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RESEARCH ARTICLE

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Reversible inactivation of macaque dorsomedial frontal cortex: effects on saccades and fixations

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Abstract Neural recording and electrical stimulation results suggest that the dorsomedial frontal cortex (DMFC) of macaque is involved in oculomotor behavior. We reversibly inactivated the DMFC using lidocaine and examined how saccadic eye movements and fixations were affected. The inactivation methods and monkeys were the same as those used in a previous study of the frontal eye field (FEF), another frontal oculomotor region. In the first stage of the present study, monkeys performed tasks that required the generation of single saccades and fixations. During 15 DMFC inactivations, we found only mild, infrequent deficits. This contrasts with our prior finding that FEF inactivation causes severe, reliable deficits in performance of these tasks. In the second stage of the study, we investigated whether DMFC inactivation affected behavior when a monkey was required to make more than one saccade and fixation. We used a double-step task: two targets were flashed in rapid succession and the monkey had to make two saccades to foveate the target locations. In each of five experiments, DMFC inactivation caused a moderate, significant deficit. Both ipsi- and contraversive saccades were disrupted. In two experiments, the first saccades were made to the wrong place and had increased latencies. In one experiment, first saccades were unaffected, but second saccades were made to the wrong place and had increased latencies. In the remaining two experiments, specific reasons for the deficit were not detected. Saline infusions into DMFC had no effect. Inactivation of FEF caused a larger double-step deficit than did inactivation of DMFC. The FEF inactivation impaired contraversive first or second saccades of the sequence. In conclusion, our results suggest that the DMFC makes an important contribution to generating sequential saccades and fixations but not single saccades and fixations. Compared with the FEF, the DMFC has a weaker, less directional, more task-dependent oculomotor influence.

Key words Saccadic eye movements · Fixations · Dorsomedial frontal cortex · Supplementary eye field · Frontal eye field · Reversible inactivation

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Introduction

The oculomotor properties of cortex near the frontal midline of macaque were first examined in detail by Schlag and Schlag-Rey (1987). They named this region the supplementary eye field. We and others (Mann et al. 1988; Bon and Lucchetti 1992; Heinen 1995) use the anatomical designation, dorsomedial frontal cortex (DMFC) (issues of nomenclature are reviewed by Tehovnik 1995 and Schall 1997). Regardless of terminology, the areas near the frontal midline that have been studied by oculomotor physiologists overlap with one another (Fig. 1A; for a more detailed comparison see Tehovnik 1995). The experiments of this report were specifically carried out on the DMFC as mapped using electrical stimulation (Tehovnik and Lee 1993; see Fig. 1A); this defines an area that includes large portions of the regions examined by other investigators.

In this report, we focus on the contribution of the macaque DMFC to the generation of saccades and fixations. Results of single unit recording and electrical stimulation studies, as reviewed below, suggest that the DMFC plays a role in these behaviors. However, the extent to which the DMFC contributes to saccadic and fixational behavior is unclear, because no studies have examined the oculomotor effects of temporarily silencing this region. The present report is the first to document these effects.

Many DMFC neurons increase their discharge before or during saccadic eye movements (Brinkman and Porter

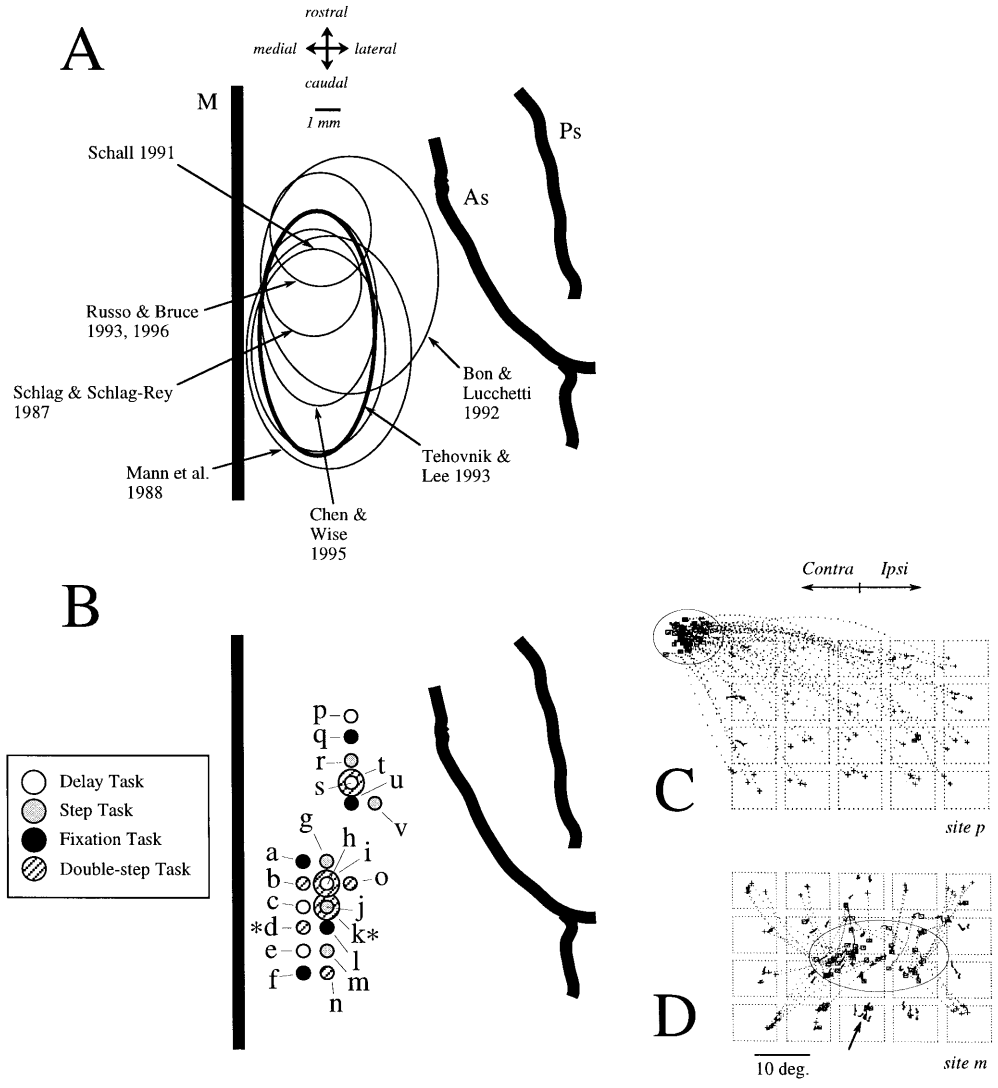


Fig. 1A–D The dorsomedial frontal cortex (DMFC). **A** A summary of DMFC regions (*ovals*) studied in seven physiological studies of saccades and fixations. Regions were approximated from investigators' figures using the midline (*M*) and the genu and superior branch of the arcuate sulcus (*As*) as references. *Ps*, Principle sulcus. Regions in both hemispheres were collapsed into a right-hemisphere representation. **B** Infusion sites (*small circles*) for the current study are shown. Sites from both monkeys (I, sites *a–o*; L, sites *p–v*) are superimposed onto histology from monkey L. For monkey I, site locations were estimated with reference to sulcal locations observed through the dura during surgery. *Legend at left* lists the symbols used to designate the tasks run during infusion at each site. For sites at which two infusions were made, the inner circle represents the earlier one. All infusions were of lidocaine, except for the two marked with an *asterisk*, which were of saline. Saccades electrically evoked from the (**C**) rostral and (**D**) caudal DMFC are shown. A monkey initially foveated an LED in one of 20 locations (*dotted boxes*) before stimulation was delivered. *Crosses*, Initial eye positions; *small squares* final eye positions; *dotted curves* samples of eye position during saccades; *ovals* approximate termination zones in which saccades converged. *Arrow* in **D** shows examples of electrically evoked fixations

1979; Schlag and Schlag-Rey 1987; Mann et al. 1988; Schall 1991a; Bon and Lucchetti 1992; Lee and Tehovnik 1995; Russo and Bruce 1996). In general, these neurons are poorly tuned for saccade direction (Schall 1991a). Of those that are tuned, a small majority prefer contraversive saccades (Schall 1991a). Other DMFC neurons fire throughout fixation, and many of these begin discharging before or during the saccade that leads to the fixation (Schlag et al. 1992; Lee and Tehovnik 1995). These fixation neurons are topographically distributed (Lee and Tehovnik 1995): neurons in rostral DMFC fire most vigorously for contralateral fixation, neurons in caudal DMFC fire most vigorously for ipsilateral fixation, neurons in medial DMFC fire most vigorously for downward fixation, and neurons in lateral DMFC fire most vigorously for upward fixation.

Electrical stimulation of DMFC can evoke saccades (Schlag and Schlag-Rey 1987; Mann et al. 1988; Schall 1991b; Bon and Lucchetti 1992; Russo and Bruce 1993; Tehovnik and Lee 1993). It can also fix the eyes, delaying visually-guided saccades (Tehovnik and Lee 1993; Tehovnik et al. 1994). The general effect of stimulating

the DMFC when the eyes initially are at rest and optimal stimulation parameters are used (Tehovnik and Lee 1993; Tehovnik and Sommer 1997b), is an evoked single saccade to a region of space (termination zone) and fixation of gaze at that location until stimulation ceases. The evoked saccades can be contra- or ipsiversive (Mann et al. 1988; Schall 1991b; Bon and Lucchetti 1992; Tehovnik and Lee 1993; Tehovnik et al. 1994; Lee and Tehovnik 1995; Tehovnik and Sommer 1996). Multiple saccades are only rarely evoked by prolonged stimulation (Schlag and Schlag-Rey 1987; Schall 1991b; Tehovnik and Lee 1993). The location of a termination zone matches the tuning of fixation cells at the site (Bon and Lucchetti 1992). Consequently, a stimulation map of termination zones exists in DMFC that corresponds to the topography of fixation cell tuning (Tehovnik and Lee 1993; Lee and Tehovnik 1995). These results suggest that DMFC uses a place code for saccades, signaling the desired final position of the eyes (Schlag and Schlag-Rey 1987; Mann et al. 1988; Schall 1991b; Schall et al. 1993; Lee and Tehovnik 1995).

We briefly note two other points regarding DMFC research. The hypothesis that DMFC uses place coding has been challenged by Russo and Bruce (1993, 1996); however, some of their results have been questioned on methodological grounds (Tehovnik and Sommer 1997b). Also, the DMFC may be involved in generating arm movements (reviewed by Tehovnik 1995) and smooth pursuit eye movements (Heinen 1995; Tian and Lynch 1995). We did not investigate either of these behaviors in the present study.

Another oculomotor region of frontal cortex, the frontal eye field (FEF), lies in the arcuate sulcus, lateral to the DMFC. The DMFC and the FEF are known to be different in many ways. Stimulation of FEF when the eyes initially are at rest evokes saccades that are almost exclusively contraversive. As initial eye position is varied, the evoked saccades usually retain similar amplitudes and directions and rarely converge on a termination zone (Mitz and Godschalk 1989; Goldberg and Bruce 1990; Schall 1991b; Russo and Bruce 1993; Tehovnik and Lee 1993). Prolonged stimulation of FEF nearly always evokes multiple saccades of similar vector (staircase saccades) (Robinson and Fuchs 1969; Schiller 1977; Schall 1991b; Tehovnik and Lee 1993). The direction tuning of FEF presaccadic neurons is mainly contraversive (Schall 1991b). These results suggest that the FEF uses a vector code for saccades, signaling the desired contraversive displacements of the eyes (Goldberg and Bruce 1990).

We had two general goals in the present study. The first was to determine whether DMFC neural activity is needed for the generation of saccades and fixations. We therefore reversibly inactivated the DMFC and examined whether saccades and fixations were affected. Our second goal was to directly compare the functions of the DMFC with those of the FEF. We therefore inactivated the DMFC using the same methods and the same monkeys as in our previous study of FEF inactivation (Sommer and Tehovnik 1997).

In the first part of this report, we document how DMFC inactivation affects single saccades and fixations. We used the same behavioral tasks as in our FEF study (Sommer and Tehovnik 1997), which showed that FEF inactivation causes severe impairments in some of these tasks, e.g., it disrupts single contraversive saccades made to briefly flashed targets. In the present study, however, we found that DMFC inactivation had little effect on behavior in these tasks. We then studied the effects of DMFC inactivation on more complicated behavior, using the double-step task (Mays and Sparks 1980; Sparks and Porter 1983; Goldberg and Bruce 1990; Goldberg et al. 1990; Barash et al. 1991). This task requires the coordinated generation of two saccades and fixations. We present the results of the double-step experiments in the second part of this report. We conclude by discussing our results and what they suggest about the oculomotor function of the DMFC and how it compares to the function of the FEF.

Materials and methods

Animals

We used the two monkeys (*Macaca mulatta*) that had been used in our FEF inactivation study (Sommer and Tehovnik 1997). For monkey I, we alternated between inactivating the DMFC and the FEF. For monkey L, we performed the DMFC inactivation experiments after the FEF experiments. Surgical details were described previously (Sommer and Tehovnik 1997). A monkey was implanted with a scleral search coil for recording eye position (Robinson 1963; Judge et al. 1980), a stainless steel post for restraining the head, and chambers for accessing the brain. For monkey L, the DMFC chamber was centered on the midline at anterior–posterior +27.5; for monkey I, it was centered 3 mm to the right of the midline at anterior–posterior +25. Monkeys received antibiotics and pain-killers (Buprenorphine) post-operatively. They were deprived of water overnight before testing and received an apple-juice reward during the experiments. The monkeys were provided for in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals and the guidelines of the Massachusetts Institute of Technology Committee on Animal Care.

DMFC mapping

We mapped the right DMFC of each monkey using electrical stimulation according to the method of Tehovnik and Lee (1993). A platinum–iridium (Pt–Ir), glass-insulated microelectrode (0.15 MΩ at 1 kHz) was introduced through the dura. Penetrations were made 1 mm apart in a grid pattern. We stimulated at the first recorded unit and then every 0.1 mm during the penetration. By periodically switching to recording mode, we verified that our electrode tip was in gray matter and we ceased stimulating when white matter was reached. We used optimal parameters for DMFC stimulation (Tehovnik and Lee 1993; Tehovnik and Sommer 1997b): biphasic pulses with a 400-μA current, 0.10-ms pulse duration, 150-Hz frequency, and 800-ms train duration. Note that the short pulse duration compensates for the use of relatively high current, such that the charge delivered per pulse is comparable with that used in other studies (Tehovnik 1996). Furthermore, the charge density at the electrode tip is similar to that generated by other investigators (Russo and Bruce 1993, see Tehovnik and Sommer 1997b).

The monkey foveated a light-emitting diode (LED) at one of 20 locations that spanned 40×30° and then the LED was extinguished, leaving the animal in darkness. In half of the trials, selected at random, electrical stimulation was then immediately delivered.

Neural recording complemented our stimulation mapping. The right DMFC of monkey L was investigated extensively using single-unit recording, as published in a previous report (Lee and Tehovnik 1995). Throughout the present study, when recording during infusion, we commonly encountered multiunit activity in both monkeys which was related to saccades, fixations, vision, or combinations of these.

General protocol

As an overview, each experiment involved the following general sequence of events. A microelectrode and needle were lowered together into the right DMFC until an acceptable multiunit site was found. The monkey was run on a task, providing "before" DMFC inactivation data. Lidocaine or saline was then infused through the needle, and "during" DMFC inactivation data were collected. Near the end of the session, "after" data were collected.

Infusion methods

We infused lidocaine (lidocaine hydrochloride, 2% solution; Steris Laboratories, Inc., Phoenix, Ariz.) or saline at a site, while monitoring the nearby neural activity. We previously have described the infusion methods (Sommer and Tehovnik 1997) and quantified the time course and spread of cortical inactivation subsequent to lidocaine infusion (Tehovnik and Sommer 1997a). In summary, a 30-gauge needle was attached to a stainless-steel cannula that was connected to a 100-µl Hamilton syringe using PE 50 tubing. A hydraulic microdrive held the needle assembly, loaded with lidocaine or saline, in parallel with a recording microelectrode (Pt–Ir, glass-coated, ~1.0 MΩ at 1 kHz), so that the needle and microelectrode moved in concert through the dura, into the brain, with their tips 1.5 mm apart. We infused 18 µl of lidocaine or saline at 4 µl/min; this volume and rate of lidocaine infusion causes short-term neural inactivation (usually for less than 40 min) 1.5 mm from the needle tip, i.e., at the microelectrode, nearly 100% of the time (Tehovnik and Sommer 1997a). Equivalent volumes and rates of saline infusion have no detectable neural effects (Tehovnik and Sommer 1997a).

We placed the needle and electrode tips approximately 1–2 mm below the first unit encountered in a DMFC penetration. Within this depth range, we found a multiunit site with a reasonably high and stable firing rate (typically more than 5 Hz, with little variation over 5 min). These criteria allowed us to detect any neural changes, i.e., inactivation and recovery, with confidence.

Stimulus presentation and data collection

The visual stimuli were the same as in our FEF inactivation study (Sommer and Tehovnik 1997). Yellow LEDs (18 cd/m^2) were fixed in a board that was curved horizontally and vertically to point the LEDs at a monkey sitting 108 cm away. The LEDs were spaced 5° apart and the array spanned 40° horizontally and 30° vertically. Prior to each experiment, we calibrated the eye-position signal by having the monkey look at LEDs illuminated for several seconds in various positions on the board. The testing room was dark, unless otherwise noted. The room light and the entire array of LEDs were turned on for several seconds between blocks of trials (approximately every 10 min) to keep the monkey alert. Occasionally the monkey was given breaks in light for 10–20 min to prevent drowsiness.

Experiments were controlled by a PDP-11 computer. The microelectrode signal was amplified (BAK, A-1B), spikes were discriminated (BAK, DIS-1), and Schmitt trigger signals corresponding to the spikes were sent to the PDP-11. Data files recorded eye position (sampled at 333 Hz), task events, and the mean firing rate during each trial.

Oculomotor tasks

Four tasks were used (Fig. 2). The step, delay, and fixation tasks were used to study single saccades and fixations. The double-step task was used to study sequences of saccades and fixations. Only one task was used during a testing session.

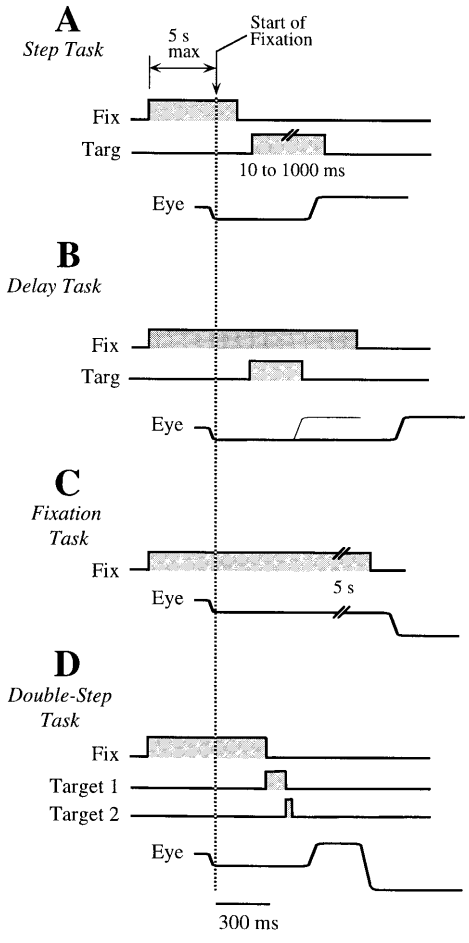


Fig. 2A–D Timing of the tasks. In each task, the monkey initially had 5 s to acquire the fixation light-emitting diode (LED) (*top*). Once fixation began, the remaining events occurred. (**A**) Step task. After the start of fixation, the fixation LED (*Fix*) disappeared, there was a brief gap, and a target LED (*Targ*) was lit. The monkey was allowed to make a saccade (*Eye*) to the target as soon as it appeared. Targets were 10–1000 ms in duration. (**B**) Delay task. After the start of fixation, a target LED was lit and then extinguished. The monkey was required to maintain fixation until the fixation LED disappeared, at which time the monkey was allowed to make a saccade to the location of the extinguished target (*Eye, thick line*). A saccade was premature if it was initiated before fixation offset (*Eye, thin line*). (**C**) Fixation task. After initial fixation of an LED, the monkey was required to maintain its eye position near the fixation LED until it disappeared 5 s later. (**D**) Double-step task. After fixation, the fixation LED disappeared and two targets were flashed in succession. The monkey was required to make sequential saccades to the target locations. Time scale is shown at *bottom*

The computer triggered task events (e.g., target onset) in synchrony with the monkey's fixations. Fixation of an LED was judged to occur if two conditions were met: the eye position was within an electronic window around the LED position and the eye velocity fell below 50°/s. Once the monkey foveated the initial fixation LED, the full sequence of task events began. As soon as the monkey fixated the target LED, a reward was delivered.

Because there is an upward drift and inherent inaccuracy for saccades made in darkness to locations of extinguished targets in delay tasks (Gnadt et al. 1991; White et al. 1994), windows around target LEDs had to be relatively large (10° horizontally, 20° verti-

cally). The same window sizes were used in all tasks to keep conditions as similar as possible between experiments. Fixation windows were 10×10° so as to be the same as those used in the FEF inactivation study, in which drifts in fixation sometimes occurred during inactivation (Sommer and Tehovnik 1997). Note that the windows were used only for triggering task events on-line. All data analysis was performed off-line, quantitatively, by comparing the eye-position data with the actual target locations. Window sizes had no effect on the quantitative results.

Step task

A fixation LED was illuminated to start a trial and was extinguished 100 ms after the monkey foveated it (Fig. 2A). After 100 ms, a target LED was illuminated. The monkey then had 2 s to move. A correct response was a single saccade to the target location. If a saccade was made before target onset, the trial was aborted. The 20 possible target locations were randomized by trial. In some experiments, three initial fixation positions (20° ipsilateral, central, and 20° contralateral) were randomized by trial, and target duration was set at 30 ms. In other experiments, target duration was randomized by trial (10, 30, 100, 315, or 1000 ms) and initial fixation was always central.

Delay task

A fixation LED appeared and was foveated (Fig. 2B). After 200 ms, a target LED appeared for 300 ms and then disappeared. After a 300-ms delay period, the fixation LED disappeared; this was the cue to move. The monkey then had 2 s to initiate a saccade. A correct response was a single saccade to the target location. If a saccade was made after target onset, but before the cue to move, it was classified as premature and was not rewarded. If a saccade was made before target onset, the trial was aborted. Twenty target locations and three initial fixation positions (20° ipsilateral, central, and 20° contralateral) were randomized by trial.

Fixation task

The monkey waited in darkness with eye position unconstrained and, after a random interval (~6 s), one LED was illuminated (Fig. 2C). This LED was chosen randomly from an array of 20 LED locations that spanned the testing space. The monkey had 5 s to foveate the LED, i.e., to fixate within the 10×10° window around it, and then had to keep its eye position within the window for an additional 5 s.

Double-step task

A fixation LED was illuminated and the monkey foveated it for 300 ms (Fig. 2D). The fixation LED was then extinguished and a target LED (target 1) was immediately illuminated for 110 ms. This was followed by the illumination of another target LED (target 2) for 20 ms. The monkey was required to make sequential saccades (saccades 1 and 2) to the respective target locations. A reward was given if saccade 1 was made to target 1 within 400 ms of its appearance, for monkey I, or within 500 ms of its appearance, for monkey L, and then if the monkeys made saccade 2 to target 2 within 800 ms after saccade 1 ended. Differences in saccade-1-latency criteria were due to slight differences in the monkeys' latency distributions, as documented in Results.

Four LEDs, at the corners of an imaginary 20×20° square surrounding the central fixation LED, were used as targets. In a trial, one LED was chosen randomly to be target 1 and one of the others was chosen randomly to be target 2, yielding 12 randomized sequences. The task was performed in dim ambient light. For monkey I, the two targets were presented in immediate succession. For monkey L there was a 35-ms gap between the offset of target 1 and the onset of target 2. These timings were chosen during training to optimize each monkey's performance, while minimizing the likelihood of the monkey beginning its saccadic sequence while target 2 was illuminated. Similar target timings have been used previously with monkeys (Mays and Sparks 1980; Sparks and Porter 1983; Goldberg and Bruce 1990; Goldberg et al. 1990; Barash et al. 1991).

Analysis

Step, delay, and fixation tasks

For the step and delay tasks, we analyzed the first saccade made after target onset. The beginning and end of the saccade were found using a 50 deg/s threshold. Saccadic error was the vectorial distance from the saccade's endpoint to the target's location. Saccadic latency was the amount of time leading to saccade initiation after target onset in the step task, or after fixation spot disappearance in the delay task. To analyze dynamics, we made main sequence graphs, plotting saccadic velocity against amplitude.

We did not analyze first saccades that had amplitudes less than or equal to 2.0°, because such saccades were within the amplitude range of fixation-related microsaccades in our monkeys. Hence, we were not confident that such saccades were attempts to reach the target location. However, we counted these *no-saccade* trials to determine whether their rates of occurrence were affected by DMFC inactivation. Corrective, secondary saccades were rare and not analyzed. Trials aborted on-line were omitted from analysis. For the fixation task, we measured the percentage of trials in which the monkey was able to foveate the fixation LED, the latency until foveation, and the distance that the eyes moved during the 5 s of foveation required.

Double-step task

We analyzed the first two saccades made after the disappearance of the fixation LED. Saccade 1 was considered correct if it began within 400 ms (for monkey I) or 500 ms (for monkey L) of target 1 onset and landed within 10° of target 1. Saccade 2 was correct if it began within 400 ms of saccade 1 ending and landed within 14.14° of target 2. These criteria were selected after examining the baseline psychophysics of the task for each monkey (documented in Results). The exact values of the spatial tolerances were arbitrary but corresponded to the task geometry; tolerance for saccade 1 to target 1 (10°) equals half the distance between targets in the cardinal directions, and tolerance for saccade 2 to target 2 (14.14°) equals the radius of a target from the fixation location.

Each trial was classified to summarize task performance. *Correct* trials were those in which both saccade 1 and saccade 2 were correct. *Saccade 1 wrong* trials were those in which saccade 1 was wrong. *Saccade 2 wrong* trials were those in which saccade 1 was correct but saccade 2 was not. Note that if saccades 1 and 2 were both wrong, it was ambiguous as to whether saccade 2 was in error solely because it followed an wrong saccade 1 or because of other factors. Because of this ambiguity, we took the conservative approach of classifying such trials as *saccade 1 wrong* trials.

"Before", "during", and "after" data sets

Monkeys were run continuously throughout a session (except during rest breaks). Three epochs of the data, "before", "during", and "after", were fully quantified and compared. "Before" data were those collected just before infusion. For lidocaine infusions, "during" data were those collected while neurons were inactivated, within 30 min subsequent to infusion. "After" data were those collected after the neurons recovered, near the end of the session. For saline infusions, "during" and "after" data sets were time-matched to respective data sets collected during lidocaine infusions.

For statistical analyses, we used a criterion of $P<0.05$ with Bonferroni correction. For saccadic error and latency data, "during"

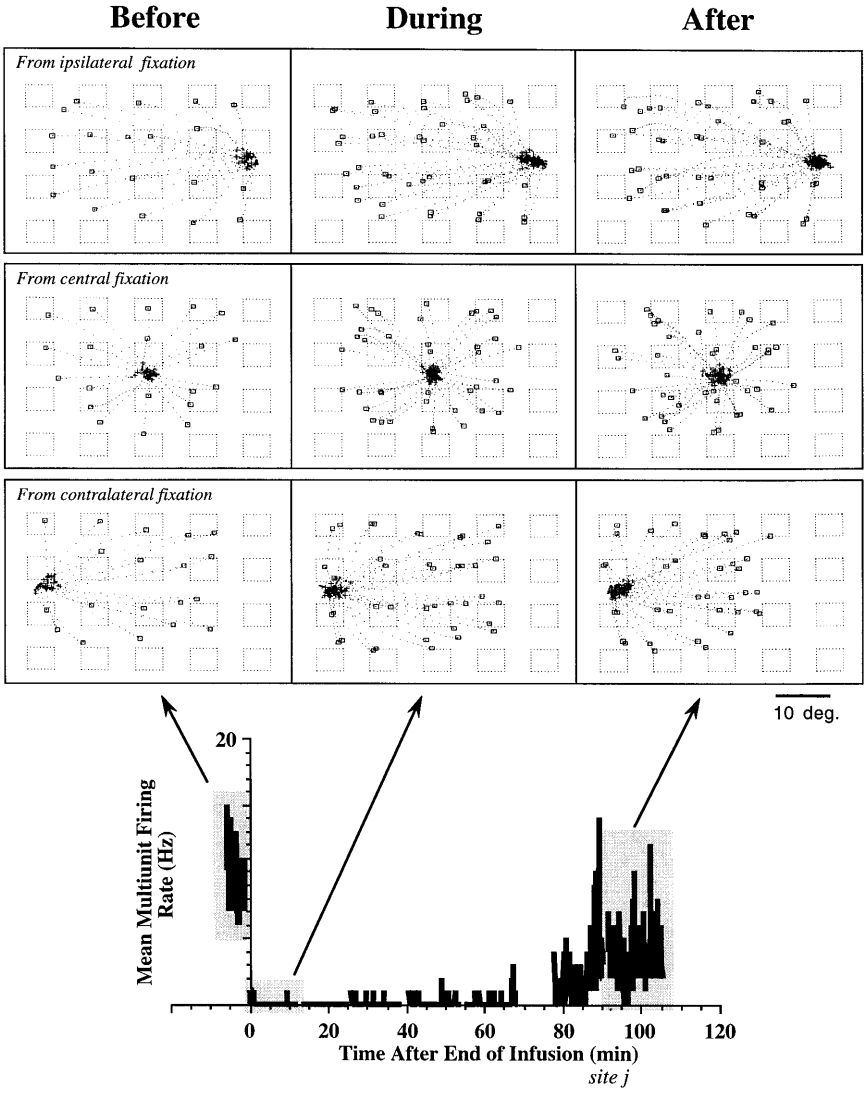


Fig. 3 Examples of saccades made in the step task. The saccades were not appreciably affected by dorsomedial frontal cortex (DMFC) inactivation. Representation of saccades is the same as in Fig. 1C, D. *Dotted boxes* represent the 20 target locations. Initial eye position was varied randomly between 20° ipsilateral (*top row*), central (*middle row*), and 20° contralateral (*bottom row*). Saccades are shown before (*left column*), during (*center column*), and after (*right column*) DMFC inactivation. At the very *bottom*, the mean multiunit firing rate 1.5 mm from the infusion site is plotted as a function of time relative to the end of the infusion (time 0). The average firing rate during every trial was plotted and data were connected with *straight lines*. *Shaded boxes* show the time periods in which before, during, and after data were collected

and "after" data sets were compared with the "before" data set using an unpaired, two-tailed Student's *t*-test with a Bonferroni correction of 2, i.e., $P<0.025$ was the adjusted criterion. To test hypotheses that percentages were different for "during" and "after" data relative to "before" data, Chi-squared or two-tailed Fisher Exact tests were used with the same Bonferroni correction. In some analyses of double-step task results, data were tested twice, once according to target-1 location and again according to target-2 location; this necessitated another Bonferroni correction of 2 and a significance criterion of $P<0.0125$ for these analyses.

Histology

Monkey L was overdosed with pentobarbital, perfused with 0.9% sodium chloride, and fixed with 4% paraformaldehyde. To estimate the locations of infusion sites, guide pins were inserted into the cortex at reference locations in the recording chamber. Monkey I is being used for additional experiments.

Results

DMFC infusion sites

We chose 19 sites for infusion (Fig. 1B). These sites were located in the DMFC topographic saccade map. For example, stimulation at site "p" in rostral and lateral DMFC evoked saccades that converged at a contralateral upward location (Fig. 1C). Stimulation at the more rostral and medial site, "m", elicited saccades toward the center (Fig. 1D). Stimulation also could fix the eyes in place (Fig. 1D). Staircase saccades only rarely were evoked during the mapping (2 of 53 sites tested), consistent with previous findings in DMFC (Schlag and Schlag-Rey 1987; Schall 1991b; Tehovnik and Lee 1993).

At the 19 DMFC sites, 20 lidocaine and 2 saline infusions were performed (at three sites we performed two infusions, separated by several weeks). One infusion also was made in the left FEF of monkey I; this monkey's FEF was mapped previously (Sommer and Tehovnik 1997).

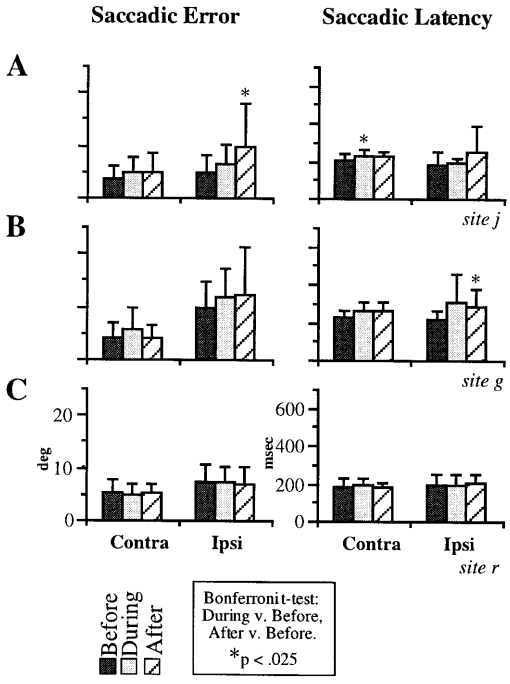


Fig. 4A–C Quantification of saccadic error and latency for all step task experiments that used a random initial fixation location and a 30-ms target duration. Results from central fixation are illustrated. Means and SDs of the saccadic error (*left column*) and the saccadic latency (*right column*) are shown before, during, and after DMFC inactivation (legend at *bottom*). Degrees of freedom ranged from 27–37

Effects of DMFC inactivation on single saccades and fixations

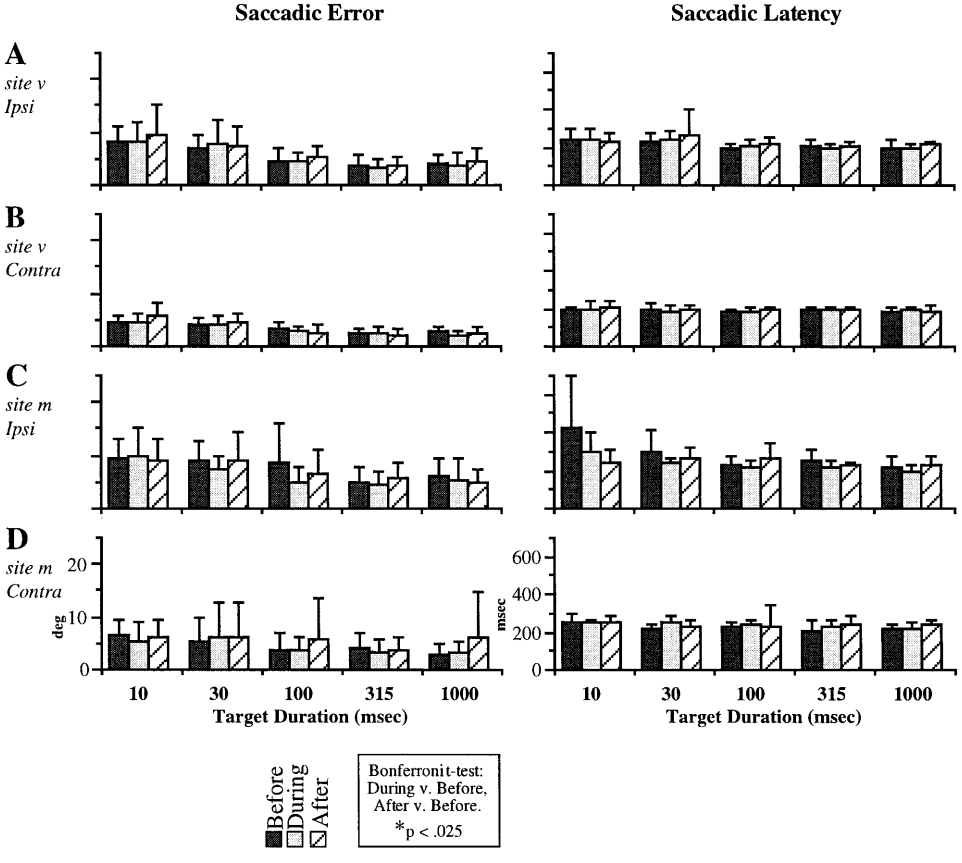
We performed 15 DMFC inactivations during tasks that required single saccades and fixations. The step, delay, and fixation tasks were each run in five experiments. The overall result was that DMFC inactivation caused negligible impairments.

Step-task results

In Fig. 3, eye movements are shown before, during, and after right DMFC inactivation. The monkey performed the step task with a target duration of 30 ms. Initial fixation location was randomized between 20° ipsilateral, central, and 20° contralateral. Before lidocaine infusion, multiple units recorded 1.5 mm away from the DMFC infusion site had a mean firing rate of ~9 Hz (Fig. 3). Subsequent to lidocaine infusion, the firing rate dropped, stayed low (less than or equal to 1 Hz) for about 1 h and then gradually recovered. One block of trials is shown before DMFC inactivation (Fig. 3) and two blocks are shown during and after inactivation. The trajectories and accuracies of saccades made from all fixation locations toward all target locations did not change appreciably throughout the experiment, despite inactivation of DMFC.

The results of all three step-task experiments that used randomized initial fixation locations and a 30-ms target

Fig. 5A–D Quantification of saccadic error and latency for both step task experiments that used random target durations. Means and SDs of the saccadic error (*left column*) and the saccadic latency (*right column*) are shown before, during, and after dorsomedial frontal cortex (DMFC) inactivation (legend at *bottom*). Results from (**A**) ipsilateral and (**B**) contralateral target trials when site *v* was inactivated are shown. Results from (**C**) ipsilateral and (**D**) contralateral target trials when site m was inactivated are shown. Degrees of freedom were 13 or 14 for each *t*-test



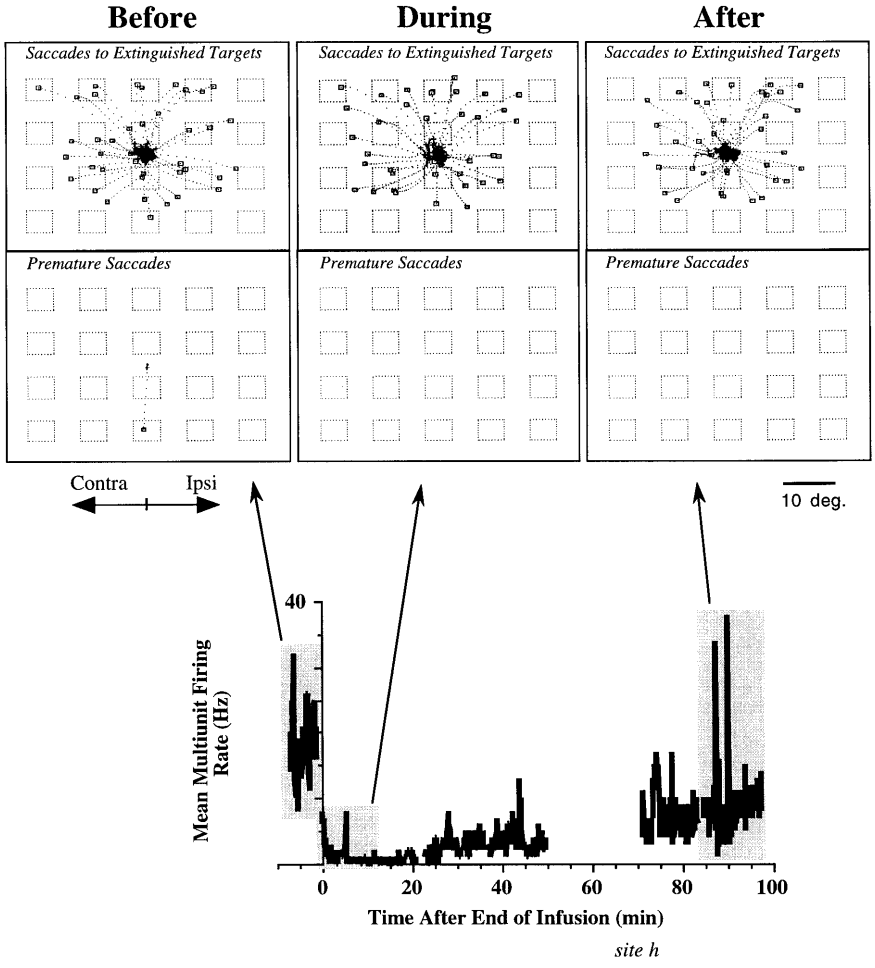


Fig. 6 Example of saccades made in the delay task during dorsomedial frontal cortex (DMFC) inactivation. *Upper panels* show saccades made to the locations of extinguished targets following the cue to move. *Lower panels* show premature saccades, made before the cue to move. See Fig. 3 for plotting conventions

duration are quantified in Fig. 4. For brevity, only results from central fixation are shown. There was only one mild deficit, in one experiment (the same experiment shown in Fig. 3): the latency of contraversive saccades increased by a small, but significant, amount during DMFC inactivation (Fig. 4A: from 210 ms to 233 ms, P=0.018). The only other significant change in the three experiments occurred at the end of sessions (in the "after" data) and probably were fatigue related. Results also were negative for trials that used eccentric initial fixation locations. The data also were analyzed by pooling within spatial quadrants rather than hemifields, to search for deficits on a smaller spatial scale; this revealed only one significant, small latency deficit during DMFC inactivation (comparable with that shown in Fig. 4A).

We performed two step-task experiments in which the target duration was randomized between 10 ms and 1000 ms and initial fixation was always central. Results are summarized in Fig. 5. Neither the saccadic error nor the saccadic latency changed significantly during DMFC inactivation for any target duration, or for saccades made to ipsilateral (Fig. 5A, C) or contralateral (Fig. 5B, D) targets. There were also no changes at the end of the experimental session ("after" data). Analyzing the data by quadrant rather than hemifield still did not reveal any significant changes during DMFC inactivation.

Delay-task results

Eye movements during a delay task experiment are shown in Fig. 6. Initial fixation location was randomized between three possible locations, as in the experiment of Fig. 3; for brevity, only the trials with central fixation are illustrated. During DMFC inactivation, there was no obvious change ("before" versus "during") in saccade metrics (Fig. 6). There was a slight decrease in velocity for saccades made to locations of contralateral, downward targets (note the closer spacing of eye position sample dots for these saccades in Fig. 6). The number of premature saccades was negligible, regardless of DMFC activity (Fig. 6).

In all five experiments that used the delay task, significant changes in error or latency were rare, small, and present only in the "after" data. This was true for all three of the randomized initial fixation locations and for analyses performed according to hemifield or quadrant. Hemifield results from central fixation for the five experiments are shown in Fig. 7. The number of premature saccades was not affected by DMFC inactivation [overall rates were 7.7% before, 5.8% during, and 6.5% after inactivation; "during" versus "before", Chi-squared (df 1) =1.20, P=0.27; "after" versus "before", Chi-squared (df 1)=0.49, P=0.48].

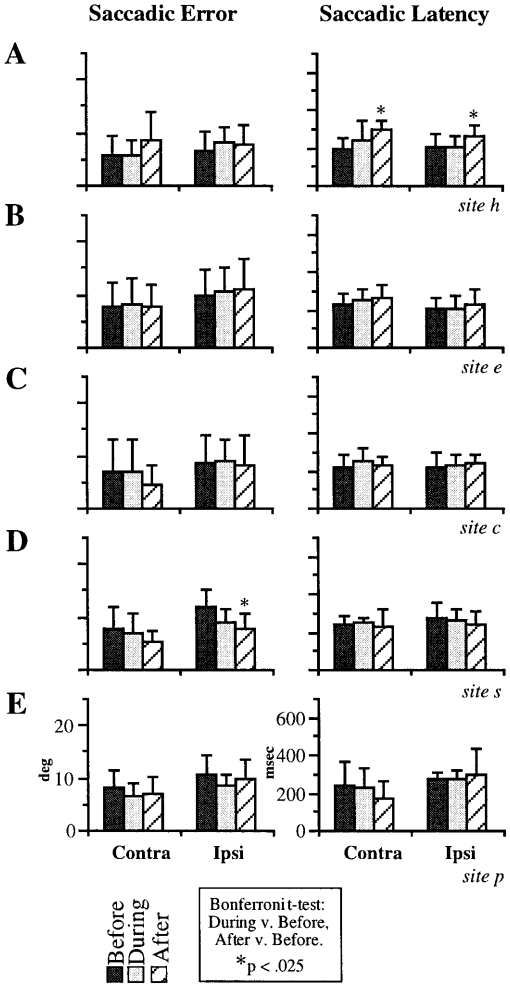


Fig. 7A–E Quantification of saccadic error and latency for all delay task experiments. See Fig. 4 for plotting conventions. Degrees of freedom ranged from 18–53

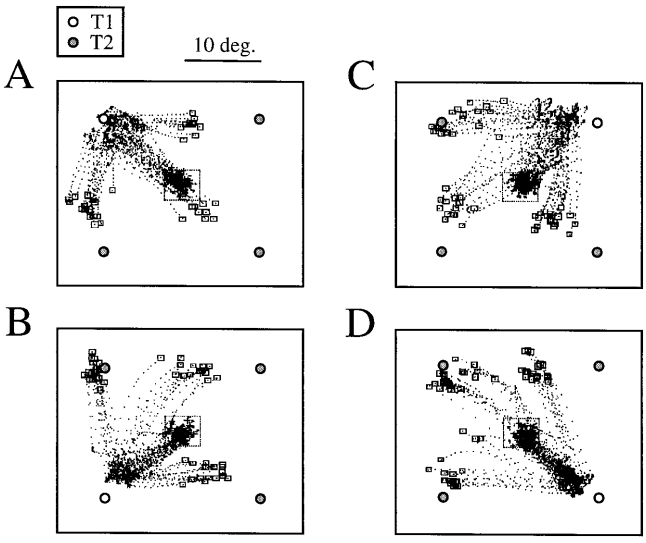


Fig. 8A–D Typical examples of saccadic trajectories in the double-step task. Trials are shown in which target 1 locations (*white circles*) were (**A**) contralateral and up, (**B**) contralateral and down, (**C**) ipsilateral and up, and (**D**) ipsilateral and down. Target 2 locations are shown by *dark circles*

Other results

The percentage of *no saccade* trials, i.e., those in which the first saccade did not occur or was less than or equal to 2.0° amplitude, was not affected by DMFC inactivation. In the step tasks, the overall percentage of *no saccade* trials was 1.0% before, 0.7% during, and 0.4% after inactivation [("during" versus "before", Chi-squared (df 1) =0.043, P=0.84; "after" versus "before", Chi-squared (df 1)=0.38, P=0.54]. In the delay task, the overall percentage of *no saccade* trials was 3.5% before, 6.1% during, and 6.1% after inactivation ["during" versus "before", Chi-squared (df 1)=3.33, P=0.07; "after" versus "before", Chi-squared (df 1)=3.70, P=0.055].

The remaining results of testing the effects of DMFC inactivation on single saccades and fixations are summarized as follows (details can be found in Sommer 1995). In one experiment using the fixation task, there were mild impairments in the latency and accuracy of foveating lower ipsilateral LEDs during DMFC inactivation; in the other four experiments, however, there were no effects. We found no reproducible changes in saccadic peak velocity attributable to DMFC inactivation. The only possible velocity deficit was that described above for the experiment of Fig. 6. Finally, the resting eye position in the dark, between trials, did not change significantly during DMFC inactivation.

Effects of DMFC inactivation on sequential saccades and fixations

To summarize the above results, DMFC neural activity is not necessary for generating single saccades and fixations. However, prior results from recording and stimulation studies do suggest that DMFC activity is involved, somehow, with saccadic and fixation behavior. We therefore studied whether DMFC inactivation impairs saccades and fixations that are components of a more complicated task. The double-step task seemed to be a logical task for testing this possibility: the monkey, instead of making one saccade and fixation, was required to link two saccades and fixations correctly into a sequence. We performed five DMFC inactivations during the double-step task.

Although other groups have used the double-step task with monkeys (Mays and Sparks 1980; Sparks and Porter 1983; Goldberg and Bruce 1990; Goldberg et al. 1990; Barash et al. 1991), there has been no quantification of the animals' behavior in this task. First, we document the baseline psychophysics of the double-step task and then we describe how DMFC inactivation perturbs performance.

Baseline psychophysics of the double-step task in monkey

In Fig. 8, typical baseline saccadic sequences made in the double-step task are shown. Many correct sequences

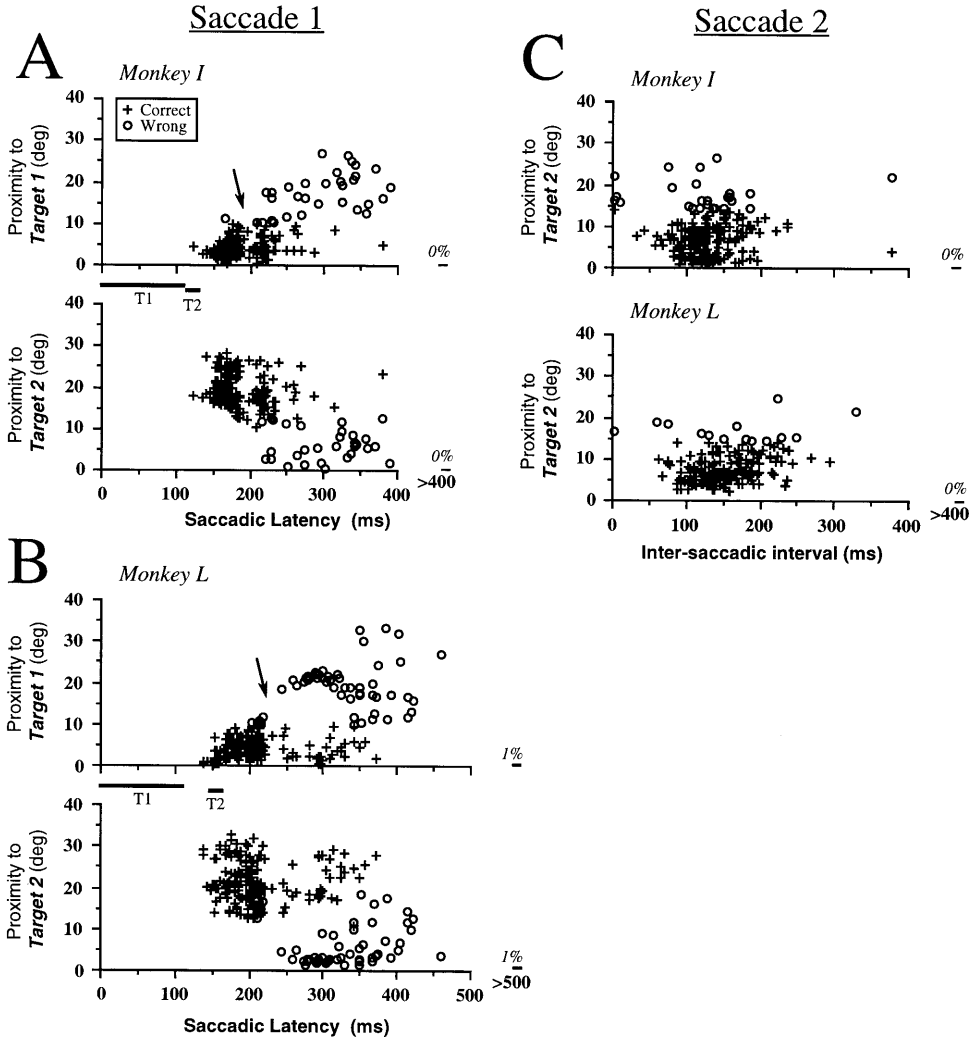


Fig. 9A–C Latencies (*abscissas*) and accuracies (*ordinates*) of saccades made in the double-step task. **A** *Upper graph* For monkey I, the latency of saccade 1 is plotted against the distance from the endpoint of saccade 1 to target 1. *Bars* below the *abscissa* show the timing of targets 1 and 2 (T1 and T2). **A** *Lower graph* Same data are shown, but ordinate is the saccadic endpoint's proximity to target 2. (**B**) Data for monkey L, in same format as in **A**, are shown. *Arrows* in **A** and **B** highlight the typical pause in saccade generation that began approximately 80 ms after target 2 onset. (**C**) Accuracy-latency characteristics of saccade 2 with respect to the inter-saccadic interval and the location of target 2, for (*top*) monkey I and (*bottom*) monkey L

from a block of trials are superimposed; sequences are sorted by target-1 location in panels A–D and by target-2 location within each panel. The first saccades begin at the center and are made to target 1. The second saccades begin at a corner (at target 1) and are made toward target 2. The saccades were highly reproducible: for each of the 12 sequences, correct saccade-1 endpoints typically formed a cluster with radius less than or equal to 7°; the same was true for correct saccade-2 endpoints.

Although precise with respect to one another, saccade-1 and saccade-2 endpoints were sometimes inaccurate with respect to the target locations. Saccade 1 tended to be correctly directed but hypometric (the gain ranged from ~0.7–1.0). Saccade 2 was more variable, with gains from ~0.5–1.0 and, for some sequences, a leftward bias. It has long been known that second saccades in remembered sequences are less accurate than first saccades (Komoda et al. 1977). Factors contributing to this probably include visual mislocalization of target 2 due to its appearance at approximately the same time as saccade 1 (Schlag and Schlag-Rey 1995; Honda 1997; Ross et al. 1997), accumulation of error from saccade 1 (Bock et al. 1995), and degradation of spatial memory over time (Gnadt et al. 1991). The leftward bias of saccade 2 in some sequences may have been due to inherent biases of the monkeys (as seen occasionally in presumably normal humans, e.g. Honda 1997) and/or minor left FEF damage from needle penetrations (Sommer and Tehovnik 1997).

In Fig. 9, baseline data are presented in more detail. Characteristics of saccade 1 are shown in panels A and B. The latency of each saccade is plotted against how far it landed from a target. For an initial examination of this figure, it is useful to overlook the different symbols. For monkey I (Fig. 9A top), if saccade 1 was initiated with a latency of 190 ms or less, it nearly always landed close (within 10°) to target 1. Then there was a pause of approximately 20 ms, during which time few saccades were made. If saccade 1 was initiated after the pause, it frequently landed far from target 1 (Fig. 9A top). By replotting the latency data with respect to target-2 location (Fig. 9A bottom), it can be seen that when saccade 1 landed far from target 1, it usually was made to target 2. A similar pattern of behavior was seen for monkey L (Fig. 9B), although its overall latencies were longer than those of monkey I.

Informed by these and other normative double-step data, we set criteria for judging whether a saccade 1 was correct or wrong (see Methods). The result of this cate-

gorization is illustrated by the symbols in Fig. 9A and B: correct saccade 1s are represented by crosses (+) and wrong saccade 1s by circles (o). The rare saccade 1s with very long latency (more than 400 ms for monkey I, more than 500 ms for monkey L) also were considered wrong; their frequency of occurrence is shown (Fig. 9A, B).

Saccade 2 exhibited simpler characteristics. In Fig. 9C the time that each saccade 2 occurred relative to the end of a correct saccade 1 is plotted against how far it landed from target 2. For both monkeys, saccade 2 generally was initiated after an inter-saccadic interval of 100–200 ms and landed within 15° of the target-2 location. From these and other normative data, criteria for classifying saccade 2 as correct or wrong were set (see Methods). Again, the frequencies of wrong saccade 2s due to excessively long latency are shown.

To summarize the double-step behavior within a certain time period, e.g., during DMFC inactivation, we used the saccade categorizations to determine the overall percentage of *correct* trials, *saccade 1 wrong* trials, and *saccade 2 wrong* trials that occurred within that interval (see Methods). We then calculated whether the percentage of each trial type changed significantly between time periods, e.g., "during" versus "before".

Effects of DMFC inactivation on double-step task performance

Figure 10 demonstrates the main result. There was a significant, moderate decrease in the percentage of correct trials during DMFC inactivation, compared with before, in all five double-step task experiments (Fig. 10A–E). Performance fully recovered after the inactivation in most experiments (Fig. 10A–C). Inactivation of the FEF, for comparison, caused an even larger deficit (Fig. 10F). Saline infusions into DMFC had no significant effects (Fig. 10G, H).

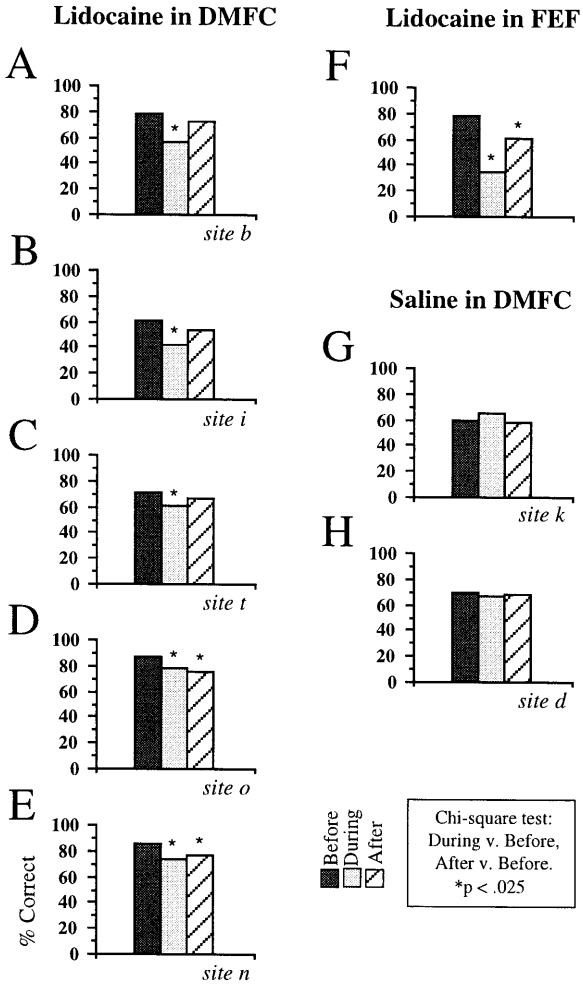


Fig. 10A–H Quantification of the percentage of correct trials for each double-step experiment. Legend at bottom right. **A–E** Results of inactivating dorsomedial frontal cortex (DMFC). **F** Results of inactivating FEF. **G, H** Results of infusing saline into DMFC. For each percentage calculation, the total number of trials ranged from 247–558

In the rest of this section, we document the specific ways in which monkeys were impaired in the double-step task during DMFC inactivation. In two experiments, the deficit was due to disruptions of saccade 1. Figure 11 shows an example of how saccadic accuracy was affected. The saccade 1 for every trial in which target 1 was in the lower right quadrant (ipsilateral–down) is shown. Before DMFC inactivation (Fig. 11), saccade 1 always landed in the lower right quadrant (67 trials). The saccade 1 endpoints were tightly grouped. During DMFC inactivation (Fig. 11), saccade 1 often was grossly misdirected, landing outside the lower right quadrant on 16 of 83 trials (19%). The saccade 1s that did land in the correct quadrant exhibited a marked scatter in their endpoint locations. After DMFC inactivation (Fig. 11), the impairment almost completely recovered: saccade 1 was misdirected in only 3 of the 66 trials (5%) and there was little scatter around target 1 location.

Figure 12 shows how latency was affected for the saccades of Fig. 11. The format is the same as that used for the top of Fig. 9A. Before DMFC inactivation, the latencies of all saccades were less than 250 ms (Fig. 12A). During the inactivation, many saccades had latencies greater than 250 ms (Fig. 12B). Fourteen of the 83 saccades (17%) had latencies of 250–400 ms, and 8 saccades (10%) had even longer latencies. After the inactivation, latencies returned almost to normal (Fig. 12C); only 4 of 66 saccades, 6%, had latencies of 250–400 ms, and only 1 saccade, 2%, had a latency greater than 400 ms.

Recall that a trial was categorized as a *saccade 1 wrong* trial if saccade 1 had excessive error or latency. For this experiment and location of target 1 (ipsilateral–down), the percentage of *saccade 1 wrong* trials increased significantly during DMFC inactivation [from 1% "before" to 29% "during", Chi-squared (df 1)=18.15, $P<0.0001$]. This significant increase is depicted graphically in Fig. 13A with a plus sign in the lower right quadrant of the saccade 1 wrong/T1 box. As can be seen, the percentage of *saccade 1 wrong* trials also increased significantly when target 1 was ipsilateral–up or contralateral–up. Overall, this meant that three of the four vectors of saccade-1 were

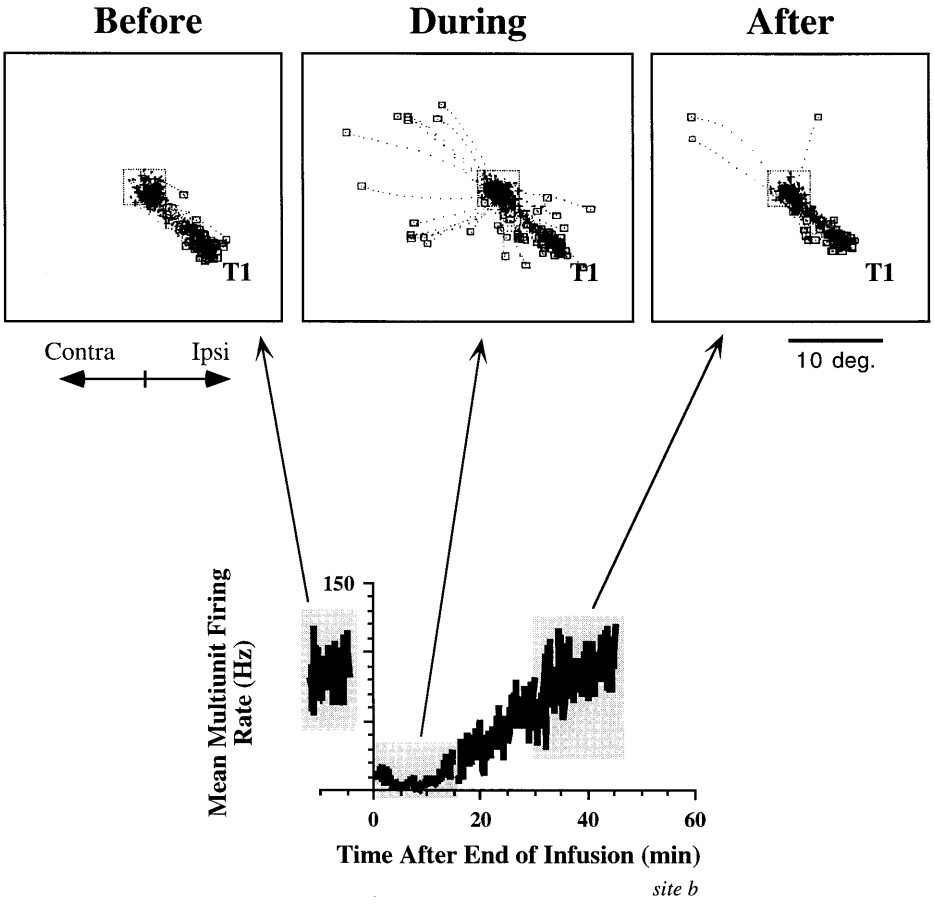


Fig. 11 Trajectories of saccade 1s made before, during, and after dorsomedial frontal cortex (DMFC) inactivation. All saccade 1s from trials in which target 1 (*T1*) was ipsilateral and down are shown. Saccade 2 of each sequence is omitted, for clarity

impaired (short arrows in Fig. 13A). Saccade 1 impairments occurred when target 2 was at any location (Fig. 13A, saccade 1 wrong/T2 box). Saccade 2 never was impaired significantly in this experiment (Fig. 13A, saccade 2 wrong boxes).

A similar deficit was seen during another DMFC inactivation (Fig. 13B). In this case, saccade 1 was impaired if target 1 was contralateral–up or ipsilateral–down, or if target 2 was contralateral–down. Two saccade-1 vectors were disrupted (contraversive–up and ipsiversive–down). Again, there was no change in the frequency of *saccade 2 wrong* trials. Both of the experiments in which saccade 1 was selectively impaired (Fig. 13A, B) occurred during inactivation of adjacent sites in DMFC (Fig. 13, sulcal map). These sites were relatively medial and near the middle of the DMFC rostrocaudal extent.

In one DMFC inactivation (Fig. 13E), saccade 2 was selectively impaired. The infusion was made in the caudal DMFC (Fig. 13, sulcal map). Figure 14 shows how saccadic accuracy was affected. Saccadic sequences are shown for all trials in which target 2 was ipsilateral–up. Before DMFC inactivation (Fig. 14), saccade 2 usually landed approximately 10° to the left of target 2. This was the normal baseline behavior (cf. Fig. 8). During DMFC inactivation (Fig. 14), saccade 2 often went elsewhere, to apparently random locations. For trials in which saccade 2 did land near the baseline location, there was an increased scatter of the saccadic endpoints. After DMFC inactivation (Fig. 14), the saccadic accuracy fully recovered.

Figure 15 shows how latency was affected for the saccades of Fig. 14. Before DMFC inactivation (Fig. 15A), inter-saccadic intervals usually were less than 200 ms, with a few longer ones (7 of 74 were greater than 400 ms). During inactivation (Fig. 15B), the inter-saccadic intervals were often greater than 200 ms; 28% (19 of 68) were greater than 400 ms. After inactivation (Fig. 15C), the inter-saccadic intervals partially recovered, with only 9% (5 of 56) greater than 400 ms.

In the remaining two DMFC inactivation experiments (Fig. 13C, D), the impaired double-step performance (recall Fig. 10C, D) could not be attributed to any specific saccadic disruption. Many small impairments, individually insignificant, summed to cause overall deficits in these two cases.

Saccade dynamics were not affected appreciably by DMFC inactivation. For example, despite being impaired by a DMFC inactivation, only a few saccade 1s (with amplitudes of 10–15°) had abnormally low peak velocity (Fig. 16A, data from the saccades of Fig. 11). Similarly, the velocity of saccade 2s impaired by a DMFC inactivation were essentially unchanged (Fig. 16B, data from the saccades of Fig. 14).

For comparison, we found that FEF inactivation caused different double-step deficits than did DMFC inactivation. First, impairments were more lateralized during FEF in-

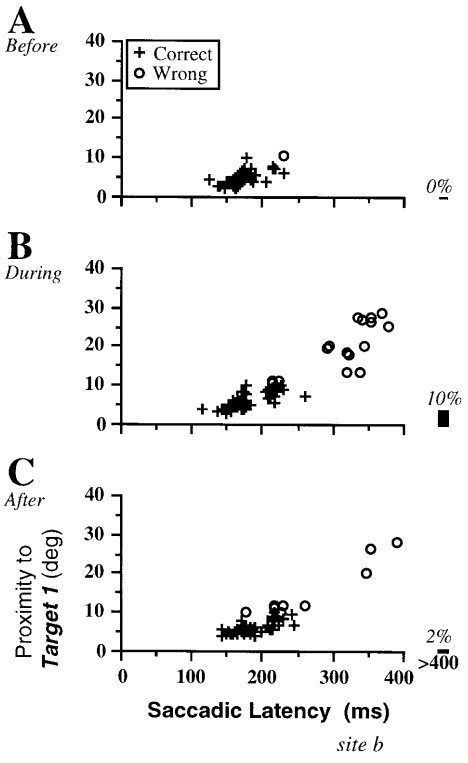


Fig. 12A–C Latencies of saccade 1s made in the dorsomedial frontal cortex (DMFC) inactivation experiment of Fig. 11. Saccades made (**A**) before, (**B**) during, and (**C**) after DMFC inactivation are represented

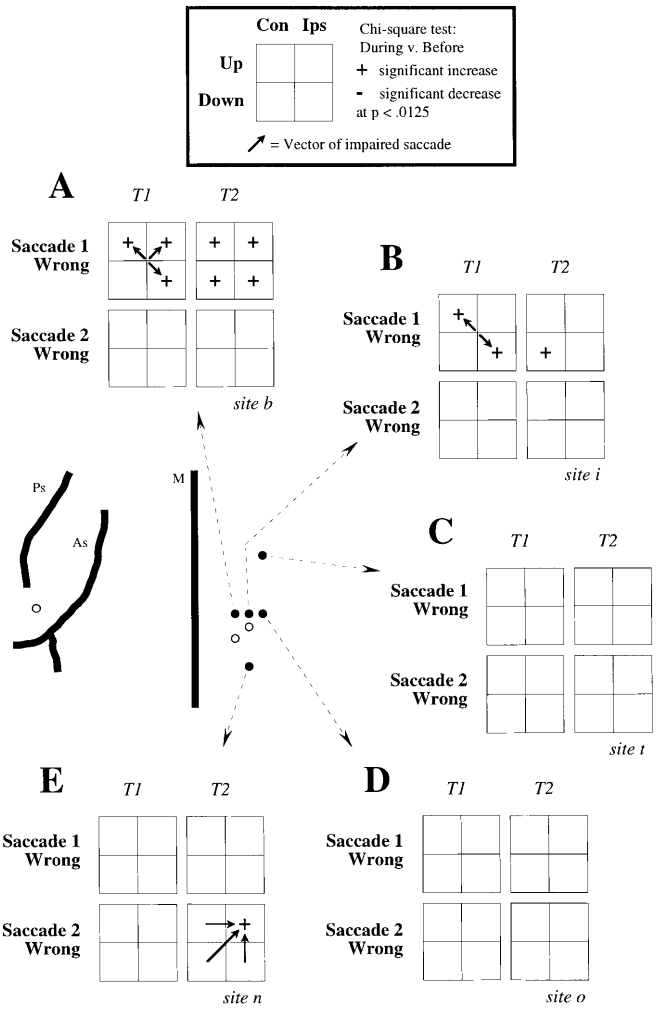


Fig. 13A–E Summary of specific impairments during all dorsomedial frontal cortex (DMFC) inactivations during the double-step task. Legend is at *top* (*Con* contralateral; *Ips* ipsilateral). For *saccade 1 wrong* and *saccade 2 wrong* trials, data were sorted and analyzed by the location of target 1 (*T1*) or target 2 (*T2*). The four quadrants of each *box* represent the four possible target locations. If the rate of making *saccade 1 wrong* or *saccade 2 wrong* trials increased significantly when T1 or T2 was in a particular location, this is marked with a plus sign (+) at the T1 or T2 location. Vectors of the impaired saccades are diagrammed explicitly using *short arrows*. At *center left*, infusion sites are reproduced from Fig. 1B, with the addition of the left FEF infusion site. *Black circles* represent sites pertaining to this figure; *white circles* show control sites (see Fig. 17)

activation, affecting only contraversive and vertical saccades (Fig. 17A). Also, FEF inactivation disrupted either saccade of the sequence. These results were as expected; the target durations in the present double-step task were 110 ms and 20 ms, and we have shown previously that contraversive and vertical saccades made to comparably brief targets are impaired by FEF inactivation (Sommer and Tehovnik 1997).

During the two saline infusions into DMFC, there were no significant impairments of saccades 1 or 2 (Fig. 17B, C). In one case, the percentage of *saccade 1 wrong* trials actually decreased for some target locations (Fig. 17B).

Discussion

We had two general goals: (1) to determine whether DMFC activity is necessary for generating saccades and fixations; and (2) in conjunction with our FEF study (Sommer and Tehovnik 1997), to directly compare the functions of DMFC and FEF by inactivating each area using the same methods and monkeys. First, we found that DMFC activity is necessary for generating sequences of saccades and fixations at normal performance levels but is not necessary for generating single saccades and fixations. Second, we found major differences between the functions of DMFC and FEF.

DMFC activity and the generation of saccades and fixations

Step, delay, and fixation tasks

In 15 experiments, DMFC inactivation was rarely associated with impairment of single saccades and fixations. Although this was a negative result, it seems well established. First, we know the infusions were made into the DMFC. We found the DMFC stimulation map of termination zones for each monkey (Tehovnik and Lee 1993; Tehovnik et al. 1994; Lee and Tehovnik 1995) and we

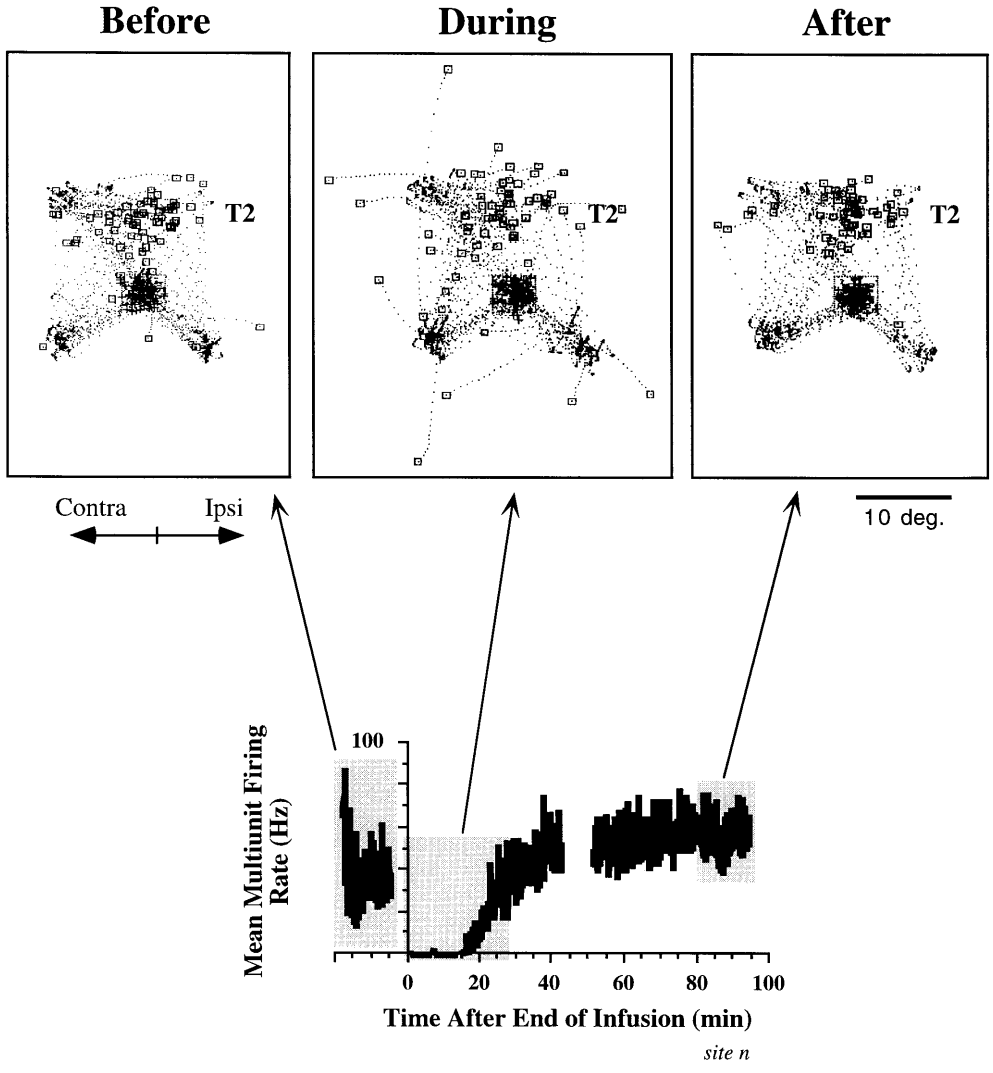


Fig. 14 Trajectories of saccade 2s made before, during, and after a dorsomedial frontal cortex (DMFC) inactivation. Saccades from trials in which target 2 (*T2*) was ipsilateral and up are shown. For each sequence, saccade 2 is the one terminated by a *small box*. Saccade 1s were from the center to the three possible locations of target 1

aimed our infusions with reference to this map. Second, the infusions silenced DMFC neurons. We always recorded multiunit activity near the infusion site, and it was always quenched by lidocaine. Third, our methods of testing were effective at revealing deficits in single saccades and fixations if they existed. Identical methods employed in the same monkeys while inactivating FEF yielded strong positive results (Sommer and Tehovnik 1997).

The one caveat to the present results is that we may have missed inactivating a special DMFC site that would have caused robust deficits. We think this possibility is remote because we studied an extensive range of the DMFC (Fig. 1A, B) and each infusion was relatively large, inactivating neurons at least 1.5 mm from the needle tip (Tehovnik and Sommer 1997a). Also, when we inactivated the same or adjacent DMFC sites during the double-step task (Fig. 1B), we did cause reliable deficits.

Our finding that DMFC inactivation had little effect on the generation of single saccades and fixations surprised us. There is much prior evidence implicating the DMFC in contributing to the generation of saccades and fixations, as reviewed in the Introduction. Neural activity originating in DMFC is sufficient to evoke saccades and fixations, as revealed by electrical stimulation. Neural activity within DMFC is correlated with saccades and fixations, as revealed by unit recording. Nevertheless, it appears that neural activity in DMFC is not necessary for generating saccades and fixations, as revealed by reversible inactivation.

Lee and Tehovnik (1995) hypothesized that DMFC fixation neurons contribute to a place signal of desired eye position that is used for generating all saccades. Because accurate saccades can be made reliably when the DMFC is inactivated, the present results seem to refute this hypothesis. The question remains, however, as to why an eye position place map exists in the DMFC (Tehovnik and Lee 1993; Lee and Tehovnik 1995). The spatial map does not appear to be used for generating all saccades and fixations, but it might be used during the generation of saccades and fixations in the context of certain tasks. For example, the map may be used for learning motor patterns that involve the eyes (Tehovnik 1995). It also might provide a common spatial frame of reference for the general coordination of the eyes and forelimbs, given that

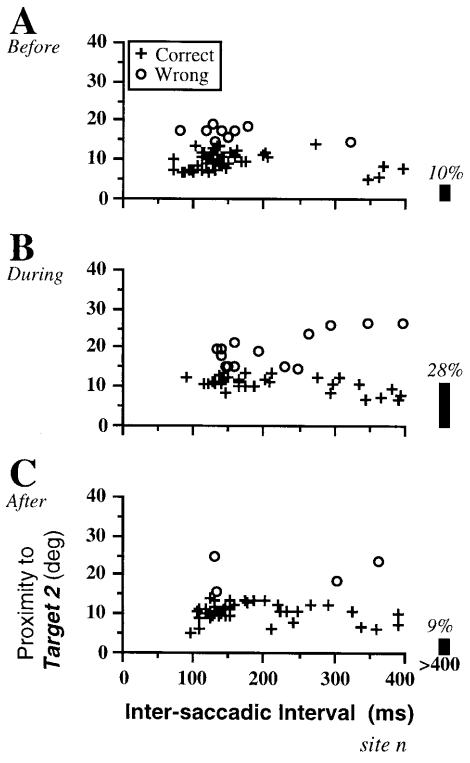


Fig. 15A–C Latencies of saccade 2s made in the experiment of Fig. 14. Saccades made (**A**) before, (**B**) during, and (**C**) after DMFC inactivation are represented

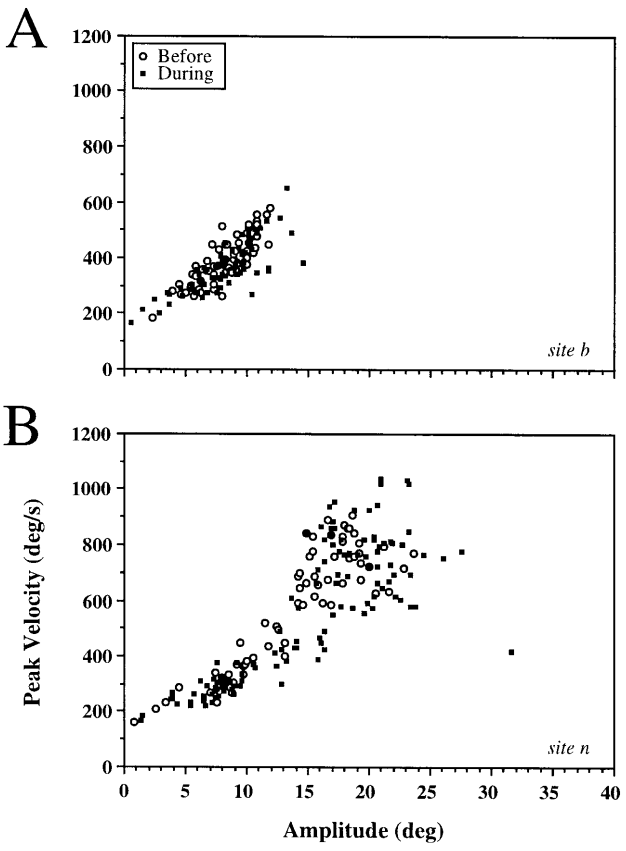


Fig. 16A, B Relationship between amplitude and peak velocity (the main sequence) for saccades affected by dorsomedial frontal cortex (DMFC) inactivation. In each graph, saccades made before and during inactivation are compared (legend at *top*). **A** Main sequence for the saccade 1s of Fig. 11 is shown. **B** Main sequence for the saccade 2s of Fig. 14 is shown

DMFC neural activity is influenced by both arm and eye movements (Mann et al. 1988; Mushiake et al. 1996; Chou and Schiller 1997a,b). In future studies it would be useful to see whether inactivation of a site within the DMFC map causes a corresponding spatial impairment in motor learning or eye–arm coordination.

Although we found that DMFC is not necessary for generating saccades and fixations in the intact monkey, it is possible that it becomes necessary for these functions after damage occurs elsewhere in the cortex. Recovery of function is a well-known phenomenon that occurs following cortical lesions. After a few weeks, the deficits from FEF lesions (Schiller et al. 1980) or combined lesions of FEF plus parietal cortex (Lynch 1992) diminish until the monkey's oculomotor abilities return to near normal levels. It is conceivable that plasticity involving the DMFC accounts for some cases of lesion recovery, but this hypothesis needs to be tested in a thorough and direct manner. Prior results do not support the hypothesis. Combined lesions of the FEF and the SC permanently devastate the generation of saccades to visual stimuli (Schiller et al. 1980), even though the DMFC and its direct projection to the brainstem omnipause region (Shook et al. 1988), an area that appears intimately involved in saccade generation, remain intact. Also, the ability to evoke saccades or fixations electrically from the DMFC does not appear enhanced in any way after lesions to the FEF (Tehovnik et al. 1994).

Double-step task

In all five experiments, DMFC inactivation caused a significant, moderate deficit in the ability to make sequential saccades to flashed targets in the double-step task. This was not due to an inability to make saccades to flashed targets, per se; single saccades made to single flashed targets were affected negligibly by DMFC inactivation (Figs. 3–5). DMFC inactivation disrupted saccades and fixations only in the task context of making a quick sequence of two saccades to two flashed targets.

A notable aspect of the double-step impairments during DMFC inactivation was the lack of directionality; contraversive, ipsiversive, and vertical saccades were all affected (Fig. 13A, B, E). The nearly omnidirectional deficits conform to prior findings that DMFC visual and presaccadic neurons are tuned for all directions (Schall 1991a) and that contraversive, ipsiversive, and vertical saccades all can be evoked from DMFC (Mann et al. 1988; Schall 1991b; Bon and Lucchetti 1992; Tehovnik and Lee 1993; Tehovnik et al. 1994; Lee and Tehovnik 1995). A slight contralateral bias in the tuning of DMFC neurons has been reported (Schall 1991a), but we did not observe a corresponding bias in our deficits. We may not

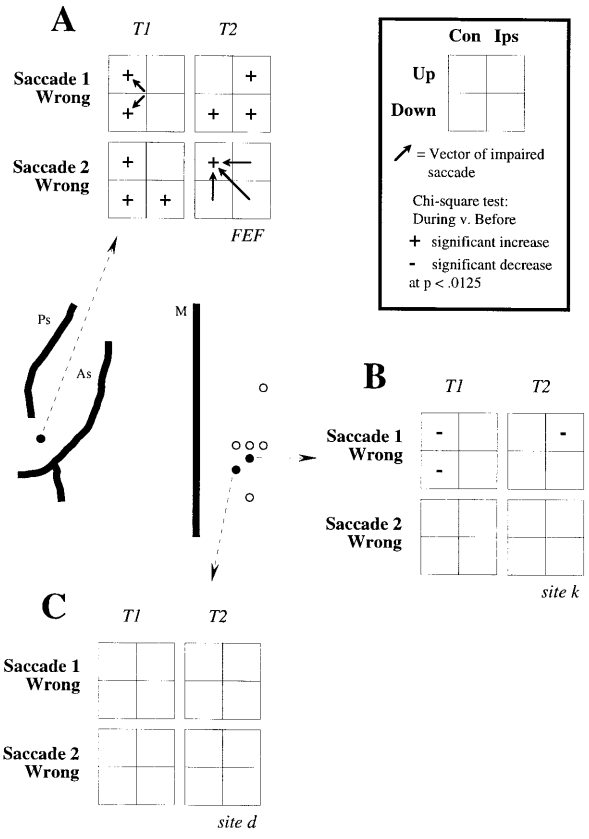


Fig. 17A–C Summary of effects found in the control experiments. See Fig. 13 for details of layout. **A** Results of the FEF inactivation experiment. **B, C** Results of the two saline infusions into dorsomedial frontal cortex (DMFC)

have tested enough target locations to uncover such a bias. Also, it has been reported that directional biases of DMFC cells are labile, changing with training (Chen and Wise 1996). We always presented ipsi- and contralateral targets with equal probability, so it may be that the population of neurons in our monkeys' DMFCs was directionally unbiased.

DMFC inactivation selectively impaired either the first or the second saccade of the sequence. During two inactivations in middle DMFC (Fig. 13A, B), only saccade 1 was impaired, and during a caudal inactivation (Fig. 13E), only saccade 2 was impaired. This hints at a topography that could be examined further with single-unit recording. For example, during the double-step task, caudal DMFC units might preferentially fire in response to target-2 presentation or saccade-2 execution. We found no clear relationship between the deficits and the known topography of termination zones (Tehovnik and Lee 1993; Lee and Tehovnik 1995).

In summary, DMFC inactivation disrupted saccades and fixations made in a rapidly executed sequence much more than saccades and fixations made in isolation. This implies that the intact DMFC contributes much more to the generation of saccadic sequences than to the generation of single saccades and fixations. In the extreme, one might think of DMFC as functionally specialized for generating sequences. This conclusion is supported by studies of reaching arm movements, another behavior in which DMFC is involved. Mushiake et al. (1991) recorded from DMFC neurons during visually-guided reaches or remembered sequences of reaches and found preferential modulation during the latter. Also, Tanji and Shima (1994) reported that many DMFC neurons fire only for arm movements that occur at a particular point in a sequence and not for identical movements that occur singly or at other points in the sequence. However, there also is evidence against the idea that DMFC is a sequencing area. If DMFC were specialized for generating saccadic sequences, electrical stimulation would be predicted to evoke saccadic sequences. This has never been demonstrated. A hallmark of stimulation in DMFC is that it nearly always evokes a single saccade, even if relatively high currents and long-train durations are used (Schlag and Schlag-Rey 1987; Schall 1991b; Tehovnik and Lee 1993).

Our conclusion, that DMFC is needed more for saccadic sequencing than for single-saccade generation is descriptive but has limited explanatory power. We still do not know exactly what the DMFC does that contributes to sequence generation. Does it help to discriminate multiple visual stimuli in space and time? Does it help to temporally order, or spatially aim, the multiple saccadic responses? More studies are needed to answer questions such as these. It would be informative to compare DMFC neural responses during saccades made singly and as part of rapid sequences. Also, an investigation into the oculomotor and visual effects of DMFC ablation needs to be done (and is underway, Schiller and Chou 1997a, b).

Comparison of DMFC and FEF

We inactivated the DMFC or the FEF (Sommer and Tehovnik 1997) in the same monkeys using identical methods. In single-saccade tasks, FEF inactivation caused reliable, severe, contralateralized impairments (Dias et al. 1995; Sommer and Tehovnik 1997). In response to flashed or extinguished targets in the contralateral hemifield (and sometimes along the vertical meridian), saccades were made with severely disrupted latency and accuracy. In the delay task, FEF inactivation caused saccades to be made prematurely to ipsilateral targets. Fixations in contralateral space were unstable, drifting upward and ipsiversively, and the resting position of the eyes in darkness shifted ipsiversively. In contrast, DMFC inactivation caused much weaker impairments. It had rare, mild effects on saccades and fixations.

In the double-step task, FEF inactivation caused a large deficit. This was predictable, because the double-step task required a monkey to make contraversive and vertical saccades to briefly flashed targets, and such saccades are known to be disrupted by FEF inactivation (Sommer and Tehovnik 1997). DMFC inactivation caused moderate, bilateral deficits in the double-step task, but these deficits could not be attributed to an underlying inability to make single saccades to flashed targets.

These results allow us to compare the functions of FEF and DMFC directly. The FEF is needed for generating contraversive saccades to flashed or extinguished targets, whether the saccades are made singly or as part of a rapid sequence. The DMFC contributes little to the generation of single saccades, but it does contribute substantially if saccades are to be generated in an accurate, rapid sequence. The FEF and DMFC are similar in that they both are needed to generate sequences of saccades. They are different in that the FEF oculomotor influence is stronger and more directional, and only the FEF is important for generating individual saccades.

As reviewed in the Introduction, unit recording and electrical stimulation studies also found differences between the properties of FEF and DMFC. Those techniques accentuated the differences in coding apparently used by the areas; FEF seems to generate saccades according to a vector code, whereas DMFC uses a place code. The present study affects those conclusions only by showing that the DMFC place code probably is not used for generating all saccades.

Another fundamental way in which the two areas differ is that the DMFC is less specialized for generating eye movements than is the FEF. The DMFC seems to have a lower density of saccade-related output neurons than does the FEF, as revealed by comparing the stimulation parameters that are optimal for evoking saccades from each area (Tehovnik and Sommer 1997b). Besides its saccade- and fixation-related activity, the DMFC also has neural activity that is modulated by visuomotor learning (Chen and Wise 1995a, b) and arm movements (Mann et al. 1988; Mushiake et al. 1996; Chou and Schiller 1997a, b). The FEF has relatively less activity related to these other functions (Chen and Wise 1995a, b; Mushiake et al. 1996).

Finally, human lesion studies provide further clues as to how FEF and DMFC compare (see review by Pierrot-Deseilligny et al. 1995). The human results generally agree with our macaque results. Sequential saccades are disrupted by both DMFC lesions (Gaymard et al. 1990, 1993) and FEF lesions (Rivaud et al. 1994). However, single saccades made to locations of extinguished targets are impaired by lesions of FEF, but not of DMFC (Pierrot-Deseilligny et al. 1991).

Conclusion

Inactivation of macaque DMFC had very little effect on the ability to make single saccades and fixations. Therefore, it appears that DMFC activity is not necessary for the general execution of saccades and fixations. DMFC activity is needed, however, for generating saccadic sequences at normal performance levels. Further work is needed to determine the precise role that DMFC plays in saccadic sequencing.

This study and our FEF inactivation study (Sommer and Tehovnik 1997) confirm that the DMFC and the FEF differ substantially in function. The FEF has a strong, dedicated role in generating contraversive saccades to flashed and extinguished targets, whereas the DMFC oculomotor role is weaker, less directional, and more task-dependent.

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