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Frontal Eye Field as Defined by Intracortical Microstimulation in Squirrel Monkeys, Owl Monkeys, and Macaque Monkeys: I. Subcortical Connections

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ABSTRACT

Intracortical microstimulation was used to define the borders of the frontal eye fields in squirrel, owl, and macaque monkeys. The borders were marked with electrolytic lesions, and horseradish peroxidase conjugated to wheat germ agglutinin was injected within the field. Following tetramethyl benzidine histochemistry, afferent and efferent connections of the frontal eye field with subcortical structures were studied. Most connections were ipsilateral and were similar in all primates studied. These include reciprocal connections with the following nuclei: medial dorsal (lateral parts), ventral anterior (especially with pars magnocellularis), central lateral, paracentral, ventral lateral, parafascicular, medial pulvinar, limitans, and suprageniculate. The frontal eye field also projects to the ipsilateral pretectal nuclei, subthalamic nucleus, nucleus of the posterior commissure, superior colliculus (especially layer four), zona incerta, rostral interstitial nucleus of the medial longitudinal fasciculus, nucleus Darkschewitsch, dorsomedial parvocellular red nucleus, interstitial nucleus of Cajal, basilar pontine nuclei, and bilaterally to the paramedian pontine reticular formation and the nucleus reticularis tegmenti pontis. Many of these structures also receive input from deeper layers of the superior colliculus and are known to participate in visuomotor function. These results (1) reveal connections that account for the parallel influence of the superior colliculus and the frontal eye field on visuomotor function; (2) suggest that there has been little evolutionary change in subcortical connections, and therefore function, of the frontal eye fields since the time that these lines of primates diverged; and (3) support the conclusion that the frontal eye fields are homologous in New and Old World monkeys.

Key words: visuomotor, superior colliculus, ventral anterior nucleus, medial dorsal nucleus, primates

Eye movements play an important role in directing our attention and movements in space. This is also true for other primates. While several cortical regions in macaque monkeys are known to participate in visuomotor function (eg., Hyvärinen and Poranen, '74; Mountcastle et al., '75; Lynch et al., '77; Schiller, '77; Sundqvist, '79; Lynch, '80; Bushnell et al., '81; Hyvärinen, '81; Keating et al., '83; Sakata et al., '83; Robinson and Petersen, '84; Shibutani et al., '84; Fox et al., '85; Guitton et al., '85; Schlag and Schlag-Rey, '85; Gould et al., '86), one of the most studied is the frontal eye field, which has been implicated in the initiation of the rapid, saccadic eye movements (Ferrier, 1875; Beevor and Horsley, 1888; Mott and Schafer, 1890; Smith, '44; Wagman et al., '61; Bizzi, '68; Robinson and Fuchs, '69; Bizzi and Schiller, '70; Kubota and Niki, '71; Mohler et al., '73; Wurtz and Mohler, '76; Schiller, '77; Marrocco, '78; Pigarev et al., '79; Schiller et al., '79, '80; Kojima, '80; Goldberg and Bushnell, '81a, '81b; Mikami et al., '82a, '82b; Keating et al., '83; Bruce and Goldberg, '84, '85; Bruce et

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al., '85; Fox et al., '85; Guitton et al., '85; Komatsu and Suzuki, '85). Despite the wealth of our knowledge of this cortical region in macaque monkeys, it has been studied very little in New World monkeys (Blum et al., '82; Gould et al., '86), and in no primate have the connections of the physiologically defined frontal eye field been comprehensively reported (but see Stanton et al., '82; Huerta et al., '85).

In the present study, intracortical microstimulation was used to define the frontal eye fields in squirrel monkeys, owl monkeys, and macaque monkeys. Following physiological definition of the borders of the field, anatomical tracers were injected within the field and the afferent and efferent connections were determined. The present findings reveal a large number of subcortical structures which are connected with the frontal eye field. Many of these structures also receive input from the deeper layers of the superior colliculus (Benevento and Fallon, '75; Harting, '77; Partlow et al., '77; Harting et al., '80), which functions in parallel with the frontal eye field in the generation and elaboration of saccadic eye movements (e.g., Schiller, '77, '84; Schiller et al., '79, '80; Albano and Wurtz, '82; Keating et al., '83). Several structures that are connected with the frontal eye field are also known to participate in skeletomotor function, which suggests that these structures are responsible for some of the interaction between oculomotor and skeletomotor behavior. Finally, our findings reveal that the majority of subcortical connections of the frontal eye field are similar in the New and Old World monkeys studied. This suggests that these systems function similarly in these primates, and further suggests that the frontal eye field, as presently defined, is homologous in New and Old World monkeys.

METHODS

The locations and subcortical connections of the frontal eye fields were investigated in three squirrel monkeys (*Saimiri sciureus*), three owl monkeys (*Aotus trivirgatus*), and three macaque monkeys (*Macaca fascicularis*). In each monkey, the frontal eye field and surrounding regions were unilaterally probed with microstimulation and an injection of horseradish peroxidase conjugated to wheat germ agglutinin (HRP-WGA) was placed in the physiologically defined frontal eye field.

All animals were anesthetized with an intramuscularly administered initial dose of 35 mg/kg body weight of ketamine hydrochloride, and received supplemental doses as needed to maintain surgical levels of anesthesia (White et al., '82). Local anesthetic (2% lidocaine) was injected subcutaneously along the midline of the dorsal surface of the head and in the region of the external auditory meatus on each side. The head was shaved and placed in a stereotaxic head holder. Throughout the experiment, a heating pad was used to help maintain the animal's rectal temperature near 37°C.

A large craniotomy was made and the underlying dura was cut to expose the brain from a point several millimeters caudal to the central sulcus (or dimple, in New World monkeys) to a point several millimeters rostral to the arcuate sulcus (or inferior arcuate dimple, in New World monkeys), and from the midline to a point several millimeters lateral to the lateral limit of the arcuate sulcus (or inferior arcuate dimple, in New World monkeys). A well of acrylic plastic was built around the rim of the craniotomy and was filled with silicone fluid in order to prevent desiccation and reduce pulsation. The well was attached to a bar mounted on the operating table, and the animal's head was removed from the holder and was suspended by the well.

Exposed regions of periarcuate cortex were explored with intracortical microstimulation via tungsten microelectrodes (1.5 MΩ at 1,000Hz). Stimulation was produced by a two-channel anapulse stimulator (WPI, model 302-T) and two photon-coupled stimulus isolator units (WPI, model 305) operated in shunt (parallel), so that constant current amplitudes could be administered. Current levels were monitored by measuring the voltage drop (via an oscilloscope) across a resistor in series with the stimulator circuit. The stimuli consisted of 40-msec trains of 0.5-msec biphasic pulses delivered at 300 Hz with constant current amplitudes, which were varied. These parameters are similar to those used by other investigators studying the frontal eye field cortex in monkeys (e.g., Schiller et al., '79).

During the experiment, microelectrode penetration sites were viewed with a dissection microscope and were marked on an enlarged photograph of the brain surface. Penetration points were usually spaced 300–1,000 μm apart in the field studied. The microelectrode was hydraulically advanced through the depths of the cortex. In most penetrations the microelectrode was oriented perpendicular to the cortical surface and, hence, to cortical laminae. In such penetrations the electrode tip was typically advanced to a depth of about 2,000 μm (which our experience revealed to be the depth at which lowest current levels produced movements) before stimulation commenced. In several penetrations in the macaque monkey, the cortex in the depths of the arcuate sulcus was explored. In these penetrations, the electrode was often oriented parallel to the cortical laminae and stimulation was produced at a number of different "depths," which were carefully noted.

Stimulation was initiated in the region rostral to the arcuate sulcus (or inferior arcuate dimple) and exploratory currents of about 100 μA were used to search for evoked movement. Movements were monitored by visual observation and, in many cases, palpation of muscles, by two observers. Once a movement was produced by stimulation, current amplitudes were decreased and threshold level of current (i.e., the lowest current amplitude at which a movement could be produced) was determined. In some cases, the remainder of the region was explored with levels of current just above threshold with more careful examination of threshold levels close to what we considered to be borders of the defined zone. In most cases, however, threshold current levels were determined for the vast majority of stimulus points.

Between penetrations, changes in types of movements (i.e., eye movements versus movements of body parts) at similar current levels or a marked (threefold) increase in threshold levels for eye movement production were used to define physiological borders. After such borders were defined, penetrations were made at these borders and a series of electrolytic lesions were produced by passing a 10-μA DC current for 7–10 seconds at 700-μm intervals along the depth of the penetration. Those lesions were later used to relate injection sites to physiologically defined borders.

We defined the frontal eye fields as the region of periarcuate cortex from which eye movements could be elicited with the lowest current amplitudes. In general, this region was situated rostral to the arcuate sulcus (or inferior arcuate dimple), but the location of the field varied widely.

Within the physiologically defined regions, HRP-WGA (0.1%, 0.06–0.18 μl) was injected over the course of 30–60 minutes via narrow glass pipettes, with tip diameters of 15–50 μm. The injection solution also contained the dye fast green so that it could be easily visualized. In some animals, injections of ^{3}H-proline (33 μCi/μl, 0.1–0.3 μl) were placed within other physiologically defined fields (including the portion of the supplementary motor area from which eye movements could be elicited with electrical stimulation; see Gould et al., '86). These autoradiographic results will be presented elsewhere.

Following injections of tracers, a plate of acrylic plastic was made to cover the craniotomy, the overlying muscle and skin were sutured, and the animal was allowed to recover. Approximately 48 hours after the tracers were injected, the animals were deeply anesthetized with sodium pentobarbitol and were transcardially perfused with normal saline followed by a 0.1 M phosphate buffer solution composed of 1.0% paraformaldehyde and 1.25% glutaraldehyde. Finally, the animal was perfused with a 0.1 M phosphate buffer solution composed of 1.0% paraformaldehyde, 1.25% glutaraldehyde, and 10.0% sucrose. The brain was then removed from the skull, and in most cases, the cerebral hemispheres were separated from the rest of the brain. The cerebral cortex was usually unfolded, flattened, and cut parallel to the flattened surface (also see Huerta et al., '87). In some cases, the cortex was sectioned coronally or parasagittally. Nevertheless, since the cerebral cortex was removed from the rest of the brain in most cases, the claustrum and corpus striatum were usually badly damaged. Thus, observations regarding these structures are not included in this report. The brainstem and thalamus were cut transversely at 50 μm on a freezing microtome. The HRP was revealed by reacting a one in five series of sections with tetramethyl benzidine according to the method of Mesulam ('78). Two of the five sections in each series were processed for autoradiography, one in five for Nissl stain, and a one-in-five series of sections was stained for cytochrome oxidase.

Cortical sections were graphically reconstructed and the extents of injection sites were related to lesions that marked physiological borders. Blood vessels and other landmarks were used to align sections.

Anterogradely and retrogradely transported label was plotted with darkfield illumination with a camera lucida. Nuclear borders were determined with lightfield illumination on adjacent sections, which were stained for Nissl substance. By aligning landmarks, such as blood vessels, the drawings of nuclear borders were superimposed on drawings of transported label.

Cytoarchitectonic borders of subcortical nuclei were drawn primarily according to the definitions of Olszewski ('52) for macaque monkeys and the similar definitions of Emmers and Akert ('63) for New World monkeys. In the case of the ventral lateral nuclei, however, we adopted the terminology of Jones ('85) because the present material closely matched his description of the cytoarchitecture of this region. Specifically, Jones considers Olszewski's nucleus ventralis lateralis pars caudalis (VL_c), nucleus ventralis lateralis pars postrema (VL_{ps}), nucleus ventralis posterior lateralis pars oralis (VPL_o) and area X (X) to constitute the posterior part of the ventral lateral nucleus (VL_p). Jones ('85) calls Olszewski's ('52) nucleus ventralis lateralis pars oralis (VL_o) the anterior part of the ventral lateral nucleus (VL_a). In the present communication, we do not distinguish between VL_a and VL_p, because they are not cytoarchitectonically distinct in our material, but we do recognize area X in the macaque monkey since it was cytoarchitectonically distinct from surrounding nuclei.

The pretectal nuclei were defined according to Hutchins and Weber ('85), and brainstem nuclei were defined in accordance with Emmers and Akert ('63).

Some of the present results have been presented in preliminary form (Huerta et al., '85).

RESULTS

Macaque monkey

Definition of the frontal eye field. In three macaque monkeys (*Macaca fascicularis*) the prearcuate cortex was explored with intracortical microstimulation. Our definition of the frontal eye field in the ketamine-anesthetized macaque monkey was similar to that used by Bruce et al. ('85) to define the field in awake macaque monkeys. Specifically, a microelectrode penetration was considered to be within the frontal eye field if rapid contralaterally directed conjugate eye movements could be elicited by stimuli with current levels of 50 μA or less at the majority of stimulated sites within that penetration. Since most of the frontal eye field is located on the anterior bank of the arcuate sulcus and since the mircoelectrode was oriented parallel to the layers of this cortex, most of the field was explored by advancing the electrode in steps of from 300 μm to 1,000 μm and stimulating at each intervening point. The frontal eye field defined this way extended about 7 mm along the length of the arcuate sulcus, as far as 8 mm into the depth of the arcuate sulcus and onto the prearcuate cortical surface as far as 3 mm from the sulcus. Typically, however, the field extended less than 1.5 mm onto the exposed prearcuate surface.

In the experiment depicted in Figure 1 (85-68), 120 points were stimulated in 26 penetrations, and threshold current levels for eliciting eye movements were determined at each point. Within the frontal eye field, eye movements could be evoked with current levels of 50 μA or less at 81% (64 of 79) of the stimulated points. At 15 points scattered throughout the field slightly higher current levels were required to produce eye movements.

Similar results were obtained from the other two experiments in macaque monkeys. In case 85-86 (Fig. 2), the frontal eye field was identified by determining threshold current levels at 132 points, spaced 500 μm apart, in 20 penetrations. Seventy-six stimulation points were within the field, and, as in case 85-68 (Fig.1), eye movements could be evoked by stimuli with current levels of 50 μA or less at about 80% (61 of 76) of these points. Eye movements could be produced by stimulating the remaining (scattered) points with currents slightly higher than 50 μA. Similarly, in the third case the frontal eye field was defined by 41 points within it and another 19 points immediately around the field.

In all three experiments in macaque monkeys, stimulation points just outside of the region of low thresholds usually required currents of at least 100 μA to produce eye movements. More often, however, eye movements could not be evoked in these penetrations unless current levels were 150 μA; at some points in these penetrations, even current levels of 250 μA did not result in eye movements. At points just outside of the frontal eye field at these current levels, other body movements were not observed.

The frontal eye fields were similar in size across cases. Nevertheless, there was a difference in the location of the field with respect to sulcal patterns in each case. For example, the field occupied a relatively medial position in one case (Fig. 1), and was situated considerably further lateral in another case (Fig. 2).

In the experiments illustrated in Figures 1 and 2, and in the third unillustrated case, penetrations were made midway between a penetration just outside of the frontal eye field and the nearest penetration within the frontal eye field. A series of electrolytic lesions were made along the depth of each of these interposed penetrations, thus marking the borders of the physiologically defined frontal eye fields. Horseradish peroxidase conjugated to wheat germ agglutinin (HRP-WGA) was injected into the physiologically defined frontal eye field in each of the three cases. Since the borders of the field were marked with electrolytic lesions, the spread of the injection site could be compared to the limits of the field. In all cases the injection site was almost completely confined to the delimited field. In the typical case illustrated in Figure 1, for example, the dense part of the injection site extended just 250 μm beyond the rostrolateral border, but the rest of the large injection site was within the physiologically determined boundaries. Thus, we are confident that the vast majority of transported label is from the physiologically defined region.

Connections of the frontal eye field. Injection of HRP-WGA in the frontal eye field labeled fibers within the ipsilateral internal capsule that formed two loosely arranged bundles at the level of the rostral pole of the dorsal thalamus. The more dorsal bundle coursed lateral-medial in the rostral thalamus across the ipsilateral reticular, ventral lateral and ventral anterior thalamic nuclei (Fig. 3, level 497) to extend caudally to connect dorsal thalamic nuclei, pretectal nuclei, and superior colliculus with the frontal eye field.

Of the nuclei that had inputs and/or outputs contributing to this bundle of fibers, the heaviest concentration of anterogradely and retrogradely transported label was in the dorsolateral portion of the medial dorsal nucleus; specifically, in pars multiformis (Fig. 4). While label extended throughout most of the rostral-caudal extent of this nucleus, it was greatest in intermediate levels (Fig. 3). The

Abbreviations

AD	Anterior dorsal nucleus
APN	Anterior pretectal nucleus
Arc	Arcuate sulcus
AV	Anterior ventral nucleus
BC	Brachium conjunctivum
BP	Brachium pontis
Cdc	Central densocellular nucleus
CG	Central gray
Cl	Central lateral nucleus
CM	Centromedian nucleus
CP	Cerebral penduncle
CS	Central superior nucleus of the raphe
Csl	Central superior lateral nucleus
Cun	Cuneiform nucleus
DBC	Decussation of the brachium conjunctivum
DLG	Dorsal lateral geniculate nucleus
DTG	Dorsal tegmental nucleus of Gudden
Fx	Fornix
Hb	Habenular nuclei
IC	Inferior colliculus
Inf Arc	Inferior limb of the arcuate sulcus or inferior arcuate dimple
INC	Interstitial nucleus of Cajal
IPul	Inferior pulvinar
Lat	Lateral fissure
LC	Locus coeruleus
LD	Lateral dorsal nucleus
Li	Nucleus limitans
LLd	Dorsal nucleus of the lateral lemniscus
LLv	Ventral nucleus of the lateral lemniscus
LP	Lateral posterior nucleus
L Pul	Lateral pulvinar
M	Medial
MD	Medial dorsal nucleus
MDmc	Medial dorsal nucleus, pars magnocellularis
MDmf	Medial dorsal nucleus, pars multiformis
MDpc	Medial dorsal nucleus, pars parvocellularis
MG	Medial geniculate nucleus
MLF	Medial longitudinal fasciculus
M Pul	Medial pulvinar
ND	Nucleus Darkschewitsch
NPC	Nucleus of the posterior commissure
NPCm	Nucleus of the posterior commissure, pars magnocellularis
niii	Oculomotor nerve
Niii	Oculomotor nucleus
niv	Trochlear nerve
Niv	Trochlear nucleus
nvi	Abducens nerve
Nvi	Abducens nucleus
ON	Olivary pretectal nucleus
O Pul	Oral pulvinar
Pb	Parabigeminal nucleus
Pcn	Paracentral nucleus
Pf	Parafascicular nucleus
Pg	Pregeniculate nucleus
PG	Pontine gray
PPN	Posterior pretectal nucleus
Princ	Principal sulcus
Pv	Principal sensory trigeminal nucleus
R	Reticular nucleus of the thalamus or rostral
Re	Nucleus reuniens
riMLF	Rostral interstitial nucleus of the medial longitudinal fasciculus
RN	Red nucleus
RTP	Nucleus recticularis tegmenti pontis
SC	Superior colliculus
Sg	Suprageniculate nucleus
SN	Substantia nigra
SNc	Substantia nigra, pars compacta
SNd	Substantia nigra, pars diffusa
SO	Superior olivary complex
St	Subthalamic nucleus
Sup Arc	Superior limb of the arcuate sulcus
Sup temp	Superior temporal sulcus
THI	Habenulointerpeduncular tract
TMT	Mammillothalamic tract
V	Ventral
VA	Ventral anterior nucleus
VAmc	Ventral anterior nucleus, pars magnocellularis
VL	Ventral lateral nucleus
VP	Ventral posterior nucleus
VPI	Vental posterior inferior nucleus
VPL	Ventral posterior lateral nucleus
VPM	Ventral posterior medial nucleus
X	Area X
ZI	Zona incerta
II	Layer two of the superior colliculus
III	Layer three of the superior colliculus
IV	Layer four of the superior colliculus
V	Layer five of the superior colliculus
VI	Layer six of the superior colliculus

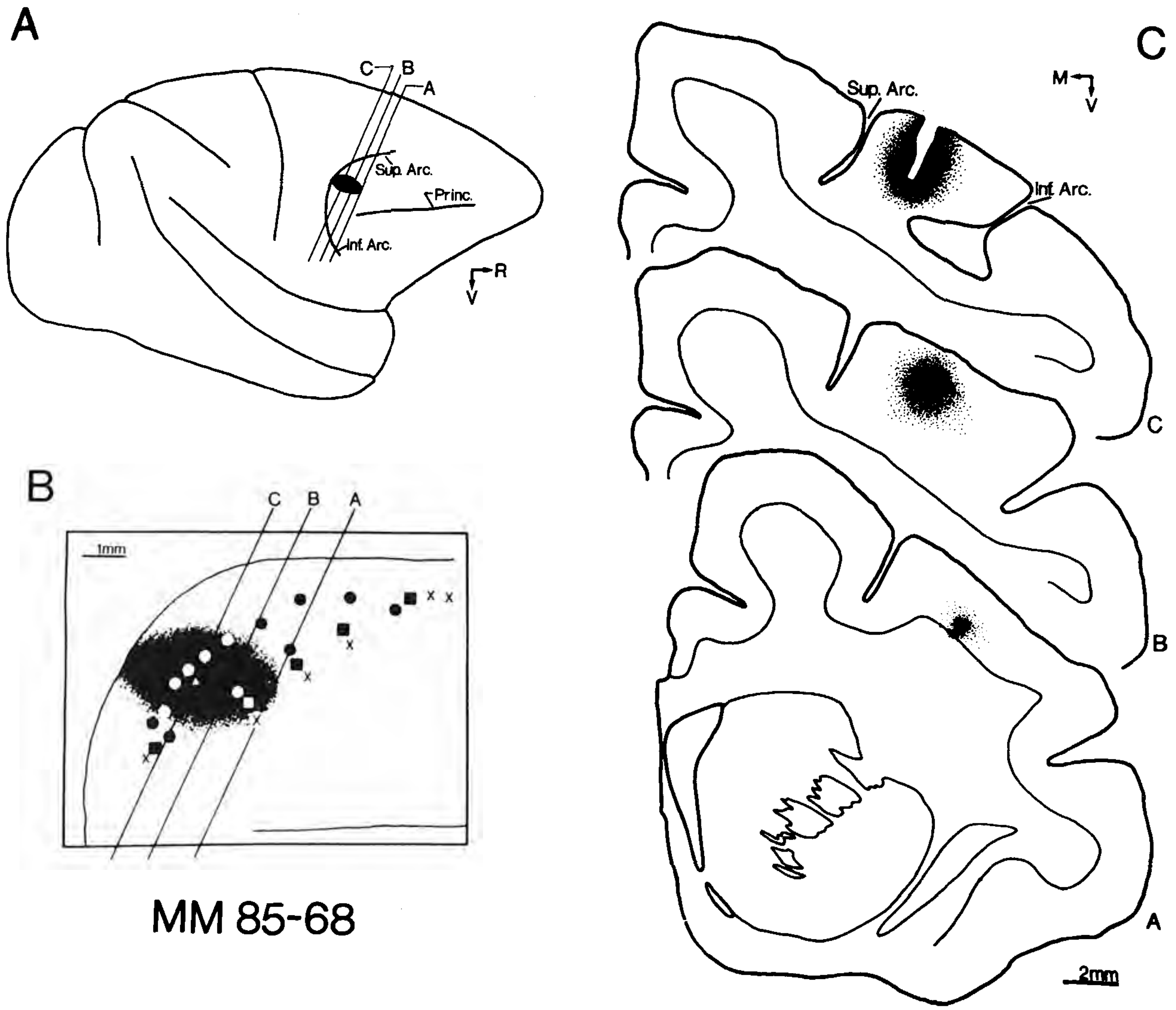

Fig. 1. Location of physiologically defined frontal eye field and extent of HRP-WGA injection site in a macaque monkey. A. Lateral view of right hemisphere with location of injection site indicated in black. Levels from which sections in panel C were taken are indicated. B. Lateral view of prearcuate cortex (drawn from brain photograph) with the location of electrode penetrations indicated as circles (sites within the frontal eye field), (sites of electrolytic lesions), and X's (sites outside of the frontal eye field). Injection site indicated by triangle with extent of reaction product shown as black stipple (reconstructed from coronal sections). Levels of sections illustrated in panel C are also indicated. C. Drawings of sections through the injection site (stipple). Transported label is not drawn.

medial part of the ventral anterior nucleus was also densely labeled, especially in pars magnocellularis. The paracentral nucleus was much less heavily labeled; in rostral levels sparse anterogradely and retrogradely transported HRP-WGA was evident throughout most of the nucleus, though caudal levels were virtually void of label. The rostral part of the central lateral nucleus had no obvious connections with the frontal eye field, but more caudal levels (at the level of the parafascicular-centromedian complex and the habenulointerpeduncular tract) contained a few retrogradely labeled cells. While the rostral part of the ventral lateral nucleus contained numerous labeled fibers, no terminal label or labeled cell bodies were apparent; however, a very few retrogradely labeled cell bodies are present in caudal portions of this nucleus. A major projection was demonstrated from the frontal eye field to the ventromedial portion of the parafascicular nucleus (Fig. 3). Despite the density of the anterogradely transported tracer, however, retrogradely labeled cells were rare in the parafascicular nucleus (only one to three were observed in any one case). Retrogradely labeled cells and anterogradely transported label occupied restricted portions of the medial pulvinar, but only a few retrogradely labeled neurons were present in the lateral pulvinar (just lateral to nucleus limitans). Nucleus limitans received dense input from the frontal eye field and also contained retrogradely labeled cells. The dorsomedial portion of the suprageniculate nucleus also had labeled terminations and cells (Fig. 3).

While each of the pretectal nuclei contained anterogradely transported tracers, only the posterior pretectal nucleus received a moderately dense projection from the frontal eye field (Fig. 3). No labeled cell bodies were ob-

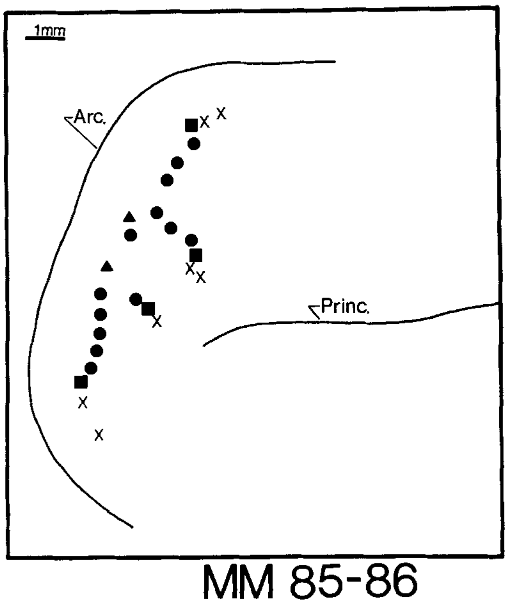

Fig. 2. Lateral view of the surface of prearcuate cortex showing the location of the physiologically defined frontal eye field in a macaque monkey. Locations of electrode penetrations indicated as circles (sites within the frontal eye field), boxes (sites of electrolytic lesions), and X's (sites outside of the frontal eye field). Injection sites of anatomical tracers are indicated by triangles. Drawn from brain photograph. Rostral is to the right, dorsal to the top of the figure.

served in any of the pretectal nuclei. Anterogradely transported label was also present in the nucleus of the posterior commissure.

The superior colliculus received a dense and expansive projection from the ipsilateral frontal eye field (Fig. 3). While label was present throughout layers three through seven, the anterogradely transported label was concentrated within layer four. Within layer four, the densest label formed a tier of loosely arranged patches near the dorsal border; more deeply in layer four, the label was also unevenly distributed. Numerous labeled fibers and possibly some labeled terminals were present in layers ventral to layer four and label just above background levels was present in layer three (Figs. 3, 5).

The second subcortical bundle of labeled fibers following an injection of HRP-WGA into the frontal eye field coursed ventrally from the internal capsule at rostral thalamic levels. At more caudal levels, fibers from this bundle were distributed to various nuclei of the subthalamus. The remaining fibers coursed within the medial part of the cerebral peduncle, and were distributed to pontine nuclei.

Subthalamic nuclei that received light to moderate input from the ipsilateral frontal eye field were the zona incerta, the rostral interstitial nucleus of the medial longitudinal fasciculus, and a small zone just medial to the rostral portion of the red nucleus (Fig. 3). Extremely sparse terminal label was found in nucleus Darkschewitsch and the interstitial nucleus of Cajal, while the subthalamic nucleus contained moderate to high levels of label (Fig. 3).

Dense input from the frontal eye field was distributed to much of the rostral-caudal extent of the ipsilateral pontine gray (Fig. 3). Medial, dorsolateral, and intermediate parts of the pontine gray contained considerable amounts of anterogradely transported tracer, usually in the form of isolated patches. In contrast to the label in the pontine gray, dense label in the nucleus reticularis tegmenti pontis was bilaterally distributed (Fig. 3, 6). Bilateral projections are strongest in medial portions of the nucleus, while label along the dorsal border is much denser ipsilaterally than it is contralaterally.

In addition to the major fiber bundles described above, labeled fibers were also apparent in the mesencephalic and pontine reticular fomation (e.g., levels 387, 332, Fig. 3). Which of the two major fiber bundles provided these scattered axons is unclear. Some of these fibers terminated in the paramedian pontine reticular formation bilaterally, but primarily contralaterally. These regions of the pontine and mesencepahlic reticular formation, as well as locus coeruleus, contained a few retrogradely labeled cells.

Squirrel monkey

Definition of the frontal eye field. In three squirrel monkeys (*Saimiri sciureus*) the periarcuate (i.e., around the inferior arcuate dimple) cortex was explored with intracortical microstimulation. Since the electrode was oriented perpendicular to the cortical laminae, the tip of the electrode was usually lowered to about 2,000 μm before stimulation commenced. As in the macaque monkey, bilateral, contralaterally directed rapid eye movements could be evoked by stimulation of a restricted region of periarcuate cortex, but unlike the macaque monkey, current levels of nearly 100 μA were usually required before eye movements could reliably be elicited. In these experiments expansive regions (40–50 mm^2) of periarcuate frontal cortex were explored with penetrations spaced 300 to 500 μm apart. The zone from which eye movements could be reliably driven with the lowest current levels was considered to be the frontal eye field. The borders of the frontal eye field were indicated by stimulation resulting in no apparent response or in body movements other than eye movements at current amplitudes that were adequate to evoke eye movements within the field. For example, if within the frontal eye field a 100-μA stimulus resulted in eye movements, whereas within a nearby penetration the same stimulus produced only a movement of the vibrissae, then the border of the frontal eye field was considered to lie between these two penetrations.

Defined in this manner, the frontal eye field of the squirrel monkey occupied an oval area that ranged from 1.0 × 1.5 mm to about 2.0 × 3.0 mm in different animals. The borders of the frontal eye field were marked with small electrolytic lesions, and small volumes (about 0.06 μl) of HRP-WGA were injected into the defined field.

As in the macaque monkeys, the location of the frontal eye field in squirrel monkeys varied between animals with respect to surface features, even though connections appeared to be identical. For example, in one case (85-30, Fig. 7C,D) the frontal eye field was situated just rostral to the dorsomedial limit of the inferior arcuate dimple. In another

Fig. 3. Drawings of a rostral (level 497) to caudal (level 332) series of frontal sections showing the distribution of anterogradely (fine stipple) and retrogradely (dots) transported label following injection of HRP-WGA into the frontal eye field of macaque monkey 85-68. The right-hand sides of the sections are ipsilateral to the injection site. Dorsal is to the top of each section.

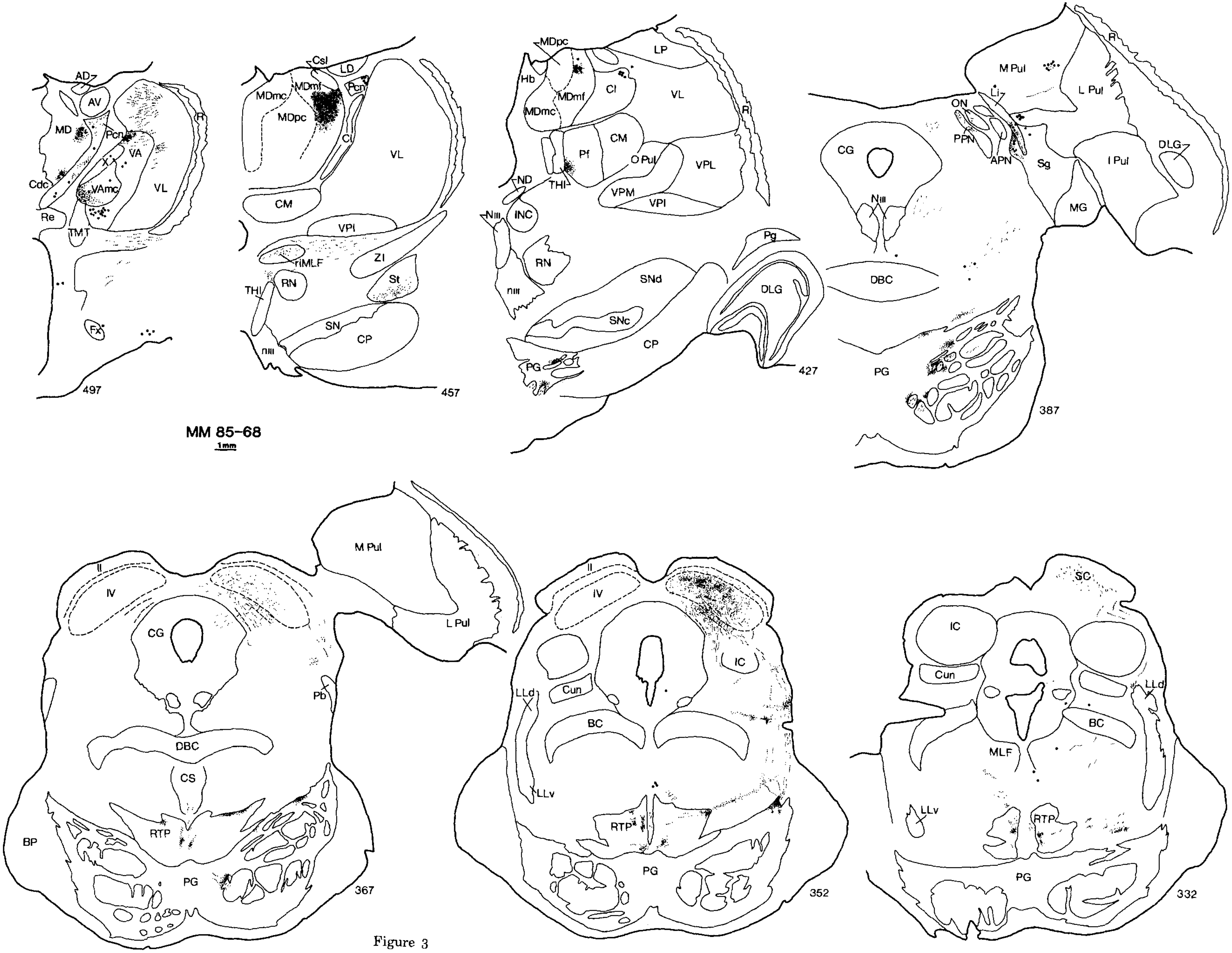
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Figure 3

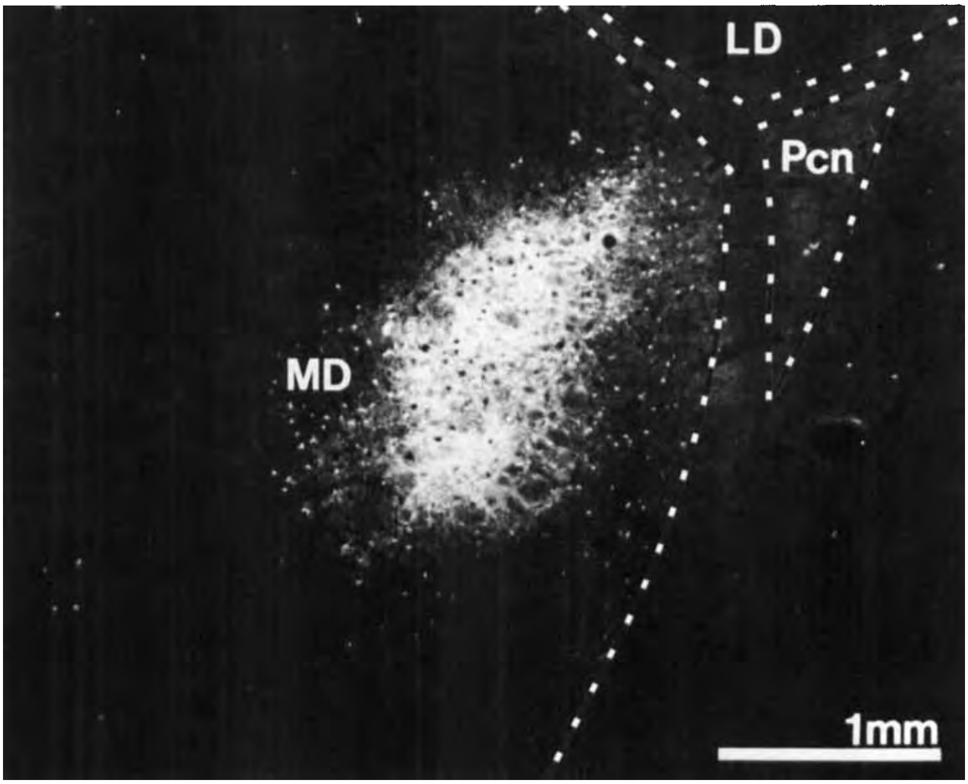


Fig. 4. Darkfield photomicrograph of dense anterogradely and retrogradely transported label in the ipsilateral pars multiformis of the medial dorsal nucleus of macaque monkey 85-68. Approximate nuclear borders are indicated. Dorsal is to the top, medial to the left of the figure.

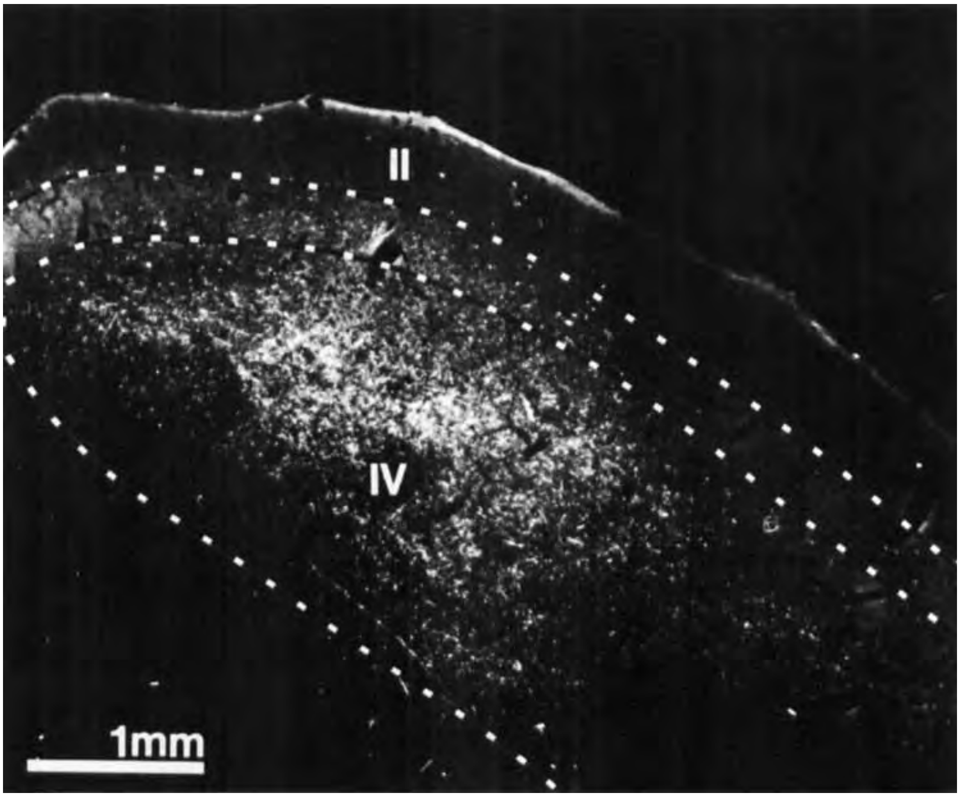


Fig. 5. Darkfield photomicrograph of anterogradely transported label in the ipsilteral superior colliculus of macaque monkey 85-68 with approximate laminar borders indicated. Dorsal is to the top, medial to the left of the figure.

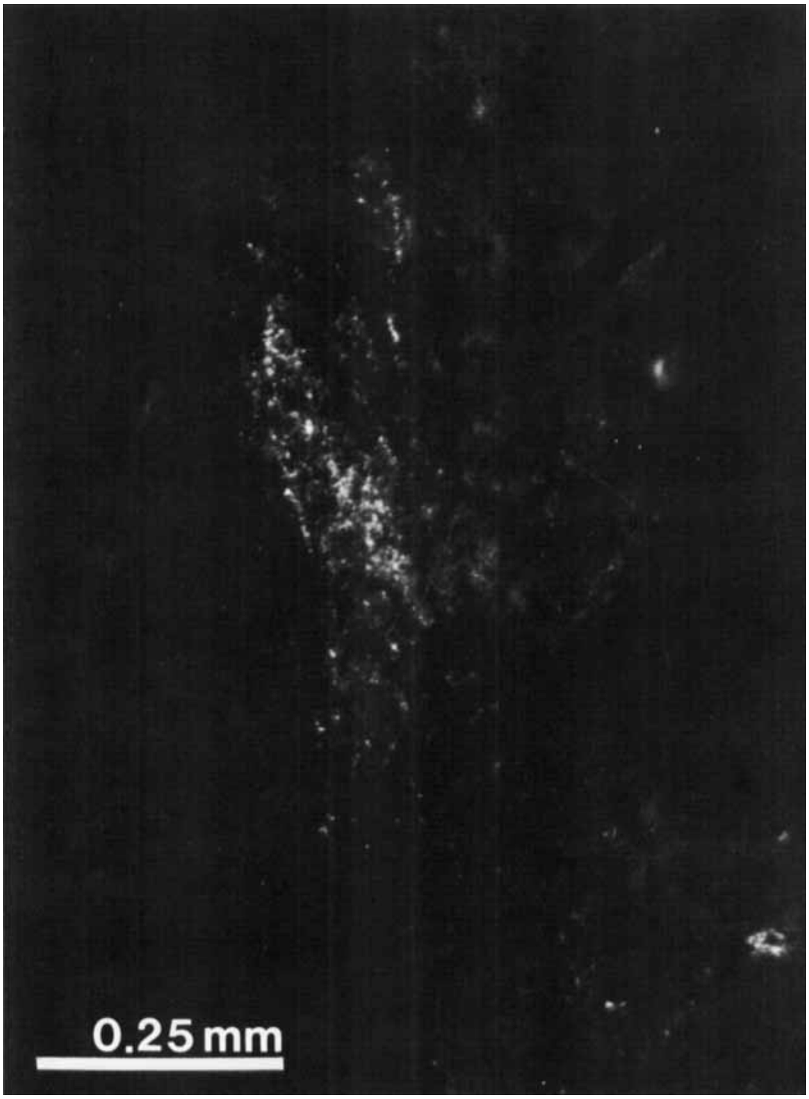


Fig. 6. Darkfield photomicrograph of anterogradely transported label in the contralateral nucleus reticularis tegmenti pontis in macaque monkey 85-68. Dorsal is to the top, medial to the right of the figure.

case (85-34, not illustrated) eye movements could not be driven from this region, but other body movements (e.g., vibrissae, pinnae) could be. Persistent exploration in this case revealed that the frontal eye field was located approximately 2.0 mm caudomedial to the dorsomedial limit of the inferior arcuate dimple.

Connections of the frontal eye field. As in the macaque monkey, there were two major bundles that carried fibers between the frontal eye field and subcortical structures in the squirrel monkey. At rostral levels the bundles are both situated in the internal capsule. Further caudal, at the level of the rostral thalamus, they became separate with one distributing to the nuclei of the dorsal thalamus, and the other coursing through the subthalamus. The thalamic bundle entered dorsal thalamic territory from the ventrolateral aspect of the dorsal thalamus (Fig. 8, levels 432, 422) rather than from the dorsolateral aspect, as this bundle did in the macaque monkey (Fig. 3). This group of axons reached the ipsilateral intralaminar and juxtalaminar thalamic nuclei rostrally, and the pretectum and superior colliculus caudally. The other bundle reached subthalamic nuclei, and at more caudal levels, distributed to pontine nuclei from the medial part of the cerebral peduncle.

The connections of the thalamic bundle include dense reciprocal connections with the lateralmost part of the medial dorsal nucleus, just medial to the internal medullary lamina (Figs. 8, 9). The anterogradely and retrogradely transported label was present throughout most of the rostral-caudal extent of the medial dorsal nucleus, but was especially heavy at intermediate levels. In a few sections, isolated label was also present in more medial parts of the medial dorsal nucleus, especially in more caudal levels (e.g., Fig. 8, level 392). The medial part of the ventral anterior nucleus was also heavily labeled, with the bulk of the label present in pars magnocellularis, which lies immediately lateral to the internal medullary lamina. Sparse and scattered label was present in the medial part of the ventral lateral nucleus. Of the intralaminar nuclei, the paracentral

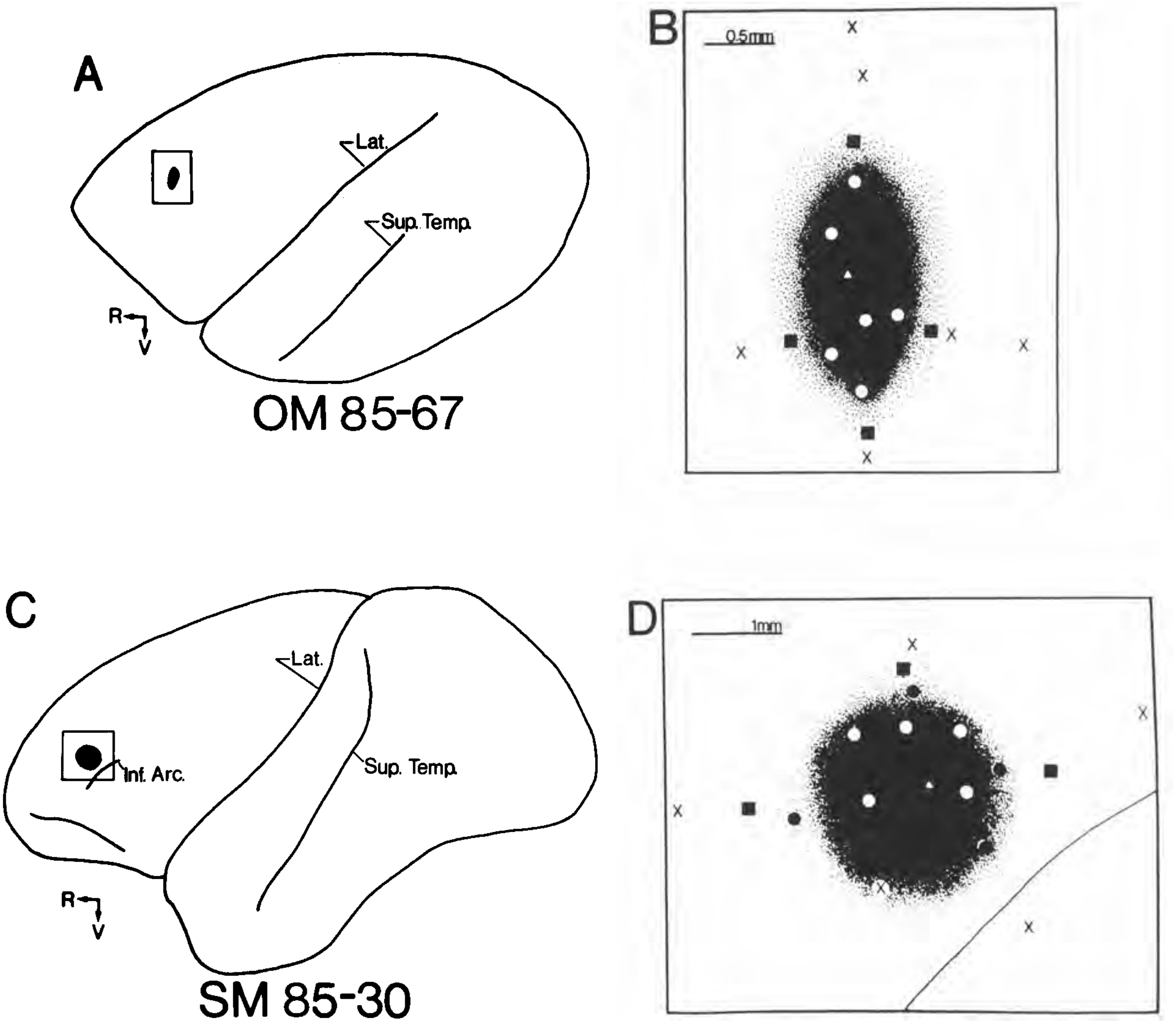


Fig. 7. Locations of physiologically defined frontal eye fields and extents of HRP-WGA injection sites in owl and squirrel monkeys. A. Lateral view of left hemisphere of owl monkey 85-67 with location and extent of injection site indicated in black. Box represents region shown in panel B. B. Enlarged view of region indicated in A (drawn from photograph) showing locations of electrode penetrations as circles (sites within the frontal eye field), boxes (sites of electrolytic lesions), and X's (sites outside of the frontal eye field). Injection site indicated by triangle with extent of reaction product shown as black stipple (reconstructed from flattened sections). C. Lateral view of left hemisphere of squirrel monkey 85-30. Same conventions as in panel A. D. Same conventions as in panel B.

nucleus had substantial reciprocal connections with the frontal eye field, whereas such connections were sparse with the central lateral nucleus (Fig. 8). The medial pulvinar contained patches of retrogradely and anterogradely transported label, and retrogradely labeled neurons were occasionally present in the rostral half of lateral posterior nucleus. The parafascicular nucleus contained a substantial amount of anterogradely transported label but only a very few labeled cell bodies (Figs. 8, 9).

At the mesodiencephalic junction, bidirectionally transported HRP-WGA was apparent in nucleus limitans and in the suprageniculate nucleus, while the pretectal nuclei contained only anterogradely transported label (Fig. 9). The anterior pretectal nucleus was the most heavily labeled pretectal nucleus. The nucleus of the posterior commissure also received input from the frontal eye field; most of the anterogradely transported label was concentrated in pars magnocellularis (Fig. 8, level 332; Fig. 9, level 327).

The frontal eye field also projected strongly to layer four of the ipsilateral superior colliculus, where the label was unevenly distributed. In one case (85-30, Fig. 10), the anterogradely transported label was concentrated medially in layer four, whereas in another case (85-42, Fig. 10), the label was heaviest in lateral parts of layer four. In a third case (Fig. 11), the frontal eye field projection filled the medial-lateral extent of layer four of the superior colliculus.

The second major bundle of fibers was distributed rostrally within the ipsilateral subthalamus. Light anterograde labeling was present within the zona incerta, the rostral interstitial nucleus of the medial longitudinal fasciculus, and nucleus Darkschewitsch. Very light label was present within the interstitial nucleus of Cajal, and the subthalamic nucleus contained only a few labeled axons.

Labeled fibers derived from the subthalamic bundle were traced caudally where they traveled in the medial part of the ipsilateral cerebral peduncle. At the level of the rostral

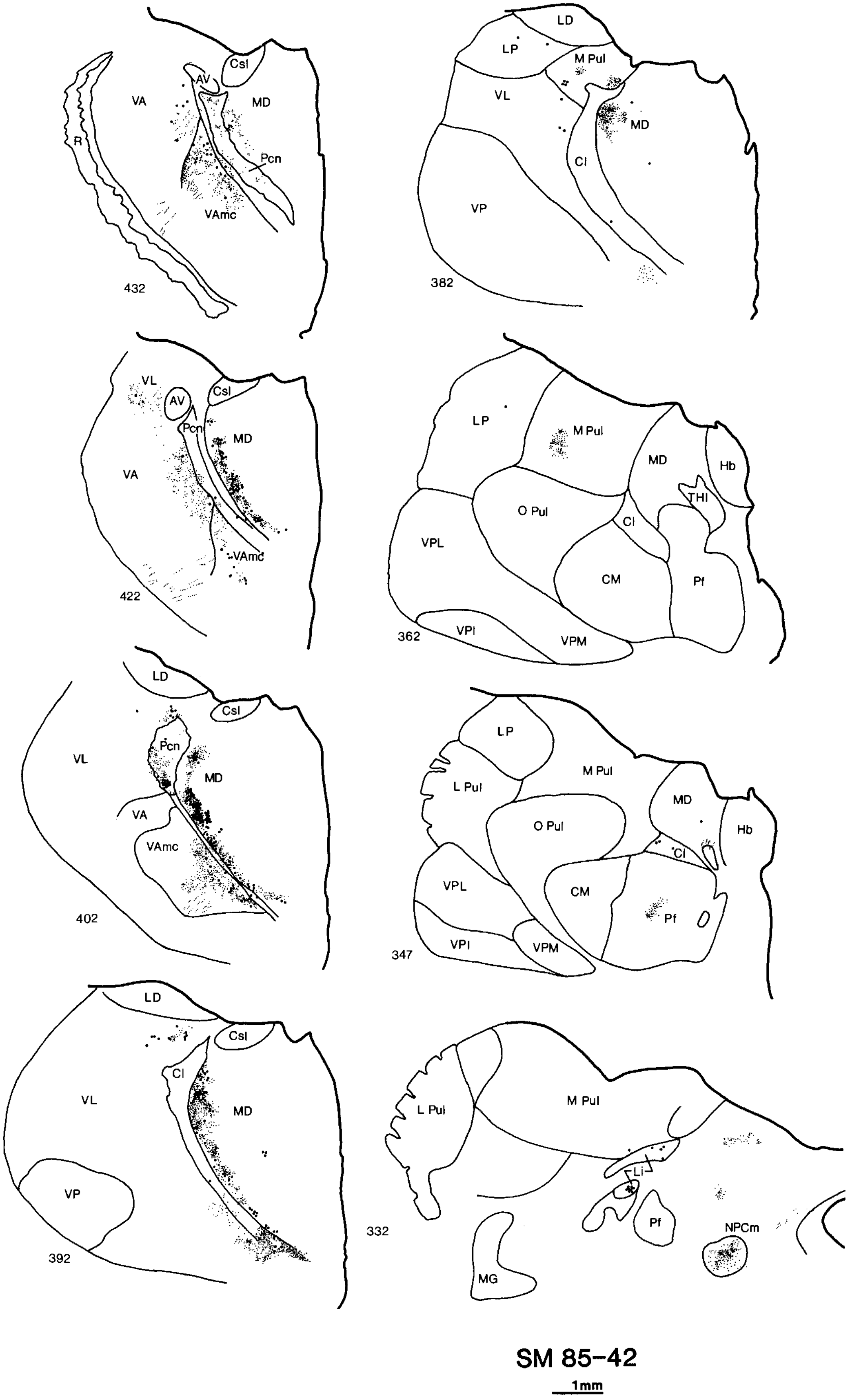


Fig. 8. Drawings of rostral (level 432) to caudal (level 332) series of frontal sections showing the distribution of anterogradely (fine stipple) and retrogradely (dots) transported label following injection of HRP-WGA into the ipsilateral frontal eye field of squirrel monkey 85-42. Dorsal is to the top, medial to the right of each section.

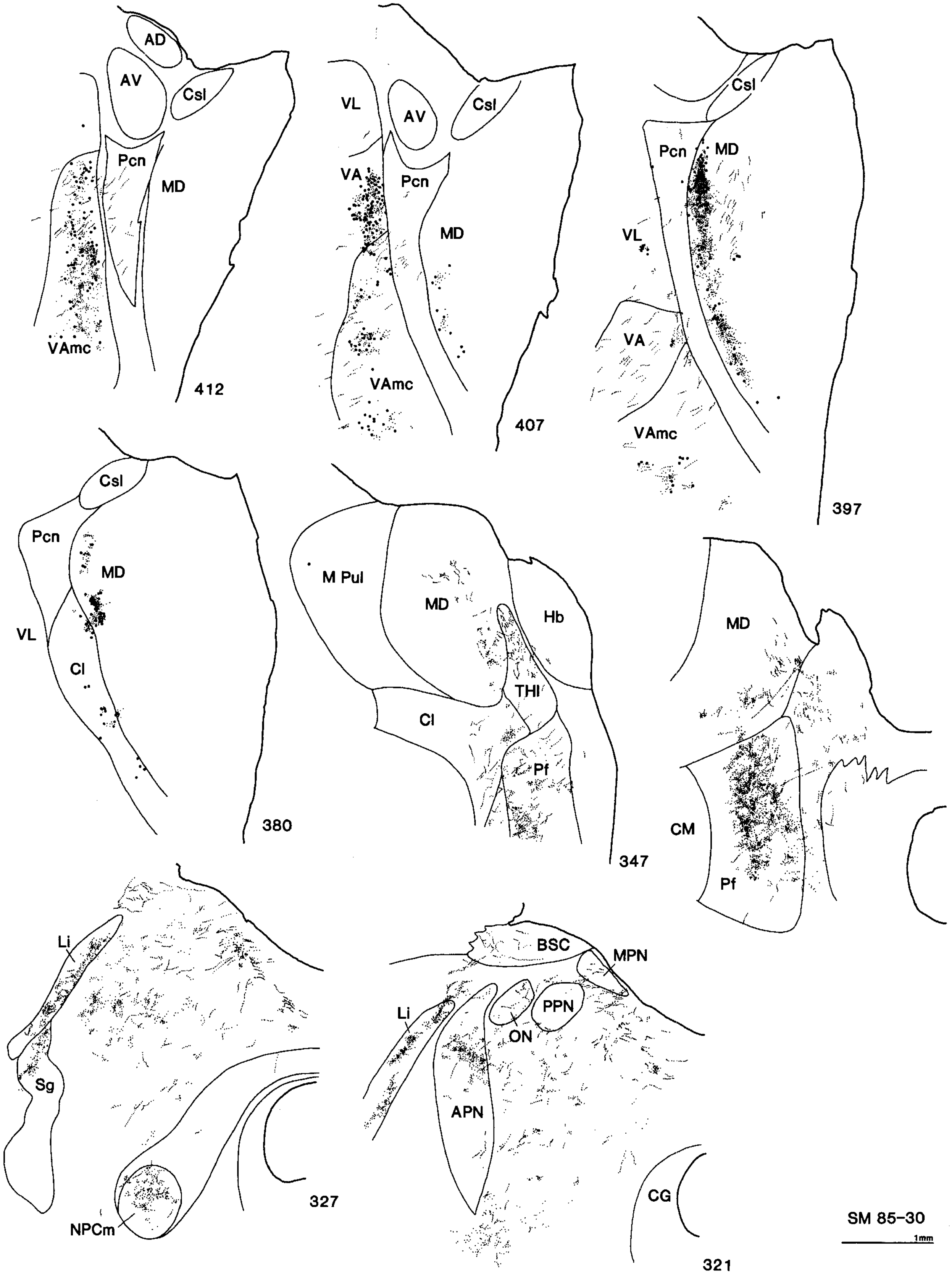


Fig. 9. Drawings of rostral (level 412) to caudal (level 321) series of frontal sections showing the distribution of anterogradely (fine stipple) and retrogradely (dots) transported label following injection of HRP-WGA into the ipsilateral frontal eye field of squirrel monkey 85-30. Dorsal is to the top, medial to the right of each section.

pons, anterogradely transported HRP-WGA was apparent in medial and dorsal parts of the ipsilateral pontine gray and within the nucleus reticularis tegmenti pontis (Fig. 11). The nucleus reticularis tegmenti pontis was heavily labeled contralaterally. The paramedian pontine reticular formation also received input from the contralateral frontal eye field (Fig. 11). No transported HRP-WGA was apparent caudal to the pons.

Owl monkey

Definition of the frontal eye field. Since the inferior arcuate dimple is often absent in owl monkeys, the frontal eye field was located with reference to the results of previous stimulation mapping studies from this laboratory (Gould et al., '86). These findings revealed that the frontal eye field of the owl monkey is located immediately rostral to the motor cortex devoted to movements of the forelimb, and that the forelimb motor representation extends as far caudal as the cortex just rostrolateral to the lateral limit of the central dimple. Thus, the central dimple served as a landmark, and the first penetration was placed relative to this dimple. After finding the motor representation of the forelimb, stimulation penetrations were made at progressively rostral sites until eye movements could be elicited. At each penetration, the electrode tip was usually lowered to about 2,000 μm deep to the pial surface before current was passed. This was the depth at which movements could usually be driven at the lowest current amplitudes. In each of the three experiments, the number of penetrations ranged from 36 to 53. Threshold levels of current were assessed for the vast majority of these.

In agreement with previous accounts of the frontal eye field in the owl monkey (Gould et al., '86), bilateral, contralaterally directed rapid eye movements were evoked by stimulation of the region just rostral to the representation of the forelimb movement. In each experiment, five or six penetrations were made within the frontal eye field, and eye movements were produced at levels as low as 10 μA. The mean threshold levels of current that resulted in eye movements in the frontal eye fields of the three owl monkeys were 43 μA, 40 μA, and 15 μA.

As in squirrel monkeys, the physiological border of the frontal eye field in owl monkeys was defined as adjacent regions in which stimulation at comparable or higher current levels resulted in no movement or in movements other than those of the eye. A typical case is illustrated in Figure 7A,B. The average threshold for penetrations within the frontal eye field in case 85-67 was about 40μA. On the other side of three of the four defined borders in this case, current amplitudes of 50μA were required to produce movement, and the movements produced were of the eyelid, ear, or vibrissae. On the other side of the fourth border, levels of up to 75 μA resulted in no apparent movement. As in other cases, the frontal eye field was delimited by a series of electrolytic lesions and HRP-WGA was injected into the field (Fig. 7A,B).

Connections of the frontal eye field. Fibers connecting the frontal eye field with subcortical structures took the same routes in owl monkeys as they did in squirrel monkeys. Thus, at the level of the rostral thalamus a group of fibers entered the dorsal thalamus from its ventrolateral aspect to distribute to dorsal thalamic nuclei, the pretectum, and the superior colliculus (Figs. 12, 14). The other major bundle traversed the subthalamus and, at caudal levels, occupied the medial part of the ipsilateral cerebral peduncle (Figs. 12, 14).

The medial portion of the ventral anterior nucleus, especially pars magnocellularis and the lateral part of the medial dorsal nucleus contained dense anterogradely and retrogradely transported label (Fig. 13). In addition, bidirectionally transported label was present within the paracentral nucleus (Fig. 12). The caudal part of the central lateral nucleus contained transported HRP-WGA, but the rostral part was void of label. The medial pulvinar and the lateral posterior nucleus contained labeled cells and terminals, whereas only anterogradely transported HRP-WGA was evident within the parafascicular nucleus (Fig. 12). At more caudal levels, the suprageniculate nucleus and nucleus limitans were labeled. Within the pretectum, anterogradely transported label was concentrated within the anterior pretectal nucleus, although very sparse label was distributed within the other pretectal nuclei. The nucleus of the posterior commissure also received input from the frontal eye field (Fig. 12). Within the ipsilateral superior colliculus, anterogradely transported HRP-WGA was unevenly distributed in layer four (Fig. 14).

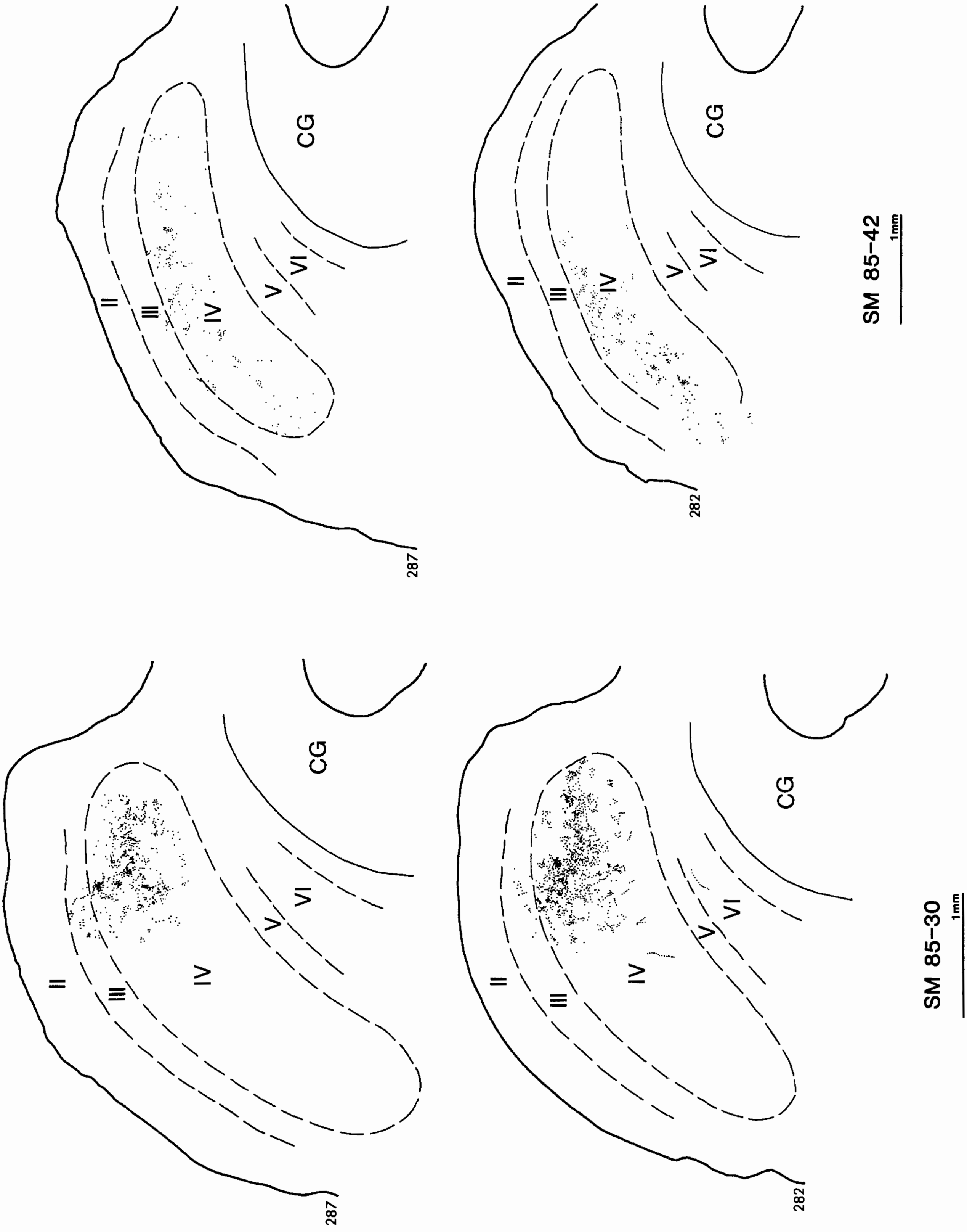
The fiber bundle that coursed through the subthalamus distributed moderate levels of anterogradely transported label to the rostral interstitial nucleus of the medial longitudinal fasciculus and to the subthalamic nucleus (Fig. 12, level 217). Similar levels of anterogradely transported HRP-WGA were evident within nucleus Darkschewitsch, but only very small amounts of transported tracers were present within the interstitial nucleus of Cajal. This bundle of fibers continued caudally within the medial cerebral peduncle (Fig. 12, levels 207–172). From this position, fibers were distributed to the ipsilateral pontine gray; the frontal eye field projected mostly to the medial pontine gray, but anterogradely transported label was also present further laterally (Fig. 14, level 112). The contralateral and ipsilateral nucleus reticularis tegmenti pontis contained anterogradely transported label, whereas most of the label within the paramedian pontine and reticular formation was contralateral (Fig. 14, level 112).

DISCUSSION

Since the frontal eye field is a physiologically defined region, the significance of the present study is that physiological methods were used to determine and mark the borders of the field and anatomical tracers were injected within these borders to demonstrate solely the connections of the field. The present report is the first full-length report of such experiments (see also Stanton et al., '82, Huerta et al., '85). Moreover, since much of our understanding of the primate's oculomotor system is based on studies of macaque monkeys, and since the present study included macaque monkeys as well as squirrel and owl monkeys, the present results can be related to other work on the primate's oculomotor system, and interspecies comparisons can be made.

Definition of the frontal eye field

While the "frontal eye fields" initially referred to expansive regions of the primate's frontal lobe from which electrical stimulation elicited eye movements (for review of early literature, see Smith, '44), the use of the term has become more restricted as physiological techniques have become more refined. Moreover, as more sensitive physio-


II
III
IV
V
VI
CG
287
282
SM 85-42
1mm
II
III
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V
VI
CG
287
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SM 85-30
1mm

Figure 10

logical techniques have been used, agreement on the location and extent of the frontal eye field has increased. Despite the variety in location and extent of the frontal eye fields that has been described in Old World monkeys, however, the region immediately rostral to the arcuate sulcus is always included (Ferrier, 1875; Beevor and Horsley, 1888; Mott and Schaeffer, 1890; Vogt and Vogt, '19; Smith, '44; Wagman et al., '61; Robinson and Fuchs, '69; Marrocco, '78; Schiller et al., '79; Bruce and Goldberg, '85; Bruce et al., '85; present results). Since this approximately corresponds with area 8 of Brodmann ('09), the frontal eye field and Brodmann's ('09) area 8 have sometimes been considered equivalent (e.g., Astruc, '71; Künzle and Akert, '77; Leichnetz, '82a). Recently, however, Bruce et al. ('85) have combined single-unit recording, intracortical microstimulation, and cytoarchitectonic analysis in macaque monkeys (*Macaca mulatta* and *M. fascicularis*) to show that the frontal eye field more likely corresponds to areas 8a and 45 of Walker ('40), which are collectively smaller than area 8 of Brodmann ('09).

More specifically, these investigators define "the low-threshold frontal eye fields as cortex yielding saccades with stimulation currents $\leqslant 50\ \mu$A" in unanesthetized monkeys (p. 714, Bruce et al., '85). The frontal eye field so defined occupies a portion of the anterior bank of the arcuate sulcus (Bruce and Goldberg, '85; Bruce et al., '85). Analysis of Nissl-stained sections (Bruce et al., '85) revealed that the frontal eye fields are located within Walker's areas 8a and 45, both of which have "fairly large" pyramidal neurons in layer V and a "faint" layer IV (Walker, '40). (Nevertheless, it should be mentioned that the extent of the frontal eye fields defined by Bruce et al., '85, appears to be less than the extent of areas 8a and 45 of Walker, '40, as depicted in surface views.) Using the same criterion level of intracortical microstimulation (50 μA) in ketamine-anesthetized macaque monkeys (*M. fascicularis*), we obtained findings that are in close agreement with these results (Bruce and Goldberg, '85; Bruce et al., '85), except that the medial-lateral extent of the frontal eye field as defined in anesthetized monkeys is slightly less than that defined in awake animals (7 mm vs. 10 mm). This difference is probably at least partially an effect of the anesthetic, since ketamine anesthesia (Duncan et al., '82), like barbiturate anesthesia (Robinson and Fuchs, '69) and drowsiness (Bruce et al., '85), decreases the responsivity of cortical neurons. The smaller size of the field as defined in the anesthetized preparation indicates that ours is a conservative estimate of the extent of the frontal eye field. Thus, even in case 85-68 (Fig. 1), in which the injection site extended slightly (250 μm) beyond the "border" of the frontal eye field, it seems reasonable that the entire injection site would have been within the frontal eye field as defined in an awake monkey.

Comparisons among the present results and similar previous studies using intracortical microstimulation (Robinson and Fuchs, '69; Bruce and Goldberg, '85; Bruce et al., '85) in macaque monkeys suggest that the same region is being defined. The question now arises as to whether this region comprises a single (functional) frontal eye field, or multiple (functional) adjacent frontal eye fields. A corollary question is whether areas 8a and 45 (Walker, '40), which correspond to the physiologically defined region, are two separate cytoarchitectonic areas, or a single area with internal variation. The present results indicate that there is no differential distribution of threshold levels that might indicate subdivisions of what has been termed the frontal eye field; nor have such differences been noted by others referring to similar regions (Robinson and Fuchs, '69; Bruce and Goldberg, '85; Bruce et al., '85). Moreover, despite the fact that numerous cell types were studied quantitatively in this region via single-unit recording, a differential distribution of such cell types has not been reported (Bizzi, '68; Bizzi and Schiller, '70; Kubota and Niki, '71; Mohler et al., '73; Wurtz and Mohler, '76; Pigarev et al., '79; Fuster, '80; Goldberg and Bushnell, '81a,b; Mikami et al., '82a, b; Bruce and Goldberg, '85; Bruce et al., '85). In addition, quantitative studies in awake monkeys reveal that the region that we have called the frontal eye field contains a single topographic representation of saccade amplitudes, with large saccades represented dorsomedially and small saccades represented ventrolaterally in this region (Robinson and Fuchs, '69; Stanton et al., '82; Bruce and Goldberg, '85; Bruce et al., '85). Finally, it has been shown that this region projects topologically to the intermediate layers of the superior colliculus (Stanton et al., '82). Specifically, the dorsomedial region of the frontal eye field, which contains a representation of large saccades, projects to the caudal part of the superior colliculus, which also contains a representation of large saccades, while the ventrolateral frontal eye field innervates the rostral superior colliculus; both regions contain representations of small amplitude saccades (Stanton et al., '82). Similar observations have been made by others exploring prearcuate cortex, but those investigators did not define the borders of the explored region physiologically or anatomically (e.g., Komatsu and Suzuki, '85). This set of observations indicates that the region defined in these studies is a single functional area. This contention, in turn, supports the conclusion that the differences between areas 8a and 45 (Walker, '40) are actually variations within a single area.

While the location and extent of the frontal eye field presently demonstrated in *Macaca fascicularis* and *Aotus trivirgatus* are similar to those described by others for these species and for *Macaca mulatta* (Robinson and Fuchs, '69; Bruce and Goldberg, '85; Bruce et al., '85; Gould et al., '86), the borders of the frontal eye field have not previously been physiologically defined in other New World monkeys. Nevertheless, it has been reported that eye movements are elicited by surface stimulation of broad regions of the frontal lobe of squirrel monkeys (*Saimiri sciureus*) and marmosets (*Callithrix jacchus*) with currents ranging from 5 to 500 μA (Blum et al., '82).

A final point regarding the definition of the frontal eye field in Old World and New World monkeys relates to the variation in location of the field between individual members of a species. Specifically, the location of the frontal eye field cannot be predicted on the basis of surface landmarks (e.g., Fig. 6, Bruce et al., '85; present results). Thus, it is necessary to use physiological methods to accurately determine the location and borders of the frontal eye field in the

Fig. 10. Drawings of the distribution of anterogradely transported label (fine stipple) in the superior colliculus following injection of HRP-WGA into two different regions of the ipsilateral frontal eye field in two squirrel monkeys. Laminae are outlined by dashed lines. Dorsal is to the top, medial to the right of each section.

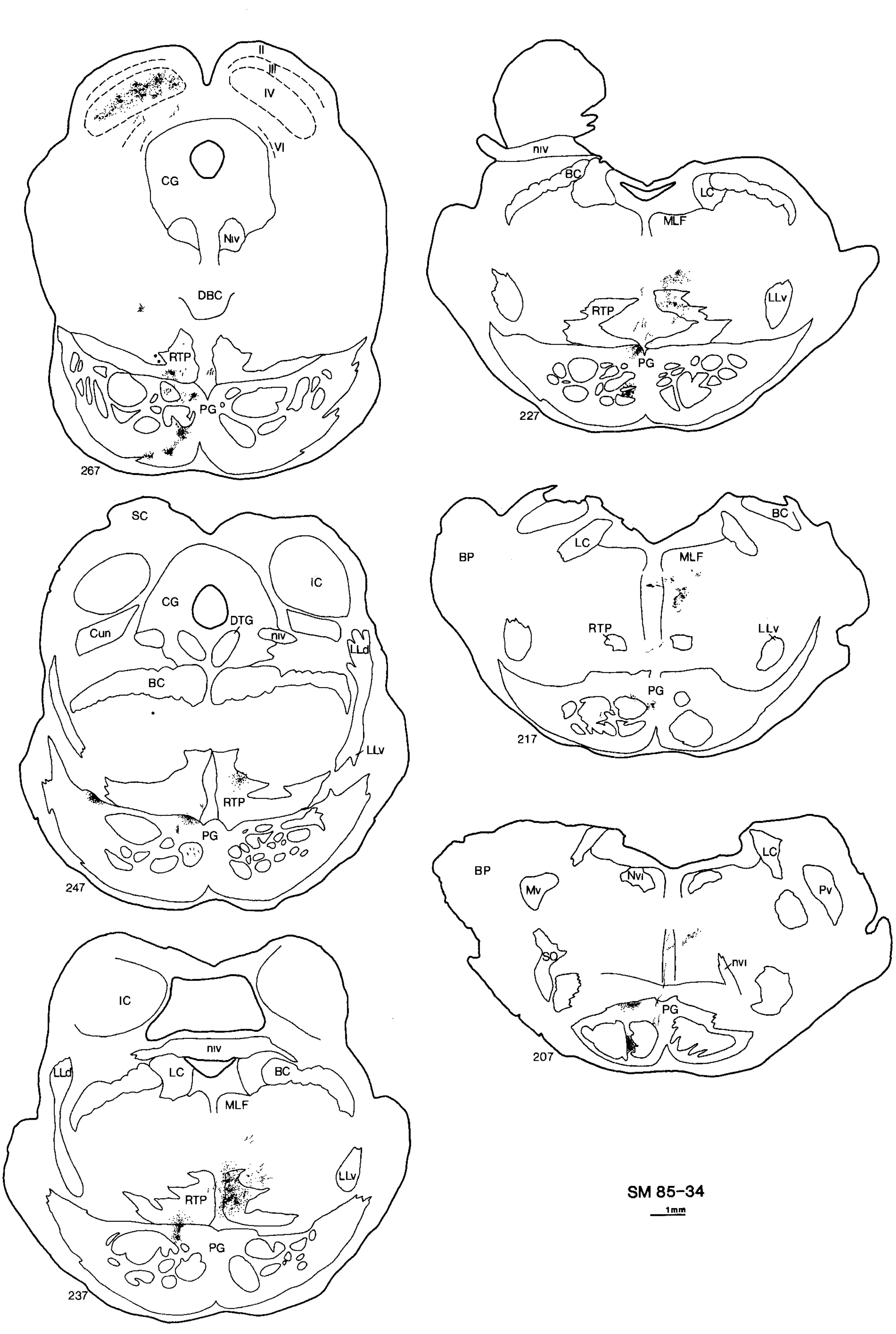

Fig. 11. Drawings of a rostral (level 267) to caudal (level 207) series of frontal sections showing the distribution of anterogradely (fine stipple) and retrogradely (dots) transported label following injection of HRP-WGA into the frontal eye field of squirrel monkey 85-34. Dorsal is to the top of each section; the left-hand side of each section is ipsilateral to the injection site.

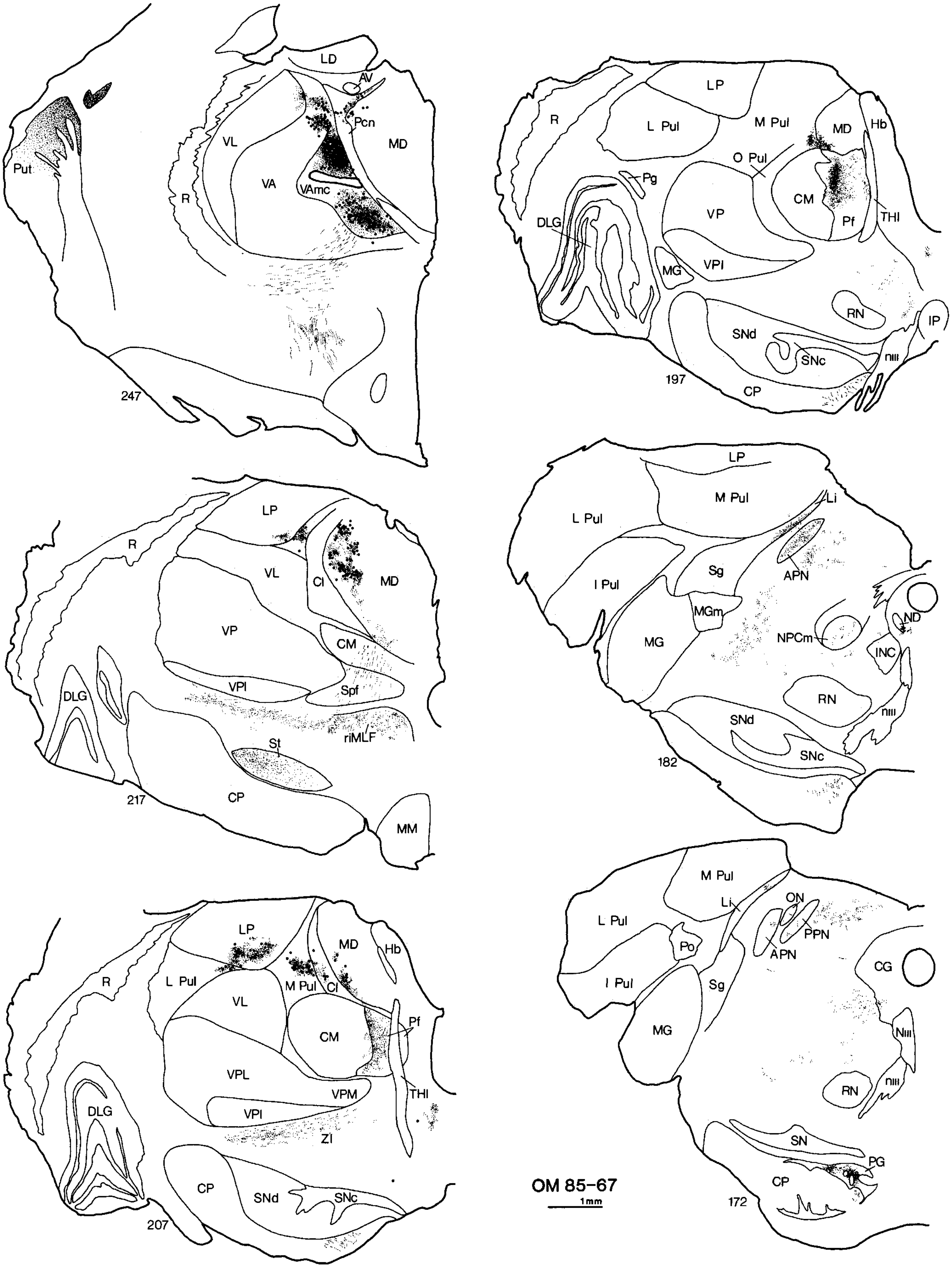

Fig. 12. Drawings of a rostral (level 247) to caudal (level 172) series of frontal sections showing the distribution of anterogradely (fine stipple) and retrogradely (dots) transported label following injection of HRP-WGA into the ipsilateral frontal eye field of owl monkey 85-67. Dorsal is to the top, medial to the right of each section.

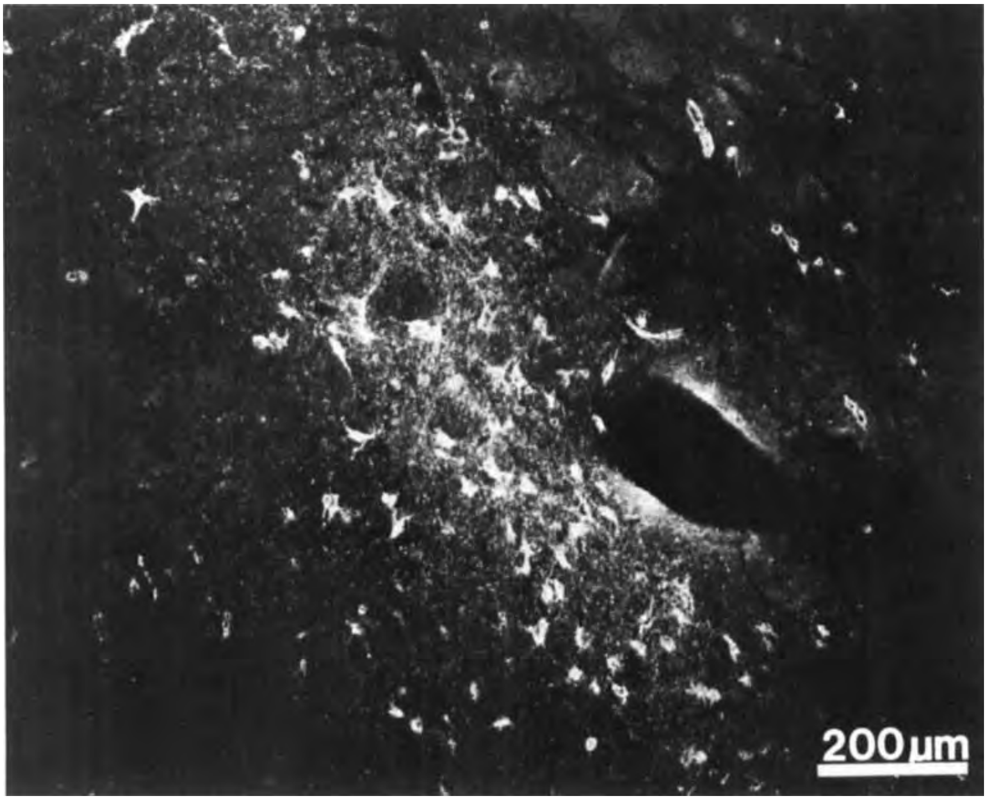

Fig. 13. Darkfield photomicrograph of anterogradely and retrogradely transported label in pars magnocellularis of the ventral anterior nucleus in owl monkey 85-67 following injection of HRP-WGA into the ipsilateral frontal eye field.

intact animal. Nevertheless, since the frontal eye field appears to correspond to areas 8a and 45 of Walker ('40; Bruce et al., '85), careful cytoarchitectonic analysis can be used to determine the borders of this field in the sectioned brain.

Previous connectional studies: Subcortical connections of prearcuate cortex

It is difficult to compare directly the presently demonstrated connections of the physiologically defined frontal eye field with previous connectional studies of "the frontal eye field" for the following reasons: First, it has only recently been shown that the physiologically defined frontal eye field corresponds to areas 8a and 45 of Walker ('40; Bruce et al., '85). Second, most previous studies of "the frontal eye field" equated this field to area 8 of Brodmann ('09), whereas areas 8a and 45 of Walker ('40) comprise only a portion of Brodmann's area 8 ('09; Walker, '40; Bruce et al., '85). Third, many studies of cortex related connectional data to surface features, such as sulci, and not to actual cytoarchitectonic areas. Thus, while injections of tracers or lesions may have included the frontal eye field (as defined physiologically and which corresponds to areas 8a and 45 of Walker, '40) in previous studies, it is very unlikely that the connections demonstrated in these studies were solely those of the frontal eye field.

Despite these difficulties, each of the connections that we have demonstrated between the physiologically defined frontal eye field and particular subcortical structures has been previously reported in one or another study of the connections of cortex immediately rostral to the arcuate sulcus in macaque monkeys (which is the general location of the presently defined frontal eye field), although no single study has demonstrated all of the connections presently shown. Thus, connections have previously been shown between the frontal eye field and pars multiformis of the medial dorsal nucleus (called paralamellaris dorsalis by Scollo-Lavizzari and Akert, '63; Astruc, '71; Tobias, '75; lateral medial dorsal nucleus, Kievet and Kuypers, '77; Künzle and Akert, '77; Barbas and Mesulam, '81; Asanuma et al., '85; Ilinsky et al., '85), pars magnocellularis and/or medial parts of the ventral anterior nucleus (Astruc, '71; Kievet and Kuypers, '77; Künzle and Akert, '77; Barbas and Mesulam, '81; Stanton et al., '82; Asanuma et al., '85), the central lateral nucleus (Astruc, '71; Künzle and Akert, '77; Barbas and Mesulam, '81; Asanuma et al., '85), the paracentral nucleus (Astruc, '71; Kievet and Kuypers, '77; Künzle and Akert, '77; Barbas and Mesulam, '81; Asanuma et al., '85; but see Stanton et al., '82), caudal portions of the ventral lateral nucleus (as defined here, see Methods; Kievet and Kuypers, '77; Künzle and Akert, '77; Barbas and Mesulam, 81; Stanton et al., '82), the parafascicular nucleus (Astruc, '71; Kievet and Kuypers, '77; Künzle and Akert, '77; Stanton et al., '82), the medial pulvinar (Trojanowski and Jacobson, '74; Bos and Benevento, '75; Kievet and Kuypers, '77; Barbas and Mesulam, '81; Stanton et al., '82; Asanuma et al., '85), nucleus limitans (Künzle and Akert, '77; Barbas and Mesulam, '81; Stanton et al., '82; Asanuma et al., '85; referred to as the pretectal nucleus of the optic

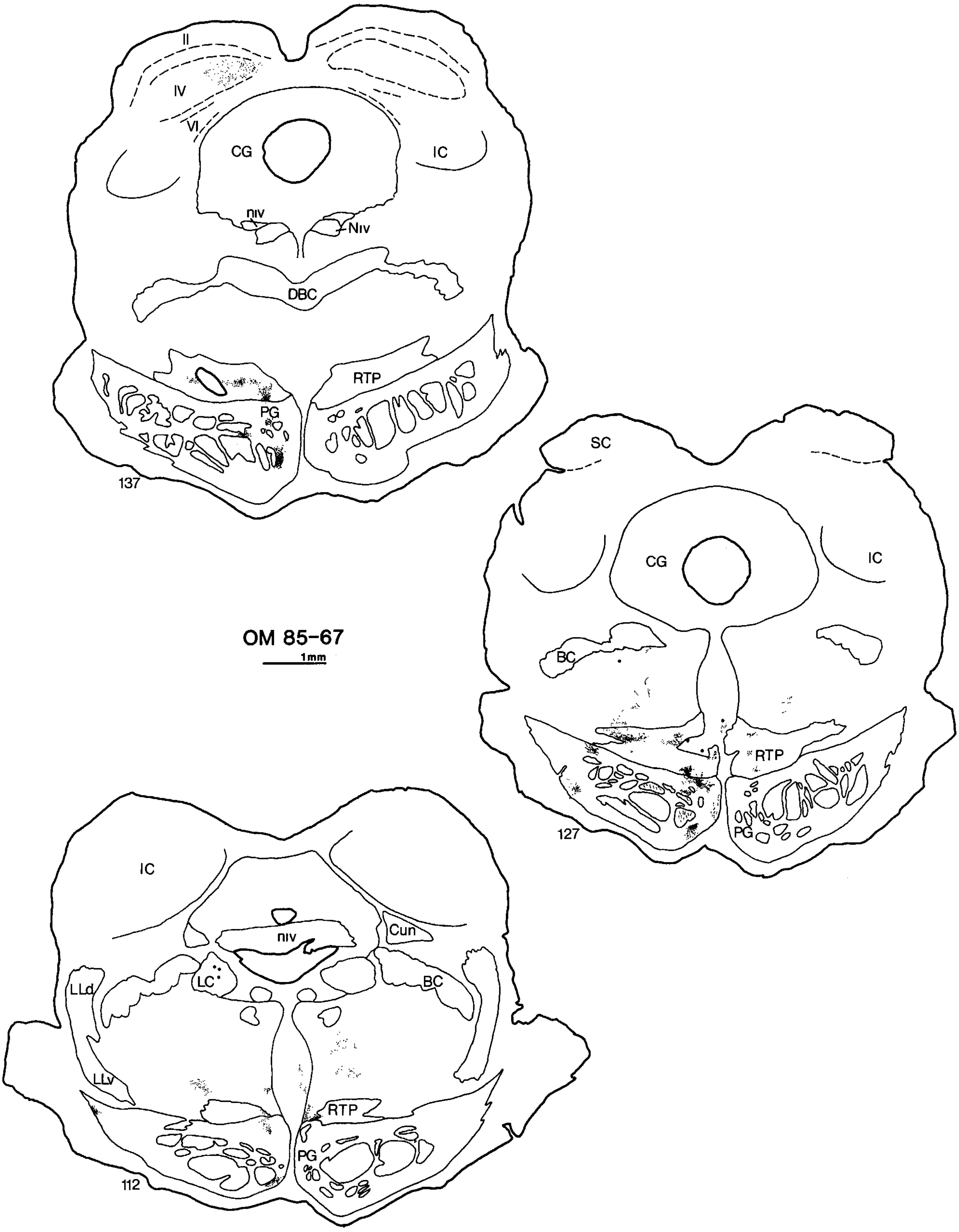

Fig. 14. Drawings of a rostral (level 137) to caudal (level 112) series of frontal sections showing the distribution of anterogradely (fine stipple) and retrogradely (dots) transported label following injection of HRP-WGA into the frontal eye field in owl monkey 85-67. Dorsal is to the top, and the left-hand side of each section is ipsilateral to the injection site.

tract, Leichnetz, '82a), the suprageniculate nucleus (Leichnetz, '82a; Asanuma et al., '85), pretectal nuclei (Astruc, '71; Künzle and Akert, '77; Leichnetz, '82a), the nucleus of the posterior commissure (Leichnetz, '82a), layer IV of the superior colliculus (Astruc, '71; Künzle and Akert, '77; Leichnetz et al., '81; Distel and Fries, '82; Stanton et al., '82; Fries, '84; Komatsu and Suzuki, '85; Lynch et al., '85), the zona incerta (Astruc, '71; Künzle and Akert, '77), the rostral interstitial nucleus of the medial longitudinal fasciculus (Leichnetz et al., '84a), the zone near the dorsomedial parvocellular portion of the red nucleus (Stanton et al., '82; Leichnetz et al., '84a; but see Astruc, '71), nucleus Darkshewitsch (Stanton et al., '82; Leichnetz et al., '84a; but see Künzle and Akert, '77), the interstitial nucleus of Cajal (Astruc, '71; Leichnetz, '84a; but see Künzle and Akert, '77), the subthalamic nucleus (Künzle and Akert, '77; Stanton et al., '82; but see Astruc, '71), and the pontine nuclei (Astruc, '71; Künzle and Akert, '77; Stanton et al., '82; Leichnetz et al., '84b; Schnyder et al., '85). Most of these connections have previously been demonstrated only in macaque monkeys, but the present results indicate that they apply to owl and squirrel monkeys as well.

In addition to these connections, previous studies in macaque monkeys have also reported connections between prearcuate cortex and the reticular nucleus of the thalamus (Astruc, '71) nucleus reuniens (Astruc, '71; Barbas and Mesulam, '81), nucleus centrum medianum (Astruc, '71; Asanuma et al., '85), the densocellular, parvocellular and/or magnocellular parts of the medial dorsal nucleus (Künzle and Akert, '77; Barbas and Mesulam, '81; Stanton et al., '82; Asanuma et al., '85; Ilinsky et al., '85), nucleus centralis superior lateralis (Barbas and Mesulam, '81), nucleus centralis densocellularis (Asanuma et al., '85), the central gray (Astruc, '71; Leichnetz, '82a), the "rostral lateral principal oculomotor" nucleus (Leichnetz, '80), the parabigeminal nucleus (Stanton et al., '82), and the medial accessory nucleus of Bechterew (Leichnetz, '82b). Possible explanations for these connections, which were not seen in any species in the present study, include the inclusion of regions beyond the frontal eye field (as presently defined) in the lesion or injection site, differential sensitivity of methods used, and/or differences in interpretation of nuclear boundaries.

Connections of subcortical targets of, and sources of input to, the frontal eye field

Two features characterize most of the subcortical structures that are connected with the frontal eye field: they are known to participate in visuomotor function and they receive direct input from the deeper layers (IV–VII) of the superior colliculus (also see Discussion in Harting et al., '80). These two features are probably related, since Schiller et al. ('80) have shown that ablation of both the frontal eye field and the superior colliculus profoundly disrupts saccades, whereas ablation of either structure alone produces few persevering eye-movement deficits. Moreover, many of the nuclei connected with the frontal eye field also have connections with various parts of the posterior parietal cortex that play important roles in visuomotor function (e.g., Hyvärinen and Poranen, '74; Mountcastle et al., '75; Lynch et al., '77; Lynch, '80; Sunqvist, '79; Sakata et al., '83; Bushnell et al., '81; Hyvärinen, '81; Mesulam, '81; Robinson and Peterson, '84; Shibutani et al., '84). Finally, many of the subcortical targets of, and sources of input to, the frontal eye field are connected with each other and with other brainstem structures that are important to visuomotor and oculmotor function. This network of connections is discussed for each subcortical structure connected with the frontal eye field, below.

Following injection of HRP-WGA into the frontal eye field in macaque monkeys, the heaviest concentration of anterogradely and retrogradely transported label is present in the laterally located pars multiformis of the medial dorsal nucleus and in the medially located pars magnocellularis of the ventral anterior nucleus. These specific nuclear subdivisions have also been shown to receive substantial input from the deeper collicular layers in macaque monkeys (Benevento and Fallon, '75; Harting et al., '80). Other connectional, as well as physiological, data in the macaque monkey implicate the lateral part of the medial dorsal nucleus and the medial part of the ventral anterior nucleus in visuomotor function. In particular, these thalamic zones receive input specifically from the lateral region of substantia nigra pars reticulata (Carpenter et al., '76; Ilinsky et al., '85), which (1) is populated by visuomotor neurons (Hikosaka and Wurtz, '81, '83a) and (2) projects to the deeper collicular layers (Jayaraman et al., '77; Beckstead et al., '81) where the nigrotectal axons tonically inhibit saccade-related neurons, probably via gamma-aminobutyric acid (Hikosaka and Wurtz, '83b, '85a,b). In addition, the magnocellular portion of the ventral anterior nucleus is reciprocally connected with the inferior parietal lobule, including area 7a (Kasdon and Jacobson, '78; Asanuma et al., '85). In accordance with their connections with visuomotor structures, single-unit recording studies in awake macaque monkeys indicate that thalamic regions corresponding to these particular parts of the medial dorsal and the ventral anterior nuclei contain several types of visuomotor neurons (Schlag-Rey and Schlag, '84; Schlag and Schlag-Rey, '84).

In light of these findings, it is interesting that the paracentral nucleus, which is interposed between pars magnocellularis of the ventral anterior nucleus and pars multiformis of the medial dorsal nucleus, also contains visuomotor neurons (Schlag-Rey and Schlag, '84; Schlag and Schlag-Rey, '84) and receives dense input from the deeper collicular layers (Benevento and Fallon, '75; Partlow et al., '77; Harting et al., '80), but has only relatively scant connections with visuomotor structures such as the lateral substantia nigra (Carpenter et al., '76; Ilinsky et al., '85), the inferior parietal lobule, including area 7 (Kasdon and Jacobson, '78; Asanuma et al., '85), and the frontal eye field (present results). While the differential connections of these rostral intralaminar and juxtalaminar nuclei suggest distinct visuomotor functions for each nucleus, such differences are not yet obvious from physiological investigations (Schlag-Rey and Schlag, '84; Schlag and Schlag-Rey, 84).

Besides the strong inputs from the frontal eye field (present study) and the deeper layers of the superior colliculus (Benevento and Fallon, '75; Partlow et al., '77; Harting et al., '80), the parafascicular nucleus of the primate has few well-characterized afferents that are clearly related to visuomotor function; nevertheless, this nucleus is known to receive input from the paramedian pontine reticular formation in the cat (Graybiel, '79), as well as from the zona incerta in the cat and rat (Kaelber and Smith, '79; Ricardo, '81). As shown in the present study, both of these afferents to the parafascicular nucleus receive input from the frontal eye field in monkeys. While the paramedian pontine reticular formation receives little input from the frontal eye field, it receives a strong projection from the deeper collicular layers in the cat and in macaque monkeys (Harting, '77; Huerta and Harting, '82b) and is paramount in saccadic eye movement functions (e.g., Fuchs et al., '85). The zona incerta receives a relatively heavy projection from the frontal eye field (present study) and from the deeper collicular layers (Benevento and Fallon, '75; Harting et al., '80), and visuomotor activity has been reported in the vicinity of the zona incerta (Hikosaka and Wurtz, '83a). According to some reports, the parafascicular nucleus has connections with the inferior parietal lobule (Divac et al., '77; Mesulam et al., '77; Kasdon and Jacobson, '78), whereas such connections have apparently not been found in other studies (Asanuma et al., '85; Yeterian and Pandya, '85). In a comprehensive study (Royce and Mourey, '85), it has recently been shown that the parafascicular nucleus of the cat projects to the zone incerta, the ventral lateral geniculate nucleus, and the dorsal hypothalamic area, all of which innervate the deeper collicular layers (Swanson et al., '74; Edwards et al., '79; Huerta and Harting, '84; Rieck et al., '86). The parafascicular nucleus also innervates the paracentral nucleus (which has been discussed, above), and the subthalamic nucleus, which projects to the substantia nigra pars reticulata (Nauta and Cole, '78) and in which visuomotor activity has been reported (Hikosaka and Wurtz, '83a; DeLong et al., '85). The subthalamic nucleus also receives a moderate amount of input from the frontal eye field in the macaque and owl monkeys. These observations indicate that while the visuomotor function of the parafascicular nucleus remains unclear, it possesses numerous connections that suggest at least an auxilliary role in eye-movement activity.

Injection of HRP-WGA into the frontal eye field results in moderate levels of anterogradely and retrogradely transported label in the medial pulvinar; this nucleus also receives a moderate amount of input from the deeper layers of the superior colliculus (Benevento and Fallon, '75; Partlow et al., '77; Harting et al., '80; Benevento and Standage, '83), and has strong connections with the cortex of the inferior parietal lobule (Baleydier and Mauguiere, '77; Divac et al., '77; Mesulam et al., '77; Kasdon and Jacobson, '78; Weber and Yin, '84; Asanuma et al., '85; Yeterian and Pandya, '85). In particular, it has recently been shown that the medial pulvinar is reciprocally connected with area 7a, and that the cells projecting to this portion of the inferior parietal lobule are different, but in proximity to, the neurons that innervate lateral prefrontal cortex (including the frontal eye field; Asanuma et al., '85). The relation of collicular input to the cells projecting either to prefrontal or posterior parietal cortex remains to be determined, although it has been suggested that such input reaches both populations of cells (Harting et al., '80).

Like most of the other nuclei connected with the frontal eye field, the suprageniculate nucleus and nucleus limitans also receive dense input from the deeper collicular layers (Benevento and Fallon, '75; Partlow et al., '77; Harting et al., '80), and are connected with posterior parietal cortex (Kasdon and Jacobson, '78; Asanuma et al., '85), specifically, with area 7a (Asanuma et al., '85). It is not clear how these visuomotor-related connections relate to the connections that these nuclei have with the granular portion of insular cortex (Burton and Jones, '76; Mufson and Mesulam, '84), which contains neurons responding to somatosensory stimuli (Robinson and Burton, '80).

In addition to the dorsal thalamic nuclei discussed above, the frontal eye field projects upon several structures that also receive deep collicular input (Harting, '77; Harting et al., '80) and that are closely involved with saccadic eye movement mechanisms. These include (1) the rostral interstitial nucleus of the medial longitudinal fasciculus, which receives input from the paramedian pontine reticular formation (Büttner-Ennever and Büttner, '78), innervates the somatic oculomotor nucleus (Büttner-Ennever and Buttner, '78; Steiger and Büttner-Ennever, '79) and which is thought to participate in vertical eye movements (e.g., Büttner-Ennever and Büttner, '78); (2) the nucleus of the posterior commissure, which contains saccade-related neurons (King et al., '81), projects to the region near, if not directly to, the somatic oculomotor nucleus (Graybiel and Hartweig, '74; Steiger and Büttner-Ennever, '79), and which also is thought to specifically participate in vertical eye movements (Carpenter and Peter, '70/'71; Carpenter et al., '70; Christoff, '74; Pasik and Pasik, '74; King et al., '81; Huerta and Harting, '82a); (3) the nucleus reticularis tegmenti pontis, which, in the particular zone that receives collicular and frontal eye field input, contains predominantly saccade-related neurons (Keller and Crandall, '81; Crandall and Keller, '85) and which projects to regions of the cerebellar vermis that have been implicated in saccadic eye movement function (Ron and Robinson, '73; but see McElligott and Keller, '84); (4) portions of the basilar pontine gray, which also project to the saccade-related cerebellar vermal lobules VII and VIII (Frankfurter et al., '77; Weber and Harting, '78; Brodal, '82); (5) the paramedian pontine reticular formation, the interstitial nucleus of Cajal, and nucleus Darkschewitsch, all of which have clear visuomotor function (e.g., King et al., '81; Fuchs et al., '85), but which receive only very sparse frontal eye field input.

Finally, the deeper collicular layers themselves receive a dense and extensive projection from the frontal eye field; much of this input is to layer four. This collicular layer is populated by neurons that discharge prior to eye movements and, as has been discussed, has numerous connections with the oculomotor apparatus of the brain (e.g., Sparks and Pollack, '77; Goldberg and Robinson, '78; Wurtz and Albano, '80; Huerta and Harting, '84; Schiller, '84; Fuchs et al., '85).

Comparisons between species

The present results reveal that the subcortical connections of the frontal eye field are similar across the three species of Old (*Macaca fascicularis*) and New (*Saimiri sciureus* and *Aotus trivirgatus*) World monkeys studied. This similarity is remarkable because it holds for a large number of thalamic and brainstem structures, and because the similarity of connections also holds for specific aspects of the connections (e.g., the lateral part of the medial dorsal nucleus is connected with the frontal eye field both in the Old World monkey, where the lateral region is cytoarchitectonically distinct, and in New World monkeys, where such distinction is not apparent; also, in all monkeys the strongest projection to the superior colliculus is to layer four). The resemblance of even the details of connections with such a large number of subcortical structures suggest that these pathways have been conserved through evolution and, further, that this widespread system of interconnections, and therefore functioning has been maintained, as a unit. Finally, the large number of similarities in subcortical connections of the frontal eye fields in Old and New World monkeys supports the conclusion that the frontal eye fields of these two groups are homologous, that is, they were also present in an ancestor common to these lines.

Despite the overall connectional resemblance across these species, there are three obvious species differences. The first is that in Old World macaque monkeys, the posterior pretectal nucleus is the primary pretectal target of the frontal eye field, whereas in New World squirrel and owl monkeys, the anterior pretectal nucleus is the most densely labeled pretectal region following injections of tracers into the frontal eye field (although both nuclei received *some* input in New and Old World monkeys). Since the differential connections and functions of the pretectal nuclei are only poorly understood (Weber, '85), however, the functional implications of these species differences are unclear. Nevertheless, the presence of differential projections to both nuclei in Old and New World monkeys suggests that while their common ancester may have had both pathways, they evolved differentially in Old and New World lines. In this regard, the projection of the frontal eye field to the pretectum of a member of the family callithricidae might suggest when such differential evolution may have begun.

The second difference is that the subthalamic nucleus receives considerable input from the frontal eye field in the owl monkey and in the macaque monkey, but virtually no such input in the squirrel monkey. Thus, the projection from the frontal eye field to the subthalamic nucleus may have been lost through the evolution of *Saimiri.* This contention would be supported if such a projection were found in a callithricid monkey. From a functional standpoint, it is interesting that threshold current amplitudes were consistently higher in squirrel monkeys (typically 100–150 μA) than in owl or macaque monkeys (typically 30–40 μA). Although these observations may not be related, the subthalamic nucleus is known to innervate the substantia nigra (Nauta and Cole, '78) which, in turn, is known to disinhibit presaccadic cells in the deeper collicular layers (Hikosaka and Wurtz, '83b, '85a,b). Moreover, the substantia nigra projects to thalamic (the ventral anterior and medial dorsal) nuclei (Carpenter et al., '76; Ilinsky et al., '85), which serve visuomotor functions (Schlag-Rey and Schlag, '84; Schlag and Schlag-Rey, '84) and which are strongly interconnected with the frontal eye field (present results). Finally, some evidence suggests that visuomotor activity is present in the subthalamic nucleus, itself (Hikosaka and Wurtz, '83a; Delong et al., '85).

A final obvious species difference is that in macaque monkeys the frontal eye field projects densely to layer four of the superior colliculus, and more sparsely to layers five through seven. In the New World monkeys, the frontal eye field distributes axons only to layer four. Since the projection to the superior colliculus in both species of New World monkeys is limited to layer four, the possibilities exist that the projection to layers five through seven (1) was independently lost in the evolution of *Aotus* and *Saimiri*, (2) was not present in the ancestor common to these ceboid monkeys, (3) was not present in the ancestor from which callithricidae and cebidae evolved, or (4) was not present in the common ancestor of Old and New World monkeys, but was acquired through the evolution of *Macaca.* An obvious experiment which would shed light on this issue would be to determine the frontal eye field projection to the superior colliculus in a member of the New World monkey family callithricidae. If the projection to layers five through seven is present in the callithricid, it would lend support to possibilities 1 or 2, whereas the absence of such a projection might lend support to possibilities 3 or 4.

Functional considerations

The present data reveal the anatomical substrate for a wealth of physiological and behavioral findings from macaque monkeys that indicate that the frontal eye field and the deeper collicular layers have similar oculomotor functions (such as the initiation of saccades), and that they exert their influence on the oculomotor system in a parallel manner (e.g., Schiller, '77; Sparks and Pollack, '77; Schiller et al., '79, '80; Wurtz and Albano, '80; Albano and Wurtz, '81; Goldberg and Bushnell, '81b; Albano and Wurtz, '82; Albano et al., '82; Keating et al., '83; Schiller, '84; Bruce and Goldberg, '85; Bruce et al., '85). Specifically, the majority of subcortical structures that receive input from the frontal eye field also receive input from the deeper collicular layers (discussed in detail in the preceding section). These structures include the paramedian pontine reticular formation, which contains preoculomotor neurons (see Fuchs et al., '85). Nevertheless, this region receives only a sparse projection from the frontal eye field and a moderate projection from the deeper collicular layers (present results; Harting, '77). In contrast, a number of other structures, including visuomotor-related thalamic and pretectal nuclei (e.g., Benevento and Fallon, '75; Schlag-Rey and Schlag, '84; Schlag and Schlag-Rey, '84; Cowey and et., '84; Kato et al., '86), receive strong convergent input from the frontal eye field and superior colliculus (Benevento and Fallon, '75; Partlow et al., '77; Harting et al., '80; present results). Thus, in agreement with behavioral data (Albano and Wurtz, '82), the anatomical data indicate that the frontal eye field and superior colliculus exert their major parallel influence on structures other than the preoculomotor neurons of the paramedian pontine reticular formation. The present findings strongly suggest that similar mechanisms are operating in New World monkeys.

In addition to having oculomotor functions, it is interesting to note that many of the structures that receive convergent input from the frontal eye field and deeper collicular layers also participate in circuits subserving skeletomotor function (e.g., Akert et al., '79; Jurgens, '84; Schell and Strick, '84). While the extent to which oculomotor and skeletomotor circuits and functions overlap remains to be carefully assessed, such an assessment would be crucial in addressing such issues as how our movements are directed in space and how particular disease states differentially affect particular oculomotor and skeletomotor functions (e.g., Teravainen and Calne, '80a,b; Arbib et al., '85).

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