Evidence That the Superior Colliculus Participates in the Feedback Control of Saccadic Eye Movements

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Soetedjo, Robijanto, Chris R. S. Kaneko, and Albert F. Fuchs. Evidence that the superior colliculus participates in the feedback control of saccadic eye movements. J Neurophysiol 87: 679–695, 2002; 10.1152/jn.00886.2000. There is general agreement that saccades are guided to their targets by means of a motor error signal, which is produced by a local feedback circuit that calculates the difference between desired saccadic amplitude and an internal copy of actual saccadic amplitude. Although the superior colliculus (SC) is thought to provide the desired saccadic amplitude signal, it is unclear whether the SC resides in the feedback loop. To test this possibility, we injected muscimol into the brain stem region containing omnipause neurons (OPNs) to slow saccades and then determined whether the firing of neurons at different sites in the SC was altered. In 14 experiments, we produced saccadic slowing while simultaneously recording the activity of a single SC neuron. Eleven of the 14 neurons were saccade-related burst neurons (SRBNs), which discharged their most vigorous burst for saccades with an optimal amplitude and direction (optimal vector). The optimal directions for the 11 SRBNs ranged from nearly horizontal to nearly vertical, with optimal amplitudes between 4 and 17°. Although muscimol injections into the OPN region produced little change in the optimal vector, they did increase mean saccade duration by 25 to 192.8% and decrease mean saccade peak velocity by 20.5 to 69.8%. For optimal vector saccades, both the acceleration and deceleration phases increased in duration. However, during 10 of 14 experiments, the duration of deceleration increased as fast as or faster than that of acceleration as saccade duration increased, indicating that most of the increase in duration occurred during the deceleration phase. SRBNs in the SC changed their burst duration and firing rate concomitantly with changes in saccadic duration and velocity, respectively. All SRBNs showed a robust increase in burst duration as saccadic duration increased. Five of 11 SRBNs also exhibited a decrease in burst peak firing rate as saccadic velocity decreased. On average across the neurons, the number of spikes in the burst was constant. There was no consistent change in the discharge of the three SC neurons that did not exhibit bursts with saccades. Our data show that the SC receives feedback from downstream saccade-related neurons about the ongoing saccades. However, the changes in SC firing produced in our study do not suggest that the feedback is involved with producing motor error. Instead, the feedback seems to be involved with regulating the duration of the discharge of SRBNs so that the desired saccadic amplitude signal remains present throughout the saccade.

INTRODUCTION

Saccades are eye movements that are used to redirect the fovea to a new object of interest quickly and accurately. Because visual acuity is reduced during saccades, these movements are executed extremely rapidly. Indeed, the peak angular velocity of saccades often reaches 1,000°/s in the monkey (Fuchs 1967). Because saccades are so fast, they cannot be guided by visual feedback. Nevertheless saccades executed within the central 20° of the visual field are quite accurate. Although visual feedback cannot guide a saccade, feedback from other sources apparently does. Saccades that are perturbed in mid-flight are accurate even when the target has been extinguished before the saccade occurs (e.g., Keller et al. 1996). After human subjects take the sedative diazepam, their saccades are much slower than normal but still are accurate, i.e., saccadic amplitude is controlled (Jürgens et al. 1981). Taken together, these kinds of experiments support the hypothesis that the saccadic system employs a feedback circuit that compares an internal representation (efference copy) of current eye position with desired eye position (Robinson 1975).

The feedback model for saccade generation proposed by Jürgens et al. (1981) is schematized in Fig. 1 (thin rectangle). When desired saccadic/gaze displacement and trigger signals, both presumably from the superior colliculus (SC), are issued to the brain stem, the omnipause neurons (OPN) free the excitatory burst neurons (EBN) to respond to the desired displacement signal. The EBN inhibits the OPN, most likely through an interneuron (Int), to maintain EBN disinhibition throughout the saccade. The EBN emits a high-frequency burst (pulse) that is relayed directly to the motoneuron (MN) to bring the eyes to the target as quickly as possible. To maintain the eyes on the target, integrator 1 (f#1, Fig. 1) integrates, in the mathematical sense, the pulse of EBN firing, which is proportional to eye velocity. This integrated signal, which is proportional to the change in eye position (step), is also relayed to the motoneuron. The combination of the EBN burst and the position-related discharge rate of integrator 1 can be identified in the motoneuron discharge, which consists of a pulse step of firing rate for saccades (Fuchs and Luschei 1970; Robinson 1970). Integrator 2 provides an efference copy of the ongoing movement, which is compared (comp) continuously with the desired displacement signal. Once the difference between desired and actual displacement, dynamic motor error (dme), reaches zero, the EBN stops discharging and disinhibits the OPN, which in turn inhibits the EBN. When the EBN stops discharging, the EBN/Evests inhibit the Ints, which, in turn, inhibit the EBNs. This feedback model provides a self-sustained oscillation to saccade generation. However, this model appears to be inadequate to explain how the velocity of saccades is controlled. Recent studies suggest that the feedback loop is not the primary controller of saccadic velocity (Fuchs and Luschei 1970; Robinson 1975; Keller et al. 1996).

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discharging, the eye automatically stops on target. The advantage of having this local feedback loop is that the brain does not have to specify in advance the duration of saccade-related activity in the EBN. Any problem with the elements of the saccade generator is corrected automatically by the feedback loop to achieve an appropriate duration. Many elements and some of the connections in this model have been known for some time (for reviews, see Fuchs et al. 1985; Moschovakis et al. 1996).

Although the SC has important roles in saccade generation (for review, Sparks and Hartwich-Young 1989), it is unclear whether the SC lies within the feedback loop of Fig. 1. If the SC receives feedback about the ongoing saccade, the discharge of its neurons will be related to the saccade dynamics. Some studies suggest that this is indeed the case. Berthoz et al. (1986) and Munoz et al. (1991) showed that the discharge of tectoreticulo-spinal neurons in the cat SC was related to saccade velocity. Waitzman et al. (1988, 1991) suggested that the discharge of saccade-related burst neurons (SRBNs) in the monkey SC is related to saccadic motor error. In addition, the discharge of the most rostral SC neurons, the fixation neurons (Munoz and Guitton 1991), is related to the termination of gaze shifts in the cat (Bergeron and Guitton 2000). All of this evidence suggests that the SC receives a feedback signal. However, the nature of this signal and how it influences the discharge of SC neurons is unclear.

A different approach to test whether the SC is within the feedback loop is to perturb neurons downstream from the SC and determine the effect of such a perturbation on the discharge of SC neurons. When a saccade was interrupted in mid-flight by brief electrical trains delivered to the OPNs, the burst of the concomitantly recorded SRBN was also interrupted (Keller and Edelman 1994). The SRBN resumed its burst ∼6 ms after the stimulation ceased and before the saccade resumed. One possible explanation of these data is that the SC receives both negative velocity and position feedback from downstream EBNs to help restart its activity because the saccade has not been completed (Arai et al. 1999). However, this experiment does not rule out the possibility that the saccade is restarted by more central structures (e.g., the frontal eye fields) or by networks internal to the SC. It also does not indicate the nature of the feedback signal. For example, it does not reveal whether feedback to the SC is related to eye velocity or to some other characteristic of the saccade (e.g., its duration).

Recent evidence suggests that the SC might receive feedback from the brain stem for quite a different reason than to create a motor error signal. Electrical stimulation in the SC shows that stimulus trains of insufficient duration produce hypometric saccades (Stanford et al. 1996). These data suggest that the burst of SC neurons must have a certain minimum duration to elicit a saccade characteristic of a particular SC site. Of course, the correct duration of the SC discharge might already be present on SC input signals. Alternatively, the duration of the SC discharge could be continued for at least the duration of the saccade if the discharge were maintained by a feedback signal from the brain stem indicating the progression of the saccade.

To determine whether the SC indeed is part of a feedback loop and to study its possible role, we slowed saccades through manipulation of the downstream brain stem burst generator and tested whether there was a concomitant change in activity of SRBNs in the SC. We slowed saccades by injecting the

![FIG. 1. Schematic of a brain stem saccade generator for horizontal saccades (after Jürgens et al. 1981). Model operation is described in the text. +, excitatory connections; −, inhibitory connections; comp, comparator; EBN, excitatory burst neuron; Int, interneuron; MN, motoneuron; OPN, omnipause neuron; SC, superior colliculus; f#1, position integrator; f#2, feedback integrator; dme, dynamic motor error.](http://jn.physiology.org/)}
therefore the duration of the desired saccadic displacement involved in ensuring that the duration of the SC burst, and parsimonious explanation of our data is that the feedback is discharged of SRBNs would also be affected. Data produced by muscimol-induced slowing of OPNs suggest that the SC indeed receives input from the burst generator. Moreover, the most parsimonious explanation of our data is that the feedback is involved in ensuring that the duration of the SC burst, and therefore the duration of the desired saccadic displacement signal, is long enough to produce an accurate saccade. Some of these results have been presented in abstract form (Soetedjo et al. 1999).

METHODS

All surgical and experimental protocols were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (1997) and in compliance with the recommendations from the Institute of Laboratory Animal Resources and the Association for Assessment and Accreditation of Laboratory Animal Care International. Specific protocols were approved by the local Animal Care and Use Committee of the University of Washington (ACC No. 2602-01).

Surgical procedures

Two juvenile male rhesus macaques (Macaca mulatta), monkeys C and D, were used in this study. Scleral search coils were implanted on the left eye of each monkey (Fuchs and Robinson 1966), and two stainless steel recording cylinders were implanted over holes that had been trephined in the monkey’s skull. A cylinder directed at the paramedian pontine reticular formation was inclined at 20° relative to the sagittal plane and aimed 2 mm dorsal to stereotaxic zero. A chamber directed at the SC was tilted caudally 38° in the mid-sagittal plane and aimed at a point 15 mm dorsal and 1 mm posterior to stereotaxic zero. The chambers were secured to the skull with titanium screws and dental acrylic.

Behavioral training and experimental procedures

The monkeys were trained to follow a jumping visual target on a tangent screen. The target, a continuously lit laser spot that was aimed at orthogonal mirrors attached to galvanometers controlled by a computer, was back-projected on the screen. The monkeys were rewarded with a drop of applesauce if their eyes made a targeting saccade within 500 ms of a target jump, if the eye stopped within ±2° of the spot and if it stayed on target for ≥700 ms. They were rewarded for every correct trial. The timing of the target jump was randomized between 2 and 4 s, and the inter-trial interval was 1 s. In each experiment, every saccade started from the same position on the screen, usually the center position. However, if the optimal amplitude of the SRBN was large (e.g., 17°), the saccade was started off center. We ensured that the monkey was satiated at the end of each experimental session.

We isolated a single unit by adjusting the depth of the tip of a microelectrode with a hydraulic microdrive. The unit activity was recorded extracellularly with tungsten microelectrodes with iron-plated tips. Action potentials from single neurons were amplified, filtered (300 Hz to 10 kHz), and displayed on an oscilloscope. Both eye- and target-position signals were low-pass filtered at 500 Hz. All analog signals and the associated neuronal activity were recorded on a PCM video tape recorder (Vetter Model 4000A) for off-line digitizing.

We explored the caudal pons to find the OPNs and then determined the extent and topographic saccadic map of the SC. To locate the OPNs, we first found the abducens nucleus and moved the electrode medially and rostrally. OPNs were identified by their constant high rate of discharge during fixation and pauses for saccades in all directions (Keller 1974; Luschei and Fuchs 1972). On the day of an injection, we recorded from both the pons and SC simultaneously to determine the location of the OPNs and to locate a SRBN. Once we determined the depth of the OPNs, we withdrew the recording electrode and cannula and replaced the electrode with an injection pipette assembly (Kaneko 1996) filled with muscimol in phosphate-buffered saline solution (2 µg/µl). Briefly, a short glass pipette that was pulled to a fine tip and broken to a ~20 µm opening was inserted over and then glued at the tip of a 30-gauge metal cannula.

The SC was identified first by the visual cells in its superficial layers and then by its saccade-related neurons, which were recorded ~1-1.5 mm deeper. The visual cells responded to the appearance of a target spot at certain locations in the contralateral visual field but did not exhibit a discharge with the subsequent targeting saccade. In contrast, saccade-related neurons discharged a burst for saccades into the neuron’s movement field (Wurtz and Goldberg 1972). Saccades to the center of the field were accompanied by the most vigorous bursts (instantaneous discharge rates often to 1,200/s) with the longest burst lead times and these were defined as optimal. Nearby nonoptimal saccades were accompanied by lower discharge rates and shorter lead times (Freedman and Sparks 1997). SC neurons that discharged a burst for saccades could also display a visual response and/or a prelude of activity that preceded the frank saccadic burst.

Once we isolated a saccade-related neuron, we determined its optimal direction as the angle halfway between those saccade vectors where the burst was the weakest, i.e., the extremes of its movement field (Munoz and Wurtz 1995a; Sparks and Mays 1980). While the monkey was making saccades in the optimal direction, we varied the size of the target step in 1° increments to find the optimal amplitude. We displayed the instantaneous firing rate on a storage oscilloscope to estimate the amplitude that produced the maximum discharge frequency. Once we had found the optimal direction and amplitude, we set the computer to produce target jumps of different sizes in the optimal direction so they bracketed the optimal amplitude. Usually we used pseudorandom target amplitudes that included the optimal amplitude and four or five amplitudes that varied in 1° steps around the optimal amplitude. This strategy allowed us to collect the largest number of optimal amplitude saccades. In a few experiments (D1 and D11), where the optimal amplitude was >15°, the target amplitude was varied in 2° steps.

After collecting preinjection saccades, we delivered muscimol (80–460 nl) into the OPN region using a pico pump (WPI) and continued to record behavioral and single-unit data for 5–105 min after the injection. The recording time depended on our ability to maintain unit isolation and the monkey’s tracking behavior. Loss of neuron isolation, death of the neuron, or a decline in the monkey’s behavior terminated the experiment. Eight to 83 min after the injection, the monkey’s horizontal saccades sometimes became hypometric. We speculate that this dysmetria was caused by the spread of muscimol to the nearby EBNs because the hypometria occurred earlier in those experiments in which more muscimol was injected. Occasionally we also observed a shift of the null position of the eyes even later in the recording period (cf. Kaneko 1996). When the animal was no longer able to make optimal vector saccades for the SRBN under study, the experiment was terminated.
Data analysis

The recorded analog signals of both horizontal and vertical eye and target positions were digitized at 1 kHz. A single action potential was digitized as a time stamp in the digitized file with 10-μs resolution. The analysis program displayed these stamps as a spike raster. Digitized data were analyzed with a customized program developed in our laboratory. Briefly, the program displays target positions, eye positions and velocities, spike rasters, and instantaneous firing rate. Figure 2 shows two examples. The program marks the saccade automatically whenever horizontal and vertical eye velocities exceed 10°/s (saccade onset) or fall below 10°/s (saccade end). Saccadic duration was measured as the interval between the earliest component onset and the latest component offset (thin vertical lines in Fig. 2). The user could override the computer selections if necessary and mark the saccade manually.

Because of the variability between trials and between neurons, we always marked the burst of neural activity manually. We marked the onset and offset of the burst when the interspike intervals of a group of consecutive spikes displayed higher rates than the surrounding spikes as revealed in both the spike raster and instantaneous firing rate. An easily identifiable burst is shown in Fig. 2A (black spikes) and one of the most difficult bursts in Fig. 2B. Because this subjective analysis might be biased, we compared it with an objective method. To determine burst onset and offset objectively, we generated a spike density function from the spike raster of each saccade trial by replacing each spike with a Gaussian function (σ = 15 ms). A spike density function generated in this way is shown in the lowest traces in Fig. 2, A and B. We defined burst onset and offset as the time when the spike density function crossed 50% of its peak value (F_max). The interval between these two times was taken as the burst duration.

We used this analysis on a neuron from each monkey, D16 (the neuron of Fig. 2B) and C3. These neurons were selected for several reasons. First, their firing rates decreased as saccades slowed so that the ends of their bursts were indistinct. Second, they exhibited pre- and postburst activity (i.e., the burst did not begin or end abruptly). Third, duration data from both experiments were evenly and widely

![Figure 2](http://jn.physiology.org/)

**Fig. 2.** Methods of analysis. A and B: single saccade trial illustrates how the saccade and SRBN burst were marked. Traces from the top are horizontal eye (HE) and target (HT) position, vertical eye (VE) and target (VT) position, horizontal (HE) and vertical (VE) eye velocity, action potential time stamps, instantaneous firing rate, and spike density function (σ = 15 ms). Arrows indicate the beginning and end of the saccadic components and the time of peak velocity. Thin vertical lines indicate saccade duration. Heavy spikes in the action potential trace are manually marked bursts. Arrows in the inset show doublets and triplets of action potentials. On the spike density function, 50% of F_max (the maximum firing rate) indicates the beginning and end of the burst to calculate objective burst duration.
distributed. And fourth, data from those two neurons were analyzed 
~1 yr apart, so we could test the consistency of our marking criteria. Results of the subjective and objective analyses are compared in Fig. 3, A and B; - - - are the lines of equality. The objective analysis tends to produce longer durations (intercepts: 20.65 and 14.95 ms). These intercepts are consistent with the width of the Gaussian function (15 ms). Most important, the visual inspection data are strongly correlated with the objective criteria data ($r = 0.76$ and 0.79). Because part of our analysis was a regression analysis between burst duration and saccade duration, we compared the regressions from data determined by the objective criterion and by visual inspection (Fig. 3, C and D). For neuron C3, the regression of saccade duration on burst duration of visual inspection data (Fig. 3C, - - -) had an intercept of 18.43, a slope of 0.73, and a regression coefficient of 0.91; the same measures for objective criteria data (Fig. 3C, - - -) were 19.59, 0.60, and 0.81, respectively. For neuron D16, the measures were 11.51, 0.71, and 0.82, respectively, for visual inspection data (Fig. 3D, - - -), and 11.47, 0.68, and 0.89, respectively, for objective criteria data (Fig. 3D, - - -). For both neurons, neither the slopes ($t$-test, $P > 0.09$) nor the intercepts ($P > 0.5$) are significantly different. We conclude that our visual inspection analysis agrees with the objective method. We preferred our method because it was not biased by replacing the spikes with Gaussian functions, did not distort the duration measurements by the arbitrary choice of Gaussian width, and better accounted for variations in individual bursts.

The magnitude of the peak firing rate during the SRBN burst was defined as the average frequency of the five consecutive spikes with the shortest total duration. We used this measure rather than the two-spike peak burst rate because the burst of SRBNs frequently contains high-frequency doublets or triplets, which produce unusually high firing rates for brief periods of time (Fig. 2, A and B, arrows in the insets). Similar closely spaced action potentials also have been recorded in cat SC neurons in response to intermediate levels of injected currents (Grantyn et al. 1983).

Because the optimal saccades of most of the SC SRBNs used in this study had oblique vectors, we compared neuronal firing with the vector properties of saccades. Vector eye amplitude ($E_v$) was calculated as

$$E_v = \sqrt{\text{Horizontal Amplitude}^2 + \text{Vertical Amplitude}^2}$$

Vector eye velocity was the numerical derivative of vector eye amplitude. We used a Matlab (Mathworks) program to produce vector eye traces and to determine instantaneous saccadic acceleration. For the initial part of the analysis, we used our laboratory-customized program to calculate the metrics of the saccades (e.g., amplitude, direction, duration, and velocity) and the relative timing of the target, saccade, and neuronal activity. Saccades were included in the analysis if they landed within ±15% of the optimal target amplitude and within ±10° of the optimal direction. The regression analysis and curve fits were done in Statview (SAS). Statistical significance was based on a Student’s $t$-test.

To chart the progression in the changes of saccadic peak velocity and duration over the course of an experiment (Figs. 6 and 7), we used Statview 5.0 to fit the magnitude of either parameter as a function of time with a piecewise linear regression called a "locally weighted
scatter plot smoother” (LOWESS) (Cleveland 1979). Briefly, in predicting a $y_i$ value from an $x_i$ value, this algorithm puts a window around the $x_i$ value and calculates the weighted least-square linear regression of the data points in the window. The weights are inversely proportional to the distance between $x_i$ and its neighboring data points within the window. A tension parameter controls the neighborhood of influential data points. Increasing this parameter tends to increase the smoothness of the fit whereas decreasing the parameter causes the fit to follow the noise of the data. A tension parameter of 70 was chosen because it smoothed the curve sufficiently and revealed the trends of the data. Before the fitting, we normalized the peak velocity and duration data by dividing them by the mean peak velocity and duration of preinjection saccades in each experiment so that the ordinates (Fig. 7) are plotted in percentage. We normalized the data to reveal any slowing that occurred during the injection of the drug.

RESULTS

We successfully maintained isolation of a SC neuron while injecting muscimol into the OPN region on 16 separate occasions. Two of the 16 injections failed to produce slower saccades so their data were not considered further. We speculate that these failures were caused by inactive muscimol because all injections of muscimol that were <1 wk old resulted in slower saccades. In the other 14 experiments, four saccade-related neurons were recorded from the left SC in animal C and 10 from the right SC in animal D. Based on their visual responses and saccade-related activity, we divided our SC neurons into three groups as illustrated in Fig. 4. Eleven of the 14 neurons exhibited a prominent burst aligned with the saccade (Fig. 4, A and B, left). These 11 neurons had either just a saccade-related discharge ($n = 2$; Fig. 4A) or, in addition, had a visual response after the target step and a prelude of activity prior to the saccade-related burst ($n = 9$; Fig. 4B, right). Although Sparks and Mays (1980) define SRBNs as exhibiting only a burst related to the saccade, like the neuron shown in Fig. 4A, we will refer to these 11 neurons as SRBNs for ease of description. Their presaccadic activity might be related to other parts of the saccadic paradigm. The remaining three neurons discharged a burst at a fixed time after the target step followed by sustained activity that did not culminate in a saccade-related burst (Fig. 4C). We performed quantitative analyses only on the 11 SC neurons with a clear saccadic burst.

The optimal vectors of the 14 neurons spanned a substantial range of directions and amplitudes. The optimal directions and amplitudes were estimated from preinjection data, except for neuron D5, for which preinjection data were lost due to a tape recorder malfunction. For this neuron we took the first 2 min of postinjection data as preinjection data. The optimal amplitudes ranged from 4 to 17° (Fig. 5). The optimal directions ranged from 0 to 256°. All oblique optimal vectors had horizontal components that were contraversive to the recording site, with the exception of neuron C1, whose vector had a slight ipsiversive component.

Effect of OPN injection on saccadic metrics

SACCADIC PEAK VELOCITY AND DURATION. Injections of muscimol into the OPNs caused the peak velocity of saccades to decrease and their duration to increase. The time course of the slowing of optimal saccades during a representative experiment (D3) is shown in Fig. 6A. Although the saccade slowed, it remained accurate and we could still elicit the optimal
Feedback control of saccades

FEEDBACK CONTROL OF SACCADES

Saccades (12° amplitude at 165°) for this particular neuron at 37 min after the injection (Fig. 6B).

Immediately after the injector valve was closed (t = 0), both saccadic duration and peak velocity were like those of preinjection saccades (Fig. 6A, Pre). Within 3–5 min, saccadic peak velocity had slowed and duration had increased. By ~25 min, peak velocity was ~50% slower and saccadic duration ~48% longer, on average, than before the injection. The time course of the changes in saccadic duration and peak velocity were fit with the LOWESS smoother described in METHODS.

Figure 7 shows the time course of the changes in peak velocity and duration of optimal saccades (those within ±15° of their optimal amplitudes and ±10° of their optimal directions) for all 14 experiments that produced saccadic slowing. Each individual fit, therefore, is of data from saccades with similar vectors. Most of the curves start below 100% because the postinjection data were normalized with the means of the preinjection data and some slowing occurred during the muscimol injection (from 1 to 11 min). During the course of the experiment, saccadic peak velocity across experiments decreased by 20.5–69.8% and saccadic duration increased by 25–192.8% relative to the means of preinjection saccades. In experiments D8 and D23, which lasted 84 and 60 min, respectively, the injection produced only gradual and modest changes in saccade duration and peak velocity. However, even in these two experiments, the postinjection saccades still were significantly slower and longer (P < 0.001).

The time course of the change of saccadic velocity and duration depended on the quantity of injected muscimol, which could not always be precisely controlled owing to the extremely small volumes involved. In the experiment that lasted the shortest amount of time (5 min), we lost the neuron. The largest amount of muscimol (460 nl) was injected in an experiment that lasted only 8 min, whereas only 80 nl of muscimol was injected in the longest experiment (83 min). The smaller doses of muscimol caused slowing to occur more gradually and produced hypometric saccades that did not differ from the optimal vector until much later in the experiment.

We think the saccadic slowing was produced by inactivation of the OPNs and not by involving other elements of the burst generator. EBNs do lie in the vicinity of OPNs (Strassman et al. 1987), but they discharge primarily for horizontal saccades and only weakly, if at all, for vertical saccades (Luschei and Fuchs 1972; Strassman et al. 1986). Therefore if our injections were influencing primarily EBNs rather than OPNs, they should have little influence on vertical saccades. However, even in experiment C1 where the SRBN had a nearly vertical optimal vector (~92°), there was a decrease in vertical saccadic velocity and a concomitant increase in saccadic duration (Fig. 7, - - -). Because OPNs pause for saccades in all directions, this experiment suggests that our injection affected primarily the OPN area rather than the nearby EBNs.

Saccadic Velocity Profile. We next investigated whether a specific portion of the saccadic time course was altered to cause the increase in saccadic duration. Saccades accelerate to a peak velocity (□) and then decelerate (▲) to stop the eyes on target (Fig. 8A, inset). Smaller saccades usually have equal acceleration and deceleration phases, but as saccades become larger, deceleration outlasts acceleration. For the saccadic data gathered while recording from neuron D1, whose optimal saccadic amplitude was 17°, the deceleration duration increased faster than the acceleration duration as saccade duration increased (Fig. 8A). The slopes were significantly different (slopes: 0.65 vs. 0.35, P < 0.01). To determine whether the deceleration duration always increased faster than the acceleration duration, we plotted the ratio of the acceleration slope to the deceleration slope (in percentage) against saccade amplitude for all 14 experiments (Fig. 8B). When muscimol slows saccades, it appears that deceleration increased as fast as or faster than acceleration in 10 of 14 experiments (slope ratio ≤ 100%).

Saccadic Acceleration. The data in Fig. 8B suggest that the velocity profile of saccades in most experiments should become more asymmetric as the saccade slows. We tried to test this suggestion by examining saccadic acceleration profiles. Because differentiating saccadic velocity produced very noisy data, we chose to average the acceleration traces of several saccades aligned on their onset. We used all optimal vector saccades from preinjection data, whereas data from the last 2–7 min postinjection were used to produce the averages of postinjection acceleration profiles (n ≥ 5). In Fig. 9, we plotted three acceleration profiles from the experiments with the least noisy data. During the slower postinjection saccades, the acceleration duration had increased less than the deceleration duration. This difference is particularly noticeable for experiments D11 and D14.

In addition, both the peak acceleration and deceleration after the injection were less than those before. For experiments D11, D12, and D14, the average peak acceleration postinjection was
FIG. 7. Fits of the time course of increases in saccade duration and decreases in peak velocity (as percentages of preinjection) for all 14 experiments. Postinjection data were normalized with the means of preinjection data. Experiments lasted 5–83 min. Each fit represents a single injection experiment on a different day. – – –, experiment C1, where the optimal direction of the neuron is 92°. In each experiment, all saccades were within ±15% of the optimal saccade amplitude and ±10° of the optimal saccade direction of the neuron under study.

FIG. 8. Changes in acceleration and deceleration times as saccades increase in overall duration. Saccadic velocity trace (inset) shows that acceleration duration is taken as the time from 0 to peak velocity (□); deceleration duration as the time from peak to 0 velocity (▲). A: in experiment D1, deceleration duration (▲) increased significantly ($P < 0.01$) faster with saccade duration than did acceleration duration. B: plot of the ratio in percentage of acceleration/deceleration slopes (calculated as in A) for all 14 experiments. —, a ratio of 100%. Each symbol represents a different experiment.
36.7, 87.8, and 45.5%, respectively, of the preinjection peak acceleration. In addition, the average postinjection peak deceleration was 31.8, 53.8, and 35.5%, respectively, of the preinjection peak deceleration. To summarize all experiments, we determined the ratio of the percentage of peak acceleration to the percentage of peak deceleration. If postinjection peak deceleration decreased more than did the peak acceleration, the ratio would be >100%, as in the three illustrated profiles. In 10 of 14 experiments, the postinjection peak deceleration was reduced as much or more than the peak acceleration (Fig. 9D). Therefore not only was deceleration duration longer than acceleration duration, but peak deceleration also was reduced more than peak acceleration. However, saccades showed both a decrease in peak deceleration and a prolonged deceleration in only 6 of 14 experiments (compare Figs. 8B and 9D).

EFFECT ON SACCADE REACTION TIME. Because the OPNs are thought to control the time when the saccadic burst generator can respond to the desired gaze displacement signal (recall Fig. 1), we examined whether saccadic reaction times changed after muscimol injection. In 9 of the 14 injections that slowed saccades, we compared the reaction times of 100 preinjection saccades with those of the last 100 postinjection saccades. For the other five injections (experiments C2, D5, D11, D12, and D23), there were only 40, 21, 73, 84, and 67 pairs, respectively, of both pre- and postinjection saccades. We did not restrict our analysis to optimal vectors because the injection slowed all saccades. In 10 of 14 experiments, there was no significant difference (percent changes were not significantly different from 0, P > 0.05) in mean saccadic reaction times before and after the injection (Fig. 10). In the remaining four experiments, three (experiments D8, D12, D14) showed significant increases in reaction time, whereas one (C1) showed a significant decrease. We conclude that OPN inactivation has no consistent effect on saccadic reaction time.

Effect of OPN injection on SRBN burst characteristics

As stated in the introduction, if the SC is in the feedback loop, we expect its SRBNs to exhibit altered bursts. Figure 11 shows the effect of OPN-induced saccadic slowing on the discharge of the SRBN recorded in experiment D3 (recall Fig. 6). As illustrated in Fig. 11B, a muscimol injection into the OPNs decreased peak vector velocity by ~40%, on average, and increased average saccadic duration by ~48% (arrows represent preinjection averages). After the injection, the burst duration of this SRBN also was longer, as can be appreciated.
in the superimposed histograms at the bottom. Similar increases in burst duration occurred for the other 10 SRBNs.

Although the duration of the burst always increased with saccadic duration, the peak of the firing rate histogram did not show consistent changes across experiments. For example, the average peak firing rates of pre- and postinjection saccadic discharge calculated in an interval around the peak of the superimposed histograms in experiment D3 (bottom, Fig. 11B, ↔) were not significantly different after the injection (P > 0.1). In contrast, the firing rate of the SRBN in experiment D16 decreased significantly during the slower postinjection saccades (Fig. 12).

In Table 1, we compare the means of preinjection data with the means of the last 2–7 min of postinjection data when the effects of the muscimol were greatest (recall Fig. 7). The mean burst duration associated with postinjection saccades were all significantly longer than preinjection (P < 0.005; Table 1, column 1). In contrast, in only 5 of 11 experiments did SRBNs show significant decreases in burst peak firing rate postinjection (P < 0.05 Table 1, column 2).

To quantify the correlations between the properties of saccades and the firing of SRBNs, we plotted saccadic duration versus burst duration and saccadic peak velocity versus burst peak firing rate in each experiment for all those saccades within ±15° in amplitude and ±10° in direction of the optimal vector. Because we obtained a wide range of saccadic velocities and durations as saccades became ever slower over the course of the experiment (recall Figs. 6 and 7) but retained their optimal vector, we were able to observe how well a single regression line accounted for all the data. Figure 13 shows linear regressions for SRBNs D3 and D16 (see Figs. 11 and 12). When all of the data (both pre- and postinjection) are fit with a linear regression, burst duration increases robustly with saccadic duration (r = 0.92 for D3 and r = 0.82 for D16). For SRBN D3, burst peak firing rate was only weakly related to saccadic peak velocity (r = 0.31), but for SRBN D16, burst peak firing rate was strongly correlated with peak eye velocity (r = 0.81).

Burst duration showed a robust linear increase with saccade duration for all 11 SRBNs (Table 1, column 4). The slopes ranged from 0.36 to 1.38 with a mean of 0.80 ± 0.27 (mean ± SD). The correlation coefficients ranged from 0.57 to 0.93, with a mean of 0.79 ± 0.14; all were significantly different from zero (P < 0.001). The burst peak firing rate also was linearly related to saccadic peak velocity, although the relation was less robust and more variable across the SRBNs (Table 1, column 5). The slopes of this relation ranged from −0.18 to 0.49/spikes, with a mean of 0.17 ± 0.18. The correlation coefficients ranged from −0.15 to 0.82, with a mean of 0.44 ± 0.34. Five neurons showed correlation coefficients of <0.5 and three of them were not significantly different from zero (P > 0.05).

Finally, we checked whether the number of spikes in the burst changed as the saccade slowed by comparing the mean number of spikes associated with pre- and postinjection sac-
For postinjection saccades, the last bursts for the unit in experiment D16. Traces and arrows as in Fig. 11.

samples, there were at least were used to calculate the average number of spikes. In all SRBNs (Table 1, *; Fig. 14, /H17040) fell near the line of slope = 1 (- - -); therefore in those experiments, the number of spikes did not change significantly as saccadic duration increased (P > 0.05). In the remaining 7 experiments, 4 showed more spikes in the burst as saccadic duration increased, whereas 3 showed less (P < 0.05). The linear regression of pre- vs. postinjection number of spikes for all 11 SRBNs (Fig. 14, —) is parallel to the line of unity slope but with an intercept of 1.86 spikes, which is not significantly different from 0 (P > 0.5). Therefore on average, our population of SRBNs showed a constant number of spikes as the saccade was stretched but retained its same size.

**Effect of OPN injection on non-SRBNs**

As mentioned earlier (Fig. 4C), we recorded three SC neurons that exhibited no clear saccade-related bursts. For those units, saccadic slowing was not accompanied by a consistent peri-saccadic change of firing. Figure 15 compares the discharge of two of them before and after an OPN injection; all traces are aligned on saccade onset. Neuron D14 showed less peri-saccadic activity after the injection. However, the decrease was not specific to the time when the saccade occurred but rather happened throughout the entire discharge pattern. The early increase in postinjection activity occurred because the postinjection saccades had a longer reaction time so the visual response of this neuron was shifted earlier in time relative to the saccade. Neuron D23 showed no significant change in peri-saccadic activity after saccadic slowing. The remaining neuron that did not burst with saccades (D12, not shown) behaved like neuron D23. Therefore we conclude that non-SRBNs of this type are not influenced by the saccadic slowing produced by OPN inactivation.

**DISCUSSION**

Two things occurred when we injected muscimol into the OPN area. First, saccades were slower although they remained essentially unchanged in size. Second, SRBNs in the SC exhibited concomitant changes in their discharge patterns as the saccade slowed. Because we slowed the saccade by manipulating the burst generator locally, the most parsimonious explanation of the changes in SRBN discharge is that a feedback path exists from the burst generator to the SC. First we will speculate on how the muscimol injections caused slower saccades, and then we will discuss the nature of the feedback and its effect on the generation of saccades.

**What produced the saccadic slowing?**

The saccadic slowing does not have a trivial explanation. For example, the muscimol could not have affected the SC directly because the OPN region is separated from the SC by >10 mm and we injected only very small amounts of muscimol (<0.5 μl; < 1.0-mm diameter sphere). Also, the slowing was not due to a general reduction in alertness. Certainly, when agents that reduce alertness, such as diazepam (a member of the benzodiazepine group), are administered systemically to primates, saccades are slowed (Jürgens et al. 1981). Indeed, benzodiazepine, like muscimol, binds at the GABA_A receptor complex (Squires 1988), which has been demonstrated to occur on OPNs (Horn et al. 1994). Like diazepam, systemic administration of the sedating drug diphenhydramin also decreases saccadic velocity but does not affect saccadic accuracy (Hopfenbeck et al. 1995). Also, both diazepam and diphenhydramin cause an increase in saccadic reaction time (Aschoff et al. 1975; Hopfenbeck et al. 1995; Roy-Byrne et al. 1993). However, in 10 of our 14 injections, there was no significant change in reaction times; although the remaining four produced significant changes, the change could be either an increase (n = 3) or a decrease (n = 1). Because reaction time was not consistently altered by our muscimol injections, saccadic slowing was probably not the result of global effects on alertness due to effects on the “reticular activating system.” Instead we believe the saccadic slowing was produced by local effects of muscimol on the pontine burst generator. Indeed it seems highly unlikely that the considerable variation in the duration of consecutive saccades that we observe in our experiments (Fig. 6, ▶) could be accounted for by moment to moment changes in alertness.

![FIG. 12. Pre- (A) and postinjection (B) saccades and their associated SRBN bursts for the unit in experiment D16. Traces and arrows as in Fig. 11.](http://jn.physiology.org/)
Furthermore it is very likely that our injections affected the OPNs specifically. Because the EBNs that lie in the vicinity of the OPNs discharge primarily for horizontal saccades and only weakly, if at all, for vertical saccades, the slowing of vertical saccades by our injections (Fig. 7, - - -) cannot be attributed to inactivation of nearby EBNs. Furthermore, there is preliminary evidence that muscimol injections into the EBN area produce slow and hypometric horizontal saccades (Scudder 1997), whereas we observed slower but accurate saccades. Taken together, these data are consistent with our conclusion that the injections affected primarily the OPNs.

FIG. 13. Saccade duration as a function of burst duration and saccadic peak velocity as a function of peak firing rate for experiments D3 and D16. ■, preinjection data; □, postinjection data. Linear regressions fit the combined pre- and postinjection data. For D3, saccade vs. burst duration: slope = 0.86, r = 0.92; saccadic peak velocity vs. burst peak firing rate: slope = 0.15, r = 0.31. For D16, saccade vs. burst duration: slope = 0.71, r = 0.82; saccadic peak velocity vs. burst peak firing rate: slope = 0.24, r = 0.81.
Irreversible OPN lesions also slow saccades (Kaneko 1996), although the saccades after our muscimol injections were much slower. Why OPN inactivation slows saccades is difficult to explain. A simulated lesion of the OPNs in the Scudder model (Scudder 1988) both slows saccades and decreases their reaction times (Kaneko 1989). Unfortunately, our OPN injections caused saccades to be much slower than those predicted by the model and saccadic reaction times were not decreased in 13 of our 14 injections. In conclusion, it appears that the slowing produced by OPN inactivation reflects a more complicated mechanism than can be simulated completely by existing models.

**Implication for feedback models**

Because saccade slowing caused by OPN inactivation produces concomitant slowing of the discharge of putative output neurons in the SC, the SC apparently is aware of the state of the ongoing saccade and changes certain aspects of its discharge (mostly its duration) accordingly. Our sample of SC neurons did not include visual or predominantly visual neurons usually found in the superficial layers of the SC but it appears that the feedback affects SRBNs (as defined by Sparks and Mays 1980) (Fig. 4A) and visuo-motor neurons (Fig. 4B), which reside in the intermediate and deep layers of the SC. We did not test our sample neurons using a remembered or delayed saccade paradigm but it seems unlikely that any were build-up neurons (Munoz and Wurtz 1995a) because they all appeared to have closed movement fields even though several displayed both visual and prelude activity.

The observation that all SRBNs were slowed suggests that the SC is part of a feedback loop involving the brain stem. In the introduction, we suggested that the SC might be involved in at least two feedback loops, which could have different goals. One feedback loop might impinge on SC neurons to create an error signal (Keller 1981), which is the difference between where the saccade wants to go and where the eye currently is. This is a modification of Robinson’s (1975) local feedback concept, with his original comparator in the brain stem shifted upstream to the SC. In the remaining paragraphs, we will discuss how the behavior of SC SRBNs would change if our inactivation experiments had affected such a feedback pathway and review the existing evidence that places this local feedback loop in the SC. Then we will suggest that the changes in activity seen in our experiments are most parsimonious with a second feedback pathway through the SC. This second pathway is not involved with creating motor error; instead, it affects the duration of the desired eye displacement signal.

**FEEDBACK TO PRODUCE MOTOR ERROR**. Waitzman et al. (1988, 1991) suggested that the linear relation between the firing rate of the declining part of the burst of SRBNs and the saccadic motor error indicates that the SC is the comparator that produces a motor error signal. If so, the discharge of SRBNs, the

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**FIG. 14.** Comparison of average numbers of spikes in the SRBN bursts of pre- and postinjection saccades. - - -, the line of equality. ○, pre- and postinjection means are not different statistically (P > 0.05). ——, regression line fit to all 11 data points: slope = 1.00, intercept = 1.86, and r = 0.74.

Irreversible OPN lesions also slow saccades (Kaneko 1996), although the saccades after our muscimol injections were much slower. Why OPN inactivation slows saccades is difficult to explain. A simulated lesion of the OPNs in the Scudder model (Scudder 1988) both slows saccades and decreases their reaction times (Kaneko 1989). Unfortunately, our OPN injections caused saccades to be much slower than those predicted by the model and saccadic reaction times were not decreased in 13 of our 14 injections. In conclusion, it appears that the slowing produced by OPN inactivation reflects a more complicated mechanism than can be simulated completely by existing models.

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**FEEDBACK TO PRODUCE MOTOR ERROR**. Waitzman et al. (1988, 1991) suggested that the linear relation between the firing rate of the declining part of the burst of SRBNs and the saccadic motor error indicates that the SC is the comparator that produces a motor error signal. If so, the discharge of SRBNs, the
likely SC output neurons, should have two characteristics. First, the duration of the SRBN burst should be well correlated with saccade duration. In previous studies, this relation has been difficult to demonstrate because natural saccades of a particular vector show little variation in duration and velocity. Here we were able to demonstrate such a correlation because the gradual slowing of saccades after OPN injections produced a wide range of saccade durations without changes in the optimal saccadic vector. The correlation between saccade and SRBN burst duration was extremely robust for all of our neurons. Second, because equal-amplitude saccades always start with the same saccadic motor error, the decline in the firing rate of the SRBN burst with motor error theoretically always should start from the same peak firing rate, regardless of saccadic velocity. However, this was true of less than half of our neurons; 5 of 11 SRBNs decreased their peak firing rates as saccadic peak velocity decreased. These latter data, therefore, are not consistent with the SC residing within the local feedback loop.

Other experiments also suggest that the SC is not the comparator. First, the linear relation between firing rate and motor error breaks down in saccade interruption studies (Goossens and van Opstal 2000; Keller and Edelman 1994). The motor error versus spike density curves of perturbed saccades followed different relations than did those of control saccades. In addition, Frens and van Opstal (1998) showed that two different SRBN firing profiles could be related to saccades of similar vectors and dynamics, and this is inconsistent with the existence of a single linear relation between firing rate and motor error. Second, if the SC was the comparator, electrical stimulation in the SC should cause the eyes to move as long as the stimulus continues because the motor error simulated by the stimulation remains constant until the stimulation ceases. In fact, prolonged electrical stimulation in the SC produces a staircase of saccades (Robinson 1972).

Another possibility is that the instantaneous motor error might be represented topographically as movement of activity on the SC. In this scenario, which has been demonstrated convincingly in the cat (Guitton et al. 1990; Munoz et al. 1991), the locus of active cells in the SC starts at a caudal site that represents a particular gaze shift and moves rostrally as the gaze shift evolves (Munoz et al. 1991; but see Kang and Lee 2000). When the rostral-ward movement reaches the “fixation zone,” the neurons there become active and terminate the saccade (Bergeron and Guitton 2000; Munoz and Guitton 1991). The moving activity model could account for the staircase of saccades produced by electrical stimulation because the rostral shift of the active locus reactivates the fixation neurons (Munoz and Istvan 1998), thereby terminating the saccade although the stimulation is still on.

Our data and those of others do not seem consistent with the moving activity scenario. First, the existence of a moving locus in the monkey is controversial because it has not been readily demonstrable by different labs (Anderson et al. 1998; Keller and Edelman 1994; Munoz and Wurtz 1995b; Port et al. 2000; Soetedjo et al. 1998). Second, to implement the moving locus, feedback models have utilized velocity feedback (Lefèvre and Galiana 1992; Optican 1995) instead of displacement feedback. However, almost half of our SC SRBNs receive an inaccurate measure of eye velocity as reflected in their poor relations between peak firing rate and peak eye velocity. These data could be taken to suggest that only some SRBN neurons are participating in local feedback. However, we prefer to interpret the ubiquitous strong correlation with duration but the less universal, more problematic relation with velocity as an indication that the SC actually is participating in another feedback circuit.

FEEDBACK TO CONTROL THE GAZE DISPLACEMENT ERROR SIGNAL. The strong correlation between the burst duration of all our SRBNs and saccade duration leads us to posit that the feedback path that reaches the SC serves primarily to regulate the burst duration of SC SRBNs. This suggestion is supported by data from other studies. First, when saccades are interrupted in mid-flight by stimulation of the OPNs, SC SRBNs show a concomitant suppression of their firing, which lasts for the duration of the stimulus train. The SRBN then resumes its burst before the saccade resumes (Keller and Edelman 1994; Keller et al. 2000). Furthermore the end of the resumed saccade is similar to the end of the resumed burst. Therefore these data suggest that the duration of SRBN discharge is related to the duration of saccades. Second, stimulus trains of increasing durations delivered to a site in the SC elicit saccades of increasing sizes until a minimum duration is reached beyond which stimulation elicits saccades of a constant vector (Paré et al. 1994; Stanford et al. 1996). These data suggest that the duration of the SC output must be maintained at least until the end of the saccade to elicit a movement characteristic of that site. Finally, during a blink-perturbed saccade, the duration of the burst of SRBNs is related to the total duration of the saccade (Goossens and van Opstal 2000). Although their data are similar to ours, the authors suggested that the prolongation of SRBN burst duration was caused by properties of an intrinsic SC network. However, because blinks also cause cessation of OPN activity (Mays and Morrisse 1993) and a reduction of EBN firing rate (Mays and Morrisse 1995), we believe the data of Goossens and van Opstal can be explained just as well by feedback from the brain stem.

Of course, a local feedback circuit with a comparator is still necessary to bring the saccade accurately onto the target. However, based on the results of our experiments, we prefer to leave the entire local feedback circuit in the brain stem (Scudder 1988). Because the local feedback circuit involves the high-gain EBN element, it would be an advantage to have the circuit localized to the brain stem. A long delay in the feedback path might introduce instability. For example, a 10° saccade lasts as little as 25 ms (Fuchs 1967), so a long synaptic or signal processing delay is problematic.

SOURCE OF DURATION-RELATED SIGNALS TO THE SC. Several lines of evidence suggest that the central mesencephalic reticular formation (cMRF) could be the source of the feedback signal. First, the cMRF makes reciprocal connections with the SC (Chen and May 2000; Cohen and Büttner-Ennever 1984; Moschovakis et al. 1988). Second, the cMRF also has reciprocal connections with the OPNs, whose pauses are related to saccadic duration (Langer and Kaneko 1983, 1984, 1990). Third, cMRF burst neurons have movement fields similar to those of SC neurons so that their activity need not undergo a temporal-to-spatial transformation to be in the same coordinate frame as SRBN activity (Handel and Glimcher 1997; Kaneko and Fuchs 1982; Waitzman et al. 1996). Fourth, inactivation of at least some parts of the cMRF causes hypometric saccades
(Waitzman et al. 2000) as would be predicted if the signal that maintained SRBN discharge had been eliminated. Other possible brain stem sources of a saccadic duration signal include burst neurons in the pontine and medullary reticular formations and the nucleus prepositus hypoglossi (NPH), which projects to the SC (Hartwich-Young et al. 1990). However, feedback from burst neurons would presumably produce an excellent relation between firing rate and saccadic velocity in all SRBNs, which doesn’t occur. Also, NPH lesions affect neither saccadic velocity nor duration (Kaneko 1997). Consequently, based on admittedly sparse evidence, we favor a feedback pathway that derives a saccadic duration signal from the OPNs and delivers it to the SC via the cMRF.

Figure 16 shows a simple schematic with the traditional brain stem feedback to produce motor error at the EBN level and our proposed second feedback loop through the SC to maintain its bursting activity during the saccade. The discharge of SRBNs could be maintained either by exciting them (a net positive feedback) or by failing to turn them off (a net negative feedback). We favor positive feedback because 5 of 11 SRBNs decreased their firing rate as saccadic velocity decreased and cMRF neurons show saccade-related bursts instead of pauses (Handel and Glimcher 1997; Waitzman et al. 1996). As stated previously, we believe that the feedback originates from the OPNs, which presumably inhibit the cMRF. During a saccade, the pause of OPNs allows cMRF neurons to burst, which in turn maintains the bursts of SC SRBNs. The significance of the SC→cMRF→OPN pathway is not well understood, although it may help trigger the saccade (Waitzman et al. 1996).

The conceptual circuit in Fig. 16 accounts nicely for our data. The reciprocal connections of the cMRF with both the SC and OPNs could produce the tight relation between SRBN burst and saccade durations that we have demonstrated. Furthermore, the feedback signal through the cMRF to the SC is not related to saccadic velocity, and indeed we find only an inconsistent relation between saccadic peak velocity and SRBN peak firing rate across our neurons. Finally, our simple schematic will also predict the saccadic staircase elicited by electrical stimulation of the SC because the local negative feedback downstream from the SC will terminate the saccade when the motor error reaches zero.

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