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Cortical afferents and efferents of monkey postarcuate area: an anatomical and electrophysiological study

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Summary. A study has been made of the cortico-cortical efferent and afferent connections of the posterior bank of the arcuate sulcus in the macaque monkey. The distribution of efferent projections to the primary motor cortex (MI) was studied by injecting three different fluorescent retrograde tracers into separate regions of MI. The resultant labeling showed a discrete and topographically organized projection: neurons lying below the inferior limb of the arcuate sulcus project into the MI face area, while neurons located in the posterior bank of the inferior limb of the arcuate sulcus and in the arcuate spur region project into the MI hand area. These findings were confirmed electrophysiologically by demonstrating that postarcuate neurons could only be activated antidromically by stimulation within restricted regions of MI. HRP injections within postarcuate cortex indicated that afferents to this region arise from a number of cortical areas. However, the largest numbers of labeled neurons were found in the posterior parietal cortex (area 7b; PF) and in the secondary somatosensory region (SII). Neurons in both 7b (PF) and SII could be antidromically activated by postarcuate stimulation. It was further shown that stimulation of area 7b (PF) gives rise to short-latency synaptic responses in postarcuate neurons, including some neurons with identified projections to MI. The results are discussed in relation to the possible function of the postarcuate region of the premotor cortex in the sensory guidance of movement.

Key words: Cortex – Monkey – Postarcuate area – Premotor area

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Introduction

Many anatomical and functional differences between the rostral and caudal parts of the monkey precentral gyrus have been reported. On purely cytoarchitectonic grounds, a distinction has been made between a rostral region (area 6) and a caudal region (area 4), but considerable disagreement exists as to where the boundary between them should be located (for a review of this question see Wise 1984). The term 'premotor' cortex (PM) was introduced to distinguish the rostral parts of the precentral gyrus from the primary motor cortex (Fulton 1935), and in early studies, the terms primary motor cortex and premotor cortex were used interchangeably with areas 4 and 6 respectively. However, the primary motor cortex or MI defined by Woolsey's stimulation experiments (Woolsey et al. 1952) clearly included the caudal part of area 6.

The application of modern techniques has emphasized important differences between PM and MI (see Wiesendanger 1981; Wise 1984). These differences can be summarized as follows:

1. There is a relative paucity of corticospinal neurons in PM (Catsman-Berrevoets and Kuypers 1976; Jones and Wise 1977; Coulter and Jones 1977; Murray and Coulter 1981; Sessle and Wiesendanger 1982).

2. Several recent studies using intracortical microstimulation in conscious monkeys have reported that significantly higher shocks are required to evoke movements from PM than from MI (Kwan et al. 1978; McGuinness et al. 1980; Sessle and Wiesendanger 1982; Weinrich et al. 1984).

3. Projections to the parvocellular red nucleus are derived from both PM and MI, but the magnocellular red nucleus receives projections only from MI (Kuypers and Lawrence 1967; Catsman-Berrevoets et al. 1979; Hartmann-von Monakow et al. 1979).

4. PM receives direct projections from areas in the posterior parietal lobe which do not project to MI (Jones and Powell 1969; Pandya and Kuypers 1969; Chavis and Pandya 1976).

5. Many PM neurons are strikingly active during preparation for visually-cued movements (Godschalk et al. 1981; Weinrich and Wise 1982; Weinrich et al. 1984). In general, these neurons exhibit a greater modulation of their activity following presentation of the visual stimulus used to cue a motor response than during the motor response itself (Godschalk et al. 1981; Weinrich et al. 1984). Although some MI neurons are influenced by sensory cues, the greatest modulation of their activity is seen during movement (Evarts and Tanji 1974; Godschalk et al. 1981).

According to these criteria, it is clear that PM includes part of the cortex which gives rise to corticospinal projections, and that MI is not co-extensive with that described by Woolsey et al. (1952), but is restricted to the caudal parts of the precentral gyrus. None of the above criteria allow a strict boundary to be drawn between MI and PM; rather they suggest a gradient of changing connectivity and neuronal properties as one passes from MI to PM.

The activity of PM neurons during preparation for movement may give an important clue to the possible functions of PM cortex. This type of pre-movement activity might reflect the use of sensory information to prepare or guide the course of the movement. PM is known to receive a variety of sensory inputs (Bignall and Imbert 1969; Rizzolatti et al. 1981b, c) and some of these may depend upon projections from the inferior parietal lobule, which has been implicated in a variety of sensory-motor functions, including spatial perception and motor guidance (Hyvärinen and Poranen 1974; Mountcastle et al. 1975; Lynch et al. 1977; Hyvärinen 1982).

Interruption of projections from the inferior parietal lobule to the frontal cortex disturbs visual guidance of movements (Haaxma and Kuypers 1975), while lesions involving the premotor area of macaque monkeys cause deficits in the ability to use sensory cues to direct movements (Moll and Kuypers 1977; Deuel 1977; Halsband and Passingham 1982; Rizzolatti et al. 1983). Premotor neurons may exert their influence over movement via projections into the primary motor cortex (Pandya and Kuypers 1969; Pandya and Vignolo 1971; Künzle 1978; Matsumura and Kubota 1979; Muakkassa and Strick 1979).

The present study was designed to investigate a) the topography of premotor cortico-cortical projections into the primary motor cortex and b) the afferent cortico-cortical projections to these same premotor regions from the inferior parietal lobule.

Materials and methods

1. Axonal transport studies

In four adult macaque monkeys, retrograde tracers were injected unilaterally into the frontal lobe. Retrograde transport of different *fluorescent tracers* injected into different parts of the primary motor cortex was used to identify *efferent* projections from the postarcuate area into MI. Injections of *HRP* into the postarcuate area were used to identify *afferent* projections to this area e.g. from the inferior parietal lobule. The non-injected hemisphere was used for either lesion or electrophysiological experiments.

Anaesthesia was induced with ketamine (10 mg/kg i.m.), and maintained with Nembutal (i.v.); the monkeys respired spontaneously. After the head had been mounted in a stereotaxic frame, a large craniotomy was made and the dura opened.

1.1. Fluorescent tracers. In four monkeys (*Macaca fascicularis* 5.2 kg, 5.0 kg and 2.1 kg; *Macaca mulatta* 5.6 kg), three different fluorescent retrograde tracers were injected into three separate areas of the primary motor cortex using glass micropipettes. After each injection, the micropipette was kept in situ for 1–2 min. After the injections had been made, the dura incision was sutured and the wound closed. The following tracers were used: Granular Blue (GB, 2% in water), True Blue (2% in water) (Bentivoglio et al. 1979), Diamidino Yellow (DY, 2% suspension in 0.2 M phosphate buffer at pH 7.2) (Keizer et al. 1983) and Fast Blue (FB, 7% in water) (Bentivoglio et al. 1980). A new tracer, 322/60 (2% in water) (synthesized by Dr. O. Dann) was also used. This compound, when viewed at 360 nm wavelength, produces a pale blue granular fluorescence of the cytoplasm and a yellow nucleus. Its transport time is similar to DY and FB (Kuypers and Keizer, unpublished observations).

In the first two monkeys we made large injections in the primary motor cortex so as to guarantee labeling of a large number of neurons in the premotor cortex. In both these monkeys, a large part of the hand area was filled with multiple injections of GB. The total volume injected was 2.6 and 1.5 µl, in the first and second monkey respectively. Multiple injections of TB (2.0 and 1.5 µl, respectively) and of DY (1.8 and 1.5 µl, respectively) were made in two separate regions of the face area in these monkeys. The depth of the penetrations over which these tracers were injected was up to 7 mm in the first monkey and up to 3 mm in the second.

In the third monkey, the objective was to make small injections in physiologically-identified regions of the primary motor cortex. Prior to the injections, the cortical motor representation was determined by intracortical microstimulation. During this procedure, Nembutal anaesthesia was discontinued and replaced by regular i.m. injections of ketamine. A tungsten stimulating microelectrode was used to explore the cortex and the movements produced by a train of 13 cathodal shocks at a frequency of 300 Hz and strengths of 5–50 µA were noted. Penetrations yielding low threshold (< 10 µA) movements of the toes, of the index finger and of the perioral and tongue muscles were noted. Subsequently these cortical loci were injected respectively with 0.6 µl of DY, FB and 322/60. The depth of these injections was 1.5 mm for DY, 3 mm for FB and 322/60.

In the fourth monkey, injections were made in a similar fashion as in the third. In this case, areas yielding low threshold movements of the toes, of the fingers and of the tongue were injected with 322/60 (0.4 µl), FB (0.6 µl) and DY (0.9 µl) respectively, all at a depth of 1.5 mm.

After 7 days the animals were deeply anaesthetized with Nembutal and transcardially perfused with hypertonic saline solution (2.7%) followed by cacodylate-buffered 10% formaline (pH 7.2) and cacodylate-buffered 7% sucrose (pH 7.2). The

injected hemisphere was photographed and 30 μm coronal frozen sections were made. Every fifth section (first and second monkeys) or every second section (third and fourth monkeys) was mounted, air dried and studied with a fluorescence microscope providing excitation ligth of 360 nm wavelength. Representative sections were charted with an x–y plotter. The location of labeled neurons was plotted on the photograph.

1.2 Horseradish peroxidase. In two monkeys (*Macaca mulatta*, 5.9 ; *Macaca fascicularis*, 3.0 kg) multiple injections of 0.1 μl horseradish peroxidase (HRP, 30% in 5% polyvinyl pyrolidon in water) were made with glass micropipettes in the posterior bank of the inferior limb of the arcuate sulcus, 1.0 mm below the surface and 1–2 mm apart. After each injection, the pipette was kept in situ for 2 min. Three days later the animals were deeply anaesthetized with Nembutal and transcardially perfused (Mesulam 1978). The injected hemisphere was photographed and 30 μm coronal frozen sections were made. Every fifth section was incubated with tetramethylbenzidine (TMB) (Mesulam 1978). A second series of sections from the injection area was incubated with diaminobenzidine (DAB) (Graham and Karnovsky 1966). Every other section was counterstained with a Nissl stain. The sections were studied microscopically under darkfield illumination, and representative sections were charted by means of an x–y plotter. The results were plotted in similar fashion to the fluorescent tracer cases.

2. Electrophysiology

Electrophysiological experiments revealed cortico-cortical connections of the periarcuate area by demonstrating either antidromic or synaptic single or multi-unit responses to electrical stimulation of different cortical areas.

Four adult monkeys (2 *Macaca fascicularis*: 5.7 and 3.0 kg; 2 *Macaca nemestrina*: 4.7 and 5.2 kg) were anaesthetised with ketamine (10 mg/kg i.m.), followed by 2–5% methoxyflurane (Penthrane) in combination with a 80% : 20% N_2O : O_2 mixture. The monkeys respired spontaneously. The head was mounted in a stereotaxic apparatus and a unilateral craniotomy carried out. The dura was opened and the exposed cortex covered with warm paraffin oil. Blood pressure, heart rate, end-tidal pCO_2 and core temperature were monitored throughout the experiment and kept within normal physiological limits.

Intracortical stimulation was performed using an array of up to 7 stimulating tungsten wires (diameter 250 μm) insulated with varnish. Electrode tip impedance was 10–50 kΩ at 1 kHz. Electrodes were mounted together in a plexiglass holder held via a ball-and-socket joint to a manipulator. Each electrode was first adjusted so that its tip touched the pial surface; the electrodes were then advanced together. Each stimulating electrode could be connected via a switch panel to the cathode of a constant-current stimulator; a rectal probe served as the anode. Stimulus width was 0.2 ms; current cancellation (Asanuma and Rosén 1973) was used to reduce stimulus artefacts.

Pyramidal tract stimulation was carried out with a tungsten electrode inserted stereotaxically into the pyramid just caudal to the pons.

Recording. Multi-unit responses were recorded with low impedance (200–500 kΩ at 1 kHz) varnish-insulated tungsten electrodes and averaged using a Neurolog NL 750 Averager. Single-unit responses were recorded with 1–2 MΩ impedance electrodes. A plexiglass pressor plate was used to improve the stability of single unit activity.

Histology. The positions of all electrode penetrations were marked during the experiment on a photograph of the exposed cortex. Tracks made by recording or stimulating electrodes were marked by electrolytic lesions (50–100 μA d.c. current for 10 s). Cortical surface landmarks were made with small injections of Alcian Blue. The hemisphere was re-photographed; 50 μm frozen sections were cut and stained with cresyl violet, and electrode tracks identified and reconstructed.

Results

1. Axonal transport studies

1.1. Fluorescent tracers. The distribution of labeled neurons in the premotor cortex after primary motor cortex injections was essentially similar in all four monkeys. However, the deep injections (up to 7 mm) made in the first monkey involved the underlying white matter and the results from this case were therefore discarded. The injections made in the second, third and fourth monkeys were confined entirely to the gray matter of MI. In the third and fourth monkeys, relatively small injections were made into clearly defined regions of MI: a detailed description of the labeling in the third monkey will be given.

Figure 1 (left) shows the overall distribution of neurons labeled with each of the three tracers. Representative transverse sections (a–e) include details of the three different injection sites. The tracer 322/60, injected laterally in the MI peri-oral representation (Fig. 1, injection 1) produced the largest injection site (Fig. 1d) and the most widespread labeling. Labeled cells were found in a wide band reaching antero-laterally from the injection site into the region between the inferior limb of the arcuate sulcus and the lateral fissure including some labeling in the posterior bank of the inferior arcuate limb (Fig. 1e). The labeled neurons were distributed in both supra- and infragranular layers of the cortex, with the former predominating in most premotor regions. Virtually no labeling was seen in the prearcuate cortex. Some labeling of postcentral cells was seen near the posterior edge of the central sulcus directly opposite the injection site; this may have resulted from direct diffusion of the injected material to the postcentral gyrus. Apart from this labeling, however, those parts of the postcentral gyrus corresponding to areas 3b and 1 (the posterior bank of the central sulcus and the anterior part of the postcentral convexity) were void of labeled cells (Fig. 1c). Some labeled cells were found deep in the central sulcus in the region corresponding to area 3a. The most lateral part of area 2, lying between the tip of the intraparietal sulcus (IPS) and the lateral fissure was heavily labeled. The labeled neurons were distributed in both supra- and infragranular laminae

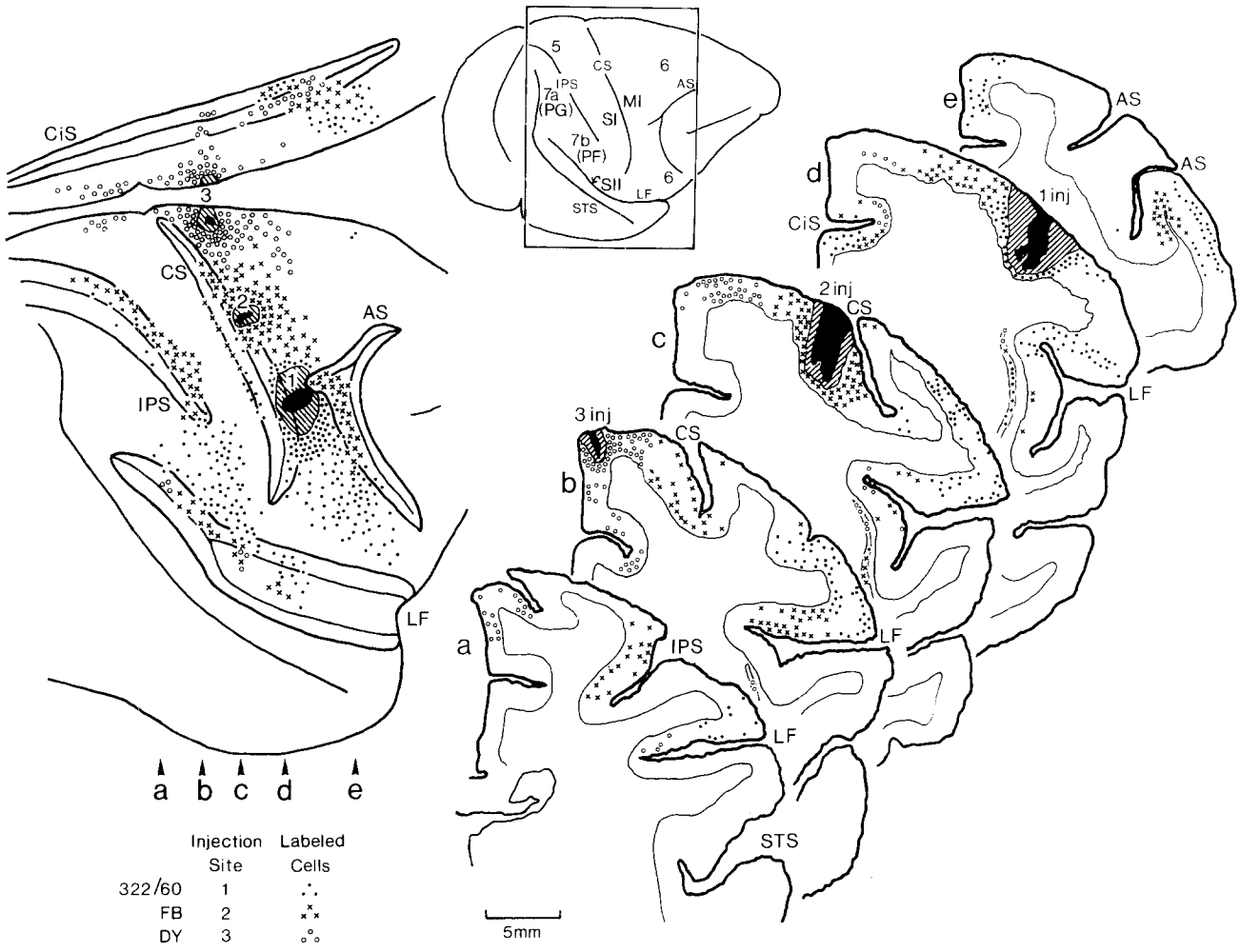

Fig. 1. Schematic representation of the distribution of labeled neurons after injection of three different retrograde fluorescent tracers (322/60; FB; DY) in the primary motor cortex. The cortical regions drawn are indicated by the frame on the inset diagram, in which various cytoarchitectonic areas are also shown. Representative transverse sections (a–e) are shown on the right. The centre of the injection sites (1 inj. etc.) are shown in black; the hatched areas represent the zone of densely labeled tissue around the injected material. In the sections shown, each symbol represents about 5 labeled neurons. AS: arcuate sulcus; CiS: cingulate sulcus; CS: central sulcus; IPS: intraparietal sulcus; LF: lateral fissure; MI: primary motor cortex; SI, II: primary and secondary somatosensory cortex; SPCS: superior precentral sulcus; STS: superior temporal sulcus

(Fig. 1c). A few labeled cells were present in the anterior part of the inferior parietal lobule.

The FB injection in the hand area (Fig. 1, injection 2) reached deep into the anterior bank of the central sulcus (Fig. 1c). Again, the band of labeled precentral neurons reached anteriorly and laterally, including the spur and the inferior limb of the arcuate sulcus. In Fig. 1e, it can be seen that FB-labeled cells were located in the posterior bank of the inferior limb of the arcuate sulcus, in contrast to the 322/60 labeling which was found predominantly in neurons located in the convexity of the precentral gyrus. The FB-neurons were particularly numerous in that part of the posterior bank which, in these monkeys, was deeply folded under the convexity of the precentral gyrus. There was little or no overlap in the precentral distribution of 322/60- and FB-labeled neurons. Once again, a limited number of postcentral neurons was labeled in the area opposite the FB injection area (Fig. 1b, c). In the posterior parietal region, there was labeling of neurons for a considerable distance along the upper bank of the IPS (areas 2 and 5 c.f. Strick and Kim, 1978). Both supra- and infragranular neurons were labeled. Once again, very few FB cells were found in the inferior parietal lobule.

The DY injection in the foot area (Fig. 1, injection 3) was very small and this probably resulted in the rather sparse labeling of cells with this tracer. However, the antero-lateral orientation of the band

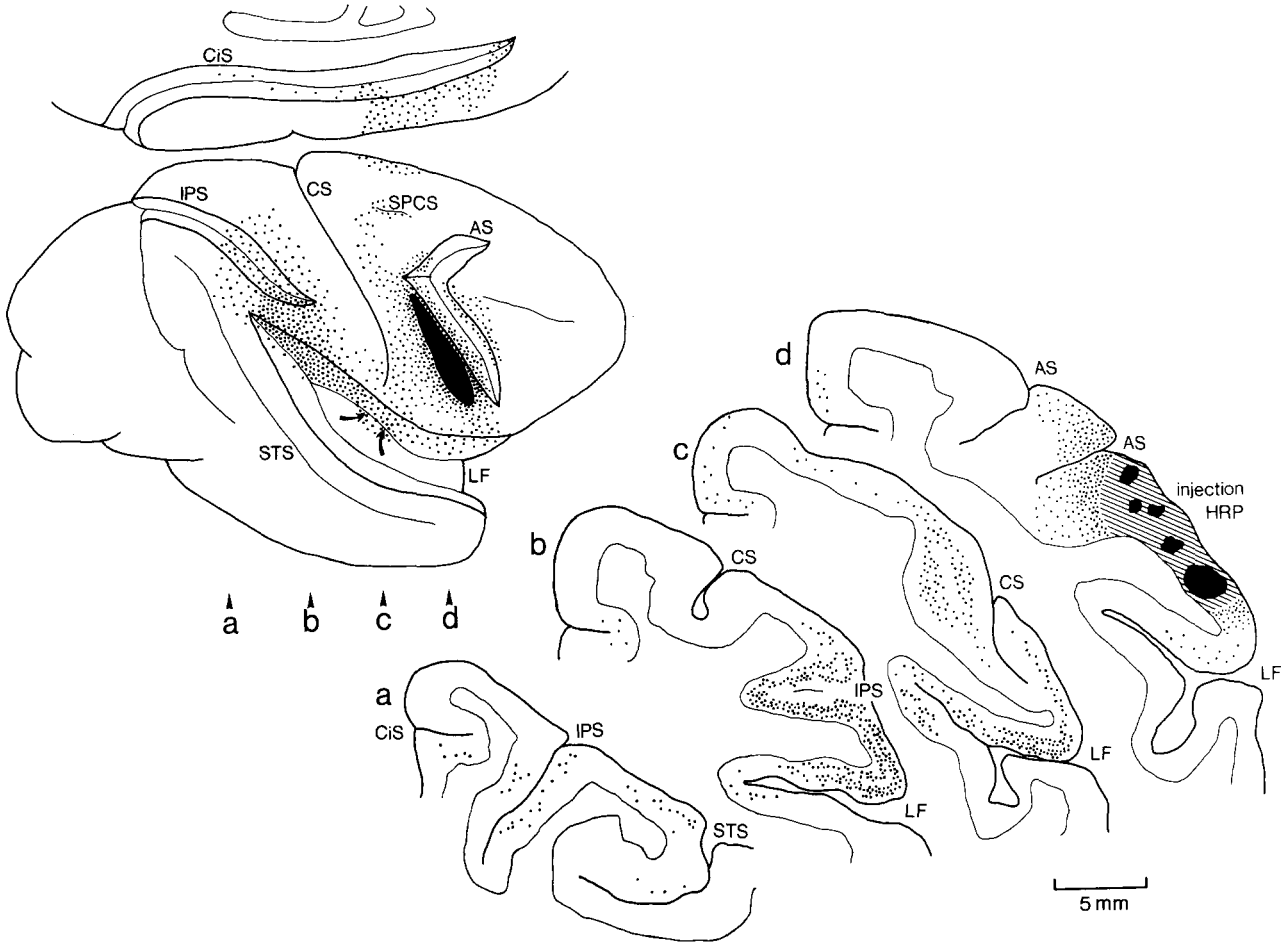

Fig. 2. Schematic representation of the distribution of labeled neurons after HRP infiltration of lateral area 6 (black and striped area). Each dot in the sections a–d represents about 10 labeled neurons

of DY-labeled neurons resembled that seen with the other two groups of labeled cells. DY-labeled cells were found anterior to the region normally occupied by the superior precentral gyrus; no labeled cells were found in the region of the arcuate sulcus. The location of labeled cells in the postcentral gyrus once again corresponds to areas 2 and 5.

Separate populations of FB-, DY- and 322/60-labeled neurons were found in the dorsal operculum of the lateral fissure (second somatosensory area, SII) and in the vicinity of the cingulate sulcus (supplementary motor area, SMA) as described by Matsumura and Kubota (1979) and Muakkassa and Strick (1979). In the contralateral hemisphere, there was little or no labeling of MI neurons with FB (hand area) or DY (foot area) whereas many 322/60-labeled neurons were seen in the contralateral MI face area and in the contralateral SMA.

In the second monkey, the injections of the different tracers into the MI face and hand areas were larger than in the above case, but there was no appreciable overlap between the injection sites. This was also true for the distribution of labeled cells in the precentral gyrus and posterior parietal cortex. which closely resembled that shown in Fig. 1. However, there was significant spread of injected material across the central sulcus, and this probably explains the fact that labeled cells were found in areas 3b and 1, as well as in areas 5 and 2.

The results obtained in the fourth monkey were similar to those described for the third monkey. The injection in the foot area was slightly larger than the corresponding injection in the case described above. The hand area injection again produced heavy labeling of cells in the spur and inferior limb of the arcuate sulcus. In addition, labeled neurons were also seen in the vicinity of the superior precentral sulcus, as reported by Muakkassa and Strick (1979). Once again, no significant labeling was observed in the postcentral SI regions corresponding to areas 3b and 1.

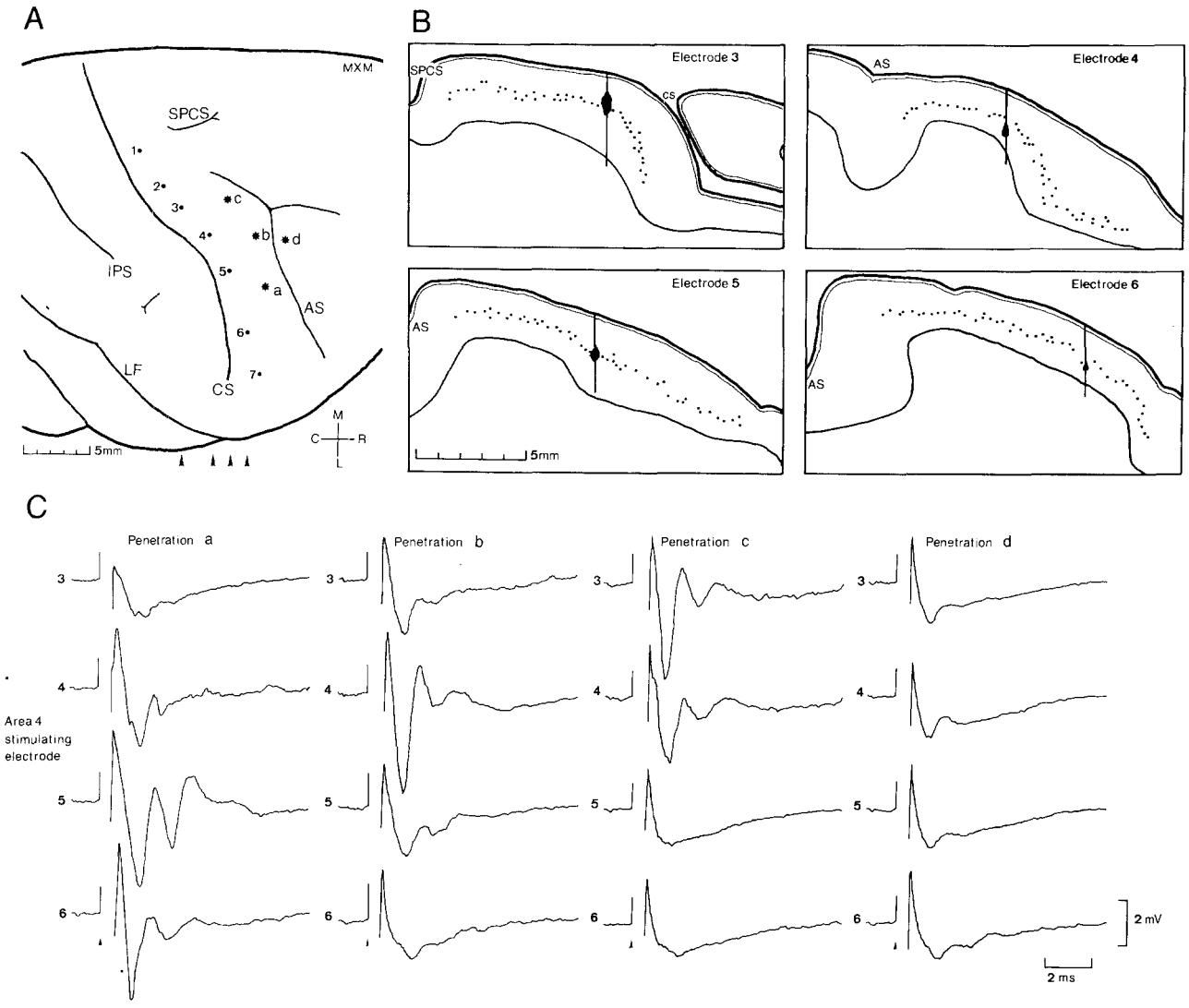

Fig. 3A–C. Topographic distribution of projections from periarcuate cortex to primary motor cortex. Mass responses. **A** Periarcuate sites (a–d) which were explored for antidromic mass responses evoked from stimulating electrodes 1–7 located in area 4. L: lateral; M: medial; C: caudal; R: rostral. Arrows indicate level of frontal sections shown in **B** to demonstrate the tracks made by four stimulating electrodes (3, 4, 5 and 6). After initial adjustments, stimulating electrode tips were left in the same position for the rest of the experiment, at the end of which the lesions shown were made electrolytically (50 μA, 10 s). Dots indicate location of Betz cells in lamina V. **C** Averages of 32 responses recorded in the four penetrations a–d shown in **A** and evoked by intracortical stimulation (300 μA, 0.2 ms) at area 4 sites 3–6. Stimulus artefacts indicated by arrows. Depth at recording sites was 1.5 mm

1.2. Horseradish peroxidase. In both cases the injection area comprised the lateral part of area 6 along the inferior limb of the arcuate sulcus. In one animal, 21 injections (total of 2.1 μl) were made in three parallel rows, within 3 mm of the arcuate sulcus. In the second animal, 17 injections (total 1.7 μl) were made in two parallel rows within 2 mm of the arcuate sulcus.

The results in the first case are shown in Fig. 2. In the injected cortex small needle tracks and lesions were present. They were surrounded by a densely-stained area (black in Fig. 2). This region was surrounded in turn by a zone containing many labeled neurons. It extended rostrally into the banks of the inferior limb of the arcuate sulcus (Fig. 2d) and extended caudally in diminishing density into the precentral gyrus from the superior precentral sulcus to the lateral fissure (Fig. 2c). However, only very few labeled cells were present in the banks of the central sulcus except at its most lateral part. Further in the frontal lobe a separate population of labeled neurons was present on the medial surface of the hemisphere in the area corresponding approximately to the supplementary motor cortex. When proceed-

ing from the injection area caudally a dense population of labeled neurons was present in the dorsal operculum of the lateral fissure (Fig. 2b). At the level of the parietal lobe it extended medially over the convexity of the hemisphere and occupied the anterior part of the inferior parietal lobule including the inferior bank of the tip of the IPS. This area was surrounded by a zone of less dense labeling which extended into both banks of the rostral half of the IPS, in the adjoining parts of the superior parietal lobule (areas 5 and 2) and in the inferior parietal lobule (area 7) up to the superior temporal sulcus (Fig. 2a). The density of labeled cells in the inferior parietal lobule and in the lower bank of the IPS was much more marked than that obtained after MI injections (compare Fig. 2b with Fig. 1a).

Most HRP-labeled cells were pyramidal in shape, but a substantial minority were stellate cells. In most areas, the labeled cells were present throughout the different cortical laminae. In those areas with pronounced labeling i.e. in the dorsal operculum and in the banks of the IPS, labeled neurons were concentrated in layer III and V.

In the second HRP case labeled neurons were less numerous than in the first monkey, but their distribution was similar.

2. *Electrophysiology*

2.1. Efferent projections from the periarcuate region to primary motor cortex

a. Antidromic mass responses. In three monkeys, potentials evoked in the periarcuate region by intracortical stimulation within the primary motor cortex (area 4) were investigated at the beginning of each experiment. Seven stimulating electrodes, spaced 3–5 mm apart were positioned in the precentral gyrus 2–3 mm rostral to the central sulcus (Fig. 3A, electrodes 1–7 and Fig. 3B). A standard stimulus of 300 μA was used. Up to 15 different recording sites close to the arcuate sulcus were then explored with a low-impedance electrode inserted to a standard cortical depth of 1.5 mm.

Figure 3C shows averages of responses evoked from four different stimulation sites (Fig. 3A and B: 3, 4, 5 and 6) and recorded from three post-arcuate sites (Fig. 3A: a–c) and one prearcuate site (d). The evoked responses usually showed a clear negative-positive wave (e.g. in penetration b from electrode 4). The peak of the negative-going wave had a latency of 1.3–2.0 ms. An earlier positive-going deflection (e.g. penetration a from electrode 4), was usually obscured by the stimulus artefact. Responses evoked in postarcuate sites from area 4 were considered to be antidromic because of their short, consistent latency and ability to follow repetitive stimuli. Their latency agrees well with that of the single unit responses described below.

Evoked responses were distributed topographically (Fig. 3C). At any given postarcuate site, the responses evoked from one MI stimulation site were significantly larger than those evoked from any other. At the most lateral recording site (penetration a), the largest response was evoked from electrode 5. Smaller responses were evoked from the adjacent electrodes 4 and 6, but no response was obtained from electrode 3. Responses evoked at more medial postarcuate recording sites (penetrations b and c) were maximal from the medial MI electrodes 4 and 3, respectively. No clear responses were evoked at a, b, or c from the most medial electrodes 1 and 2, or from the most lateral, 7. Finally, no responses were evoked at the prearcuate recording site (penetration d) from any MI electrode.

b. Antidromic responses from single neurons. After mapping of the mass responses, the MI stimulating electrodes were left in place and, using a hunting stimulus of 500 μA, a search was made of the periarcuate region for antidromic responses from single neurons. In 47 microelectrode penetrations, antidromic responses were recorded from 52 single neurons. Figure 4A (third trace) shows a typical antidromic response in a postarcuate neuron (penetration F, Fig. 4D).

All 52 neurons were found in postarcuate penetrations. They exhibited short-latency antidromic responses (Fig. 4B; mean 1.2 ms, range 0.6–2.1 ms).

Fig. 4A–E. Topographic distribution of projections from periarcuate cortex to area 4. Single neuron responses. **A** Recording from single neuron in postarcuate cortex (penetration F in **D**) activated antidromically by intracortical stimulation within area 4 (electrode 6); antidromic spike indicated by asterisk. Four sweeps at threshold stimulus strength (150 μA) have been superimposed together with one at sub-threshold strength. Stimulation at three adjacent sites (electrodes 4, 5, 7) with 500 μA did not excite the cell; 5 superimposed sweeps are shown in each case. Arrows indicate stimulus artefacts. Antidromic nature of response evoked from electrode 6 is confirmed by collision with orthodromic spike. **B** and **C** Distribution of antidromically-activated postarcuate neurons according to antidromic latency (**B**) and depth (**C**). **D** and **E** show postarcuate penetrations (indicated by ⊙) made in two monkeys in which neurons activated by area 4 stimulation were recorded. Straight lines link these penetrations with stimulus site giving antidromic responses at low threshold (**D** < 100 μA; **E**: < 200 μA). Dots indicate penetrations in which neurons with antidromic responses could not be found

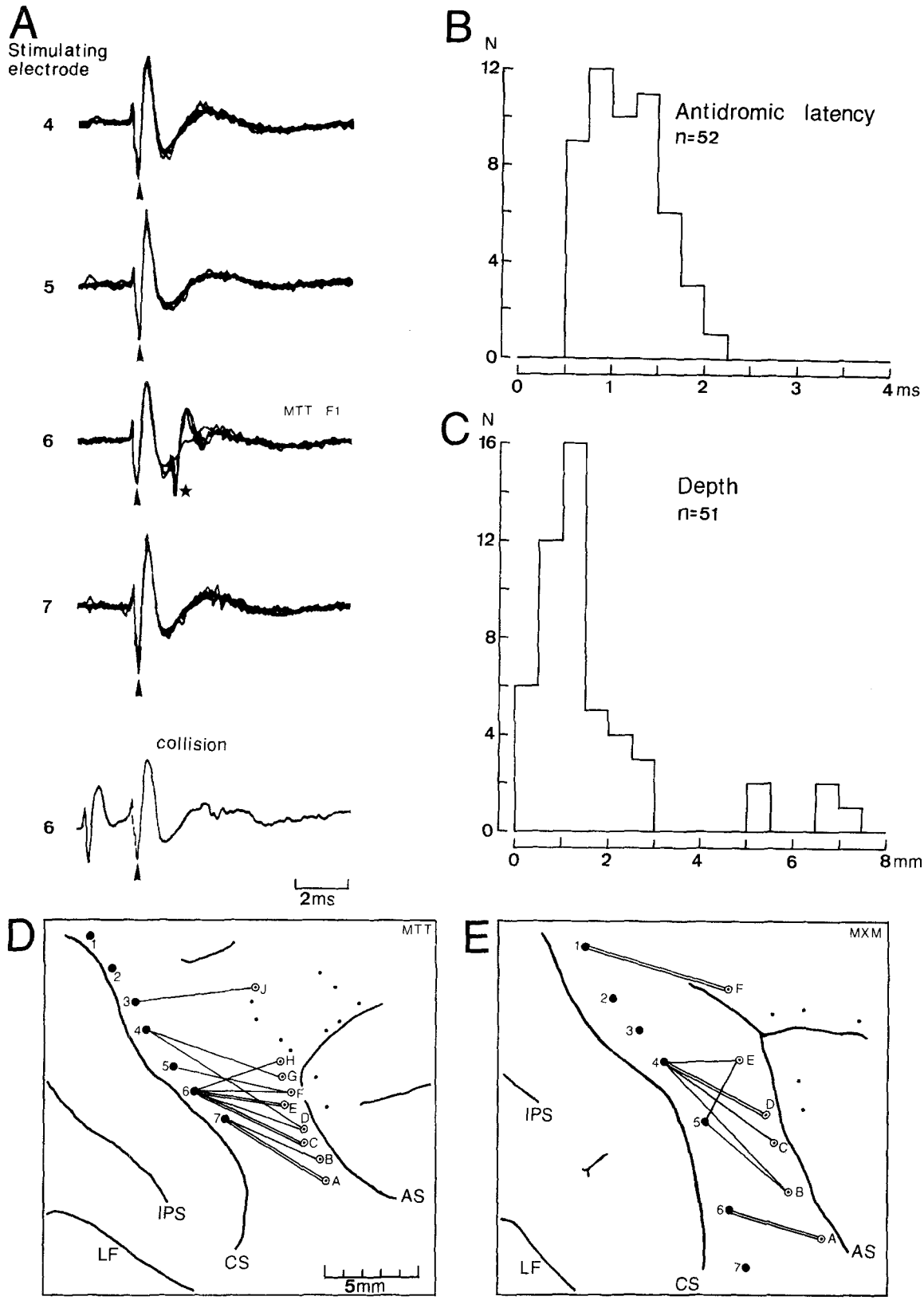
A
Stimulating electrode
4
5
6
MTT F1
7
collision
6
2ms
B
N
12
8
4
0
Antidromic latency
n=52
0
1
2
3
4 ms
C
N
16
12
8
4
0
Depth
n=51
0
2
4
6
8mm
D
MTT
1
2
3
4
5
6
7
J
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Fig. 4

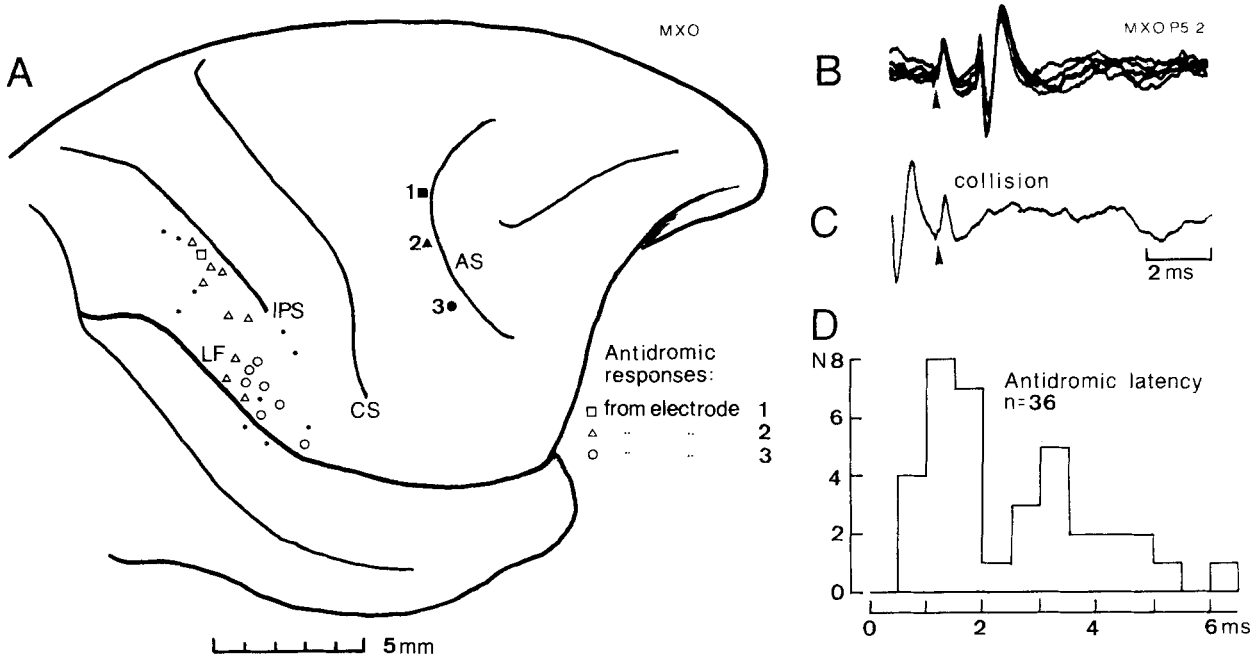

Fig. 5A–D. Posterior parietal projections to postarcuate region. **A** Filled symbols (1, 2, 3) indicate location of three stimulating electrodes located at a depth of 1.5–2.0 mm within the postarcuate region. Open symbols indicate penetrations in which neurons were found which responded antidromically to stimulation from only one of these three sites at a shock strength of 500 μA or less. Dots indicate penetrations lacking neurons with antidromic responses. **B** and **C** Antidromic response (**B**) of posterior parietal neuron to stimulation at site 2 (50 μA) confirmed by collision test (**C**). Arrows indicate stimulus artefacts. **D** Antidromic latency distribution of 36 posterior parietal neurons

Most of them were found superficially in the cortex (0.3–1.5 mm; Fig. 4C); histological reconstruction suggested that they lay in lamina III. Many other neurons were recorded in deeper laminae, and in the depth of the banks of the arcuate sulcus, but very few of these deeply-lying neurons responded antidromically (Fig. 4C).

The threshold for antidromic excitation of the 52 postarcuate neurons ranged from 25 to 500 μA; 14/52 had thresholds of 100 μA or less and 40/52, 300 μA or less. In general, the stimulating electrodes were kept at the same height throughout the experiment: no systematic tracking was made to find the optimal stimulation depth for a given antidromic response. With a maximum shock of 500 μA, 43/52 neurons could be antidromically excited from only one area 4 stimulus site. For example, the neuron in Fig. 4A was excited only from stimulation electrode 6 (see Fig. 4D). For the 9 neurons excited from more than one site, 7 were excited from two adjacent stimulating electrodes. None of the 52 postarcuate neurons activated from area 4 could be antidromically driven from the pyramidal tract.

Figure 4D and E show the distribution, in two monkeys, of postarcuate neurons with projections into MI. The straight lines link the penetrations in which they were found to the area 4 stimulation site from which they were antidromically activated. A topographic distribution of these single unit responses is evident, with projections of postarcuate neurons into the primary motor cortex frequently running in a postero-medial direction (Fig. 4D, E).

Although the superior limb of the arcuate sulcus was fully investigated in all 3 monkeys, no antidromically-activated neurons were found. Prearcuate penetrations also failed to yield any neurons with antidromic responses to area 4 stimulation.

2.2. Afferent projections to the postarcuate region from the inferior parietal lobule

These experiments were guided by previous anatomical findings (Pandya and Kuypers 1969; Chavis and Pandya 1976) and the present HRP findings (see 1.2). The object was to discover whether the postarcuate region which projects into MI receives afferents from the inferior parietal lobule (IPL). This was confirmed in one monkey by antidromically invading IPL neurons from electrodes placed in the postarcuate cortex. In a second monkey, excitatory synaptic responses were demonstrated in postarcuate neurons following stimulation of IPL.

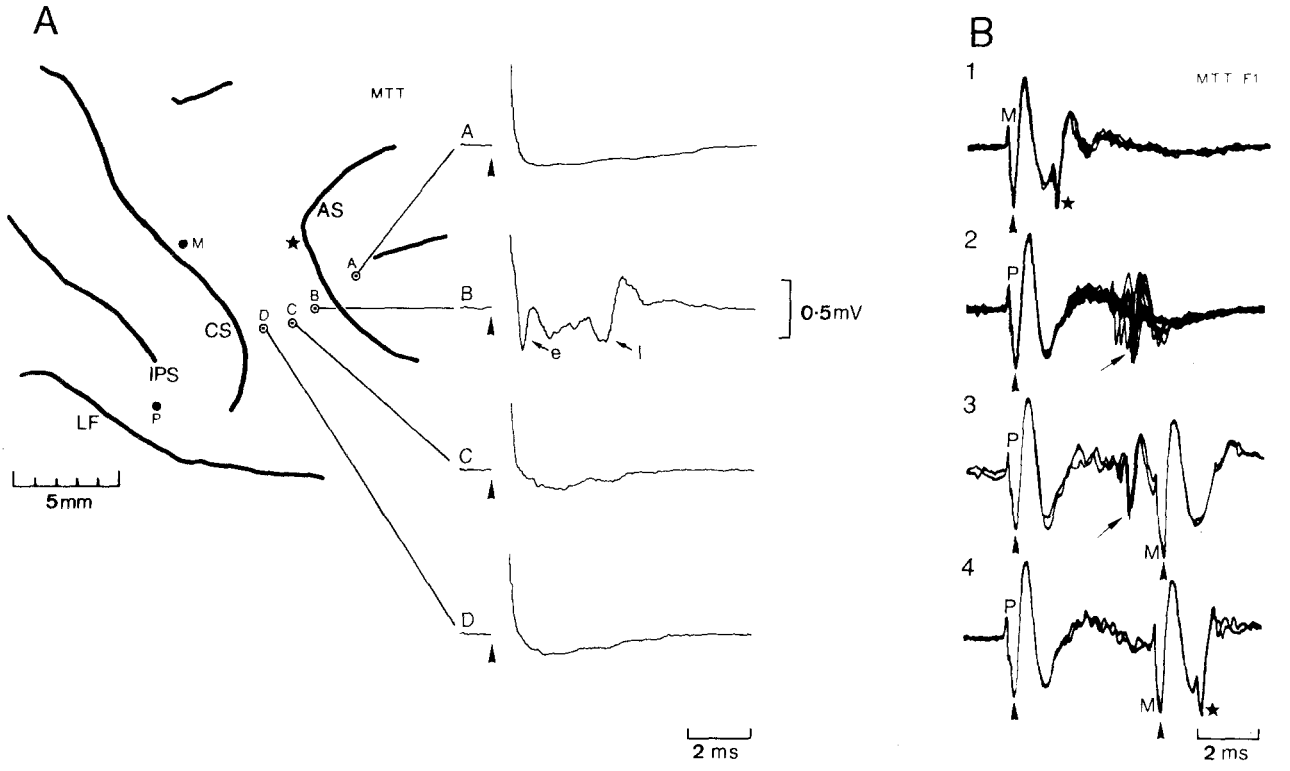

Fig. 6A and B. Excitatory projections from posterior parietal cortex to postarcuate neurons. **A** Mass responses. These were recorded from 4 different sites A–D and averaged (n = 32) following stimulation at location P (300 μA). Note early (e) and late (l) components in response evoked from the postarcuate site, B. **B** Single neuron responses. Records from a single postarcuate neuron recorded in a penetration marked with the star. Trace 1 shows that this neuron was antidromically activated by stimulation within the motor cortex at site M (150 μA). The antidromic spike is marked with a star. Trace 2 shows synaptic responses (arrowed) evoked by parietal stimulation at point P (250 μA). Traces 1 and 2 show five superimposed responses. Trace 3 and 4 (2 superimposed sweeps) show that both antidromic and synaptic responses came from the same neuron. The synaptic spike collided the antidromic spike (trace 3) when the parietal shock (P) preceded the motor cortex shock (M). No collision was observed when the parietal shock failed to elicit a synaptic response from the neuron (trace 4)

a. Antidromic excitation of inferior parietal lobule neurons. Three stimulating electrodes, spaced 2–3 mm apart, were driven into the postarcuate cortex (Fig. 5A, electrodes 1–3). The tips were located superficially (1.5–2.0 mm below the surface) so as to be close to those periarcuate neurons projecting to MI (see Fig. 4C). The IPL was then explored for single neurons yielding antidromic responses to stimulation of the postarcuate cortex with shocks of up to 500 μA. In all, 27 IPL penetrations were made (Fig. 5A) and several spontaneously-active neurons were found in each penetration; 17 penetrations yielded a total of 36 neurons with antidromic responses to postarcuate stimulation (see Fig. 5B, C). Their antidromic thresholds varied from 50 to 500 μA; 7 neurons had thresholds of 100 μA or less and 25, 300 μA or less. 30 neurons could be activated from only one postarcuate electrode; their locations are plotted in Fig. 5A. The distribution suggests that posterior parietal neurons located in the dorsal operculum of the lateral fissure together with those lying on the convexity of the inferior parietal lobule project to the inferior limb of the arcuate sulcus (electrode 3, circles), while those recorded immediately lateral to the IPS project more medially along the arcuate sulcus (Fig. 5A: electrode 2, triangles) i.e. in the region normally occupied by the spur. Electrode 1 (squares), in the superior limb of the arcuate sulcus, was generally ineffective in exciting antidromic responses in the above parietal areas.

Neurons located rostral and lateral to the tip of the IPS were not excited antidromically by postarcuate stimulation; the same was true of neurons lying caudal and medial in the inferior parietal lobule (area 7a; Hyvärinen 1982). In penetrations made in the convexity of the inferior parietal lobule, neurons were encountered either superficially (0.5–1.3 mm; 9 neurons) or slightly deeper (2.0–2.6 mm; 7 neurons); they may represent cortico-cortical projection neurons lying in lamina III and V, respectively (Jones and Wise 1977), both of which were labelled in the HRP experiments (see Sect. 1.2). A further 4

neurons were found deep (4.0–7.0 mm) in the superior bank of the lateral fissure and 11 neurons were found deep in the posterior bank of the IPS.

b. Synaptic excitation of postarcuate neurons by stimulation in the inferior parietal lobule. Evidence was first sought from mass potentials recorded from various locations in the precentral gyrus and periarcuate region and evoked by stimulation at different sites in the IPL (see Fig. 6). Intracortical parietal stimulation (300 μA) at the point P (Fig. 6A), just lateral to the tip of the intraparietal sulcus evoked only weak responses within primary motor cortex (Fig. 6A, penetrations C, D), and no responses in the prearcuate penetration (A). In marked contrast, recordings made from a postarcuate site (B) in the inferior limb of the arcuate sulcus yielded a complex response consisting of early (latency 1.0 ms) and late (3.5 ms) components. The early wave probably represents the antidromic response of arcuate neurons projecting to the IPL.

The late wave recorded in penetration B probably reflects synaptic excitation of arcuate neurons from the parietal site, and single neuron recording in the same monkey did indeed yield 14 postarcuate neurons which responded synaptically to parietal stimulation. Reproducible synaptic responses were obtained with single shocks of 200–350 μA; repetitive stimulation (2–3 shocks at 300 Hz) gave more powerful and more consistent responses. Response latency varied from 2.5–7.0 ms, which is comparable with the latency of the late wave shown in Fig. 6A, trace B. None of the 14 neurons was identifiable as a pyramidal tract neuron.

Of the 14 synaptically-activated neurons, 4 were also antidromically excited from MI. Thus some neurons receiving afferent input from the IPL project directly to MI. An example is shown in Fig. 6B.

2.3. Projection of postarcuate neurons to the inferior parietal lobule

During the course of the above experiments, 5 postarcuate neurons were encountered which responded *antidromically* to stimulation of the IPL. These neurons presumably belong to the population which provides the reciprocal projection to that described above i.e. *from* the arcuate region to the IPL (Pandya and Kuypers 1969; Stanton et al. 1977). All 5 neurons responded at short-latency (0.8–1.2 ms), which is comparable with the latency of the early 'antidromic' wave (Fig. 6A, trace B) seen in the evoked response study.

Discussion

1. The postarcuate area of the premotor cortex

The findings presented here concern the connectivity of neurons in the postarcuate cortex: the posterior bank of the inferior limb of the arcuate sulcus, and the convexity of the precentral gyrus both inferior to the sulcus and in the region of the arcuate spur. Before discussing the possible significance of these findings, it is important to establish the identity of the postarcuate area within the context of the premotor cortex (PM) and the primary motor cortex (MI).

As pointed out in the introduction, there are a variety of criteria which can be used to distinguish PM from MI. However, since the MI cortex lying inferior to the arcuate sulcus does not project to the spinal cord (Catsman-Berrevoets and Kuypers 1976), the relative lack of corticospinal neurons in lateral PM cannot be used to distinguish it from MI. A similar difficulty arises over the identity of the projections from the MI face area to the magnocellular part of the red nucleus (see Kuypers and Lawrence 1967) and whether or not the presence of such projections can be used to differentiate the lateral parts of PM from the MI face area, as they have been used for the precentral gyrus lying above the arcuate sulcus (see Introduction).

Examination of other criteria, however, clearly indicates that the postarcuate area investigated in the present study should be considered as part of the premotor cortex. Thus, several investigations have shown that low-threshold intracortical microstimulation in the postarcuate area of conscious monkeys fails to produce movements (McGuinness et al. 1980; Sessle and Wiesendanger 1982; Weinrich et al. 1984). It is clear from a comparison of Fig. 1 (section c) and Fig. 2 (section b) that the postarcuate region receives strong projections from parts of the inferior parietal lobule which do not project to the primary motor cortex. Finally, the premotor identity of the postarcuate region is supported by single neuron recording in conscious monkeys which shows that postarcuate neurons are responsive to visual stimuli (Rizzolatti et al. 1981a, c), particularly those associated with conditioned movements (Godschalk et al. 1981; Godschalk and Lemon 1983; Weinrich et al. 1984).

2. Efferent projections from the postarcuate area

The present findings confirm the direct projections of postarcuate neurons into MI (Pandya and Kuypers 1969; Pandya and Vignolo 1971; Künzle 1978). The HRP studies of Matsumura and Kubota (1979) and of

Muakkassa and Strick (1979) clearly indicate that this projection is topographically organized. This has now been confirmed using retrograde transport of three different fluorescent tracers in the same monkey, and indicates that there is little or no overlap in the projections from different regions of the postarcuate cortex to MI.

Stimulation within MI evoked antidromic responses from 52 postarcuate neurons. 14 of these neurons were excited with shocks of between 25 and 100 μA; shocks of this strength are unlikely to have spread far enough to excite the underlying white matter (Ranck 1975). A further 26 neurons were excited by shocks of 100–300 μA, and the remaining 12 neurons with shocks of 300–500 μA. These higher currents may have spread to the cortical white matter. Nevertheless, the relatively restricted projection pattern of the postarcuate neurons is readily confirmed by the observation that 43/52 of them could be excited from only one MI stimulation site, even when shocks of 500 μA were tested. Since all of these sites were known to be effective (i.e. antidromic responses could be elicited from every electrode, but from different neurons) and since the spacing between these electrodes was only 3–5 mm, this result argues for a projection to limited territories within MI. If such a projection pattern exists, it suggests that the higher threshold of some of the antidromic responses may have resulted from the relatively small number of stimulating sites within MI. Some low-threshold responses may have been missed because no systematic tracking with the stimulating electrodes was carried out.

The short latency of the antidromic responses is evidence for a rapid pathway for premotor inputs to MI. Most of these antidromic responses were recorded from neurons lying superficially in the postarcuate cortex and they are probably cortico-cortical neurons located in lamina III (Jones and Wise 1977; Sloper and Powell 1979; Sloper et al. 1979). In confirmation of earlier studies (Catsman-Berrevoets and Kuypers 1976; Jones and Wise 1977; Murray and Coulter 1981), we also found a few pyramidal tract neurons within PM, but these neurons did not project into MI, nor did they respond synaptically to stimulation of the posterior parietal cortex.

The postarcuate projection to MI appears to be organized in an oblique postero-medial fashion. Thus neurons located in the convexity of the cortex inferior to the arcuate sulcus project into the face region of MI, while those lying in the posterior bank of the sulcus project more medially, with the spur region projecting to the hand area of MI (c.f. Muakkassa and Strick 1979). This pattern of projections was most striking in the experiment shown in Fig. 4D, which is based upon antidromic responses of postarcuate neurons elicited with MI shocks of 100 μA or less. As discussed above, with currents of this strength, the projection of such neurons to MI is not in any doubt.

The lack of direct projections from prearcuate areas 8 and 9 to MI is indicated by both the fluorescent tracer and electrophysiological results, and confirms earlier degeneration and autoradiographic findings (Pandya and Kuypers 1969; Pandya and Vignolo 1971; Künzle 1978).

3. Afferent cortical projections to the postarcuate area

The direct projection of postarcuate premotor neurons to MI may provide a unique pathway for the different types of sensory information required for programming and guidance of movements (Jacobsen 1934; Geschwind 1965). Our electrophysiological experiments have therefore concentrated on the afferent projections to this postarcuate region.

In confirmation of earlier findings (Ward et al. 1946; Pandya and Kuypers 1969; Chavis and Pandya 1976) there appear to be projections to the postarcuate cortex from at least four parietal areas (see Fig. 1, inset): 1. from the convexity of postcentral gyrus immediately above the intraparietal sulcus (IPS); 2. from the banks of the IPS (area 7; area POa of Seltzer and Pandya 1980); 3. from the convexity of the rostral part of the inferior parietal lobule (area 7b or PF) and 4. from the dorsal operculum of the lateral fissure (SII; Jones and Burton 1976). The largest numbers of labeled neurons were found in area 7b and in SII, and the electrophysiological results suggest a topographical projection from these regions into the postarcuate area (Fig. 5). It is interesting that SII, as well as projecting to the postarcuate region, also projects to area 7b (Stanton et al. 1977).

The electrophysiological results also confirm the reciprocal projection of the postarcuate area to area 7b (Pandya and Kuypers 1969; Pandya and Vignolo 1971; Künzle 1978).

Stimulation of the postarcuate cortex did not evoke antidromic responses in neurons located in the caudal part of the inferior parietal lobule (area 7a or PG), which agrees with earlier degeneration findings (Pandya and Kuypers 1969; Chavis and Pandya 1976). Barbas and Mesulam (1981) recently showed that area 7a projects to the prearcuate areas 8 and 9. In the present study, we were careful to avoid deep injections of HRP in the caudal bank of the arcuate sulcus which might have injured fibers passing under the sulcus and terminating in these prearcuate areas.

The absence of labelled neurons in area 7a suggests that no such contamination occurred.

4. *Functional significance of postarcuate connectivity*

The afferent projections to the postarcuate area revealed in the present experiments would help to explain the polysensory nature of this area, as originally described by Bignall and Imbert (1968). These projections would provide somatosensory inputs from SII (Robinson and Burton 1980a–c) and mixed visual/somatic inputs from areas 7b (PF) and POa (Leinonen et al. 1979; Leinonen and Nyman 1979; Hyvärinen and Shelepin 1979; Robinson and Burton 1980b,c). Area POa is particularly interesting in terms of visual guidance of movement since, unlike area 7b (PF), it receives a direct projection from the prestriate cortex (area OA; Seltzer and Pandya 1980). There is also a report of projections from auditory association cortex (area Tpt) to the posterior bank of the inferior limb of the arcuate sulcus (Galaburda and Pandya 1982).

The properties of single neurons within the postarcuate area are consistent with the afferent inputs described above. These neurons are responsive to visual stimuli (Kubota and Hamada 1978; Sakai 1978; Rizzolatti et al. 1981c; Godschalk et al. 1981; Godschalk and Lemon 1983; Weinrich et al. 1984) and to somatosensory stimuli (Rizzolatti et al. 1981b), although in the conscious monkey, the proportion of neurons responsive to the latter is lower than in MI (Brinkman and Porter 1979; Godschalk and Lemon, unpublished observations; see Weinrich et al. 1984).

Different types of sensory information, integrated within PM, could directly influence MI via the fast and specific projections from PM to MI revealed in the present study. Such an organization is well illustrated by the presence of postarcuate neurons which project into MI and which also respond to excitatory synaptic inputs from area 7b (Fig. 6B). However, it is still uncertain as to which type of sensory-motor function should be assigned to postarcuate neurones, and to the projections they receive from area 7b and from SII. These projections may be involved in the animal's general awareness of the location of interesting visual and somatic stimuli within extrapersonal space. It is unclear whether or not this system is also used for the visual guidance of movements within that space (Haaxma and Kuypers 1975; Hyvärinen 1982).

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