ELECTROPHYSIOLOGICAL CHARACTERIZATION OF THE DORSOMEDIAL FRONTAL CORTEX OF THE RHESUS MONKEY.

by

Kyoungmin Lee

M.D., Seoul National University, Seoul, Korea
(1987)

Submitted to the Department of
Brain and Cognitive Sciences
in partial fulfillment of the requirements
for the degree of

Doctor of Philosophy in Neuroscience

at

the Massachusetts Institute of Technology
September, 1992

Signature of Author .....
Department of Brain and Cognitive Sciences
September, 1992

Certified by .....
Peter H. Schiller
Professor, Dept. of Brain and Cognitive Sciences
Thesis Supervisor

Accepted by .....
Emilio Bizzi, Chairman
Department of Brain and Cognitive Sciences

Electrophysiological Characterization of the
Dorsomedial Frontal Cortex of the Rhesus Monkey.
by

Kyoungmin Lee

Submitted to the Department of Brain and Cognitive Sciences
on June 17, 1992 in partial fulfillment of the
requirements for the Degree of Doctor of Philosophy in Neuroscience

ABSTRACT

The dorsomedial frontal cortex (DMFC) of monkeys has been implicated in controlling eye movements. The purpose of this study was (1) to examine saccadic evocation by electrical stimulation of the DMFC and (2) to record from units in order to identify neural correlates of the evoked behavior.

Electrical stimulation of the DMFC typically produced saccades that terminated within a region of visual space, the termination zone. The latency to evoke a saccade varied with eye position such that it increased monotonically the closer the fixation spot was to the termination zone. The probability to evoke a saccade decreased the closer the fixation spot was to the termination zone. Changing head position with respect to the body did not change the location of a termination zone with respect to the head. The DMFC was found to contain a topographic codification of termination zones with rostral sites representing zones in extreme contralateral visual space and caudal sites representing zones closer to the midline. Lateral sites represented zones in upper visual space, whereas medial sites represented zones in lower visual space. Once the eyes were positioned within a termination zone, further stimulation fixed the eyes and inhibited visually-evoked saccades. Following release from inhibition, the saccades reached the visual target accurately. This shows that the stimulation delayed the execution of the saccades without actually aborting their execution.

A large proportion of units in the DMFC were found to have activity modulated by a monkey's fixation behavior. Many of the units fired maximally when the eyes fixated a target in a particular zone of visual space. As a group, units in the rostral DMFC fired more with the eyes fixating contralaterally, while those in the caudal DMFC fired more with the eyes fixating ipsilaterally. This rostro-caudal difference in unit activity is consistent with the arrangement of termination zones of saccades evoked by electrical stimulation of the region.

In conclusion, the DMFC contains a map of eye position in craniotopic coordinates, and this map seems to be utilized to fixate at the position.

Thesis Supervisor: Peter H. Schiller, Ph.D.
Title: Professor, Department of Brain and Cognitive Sciences.

To my parents,

Acknowledgements.

I thank Professor Peter H. Schiller for his generous support and supervision on my study at M.I.T.. I am deeply grateful to Dr. Edward J. Tehovnik, with whom the experiments described in this thesis has been conducted. I thank Robert Dolan for his kind help in solving many technical problems. I appreciate the numerous helpful suggestions and comments on this thesis by Drs. James T. McIlwain and Richard A. Andersen. I thank my parents, my brother, my sister, and my wife for their ever-loving care of me. Finally, and most importantly, I thank God for His love that fulfills my life.

Table of Contents

Chapter 1. Introduction.

Eye movements are evoked by electrical stimulation of the frontal cortex of primates. Since studies by Ferrier (1874, 1875), efforts to localize the sites of excitation in the frontal lobe by using microstimulation resulted in the identification of two distinct areas that subserve saccadic eye movements: the frontal eye fields (FEF), which are at the anterior bank of the arcuate sulcus (Bruce et al. 1985; Robinson and Fuchs 1969) and the supplementary eye fields, which are in the dorsomedial frontal cortex (DMFC) (Schlag and Schlag-Rey 1987).

The supplementary eye fields in the DMFC, which is the subject of this thesis, are located at a region of the superior frontal convexity that is medial to the upper branch of the arcuate sulcus and close to the midline (Mann et al. 1988; Schall 1991; Schlag and Schlag-Rey 1987) (Fig. 1-1). This region coincides with rostral parts of the supplementary motor area where Penfield and Welch (1951) found that electrical stimulation of a homologous region in humans evokes contraversive eye, head, and body movements as well as contraversive limb movements.

That the DMFC of the primate brain contains another eye field is further established by the finding that activity of units in this area is modulated by saccadic eye movements (Mann et al. 1988; Schall 1991; Schlag and Schlag-Rey 1987). Presaccadic activity occurred with self-initiated as well as with visually triggered saccades (Schlag and Schlag-Rey 1987). Also units were found whose activity was related to visual and auditory stimuli,

to the anticipation of predictable target presentation, or to visually-guided reaching movements of the eyes and forelimb (Mann et al. 1988; Schall 1991).

Anatomical studies have demonstrated that the DMFC of the primate has connections with other brain regions that are involved in generation of eye movements (Huerta and Kaas 1990; Shook et al. 1990, 1991). The supplementary eye field (SEF) in the DMFC is connected with subcortical structures such as the superior colliculus, rostral interstitial nucleus of the medial longitudinal fasciculus, cuneiform nucleus, mesencephalic reticular formation, and nucleus reticularis pontis oralis (Huerta and Kaas 1990). Also the SEF projects to the nucleus prepositus hypoglossi and nucleus raphe interpositus, which project with the motoneurons and the omnipause neurons, respectively (Shook et al. 1990).

The SEF also has extensive cortico-cortical connections with structures implicated with oculomotor control. It has reciprocal and bilateral connections with periprincipal and inferior prefrontal cortex, periarcuate cortex including the FEF, postarcuate premotor cortex, and the supplementary motor area which surrounds the SEF. The SEF is also reciprocally connected ipsilaterally with cortex in and around the cingulate sulcus and the intraparietal sulcus, and cortex within the superior temporal sulcus projects to the SEF (Huerta and Kaas 1990).

Overall patterns of connectivity are similar between the FEF and SEF, and the pathways by which the SEF can control eye movements are as direct

as those demonstrated for the FEF (Shook et al. 1990, 1991). Comparative study of subcortical connections of the FEF and the SEF showed that the major thalamic pathways of the SEF are with the ventral anterior and medial dorsal nuclei of the thalamus, whereas the most robust pathway of the FEF is with the medial dorsal rather than the ventral anterior nucleus. In the caudate, projections from the two eye fields were found to be restricted to a central longitudinal core, while their projections to the putamen were restricted to the region representing the face (Shook et al. 1991).

One of the important observations made of the DMFC that, among others, motivated this study is that saccades elicited by electrical stimulation of the region terminate within a certain region of visual space irrespective of initial eye position (Mann et al. 1988; Mitz and Godschalk 1989; Schall 1991; Schlag and Schlag-Rey 1987; Wagman 1964). This is in contrast with results obtained by electrical stimulation of other oculomotor areas, such as the FEF or the superior colliculus. Saccadic eye movements evoked by electrical stimulation of these areas have constant direction and amplitude regardless of initial eye position, and do not terminate in a common space (Bruce et al. 1985; Robinson 1972; Robinson and Fuchs 1969; Schiller and Stryker 1972). The difference between saccades evoked by DMFC stimulation and those evoked by stimulation of either the FEF or superior colliculus is interesting because it may reflect the difference in the coordinate systems utilized by those areas in generating eye movements (Robinson 1972).

The question of what coordinate system is utilized in making saccadic eye movements has been an issue of much debate, since Robinson (1975) proposed his local-loop feedback model of saccade generator. In the model, target position represented in head-centered or craniotopic coordinates is considered as the input needed to drive the burst neurons in the brainstem. Identifying this input has been a central problem in oculomotor research, because the FEF or the superior colliculus, both of which have been studied extensively in this regard, seem to be unable to provide neural correlates of target position in a craniotopic coordinate system. Electrical stimulation of such areas indicated that these areas are coded in retinotopic coordinates (Bruce et al. 1985; Robinson 1972; Robinson and Fuchs 1969; Schiller and Stryker 1972).

Subsequently, attempts have been made to get around this problem. In his modification of the Robinson model, Scudder (1988) proposed that what is given as the input to the local feedback loop to generate saccades is not the target position in head-centered space but the amount of eye displacement to acquire the target. It was suggested that saccades to the target can be accurately made with this code of eye displacement alone, if the system has a resettable integrator of eye position in the feedback pathway of the neural circuit. According to this model, the integrator is reset after each saccade to eliminate the possible mismatch between eye position and its internal neural correlates (Jurgens et al. 1981; Tweed and Villis 1985). Some have

questioned the necessity of representing target position in space and proposed that spatially accurate saccades could be generated by cumulatively updating previous eye movements (Goldberg and Bruce 1990). According to this model, records of previous saccades and retinal error of the visual target are sufficient to acquire the target accurately.

Nevertheless, there is evidence that the oculomotor system utilizes head-centered representation of the target position to make saccades. One can direct the eyes to a target whose position is not given by its retinal error. In order to make an accurate saccade to a source of sound, for example, the position of the source needs to be represented with respect to the head, and then current eye position with respect to the head should be subtracted from it to compute the amount of required eye displacement (Robinson 1975). Moreover, it is demonstrated that specifying eye movements correctly about the three axes of eyeball rotation in the orbit requires the target to be represented with respect to the head (Nakayama 1975; Westheimer 1981). Furthermore, studies of the posterior parietal cortex showed that the activity of units in the region is modulated as a function of eye position, suggesting that the posterior parietal cortex transforms the visual input from a retinocentric to a craniocentric coordinate system (Andersen 1987). It is more likely, therefore, that the oculomotor system utilizes the representation of the target in craniocentric coordinates to make eye movements.

The observation that saccades evoked by DMFC stimulation stops at

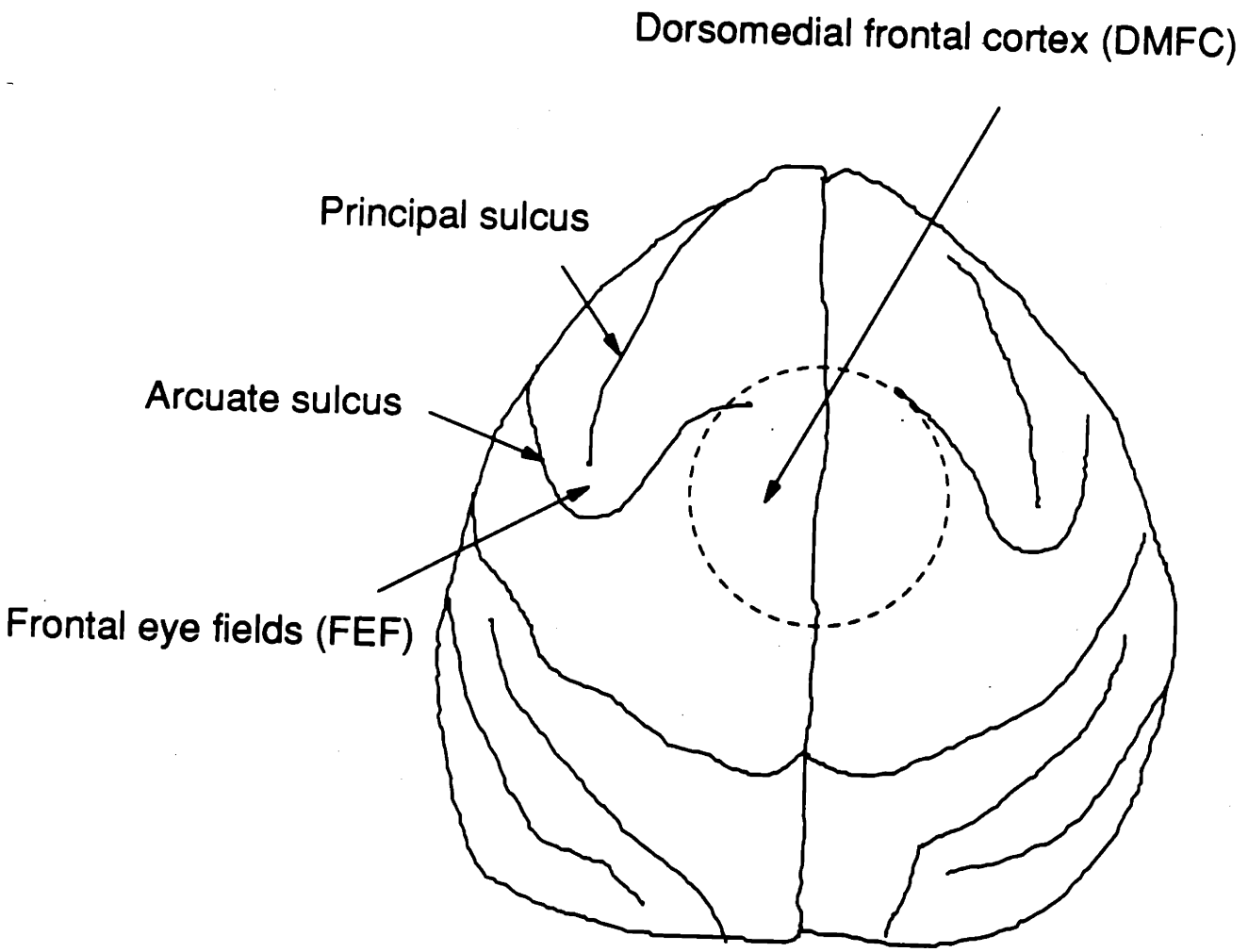
a certain space irrespective of initial eye position is quite interesting in this regard. It suggests that the DMFC may provide a neural signal for saccadic eye movements specified according to a coordinate system fixed with respect to the head (Robinson 1972).

Therefore, the following electrophysiological characterization of the DMFC was conducted in an effort to understand the role played by the area of the brain in controlling saccadic eye movements. First, the DMFC was electrically stimulated in order to examine the characteristics of evoked eye movements. Second, units in the DMFC were recorded in order to identify the neural elements that may account for results obtained by electrical stimulation of the area. Third, the frontal eye fields were studied for comparison.

Figure.

FIG. 1-1. A top-down view of the cerebral cortex of monkey Q. The locations of the frontal eye fields and the supplementary eye fields in the dorsomedial frontal cortex are indicated.

Figure 1-1


Dorsomedial frontal cortex (DMFC)
Principal sulcus
Arcuate sulcus
Frontal eye fields (FEF)

Chapter 2. Electrical stimulation of the DMFC.

1. Methods.

a) Subjects.

Three male, adult rhesus monkeys (Macaca mulatta), A, Q, 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.

b) Surgery.

Monkeys were anesthetized with pentobarbital (30 mg/kg). 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 Q and Y, a recording chamber was implanted over the midline and centered over the DMFC. For monkey Q, a second recording chamber was implanted over the left frontal eye field (FEF).

c) Behavioral Tasks.

i) Fixation task:

The monkey faced a TV screen usually with his head fixed (Fig. 2-1a). He had to fixate for 600 ms (milliseconds) a spot of light that appeared on the TV screen (Fig. 2-1b). During fixation, the monkey had to keep his eyes within a 1x1 degree area otherwise the trial was terminated. Fixation was rewarded with a drop of apple juice. This task allowed us to control the position of a monkey's eyes before electrical stimulation was delivered. Stimulation began 200 ms after fixation began. Typically, the monkey was stimulated on every second trial.

On some stimulation trials, the monkey's head was free to move within 30 degrees to the left or right along the horizontal plane during the fixation task. The head holder could be fastened so that the monkey's head could be fixed at various orientations with respect to the body. Because only horizontal head movements were possible, stimulation was restricted to that part of the DMFC that when stimulated evoked eye movements with trajectories falling along the horizontal meridian.

ii) Detection task:

The monkey fixated a spot for 600 ms after which a punctate target appeared 3 degrees to the left or right of the fixation spot (Fig. 2-1c). A correct saccade was recorded when the monkey's eyes entered a 2x2 degree 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 stimulation offset, the monkey had 800 ms to saccade to a target; on non-stimulation trials, the monkey had 800 ms to saccade to a target following target appearance. This paradigm was used to test the monkey on stimulation-evoked saccadic inhibition.

d) 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 unit responses (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 maximal velocity of at least 200 degrees/sec (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.

e) Electrical Stimulation.

Glass-coated platinum-iridium electrodes with an impedance of 0.5 to 1.0 MΩ (megohms) at 1 KHz (kilohertz) were used. Electrode-tips were 40 μm long and 14 μm wide at the base etched to a fine taper to yield a surface area of 880 μm^2. Use of tips this size reduces the current density at the tip thereby decreasing the probability of tissue damage (Yeomans 1990). The integrity of the electrode tip was checked periodically by visual examination under a microscope and by monitoring impedance. Constant-current biphasic pulses were delivered to the tissue using a Grass S88 stimulator attached to a pair of constant-current, stimulus isolation units (Grass PSIU6B). For each stimulation pulse, a cathodal was followed immediately by an anodal pulse. 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 read as the amplitude of one pulse (cathode or anode) of a biphasic pair. The current, pulse duration, frequency, and train duration were held constant (unless specified) at 400 μA, 0.1 ms, 150 Hz, and 400 ms, respectively. These values were chosen following parametric tests conducted to optimize the stimulation-evoked responses (see Appendix for details).

Typically, electrodes were introduced vertically through the dura with a hydraulic microdrive. The action potentials were amplified (Bak A-1B), filtered (Krohn-Hite 3750), and discriminated (WP Instruments 121). The

best stimulation sites were encountered at 2 to 5 mm lateral to the midline of the DMFC and immediately below the first unit encountered on an electrode pass. A total of 270 penetrations were made in the three monkeys. For each penetration, stimulation tests were typically conducted every 0.5 mm over a depth of 6 mm. For monkey A, electrodes were introduced through the dura at 25 degrees to the vertical and aimed at the medial bank of the DMFC.

f) Histology.

Monkeys were overdosed with pentobarbital, perfused with 0.9% NaCl, and fixed with 4% para-formaldehyde. Guide pins were inserted into the cortex at specific positions around the recording chamber. The locations of the electrode tracts were estimated relative to the pins. Tissue shrinkage, which was about 5%, was taken into account in the anatomical reconstructions. The brains were photographed and sectioned coronally at 40 µm and stained with cresyl violet. Monkey A has been retained for future study.

2. Eye movements evoked by electrical stimulation of the DMFC.

Eye movements evoked by DMFC stimulation are similar to saccadic eye movements in terms of properties such as peak velocity. In Figure 2-2a, duration of eye movements evoked by DMFC stimulation is plotted as a function of their amplitude. Comparing this plot with that of visually-guided saccades as in Figure 2-2b reveals that the two kinds of eye movements do not differ from each other in their duration-amplitude relationship. Therefore, eye movements evoked by DMFC stimulation will be considered saccades.

3. Eye position dependency of saccades evoked by DMFC stimulation.

a) The final position of evoked saccades: the termination zone.

The size of a saccade evoked by electrical stimulation of the DMFC varied with fixation position. As the fixation position changed from the ipsilateral to the contralateral hemifield, the amplitude of a saccade decreased with the final position of the saccade approaching a certain region of visual space, which we call a termination zone (Fig. 2-3a). Vertical and horizontal eye movement traces are illustrated for a site of the DMFC in monkey Q (Fig. 2-4a). For a 24 degree fixation position, which was positioned maximally away from the termination zone of the site, the saccades were the largest (40 to 50 degrees). As the fixation position neared the termination zone, which was situated beyond the -8 degree fixation position, the size of the saccades decreased until no eye movements were evoked at the -24 degree fixation position.

In contrast to saccades elicited from the DMFC, those elicited from the FEF exhibited staircase properties and their maximal excursion and direction did not vary with fixation position (Fig. 2-3b and 2-4b).

b) Probability of evoking saccades.

Not only did the amplitude of the saccadic eye movements evoked from the DMFC vary with fixation position, but the probability of evoking a

saccade and saccadic latency also varied. When the fixation position approached the termination zone (moving from fixation position 24 to -24), the probability of evoking a saccade decreased once the eyes were within the termination zone of each site of the DMFC (Fig. 2-5a). Yet for the FEF, the probability of evoking saccades did not vary with fixation position and always remained at 100% (Fig. 2-5b).

c) Latency of evoked saccades.

Figure 2-6 shows the latency between stimulation onset and saccade onset, the saccadic latency, plotted as a function of fixation position for the DMFC and the FEF. The latency to evoke saccades from the DMFC increased as the fixation position neared the termination zone. In Figure 2-6, data from three sites in the DMFC are plotted. Site C is the same site from which the data shown in Figures 2-3a, 2-4a and 2-5a were obtained. Note that, for sites C and E, saccadic latency could not be measured when fixation position was at -8 and -24 degree, because too few saccades were evoked by the stimulation. For the FEF, however, the latency to evoke a saccade did not vary with fixation position (the FEF curve in Figure 2-6). The observed latencies are consistent with those reported by other investigators (Bruce et al. 1985; Marrocco 1978; Robinson and Fuchs 1969).

For DMFC stimulation, saccadic latency was found to decrease monotonically with saccadic amplitude for monkey Q (Fig. 2-7). Saccadic

amplitude is the distance between the fixation position and the termination zone. As already noted in Figure 2-6, the closer the eyes were to the termination zone the longer the latency. Once the eyes were within 10 degrees of the termination zone, the number of saccades evoked decreased dramatically and, instead, saccades were inhibited by the stimulation, as will be discussed later in detail. Therefore, no saccades shorter than 10 degree arc were observed. The same amplitude-latency relationship was also observed for monkeys A and Y.

4. Arrangements of termination zone in the DMFC.

a) Rostrocaudal axis of the DMFC.

Vector-representations of saccadic eye movements evoked from 5 sites in the DMFC of monkey Q (Fig. 2-8) are illustrated (Fig. 2-9). For all sites shown, the saccades were contraversive with respect to the side of stimulation.

Systematic exploration of the DMFC revealed that different portions of the DMFC coded for different termination zones: As the electrode was moved from anterior to posterior sites in the DMFC, i.e., from sites A to E, the termination zone moved systematically from the extreme contralateral hemifield to a position closer to the midline. These observations were made for both hemispheres of monkeys Q and Y, and for the left hemisphere of monkey A.

The termination zone was not confined to a punctate area of visual space but had an area ranging from 9.1 to 40.3 deg.^{2} of visual space (Table 2-1) for sites marked by A through to E in the DMFC. The zone filled for the FEF was appreciably larger at 669.1 deg.^{2} (for the data in Figure 2-3b), which indicated that the concept of termination zone was not applicable to the FEF. For the DMFC, the convergence was more prominent along the horizontal than along the vertical dimension. The size of the termination zone in the horizontal dimension ranged from 1.4 to 3.3 deg., whereas it ranged from 6.5

to 12.2 deg in the vertical dimension.

As the electrode was moved from anterior to posterior DMFC sites (A to E), the overall probability of evoking saccades decreased as the termination zone shifted toward the midline (Fig. 2-10). This decrease was most noticeable for contralateral fixation positions (i.e., -24 and -8 degrees). Furthermore, as the electrode was moved from anterior to posterior sites in the DMFC, the overall latency increased (curves marked as site A, C, and E in Figure 2-6).

b) Lateromedial axis of the DMFC.

In monkey A, the bank of the left DMFC was stimulated to determine whether termination zones along vertical space are represented along the lateral-medial axis of the DMFC. Saccades evoked from lateral to medial sites in the DMFC are shown for anterior (Fig. 2-11), middle (Fig. 2-12), and posterior (Fig. 2-13) regions of the DMFC. The anterior region and middle region were 5 and 3 mm anterior to the posterior region, respectively. The top left corner of each figure shows a coronal section of the DMFC with 4 stimulation sites A through to D. Panels A through D show saccades evoked from the corresponding site while the monkey fixated different positions. As the electrode was positioned more medially and deeply in the DMFC, the direction of saccades changed from an upward trajectory to a downward trajectory. This was most apparent for anterior and middle regions (Fig. 2-11

and 2-12), and less so for posterior regions (Fig. 2-13). A similar medial to lateral topography representing saccadic direction was observed in monkey Y.

Stimulation of sites deep within the bank of the DMFC was aversive. During such stimulations, monkey A tended to break fixation thereby making the evoked saccades more erratic (Fig. 2-11, site D).

Finally, stimulation of posterior sites in the DMFC of monkey A evoked convergent saccades (Fig. 2-13, sites A, B, & C). The contraversive saccades always occurred at a shorter latency and had a higher probability of occurrence than did the ipsiversive saccades.

5. Saccadic inhibition by DMFC stimulation.

Once the stimulation-evoked saccades reached their termination zone, further stimulation fixed the eyes in the termination zone and inhibited visually-evoked saccades. After the termination zone was found (Fig. 2-14), monkey Y was required to do the detection task with the fixation spot positioned within the termination zone. Horizontal eye traces are shown for different episodes of stimulation while monkey Y performed the detection task (Fig. 2-15). The eyes remained on the fixation spot for the duration of stimulation, and only after stimulation did the monkey make a saccade to the target. Moreover, saccadic latency was found to increase linearly with train duration (Fig. 2-16a). After stimulation, the monkey was still able to perform the detection task at an accuracy rate of 100% (Fig. 2-16b). On trials without stimulation, monkey Y made brisk visually-evoked saccades that exhibited latencies well below 300 ms.

The same experiment was conducted on monkey Q for 3 different sites in the DMFC. As with monkey Y, when the fixation spot was positioned in a termination zone, eye position was maintained for the duration of stimulation up to 1.2 seconds (Fig. 2-17a). Also the performance level remained high at above 90% (Fig. 2-17b). Beyond a train duration of 1.2 seconds, monkey Q tended to break fixation: the saccadic latency was less than the train duration and the performance level dropped below 80%.

To test how saccadic inhibition varies as a function of fixation position, an 800 ms train of stimulation was delivered to the right DMFC of monkey Q as he performed the detection task. The possible locations of the fixation positions and targets are illustrated in Figure 2-18a. When no current was applied, the latency of visually-evoked saccades was between 200 and 250 ms for all fixation positions tested (Fig. 2-18b, 0 μA). When a 100 μA current was applied, the latency of visually-evoked saccades was increased for all positions (Fig. 2-18b, 100 μA). When the current was increased to 400 μA an entirely different pattern emerged. Contraversive, leftward saccades were now evoked from all fixation positions except from the position that fell within the termination zone (Fig. 2-18b, 400 μA). For this position (at -24 degree in the lower field) the saccadic latency just surpassed 800 ms, the duration of stimulation.

6. Stimulation during head-free conditions.

Anterior and posterior sites, separated by 5 mm along the rostrocaudal axis, were stimulated in the left DMFC of monkey A while he fixated targets presented along the horizontal meridian. The head was free to move left and right within 30 degrees of the midline. Head movements were not evoked from any of the sites stimulated in the DMFC, while the monkey fixated targets located at 30 and 15 degrees to the left and right of center of gaze. Saccadic eye movements, however, were evoked from all sites tested and these saccades were similar to those described above.

Finally, changing the position of the head with respect to the body did not change the position of a termination zone with respect to the head.

Table and Figures.

TABLE 2-1. The size of a termination zone in vertical and horizontal space is listed for each of five sites of the DMFC and one site in the FEF of monkey Q. A mean final position of the eyes in X and Y coordinates was determined following stimulation from each fixation position. The standard deviations for these means were always less than 3.6 degrees. For a given site, these means provide a range of final positions along vertical and horizontal space.

Site	Vertical (deg.)	Horizontal (deg.)	Estimated Area ($deg.^2$)
A	12.2	3.3	40.3
B	6.5	1.4	9.1
C	10.9	2.4	26.2
D	8.6	1.5	12.9
E	6.5	3.3	21.5
FEF	17.2	38.9	669.1

Figure legends.

FIG. 2-1. (a) TV monitor (Mitsubishi Color Display Monitor) showing the positions of the fixation spot. The monitor was moved left and right to increase the size of the field tested. Sixteen degrees in the vertical dimension were tested. For some experiments the monitor was moved along the vertical dimension to further increase the field of testing.

(b) The fixation task is illustrated 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. (c) The detection task is illustrated for different stages of a trial. A trial began with the onset of the fixation spot. At the offset of the fixation spot, the target and electrical stimulation were presented. A reward was delivered after a saccade was made to the target.

FIG. 2-2. (a) Duration of eye movements evoked by DMFC stimulation of monkey L is plotted as a function of the amplitude. (b) The same kind of plot is drawn for visually-guided saccades made by the same monkey.

FIG. 2-3. (a) Eye movement traces that were obtained by electrical stimulation of a DMFC site of monkey Q are shown. For comparison, saccadic eye movements evoked from a site in the FEF of the same monkey are illustrated in (b). For each plate, an upright rectangle depicts a fixation

position. Each dotted line, starting from a rectangle, represents the entire excursion of the eyes during the 400 ms train of stimulation. Each line represents one saccade. The dots confined to a rectangle indicate that eye movements were not evoked from those positions. A monkey always faced the region between the four central fixation positions such that four fixation positions occurred to the right of the monkey and four occurred to the left. Eye movements evoked by DMFC stimulation are single saccades only; whereas for the FEF, each line represents numerous saccades since for the train duration used staircase saccades were evoked.

FIG. 2-4. (a) Vertical and horizontal eye movement traces are shown for the same DMFC site as in Figure 2-3a. The traces represent eye movements evoked from the four fixation positions. Saccades evoked from fixation positions located at 24 and 8 degrees in the ipsilateral hemifield (with respect to the side of stimulation) are shown in plate (24 deg) and (8 deg), respectively. Saccades evoked from fixation positions located at 24 and 8 degrees in the contralateral hemifield are shown in plate (-24 deg) and (-8 deg), respectively. In each plate, the top profile indicates the horizontal eye positions and the bottom profile indicates the vertical eye positions. The ordinate of each profile represents the amplitude of an eye movement, and the abscissa represents the time following fixation onset. Rightward, leftward, upward, and downward movements are indicated by R, L, U, and

D, respectively. The two vertical lines set at 200 and 600 ms, respectively, show the time of stimulation onset and offset.

(b) Vertical and horizontal eye movement traces are shown for the same FEF site as in Figure 2-3b. The traces represent eye movements evoked from the 4 top fixation positions. Details of the figure is the same as in (a).

FIG. 2-5. The probability of evoking a saccade by DMFC stimulation (a) and FEF stimulation (b) is plotted as a function of fixation position. The probability was determined by dividing the number of trials during which a saccade was evoked over the total number of stimulation trials, which was 20. The fixation positions that occurred in the ipsilateral hemifield are indicated by 24 and 8 degrees, and those that occurred in the contralateral hemifield are indicated by -24 and -8 degrees The plots are based on the saccades depicted in Figures 2-3 and 2-4. Since the saccades evoked from the top and bottom fixation positions were similar, the probability values from each were combined.

FIG. 2-6. Saccadic latency is plotted as a function of fixation position for the FEF and three sites in the DMFC. Fixation positions in the ipsilateral hemifield are represented by the 8 and 24 degree positions, and those in the contralateral hemifield are represented by the -8 and -24 degree

positions. The data marked by site C were obtained from the same DMFC site as in Figures 2-3a and 2-4a. The latencies are based on 20 trials. Standard error bars are shown when the errors are larger than the symbols. If fewer than 3 saccades were evoked from a fixation position, as was the case for fixation positions occurring in the contralateral hemifield for sites C and E of the DMFC, then a latency value was not computed.

FIG. 2-7. Saccadic latency is plotted as a function of saccadic amplitude for the DMFC of monkey Q. These data are based on saccades illustrated in Figure 2-9, namely, those evoked from sites A, B, C, D, and E of the DMFC, as shown in Figure 2-8. The data (N = 230) are fitted to a power function ($y = 20570\ x^{-1.55}$, N = 230) which accounts for 67% of the variance ($R^2 = 0.67$). The R value, 0.82, is significantly different from zero ($p < 0.01$). Other functions tested (i.e., linear, log, and exponential) accounted for less variance.

FIG. 2-8. A top view of the cortex is shown for monkey Q. The circle demarcates the region investigated in the DMFC. Each recording site, which is represented by a letter, was separated from an adjacent site by 2 mm. Each site was 4 to 5 mm off the midline. Sites A, B, and C were situated anterior to the posterior tip of the arcuate, and sites D and E were situated posterior to the tip.

FIG. 2-9. Saccadic eye movements evoked from sites A through to E of the DMFC of monkey Q are shown. The location of the DMFC sites are illustrated in Figure 2-8. The data from site C were shown also in Figure 2-3a. Details of the figure are the same as in Figure 2-3a, except that vector representation of saccades, instead of actual eye movement traces, are drawn here.

FIG. 2-10. The probability of evoking a saccade is plotted as a function of fixation position for each site of the DMFC as marked. Site A, C, and E refer to the sites as illustrated in Figure 2-8. The data from site C were shown also in Figure 2-5a. See legends of Figure 2-5 for details in the calculation of the probability.

FIG. 2-11. Saccades evoked from an anterior region of the DMFC are shown. The top left plate represents a coronal section through the DMFC of monkey A. Since monkey A is being used for further study, the locations of sites A through to D indicated on the section were estimated. Panels A through to D show the vector representations of saccades evoked from corresponding sites in the DMFC. Each of the 12 rectangles illustrated in a plate represents a fixation position. The monkey was facing a position between the central two boxes.

FIG. 2-12. Saccades evoked from a middle region of the DMFC are shown. See figure 2-11 for details.

FIG. 2-13. Saccades evoked from a posterior region of the DMFC are shown. See figure 2-11 for details.

FIG. 2-14. The bottom portion of the figure shows saccadic eye movements evoked from different fixation positions following stimulation of the right DMFC of monkey Y. Each rectangle represents a fixation position. The saccades, represented here by the vectors, converge onto a region in space, 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 inset. The monkey was required to make a saccade to either the left or right target (depicted by a circle) that was 3 degrees from the fixation spot. Electrical stimulation to the DMFC was delivered 5 ms after the target was presented, to test for saccadic inhibition.

FIG. 2-15. Horizontal eye movement traces of visually-evoked saccades are shown for different train durations of electrical stimulation while monkey Y performed the detection task (Fig. 2-14). Going from the top to the bottom trace, eye movements are shown for 0, 1, 2, and 3 second bouts of stimulation. Fixation is represented by 'f' and the target is represented by 't'. The arrows

represent the time of target onset. The horizontal black bars represent time of stimulation.

FIG. 2-16. Saccadic latencies and performance scores are shown for monkey Y, while he performed the detection task (Fig. 2-14).

a) 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. The dotted line is a reference y = x axis.

b) Percent correct is plotted as a function of train duration for the same stimulation trials represented in (a). Following electrical stimulation, the monkey was given 800 ms to make a saccade to the target. The dotted line represents the 80% performance level, the criterion achieved before testing began.

FIG. 2-17. Saccadic latencies and performance scores are shown for monkey Q, while he performed the detection task. The results from three different sites in the DMFC are shown.

a) Saccadic latency is plotted as a function of train duration. Each point represents 20 trials. Standard errors are shown when they are greater than the size of a data point. The reference y = x axis is illustrated.

b) Percent correct is plotted as a function of train duration for the same trials as in (a). Following electrical stimulation, the monkey was given 800

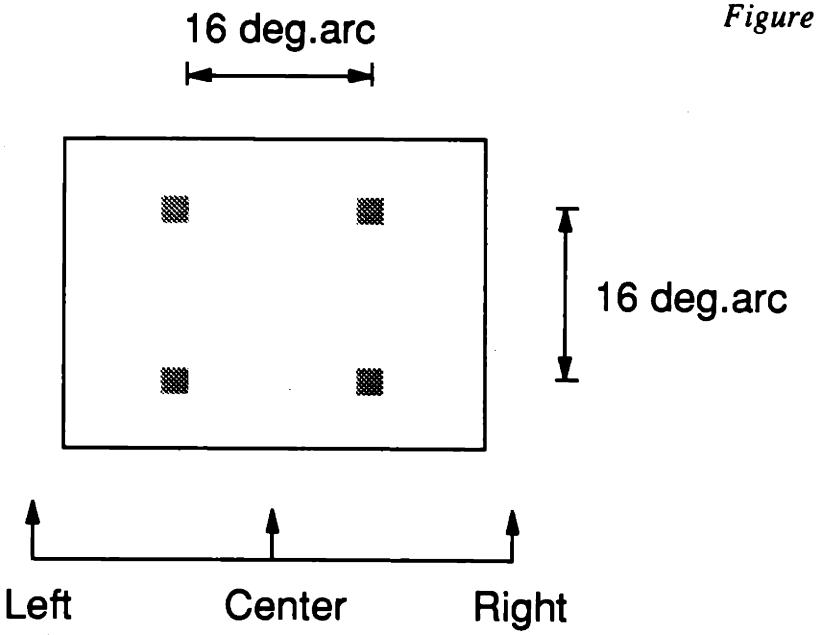
ms to make a saccade to the target.

FIG. 2-18. a) Fixation and target positions are shown for the detection task. The fixation spot is represented by the smaller square in the center of a set of three squares, and the target is represented by a larger square on either side of the fixation spot. The target occurred 3 degrees to the left or right of the fixation spot. The circle at the left bottom corner indicates the approximate location of the termination zone for the DMFC site from which the data shown in (b) were obtained.

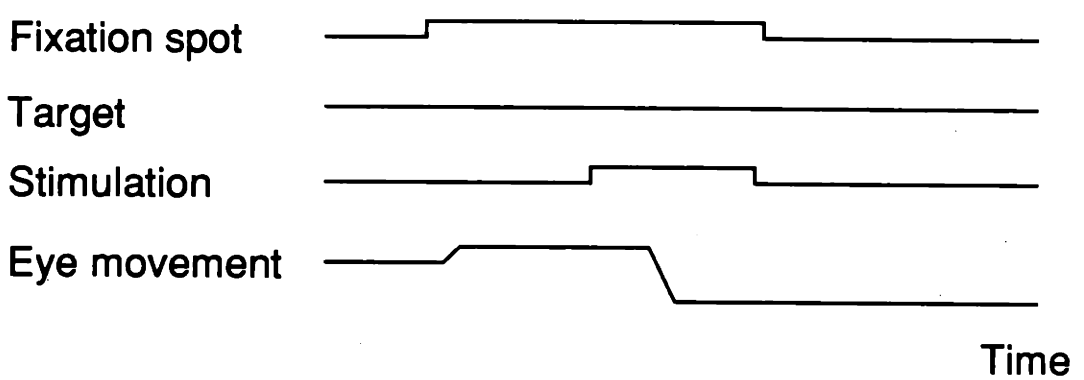
b) Saccadic latency is plotted as a function of fixation position. Each bar is based on 10 trials, and standard error bars are shown. Each plate represents data obtained at a given current: 0, 100, or 400 μA.

Figure 2-1

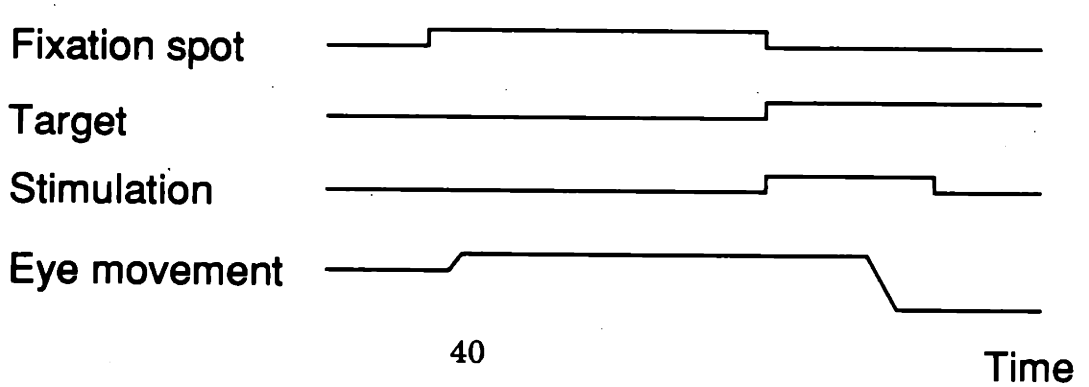
a)



b) Fixation task



c) Detection task



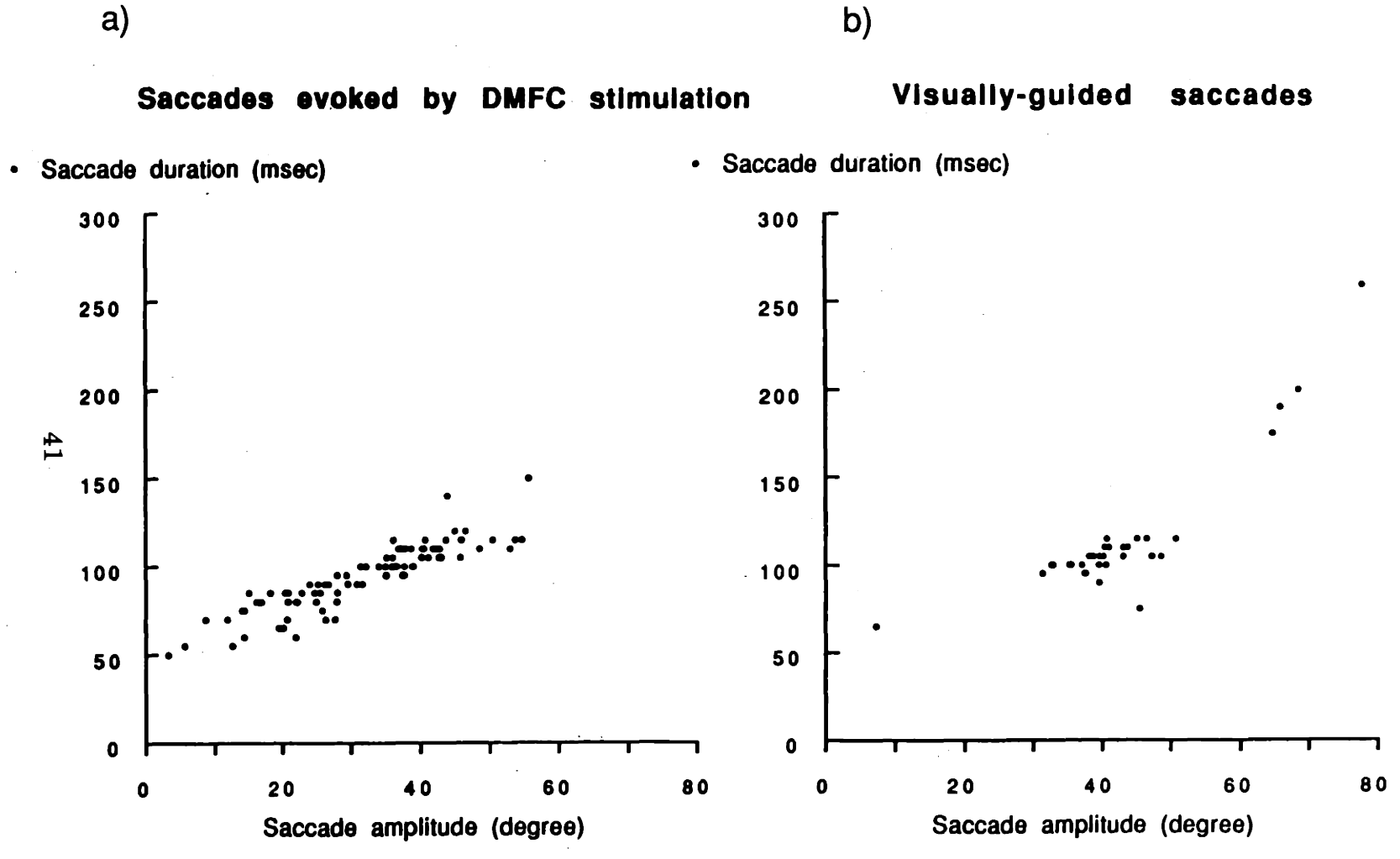
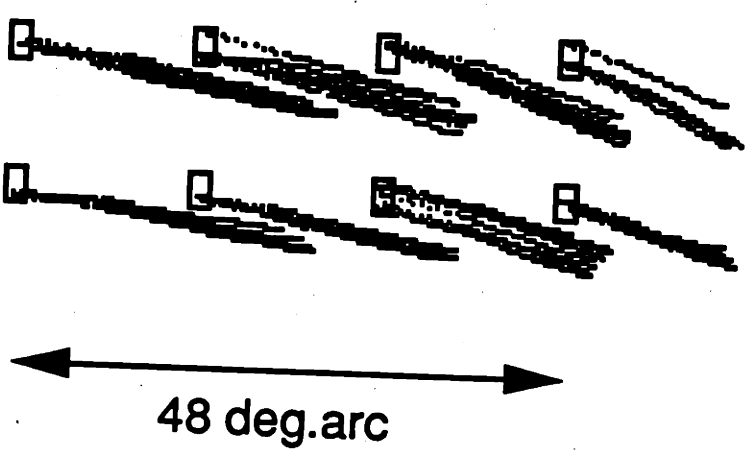

a)
Saccades evoked by DMFC stimulation
• Saccade duration (msec)
300
250
200
150
100
50
0
0
20
40
60
80
Saccade amplitude (degree)
b)
Visually-guided saccades
• Saccade duration (msec)
300
250
200
150
100
50
0
0
20
40
60
80
Saccade amplitude (degree)

Figure 2-2

Figure 2-3

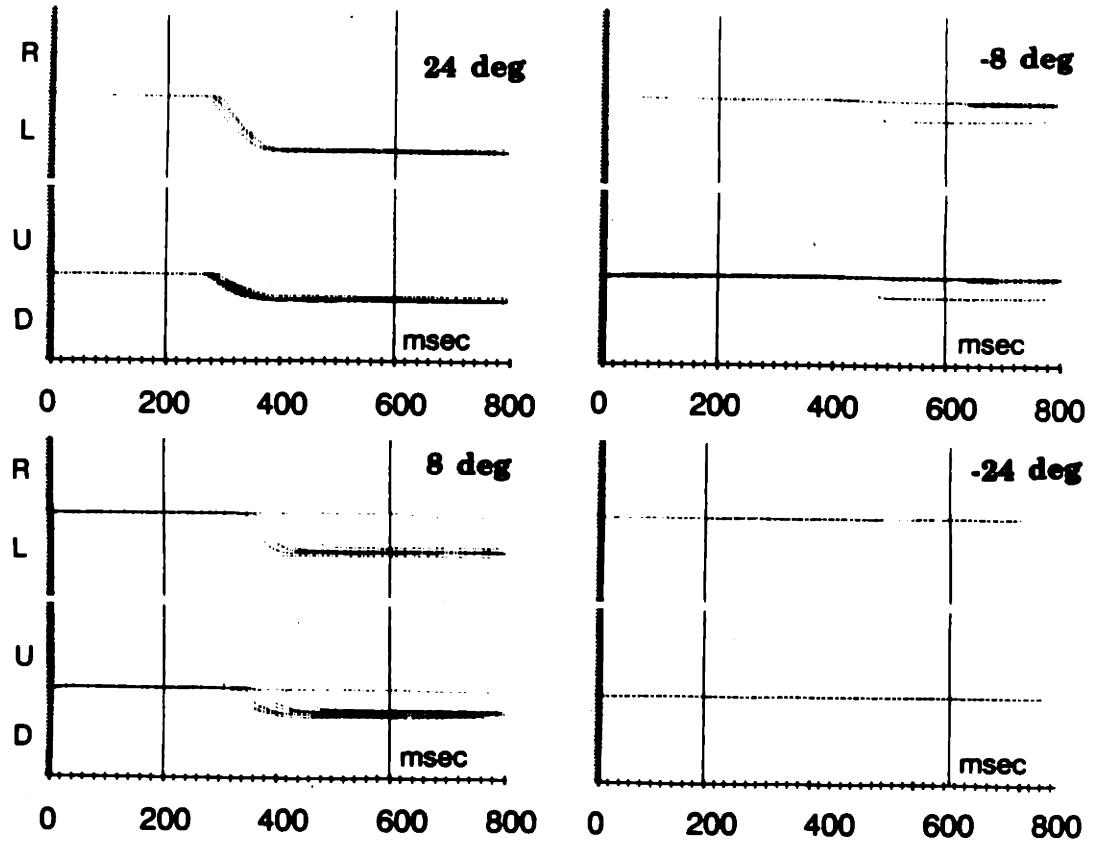
a) DMFC stimulation

b) FEF stimulation



a) DMFC stimulation

Figure 2-4



b) FEF stimulation

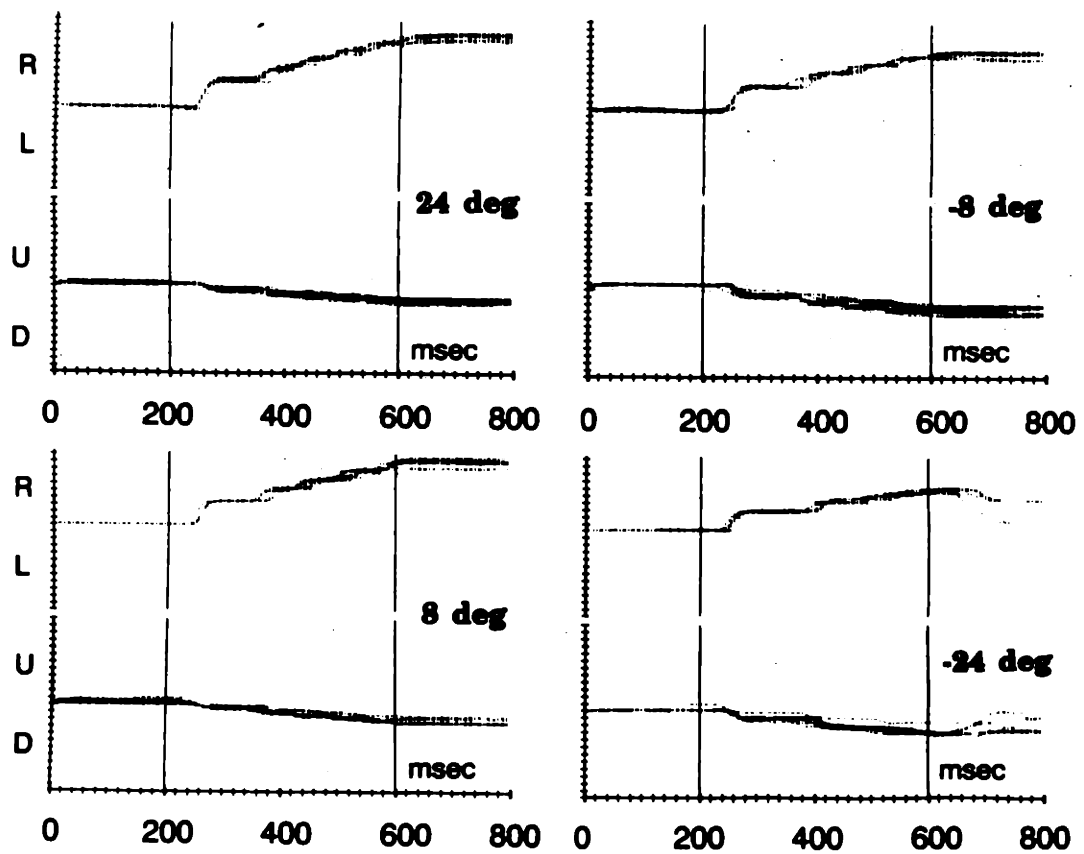
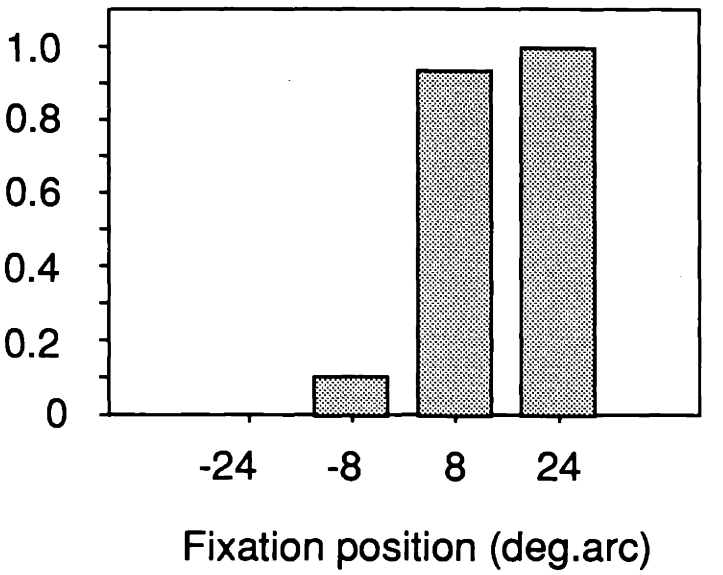


Figure 2-5

a) Probability of evoking a saccade from the DMFC



b) Probability of evoking a saccade from the FEF

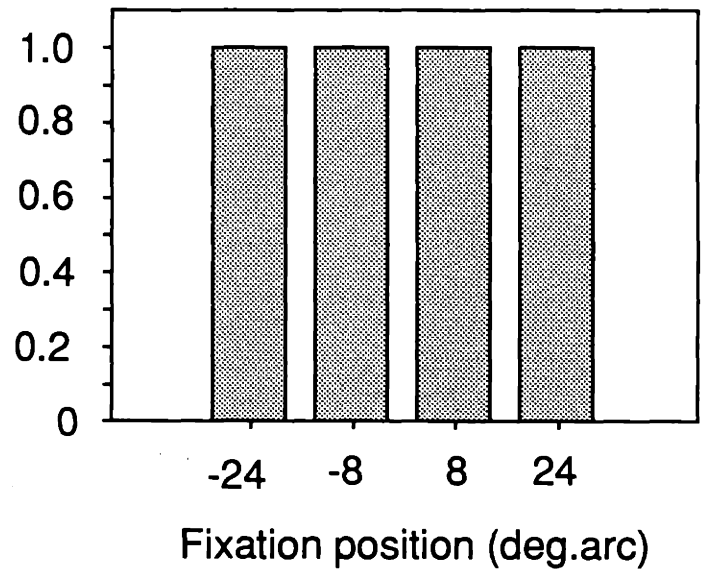


Figure 2-6

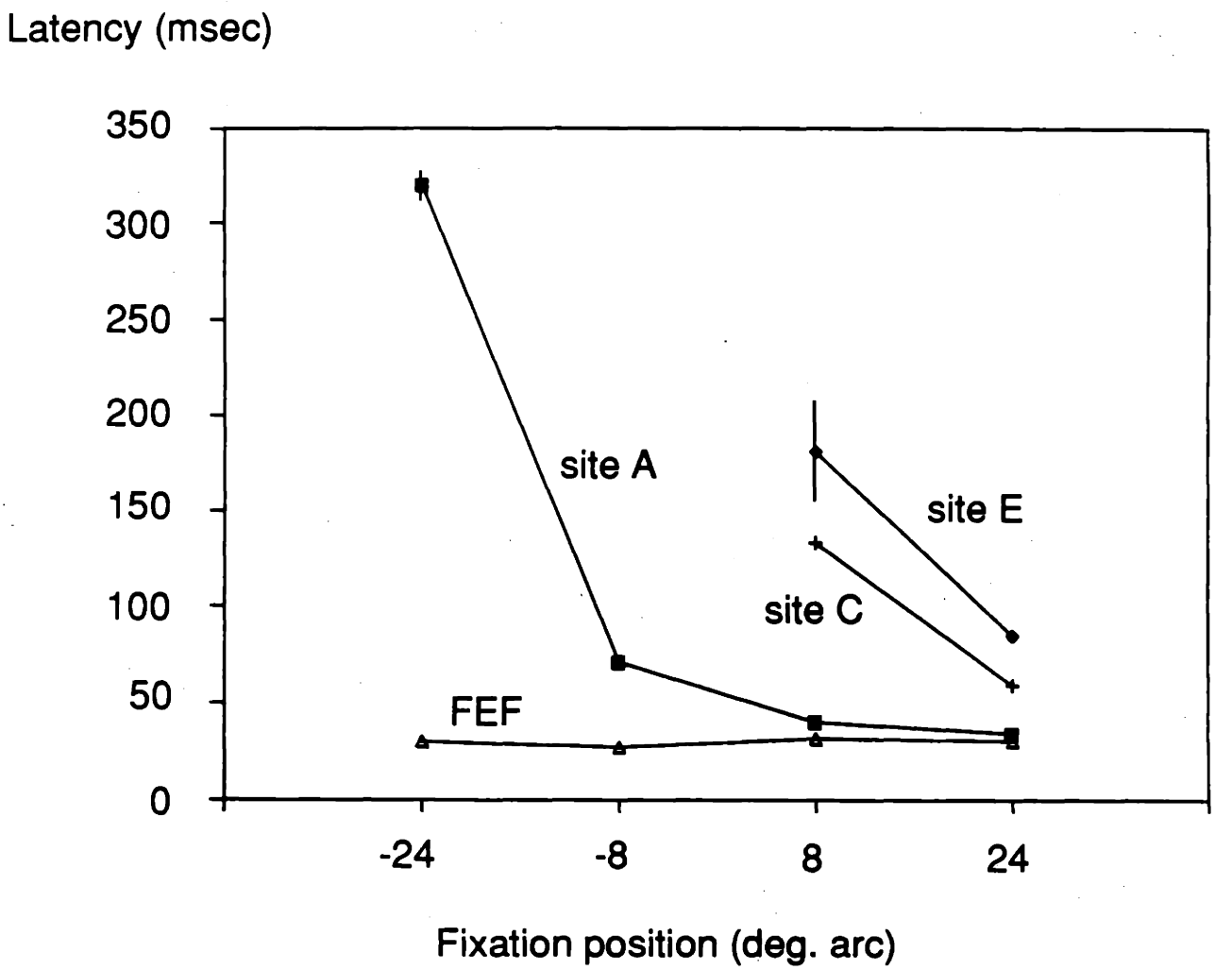

Latency (msec)
350
300
250
200
150
100
50
0
site A
site E
site C
FEF
-24
-8
8
24
Fixation position (deg. arc)

Figure 2-7

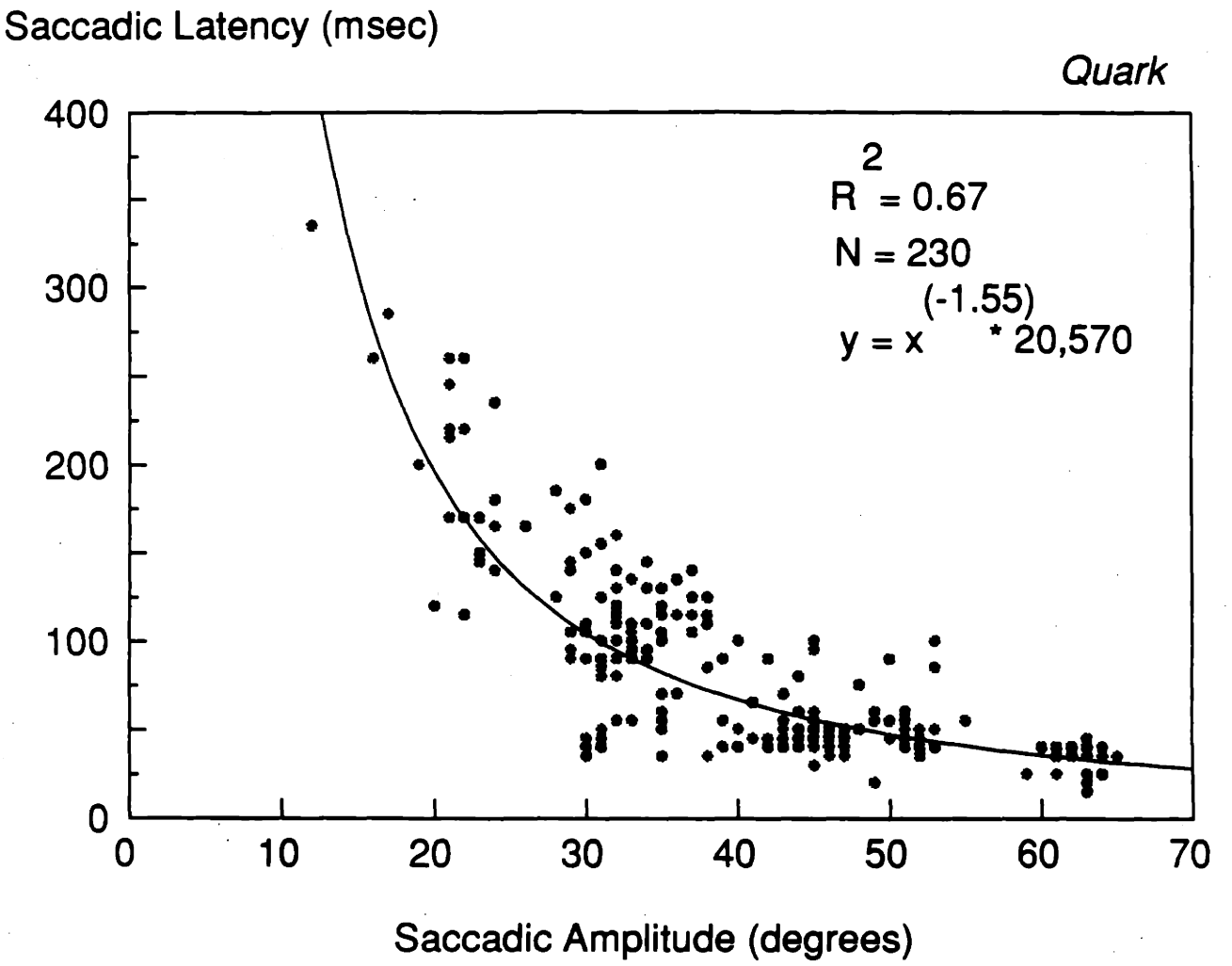

Saccadic Latency (msec)
Quark
400
300
200
100
0
0
10
20
30
40
50
60
70
2
R = 0.67
N = 230
(-1.55)
y = x * 20,570
Saccadic Amplitude (degrees)

Figure 2-8

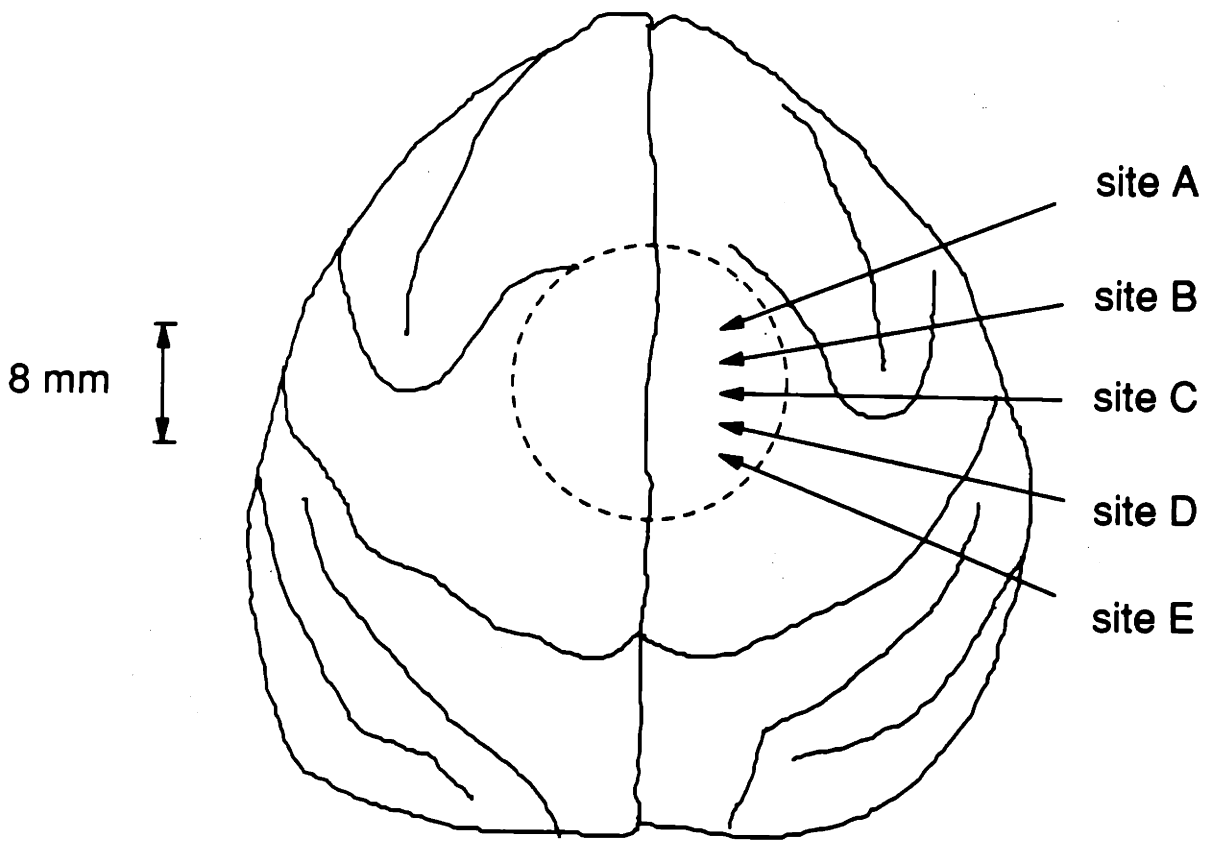


Figure 2-9

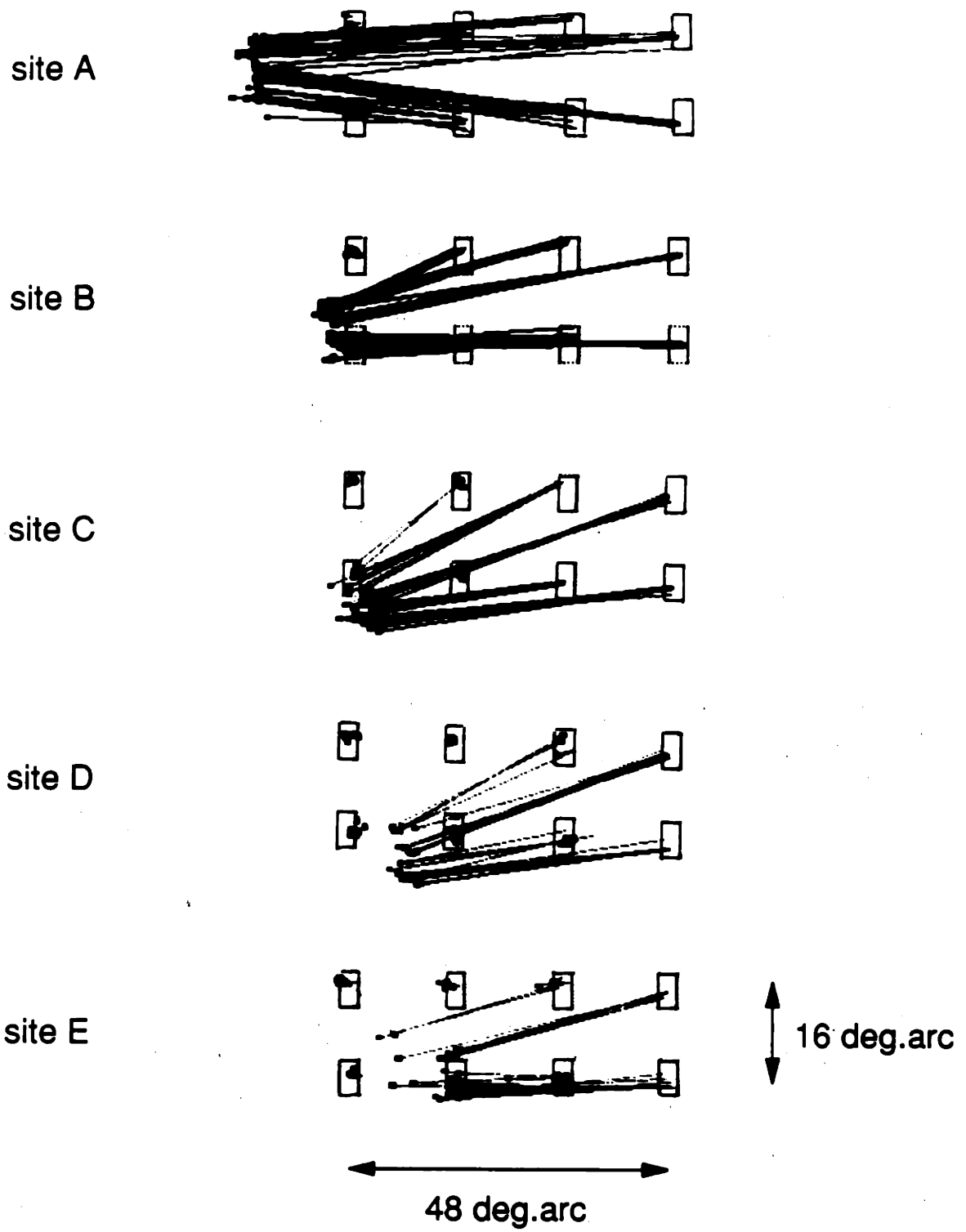


Figure 2-10

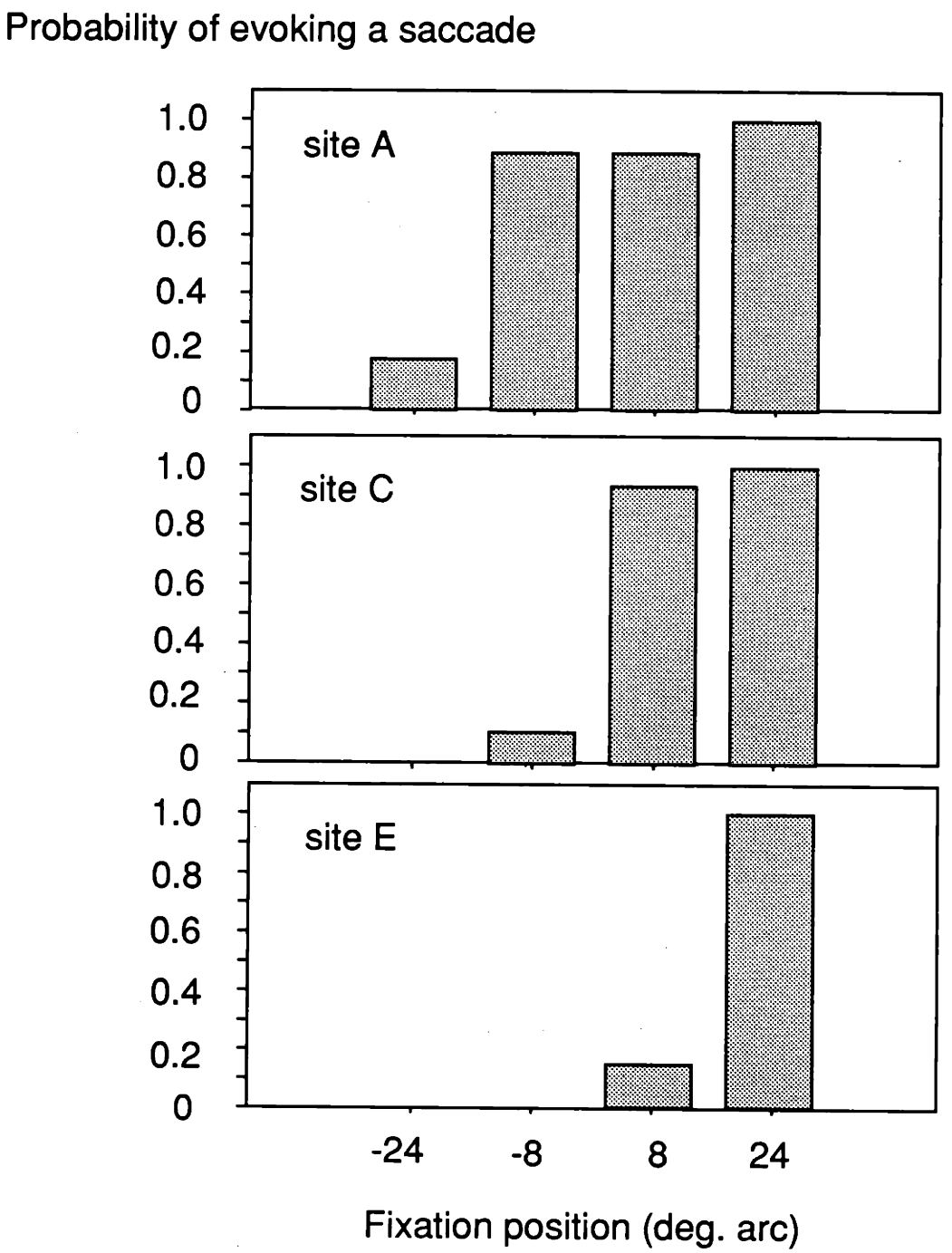

Probability of evoking a saccade
1.0
0.8
0.6
0.4
0.2
0
site A
site C
site E
-24
-8
8
24
Fixation position (deg. arc)

Figure 2-11

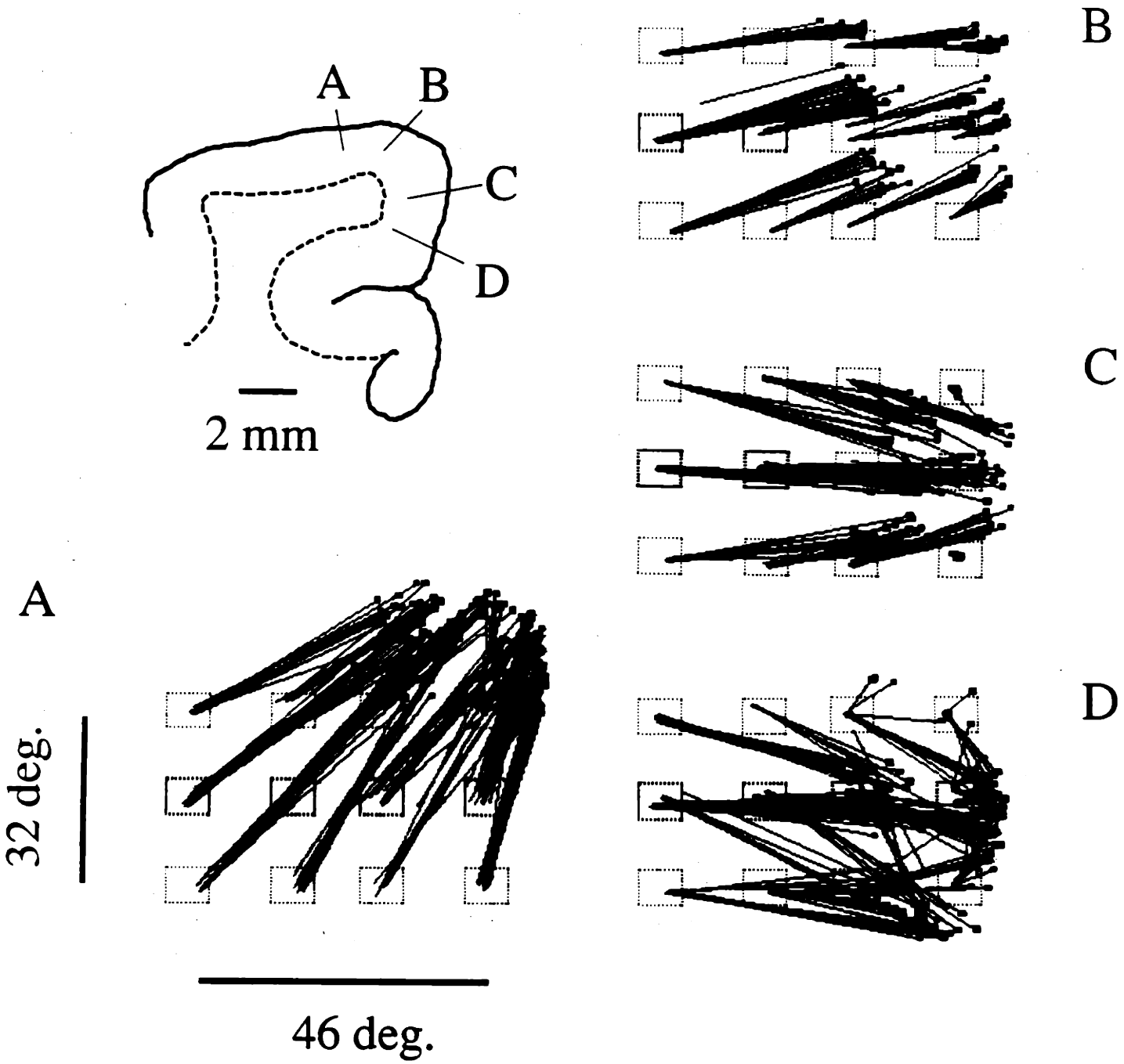


Figure 2-12

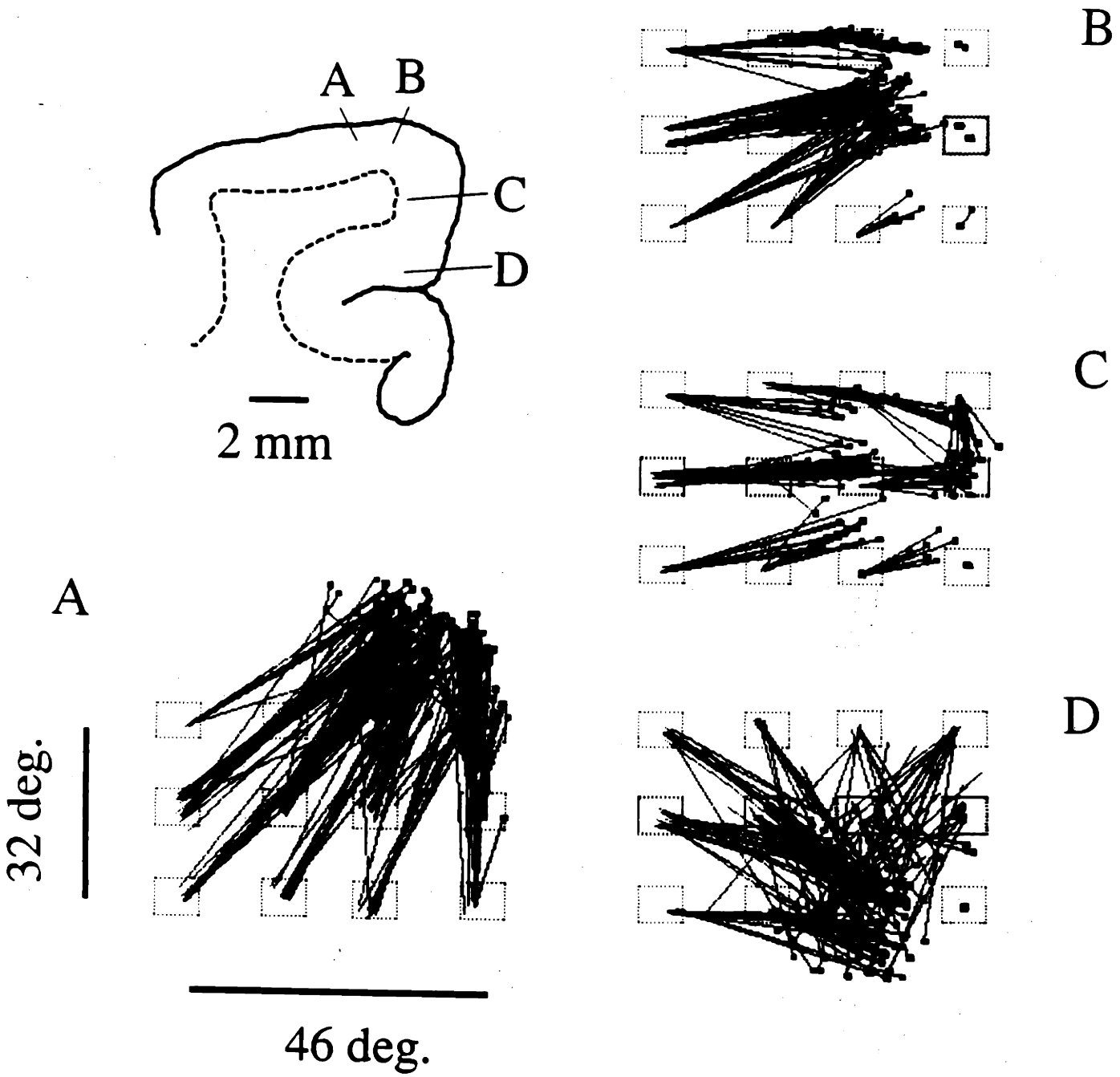


Figure 2-13

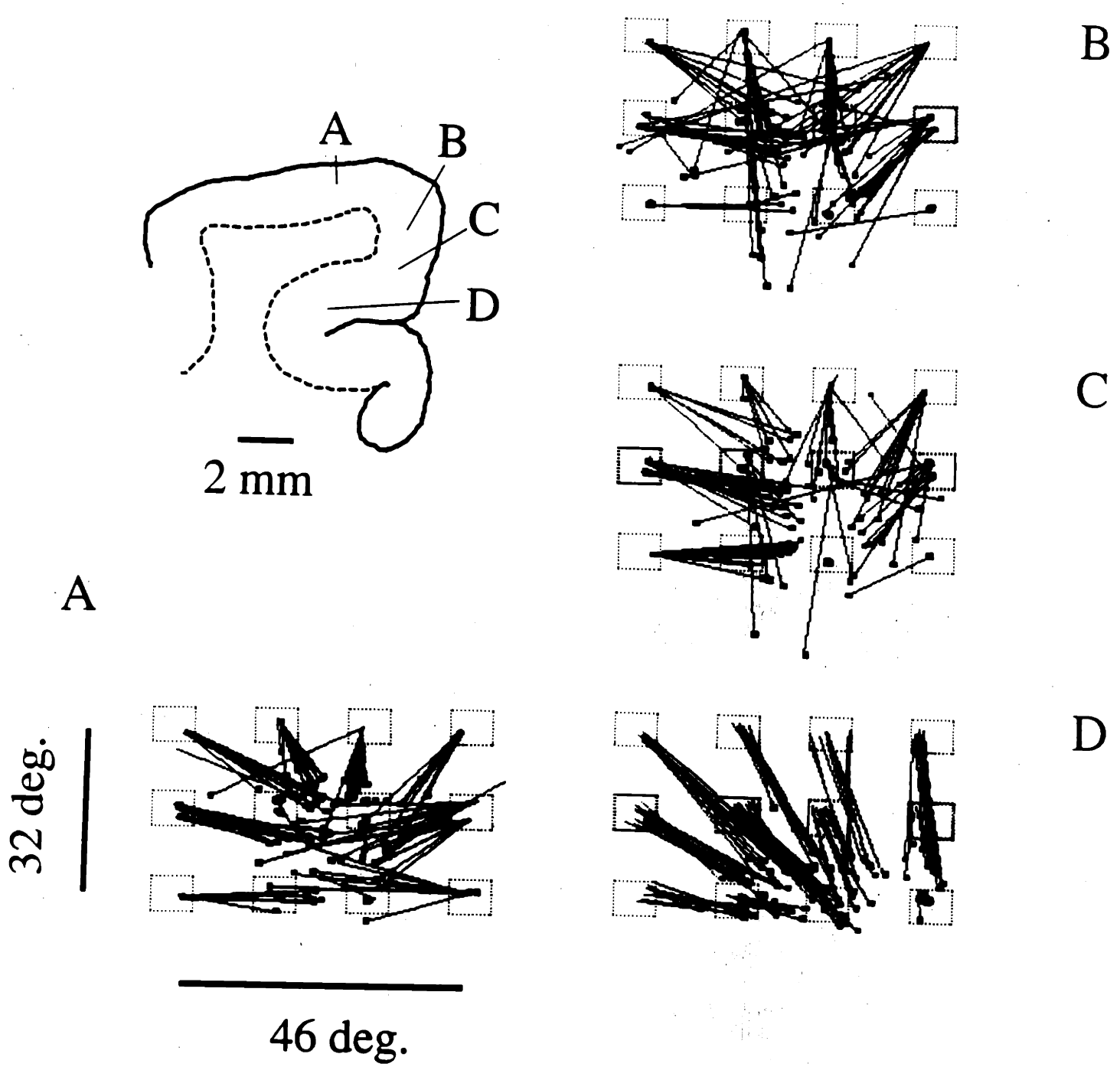


Figure 2-14

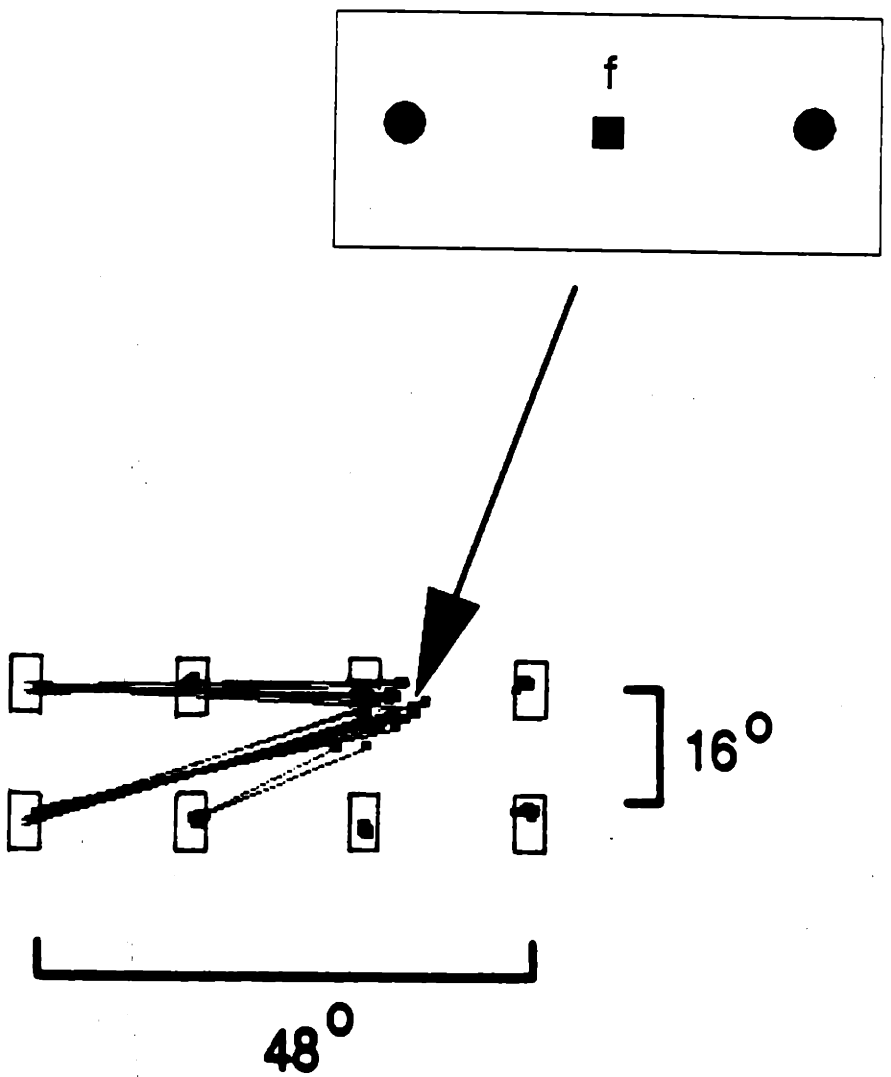


Figure 2-15

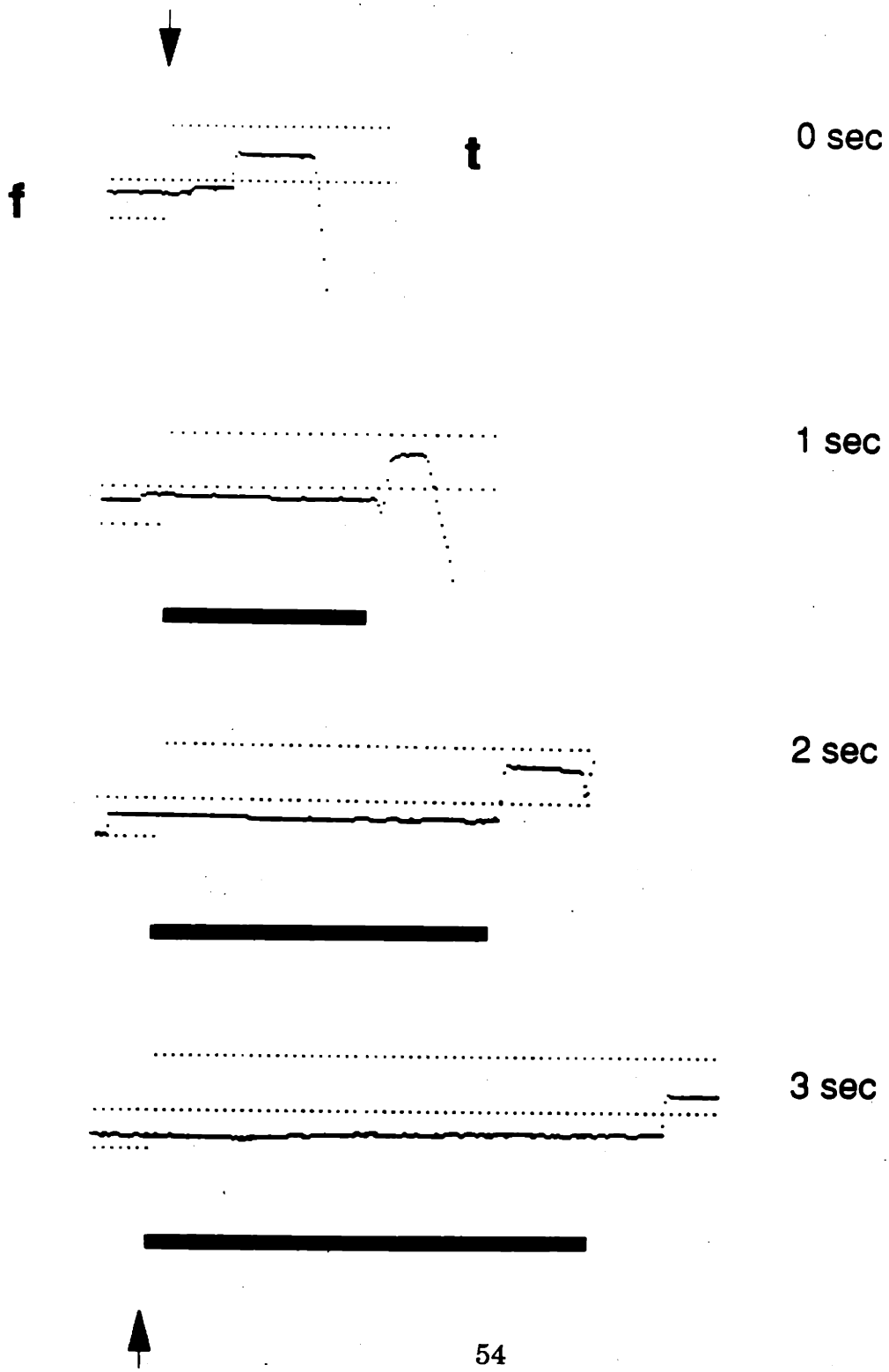
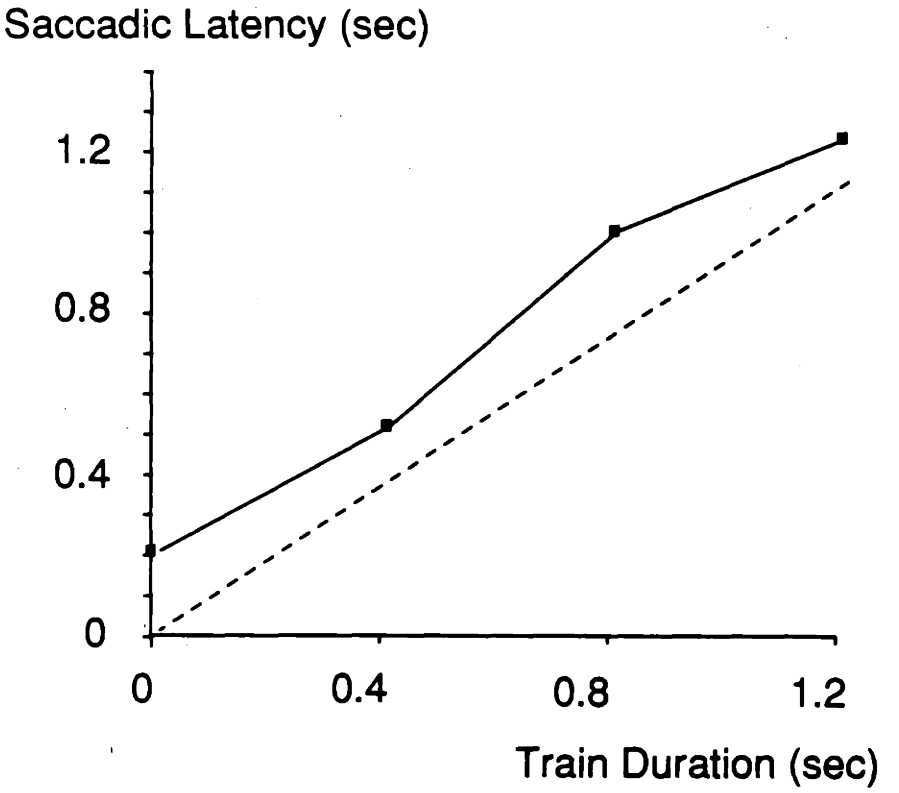


Figure 2-16

a)



b)

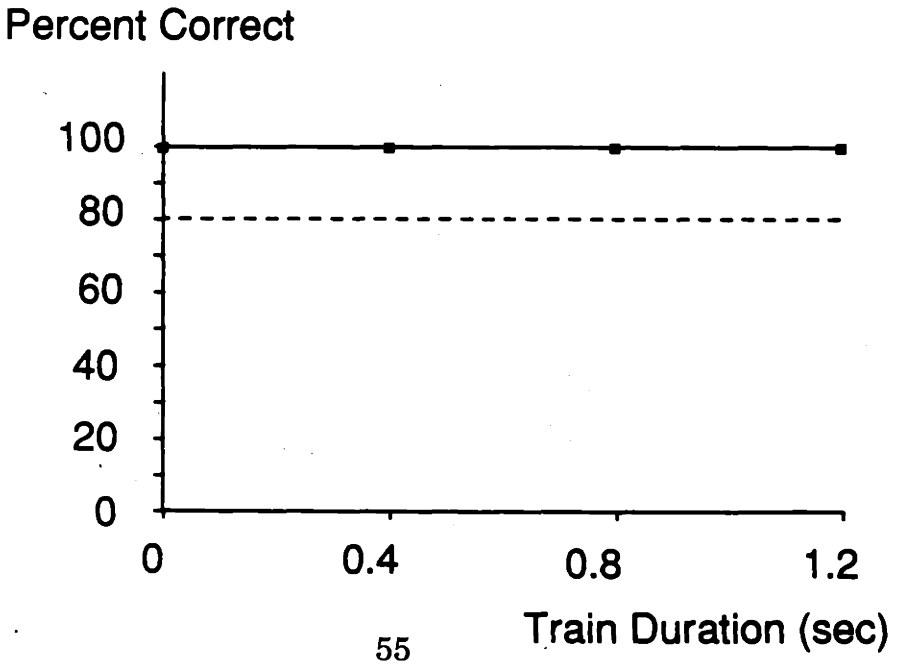


Figure 2-17

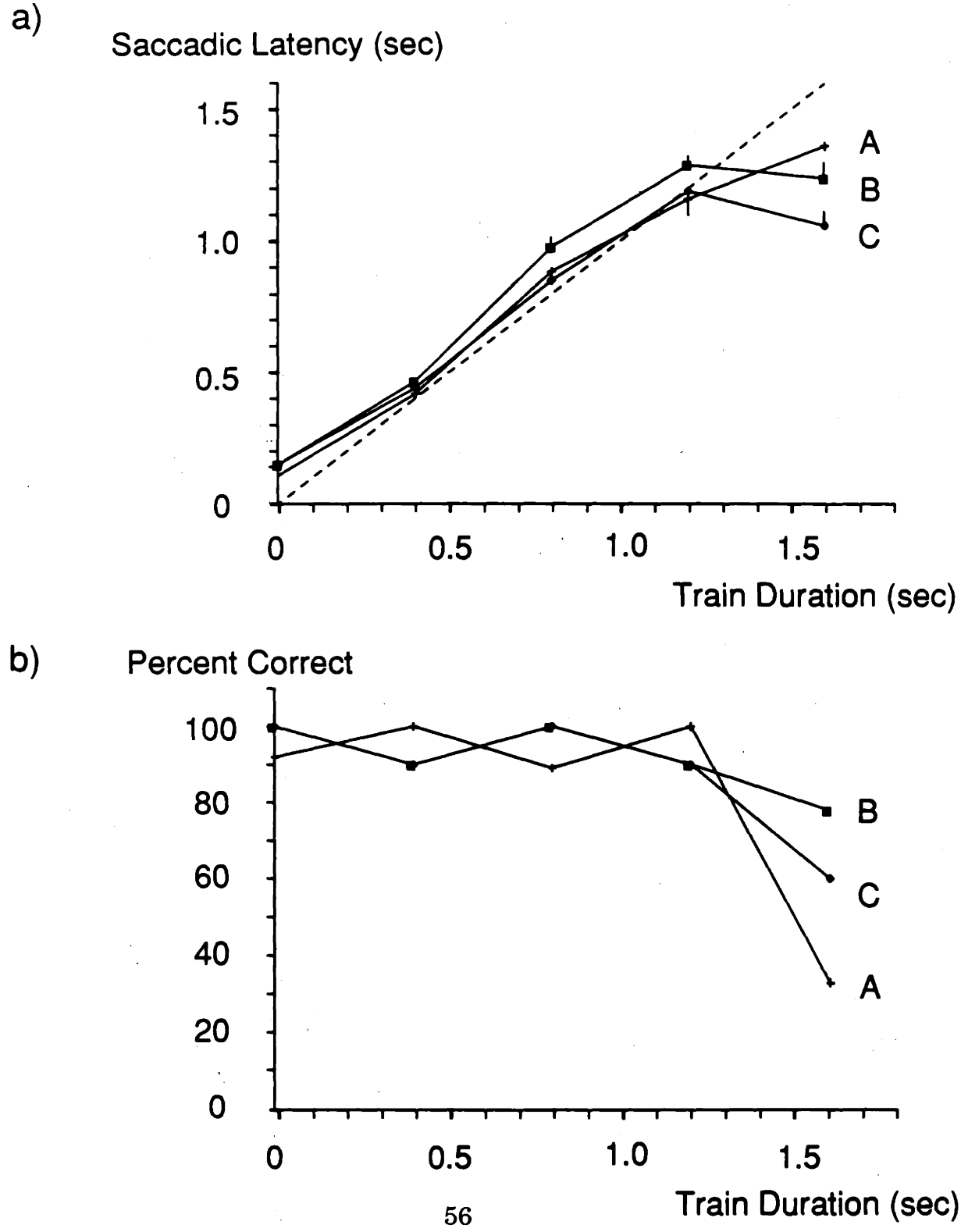
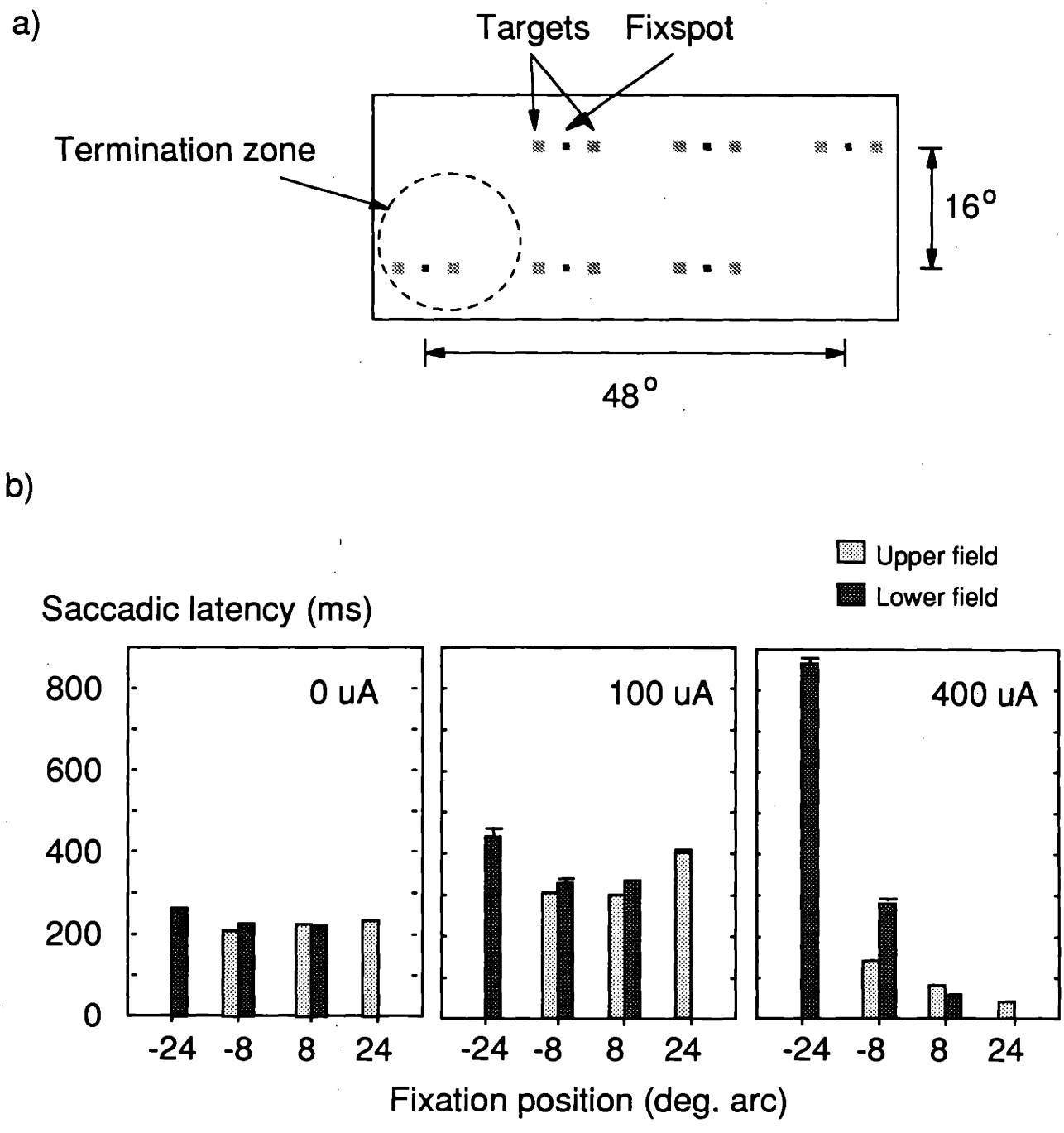

a)
Saccadic Latency (sec)
1.5
1.0
0.5
0
A
B
C
0
0.5
1.0
1.5
Train Duration (sec)
b)
Percent Correct
100
80
60
40
20
0
B
C
A
0
0.5
1.0
1.5
Train Duration (sec)

Figure 2-18


a)
Targets
Fixspot
Termination zone
16°
48°
b)
Upper field
Lower field
Saccadic latency (ms)
800
600
400
200
0
0 uA
100 uA
400 uA
-24
-8
8
24
Fixation position (deg. arc)

Chapter 3. Unit recording in the DMFC.

1. Methods.

a) Animal preparation and experimental set-up.

Three monkeys (*Macaca mulatta*), Y, A, and L, were prepared for single-unit recording as well as for electrical stimulation of the DMFC. A second recording chamber was implanted over the left FEF of Monkey L.

The reader is referred to the method section of the preceding chapter for a detailed description of the surgical procedure and other aspects of the experimental set-up.

A PDP 11/73 computer was used to record unit firing in real-time, to collect eye movements and to record other task-related events.

b) Behavioral tasks.

In an experimental session, an electrode was lowered into the DMFC. Single-unit recordings were conducted on downward passes only and electrical stimulation was conducted on upward passes. When a unit was isolated, three different tasks were used to study the unit (Fig. 3-1a, b, and c).

For all tasks, a fixation spot was presented by turning on a light-emitting diode (LED) after the intertrial interval of about 2000 msec. The animal had to fixate the fixation spot until its offset, which was the cue to make a saccade to a target. The target was given by turning on a second LED. A successful saccade to the target was rewarded with apple juice. The

interval from the start of fixation to fixation spot offset varied randomly between 800 and 1600 msec. The fixation spot and visual target were displayed using an LED board that was 60 degrees wide and 40 degrees high when put at 60 cm in front of an animal (Fig. 3-1d). The location of the fixation spot and the target were varied randomly from trial to trial. All experiments were conducted in complete darkness to prevent ambient visual cues from affecting unit activity.

The three tasks were as follows: 1) A fixation task was used in which a target was presented at the time of fixation spot offset (Fig. 3-1a). This paradigm was used to study the fixation-position dependency of a unit. 2) A delayed-saccade task was used in which a target was presented 400 msec after the animal acquired the fixation spot and the target remained on until the end of the trial (Fig. 3-1b). The interval between target onset and fixation spot offset, the hold time, was varied from 400 to 1200 msec. With this paradigm the visual response of a unit to the presentation of a target could be separated from the unit activity related to eye movements. 3) A memory-guided-saccade task was used in which a target was presented for 100 msec while the animal was fixating at a fixspot (Fig. 3-1c). At fixation spot offset, the animal had to make a saccade to the remembered location of the target. This paradigm was tried only on units that had activity correlated with target presentation rather than eye movement in order to see if the activity related to target presentation was sustained after target offset.

Comparing the activity profiles obtained by using the three different tasks allowed us to determine whether a unit was correlated with fixation, with the onset of a target, with fixation spot offset, or with saccadic eye movements, or some combination of each.

c) Analysis of unit activity.

An average firing frequency (spikes/sec) of a unit was computed for each of the following intervals: (1) the intertrial interval from the start of a trial to the time of fixation spot onset; (2) the fixation period from the time the animal fixates at the fixation spot to the time the spot disappears; and (3) the saccade period from the fixation spot offset until the end of a saccade to the target.

The firing frequency of a unit during the intertrial interval was used as the baseline activity of the unit. Unit activity was correlated with fixation behavior if the activity during the fixation period differed by one standard deviation from the baseline activity. Similarly, unit activity was correlated with saccades if the activity during the saccadic period differed by one standard deviation from the baseline activity.

d) The fixation-position index.

Once data were collected for a unit, fixation-position dependency of a unit was quantified by computing the fixation-position index (FI) for the unit

by the following equation:

$$FI = (f_c - f_i) / (f_c + f_i).$$

where f_c and f_i are the firing frequencies (spikes/sec) of a unit for fixation at a fixation spot in the contralateral and ipsilateral hemifields, respectively. FI can vary between +1 and -1. An FI of +1 means that the unit fired only when the animal fixated in the contralateral hemifield, whereas an FI of -1 indicates that the unit fired only when the animal fixated in the ipsilateral hemifield[1].

To analyze FI for a group of units, a mean and a standard deviation of FI's were calculated for the group. Assuming that all DMFC units are excitable equally by electrical stimulation, all units that were recorded from a site were included in the calculation of FI for the group of units, regardless of their individual response characteristics.

---

[1] The FI is just one way of quantifying the effect of eye position on unit activity, given the limited number of fixation positions tested. It simply reflects the ratio of unit activity between the fixation at the contralateral and ipsilateral positions. The FI is very useful for the analysis of the DMFC units because the 'position' field of most units were not clearly defined but the unit activity changed monotonously as a function of eye position at the first level of approximation.

Note that when the FI is zero it is ambiguous whether the unit activity does not show eye-position dependency or the computation of FI does not include the optimal position for the unit, e.g. the center position. It is our observation, however, that there is few, if any, units in the DMFC that have their optimal position around the center. Therefore, it is safe to say that, if FI is zero, the unit does not show eye position dependency in the horizontal dimension. Nevertheless, such units may well be tuned in the vertical dimension instead.

2. Response characteristics of units in the DMFC.

A total of 274 units were recorded from the DMFC's of three animals. In characterizing the responses of these units, fixation and saccadic eye movement were the focus of our study. Examples of typical DMFC units that were modulated by the tasks are shown in Figures 3-2 to 3-4.

Figure 3-2 shows the firing of a DMFC unit that had activity modulated by the animal's fixation behavior. The rasters of unit activity are aligned with respect to various events of the fixation task. The unit became active when the animal fixated a fixation spot. When the animal made a saccade to a target, the activity dropped to baseline. Note that the activity started about 100 msec after the onset of the fixation spot, but preceded the acquisition of the spot. The temporal relationship between the onset of unit activity and the fixation, however, varied considerably from unit to unit. In about a half (49%, 41/84) of DMFC units that had activity modulated by fixation, the onset of activity preceded the acquisition of the fixation spot[2].

In Figure 3-3 are other examples of units that were modulated by fixation. The activity was correlated with fixation for all of these units, but the temporal patterning of the activity was variable among them: some

[2] The temporal patterning of unit activity varied from one unit to another and the onset time changed as a function of fixation position for some units. Therefore, we determined whether the activity onset occurred before or after the acquisition of the fixation spot, without attempting to measure the exact interval between the two events.

exhibited sustained activity throughout the fixation period (Fig. 3-3a); others exhibited activity that increased gradually until a saccade was made (Fig. 3-3b); and still other units reached the maximum rate of firing at the start of fixation and the activity declined over the fixation period (Fig. 3-3c). Units that were inhibited during fixation were also found (Fig. 3-3d). Such inhibitory units were very active during the intertrial interval when the animal was waiting for a fixation spot to appear. As soon as the animal made a saccade to the spot, they became silent. When fixation was interrupted by a saccadic eye movement, the activity level returned to baseline. Quite often inhibitory units were found near excitatory units.

Most common in the DMFC were the types of fixation units that had activity sustained or increased during fixation, although the proportion of such units could be known only roughly because there were many units that fell between the categories.

Among the heterogeneous units in the DMFC, the activity of some units was correlated predominantly with saccadic eye movements (Fig. 3-4)[3], as has been described by earlier investigators (Mann et al. 1988; Schlag and Schlag-Rey 1987; Shall 1991). Most saccade units were direction-selective

[3] It should be noted that, although the activity profile of these saccadic units looks similar to that of inhibitory fixation units (Fig. 3-3d), they are very different from each other when their activity during the intertrial interval is compared. Saccadic units get more active than the baseline activity when the animal makes a saccade to a target, whereas the activity of inhibitory fixation units returns to baseline with the interruption of fixation by saccades.

and also tuned for the saccadic amplitude. These units were driven best by saccades larger than twenty degrees of visual angle[4]. Saccade units were better correlated with eye movements than with the target onset (compare Fig. 3-4b and c). There were some saccade units, however, that had activity related to target onset as well.

A majority (74%, 202/274) of DMFC units had responses modulated by fixation and/or saccadic eye movement (Table 3-1). Of the total 274 units, 167 units showed change in activity during fixation (61%), 139 units showed change in activity during saccadic eye movement (51%) including 104 units that were modulated by both fixation and saccadic eye movement (38%).

For comparison, we recorded from the left FEF of Monkey L. Of the total 41 units recorded, a vast majority (73%, 30/41) were modulated by saccades. This is consistent with what previous investigators of this area had found (Bizzi 1968; Bizzi and Schiller 1970; Bruce and Goldberg 1985). Units that showed change in activity during fixation were significantly less in the frontal eye field (41%, 17/41) than in the DMFC (61%, 167/234) ($p < 0.05$). Of these units with modulation by fixation, 12 units were modulated by saccadic eye movement as well (29%, 12/41). Furthermore, it is noteworthy

[4] For this reason, it was difficult to obtain the direction tuning curve for most DMFC units and test whether the direction tuning changed as a function of eye position. Nevertheless, the unit activity related with saccades of the same amplitude and direction were observed to change depending on the initial eye position, as had been observed for units in the posterior parietal cortex (Andersen et al. 1990).

that none of the fixation units that we recorded from the FEF had activity sustained or increased over the fixation period, whereas such types of units were predominant in the DMFC.

3. Fixation-position dependency of DMFC units.

The activity of fixation units in the DMFC as described above depended upon the position of fixation in visual space. A typical example of such dependency is shown in Figure 3-5. The optimal fixation-position, where the unit fired maximally, was at 30 degrees to the right and 20 degrees below the center of visual space, position E of Figure 3-1d. In Figure 3-6, the firing frequency during fixation period is plotted as a function of fixation position, for another unit. The unit activity increased abruptly beyond 20 degrees arc to the right. This profile of unit activity resembling a step-function was typical of most DMFC units.

The fixation-position dependency manifested itself in a number of different ways depending on the different activity patterns that were described in the previous section. If a unit had an increasing pattern of activity (as in Fig. 3-3b), the fixation-position dependency affected the time between the acquisition of the fixation spot and the onset of activity build-up, such that for the optimal fixation position this period was shorter than for the non-optimal fixation positions (compare Fig. 3-7a and b). When a unit happened to be of the inhibitory type as was the example in Figure 3-3d, the degree of inhibition changed as a function of fixation-position (compare Fig. 3-7c and d). The fixation position of the lowest activity was considered the optimal fixation position for such a unit.

In Figure 3-8 we present an example of a unit that had memory-like properties, something similar to units in the prefrontal cortex (Fuster 1973). The unit activity related with target onset persisted for the duration of fixation, regardless of whether the target was presented briefly (Fig. 3-8b) or maintained (Fig. 3-8a). Such memory-like activity was also subject to the influence of fixation position. The unit activity related to the target onset was much higher when the fixation spot and the target were in the right hemifield (Fig. 3-8d) than when it was in the left hemifield (Fig. 3-8c). These kinds of units were rare in the DMFC (2/234).

4. The distribution of fixation-position dependent units in the DMFC: Comparison with results of electrical stimulation.

Given that 61% of units in the DMFC were modulated by fixation position, we set out to see whether the distribution and position tuning of such units is congruent with the results obtained by the electrical stimulation of the region. Electrical stimulation recruits all excitable elements within the volume of tissue where the current density exceeds the threshold of excitation. Assuming that units recorded are recruited equally by electrical stimulation, a population analysis of units found at a DMFC site seems more appropriate, than dwelling on individual properties of units found at various sites. A population analysis allows for a better comparison with the result of electrical stimulation. After we computed the individual FI of each unit among a group of units recorded from a DMFC site, an average and standard error of these FI's were calculated to serve as an estimate of the overall position tuning of the group of units at the site.

The result of such an analysis for monkey A is plotted in Figure 3-9. The group FI changed as a function of the rostro-caudal location of a DMFC site, with positive FI at rostral sites and negative FI at caudal sites. A positive FI indicates that the group of units at the site was most active when the animal fixated in the contralateral hemifield, whereas a negative FI indicates that that group was most active when the fixation was in the

ipsilateral hemifield. Therefore, this is consistent with results obtained by electrical stimulation where the termination zone of evoked saccades was in the contralateral side for rostral sites and in the ipsilateral side for caudal sites. Eye movement traces obtained by stimulation of the DMFC sites are provided in the bottom of the figure. The correspondence between the FI changes and the location of termination zone of stimulation-evoked saccades was observed over the rostrocaudal axis of the DMFC in monkey Y that was also tested with this analysis.

Table and Figures.

TABLE 3-1. The number and percentage of units recorded from the DMFC and FEF are listed. Units are classified by their responses correlated with fixation and saccadic eye movements. Units that have activity modulated by fixation are further classified by their activity during saccadic eye movements.

	DMFC	FEF
Fixation unit	202 (74%)	17 (41%)
without saccadic activity	98 (36%)	5 (12%)
with saccadic activity	104 (38%)	12 (29%)
Saccade unit	35 (13%)	18 (44%)
Uncorrelated	37 (14%)	6 (15%)
Total	274 (100%)	41 (100%)

Figure legends.

FIG. 3-1. (a)-(c) Three behavioral tasks were used to study units. Each plate, (a) a fixation task, (b) a delayed-saccade task and (c) a memory-guided-saccade task, shows the onset and offset of a fixation spot and a target depicted by the shifts of corresponding lines. Eye movement is also depicted by a line to show its approximate occurrence relative to the time of the cues. The time periods during which the firing frequency of a unit is computed are also marked: ITI is the intertrial interval from the start of a trial to the onset of a fixation spot; FP is the fixation period from the start of the fixation to the fixation spot offset; SP is the saccade period from the end of fixation period to the end of a saccade made to the target; and HT is the hold time between a target onset and the offset of a fixspot. ITI, FP, and HT were 2000 msec, 1200 msec (ranging from 800 to 1600 msec), and 800 msec (ranging from 400 to 1200 msec), respectively. FP and HT were randomly varied from trial to trial, as were the locations of the fixation spot and target.

(d) A drawing illustrates the position of five LED's (light-emitting diodes) that were used to present the fixation spot and target.

FIG. 3-2. An example of a unit whose activity was modulated by the fixation behavior is shown. Rasters of the unit firing are shown aligned with respect to the onset of the fixation spot (a), the fixation at the fixation spot

(b), the onset of a target (c), and the saccade to the target (d). Each panel also contains the firing frequency curve, and traces of horizontal eye movements. The fixation spot was at the right-bottom of the visual field, position E of Figure 3-1d.

FIG. 3-3. Examples of units that had activity modulated by fixation are shown. Each panel of this figure and the following figures contains rasters of unit firing, the firing frequency curve, and traces of horizontal eye movements, all aligned on the start of saccadic eye movements to a target (unless stated otherwise). The target onset is indicated by a longer tick mark on the unit raster. The locations of the fixation spot and target are written at the bottom of each panel.

Four types of units are illustrated: (a) a unit that showed increased activity while the animal fixated at a fixspot and remained active during the fixation period; (b) a unit whose activity was increased gradually during the fixation period; (c) a unit whose activity declined during the fixation period; and (d) a unit that had activity inhibited throughout the fixation period.

FIG. 3-4. (a) A unit whose activity was best correlated with saccadic eye movements is shown. The peak activity of the unit occurred at the start of the saccades. Another saccade unit that was tested with the fixation task (b) and the delayed-saccade task (c) is illustrated.

FIG. 3-5. Raster display shows unit firing modulated by fixation at one of the five fixation positions as shown in Figure 3-1d. The data were obtained from the same unit as in Figure 3-2.

FIG. 3-6. The firing frequency during the fixation period is plotted as a function of fixation position, for a unit that had activity modulated by the fixation.

FIG. 3-7. Raster display shows the activity of a unit that increased during the fixation period when the fixation was in the ipsilateral hemifield (a) or when the fixation was in the contralateral hemifield (b).

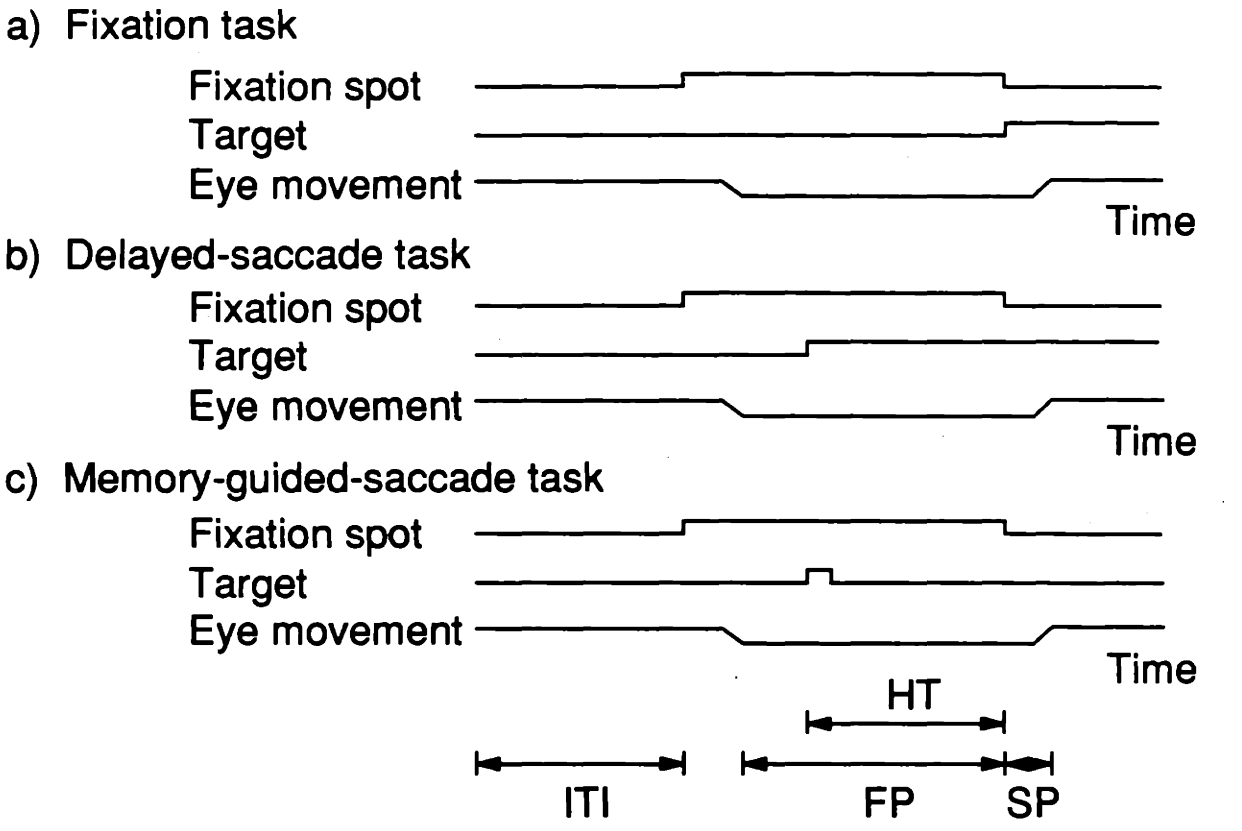
Raster display of another unit that had activity inhibited during the fixation period when the fixation was in the ipsilateral hemifield (c) or when the fixation was in the contralateral hemifield (d) is shown.

FIG. 3-8. An example of a unit that had memory-like activity. The unit activity related with target presentation was not different whether the target was continuously visible (a) or turned off 100 ms after the onset (b). The onset and offset of the target are marked by the first and the second taller tick marks on the rasters of unit firing. The rasters are aligned with respect to the target onset. The unit activity of the same unit was recorded with the fixation spot on the left side (c) or on the right side (d). The target

was presented at the same retinotopic location, straight up from the fixation spot, in both cases.

FIG. 3-9. (a) FI of a group of units is plotted as a function of the rostro-caudal location of the units. An average FI of 8 to 10 units found at each DMFC site of monkey A is illustrated. Standard error bars are shown. These data are-statistically significant according to correlation analysis ($n = 48$, $p < 0.01$). (b) Each panel shows saccades evoked by electrical stimulation of the corresponding DMFC site. The saccades started from the five fixation positions as illustrated in Figure 3-1d.

Figure 3-1


a) Fixation task
Fixation spot
Target
Eye movement
Time
b) Delayed-saccade task
Fixation spot
Target
Eye movement
Time
c) Memory-guided-saccade task
Fixation spot
Target
Eye movement
Time
HT
ITI
FP
SP

d)

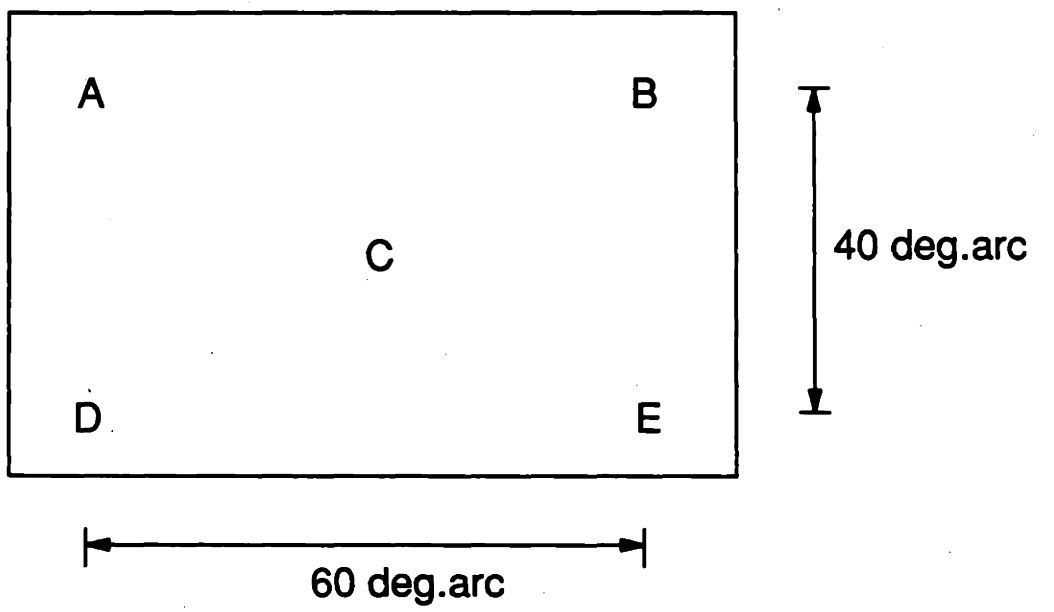

A
B
C
D
E
40 deg.arc
60 deg.arc

Figure 3-2

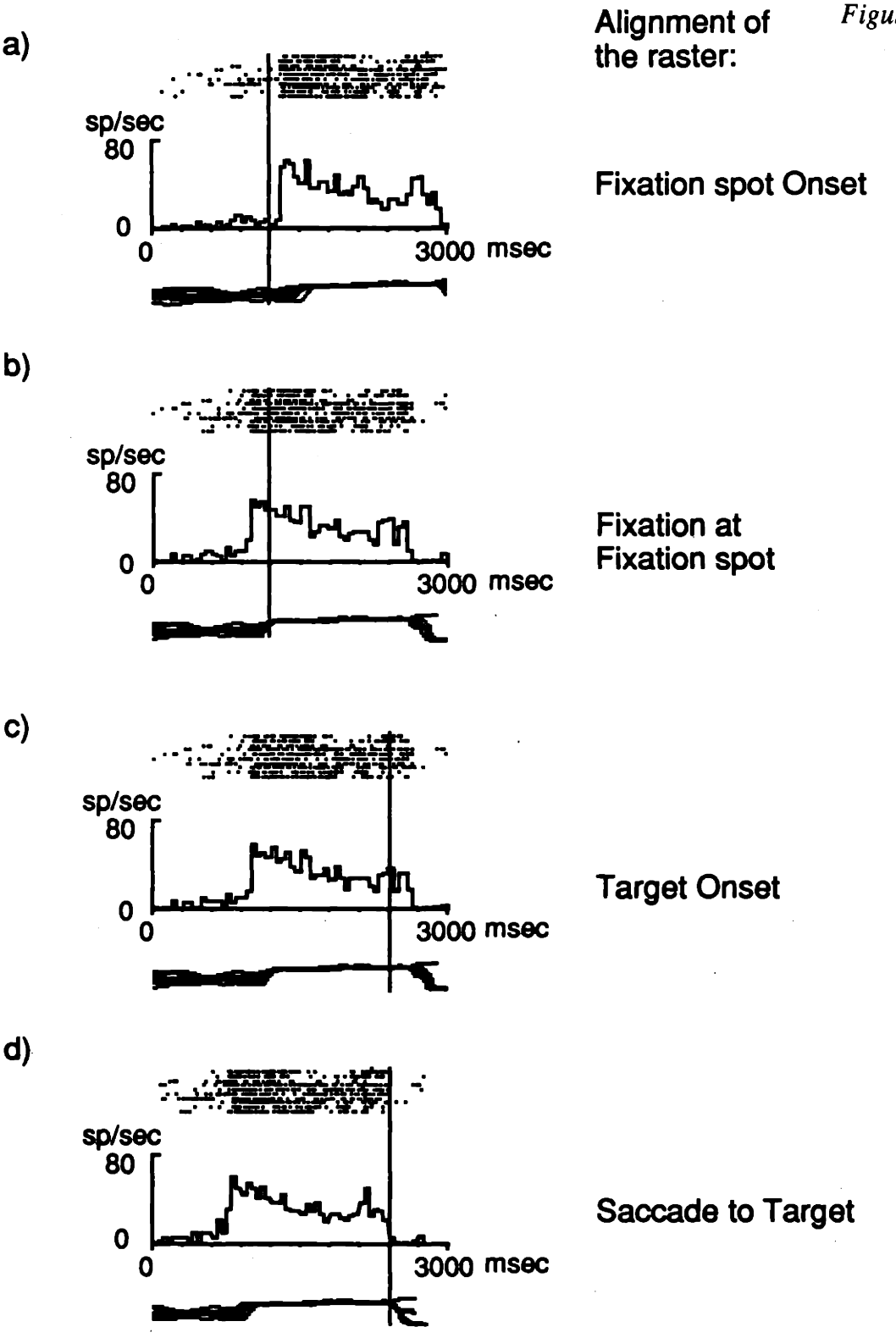
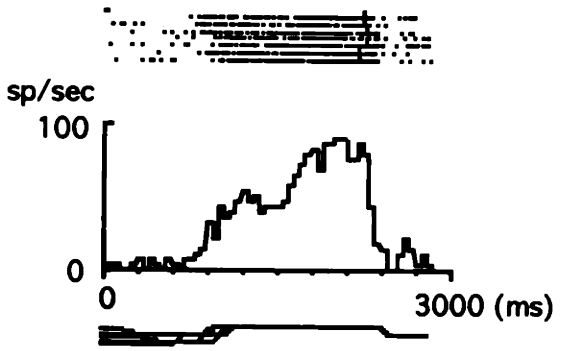

a)
sp/sec
80
0
0
3000 msec
Alignment of the raster:
Fixation spot Onset
b)
sp/sec
80
0
0
3000 msec
Fixation at Fixation spot
c)
sp/sec
80
0
0
3000 msec
Target Onset
d)
sp/sec
80
0
0
3000 msec
Saccade to Target

Figure 3-3

a)

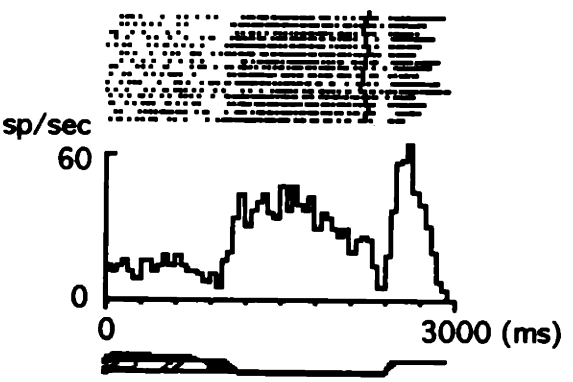
Fixation spot at Center
Target at Right-top

b)



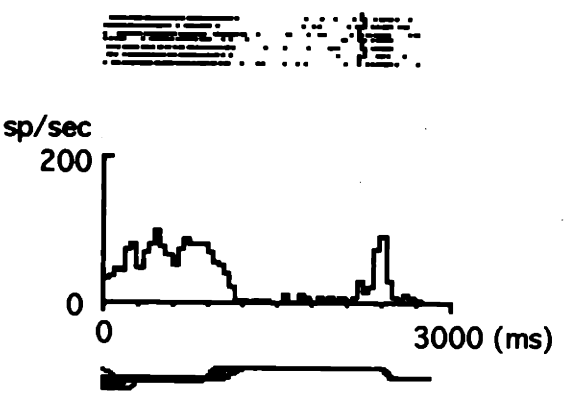
Fixation spot at
Right-bottom
Target at Center

c)



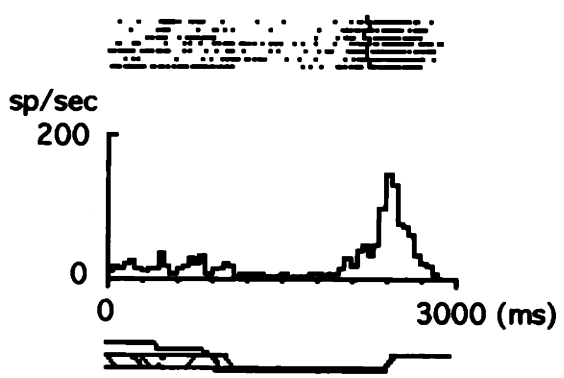
Fixation spot at Center
Target at Left-bottom

d)

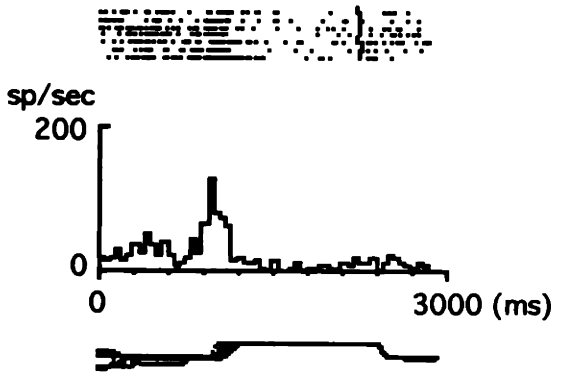


Fixation spot at Right-top
Target at Center

a)

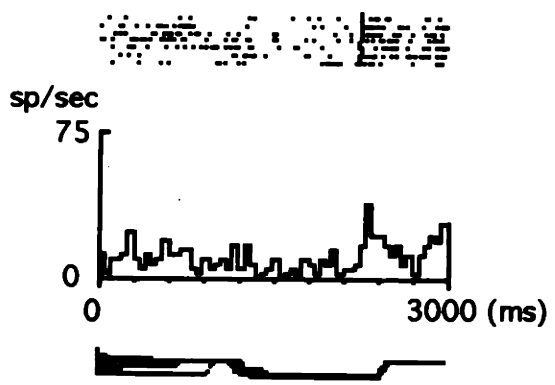


Fixation spot at Left-bottom
Target at Center

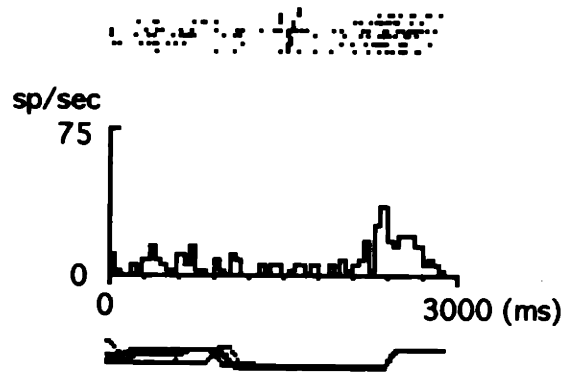


Fixation spot at Right-top
Target at Center

b) Fixation task



c) Delayed-saccade task



Fixation spot at Left-bottom
Target at Center

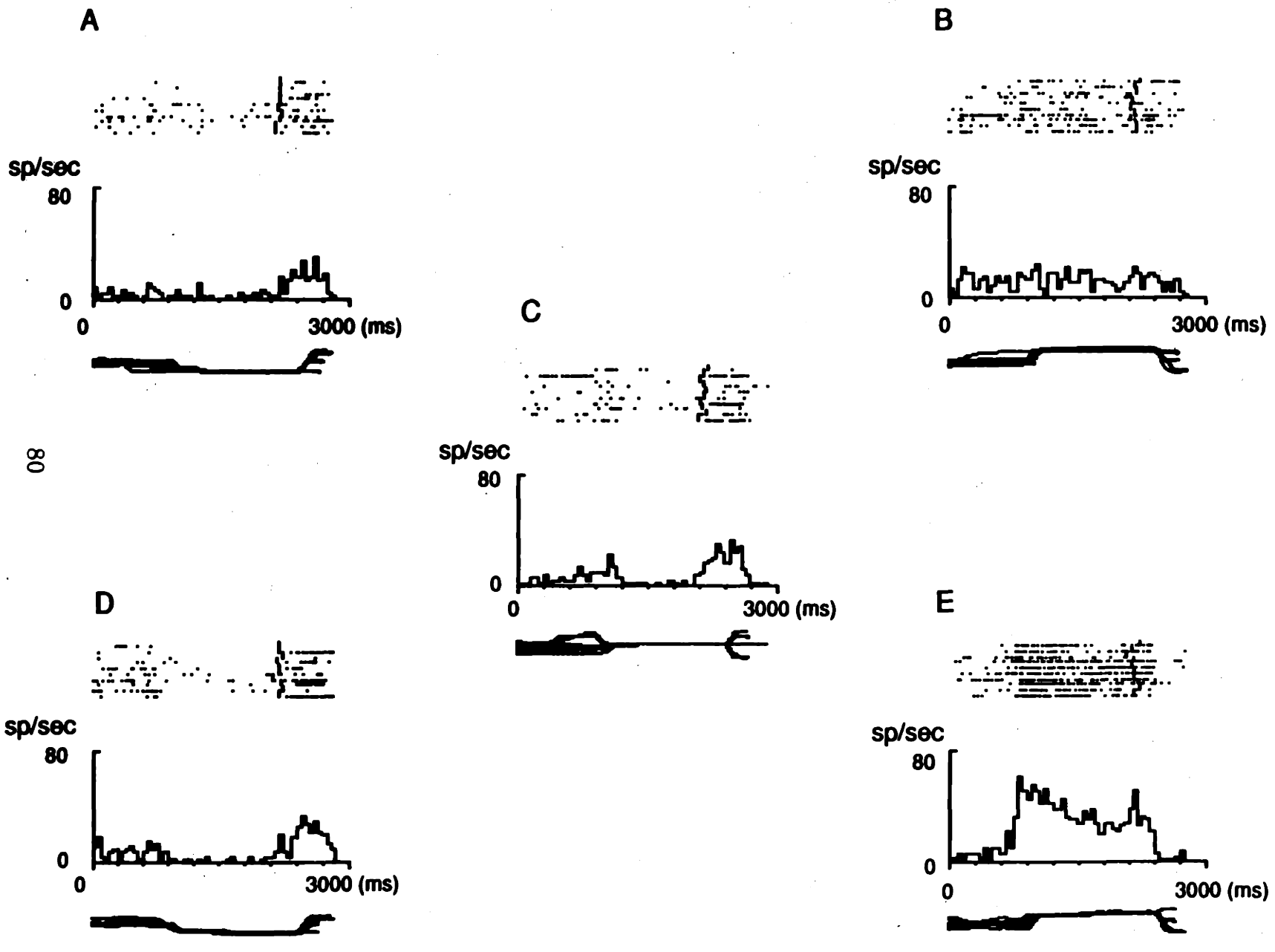

A
sp/sec
80
0
0
3000 (ms)
B
sp/sec
80
0
0
3000 (ms)
C
sp/sec
80
0
0
3000 (ms)
D
sp/sec
80
0
0
3000 (ms)
E
sp/sec
80
0
0
3000 (ms)

Figure 3-5

Figure 3-6

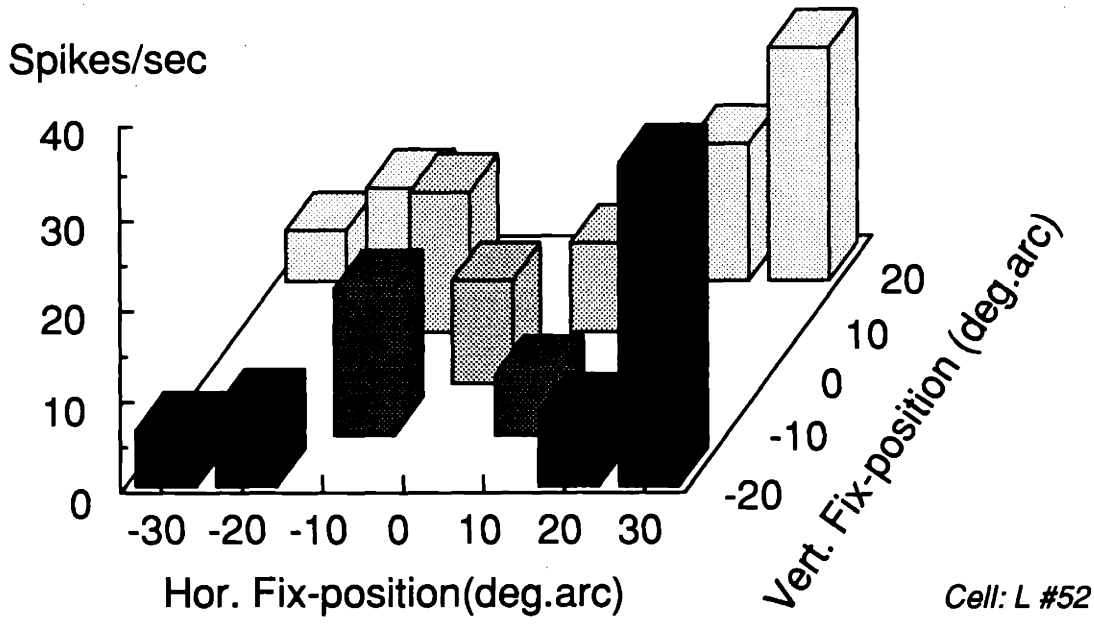
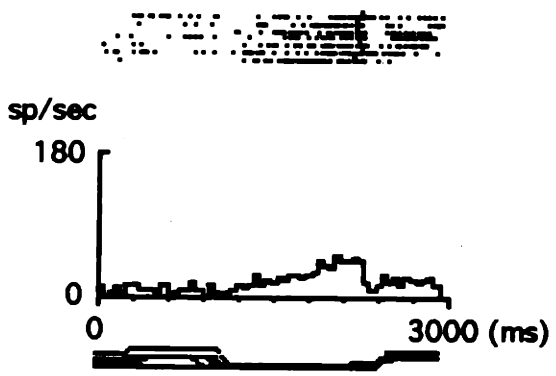

Spikes/sec
40
30
20
10
0
-30 -20 -10 0 10 20 30
Hor. Fix-position(deg.arc)
20
10
0
-10
-20
Vert. Fix-position (deg.arc)
Cell: L #52

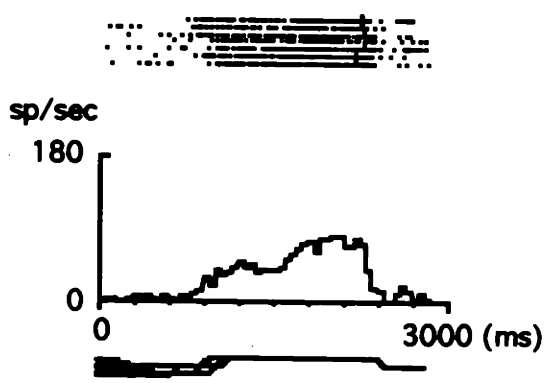
Figure 3-7

a)



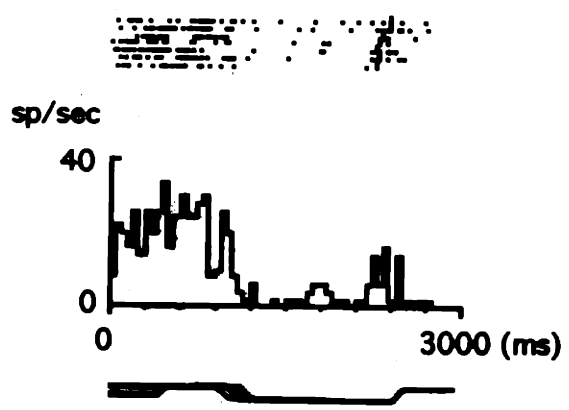
Fixation spot at Left-top
Target at Center

b)



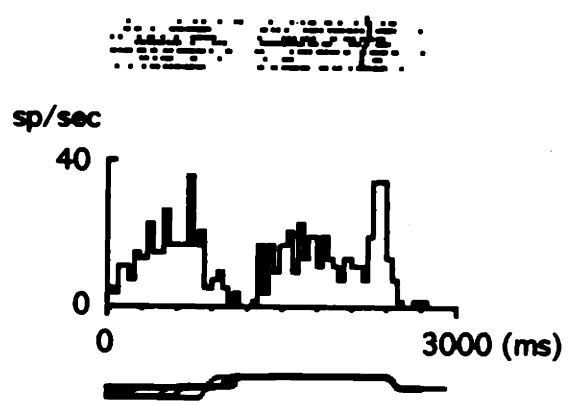
Fixation spot at Right-bottom
Target at Center

c)



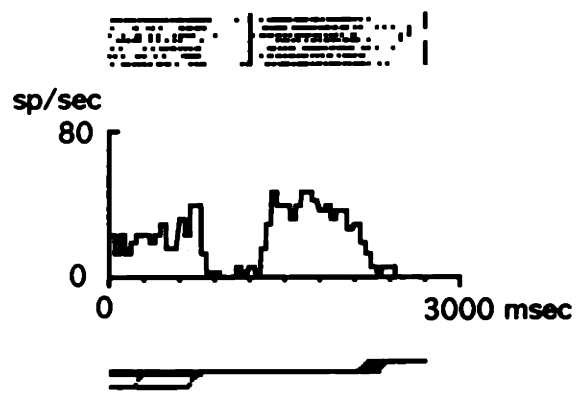
Fixation spot at Left-bottom
Target at Center

d)

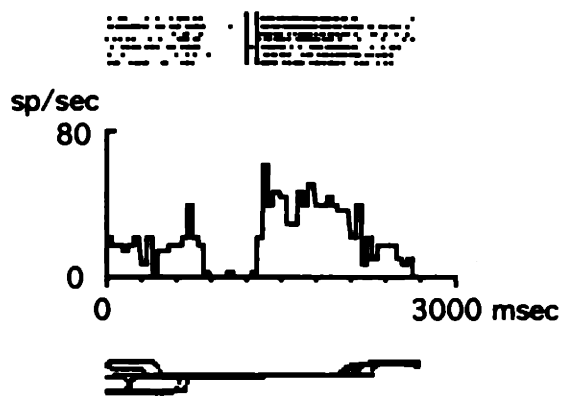


Fixation spot at Right-top
Target at Center

a) Delayed-saccade task

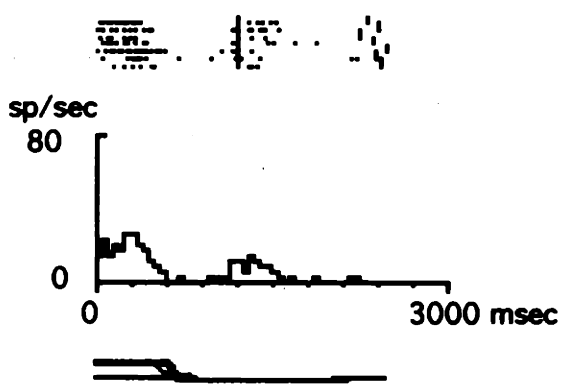


b) Memory-guided saccade task



Fixation spot at Center
Target at Right-top

c)



Fixation spot at Left-bottom
Target at Left-top

d)

Fixation spot at Right-bottom
Target at Right-top

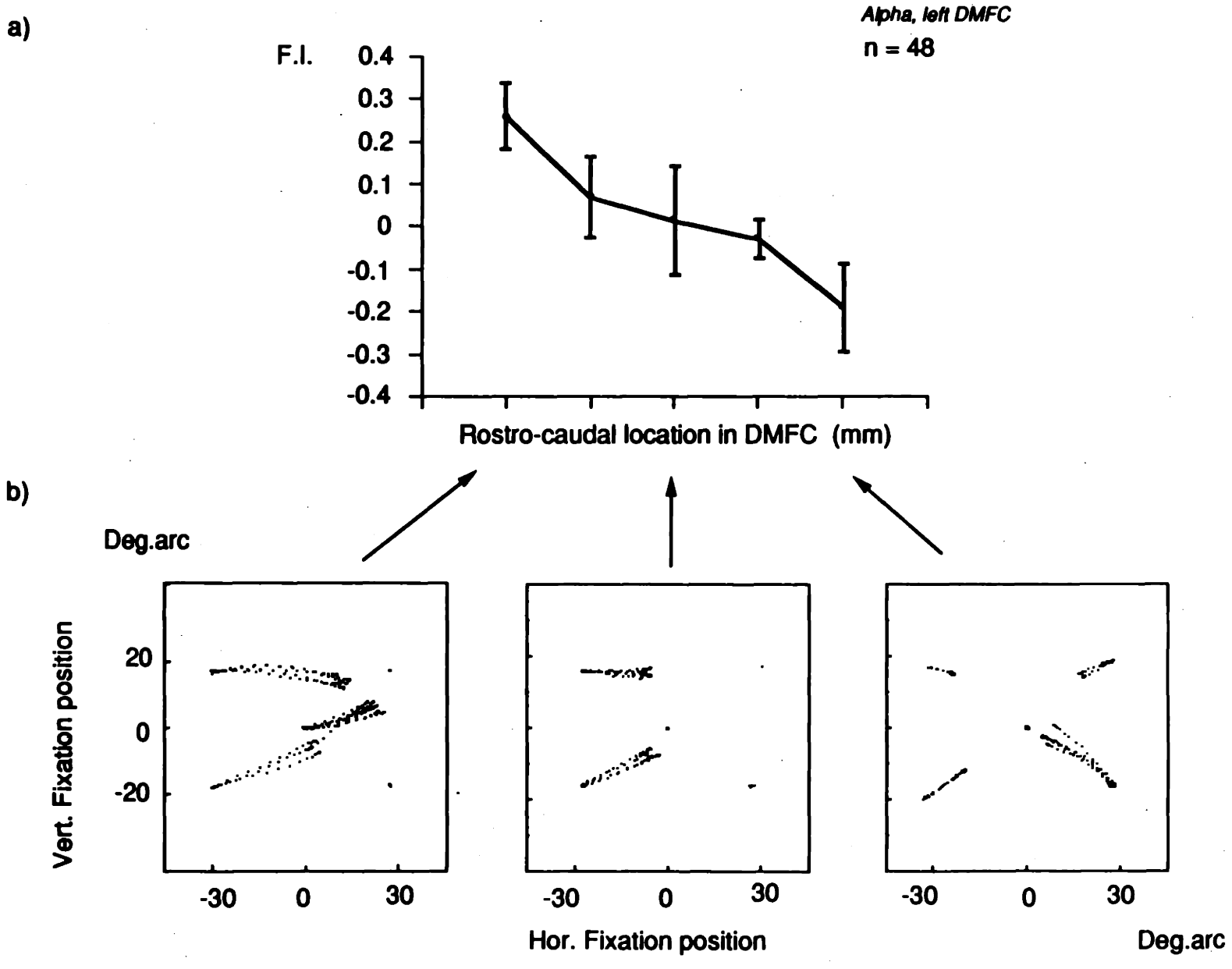

a)
Alpha, left DMFC
n = 48
F.I.
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
Rostro-caudal location in DMFC (mm)
b)
Deg.arc
Vert. Fixation position
20
0
-20
-30
0
30
Hor. Fixation position
Deg.arc

Figure 3-9

Chapter 4. Discussion.

1. Saccades evoked by DMFC stimulation.

Termination zone.

One of the distinguishing features of the DMFC is that electrical stimulation of the region evokes saccades that bring the eyes to a restricted range of position well within the oculomotor range, the termination zone, irrespective of initial eye position. These kinds of saccadic eye movements have been described as goal directed (Hyde and Eason 1959; Robinson 1975), as opposed to saccades of fixed vectors whose final positions are not restricted and whose direction and amplitude are invariant to initial eye position. Fixed-vector saccades are evoked by stimulation of other oculomotor areas, such as the FEF or the superior colliculus (Bruce and Goldberg 1984; Robinson and Fuchs 1969; Robinson 1972; Schiller and Stryker 1972; Sparks 1986).

The significance of distinguishing these two types of stimulation-evoked saccades is that they may reveal the nature of neural code generated by the stimulated area (Robinson 1972). That is, saccades approaching a termination zone indicate that signal from the stimulated area is coded in a coordinate system fixed with respect to the head, whereas fixed-vector saccades indicate that the physiological neural signal from the stimulated area is coded in a coordinate system that moves with the retina.

Therefore, that electrical stimulation of the DMFC evokes saccades

approaching a termination zone suggests that the area generates neural code in craniocentric coordinates. Furthermore, the observation that changing the position of the head with respect to the body did not change the position of the termination zone with respect to the head confirms that the DMFC is indeed organized according to head-centered coordinates, but not according to body-centered coordinates.

Comparison with goal-directed saccades evoked in the cat.

Goal-directed saccades evoked by electrical stimulation have rarely been observed in the primate. Other than from the DMFC (Mitz and Godschalk 1989; Schlag and Schlag-Rey 1987), such saccades have been evoked from the floor of the intraparietal cortex (Thier and Andersen 1991). In the cat, however, they are much more commonly observed. Stimulation of the caudal superior colliculus evokes such saccades (Guitton et al. 1980; McIlwain 1986; Roucoux and Crommelinck 1976; Roucoux et al. 1980). Stimulation of sites in the lateral subregion of the frontal oculomotor area also evokes such saccades (Guitton and Mandl 1978).

The goal-directed saccades obtained from the cat were similar to those obtained from the monkey in this study. Nevertheless, head movements were evoked accompanying goal-directed saccades in the cat (Roucoux et al. 1980), but no head movements were observed from the DMFC stimulation in the monkey. Even though early stimulation experiments have implicated the

DMFC in head-movement control (Brown 1922; Levinsohn 1909; Penfield and Welsh 1951), we were unable to evoke head movements from the DMFC while a monkey fixated different positions in visual space. These results are similar to those reported by Schlag and Schlag-Rey (1987). This led them to the conclusion that the DMFC is primarily an eye field. Our results support their interpretation. Therefore, that goal-directed saccades are part of a coordinated head-eye orienting response (Guitton et al. 1978, 1980; Roucoux et al. 1980) is not supported by the current results.

Topographic organization.

The current study shows that the DMFC is topographically organized with respect to the final position of electrically-evoked saccadic eye movements, with the anterior DMFC coding for termination zones in the extreme contralateral hemifield and with the posterior DMFC coding for termination zones close to the midline. Furthermore, the lateral DMFC codes for termination zones in the upper field, whereas the medial DMFC codes for termination zones in the lower field. This topography is supported by the finding that a group of units in the anterior DMFC discharge most actively when the eyes fixate targets in the contralateral hemifield, whereas a group of units in the posterior DMFC discharge most actively when the eyes fixate targets in the ipsilateral hemifield.

Eye-position dependency of saccades.

Another interesting feature of saccades evoked by DMFC stimulation is that they are highly dependent upon initial eye position. The probability of evoking a saccade decreased and the latency to the evoked saccade increased as the initial eye position got closer to the termination zone as defined by the stimulation.

These properties of saccades evoked from the DMFC differ from those of the FEF and superior colliculus. Whereas saccades evoked from the FEF and superior colliculus have latencies that range between 15 and 60 ms and are insensitive to initial eye position (Bruce et al. 1985; Marrocco 1978; Robinson 1972; Robinson and Fuchs 1969; Schiller and Stryker 1972), latencies ranging between 15 and 400 ms were observed for the DMFC and they depend upon initial eye position. Furthermore, it is conceivable that longer latencies would have been observed if train durations longer than 400 ms had been used (see Fig. 2-7).

A dissociation between eye-position dependency and goal-directedness of saccades was shown in the stimulation study of the visual cortex in the cat (McIlwain 1988). Saccades evoked by stimulation of the cat visual cortex showed dependency upon initial eye position but were not goal directed. In contrast, saccades evoked by DMFC stimulation were not only dependent upon initial eye position, but they also approach a common space in the visual field.

2. Unit responses in the DMFC.

The fixation units.

Units modulated by fixation behavior abound in the DMFC. Over 55 percent of the DMFC units were found to have such properties. Although others have reported the presence of units in the DMFC related to fixation (Bon and Lucchetti 1990; Schall 1991; Schlag and Schlag-Rey 1985), the prevalence of these units varied enormously from paper to paper. In our study, we lengthened the fixation period so that eye-position dependency of a unit could be observed rather easily. Also, we observed the different temporal patterns of fixation-related activity by looking at the unit activity during a long fixation period that was typically over 1000 msec. Finally, it was necessary to test almost all the oculomotor range (60 x 40 degree arc square) since these fixation units were broadly tuned.

Units that are similar to the fixation units found in the DMFC have also been found in V3A (Galletti and Battaglini 1989), posterior parietal lobe (Lynch et al. 1977; Mountcastle et al. 1981; Robinson et al. 1978; Sakata et al. 1980), caudate nucleus (Hikosaka et al. 1989), and in central thalamus (Schlag and Schlag-Rey 1984; Schlag-Rey and Schlag 1984). Although many areas contain cells that are modulated by various types of fixation, it cannot be over-emphasized that the abundance of these cells varies from one structure to another.

The following observations made on the fixation units in the DMFC seem relevant to the results obtained by electrical stimulation of the region: 1) Individual fixation units are highly dependent upon eye position for their activity, as are saccades evoked by electrical stimulation. 2) The tuning distribution of fixation units in the DMFC is consistent with the topographic map of the termination zones of saccades evoked by stimulation of the region. 3) The activity of most fixation units is maintained throughout the fixation, which can be thought of as similar to sustained electrical stimulation that fixates the eyes in a termination zone (Figure 2-15). These observations show that the DMFC harbors neural correlates that may account for oculomotor behaviors evoked by electrical stimulation of the region.

Heterogeneity of unit responses.

Although the fixation units were predominant, other types of units also existed in the DMFC. Furthermore, unit responses were remarkably heterogeneous among units that were modulated by fixation as well as those that were not. In fact, this was well demonstrated by our occasional observation of units that fired in anticipation of juice delivery. Interestingly, information concerning eye position seemed to be available even to those units because the unit activity changed as a function of eye position (data not shown). Such heterogeneity of unit responses in the DMFC implies that this area may be involved in functions that require other information in addition

to eye position signal, such as spatial learning and memory.

Eye-position dependency of DMFC units.

One of the most interesting properties of units in the DMFC is that their activity is highly dependent upon eye position. Fixation-related units are maximally active only when the eyes fixate a target within a certain region of visual space. The property that unit firing changes as a function of eye position, however, is not confined to the fixation units. Such eye position dependency is also exhibited by other types of units in the region, although it is most conspicuously demonstrated in units that has fixation-related activity.

Units modulated by eye position exist also in other parts of the brain, such as the posterior parietal cortex (Andersen and Mountcastle 1983; Andersen et al. 1985, 1990; Lynch et al. 1977; Sakata et al. 1980). The posterior parietal cortex has been implicated in transforming visual input from a retinocentric to a craniocentric coordinate system (Andersen et al. 1987). The craniocentric representation would be important in acquiring a stable perception of the outside world and generating spatially accurate eye movements (Andersen 1987).

The finding that unit responses in the DMFC were highly dependent upon fixation position suggests that this region is also organized in craniocentric coordinates. Visual responses of DMFC units, however, were

much weaker and more loosely coupled with sensory cues than those of units in the parietal cortex. In fact, units that had visual responses strong enough to map out their receptive fields were extremely rare in the DMFC. It was the fixation-related activity of units that was most conspicuously under influence of eye position. Therefore, the DMFC seems to be utilizing the representation of space on the 'motor' side of oculomotor control rather than constructing such representation from the 'sensory' information.

3. Neural code generated by the DMFC.

Neural signal from the DMFC appears to concern eye position. The final position of evoked saccades was coded for by the area. Also, initial eye position had crucial influence upon evoking a saccade by electrical stimulation of the DMFC. Furthermore, the activity of DMFC units was heavily dependent upon the fixation position.

According to the Robinson model of saccade generator, an eye-position signal plays an important role in making a spatially accurate saccade (Robinson 1975). In the model, neural signal of current eye position (E_0) is added to the retinal error (e_r) of a saccadic target in order to internally represent the target position in space (T_h). Comparing T_h with E_0 produces an error signal (e_h) that will drive the burst neurons until it becomes zero.

Now that the DMFC codes for the final positions of evoked saccades, it is an attractive idea that the area may provide the signal representing T_h. Unit data from this region also seem to support this idea. There are units in the DMFC whose activity during fixation is dependent upon eye position. The tuning distribution of such eye-position dependency is consistent with the coding of final position as revealed by electrical stimulation. Furthermore, about a half (49%, 41/84) of units whose activity was modulated by fixation started to fire before the eyes actually acquired the fixation position (Fig. 3-2). The activity of such units may represent T_h for the saccade to the fixation

spot. Therefore, it is possible that the DMFC codes for the target position in space in the way that the Robinson model would predict.

It seems, however, that the DMFC is not only involved in coding for target position to make saccades, but also important in maintaining fixation at the target. This is suggested by the fact that most DMFC units continued to fire over the fixation period after the saccade to the fixation spot had been completed.

The involvement of the DMFC in maintenance of fixation is further supported by the observation that DMFC stimulation inhibited visually-guided saccades if the eyes were fixated within a termination zone as defined by the stimulation. This stimulation did not abort the visual responsiveness of the monkey. Once the monkey was released from inhibition, it produced saccades to targets accurately, suggesting that holding the eyes by DMFC stimulation might have mimicked a physiological situation.

Moreover, the intralaminar nuclei of the thalamus, in which neurons respond during attentive fixation (Schlag and Schlag-Rey 1984; Schlag-Rey and Schlag 1984), send extensive projections to the DMFC (Huerta and Kaas 1990; Wiesendanger and Wiesendanger 1985).

The hypothesis that the DMFC codes for the eye position to fixate is also consistent with the finding that DMFC stimulation brought eyes to a termination zone. It appears that DMFC stimulation created a neural signal that the system interpreted as indicating that the eyes should be brought to

a certain position as defined by the stimulation. When the error between the current eye position and the eye-position signal created by the stimulation exceeded a threshold, the saccade generator would trigger a saccade to reduce the error. This may explain why the probability of evoking a saccade increased and the latency to the evoked saccades decreased as initial eye position got farther from the termination zone, with an additional assumption that the effect of DMFC stimulation is temporally cumulative.

Anatomical studies show that there are neuronal projections that support this interpretation. First, the DMFC innervates the nucleus prepositus hypoglossi (Shook et al. 1990) which has been implicated in providing an eye position signal to the motoneurons (Lopez-Barneo et al. 1982). This connection may be one of the pathways through which the artificial signal of eye position created by DMFC stimulation is conveyed. Second, the DMFC neurons send axons to the raphe interpositus of the brainstem (Huerta and Kaas 1990; Shook et al. 1988), which harbors the omnipause neurons (Buttner-Ennever et al. 1988). The omnipause neurons play an important role in triggering saccades (Fuchs et al. 1985). Therefore, DMFC stimulation may trigger a saccade through this connection. Third, other neuronal pathways for triggering saccades include one from the DMFC to the brainstem, via the central mesencephalic reticular formation (Edwards 1975; Huerta and Kaas 1990; Shook et al. 1990). Saccadic evocation by electrical stimulation of the ventral part of the central mesencephalic

reticular formation was also shown to be dependent upon eye position (Cohen et al. 1985).

The coding of fixation position by the DMFC is coarse as revealed by the broad tuning of fixation units. A fixation unit gets active when the animal fixates within a rather large zone of visual space. That such a coarse code can be utilized to specify behavioral responses accurately is commonly observed in the brain. The neurons in the motor cortex are coarsely tuned for the direction of arm movements and it has been shown that this tuning can specify accurately the trajectory of an arm movement by a vector average of the activity of the neuronal population (Georgopoulos 1987). Similarly, the movement fields of saccade-related neurons in the superior colliculus are large and coarsely tuned, and a saccadic eye movement is accurately specified by the weighted average of the vector contribution of each neuron (Lee et al. 1988). Such a coarse coding may also be utilized by the DMFC in specifying and maintaining fixation position in a punctate region of visual space.

Electrical stimulation of one hemisphere typically produced contraversive saccades. Once the eyes fixated a position within the termination zone it was most often the case that saccades could no longer be evoked from fixation positions in a large part of the contralateral hemifield, and sites from which ipsiversive saccades were evoked were rare. It is likely, therefore, that activation of both hemispheres might be required to define a punctate area of visual space. That both hemispheres of the DMFC

participate in the execution of visuomotor behavior is also suggested by the finding that unilateral damage of the DMFC in man interrupts the generation of sequences of saccades bilaterally (Gaymard et al. 1990).

It remains to be seen whether a lesion confined to the DMFC disrupts oculomotor behavior. Nonetheless, studies have been conducted that address this issue indirectly. Humans with lesioned frontal lobes have been tested on the anti-saccade task, a task that requires a subject to make a saccade away from a visual target. To perform such a task efficiently, it is necessary to first suppress a saccade to the visual target, namely, fixation has to be maintained before the antisaccade can be generated. Results from such studies with respect to the DMFC have proved equivocal, however. Whereas Gaymard et al. (1990) reported that lesions confined to the DMFC of humans do not disrupt performance on the antisaccade task, Guitton et al. (1985) showed that such lesions gravely impair performance such that patients have difficulty suppressing reflexive saccades to the visual target.

Chapter 5. Summary and Conclusions.

In summary, the following observations were made on the DMFC from the experiments of this study.

1) Electrical stimulation of the DMFC evoked eye movements, which were highly dependent upon eye position at the time of the stimulation. The probability of evoking a saccade and the latency of the evoked saccade varied as a function of eye position.

2) Saccades evoked by DMFC stimulation approached a common region of visual space, the termination zone. This termination zone was coextensive with the region of visual space where the probability of evoking a saccade was low and the latency of evoked saccades was long.

3) Once eyes were within the termination zone, electrical stimulation delayed visually-guided saccades by holding the eyes at the initial position.

4) Changing head position with respect to the body did not change the location of the termination zone with respect to the head, confirming that the DMFC was organized according to craniotopic coordinates.

5) The location of the termination zone was systematically coded for by sites in the DMFC. The rostral part of the DMFC coded for a termination zone at an extreme contralateral position and the caudal part around the midline. The lateral part of the DMFC represented an eye position in the upper visual space, whereas the medial part represented an eye position in the lower visual space.

6) Units whose firing was modulated by fixating at a visual target

abounded in the DMFC. The unit activity during fixation might be maintained high, increase steadily, decline over time, or be inhibited throughout the period.

7) The activity of units in the DMFC was highly dependent upon eye position. The fixation-related activity changed as a function of fixation position. Some units showed eye-position dependent modulation of their activity related with saccadic eye movement or memory of a visual target.

8) A population tuning for eye position was distributed in the DMFC in a manner that was consistent with the arrangement of termination zones in the same region of the brain, as discovered by electrical stimulation.

From these observations, two conclusions are drawn as follows: First, the DMFC contains a map coding for eye position that is organized according to a craniotopic coordinate system. Second, this map is utilized to maintain fixation at the coded eye position.

Appendix.

Parametric tests for electrical stimulation of the DMFC.

Since it is claimed that stimulation of the DMFC does not evoke behavioral responses reliably (Macpherson et al. 1982; Mitz and Wise 1987), we carried out parametric tests to optimize saccadic responses.

1. Pulse Duration.

Figure A-1a shows strength-duration functions (current traded off against pulse duration) representing a 50% probability of evoking a saccade from 6 different sites in the DMFC. Each site is represented by letter in the figure. The curves decline rapidly between pulse durations of 0.05 and 0.2 ms. Beyond 0.2 ms the curves level off.

Figure A-1b illustrates the same strength-duration curves normalized with fitted power functions wherein current is expressed as a threshold value over the rheobase current (Table A-1). Rheobase current was defined as the current necessary to evoke a threshold response at a 0.5 ms pulse duration. The chronaxie was estimated for each curve by determining the pulse duration at twice the rheobase current. For all sites, these values ranged between 0.1 and 0.2 ms with a mean of 0.15 ms and standard deviation of 0.02 ms. The behaviorally-determined chronaxies are well within the range of those found for CNS units (Asanuma et al. 1976; Hentall et al. 1984b; Ranck 1975; Shizgal et al. 1991; West and Wolstencroft 1983). For our

experiments, we selected a pulse duration that equaled the lower limit of the chronaxie range, 0.1 ms.

We chose a short pulse-duration to be used in subsequent experiments for the following reasons: (1) Long-duration cathodal-pulses can generate multiple action potentials per single cathodal-pulse (Matthews 1978), and such pulses are known to increase the refractory period of stimulated axons (Shizgal et al. 1991). (2) Cathodal pulse-durations must be less than the absolute refractory period of the most excitable axons, which is always greater than 0.3 ms (Hursch 1939; Paintal 1978; Swadlow and Waxman 1978), to increase the probability of a one-to-one ratio between the number of pulses delivered and the number of action potentials evoked (Yeomans 1990). (3) Most importantly, shorter pulse durations lower the probability of damaging neuronal tissue (Yeomans 1990).

2. Current.

Figure A-2 shows the effect of current on saccades evoked from an anterior (A), a middle (B), and a posterior (C) electrode site in the left DMFC of monkey A from 3 fixations positions. The pulse duration, frequency, and train duration were set at 0.1, 150 Hz, and 400 ms, respectively. The electrode sites were spaced by 2 mm and the monkey faced the center fixation position. The left plate shows saccades elicited at currents that evoked a

saccade on 50% of stimulation trials. The threshold currents tended to be lowest (ranging from 100 to 160 μA) for the left fixation position, and increased as the fixation position was situated rightward in contralateral hemispace. For all 3 sites, saccades were not evoked from the right fixation position for currents as high as 800 μA.

The right plate of figure A-2 shows saccades elicited from sites A, B, and C at a fixed current of 400 μA. Compared with the threshold-current condition, the saccades were of a larger amplitude, and the saccades evoked from the left and center fixation positions for sites A and B terminated in a similar location. Further increases in current up to 800 μA did not increase the amplitude or change the direction of the saccades.

Therefore, current was fixed at 400 μA for all experiments to maximize the amplitude of saccades thereby better defining saccadic termination. A fixed current was used to ensure that a similar volume of tissue was being activated for different sites in the DMFC. The latter is based on the assumption that the excitable elements in the DMFC are homogeneously distributed with a similar distribution of current-distance constants (K).

The passive spread of a 400 μA current was estimated to range from 0.3 to 1.0 mm by using the formula, radius = $(\text{current}/K)^{1/2}$ (Hentall et al. 1984a; Stoney et al. 1968; Yeomans 1990). K values computed by Stoney et al. (1968) for pyramidal tract neurons of cats were used in the estimation of current spread. Since the K values computed by Stoney et al. (1968), which

ranged between 250 and 3500 $\mu A/mm^2$, were based on a pulse duration of 0.2 ms, a slight modification was necessary since 0.1 ms pulse durations were used in the present study. The current used to evoke saccades at a 0.1 pulse duration was 1.7 times greater (on average) than the current used to evoke a saccade at a pulse duration of 0.2 ms (Fig. 2). Therefore, the values of Stoney et al. (1968) were adjusted by multiplying each K value by 1.7 to yield a range between 400 to 6000 $\mu A/mm^2$.

3. Train Duration

The train duration of stimulation was always fixed at 400 ms. The reason for selecting this longer-than-usual train duration was that the latency to evoke saccades from some sites in the DMFC, particularly posterior sites, was over 200 ms. Changes in train duration did not have any noticeable effect on the amplitude and direction of evoked saccades.

4. Pulse Frequency

The optimal stimulation frequency was determined by studying the effect of frequency on the probability of evoking a saccade and on inhibiting a visually-evoked saccade. For these experiments, the current, pulse duration, and train duration were set at 400 μA, 0.1 ms, and 400 ms,

respectively. Figure A-3 shows that the probability of evoking a saccade increased rapidly at 80 Hz and began to drop beyond 200 Hz.

Figure A-4 shows saccadic latency plotted as a function of stimulation frequency for 3 sites when the eyes were positioned in a termination zone and while a monkey generated visually-evoked saccades. The optimal frequency for inhibiting the saccades occurred between 60 and 200 Hz; for these trials the saccadic latency was greater than the train duration.

In summary, for both saccadic excitation and inhibition the optimal stimulation frequency was between 60 and 200 Hz. The stimulation frequency was fixed at 150 Hz.

Table and figures.

TABLE A-1. The R^2 values, sample size (N), and power functions for the normalized strength-duration curves illustrated in figure 2 are listed. The R values are significantly different from zero ($p < 0.01$).

Curve	R^2	N	Equation
A	0.89	6	$y = x^{-0.5} * 0.67$
B	0.93	6	$y = x^{-0.6} * 0.64$
C	0.93	6	$y = x^{-0.6} * 0.59$
D	0.98	6	$y = x^{-0.6} * 0.59$
E	0.98	6	$y = x^{-0.7} * 0.60$
F	0.96	6	$y = x^{-0.7} * 0.62$

Figure legends.

FIG. A-1. (a) Current is plotted as a function of pulse duration for a 50% probability of evoking a saccade. For a given pulse duration (i.e., the duration of one pulse of a symmetrical biphasic pair), an ascending and descending series of currents were tested. The current that produced 5 saccades over 10 stimulation trials was selected as the datum. This current was calculated by interpolating from the ascending and descending series of currents and by computing a mean of the values obtained from both series. The frequency was 150 Hz, and the train duration was fixed at 400 ms. Each curve represents data from one stimulation site in the DMFC. Curve A is from monkey Y, and curves B to F are from monkey Q. Using the fixation task, the monkeys were required to fixate a target in the hemifield ipsilateral to the side of stimulation. The same fixation position was tested for each site.

(b) Strength-duration functions of (a) are normalized and fitted to power functions, which account for more of the variance than linear, log, or exponential functions. R^2 for each curve is shown in Table A-1. Current is represented as the threshold current over the rheobase current.

FIG. A-2. Vector representations of saccadic eye movements evoked from sites A, B, and C of the left DMFC of monkey A are shown. Each upright rectangle represents a fixation position. The same 3 fixation

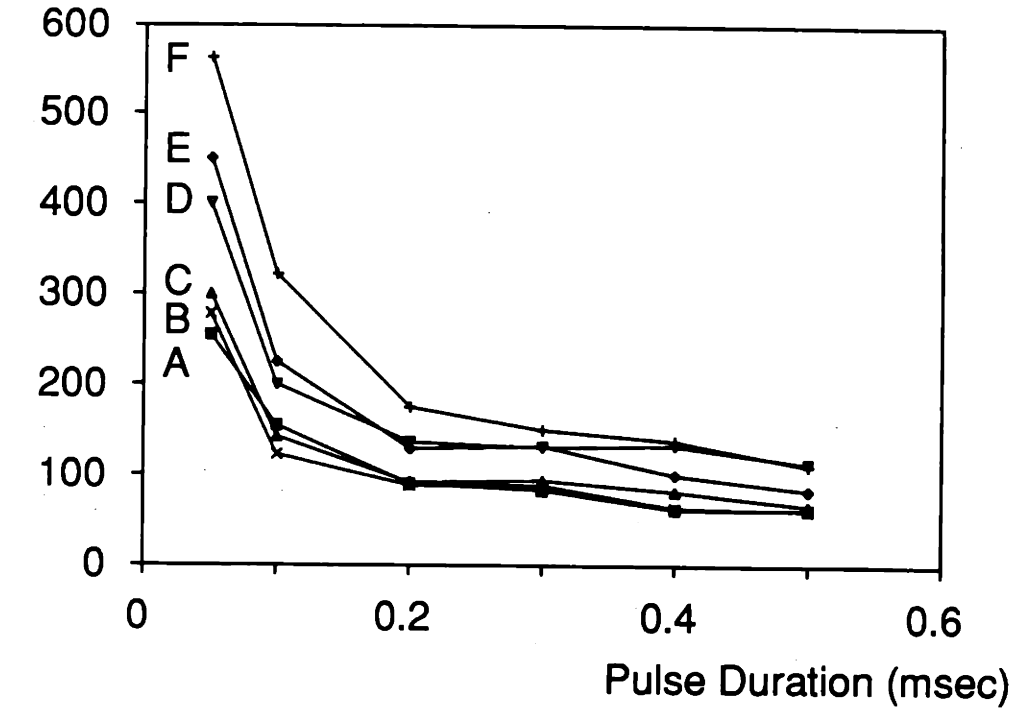
positions were tested for each site. In the left plate are shown saccades evoked at currents that elicited saccades on 50% of the stimulation trials. The threshold currents for site A were 104 and 170 μA for the left and center fixation positions, and those for sites B were 160 and 240 μA. The threshold current for site C was 100 μA for the left fixation position. Saccades were not evoked for the remaining fixation positions with currents as high as 800 μA. In the right plate are shown saccades evoked from the same combination of sites and fixation positions while using a fixed current of 400 μA.

FIG. A-3. The probability of evoking a saccade is plotted as a function of pulse frequency for 3 sites in the DMFC. For frequencies ranging from 10 to 800 Hz, the probability was determined by dividing the number of stimulation trials during which a saccade was evoked over the total number of stimulation trials. Each letter in the figure represents a different stimulation site and C1 through to C4 represents 4 replications for one site. Curves A and B were obtained from monkey Y, and curves C1 through C4 were obtained from monkey Q. The pulse duration, train duration, and current were set at 0.1 ms, 400 ms, and 400 μA, respectively. Using the fixation task, monkeys were required to fixate a target in the hemifield ipsilateral to the side of stimulation. The same fixation position was tested for each site.

FIG. A-4. Saccadic latency is plotted as a function of frequency of stimulation for 3 sites in the DMFC. Train duration, pulse duration, and current were fixed at 800 ms, 0.1 ms, and 400 μA, respectively. Using the detection task, the monkeys were required to fixate a target positioned in a termination zone. For each site, the termination zones was always located in the hemifield contralateral to the side of stimulation.

Figure A-1

a)


Current (uA)
600
500
400
300
200
100
0
F
E
D
C
B
A
0
0.2
0.4
0.6
Pulse Duration (msec)

b)

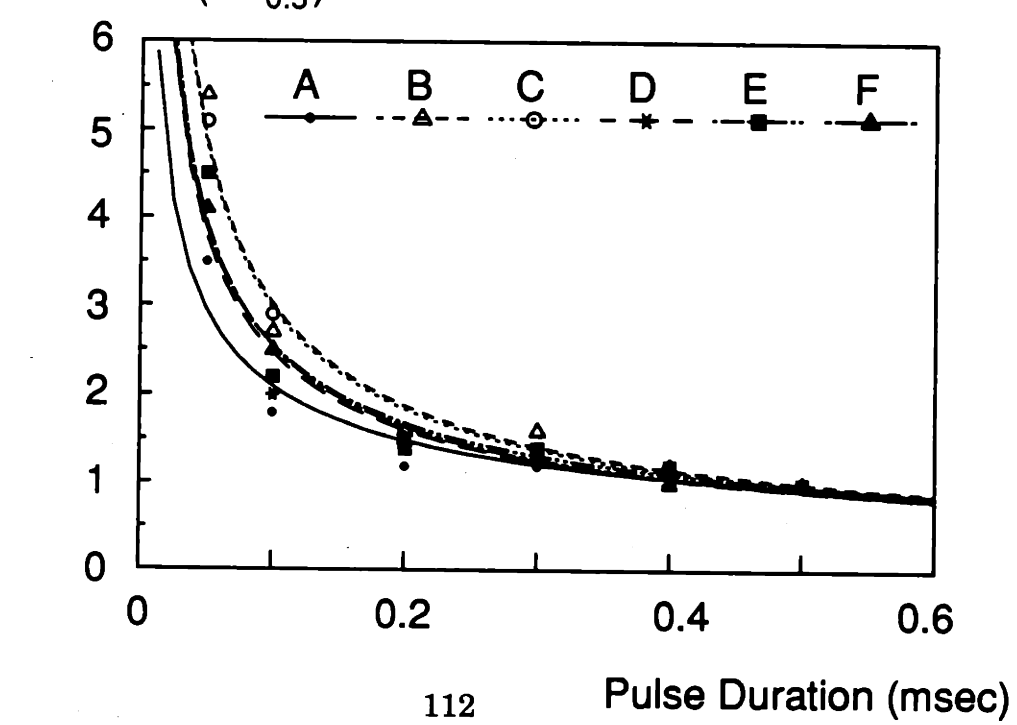
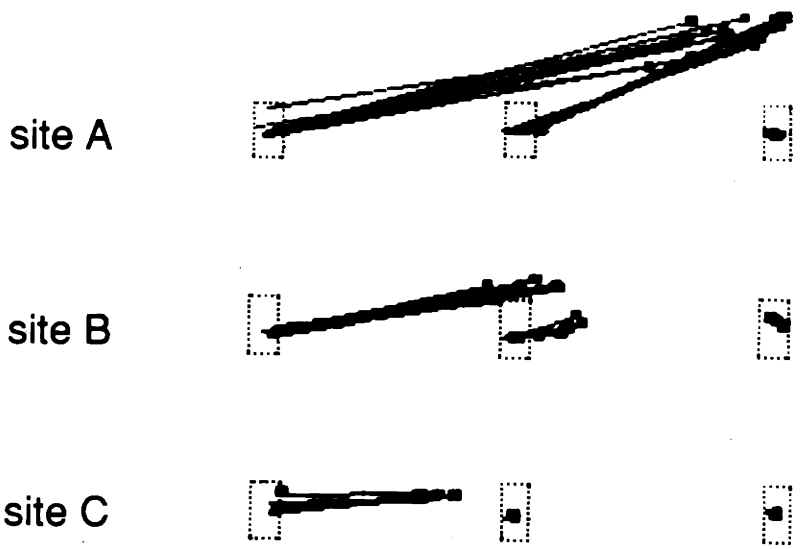

Threshold (I / I0.5)
6
5
4
3
2
1
0
A
B
C
D
E
F
0
0.2
0.4
0.6
Pulse Duration (msec)

Figure A-2

a) 400 uA current



b) Threshold current

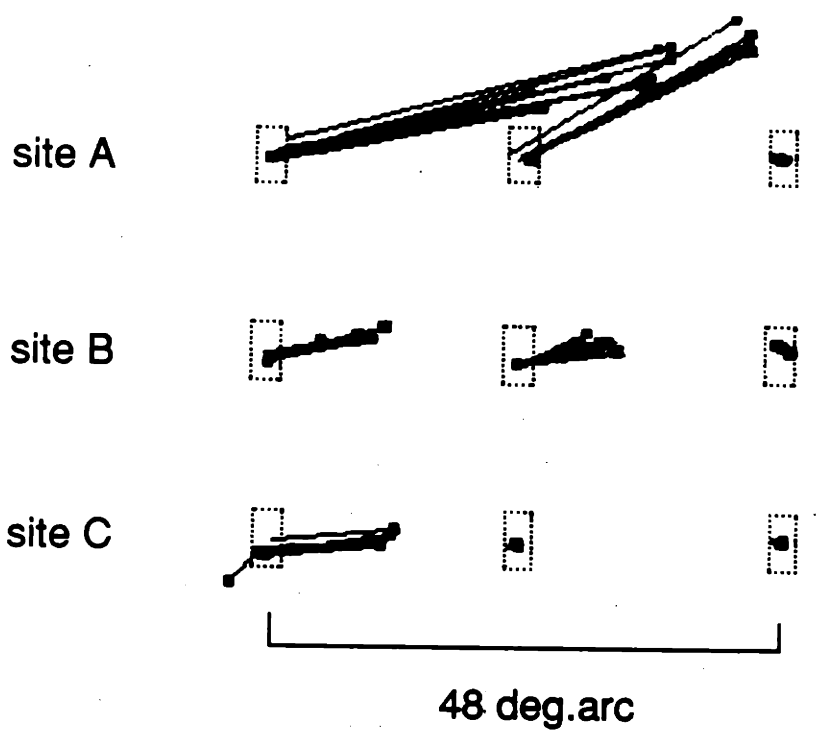


Figure A-3

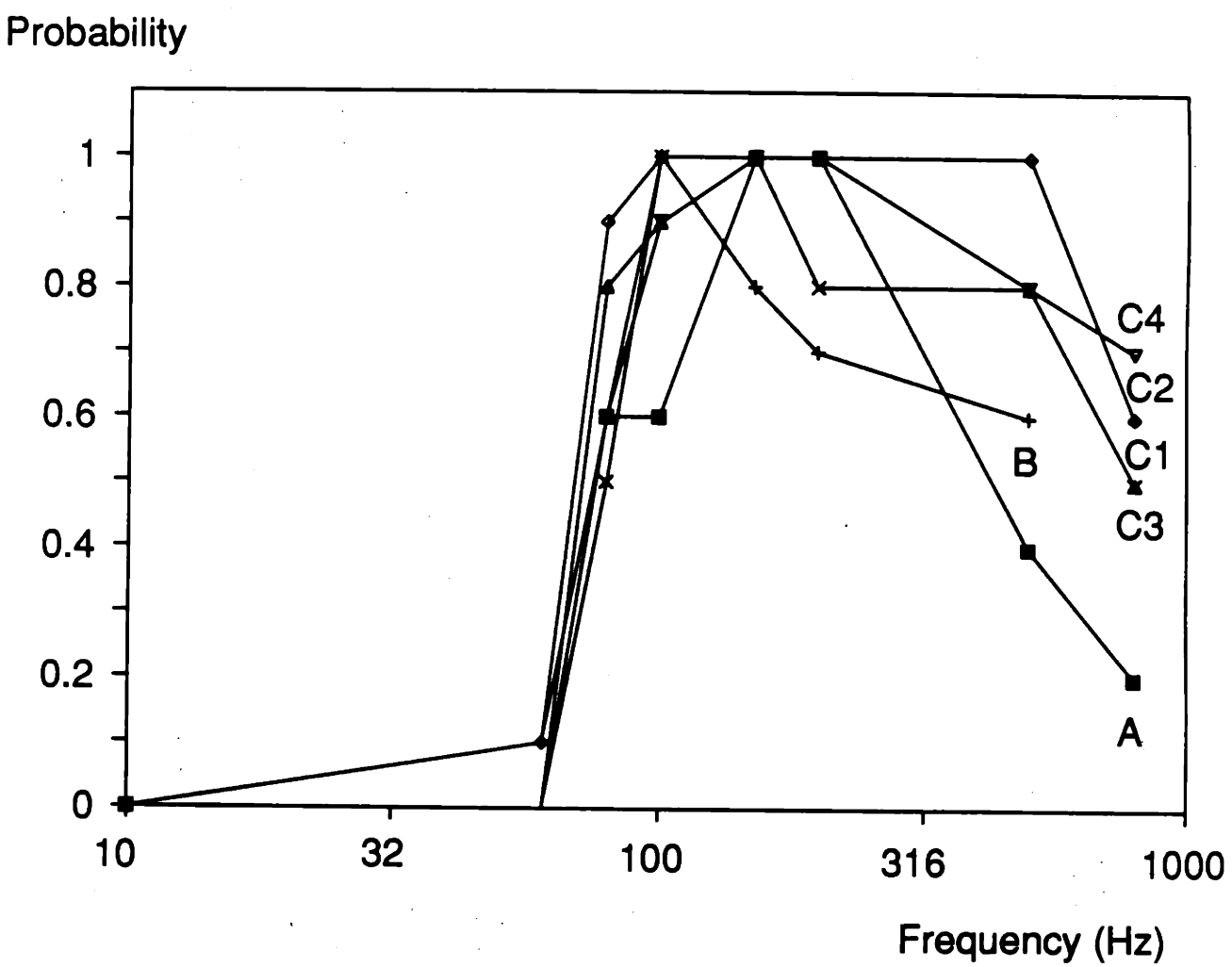
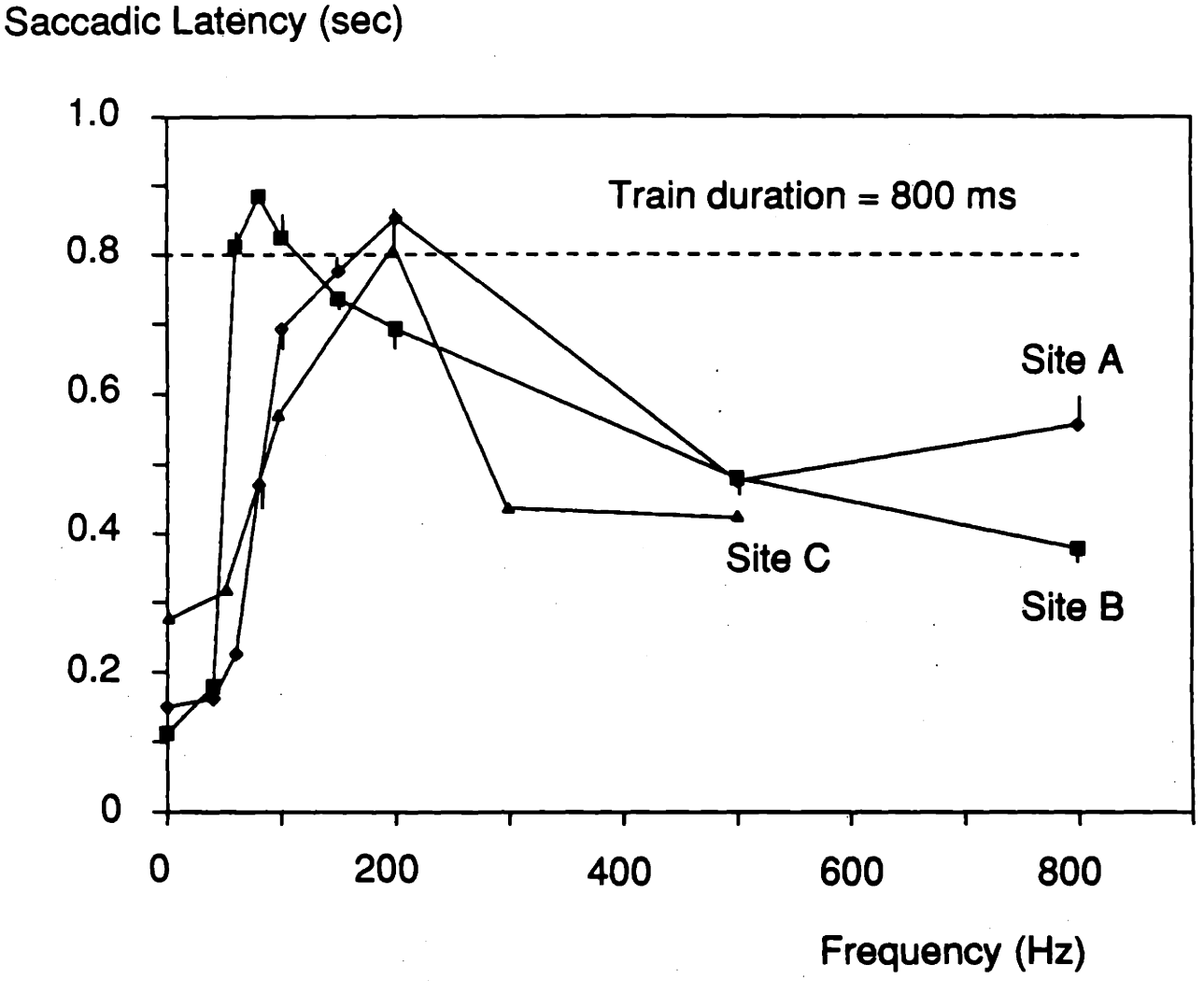

Probability
1
0.8
0.6
0.4
0.2
0
10
32
100
316
1000
Frequency (Hz)
C4
C2
C1
C3
B
A

Figure A-4


Saccadic Latency (sec)
1.0
0.8
0.6
0.4
0.2
0
Train duration = 800 ms
Site A
Site C
Site B
0
200
400
600
800
Frequency (Hz)

Bibliography.

Andersen, R. A. The role of the inferior parietal lobule in spatial perception and visual-motor integration. In *The Handbook of Physiology. Section 1: The Nervous System. Volume IV. Higher Functions of the Brain. Part 2*, F. Plum, V. B. Mountcastle, and S. T. Geiger, eds., pp. 483-518, American Physiological Society, Bethesda, MD. 1987.

Andersen, R. A., Bracewell, R. M., Barash, S., Gnadt, J. W., and Fogassi, L. Eye position effects on visual, memory, and saccade-related activity in areas LIP and 7a of macaque. *J. Neurosci.* 10:1176-1196, 1990.

Andersen, R. A., Essick, G. K., and Siegel, R. M. Encoding of spatial location by posterior parietal neurons. *Science* 230:456-458, 1985.

Andersen, R. A. and Mountcastle, V. B. The influence of the angle of gaze upon the excitability of the light-sensitive neurons of the posterior parietal cortex. *J. Neurosci.* 3:532-548, 1983.

Asanuma, H., Arnold, A., and Zarzecki, P. Further study on the excitation of pyramidal tract cells by intracortical microstimulation. *Exp. Brain Res.* 26:443-461, 1976.

Bizzi, E. Discharge of frontal eye field neurons during saccadic and following

eye movements in unanesthetized monkeys. *Exp. Brain Res.* 6:69-80, 1968.

Bizzi, E. and Schiller, P. H. Single unit activity in the frontal eye fields of unanesthetized monkeys during eye and head movement. *Exp. Brain Res.* 10:151-158, 1970.

Bon, L and Luchetti, C. Neurons signalling the maintenance of attentive fixation in frontal area 6ab of macaque monkey. Exp. Brain Res. 82:231-233, 1990.

Brown, T. G. Reflex orientation of the optical axes and the influence upon it of the cerebral cortex. *Arch. Neerl. Sci. Ex. Nat.* Series 3C. 7:571-578, 1922.

Bruce, C. J. and Goldberg, M. E. Physiology of the frontal eye fields. *Trends Neurosci.* 7:436-441, 1984.

Bruce, C. J. and Goldberg, M. E. Primate frontal eye fields. I. Single neurons discharge before saccades. *J. Neurophysiol.* 53:603-635, 1985.

Bruce, C. J., Goldberg, M. E., Bushnell, M. C., and Stanton, G. B. Primate frontal eye fields. II. Physiological and anatomical correlates of electrically evoked eye movements. *J. Neurophysiol.* 54:714-734, 1985.

Buttner-Ennever, J. A., Cohen, B., Pause, M. and Fries, W. Raphe nucleus of the pons containing omnipause neurons of the oculomotor system in the monkey, and its homologue in man. *J. Comp. Neurol.* 267:307-321, 1988.

Cohen, B., Matsuo, V., Fradin, J., and Raphan, T. Horizontal saccades induced by stimulation of the central mesencephalic reticular formation. *Exp. Br. Res.* 57:605-616, 1985.

Edwards, S. B. Autoradiographic studies of the projections of the midbrain reticular formation: Descending projections of nucleus cuneiformis. *J. Comp. Neurol.* 161:341-356, 1975.

Ferrier, D. The localization of function in the brain. *Proc. R. Soc. London Ser. B* 22:229-232, 1874.

Ferrier, D. Experiments on the brains of monkeys. *Philos. Trans. London* 165:433-488, 1875.

Fuchs, A. F., Kaneko, C. R. S., and Scudder, C. A. Brainstem control of saccadic eye movements. *Ann. Rev. Neurosci.* 8:307-337, 1985.

Fuster, J. M. Unit activity in the prefrontal cortex during delayed-response

performance: neuronal correlates of transient memory. *J. Neurophysiol.* 36:61-78, 1973.

Galletti, C. and Battaglini, P. P. Gaze-dependent visual neurons in area V3A of monkey prestriate cortex. *J. Neurosci.* 9:1112-1125, 1989.

Gaymard, B., Pierrot-Deseilligny, C., and Rivaud, S. Impairment of sequences of memory-guided saccades after supplementary motor area lesions. *Ann. Neurol.* 28:622-626, 1990.

Georgopoulos, A. P. Spatial coding of visually guided arm movements in primate motor cortex. *Can. J. Physiol. Pharmacol.* 66:518-526, 1987.

Goldberg, M. E. and Bruce, C. J. Primate frontal eye fields. III. Maintenance of a spatially accurate saccade signal. *J. Neurophysiol.* 64:489-508, 1990.

Guitton, D., Buchtel, H. A., and Douglas, R. M. Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp. Brain Res.* 58:455-472, 1985.

Guitton, D., Crommelinck, M., and Roucoux, A. Stimulation of the superior colliculus in the alert cat. I. Eye movements and neck EMG activity evoked

when the head is restrained. *Exp. Brain Res.* 39:63-73, 1980.

Guitton, D. and Mandl, G. Frontal 'oculomotor' area in alert cat. I. Eye movements and neck activity evoked by stimulation. *Brain Res.* 149:295-312, 1978.

Hentall, I. D., Zorman, G., Kansky, S., and Fields, H. L. Relations among threshold, spike height, electrode distance, and conduction velocity in electrical stimulation of certain medullospinal neurons. *J. Neurophysiol.* 51:968-977, 1984a.

Hentall, I. D., Zorman, G., Kansky, S., and Fields, H. L. An estimate of minimum number of brain stem neurons required for inhibition of a flexion reflex. *J. Neurophysiol.* 51:978-985, 1984b.

Hikosaka, O., Sakamoto, M., and Usui, S. Functional properties of monkey caudate neurons. III. Activities related to expectation of target and reward. *J. Neurophysiol.* 61:814-832, 1989.

Huerta, M. F. and Kaas, J. H. Supplementary eye field as defined by intracortical microstimulation: connections in macaques. *J. Comp. Neurol.* 293:299-330, 1990.

Hursch, J. B. Conduction velocity and diameter of nerve fibers. *Am. J. Physiol.* 127:131-139, 1939.

Hyde, J. E. and Eason, R. G. Characteristics of ocular movements evoked by stimulation of brainstem of cat. *J. Neurophysiol.* 22:666-678, 1959

Judge, S. J., Richmond, B. J., and Chu, F. C. Implantation of magnetic search coils for measurement of eye position: an improved method. *Vision Res.* 20:535-538, 1980.

Jurgens, R., Becker, W., and Kornhuber, H. Natural and drug-induced variations of velocity and duration of human saccadic eye movements: Evidence for a control of the neural pulse generator by local feedback. *Biol. Cybern.* 39:87-96, 1981.

Lee, C., Rohler, W. H., and Sparks, D. L. Population coding of saccadic eye movements by neurons in the superior colliculus. *Nature* 332:357-360, 1988.

Lee, K. M. and Tehovnik, E. J. The dorsomedial frontal cortex of the rhesus monkey. II. Eye-position dependent activity of units in relation to visual fixation. *J. of Neurophysiol.*, (submitted).

Levinsohn, G. Uber die Beziehungen der Grosshirnrinde beim Affen zu den Bewegungen des Auges. *Graefe Arch. Ophthalm.* 71:313-378, 1909.

Lopez-Barneo, J., Darlot, C., Berthoz, A., and Baker, R. Neural activity in prepositus nucleus correlated with eye movement in the alert cat. *J. Neurophysiol.* 47:329-352, 1982.

Lynch, J. C., Mountcastle, V. B., Talbot, W. H., and Yin, T. C. T. Parietal lobe mechanism for directed visual attention. *J. Neurophysiol.* 40:362-389, 1977.

Macpherson, J. M., Marangoz, C., Miles, T. S., and Wiesendanger, M. Microstimulation of the supplementary motor area (SMA) in the awake monkey. *Exp. Brain Res.* 45:410-416, 1982.

Mann, S. E., Thau, R., and Schiller, P. H. Conditional task-related responses in monkey dorsomedial frontal cortex. *Exp. Brain Res.* 69:460-468, 1988.

Marrocco, R. T. Saccades induced by stimulation of the frontal eye fields: interaction with voluntary and reflexive eye movements. *Brain Res.* 146:23-34, 1978.

Matthews, G. Strength-duration properties of single units driven by electrical stimulation of the lateral hypothalamus in rats. *Brain Res. Bull.* 3:171-174, 1978.

McIlwain, J. T. Effects of eye position on saccades evoked electrically from superior colliculus of alert cats. *J. Neurophysiol.* 55:97-112, 1986.

McIlwain, J. T. Saccadic eye movements evoked by electrical stimulation of the cat's visual cortex. *Visual Neurosci.* 1:135-143, 1988.

McIlwain, J. T. Effects of eye position on electrically evoked saccades: a theoretical note. *Visual Neurosci.* 1:239-244, 1988.

Mitz, A. R. and Godschalk, M. Eye-movement representation in the frontal lobe of rhesus monkeys. *Neurosci Let.* 106:157-162, 1989.

Mitz, R. A. and Wise, S. P. The somatotopic organization of the supplementary motor area: intracortical microstimulation mapping. *J. Neurosci.* 7:1010-1021, 1987.

Mountcastle, V. B., Andersen, R. A., and Motter, B. C. The influence of attentive fixation upon the excitability of the light-sensitive neurons of the

posterior parietal lobe. *J. Neurosci.* 11:1218-1235, 1981.

Nakayama, K. Coordination of extraocular muscles. In *Basic Mechanisms of Ocular Motility and their Clinical Implications*, G. Lennerstrand and P. Bach-y-Rita, eds., pp.193-207, Pergamon, Oxford, UK, 1975.

Paintal, A. S. Conduction properties of normal peripheral mammalian axons. In: *Physiology and Pathobiology of Axons*, Raven Press: New York, 131-144, 1978.

Penfield, W. and Welch, K. The supplementary motor area of the cerebral cortex. *Arch. Neurol. Psychiat.* 66:289-317, 1951.

Ranck Jr., J. B. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Res.* 98:417-440, 1975.

Robinson, D. A. Oculomotor unit behavior in the monkey. *J. Neurophysiol.* 33:393-404, 1970.

Robinson, D. A. Eye movements evoked by collicular stimulation in the alert monkey. *Vision Res.* 12:1795-1808, 1972.

Robinson, D. A. Oculomotor control signals. In: *Basic Mechanisms of Ocular Motility and their Clinical Implications,* edited by G. Lennerstrand and P. Bach-y-Rita. Oxford, UK: Pergamon, 1975, p. 337-374.

Robinson, D. A. and Fuchs, A. F. Eye movements evoked by stimulation of frontal eye fields. *J. Neurophysiol.* 32:637-648, 1969.

Robinson, D. L., Goldberg, M. E., and Stanton, G. B. Parietal association cortex in the primate: sensory mechanisms and behavioral modulation. *J. Neurophysiol.* 41:910-932, 1978.

Roucoux, A. and Crommelinck, M. Eye movements evoked by superior colliculus stimulation in the alert cat. *Brain Res.* 106:349-363, 1976.

Roucoux, A., Guitton, D., and Crommelinck, M. Stimulation of the superior colliculus in the alert cat. II. Eye and head movements evoked when the head is unrestrained. *Exp. Br. Res.* 39:75-86, 1980.

Sakata, H., Shibutani, H., and Kawano, K. Spatial properties of visual fixation neurons in posterior parietal association cortex of the monkey. *J. Neurophysiol.* 43:1654-1670, 1980.

Schall, J. D. Neuronal activity related to visually guided saccadic eye movements in the supplementary motor area of rhesus monkeys. *J. Neurophysiol.* 66:530-558, 1991.

Schiller, P. H. The superior colliculus and visual function. In: *Handbook of Physiology*. The Nervous System. Sensory Processes, sect. 1, vol. III, pt. 1, chapt. 11, 457-505, 1984.

Schiller, P. H. and Stryker, M. Single-unit recording and stimulation in superior colliculus of the alert rhesus monkey. *J. Neurophysiol.* 42:1124-1133, 1972.

Schlag, J. and Schlag-Rey, M. Visuomotor functions of central thalamus in monkey. II. Unit activity related to visual events, targeting, and fixation. *J. Neurophysiol.* 51:1175-1195, 1984.

Schlag, J. and Schlag-Rey, M. Eye fixation units in the supplementary eye field of monkey. *Soc. Neurosci. Abstr.* 11:82, 1985.

Schlag, J. and Schlag-Rey, M. Evidence for a supplementary eye field. *J. Neurophysiol.* 57:179-200, 1987.

Schlag-Rey, M. and Schlag, J. Visuomotor functions of central thalamus in monkey. I. Unit activity related to spontaneous eye movements. *J. Neurophysiol.* 51:1149-1174, 1984.

Scudder, C. A. A new local feedback model of the saccadic burst generator. *J. Neurophysiol.* 59:1455-1475, 1988.

Shizgal, P., Conover, K., and Schindler, D. Medial forebrain bundle units in the rat: dependence of refractory period estimates on pulse duration. *Behav. Brain Res.* 42:151-160, 1991.

Shook, B. L., Schlag-Rey, M., and Schlag, J. Direct projection from the supplementary eye field to the nucleus raphe interpositus. *Exp. Brain Res.* 73:215-218, 1988.

Shook, B. L., Schlag-Rey, M., and Schlag, J. Primate supplementary eye field: I. Comparative aspects of mesencephalic and pontine connections. *J. Comp. Neurol.* 301:618-642, 1990.

Shook, B. L., Schlag-Rey, M., and Schlag, J. Primate supplementary eye field: II. Comparative aspects of connections with the thalamus, corpus striatum, and related forebrain nuclei. *J. Comp. Neurol.* 307:562-583, 1991.

Sparks, D. L. Translation of sensory signals into commands for control of saccadic eye movements: role of primate superior colliculus. *Physiol. Rev.* 66:118-171, 1986.

Stoney, S. D., Tompson, W. D., and Asanuma, H. Excitation of pyramidal tract cells by intracortical microstimulation: effective extent of stimulating current. *J. Neurophysiol.* 31:659-669, 1968.

Swadlow, H. A. and Waxman, S. G. Activity-dependent variations in the conduction properties of central axons. In: *Physiology and Pathobiology of Axons*, Raven Press: New York, 191-202, 1978.

Tehovnik, E. J. and Lee, K. The dorsomedial frontal cortex of the rhesus monkey. I. Topographic representation of saccades evoked by electrical stimulation. *J. Neurophysiol.* (submitted).

Thier, P. and Andersen, R. A. Electrical microstimulation delineates 3 distinct eye-movement related areas in the posterior parietal cortex of the rhesus monkey. *Soc. Neurosci. Abst.* 17:1281, 1991.

Tweed, D. and Villis, T. A two dimensional model for saccade generation. *Biol. Cybern.* 52:219-227, 1985.

Wagman, I. H. Eye movements induced by electrical stimulation of cerebrum in monkeys and their relationship to body movements. In: *The Oculomotor System*, Harper and Row Publishers: New York, 17-39, 1964.

West, D. C. and Wolstencroft, J. H. Strength-duration characteristics of myelinated and non-myelinated bulbospinal axons in the cat spinal cord. *J. Physiol.* 337:37-50, 1983.

Westheimer, G. Donders', Listing's, and Hering's laws and their implications. In *Models of Oculomotor Behavior and Control*, B. L. Zuber, ed., pp.149-160, CRC Press, Boca Raton, FL, 1981.

Wiesendanger, R. and Wiesendanger, M. The thalamic connections with medial area 6 (supplementary motor cortex) in the monkey (Macaca fascicularis). *Exp. Brain Res.* 59:91-104, 1985.

Yeomans, J. S. *Principles of Brain Stimulation*, Oxford University Press: New York, 1990.