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Stimulation-evoked saccades from the dorsomedial frontal cortex of the rhesus monkey following lesions of the frontal eye fields and superior colliculus

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Abstract This study examined whether signals for the generation of eye movements from the dorsomedial frontal cortex (DMFC) reach brainstem oculomotor centers either through the frontal eye fields (FEF) or through the superior colliculi (SC). The DMFC was stimulated when the monkeys studied were intact and after either one FEF or one SC was ablated. Following lesions of either the FEF or SC, the topographic order of the DMFC was largely preserved. After either lesion, stimulation of anterior DMFC sites still evoked saccades that terminated in contralateral space, and stimulation of posterior DMFC sites still evoked saccades that terminated in central space. The probability of evoking saccades decreased and the latency to evoke saccades increased as fixation neared the termination zone (a restricted region within craniotopic space) both before and after either lesion. Ablation of the SC, but not of the FEF, eliminated the saccadic inhibition to visual targets which resulted when the DMFC was stimulated in the intact animal. The findings suggest that additional channels besides those coursing through the FEF and SC are utilized by the DMFC to access the saccade generator in the brainstem.

Key words Dorsomedial frontal cortex
Frontal eye fields · Superior colliculus · Saccades · Monkey

Introduction

Electrical stimulation of the superior colliculus (SC), the occipital cortex, and the frontal eye fields (FEF) elicits saccadic eye movements whose direction and amplitude depend on the particular region stimulated within each of these structures (Bruce et al. 1985; Keating and Gooley 1988; Robinson 1972; Robinson and Fuchs 1969; Schiller 1977; Schiller and Stryker 1972). The metrics of the evoked saccades are largely independent of initial eye position. Prolonged stimulation at any site produces a staircase of similar saccades as if the same command were executed repeatedly. These findings suggest that the visual cortex, the FEF, and the SC utilize a vector code for the generation of saccadic eye movements. Subsequent work has established that ablation of the SC eliminates stimulation-elicited saccades from the occipital cortex but not from the FEF (Keating et al. 1983; Schiller 1977), and that paired ablation of the FEF and the SC abolish visually guided eye movements (Schiller et al. 1980). These findings led to the hypothesis that two major parallel pathways are involved in the generation of visually guided saccadic eye movements and that these pathways reach the brainstem eye-movement control centers either through the SC or the FEF.

Recently, another area involved in eye-movement control has been identified. This area, located in the dorsomedial frontal cortex (DMFC), uses a different coding operation from that of the FEF and the SC. Electrical stimulation of the DMFC elicits saccadic eye movements that bring the center of gaze to a restricted location in visual space (Bon and Lucchetti 1992; Mann et al. 1988; Schlag and Schlag-Rey 1987; Tehovnik and Lee 1993) which we call the termination zone. The termination zone is expressed in craniotopic space and is synonymous with eye position in orbit. The DMFC is topographically ordered (Tehovnik and Lee 1993): anterior sites represent termination zones located in extreme contralateral craniotopic space, whereas posterior sites represent central or ipsilateral craniotopic space; lateral sites represent upper and medial sites represent lower portions of craniotopic space. It may be said, therefore, that a spatial code resides in the DMFC.

The question this paper addresses is how the signals through DMFC reach the brainstem areas involved in the generation of saccadic eye movements. If there are only two major pathways involved as noted above, the signals from the DMFC would be expected to pass through either the FEF or the SC; therefore, ablation of

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either one or the other of these areas should disrupt stimulation-evoked saccades from the DMFC. On the other hand, failure of the lesions to affect stimulation-elicited saccades from the DMFC would suggest the involvement of other pathways. Anatomical results have not provided clear alternatives, as they have shown connections between the DMFC and the FEF, the SC, and the caudate nucleus, as well as direct connections to the brainstem (Huerta and Kass 1990; Parthasarathy et al. 1992; Schall et al. 1993).

In this study we examined how ablation of either the FEF or the SC affects electrically elicited saccades from the DMFC. Stimulation-evoked saccades were not abolished by either lesion, suggesting that other pathways play a major role in getting signals from the DMFC to the brainstem. A brief report has appeared earlier (Schall et al. 1987; Tehovnik et al. 1991).

Materials and methods

Subjects

Four adult rhesus monkeys (*Macaca mulatta*), A, AB, M, and Y, were used. Throughout this study food was freely available. The monkeys were water deprived overnight before each day of experimental testing. After testing, they were allowed to drink to satiation before being returned to the vivarium. The monkeys were provided for in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the guidelines of the Massachusetts Institute of Technology Committee on Animal Care.

Surgery

Monkeys were anesthetized with pentobarbital (30 mg/kg) intravenously. A scleral search coil was implanted subconjunctivally (Judge et al. 1980), and a stainless-steel post to restrain the head was attached to the skull with head bolts and acrylic cement. For monkey A, a recording chamber was implanted over the left DMFC; for monkeys AB, M, and Y, a chamber was implanted over the midline and centered over the DMFC.

The FEF was located by visual inspection after craniotomy and was ablated by suction under aseptic conditions. The SC was located by single unit recording and ablated using radio-frequency lesions employing methods of Schiller et al. (1980).

The right FEF was lesioned in monkeys AB and Y, the left FEF was lesioned in monkey M, and the left SC was lesioned in monkey A. Many months after these lesions were conducted and after behavioral testing was completed, monkeys AB and M were given SC lesions: the left SC was lesioned in monkey AB, and the right SC was lesioned in monkey M.

Behavioral tasks

Fixation task

A monkey faced a color monitor (Mitsubishi Color Display Monitor) with the head fixed. The animal had to fixate a square spot of light that measured 0.5×0.5 deg of visual angle (Fig. 1A) for 600 ms, and the fixation spot could appear anywhere on the monitor. During fixation, a monkey had to keep his eyes within a 1×1 deg area as assured by electronic windows, otherwise the trial was terminated. Fixation was rewarded with a drop of apple juice. This task allowed us to control the fixation position of a monkey's eyes before electrical stimulation was delivered. Stimulation began

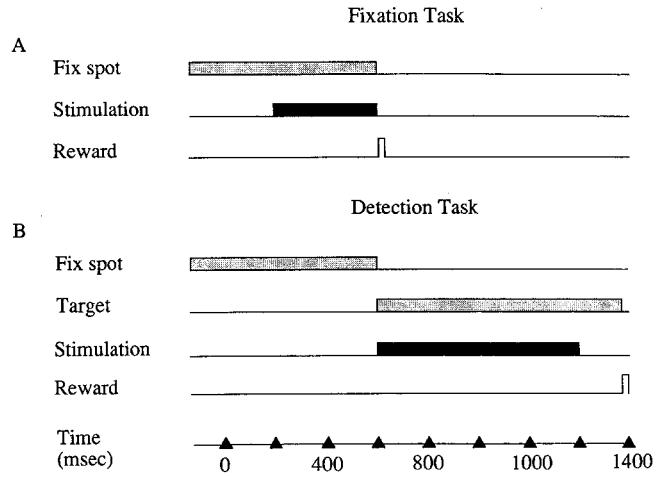

Fig. 1 **A** The fixation task for different stages of a trial. A trial began with the onset of the fixation spot. Electrical stimulation and reward were then delivered in succession. **B** The detection task for different stages of a trial. A trial began with the onset of the fixation spot. At the termination of the fixation spot, the target and electrical stimulation were presented. A reward was delivered after a saccade was made to the target

200 ms after the initiation of fixation. All testing was done in darkness.

Detection task

A monkey fixated the fixation spot for 600 ms after which a punctate target (measuring 0.5×0.5 deg of visual angle) appeared 3 deg to the left or right of the fixation spot (Fig. 1B). A correct saccade was recorded when the monkey's eyes entered a 2×2 deg area about the target location, and such a saccade was rewarded with a drop of apple juice. The order of presentation of the left and right targets was randomized. Stimulation was delivered to the DMFC on every second trial, 5 ms following the appearance of the target. After terminating the stimulation, a monkey had 800 ms to make a saccade to a target; on non-stimulation trials, a monkey had 800 ms to make a saccade to a target following target appearance. This paradigm was used to test monkeys on stimulation-evoked saccadic inhibition.

Data collection and analysis

A PDP 11/73 computer controlled the presentation of visual stimuli, the delivery of electrical stimulation, the display and collection of single units (sampled at 1000 Hz), the assessment of correct saccadic responses using target windows, the storage of task-related events, and the collection of eye movements (sampled at 200 Hz).

During off-line analysis, an algorithm was used to sort out saccades from non-saccades. To qualify as a saccade, the eye movement had to achieve a velocity of at least 200 deg/s (Robinson 1970). An eye movement had to occur during the train of stimulation to qualify as a stimulation-evoked saccade. To qualify as a visually evoked saccade, the eye movement had to occur during the period of target appearance.

Electrical stimulation

Glass-coated platinum-iridium electrodes with an impedance of 0.5–1.0 mΩ at 1 KHz were constructed. The impedance of these electrodes dropped during electrical stimulation. Constant-cur-

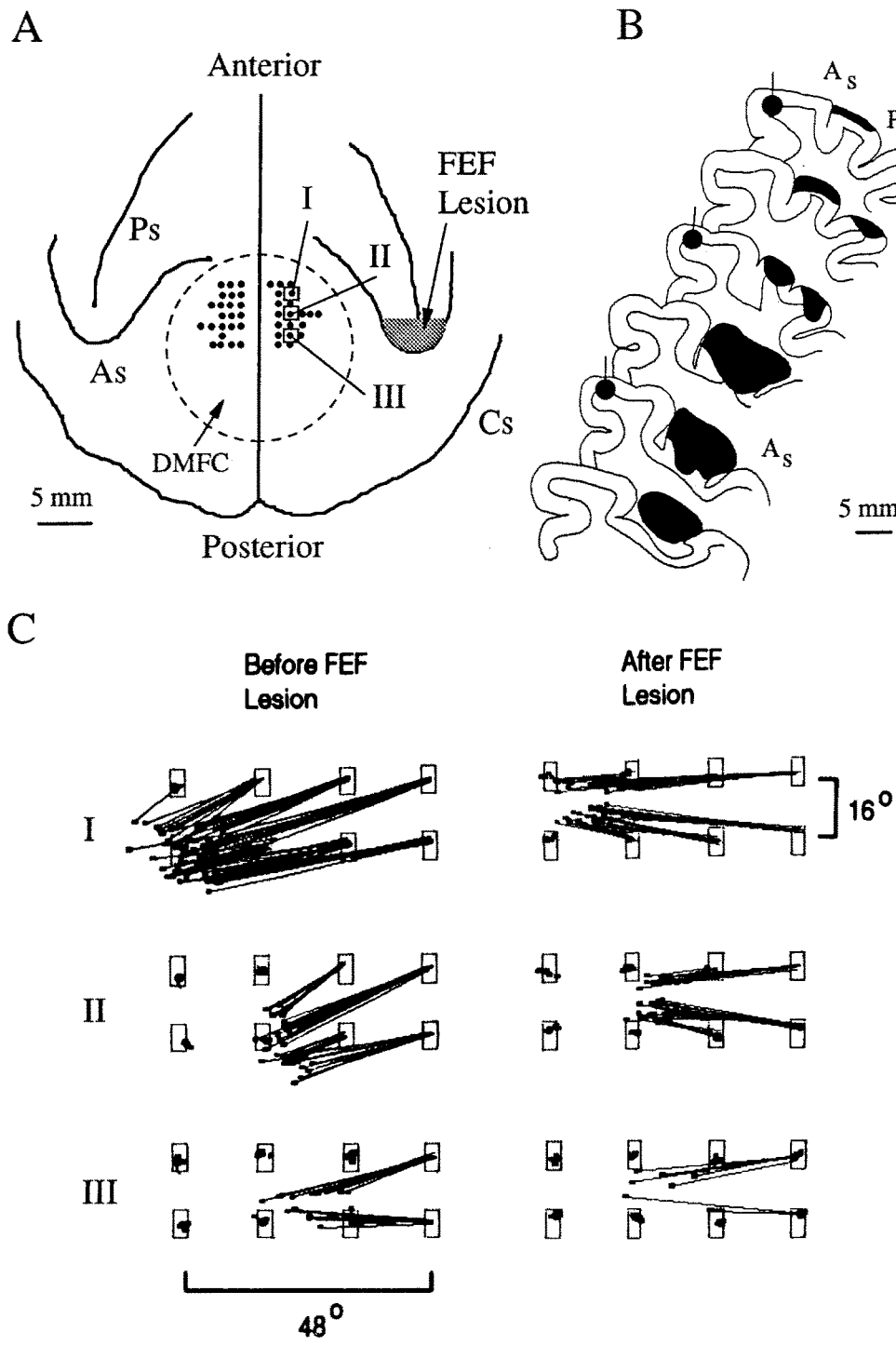

Fig. 2 **A** An overhead view of the DMFC and FEF of monkey Y. Each *symbol* represents the location of one or more electrode penetrations made into the DMFC. Sites from which saccades were evoked electrically are illustrated as *filled circles*. The saccades were evoked while the monkey performed either the fixation task or the detection task. Sites from which extensive testing was done are marked I, II, and III. The extent of the FEF lesion is shown. (*Ps* principal sulcus, *As* arcuate sulcus, *Cs* central sulcus). **B** Schematic representations of coronal sections obtained from the left DMFC and FEF of monkey Y. Each section is spaced by 1 mm. Electrode sites in the DMFC are represented by *dark circles*. A *dark circle* shows the maximal field of stimulation, estimated to be 1 mm from the electrode tip for a 400 μA current that is activating low-threshold elements with a current-distance constant (K) of 400 $\mu A/mm^2$ (Tehovnik and Lee 1993). The formula, radius = $(current/K)^{1/2}$, was used for the calculation. The extent of the FEF lesion is marked in *black*. (*As* arcuate sulcus, *Ps* principal sulcus). **C** Vector representations of saccadic eye movements evoked from sites I, II, and III of the right DMFC of monkey Y (see **A**) before and after the FEF lesion. For each panel, an *upright rectangle* depicts a fixation position. *Each line starting at a rectangle* represents the entire excursion of the eyes during the 400-ms train of stimulation. Each line represents one saccade only. The *dots confined to a rectangle* indicate that eye movements were not evoked from that position. The monkey always faced the region between the four central fixation positions, such that four fixation positions were located to the right of the monkey and four to the left

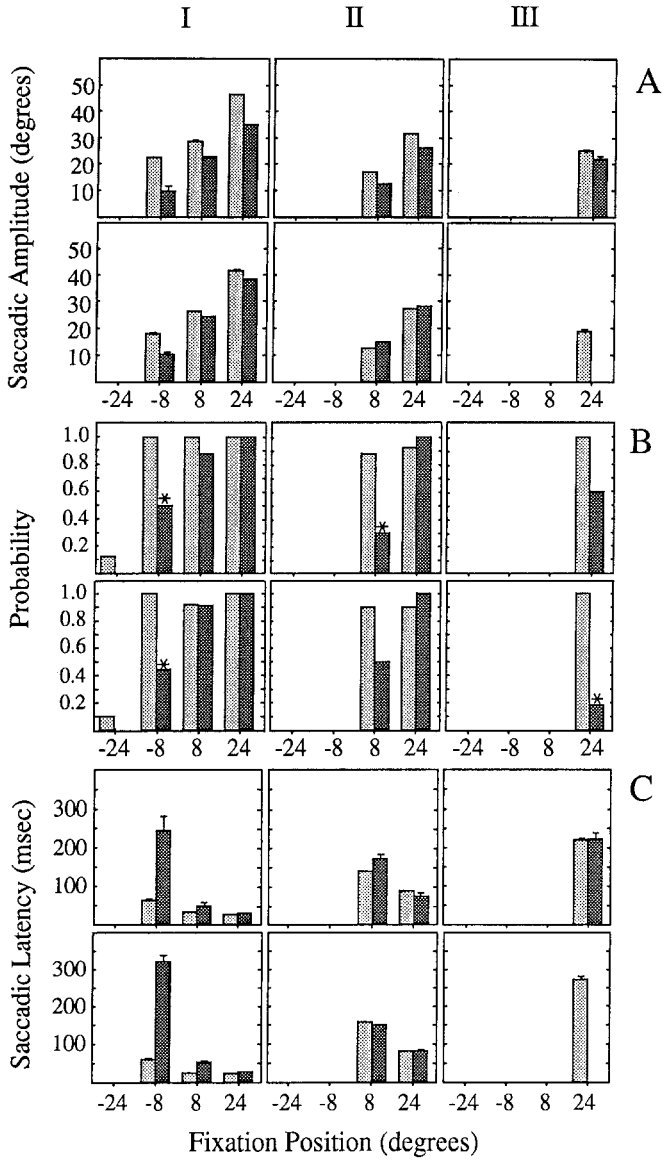

Fig. 3 **A** Saccadic amplitude plotted as a function of fixation position for sites I, II, and III of the DMFC of monkey Y. These data are based on saccades illustrated in Fig. 2C. The *light-gray bars* represent mean amplitudes of saccades evoked before the FEF lesion, and the *dark-gray bars* represent mean amplitudes of saccades evoked after the FEF lesion. The mean amplitudes are based on ten stimulation trials. Amplitude values were computed only when more than three saccades were evoked from a fixation position. The fixation positions that occurred in the ipsilateral hemifield are indicated by 24 deg and 8 deg, and those that occurred in the contralateral hemifield are indicated by −24 deg and −8 deg. The *top bar graphs* represent amplitudes of saccades evoked from top fixation positions, and the *bottom bar graphs* represent amplitudes of saccades evoked from bottom fixation positions. Standard error bars are shown for errors greater than 1 deg of visual angle. Overall, the mean saccadic amplitudes did not show a significant decrease following the FEF lesion as evidenced by a paired *t*-test ($t(10)=1.82$, $p>0.01$). **B** The probability of evoking a saccade plotted as a function of fixation position for sites I, II, and III of the DMFC of monkey Y. These data are based on saccades illustrated in Fig. 2C. Probability was determined by dividing the number of trials during which a saccade was evoked by the total number of stimulation trials, which was ten. The *light-gray bars* represent the probability of saccades evoked before the FEF lesion, and the *dark-gray bars* represent the probability of saccades evoked after the FEF lesion. The fixation positions that occurred in the ipsilateral hemifield are indicated by 24 deg and 8 deg, and those that occurred in the contralateral hemifield are indicated by −24 deg and −8 deg. The *top bar graphs* represent the probability of saccades evoked from top fixation positions, and the *bottom bar graphs* represent the probability of saccades evoked from bottom fixation positions. A *star* over a dark-gray bar indicates that the post-lesion probabilities are significantly different from the pre-lesion probabilities by $p<0.01$ using a standard score statistic, Z (Johnson 1976). Overall, the probabililty of evoking saccades did not decrease significantly following the FEF lesion as evidenced by a paired *t*-test ($t(13)=1.4$, $p>0.01$). **C** Saccadic latency plotted as a function of fixation position for sites I, II, and III in the DMFC of monkey Y. These data are based on saccades illustrated in Fig. 2C. Saccadic latency is the time between stimulation onset and saccade execution. The *light-gray bars* represent the mean latency of saccades evoked before the FEF lesion, and the *dark-gray bars* represent the mean latency of saccades evoked after the FEF lesion. The mean latencies are based on ten stimulation trials. When fewer than three saccades were evoked from a fixation position, a latency value was not computed. The fixation positions that occurred in the ipsilateral hemifield are indicated by 24 deg and 8 deg, and those that occurred in the contralateral hemifield are indicated by −24 and −8 deg. The *top bar graphs* represent the latency of saccades evoked from top fixation positions, and the *bottom bar graphs* represent the latency of saccades evoked from bottom fixation positions. Standard error bars are shown for cases greater than the data point. Overall, the mean saccadic latencies did not show a significant increase following the FEF lesion as evidenced by a paired *t*-test ($t(10)=1.68$, $p>0.01$)

rent biphasic pulses were delivered to the brain tissue using a Grass S88 stimulator attached to a pair of constant-current, stimulus isolation units (Grass PSIU6B). For each biphasic pulse, a cathodal and anodal pulse followed in immediate succession. Both pulses had the same amplitude and duration. Current was monitored by the voltage drop across a 1000 Ω resistor that was in series with the return lead of the stimulator. The current was monitored using a Tektronix Oscilloscope (model 5103N), and was read as the amplitude of one pulse (cathode or anode) of a biphasic pair. To study the DMFC, current, pulse duration, frequency, and train duration were set (unless specified) at 400 μA, 0.1 ms, 150 Hz, and 400 ms, respectively. These values were chosen following parametric tests conducted on the DMFC to optimize the stimulation-evoked responses (Tehovnik and Lee 1993).

Typically, electrodes were introduced perpendicular to the dura surface with a hydraulic microdrive. The action potentials were amplified (Bak A-1B) and filtered (Krohn-Hite 3750). A total of 241 penetrations were made into the DMFC of the four monkeys. For each penetration, stimulation tests were conducted every 0.5 mm over a depth of 6 mm.

Histology

Monkeys were overdosed with pentobarbital, perfused with 0.9% NaCl, and fixed with 4% paraformaldehyde. Guide pins were inserted into the cortex at specific positions around the recording chamber. The location of the electrode tracts were estimated relative to the pins. The brains were photographed and sectioned coronally at 50 μm and stained with cresyl violet.

Results

Effect of FEF lesion

Saccadic excitation

Following unilateral lesions of the FEF in monkeys AB, M, and Y, saccades were evoked during stimulation of the DMFC ipsilateral (or contralateral) to the side of the lesion.

Vector representations of saccadic eye movements evoked from three sites (I, II, and III) in the right DMFC of monkey Y (Fig. 2A) before and 1 month after a right FEF lesion (Fig. 2B) are shown (Fig. 2C). The same sites were stimulated in the DMFC before and after the FEF lesion by placing the electrode at the same head-stage coordinates and by stimulating at the same depth within the DMFC at which units were first encountered. Saccades evoked from the DMFC before and after the FEF lesion were quite similar: (1) the saccades were contraversive with respect to the side of stimulation; (2) the size of a saccades decreased as the fixation position changed from the ipsilateral to the contralateral hemifield; (3) the saccades converged onto a termination zone; and (4) as the electrode was moved from anterior to posterior sites in the DMFC (i.e., from sites I to III), the termination zone moved systematically from the extreme contralateral hemifield to the straight-ahead position. The amplitude of saccades decreased somewhat following the FEF lesion; however, this was not statistically significant (Fig. 3A).

Both before and after the FEF lesion, the probability of evoking a saccade decreased as the fixation position entered the termination zone (Fig. 3B: moving from fixation position 24 to −24). Moreover, the overall probability of evoking saccades was greater for anterior (I) than for posterior (III) sites. For fixations immediately outside of a termination zone (e.g., site I, fixation position −8; site II, fixation position 8; site III, fixation position 24), the probability of evoking saccades dropped after the FEF lesion, yet the overall probability of evoking saccades did not decrease.

Figure 3C shows the latency between stimulation onset and saccade onset, the saccadic latency, plotted as a function of fixation position before and after the FEF lesion. The latency to evoke a saccade increased as the fixation position neared the termination zone. Furthermore, as the electrode was moved from anterior to posterior sites in the DMFC, the overall latency increased. The latencies before and after the lesion remained similar, with the exception of site I (fixation position −8) where the latency increased dramatically.

Figure 4 shows that maximum saccadic velocity increased with the amplitude of the stimulation-evoked saccades, and that the FEF lesion did not effect this relationship.

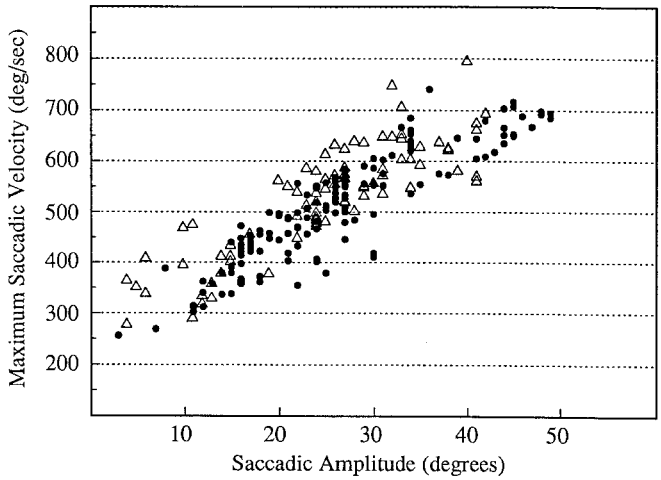

Fig. 4 Maximum saccadic velocity plotted as a function of saccadic amplitude of saccades evoked from the DMFC of monkey Y before (*black dots*) and after (*open triangles*) the FEF lesion. The pre-lesion data ($n = 145$) overlap with the post-lesion data ($n = 80$). These data are based on saccades illustrated in Fig. 2C

Saccadic inhibition

Once stimulation-evoked saccades reach a termination zone, further stimulation fixes the eyes in orbit and inhibits visually evoked saccades (Tehovnik and Lee 1993). After the termination zone was found by stimulating the DMFC contralateral to the FEF lesion (Fig. 5A), monkey Y was required to detect a target with the fixation spot positioned within the termination zone. The eyes remained on the fixation spot for the duration of electrical stimulation (Fig. 5B); only after termination of stimulation did the monkey make a saccade to the target. On trials without stimulation, monkey Y made visually evoked saccades with latencies well below 300 ms. After stimulation, monkey Y made saccades to a target with an accuracy rate of 100% (Fig. 5C).

After the termination zone was found by stimulating the DMFC ipsilateral to the FEF lesion (Fig. 5D), monkey Y was required to perform the detection task while electrical stimulation was delivered. The FEF lesion did not interrupt the inhibition of visually evoked saccades (Fig. 5E); nor did it affect the monkey's performance on the detection task (Fig. 5F).

Effect of SC lesion

Saccadic excitation

Following unilateral lesions of the SC in monkeys A, AB, and M, saccades were still evoked following stimulation of the DMFC ipsilateral (or contralateral) to the side of the lesion.

Vector representations of saccadic eye movements evoked from three sites (I, II, and III) in the left DMFC of monkey A (Fig. 6A) before and 1 month after a left SC lesion (Fig. 6B) are shown (Fig. 6C). The same sites

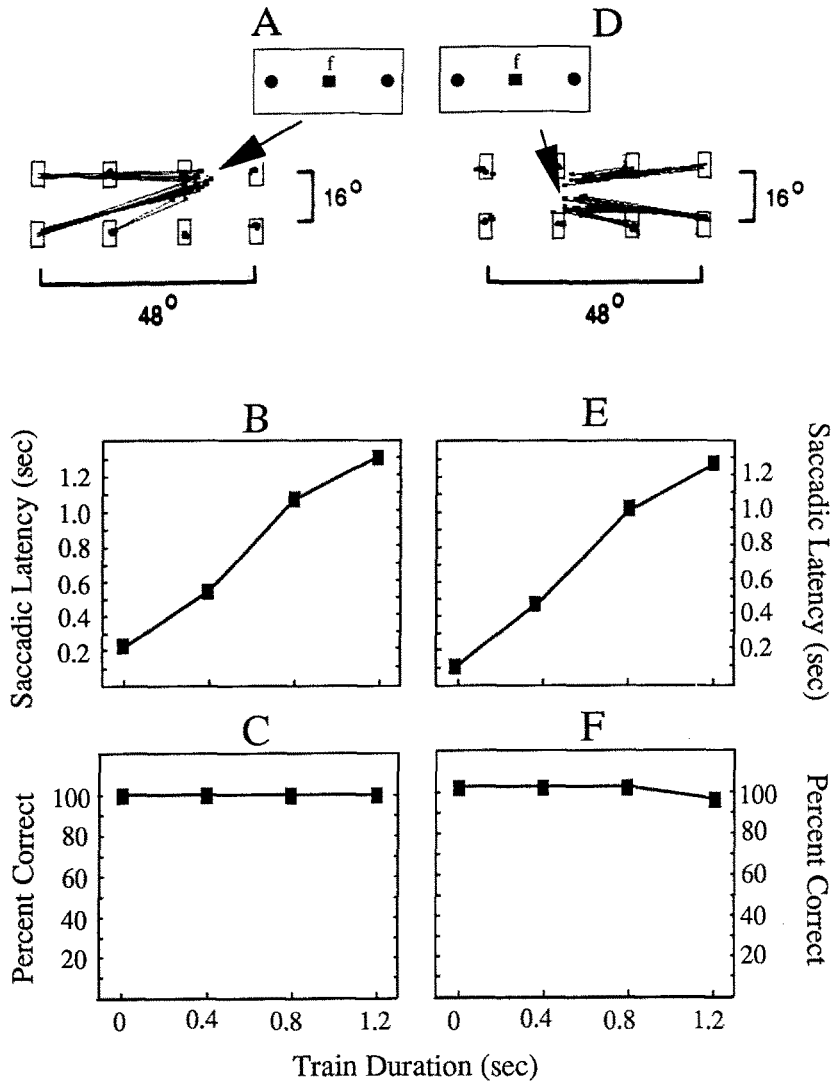

Fig. 5 **A** Saccadic eye movements evoked from different fixation positions following stimulation of the left DMFC of monkey Y on the non-lesioned side. Each *rectangle* represents a fixation position. The saccades, represented here by the vectors, brought the eyes to the termination zone. The *top portion* of the figure shows a magnified version of the detection task. The fixation spot (*f*) was centered within the termination zone, as shown by the *arrow*. The monkey was required to make a saccade to either the left or right target (*circle*) which was 3 deg from the fixation spot. Five milliseconds after the target was presented, electrical stimulation was delivered to the DMFC to test for saccadic inhibition. **B** Saccadic latencies shown for monkey Y while he performed the detection task. Saccadic latency is plotted as a function of train duration. Each *point* represents 20 trials. Standard errors are not shown, since they are less than the size of the data points. **C** Performance scores are shown for monkey Y while he performed the detection task. Percent correct is plotted as a function of train duration for the same stimulation trials represented in **B**. Following electrical stimulation, the monkey was given 800 ms to make a saccade to the target. **D** Saccadic eye movements evoked at different fixation positions following stimulation of the right DMFC of monkey Y after an FEF lesion of the right side. See **A** for details. **E** Saccadic latency plotted as a function of train duration. Each *point* represents 20 trials. See **B** for details. **F** Percent correct is plotted as a function of train duration for the same stimulation trials represented in **E**. See **C** for details

were stimulated in the DMFC before and after the SC lesion by placing the electrode at the same head-stage coordinates and by stimulating at the same depth within the DMFC at which units were first encountered. Saccades evoked from the DMFC before and after the SC lesion were similar: (1) the saccades evoked from sites I and II were contraversive, and those evoked from site III were contraversive or ipsiversive depending on the fixation position; (2) the saccades converged onto a termination zone; and (3) as the electrode was moved from anterior to posterior sites in the DMFC (i.e., from sites I to III), the termination zone moved from the contralateral hemifield toward the midline. Although the trajectory of the saccades did not change following the lesion, the amplitude of the saccades was decreased significantly for all stimulation sites at all fixation positions (Fig. 7A). In fact, saccades exhibited amplitude reductions averaging 45% (SD = 6.5%, $n = 16$) following the lesion.

In Fig. 7B, the probability of evoking a saccade dropped when the fixation position entered the termination zone before and after the SC lesion. The overall probability of evoking saccades was greater for anterior

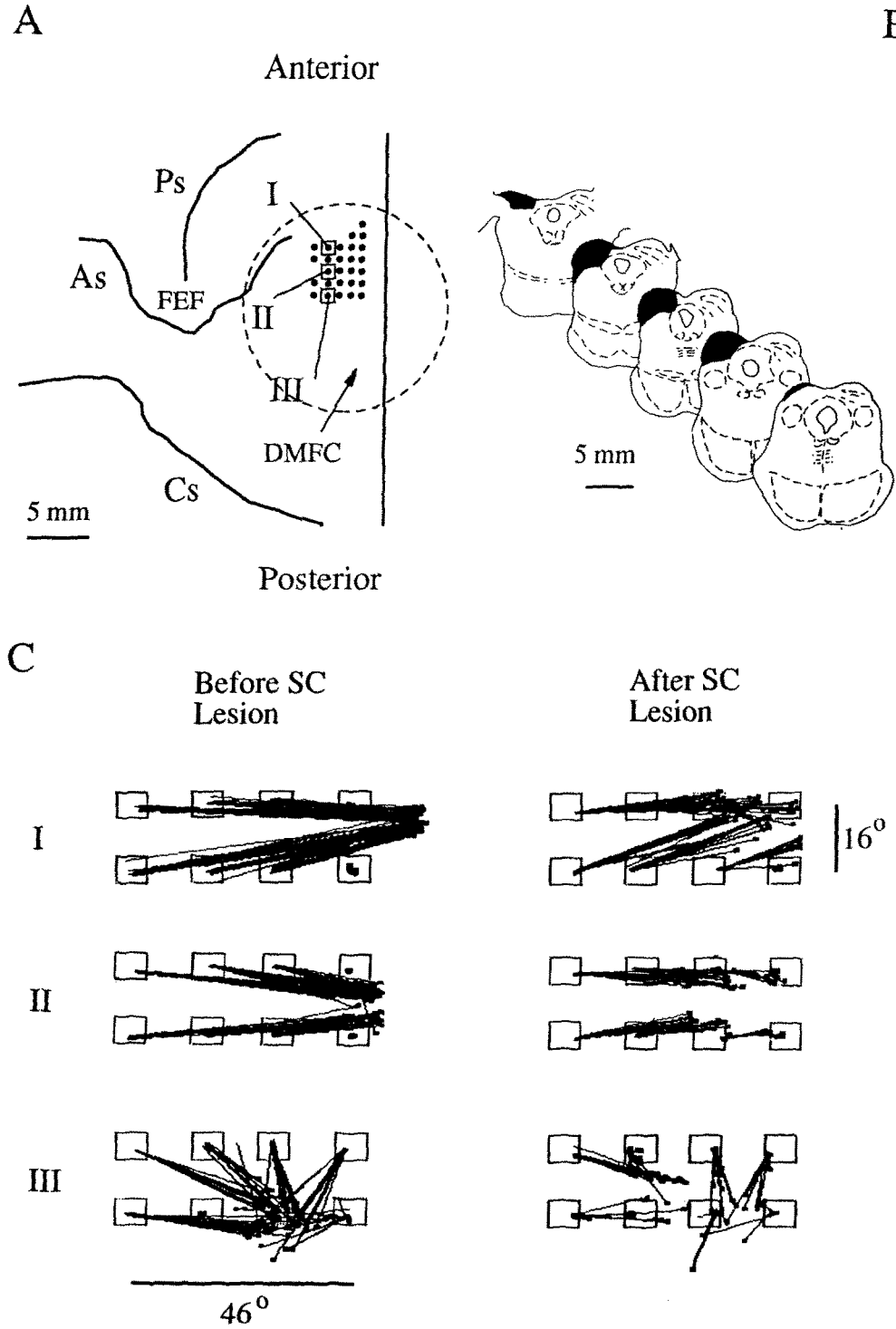

Fig. 6 **A** An overhead view of the DMFC of monkey A. Each *mark* represents the location of one or more electrode penetrations made into the DMFC. Sites from which saccades were evoked electrically are illustrated as *filled circles*. The saccades were evoked while the monkey performed either the fixation task or the detection task. Sites from which extensive testing was done are marked I, II, and III. (*FEF* frontal eye field, *Ps* principal sulcus, *As* arcuate sulcus, *Cs* central sulcus). **B** Schematic representations of coronal sections obtained from the SC of monkey A. Sections are 1 mm apart with the *top left section* representing the anterior midbrain and the *bottom right section* representing the posterior midbrain. The extent of the SC lesion is marked in *black*. The lesion included both the intermediate and deep layers of the SC, both of which receive the most robust projections from the DMFC (Huerta and Kaas 1990; Parthasarathy et al. 1992). **C** Vector representations of saccadic eye movements evoked from sites I, II, and III of the left DMFC of monkey A before and after the SC lesion. For each panel, a *square* depicts a fixation position. *Each line starting at a rectangle* represents the entire excursion of the eyes during the 400-ms train of stimulation. Each line represents one saccade only. The *dots confined to a square* indicate that eye movements were not evoked from that position. The monkey always faced the region between the four central fixation positions such that four fixation positions were located to the right of the monkey and four to the left

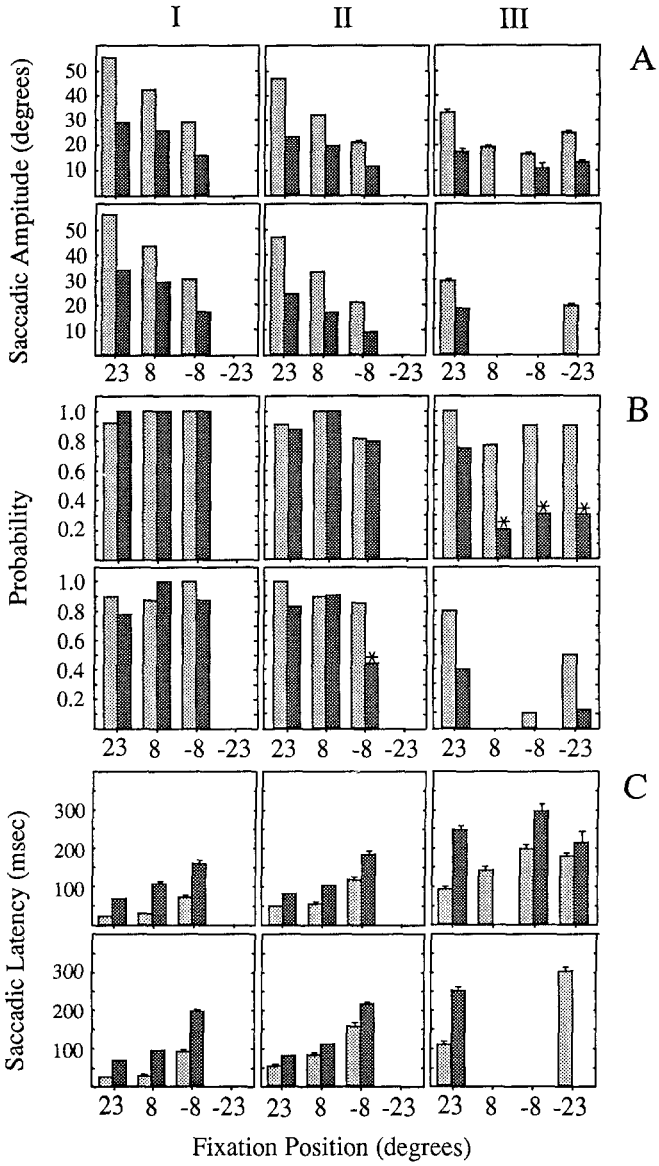

Fig. 7 **A** Saccadic amplitude plotted as a function of fixation position for sites I, II, and III of the DMFC of monkey A. These data are based on saccades illustrated in Fig. 6C. The *light-gray bars* represent mean amplitudes of saccades evoked before the SC lesion, and the dark-gray bars represent mean amplitudes of saccades evoked after the SC lesion. The mean amplitudes are based on ten stimulation trials. Overall, the mean saccadic amplitudes showed a significant decrease following the SC lesion as evidenced by a paired *t*- test ($t(15) = 10.8$, $p < 0.0005$). See Fig. 3A for details. **B** The probability of evoking a saccade plotted as a function of fixation position for sites I, II, and III of the DMFC of monkey A. These data are based on saccades illustrated in Fig. 6C. The *light-gray bars* represent the probability of saccades evoked before the SC lesion, and the *dark-gray bars* represent the probability of saccades evoked after the SC lesion. A *star* over a dark-gray bar indicates that the post-lesion probabilities are significantly different from the pre-lesion probabilities by $p < 0.01$ using a standard score statistic, Z (Johnson 1976). Overall, the probabililty of evoking saccades did not decrease following the SC lesion as evidenced by a paired *t*-test ($t(18) = 1.59$, $p > 0.01$). See Fig. 3B for details. **C** Saccadic latency plotted as a function of fixation position for sites I, II, and III in the DMFC of monkey A. These data are based on saccades illustrated in Fig. 6C. The *light-gray bars* represent the mean latency of saccades evoked before the SC lesion, and *dark-gray bars* represent the mean latency of saccades evoked after the SC lesion. The mean latencies are based on ten stimulation trials. Overall, the mean saccadic latencies showed a significant increase following the FEF lesion as evidenced by a paired *t*-test ($t(15) = 7.27$, $p < 0.0005$). See Fig. 3C for details

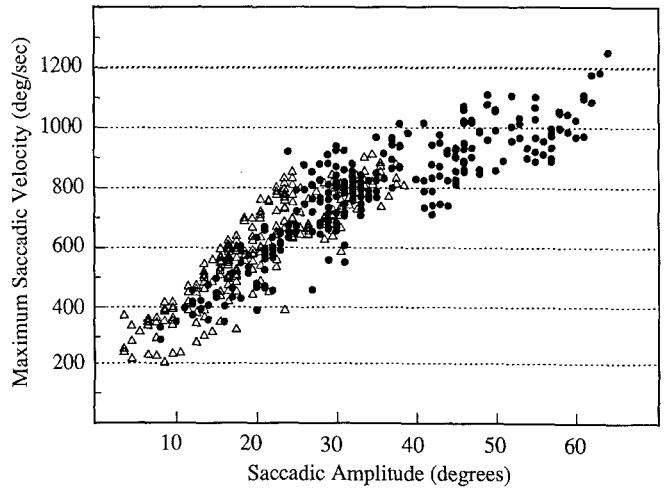

Fig. 8 Maximum saccadic velocity plotted as a function of saccadic amplitude of saccades evoked from the DMFC of monkey A before (*black dots*) and after (*open triangles*) the SC lesion. The pre-lesion data ($n = 284$) overlap with the post-lesion data ($n = 246$). These data are based on saccades illustrated in **Fig. 6C**

(I) than for posterior (III) sites. The probability of evoking saccades decreased after the SC lesion for site III, but remained relatively unchanged for sites I and II. The overall probability of evoking a saccade did not decrease following the lesion.

Saccadic latency is plotted as a function of fixation position both before and after the SC lesion in Fig. 7C. The latency to evoke a saccade increased as the fixation position neared the termination zone. Following the SC lesion, the latency was found to increase for all sites at every fixation position.

Figure 8 illustrates that maximum velocity of saccades increased with saccadic amplitude both before and after the SC lesion. The lesion had no effect on this relationship except that saccades larger than 40 deg were no longer evoked.

Saccadic inhibition

Monkey A was required to detect a target with the fixation spot positioned within the termination zone before (Fig. 9A, top panel) and after (Fig. 9A, bottom panel) the SC lesion. The same site within the DMFC (ipsilateral to the side of the SC lesion) was stimulated before and after the lesion. Before the SC lesion, the eyes remained on the fixation spot for the duration of electrical stimulation (Fig. 9B, top left panel), and only after termination of stimulation did the monkey generate a saccade to the target. After stimulation, the monkey performed the detection task at an accuracy rate of over

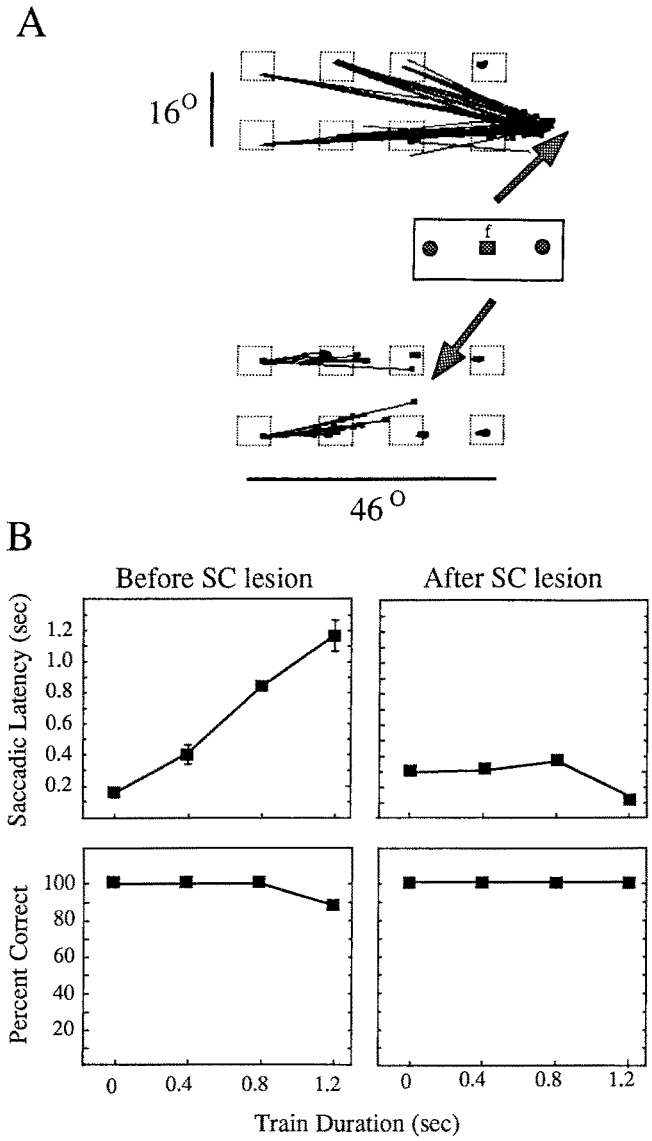

Fig. 9 **A** Saccadic eye movements evoked from different fixation positions following stimulation of the left DMFC of monkey A before (*top panel*) and after (*bottom panel*) the SC lesion which was located ipsilateral to the side of stimulation. Each *square* represents a fixation position. The saccades, represented here by the vectors, brought the eyes to the termination zone. The *right portion* of the figure shows a magnified version of the detection task. The fixation spot (*f*) was centered within a termination zone, as shown by the *arrows*. The monkey was required to make a saccade to either the left or right target (*circle*) which was 3 deg from the fixation spot. Five milliseconds after the target was presented, electrical stimulation was delivered to the DMFC to test for saccadic inhibition. **B** Saccadic latencies and performance scores are shown for monkey Y before and after the SC lesion, collected while the animal performed the detection task (**A**). Saccadic latency is plotted as a function of train duration in the top panels before and after the SC lesion. Each *point* represents ten trials. Standard errors are shown. Percent correct is plotted as a function of train duration before and after the SC lesion in the *bottom panels*. Following electrical stimulation, the monkey was given 800 ms to make a saccade to the target

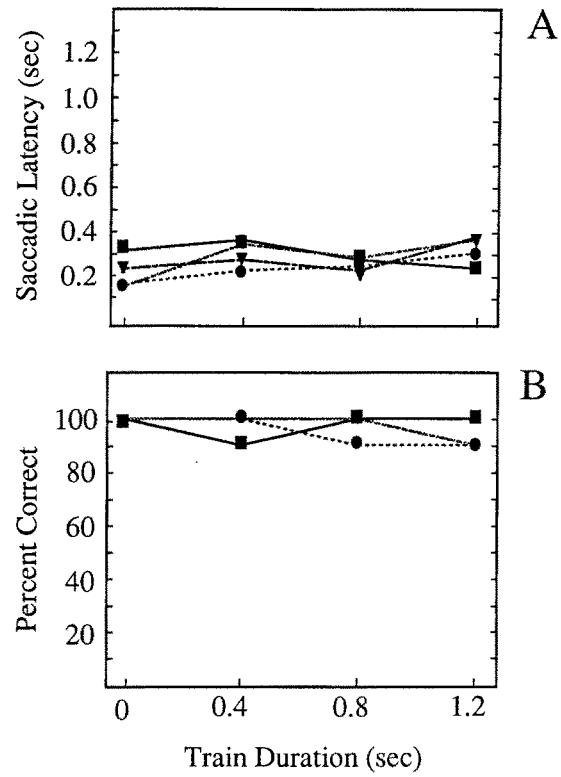

Fig. 10 **A** Saccadic latency plotted as a function of train duration. Each curve represents one of four stimulation sites, and each point represents ten trials. Standard errors were always less than 35 ms and are not shown for clarity. **B** Percent correct plotted as a function of train duration for the same stimulation sites and trials represented in **A**

80% (Fig. 9B, bottom left panel). A lesion of the SC ipsilateral to a DMFC stimulation site abolished the stimulation evoked inhibition of visually evoked saccades (Fig. 9B, top right panel) and decreased the amplitude of saccades directed contralateral to the side of the lesion, but did not affect the monkey's performance on the detection task (Fig. 9B, bottom right panel). These results were replicated for four other stimulation sites ipsilateral to the SC lesion (Fig. 10).

Discussion

Stimulation-evoked saccades

The results of this study show that following lesions of either the FEF or the SC, the topographic organization of the DMFC is largely preserved. Lesions of the FEF had negligible effects on the probability of evoking saccades from the DMFC and on the amplitude and latency of stimulation-elicited saccadic eye movements. Also, lesions of the SC did not effect the probability of evoking saccades from the DMFC.

A positive correlation has been reported between the firing rate of SC units and saccadic velocity (Rohrer et al. 1987). The velocity of visually evoked saccades was

shown to decrease following SC lesions (Lee et al. 1988; Schiller et al. 1980). In the current study, lesions of the SC and the FEF did not affect the maximum velocity of saccades generated following DMFC stimulation.

Nevertheless, following SC lesions the overall latency and overall amplitude of stimulation-evoked saccades was slightly altered: the amplitude became shorter and the latencies longer at all stimulation sites tested in the DMFC. Latency increases to visually guided eye movements, as previously shown (Albano and Wurtz 1982; Schiller et al. 1987), were also observed in the animals in this study following SC lesions, which typically led to an increase of about 20–25 ms for visual stimuli that produce saccadic latencies of around 180 ms in the intact animal. The amplitude of the visually guided saccades was also decreased, as shown in the current and previous studies (Albano and Wurtz 1982; Schiller et al. 1980). Saccades evoked from the DMFC exhibited amplitude reductions averaging 45% following SC lesions. Similarly, the amplitude of saccades made to visual targets falling within a 60 × 60 deg field have been found to decrease by 44% following SC lesions (Schiller et al. 1980, Fig. 4).

These findings suggest that pathways other than those involving the FEF and SC convey the signals from the DMFC to the brainstem. One pathway that subserves this function may course through the central mesencephalic reticular formation which innervates brainstem regions harboring the saccade generator (Cohen et al. 1981; Edwards 1975; Raybourn and Keller, 1977). The DMFC innervates the mesencephalic reticular formation directly (Huerta and Kass 1990) as well as indirectly via a striatonigral path (Hikosaka et al. 1989; Parthasarathy et al. 1992). In further support of this idea is the finding of Cohen et al. (1985) who have shown that stimulation of the central mesencephalic reticular formation evokes saccades that converge onto a termination zone as does stimulation of DMFC. Cohen et al. also found that simultaneous bilateral stimulation caused the eyes to remain fixated. Single-cell recordings in this area disclosed cells that are active both before visually evoked saccades and during the fixation of visual targets (Cohen et al. 1986; Waitzman and Cohen 1979), again much like the cells in the DMFC (Bon and Lucchetti 1992; Lee and Tehovnik 1991; Schlag et al. 1992).

The contribution of the central mesencephalic reticular formation may be partial, however, since current evidence suggests that it mediates horizontal saccades only (Cohen et al. 1986; Waitzman and Cohen 1979). A second candidate which might provide a relay between the DMFC and the saccadic generator in the brainstem that can mediate both horizontal and vertical saccades is the nucleus reticularis tegmenti pontis. This nucleus is innervated directly by the DMFC (Huerta and Kaas 1990) and is comprised of neurons that discharge before visually evoked saccades (Crandall and Keller 1985). Most importantly, a subgroup of these neurons is sensitive to changes in starting eye position. Direct projections between nucleus reticularis tegmenti pontis and the saccade generators in the brainstem have never been reported (Buttner-Ennever and Henn 1976). Nevertheless, this nucleus sends a robust projection to the cerebellum (Lafleur et al. 1974), which innervates the saccade generator in the brainstem (Batton et al. 1978; Precht 1977) and which contains neurons, situated in the posterior vermis and the flocculus, that are modulated by eye position (Kase et al. 1980; Noda and Suzuki 1979). An ablation of the posterior vermis produces eye-position-dependent dysmetria (Ritchei 1976) and ablation of the flocculus produces a deficit in holding eccentric positions of gaze (Zee et al. 1981). Stimulation of the posterior vermis elicits saccades that are dependent on starting eye position (McElligott and Keller 1984; Ron and Robinson 1973) and that are similar to those observed following DMFC stimulation (Tehovnik and Lee 1993).

It might be argued, however, that the DMFC still utilizes either the FEF or SC for the generation of saccadic eye movements, since in the current experiments either the FEF or SC of the same side always remained intact. Unfortunately, in order to test whether the craniotopic representation of the DMFC is preserved following brain lesions it is necessary for monkeys to be able to generate saccades to visual targets presented in various parts of craniotopic space, something that is not possible following combined FEF and SC lesions (Schiller et al. 1980).

Stimulation-evoked inhibition

The stimulation-evoked inhibition found in intact animals that results when the DMFC is stimulated and when the eyes are positioned within the termination zone was abolished after SC lesions. Under normal conditions such stimulation prevents the initiation of visually elicited eye movements as long as current is passed (Tehovnik and Lee 1993). Following SC lesions, animals were able to make saccadic eye movements to visual targets even while the DMFC was continually stimulated.

One possible explanation of this effect is the following: Neurons in the rostral pole of the SC discharge tonically when a monkey actively fixates a visual target and they remain silent during the execution of saccadic eye movements (Munoz and Wurtz 1992). Moreover, when the rostral SC is deactivated with muscimol, a monkey is less able to suppress the execution of saccades. Stimulation of the DMFC may activate the SC fixation cells directly via corticotectal fibers (Huerta and Kaas 1990) once the eyes are positioned in a termination zone. If the stimulation-evoked inhibition is mediated by these fixation cells, lesions confined to the anterior SC should be sufficient to interrupt the inhibition evoked from the DMFC.

Parallel pathways for visually guided saccades

Schiller et al. (1980) proposed that two parallel pathways mediate visually evoked saccades in primates, one of which involves the FEF and the other of which involves the SC. It was necessary to ablate both the FEF and SC to severely debilitate visually evoked saccades. Albano and Wurtz (1982) observed a similar deficit when large ablations were made of the SC which most likely transected the cortico-mesencephalic pathway emanating from the FEF (Leichnetz 1981). Albano and Wurtz (1982) concluded that their large lesions interrupted not only signals related to retinal error mediated by the FEF and SC, but also signals related to target or eye position, since their animals always undershot the position of a target and never made corrective saccades to the target.

We propose that their large lesions also interrupted cortico-mesencephalic fibres originating from the DMFC (Huerta and Kaas 1990), which we have argued conveys eye-position information to the saccade generator in the brainstem (Lee and Tehovnik 1991). That the DMFC mediates eye position is supported by the following observations: First, neurons within the DMFC are modulated by changes in eye position (Bon and Lucchetti 1992; Schlag et al. 1992), which are topographically organized (Lee and Tehovnik 1991; Tehovnik and Lee 1993). Continued electrical stimulation of the DMFC fixes the eyes within a termination zone for the duration of stimulation without aborting subsequent saccadic responses.

Second, monkeys are able to generate saccades to remembered positions of craniotopic space after their eyes have been displaced involuntarily by electrical stimulation of either the FEF or SC (Mays and Sparks 1980; Schiller and Sandell 1983). Furthermore, monkeys with SC lesions execute such saccades accurately after displacement via FEF stimulation, and monkeys with FEF lesions execute such saccades accurately after displacement via SC stimulation. Thus, monkeys have access to an eye-position signal that is not dependent on the integrity of the FEF or SC. Preliminary evidence suggests that stimulation of the DMFC immediately before the execution of memory-guided saccades disrupts saccadic performance (K. M. Lee and E. J. Tehovnik, unpublished observation).

Third, following combined FEF and SC lesions, animals reach accurately to visual targets presented within 60×60 deg of craniotopic space, even though they can only evoke eye movements within a limited central region of craniotopic space (Schiller et al. 1980). This indicates that the eye-position information to compute an arm movement to a visual target is still available following the combined lesions. Hence, we predict that visually guided arm movements should be impaired following large SC lesions that transect cortico-mesencephalic projections from the FEF and DMFC or following combined lesions of the FEF, SC, and DMFC.

Conclusion

Stimulation-evoked saccades elicited from the DMFC are not abolished following lesions of the FEF or SC. However, stimulation-evoked inhibition, which occurs once the eyes are positioned within a termination zone, is eliminated following SC lesions.

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