Effects of Partial Lidocaine Inactivation of the Paramedian Pontine Reticular Formation on Saccades of Macaques

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[1]*Division of Neuroscience, Baylor College of Medicine, Houston, Texas 77030;* [2]*Department of Physical Therapy, The College of St. Scholastica, Duluth, Minnesota 55811; and* [3]*Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213*

Barton, Ellen J., Jon S. Nelson, Neeraj J. Gandhi, and David L. Sparks. Effects of partial lidocaine inactivation of the paramedian pontine reticular formation on saccades of macaques. *J Neurophysiol* 90: 372–386, 2003. First published February 12, 2003; 10.1152/jn.01041.2002. To investigate the brain stem control of saccadic eye movements, the paramedian pontine reticular formation (PPRF) in rhesus monkeys was temporarily and partially inactivated with the local anesthetic lidocaine. The influence on ipsilesional, contralesional, and upward saccades was examined. While the effects of the inactivation on contralesional and upward saccades were inconsistent and small, consistent and marked modifications were observed for ipsilesional movements. For ipsilesional, horizontal saccades, all lidocaine injections caused a decrease in peak velocity and a proportional increase in duration, which substantially altered the shape of the velocity profile. The rise in duration usually fell short of preventing hypometric saccades at the peak of the effect. However, as the lidocaine effect dissipated, the amplitude often returned to control, even though the velocity and duration remained compromised. For ipsilesional, oblique saccades, the effect of lidocaine on the horizontal component was similar to that for horizontal saccades. The vertical component of oblique saccades was also influenced, albeit to a much lesser extent: the duration of the vertical component typically increased, while the vertical peak velocity either decreased or exhibited no significant change. These results were compared with simulations of three prominent models for cross-coupling oblique saccades. In general, these results of the temporary inactivation of PPRF are consistent with the predictions of local feedback models for saccadic control.

INTRODUCTION

Physiological studies have shown that the paramedian pontine reticular formation (PPRF) is a critical premotor region for producing horizontal saccades. Unilateral lesions of the PPRF in monkeys have eliminated ipsilateral, horizontal saccades (Cohen et al. 1968; Goebel et al. 1971; Henn et al. 1984; Jaeger et al. 1981). Vertical and contralesional horizontal saccades persisted, although their accuracy was not examined in detail. Bilateral lesions of the caudal or rostral PPRF have caused complete paralysis of horizontal saccades with the vertical saccades largely disabled for caudal lesions but only slightly slowed for rostral lesions (Henn et al. 1984). Single-unit recording studies have found that the PPRF contains excitatory burst neurons (EBNs), which make excitatory, monosynaptic connections with the ipsilateral abducens nucleus (Sasaki and Shimazu 1981; Strassman et al. 1986), and that the EBN activity codes the metrics and dynamics of horizontal saccades (for review, see Moschovakis et al. 1996). Finally, all horizontal saccades are preceded and accompanied by EBN bursts.

To describe the neural control of horizontal saccades, Robinson (1975) proposed a model whereby a pulse-step signal sent to the motoneurons causes saccades, and the pulse, produced by EBNs, is modulated by an internal, continuous feedback loop. This nonvisual feedback allowed a comparison between desired eye position and a corollary discharge of current eye position to determine the motor error, which then dictates the duration of the pulse required to bring the eyes on target. The internal feedback loop has since been supported by substantial behavioral and physiological observations (for review, see Scudder et al. 2002). Because of experimental data available subsequent to the Robinson model, later models compare current and desired eye *displacements* (Jürgens et al. 1981).

Sparks et al. (1987) conducted experiments that support the notion of local feedback control. They stimulated at various sites within the PPRF before monkeys made saccades to briefly flashed visual targets. The monkeys compensated for the perturbation by making a subsequent saccade to the location of the disappeared target for the majority of PPRF stimulation sites, but compensation did not occur for a minority of sites. This suggests that the PPRF contains neurons located before or at the site where the feedback signal is derived and also a minority of neurons beyond it. This study examined the feedback control of the saccadic system by exciting a population of PPRF neurons. Logically, inactivating a population of neurons within the PPRF should provide an alternative means to examine feedback control. If it is true that a substantial division of the PPRF resides within or before the site of feedback signal derivation, compensation for the affected saccades should occur.

Arguing that local feedback is unnecessary and not sufficiently supported by experimental observations, Kaneko proposed a model without local feedback (Kaneko 1996). This model predicts a lack of compensation for damage to the

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EBNs. If it is correct, inactivating part of the PPRF should produce saccades reduced in velocity but without a concomitant increase in duration and therefore reduced in size. Conversely, if feedback does exist, the saccades should be slowed because of the defective burst generator but with an increase in duration due to feedback compensation. To test these hypotheses, we temporarily inactivated regions of the PPRF using the local anesthetic lidocaine and examined the influence on horizontal saccades.

Oblique saccades

The inactivations also provide an opportunity to test models for the production of oblique saccades. There are two variants: cross-coupling and common source models. Both account for "component stretching," i.e., increased duration and decreased velocity of the smaller of the orthogonal components. Grossman and Robinson (1988) proposed a cross-coupling model where component stretching arises because the output of each burst generator reduces the gain of the orthogonal system. This approach has multiple discrepancies with the behavioral data (as pointed out previously, Becker and Jürgens 1990; Smit et al. 1990). To correct the problems of the Grossman and Robinson model, Becker and Jürgens (1990) proposed an alternative cross-coupling model where the input to each burst generator, the motor error, attenuates the instantaneous motor error of the orthogonal system. These two versions of the cross-coupling approach make disparate predictions regarding what will happen to the vertical component of oblique saccades when the horizontal burst generator is weakened. According to the Grossman and Robinson (1988) model, the inhibition of the vertical burst gain will shrink, causing the vertical component to speed up. With the Becker and Jürgens (1990) model, the rate at which the horizontal motor error subsides will be reduced, and this slower decay will produce a greater temporary attenuation of the input to the vertical pulse generator. Hence the vertical component will slow down. With both models, separate feedback controllers for the horizontal and vertical burst generators will adjust the duration of each component to improve accuracy.

Scudder (1998) presented a local feedback model in which the horizontal and vertical burst generators are coupled indirectly through shared omnipause neurons (OPNs). When long-lead burst neurons (LLBNs) of either component reach a threshold level, they inhibit the OPNs, which disinhibits the EBNs of both components. For an oblique saccade with a larger horizontal than vertical component, the horizontal LLBNs reach threshold faster. This causes earlier disinhibition of the vertical EBNs than for purely vertical saccades of the same vertical amplitude, which stretches the vertical component. Because primarily the LLBNs control the coupling, weakening the horizontal EBNs, which are modeled as separate from the LLBNs, would have no noticeable effect on the vertical component. Lesioning the LLBNs would slow the rate that the LLBNs reach threshold, thereby, reducing the capacity of the horizontal component to stretch the vertical component. In this case, the vertical component will speed up.

The common source model suggests that a common vectorial pulse generator produces a vectorial velocity signal, which is then trigonometrically decomposed into horizontal and vertical components (Van Gisbergen et al. 1985; Van Gisbergen

and Van Opstal 1989). This approach produces straight trajectories and generates exactly equal durations for the orthogonal components instead of the observed slightly curved saccades, with asynchronous durations and timing of peak velocities (as pointed out elsewhere: Becker and Jürgens 1990; Grossman and Robinson 1988; King et al. 1986). Feedback must be added to the common source model to produce curvature and accuracy (Becker and Jürgens 1990). The two, leading approaches to feedback are to use separate control for each component through independent horizontal and vertical comparators or to use a common, vectorial comparator (for discussion, see Nichols and Sparks 1996a). The separate feedback approach better accounts for the behavioral and physiological data (Nichols and Sparks 1996a). In the case of a common source model with separate feedback, no influence on the vertical component would result from partial inactivation of the PPRF. This follows because the inactivation would not directly impact the vectorial velocity signal and no modulation of the vertical burst generator would come from coupling with the PPRF or a common feedback control.

We tested these hypotheses for the generation of oblique saccades by examining the effects of partially disabling the PPRF on oblique saccades. We also report the results of partially inactivating the PPRF on upward and contralesional horizontal saccades, which indicate that the effects on ipsilesional saccades were not caused by unintentional inactivation of the OPNs. A preliminary report of part of this study was presented previously (Sparks and Nelson 1997).

METHODS

Surgical and behavioral procedures

Two rhesus monkeys (*Macaca mulatta*) served as subjects (*H* and *M*). In sterile surgery, a stainless steel post was secured to the skull with surgical stainless steel screws and dental cement to provide a means for head restraint. For recording eye position signals, a scleral search coil was implanted under the conjunctiva (Fuchs and Robinson 1966; Judge et al. 1980). In a separate surgery, a stainless steel cylinder was cemented over a 15-mm craniotomy to access the PPRF. This allowed a hydraulic microdrive to be mounted on the cylinder and electrodes to be placed within a 10×10 mm^2 area. The cylinder was oriented at an 18° angle to the sagittal plane, offset from the midline by 4 mm at 1 mm posterior to AP zero. All animal experimental and care procedures were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

The monkeys were trained to acquire and fixate small (0.1°) visual targets for a liquid reward. Their heads were immobilized throughout the training and experiments. Horizontal and vertical eye positions were sampled every 2 ms and stored for later analysis. The targets consisted of LEDs located in a rectangular array on a tangent screen. The location of the targets will be reported in Cartesian coordinates without a tangent correction. Positive values correspond to up or right target displacements and negative values to down or left.

Data were obtained while the monkeys performed a single oculomotor task. The monkeys had 1 s to acquire the initial fixation position (F), which was always in the "straight ahead" position. After fixating F for 500 ms, the saccade target (T) appeared and F disappeared. They were required to look to T and maintain fixation of T for 500 ms to receive the reward. Both monkeys received at least 3 mo of experience with this task before these experiments took place. Control data were collected each experimental session for all of the targets used in that session. A variety of target displacements were randomly interleaved

for each recording session. Because the lidocaine effect decays quickly, not all targets could be studied for every injection. Ipsilesional, horizontal, and oblique target displacements were always presented. Usually upward target displacements were also presented and, in some cases, contralesional horizontal (both 20° target displacements). The ipsilesional horizontal saccades were to 20° target displacements and, in some cases, 10° target displacements were also used. Oblique saccades analyzed were to two target displacements [$H = 20°$ (ipsilesional), $V = 10°, 20°$]. If a particular target displacement had a shortage of associated trials for any injection, the results for that target were excluded from the analysis. The eye traces were usually measured with a 30°/s on and off criteria with manual adjustments when necessary.

Physiological procedures and data analysis

The use of a metal-coated glass pipette (Malpeli and Schiller 1979) allowed recordings, stimulations, and injections to occur in the same session using a single electrode penetration. To control the amount of 2% lidocaine hydrochloride injected, the investigator examined the movement of the meniscus at a portion of bare glass, with 1-mm travel of the meniscus corresponding to approximately 100 nl of fluid. The injection volumes, which varied between experiments, are listed in the second column of each table (1–5) in chronological order. Injections done on the same day are referred to in the text by the same number, but different letter suffix.

The location of the PPRF had been physiologically characterized before the injections occurred. At the start of the experiment, the investigator lowered the electrode until reaching a region of short-lead burst neurons (SLBNs). The PPRF was located with respect to the abducens nucleus in both monkeys. The injections in *H* were located in an area of SLBNs where LLBNs were not observed. The injections in *M* were located in an area of SLBNs where LLBNs were also sometimes encountered. Furthermore, when the superior colliculus was stimulated at a site 2 mm posterior to the injections in *M,* saccades of about 10° were evoked. On a single day, usually 2 (in 1 case, 3) injections were made, either at the same site or at different depths on the same track. The results of 15 lidocaine injections are described, 9 in the right PPRF of H and 6 in the left PPRF of *M*. The apparatus did not provide the precision to exactly compare the depths for recording sessions on separate days. The electrode was situated in the same location within the *x-y* positioner for the injections done in each monkey. For both monkeys, an electrolytic lesion was attempted in the area of the injections before the animal was killed under pentobarbital sodium. For *H,* a lesion was also made in the abducens nuclei. The brain was fixed, cut into 50-μm sections in the sterotaxic plane and stained with cresyl violent.

All statistical analyses were done with the STATISTICA program. Comparisons between group means were done with the *t*-test. When the variances in the two groups were significantly different, the *t*-test with separate variance estimates was used. The results of all the analyses were deemed significant by the conventional significance level of $P < 0.05$.

To obtain an index of curvature magnitude during the saccade, the end points of the movement were connected with a straight line. The area between the curve traced by the saccade trajectory and the straight line was divided by the length of the line. This value was taken as the index of curvature.

Simulations

A model that simulated oblique saccades was constructed using SIMULINK (The Mathworks). Coupling interactions between the horizontal and vertical burst generators were implemented as based on the Grossman and Robinson (1988) model, where a constant (λ) was used to vary the cross-coupling. In addition, we implemented interactions at the level of the dynamic motor error, as suggested by

Becker and Jürgens (1990). The dynamic motor error computed at the horizontal comparator was multiplied by $1/[1 + c(\text{dynamic vertical motor error})]$, and vice versa, where c is the cross-coupling constant. When simulating the Grossman and Robinson model, we set $c = 0$ and tested the model for different values of the coupling constant (λ). When simulating the Becker and Jürgens (1990) model, we set $λ = 0$ and varied c. The elements downstream of the burst generators, namely the neural integrator, motoneurons, and eye plant were modeled as shown in Kaneko (1997). Some parameters of the plant element were tweaked to match the behavior of saccades observed in our monkeys. Compared with the conditions used to simulate control saccades, two major modifications were implemented to simulate saccades after a lesion to the right PPRF. First, we attenuated the right burst element by dividing its output by three. This parameter was chosen to replicate the difference observed in our experimental data. Second, we lengthened the duration of the trigger, and therefore the inhibition of OPNs, to allow the slower saccades to reach completion.

The Scudder (1988) model was also simulated using SIMULINK. In this model, the EBNs and LLBNs are separate entities. We examined the model with simulated lesions in the right EBNs and/or LLBNs by varying the gains of each. For the effects presented on vertical peak velocity of oblique saccades, we multiplied the right EBN gain by 0.4 and the right LLBN gain by 0.75 and 0.5, which approximately replicated the experimental data.

RESULTS

Ipsilesional horizontal target displacements (20°)

When lidocaine was injected into the PPRF, it caused an increase in duration and a decrease in peak velocity for the horizontal component of saccades to ipsilesional, horizontal (20°) target displacements. This occurred for both monkeys and all 14 injections. (For this target, the 15th injection, 3b, was excluded because of insufficient trials.) The magnitude of the effect depended on the amount of lidocaine and the location of the injection within the PPRF. The prolonged duration compensated for the decreased velocity but usually not enough to prevent hypometric saccades. Figure 1 illustrates the position and velocity profiles for one injection of each monkey. Five control trials (—) and five trials at the height of the effect
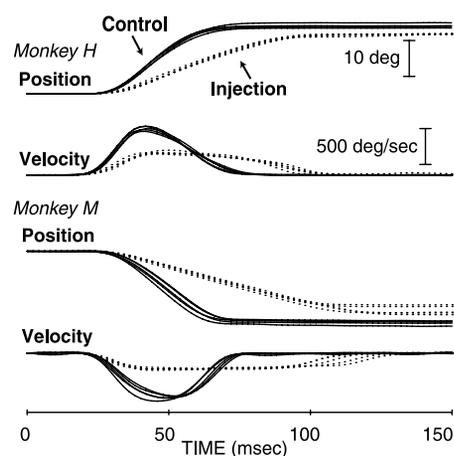

FIG. 1. Position and velocity profiles of the horizontal component for 1 injection in each monkey. Five control trials (—) and 5 trials from the peak of the inactivation (···; each ● corresponds to 2-ms sample time) are superimposed in each plot. Upward deflection of position curve corresponds to rightward movement and downward deflection to leftward. All target displacements were 20° in the ipsilesional direction (rightward for *H,* leftward for *M*). Injections 2a is shown for *H* and 7a for *M*. The traces are aligned on 25 ms before the measured saccade onset (30°/s).

($\cdots$) are superimposed in each plot. The decrease in velocity and stretch in duration are obvious. Yet some hypometria still occurred. When saccades fell short of the target, both monkeys made corrective saccades (not shown) toward the continuously lit target. The injections did not induce substantial (>1.5°) changes in saccadic direction.

Figure 2 shows the changes across saccades as a function of time for an injection in H (A–C) and an injection in M (D–F). Horizontal peak velocity and duration are shown on the same graph in A and D. Both injections caused a pronounced drop in peak velocity and a concomitant increase in duration, which gradually dissipated over the course of roughly 20 min. For 12/14 injections, the extended duration did not completely balance the reduced velocity as seen in the hypometria (Fig. 2B). Even though hypometria occurred for the majority of injections, this does not necessarily imply that the system undercompensated the entire time of the inactivation. In most cases, amplitude returned to control faster than peak velocity and duration, e.g., Fig. 2B, and this point will be covered in a later section. For 2/14 injections, there was no change in horizontal amplitude, as seen in Fig. 2E. This does not imply that peak velocity*duration remained constant for these two injections since the shape of the velocity profile changed (see Fig. 1).

The velocity profile shape can be described by the ratio (C) of peak velocity and average velocity (the latter is computed as amplitude/duration), where a transition from triangular to rectangular velocity profiles shifts C, a dimensionless constant, from 2 to 1 (Van Opstal and Van Gisbergen 1987). The average C of all control data sets was 1.7 for H and 1.6 for M. Figure 2, C and F, illustrates the effect of lidocaine on C for the same injections shown above. The ratio dropped during the inactivations, indicative of the waveform becoming more rectangular, for both hypometric and accurate saccades.

The relationship between saccade duration and peak velocity was well described by linear regression. The correlation coefficients and slopes for all injections are listed in Table 1. Only one injection site (2) produced $r < 0.90$, and these injections were associated with the lowest slopes. The average r and slope for the 14 inactivations were -0.90 and -0.08 (H) and -0.94 and -0.11 (M). Thus on average, an increase in duration of 33 ms accompanied a decrease in peak velocity of 300°/s for M.

To assess the maximum effects on the horizontal component for each injection, amplitude, duration, peak velocity and C were each plotted as a function of time and a moving average plot was fit to the data with a 4-min window size. Figure 3 illustrates the analysis for one injection. The moving average plots for the four data sets each had the same 4-min step size and started at the same point in time. The control data appear in the figure, with the vertical, dashed line indicating the transition from control to injection data points. The velocity
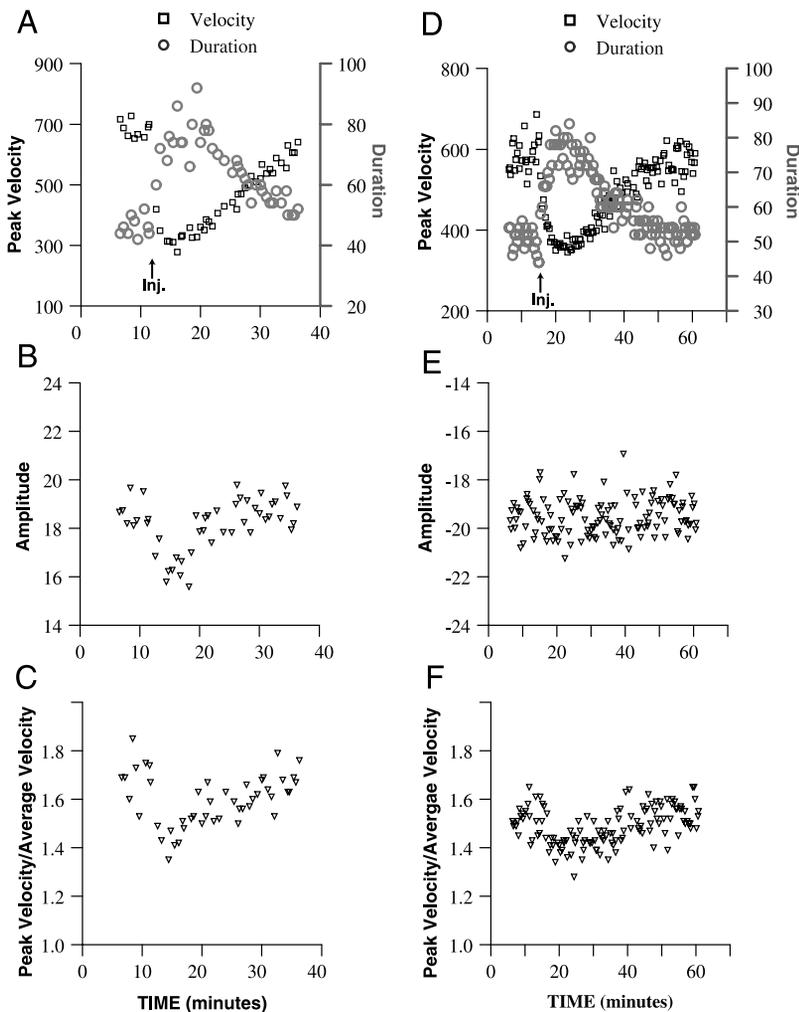

FIG. 2. Effect of lidocaine on saccades to horizontal target displacements of 20° in the ipsilesional direction (arrow indicates injection). Plot contains all saccades for that target. A: peak velocity (°/s) of the horizontal component, shown on the left y axis (black squares), is plotted as a function of time (min) for saccades of injection 2a in H. Horizontal duration (ms), shown on the right y axis (gray circles), is plotted for the identical saccades. B: horizontal amplitude (°) is plotted as a function of time (min) for the same saccades shown above. C: the ratio peak velocity/average velocity (C) is plotted as a function of time for the same saccades. D–F: The variables plotted are identical to A–C but for the saccades of injection 6b in M.

TABLE 1. *Horizontal, ipsilesional saccades (20°)*

Injection No.	Lido, nl	ΔH_{am}, °	ΔH_{vel}, °/s	ΔH_{dur}, ms	ΔC	Velocity Vs. Duration	Velocity Vs. Amplitude
1a	50–75	−2.4	−390.4	30.7	−0.25	−0.97 (−0.08)	0.66
1b	75–100	−4.0	−452.9	41.7	−0.32	−0.94 (−0.08)	0.83
2a	100	−2.3	−364.0	32.9	−0.22	−0.93 (−0.09)	0.65
2b	100	−3.0	−400.4	35.8	−0.21	−0.93 (−0.09)	0.82
2c	200	−6.7	−479.2	39.6	−0.20	−0.92 (−0.09)	0.89
3a	150	−0.7	−163.9	14.2	0.02*†	−0.90 (−0.07)	0.46
4a	150	−1.2	−186.4	13.3	−0.07*†	−0.76 (−0.05)	0.51
4b‡	150	−1.4	−215.1	13.3	−0.07*†	−0.85 (−0.05)	0.79
5a	100	−4.4	−466.3	51.8	−0.27	−0.95 (−0.10)	0.80
5b	100	−3.2	−423.5	54.0	−0.26	−0.93 (−0.13)	0.67
6a	100	0.6*†	−250	23.1	−0.13	−0.93 (−0.08)	0.02*
6b	?	0.2*†	−210.7	24.9	−0.09	−0.95 (−0.11)	−0.10*
7a	150	−3.4	−391.6	35.3	−0.25	−0.96 (−0.09)	0.72
7b‡	200	−3.1	−406.9	46.0	−0.18	−0.94 (−0.12)	0.72

Data from *H* and *M*, respectively, separated by the border. All saccades were to targets 20° in the ipsilesional direction. The injections with the same number and a different letter suffix correspond to sequential injections done in the same recording session. The second column shows the approximate amount of 2% lidocaine hydrochloride used. For 6b, clogging occurred and probably only part of the intended 200 nl was delivered. The next four columns list the maximum shift in amplitude, peak velocity, duration, and *C* (peak velocity/avg. velocity) of the horizontal component from the control data. The last columns list the correlation coefficient and slope for the line describing duration as a function of peak velocity and the correlation coefficient for amplitude as a function of peak velocity. * Not significant; † there was no apparent change of this variable and so the values compared to control were taken from the epoch synchronous with the maximal change in peak velocity; ‡ The injections were done in the same session as the previous injection, but at a different depth: 7b was approximately 1 mm higher than 7a; 4b was 0.25 mm lower than 4a.

and duration plots display obvious drops and increases, respectively, (Fig. 3, *A* and *B*), which occurred for every injection. The average values of peak velocity and duration associated with the 4-min periods producing the greatest effect were noted (horizontal, dashed lines). A similar analysis was done for amplitude (Fig. 3*C*) and for *C* (Fig. 3*D*), which both usually exhibited an obvious drop.

Table 1 lists the magnitude of the maximum shift for each variable and the amount of lidocaine used. To determine the maximum effects, the average value associated with the control data (number of control trials 9–30, average 17) was subtracted from the average value associated with the period of maximum effect for each of the four variables. A *t*-test was used to determine whether the data in the period of maximum shift
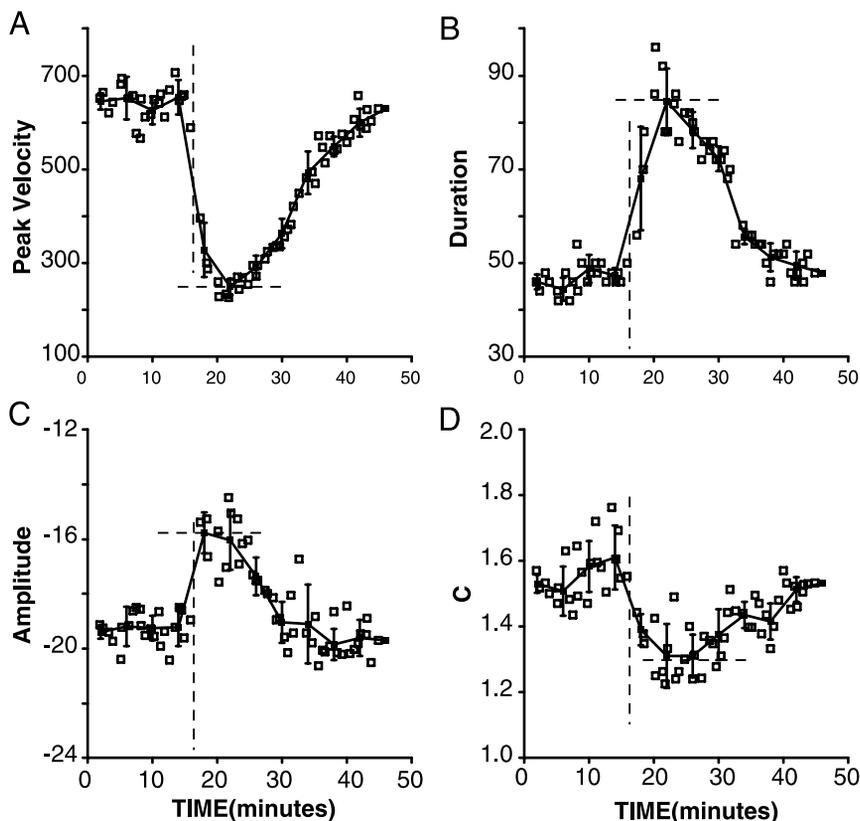

FIG. 3. Moving average plots superimposed on the data with a 4-min step size. *A–D*: peak velocity (°/s), duration (ms), amplitude (°), and *C* (dimensionless), respectively, of the horizontal component plotted as a function of time (min). The 4 moving average plots are aligned in time. The vertical dashed line marks the transition from control to injection data. Because of the 4-min smooth, the vertical line appears to cross the moving average plot after the inactivation occurred. The horizontal dashed line indicates the point of maximum effect according to moving average plot. The periodic vertical bars represent the SD for each average. Data from injection 7a in *M*.
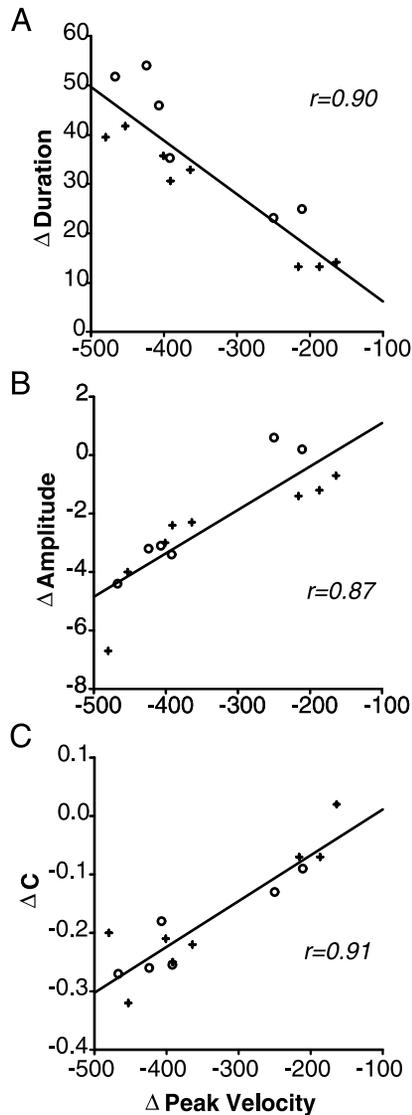
FIG. 4. The maximum effect of lidocaine (peak effect minus control) on the horizontal component across injections. The values are taken from Table 1. Positive values indicate increase from control. *A*–*C*: maximum change in duration (ms), amplitude (°), and *C* (dimensionless), respectively, as a function of maximum change in peak velocity (°/s). Each data point represents 1 injection (+, *H*; ○, *M*).

to the maximum effect were used for the statistical analysis to have sufficient trials. Generally this reduced the difference a small amount since the peak effect did not usually last for 8 min (see Fig. 3). Accordingly, the degree of significance represents a conservative estimate. Nonetheless, all the difference values for peak velocity, duration and amplitude in Table 1 were found to be significant, except for the two injections that produced no apparent change in horizontal amplitude.

Figure 4 summarizes the maximum changes in duration (*A*), amplitude (*B*), and *C* (*C*) as a function of the maximum change in peak velocity for the 14 injections (data from Table 1; *H,* +; *M,* ○). The change in duration is roughly inversely proportional to the change in peak velocity ($r = -0.90$, $P < 0.0001$). In addition, the drop in amplitude tended to increase as the drop in peak velocity increased ($r = 0.87$ $P < 0.0001$). Therefore the lengthening of duration tended to increase as the reduction in peak velocity grew, but not sufficiently and the hypometria also increased. As duration increased and peak velocity diminished, the velocity profile became more rectangular, hence, *C* dropped ($r = 0.91$, $P < 0.00001$).

The injections increased saccadic latency in a manner that varied across injections and monkeys. Moving average plots were fit to the latency data in the same way as for the other variables. The injections in *M* caused the greatest increase in latency (range: 31.1–54 ms; average = 43.1 ms, 6/6 significant). The influence on latency for injections in H was much less pronounced than for *M* with 7/8 exhibiting a consistent, but small increase (range: 11.8–18.5 ms; average = 13.2 ms, 6/7 significant). *H* exhibited a shorter normal latency than *M* in the control data [average of 3 control data sets: 150.8 (*H*); 186.7 (*M*)].

Timing of return to accuracy

When lidocaine caused a drop in horizontal amplitude, the time following the injection at which amplitude returned to control values was usually faster than the time that duration and peak velocity returned to control values (see Figs. 2 and 3). Therefore accurate saccades were made, while lidocaine still influenced the shape of the velocity profile. Amplitude can be related to peak velocity and duration by the following formula (Van Opstal and Van Gisbergen 1987)

$$\text{amplitude} = \frac{\text{peak velocity}*\text{duration}}{C}$$

Therefore if peak velocity*duration and *C* both decrease by a similar fraction from control, then amplitude would be normal, but the waveform would still be abnormal.

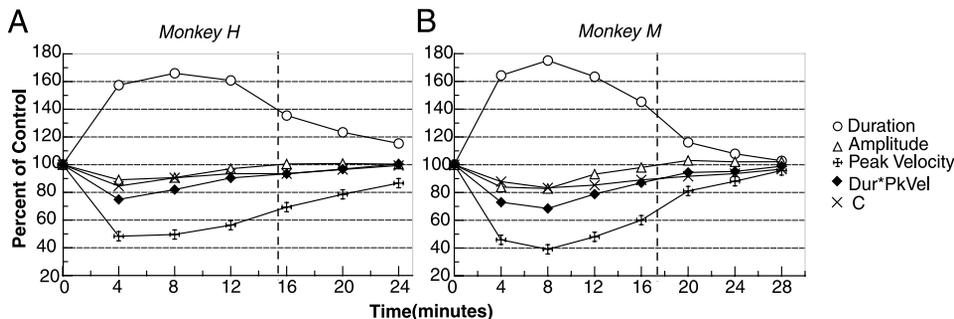Figure 5 illustrates the percentage change in peak velocity,

were significantly different from control. The number of trials in the maximum 4-min period for this target depended on the data set with a range of 5–10. When less than 10 trials occurred, the trials during both the period producing the largest effect and the adjacent period that produced the results closest

FIG. 5. The change in horizontal peak velocity, duration, amplitude, *C,* and peak velocity*duration across time for 2 injections (same injections as in Fig. 1) *A* (2a), *B* (7a). Each variable is plotted as a percent of the control data: duration (○), peak velocity (+), amplitude (△), *C* (×), peak velocity*duration (◆). Each data point was taken from the moving average plot and divided by the control value.

duration, amplitude, *C,* and peak velocity*duration across time for one injection in each monkey. For Fig. 5*A* (injection 2a), when duration and peak velocity were at about 138.5 and 67.5%, respectively, amplitude crossed the 100% line (vertical dashed line) because peak velocity*duration and *C* were both at similar points, approximately 93%. For Fig. 5*B* (7a), amplitude returned to 100%, while duration and peak velocity were still at 133.5 and 68%, respectively, because peak velocity*duration and *C* were both at 90%. The hypometria at the peak effect occurred because the drop in peak velocity*duration was greater than the drop in *C.* The point where peak velocity*duration intersected *C* is where amplitude returned to normal. Both monkeys exhibited variation across injections in the time that amplitude returned to control when compared with duration and peak velocity. Hence, peak velocity and duration were not tightly linked to amplitude because of the changing shape of the waveform. Accordingly, the correlations of amplitude and peak velocity were much less than of duration and peak velocity: *H,* average = 0.68, range: 0.46–0.89; *M,* average = 0.47, range: −0.10–0.80 (see Table 1, column 8).

Ipsilesional horizontal target displacements (10°)

To examine if lidocaine has a similar effect on smaller saccades, 10° horizontal target displacements were also presented for six inactivations in *H.* As with the larger saccades, there was a drop in peak velocity and a simultaneous rise in duration, with *C* usually dropping significantly. Usually, the resulting saccades were also slightly hypometric. In some cases, amplitude clearly returned to control values before peak velocity and duration. Table 2 summarizes the maximum effects, which were determined in the same manner as for the larger saccades. The magnitude of the effect varied across injections, similar to Table 1.

Ipsilesional oblique saccades

Saccades to two oblique target displacements were examined (20° ipsilesional horizontal component, *V* = 10°, 20°). Figure 6 illustrates the position and velocity profiles of oblique saccades (*V* = 20°) for the same injections shown in Fig. 1. The control (—) and injection trials (···) are superimposed on the same plot. The horizontal component velocity decreased and horizontal component duration increased, with the result-
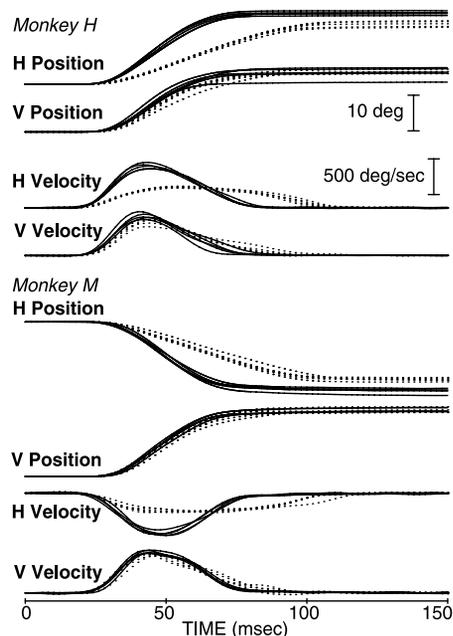

FIG. 6. Position and velocity profiles of oblique saccades. All target displacements were 20° in ipsilesional direction and 20° upward. Five control trials (—) and 5 trials from the peak of the inactivation (···; each ● corresponds to 2-ms sample time) are superimposed in each plot [same injections as Fig. 1: 2a (*H*), 7a (*M*)]. Upward shift of horizontal position curve corresponds to rightward movement and downward shift to leftward movement. Vertical position curve always indicates upward movement. The traces are aligned on 25 ms before the measured saccade onset (30°/s).

ing saccades still slightly hypometric, similar to pure horizontal saccades. The vertical component displayed a significant increase in duration and decrease in peak velocity but much less than for the horizontal component. Figure 7 illustrates the influence of the inactivation on all saccades of a different injection in *H.* Here again, the lidocaine caused a drop in horizontal peak velocity and an insufficient rise in horizontal duration (*A*), resulting in hypometria (*B*). For the same saccades, a smaller reduction in vertical peak velocity was observed in association with a smaller increase in vertical duration (*C*). The increase in vertical duration largely compensated for the drop in vertical peak velocity, which is reflected in the amplitude data (*D*).

The changes in the horizontal and vertical component of oblique saccades were analyzed separately. As with the analysis on horizontal saccades, each variable examined was plot-

TABLE 2. *Horizontal, Ipsilesional Saccades (10°)*

Injection No.	Lido, nl	ΔH_{am}, °	ΔH_{vel}, °/s	ΔH_{dur}, ms	ΔC	Velocity vs. Duration	Velocity vs. Amplitude
1a	50–75	−1.0	−318.4	26.3	−0.28	−0.94 (−0.09)	0.51
1b	75–100	−1.3	−372.8	39.3	−0.38	−0.92 (−0.10)	0.57
2a	100	−1.4	−319.7	25.2	−0.37	−0.91 (−0.08)	0.43
2b	100	−1.3	−337.6	31.5	−0.34	−0.80 (−0.09)	0.43
3a	250	−0.6	−135.3	10.5	−0.05*†	−0.76 (−0.07)	0.43
3b	150	−0.4*	−103.3	11.5	−0.06*†	−0.64 (−0.06)	0.52

All saccades were to targets 10° in the ipsilesional direction. Columns 3–6 list the maximum shift in amplitude, peak velocity, duration and *C* (peak velocity/avg. velocity) of the horizontal component from control (avg. number of trials for control = 15.6, range of trials in peak 4-min epoch = 4–7). Column 7 lists the correlation coefficient and slope for the line describing duration and as a function of peak velocity. Column 8 lists the correlation coefficient for amplitude as a function of peak velocity. * not significant; † there was no apparent change of this variable and so the values compared to control were taken from the epoch synchronous with the maximal change in peak velocity.
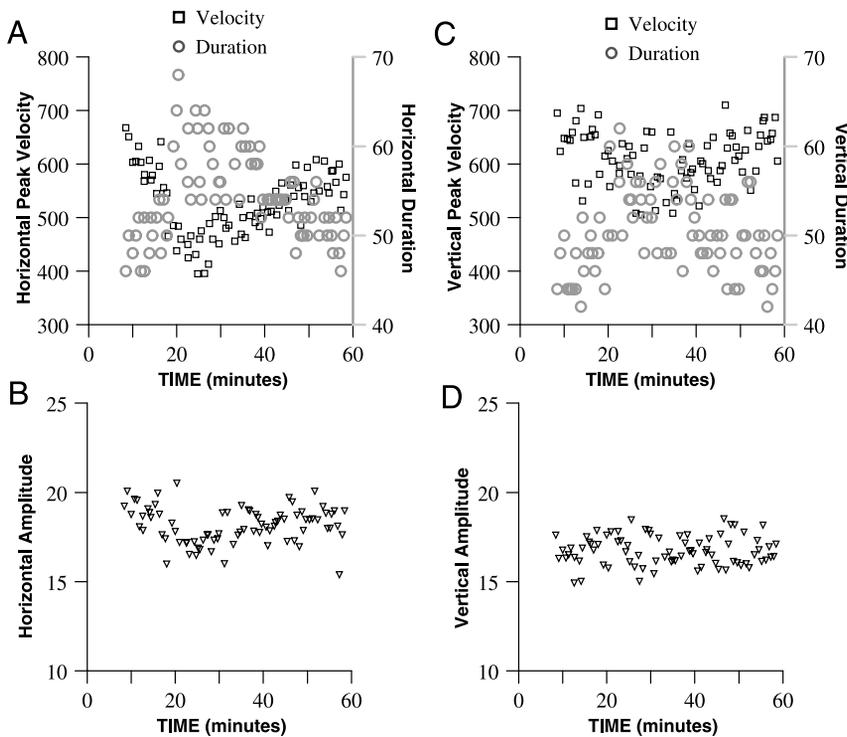
FIG. 7. Effect of lidocaine on oblique saccades, injection 4a of H. The target displacement was always $H = 20°$, $V = 20°$. Data in all 4 panels are from the same saccades. A: the peak velocity (□, left y axis) and duration (○, right y axis) of the horizontal component as a function of time. C: peak velocity (□, left y axis) and duration (○, right y axis) of the vertical component as a function of time. Amplitude of the horizontal (B) and vertical (D) component as a function of time.

ted as a function of time and a moving average plot was fit to the data.

In general, the pattern of impact on the horizontal component of oblique saccades was similar to that for pure horizontal saccades. The relationship between horizontal duration and horizontal peak velocity for oblique saccades of each injection could usually be described well by linear regression, but the correlations were somewhat lower than for pure horizontal saccades [average r: ($V = 20°$) -0.84 (H), -0.84 (M); ($V = 10°$) -0.88 (H), -0.93 (M)]. Across injections, the maximum decrease in horizontal peak velocity for horizontal targets was highly correlated with the maximum decrease in horizontal peak velocity for either oblique target ($V = 20°$, $r = 0.97$; $V = 10°$, $r = 0.98$) and the means of these comparisons were not significantly different (*t*-test). (Injections with data from both targets were included in comparison). Similarly, the maximum increase in horizontal duration was significantly correlated for horizontal and oblique saccades ($V = 20°$, $r = 0.84$; $V = 10°$, $r = 0.88$), and the means of these comparisons were not significantly different. While the means of the comparisons above were not statistically different, usually horizontal duration increased and horizontal velocity decreased more during horizontal than oblique saccades (see Tables 1, 3, and 4). The maximum change in C was correlated for the horizontal and oblique saccades ($V = 20°$, $r = 0.83$; $V = 10°$, $r = 0.87$) and their means were not significantly different. The increase in latency for oblique saccades was similar to the increase for horizontal saccades for *monkey M* [5 common injections: average 40.9 ms $(20°,0°)$ 35.4 ms $(20°,20°)$ 43.4 ms $(20°,10°)$]. For *H,* there was usually no discernible effect on latency for oblique saccades with only one injection (2a) showing a consistent increase, 26.2 ms, for target $(20°,20°)$ and two injections for target $(20°,10°)$ (2a, 21.1 ms, 1b, 16.1 ms).

Table 3 lists the maximal changes in main sequence variables for the horizontal and vertical component of saccades to

targets with equal component amplitudes $(20°)$. It shows a clearly larger effect for the horizontal than vertical component, especially for peak velocity. The vertical peak velocity decreased significantly for 9/14 injections (average $= 91.9°/s$): 6/9 in H and 3/5 in M. The remaining five injections caused no significant change in vertical peak velocity. The maximum change in peak velocity of the orthogonal components was significantly correlated for *monkey H* ($r = 0.81$). Accordingly, the vertical peak velocity tended to drop further when the horizontal peak velocity dropped further (number of injections in M were not sufficient for regression analysis). Every inactivation caused the duration of both components to lengthen (average $\Delta H_{dur} = 21.7$ ms, $\Delta V_{dur} = 12.7$ ms). The maximum shift in duration for the two components was correlated for *monkey H* ($r = 0.96$). For 7/14 injections where the vertical amplitude increased a small but significant amount, there was an inappropriate increase in vertical duration, i.e., the rise in vertical duration either overcompensated for a reduced vertical peak velocity or occurred without any drop in peak velocity.

The maximum changes for saccades to targets with a 20° horizontal and 10° vertical component, shown in Table 4, were similar to those for equal component amplitudes, with a consistently larger effect on the horizontal than vertical component. For *H,* the vertical peak velocity dropped significantly for all eight injections (average $= 94.7°/s$) and was correlated with the reduction in horizontal peak velocity ($r = 0.79$). No significant change in vertical peak velocity occurred for 4/5 injections in *M,* with one injection displaying an increase in peak velocity. Every injection caused an increase in the duration of both components (average $\Delta H_{dur} = 28$ ms, $\Delta V_{dur} = 14.6$ ms), with the changes in the orthogonal durations correlated for *monkey H* ($r = 0.99$). Across injections, the maximum changes in each variable (horizontal peak velocity, horizontal duration, horizontal amplitude, vertical peak velocity, vertical duration,

TABLE 3. *Oblique, ipsilesional saccades (20,20)*

Injection No.	Lido, nl	ΔH_{am}, °	ΔH_{vel}, °/s	ΔH_{dur}, ms	ΔV_{am}, °	ΔV_{vel}, °/s	ΔV_{dur}, ms
1a	50–75	−3.4	−338.7	33.1	0.6†	−128.6	21.5
1b	75–100	−6.0	−396.0	34.7	0.8†	−163.2	26.1
2a	100	−3.4	−300.5	25.6	−0.3*†	−77.1	12.6
2b	100	−6.3	−330.3	20.0	−0.3*†	−64.2	12.3
2c	200	−9.5	−386.9	17.6	−1.0*	−90.5	11.5
3a	250	−1.6	−133.8	9.5	0.8	−3.3*†	7.5
3b	150	−0.8	−101.9	8.9	0.8	22.4*†	6.4
4a	150	−1.9	−166.2	10.0	0.9*†	−86.0	6.9
4b‡	150	−2.3	−174.6	11.3	1.9	−44.8*	8.6
5a	100	−3.7	−338.1	32.7	1.2	−75.0	11.4
6a	100	1.6	−208.4	17.1	1.5	−44.1*†	13.3
6b	?	1.5	−165.4	22.2	1.5	−49.2†	15.0
7a	150	−3.2	−302.5	23.7	0.7	−65.6	10.4
7b‡	200	−2.2	−296.3	37.2	0.4*	−29.6*†	13.7

Oblique targets: 20° upward and 20° horizontal. Data from *H* and *M*, respectively, separated by border. Columns 3–5 show the maximum shift in amplitude, peak velocity, and duration for the horizontal component from the control data. Columns 6–8 list the same variables for the vertical component (average number trials for control = 14.4; range of trials in peak 4-min epoch = 4–10). * Not significant; † there was no apparent change related to the injection. The trials compared to control were taken from the epoch synchronous with the maximal value for the corresponding horizontal variable. For 6b, the significant vertical peak velocity change did not appear related to the injection because it lasted only one 4-min epoch and seemed to be a brief shift in alertness that coincided with the maximum shift in horizontal peak velocity. ‡ Injection 7b was approximately 1 mm higher than 7a; 4b 0.25 mm lower than 4a.

and vertical amplitude) were not statistically different for the two oblique targets (*t*-test).

It follows that as the inactivation caused horizontal duration to increase more than vertical duration, the saccades became curved. For example, Fig. 8*A* portrays the path of straight control saccades and highly curved saccades at the peak of the inactivation (injection 7a). In Fig. 8*B,* index of curvature is plotted as a function of time for the two injections during this session (7a and 7b). The curvature increased as horizontal peak velocity decreased and duration increased. In fact, the correlation coefficients describing index of curvature plotted as a function of horizontal peak velocity for these two injections are 0.90 and 0.91.

Upward and contralesional saccades

The influence of lidocaine on the vertical component of saccades to pure upward targets (20°) was relatively inconsistent and small. The effect was examined for eight injections, *H*

(4) and *M* (4). Moving average plots were fit to the data for duration, peak velocity and amplitude of the vertical components as with horizontal saccades. The results are listed in Table 5. The most consistent effect was a small, but significant increase in vertical duration for 7/8 injections (4.8 ms), which often caused a small increase in amplitude. There was no consistent influence on vertical peak velocity for the eight injections (average ΔV_{pk} = 8.5°/s), with only one causing a significant drop (1b). One inactivation resulted in a significantly prolonged latency (6a, 25.1ms). For an additional three injections (2a, 2b, 2c), there were not sufficient trials for detailed analysis, but it was clear that the injections did not cause a noticeable drop in vertical peak velocity. The effects on the small horizontal component of upward saccades were small, and the shifts in horizontal amplitude that appeared were, on average, roughly a degree.

Similarly, the effects of lidocaine on horizontal saccades to contralesional targets (20°) were inconsistent and small. Of the

TABLE 4. *Oblique, ipsilesional saccades (20,10)*

Injection No.	Lido, nl	ΔH_{am}, °	ΔH_{vel}, °/s	ΔH_{dur}, ms	ΔV_{am}, °	ΔV_{vel}, °/s	ΔV_{dur}, ms
1a	50–75	−1.9	−372.6	33.7	0.2*†	−129.9	21.1
1b	75–100	−4.6	−441.1	44.0	0.3*†	−164.7	24.8
2a	100	−2.1	−344.7	27.3	−0.2*†	−91.0	16.7
2b	100	−3.7	−384.5	27.8	−0.6*†	−95.5	16.4
2c	200	−11.0	−457.6	26.0	−1.0*	−97.3	16.1
3a	250	−1.6	−180.1	14.2	0.4†	−93.7	8.8
4a	150	−2.1	−167.6	10.5	0.0*†	−35.8	8.6
4b‡	150	−1.7	−181.6	12.5	0.3*†	−49.9	7.0
5a	100	−3.9	−392.1	39.1	1.6	52.4	17.3
6a	100	1.1	−213.2	22.3	1.1	−15.1*†	14.2
6b	?	1.2	−183.2	25.4	1.4	−8.1*†	11.8
7a	150	−3.5	−353.2	39.7	0.6†	−31.4*†	13.4
7b‡	200	−2.2	−372.5	41.7	0.9	−10.1*†	13.4

Oblique targets: 10° upward and 20° horizontal. Other conventions as in Table 3. Average number of trials for control = 18.2; range of peaks in 4-min epoch = 5–11.
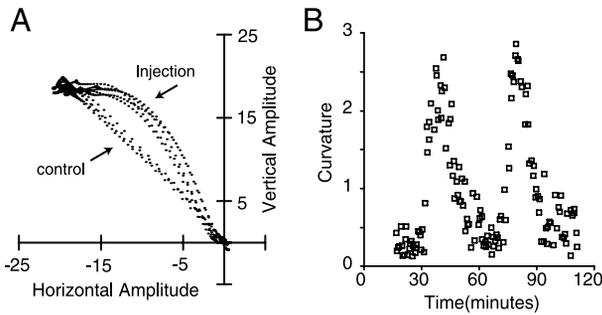
FIG. 8. Curvature of oblique saccades. *A*: the spatial trajectory of control saccades and saccades at the peak of inactivation 7a. Five trials of each are superimposed. Each dot in the eye movement trace corresponds to the 2-ms sample time. *B*: the index of curvature plotted as a function of time for 2 injections in *M* (7a and 7b).

seven injections, three (4a, 4b, 5b) caused no changes in any of the variables examined, i.e., amplitude, peak velocity, duration, and latency of the horizontal component. Two injections induced an increased latency, with only one statistically significant (7b, 31.8 ms; 7a, 28.2 ms). One injection (5a) caused a small increase in peak velocity (33.7°/s) and amplitude (1.3°), but the slight change in duration was not significant (1.8 ms). Another (6a) lengthened the amplitude (0.9°) because of an increase in peak velocity (31.4°/s), without an influence on duration. Only one injection (7b) produced a significant, but mildly prolonged duration (3.8 ms), which increased the amplitude (1.1°) without a rise in peak velocity.

Histology

Lesions in the PPRF and the abducens nucleus of *H* were made from separate tracks on the same day. Figure 9 shows the center of the abducens lesion (*A*) and of the PPRF lesion (*B*) with the electrode track for each lesion visible in both. The center of the abducens lesion was approximately 2.3 mm posterior to the center of the PPRF lesion, in the plane of the coronal sections. The PPRF lesion center was approximately 1.6 mm anterior from the anterior border of the abducens.

EBNs and LLBNs were recorded around the site of the

TABLE 5. *Vertical saccades (20°)*

Injection No.	Lido	ΔV_{am}, °	ΔV_{vel}, °/s	ΔV_{dur}, ms
1a	50–75	1.2	−27.2*	5.6
1b	75–100	1.6†	−54.8	3.9
4a	150	0.8†	3.3*†	3.0
4b	150	0.6†	20.4*†	−1.2*†
6a	100	2.9	36*	6.7
6b	?	2.1	6.3*†	5.4
7a	150	1.5	48.1*†	3.6
7b	200	1.1	35.9*†	5.6

Columns 3–5 list the maximum changes in amplitude, peak velocity, and duration, respectively, of the vertical component. (average number of trials in control = 24, range of trials for peak epoch = 5–10). * Not significant; † No apparent change related to the injection and so the values compared to the control were taken from the epoch synchronous with the maximal change for the corresponding horizontal variable of horizontal saccades. For 1b and 7a, the significant change in amplitude and peak velocity, respectively, were considered not related to the injection because it lasted for only one epoch and appeared to be a transient change in alertness.
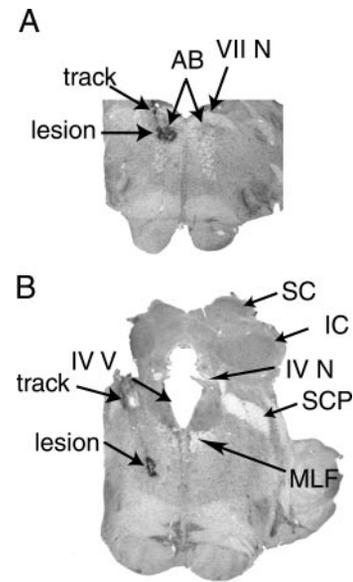

FIG. 9. Histology. *A*: abducens lesion indicated by the arrow on the left. *B*: paramedian pontine reticular formation (PPRF) lesion indicated by arrow on left. The coronal section shown in *B* is 2.3 mm anterior to the section shown in *A*. The electrode track used for the lesions is visible in both. Abducens nucleus (AB), facial nerve (VII N), superior colliculus (SC), inferior colliculus (IC), superior cerebellar peduncle (SCF), fourth ventricle (IV V), medial longitudinal fasciculus (MLF), trochlear nerve (IV N).

PPRF lesion, unlike the area of the injections, where LLBNs were not obvious. Therefore it seems that the lesion center was farther rostral than the injections because LLBNs occur more often rostrally. The *x-y* positioner was not more anterior, but the lesions were done before sacrificing the animal, one year after the injections. It is likely that changes in the brain caused the electrode to travel a different path to the PPRF, such that the final position was farther rostral. The difficulty in arriving at a site along the path directed by the *x-y* positioner is illustrated by the fact that the two lesions were about 2.3 mm apart in the brain stem, but the tracks were only 1 mm apart in the *x-y* positioner (anterior-posterior axis).

For *M*, no lesion was found, suggesting that an error occurred in the lesion delivery; however, the electrode tracks indicate the approximate injection location. The injections were done at the most anterior and the most lateral tracks used. Consistently, the most anterior tracks recovered were also the most lateral. These tracks were obvious until approximately 1.2 mm anterior to the anterior abducens border and continued faintly for another 0.4 mm. Hence, the injections should have been within this range.

Simulations

To compare the present results to the predictions of the Grossman and Robinson (1988) model and the Becker and Jürgens (1990) model, we simulated the models for the two oblique targets used in these experiments ($H = 20°$, $V = 10°$ and $H = 20°$, $V = 20°$). For both models, the lesions caused horizontal peak velocity to drop and horizontal duration to increase for each target. The feedback completely corrected for the reduced peak velocity such that no hypometria occurred. However, the trigger signal was lengthened to keep the pause cells off for the full duration of the saccade. Before the trigger

signal was lengthened, substantial hypometria occurred for the horizontal component of horizontal and oblique ipsilesional saccades. Stronger coupling produced a smaller change in the horizontal peak velocity after the lesion primarily because the increased coupling slowed the control saccades. Figure 10 illustrates the results of simulating saccades to target $H = 20°$, $V = 10°$ for the Becker and Jürgens model. The results of two coupling constants are shown for the control and after the lesion (gain of the horizontal burst generator one-third of the control value). The drop in horizontal velocity and increase in duration is obvious (Fig. 10A), as is the complete compensation (Fig. 10C).

The simulated lesions caused the vertical peak velocity to increase for the Grossman and Robinson model but decrease for the Becker and Jürgens (Fig. 10B) model. For both models, the magnitude of the change in vertical peak velocity depended on the size of the lesion and the strength of the coupling, with larger lesions and coupling constants producing more change. In the original Grossman and Robinson (1988) model, the coupling constant, λ, was set to 0.7 to achieve straight saccades. In our simulations, $\lambda = 0.7$ and lesion = 1/3 produced an increase in vertical peak velocity of 167 and 133°/s for targets (20°,20°) and (20°,10°), respectively. Furthermore, the vertical duration decreased slightly: 4 ms for (20°,20°) and 7 ms for (20°,10°). The saccades of equal component amplitude

were always straight in our simulations, but for target (20°,10°), the control saccades were still somewhat curved with this value of λ. Increasing λ to 0.8 produced straight control saccades and, after the simulated lesion, even larger increases in vertical peak velocity and decreases in vertical duration. Clearly these effects are inconsistent with the results of the present experiments.

In the original Becker and Jürgens (1990) model, the coupling constant, c, was set to 0.05. In our control simulations, this value produced quite curved saccades (Fig. 10E). After the lesion, insubstantial decreases in vertical peak velocity and increases in vertical duration occurred: (20°,20°), –30°/s, 1.5 ms; (20°,10°), −17°/s, 2 ms. When c was increased to 0.3, the control saccades became approximately straight (Fig. 10E). Postlesion with this c, the drop in vertical peak velocity and rise in duration increased greatly, with similar values for the two targets: (20°,20°), −57°/s, 17 ms; (20°,10°), −61°/s, 19 ms. Furthermore, the rise in vertical duration was much less than the horizontal duration such that the saccades were still strikingly curved (Fig. 10E). Consequently, these effects resemble much of the present data.

For the Scudder (1988) model, horizontal peak velocity dropped and horizontal duration increased for simulated lesions in either the EBNs or LLBNs but much more so for EBNs. This occurred for both horizontal and oblique saccades.
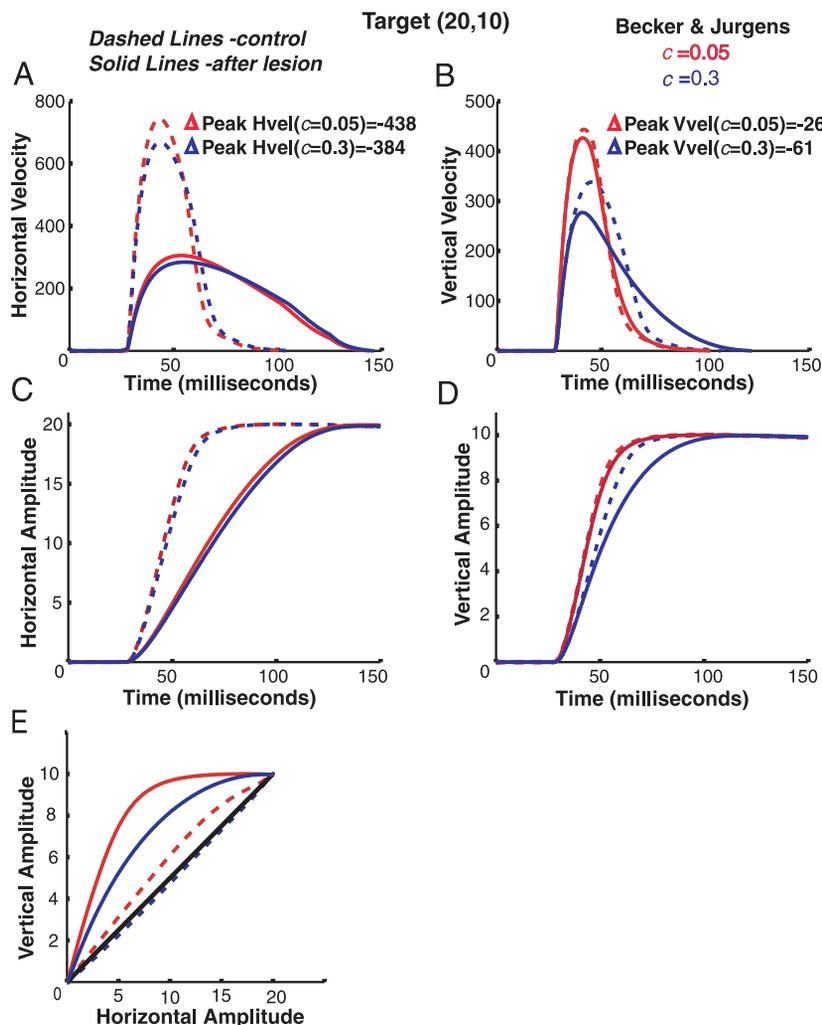

FIG. 10.   Simulations of the Becker and Jürgens (1990) model for saccades to target $H = 20°$, $Y = 10°$, control (- - -) and postlesion (—). The results of 2 values for the coupling constant, c, are superimposed. A: horizontal velocity as a function of time. The difference that the lesion caused in horizontal peak velocity for each value of c is listed in the *inset*. B: vertical velocity as a function of time. The difference that the lesion caused in vertical peak velocity is listed in the *inset*. C and D: horizontal and vertical amplitude as a function of time, respectively, for the same saccades shown above. E: the trajectory of the saccades.

The compensation was incomplete with hypometria occurring to an increasing degree as the lesion size in either the LLBNs or EBNs increased. The hypometria occurred because the OPNs, inhibited by the SC and IBNs, resumed activity prematurely. The early disinhibition was caused by the SC output, which was unaffected by the lesion and so insufficient, and the decreased signal in the IBNs.

With this model, the effect on the vertical component of oblique saccades depended on the magnitude of the lesion in the horizontal LLBNs and the target. Nearly identical vertical components occurred regardless of EBN lesion size. For target $H = 20°$, $V = 10°$, the vertical peak velocity increased by 21 and 51°/s with the LLBN gain set to 0.75 and 0.5, respectively. Only minute changes in vertical duration (less than 1 ms) and amplitude ($<0.2°$) appeared. For equal component amplitudes (20°, 20°), the results were similar for both lesions, with vertical peak velocity approximately constant ($\Delta V_{pk} < 0.3°/s$), and slight increases in vertical amplitude (0.6°) and duration (5 ms). Hence, vertical LLBNs reached threshold at the same time as control for this large vertical input. (When smaller targets of equal component amplitude were tested, a small increase in the vertical peak velocity occurred.) Because the simulated lesions never caused a drop in vertical peak velocity, the results from H are inconsistent with the simulations. The increase in vertical peak velocity associated with inactivating only 25% of the LLBNs (21°/s) would not amount to statistically significant effects, but the increase for 50% inactivation (51°/s) would. We don't know the percent of the LLBNs inactivated in M, but given the injection size, it probably was less than half (Sandkühler et al. 1987). Therefore the results in M, which usually displayed no change, could still fit with this model.

DISCUSSION

Ipsilesional horizontal saccades

To summarize, every lidocaine injection in the PPRF caused a decrease in horizontal peak velocity and increase in horizontal duration for saccades to horizontal (ipsilesional) target displacements. Generally, across injections in each monkey, the amount duration lengthened was roughly proportional to the magnitude of the drop in peak velocity (Fig. 4). When the decrease in peak velocity was large, the velocity profile became strikingly more rectangular. While the effect of the injection was at or near the peak, the rise in duration usually fell short of preventing hypometric saccades. However, the amplitude of the saccades often returned to control values faster than velocity and duration. The inactivations also prolonged saccadic latency. The amount of lidocaine and the injection site within the PPRF affected the extent of the influence on kinematics and latency, with considerable variability occurring across injections.

Inactivated omnipause neurons (OPNs) do not seem to account for the slowing and prolonging of saccades described herein. These neurons, which pause immediately before and during all saccades but discharge at a steady rate otherwise, inhibit EBNs (reviewed in Moschovakis et al. 1996). Ibotenic acid lesions of the OPNs have caused a decrease in peak velocity and increase in duration for ipsilesional, contralesional, and vertical saccades (Kaneko 1996). Muscimol inactivations of the OPNs also slowed and prolonged horizontal,

oblique, and vertical saccades (Soetedjo et al. 2002). It is possible that the present lidocaine injections in the PPRF inadvertently inactivated nearby OPNs. However, this does not seem to have occurred to a noticeable degree because the saccades to purely vertical target displacements were usually not slowed with only one injection causing a significant drop in peak velocity. In addition, the contralesional saccades did not display a reduced peak velocity and only one injection induced a significant but quite small increase in duration.

Visual information from before the saccade must have been used to create the retinal error signal, but visual feedback during the saccade does not seem responsible for the lengthened duration that occurred with the inactivations. The visually related burst of SC cells have latencies of 70–80 ms when using the LEDs of the present experiments (Sparks et al. 2000). With an efferent delay of at east 8 ms (Miyashita and Hikosaka 1996), the visual system would require 80–90 ms to respond. Most saccades (all saccades for target 10°,0°) were completed before this period. When the saccades lasted more than 80–100 ms, visual feedback may have assisted the compensation. However, it could only assist in the later part of the saccade and only for the saccades occurring during the fraction of the inactivation producing these long durations, i.e., the peak effect. The saccades of such long durations displayed the worst compensation, which seems inconsistent with the notion that visual feedback aided these saccades.

Saccadic adaptation could not have accounted for the increased duration. The increase in duration occurred simultaneously when the peak velocity dropped. The injection effects often peaked in only 4–8 min and gradually dissipated over the course of 30 min. During this time, the increase in duration peaked and dropped off in a manner that matched the reduction in peak velocity and only for the ipsilesional targets. Moreover, the incremental change in duration could be seen on a trial-by-trial basis (Figs. 2 and 3) without sufficient time for adaptation. It is possible that when the saccadic amplitude returned to normal before the dynamics, roughly 16 min into the injection, adaptation may have been involved. This would require a remarkably resilient adaptation mechanism that could adjust the duration, even trial by trial, based on the past rate of change in the error.

Local feedback models for saccadic control, which maintain that feedback controls saccade accuracy through adjusting the time course, predict longer durations when a crippled burst generator produces abnormally slow saccades. For the present experiments, all inactivations caused the duration to increase, in a manner proportional to the drop in velocity. One might expect a feedback system to be consistently accurate, which did not occur. Hypometria resulted during 12/14 and 5/6 inactivations for saccades to 20° and 10° target displacements, respectively. Still, this hypometria was a small fraction of what would have occurred without the average increase in duration of 34.1 ms (20° target displacements) and 24.1 ms (10° target displacements) for those same injections. The control saccades to 20° and 10° target displacements were roughly 48 and 34 ms, respectively; thus the injections caused an approximately 71% increase in duration from control, on average, for each target. Hence, the results of these experiments are generally consistent with the predictions of local feedback models for saccadic control and inconsistent with models postulating that damage to the PPRF will cause the resulting saccades to reflect

the damage due to the lack of a compensatory signal (Kaneko 1996).

If a feedback mechanism produced the incomplete compensation either it did not evolve to correctly compensate for such large, abnormal errors or the inactivations compromised the feedback process. We consider three possible hypotheses, not necessarily mutually exclusive, to explain a compromised feedback process.

The injections that caused the greatest slowing also generally resulted in the most severe hypometria. When the volume of lidocaine injected at a particular site increased, the peak velocity decreased even more (injection sites 1–3). Perhaps the larger the PPRF region inactivated, the more incomplete the compensation. Results of the microstimulation study of Sparks et al. (1987) were interpreted as evidence that most of the PPRF sites examined were at or before the site of derivation of the feedback signal, while some sites were beyond it. If this is true, the hypometria could have arisen because a subset of the PPRF area inactivated was outside the feedback loop. If the sites outside were farther from the electrode tip than those inside, this could cause the compensation to worsen as the inactivated region increased. It could also cause the amplitude to return to control before the velocity profile because the width of lidocaine injections decreases at longer postinjection times (Martin 1991). Hence, more distant, uncompensated regions should resume full functioning earlier. In like manner, the lesions could have encroached on the abducens nerve or nucleus and this component of the effect could have gone uncompensated.

Second, the hypometria could be related to an indirect effect of the injection on the (OPNs). Once a saccade starts, inhibition of OPNs is necessary until the saccade terminates (Yoshida et al. 1999). It has been postulated that EBNs (Robinson 1975; Van Gisbergen et al. 1981) or LLBNs (Scudder 1988) maintain the suppression of OPNs through inhibitory burst neurons (IBNs). During the lidocaine inactivations, the activity generated by EBNs and LLBNs is reduced, and the discharge near the end of the saccade, assumed to be critical for maintaining the suppression of the OPNs, is probably much lower than usual. If OPNs resume firing when the burst activity reaches a particular diminished level but not zero, then during the inactivations, the OPNs would restart when the eyes were farther from the goal than under normal conditions.

Third, in existing models of the saccadic system, continuation of a saccade is dependent on a signal of desired displacement being sustained until movement completion. This notion is supported by the experimental observation that when electrical stimulation in the superior colliculus (SC) terminates early, movements are hypometric (Stanford et al. 1996). In addition, when saccades are slowed through OPN inactivation (Soetedjo et al. 2002) or interrupted through OPN stimulation (Keller and Edelman 1994; Keller et al. 2000), the duration of SRBNs in the SC changes concomitantly, reflecting the altered saccade duration. This indicates that the SC receives feedback from downstream neurons that Soetedjo et al. (2002) suggest is used to maintain the desired displacement signal. If the inactivations caused an inaccurate feedback signal that led to an insufficient desired displacement signal, this could cause hypometria.

Because the lidocaine inactivations usually produced a significant increase in ipsilesional saccadic latency, this suggests

that the lesions affected the trigger signal, which inhibits the OPNs to initiate the saccade (reviewed in Hepp et al. 1989). LLBNs in the medullary reticular formation (MdRF) and/or the PPRF may be involved in generating the trigger signal (Hepp and Henn 1983; Hepp et al. 1989; Kamogama et al. 1996; Raybourn and Keller 1977; Scudder et al. 1988). The volumes of lidocaine injected preclude any inactivation of LLBNs in the MdRF (Sandkühler et al. 1987) but probably indirectly affected the MdRF (Strassman et al. 1986). Moreover, the injections directly affected the LLBNs of the PPRF; thus it is conceivable that the trigger could have taken longer to inhibit the OPNs because of its weaker input.

The histology indicates that the injections of both monkeys were no more than approximately 1.6 mm anterior from the abducens anterior border, which lies in the caudal half of the PPRF (Keller 1991; Strassman et al. 1986). We speculate that the injections in *M* were probably more rostral that those in *H* because the physiological observations, at the time of the injections, suggest that the inactivations in *M* occurred where LLBNs were sometimes encountered, and LLBNs have been found more rostrally (Hepp et al. 1989). This is consistent with the above hypothesis that inactivated LLBNs caused the increased latency because the latency increased much more for the injections in *M* than *H*.

Oblique saccades

To recapitulate, the effect of lidocaine on saccades to ipsilesional, oblique target displacements was examined for two targets (20°,20°) and (20°,10°). The change in the horizontal component was similar to that for horizontal saccades. Every injection significantly prolonged the duration of the vertical component of oblique saccades. Most of the nine injections in *H* caused a significant drop in vertical peak velocity for both targets with the exception of three injections that caused no significant change for one target. Most of the five injections in *M* caused no significant change in vertical peak velocity with the exception of two that produced a significant drop for one target and one that caused a significant rise for one target. The kinematics always changed less for the vertical than the horizontal component. Usually, the increase in vertical duration compensated for a decrease in vertical velocity. However, slightly hypermetric vertical components did frequently occur due to either an excessive lengthening of vertical duration or a small rise in vertical duration without a reduction in peak velocity. Similarly, saccades to vertical target displacements routinely displayed a small increase in vertical duration without a concomitant drop in velocity.

The influence on the vertical component of oblique saccades does not seem to have resulted from unintentional inactivation of nuclei involved in the generation of upward saccades [the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), the interstitial nucleus of Cajal (NIC), or the oculomotor nuclei (OMN)] (for review, see Moschovakis et al. 1996) because they are too far away (Keller 1991) to have been inactivated by the injection volumes used (Sandkühler et al. 1987). Moreover, for the injections where data on both vertical and oblique saccades were collected, the inactivations that produced the obvious drop in peak velocity and rise in duration for the upward component of oblique saccades did not produce the same influence on upward saccades. Since the PPRF

projects to the riMLF ipsilaterally (Büttner et al. 1977), the inactivations could have indirectly produced modulation of the vertical component through this connection.

One possible explanation for the effect on the vertical component of oblique saccades is cross-coupling of the burst generators. As stated in the INTRODUCTION, cross-coupling in the manner of the Grossman and Robinson (1988) model should cause an increase in vertical peak velocity, but with the Becker and Jürgens (1990) model, it should cause a decrease. In addition, the feedback signal will shorten the vertical duration in the former model and prolong it in the latter to produce accurate saccades. In our simulations of the two models, using SIMULINK, these effects were seen. The results of the Grossman and Robinson model simulations are obviously not consistent with our results. Nichols and Sparks (1996b) speculated that the Grossman and Robinson model could be modified to better account for the behavioral data if the outputs were inhibited not by the orthogonal burst but by the difference in the bursts of the two populations. Such an approach would still cause the vertical peak velocity of saccades that had a larger horizontal than vertical component to increase when the horizontal burst generator is impaired, which is inconsistent with the present results. When we increased the coupling constant of the Becker and Jürgens model until straight control saccades occurred, the lesion produced substantial drops in vertical peak velocity and increases in vertical duration. These results were usually similar to the results of the inactivations in *H*. We conclude that the present experiments provide further evidence that component stretching does not arise because the outputs of the burst generators are coupled and support the notion that the inputs might be coupled.

With the Scudder (1988) approach of indirectly coupling the burst generators through shared OPNs, simulated EBN lesions produced nearly identical vertical components, but lesioning, at least, half of the LLBNs caused a significant rise in vertical peak velocity for one target (20°,10°). These experiments were not designed to inactivate as much as half of the LLBNs and so the latter prediction of the model was not tested. However, the results from *H* of a drop in vertical peak velocity are inconsistent with the simulations. We conclude that the experimental observations do not well support the Scudder approach to coupling and that more rostral, larger inactivations would complement the test of the model.

As stated in the INTRODUCTION, the common source model (Van Gisbergen et al. 1985) with independent feedback control would not cause modulation of the vertical component during partial inactivation of the horizontal burst generator. The injections in *M* often did not significantly affect vertical peak velocity. Because the small increase in vertical duration, which occurred for both upward and oblique saccades, may have come about through a process apart from component stretching, the effects of these inactivations are more consistent with the predictions of the vectorial model. The differences in the results for the two monkeys are most likely explained by the inactivations occurring in somewhat different regions of the PPRF.

All the models examined in this paper employ independent feedback control for the orthogonal components, which implies separate comparators. However, vectorial comparator models using the common source model (Van Opstal and Kappen 1993) and a cross-coupling model (Arai et al. 1994)—in the manner of Grossman and Robinson—for component stretching have been proposed. The results from the oblique saccades of our study do not support the vectorial comparator hypothesis. The duration of the vertical component frequently increased far less than the horizontal component. For two injections, the vertical component ended more than 20 ms before the horizontal. A vectorial comparator would not provide the capability to cause such disparities in the durations of the orthogonal components.

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