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Conditional task-related responses in monkey dorsomedial frontal cortex

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Summary. Dorsomedial frontal cortex (DMFC) was studied in monkeys trained to make visually guided eye or arm movements. Portions of DMFC are involved in the execution of learned, goal-directed behaviors. Many neurons discharge with both eye and hand movements as well as when motor responses are withheld, provided these behaviors are related to the successful execution of the learned task. Similar movements, when carried out at times unrelated to the task, are not accompanied by neuronal activity. Electrical microstimulation produces either arrest of task-related, but not task-unrelated motor acts, or triggers task-related movements. The nature of stimulation elicited responses depends on the task the animal has been trained on and is altered by new training.

Key words: Dorsomedial frontal cortex – Supplementary motor area – Eye movements – Learning – Goal directed movements

Introduction

The dorsomedial frontal cortex of primates (DMFC) is thought to be involved in the planning and execution of movements (Goldberg 1985). Evidence has been gathered to the effect that one portion of this region, the so called supplementary motor area, has several subdivisions, each concerned with different parts of the motor system (Macpherson et al. 1982; Fox et al. 1985; Gould et al. 1986). Our interest in this area was triggered by a recent study by Schlag and Schlag-Rey (1985) which has shown that a surprisingly large portion of it is involved in saccadic eye movement generation. We set out to compare neuronal activity in DMFC with that of the frontal eye fields and the superior colliculi, areas which we have studied extensively earlier (Schiller and Stryker 1972; Schiller and Sandell 1983). Our study of DMFC using a variety of behavioral paradigms reveals a more labile organization than has so far been reported and shows that this organization is quite unlike that which is found in the frontal eye fields and in the superior colliculi. Our results show that what is seen in DMFC using single-unit recording and microstimulation depends crucially on what the animal has been trained to do; the activity within this area appears to be linked to those motor acts that are relevant to the successful execution of learned tasks and appears to become reorganized when the animal is retrained on a modified task. The learned tasks appear to be spatially coded. Abstracts of this work have appeared earlier (Schiller et al. 1986; Mann et al. 1986).

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Methods

Three rhesus monkeys were trained for this experiment. The basic procedures have been previously described by Schiller et al. (1987). Responses to visual targets were assessed using a scleral search coil to measure eye movements and a touch panel to assess touch locations (Robinson 1963; Schiller et al. 1980). The animals faced a screen into which an array of LEDs was embedded. Following the appearance and fixation of a central stimulus, one or two peripheral targets appeared in succession and the animal's task was either to saccade to these targets or to touch them. Correct target acquisition, as detected by electronic windows in the case of eye movements and by the touch panel in the case of touches, was rewarded with drops of apple juice. For one of the animals the cue for the movement was the dousing of the fixation light which occurred 240 to 560 ms after the appearance of the targets. This animal was trained only on the eye-movement task. The other two animals learned both the eye-movement and touch tasks. For these two monkeys a go/no-go paradigm was used; the fixation spot was yellow which subsequently turned either green or red. When it turned green (the go condition), the animal had to make an eye or hand movement to the target(s); when it turned red (the no-go condition), the animal had to maintain fixation or touch, that is to

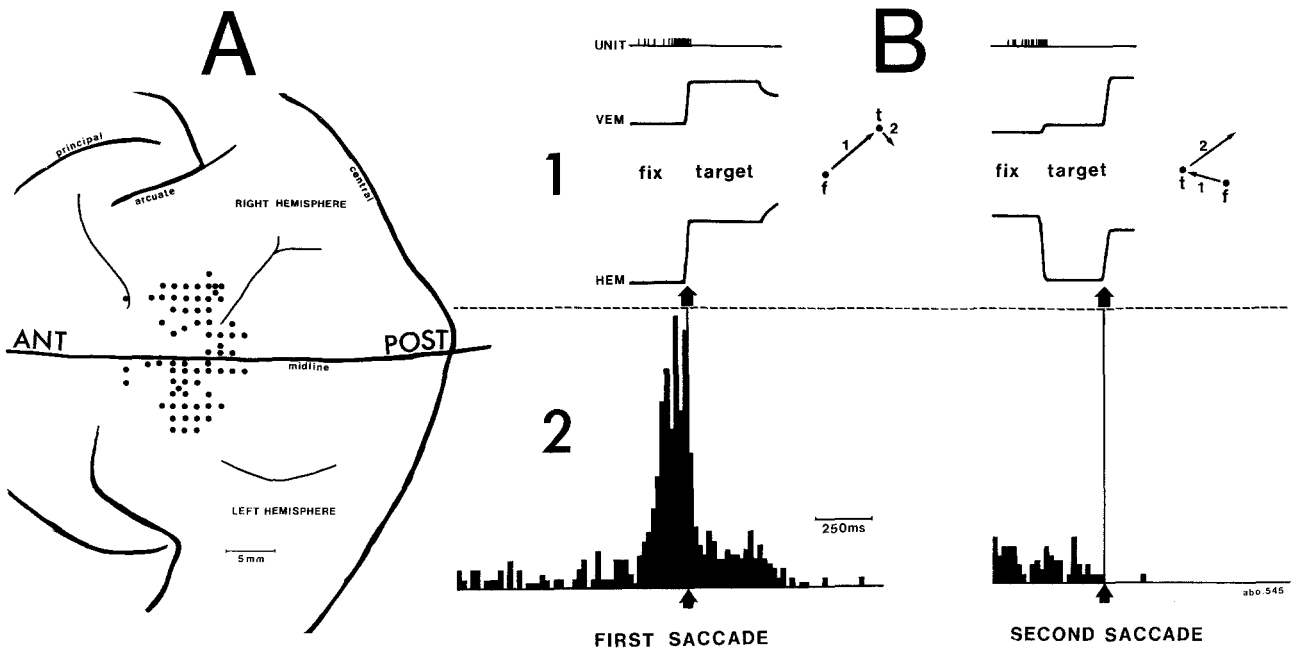

Fig. 1. **A** Surface view of the location of the penetrations in the DMFC of two of the three monkeys studied. **B** Unit responses during the one-saccade task. **B1** Eye-movement and unit responses for two trials; spatial arrangement of the stimuli and saccades shown to the right of each trial. VEM, HEM = vertical and horizontal eye movements, f = fixation spot, t = target. Small numbers indicate temporal order of saccades. **B2** Cumulative histogram for same unit showing responses to first and second saccades. The data are aligned with the saccades (arrows)

make no overt motor response, in order to get rewarded. In both cases the target stimuli appeared 240 to 560 ms before the yellow stimulus changed to either green or red. The experiment was controlled by a PDP 11/34 computer, which kept track of the eye movements, of the touches and set electronic windows around the correct targets thereby necessitating accurate motor responses. During the recording experiments four target locations were used, which were presented either singly or in successive pairs in randomized order. In most cases the targets were arranged to form the corners of a rectangle with each target 12 degrees from the fixation spot in the center. During some of the recordings several other target locations were also examined, however, especially in the first monkey which was trained only on the eye movement task; this allowed for a larger area of visual space to be explored than in case of the other two animals where stimuli had to be confined to an area reachable by the arm.

Single-unit recordings and microstimulation were made through an implanted chamber with glass-coated platinum-iridium microelectrodes using methods previously described (Schiller and Stryker 1972). Trial by trial performance was displayed on-line for examination of ongoing behavior and unit responses, and was stored for subsequent analysis. In two of our animals recordings were also made in the frontal eye fields the results of which will be reported elsewhere.

Results

Single-unit recordings

More than 600 single cells were studied in the DMFC of three monkeys. The location of the electrode penetrations, which spanned the range of the Horsley-Clark anterior-posterior coordinates of 18 to 32 mm, is shown for two monkeys in Fig. 1A. In our sample of single cells most of the neurons which responded with saccades did so only during the performance of the task (428 out of 442), discharging before, during or just after the eye movements. Saccades of similar dimensions made at other times were not accompanied by neuronal activity. An example of this appears in Fig. 1 for a cell which during the target acquisition task discharged before saccades to all four target locations. Figure 1B1 shows two individual trials to two different target locations. On each of these trials the cell responded vigorously before the saccade to the target, but did not discharge with the saccade occurring after target acquisition, even though the size and direction of the second saccade on the trial shown on the right was similar to that of the first saccade on the trial shown on the left. In 1B2 cumulative histograms for task-relevant first saccades and task-irrelevant second saccades are shown. Only the first, task-related saccade elicited responses.

Figure 2A shows the responses of another cell in DMFC which was obtained from an animal trained to make either one or two saccades to one or two successively appearing targets. The upper histogram shows the cell's activity during the one-saccade task.

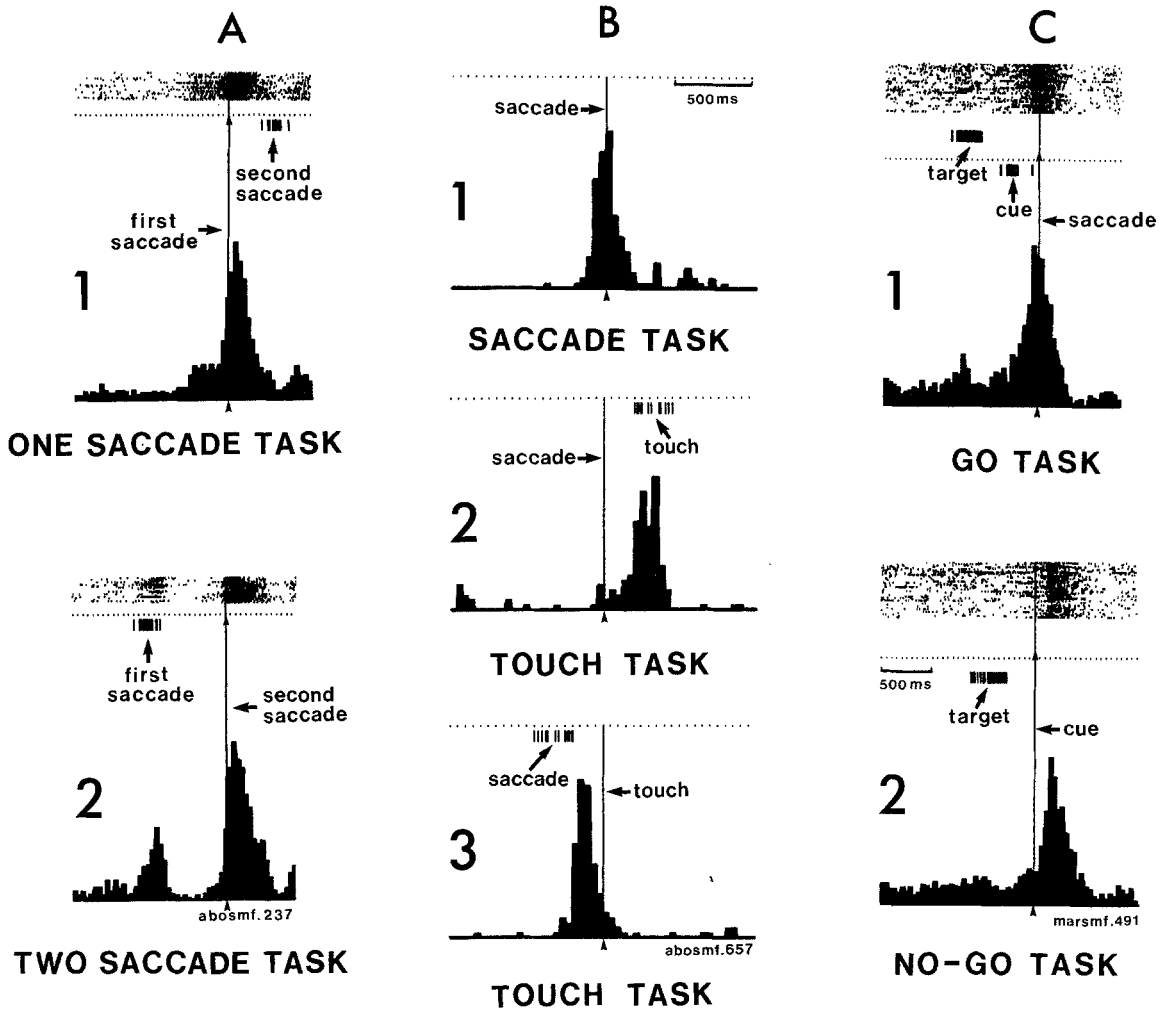

Fig. 2. A Trial-by-trial rasters and cumulative histograms obtained from one cell during the one-saccade (**A1**) and two saccade tasks (**A2**), aligned on the first and second saccades respectively. Above the histograms are time lines with dots 50 ms apart. **B** Cumulative histograms from one cell during the saccade task and the touch task. In **B1** (saccade task) and in **B2** (touch task) the data are aligned on the saccade. In **B3** the same data shown in **B2** are aligned on the touch. Events on which histograms are not aligned are shown by tick marks. **C** Trial by trial unit activity and cumulative histograms obtained from a cell during the go and no-go tasks. Cumulative data are aligned on the saccade for the go task and on the onset of the cue (when the central fixation spot changes from yellow to red) for the no-go task. A set of tick marks in **C1** also shows when the target was turned on to demonstrate that this stimulus did not affect unit activity

The data are similar to those shown in Fig. 1B: there is a vigorous response with the first saccade which brought the eye to the appropriate target location and there is no response with the subsequent saccade which is not directly related to the execution of the task. The lower portion of Fig. 2A shows the responses of this same unit when the animal performed on the two-saccade task, where he was rewarded only after correctly saccading to two targets in succession. The response of the unit changed dramatically: The activity associated with the first saccade is now smaller and a vigorous response is evident with the second saccade. The task-related saccadic neural activity of this cell begins just prior to the saccade, reaches a peak immediately after saccade completion and then terminates rather rapidly. The majority of cells we examined with both the one- and the two-saccade tasks discharged with the second saccade when it became task relevant (111 of 125).

We next proceeded to determine the extent to which the responses we have obtained in DMFC are specifically tied to the oculomotor system. We therefore trained animals on an arm-movement task in addition to the eye-movement task so that they now had to touch the visual stimuli to be rewarded. The comparison between the two tasks showed that while some cells continued to fire with eye movements during the touch task, others altered their responses

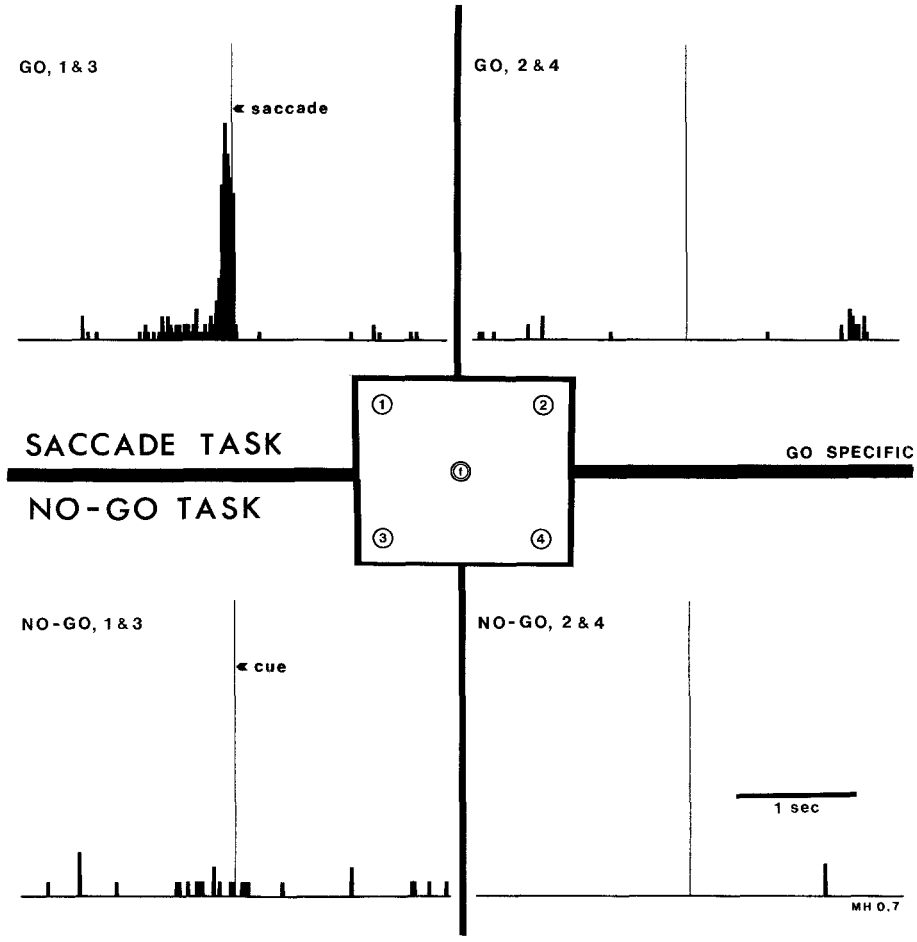

Fig. 3. Response histograms obtained from a single cell which responds specifically with leftward saccades to targets 1 and 3 as shown in the inset. The cell does not respond during the no-go task. Top left and right histograms show cumulative data obtained for left saccades (targets 1 and 3) and right saccades (targets 2 and 4) respectively during the go task. Bottom histograms shows cumulative data obtained during the no-go task for the same set of targets

and now discharged when the targets were touched. An example of such a cell is shown in Fig. 2B. The top histogram shows the activity of the cell during the saccade task. The middle and lower histograms show the responses made during the touch task. For the trials shown on the touch task the animal's saccades occurred well before the touch, as indicated by the tick marks in the figure. The data are displayed twice to make this point, once aligned with the touches and once with the saccades. These kinds of cells exhibit what may be called motor equivalency: They respond with eye movements during the eye-movement task and with touches during the touch task. Of the 152 movement-related cells studied with both eye and hand movement, 67 were motor equivalent.

Using the go/no-go paradigm we found that of 178 cells so studied, 100 responded both when an overt motor act was made and when the motor act was withheld. An example of such a cell appears in Fig. 2C in which the go and no-go trials, randomized during data collection, are shown separately. These kinds of cells are not specifically tied to the execution of a particular motor act. Some of the cells studied with the go/no-go paradigm did show considerable specificity. Examples of this are shown in Figs. 3 and 4. The cell in Fig. 3 discharges with saccades during the go task but does not discharge during the no-go task (N = 78). Figure 4 shows the converse: a cell that discharges during the no-go hold but not during the go task (N = 15). In these two figures data are shown separately for targets appearing to the left and to the right of fixation to make another point: in addition to being specific for go and no-go trials, these two cells were also spatially selective in that they responded during trials in which the targets appeared on the left but not on the right. Spatial specificity was also evident in 31 of the 100 cells which responded both in the go and no-go conditions. In all 74 of 178 cells studied using this paradigm showed spatial specificity.

To further test the hypothesis that events are spatially coded in the DMFC, as suggested by the data in Figs. 3 and 4, we examined whether cells which respond with saccades are selective for the size and direction of these saccades or for the reaching of specific target locations in space. To accomplish this we compared trials on which the animals made similar saccades to foveate different target locations.

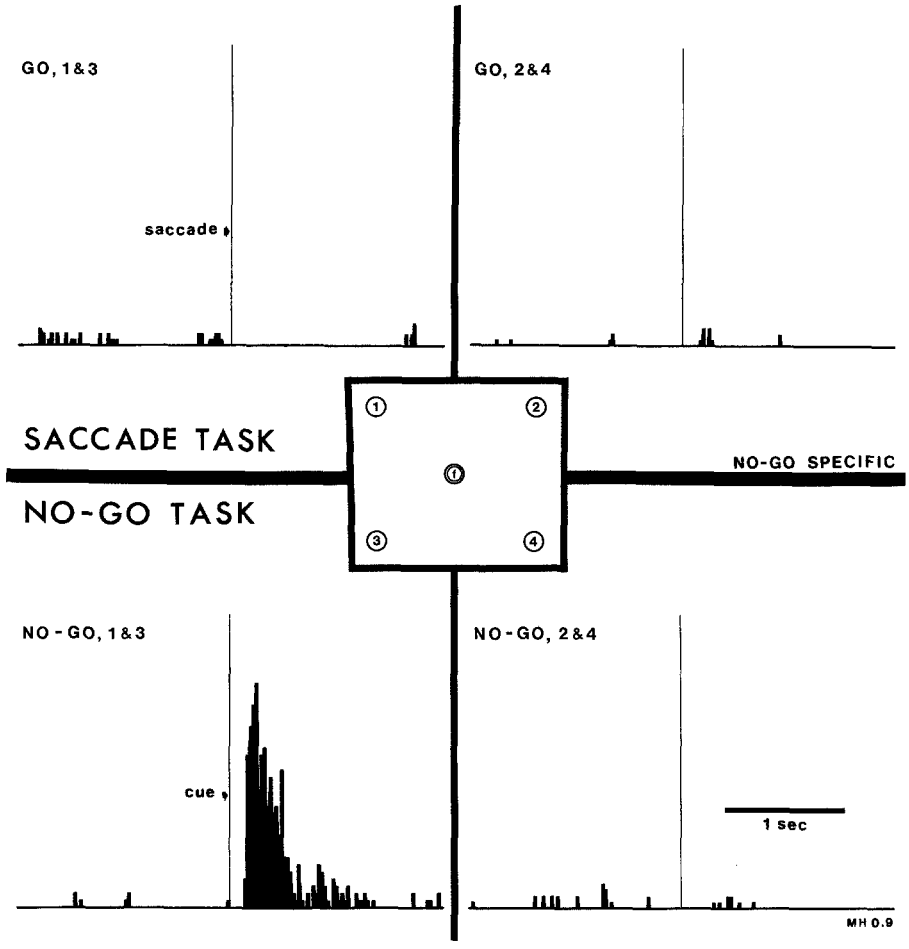

Fig. 4. Response histograms obtained from a single-cell which discharges specifically to leftward targets during the no-go task. Parameters as in Fig. 3

An example of such a comparison appears in Fig. 5. The size and direction of the saccades shown in the two panels are identical but the target locations are different. The figure shows a cell which discharges much more vigorously when the saccades terminate on the lower right target than when they terminate on the other targets, suggesting that a specific location in space is coded relative to the movement rather than a specific saccade size and direction. Of 428 cells studied in this fashion 146 showed spatial selectivity of the sort shown in Fig. 5. The remaining 282 cells did not exhibit obvious spatial selectivity in that they responded in association with saccades to all target locations during the execution of the task. The cells which have been shown in Figs. 1 and 2a fell into this category.

The majority of cells we recorded from in DMFC responded to various aspects of the task on which the monkey performed. In addition to the cells just described, we have found neurons which discharged to the visual stimuli (N = 48) and neurons which fired when the animal was rewarded (N = 81). Most of the reward-related cells did not respond when juice was dispensed unexpectedly between trials; thus the responses of these cells were also conditional and were not invariantly tied to the muscles of the mouth and throat.

Not all cells we studied gave excitatory responses of the sorts shown in the figures so far. Also common were neurons with relatively high spontaneous activity which stopped firing at various times in relation to the performance of the task. For each of the excitatory cell types we have described, it was possible to find an inhibitory counterpart. We had 84 inhibitory cells in our sample.

Electrical stimulation

We stimulated several sites in each of 58 penetrations in DMFC using 250–300 Hz, 50–800 ms duration, monophasic cathodal, 20–300 μA current parameters. Stimulation caused either arrest in ongoing behavior or specific activation of motor acts. Arrest in motor behavior was most common when during the early parts of the penetration the upper layers of cortex were stimulated. Such arrest was typically task specific and persisted for the duration of the stimula-

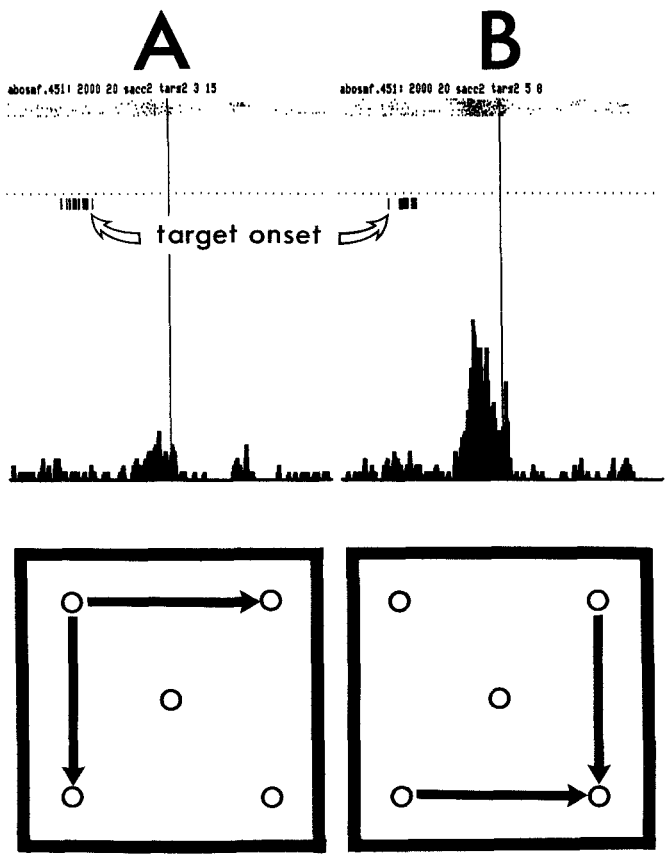

Fig. 5A, B. The responses of a single cell during saccades of identical sizes and directions but with different endpoints. The histograms in **A, B** are both aligned on the saccade (vertical line); the tick marks show the time of target onset. Below each histogram are shown the saccade vectors on which the data are based

tion. When the animal performed on the saccade task, eye movements were arrested, and when he performed on the touch task the arm movements, but not concurrent eye movements, were arrested; stimulation between trials produced no discernible effects. Deeper in the penetrations motor responses were commonly elicited. The kind of movement produced by the stimulation at the majority of sites depended on the task the monkey was working on: eye movements were triggered while the animal performed the saccade task and arm movements while he performed the touch task. As in the upper layers, electrical stimulation was less effective or ineffective when it was administered during the intertrial interval. Electrically triggered responses were studied most extensively in conjunction with the eye-movement task. At most deeper locations (in 40 of 58 penetrations) the stimulation triggered goal-directed eye movements with latencies of 100 to 150 ms with currents as low as 50 μA. That is, stimulation elicited not saccades of invariant directions and amplitudes, as it does in the

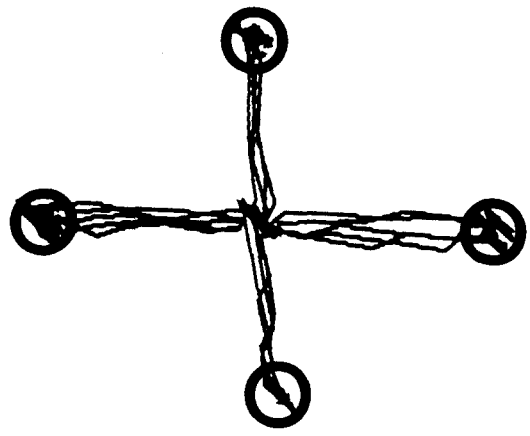

Fig. 6. Eye movement traces produced by electrical stimulation of one DMFC site while the animal fixated each of the four target LEDs shown by the circles. Stimulation elicited saccades at 50 μA and 500 ms duration are superimposed for 15 successive trials. In all cases the effect of the stimulation is to bring the eye to the center of the field where the fixation spot it located

frontal eye fields and the superior colliculi (Robinson and Fuchs 1969; Robinson 1972; Schiller and Stryker 1972), but saccades converging on a specific point in space. An example of this is shown in Fig. 6 as obtained from one of our monkeys after training on a display consisting of a central fixation spot and four targets which appeared above, below, to the left and to the right of fixation. Stimulation was initiated whenever the monkey foveated one of the targets. The result of such stimulation was to bring the eye to the central LED with a latency of 100–130 ms.

Following extensive training on the original diagonal array of targets described in the methods section, we found that at each of the 40 sites we stimulated in the DMFC of one of our animals, we elicited saccades which terminated in the vicinity of one of the five LED locations. Since the probability of this occurring by chance is rather low, we went on to examine the hypothesis that a coding relative to the spatial location of the targets used in the task – hence a learned spatial code – is contained in this area, as already suggested by our single-unit data. To test this idea we retrained this same animal for several days on just two targets, which were placed above and below fixation, thereby requiring the monkey to make vertical eye-movements to get rewarded. After such training the stimulation-elicited saccades at most sites were directed to one or the other of the new vertical targets. We then retrained the animal on a pair of horizontal targets, and found that the goal-directed saccades elicited by stimulation shifted their endpoint to coincide with the locations of the new targets. One to three days of new training (2000–6000 trials) were needed for this shift to occur.

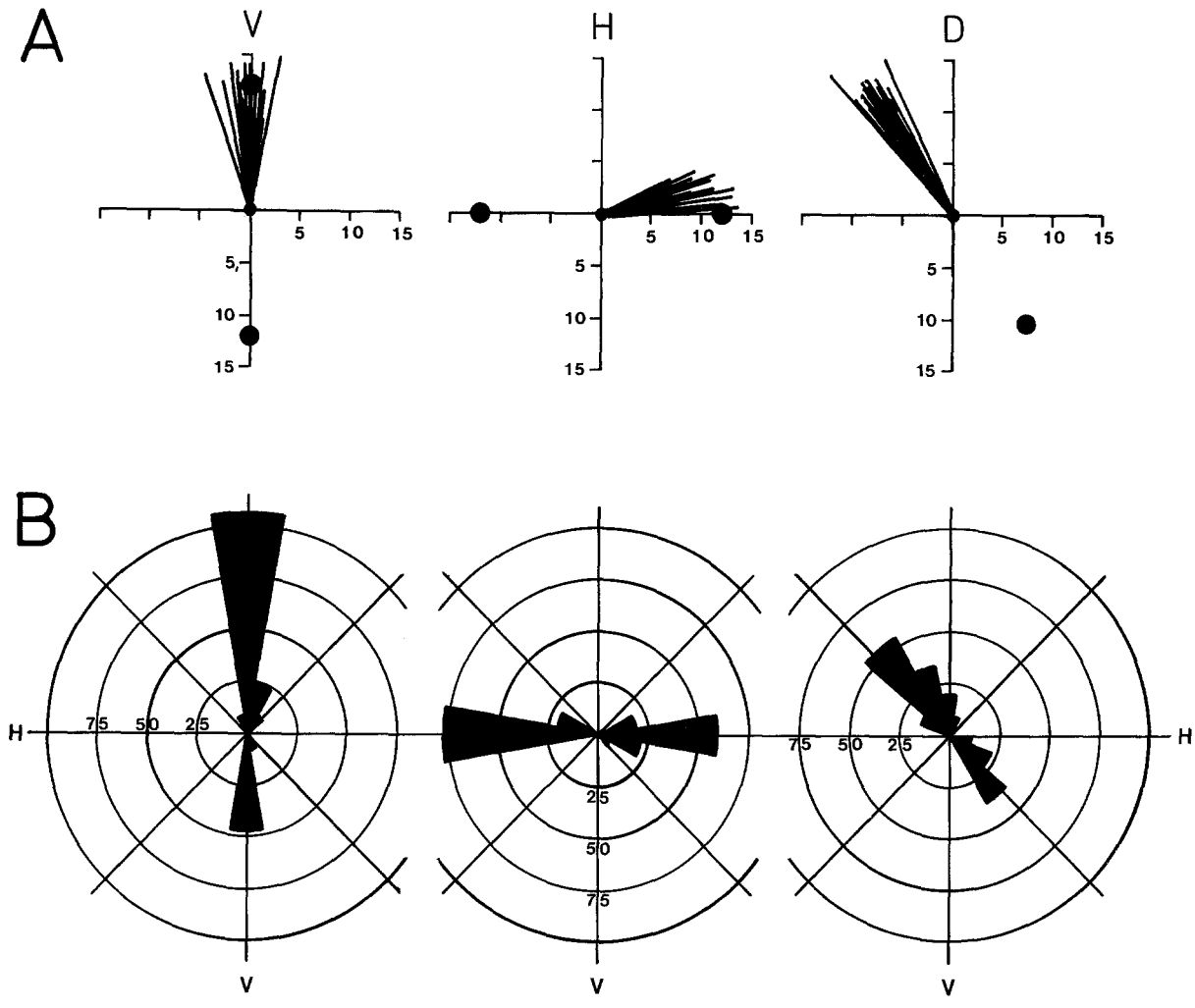

Fig. 7A, B. The effect of electrical stimulation following training on each of three differently positioned pairs of targets. **A** Size and direction of saccades elicited from one site after training on a vertical set (V), horizontal set (H) and diagonal set (D) of targets. Disks: location of targets; Numbers: degree of visual angle. **B** Polar histograms of the number of stimulation elicited saccades for each of 18 directions (binwidth 20 degrees) after training on each set of the vertically, horizontally and diagonally placed stimuli. The data are based on stimulation of the same 10 sites after each of the three sets of training sessions. Polar coordinate numbers indicate number of stimulation elicited saccades (N = 200 for each training condition)

The results of these manipulations are shown in Fig. 7. Stimulation was applied after the animal fixated the center light but before the onset of the target light. The upper set of figures (A) shows the size and direction of saccades elicited from one site after several days of training on each of a pair of vertical, horizontal and diagonal targets respectively. The lower figure (B) shows cumulative polar histograms of saccade directions produced by electrical stimulation of 10 sites after training with each pair of targets. The same 10 sites were stimulated after each new training regimen. At each of these sites the effect of stimulation was contingent on the target positions the animal had just been trained on.

Discussion

The results of this study allow for five generalizations about the organization of DMFC: (1) Single cells in this area respond in a conditional fashion; most neurons which discharge in association with certain motor acts do so only within the context of the task. This observation is further supported by the fact that the effectiveness of electrical stimulation is much greater when it is administered in close temporal proximity with the execution of the task. (2) In many regions of DMFC the activity of neurons is not tied to a specific motor apparatus; such cells discharge in association with saccades during the saccade task and

with arm and hand movements during the touch task and many also discharge when reward is contingent upon withholding motor acts. This assertion is further supported by our observation that the motor acts triggered by electrical stimulation depend on the particular task the animal performs. (3) A spatial code is represented in DMFC; many single neurons in this region discharge in association with task performance relative to specific spatial locations. Electrical stimulation supports this observation in showing that it elicits motor acts which bring the eye or hand to specific task-defined locations in space. (4) The organization of this area depends on what the animal has learned and is modified upon new learning. (5) Neuronal representation in this area can be found for all aspects of the task the animal has learned. In our situation this includes cells which discharge to the visual stimuli, cells which discharge with motor acts related to these targets and cells which discharge upon receipt of the reward.

The conditional nature of neuronal responses in the DMFC is suggested also by some of the findings of Brinkman and Porter (1979) and Tanji and Kurata (1985) and is similar to what has been reported in the caudate nucleus by Hikosaka and Sakamoto (1986). However, an important difference is notable in comparison with the study by Schlag and Schlag-Rey (1985) who found most eye-movement related cells in DMFC to discharge with saccades under all conditions. Schlag used a different kind of task, however, in which animals had to continually search the screen for targets. This difference in our respective studies may be interpreted to further support the idea that the nature of neuronal organization in this area depends heavily on what is learned by the animal.

Our hypothesis that DMFC encodes actions in terms of goals irrespective of their underlying motor apparatus is supported by several lines of evidence: (1) Examination of the efferent connections of the DMFC by Mauritz et al. (1986) revealed that single neurons in this area send their axons to multiple motor areas. (2) Roland et al. (1980) have shown that high metabolic activity, as reflected by the rate of blood flow, occurs in DMFC both when a motor act is performed and when it is imagined. (3) Patients with damage to this area cannot learn to make movements that do not require the achievement of specific loci in space such as waving goodbye (Watson et al. 1986). (4) In humans electrical stimulation of this area either arrests ongoing voluntary movements or evokes learned motor acts such as the repetition of words, complex arm movements and even piano-playing movements with the fingers (Chavel 1976). (5) Gemba and Sasaki (1984) showed that in animals trained to make visually guided arm movements the onset of task-related stimuli evoked a field potential in the DMFC even when the monkey made no overt motor responses; in untrained animals these same stimuli produced no change in DMFC activity.

Lastly our results make evident the fact that the eye-movement control functions of DMFC are quite different from those of the superior colliculi and the frontal eye fields where stimulation-elicited eye-movements, which are initiated within 20–40 ms, are not goal directed and appear unaltered by learning (Bruce et al. 1985; Robinson and Fuchs 1969; Schiller and Stryker 1972).

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