# Frontal Eye Field as Defined by Intracortical Microstimulation in Squirrel Monkeys, Owl Monkeys, and Macaque Monkeys  II. Cortical Connections

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## ABSTRACT

Physiological (intracortical microstimulation) and anatomical (transport of horseradish peroxidase conjugated to wheat germ agglutinin as shown by tetramethyl benzidine) approaches were combined in the same animals to reveal the locations, extents, and cortical connections of the frontal eye fields (FEF) in squirrel, owl, and macaque monkeys. In some of the same owl and macaque monkeys, intracortical microstimulation was also used to evoke eye movements from dorsomedial frontal cortex (the supplementary motor area). In addition, in all of the owl and squirrel monkeys, intracortical microstimulation was also used to evoke body movements from the premotor and motor cortex situated between the central dimple and the FEF. These microstimulation data were directly compared to the distribution of anterogradely and retrogradely transported label resulting from injections of tracer into the FEF in each monkey. Since the injection sites were limited to the physiologically defined FEF, the demonstrated connections were solely those of the FEF. To aid in the interpretation of areal patterns of connections, the relatively smooth cortex of owl and squirrel monkeys was unfolded, flattened, and cut parallel to the flattened surface. Cortex of macaque monkeys, which has numerous deep sulci, was cut coronally.

Reciprocal connections with the ipsilateral frontal lobe were similar in all three species: dorsomedial cortex (supplementary motor area), cortex just rostral (periprincipal prefrontal cortex) to the FEF, and cortex just caudal (premotor cortex) to the FEF. In squirrel and owl monkeys, extensive reciprocal connections were made with cortex throughout the caudal half of the lateral fissure and, to a much lesser extent, cortex around the superior temporal sulcus. In macaque monkeys, only sparse connections were present with cortex of the lateral fissure, but extensive and dense connections were made with cortex throughout the caudal one-third to one-half of the superior temporal sulcus. In addition, very dense reciprocal connections were made with the cortex of the lateral, or inferior, bank of the intraparietal sulcus. Contralateral reciprocal connections in all three species were virtually limited to regions that correspond in location to the FEF and the supplementary motor area.

The results of this study reveal connections between the physiologically defined frontal eye field and cortical regions known to participate in higher

order visual processing, short-term memory, multimodal, visuomotor, and skeletomotor functions. Some of the demonstrated pathways may contribute to functional interactions between oculomotor and skeletomotor systems, perhaps facilitating the planning and coordination of related eye, head, and hand movements.

**Key words: primate cortex, oculomotor, visuomotor, skeletomotor, vision, flattened cortex**

More than a century ago, Ferrier demonstrated that eye movements could be evoked by electrical stimulation of the prearcuate cortex in macaque monkeys (Ferrier, 1874, 1875). Other early studies generally confirmed these observations in macaque monkeys (Beevor and Horsley, 1888; Mott and Schaefer, 1890) and revealed similar "frontal eye fields" in other primates as well (*Cercopithecus*: Vogt and Vogt, '07, '19; *Pongo*: Beevor and Horsley, 1890; Leyton and Sherrington, '17; *Homo*: Bechterew, 1899). Although accumulating evidence continued to implicate the frontal eye field in the control of voluntary eye movements (Smith, '44; Wagman et al., '61; Robinson and Fuchs, '69), single unit studies revealed that frontal eye field neurons did not discharge prior to voluntary spontaneous eye movements (Bizzi, '68; Bizzi and Schiller, '70). This suggested that such eye movements were not being initiated in the frontal eye field. Nevertheless, most recent evidence shows that whereas the frontal eye field is not involved in the initiation of all types of eye movements, this cortical region does play a role in the initiation of a particular type of saccadic eye movement. Specifically, frontal eye field neurons discharge prior to "purposive" saccades, i.e., saccades to targets that are of behavioral importance to the organism (Bruce and Goldberg, '85). In addition to participating in the initiation of certain types of eye movements, the macaque monkey's frontal eye field has also been implicated in the coordination of eye and head movements (Bizzi and Schiller, '70; Van der Steen et al., '86). Such coordination is necessary for accurate gaze changes in primates.

Since much of primate, including human, behavior depends on purposive saccades and accurate changes of gaze, the frontal eye field clearly serves an important function. Despite this importance, however, the cortical connections of the frontal eye field, as defined and delimited physiologically, have not been fully reported (but see Huerta et al., '85; Stanton, '86). Because the frontal eye field is relatively small and variable in location (present results; also see Bruce et al., '85; Huerta et al., '86), it is important that anatomical methods be used in concert with physiological methods to assure that the injection site is limited to the frontal eye field and, therefore, that the connections demonstrated are solely those of the frontal eye field.

In the present study, anatomical and physiological methods were combined in the same individuals to determine the cortical connections of the physiologically defined frontal eye field (subcortical connections have been reported previously, Huerta et al., '86). Squirrel monkeys, owl monkeys, and macaque monkeys were studied, which allowed direct interspecies comparisons. In each experiment, intracortical microstimulation was used to define the borders of the frontal eye field. These borders were marked by small electrolytic lesions to facilitate correlation of physiological and anatomical data, and the field received an injection of horseradish peroxidase conjugated to wheat germ agglutinin (HRP-WGA). In these same animals, electrical stimulation was also used to explore other motor-related cortex, including the supplementary motor area, premotor cortex, and primary motor cortex; lesions were also placed strategically in these fields.

The present results indicate that the well-known sensorimotor properties of the frontal eye field are reflected in its cortical connections. Thus, the frontal eye field has connections with cortex related to higher order visual processing, multimodal, and visuomotor functions. In addition, the frontal eye field has connections with periprincipal prefrontal cortex, the supplementary motor area, and premotor cortex. Since these latter connections are the least variable between species, an important function of the frontal eye field may be to link oculomotor and skeletomotor functions, perhaps in planning and coordinating eye, head, and hand movements (see Discussion).

## METHODS

The locations and connections of the frontal eye fields were studied in three squirrel monkeys (*Saimiri sciureus*), three owl monkeys (*Aotus trivirgatus*), and three macaque monkeys (*Macaca fascicularis*). In each animal, the frontal eye field was unilaterally explored and defined with intracortical electrical microstimulation; borders were then marked with small electrolytic lesions, and an injection of horseradish peroxidase conjugated to wheat germ agglutinin (HRP-WGA) was placed within the physiologically defined front eye field. The subcortical connections demonstrated by these experiments have been published previously (Huerta et al., '86), and methodological details not presented here can be found in that report.

### Surgical, experimental, and histological procedures

All surgical procedures were carried out with aseptic precautions on animals that were initially anesthetized with intramuscular injections of 35 mg/kg body weight of ketamine hydrochloride. Supplemental doses were administered to maintain surgical levels of anesthesia (White et al., '82). In each animal a large craniotomy was made over the periarcuate cortex, and the underlying dura resected. A well of acrylic plastic was built around the craniotomy and filled with silicone fluid. Locations of microelectrode penetrations were marked on a photographic print of the surface of the exposed cortex.

Stimulation was delivered via a tungsten microelectrode (1.5 M Ω at 1,000 Hz), and generated by a two-channel anapulse stimulator with two photon-coupled stimulus isolator units operated in parallel. The constant current levels were monitored on an oscilloscope by measuring the voltage drop across a resistor of known impedance in series with the stimulator circuit. Stimuli consisted of biphasic, square

*Abbreviations*

| | |
|---|---|
| A–I | primary auditory area |
| AL | anterolateral area |
| Ant somat | anterior somatosensory cortex |
| Arc S | arcuate sulcus |
| AS | arcuate sulcus |
| C | central sulcus |
| Ca | calcarine sulcus |
| CaS | calcarine sulcus |
| caud | caudal |
| CC | corpus callosum |
| Cd | caudate nucleus |
| CD | central dimple |
| Cg | cingulate sulcus |
| CgS | cingulate sulcus |
| Cl | claustrum |
| CS | central sulcus |
| D | dorsal |
| db | dorsal bank of the lateral fissure |
| DI | dorsal intermediate area |
| DL | dorsolateral area |
| DM | dorsomedial area |
| dorsomed | dorsomedial |
| FEF | frontal eye field |
| FV | frontal ventral area |
| IA | inferior limb of the arcuate sulcus |
| IO | inferior occipital sulcus |
| IOS | inferior occipital sulcus |
| IP | intraparietal sulcus |
| IPS | intraparietal sulcus |
| ITc | caudal inferotemporal area |
| ITp | polar inferotemporal area |
| ITr | rostal inferotemporal area |
| ITS | inferior temporal sulcus |
| L | lunate sulcus |
| Lat fiss | lateral fissure |
| LF | lateral fissure |
| LIP | lateral intraparietal area |
| LS | lunate sulcus |
| MST | medial superior temporal area |
| MT | middle temporal area |
| OS | orbital sulcus |
| OT | occipital temporal sulcus |
| P | principal sulcus |
| PL | posterolateral area |
| PMT | posterior middle temporal sulcus |
| PMTS | posterior middle temporal sulcus |
| PP | posterior parietal area |
| Princ. S. | principal sulcus |
| PS | principal sulcus |
| Pul | pulvinar |
| Put | putamen |
| R | rostral, rostral area |
| rost | rostral |
| Rt | reticular nucleus |
| SA | superior limb of the arcuate sulcus |
| SMA | supplementary motor area |
| ST | superior temporal sulcus, superior temporal area |
| STP | superior temporal polysensory area |
| STS | superior temporal sulcus |
| TE | area TE |
| TEO | area TEO |
| TP | temporal posterior area |
| V | ventral area |
| vb | ventral bank of the lateral fissure |
| ventrolat | ventrolateral |
| VP | ventral posterior area |
| V-I | primary visual area |
| V-II | secondary visual area |
| V4 | fourth visual area |
| 5 | area 5 |
| 5a | area 5a |
| 5b | area 5b |
| 7a | area 7a |
| 7b | area 7b |

wave, symmetric 0.5 msec pulses delivered at 300 Hz in 40 msec trains. Constant current amplitudes were varied systematically to determine threshold levels of effective stimuli. These parameters are similar to those used by others studying the frontal eye field (e.g., Schiller et al., '79; Bruce et al., '85; Goldberg et al., '86).

Microelectrode penetrations were spaced 300–1,000 μm apart; in most cases the microelectrode was oriented perpendicular to the cortical surface. In these perpendicular approaches, the microelectrode tip was hydraulically driven to a depth of about 2,000 μm before stimulation was delivered. The depths of the arcuate sulcus of the macaque monkey were probed with the microelectrode oriented parallel to the surface of the sulcal cortex. In these cases, stimulation was produced at several different depths along the same penetration, with the depths being carefully noted.

At each stimulation point, exploratory currents of 100 μA were delivered with current levels usually being increased or decreased to determine threshold levels of current that elicited movements. Stimulation-evoked movements were monitored by two observers and carefully noted.

In general, the borders of the frontal eye field were marked by either a change in movement type (i.e., eye movements versus movements of other body parts) or a great increase (e.g., threefold) in threshold levels for eye movements between penetrations. How borders were defined in various primates are detailed in Results and have been discussed elsewhere (Huerta et al., '86). Small electrolytic lesions were made at the physiologically defined borders to allow the injection site location and extent to be related to these borders.

Volumes of 0.06–0.18 μl of 0.1% HRP-WGA were injected within the physiologically defined borders in each monkey. Next, the craniotomy was closed, the animal recovered from anesthesia, and 48 hours later, the animal received a lethal dose of sodium pentobarbitol. The animal was then transcardially perfused with saline followed by a 0.1 M phosphate buffer solution comprising 1.0% paraformaldehyde, 1.25% glutaraldehyde, and, finally, a similar solution, which also contained 10.0% sucrose. The brain was removed from the skull and, except for macaque monkeys, the cerebral hemispheres were separated from the rest of the brain, unfolded, flattened, and cut parallel to the flattened surface (details below). Removing the cerebral cortex badly damaged the claustrum and the corpus striatum; thus, observations regarding these structures are not included. A one-in-five series of sections was treated with tetramethyl benzidine (TMB; Mesulam, '78) to reveal the HRP-WGA, and other series were processed for autoradiography, stained for myelin, Nissl substance, and/or cytochrome oxidase. The sections treated with TMB were plotted under dark-field illumination with a camera lucida and were graphically reconstructed.

### Procedure for unfolding and flattening cortex

The cerebral hemispheres of owl monkeys and squirrel monkeys were removed, unfolded, flattened, and cut in a plane parallel to the flattened surface so that areal patterns of labeled connections could be viewed directly. The general sequence of unfolding the left cerebral hemisphere of a squirrel monkey is shown in Figure 1. It should be noted that slight differences in the location of the various cuts can result in very different appearances of the final product. As indicated in Figure 1A (1), a cut is first made along the floor of the lateral fissure, with the blade of the scalpel
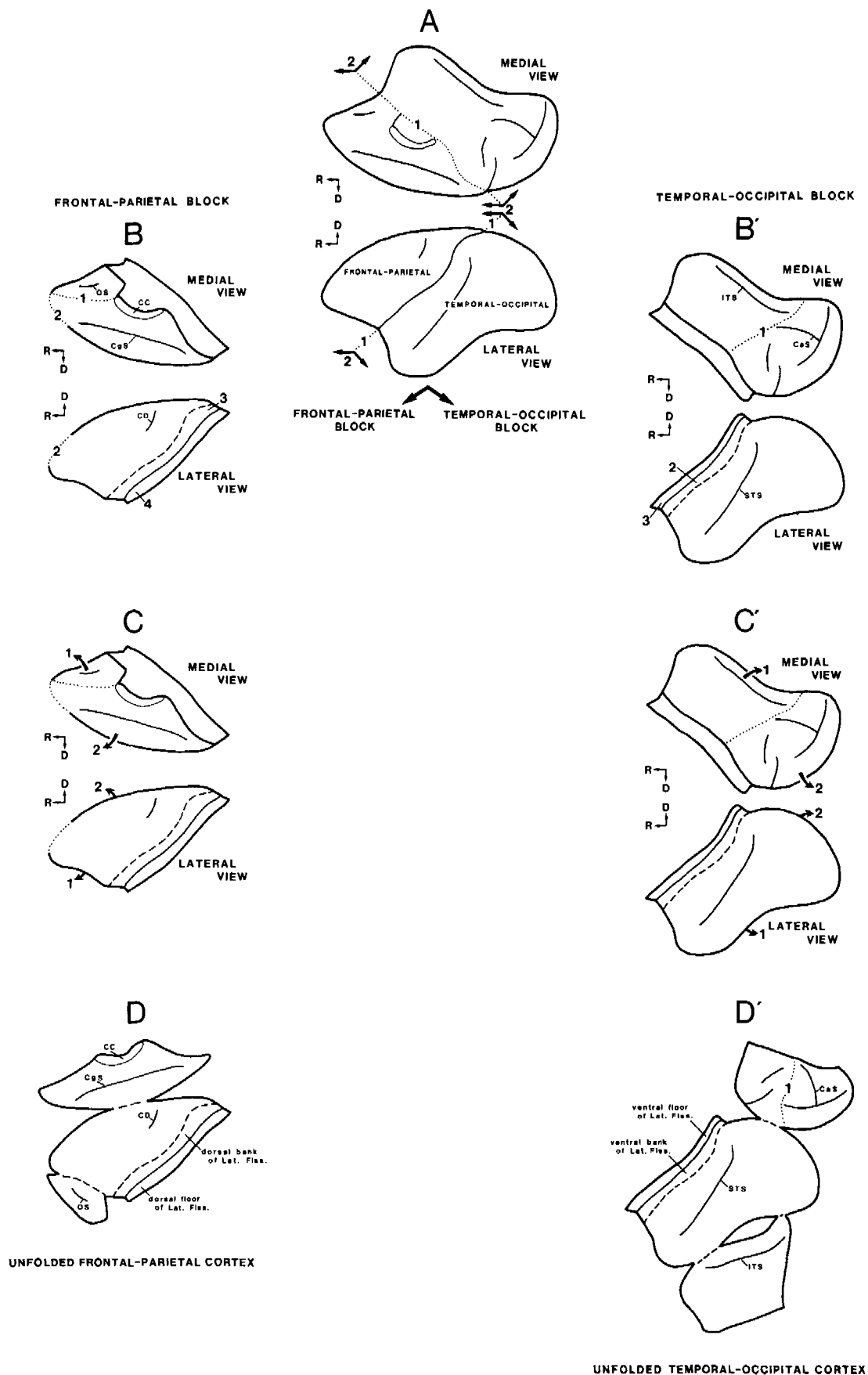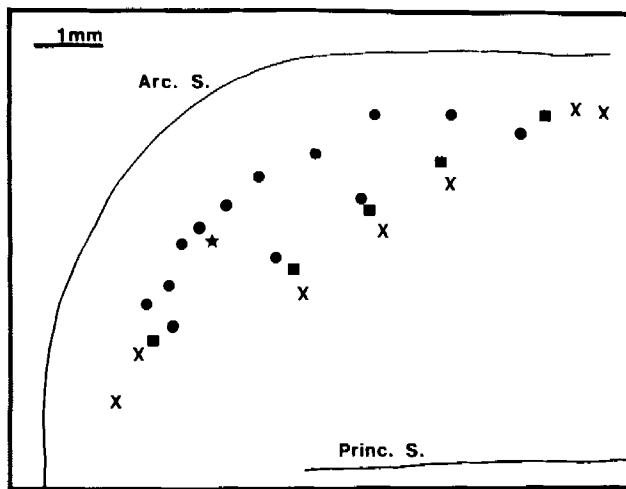
Fig. 1. Procedure for unfolding the cerebral cortex of the squirrel monkey. Same procedure used for unfolding the cortex of the owl monkey. Dotted lines, cuts; dashed lines, folds. (See Methods for details.)

**●** Threshold ≤ 50 µA
**X** Threshold ≥ 100 µA
**■** Lesion
**★** HRP-WGA injection                                    MM 85-68

Fig. 2. Location of the physiologically defined frontal eye field in macaque monkey 85-68. At the bottom is a drawing of the right cerebral hemisphere with the frontal eye field region indicated and enlarged at the top of the figure (drawn from brain photograph). Circles represent penetration sites in which the majority of stimulus points evoked contralateral rapid, conjugate eye movements at current levels of 50 µA at most (within the frontal eye field). Penetration sites from which eye movements were not evoked with currents less than 100 µA are indicated by X's (outside of the frontal eye field). Squares indicate penetration sites in which electrolytic lesions were placed (physiologically defined border). Star represents location of pipette tip through which HRP-WGA was injected. Rostral is to the right and dorsal is to the top of the figure.

With regard to the temporal-occipital tissue block, after it is removed from the frontal-parietal block, a cut is made on the ventromedial aspect of the temporal cortex (Fig. 1B'(1), and the ventral bank of the lateral fissure (Fig. 1B'(2) and the ventral half of the floor of the lateral fissure (Fig. 1B'(3) is unfolded. The ventromedial temporal cortex (Fig. 1C'(1) and the cortex containing the occipital region (Fig. 1C'(2) are unfolded resulting in a block of tissue that has white matter on one side and the pial surface on the other side (Fig. 1D'). In some cases, the pericalcarine cortex was removed (Fig. 1D'(1) and cut separately. Each block can now be flattened.

To flatten the cortex, each block is placed in the inverted "top" (i.e., larger) part of a petri dish containing a 0.1 M phosphate buffer solution, which is 30% sucrose. The "bottom" (i.e., smaller) part of the petri dish is then placed on the unfolded cortex. Weights of 75-100 g are placed on the "bottom" part of the petri dish and the preparation stored in a refrigerator overnight. The next morning, the unfolded flattened block is placed on the stage of a freezing microtome with the white matter-side facing the stage and the pial surface-side facing the blade. Immediately after placing the block on the stage, a large glass slide is pressed upon the block so that the pial surface is flat, with the flat
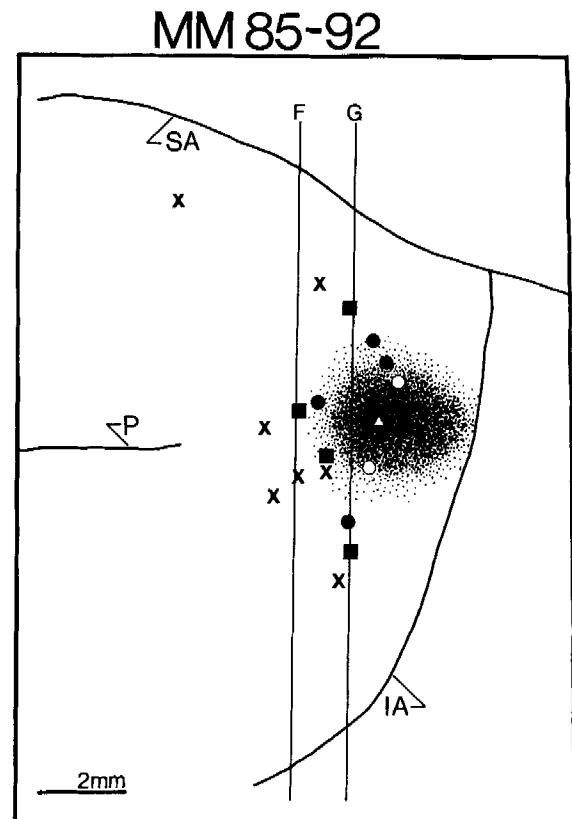
## MM 85-92



Fig. 3. Lateral view of the prearcuate cortex of the left hemisphere in macaque monkey 85-92 showing the location of the physiologically defined frontal eye field (drawn from brain photograph) and the extent of the HRP-WGA injection site shown as stipple (reconstructed from coronal sections). Symbols indicate penetration sites within (circles), outside (X's), and on the border (squares) of the physiologically defined frontal eye field. Triangle represents location of injection pipette tip. Levels from which frontal sections F and G of Figure 5 were taken are indicated. Note that these levels pass through electrolytic lesions marking the border of the frontal eye field. Rostral is to the left and dorsal is to the top of the figure.

extending into the medial cortical surface. Next (Fig. 1A(2), the block comprised of frontal and parietal cortex is separated from the block comprised of temporal and occipital cortex. On the frontal-parietal block (Fig. 1B(1), a cut is made along the ventromedial cortex from the rostrum of the corpus callosum to the frontal pole, and continued (Fig. 1B(2) along the dorsal ridge of frontal cortex. The dorsal bank of the lateral fissure (Fig. 1B(3) and the dorsal half of the floor of the lateral fissure (Fig. 1B(4) are then unfolded. The ventromedial cortex (Fig. 1C(1) and the cortex around the cingulate sulcus (Fig. 1C(2) are unfolded, resulting in the pial surface of all of the frontal-parietal cortex facing one side of the block and the white matter facing the other side (Fig. 1D).

surface parallel to the trajectory of the microtome blade. (For further details regarding procedures for flattening the occipital cortex of monkeys, see Tootell and Silverman, '85, and of cats, see Olavarria and Van Sluyters, '85).

# RESULTS

In each experiment, intracortical electrical microstimulation was used to define the frontal eye field, which received an injection of horseradish peroxidase conjugated to wheat germ agglutinin (HRP-WGA). In the same animal, microstimulation was also used to indicate the locations of other motor-related fields, such as the primary motor cortex, the supplementary motor cortex, and premotor cortex. Electrolytic lesions placed at physiologically determined borders were used to correlate these physiological data with the extent of the injection site and the distribution of transported tracer. In this section, microstimulation data are presented for each species, followed by a description of the cortical connections of the physiologically defined frontal eye field. In general, ipsilateral connections with frontal, parietal, and temporal cortex are described, followed by a description of connections with contralateral cortex. Because the frontal eye field has been studied most thoroughly in macaque monkeys and because this is the only primate for which the frontal eye field has been formally defined according to intracortical microstimulation criteria, results from the macaque monkeys are considered first below.

## Macaque monkey

*Definition of the frontal eye field and other intracortical microstimulation data.* In each macaque monkey, much of the physiologically defined frontal eye field was located on the rostral bank of the arcuate sulcus (although the specific borders of the field varied between individuals). Thus, many of the microelectrode penetrations used to define the field were oriented parallel to cortical laminae, with each of these penetrations containing multiple stimulation points. Stimulation points were separated by 300 $\mu$m to 1,000 $\mu$m, and a penetration was considered to be within the frontal eye field if the majority of stimulation points in that penetration evoked contralateral, conjugate rapid eye movements at current levels of 50 $\mu$A or less (further details in Huerta et al., '86). This level is similar to that used by Bruce et al. ('85) to define the frontal eye field borders in awake macaque monkeys. Functional significance of this criterion level is suggested by the fact that in penetrations just outside (300–500 $\mu$m) the so defined field, the level of current required to evoke eye movements increases to at least 100 $\mu$A or more (Fig. 2; also see Huerta et al., '86).

The frontal eye fields in three macaque monkeys were defined by a total of 312 stimulation points, 196 of which were within the field (further details in Huerta et al., '86). The borders of the field were defined as points between a penetration within the field and the nearest penetration outside of the field; many borders were marked with electrolytic lesions [Figs. 2, 3, 4A(G), 5F,G; also Figs. 1, 2, Huerta et al., '86], and horseradish peroxidase conjugated to wheat germ agglutinin (HRP-WGA) was injected into the field. Comparison of the extent of the injection site to the location of the electrolytic lesions in histological sections revealed that the injection site in each macaque monkey was virtually confined to the physiologically defined frontal eye field [Figs. 3, 4A(G), B(H,I), 5F,G; also Fig. 1, Huerta et al., '86].

In one of the macaque monkeys (case 85–92; Figs. 3, 5, see also Fig. 7), intracortical microstimulation was also used to explore cortex located along the dorsomedial margin of the ipsilateral hemisphere just medial to the rostral tip of the superior limb of the arcuate sulcus. Previous studies on awake monkeys have implicated this zone in saccadic eye movement function (Schlag and Schlag-Rey, '85), and this zone appears to be the most rostral part of the supplementary motor area (see Discussion). In monkey 85–92, eye movements could be evoked from the dorsomedial-most cortex depicted in level C of Figure 5, as well as in slightly more rostral levels. Such movements were elicited with current levels of 75–100 $\mu$A. Because of the configuration of the craniotomy, dorsomedial cortex caudal to level C in Figure 5 was not explored with intracortical stimulation.

*Connections of the frontal eye field.* Intrinsic connections were concentrated approximately 1.5 mm from the edge of the injection site within the frontal eye field and were manifest as clusters of anterogradely and retrogradely transported label [Fig. 4A(G), B(H,I)]. Most of this label appeared to occupy supragranular layers; however, the plane of section in caudal parts of the sulcus was tangential to cortical laminae, making laminar interpretation difficult.

Extrinsic connections with the ipsilateral frontal lobe extended as far rostral as the cortex along the caudal one-half to two-thirds of the principal sulcus. Label was concentrated in the cortex of the dorsal bank of the sulcus, especially near the top of the sulcus [Figs. 4A(A–D), 5A,B], whereas the generally sparser label in the ventral bank was situated close to the fundus [Fig. 4A(D)]. In the cortex of the principal sulcus, anterogradely transported label and retrogradely labeled cells were present in superficial and deeper cortical layers, with anterogradely transported label also present in layer IV [Figs. 4A(G), 5A,B]. Retrogradely labeled neurons were slightly more numerous in superficial laminae. Also at these rostral levels, a few labeled cells were scattered in the ipsilateral cortex of the superior concavity of periprincipal region, i.e., cortex immediately superior or dorsomedial to the principal sulcus [Fig. 4A(B)] and in the dorsal bank of the ipsilateral cingulate gyrus [Figs. 4A(C,D), 5B].

At more caudal levels, near the caudal extent of the principal sulcus and the rostral extent of the limbs of the arcuate sulcus, very dense label was present in ipsilateral cortex of the inferior concavity (i.e., cortex immediately inferior or ventrolateral to the principal sulcus), with most of the anterogradely and retrogradely transported label situated in supragranular laminae [Figs. 4A(E,F), 5C–E]. Immediately rostral to the physiologically determined borders of the frontal eye field, bidirectionally transported HRP-WGA was extremely dense and, like the label in the cortex of the ipsilateral inferior concavity, was densest in supragranular layers [Figs. 4A(F), 5E,F]. The adjacency of this dense label to the rostral border of the frontal eye field is illustrated in Figure 5, where F contains an electrolytic lesion (arrowhead) marking the rostral border of the field. This lesion is situated within (Fig. 5F) and just caudal to (Fig. 5E) a heavily labeled zone. In addition to label immediately rostral to the defined frontal eye field, label was distributed in what appear to be two separate foci: one medially, near the superior limb of the arcuate sulcus, and one laterally, near the inferior limb of the arcuate sulcus (Fig. 5F). Further caudal, moderately labeled regions were also present medially and laterally, just outside of the physiologically defined borders of the frontal eye field [Figs. 4(G,H), 5G; dashed lines represent locations of borders].
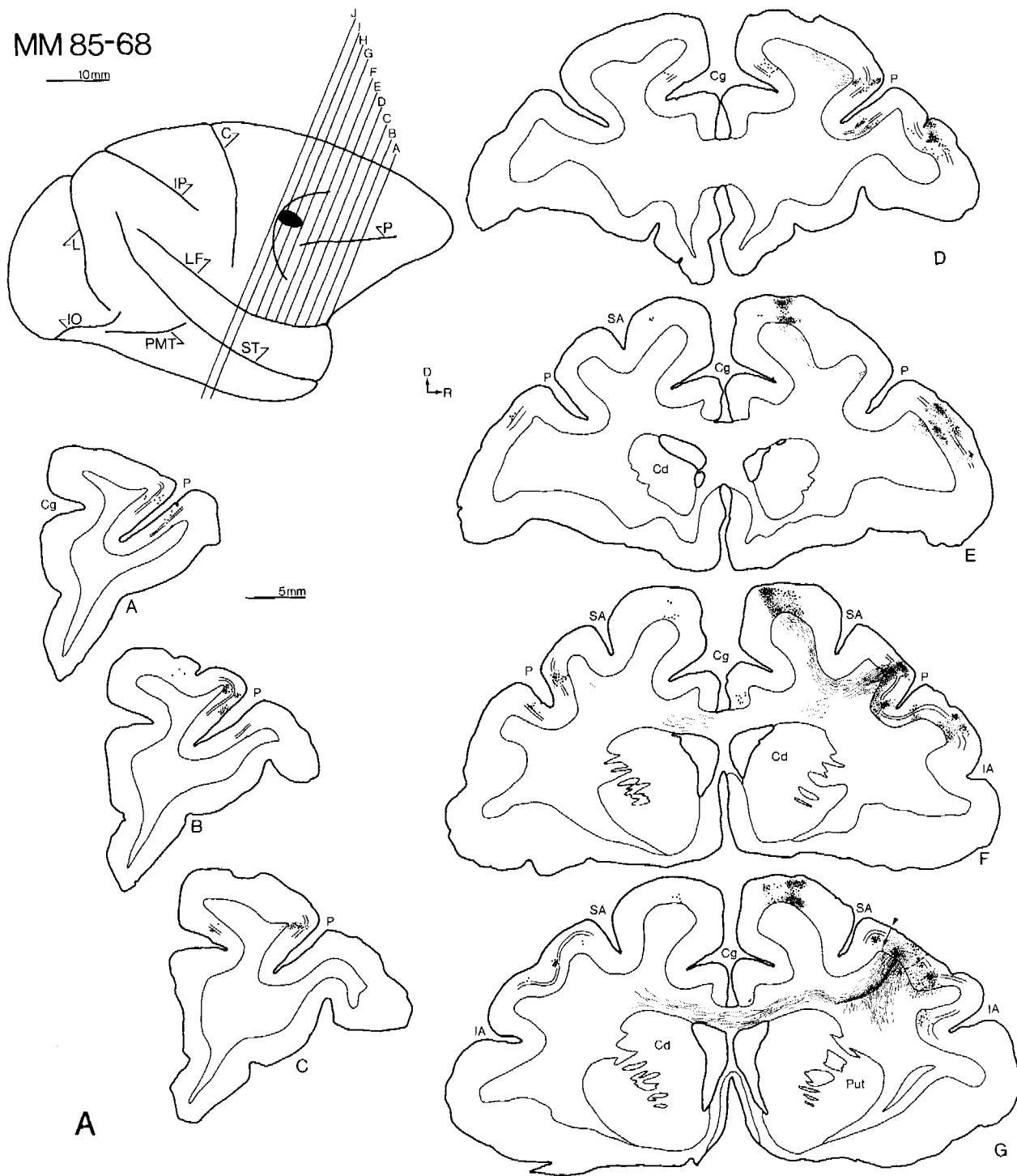
Fig. 4. Frontal lobe connections of the physiologically defined frontal eye field in macaque monkey 85–68. Cortical layer IV is indicated by parallel lines. A. At top left is a lateral view of right hemisphere with the HRP-WGA injection site indicated in black and with levels from which frontal sections were taken indicated as lettered, oblique lines. Corresponding frontal sections are drawn with the hemisphere ipsilateral to the injection site to the right and dorsal to the top. B. Continuation of A. Injection site is drawn in levels G, H, and I. Borders of physiologically defined frontal eye field are represented by dashed lines, and marker lesion is indicated by arrowhead (G). Anterogradely transported label is drawn as fine stipple and retrogradely transported label is drawn as larger dots.
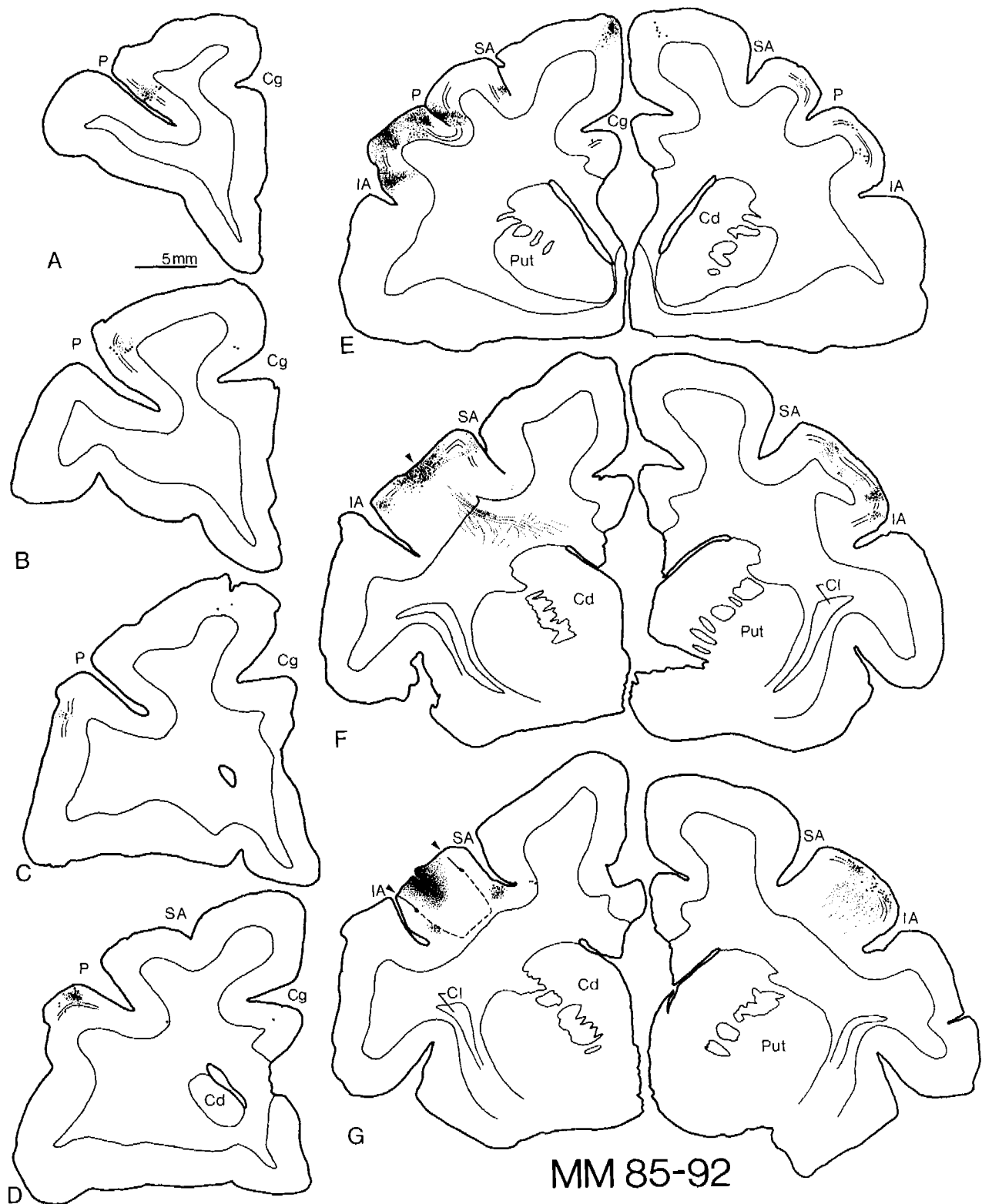
Figure 4 continued

Fig. 5. Frontal lobe connections of the physiologically defined frontal eye field in macaque monkey 85–92. (A lateral view of the left hemisphere of this case, with the HRP-WGA injection site indicated in black and with levels from which frontal sections were taken indicated as oblique lines lettered A–G, is shown in Fig. 7.) Frontal sections are drawn with the hemisphere ipsilateral to the injection site on the left and dorsal to the top.

Injection site drawn in level G. Borders of the physiologically defined frontal eye field are represented by dashed lines, and marker lesions are indicated by arrowheads (F and G). Anterogradely transported label is drawn as fine stipple and retrogradely transported label is drawn as larger dots. Cortical layer IV is indicated by parallel lines.

At levels near the rostral extent of the superior limb of the arcuate sulcus, ipsilateral cortex along the dorsomedial ridge of the hemisphere contained dense label that was concentrated in supragranular and infragranular layers, but that spanned all cortical laminae [Figs. 4(E–G), 5E, see also Fig. 8A]. This labeled dorsomedial zone corresponds to the location of the supplementary motor area (see Discussion). In monkey 85–92, eye movements were evoked by intracortical microstimulation of the dorsomedial cortex depicted in C of Figure 5. Such movements might be expected to be elicited by stimulation of the most rostral part of the supplementary motor area (see Discussion). Since a micropipette (used to inject $^3$H-proline) severely damaged the tissue in this particular zone in this case (Fig. 5C), only a few retrogradely labeled cells were apparent following injection of HRP-WGA into the ipsilateral frontal eye field. Nevertheless, the dorsomedial cortex, immediately caudal to this damaged region, contained dense bidirectionally transported label (Fig. 5). The densely labeled dorsomedial cortex depicted in E of Figure 5 is about two millimeters caudal to the damaged zone from which eye movements were evoked (i.e., Fig. 5C). In monkey 85–68 (Fig. 4, see also Fig. 8A), which had a larger injection site than monkey 85–92 (Fig. 5) and in which dorsomedial cortex was not damaged by the introduction of microelectrodes or micropipettes, the ipsilateral dorsomedially located label occupied a region that extended 3 mm in the rostral-caudal dimension and 5 mm in the medial-lateral dimension [Fig. 4(E–G), see also Fig. 8A]. In all cases, the dorsomedial cortex was reciprocally connected with the frontal eye field.

At similar rostral-caudal levels, a few scattered labeled cells were present in the ventral bank of the ipsilateral cingulate sulcus [Figs. 4(F,G), B(H,I), 5D,E]. The most caudally located label in the ipsilateral frontal lobe is in the caudal bank of the arcuate cortex [Fig. 4B(J)], corresponding to the location of the premotor cortex (see Discussion).

Label in the parietal lobe was concentrated in the ventral, or lateral, bank of the ipsilateral intraparietal sulcus. In any given section, two foci of very dense anterogradely and retrogradely transported label occupied the cortex of the intraparietal sulcus, with one focus located near the fundus (see Fig. 8B) and another situated closer to the top of the sulcus (Figs. 6C–G, 7I–K). These labeled regions correspond to the location of the ventral intraparietal and lateral intraparietal areas (see Discussion). Transported label in the cortex of the intraparietal sulcus spanned all cortical laminae, but was concentrated in supragranular and infragranular layers (e.g., Fig. 8B). There was virtually no transported label in other parts of the parietal lobe.

In the ipsilateral temporal lobe, anterogradely and retrogradely transported label was distributed throughout much of the dorsal bank (Fig. 9) and floor of the caudal one-third to one-half of the superior temporal sulcus (Figs. 6, 7). This labeled region corresponds to the locations of the middle temporal, the medial superior temporal, the fundal superior temporal, and the superior temporal polysensory areas (see Discussion). In the present material, however, only the heavily myelinated middle temporal area could be unequivocally identified (Figs. 6D,E, 7I,J). Throughout the labeled cortex of the superior temporal sulcus, most of the retrogradely labeled cells occupy the supragranular layers. Although the sections illustrated in Figures 6 and 7 suggest multiple separate foci of label, the distribution of label is actually rather continuous when adjacent sections are considered.

Finally, sparse bidirectionally transported label was also present in the ipsilateral cortex just medial to the occipitotemporal sulcus (Figs. 6D, 7I) and along the ventromedial (Fig. 7I) and ventrolateral (not illustrated) aspects of the caudal temporal cortex.

With regard to the interhemispheric connections of the frontal eye field, bidirectionally transported label was present in the cortex that corresponds to the location of the contralateral frontal eye field [Figs. 4B(H,I), 5G], as well as regions rostrolateral and rostromedial to the presumed location of the contralateral frontal eye field [Figs. 4A(G), 5F]. Label in these regions was concentrated in supragranular laminae. Reciprocal connections were also present with the contralateral caudal periprincipal cortex [Figs. 4A(F), 5E], and in the contralateral dorsomedial cortex, which corresponds to the location of the supplementary motor area [Figs. 4A(F,G), 5E]. Finally, retrogradely labeled cells were occasionally scattered in the banks of the contralateral cingulate sulcus [Fig. 4A(D–G), B(H,I)], and in the caudal bank of the contralateral arcuate sulcus, which corresponds to the location of the premotor cortex [Fig. 4B(I)].

## Squirrel monkey

*Definition of the frontal eye field and other intracortical microstimulation data.* In each squirrel monkey, the physiologically defined frontal eye field was located near the inferior arcuate dimple (also see Huerta et al., '86). Nevertheless, the spatial relationship between the field and the dimple varied tremendously between individuals. For example, in one case (see Fig. 11), the frontal eye field is located just rostral and dorsomedial to the caudal limit of the inferior arcuate dimple. In contrast, in the other case (see Fig. 12), the frontal eye field is "displaced" several millimeters relative to the caudal limit of the dimple. In each case, 40–50 mm$^2$ of periarcuate cortex was explored with intracortical microstimulation, and the cortex from which contralateral, conjugate rapid eye movements could be consistently evoked with the lowest current amplitudes was considered to be the frontal eye field. Since cortical and subcortical connections were similar in each case, it appears that in squirrel monkeys, the location of the frontal eye field relative to the inferior arcuate dimple varies by as much as 2–3 mm (also see Huerta et al., '86).

Unlike the macaque (and owl) monkeys, current levels of nearly 100 μA were often required to reliably evoke eye movements from the frontal eye fields of squirrel monkeys. The borders of the field were indicated by evoked movements of body parts other than the eyes (also see Huerta et al., '86). These borders were marked with electrolytic lesions (Fig. 10; depicted as circles in periarcuate cortex in Figs. 11, 12), and the field received an injection of HRP-WGA (Fig. 10; also see Huerta et al., '86, Fig. 7). As indicated in Figures 10, 11, and 12, the injection sites were confined to the physiologically defined field.

In addition to the periarcuate cortex, the cortex between the central dimple and the inferior arcuate dimple was explored with intracortical microstimulation in all three squirrel monkeys. In squirrel monkey 85–30 (Fig. 11), for example, contralateral body movements were evoked by exploratory current levels of 50 μA in an expanse of cortex that measured 9–10 mm in the rostral-caudal dimension and that had the central dimple as its caudal border. Rostral to this "low threshold motor region," current levels required to elicit movements increased at least threefold. The rostral border of the "low threshold motor region" was
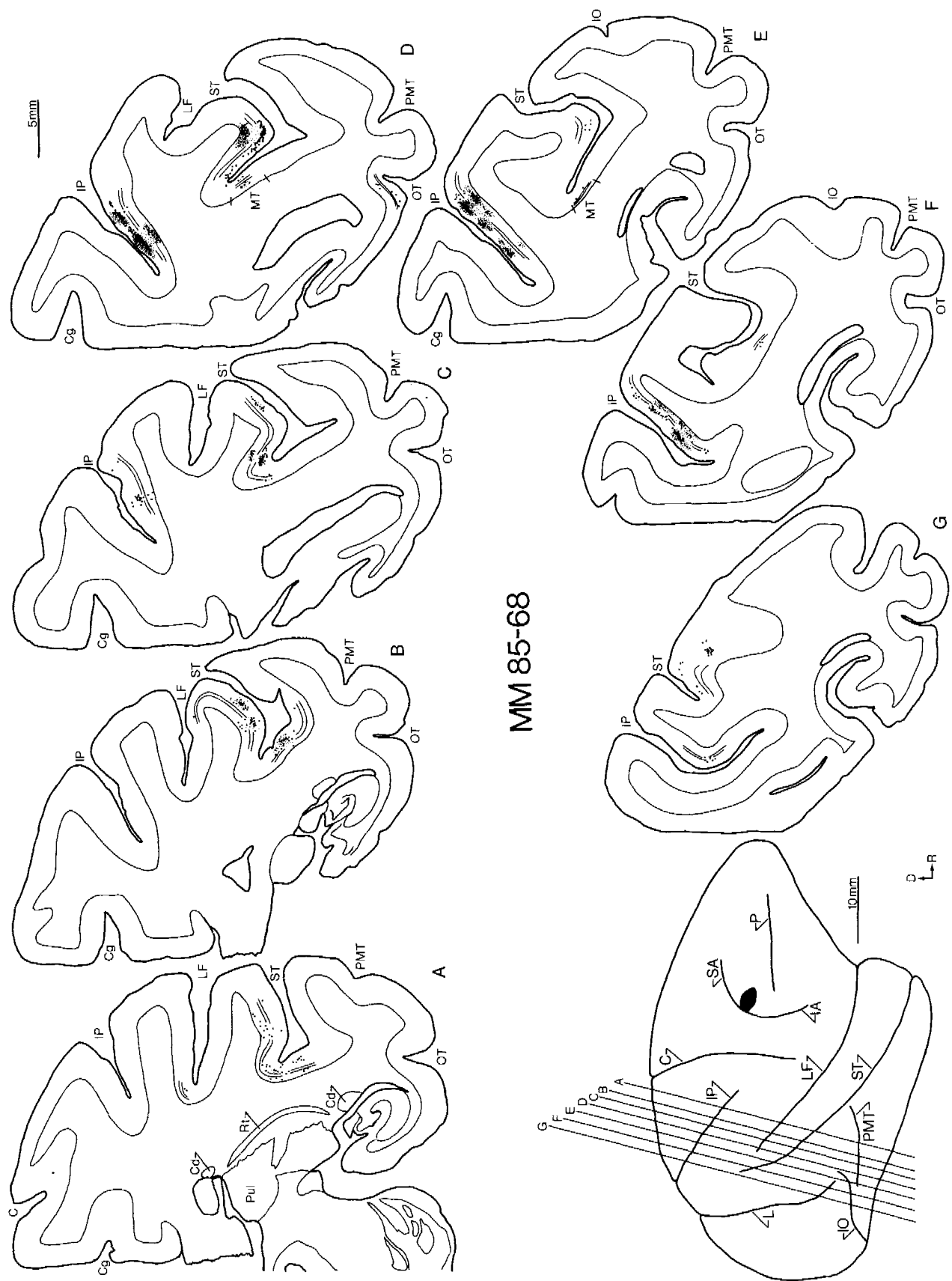
MM 85-68

Figure 6

marked by two electrolytic lesions (depicted as two circles 9-10 mm rostral to the central dimple in Fig. 11). Thus, proceeding rostral from the central dimple, the cortex was subdivided into a 9-10 mm "low threshold motor region," a 2-3 mm "high threshold motor region," and farthest rostral, the frontal eye field. More specifically, the frontal eye field was situated immediately rostral to the part of the "high threshold motor region" from which ear and eyelid movements could be evoked. This "high threshold motor region," in turn, was located immediately rostral to the "low threshold motor region" from which forelimb movements could be evoked.

*Connections of the frontal eye field.* Since the injection site virtually filled the physiologically defined frontal eye field in each of the three squirrel monkeys (e.g., Figs. 10, 11, 12), the intrinsic connections were obscured. As in the macaque monkey, extrinsic connections with the ipsilateral frontal lobe were concentrated in the cortex at or rostral to the rostral-caudal level of the frontal eye field (Figs. 11, 12, see also Fig. 15). Rostral and rostrolateral to the level of the frontal eye field, bidirectionally transported label was distributed in several foci (Figs. 11, 12, see also Fig. 15). Reciprocal connections were also made with ipsilateral cortex ventrolateral to the frontal eye field (most easily seen just rostral to the inferior arcuate dimple in Fig. 12, but also present in Fig. 11; see also Fig. 15). Dorsomedial to the frontal eye field, near the dorsomedial ridge of the ipsilateral hemisphere, anterogradely and retrogradely transported label was distributed in two (Fig. 11) or more (Fig. 12) foci. This dorsomedial cortex corresponds to the location of the supplementary motor cortex (see Discussion).

There was a considerable amount of label immediately surrounding the injection site (but outside of the physiologically defined field) and patches of transported label caudal and caudolateral to the frontal eye field (Figs. 11, 12, see also Fig. 15). The caudal patch of label was immediately rostral to the rostral border of the "low threshold motor region" (described above). This is clearly depicted in Figure 11. The "low threshold motor region" contained little or no transported label. In one case, reciprocal connections were made with the ventromedial cortex lateral to the orbital sulcus (Fig. 11), but this region did not contain label in the other two squirrel monkeys.

On the medial wall of the ipsilateral parietal cortex, anterogradely and retrogradely transported label occupies the ventral bank of the caudalmost part of the cingulate gyrus (Figs. 11, 12). Farther caudal on the medial wall were several other labeled zones that extended to the parietal cortex rostral to the parietal occipital sulcus (Figs. 11, 12).

Bidirectionally transported label was also present in widespread regions of the cortex of the caudal half of the ipsilateral lateral fissure, including the dorsal bank (Figs. 11, 12, see also Fig. 15), the floor (Figs. 11, 12, see also Figs.

14, 15), and the ventral bank (see Figs. 14, 15). Most label in the lateral fissure, however, was situated in the dorsal bank. In addition to label in the caudal part, sparse label was also present farther rostral, in the floor of the ipsilateral lateral fissure (see Fig. 15, levels 141, 151). Most label in the ipsilateral temporal lobe was distributed in the cortex rostral to, and in the rostral bank of, the superior temporal sulcus [see Figs. 14, 15(131, 141, 151)]. Nevertheless, sparse label was also present in the cortex just caudal to this sulcus, in a region that stained densely for cytochrome oxidase and that probably corresponds to the middle temporal area [see Figs. 14, 15(186)].

Transported label in the contralateral hemisphere was restricted to the frontal lobe, with reciprocal connections present in cortex corresponding to the locations of the frontal eye field and the supplementary motor area (Fig. 13).

## Owl Monkey

*Definition of the frontal eye field and other intracortical microstimulation data.* Since the inferior arcuate sulcus is not always present in owl monkeys, other means were used to grossly locate the frontal eye field region. Our stimulation data from squirrel monkeys (above) and previous intracortical microstimulation studies of owl monkeys (Gould et al., '86) indicated that the frontal eye field is situated 2-3 mm rostral to the cortex from which forelimb movements could be elicited with low current levels. Thus, intracortical microstimulation was used to locate this "low threshold motor region" in the precentral cortex. After locating this forelimb representation, stimulation was used to explore more rostral regions until cortex from which eye movements could be evoked was found (also see Huerta et al., '86). Such cortex was studied with closely spaced penetrations, and threshold current levels were carefully noted.

The region from which eye movements could be evoked with the lowest current levels was considered to be within the frontal eye field. Cortex from which no movements, or movements of other body parts, were elicited with comparable current levels were considered to be outside the frontal eye field. Data regarding the definition of the frontal eye field in owl monkey 85-67 are shown in Figure 16. Thus, in the frontal eye field of this monkey, eye movements were consistently evoked with current levels of from 20-60 $\mu$A. Immediately outside of the field, comparable levels of current produced no movement, or movements of the ear or vibrissae (Fig. 16). As in all monkeys, the borders of the frontal eye field were marked by electrolytic lesions (depicted as boxes in Fig. 16) and received an injection of HRP-WGA (injection site depicted as a star in Fig. 16; also see Huerta et al., '86, Fig. 7).

In addition to exploring the frontal eye field region and precentral cortex ("low threshold motor region") with intracortical microstimulation, the frontal cortex near the dorsomedial ridge of the ipsilateral hemisphere was also studied with stimulation in the same animals. In each of all three owl monkeys, a small zone of dorsomedial frontal cortex (supplementary motor area, Gould et al., '86) was found from which eye movements were evoked with current levels similar to those used to define the frontal eye field. The borders of this dorsomedial eye movement-related region were defined and marked with electrolytic lesions (set of four circles in the dorsomedial cortex depicted in Fig. 17).

*Connections of the frontal eye field.* The cortical connections of the frontal eye field in a typical owl monkey case are shown in Figures 17 and 18. In general, these connections strongly resemble those of the squirrel monkey. Spe-

Fig. 6. Parietal and temporal lobe connections of the physiologically defined frontal eye field in macaque monkey 85-68. At the bottom left is a lateral view of the right hemisphere with the HRP-WGA injection site indicated in black and with levels from which frontal sections were taken indicated as lettered, oblique lines. Corresponding frontal sections through the right hemisphere ipsilateral to the injection site are drawn with medial to the left and dorsal to the top. Anterogradely transported label is drawn as fine stipple, and retrogradely transported label is drawn as larger dots. Cortical layer IV is indicated by parallel lines. Visual area MT, as defined by myeloarchitecture, is indicated in levels D and E.
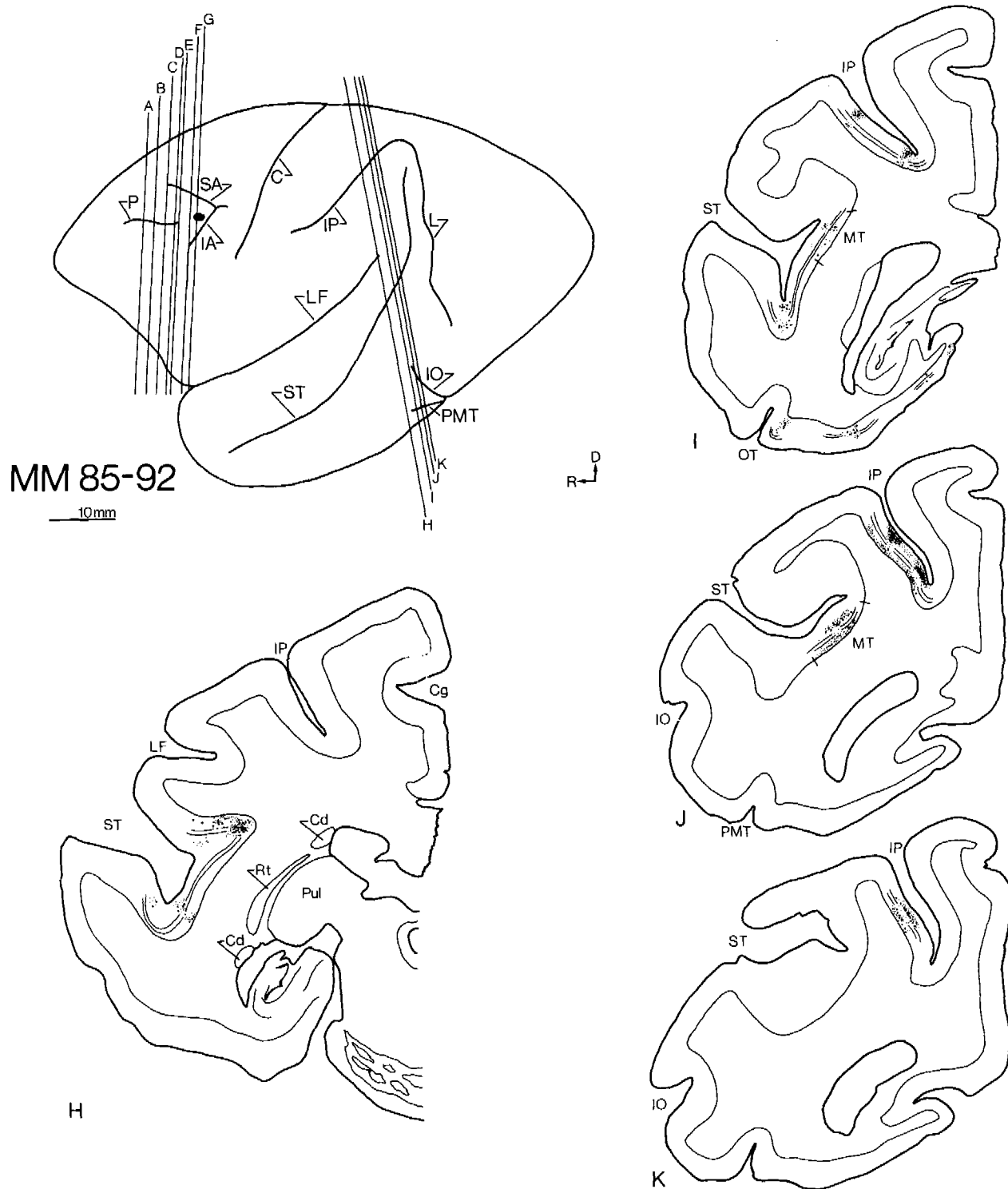
Fig. 7. Parietal and temporal lobe connections of the physiologically defined frontal eye field in macaque monkey 85–92. At the top left is a lateral view of the left hemisphere with the HRP-WGA injection site indicated in black and with levels from which frontal sections were taken indicated as oblique lines lettered **H-K**. Corresponding frontal sections through the hemisphere ipsilateral to the injection site are drawn with medial to the right and dorsal to the top. Anterogradely transported label is drawn as fine stipple and retrogradely transported label is drawn as larger dots. Cortical layer IV is indicated by parallel lines. Visual area MT, as defined by myeloarchitecture, is indicated in I and J.
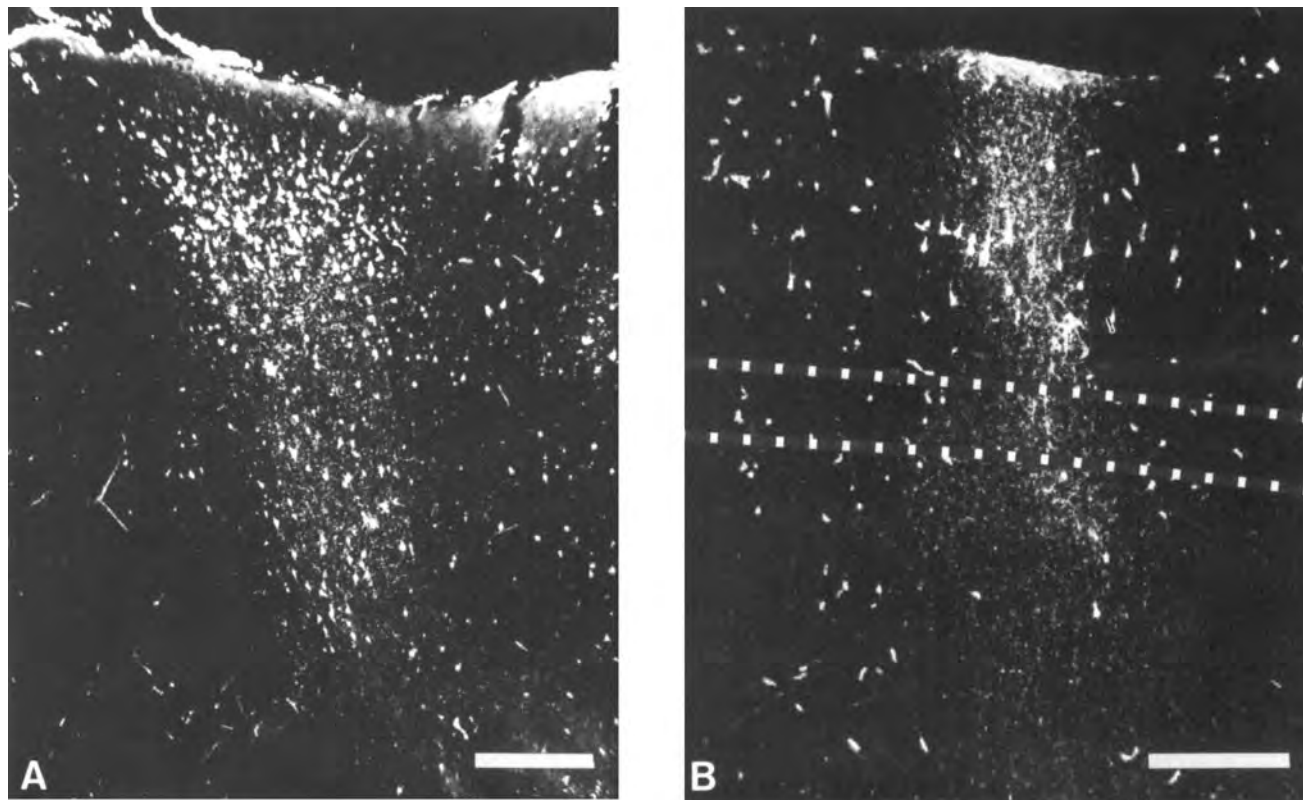
Fig. 8. A. Dark-field photomicrograph of anterogradely and retrogradely transported label in the ipsilateral supplementary motor cortex in macaque monkey 85–68 following injection of HRP-WGA into the physiologically defined frontal eye field. Medial is to the left, dorsal to the top. Scale bar is 500 μm. B. Dark-field photomicrograph of anterogradely and retrogradely transported label in the ipsilateral cortex of the lateral bank of the intra-parietal sulcus near the fundus in macaque monkey 85–92 following injection of HRP-WGA into the physiologically defined frontal eye field. Dorsomedial is to the top and dorsolateral is to the left of the figure. Cortical layer IV is indicated by dotted lines. Scale bar is 500 μm.
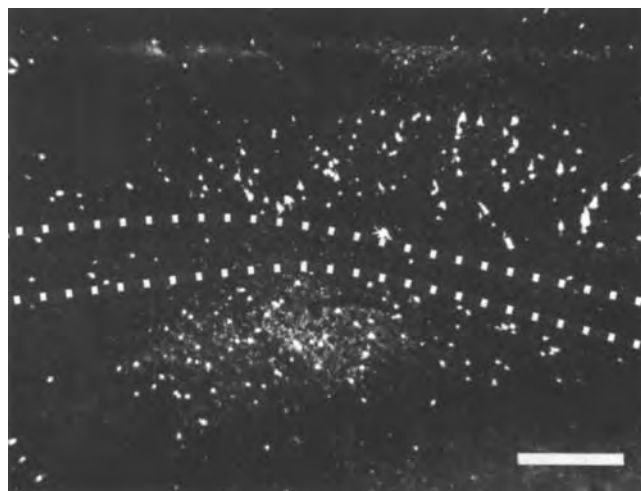


Fig. 9. Dark-field photomicrograph of anterogradely and retrogradely transported label in the ipsilateral dorsal bank of the superior temporal sulcus following injection of HRP-WGA into the physiologically defined frontal eye field in macaque monkey 85–68. Ventromedial is to the top, ventrolateral to the left of the figure. Scale bar is 500 μm.

cifically, most of the connections between the physiologically defined frontal eye field and the rest of the frontal lobe are with cortex at or rostral to the rostral-caudal level of the frontal eye field (Fig. 17). Ventrolateral, rostrolateral, and rostral to the frontal eye field, anterogradely and retrogradely transported label was distributed in several ipsilateral foci (Fig. 17). Dorsomedial to the physiologically defined frontal eye field were three distinct clusters of bidirectionally transported tracer. The most rostral of these was confined to a zone delimited by four lesions. These lesions marked the boundaries of cortex from which eye movements were elicited with intracortical microstimulation (described above). Immediately caudal to this focus of label was one continuous focus (unillustrated case) or two separate foci of label (Fig. 17). All of these dorsomedial patches were rostral to the "low threshold motor region" defined by microstimulation in these monkeys.

The cortex immediately surrounding the injection site, and physiologically defined frontal eye field, was densely labeled, as was a patch of cortex approximately 0.5 mm caudal to the border of the frontal eye field (Fig. 17). This caudal focus of label was rostral to the "low threshold motor" representation of the forelimb as defined with intra-
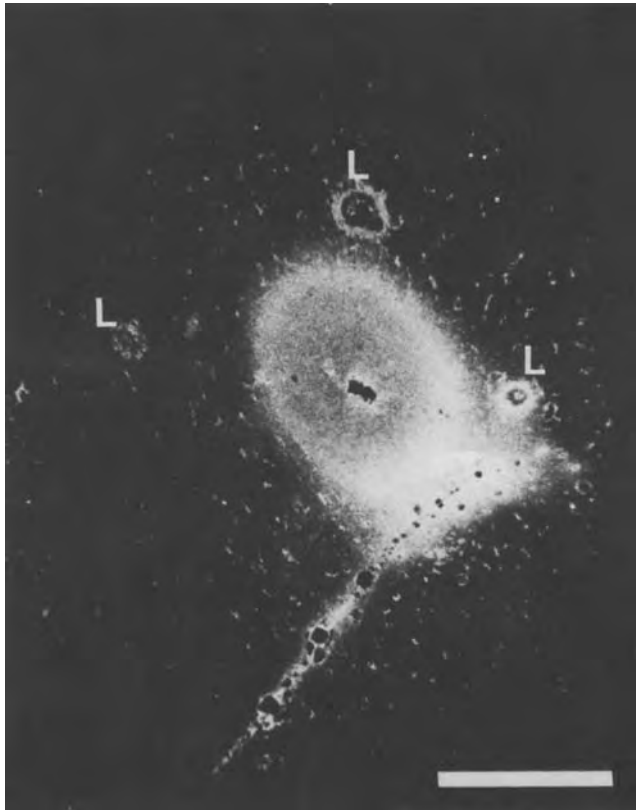
Fig. 10. Dark-field photomicrograph of flattened section of cortex in squirrel monkey 85–30 showing the extent of the HRP-WGA injection site in relation to electrolytic lesions (L), which mark the physiologically defined borders of the frontal eye field. Rostral is to the left and dorsomedial to the top of the figure. Scale bar is 1.0 mm.

cortical microstimulation (described above). In addition, sparse anterogradely transported label was present caudolateral to the physiologically defined field. Reciprocal connections were also made with cortex located in the lateralmost part of the ventromedial cortex in all three owl monkeys.

Bidirectionally transported label in the parietal lobe was distributed in the cortex of the medial wall and throughout much of the caudal half of the dorsal bank of the lateral fissure (Fig. 17). The corresponding caudal floor and ventral bank of the lateral fissure also contained numerous zones of anterogradely and retrogradely transported label (Fig. 18). Reciprocal connections were also made with the cortex of the lateral surface of the temporal lobe, just caudal to the bank of the lateral fissure. Temporal lobe label was also present, although sparse, in cortex caudal to the superior temporal sulcus and within the caudal bank of the sulcus.

Contralateral connections were made reciprocally with cortex corresponding to the location of the frontal eye field and the dorsomedially situated supplementary motor area.

## DISCUSSION

The present report is the first to comprehensively describe the cortical connections of the physiologically defined frontal eye fields in primates. The combination of anatomical and physiological approaches in individual animals as-

sures that the connections demonstrated are solely those of the frontal eye field. Such assurance, in turn, allows greater confidence in making interspecies comparisons and in relating the present anatomical data to functional issues.

In the following discussion the present data are compared to previous studies of the cortical connections of prearcuate cortex, most of which were carried out in macaque monkeys. Next, the cortical connections of the physiologically defined frontal eye fields in squirrel monkeys, owl monkeys, and macaque monkeys are compared. Finally, the results of the present study are considered in the context of our knowledge of the functions of the frontal eye field and cortical regions with which they are connected.

### Previous connectional studies

Since virtually all previous studies of the cortical connections of the frontal eye field have been limited to macaque monkeys, so, too, is this section. The definition of the frontal eye field in macaque monkeys has recently been discussed at length elsewhere (Bruce et al., '85; Huerta et al., '86). Nevertheless, it is important to stress that whereas the frontal eye field has traditionally been considered to correspond to cytoarchitectonic area 8 of Brodmann ('09), or to rather expansive portions of prearcuate cortex, combined physiological and anatomical analyses indicate that the frontal eye field is actually much less extensive, roughly corresponding to Walker's ('40) areas 8a and 45 (Bruce et al., '85; Huerta et al., '86). Thus, connections that have been described as those of the frontal eye field are likely to include connections of nearby cortex lying outside of the frontal eye field. This is reflected by the fact that whereas most of the connections presently demonstrated have been described by others (see below), there are connections that were not observed in the present material but that were reported by others to exist with the frontal eye field.

The presently demonstrated connections of the physiologically defined frontal eye field in macaque monkeys are consistent with the results of numerous previous connectional studies of prearcuate cortex. Specifically, connections with the frontal eye field region have been described for: 1) the cortex in the banks of the ipsilateral principal sulcus (Pandya and Kuypers, '69; Jones and Powell, '70; Kunzle and Akert, '77; Barbas and Mesulam, '81, '85), 2) the cortex along the banks of the contralateral principal sulcus (Anderson et al., '85), 3) the cortex along the dorsomedial ridge of the ipsilateral hemisphere in rostral-caudal levels around the rostral limit of the superior limb of the arcuate sulcus (Jones and Powell, '70; Kunzle and Akert, '77; Barbas and Mesulam, '81; Stanton, '86), 4) the corresponding dorsomedial cortex in the contralateral hemisphere (Anderson et al., '85), 5) the contralateral cortex corresponding to the location of the frontal eye field (Kunzle and Akert, '77; Anderson et al., '85), 6) the cortex immediately caudal to the frontal eye field, in the ipsilateral postarcuate region (Pandya and Kuypers, '69; Jones and Powell, '70; Barbas and Mesulam, '81; Godschalk et al., '84), 7) the cortex of the inferior or lateral bank of the ipsilateral intraparietal sulcus (Pandya and Kuypers, '69; Chavis and Pandya, '76; Kunzle and Akert, '77; Mesulam et al., '77; Barbas and Mesulam, '81; Petrides and Pandya, '84; Anderson et al., '85), 8) the cortex in the depths of the most caudal part of the ipsilateral lateral fissure (Barbas and Mesulam, '81; Petrides and Pandya, '84; Anderson et al., '85), 9) the cortex throughout much of the caudal one-third to one-half of the ipsilateral superior temporal sulcus (Pandya and Kuypers,
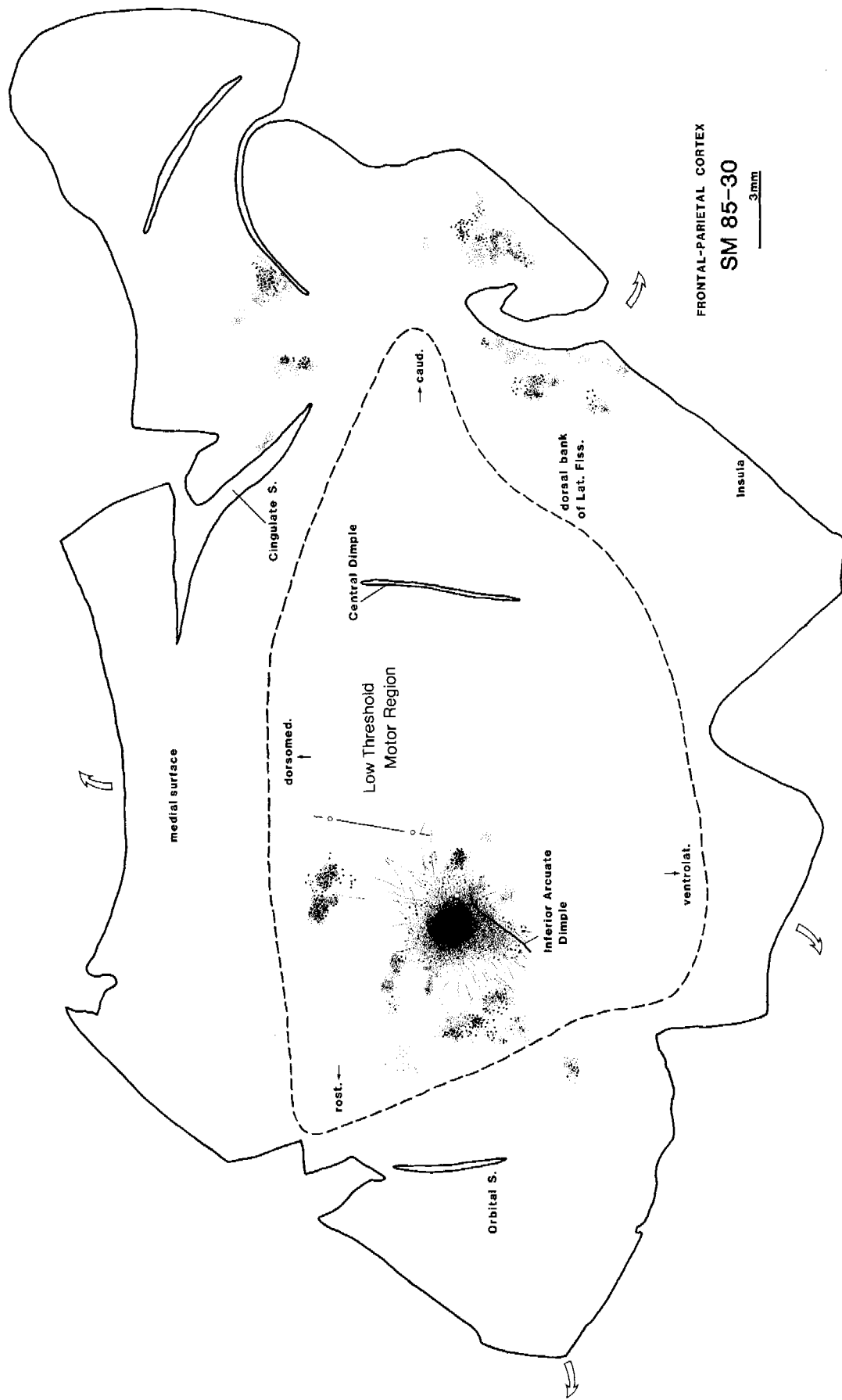
FRONTAL-PARIETAL CORTEX

SM 85-30

3mm

Fig. 11. Results of an experiment in which HRP-WGA was injected into the physiologically defined frontal eye field in squirrel monkey 85-30. In this flattened cortex preparation, the lateral surface of the frontal and parietal cortex is outlined by the dotted line. As illustrated in Figure 1, cortex of the medial wall is at the top, cortex of the orbital surface at the left, and cortex normally situated in the depth of the lateral fissure is at the right of the figure. Three lesion sites marking the physiologically defined borders of the frontal eye field are indicated as open circles around the injection site (see photomicrograph in Fig. 10). Two other lesions mark the rostral border of a low threshold motor region, located about 9 mm rostral to the central dimple. Anterogradely transported label drawn as fine stipple and retrogradely transported label drawn as larger dots.

FRONTAL-PARIETAL CORTEX

SM 85-34

3mm

medial surface

Cingulate S.

Central Dimple

Area 3b

caud.

dorsomed.

lateral surface

dorsal bank of Lat. Fiss.

Insula

Inferior Arcuate Dimple

ventrolat.

rost.

Orbital S.

FRONTAL-PARIETAL CORTEX

SM 85-34

3mm

medial surface

Cingulate S.

dorsomed.

caud. ←

Central Dimple

lateral surface

SMA

→ rost.

FEF

dorsal bank
of Lateral Fissure
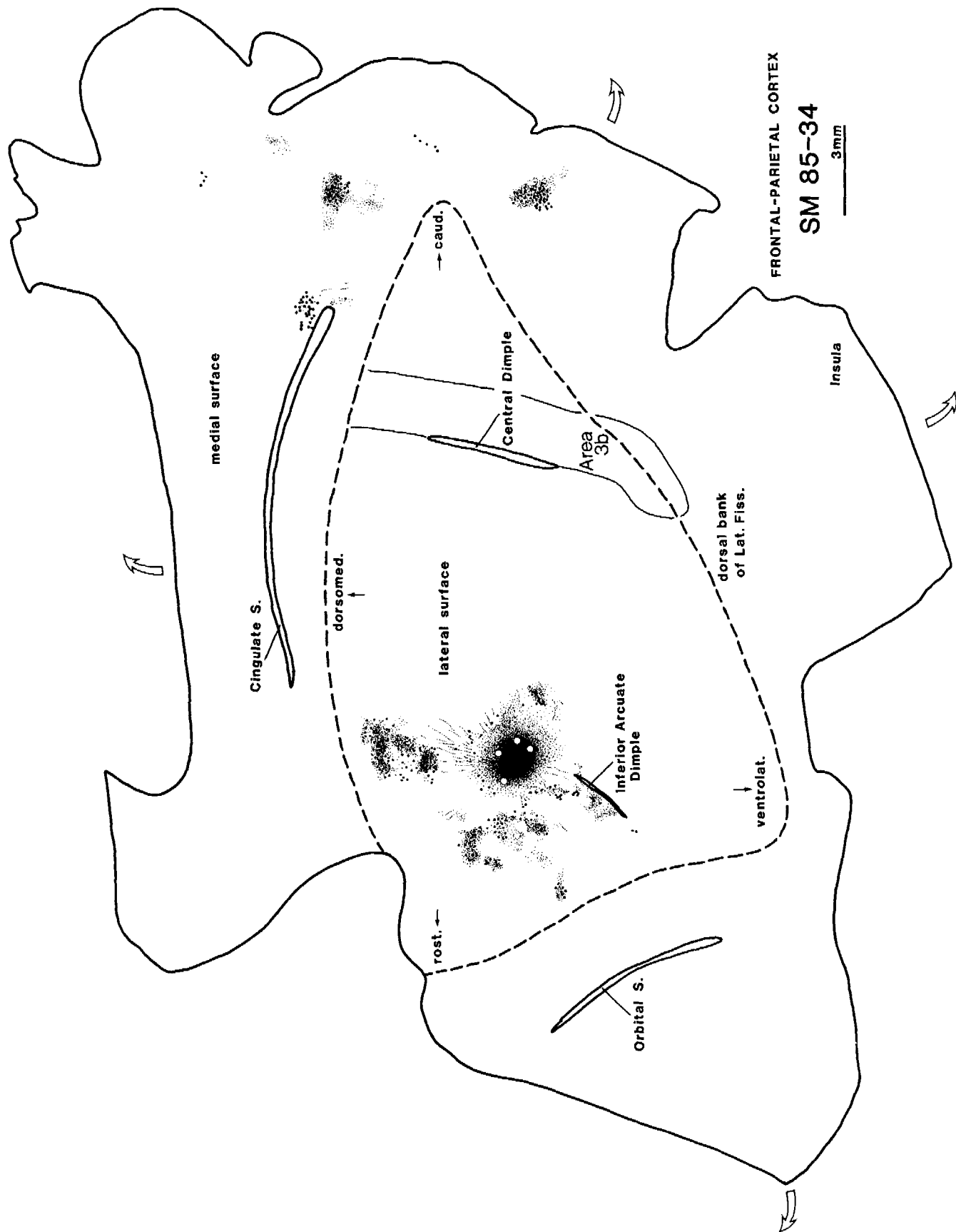
ventrolat.

Orbital S.

Insula

Fig. 13. Anterogradely and retrogradely transported label in frontal and parietal cortex contralateral to the injection site in the frontal eye field in squirrel monkey 85-34. Probable locations of supplementary motor area and frontal eye field are indicated. Other conventions the same as Figure 11.

'69; Chavis and Pandya, '76; Kunzle and Akert, '77; Barbas and Mesulam, '81; Maioli et al., '83; Anderson et al., '85; Ungerleider and Desimone, '86), 10) the cortex just ventrolateral to the ipsilateral posterior middle temporal sulcus (Pandya and Kuypers, '69; Jones and Powell, '70; Barbas and Mesulam, '81), 11) the cortex just medial to the ipsilateral occipitotemporal sulcus (Barbas and Mesulam, '81), 12) the cortex in the banks of the ipsilateral cingulate sulcus (Pandya and Kuypers, '69; Kunzle and Akert, '77; Barbas and Mesulam, '81), and 13) the cortex just rostrolateral to the rostral tip of the lower limb of the ipsilateral arcuate sulcus (Barbas and Mesulam, '81). In addition, cortex in the caudal part of the superior temporal sulcus, in visual area ST, has been described as projecting to the frontal eye field

Fig. 12. Ipsilateral connections of physiologically defined frontal eye field in squirrel monkey 85-34. Cortical area 3b, as defined by myeloarchitecture, is indicated. Same conventions as in Figure 11.

in the owl monkey (Weller et al., '84), and the relationship between the total pattern of interhemispheric connections of the physiologically defined frontal eye field has been described in this New World monkey (Gould et al., '86). Finally, in the squirrel monkey ipsilateral reciprocal connections have been demonstrated between the dorsomedial cortex of the frontal lobe, corresponding to the location of the supplementary motor area, and the region of the frontal eye field (Jürgens, '84).

Despite the consistency of the present findings with the results of others just described, there are also reports of prearcuate connections that were not observed in the present material (in which the injection sites of tracer were confined to the physiologically defined frontal eye field). Specifically, in macaque monkeys, ipsilateral projections to prearcuate cortex have been described as arising from: 1) the medial wall of the caudalmost part of the lateral fissure (Petrides and Pandya, '84), 2) the cortex just lateral to the intraparietal sulcus on the surface of the hemisphere (Pe-
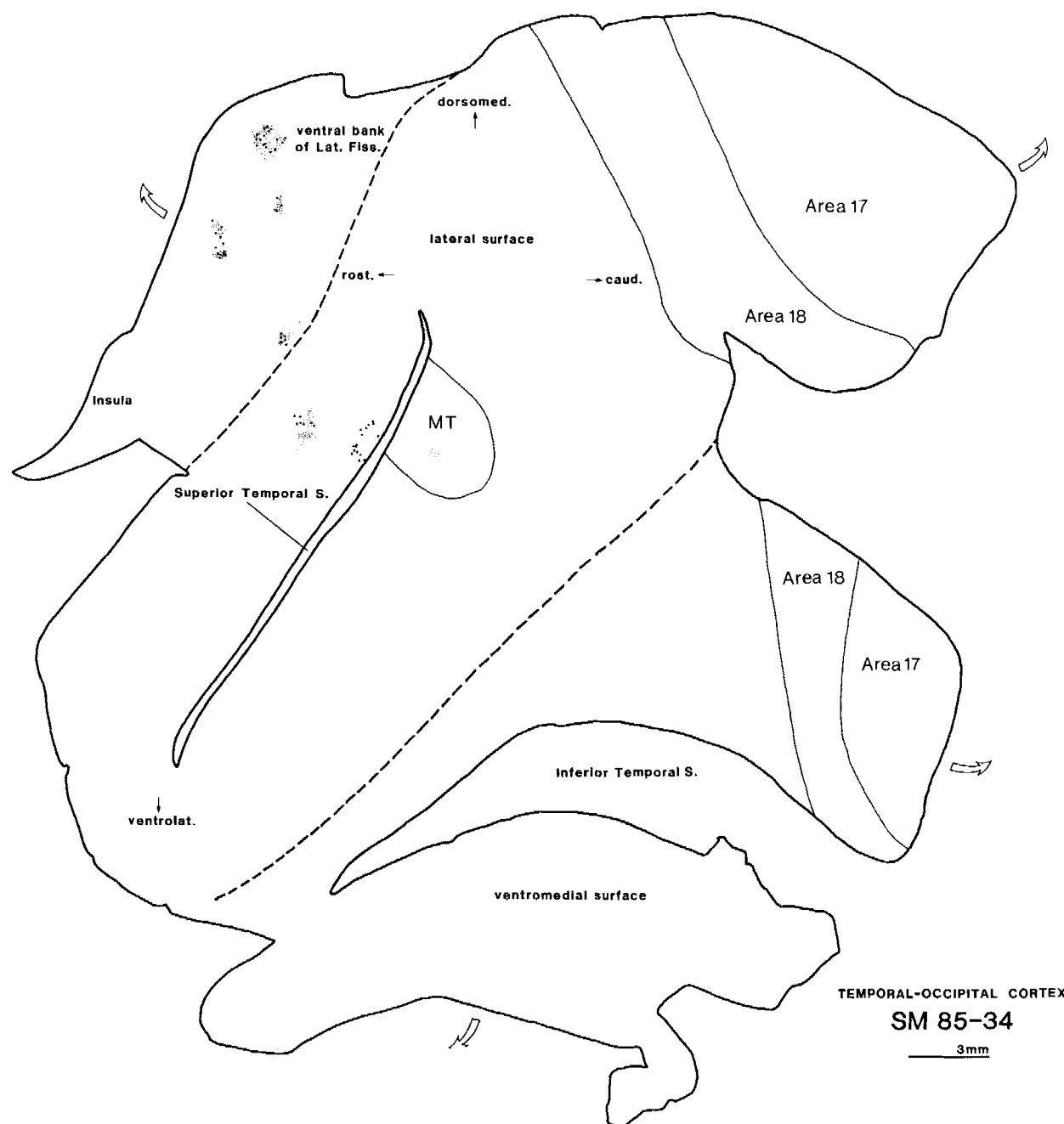
Fig. 14. Results of an experiment in which HRP-WGA was injected into the physiologically defined frontal eye field in squirrel monkey 85–34. In this flattened cortex preparation the lateral surface of the temporal lobe is outlined by the dashed line. As illustrated in Figure 1, cortex normally situated in the depth of the lateral fissure is at the left, dorsomedial cortex at the top right, and cortex of the ventromedial surface of the temporal lobe at the bottom right of the figure. Visual areas MT, 18, and 17, as defined by a stain for cytochrome oxidase, are indicated. Anterogradely transported label drawn as fine stipple and retrogradely transported label drawn as larger dots.

trides and Pandya, '84; Anderson et al., '85), 3) the cortex between the lateral fissure and the superior temporal sulcus (Chavis and Pandya, '76; Barbas and Mesulam, '81), 4) the postcentral gyrus (Pandya and Kuypers, '69), 5) prelunate and postlunate cortex (Barbas and Mesulam, '81), and 6) peristriate cortex, including area 18 of Brodmann ('05; Barbas and Mesulam, '81). There are several possible reasons that these connections were not observed in the present material. First, in studies in which connections were revealed by retrograde transport of tracer (Barbas and Mesulam, '81; Anderson et al., '85), it is likely that the injection site of tracer extended beyond the limits of what would correspond to the frontal eye field as defined presently and elsewhere (Bruce et al., '85; Huerta et al., '86). Second, in studies utilizing anterograde transport (Petrides and Pandya, '84) or anterograde degeneration (Pandya and Kuypers, '69; Jones and Powell, '70; Chavis and Pandya, '76) techniques, it is possible, and in some cases probable, that
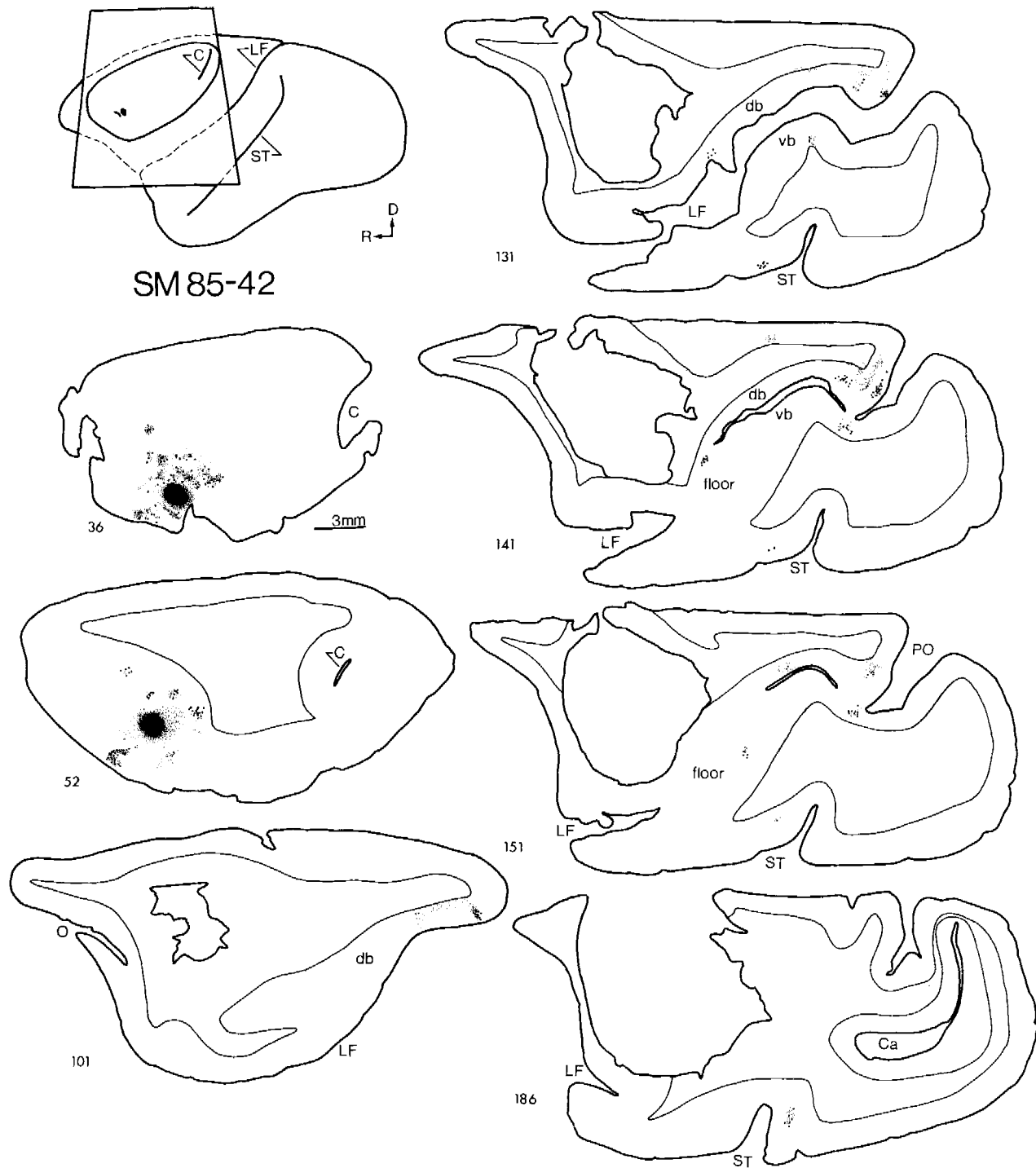
Fig. 15. Ipsilateral cortical connections of the frontal eye field in squirrel monkey 85–42. At the top left is a lateral view of left hemisphere with HRP-WGA injection site indicated in black. The plane of section, which is between parasagittal and horizontal planes, is also indicated. Anterogradely transported label drawn as fine stipple and retrogradely transported label drawn as larger dots.

the lesion site or injection site encroached upon cortex that has presently been demonstrated to innervate the frontal eye field. Finally, of course, some or all of the discrepancies listed above may be due to the fact that injection sites in the present material were relatively small and all connec-

tions of the frontal eye field may not have been demonstrated. The possibility of this explanation, however, is diminished by the facts that the injection site virtually filled the frontal eye field as defined physiologically and that the method presently employed is extremely sensitive

100V
·

50V
·

50EL
⊡

60E
·

50E
·

25E
☆

20E  40E
·      ·
        50Ea    .50Ea
100E    ⊡
75NR   ⊡            100Ea,EL
·       40E           ·
        ·

30E
·

75E
⊡
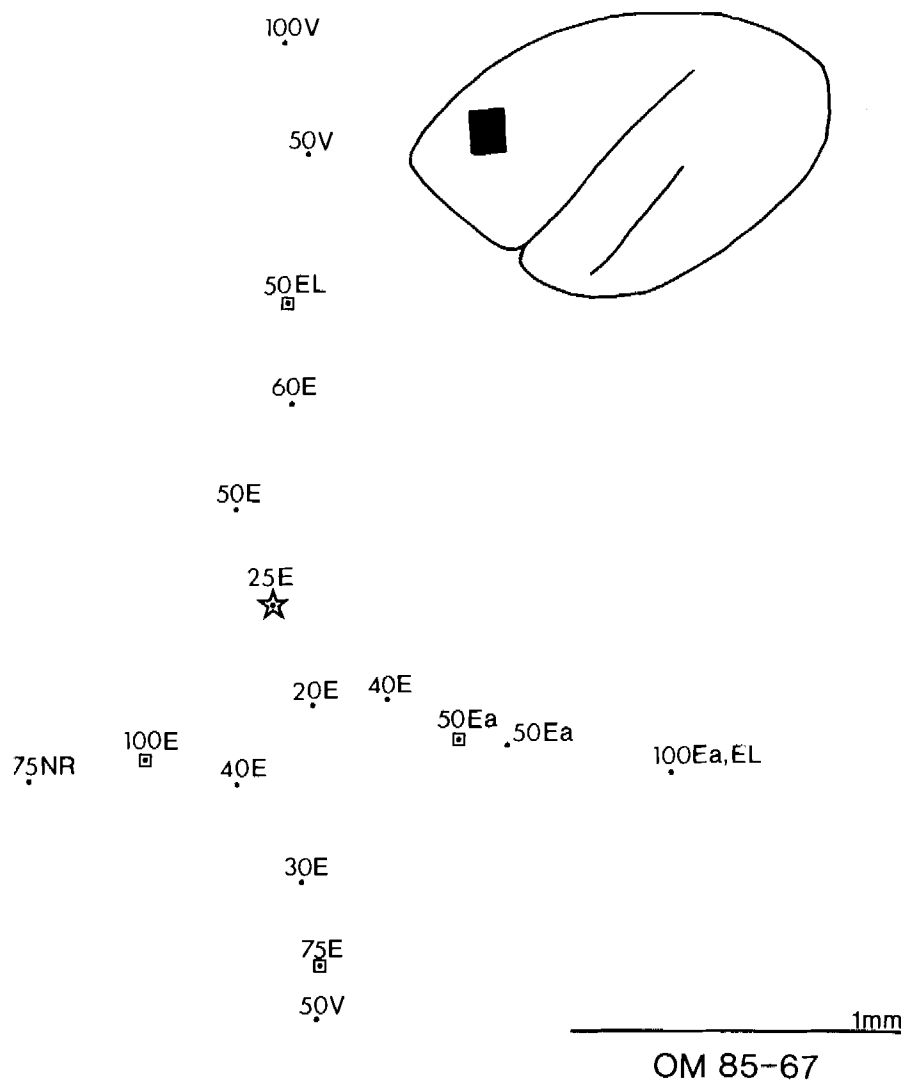
50V
·                          _____1mm

OM 85-67

Fig. 16. Physiological data from the frontal eye field region (blackened square) in owl monkey 85-67 showing the locations of electrode penetrations (dots) and threshold levels of current (in μA) needed to evoke movements of the eyes (E), eyelid (EL), ear (Ea), vibrissae (V), or from which no response (NR) could be elicited with currents as high as 75 μA. Locations of lesions indicated by squares; location of injection pipette tip indicated by star.

compared to other techniques used by most of the studies reviewed above.

## Comparisons between species

As reported previously, the subcortical connections of the physiologically defined frontal eye fields are remarkably similar in squirrel monkeys, owl monkeys, and macaque monkeys (Huerta et al., '86). The present data indicate that the connections between the physiologically defined frontal eye field and other parts of the frontal lobe are also very similar in these three species (Fig. 19). Thus, in each monkey the frontal eye field makes connections with multiple foci rostral and rostrolateral to the physiologically defined field. In macaque monkeys, these lie in the cortex of the banks of the principal sulcus as well as the cortex of the inferior and superior concavities of the prefrontal region (i.e., cortex immediately ventrolateral and dorsomedial to the principal sulcus, respectively). Although owl monkeys

and squirrel monkeys lack clear prefrontal sulcal features, a similar expanse of cortex and a similar number of foci are connected with the frontal eye fields in the New and Old World species examined. The frontal eye fields are also connected with cortex just caudal (all monkeys) and/or caudolateral (New World monkeys) to the physiologically defined region. Another feature of frontal eye field connectivity that is shared by all three species studied is the extensive, dense connections made with cortex dorsomedial to the frontal eye field, both ipsilateral and contralateral to the injection site. Finally, the frontal eye field appears to make homotopic contralateral connections in squirrel monkeys, owl monkeys, and macaque monkeys.

Connections of the frontal eye field with other cortical regions do appear to vary between the three species, with the greatest differences being between either of the two species of New World monkeys and the macaque monkeys. Specifically, in the Old World monkeys, many connections
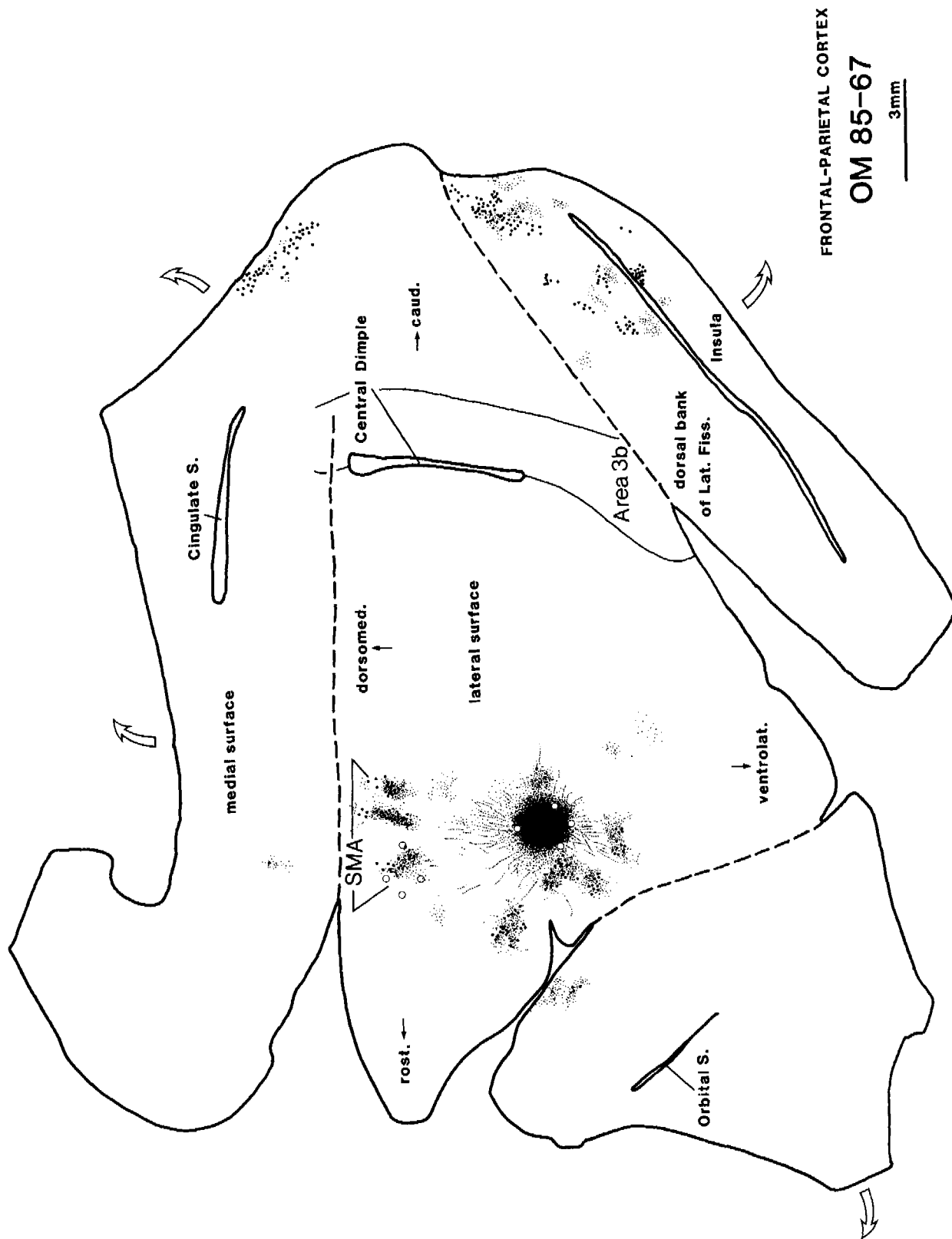
Fig. 17. Ipsilateral frontal and parietal connections of the physiologically defined frontal eye field in owl monkey 85–67. Flattened cortex preparation. Lesions (open circles) mark the border of the physiologically defined frontal eye field (with injection site) and the borders of the physiologically defined eye movement representation of the supplementary motor area. Cortical area 3b, as defined by myeloarchitecture, is indicated. Conventions as in Figure 11.

TEMPORAL-OCCIPITAL CORTEX

OM 85-67

3mm

Area 17

Inferior Temporal S.

caud.

dorsomed.

lateral surface

rost.

MT

Superior Temporal S.

ventral bank of Lat. Fiss.

ventrolat.

ventromedial surface

Insula

# SQUIRREL MONKEY

Central Dimple

Ant. Somat.

SMA
Motor and Premotor
MT
V-II
V-I
FEF
FV
Lat. Fiss.
dorsal bank
STS
floor
ventral bank

# OWL MONKEY

Central Dimple

SMA
Motor and Premotor
Ant. Somat.
5
PP
DM
FEF
DI
TP
V-II
V-I
FV
Lat. Fiss.
ST
DL
PL
MT
A-I
R
V
AL
ITc
dorsal bank
ventral bank
STS
ITp
ITr

# MACAQUE MONKEY

IPS
Ant. Somat.
5b
LIP
VIP
SMA
Motor and Premotor
CS
5a
7a
LS
AS
7b
FEF
MT
V-I
PS
MST
(ST)
V4 (DL)
FV
STP
IOS
V-II
VP (V)
TEO
PMTS
Lat. Fiss.
STS
TE

Fig. 19. Summary of ipsilateral cortical connections of the physiologically defined frontal eye fields in New and Old World monkeys, with some sulci graphically unfolded. Excluded are connections with medially situated cortex.
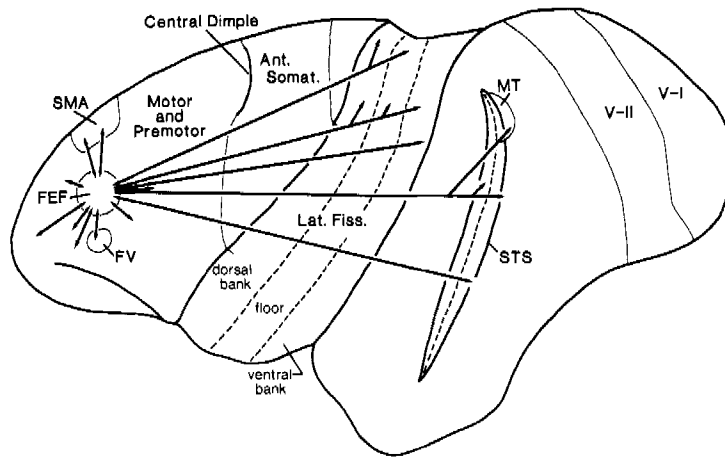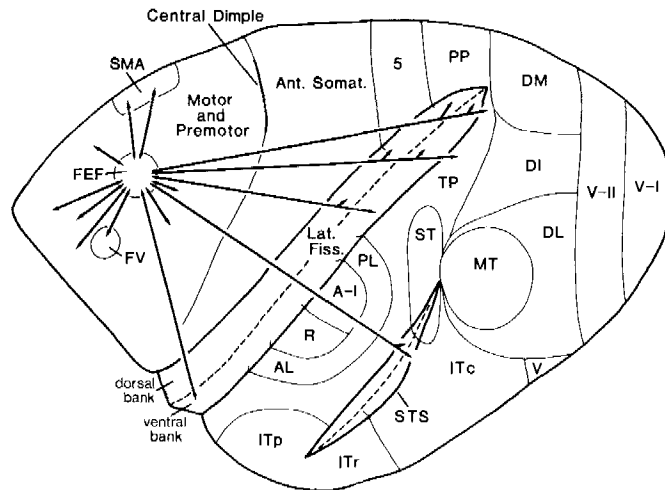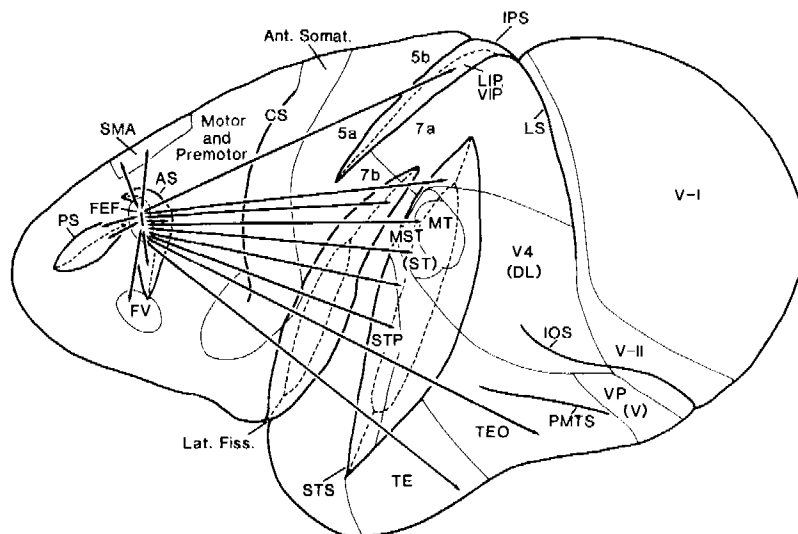
Fig. 18. Ipsilateral temporal lobe connections of the physiologically defined frontal eye field in owl monkey 85-67. Flattened cortex preparation. Visual area 17, as indicated by Nissl stain, and probable location of area MT are indicated. Conventions as in Figure 14.

are made with much of the cortex within the superior temporal sulcus, and only very sparse connections are present with cortex of the lateral fissure. In each of the New World species studied, the converse is true: cortex of the lateral fissue is heavily connected with the physiologically defined frontal eye field, whereas the cortex of the superior temporal sulcus has very few frontal eye field connections.

The main connectional differences between the squirrel monkeys and the owl monkeys is that in the former, connections are made with cortex rostral to the superior temporal sulcus and, apparently, with the middle temporal area; such connections were not found in owl monkeys. Also, the frontal eye field of owl monkeys is connected with cortex of the ventral bank of the rostrolateral part of the lateral fissure, whereas such connections were not observed in squirrel monkeys.

In summary, the connections of the frontal lobe are similar in all three species, suggesting homology and conservation or convergent evolution. Connections with other cortical regions are consistent with the phylogeny of these monkeys. Thus, connectional patterns in the more closely related squirrel and owl monkeys are more similar to each other than either is to the connectional pattern of the more distantly related macaque monkey (Fig. 19).

## Functional considerations

In primates, including humans, interaction with the environment usually begins with a gaze shift to the environmental feature of interest. Such gaze shifts are often the product of saccadic eye and head movements. Evidence from several lines of inquiry indicates that saccadic eye movements to behaviorally significant parts of visual space are governed by the frontal eye field (Bruce and Goldberg, '85; Fox et al., '85; Guitton et al., '85). Specifically, the frontal eye field participates in the initiation of saccades that are made to a behaviorally important target indicated by a visual or an auditory cue, or by the memory of a previous target (Bruce and Goldberg, '85). Moreover, the frontal eye field has been implicated in the coordination of eye and head movements necessary for accurate gaze changes (Bizzi and Schiller, '70; Van der Steen et al., '86). Finally, when attempting to acquire a behaviorally significant visual goal, eye, head, and arm movements appear to be initiated almost simultaneously (Bigauer et al., '82), and eye movement latency is affected by the laterality of the limb used to reach a visual target (Fisk and Goodale, '85). This set of observations strongly suggests that the neural apparatus responsible for generating purposive eye movements not only requires interaction with visual and oculomotor structures, but also requires interaction with structures participating in auditory, mnemonic, and skeletomotor functions. Since the frontal eye field is an important element in the generation of purposive eye movements (e.g., Bruce and Goldberg, '85), it might be expected to interact with these systems. The presently demonstrated cortical connections that might facilitate such interactions are discussed below (subcortical connections are discussed in Huerta et al., '86).

The prefrontal cortex, including the frontal eye field, of New and Old World monkeys receives multimodal sensory input (Bignall and Imbert, '69; Mohler et al., '73; Schecter and Murphy, '75; Goldberg and Bushnell, '81; Mikami et al., '82; Suzuki and Azuma, '83; Bruce and Goldberg, '85). Whereas it has been suggested that deep tecto-thalamo-cortical channels bring such information to the frontal eye

field (Harting et al., '80), there are also several corticocortical routes through which various types of sensory information can reach this structure. In owl monkeys, several cortical regions in the temporal and parietal lobes may send visual information to the frontal eye field; these include the posterior parietal (PP), temporal posterior (TP), and superior temporal (ST) visual areas (e.g., Fig. 19; Kaas, '78; Weller et al., '84). In squirrel monkeys, similar regions are connected with the physiologically defined frontal eye field, but the visual cortex of squirrel monkeys has not been studied as extensively as that of owl monkeys and, therefore, such comparisons should be made with caution (but see Cusick and Kaas, '87).

In macaque monkeys there appear to be numerous vision-related cortical areas that interconnect with the physiologically defined frontal eye field. Specifically, cortex throughout the caudal one-half to two-thirds of the superior temporal sulcus is densely connected with the frontal eye field (Figs. 6, 7, 19); physiological studies have revealed this region to contain multiple visual areas (e.g., Zeki, '69; Van Essen et al., '81; Van Essen, '85; Desimone and Ungerleider, '86; Bruce et al., '86; Mikami et al., '86a,b; Newsome et al., '86; Saito et al., '86; Tanaka et al., '86). On the basis of location within the superior temporal sulcus, it appears that the middle temporal (MT), medial superior temporal (MST, which may correspond to the superior temporal area of owl monkeys), fundal superior temporal (FST), and the superior temporal polysensory (STP) areas may all send visual information to the frontal eye field. Many neurons in these areas are sensitive to moving stimuli, and many are directionally selective (Van Essen et al., '81; Bruce et al., '82; Van Essen, '85; Desimone and Ungerleider, '86; Mikami et al., '86a,b; Newsome et al., '86; Saito et al., '86; Tanaka et al., '86). In addition, several of these areas (MT, MST, STP) are thought to play a role in "spatial" vision (Bruce et al., '82; Ungerleider and Mishkin, '82; Weller et al., '84), and appear to project to the superior colliculus (Fries, 84). Finally, the proposed projection from the superior temporal polysensory area to the frontal eye field might also contribute to the auditory responses that have been found in some neurons of the frontal eye field (Bruce et al., '82; Bruce and Goldberg, '85).

Another cortical region that contains neurons responsive to auditory or visual stimuli and that is reciprocally connected with the physiologically defined frontal eye field is the zone just rostral and rostrolateral to the frontal eye field (squirrel monkey: Bignall and Imbert, '69; Schecter and Murphy, '75; macaque monkey: Bignall and Imbert, '69; Mikami et al., '82; Suzuki and Azuma, '83; Azuma and Suzuki, '84). In macaque monkeys, this cortex constitutes the periprincipal region (i.e., around the principal sulcus) and has been studied rather extensively. Despite the fact that this region is sensorially multimodal, it probably does not play a major role in simple sensory processing. Rather, on the basis of physiological, behavioral, and clinical data (Fuster, '73, '80, '85; Bauer and Fuster, '76; Niki and Watanabe, '76; Matsunami and Kubota, '83; Kubota, '84; Milner et al., '85), this cortical region is thought to participate in complex functions and so may impart related information to the frontal eye field. Specifically, it has been proposed (e.g., Fuster, '85) that this prefrontal region allows the recognition of contingencies that occur at disjunctive times; supporting this proposal are data that have been interpreted to indicate that prefrontal cortex participates in the control of interference, preparatory set, and short-term memory (Kubota, '84; Guitton et al., '85; Fuster, '85).

With regard to preparatory set and short-term memory, some cells of the frontal eye field that discharge in association with saccades have anticipatory activity, i.e., activity that precedes the presentation of a saccade target or cue and that builds over numerous, repetitive, rewarded trials. Anticipatory activity of frontal eye field neurons has been likened to that found in periprincipal prefrontal cortex (Bruce and Goldberg, '85) and may be, at least in part, a consequence of interconnections between the fields. In addition, these interconnections might be the route over which some cells of the frontal eye field access the short-term memory, which presumably is necessary for their activity changes prior to saccades made to "learned" targets (Bruce and Goldberg, '85). With regard to the function of interference control of the prefrontal periprincipal cortex and its conveyance to the frontal eye field, it has been observed that in a monkey that is attentively fixating on a moving (Marrocco, '78) or a stationary (Schiller and Sandell, '83; Goldberg et al., '86) visual target, it is more difficult to elicit saccades with intracortical electrical microstimulation than when the animal is not actively fixating. Moreover, clinical data suggest that the cortex that includes the frontal eye field helps to suppress saccades to visual targets that interfere with a particular oculomotor task (Guitton et al., '85). Thus, it appears that the salient functional features of periprincipal prefrontal cortex that are reflected in frontal eye field function are at least partly due to direct interconnections.

The cortex of the intraparietal sulcus in the macaque monkey also participates in complex functions and is densely connected with the physiologically defined frontal eye field (Figs. 6, 7, 16). Such connections are made specifically with cortex of the inferior, or lateral, bank of the intraparietal sulcus. This region corresponds to the location of the ventral intraparietal (VIP) and lateral intraparietal (LIP) areas (Maunsell and Van Essen, '83; Van Essen, '85; Anderson et al., '85). The ventral intraparietal area is situated near the fundus of the intraparietal sulcus and is characterized by the dense input it receives from the middle temporal area (Maunsell and Van Essen, '83). Thus, the ventral intraparietal area, like the middle temporal area, is implicated in "spatial" vision. The lateral intraparietal area is located more dorsal in the sulcus and forms part of the zone (perhaps including VIP) that is thought to participate in spatial integration, selective attention, and visuomotor functions (Mountcastle et al., '75, '81, '84; Yin and Mountcastle, '77; Lynch et al., '77; Robinson et al., '78; Petrides and Iversen, '79; Lynch, '80; Motter and Mountcastle, '81; Bushnell et al., '81; Hyvärinen, '81, '82; Keating et al., '83; Shibutani et al., '84; Faugier-Grimaud et al., '85). This region is also polysensory (e.g., Hyvärinen, '81) and has strong connectional associations with the deep layers of the superior colliculus (Harting et al., '80; Weber and Yin, '84; Lynch et al., '85). Specifically, like the frontal eye field (Huerta et al., '86), the cortex of the inferior (or lateral) bank of the intraparietal sulcus has connections with numerous subcortical structures (Weber and Yin, '84) that also receive input from the deeper collicular layers (Harting et al., '80). Also, like the physiologically defined frontal eye field (Huerta et al., '86), cortex of the lateral bank of the intraparietal sulcus densely innervates the deeper (i.e., intermediate and deep) layers of the superior colliculus (Lynch et al., '85). Unlike the frontal eye field, however, eye movements elicited by electrical stimulation of intraparietal cortex depend upon the integrity of the superior colliculus

(Keating et al., '83). Thus, whereas the frontal eye field works in parallel with the superior colliculus (Schiller et al., '80; Albano et al., '82), visuomotor information from the intraparietal cortex appears to be serially processed through the superior colliculus (Keating et al., '83).

As mentioned at the outset of this section, there are intimate behavioral relationships between eye, head, and hand movements toward significant environmental features (Bigauer et al., '82; Fisk and Goodale, '85; Van der Steen et al., '86; Fischer, '86). Results from the present study suggest that links between oculomotor and skeletomotor functions are facilitated by connections that the frontal eye field has with skeletomotor cortical regions, as well as with subcortical structures that participate in skeletomotor functions (Huerta et al., '86). Specifically, in all three species, the physiologically defined frontal eye fields are reciprocally connected with regions of cortex just caudal to, and with regions just dorsomedial to, the eye field; as discussed below, these zones correspond to premotor cortex and the supplementary motor area, respectively (e.g., Fig. 19).

In macaque monkeys, the caudal region with which the frontal eye field is connected is called postarcuate cortex; this region is considered part of premotor cortex (see Wise, '84 for review). Premotor cortex is located rostral to precentral, or primary, motor cortex and is distinguished from the latter on the basis of cytoarchitecture, although this border is not clear (Weinrich and Wise, '82; Sessle and Wiesendanger, '82). Premotor cortex is also distinguished from primary motor cortex by the fact that threshold levels of current necessary to evoke movements are higher in premotor cortex than in primary motor cortex (Weinrich and Wise, '82). Postarcuate premotor cortex is connected with primary motor cortex (Matsumura and Kubota, '79; Muakkassa and Strick, '79) as well as with the cortex of the lateral, or inferior, bank of the intraparietal sulcus (Godschalk et al., '84), which also shares connections with the frontal eye field (see above). Moreover, postarcuate premotor cortex, but not many other parts of premotor cortex, projects to the deeper collicular layers (Fries, '84), which are connectionally related to the frontal eye field and intraparietal cortex (see above).

Premotor cortex (which appears to be connectionally heterogeneous; Muakkassa and Strick, '79) contains neurons whose activity is apparently related to establishing or changing motor programs as well as to the movement itself (Weinrich and Wise, '82; Weinrich et al., '84). Some cells of premotor cortex, like cells of the frontal eye field, are responsive to visual stimuli (Weinrich and Wise, '82; Gentilucci et al., '83) and exhibit anticipatory activity (Mauritz and Wise, '86). A variety of evidence indicates that the particular part of premotor cortex that is connected with the frontal eye field, i.e., the postarcuate cortex, participates in movements of the forelimb (Matsumura and Kubota, '79; Sessle and Wiesendanger, '82; Rizzolatti et al., '83; Kurata et al., '85). The connections between the frontal eye field and postarcuate cortex may, therefore, allow direct interactions between hand and eye movements; specifically, information about behaviorally significant visual space (frontal eye field) may interact with information about a visually guided hand movement (premotor cortex). Such interactions might relate to the observations that neural commands for coordinated movements of the eyes, head, and arm toward a visual target are given almost simultaneously (Bigauer et al., '82) and that latencies of saccades

to visual targets can be correlated with the laterality of the forelimb used in a reaching task (Fisk and Goodale, '85).

In squirrel monkeys and owl monkeys, the physiologically defined frontal eye field is connected with cortex caudal to the eye field but rostral to the "low threshold motor" region as determined in the same animal by intracortical microstimulation (see Results). This caudal region in squirrel monkeys and owl monkeys resembles the postarcuate premotor cortex of macaque monkeys in several ways. It is located just caudal to the frontal eye field and just rostral to the forelimb representation of the "low threshold" (primary) motor region, and it is reciprocally connected with the frontal eye field. Moreover, in both New and Old World monkeys, movements of body parts other than the eyes can be elicited from this "premotor" region, and in both New and Old World monkeys, relatively high levels of current are usually necessary to elicit such movement (e.g., Fig. 13). (In owl monkeys, however, this region is not *always* apparent as a "higher threshold" strip of cortex separate from primary motor cortex; see Gould et al., '86.) One difference between New and Old World monkeys is that the "premotor" region that is interconnected with the frontal eye field appears to participate largely in movements of the ears, eyelids, and other parts of the face in the New World monkeys (present results, also see Gould et al., '86), whereas in macaque monkeys premotor cortex connected with the frontal eye field (i.e., postarcuate premotor cortex) participates in forelimb movements (see above). Perhaps this difference relates to behavioral differences between New and Old World monkeys. Nevertheless, the main point is that the interconnections demonstrated between the frontal eye field and premotor cortex in New and Old World monkeys represent links between oculomotor and skeletomotor cortex and, presumably, between oculomotor and skeletomotor functions.

The physiologically defined frontal eye fields of squirrel monkeys, owl monkeys, and macaque monkeys are bilaterally connected with cortex dorsomedial to the frontal eye field, along the midline of the hemispheres. In the macaque monkey, this dorsomedial region corresponds to the location of the supplementary motor area (Woolsey et al., '52; Brinkman and Porter, '79; Macpherson et al., '82; Wise, '84). Electrical stimulation of the rostral supplementary motor area in macaque monkeys results in eye movements (Woolsey et al., '52; Schlag and Schlag-Rey, '85; present results; also in humans, Tailairach and Bancaud, '66), and neurons in this region discharge in association with eye movements (Brinkman and Porter, '79; Schlag and Schlag-Rey, '85; also see Fox et al., '85), including just prior to spontaneous saccades made in the dark (unlike neurons of the frontal eye field, which only fire before saccades made to behaviorally significant parts of visual space; Schlag and Schlag-Rey, '85; Bruce and Goldberg, '85). That this dorsomedial region is probably the supplementary motor area is further supported by the facts that the supplementary motor area is considered to function bilaterally (Woolsey et al., '52; Travis, '55; Brinkman and Porter, '79; Roland, '80) and that this is the only region that has substantial bilateral connections with the frontal eye field, besides the eye field itself (in all three species, see Results).

In one macaque monkey, eye movements were evoked from the dorsomedial zone in the supplementary motor area; this zone then received an injection of tritiated proline (results not described here). Although the introduction of the micropipette severely damaged this tissue, connections

were demonstrated between this physiologically defined dorsomedial eye movement representation and the physiologically defined frontal eye field (which received an injection of HRP-WGA; Fig. 5C). In addition, connections between the frontal eye field and dorsomedial cortex were present as far caudal as 2.5 mm from the eye movement representation (Fig. 5E). In another case, in which the dorsomedial cortex was disturbed by neither electrode nor pipette penetrations (Fig. 4), the physiologically defined frontal eye field made connections with about 3.0 mm of the rostral-caudal extent of the dorsomedial cortex. This is a similar expanse as that demonstrated in the case described above (Fig. 5). Given the fact that the most rostral part of the dorsomedial cortex, which is connected with the frontal eye field, is a representation of eye movements (present results), and assuming that this comprises the most rostral part of the supplementary motor area (Brinkman and Porter, '79; Fox et al., '85; Schlag and Schlag-Rey, '85), it appears that the physiologically defined frontal eye field is also connected with more caudal parts of the supplementary motor area, which participate in head and hand movements (Brinkman and Porter, '79; Fox et al., '85).

Like premotor cortex, the supplementary motor area appears to function in motor set, or making neural preparations for a particular movement (Tanji et al., '80; Deeke and Kornhuber, '78; Fox et al., '85; Tanji and Kurata, '82, '85; Wise, '84; Brinkman and Porter, '79; Wiesendanger, '86). More specifically, the supplementary motor cortex is thought to make preparations for movements that are internally generated and that, to some extent, are made despite, rather than because of, sensory stimuli (Wise, '84; Tanji and Kurata, '85; Guitton et al., '85; Tanji et al., '85; Wiesendanger, '86, but see Kurata and Wise, '86). Thus, connections between the frontal eye field and the supplementary motor area may serve to initiate and coordinate eye, head, and hand movements to targets that are significant to the individual, but that are less obvious than other "interfering" stimuli in the environment. This type of interaction is supported by the findings of Guitton et al. ('85) who reported that patients with lesions of the frontal eye field and the supplementary motor area find it very difficult to suppress wanted saccades to visual stimuli or to initiate saccades to a known, but not yet visible, target.

Whereas the functional characteristics of the supplementary motor area in New World monkeys are not known in as much detail as in macaque monkeys, its existence has been demonstrated in owl monkeys (Gould et al., '86) and squirrel monkeys (Welker et al., '57; Jürgens, '84). As in macaque monkeys, the supplementary motor area in these New World monkeys occupies the cortex directly dorsomedial to the location of the frontal eye field (Gould et al., '86; Welker et al., '57; Jürgens, '84; present results), and is topographically organized on the basis of electrical stimulation studies (Welker et al., '57; Gould et al., '86). Thus, the representation of eye movements is situated rostrally, whereas movements of the face, forelimb, and hindlimb are represented progressively more caudal in the area (Welker et al., '57; Gould et al., '86). In the present study, intracortical microstimulation was used to evoke eye movements from the dorsomedial cortex in three owl monkeys. As described in the results, this physiologically determined eye movement representation is reciprocally connected with the physiologically defined frontal eye field. Moreover, cortex immediately caudal to the dorsomedial eye movement representation was also connected with the frontal eye field,

as was a correspondingly located region of cortex in the contralateral hemisphere. Whereas intracortical micro-stimulation was not used to explore dorsomedial cortex in the squirrel monkeys, this cortex is bilaterally and recipro-cally connected with the physiologically defined frontal eye field in these monkeys (see Results). Thus, it appears that in squirrel monkeys and in owl monkeys, the physiologi-cally defined frontal eye field has connections not only with the eye movement representation of the supplementary motor area, but also with parts of that area that participate in movements of the forelimb, including the hand.

In conclusion, the present study demonstrates that the physiologically defined frontal eye fields in New and Old World monkeys have numerous pathways that allow inter-action with cortex involved with: higher order visual pro-cessing, visuomotor functions, selective attention, short-term memory, control of interference, and the planning and execution of movements of the eyes, head, and hand. It is interesting that frontal eye field connections with the fron-tal lobe, i.e., with the supplementary motor area, premotor cortex, and periprincipal prefrontal cortex, appear to vary the least between species. This suggests that among the most conserved functions of the frontal eye field may be a role as a link between oculomotor and skeletomotor sys-tems, perhaps facilitating the planning and coordination of eye, head, and hand movements.

## ACKNOWLEDGMENTS

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