion signals project directly to the SC superficial layers (Ungerleider et al. 1984) and that superficial layer visual neurons themselves convey motion signals (Davidson and Bender 1991).

To explicitly test the hypothesis that the pursuit effects resulted from activation of the overlying visual neurons in the SC, we measured smooth-pursuit eye movements in response to target ramps of 15°/s in two conditions. In the first condition, monkeys pursued a moving target, and on interleaved trials, we presented a train of stimulation to the intermediate layers of the SC at sites where saccades could be affected at low thresholds. In the second condition, we moved the electrode dorsally, into the superficial layers, confirmed that the electrode was located within the same region of the visual field representation by recording multiunit activity, and then interleaved stimulation trials using the same parameters. In both conditions, the stimulation was presented simultaneously with the onset of the target motion.

Comparing smooth-pursuit eye speed with and without stimulation of the SC in a single penetration revealed different effects on the eye movement depending on whether the stimulation occurred within the superficial layers or the intermediate and deep layers of the SC (Fig. 12). Stimulation of the superficial layers of the SC at a site very close to the representation of the fovea, increased ipsiversive pursuit speed (Fig. 12A, top left), whereas contraversive pursuit was relatively unaffected (Fig. 12A, top right). In marked contrast, stimula-

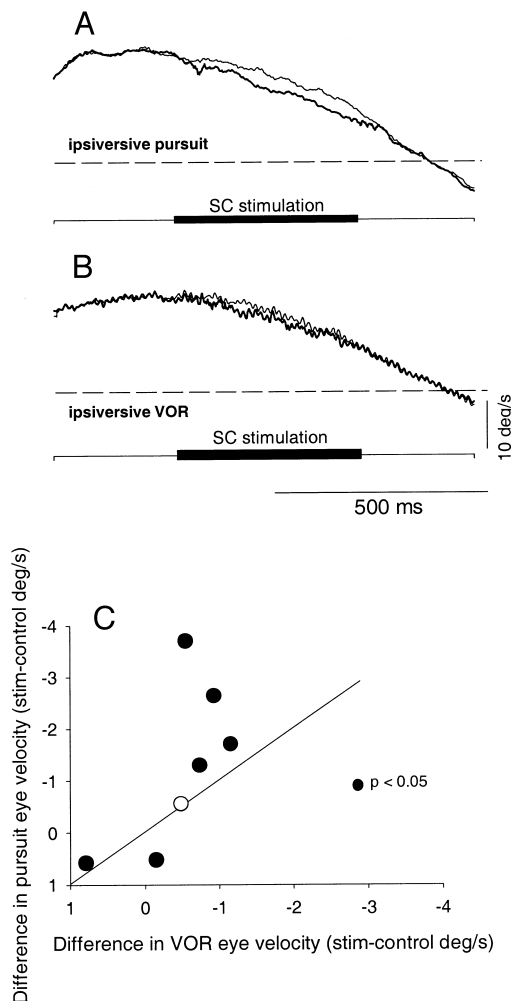


FIG. 11. Differential effects of SC stimulation on vestibular-ocular reflex (VOR) in the dark and sinusoidal pursuit. *A*: eye velocity during sinusoidal smooth pursuit (0.4 Hz, 20° peak-to-peak amplitude) ipsiversive to the site of SC stimulation is plotted with and without stimulation. *B*: ipsiversive eye velocity in response to whole body passive rotation in the dark (0.4 Hz, 20° peak-to-peak amplitude). Thick lined traces, with stimulation; thin lined traces, without stimulation. Saccades have been removed (see METHODS) Horizontal dashed lines indicate 0°/s. Filled bars indicate the duration of the SC stimulation. *C*: the average difference in ipsiversive pursuit eye velocity between stimulation and no-stimulation trials measured over the 150-ms interval of SC stimulation beginning 100 ms after the onset of the stimulation is plotted against the average eye velocity over the same interval during VOR. Six of the 7 cases had significantly different effects of stimulation between pursuit and VOR. In all cases, the VOR effect was smaller. For this example case, there was a statistically significant difference in eye velocity with SC stimulation ($P < 0.014$). None of the other 6 cases was statistically significant.

tion right below this site in the intermediate and deep layers suppressed pursuit eye speed in both directions (Fig. 12*A*, *bottom*). Thus for this site, the effect of superficial layer stimulation on ipsiversive pursuit was *opposite* that seen for the same direction of pursuit with intermediate and deep layer stimulation, and there was no effect on contraversive pursuit with stimulation of the superficial layers.

We replicated this experiment at eight sites in two monkeys and found similar effects in all cases. We plotted the difference in eye speed between the stimulation and no-stimulation conditions for each of the paired sites, one in the superficial layers and one in the intermediate and deep layers (Fig. 12*B*). For ipsiversive pursuit, all eight sites had statistically significant

differences in eye speed between stimulation in the intermediate and deep layers compared with the superficial layers. For contraversive pursuit, seven of the eight sites were significantly different in the two conditions. Thus the pursuit effects we report cannot be explained by the activation of superficial layer visual neurons.

Muscimol inactivation of the SC

In contrast to electrical stimulation, which activates the underlying neuronal elements, muscimol injections should re-

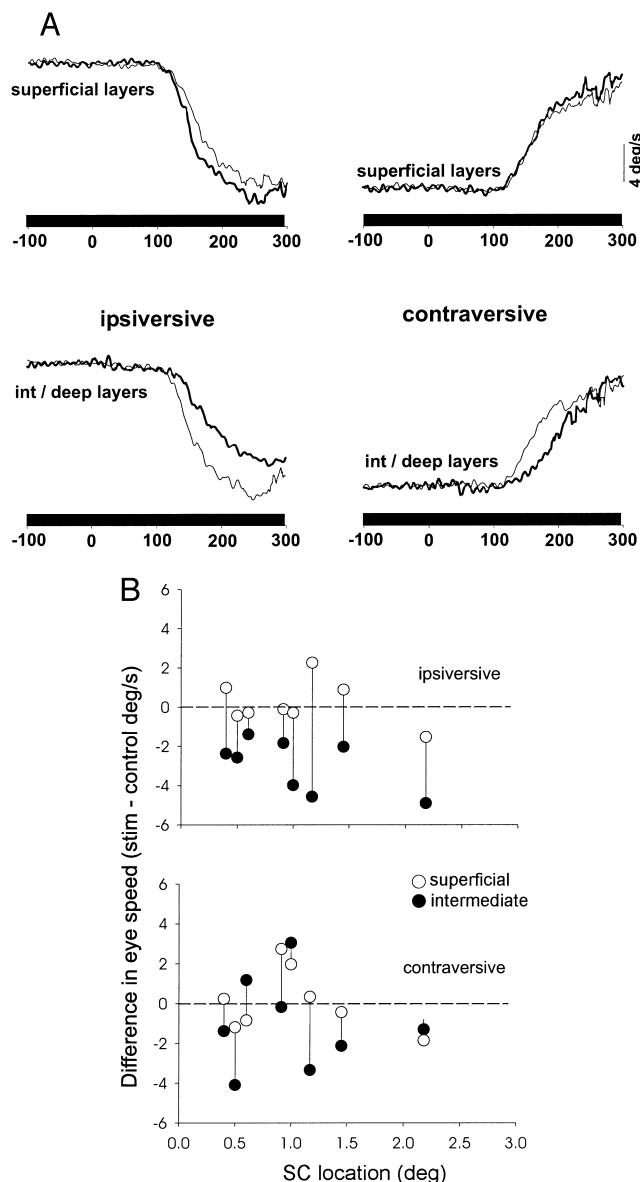


FIG. 12. Differential effects of intermediate and superficial layer stimulation of the rostral SC on pursuit eye velocity. *A*: pursuit eye velocity with stimulation (thick lined traces) and without stimulation (thin lined traces) for both directions of pursuit. The filled bars indicate the duration of the SC stimulation. *Top*: traces are with intermediate layer stimulation; *bottom*: traces are with superficial layer stimulation. *B*: the average eye speed in the 2nd 50 ms of pursuit initiation is plotted as a function of SC stimulation site. *Top*: ipsiversive pursuit; *bottom*: contraversive pursuit. Eight of 8 ipsiversive cases had significantly different effects on the eye movement between the superficial and intermediate layer stimulation. Seven of 8 cases differed significantly in the contraversive direction.

duce the activity of the underlying neurons and produce opposite behavioral effects. Therefore if the signal generated by SC neuronal activity is used by the smooth-pursuit system, we expect unilateral inactivation of the SC to produce a reduced smooth eye velocity when the pursuit target is located within the region of visual space represented by the inactivated part of the SC (Fig. 13). To determine this, we inactivated the SC while monkeys performed smooth-pursuit eye movements in both directions. For these experiments, we switched to the step-ramp paradigm so that we could independently assess the interactions between the location of the target step and the direction of target motion with the location of the SC map inactivated.

SACCADES. As we did with electrical stimulation, we first confirmed that our muscimol injections affected saccade generation as has been reported previously (e.g., Aizawa and Wurtz 1998; Quaia et al. 1998). To do this, we interleaved with the pursuit trials target step trials with stimuli located at 2, 5, 10, and 20° along the horizontal meridian in both hemifields and measured the saccades made to the target steps before and after the injections. We observed effects on saccades similar to those reported previously. First, contralateral saccades were hypometric, had reduced velocities and increased latencies. Second, for many sites, even though the injection was centered on a site evoking a 1° saccade with stimulation, saccades as large as 10° were affected by the muscimol. Third, in some cases, ipsilateral saccades occurred with a slightly shorter latency (data not shown). Finally, shortly after the injection

(within 5 min), a static fixation offset into the ipsilateral hemifield developed (see also Hikosaka and Wurtz 1983).

PURSUIT. We made eight unilateral SC injections in two monkeys. Seven of the injections were between 0.2° and 3.5° sites. One injection was made at an 8.8° site (see Table 1). Eye-velocity traces before and after a single muscimol injection into the rostral SC are shown in Fig. 14 and reflect a typical finding. For contraversive pursuit initiation, reduced eye velocity was observed, sometimes even when the target started slightly in the ipsilateral hemifield (Fig. 14G). For large steps into the ipsilateral visual field, pursuit was frequently enhanced (Fig. 14F). In contrast, an injection made more caudally had no effect and an injection made in the superficial layers had effects of the opposite sign (not shown).

To quantify the effects of inactivation of smooth-pursuit eye movements, we measured pursuit eye velocity in the second 50 ms of the initial 100 ms, open-loop pursuit response. We made this measurement before and after the injections of muscimol and plotted the average eye speed after the injection against the average eye speed before the injection. We divided the data points into four categories corresponding to the four plots in Fig. 15. The categories were: data in which the target stepped into the contralateral hemifield and moved contraversively (Fig. 15A), data in which the target stepped into the contralateral hemifield and moved ipsiversively (Fig. 15B), data in which the target stepped into the ipsilateral hemifield and moved ipsiversively (Fig. 15C), and data in which the target

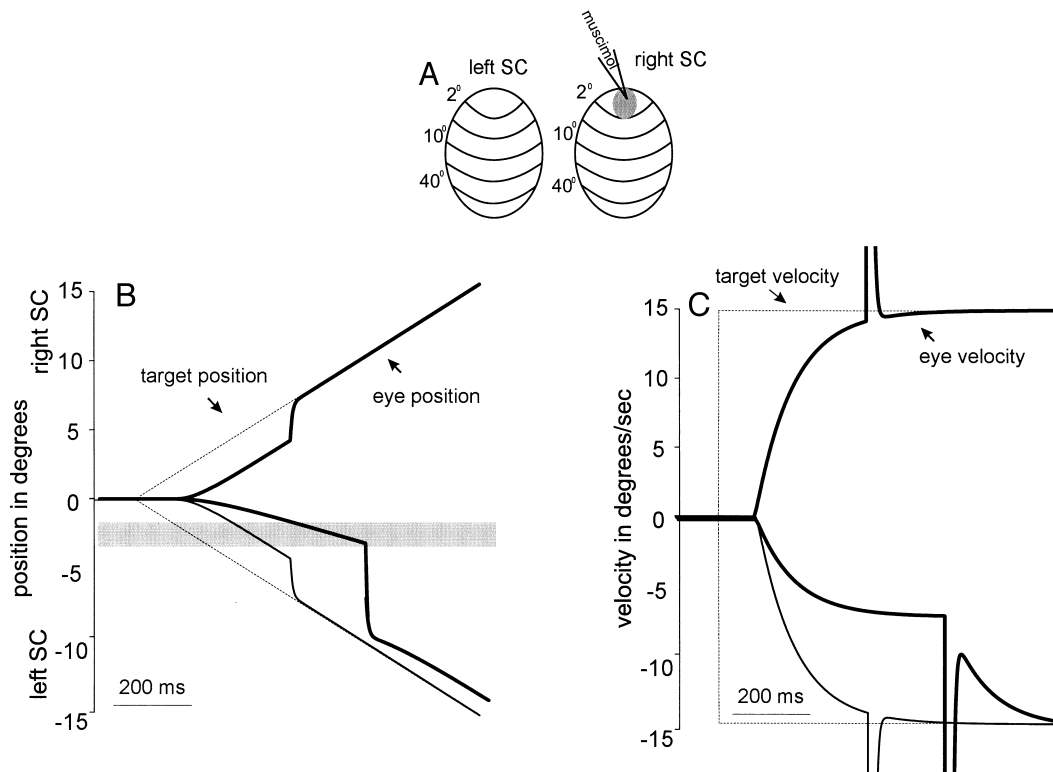


FIG. 13. A schematic representation of what would be expected of pursuit if the signal generated in the SC were removed with muscimol. *A*: the ovals represent the SC map showing an example injection site in the right SC where stimulation would evoke a 2.0° leftward saccade. This is a schematic injection and does not indicate the actual spread of muscimol, particularly since injections centered on this location affected saccades as large as 10° (see RESULTS). *B*: the vertical line indicates the degrees of visual angle with negative values indicating leftward positions represented in the right SC. The effect on pursuit is represented by the position traces; thick lines, eye position expected after the injection; thin lines, the eye position before the injection. Upward traces are rightward eye movements. With a visual target moving 20°/s leftward (dotted line beginning at "target onset") and inactivation of 2.0° leftward site in the SC, we would expect to slow down leftward pursuit. In contrast, rightward pursuit would remain unchanged. *C*: the same example is provided but in the velocity domain. The conventions are the same as in *B*.

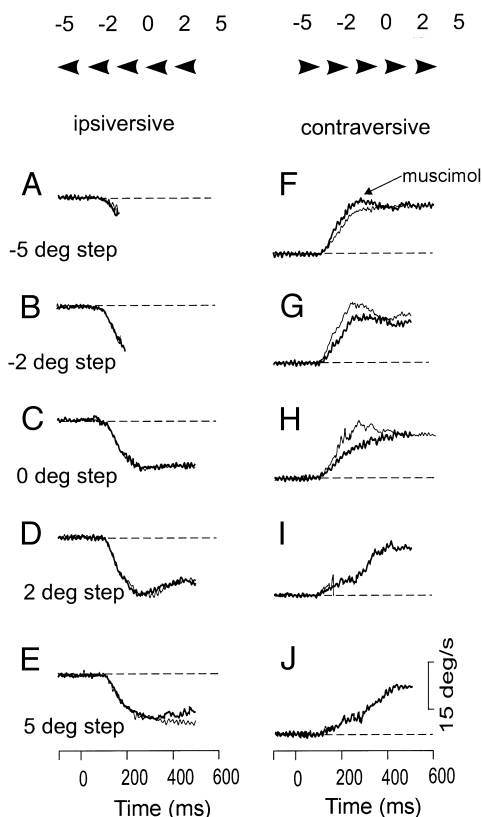


FIG. 14. Muscimol inactivation of the SC influences smooth pursuit. The schematic depicts the location of the target onset and direction of target motion. Negative values indicate target steps into the ipsilateral hemifield and positive values indicate target steps into the contralateral hemifield. Thick lines, eye-velocity traces after the injection; thin lines, before the injection. *Left*: ipsiversive pursuit velocities; *right*: contraversive eye velocities. The traces were truncated at the time of saccade occurrence. Horizontal dashed lines indicate 0%.

stepped into the ipsilateral hemifield and moved contraversively (Fig. 15D). This allowed us to determine whether the effects of rostral SC inactivation depended on the direction of pursuit or the location of the target step, similar to but not identical to, the directional and retinotopic distinctions found with MT and MST lesions (e.g., Dürsteler and Wurtz 1988; Dürsteler et al. 1987).

The reduction of pursuit eye velocity when monkeys tracked a target moving in the contralateral hemifield was evident in virtually every case (Fig. 15A). Furthermore many of the injections (not in the example case shown) revealed that eye speed was enhanced during ipsiversive pursuit (Fig. 15C), suggestive of a directional deficit in smooth-pursuit eye movements. However, comparing the cases when the target stepped into the contralateral hemifield and moved ipsiversively revealed a trend toward a reduction in pursuit eye speed, indicating that step location was important (Fig. 15B). When the target stepped into the ipsilateral hemifield and moved contraversively, a trend toward enhanced pursuit eye speed was evident (Fig. 15D). In sum, these results suggest that direction and location are both affected by SC inactivation. However, the direct comparison of both variables reveals a dominant effect from the location of the step (cf. Fig. 15, A and D).

There are a few points in the plots inconsistent with that interpretation; however, consideration of additional facts reveals most are consistent. First, one statistically significant

point in the contralateral-contraversive condition falls above the line, indicating that the eye speed was enhanced (Fig. 15A). Additionally, in the ipsilateral-ipsiversive condition one point, which was statistically significant, falls below the line, indicating pursuit eye speed was reduced. These points come from the same injection that was made slightly more dorsal to the site influencing saccades. This result may have occurred due to inactivation of superficial layer neurons. Second, in the contralateral-ipsiversive plot (Fig. 15B), there is one statistically significant point above the unity line, indicating pursuit eye speed was enhanced. This injection site was centered on a location very close to the fovea (0.2°) and may reflect an inactivation of neurons coding slightly ipsilateral target locations, tuning that is seen in some rostral SC neurons (Krauzlis et al. 1997c, 2000). Alternatively, since the injection site was so close to zero and the step location was large for this point, the result may reflect a disinhibition of SC locations *beyond* the inactivated region (Munoz and Istvan 1998). Finally, there are two statistically significant points falling below the unity line in the ipsilateral-contraversive plot (Fig. 15D), demonstrating that pursuit eye speed was reduced. Both of these points are from two different cases in the condition in which the target step was 2° . With the static fixation offset resulting from the injection averaged across trials, the target step was actually located at 1° ipsilateral. Except for the fact that the target would soon be in the contralateral hemifield, it is unclear why this resulted in a reduction in pursuit eye speed.

In sum, after inactivation of the rostral SC, contraversive pursuit is reduced and ipsiversive pursuit is frequently enhanced. For most points, the location of the target step was a better predictor of the pursuit deficit than was the direction of pursuit. An injection made more dorsally increasing the likelihood of affecting superficial layer neurons, affected pursuit in a manner predicted by the stimulation results namely, ipsiversive pursuit was *suppressed* and contraversive pursuit was *enhanced*. Finally, an injection located in the more peripheral representation was ineffective at influencing pursuit eye movements, also consistent with the stimulation results and indicating that the inactivation is not a nonspecific effect of reduced SC activity. Inactivation of the rostral SC influences pursuit in a manner opposite the effects resulting from electrical stimulation, namely pursuit in the ipsilateral hemifield is reduced with electrical stimulation and pursuit in the contralateral hemifield is occasionally enhanced with electrical stimulation. Thus we conclude that the activity of the rostral SC influences smooth-pursuit eye movements.

DISCUSSION

The results of our experiments demonstrate that the rostral SC influences smooth-pursuit eye movements. Activation of the rostral SC with electrical stimulation modifies pursuit in a manner similar to that for saccades (Fig. 2). Such stimulation reduces smooth-pursuit eye velocity ipsilaterally to the site of stimulation and in some cases, also contralaterally. Depending on the site of the stimulation, contraversive smooth eye velocity also could be slightly enhanced. We demonstrated a number of stimulation effects: the stimulation effects vary with the location of the stimulation on the SC map with most rostral sites producing the most effective suppression of ipsiversive pursuit (Figs. 4 and 5); the effects can occur immediately with the onset of pursuit (Figs. 6); pursuit eye movements are more

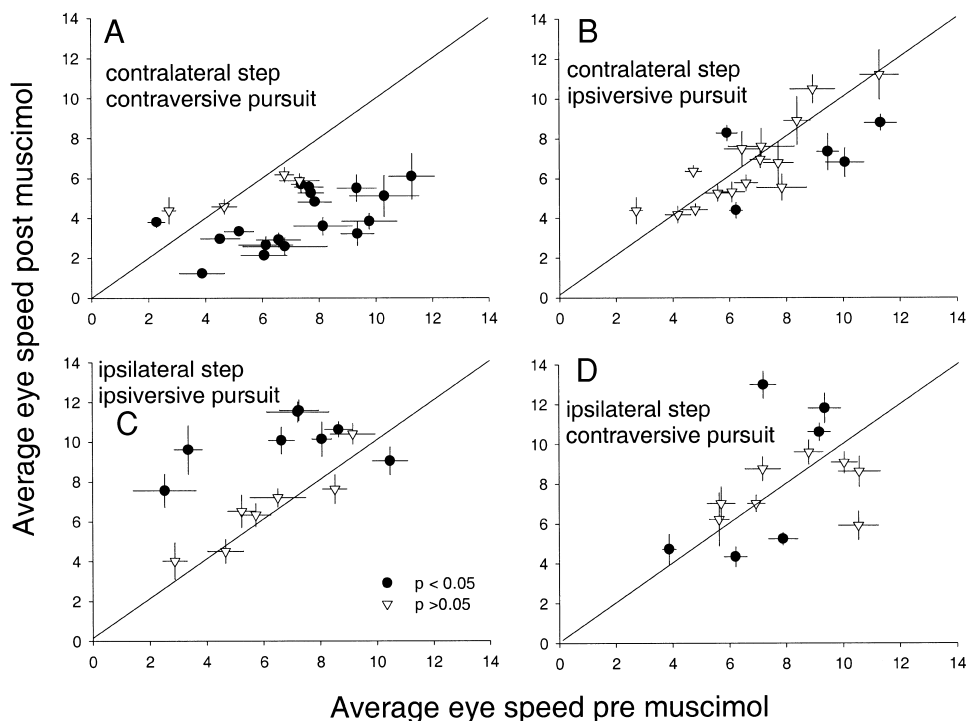


FIG. 15. Muscimol effects depended mostly on the location of the target step rather than the direction of pursuit. Average eye speed, taken from desaccaded traces, in the 1st 100 ms of pursuit after the muscimol injection is plotted against the same interval before the muscimol injection. Each plot contains 3 points per injection site. Two points are for the step-ramp conditions in which the target stepped into either hemifield, and 1 point is for the ramp condition when the target motion began at the fovea. The data are taken from 7 injections in 2 monkeys. The injection site at 8.8° on the SC map is not indicated. A and C: data from ipsiversive pursuit trials; B and D: data from contraversive pursuit trials.

affected as pursuit speed increases and are not evoked by stimulation during fixation (Figs. 7 and 8); the stimulation effects are evident for both pursuit initiation and maintenance (Figs. 9 and 10); the effects are not due to a generalized suppression because smooth eye movements evoked by head rotations are largely unaffected (Fig. 11); and it is the intermediate and deep layers of the SC that are responsible for the effects since superficial layer stimulation had either the opposite or no effect on pursuit (Fig. 12). In contrast to the stimulation, reduction in the activity of the rostral SC by injection of muscimol affects pursuit in an opposite manner; such injections reduce contraversive pursuit velocity and ipsiversive pursuit velocity is frequently enhanced (Figs. 14 and 15). These results of activating and inactivating the neurons in the rostral SC indicate that the activity of SC neurons contributes to smooth-pursuit eye movements. Moreover the results are consistent with the interpretation that the SC provides a position signal that can be used to drive the pursuit response.

The relationship of the results to the predictions of the position signal hypothesis outlined in the previous paper is not always obvious so we will consider the relationship in several steps. First, we will compare the effects of the rostral SC alterations on pursuit with those we obtained for saccades to compare the deficits of the pursuit system to those of the saccadic system, which is known to be driven by position signals. Next we will consider the extent to which the results of the pursuit experiments fit with the position signal hypothesis. Finally, we consider the possibility that the signal we are altering in the SC is a motion signal rather than a position signal.

Pursuit and saccade effects are similar

The first indication that effects on pursuit result from SC activity related to position is the similarity of activation and inactivation of the rostral SC on pursuit and saccades. For

pursuit of targets moving in the ipsiversive direction, activation of the rostral SC slows pursuit of moving targets just as such stimulation suppresses saccades to ipsilateral stationary targets. In contrast, for pursuit of targets moving in the contraversive direction, activation of the rostral SC either increases pursuit speed or has little effect just as such stimulation has less effect on saccades made to large, contralateral stationary targets. When the SC is inactivated by muscimol injections, the results are largely opposite the stimulation results for both pursuit and saccades. Inactivation of the rostral SC leaves pursuit of ipsiversive targets unaffected or speeds it. Saccades to stationary, ipsilateral targets are largely unaffected or occur with a slightly shorter latency (see also, Aizawa and Wurtz 1998; Quaia et al. 1998). Inactivation decreases pursuit speed to contraversive targets and small, contralateral saccades are hypometric. Our experiments show that activation and inactivation have opposite effects on pursuit, that these effects are different for ipsiversive and contraversive movements, and that the type of change is similar for both pursuit and saccades. Thus the current results provide evidence that the activity in rostral SC influences pursuit comparable to the previous evidence that this region influences saccades. Moreover these results suggest that the two types of eye movements are influenced by the same signal coded by rostral SC neurons.

The nature of the activity in the rostral SC fixation neurons has been proposed to signal attentive fixation (Munoz and Wurtz 1993a,b). The tonic activity of rostral neurons during fixation, the pause in activity of these neurons during saccades, the suppression of saccadic eye movements with electrical stimulation, and the shorter latency of large saccadic eye movements resulting from temporary inactivation of these neurons support that interpretation. Our results on pursuit are very similar to those for saccades, and it is therefore possible that the effects we see on pursuit result from a general signal that acts to suppress eye movements—pursuit as well as saccades—and produce fixation. In the present experiments, when the

stimulation was as close to the representation of 0° eccentricity on the SC map as was possible, we also found suppression of pursuit and saccades both ipsiversively and contraversively. We think this activity reflects small target positions adjacent to the fovea as described in our previous papers (Krauzlis et al. 1997, 2000) rather than a static fixation command for three reasons. First, despite a suppression of pursuit in both directions, the effects were asymmetrical—stimulation reliably suppressed ipsiversive pursuit more than contraversive pursuit. Second, for some stimulation sites where fixation neurons could be recorded, stimulation suppressed ipsiversive saccades and pursuit but facilitated contraversive pursuit, albeit modestly. Thus one stimulation site both increased and decreased pursuit. Third, smooth eye movements produced by head rotations were largely unaffected by rostral SC stimulation, precluding the interpretation that these neurons code a signal to fixate or to suppress *all* eye movements. It is important to note therefore that we interpret the present pursuit result and the previous saccade result in the same fashion. Specifically, the stimulation mimics a small, contralateral target position signal that interacts with the actual visual target. Thus during a 15° eccentric ipsiversive saccade, or during pursuit of a target moving at 15°/s, stimulation of the rostral SC representing a small, contralateral target provides a position signal in the direction opposite the one indicated by the visual stimulus and results in a reduced or suppressed movement.

SC provides a position signal for pursuit

Since the SC has long been known to provide a position signal for the saccadic system, the most likely interpretation of the effects of electrical stimulation and reversible inactivation of the rostral SC on pursuit eye movements is that it affects a position signal that is used by the pursuit system. We shall first describe the behavioral effects of imposed position signals on pursuit and then describe how we think the results of our experiments are consistent with this interpretation.

The smooth-pursuit response is generated primarily by visual motion signals (see for review Lisberger et al. 1987). There is evidence in both humans (Barnes and Asselman 1992; Barnes et al. 1987; Carl and Gellman 1987; Heywood and Churcher 1971, 1972; Pola and Wyatt 1980) and monkeys (Krauzlis and Miles 1996; Morris and Lisberger 1987; Segraves and Goldberg 1994) that smooth-pursuit eye movements are also influenced by visual position signals. For example, in humans, stepping a target to either side of the fovea creating a small offset of the target with respect to the fovea results in changes in smooth eye velocity in the direction of the target displacement (Pola and Wyatt 1980). Similarly, in monkeys, during open-loop pursuit of a stabilized image, small steps in the direction of target motion producing a static displacement of the target relative to the fovea result in slight increases in smooth eye velocity. Similarly stepping the target in the direction opposite the ongoing target motion results in large decreases in smooth eye velocity (Morris and Lisberger 1987).

Whereas these results in monkeys demonstrate the use of a position signal during *maintained* pursuit of a stabilized image, recently position signals were shown to influence pursuit during *initiation* in monkeys as well (for similar experiments in humans, see also Carl and Gellman 1987; Krauzlis and Miles 1996). During step-ramp target motion, small perturbations in target position were imposed at different times during the first

100 ms of presentation of the target motion. For example, a target would initially step to the left and then ramp to the right at constant velocity. At different times during the presentation of the constant velocity target motion the target position was changed either forward in the direction of ongoing target motion or backward, opposite the direction of ongoing target motion. When the target stepped forward, pursuit was initiated with a slightly higher velocity than when no target step was presented. In contrast, when the target stepped backward, pursuit was initiated with a much slower eye velocity relative to the no step condition.

A number of our results with SC manipulation are consistent with the interpretation that the stimulation is acting to impose a slight contralateral visual position error that influences the response of the pursuit system. First, neurons in the rostral SC are tuned for small contralateral target positions in both their visual and premotor responses (Krauzlis et al. 1997, 2000). Second, we obtained different effects of SC stimulation at different locations on the map where different target positions are located. For example, sites very close to the fovea suppressed pursuit bilaterally but the effects were always greater for ipsiversive than contraversive pursuit. This is consistent with imposing a small contralateral position signal producing a backward position error for both directions of pursuit but a larger backward error for ipsiversive pursuit and thus a larger slowing of eye velocity. A site slightly further caudal, representing a slightly more contralateral position signal, suppressed only ipsiversive pursuit, consistent with providing a large backward position error for ipsiversive pursuit and no net position error for contraversive pursuit.

In humans, position offsets created with retinal afterimages can *initiate* pursuit (Heywood and Churcher 1971, 1972; Pola and Wyatt 1980), whereas in monkeys, position offsets alone are less likely to initiate pursuit (Morris and Lisberger 1987). Our observations are consistent with this since stimulation of the SC during fixation either evoked small saccades or failed to evoke any response. We were never able to initiate smooth pursuit with stimulation of the rostral SC during fixation. This is in contrast to the findings in cat in which SC stimulation may evoke smooth eye movements (Missal et al. 1996; but see also Breznen and Gnadt 1997). Moreover, Segraves and Goldberg (1994) demonstrated that position signals as large as 3° can influence pursuit and we obtained maximal effects on pursuit within this region of the SC map. Although we did not systematically test sites further caudal on the map, one site where we injected muscimol at 8° failed to influence our step-ramp configuration of pursuit trials.

Finally, the results of our muscimol injections are also consistent with the position signal hypothesis. For example, when the target was stepped into the contralateral hemifield, in step-ramp pursuit trials, pursuit was suppressed in both directions. This demonstrates that the effects of the SC stimulation on pursuit is less influenced by the direction of pursuit but rather mostly depends on the location of the target step.

Indeed the idea that a position signal is used to drive a pursuit response is not new. A number of models of the pursuit system incorporate a position-error signal as a drive for the pursuit system (see Lisberger et al. 1987; Pola and Wyatt 1980). More recent models of oculomotor control have incorporated both the position-error signal and the idea that the SC was providing the position-error signal necessary to drive both types of movements (Cova and Galiana 1995; Lefèvre et al.

1994). Our single neuron evidence, that the neurons are tuned for small positions of a visual target close to the fovea (Krauzlis et al. 1997, 2000), and the stimulation effects on pursuit as well as the inactivation of these neurons resulting in pursuit deficits lend significant support to the hypothesis that the rostral SC is involved in pursuit and that the SC provides a position signal that assists in the drive for smooth-pursuit eye movements.

Motion signal in SC?

We think that the effects of activation and inactivation are consistent with a role for the SC in smooth-pursuit eye movements based on a position signal conveyed by neurons in the rostral SC (Krauzlis et al. 1997c, 2000). However, it is still possible that our experiments alter a visual motion signal, and there are several ways in which this might come about.

First, the manipulation of the rostral SC may be efficacious on pursuit due to the anatomical proximity and connections (Büttner-Ennever et al. 1996) with the nucleus of the optic tract (NOT), a structure intimately involved in smooth eye-movement generation (Schiff et al. 1988, 1990). Our results cannot be explained by this possibility for a number of reasons. First, stimulation of NOT produces ipsiversive slow eye movements while the monkey fixates, consistent with its role in generating the slow phase of optokinetic nystagmus (Schiff et al. 1988). We were never able to evoke smooth eye movements with stimulation of the SC while the monkey was maintaining fixation. Second, stimulation of NOT produces ipsiversive pursuit (Schiff et al. 1988) while the effects of SC stimulation typically produce the opposite, a *suppression* of ipsiversive pursuit. Third, muscimol inactivation of NOT impairs ipsiversive smooth eye movements (Schiff et al. 1990), whereas muscimol inactivation of the SC, *impairs contraversive* smooth pursuit. Fourth, NOT inactivation very rapidly (within 5 min) produces nystagmus with contralateral slow phases (Schiff et al. 1990), whereas, in our experiments, if nystagmus developed it occurred typically 30–45 min after an injection, consistent with diffusion into NOT. Thus our results are not at all consistent with the interpretation that the effects result from invasion of NOT.

A second possible way in which our experimental alterations in neuronal activity might reflect changes in motion signal processing is by altering the activity of superficial layer neurons. The superficial layers of the SC are known to receive inputs from visual cortical areas where the neurons are clearly related to the direction and speed of target motion as well as to pursuit eye movements such as MT and MST (Boussaoud et al. 1992; Ungerleider et al. 1984). Moreover neurons in the superficial layers show an effect of relative motion (Davidson and Bender 1991), and this may explain the results we obtained on pursuit. When we tested the hypothesis that the visual superficial layers were responsible for the effects on pursuit by stimulating the superficial layers directly, we found that this effect on pursuit was opposite to the stimulation of the intermediate and deep layers. Furthermore our one muscimol injection located more dorsally, perhaps inactivating the superficial layers preferentially, also had opposite effects to those seen after inactivation of intermediate and deep layer neurons. Therefore we are confident that the effects on pursuit with manipulation of the intermediate and deep layer SC neurons in our experiments do not result from altering superficial layer activity.

Another possibility is that both our activation and inactiva-

tion experiments are still acting on a visual motion signal but that motion signal is in the intermediate and deep layers of the SC. This possibility is relevant because recent experiments have shown that neurons in the intermediate and deep layers of the SC can, with extensive training in a visual motion discrimination task, display responses to motion and directional tuning (Horwitz and Newsome 1999). If we were altering a visual motion signal in the intermediate and deep layers, then we should get the same effects with stimulation as those seen in MT and MST where the neurons are clearly related to the direction and speed of motion. We see the opposite. In MT/MST stimulation of the foveal region leads to an *increase in ipsiversive* pursuit speed (Komatsu and Wurtz 1989), whereas we find that stimulation of the rostral SC leads to a *decrease in ipsiversive* pursuit speed. Similarly, inactivation of foveal MT/MST leads to a decrease in pursuit speed to ipsiversive targets (Dürsteler and Wurtz 1988), but we frequently obtained an increase in ipsiversive pursuit. These observations make it unlikely that the effects of activation and inactivation of the rostral SC are the result of altering the processing of motion information.

The role played by these neurons in pursuit seems to be similar to that played in saccades; they convey a position rather than a motion signal. This position signal used by both the saccadic and pursuit systems might reflect a mechanism for modulating the gain of pursuit eye movements seen with saccadic eye movements (Lisberger 1998). Alternatively, and since we demonstrated that the signal is independent of the actual movement made, this position signal might reflect a mechanism for selecting visual targets to serve as common goals for these two eye-movement systems (Krauzlis and Stone 1999; Krauzlis et al. 1997c). Increasing the activity of the neurons results in biasing both the saccadic and pursuit systems toward the location of target represented by the stimulation. Similarly, reducing the activity of the neurons biases the two eye movement systems away from the target location represented by the zone of inactivation. Finally it is worth noting, that for the activation or inactivation of the brain areas we have considered, the effects fall into two categories depending on whether the area carries a position or a motion signal. The effects of altering these areas are so different that they might be useful for diagnosis of damage in the oculomotor pathways, at least in the cortex and upper brain stem. If the error conveyed by a region is one of position, the deficit will be greater for movement to the *contralateral field* for either saccades or for pursuit guided by position. If the signal conveyed by an area is one for motion, the deficit will be greater for movement in the *ipsiversive direction*. Pursuit may show a deficit in either the contralateral field or the ipsiversive direction depending on the signal used or compromised by damage.

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