

Interaction of the Frontal Eye Field and Superior Colliculus for Saccade Generation

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Hanes, Doug P. and Robert H. Wurtz. Interaction of the frontal eye field and superior colliculus for saccade generation. *J Neurophysiol* 85: 804–815, 2001. Both the frontal eye field (FEF) in the prefrontal cortex and the superior colliculus (SC) on the roof of the midbrain participate in the generation of rapid or saccadic eye movements and both have projections to the premotor circuits of the brain stem where saccades are ultimately generated. In the present experiments, we tested the contributions of the pathway from the FEF to the premotor circuitry in the brain stem that bypasses the SC. We assayed the contribution of the FEF to saccade generation by evoking saccades with direct electrical stimulation of the FEF. To test the role of the SC in conveying information to the brain stem, we inactivated the SC, thereby removing the circuit through the SC to the brain stem, and leaving only the direct FEF–brain stem pathway. If the contributions of the direct pathway were substantial, removal of the SC should have minimal effect on the FEF stimulation, whereas if the FEF stimulation were dependent on the SC, removal of the SC should alter the effect of FEF stimulation. By acutely inactivating the SC, instead of ablating it, we were able to test the efficiency of the direct FEF–brain stem pathway before substantial compensatory mechanisms could mask the effect of removing the SC. We found two striking effects of SC inactivation. In the first, we stimulated the FEF at a site that evoked saccades with vectors that were very close to those evoked at the site of the SC inactivation, and with such optimal alignment, we found that SC inactivation eliminated the saccades evoked by FEF stimulation. The second effect was evident when the FEF evoked saccades were disparate from those evoked in the SC, and in this case we observed a shift in the direction of the evoked saccade that was consistent with the SC inactivation removing a component of a vector average. Together these observations lead to the conclusion that in the nonablated monkey the direct FEF–brain stem pathway is not functionally sufficient to generate accurate saccades in the absence of the indirect pathway that courses from the FEF through the SC to the brain stem circuitry. We suggest that the recovery of function following SC ablation that has been seen in previous studies must result not from the use of an already functioning parallel pathway but from neural plasticity within the saccadic system.

INTRODUCTION

A complete understanding of the systems within the brain that underlie behavior depends on a series of experimental steps that include the determination of the relation of neuronal activity to the behavior, the localization of these neurons within regions of the brain, the verification of the anatomical connections between the areas, and the determination of the

functional interactions between these areas. One of the systems that is close to meeting these demanding criteria is that for the visual guidance of rapid or saccadic eye movements, a system that extends from cerebral cortex through the superior colliculus (SC) to the midbrain and pons (for reviews see Andersen et al. 1997; Colby and Goldberg 1999; Moschovakis and Highstein 1994; Schall 1997; Sparks and Hartwich-Young 1989). Within the saccadic system, two of the most intensively studied areas are the frontal eye field (FEF) in prefrontal cortex and the SC on the roof of the midbrain, and in the present experiments we have concentrated on the functional interaction between these two areas in the monkey.

Investigating this interaction is possible because of the substantial knowledge already available on the FEF and SC. Both structures are well identified in the monkey, and maps of the visual receptive fields and movement fields are established for the SC (Ottes et al. 1986; Robinson 1972) and are known at least in outline form for the FEF (Bruce and Goldberg 1985; Bruce et al. 1985; Sommer and Wurtz 2000; Suzuki and Azuma 1983). Neurons in both the FEF and SC respond to visual stimuli, change their discharge in association with the initiation of saccades, and continue to discharge during the period in between (for reviews see Schall 1997; Sparks and Hartwich-Young 1989). Electrical microstimulation of either the FEF or SC elicits saccades whose vectors depend on the site of stimulation and are consistent with the vectors represented by neurons in the region stimulated (Bruce et al. 1985; Robinson 1972; Robinson and Fuchs 1969; Schiller and Stryker 1972). Reversible inactivation of either area results in temporary deficits for saccades made to visual or remembered targets (Aizawa and Wurtz 1998; Dias and Segraves 1999; Dias et al. 1995; Hikosaka and Wurtz 1985, 1986; Lee et al. 1988; Sommer and Tehovnik 1997), although ablations of either area generally lead to only transient deficits (reviewed by Schiller 1998). Finally, the close anatomical connections between the two areas are well established (Komatsu and Suzuki 1985; Stanton et al. 1988), as are the physiological connections (Everling and Munoz 2000; Schlag-Rey et al. 1992; Segraves and Goldberg 1987; Sommer and Wurtz 2000).

The major evidence concerning the possible functional interactions of the two areas has come from ablation studies. These studies have shown that while the ability to generate saccades survives the ablation of either the FEF or SC (Albano

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et al. 1982; Lynch 1992; Schiller and Chou 1998; Schiller et al. 1980, 1987; Wurtz and Goldberg 1972) when both structures are ablated, saccade generation is severely impaired (Schiller et al. 1980). Consistent with this conclusion is the added finding that ablation of the SC has no effect on saccades generated by stimulating FEF (Schiller 1977), which was in contrast to the elimination of saccades evoked by stimulation of occipital cortex following SC ablation (Keating and Gooley 1988a; Schiller 1977). The amalgamation of these studies has led to the hypothesis that two parallel pathways may control saccades to visual targets (Keating and Gooley 1988a,b; Keating et al. 1983; Schiller 1977; Schiller and Chou 1998; Schiller et al. 1980, 1987). One pathway goes directly from the FEF to the brain stem premotor circuitry, where saccades are ultimately generated, and the other goes through the SC and then to the brain stem premotor circuitry.

In the course of experiments on the recovery of the ability to make saccades following SC lesions, we made several observations that suggested that this parallel relation between FEF and SC may not be as robust as implied by these previous experiments. In the experiments described here, we tested the contribution of the pathway from the FEF to the brain stem that bypasses the SC. We assayed the contribution of the FEF to saccade generation by evoking saccades with direct electrical stimulation of the FEF. To test the role of the SC in conveying this information to the brain stem saccade generating circuits, we inactivated the SC, thereby removing the circuit through the SC to the brain stem, and leaving only the direct FEF–brain stem pathway. This brief and immediate inactivation of the SC, in contrast to previous ablation experiments, allowed a test of the contribution of the direct FEF–brain stem pathway before any compensatory mechanisms could mask the effect of removing the SC. If the direct FEF to brain stem pathway is sufficient for the generation of saccades, the injection of lidocaine into the SC at a site that represents a saccadic vector similar to the one represented at the FEF stimulation site should not alter the ability to electrically evoke saccades from FEF. The logic of the experiment is illustrated by the schematic drawing of the SC map shown in Fig. 1. The hypothetical extent of SC neurons activated by FEF stimulation (Fig. 1A), which produces a horizontal 10° saccade, is represented by the dark gray circle on the SC movement map. The extent of a hypothetical lidocaine injection made at the same location on the SC map (Fig. 1B) is represented by the light gray circle around the area activated from the FEF. The empirical question is whether saccades of such amplitude and direction can still be evoked from the FEF after that part of the SC has been inactivated.

We found that SC inactivation substantially altered saccades evoked by FEF stimulation, and we conclude that this alteration is more consistent with the FEF interacting with the SC than being parallel to it. Among the reasons we consider for the difference in the current observations and the conclusions of previous experiments is that our SC inactivations were brief and allowed very little time for recovery, whereas the previous observations probably did allow time for such recovery and reorganization.

A brief report has been published previously (Hanes and Wurtz 1999).

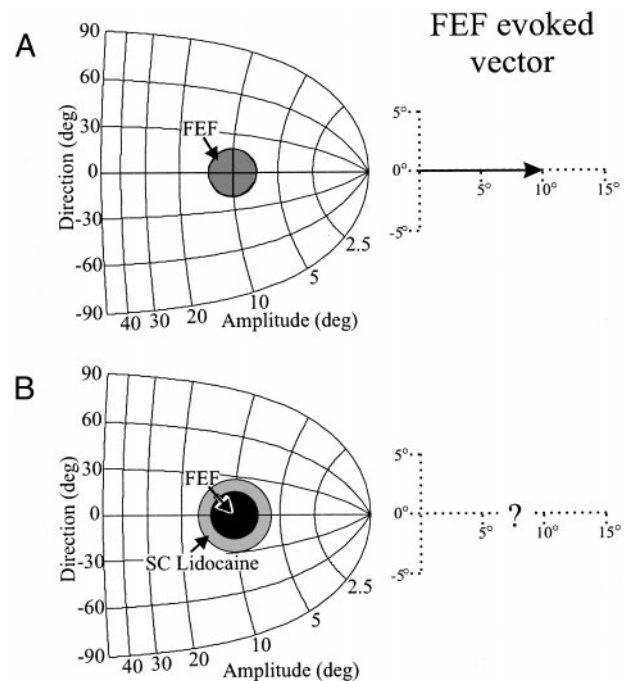


FIG. 1. Hypothetical superior colliculus (SC) lidocaine injection in which the frontal eye field (FEF) and SC sites represent similar vectors. Relative target positions and saccade vectors are expressed in polar coordinates (i.e., direction and amplitude). An angle of 0° indicates the right horizontal direction, 90° up direction, and -90° down direction. A: projection of right hemifield on to the left SC based on a parametric fit (Ottes et al. 1986) to Robinson's stimulation map (Robinson 1972). Isoamplitude lines run from 2.5 to 50° and isodirection lines run from 90 to -90°. The hypothetical extent of SC neurons activated by stimulation of a FEF site that evokes 10° horizontal saccades is indicated by the dark gray circle. B: a hypothetical lidocaine injection was made at a SC site that represents a similar vector to that evoked by FEF stimulation. The light gray circle indicates the extent of the zone inactivated by the lidocaine. The black region indicates the SC neurons that are normally activated by stimulation of this FEF site, but which are temporarily inactivated by the lidocaine injection. The size of the lidocaine injection was greater than the extent of SC cells activated by FEF stimulation.

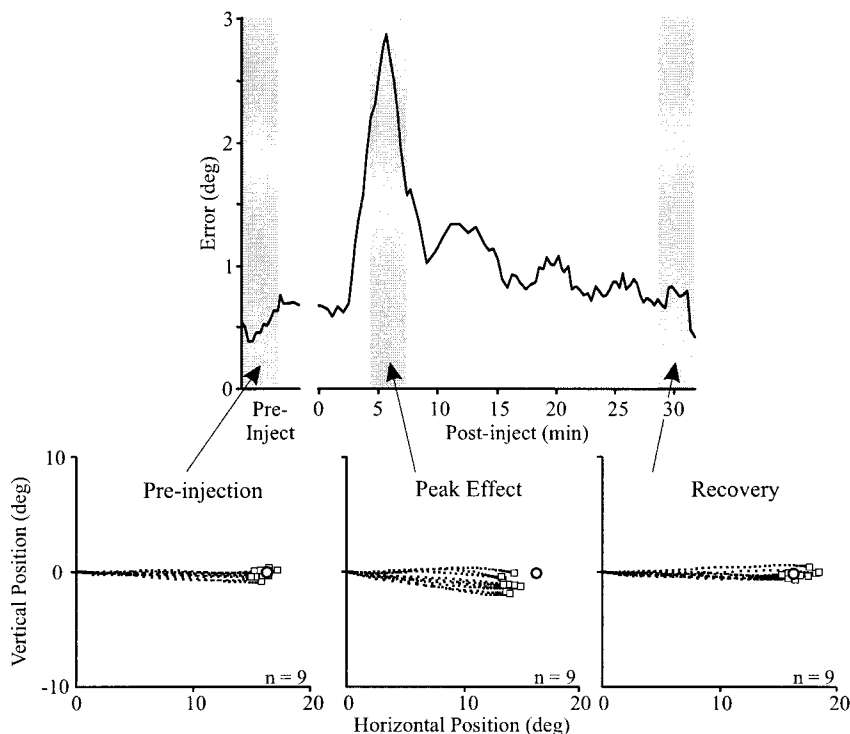
METHODS

In two monkeys, we used standard electrophysiological techniques to record single cells, electrically stimulate and reversibly inactivate the SC or FEF, and monitor eye movements as described previously (Aizawa and Wurtz 1998; Basso and Wurtz 1998). All protocols were approved by the Institute Animal Care and Use Committee and complied with the Public Health Service Policy on the humane care and use of laboratory animals.

FEF and SC were first located anatomically with magnetic resonance imaging (MRI). MRI images of tungsten microelectrodes placed in the grids (Crist et al. 1988) over FEF or SC guided exploration of each structure. The two areas were then identified physiologically by recording from saccade-related neurons and by evoking saccades at $<50 \mu\text{A}$ threshold. We first mapped the movement fields of neurons in the FEF and SC by noting where the neural activity in each area increased before the initiation of saccadic eye movements to visual targets. We then used electrical stimulation through the microelectrodes in both FEF and SC to estimate the net vector of saccades represented by the neuronal population near the stimulating microelectrode's tip (biphasic pulses, pulse duration 0.2 ms per phase, and a rate of 350 Hz; ~ 20 trials). The duration of stimulation was set to be the maximum duration that evoked only one saccade using suprathreshold stimulation (usually 70–80 ms). The duration was held constant for the remainder of the experiment.

We injected lidocaine hydrochloride (2%), muscimol ($5 \mu\text{g}/\mu\text{l}$), or

A



B

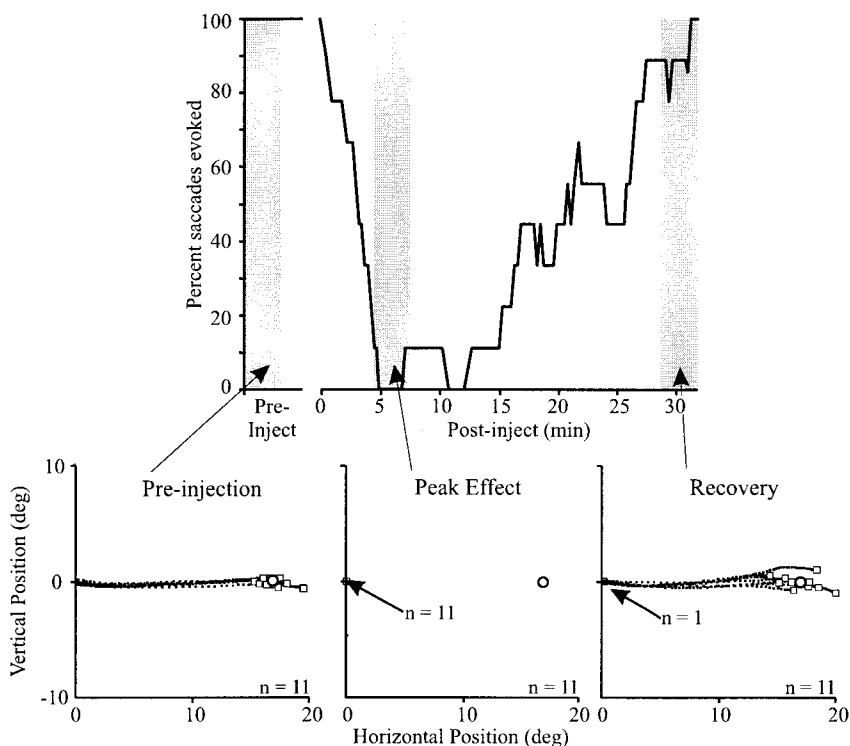


FIG. 2. Deficits in visually guided saccades (A) and saccades evoked by FEF stimulation (B) resulting from a 2.4- μ l lidocaine injection into the SC. A: the graph shows the distance between the endpoint of each visually guided saccade and the visual target (referred to as "error"). The individual trial data were convolved with a 9-trial running boxcar average to provide a smooth representation. *Time 0* indicates the onset of the lidocaine injection. The 3 bottom panels show superimposed traces of FEF stimulation evoked saccades made prior to the SC lidocaine injection (*left*, preinjection), during the peak lidocaine effect (*middle*, peak effect), and after recovery (*right*, recovery). Nine trials in each panel. The grayed regions in the top plot indicate the time of occurrence of the trials shown in the bottom 3 panels. The dots indicate eye position at 1-ms intervals. An open circle in each of the lower 3 plots indicates the mean final eye position during the preinjection period for visually guided saccades. Open squares indicate the endpoint of saccades. B: the graph shows the percent of saccades evoked by FEF stimulation during the same time period shown in A. Conventions as in A. The 3 panels below the graph show that in the preinjection period 11 of 11 saccades were evoked by FEF stimulation, during the peak effect 0 of 11 saccades were evoked, and after recovery 10 of 11 saccades were evoked. The circle in the 3 panels below the graph indicates the mean final eye position during the preinjection period for FEF stimulation evoked saccades. During the recovery period saccades were elicited in almost all trials; however, there was more variability in the endpoints of the evoked saccades. The absence of stimulation-evoked saccades during the peak effect suggests that the FEF is dependent on the SC for saccade generation in the normal monkey.

saline into the SC using a previously described technique (Crist et al. 1988). For each injection we collected pre- and postinjection files while the monkey performed three interleaved behavioral tasks. In the delayed visually guided saccade task, after fixation of a central spot (within $\pm 1.5^\circ$) for 500–800 ms, the peripheral visual target appeared

and remained present through the end of the trial. After either a 300- to 500-ms or a 500- to 1,000-ms delay, the fixation spot disappeared, instructing the monkey to generate a saccade within 1,000 ms to the target. The target was always located at approximately the same position as the endpoint of the evoked saccade from the FEF site being

TABLE 1. *Effect of SC injections on the ability to evoke saccades from the FEF*

Injection Number	Monkey	Volume, μl	SC Amplitude, deg	SC Direction, deg	FEF Amplitude, deg	FEF Direction, deg	SC-FEF Distance, mm	Current Ratio	Fail to Evoke
<i>Large volume lidocaine</i>									
1	<i>H</i>	4.0	9.0	1.0	5.9	-20.8	0.6	2.0	Yes
2	<i>H</i>	3.3	16.5	31.8	5.2	-17.1	1.7	2.0	Yes
3	<i>H</i>	3.3	19.2	31.8	4.8	-2.7	1.7	2.0	Yes
4	<i>H</i>	3.0	6.3	-2.9	7.7	-21.4	0.5	1.9	Yes
5	<i>B</i>	2.4	29.0	29.6	18.0	1.9	0.9	1.7	Yes
<i>Medium volume lidocaine</i>									
6	<i>B</i>	2.0	31.4	29.6	17.5	65.5	1.3	2.0	No
7	<i>H</i>	1.6	3.3	52.3	9.0	27.4	1.1	2.2	No
8	<i>H</i>	1.6	3.3	52.3	7.9	51.0	0.9	2.2	No
9	<i>B</i>	1.5	16.4	8.1	17.8	9.0	0.1	2.2	Yes
10	<i>B</i>	1.5	16.4	8.1	17.4	7.4	0.1	2.2	Yes
11	<i>B</i>	1.5	16.4	8.1	18.2	-58.0	1.8	2.0	No
12	<i>B</i>	1.5	16.4	8.1	17.0	-53.7	1.7	2.0	No
<i>Small volume lidocaine</i>									
13	<i>B</i>	0.4	22.0	-51.0	15.2	-39.7	0.6	1.3	No
14	<i>B</i>	0.4	22.0	-51.0	19.8	-50.0	0.1	2.0	No
<i>Muscimol</i>									
15	<i>B</i>	0.8	21.9	-46.8	13.5	-44.5	0.6	1.5	Yes
16	<i>B</i>	0.4	21.9	-46.8	20.5	-50.0	0.1	2.0	Yes
17	<i>B</i>	0.4	21.9	-46.8	14.2	-42.4	0.5	1.5	Yes
18	<i>H</i>	0.5	11.5	0.5	10.7	3.5	0.1	2.5	Yes
<i>Saline</i>									
19	<i>B</i>	0.4	21.2	-45.0	20.8	-51.0	0.2	2.3	No
20	<i>B</i>	0.4	21.2	-45.0	14.5	-47.3	0.5	1.3	No
21	<i>H</i>	0.8	12.4	14.0	12.6	18.4	0.1	1.9	No

The saccade amplitude and direction were determined by recording the multiple unit activity and electrical stimulation at each stimulation and injection site within the frontal eye field (FEF) and superior colliculus (SC), respectively. The lidocaine injections are ordered by injection volume. The SC-FEF distance was calculated using the parametric fit by Ottes et al. (1986) to Robinson's (1972) stimulation map. Current ratio indicates the ratio of the current level used during the injection to the threshold current level. "Yes" in the Fail to Evoke column indicates that post-injection we failed to evoke saccades from the FEF site at suprathreshold current levels. Injection 5 is shown in Fig. 2, injection 13 is shown in Fig. 5, and injection 7 is shown in Fig. 6.

studied. The monkey was given a liquid reward if the saccade landed within $\pm 8^\circ$ of the visual target. In the fixation-stimulation task, the central spot was extinguished after fixation for 500–800 ms, and electrical stimulation was given 25–125 ms later. Monkeys received a liquid reward 200 ms after stimulation offset. In the fixation-blink task, after fixation of the central spot for 500–800 ms, the central spot was turned off for 400–600 ms, and the monkey was required to maintain the same eye position. After this delay, the fixation spot reappeared, requiring the monkey to maintain fixation on the central spot for another 500 ms. A liquid reward was then given. The fixation-blink task served only as a control to keep the monkey fixating in the absence of a visual stimulus, and the data from this task will not be discussed further.

Stimulation and injection sites within the FEF and the ipsilateral SC, respectively, were selected so that saccades were evoked by low-threshold stimulation in both areas (~ 5 – $10 \mu\text{A}$ in the SC and ~ 40 – $60 \mu\text{A}$ in the FEF). Once two sites were selected, we determined the current required to evoke saccades from the FEF site during 50% of the fixation-stimulation trials. During data acquisition we stimulated the FEF at currents between 1.3 and 2.3 times this threshold current. Next, we lowered the syringe to approximately 3 mm above the SC and collected the *preinjection* data. The syringe was then lowered to the SC while stimulating through the internal wire. Once the lowest threshold region of the SC was located, we advanced

the syringe 500 μm to compensate for the wire extension beyond the syringe tip and began to pressure inject the liquid into the SC and collect the *postinjection* data. Volumes ranged from 0.4–4.0 μl for lidocaine and from 0.4–0.8 μl for muscimol. We injected at a rate of 0.3 μl per 30 s. Once the injection was completed and a behavioral effect (e.g., a change in saccade latency or accuracy) on visually guided saccades was evident, the syringe was retracted to ~ 3 mm above the SC.

RESULTS

Elimination of saccades evoked by FEF stimulation

The first set of experiments tested whether saccades can still be evoked from the FEF after part of the SC has been inactivated as outlined in Fig. 1. Figure 2 shows the results of an experiment (2.4 μl injection) that addressed this question. We first located regions in the SC and FEF where neurons were active before saccades to approximately the same part of the visual field, and determined the amplitude and direction of saccades evoked by stimulation through the microelectrode. In this experiment stimulation in the SC evoked saccades to the right with an angle of 30° above the horizontal and amplitude

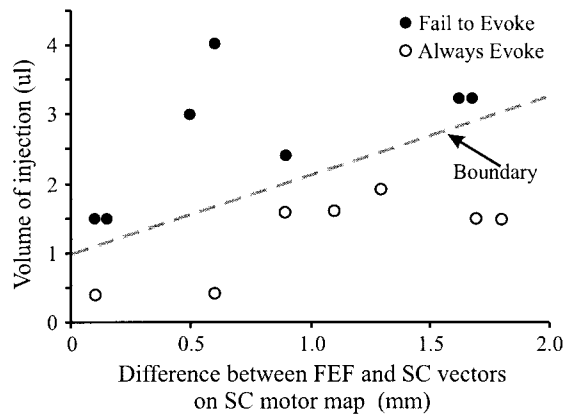


FIG. 3. Plot of whether saccades were evoked from FEF following SC inactivation as a function of proximity of the FEF and SC sites and injection volume. Saccades failed to be evoked (●) during injections in which the distance between the FEF and SC sites was small or volumes were large. Saccades continued to be evoked (○) during injections in which the distance between the FEF and SC sites was large or volumes were small. The dotted line simply indicates the boundary between the “always evoke” and “fail to evoke” data points.

of 29° . This location on the SC map would represent the center of the inactivated region following the lidocaine injection. Stimulation of the FEF evoked saccades to the right that had an average direction of 2° above horizontal and amplitude of 18° . Although these vectors appear slightly disparate, they would correspond to a separation of only ~ 0.9 mm on the SC motor map (Ottes et al. 1986) if the projection from FEF to SC is topographically aligned. This assumption of topography is supported by both anatomical (Komatsu and Suzuki 1985; Stanton et al. 1988) and physiological data (Schlag-Rey et al. 1992; Segraves and Goldberg 1987; Sommer and Wurtz 2000).

We next determined that the lidocaine injection had inactivated the SC by measuring how the saccades generated in a delayed visually guided saccade task were modified after the injection (Fig. 2A). This behavioral assay has been shown previously to be a sensitive indicator of SC inactivation (Aizawa and Wurtz 1998; Hikosaka and Wurtz 1986; Lee et al. 1988). For this experiment we placed the visual target to the right on the horizontal at an amplitude of 17° , close to the endpoint of saccades evoked by FEF stimulation, but slightly offset from the center of the inactivated zone within the SC. As shown in the *top panel* of Fig. 2A, prior to the injection the endpoints of the saccades were within $\sim 0.5^\circ$ of the 17° visual target. Within 2–3 min postinjection the error in the saccade endpoints began to increase, and by about 6 min postinjection the error in the saccade endpoints peaked at $\sim 3^\circ$. The three panels below the graph show the actual eye movements during the preinjection period, the peak effect period, and during recovery. During the peak of the effect, the saccades were consistently short and rotated slightly down; the mean error was 2.45° , which was significantly different from the 0.48° error in the preinjection period (t -test, $t = 19.9$, $df = 17$, $P < 0.01$). The observed hypometria and slight rotation downward would be predicted by the vector averaging hypothesis of Lee et al. (1988) since the inactivated zone on the SC was of slightly larger amplitude and rotated up compared with the zone activated by the visual target. The monkey's reaction time to the presentation of the target also increased significantly (mean preinjection = 184 ms, mean peak effect = 236 ms, $t =$

3.5 , $df = 17$, $P < 0.01$), while the saccadic peak velocity decreased significantly (mean preinjection = $656^\circ/\text{s}$, mean peak effect = $584^\circ/\text{s}$, $t = 2.8$, $df = 17$, $P < 0.01$). These impairments indicate that the lidocaine had inactivated the region of the SC that includes vectors that are the same as the vector of saccades evoked by stimulation of the FEF site.

Figure 2B shows the effect of this SC lidocaine injection on the ability to evoke saccades by FEF stimulation. As shown in the *top panel*, suprathreshold (1.7 times threshold) stimulation at this FEF site prior to the injection elicited saccades during

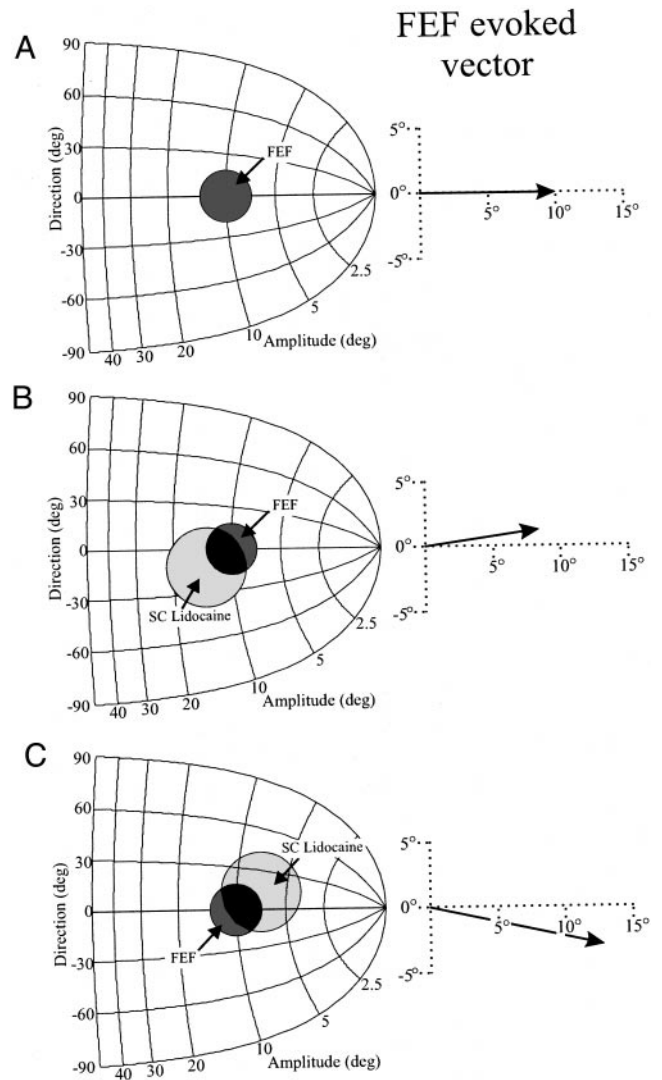


FIG. 4. Hypothetical SC lidocaine injection in which the FEF and SC sites represent disparate vectors. *A*: the hypothetical extent of SC neurons activated by stimulation of an FEF site that evokes 10° horizontal saccades is indicated by the dark gray circle. *B*: predicted effect of a lidocaine injection at a SC site that represents vectors slightly longer, and rotated down, than the FEF site. The light gray circle indicates the extent of the zone inactivated by the lidocaine injection. The black region indicates the SC neurons that are normally activated by stimulation of this FEF site, but which are temporarily inactivated by the lidocaine injection. The dark gray crescent indicates the remaining SC neurons that are activated by FEF stimulation following the injection into the SC. If a vector-averaging scheme is correct, this should result in an evoked saccade that is shorter and rotated up compared with the preinjection vector. *C*: predicted effect of an injection of lidocaine at a SC site that represents vectors slightly shorter, and rotated up, than the FEF site. This should result in an evoked saccade that is longer and rotated down compared with the preinjection vector.

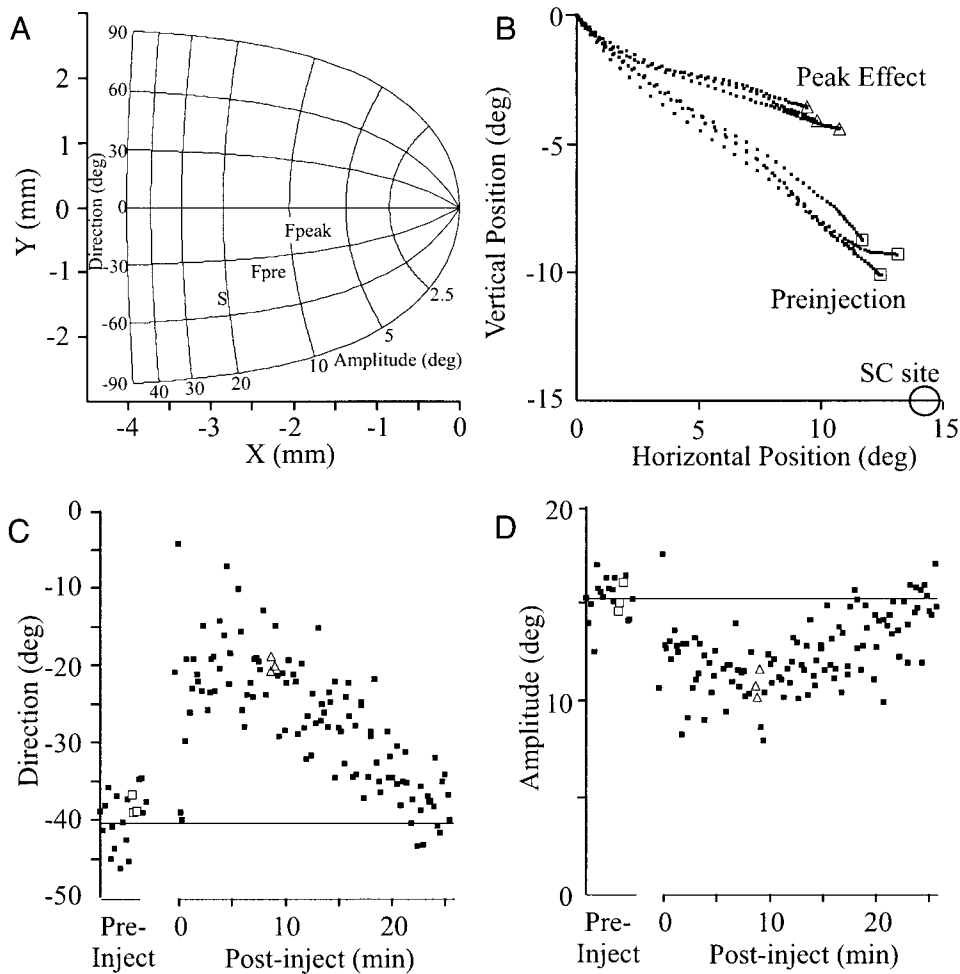


FIG. 5. Changes in direction and amplitude of saccadic vectors evoked by FEF stimulation following a SC lidocaine injection in which saccades continued to be evoked. A: an SC map as in Fig. 1, but here the abscissa represents the distance along the rostral-caudal axis of the SC in mm, and the ordinate represents the distance along the medial-lateral axis of the SC in mm. Medial (corresponding to upward saccades) is plotted as a positive distance, and lateral (corresponding to downward saccades) is plotted as a negative distance. Rostral (corresponding to small saccades) is plotted as zero on the abscissa. Locations of the vector represented at the site of the SC injection (S) and the vector evoked from FEF preinjection (Fpre) and during the peak lidocaine effect (Fpeak) are projected onto the left SC. A 9-trial running boxcar average of direction and amplitude was used to determine the time of the peak effect. B: superimposed traces of stimulation evoked saccades made prior to a SC lidocaine injection and during the peak effect (conventions as in Fig. 2). The circle indicates the vector evoked by stimulation at the SC injection site. Before the injections, saccades evoked by FEF stimulation had an average direction and amplitude of -40° and 15° , respectively, while at the peak of the injection effect, the evoked saccades had an average direction and amplitude of -16° and 11° . The direction (C) and amplitude (D) of saccades evoked following FEF stimulation are shown as a function of time from injection onset. Each point in C and D represents data from a single trial. The horizontal line in these panels indicates the mean value of the preinjection data for that panel. Open squares and triangles indicate the trials shown in B. These results show that the vector of the evoked saccade is modified in the way that would be predicted by the vector-averaging hypothesis.

100% of the fixation-stimulation trials. Within 1–2 min postinjection the percent of saccades evoked began to decline, and by about 5 min postinjection, saccades were rarely made. The three panels below the graph show the actual evoked eye movements; during the peak effect no saccades were elicited.

To determine whether the absence of evoked saccades was simply due to a threshold shift, we increased the current level to 4.3 times threshold ($150 \mu\text{A}$) for a few trials during the peak lidocaine effect. We did not evoke saccades even at these high current levels. We did not test currents higher than this level for fear of causing tissue damage. Thus this inactivation/stimulation result suggests that the direct FEF–brain stem pathway is *not* sufficient to generate stimulation-induced saccades in the absence of the pathway that projects through the SC to the brain stem.

One question that inevitably arises when looking at the results shown in Fig. 2 is why the monkey was able to make visually guided saccades after inactivation of the SC at the same time that FEF stimulation failed to evoke them. If the FEF output for generating saccades passes through the SC, how can this be? The first point to emphasize is that the monkey did *not* make normal visually guided saccades: they were hypometric, had lower velocity, and had longer latency. The second point is that, unlike the classic ablation experiments, we are not removing all of the SC, just the region centered on the saccadic vector that is close to that of the

saccade resulting from FEF stimulation. The rest of the SC remains intact and since the area active before each saccade may be as large as a quarter of the SC (Munoz and Wurtz 1995), there should be unaltered SC available to make a visually guided saccade. The saccades should not be accurate, however, and they are not. The third point is that with FEF stimulation only the contribution of this area to saccade generation is invoked, whereas for the visually guided saccades the presentation of the visual target is activating the entire oculomotor system. One might hypothesize that the amount of SC recruited by the entire oculomotor system for a visually guided saccade may be greater than during a FEF stimulation-evoked saccade. This could easily result in the monkey continuing to produce visually guided saccades, although quite inaccurate, at the same time that FEF stimulation fails to evoke saccades.

Two factors that should influence the ability of FEF stimulation to evoke a saccade after a SC lidocaine injection are the proximity of the FEF and SC sites and the size of the injection. The probability of FEF stimulation failing to evoke a saccade should increase with closer proximity of FEF and SC sites and with larger SC injections. This is what we found (Table 1). For ease of presentation, we divided the 14 lidocaine injections into three groups based on the volume: large ($>2 \mu\text{l}$), medium ($\leq 2 \mu\text{l}$, but $>1 \mu\text{l}$), small ($\leq 1 \mu\text{l}$). During all five large volume injections, FEF suprathreshold stimulation failed to evoke saccades postinjection. The average distance between

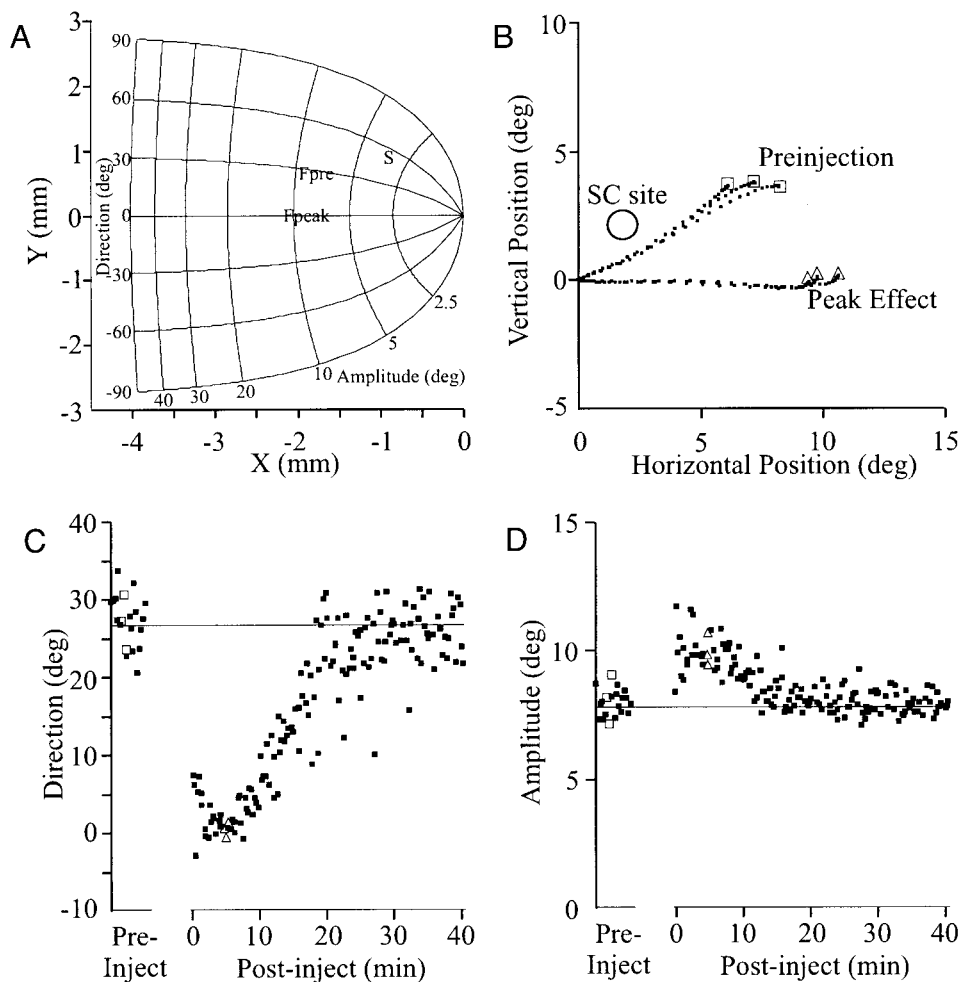


FIG. 6. Changes in direction and amplitude of saccadic vectors evoked by FEF stimulation following a SC lidocaine injection in which saccades continued to be evoked and the FEF evoked vector was below and of longer amplitude than the SC vector. Before the injections, saccades evoked by FEF stimulation had an average direction and amplitude of 27 and 9°, respectively, while at the peak of the injection effect, the evoked saccades had an average direction and amplitude of 1 and 11°. Conventions as in Fig. 5.

the FEF and SC sites for these five injections was 1.1 mm. During two of seven medium volume injections, FEF supra-threshold stimulation failed to evoke saccades postinjection. The average distance between the FEF and SC sites for these two medium volume injections was 0.1 mm, while the average distance was 1.4 mm for the other five injections during which saccades were always evoked. Thus for medium volume injections, when the distance between the FEF and SC sites was shorter, the likelihood of failing to evoke saccades from FEF postinjection was greater. Finally, we always evoked saccades from the FEF for the two smallest injections (average FEF-SC distance was 0.4 mm). Figure 3 shows these same relationships on a graph that relates distance between injections sites (as indicated by the difference in the vectors) and injection volumes with a boundary line drawn between those injections that did and did not lead to the failure of FEF stimulation to evoke saccades.

One alternative interpretation of these results is that the SC injections result in the inability to evoke saccades from the FEF because the lidocaine is deactivating fibers that pass from the FEF deeper into the brain stem premotor circuitry just rostral to the SC (Leichnetz 1981). To control for this, we made four injections of the GABA agonist muscimol, which acts on the GABA receptors found on the cell body but not the axon. The muscimol injections also resulted in the inability to evoke saccades from the FEF (although the effect of muscimol gen-

erally lasted around 6 h; Table 1), which is consistent with lidocaine acting on cell bodies within the SC rather than axons of passage. Three saline injections had negligible effects (Table 1), indicating that pressure injection alone did not produce the deficit.

Change of saccadic vector evoked by FEF stimulation

The results so far are consistent with the SC lying in the functional pathway between the FEF and the brain stem premotor circuits because inactivation of the SC with well-positioned large injections of lidocaine blocked the effect of FEF stimulation. In the other experiments where the SC lidocaine injections did not block the evoked saccades (7 of the 14 lidocaine injections; see Table 1 and Fig. 3), we would still expect to see a change in the saccades evoked from the FEF after the SC inactivation. There should be a predictable rotation caused by inactivation of *part* of the SC map that is normally activated by FEF stimulation. We can predict what the nature of the rotation should be by returning to the example used previously that considered the hypothetical extent of SC neurons activated by stimulation of an FEF site that represents 10° horizontal saccades (Fig. 4A). Now, however, we consider SC injection sites that represent vectors below (Fig. 4B) and above (Fig. 4C) the FEF stimulation site, and assume that the interaction of the FEF and SC follow the vector averaging hypoth-

esis of Lee et al. (1988). This hypothesis, which has been supported empirically by experiments on SC (Lee et al. 1988), holds that the computation of the metrics of the saccade is based on a weighted average of the saccade-related discharges of the entire active population. If this hypothesis is correct, the consequence of the inactivation of the SC site representing saccadic vectors below and longer than those produced by FEF stimulation (Fig. 4B) should be a rotation of the net vector upward because the component vectors pointing to the lower part of the field had been blocked. Additionally, one would expect a decrease in the amplitude of the FEF-evoked vector because the site representing longer saccades had been inactivated by the injection. In contrast, Fig. 4C shows a hypothetical injection that was made at a SC site that represents vectors above and of shorter amplitude than the FEF site. In this case, FEF-evoked saccades after the injection should be rotated down and be of longer amplitude than the FEF preinjection saccades.

Figure 5 shows the results of an experiment in which such a rotation was observed following a small lidocaine injection ($0.4 \mu\text{l}$) in which saccades were always evoked by FEF stimulation. Preinjection saccades evoked from the FEF site had an average direction of -40° (down-right) and amplitude of 15° (Fig. 5A, Fpre), while saccades evoked from the SC site had an average direction and amplitude of -51 and 22° , respectively (Fig. 5A, S). This corresponds to a separation of 0.6 mm on the SC map. The mean direction and amplitude during the visually guided saccade trials (not shown) were not altered noticeably after the injection, although reaction time became more variable and the peak saccadic velocity was decreased. Figure 5B shows examples of saccades evoked by FEF stimulation preinjection and during the peak injection effect. Immediately after the injection, the vector of the FEF-evoked saccade rotated upward toward the horizontal meridian and the amplitude decreased (Fig. 5, C and D). At the time of the peak effect, saccades evoked by FEF stimulation had an average direction and amplitude of -16 and 11° , respectively. Thus the evoked vector rotated upward 24° and the amplitude decreased by 4° .

Figure 6 shows the results of another experiment in which the FEF-evoked vector rotated following a lidocaine injection ($1.6 \mu\text{l}$). Preinjection saccades evoked from the FEF site had an average direction of 27° (up-right) and an amplitude of 9° (Fig. 6A, Fpre), while saccades evoked from the SC site had an average direction and amplitude of 52 and 3° (Fig. 6A, S), corresponding to a separation of 1.1 mm on the SC map. Immediately after the injection, the vector of the FEF-evoked saccade rotated downward toward the horizontal meridian (Fig. 6, B and C), and the amplitude increased (Fig. 6, B and D). At the time of the peak effect, the evoked vector had rotated downward 26° , and the amplitude increased by 2° .

A change in the direction and amplitude of the FEF-evoked vector following a lidocaine injection was observed in all seven injections during which saccades continued to be evoked from the FEF after an SC injection (Fig. 7). Figure 7A plots the size and direction of the rotation on the ordinate so that upward rotation is indicated by positive values, downward by negative values. The abscissa shows the relative direction of the FEF and SC vectors. Cases where the FEF vector was below that of the SC are given minus values in the *left half of the graph*, and those in which the FEF vector was above the SC vector are positive and on the *right*. From the logical consideration of the

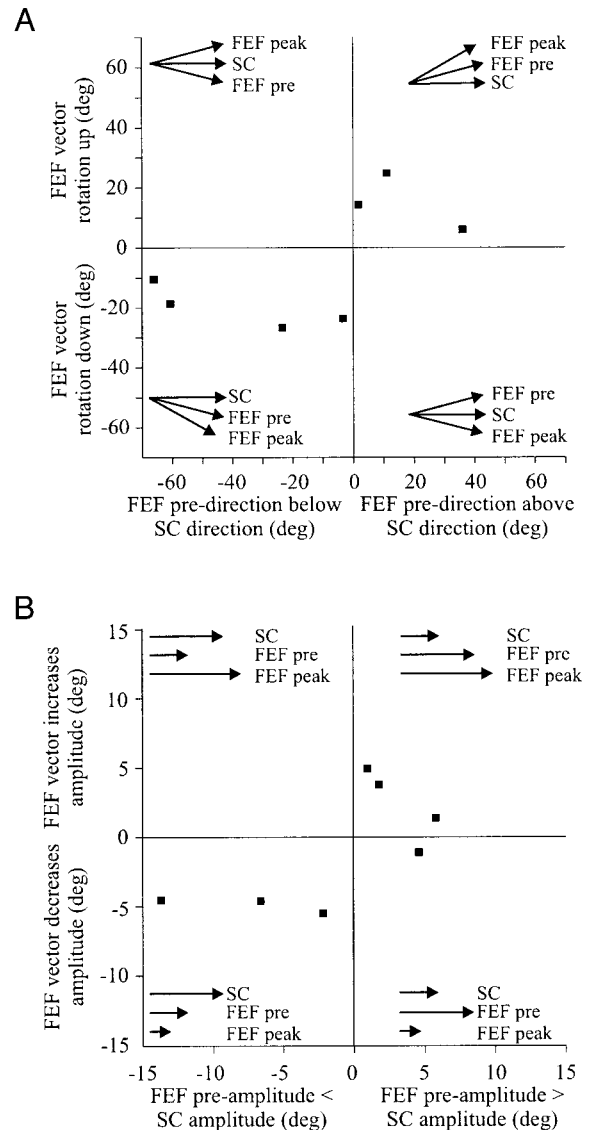


FIG. 7. Direction and amplitude changes of FEF evoked saccades for the 7 SC lidocaine injections in which FEF evoked saccades were not eliminated. A: direction of FEF vector rotation following SC lidocaine injections. Each filled square indicates 1 injection. The ordinate shows the change of saccade direction evoked by FEF stimulation from preinjection to postinjection as a rotation down (negative numbers) or up (positive numbers). The abscissa shows the difference between the direction of the FEF preinjection vector and the direction of the vector evoked at the SC injection site. The value is negative if the direction of the FEF vector was below that evoked by SC stimulation and is positive if the FEF direction is above the SC direction. The schematic arrows in each quadrant of the graph represent the combination of an initial FEF evoked direction (above or below that evoked from the SC) and a direction of rotation (up or down). SC is always shown as horizontal in the insets for simplicity. Each data point is based on 10–16 FEF preinjection trials, 9 peak effect trials, and 8–10 SC stimulation trials. See text of RESULTS for description of significance of quadrants. Conventions for nomenclature are as in Fig. 5. B: change in amplitude of the FEF-evoked vector following the SC lidocaine injections. Each filled square indicates 1 injection. The change in amplitude of the FEF evoked saccade (ordinate) is shown as a function of the difference between the amplitude of the SC-evoked saccade and the FEF preinjection-evoked saccade (abscissa). Same organization of the 4 quadrants as in A. The magnitude of the rotation or amplitude change was determined by taking the difference between the preinjection and the peak effect values. The peak effect was determined using a 9-trial running boxcar average.

direction of rotation that should result from vector averaging, we would expect the points to fall into only two quadrants of the graph. The *bottom left quadrant* should contain data points where the FEF preinjection vectors were below the SC vector, and the rotation following the injection was down. The *top right quadrant* should contain data points where the FEF preinjection vector was above the SC vector, and the rotation following the injection was up. This is what we found: all of the points in Fig. 7A fell into these two quadrants. The FEF vector never rotated down when the FEF preinjection vector was above the vector evoked at the SC site (*bottom right quadrant*) and never rotated up when the FEF preinjection vector was below the vector evoked at the SC site (*top left quadrant*). A similar effect occurred with the amplitude of the FEF evoked vector (Fig. 7B). The amplitude of the FEF vector decreased during the three injections in which the amplitude of the FEF preinjection vector was less than the vector evoked at the SC site (*bottom left quadrant*). Additionally, the amplitude of the FEF vector increased during three of four injections in which the amplitude of the FEF preinjection vector was greater than the vector evoked at the SC site (*top right quadrant*). These results show that the vector of the evoked saccade is modified in the way that would be predicted by the vector-averaging hypothesis.

DISCUSSION

We stimulated the FEF before and after reversibly inactivating the SC to investigate the relative contributions of the direct pathway from FEF to the brain stem premotor circuitry and the indirect pathway through the SC. Our logic was that by inactivating the SC we temporarily removed the indirect pathway and thereby revealed the contribution of the direct pathway. We found that inactivation of the SC alters the effect of FEF stimulation, and we made two principle observations. First, the FEF-evoked saccades were eliminated when the FEF and SC vectors were similar or when the volume injected into the SC was large. Second, SC inactivation did not eliminate saccades evoked by FEF stimulation when the FEF and SC vectors were more widely separated, or the injection was small. Instead, the inactivation led to a rotation of the vectors of the FEF-evoked saccades away from the vector represented at the SC injection site. We think that these observations provide insight into the relative contributions of the direct and indirect FEF pathways to the brain stem premotor circuits, the interaction between the signals conveyed by the FEF and SC, and the nature of the recovery process following lesions, and we will discuss each in turn.

Do the FEF and SC represent parallel pathways?

When the SC region that we inactivated represented nearly the same saccadic vector as the saccade evoked from the FEF, we were able to block the saccades normally elicited by FEF stimulation. Whatever remaining pathways outside of this inactivated region of the SC that pass from the FEF to the brain stem premotor circuits were not sufficient to generate saccades. We conclude that this does not support the idea of the direct and indirect pathways functioning in parallel but rather is more consistent with the output of the FEF being dependent on the pathway through the SC.

There are, however, several assumptions in our experiments that have to be made before such a conclusion can be accepted. With respect to the FEF, we assume that evoking saccades by electrical stimulation, rather than relying on those naturally occurring, does not in some substantial fashion alter the way in which the FEF communicates with the brain stem. We did such stimulation to specifically involve one brain region, as has been done in many previous FEF experiments (e.g., Robinson and Fuchs 1969; Schiller 1977; Schlag and Schlag-Rey 1990). We cannot, however, reject the notion that this produces abnormal output from the area. For the SC inactivation that eliminated the effect of FEF stimulation, we assume that the lidocaine injection functionally removes neurons with the same set of saccade vectors as the area stimulated in the FEF, but since we do not know the exact size of each injection, we can only infer that this was the case. In fact the necessity of indicating not only the alignment of the FEF and SC vectors but the size of the injection as well serves to emphasize this uncertainty. We tested the efficacy of the injection by the effect on visually guided saccades to targets in the region of the visual field that should have been affected by the injection, but the limited points tested due to the brevity of the lidocaine effect limited our assessment of the size of the inactivated area. The finding that larger lesions were required to eliminate the effect of the FEF stimulation makes sense in that a larger lesion should remove a larger fraction of neurons that share vectors with the site of FEF stimulation. Finally, with the SC lidocaine injections, we also assume that we are inactivating the pathway through the SC and not inadvertently the direct pathway. The opportunity for this to occur would lie primarily in the spread of the lidocaine into fibers passing below the SC. While the brevity of the lidocaine effect makes substantial spread unlikely, we also did several experiments using muscimol, a GABA agonist that would act on synapses not on fibers of passage, and we obtained essentially the same results as with lidocaine. The possibility also exists that the lidocaine could spread to the burst neurons in the brain stem; however, given the brevity of the injection and the distance that the lidocaine would need to spread to influence the burst neurons, this possibility seems implausible. Thus while our experiments require specific assumptions for their interpretation, we regard the assumptions as both reasonable and frequently made.

Our conclusion that the failure to elicit saccades from the FEF following inactivation of the SC indicates that the direct FEF to brain stem pathway is not sufficient to generate saccades is clearly in conflict with the previous conclusions based on joint FEF and SC lesions and the effect of FEF stimulation following SC ablation (see review by Schiller 1998). We believe that this apparent conflict can be explained by differences in the experiments, particularly in the time at which the FEF function was tested after removal of the SC.

The previous stimulation/lesion results (Keating and Gooley 1988a; Schiller 1977) or the paired lesion results of Schiller et al. (1980; see review by Schiller 1998) are well established and based on not one but a series of related experiments. Several permanent lesion experiments have shown that ablation of the SC or FEF alone largely spared the monkey's ability to make saccades to simple visual targets (Albano et al. 1982; Lynch 1992; Schiller and Chou 1998; Schiller et al. 1980, 1987; Wurtz and Goldberg 1972). Several other combinations of lesion and stimulation experiments have also lent support to the

concept of parallel pathways. In a series of experiments that tested the ability of occipital and parietal cortex stimulation to evoke saccades following combinations of posterior parietal, FEF, and SC lesions, Keating and Gooley (1988a) concluded that visual cortex appears to guide saccades through either of two routes, one through the tectum and the other through the frontal lobe (see Keating et al. 1983; Schiller 1977). Similarly, Lynch (1992) showed that ablation of FEF and posterior parietal cortex also precludes initiation of visually guided saccades that could be interpreted as eliminating both the parietal pathway through the SC and the pathway from FEF that does not require the SC. Thus the picture that emerges from this series of ablation experiments is that there is one pathway from occipital and parietal cortex that is dependent on the SC and another pathway that emanates from the frontal cortex that is not.

A common characteristic of these experiments, which might be critical in comparing those results to the present results, is that the ablations were followed by a period of days to weeks before the behavioral effects of the lesions on the saccadic system were tested. This time interval may have been sufficient to allow recovery that involves more efficient use of existing pathways or a reorganization of those pathways. These pathways would then be sufficient for the generation of saccades after this recovery even though they are *not* sufficient in the intact animal. In contrast in our experiments, the lidocaine injection removed the SC functionally within minutes, allowing very little time for recovery, and may have thus revealed the nature of the interactions in the normal monkey more accurately. We cannot rule out the possibility that short-term plastic changes, such as second-messenger systems up- or down-regulating various receptor mechanisms, may occur during the lidocaine injections. The fact that SC inactivation precluded FEF stimulation, however, suggests that these short-term changes did not significantly influence the neural system. Only one previous experiment has looked at the interaction of the FEF and SC without such time for recovery. In an elegant dual cooling probe experiment, Keating and Gooley (1988b) explored the effects of separate and combined inactivation of both structures. As in the previous ablation experiments, inactivation of either structure produced mild saccadic deficits, and the deficits were greater when the FEF and SC were cooled simultaneously. While inactivation of both FEF and SC did not eliminate visually guided saccades as might be expected if the two areas act in parallel, on this point the experiment is inconclusive because the inactivated regions only partly overlapped. As shown in Fig. 3 of Keating and Gooley (1988b), the FEF probe affected mainly saccades to the upper left hemifield while the SC probe affected the lower left hemifield. The additive effect of cooling both the FEF and SC does not preclude the FEF and SC being entirely serial. From the visual field deficit map it is apparent that part of the SC remains intact, and since the area active before each saccade may be as large as a quarter of the SC (Munoz and Wurtz 1995), there should be unaltered SC available to make a visually guided saccade. If the input to the remaining active SC comes from the FEF and those inputs are cooled, one would expect to see an increase in the saccadic deficit as they found. If this interpretation of their results is correct, we would also expect the affected zone of the visual field to increase in size following the combined FEF and SC inactivation, and this is in fact what

they observed. While these experiments do not unequivocally support a serial organization of the FEF and SC, they also do not lend support to a parallel organization either, nor were they designed to do so.

It is important to point out that we are not suggesting that the FEF has no influence on saccade generation in the nonablated monkey. Brief inactivations of the FEF (Dias and Segraves 1999; Dias et al. 1995; Sommer and Tehovnik 1997) or the SC (Aizawa and Wurtz 1998; Hikosaka and Wurtz 1985, 1986; Lee et al. 1988) have shown substantial changes in the monkey's ability to generate saccades, which in itself suggests that the direct and indirect pathways from FEF to the brain stem are not strictly parallel. Our results simply imply that in the nonablated monkey the direct FEF to brain stem pathway is not sufficient to generate a saccade. Thus we conclude that the predominate functional output from the FEF to the brain stem is funneled through the SC. This conclusion is consistent with both of the two principle findings of the present experiments and with a number of previous observations. First, the anatomical connections to the SC from the FEF are clear and prominent and repeatedly demonstrated (Huerta et al. 1986; Komatsu and Suzuki 1985; Leichnetz 1981; Stanton et al. 1988). Second, the physiological connections between FEF and SC have been demonstrated by antidromic stimulation (Segraves and Goldberg 1987), and these are topographically organized (Schlag-Rey et al. 1992; Sommer and Wurtz 2000).

The implication is that over time after SC ablation the connections other than those through the SC would become more efficient, and the metrics of saccades would return to almost normal values. The exact nature of the pathways participating in such a recovery following SC lesions has not been determined. Anatomical studies (Büttner-Ennever and Horn 1997; Moschovakis and Highstein 1994) have shown that the FEF projects directly to the omnipause neurons in the brain stem, and this has been confirmed physiologically (Segraves 1992). Neither anatomy nor physiology has revealed any *direct* projection from FEF to the brain stem burst neurons that ultimately generate saccades in a given direction. The direct projection to the omnipause neurons could *not* convey the directional information necessary for saccade generation since, by definition, they discharge for saccades of all directions. Other multi-step pathways are available, however, and might be strengthened over time. One such multi-step pathway would pass through the nucleus reticularis tegmenti pontis (Huerta et al. 1986; Stanton et al. 1988), and a lesion along this pathway in conjunction with one in the SC would be expected to eliminate saccade generation, as does the joint FEF and SC lesion. On the other hand, if the SC were only partially instead of completely removed, as is the case in many of the lesion experiments (for example, Wurtz and Goldberg 1972), then the reorganization may occur within the SC itself. Neither of these mechanisms of recovery has yet been investigated.

Interaction of FEF and SC

Our second principle finding is that when the vector of the saccade resulting from FEF stimulation was not well aligned with the net vector of the area removed by the SC inactivation, a saccade was always evoked from the FEF stimulation, but its vector was rotated. The rotation was consistent with the removal of a fraction of the SC movement map that is normally

activated by FEF stimulation (Figs. 5–7). The nature of this rotation is what would be expected if the region activated by the FEF stimulation had its effect on saccade generation by acting directly on the SC movement map. In fact, these interactions between the FEF and SC vectors in our experiments are remarkably similar to the interactions within the SC shown by Lee et al. (1988) following SC inactivation, and lend indirect support to their interpretation of vector averaging within the SC. This vector average effect is also consistent with the vector averaging effects seen between two stimulation sites in the SC (Robinson 1972) and, more importantly, the vector average seen with combined stimulation of FEF and SC (Schiller et al. 1979).

A series of stimulation and recording experiments by Schlag, Schlag-Rey, and their collaborators (summarized in Dominey et al. 1997) revealed several features of the interaction of FEF and SC, some of which are directly relevant to the present observations. First, they found that stimulation of FEF produced excitation in SC neurons that had the same vector as the site stimulated in the FEF (Schlag-Rey et al. 1992), and this observation was one of the key facts in designing our experiments. Second, evidence obtained with the use of the colliding saccade paradigm (see review by Schlag and Schlag-Rey 1990) provides evidence for an interaction between FEF and SC that occurs below the level of the SC, and would appear to be evidence for a direct pathway from FEF to the brain stem premotor circuits. In this paradigm, FEF stimulation given while another saccade is in flight can generate a saccade that has a different vector than the one that would be elicited from the FEF when the eye is stationary. When neurons were recorded in the SC during such colliding saccades (Schlag-Rey et al. 1992), their activity followed that expected for the site of FEF stimulation and not the actual saccade made. Thus since there is an apparent conflict between the signals generated by the FEF and SC, the authors conclude that the FEF overrides the signal generated by the SC (Dominey et al. 1997). If this were the case, in our experiment FEF stimulation should continue to evoke saccades following SC inactivation. Additionally, in the seven cases in which saccades continued to be evoked following SC inactivation, the vector should not rotate as we observed because the FEF should override the SC (Dominey et al. 1997). Further experiments will be required to resolve this issue.

Our experiments, however, do not preclude the possibility that the interaction of the FEF and SC occurs at a point other than within the SC. For example, one possibility is that the interaction of FEF and SC occurs at a brain stem site where the SC and the FEF pathways come together. If this were the case, this target site would require that the projections from FEF and SC be in register (but not necessarily on a SC-like map) to obtain the vector rotations we found following SC inactivation. Another possible interaction between the FEF and SC is that the brain stem premotor circuit must receive input from both the FEF and SC to initiate a visually guided saccade. In one variant of this interaction, SC inactivation would result in a localized suppression within the brain stem so that a saccade could not be generated from FEF activation. Note that such a hypothesized suppression would have to be localized because it is only saccades to one part of the visual field that are modified. Note also that, while both of these interpretations (i.e., that the FEF and SC interact within the SC or outside of

the SC) are viable given our results and current knowledge of the saccadic system, in both interpretations the normal functioning of the FEF is still dependent on the integrity of the SC.

Recovery of function

Our inference is that over time reorganization within the saccadic system can compensate for the loss of the SC and produce the apparent parallel pathways that have been clear when the behavioral effects of permanent lesions have been tested weeks to months after the lesions. If this inference is correct, then the recovery of function is due to neural plasticity within the saccadic system, and this reorganization opens the possibility of using this system as a model to study recovery of function following brain damage. The precision in measuring the output of the saccadic system, the outline of a circuit in the brain that underlies it, and the identity of a number of areas that interact provides a system that can be evaluated for changes following brain damage. Such issues as where the plasticity occurs (e.g., within the SC) and what factors control recovery (e.g., behavioral practice) can be directly investigated.

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