Brain Research Bulletin, Vol. 19, pp. 203–221. © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0361-9230/87 $3.00 + .00

Efferent Connections of the Rostral Portion of Medial Agranular Cortex in Rats

R. L. REEP,* J. V. CORWIN,† A. HASHIMOTO‡ AND R. T. WATSON§

**Departments of Physiological Sciences and Neuroscience, J-144, JHMHC*
University of Florida, Gainesville, FL 32610
†Department of Psychology, University of New Orleans, Lakefront, New Orleans, LA 70148
‡Department of Neuropsychiatry, Kinki University, Osaka 589, Japan
§Department of Neurology, College of Medicine, J-236, JHMHC
University of Florida, Gainesville, FL 32610

Received 23 April 1986

REEP, R. L., J. V. CORWIN, A. HASHIMOTO AND R. T. WATSON. *Efferent connections of the rostral portion of medial agranular cortex in rats.* BRAIN RES BULL **19**(2) 203–221, 1987.—This study of the rostral part of medial agranular cortex (AGm) was undertaken with two principal aims in mind. First, to delineate the efferent connections of AGm and compare these with the pattern of afferents defined by us in a previous study. Second, to provide a firmer basis for anatomical and functional comparisons with cortical regions in monkeys. Autoradiographic, horseradish peroxidase, and fiber degeneration techniques were used. Rostral AGm has a variety of corticocortical connections—with lateral agranular motor cortex (AGl); visual, auditory, and somatic sensory regions; and limbic/paralimbic areas including orbital, insular, perirhinal, entorhinal, retrosplenial and presubicular fields. The projections to orbital, perirhinal and entorhinal cortices are bilateral. Thalamic projections of rostral AGm are concentrated in the ventral lateral, central lateral, paracentral, mediodorsal and ventromedial nuclei. Moderate terminal fields are consistently seen in the reticular, anteromedial, central medial, gelatinosus, parafascicular, and posterior nuclei. More caudal projections reach the central gray, superior colliculus and pontine gray. The efferents of the adjacent AGl were also examined. Although many of these overlapped those of rostral AGm, there were no efferents to visual or auditory cortex and limbic/paralimbic projections were reduced. Thalamic projections were more focused in the ventral lateral and posterior nuclei and there were no terminal fields in the central gray or superior colliculus. Based on its afferent and efferent connections, role in contralateral neglect, and the results of microstimulation studies, rostral AGm can be viewed as a multimodal association area with strong ties to the motor system. On these structural and functional grounds, rostral AGm bears certain striking resemblances to the frontal eye field, supplementary motor, and arcuate premotor areas of monkey cortex.

Rat cerebral cortex Association cortex Frontal eye field Supplementary motor cortex
Autoradiography Efferents Neglect

MEDIAL agranular cortex (AGm) is a thin longitudinal strip of cortex positioned between the cingulate and lateral agranular areas. It overlies the cingulum bundle and extends from the frontal pole to the beginning of retrosplenial cortex. Cytoarchitecturally, AGm is characterized by its agranularity and pale staining layer III [13, 31, 44]. Zilles and his colleagues recognize a similarly located field which they refer to as Prcm [72] or, more recently, Fr2 [71]. The rostral portion of AGm (that part rostral to the anterior commissure) was called the 'shoulder cortex' by Leonard, and identified as part of prefrontal cortex due to its reciprocal connections with the mediodorsal thalamic nucleus [38]. This lesion-degeneration study was followed by the autoradiographic work of Krettek and Price [31]. Using the terminology of Rose, they referred to this cortical region as medial precentral cortex. Like Leonard, Krettek and Price found that the rostral portion of AGm receives input from MD, specifically from its lateral segment. We recently confirmed this in a retrograde tracing study [48], but found that most of the thalamic input to rostral AGm originates in the central lateral and ventral lateral nuclei rather than in MD. These results, together with several functional studies, emphasize a motor rather than prefrontal role for AGm.

Recent microstimulation mapping studies have shown that AGm is a component of sensorimotor cortex, involved primarily with movements of the vibrissae, eyes, head, upper lip and rhinarium [13, 17, 44, 53]. These observations have prompted the suggestion that AGm represents the frontal eyefield in rats [13, 17, 44]; this was first proposed by Leonard [38] on anatomical grounds. Rostral AGm also contains a secondary hindlimb area which lies adjacent to a more laterally placed secondary forelimb area [44]. Together, these secondary representations may constitute a rodent supplementary motor area, as suggested by Neafsey *et al.* [44]. This interpretation is consistent with the views of Donoghue and Wise [13] and Sanderson *et al.* [53].

ABBREVIATIONS

AC	anterior cingulate cortex
ac	anterior commissure
ACC	nucleus accumbens
AGl	lateral agranular motor cortex
AGm	medial agranular cortex
Ald	dorsal agranular insular cortex
Alp	posterior agranular insular cortex
AM	anteromedial thalamic nucleus
AOP	anterior olfactory nucleus, posterior part
APA	arcuate premotor area
AV	anteroventral thalamic nucleus
BL	basolateral amygdala
CG	central gray
cg	cingulum bundle
CL	central lateral thalamic nucleus
CLA	claustrum/endopiriform nucleus
CP	caudate-putamen
cp	cerebral peduncle
DR	dorsal raphe nucleus
ERC	entorhinal cortex
fm	forceps minor of corpus callosum
fr	fasciculus retroflexus
FS	fundus striati
fx	fornix
G	gelatinosus thalamic nucleus
GP	globus pallidus
IAM	interanteromedial thalamic nucleus
ic	internal capsule
Ig	granular insular cortex
IL	infralimbic cortex
LD	lateral dorsal thalamic nucleus
LP	lateral posterior thalamic nucleus
mcp	middle cerebellar peduncle
MD	mediodorsal thalamic nucleus
MG	medial geniculate
ml	medial lemniscus
MO	medial orbital cortex
mt	mamillothalamic tract
P	posterior thalamic nucleus
PC	paracentral thalamic nucleus
PF	parafascicular thalamic nucleus
PN	pontine nuclei
PR	perirhinal cortex
Pr5	principal sensory nucleus, trigeminal nerve
PS	presubicular cortex
RH	rhomboid thalamic nucleus
RSag	retrosplenial cortex, agranular part
RSg	retrosplenial cortex, granular part
RT	reticular thalamic nucleus
SI	first somatic sensory cortex
SII	second somatic sensory cortex
SCdg	superior colliculus, deep gray
SCig	superior colliculus, intermediate gray
SCiw	superior colliculus, intermediate white
SCo	superior colliculus, optic nerve layer
SCsg	superior colliculus, superficial gray
scp	superior cerebellar peduncle
sm	stria medullaris
SMA	supplementary motor area
SNc	substantia nigra, pars compacta
SNr	substantia nigra, pars reticulata
ST	subthalamic nucleus
st	stria terminalis
s5	sensory root, trigeminal nerve
TE	cortical area TE
V	visual cortex
VA	ventral anterior thalamic nucleus
VL	ventral lateral thalamic nucleus
VLO	ventrolateral orbital cortex
VM	ventromedial thalamic nucleus
VO	ventral orbital cortex
VPM	ventral posterior medial thalamic nucleus
ZI	zona incerta

In an earlier study, we found that rostral AGm receives extensive cortical input from primary sensory areas [48]. This and other afferent patterns, a suspected projection to superior colliculus first noted by Leonard [38], and its functional role in eye and head movements, suggested to us that rostral AGm may correspond, in some essential structural and functional aspects, to specific regions of monkey arcuate cortex. Furthermore, unilateral lesions of rostral AGm result in neglect to visual, auditory and somatic sensory stimuli presented in the contralateral hemispace [7–9]; lesions of arcuate cortex also produce neglect [62,64].

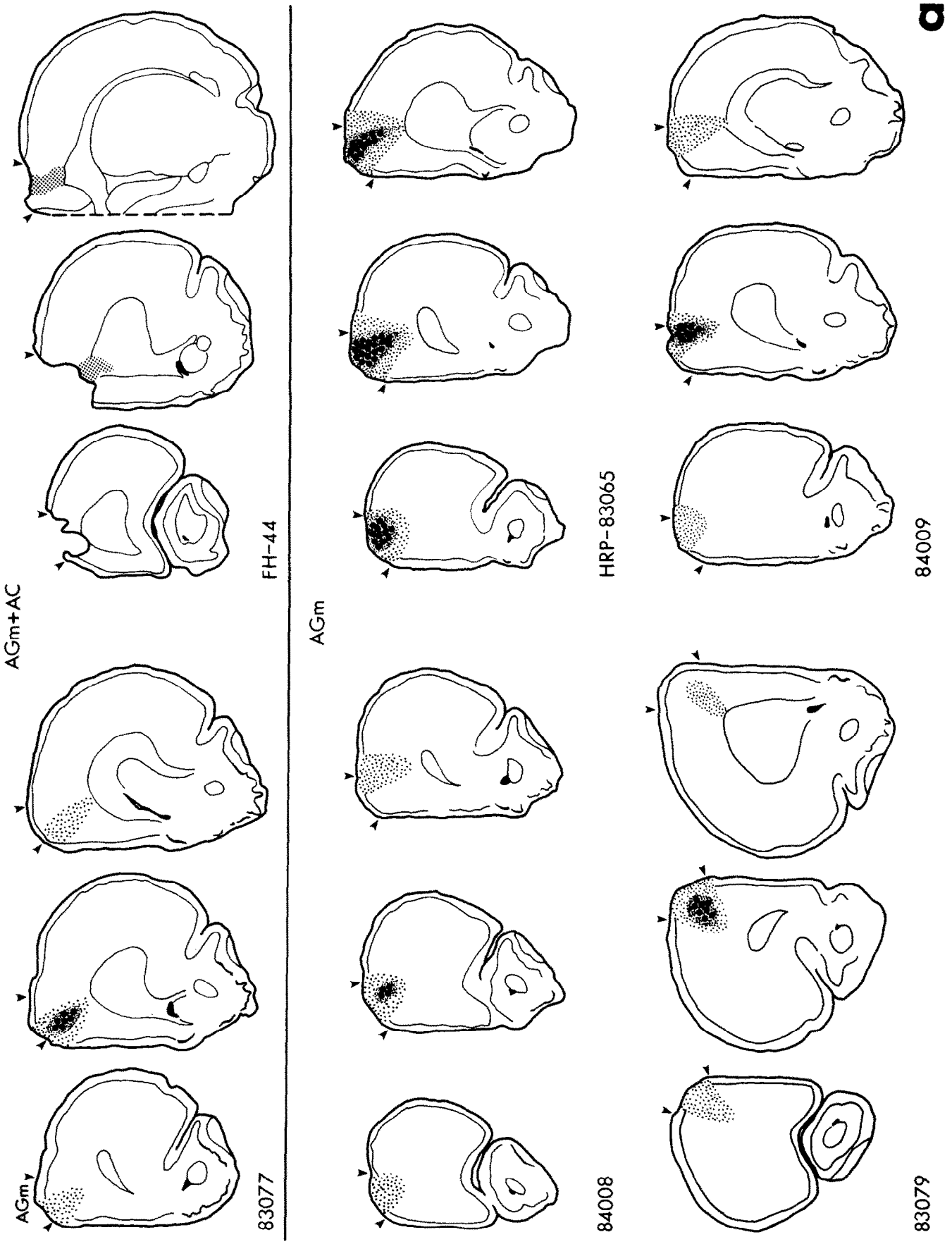
The present study of the rostral part of AGm was undertaken with two principal aims in mind. First, to further delineate the neuronal connections of this region and compare the pattern of its efferent connections with the afferents defined by us in a previous study [48]. Second, to provide a firmer basis for anatomical comparison with cortical regions in monkeys.

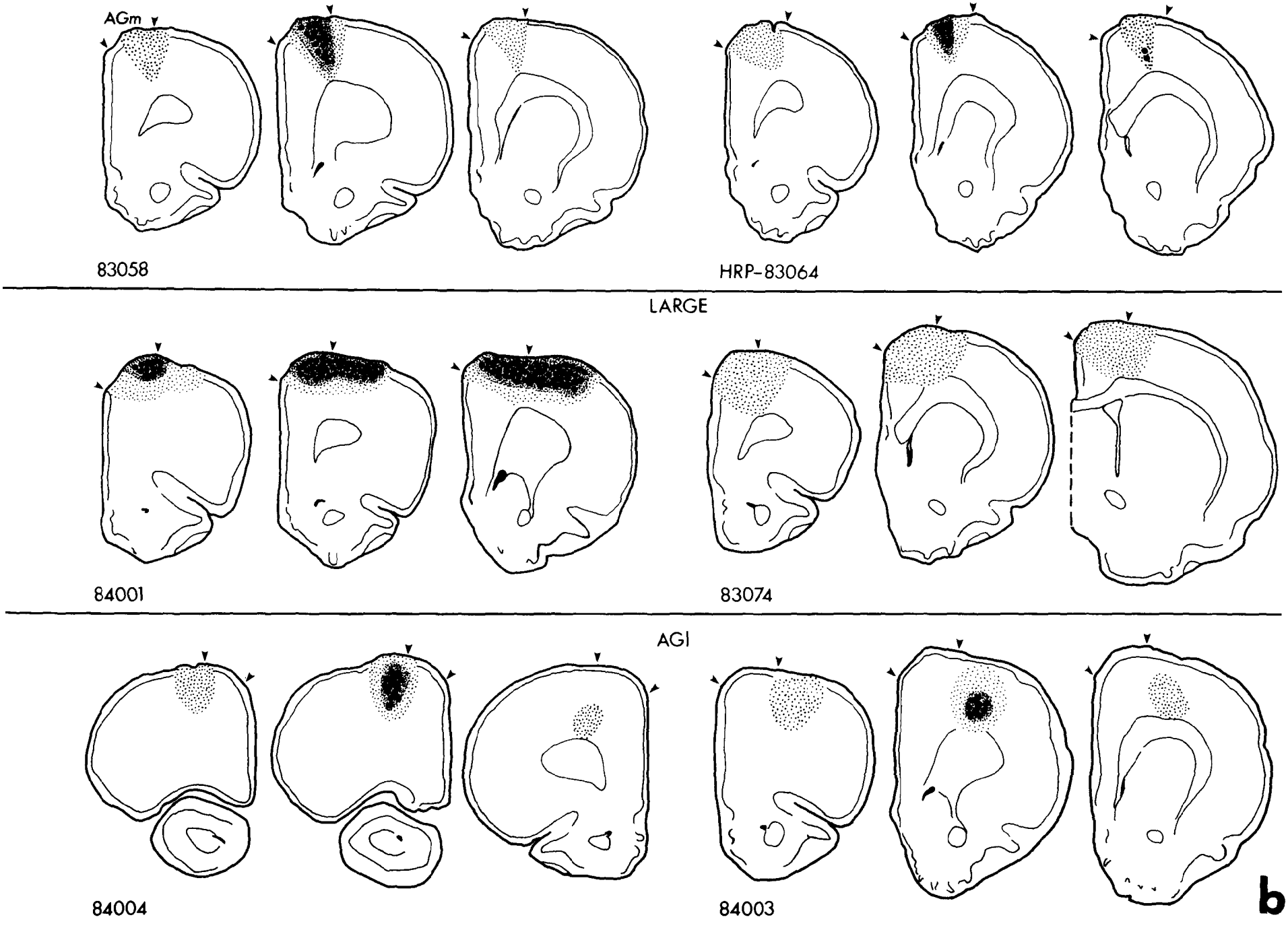
METHOD

Three techniques were employed in this study—degeneration argyrophilia, anterograde transport of tritiated

FACING AND FOLLOWING PAGES

FIG. 1. Selected injection sites arranged in four mediolateral categories, ranging from those which encroached medially upon anterior cingulate cortex (AGm + AC) to those centered in lateral agranular cortex (AGl). Within each category, brains are arranged according to rostro-caudal position of the injection site, with three sections per brain. All injections were on the right side except for brains 83079 and 84004. One lesion case (FH-44) is presented, as well as two HRP cases (HRP-83064, HRP-83065). The remaining cases are injections of ^{3}H-amino acids. Large dots represent zone 1; dense stipple, zone 2; light stipple, zone 3 (see text).


AGm+AC
AGm
AGm
83077
FH-44
84008
HRP-83065
83079
84009
a


AGm
83058
HRP-83064
LARGE
84001
83074
AGl
84004
84003
b

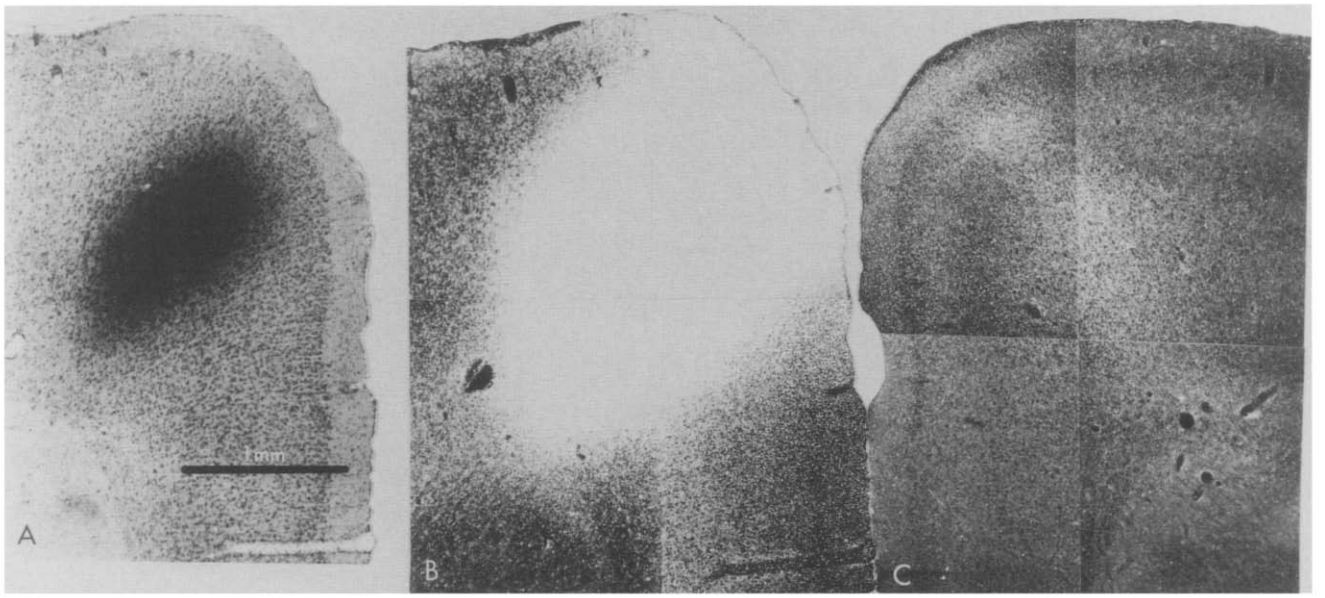


FIG. 2. The areal size of terminal field labeling in contralateral AGm indicates that the effective size of the injection site is best represented by its brightfield image. (A) Brightfield photomicrograph of the injection site in brain 83079. (B) Darkfield image of the same injection site. (C) Darkfield image of contralateral side of the same section. In case 83079, ^{3}H-leucine was delivered iontophoretically into AGm, with 6 day survival time.

amino acids, and anterograde transport of horseradish peroxidase (HRP).

In the brains of six hooded (Long Evans) rats with contralateral neglect produced by unilateral lesions of AGm, the pattern of degeneration was examined using the method of Fink and Heimer [15]. After 5–7 days post-surgical survival the subjects were perfused intracardially with buffered saline followed by 10% formalin. After 7 days fixation in 10% formalin, the brains were placed in 30% sucrose/10% formalin until they sank (2–3 days). They were then embedded in gelatin-albumin and frozen sections cut at 25 μm in the coronal plane. Sections were placed in 5% formalin and after refrigeration for 7 days at 5°C, were stained using procedure 1 of Fink and Heimer [15]. The distribution (and overlap) of fiber vs. terminal degeneration was used to guide the interpretation of autoradiographic and horseradish peroxidase material, in which this distinction is often difficult or impossible to make.

Fifteen animals (albino and hooded) were used in the analysis of autoradiographic material. Stereotaxic injections of ^{3}H-leucine or an equal mixture of ^{3}H-leucine/^{3}H-proline (New England Nuclear or ICN; 20–50 μCi/μl) were made using pressure injections of 0.05–0.10 μl volumes through a Hamilton syringe, or iontophoretic delivery through glass pipettes having tip diameters of 10–25 μm, and using 1–2 μA current pulses (0.5 sec duration, 1 pulse/sec, over 10–20 min). A range of survival times from 2–6 days was used. Following intracardial perfusion with buffered saline and 10% formalin, post-fixation for one week, and 2–3 days in 30% sucrose/10% formalin, frozen coronal sections were cut at 30 μm thickness. Further processing for autoradiography, and the designation of observed label as being in fiber bundles or terminal fields, was done the same as in previous studies [50].

Eight animals (albino and hooded) were used in the anterograde analysis of horseradish peroxidase material. Briefly, 50% HRP (Sigma type VI) or 5% WGA-HRP (Sigma) was deposited in AGm using 1–2 μA current pulses delivered through glass pipettes of 10–25 μm tip diameter. Two day survival times were used and processing done as described previously [49], using the low temperature tetramethylbenzidine method of deOlmos [45].

In this report we have defined cortical areas according to several sources in an attempt to combine the best maps from different studies. Frontal pole regions are delineated according to Krettek and Price [31], somatic sensory and motor areas according to Donoghue and Parham [12] and Sanderson *et al.* [53], cingulate and retrosplenial fields according to Vogt and Peters [61], and most remaining areas according to Zilles and co-workers [71,72]. Thalamic nuclear boundaries were determined by reference to the maps of Bold *et al.* [5], Herkenham [21], Jones and Leavitt [24], and Paxinos and Watson [46]. Spinal projections were not examined in this study.

RESULTS

Injection Sites

Selected injection sites used in the present analysis are illustrated in Fig. 1. For descriptive purposes, three zones are delineated within the injection sites. Large dots indicate the central core of the autoradiographic or HRP injection site

FOLLOWING PAGES

FIG. 3. Distribution of autoradiographic label in brain 83058, as illustrated on tracings of spaced coronal sections. This case represents a pressure injection of ^{3}H-leucine, with 2 day survival time.

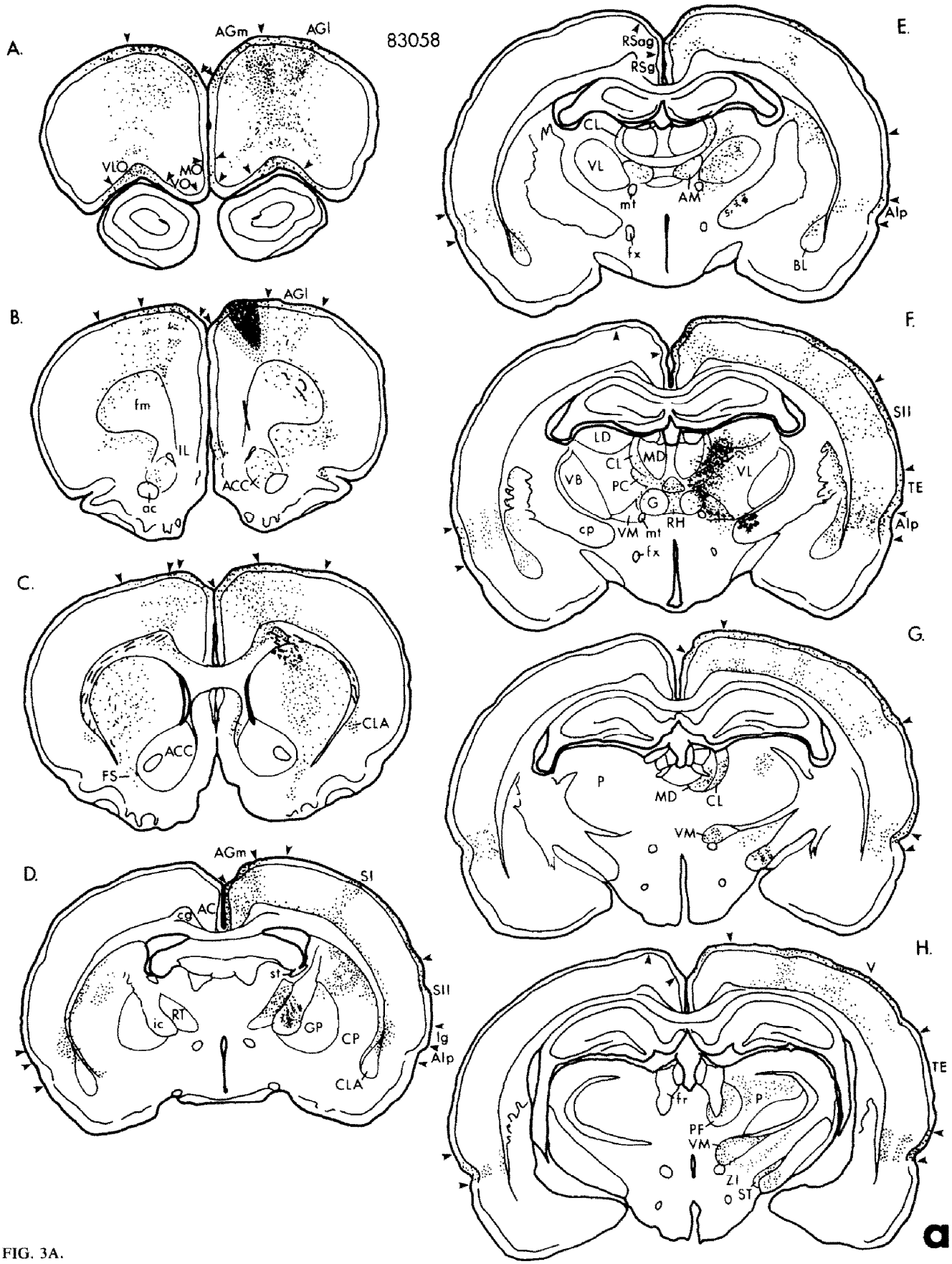
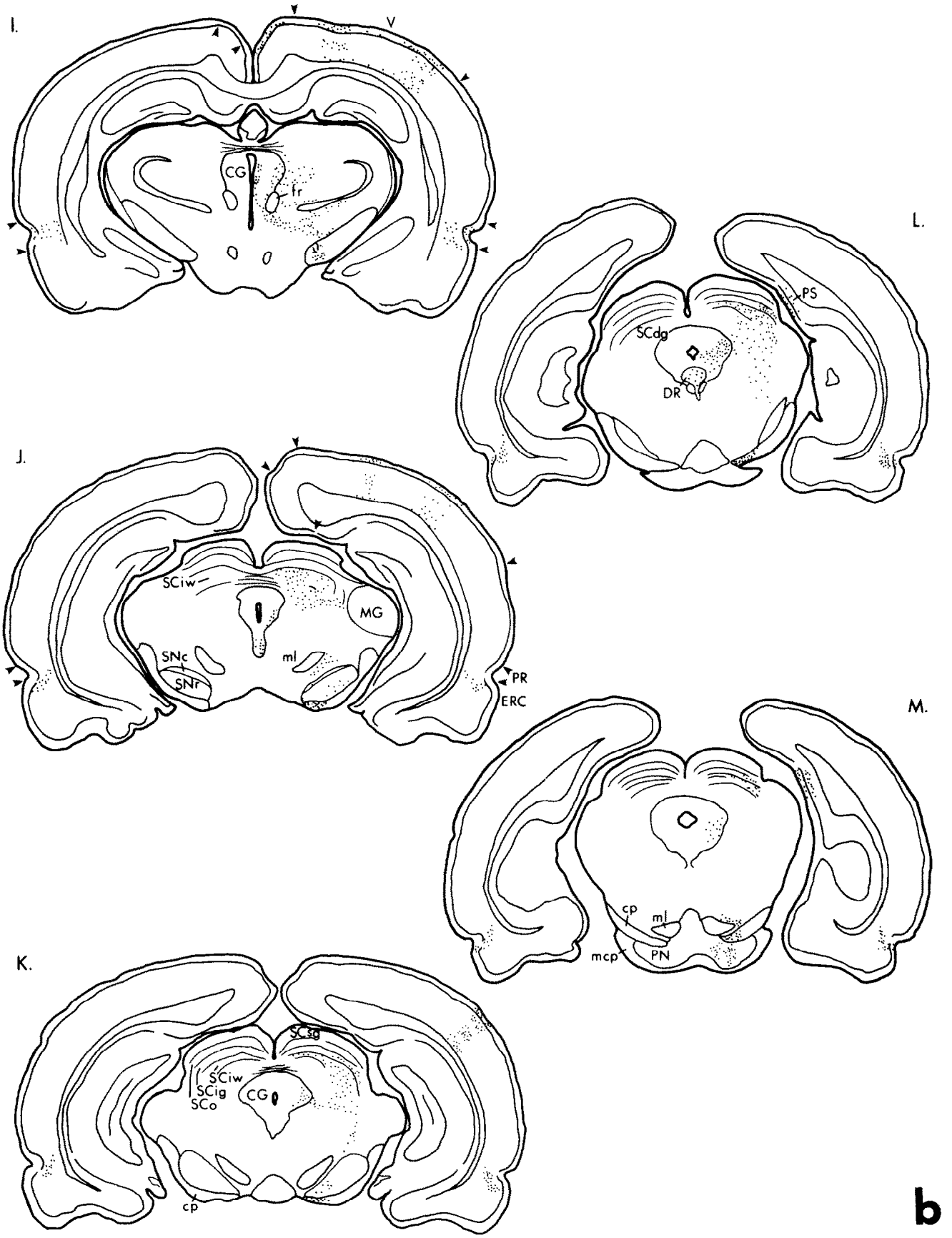

A.
AGm
AGl
83058
VLO
MO
VO
B.
AGl
fm
IL
ac
ACC
C.
CLA
ACC
FS
D.
AGm
SI
cg
AC
st
SII
ic
RT
GP
CP
Ig
Alp
CLA
E.
RSag
RSg
CL
VL
mt
AM
Alp
fx
BL
F.
SII
LD
MD
CL
VL
VB
PC
TE
G
Alp
cp
VM
mt
RH
fx
G.
P
MD
CL
VM
H.
V
TE
fr
P
PF
VM
ZI
ST
a

FIG. 3A.


I.
V
CG
fr
L.
PS
SCdg
DR
J.
SCiw
MG
SNc
SNr
ml
PR
ERC
M.
cp
ml
mcp
PN
K.
SCsg
SCiw
SCig
SCo
CG
cp

b

FIG. 3B.

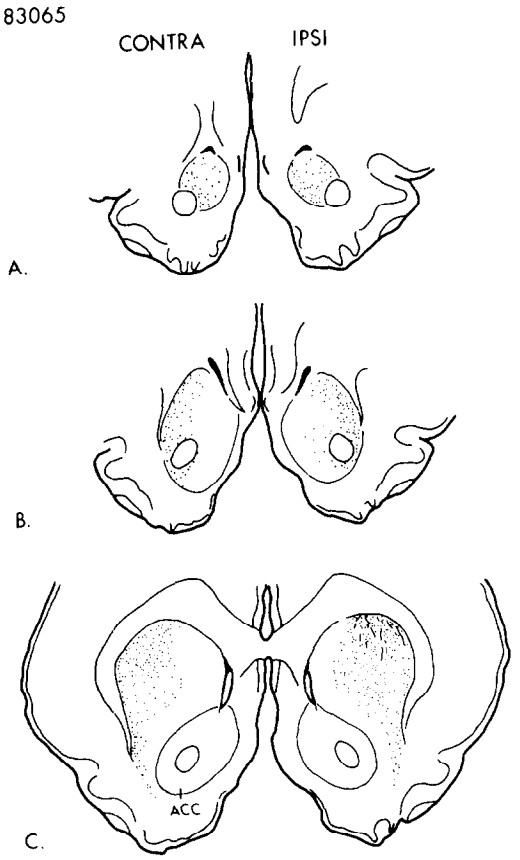


FIG. 4. Anterograde horseradish peroxidase label in nucleus accumbens and surrounding area, brain 83065. HRP was delivered iontophoretically into AGm, with 2 day survival time.

(zone 1), which is seen upon brightfield examination to contain dense label in cell bodies and the surrounding neuropil. Dense stipple denotes zone 2, which contains lightly labeled cells and neuropil. Light stippling illustrates the extent of zone 3, an outer halo of moderate to sparse neuropilar label visible upon darkfield examination. In autoradiographic brains, the distribution of contralateral homotopical cortical labeling indicates that significant corticocortical transport appears to occur only from zones 1 and 2, and to a greater extent from zone 1 than 2 [50]. This conclusion is also supported by Fig. 2, where the areal size of contralateral labeling corresponds more closely to the brightfield than the darkfield image of the injection site. Although it is not possible to directly compare autoradiographic and HRP injection sites in this regard, a similar relationship appears to hold between HRP injection sites and the distribution of contralateral homotopical label, in our material.

Efferent Projections of AGm

Brain 83058. The overall pattern of projections from the rostral portion of AGm is well illustrated by brain 83058, in which the injection site is centered in rostral AGm with slight encroachment of AGl by zone 3 (Fig. 1). Zones 1 and 2 of this injection site extend through all the cortical layers of AGm. Contralateral homotopical label is largely restricted to AGm (Fig. 3A–C), indicating the effective size of the injection site.

Rostrally, there is a strong bilateral projection to ventral lateral orbital cortex (VLO), heavier ipsilaterally (Fig. 3A,B). A similar labeling pattern is found in the claustrum and overlying posterior insular cortex (Fig. 3C–I). More caudally, this bilateral system of fibers terminates in the ventral perirhinal cortex and the most dorsal portion of lateral entorhinal cortex (Fig. 3J–M). It appears that fibers reach VLO by curving around the head of the forceps minor, traversing the deep gray matter of the frontal pole (Fig. 3A,B), while those to the claustrum, insular cortex and perirhinal/entorhinal cortex travel in the white matter of the forceps minor (Fig. 3B,C).

Another bilateral system of fibers distributes to the ventral and dorsal striatum, and amygdala. As shown in Fig. 3B, the most rostral portion of nucleus accumbens receives light input from AGm, more prominent ipsilaterally, with fibers apparently arriving via the descending limb of the cingulum bundle [11]. The density of labeling in nucleus accumbens is greater in brain 84008, in which the injection site is centered in far rostral AGm. As shown by anterograde transport of HRP in brain 83065 (Fig. 4), label is uniformly distributed throughout the most rostral portion of nucleus accumbens, but quickly assumes a lateral position and eventually merges with label in the fundus striati as one proceeds caudally. The dorsal central region of the head of the caudate-putamen contains a dense accumulation of label, with a moderate contingent of more laterally placed fibers that enter the fundus striati, and more caudally, the basolateral amygdala (Fig. 3C–F).

Ipsilateral cortico-cortical projections include light terminal fields in medial orbital and infralimbic cortex (Fig. 3A–C), and a moderate to dense field in the lateral agranular cortex (AGl) adjacent to AGm (Fig. 3A–C). Rostral AGm projects to caudal AGm ipsilaterally, but not contralaterally (Fig. 3D). Caudally, this label is continuous with a projection to the agranular portion of retrosplenial cortex [61] (Fig. 3E–H). Further caudally, there is a light terminal field seen in the presubicular cortex (Fig. 3L,M), but it is not clear by what route fibers reach this region.

Widespread projections from AGm to somatic sensory areas SI and SII (see [13,65]) terminate in well defined columnar patches which extend through all cortical layers (Fig. 3D–F). Many of these patches are found in dysgranular regions, which are characterized by a relatively sparse concentration of granule cells in layer IV. Similar columns are found in visual cortex areas 17,18a and 18b (Fig. 3G–K), but mostly in granular rather than dysgranular regions.

Fibers to all ipsilateral cortical areas travel in the deep cortical gray matter just superficial to the white matter of the corpus callosum and external capsule, rather than in the cingulum bundle or other white matter.

Projection fibers from AGm to subcortical nontelencephalic structures traverse the caudate-putamen and then collect in the internal capsule (Fig. 3C,D). Within the thalamus, the most rostral label is located in the reticular nucleus (Fig. 3D). However, since fibers destined for VL and other more medially placed thalamic nuclei obviously traverse the reticular nucleus, much of this label probably represents fiber labeling rather than a terminal field (see discussion of brain FH-44 below).

A dense accumulation of grains is found bilaterally (though much heavier ipsilaterally) in the intralaminar paracentral and central lateral nuclei. Moderate bilateral labeling extends rostrally into the anteromedial nuclei and ventrally into the gelatinosus and ventromedial nuclei. The closely related midline central medial and rhomboid nuclei contain

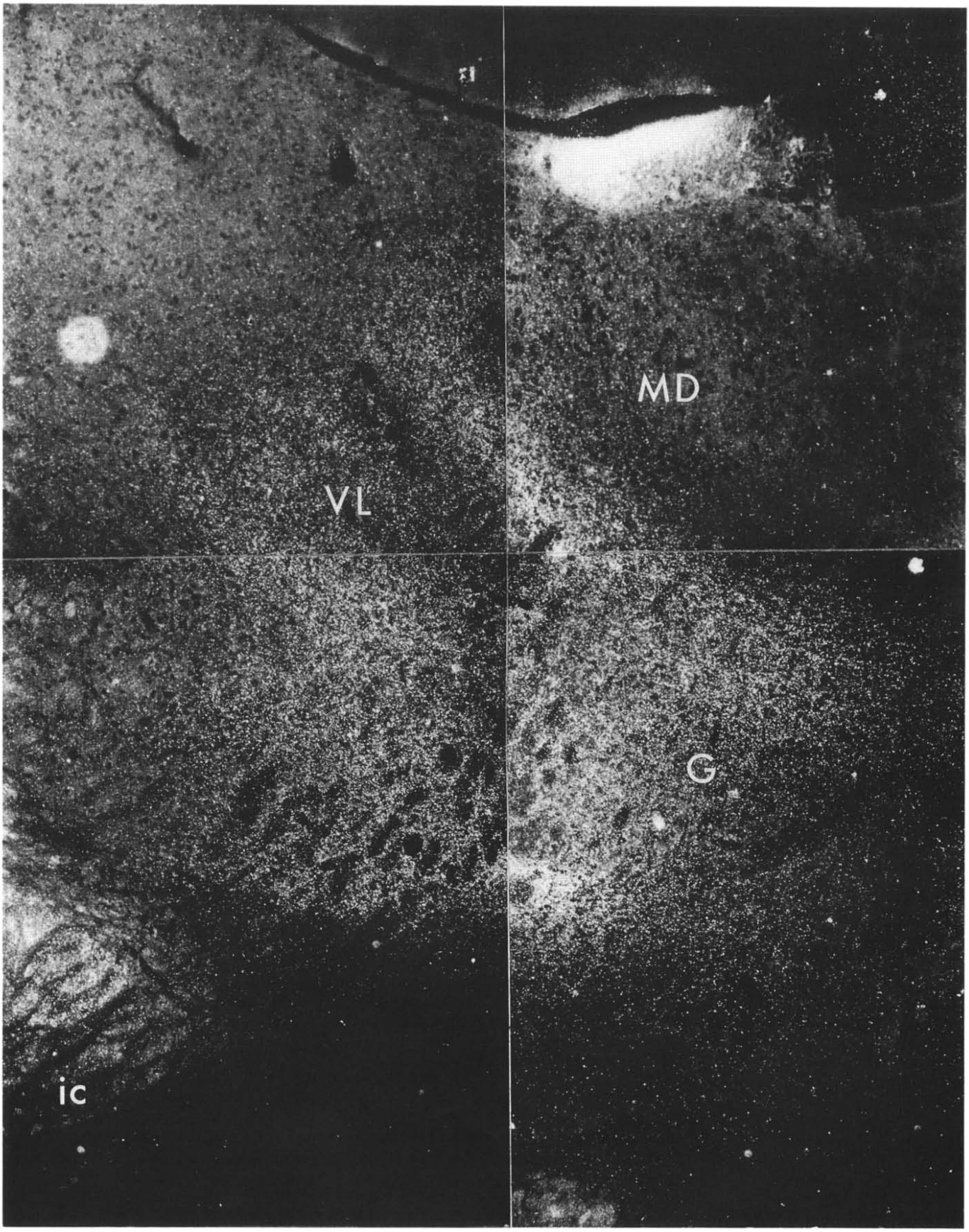


FIG. 5. Distribution of autoradiographic silver grains in the rostral thalamus of brain 83079. In addition to widespread labeling in the ventral lateral and gelatinosus nuclei, note the dense band of silver grains in the paracentral and central lateral nuclei, between MD and VL. Bright region dorsal to MD is stria medullaris. Darkfield photomicrograph of label on the ipsilateral side. Iontophoretic injection of ^{3}H-leucine, 6 day survival time.

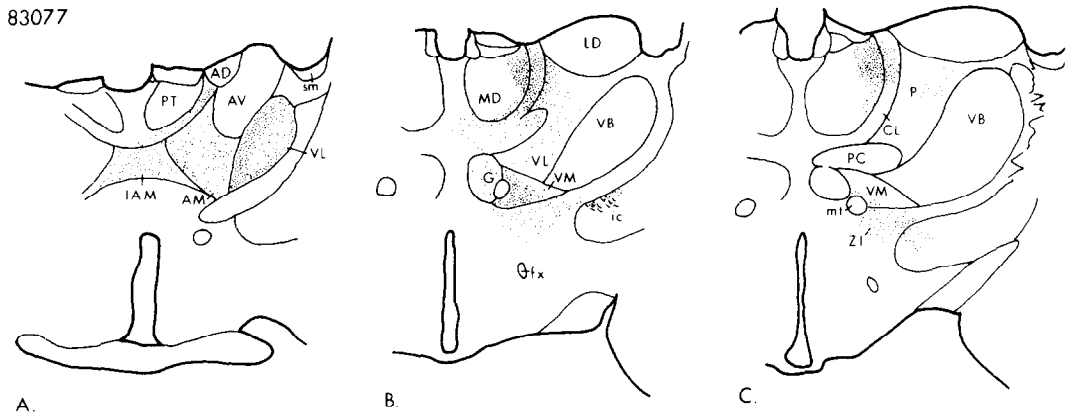


FIG. 6. Principal thalamic labeling in brain 83077. This medially placed injection resulted in a rostromedial shift in thalamic labeling, with heavier involvement of the anterior and mediodorsal nuclei compared to cases with injections centered in AGm. This case involved iontophoretic delivery of ^{3}H-leucine, with 4 day survival time.

moderate label as well. Ipsilateral thalamic labeling is prominent in the ventral lateral nucleus, widespread rostrally (Fig. 3E) and localized to medial VL more caudally (Fig. 3F). Moderate ipsilateral label is present in the posterior portion of paralamellar MD, ventral LD, the parafascicular nucleus, and posterior nucleus. Label in the parafascicular nucleus appears to continue medially into the rostral central gray (Fig. 3I).

As fibers continue caudally in the medial part of the internal capsule, they distribute lightly to the subthalamic nucleus and moderately to the region of zona incerta and the fields of Forel (Fig. 3F–I). From caudal zona incerta, fibers reach the midbrain central gray and dorsal raphe nuclei by two routes. As shown in Fig. 3I, one group of fibers takes a medial course, passing beneath fasciculus retroflexus to enter the rostral central gray. The second group sweeps dorsomedially and terminates more caudally (Fig. 3I–M). Both groups of fibers appear to intermingle with those continuing to this region from the parafascicular and posterior nuclei of the thalamus.

Fibers leaving the cerebral peduncle terminate sparsely in substantia nigra pars reticulata (Fig. 3J,K) and moderately in the medial pontine nuclei (Fig. 3M). No labeling was seen caudal to this region.

The superior colliculus receives a moderate projection from AGm, via a fiber bundle continuing caudally from the posterior thalamus, and another which sweeps dorsally from the caudal region of zona incerta (Fig. 3J–M). The former bundle's contribution is apparently much greater, as evidenced by its much greater density. Within the superior colliculus, label is most concentrated in the intermediate white matter layer (heavier laterally), and the lateral portion of the intermediate gray layer.

Results From Other AGm Brains

Among the other brains in the AGm group (Fig. 1), the pattern of thalamic projections was virtually identical to that described above for case 83058. This was true for HRP as well as autoradiographic cases. However, parafascicular and central gray labeling was not seen in brain 84009. Figure 5 illustrates thalamic labeling in brain 83079, at a level corresponding to Fig. 3F. In brain 83077 the injection site is located in far medial AGm and encroaches somewhat on anterior cingulate cortex (Fig. 1). As shown in Fig. 6, the ventral lateral, intralaminar, and posterior nuclei receive less dense projections in this case than in brains such as 83058 and 83079, where the injection site is centered in AGm. However, the projection to MD is much denser and more rostrally located than in these other cases. There is also a more widespread, though moderate, projection to AM and IAM.

The pattern of corticocortical labeling showed some variation among the brains in the AGm group. The projections to the claustrum, VLO, AGl, RS, PR/ERC and visual cortex were the most consistent, while there was more variable involvement of the somatic sensory and auditory areas. For example, in brains 84008 and 84009 the VLO and RS projections were robust but other corticocortical labeling was much less pronounced than in case 83058. This may be due to the somewhat rostral location of the injection sites in these two brains, since cases HRP-83065 and 83079 also had relatively light corticocortical labeling and rostral injection sites. Conversely, brains 83058 and HRP-83064 had well defined labeling in all the cortical areas described and also had relatively caudal injection sites.

Labeling of the superior colliculus showed considerable variability. The brains with the clearest SC label were 83058, 83074, 83079 and 84001. In all these cases silver grains were present over the intermediate and deep layers of lateral SC, as described above for cases 83058. Aside from labeling in the central gray, SC and the pontine gray, no other brainstem labeling was seen in the AGm group.

Brain FH-44. Animal FH-44 represents a case in which behavioral testing revealed contralateral multimodal neglect following a unilateral lesion of rostral AGm [7]. The lesion (Fig. 1) extends through the entire extent of rostral AGm, encompassing the PCm component of MD projection cortex as defined by the study of Krettek and Price ([31]; see their Figs. 5 and 7). The bulk of the lesion is indicated in Fig. 1 by missing cortical tissue, while adjacent gliotic tissue is shown hatched. The primary lesion did not encroach upon the white matter, although the area of gliosis does include the cingulum bundle and forceps minor to some extent. The distribution of degeneration profiles is illustrated in Fig. 7.

In most regions, the labeling pattern is very similar to that seen in the autoradiographic and HRP brains mentioned above. A principal exception to this is the absence of appar-

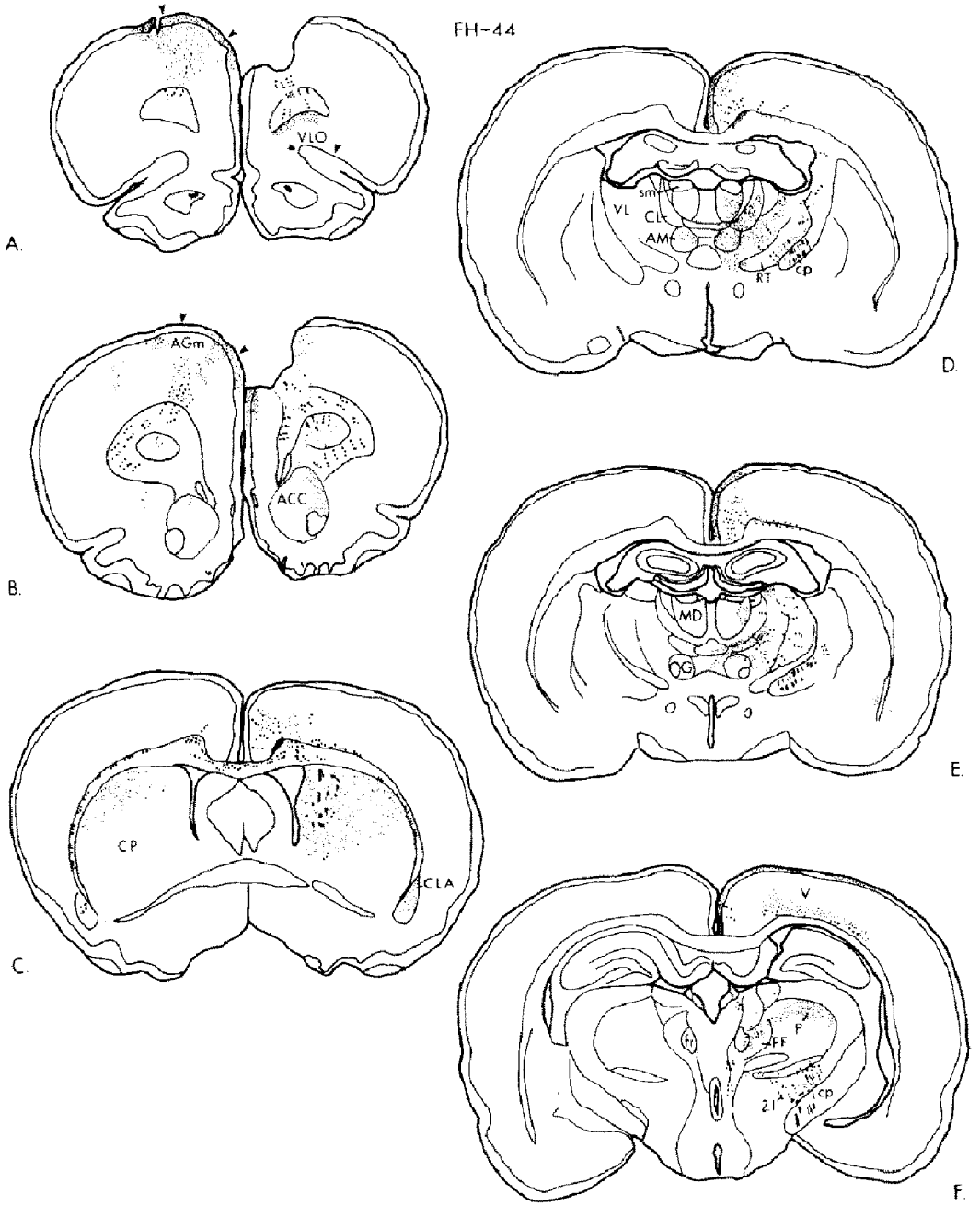


FIG. 7. Distribution of argyrophilia from fiber (dots and lines) and terminal (stipple) degeneration products in brain FH-44. Suction lesion of AGm, with 7 day survival time.

ent label in somatosensory, insular and entorhinal cortices. However, label is present in contralateral AGm, ipsilateral caudal AGm, VLO, and visual cortex. This may indicate a relatively light innervation density in the 'missing' cortical regions or less sensitivity of the lesion-degeneration technique. Another unexplained variation is the lack of apparent label in the superior colliculus.

The presence of fiber and terminal degeneration in the thalamic reticular nucleus (Fig. 7D) suggests that in addition to fibers passing medially to distribute to other thalamic nuclei, some terminations are made in the reticular nucleus. Similar logic applies to mixed fiber and terminal degeneration seen in zona incerta and the deepest layer of visual cortex (Fig. 7F).

FOLLOWING PAGES

FIG. 8. Distribution of autoradiographic label in brain 84003, charted on spaced coronal sections. ^{3}H-leucine was delivered by pressure injection, and a 5 day survival time used.

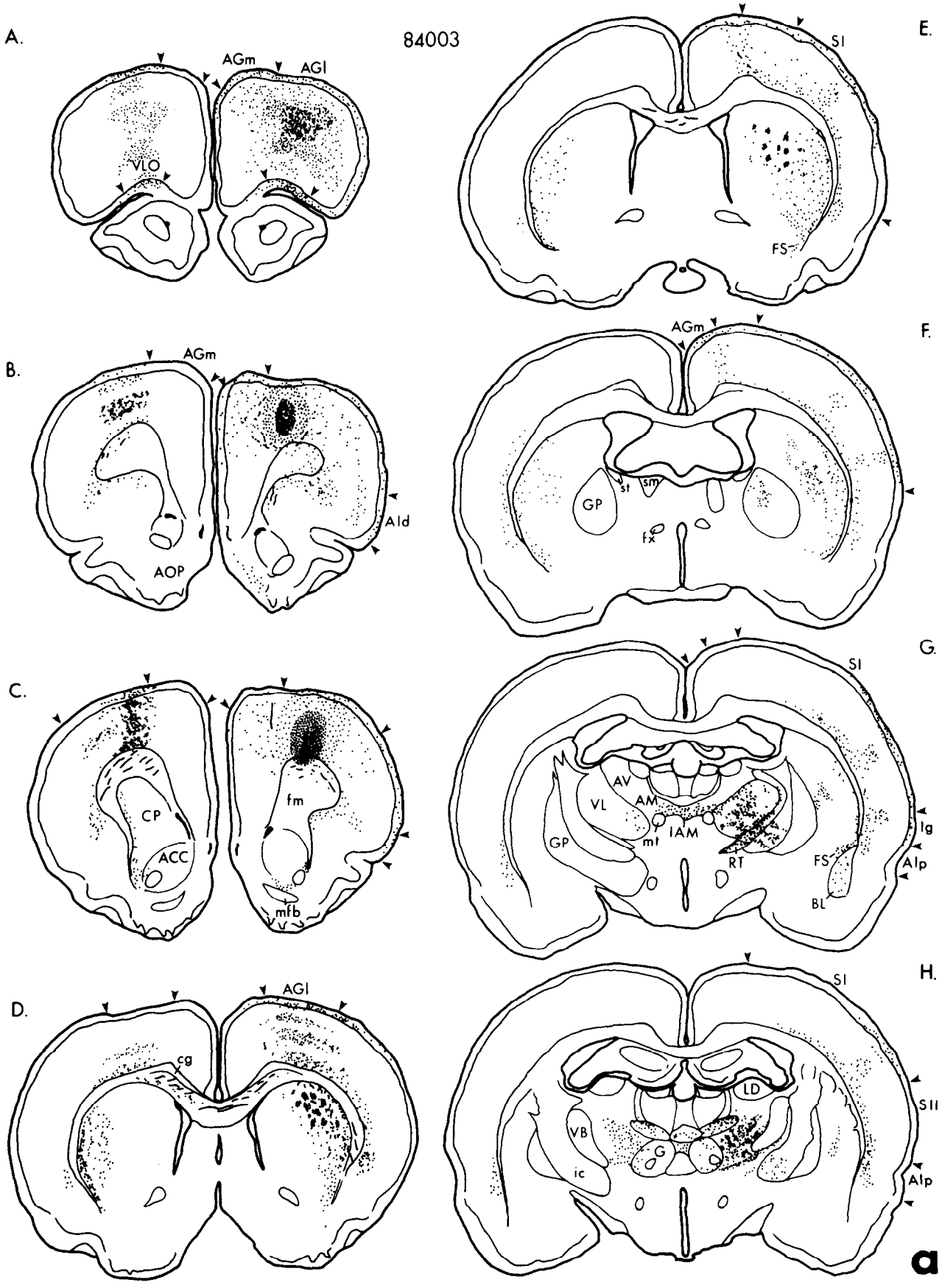

A.
84003
AGm
AGl
VLO
B.
AGm
AId
AOP
C.
CP
ACC
fm
mfb
D.
AGl
cg
E.
SI
FS
F.
AGm
GP
sf
sm
fx
G.
SI
AV
VL
AM
GP
mt
IAM
RT
FS
BL
lg
Alp
H.
SI
LD
VB
ic
G
SII
Alp
a

FIG. 8A.

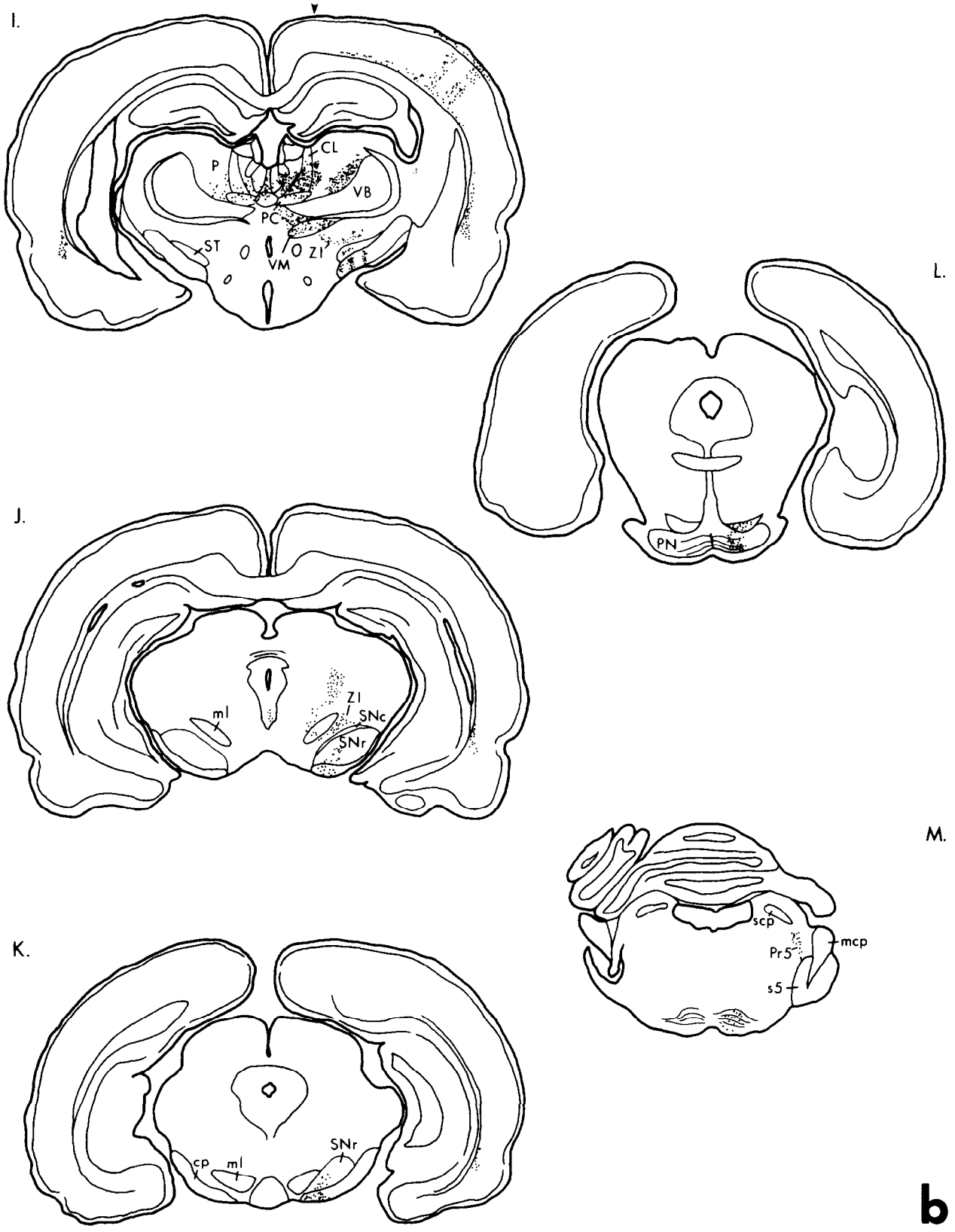


FIG. 8B.

Efferent Projections of AGl

Brain 84003. Lateral agranular cortex lies laterally adjacent to AGm, and the injection site in brain 84003 affects AGl with little or no encroachment on AGm (Fig. 1). This is illustrated in Fig. 8A–D, where contralateral homotopical label is present over AGl but not AGm.

Bilateral projections reach VLO, the claustrum, and insular cortex, as was described above for AGm. Ipsilaterally, moderate to dense label is seen in the entire extent of AGl, and in the ventrally adjacent dorsal agranular insular cortex (Fig. 8A–D). AGm and anterior cingulate cortex receive a lighter innervation. As shown most clearly in Fig. 8A, the cortico-cortical projections to VLO, AGl and AGm travel via the deepest portion of the polar gray matter, just rostral to the white matter of the forceps minor. Fibers to the claustrum and insular cortex reach their destinations via the forceps minor (Fig. 8B,C). These differing trajectories were noted above in similar projections from AGm. Curiously, the posterior portion of the anterior olfactory nucleus is lightly labeled (Fig. 8B, C), though it is not clear by what route fibers reach this nucleus.

A bilateral system of fibers distributes to the caudate-putamen, continues through the fundus striati, and sends a very light projection to the ipsilateral amygdala (Fig. 8C–H).

Somatic sensory cortex (SI) receives extensive input from AGl, terminating in spaced columns (Fig. 8E–I). Some of these are located in dysgranular regions. The posterior component of taste cortex, area Ig is also moderately labeled (Fig. 8G). There is no label seen in area TE, retrosplenial or visual cortex.

Thalamic labeling is seen most rostrally in the reticular, interanteromedial, and ventral lateral nuclei (Fig. 8G). Bilateral label continues caudally in the ventral lateral nucleus and appears to be denser and more widely distributed than in the AGm projection to VL. Moderate to dense bilateral terminal fields are also seen in the paracentral and central lateral intralaminar nuclei and in posterior MD, while the gelatinosus nuclei are only lightly labeled (Fig. 8H,I). Midline labeling continues caudally from the interanteromedial nucleus into the central medial and paraventricular nuclei (Fig. 8G–I). Ipsilateral label is fairly dense in the posterior and ventromedial nuclei, light in zona incerta and the subthalamic nucleus. From caudal zona incerta, label may be seen traversing the medial lemniscus and terminating more dorsally in a region which is transitional in location between the posterior thalamic nucleus and the midbrain reticular formation (Fig. 8J).

Continuing caudally, light fiber labeling is seen in the pars reticulata of substantia nigra, the medial pontine nuclei, and the principal sensory nucleus of the trigeminal nerve (Fig. 8J–M). No label was seen in the superior colliculus.

Other Brains. In case 84004 the injection site is centered in AGl but encroaches upon the lateral part of AGm. The pattern of projections was quite similar to that seen in case 84003, however the caudate projection was more dorsocentral in location and there was a more prominent projection to the posterior nucleus of the thalamus. In cases 84001 and 83074, both AGl and AGm are affected throughout all layers. In both these brains there is extensive cortical and subcortical labeling in areas projected to by AGl and AGm alone. For instance, retrosplenial and visual cortex contain prominent label characteristic of projections from AGm. Also, somatic sensory cortex (SI) is heavily labeled, more typical of projections from AGl.

DISCUSSION

Our present findings relate to three principal themes which are treated in further detail below. First, the connections of AGm are distinct from those of the adjacent areas AGl and AC, though there is some overlap among them. Second, rostral AGm is unique among rodent MD projection fields on anatomical grounds. Third, common organizational features appear when the connections and known functions of rostral AGm are compared with those of certain cortical areas in monkeys and cats.

Mediolateral Topography

The pattern in which the efferents from rostral AGm are distributed provides further anatomical evidence that this cortical area is distinct from the laterally adjacent AGl (lateral agranular motor cortex) and medially adjacent anterior cingulate cortex (AC). Although there is considerable overlap in the projections from AGm and AGl, striking differences exist. Most notably, AGl has no direct connections with the retrosplenial, visual or auditory cortices, or with the superior colliculus, while AGm does. Compared to AC [3,4], AGm has much more extensive corticocortical connections, and major thalamic connections with VL and the intralaminar nuclei rather than with the anterior nuclear group. However, both AGm and AC have reciprocal connections with MD ([3, 4, 48, 58], present report). Other connections of AGm and AC overlap in retrosplenial and visual cortex [60], and in the superior colliculus [4], though they have differing topographical distributions within these regions. Thalamic topography is treated in greater detail below.

Corticocortical Connections

Traditionally, prefrontal cortex has been defined as the cortical projection field of the thalamic mediodorsal nucleus (MD). More recently, a variety of findings have necessitated reevaluation of this concept [47], and our findings concerning AGm further illustrate this need with regard to the organization of rat frontal cortex. For example, if rostral AGm is viewed as part of rodent prefrontal cortex by virtue of being a component of the MD projection field, it must be distinguished from the other MD projection areas because of its more extensive corticocortical connections. On the basis of topographic location, cytoarchitecture and connections, most areas of rodent MD projection cortex can be classified as paralimbic [47, 49, 50]. The prelimbic, anterior cingulate and agranular insular components of the MD projection field have reciprocal connections among themselves and with limbic or paralimbic regions such as the retrosplenial, presubicular, perirhinal and entorhinal cortices [3, 4, 49, 50]. Rostral AGm exhibits similar limbic/paralimbic connections with the retrosplenial, presubicular, ventrolateral orbital, insular and perirhinal/entorhinal areas. However it also has reciprocal connections with visual, auditory and somatic sensory cortex, as described here and in a previous report [48]. Thus, rostral AGm may represent the only multimodal association field of rodent MD projection cortex; certainly its corticocortical connections are consistent with this view. Thus, there may be little significance in referring to 'MD projection cortex' as a unitary entity [28,47]. As discussed in another section below, it may be more accurate on a variety of grounds to consider AGm as a premotor or supplementary motor area.

Previous studies have shown that cortical projections to the perirhinal/entorhinal region arise from a variety of areas, several of which are components of the MD projection field. Efferents from AGm to perirhinal/entorhinal cortex were previously reported by Deacon *et al.* [10]. They found that while other cortical projections are directed solely to ipsilateral PR/ERC, AGm has a bilateral projection. On the other hand, fluorescent tracer studies indicate that bilateral projections to the perirhinal region originate not only from AGm, but also from the medial, orbital, and agranular insular portions of MD projection cortex [39,54]. This is confirmed to some extent by the findings of Beckstead [4]. Sarter and Markowitsch [54] found that efferents from AGm (identified by them as AGl) originate from columns of neurons that extend through all the layers of AGm. With respect to topography, cases ER5 and ER8 of Deacon *et al.* [10] (see their Figs. 6 and 7) confirm our present finding that fibers from AGm terminate in the ventral perirhinal/dorsal entorhinal area, thus overlapping the projections from VLO and agranular insular cortex (see their Figs. 8, 12 and 13; [50]). Interestingly, they also found that a small parietal field projects to this same region (see their Fig. 13i). We have found a similarly located parietal area that has reciprocal connections with AGm (see Fig. 2F of [48]; Fig. 3F,G of the present report). Since this region appears to be in the border zone between somatic sensory and visual cortex, it may represent a higher order association area. This would be consistent with Jones and Powell's [25] finding in monkeys that perirhinal cortex receives direct input from association isocortex (as well as from certain limbic and paralimbic regions).

AGm participates in a network of cortical connections which may be viewed in terms of visual/paralimbic interactions. Complex reciprocal connections exist among visual, retrosplenial, cingulate, and para/postsubicular cortical areas in rats, as discussed by Vogt and Miller [60]. They also showed that VLO receives input from visual area 18b and projects to retrosplenial cortical areas 29c,d. Our present findings and those of other studies [4, 40, 48] demonstrate that AGm interacts with this circuitry via reciprocal connections with visual (areas 17, 18a, 18b) and retrosplenial cortices, and the intriguing bilateral reciprocal connections with VLO. AGl (at least its medial portion) projects bilaterally to VLO, but apparently this is non-reciprocated [12]. Projections from AGm to retrosplenial cortex (areas 29c,d) were previously found by Vogt and Miller [60] using retrograde tracing. Likewise, case ER5 of Deacon *et al.* [10] represents a ^{3}H-amino acid injection that affects AGm. Terminal field label was seen in retrosplenial and visual cortex (in addition to projections to orbital and perirhinal/entorhinal fields). Comparing AGm with neighboring cortical regions, there is also a strong projection to RS from the medially adjacent anterior cingulate cortex [14,60], but not from the laterally adjacent AGl (present report).

Overall, the cortical efferents of AGm are more widespread than its cortical inputs. This is illustrated by the non-reciprocated projections from AGm to the posterior insular, entorhinal, and presubicular cortices [48]. All of these areas may be considered limbic or paralimbic cortex [47], and are sites of convergence for multimodal cortical projections [25].

It is intriguing to speculate on the relationship between the multimodal corticocortical connections of AGm and the fact that multimodal neglect results from unilateral lesions of AGm [7–9]. Our present results and those of an earlier study [48] indicate that AGm has strong ties to the motor system. Since neglect has been shown to have sensory and motor components in primates and humans [62–64], it is possible that in some way AGm is a key link between multimodal sensory inputs and organized motor output.

Thalamus and Zona Incerta

Two major trends may be noted in the topographic pattern of thalamic labeling. First, the efferents of AGm are densest in those thalamic regions which provide input to AGm. These include the central medial, central lateral, mediodorsal, ventral lateral, ventromedial, and gelatinosus nuclei [21,48]. Our present results, together with those of Donoghue and Parham [12], indicate that the same pattern applies for AGl, in which case reciprocal connections are made with the ventral lateral, central lateral, ventromedial, and posterior nuclei. Second, there is a distinct mediolateral topography in the pattern of distribution of corticothalamic projections which originate from AC, AGm, and AGl. Efferents from AC terminate predominately in the anteromedial, parataenial, mediordorsal, and reuniens nuclei [4]. Those from medial AGm (encroaching on AC) terminate most heavily in rostral VL, CL, and MD, more lightly in AM, VM, and the posterior nucleus (see Fig. 6). From central and lateral AGm, efferents are heaviest in intermediate VL, PC, CL, VM, and the posterior nucleus (see Fig. 3). From AGl, the projection is widespread in VL, caudal CL, and P, moderate in VM (see Fig. 8). Thus, in the projections from AC, AGm and AGl, there is a mediolateral shift in terminal field location from AM and MD to CL, VL and P. This is clearly seen by comparing Figs. 6B, 3F, and 8H (the sections representing maximal thalamic labeling from AC/medial AGm, central-lateral AGm, and AGl, respectively). This overlapping topographical corticothalamic pattern closely resembles the organization of thalamic afferents to these cortical areas [3, 12, 24, 48]. Furthermore, it is reminiscent of Kievit and Kuypers' [28] description of monkey thalamocortical relationships, wherein each cortical region of the frontal lobe is associated with a longitudinal band of cells that traverses several thalamic nuclei, and more rostral cortical areas receive input from more medial bands of cells. Siegel *et al.* [58] previously found labeled cells in anterior cingulate cortex, AGm, and medial AGl following an HRP injection which was centered in MD but apparently encroached upon the central lateral nucleus (see their Fig. 1). This distribution is consistent with the known thalamic relationships of these cortical areas as described above.

Labeling in the thalamic reticular nucleus probably represents, in part, terminal fields. This nucleus receives input from a variety of cortical areas, and these projections are organized in a topographic, overlapping fashion. Carman *et al.* [6] made cortical lesions in rabbits, and found dense fiber degeneration and fine preterminal degeneration in the thalamic reticular nucleus. Projections from the general region including AGm and AC were found to terminate in the rostral portion of the thalamic reticular nucleus (see their cases RR1, R71, and R82). Jones [23] concluded that in rats, cats and monkeys, terminations are made in the reticular nucleus as corticothalamic fibers traverse it on their way to more medially placed thalamic targets. Furthermore, he found topographic relationships among the cortex, reticular nucleus, and dorsal thalamic nuclei. For instance, in cats the rostral portion of the reticular nucleus surrounds the ventral anterior nucleus (a position corresponding to that to which rat AGm projects most heavily), and receives input from fibers whose major thalamic targets are MD, CM, CL, and VM (see his Fig. 8).

We found that zona incerta receives moderate projections from AGm and AGl, as described above (Figs. 3, 8, 9). Retrograde labeling studies have shown that frontal cortical inputs to zona incerta arise from AC, AGm, and AGl, while more caudal cortical projections originate in retrosplenial cortex, SI, and area 18 of visual cortex [52,57]. Kawana and Watanabe [27] have identified six subdivisions of zona incerta. While the distribution of label is generally diffuse in our material, it is somewhat localized to the dorsal subregion in brain 83058 (Fig. 3H,I), and to the ventral subregion in brain 84003 (Fig. 9I). In both cases label extends caudally into the pars caudalis and pars retro-polaris of Kawana and Watanabe. However, in brain 83058 this label continues dorsally to reach the superior colliculus, and medially into the central gray (Fig. 3, I–K). In our autoradiographic material it is not possible to distinguish fiber from terminal labeling within zona incerta; however, both fiber and terminal degeneration were identified in this region in brain FH-44.

Superior Colliculus

Leonard [38] indicated the existence of a projection in rats from the 'shoulder' cortex (which includes rostral AGm) to the deep layers of the superior colliculus (SC). More recently, it has been found [4, 18, 20, 70] that the prelimbic, anterior cingulate and somatic sensory cortices project to the intermediate and deep layers of SC. The prelimbic and anterior cingulate terminal fields are densest in the medial three-quarters of the intermediate gray layer (see Figs. 2, 4, 5 of [4]), while the projection from somatic sensory cortex terminates patchily in the central portion of the intermediate layer [70]. In the present study, we have found that the AGm terminal field is localized to the lateral one-quarter of the intermediate gray (Fig. 3, K–M). Roger and Cadusseau [52] reported that extensive input reaches zona incerta from the intermediate and deep layers of lateral superior colliculus in rats. Thus in rats there is interconnection between rostral AGm, zona incerta, and the intermediate and deep layers of lateral superior colliculus. In cats, neurons in the far lateral portion of SC play a significant role in motor aspects of head orientation [56]. If this is true in rats as well, it is interesting to note that this is the same response being tested in the behavioral neglect paradigm [7].

In monkeys the corticotectal projection originates from several frontal regions, including arcuate cortex (areas 8 and 45), the dorsal and ventral components of area 6 (which includes the supplementary motor and arcuate premotor areas), cortex dorsal and ventral to the principal sulcus and in its depths, and a portion of the rostral medial wall [32,37]. Terminals distribute throughout the laminae of SC in monkeys [34,37], but only to the intermediate and deep layers in rats (present report; [4, 38, 70]) and cats [30,56]. Illing and Graybiel [22] report that in cats, frontotectal and nigrotectal fibers converge upon acetylcholinesterase-rich zones of the intermediate gray. Although terminals are distributed throughout all layers of monkey SC, a superficial to deep topography exists such that inferior arcuate cortex (areas 45 and 8A) projects most heavily to superficial and intermediate layers; middle and dorsal arcuate cortex (areas 8A and 8B) to the intermediate layers [1, 34, 37]. The cortex dorsal to the principal sulcus projects mainly to the deep intermediate layer, deep layer, and central gray; cortex of the dorsal convexity and medial wall to the deep layer and central gray [37].

Mediolateral topography was suggested by the findings that inferior arcuate cortex projects most heavily to lateral SC, while more dorsal arcuate cortex projects medially [37]. Komatsu and Suzuki [29] found that the lateral projection is focused in rostral superior colliculus, and note that functionally, rostral SC and inferior arcuate cortex are concerned with the central visual field, lateral SC with the lower part of the visual field. Similarly, the medial projection is located in caudal SC, and both caudal SC and dorsal arcuate cortex are associated with the peripheral visual field, medial SC with the upper visual field. The supplementary motor portion of area 6 projects to far medial SC, while the arcuate premotor component of area 6 terminates in a small far lateral field [32].

It appears that on the basis of laminar termination, AGm corresponds most closely to the 8A–8B border zone, while according to mediolateral topography it resembles the more ventral 8A proper, and the arcuate premotor area.

Leichnetz *et al.* [37] described two trajectories by which corticotectal fibers reach SC in monkeys. A dorsal transthalamic system distributes to the thalamus and at the level of fasciculus retroflexus divides into a medial component which enters the central gray, and a lateral component that continues to the posterior thalamus and SC. A ventral pedunculotegmental system leaves the medial cerebral peduncle and courses dorsally, just lateral to the medial lemniscus, terminating in SC and the lateral central gray. We have identified both of these fiber systems in the rat (Fig. 3) and corroborate their finding that the dorsal transthalamic system appears to contribute most heavily to the corticotectal projection.

Central Gray and Brainstem

Our finding of a projection to the central gray from AGm but not AGl is consistent with the retrograde results of Hardy and Leichnetz [20]. They found labeled small pyramidal cells in layer V of the orbital, insular, prelimbic, anterior cingulate and medial agranular cortices, but not in AGl, after HRP injections into the central gray. Anterograde studies [4,50] likewise confirm this organization. Together, these cortical areas constitute the MD-projection cortex in rats. In monkeys cortical projections to the central gray originate in all areas of prefrontal cortex except the rostral inferior convexity and most of orbital cortex; the superior temporal gyrus also projects to the central gray [19].

Our finding that projections from AGm and AGl to the pons are localized to the medial half of the pontine nuclei is congruent with the conclusion of Wiesendanger and Wiesendanger [67,68] that frontal cortical regions project to medial portions of the pontine nuclei, while posterior cortical areas project more laterally. Furthermore, we corroborate their finding that there is a patchy distribution of corticopontine terminations (compare our Fig. 3M with Fig. 8 of [68]).

General Comparison with Monkeys and Cats

Rostral AGm shares functional and anatomical features with certain areas of monkey cerebral cortex, most notably supplementary motor cortex (SMA-the medial wall portion of area 6), the arcuate premotor area (APA-the ventral convexity region of area 6), and area 8 (arcuate cortex). However, compared to these areas of monkey cortex, AGm has limited brainstem connections. This is particularly true with respect to regions associated with cranial nerve motor nuclei [32, 35, 36]. Therefore, direct anatomical comparison of AGm with regions of monkey cortex must rely primarily upon cortical, thalamic and collicular connections.

SMA. Rostral AGm is related to monkey SMA in that

both are laterally adjacent to anterior cingulate cortex, are agranular, have corticospinal projections and a relatively high stimulation threshold for producing topographically organized motor movements [13, 16, 53, 66]. In macaque and squirrel monkeys, reciprocal thalamic connections of SMA are made with VA, VL, paralamellar MD and posterior thalamus [26, 32, 55, 69]. In macaques, it has been shown that thalamic afferents to rostral SMA involve the intralaminar nuclei and MD to a greater extent than do the afferents to caudal SMA [69]. Other subcortical connections of SMA differ between macaque and squirrel monkeys. In macaques, SMA efferents reach zona incerta, the dorsal central gray, medial superior colliculus, and the pontine gray, but not the intralaminar nuclei [32]. In squirrel monkeys, there are bilateral reciprocal connections with intralaminar nuclei and the claustrum, and projections from SMA to zona incerta and the pontine gray, but not to superior colliculus [26]. Both macaque and squirrel monkeys have projections from the region of SMA to various brainstem areas associated with oculomotor function [26, 32, 35, 36].

With respect to corticocortical connections, the anatomical study of Jurgens [26] in squirrel monkeys has shown SMA to receive cortical afferents from ventrolateral orbital cortex, arcuate and motor cortex, prefrontal areas 9 and 44, cingulate cortex, and parietal areas 5 and 7. SMA cortical efferents distribute primarily to motor, arcuate, and cingulate cortex. In rhesus monkeys, Kunzle [32] found cortical projections from SMA to dorsomedial prefrontal cortex, arcuate and motor cortex, the cingulate and retrosplenial areas, and parietal cortex.

In cats, the medial wall portion of area 6aβ appears to correspond to SMA (see [52]). Like rostral AGm, this cortical area borders anterior cingulate cortex and is the most dorsal portion of MD projection cortex (see [47]). Horseradish peroxidase studies have shown that area 6aβ receives thalamic input from VA, VL, CL, MD, VM, the parafascicular-centromedian nucleus, and the posterior thalamus [41, 43, 59]. Rinvik's [51] anterograde degeneration study indicates corticothalamic projections fron 6aβ to the reticular nucleus, VA, VL, CL, lateral MD, parafascicular-centromedian nucleus, and VPM. On the basis of these thalamic relationships, and its projection to the superior colliculus, the medial wall portion of cat area 6aβ closely resembles rostral AGm.

APA. The arcuate premotor area (APA) was identified by Muakkassa and Strick [42] as one of four somatotopically organized premotor areas having direct input to motor cortex. Like SMA, APA has thalamic connections with VA, VL, CL, paralamellar MD and zona incerta, but topographically these are somewhat different [55]. Kunzle's [32] case 75-163 indicates that cortical projections of APA are directed primarily to orbital cortex, and inferior convexity of prefrontal cortex, motor cortex, and insula and perirhinal cortex. In addition to oculomotor-related brainstem projections [35,36], other brainstem efferents include the ventral central gray and far lateral superior colliculus.

Area 8. Within area 8, Barbas and Mesulam [2] identified a rostral (superior) field on the border of 8A and 8B, and a caudal (inferior) field consisting of 8A proper. The subcortical afferents to these two areas are similar; both receive thalamic input from lateral MD, PC, VL and the pulvinar, but only the caudal field also receives input from VA and the claustrum. Projections from area 8 reach VA, VL, dorsolateral MD, PF and zona incerta in the thalamus, and to the central gray, superior colliculus and pontine gray [1,33]. In addition, area 8 has widespread projections to brainstem regions involved with oculomotor function [35,36]. Regarding corticocortical connections, the rostral field of area 8 has principal input from auditory association, retrosplenial, and orbital cortex, while the caudal field receives input predominately from visual association and intraparietal sulcus cortices [2]. Kunzle and Akert [33] found that area 8 projects to the dorsal bank of the principal sulcus, the depths of the intraparietal sulcus, and to the region of the superior temporal sulcus.

Although it is not possible to directly compare the connections of rat and monkey cerebral cortex, it is clear that the pattern of connections embodied by rostral AGm is not represented by a single cortical field in monkeys. Instead, within the more differentiated primate brain are several cortical regions that possess one or more of the key traits which together uniquely identify rostral AGm in rats. In broad terms, SMA, APA and area 8 are all similar to AGm with regard to claustral, diencephalic, central gray and collicular connections. However, in reference to the topographical distribution and relative density of these subcortical connections, AGm appears to resemble most closely caudal area 8 of the rhesus monkey and SMA of the squirrel monkey. Rostral area 8 has no claustral input and its afferents from MD originate more centrally than do those to caudal area 8 [2]. The efferents of rhesus SMA do not appreciably involve the intralaminar nuclei, and there is little if any terminal field in zona incerta. Similarly, the projection from APA does not heavily involve the intralaminar nuclei, and is more ventrally located in MD than the projections to this nucleus from SMA and area 8.

Several conclusions may be drawn with reference to corticocortical connections. First, no single area of primate cortex embodies the corticocortical pattern seen in AGm. In a broad sense, visual connections are most extensive in caudal area 8; auditory in rostral area 8, somatic sensory in SMA, motor in SMA and APA, and paralimbic in rostral area 8, SMA and APA. Second, primate isocortical connections of SMA, APA and area 8 are made with association areas of the occipital, temporal and parietal regions, whereas AGm has connections with primary sensory fields. This is reasonable considering that secondary and high order sensory areas are small or absent in the rat brain.

In summary, rostral AGm is similar to area 8A of monkey arcuate cortex in the overall pattern of its cortical and thalamic connections, and in its projection to the superior colliculus. The thalamic connections of rostral AGm are strikingly like those of monkey SMA, however the cortical projections of SMA emphasize motor and cingulate cortex rather than frontal, parietal and temporal association areas (or primary sensory areas). Finally, rostral AGm and monkey APA both have projections to orbital, insular, perirhinal and motor cortices, and the far lateral superior colliculus. Functionally, rostral AGm shows characteristics of both SMA and the arcuate cortex. As noted previously, these include a relatively high threshold for eye and head movements upon microstimulation, and contralateral neglect following lesions. We conclude that rostral AGm in rats is a multimodal association area whose structural and functional attributes correspond in essential ways to SMA, APA and area 8A in monkeys.

ACKNOWLEDGEMENTS

We thank Laura Line Reep for her artistic contributions on the figures. This research was supported by the University of Florida Division of Sponsored Research and by the Maxwell Fund.

REFERENCES

1. Astruc, J. Corticofugal connections of area 8 (frontal eye field) in Macaca mulatta. *Brain Res* **33:** 241–256, 1971.
2. Barbas, H. and M-M. Mesulam. Organization of afferent input to subdivisions of area 8 in the rhesus monkey. *J Comp Neurol* **200:** 407–431, 1981.
3. Beckstead, R. M. Convergent thalamic and mesencephalic projections to the anterior medial cortex in the rat. *J Comp Neurol* **166:** 403–416, 1976.
4. Beckstead, R. M. An autoradiographic examination of corticocortical and subcortical projections of the mediodorsal-projection (prefrontal) cortex in the rat. *J Comp Neurol* **184:** 43–62, 1979.
5. Bold, E. L., A. J. Castro and E. J. Neafsey. Cytoarchitecture of the dorsal thalamus of the rat. *Brain Res Bull* **12:** 521–527, 1984.
6. Carman, J. B., W. M. Cowan and T. P. S. Powell. Cortical connexions of the thalamic reticular nucleus. *J Anat* **98:** 587–598, 1964.
7. Corwin, J. V., S. Kanter, R. T. Watson, K. M. Heilman, E. Valenstein and A. Hashimoto. Apomorphine has a therapeutic effect on neglect produced by unilateral dorsomedial prefrontal cortex lesions in rats. *Exp Neurol* **94:** 683–698, 1986.
8. Crowne, D. P. The frontal eye field and attention. *Psychol Bull* **93:** 232–260, 1983.
9. Crowne, D. P., C. M. Richardson and G. Ward. Brief deprivation of vision after unilateral lesions of the frontal eye field prevents contralateral inattention. *Science* **200:** 527–530, 1983.
10. Deacon, T. W., H. Eichenbaum, P. Rosenberg and K. W. Eckmann. Afferent connections of the perirhinal cortex in the rat. *J Comp Neurol* **220:** 168–190, 1983.
11. Domesick, V. B. The fasciculus cinguli in the rat. *Brain Res* **20:** 19–32, 1970.
12. Donoghue, J. P. and C. Parham. Afferent connections of the lateral agranular field of the rat motor cortex. *J Comp Neurol* **217:** 390–404, 1983.
13. Donoghue, J. P. and S. P. Wise. The motor cortex of the rat: cytoarchitecture and microstimulation mapping. *J Comp Neurol* **212:** 76–88, 1982.
14. Finch, D. M., E. L. Derian and T. L. Babb. Afferent fibers to rat cingulate cortex. *Exp Neurol* **83:** 468–485, 1984.
15. Fink, R. P. and L. Heimer. Two methods for selective silver impregnation of degenerating axons and their synaptic endings in the central nervous system. *Brain Res* **4:** 369–374, 1967.
16. Goldberg, G. Supplementary motor area structure and function: review and hypotheses. *Behav Brain Sci* **8:** 567–615, 1986.
17. Hall, R. D. and E. P. Lindholm. Organization of motor and somatosensory neocortex in the albino rat. *Brain Res* **66:** 23–38, 1974.
18. Hardy, S. G. P. Projections to the midbrain from the medial versus lateral prefrontal cortices of the rat. *Neurosci Lett* **63:** 159–164, 1986.
19. Hardy, S. G. P. and G. R. Leichnetz. Frontal cortical projections to the periaqueductal gray in the monkey: a retrograde and orthograde horseradish peroxidase study. *Neurosci Lett* **22:** 97–101, 1981.
20. Hardy, S. G. P. and G. R. Leichnetz. Frontal cortical projections to the periaqueductal gray in the rat: a retrograde and orthograde horseradish peroxidase study. *Neurosci Lett* **23:** 13–17, 1981.
21. Herkenham, M. The afferent and efferent connections of the ventromedial thalamic nucleus in the rat. *J Comp Neurol* **183:** 487–518, 1979.
22. Illing, R.-B. and A. M. Graybiel. Convergence of afferents from frontal cortex and substantia nigra onto acetylcholinesterase-rich patches of the cat's superior colliculus. *Neuroscience* **14:** 455–482, 1985.
23. Jones, E. G. Some aspects of the organization of the thalamic reticular complex. *J Comp Neurol* **162:** 285–308, 1975.
24. Jones, E. G. and R. Y. Leavitt. Retrograde axonal transport and the demonstration of non-specific projections to the cerebral cortex and striatum from thalamic intralaminar nuclei in the rat, cat and monkey. *J Comp Neurol* **154:** 349–378, 1974.
25. Jones, E. G. and T. P. S. Powell. An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain* **93:** 793–820, 1970.
26. Jurgens, U. The efferent and afferent connections of the supplementary motor area. *Brain Res* **300:** 63–81, 1984.
27. Kawana, E. and K. Watanabe. A cytoarchitectonic study of zona incerta in the rat. *J Hirnforsch* **22:** 535–541, 1981.
28. Kievit, J. and H. G. J. M. Kuypers. Organization of the thalamo-cortical connexions to the frontal lobe in the rhesus monkey. *Exp Brain Res* **29:** 299–322, 1977.
29. Komatsu, H. and H. Suzuki. Projections from the functional subdivisions of the frontal eye field to the superior colliculus in the monkey. *Brain Res* **327:** 324–327, 1985.
30. Konno, T. Patterns of organization of the corticotectal projection of cats studied by means of the anterograde degeneration method. *J Hirnforsch* **20:** 433–444, 1979.
31. Krettek, J. E. and J. L. Price. The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat. *J Comp Neurol* **171:** 157–192, 1977.
32. Kunzle, H. An autoradiographic analysis of the efferent connections from premotor and adjacent prefrontal regions (areas 6 and 9) in Macaca fascicularis. *Brain Behav Evol* **15:** 185–234, 1978.
33. Kunzle, H. and K. Akert. Efferent connections of cortical area 8 (frontal eye field) in Macaca fascicularis. A reinvestigation using the autoradiographic technique. *J Comp Neurol* **173:** 147–164, 1977.
34. Kunzle, H., K. Akert and R. H. Wurtz. Projection of area 8 (frontal eye field) to superior colliculus in the monkey. An autoradiographic study. *Brain Res* **117:** 487–492, 1976.
35. Leichnetz, G. R., D. J. Smith and R. F. Spencer. Cortical projections to the paramedian tegmental and basilar pons in the monkey. *J Comp Neurol* **228:** 388–408, 1984.
36. Leichnetz, G. R., R. F. Spencer and D. J. Smith. Cortical projections to nuclei adjacent to the oculomotor complex in the medial dien-mesencephalic tegmentum in the monkey. *J Comp Neurol* **228:** 359–387, 1984.
37. Leichnetz, G. R., R. F. Spencer, S. G. P. Hardy and J. Astruc. The prefrontal corticotectal projection in the monkey; an anterograde and retrograde horseradish peroxidase study. *Neuroscience* **6:** 1023–1041, 1981.
38. Leonard, C. M. The prefrontal cortex of the rat. I. Cortical projection of the mediodorsal nucleus. II. Efferent connections. *Brain Res* **12:** 321–343, 1969.
39. Markowitsch, H. J. and W. O. Guldin. Heterotopic interhemispheric cortical connections in the rat. *Brain Res Bull* **10:** 805–810, 1983.
40. Miller, M. W. and B. A. Vogt. Direct connections of rat visual cortex with sensory, motor and association cortices. *J Comp Neurol* **226:** 184–202, 1984.
41. Moran, A., C. Avendano and F. Reinoso-Suarez. Thalamic afferents to the motor cortex in the cat. A horseradish peroxidase study. *Neurosci Lett* **33:** 229–233, 1982.

42. Muakkassa, K. F. and P. L. Strick. Frontal lobe inputs to primate motor cortex: evidence for four somatotopically organized 'premotor' areas. *Brain Res* **177:** 176–182, 1979.
43. Nakano, K., M. Kohno, Y. Hasegawa and A. Tokushige. Cortical and brain stem afferents to the ventral thalamic nuclei of the cat demonstrated by retrograde transport of horseradish peroxidase. *J Comp Neurol* **231:** 102–120, 1985.
44. Neafsey, E. J., E. L. Bold, G. Haas, K. M. Hurley-Gius, G. Quirk, C. F. Sievert and R. R. Terreberry. The organization of the rat motor cortex: a microstimulation mapping study. *Brain Res Rev* **11:** 77–96, 1986.
45. de Olmos, J. Tetramethylbenzidine (TMB) method. In: *Neuroanatomical Tract-Tracing Methods,* edited by L. Heimer and M. J. RoBards. New York: Plenum Press, 1981.
46. Paxinos, G. and C. Watson. *The Rat Brain in Stereotaxic Coordinates*. New York: Academic Press, 1982.
47. Reep, R. L. Relationship between prefrontal and limbic cortex: a comparative anatomical review. *Brain Behav Evol* **25:** 1–80, 1984.
48. Reep, R. L., J. V. Corwin, A. Hashimoto and R. T. Watson. Afferent connections of medial precentral cortex in the rat. *Neurosci Lett* **44:** 247–252, 1984.
49. Reep, R. L. and S. S. Winans. Afferent connections of dorsal and ventral agranular insular cortex in the hamster, Mesocricetus auratus. *Neuroscience* **7:** 1265–1288, 1982.
50. Reep, R. L. and S. S. Winans. Efferent connections of dorsal and ventral agranular insular cortex in the hamster, Mesocricetus auratus. *Neuroscience* **7:** 2609–2635, 1982.
51. Rinvik, E. Organization of thalamic connections from motor and somatosensory cortical areas in the cat. In: *Corticothalamic Projections and Sensorimotor Activities,* edited by T. Frigyesi, E. Rinvik and M. D. Yahr. New York: Raven Press, 1972, pp. 57–90.
52. Roger, M. and J. Cadusseau. Afferents to the zona incerta in the rat: a combined retrograde and anterograde study. *J Comp Neurol* **241:** 480–492, 1985.
53. Sanderson, K. J., W. Welker and G. M. Shambes. Reevaluation of motor cortex and of sensorimotor overlap in cerebral cortex of albino rats. *Brain Res* **292:** 251–260, 1984.
54. Sarter, M. and H. J. Markowitsch. Convergence of intra- and interhemispheric cortical afferents: lack of collateralization and evidence for a subrhinal cell group projecting heterotopically. *J Comp Neurol* **236:** 283–296, 1985.
55. Schell, G. R. and P. L. Strick. The origin of thalamic inputs to the arcuate premotor and supplementary motor areas. *J Neurosci* **4:** 539–560, 1984.
56. Segal, R. L., R. M. Beckstead, K. Kersey and S. B. Edwards. The prefrontal corticotectal projection in the cat. *Exp Brain Res* **51:** 423–432, 1983.
57. Shammah-Lagnado, S. J., N. Negrao and J. A. Ricardo. Afferent connections of the zona incerta: a horseradish peroxidase study in the rat. *Neuroscience* **15:** 109–134, 1985.
58. Siegel, A., T. Fukushima, R. Meibach, L. Burke, H. Edinger and S. Weiner. The origin of the afferent supply to the mediodorsal nucleus: enhancement of HRP transport by selective lesions. *Brain Res* **135:** 11–23, 1977.
59. Vedovato, M. Identification of afferent connections to cortical area 6aβ of the cat by means of retrograde horseradish peroxidase transport. *Neurosci Lett* **9:** 303–310, 1978.
60. Vogt, B. A. and M. W. Miller. Cortical connections between rat cingulate cortex and visual, motor and postsubicular cortices. *J Comp Neurol* **216:** 192–210, 1983.
61. Vogt, B. A. and A. Peters. Form and distribution of neurons in rat cingulate cortex: areas 32, 24, and 29. *J Comp Neurol* **195:** 603–625, 1981.
62. Watson, R. T., B. D. Miller and K. M. Heilman. Nonsensory neglect. *Ann Neurol* **3:** 505–508, 1978.
63. Watson, R. T., E. Valenstein, A. Day and K. M. Heilman. Normal tactile threshold in monkeys with neglect. *Neurology,* **36:** 636–640, 1986.
64. Welch, K. and P. Stuteville. Experimental production of unilateral neglect in monkeys. *Brain* **81:** 341–347, 1958.
65. Welker, C. and M. M. Sinha. Somatotopic organizations of SmII cerebral neocortex in albino rat. *Brain Res* **37:** 132–135, 1972.
66. Wiesendanger, M. The organization of secondary motor areas of cerebral cortex. In: *Handbook of Physiology. The Nervous System. II. Motor Control,* edited by V. B. Brooks. Bethesda: American Physiological Society, 1981, pp. 1121–1147.
67. Wiesendanger, R. and M. Wiesendanger. The corticopontine system in the rat. I. Mapping of corticopontine neurons. *J Comp Neurol* **208:** 215–226, 1982.
68. Wiesendanger, R. and M. Wiesendanger. The corticopontine system in the rat. II. The projection pattern. *J Comp Neurol* **208:** 227–238, 1982.
69. Wiesendanger, R. and M. Wiesendanger. The thalamic connections with medial area 6 (supplementary motor cortex) in the monkey (macaca fascicularis). *Exp Brain Res* **61:** 91–104, 1985.
70. Wise, S. P. and E. G. Jones. Somatotopic and columnar organization in the corticocortical projection of the rat somatic sensory cortex. *Neurosci Lett* **133:** 223–235, 1977.
71. Zilles, K. and A. Wree. Cortex: Areal and laminar structure: In: *The Rat Nervous System,* edited by G. Paxinos. New York: Academic Press, 1985, pp. 375–415.
72. Zilles, K., B. Zilles and A. Schleicher. A quantitative approach to cytoarchitectonics VI. The areal pattern of the cortex of the albino rat. *Anat Embryol* **161:** 335–360, 1980.