

# Rostrocaudal Distinction of the Dorsal Premotor Area Based on Oculomotor Involvement

NAOTAKA FUJII, HAJIME MUSHIAKE, AND JUN TANJI

*Department of Physiology, Tohoku University School of Medicine, Sendai 980, Japan*

**Fujii, Naotaka, Hajime Mushiake, and Jun Tanji.** Rostrocaudal distinction of the dorsal premotor area based on oculomotor involvement. *J. Neurophysiol.* 83: 1764–1769, 2000. To investigate functional differences between the rostral and caudal parts of the dorsal premotor cortex (PMd), we first examined the effects of intracortical microstimulation (ICMS) while monkeys were performing oculomotor and limb motor tasks or while they were at rest. We found that saccades were evoked from the rostral part (PMdr) whereas ICMS in the caudal part (PMdc) predominantly produced forelimb or body movements. Subsequently, we examined neuronal activity in relation to the performance of visually cued and memorized saccades while monkeys reached an arm toward a visual target. We found that roughly equal numbers of PMdr neurons were active during performance of the oculomotor and limb motor tasks. In contrast, the majority of PMdc neurons were related preferentially to arm movements and not to saccades. In the subsequent analysis, we found that the oculomotor effects evoked in the PMdr differ from the effects evoked in either the frontal eye field (FEF) or supplementary eye field (SEF). These findings suggest that the PMdr is involved in oculomotor as well as limb motor behavior. However, the oculomotor involvement of the PMdr seems to have a functional aspect different from that operating in the FEF and SEF.

## INTRODUCTION

The premotor cortex is divided into dorsal and ventral parts termed the PMd and PMv, respectively. Anatomic studies suggest that the PMd can be further divided into rostral and caudal subregions. Cytoarchitectonic and myeloarchitectonic studies show that the anatomic connectivity in these two areas is different. Barbas and Pandya (1987) called the rostral area the PMdr (approximately corresponding to F7 of Matelli et al. 1998) and the caudal area the PMdc (F2 of Matelli et al. 1998). Only the PMdc sends its output to the primary motor cortex (MI) and spinal cord (Dum and Strick 1991; He et al. 1993) whereas only the PMdr receives prominent input from the dorsolateral prefrontal cortex (Lu et al. 1994). The parietal inputs to the PMdr and PMdc are also different (Ghosh and Gattera 1995; Matelli et al. 1998). Although these anatomic differences have been identified, little is known about the functional or physiological differences between the two areas. It appears as though neurons in the PMdr may be characterized by their responses to visual signals and activities related to motor preparation (Johnson et al. 1996) or the anticipation of visual cues (di Pellegrino and Wise 1991).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

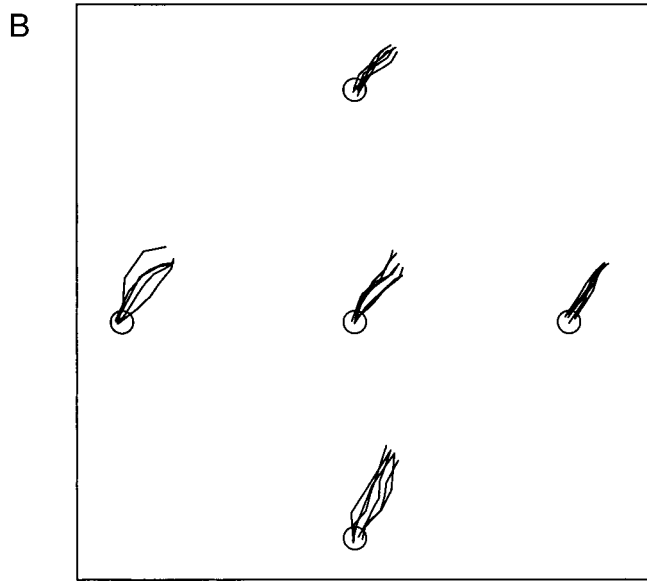
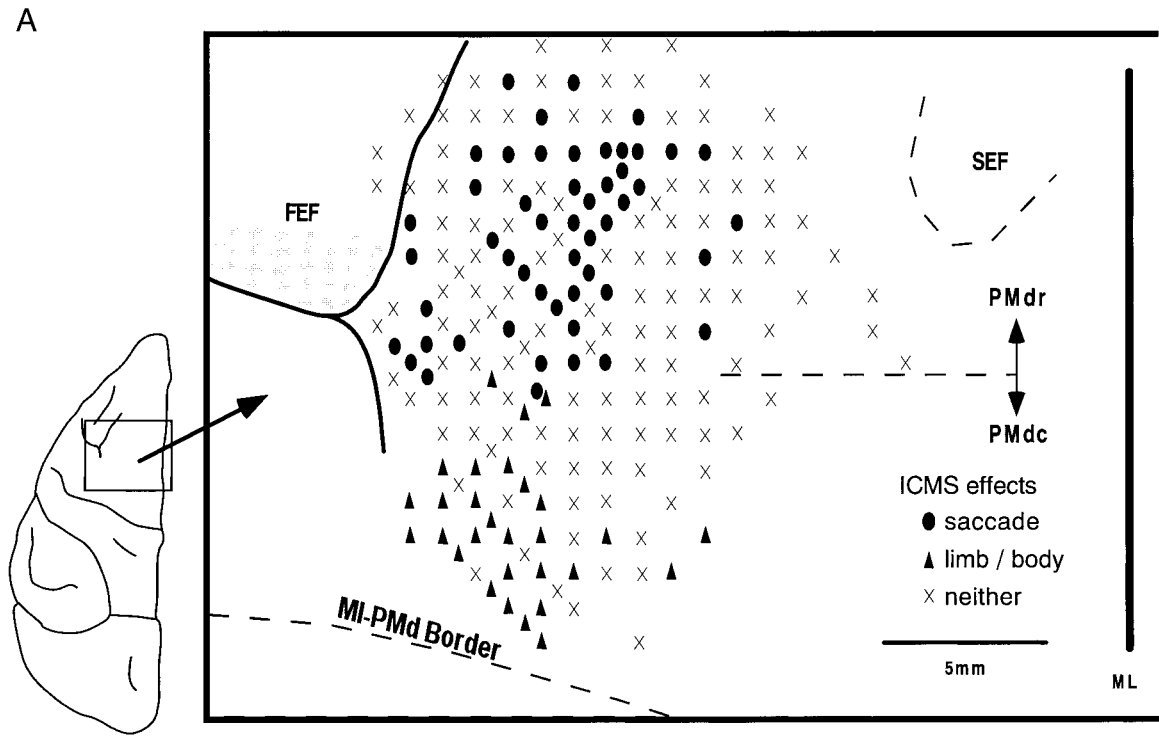
In this study, we compared the oculomotor involvement of the PMdr and the PMdc. We found profound differences in the oculomotor effects of intracortical microstimulation (ICMS) and in the neuronal activity related to visually cued saccades and arm movements.

## METHODS

Two monkeys (*Macaca fuscata*) were trained to perform a delayed saccade task and an arm-reaching task. A monkey sat in a primate chair facing a panel containing five light-emitting diodes (LEDs); one LED was located in the center of the panel and the other four were positioned 20° above, below, right, and left of the central LED. The monkey's eye position was monitored with an infrared reflecting monitor system with a resolution of 4 ms. The task began when the monkey placed its hand on the holding switch and fixated on the LED that was illuminated as the fixation point. The monkey was required to fixate on the LED for 1.5–2 s (precue period). In the saccade task, a second LED, which served as the cue for the future saccade target, was illuminated for 100 ms after the precue fixation period. If the animal maintained fixation on the original LED for an additional 500–800 ms (delay period), the original LED was dimmed. This served as the GO signal. The monkey was rewarded if the second LED was captured with a saccade within 400 ms of the GO signal. In the arm-reaching task, the color of the fixation target was changed from red to green after the monkey had maintained fixation on the fixation target for 1.5–2.0 s (precue period). This change in color served as the GO signal for the arm-reaching task; the monkey was required to release the hold switch (movement onset) and touch the fixation target within 500 ms. The saccade and arm-reaching tasks were randomly selected so that the monkey did not know the type of task or the target until the precue period was over. While the monkey performed the saccade task, we applied ICMS (330 Hz, 10–50 pulses, 0.2 ms duration) under two different conditions. The first condition was that ICMS was delivered 500 ms after the onset of fixation (fixation ICMS). The second condition was that the initiation of ICMS was timed to occur during the delay period and before the GO signal (pre-GO ICMS). We used conventional electrophysiological techniques to record single unit activity and ICMS (Fujii et al. 1998a,b; Mushiake et al. 1996).

During the initial sessions of this study, we explored the MI and PMd to identify and map the arm and body representation areas. For this purpose, we examined ICMS effects while a monkey sat quietly in the chair with unrestrained limbs, at times consuming fruit or vegetables. We used stimulus currents of 5–40  $\mu\text{A}$  in the MI and 40–80  $\mu\text{A}$  in the PMd. ICMS was delivered at 500- $\mu\text{m}$  intervals from the surface. The current with which skeletal or eye movements were evoked with 50% probability was defined as the threshold at each site.

In subsequent sessions, we let the same monkeys perform the trained motor task and examined the entire PMd, supplementary eye field (SEF), and frontal eye field (FEF) by delivering ICMS (40–80  $\mu\text{A}$  in the PMd and SEF, 20–40  $\mu\text{A}$  in the FEF). We explored the



**Saccades evoked at 5 fixation points**

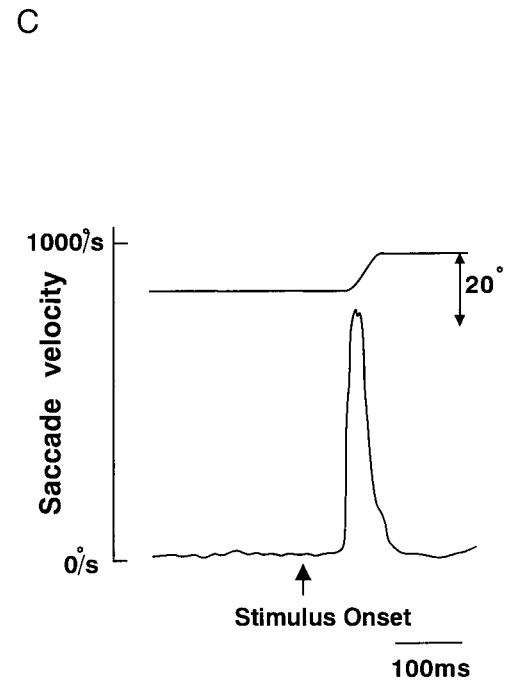


FIG. 1. *A*: stimulation map of the right dorsal premotor cortex (PMd). ●, saccade-evoking sites; ▲, sites where arm or body movements were evoked; ×, sites where no response was evoked. *B*: saccades evoked from 5 different initial fixation points (○). Note that the evoked saccades are a fixed vector type. *C*: eye movement velocity. The evoked eye movements are saccadic eye movements, not slow eye movements.

lateral surface of the frontal cortex from the central sulcus to the anterior edge of the superior limb of the arcuate sulcus at intervals of 0.5–1 mm. After examining the ICMS effects, we recorded the dis-

charges of single cells during performance of the trained task using the same electrode as was used for the ICMS studies.

We statistically analyzed the neuronal activity related to either the

saccade or arm-reaching movement. First, we calculated the mean firing rate and its standard deviation during a control period of 1 s at the end of the fixation period. If the mean firing rate during the premovement period (from the GO signal to the start of the eye or arm movement) exceeded the mean firing rate during the control period by more than two standard deviations, we identified the neuronal activity as premovement-related. We then compared the premovement-related neuronal discharges during the saccade and arm-reaching tasks. The number of discharges during the premovement period was analyzed statistically (Mann-Whitney U test).

If statistically significant activity changes were observed during the premovement period under only one of the two conditions, the PMd neurons were defined as being related to that condition only (saccade only or reach only). If the changes in activity were significantly different under both task conditions ( $P < 0.01$ , Mann-Whitney U test), the PMd neurons were defined as being predominantly related to saccades (saccade > reach) or predominantly related to arm-reaching (reach > saccade). The remaining PMd neurons for which premovement-related activity was not statistically different under both task conditions were defined as being related to both movements (both).

RESULTS

Before recording neuronal activity from the PMd, we identified the MI, FEF, and SEF on the basis of ICMS effects. The FEF was located in the anterior wall of the arcuate sulcus. The SEF was found in the dorsal frontal cortex approaching the medial wall (Fujii et al.1995; Schlag and Schlag-Rey 1987). We also found a site near the spur of the arcuate sulcus where ICMS evoked slow eye movements. Weak currents in the MI evoked skeletomotor responses in the forelimb ( $<40 \mu A$ , 10 pulses) whereas relatively stronger currents ( $>40 \mu A$ ) and longer pulse trains ( $>20$  pulses) were required in the PMd to evoke skeletomotor responses in the forelimb and body. Figure 1A shows the effects of ICMS in the left PMd, which is defined as the dorsal convexity of the frontal cortex rostral to the MI and caudal to the anterior edge of the upper limb of the arcuate sulcus, excluding the anterior and posterior banks of the arcu-

ate sulcus (cf. Fig. 2 in Russo and Bruce 1993). The border between the PMd and MI was drawn according to previously proposed physiological and cytoarchitectonic criteria (Kurata and Tanji 1986; Weinrich 1982). According to these criteria, muscle contractions are readily observed caudal to the border between the PMd and the MI with stimulus currents  $<40 \mu A$ . This border approximately corresponds to the cytoarchitectonic border based on the concentration of large-diameter pyramidal cells in layer V. In the PMd, we defined the effect of ICMS as positive when ICMS evoked eye movements or skeletomotor responses with  $>50\%$  probability. We looked for both skeletal and eye movements in all penetrations with currents  $\leq 80 \mu A$ . In the PMd, the threshold that was needed to elicit eye movements ranged from 60 to 80  $\mu A$  and the threshold for skeletal movements ranged from 40 to 60  $\mu A$ . Within this range of stimulus currents, we did not find any stimulus sites from which ICMS evoked both eye and skeletal movements. The PMd extended from the area just rostral to the MI to the rostral end of the upper limb of the arcuate sulcus, excluding the posterior wall of the arcuate sulcus. As shown in Fig. 1A, the effects of ICMS in the rostral part of the PMd differed from the effects in the caudal part. The rostral part evoked saccades whereas the caudal part evoked predominantly limb or body movements. The genu of the arcuate sulcus corresponded approximately to the border between the two regions. The evoked eye movements were saccadic and not slow and their velocities exceeded  $700^\circ/s$  (Fig. 1C). The evoked saccades were always directed toward the contralateral side (Fig. 1B) and were little influenced by eye position. Based on these ICMS results, we divided the PMd into the PMdr and the PMdc.

In a subsequent study, we examined whether or not ICMS evoked different effects in the PMdr than those evoked in the FEF and SEF. When ICMS was applied during the fixation period, we found no differences in the saccades evoked in the PMd, FEF, and SEF. Constant-vector-type saccades were evoked and the gaze returned to the fixation point. However,

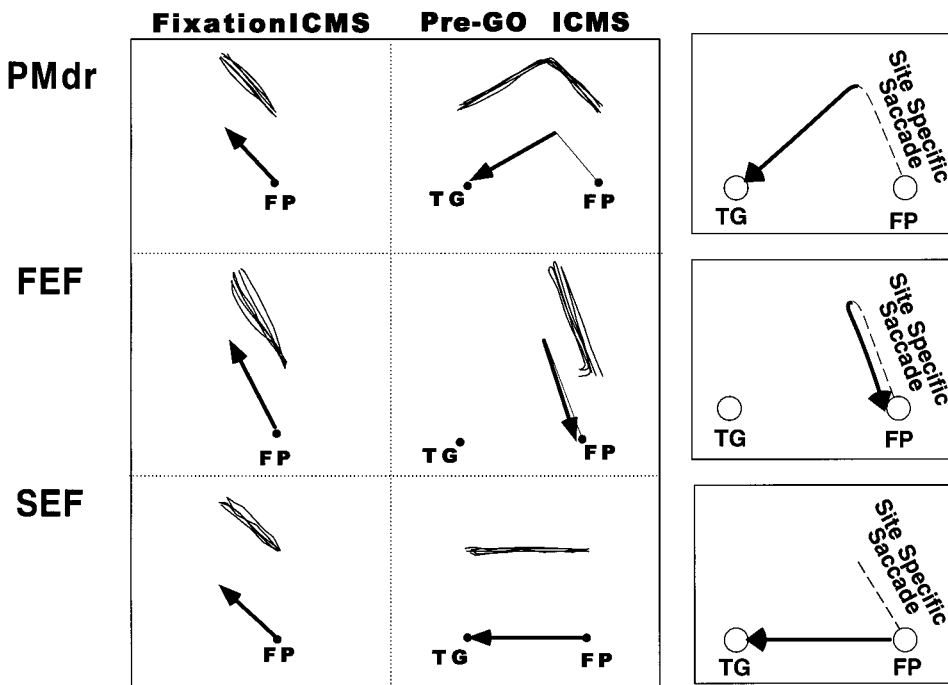


FIG. 2. Top: saccades elicited by stimulation of the PMd. Left: saccades evoked during the fixation period. Right: saccades evoked during the delay period and return saccades. Far right: schematic diagram of an evoked saccade. Middle: saccades elicited by stimulating the frontal eye field. Bottom: saccades elicited by stimulating the supplementary eye field. To facilitate comparison of pre-GO intracortical microstimulation (ICMS) effects, we selected stimulus sites from which fixation ICMS evoked saccades in similar directions. The duration of the ICMS train was 150 ms in these examples. FP, fixation point; TG, target.

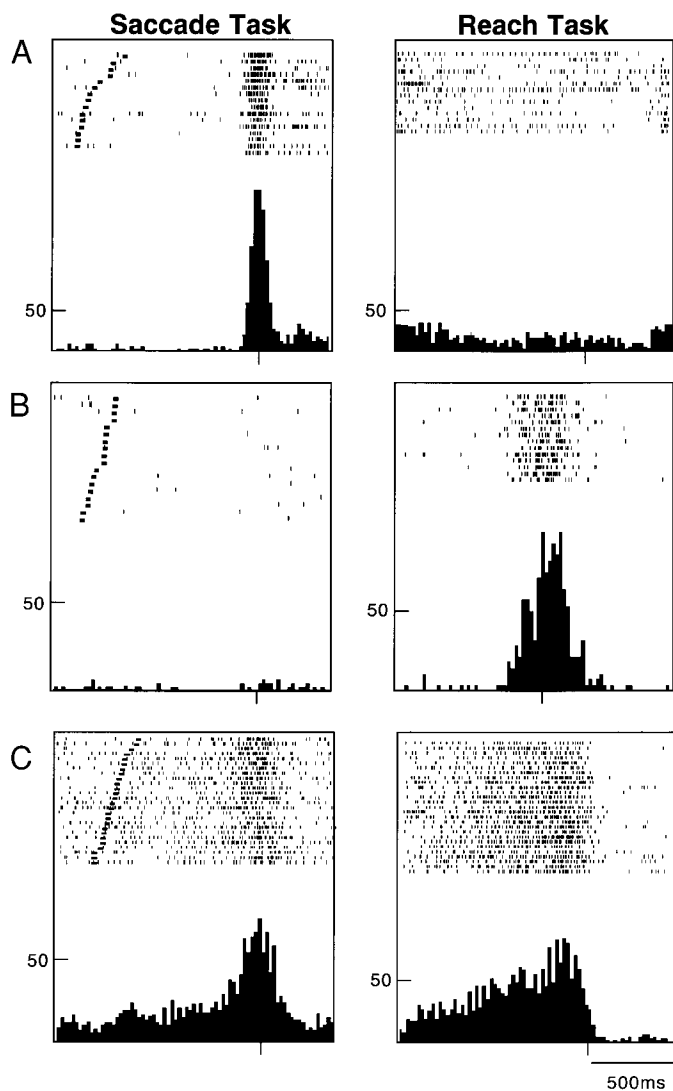


FIG. 3. Examples of 3 types of rostral PMd neurons involved in the 2 behavioral tasks. *A*: neuron is selectively active during the saccade task. *B*: neuron is selectively active during the arm-reaching task. *C*: neuron is equally active in response to saccades and arm reaching. Each row in the raster display indicates a trial, with each dot representing an individual discharge. Each histogram is the sum of the data in each raster. The raster displays and histograms are aligned with either the onset of the saccade or the onset of arm movement. The binwidth is 20 ms. Thick bars in the *left panel* represent onset of the target cue. Neuronal activity during the saccade task to the preferred direction is shown on the *left* whereas activity during the arm-reaching task to the preferred direction is shown on the *right*.

when ICMS was applied during the delay period and before the onset of the GO signal (pre-GO ICMS), we found that the effects of ICMS differed. Specifically, we found a difference in the return movement from the evoked saccades. When we applied ICMS to the PMdr 100 ms before the GO signal, the evoked saccades starting from the fixation point were followed by saccades aimed at the target specified by the cue LED (Fig. 2, *top*). The target was captured in 93% of the cases. The average latency of return saccades was  $173 \pm 49$  ms (SD) after the termination of saccades evoked by ICMS. In contrast, when ICMS was delivered to the FEF, the return saccades brought the line of sight to the fixation point in 63% of the cases (Fig. 2, *middle*). The mean latency of the return saccade was  $152 \pm$

48 ms after termination of the saccades evoked by ICMS. On the other hand, when ICMS was delivered to the SEF during the delay period, saccades were evoked directly to the saccade target (Fig. 2, *bottom*), as shown in Fujii et al. (1995). These data demonstrated that the effects of ICMS to the PMdr differed from those of ICMS to the FEF and SEF.

In addition to the analysis of ICMS effects, we examined neuronal activity in the PMd of the same animals, focusing on the appearance of saccade-related, as opposed to arm-movement-related, activity during performance of the trained task. We classified PMd neurons into five types: 1) exclusively related to saccades (Fig. 3*A*), 2) exclusively related to arm reaching (Fig. 3*B*), 3) predominantly related to saccades, 4) predominantly related to arm reaching, and 5) related to both movements (Fig. 3*C*). We recorded movement-related neuronal activity from 194 PMdr neurons and 347 PMdc neurons. As shown in Table 1, as many as 43% of the neurons in the PMdr showed a preference for the saccade task. In contrast, most (95%) of the PMdr neurons showed a preference for the arm-reaching task.

#### DISCUSSION

In the present study, we found that the effects of ICMS with low currents appeared to differ in the PMdr and the PMdc. The former evoked saccades whereas the latter evoked predominantly limb and body movements. Furthermore, we found that the properties of neuronal activity in relation to the trained oculomotor and arm motor tasks also differed in the two areas. Roughly equal numbers of neurons were active in the PMdr while the eye and arm tasks were being performed whereas most neurons in the PMdc were primarily related to the arm-reaching task. The neuronal activity may indicate further involvement of the PMdr in oculomotor tasks, although we admit that other differences in our task conditions may have contributed to the activity differences (e.g., the saccade task involved an instruction delay whereas there was no delay in the arm-reaching task). These findings provide a physiological basis for dividing the PMd into rostral and caudal parts. This accords with the anatomic view that the PMd includes two cytoarchitecturally separable areas, defined as PMdr and PMdc (Barbas and Pandya 1987).

In the present study, the cortical territory in the PMdr that evoked saccades was separated from the SEF by 5–6 mm of cortex where ICMS evoked no movements, at least with the low current that we employed. Thus the saccade-evoking area in the PMd appears to be a cortical territory distinct from the

TABLE 1. Comparison of the movement-related activity of PMdr and PMdc neurons during saccade and arm-reaching tasks

| Type            | PMdr      | PMdc      |
|-----------------|-----------|-----------|
| Saccade only    | 60 (31)   | 6 (2)     |
| Saccade > reach | 24 (12)   | 1 (0.2)   |
| Both            | 18 (9)    | 9 (3)     |
| Reach > saccade | 21 (11)   | 29 (8)    |
| Reach only      | 71 (37)   | 302 (87)  |
| Total           | 194 (100) | 347 (100) |

Values denote the number of each different type of neuron. Values in parentheses denote the percentage of each type.

SEF. A report by Shook et al. (1991) also supports the view that the the PMdr and the SEF are separate entities. They demonstrated that these two areas have separate anatomic connections with the thalamus, striatum, and forebrain nuclei. The PMdr is also separate from the FEF, which is located in the bank of the arcuate sulcus. It is important to note that the oculomotor effects evoked in the PMdr in our study were different from the effects evoked in the SEF and FEF. This suggests that the PMdr is involved in oculomotor behavior in a manner different from the SEF and the FEF.

We interpret the ICMS effects in the three areas in the following way: ICMS to the FEF evokes stimulus-site-specific saccades that override instructed saccades. In contrast, ICMS to the SEF evokes instructed saccades that override stimulus-site-specific saccades. In the PMdr, the stimulus evokes the stimulus-site-specific saccade first, followed by saccades to instructed targets. Mitz and Godschalk (1989) hinted at the oculomotor involvement of the PMdr. However, they evoked saccades primarily from a region rostral to the PMd. In their cortical map, the saccade-evoking sites were located on the medial part of the prefrontal cortex, rostral to the anterior end of the upper limb of the arcuate sulcus. More recently, Boussaoud et al. (1998) found that eye position modulated neuronal activity in the PMdr; however, the role of the PMd in oculomotor control was not studied. Interestingly, in the cebus monkey, ICMS of the area dorsal to the upper limb of the arcuate sulcus was reported to evoke slow eye movements (Tian and Lynch 1996, 1997). In macaque monkeys, however, the cortical site from which slow eye movements are evoked is located immediately posterior to the arcuate sulcus, close to its spur (Gottlieb et al. 1993, 1994; Tanaka and Fukushima 1998). There appears to be a species difference; the slow-eye part of the FEF in the cebus monkey is located dorsal to the upper limb of the arcuate sulcus and the PMdr is located elsewhere.

Previous reports on the corticocortical connections to the two portions of the PMd revealed that the PMdr, but not the PMdc, receives the output from the FEF (Ghosh and Gattera 1995; Stanton et al. 1993) whereas the parietal cortex caudal to the intraparietal sulcus projects to the PMdr but not to the PMdc (Ghosh and Gattera 1995; Johnson et al. 1996). These reports on anatomic connectivity accord with our findings of oculomotor involvement of the PMdr. We hypothesize that the PMdr, with additional input from the prefrontal cortex (periprincipal sulcus part) (Arikuni et al. 1988; Barbas and Pandya 1987; Lu et al. 1994), plays a role in coordinating eye and arm movements in a context that requires cognitive behavioral control. Further studies are needed to reveal the actual aspects of behavioral factors that call for the involvement of this area.

We thank M. Kurama and Y. Takahashi for technical assistance.

This work was supported by Japan Science and Technology Corporation (Core Research for Evolutional Science and Technology), the Ministry of Education, Science and Culture of Japan (09680809, 11145205, and 11170205), and The Cooperation Research Program of Primate Research Institute, Kyoto University.

Received 26 July 1999; accepted in final form 30 November 1999.

## REFERENCES

- ARIKUNI, T., WATANABE, K., AND KUBOTA, K. Connections of area 8 with area 6 in the brain of the macaque monkey. *J. Comp. Neurol.* 277: 21–40, 1988.
- BARBAS, H. AND PANDYA, D. N. Architecture and frontal cortical connections of the premotor cortex (area 6) in the rhesus monkey. *J. Comp. Neurol.* 256: 211–228, 1987.
- BOUSSAOU, D., JOUFFRAIS, C., AND BREMMER, F. Eye position effects on the neuronal activity of dorsal premotor cortex in the macaque monkey. *J. Neurophysiol.* 80: 1132–1150, 1998.
- 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.
- DI PELLEGRINO, G. AND WISE, S. P. A neurophysiological comparison of three distinct regions of the primate frontal lobe. *Brain* 114: 951–978, 1991.
- DUM, R. P. AND STRICK, P. L. The origin of corticospinal projections from the premotor areas in the frontal lobe. *J. Neurosci.* 11: 667–689, 1991.
- FUJII, N., MUSHIAKE, H., AND TANJI, J. Microstimulation of the supplementary eye field during saccade preparation. *Neuroreport* 6: 2565–2568, 1995.
- FUJII, N., MUSHIAKE, H., AND TANJI, J. Intracortical microstimulation of bilateral frontal eye field. *J. Neurophysiol.* 79: 2240–2244, 1998a.
- FUJII, N., MUSHIAKE, H., AND TANJI, J. An oculomotor representation area within the ventral premotor cortex. *Proc. Natl. Acad. Sci. USA* 95: 12034–12037, 1998b.
- GHOSH, S. AND GATTERA, R. A comparison of the ipsilateral cortical projections to the dorsal and ventral subdivisions of the macaque premotor cortex. *Somatosens. Mot. Res.* 12: 359–378, 1995.
- GOTTLIEB, J. P., BRUCE, C. J., AND MACAVOY, M. G. Smooth eye movements elicited by microstimulation in the primate frontal eye field. *J. Neurophysiol.* 69: 786–799, 1993.
- GOTTLIEB, J. P., MACAVOY, M. G., AND BRUCE, C. J. Neural responses related to smooth-pursuit eye movements and their correspondence with electrically elicited smooth eye movements in the primate frontal eye field. *J. Neurophysiol.* 72: 1634–1653, 1994.
- HE, S. Q., DUM, R. P., AND STRICK, P. L. Topographic organization of corticospinal projections from the frontal lobe: motor areas on the lateral surface of the hemisphere. *J. Neurosci.* 13: 952–980, 1993.
- JOHNSON, P. B., FERRAINA, S., BIANCHI, L., AND CAMINITI, R. Cortical networks for visual reaching: physiological and anatomical organization of frontal and parietal lobe arm regions. *Cereb. Cortex* 6: 102–119, 1996.
- KURATA, K. Information processing for motor control in primate premotor cortex. *Behav. Brain Res.* 61: 135–142, 1994.
- KURATA, K. AND TANJI, J. Premotor cortex neurons in macaques: activity before distal and proximal forelimb movements. *J. Neurosci.* 6: 403–411, 1986.
- LU, M. T., PRESTON, J. B., AND STRICK, P. L. Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. *J. Comp. Neurol.* 341: 375–392, 1994.
- MATELLI, M., GOVONI, P., GALLETI, C., KUTZ, D. F., AND LUPPINO, G. Superior area 6 afferents from the superior parietal lobule in the macaque monkey. *J. Comp. Neurol.* 402: 327–352, 1998.
- MITZ, A. R. AND GODSCHALK, M. Eye-movement representation in the frontal lobe of rhesus monkeys. *Neurosci. Lett.* 106: 157–162, 1989.
- MUSHIAKE, H., FUJII, N., AND TANJI, J. Visually guided saccade versus eye-hand reach: contrasting neuronal activity in the cortical supplementary and frontal eye fields. *J. Neurophysiol.* 75: 2187–2191, 1996.
- PREUSS, T. M., STEPNIWSKA, I., AND KAAS, J. H. Movement representation in the dorsal and ventral premotor areas of owl monkeys: a microstimulation study. *J. Comp. Neurol.* 371: 649–676, 1996.
- RUSO, G. S. AND BRUCE, C. J. Effect of eye position within the orbit on electrically elicited saccadic eye movements: a comparison of the macaque monkey's frontal and supplementary eye fields. *J. Neurophysiol.* 69: 800–818, 1993.
- SCHLAG, J. AND SCHLAG-REY, M. Evidence for a supplementary eye field. *J. Neurophysiol.* 57: 179–200, 1987.
- 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.
- STANTON, G. B., BRUCE, C. J., AND GOLDBERG, M. E. Topography of projections to the frontal lobe from the macaque frontal eye fields. *J. Comp. Neurol.* 330: 286–301, 1993.

- TANAKA, M. AND FUKUSHIMA, K. Neuronal responses related to smooth pursuit eye movements in the periarculate cortical area of monkeys. *J. Neurophysiol.* 80: 28–47, 1998.
- TANJI, J. The supplementary motor area in the cerebral cortex. *Neurosci. Res.* 19: 251–268, 1994.
- TIAN, J. R. AND LYNCH, J. C. Functionally defined smooth and saccadic eye movement subregions in the frontal eye field of Cebus monkeys. *J. Neurophysiol.* 76: 2740–2753, 1996.
- TIAN, J. R. AND LYNCH, J. C. Subcortical input to the smooth and saccadic eye movement subregions of the frontal eye field in Cebus monkey. *J. Neurosci.* 17: 9233–9247, 1997.
- WEINRICH, M. AND WISE, S. P. The premotor cortex of the monkey. *J. Neurosci.* 2: 1329–1345, 1982.
- WISE, S. P. The primate premotor cortex: past, present, and preparatory. *Annu. Rev. Neurosci.* 8: 1–19, 1985.
- WISE, S. P., BOUSSAOD, D., JOHNSON, P. B., AND CAMINITI, R. Premotor and parietal cortex: corticocortical connectivity and combinatorial computations. *Annu. Rev. Neurosci.* 20: 25–42, 1997.