

Insula of the Old World Monkey. III: Efferent Cortical Output and Comments on Function

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ABSTRACT

The insula sends neural efferents to cortical areas from which it receives reciprocal afferent projections. A collective consideration of afferents and efferents indicates that the insula has connections with principal sensory areas in the olfactory, gustatory, somesthetic (SI and SII), and auditory (AI and AII) modalities. There are additional connections with association areas for the visual (TE_m), auditory (supratemporal plane), and somesthetic (posterior parietal cortex) modalities; with paramotor cortex (area 6 and perhaps MII); with polymodal association cortex; and with a wide range of paralimbic areas in the orbital, temporopolar, and cingulate areas.

The topographic distribution of these connections suggests that the posterodorsal insula is specialized for auditory-somesthetic-skeletomotor function whereas the anteroventral insula is related to olfactory-gustatory-autonomic function. Most of the insula, especially its anteroventral portions, have extensive interconnections with limbic structures. Through its connections with the amygdala, the insula provides a pathway for somatosensory, auditory, gustatory, olfactory, and visceral sensations to reach the limbic system.

The cortical areas connected with the granular sector of the insula are also granular in architecture whereas virtually all the connections of the agranular insula arise from allocortical, agranular, or dysgranular areas. Thus, there is a correspondence between the architecture of insular sectors and the areas with which they have connections. The insula is heavily interconnected with temporopolar and lateral orbital areas. Furthermore, many cortical connections of the lateral orbital cortex are quite similar to those of the insula. These common connectivity patterns support the conclusion, based on architectonic observations, that the insulo-orbito-temporopolar component of the paralimbic brain should be considered as an integrated unit of cerebral organization.

The architectonic organization of the insula and the pattern of afferent cortical input that it receives have been reported previously (Mesulam and Mufson, '82; Mufson and Mesulam, '82). In this paper, we will describe the efferent projections which connect the insula with other cortical regions.

METHODS

This report is based on information obtained from 18 male rhesus monkeys in the adolescent-adult age range. In ten of these, tritiated amino acids (TAA) were injected into the insula under direct visual guidance. The surgical procedure, the composition of the injectate, and the autoradiographic method have been described in a companion paper (Mufson and Mesulam, '82). In each case, representative sections spanning the whole brain were

examined microscopically with darkfield illumination for the detection of label and with brightfield illumination for cytoarchitectonic identification. This information was transferred onto graph paper with an X-Y plotter electronically coupled to the mechanical stage of a compound microscope. The injection site was defined as the region around the needle track where the label was uniformly intense over perikarya as well as over the neuropil. Other areas where the labeling was substantially and consistently above the background level were considered to receive efferent projections from the injection site. The intensity of labeling was then described as light, moderate, or heavy.

Accepted May 18, 1982.

Several intrinsic difficulties are encountered in tracing neural efferents with TAA autoradiography. First, the effective injection site is difficult to define with precision (Graybiel, '75), a limitation of considerable relevance to this study because of the proximity of the claustrum to the insula. Second, the distinction between labeled fibers of passage and terminal fields may be difficult. This problem may lead to incorrect estimates of neural projections. Third, the presence of transsynaptic anterograde transport (Grafsstein, '71) raises the possibility that the labeling may not be confined to monosynaptic projections from the injection site.

In order to decrease the impact of these limitations, we examined eight additional cases (1h-8h) with cortical horseradish peroxidase (HRP) injections. In each of these cases the HRP injection site included one of the regions where anterograde label had been observed following TAA injections into the insula. The presence of retrograde labeling in the insula in these confirmatory cases precluded the possibility that the projection observed in the TAA cases reflected spread of the injection into the claustrum, label in passing fibers, or transsynaptic transport. The method of HRP injection, the histological procedures, and the considerations relevant to the interpretation of HRP labeling have been described previously (Mufson and Mesulam, '82). Our interpretation of architectonic subdivisions in the insula and adjacent regions was based on a map that we described elsewhere (Mesulam and Mufson, '82).

RESULTS

Of the ten animals with insular TAA injections, three representative cases will be described in detail.

Case A—TAA in anterior insula

Injection site. The injection site was in the anterior insula (Figs. 1, 2A). It extended into the agranular (Ia-p) and adjacent dysgranular (Idg) sectors. The underlying claustrum was partially included within the injection site but not prepiriform olfactory cortex (POC). A narrow strip of opercular cortex was damaged during the surgical approach.

Frontal lobe. A projection of moderate intensity was seen in a strip of granular prefrontal cortex corresponding to areas 46 and 12 of Walker ('40). The majority of frontal projections in this case were found in the lateral orbital region and in the opercular area (Fig. 1, sections 3-5). Heavy projections were seen within granular cortex (OFg) in the anterior part of the lateral orbital area. This projection had two foci, one just lateral to MOS (areas 11 and 13 of Walker ('40)) and the other more lateral, in the most anterior part of Walker's ('40) area 12. Additional orbital labeling was present in the agranular (OFa-p) and dysgranular (OFdg) sectors of the caudal orbitofrontal region (Fig. 1, section 5). The frontal operculum (OFO and Proco of Roberts and Akert ('63)) also contained heavy concentrations of label. Some of this opercular label appeared to extend into the ventral portion of area 6 (Fig. 1, sections 4 and 5).

Prepiriform olfactory cortex. Heavy labeling was present in layers 1b, 2, and 3 within the frontal, temporal, and insular extensions of prepiriform olfactory cortex (POC). The absence of anterograde labeling in the olfactory tract provided additional evidence that POC had not been included in the injection site (Fig. 1, section 6).

Insula. Heavy projections emanated from the injection

Abbreviations

AC	Anterior commissure	PA	Postauditory cortex ⁶
a-p	Insula, agranular periallocortical ¹	PF	Anterior inferior parietal cortex ⁶
AS	Arcuate sulcus	PG	Caudal inferior parietal cortex ⁶
AI	First auditory area	PI	Parainsular cortex ⁵
AII	Second auditory area	POC	Prepiriform portion of olfactory cortex
amg	Amgydala	PoD	Postcentral dimple
cd	Caudate	POS	Parietal occipital sulcus
CF	Calcarine fissure	Prco	Precentral operculum ⁴
CGS	Cingulate sulcus	PS	Principal sulcus
CL	Clastrum	pt	Putamen
CS	Central sulcus	RI	Retroinsular cortex ⁵
dg	Insula, dysgranular ¹	RS	Rhinal sulcus
FOS	Frontorbital sulcus	SI	First somatosensory cortex
G	Gustatory cortex ²	SII	Second somatosensory cortex
g	Insula, granular ¹	SPS	Subparietal sulcus
H	Hippocampus	STS	Superior temporal sulcus
IC	Internal capsule	STPg	Superior temporal cortex, granular ¹
Ia-p	Insula, agranular periallocortical ¹	TEm	Medial portion of inferior temporal gyrus ⁷
Idg	Insula, dysgranular ¹	TO	Olfactory tract
Ig	Insula, granular ¹	TPa-p	Temporopolar cortex, agranular-periallocortical ¹
IOS	Inferior occipital sulcus	TPdg	Temporopolar cortex, dysgranular ¹
IPS	Intraparietal sulcus	V	Lateral ventricle
LF	Lateral fissure	3, 1-2	Areas 3, 1, 2 ⁸
lgn	Lateral geniculate nucleus		
LOS	Lateral orbitofrontal sulcus		
LS	Lunate sulcus		
MII	Secondary motor area ³		
MOS	Medial orbital sulcus		
OFa-p	Orbitofrontal cortex, agranular periallocortical ¹		
OFdg	Orbitofrontal cortex, dysgranular ¹		
OFg	Orbitofrontal cortex, granular ¹		
OFO	Opercular cortex ⁴		
OIS	Orbitoinsular sulcus ¹		
OT	Optic tract		
OTS	Occipitotemporal sulcus		

¹According to Mesulam and Mufson ('82).

²According to Sanides ('68).

³According to Woolsey ('65).

⁴According to Roberts and Akert ('63).

⁵According to Jones and Burton ('76).

⁶According to Bonin and Bailey ('47).

⁷According to Turner et al. ('80).

⁸According to Brodmann ('05).

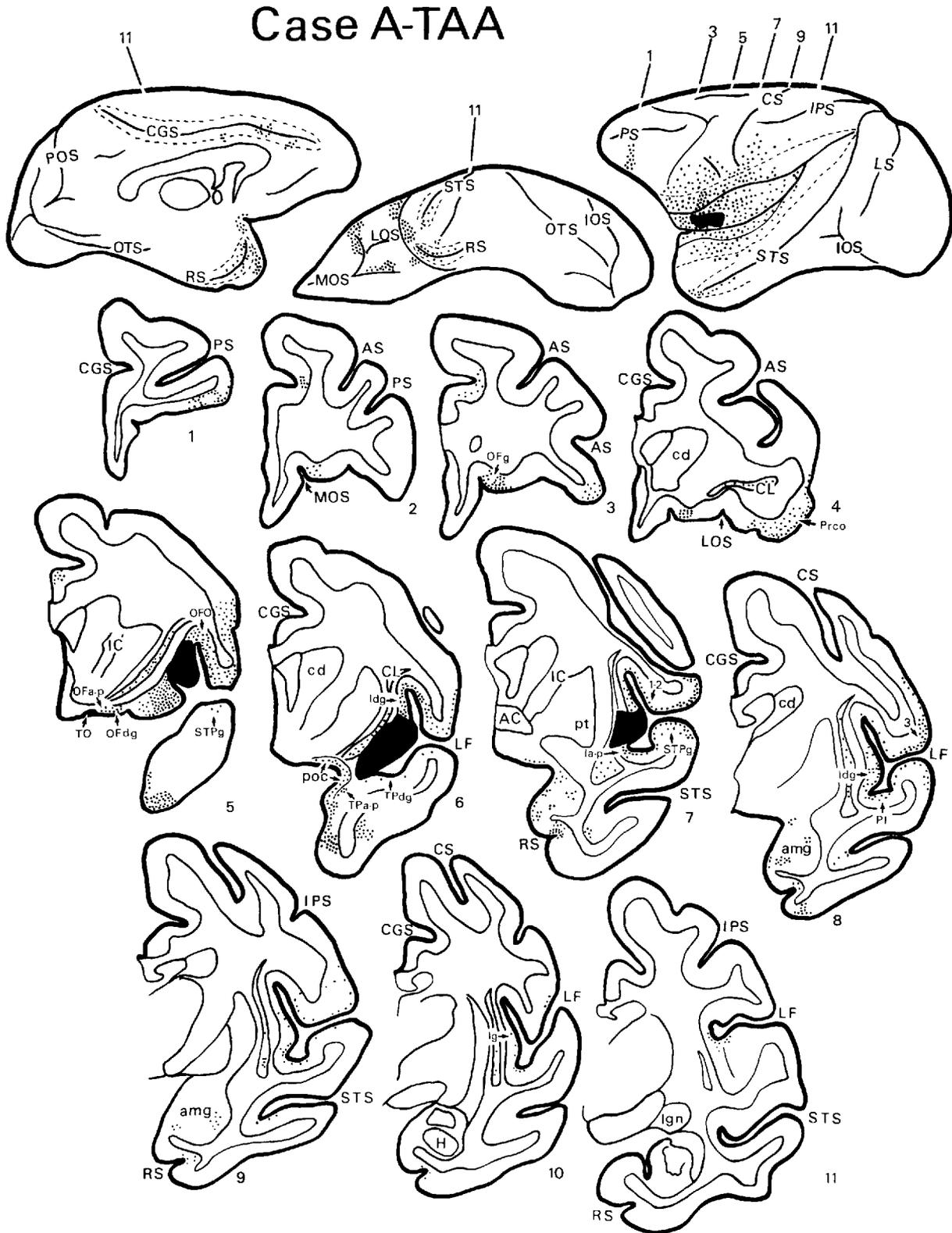


Fig. 1. Case A with TAA injected into the anterior insula. The injection site is shown as solid black. The labeled areas are indicated with black dots. At the top of the figure the medial, ventral, and lateral surfaces of the macaque brain are illustrated from left to right. The areas between dotted and solid lines represent cortex along the banks of sulci. The lateral

(Sylvian) fissure has been opened on the lateral view to show the inner face of the operculum, insula, parainsular belt, and supratemporal plane. The architectonic designations for intra-Sylvian regions containing label are included in the coronal sections and are based on Figure 1A of Mesulam and Mufson ('82).

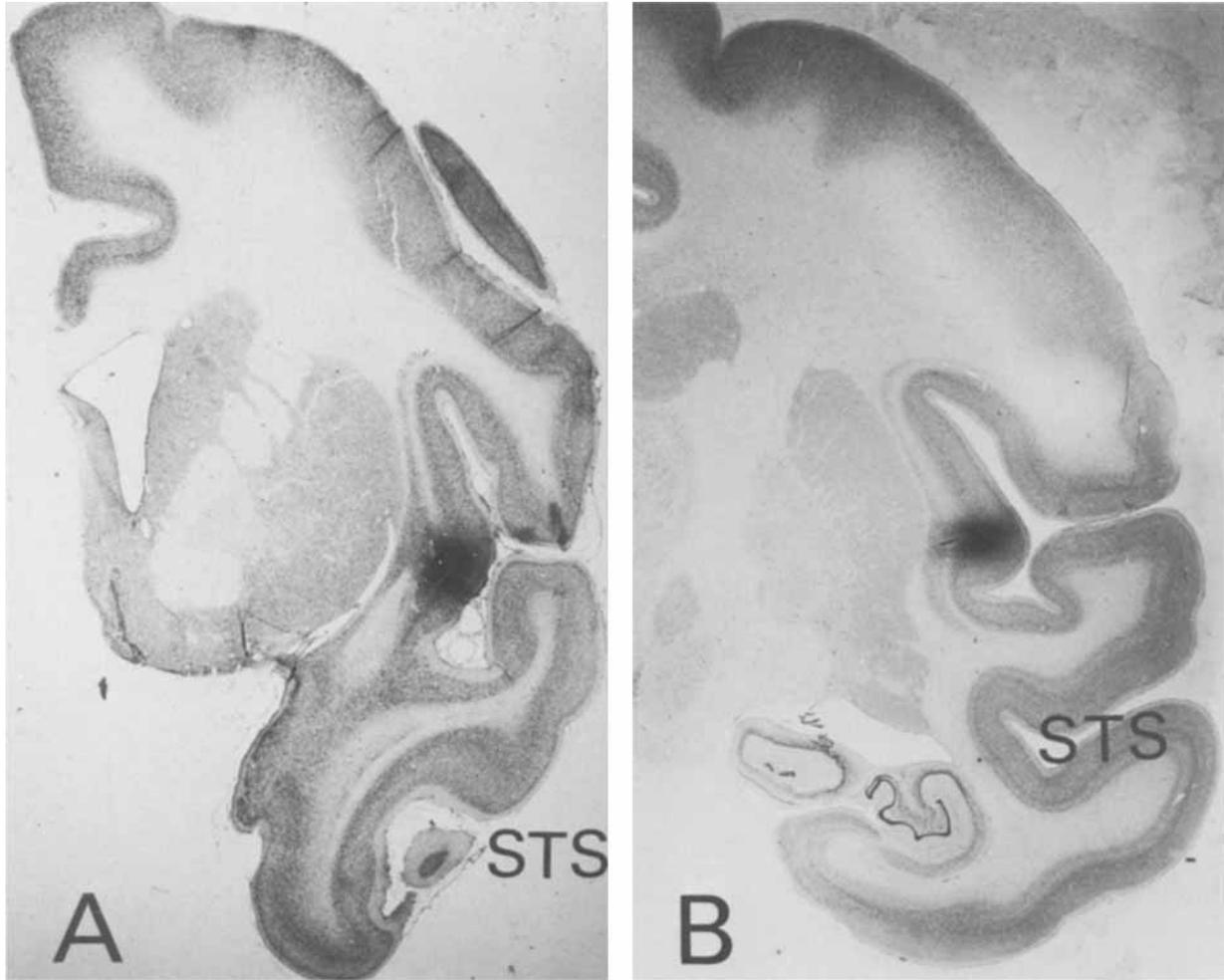


Fig. 2. A. Injection site of case A. B. Injection site of case C. $\times 3$.

site and reached surrounding portions of Ia-p and Idg. Less heavy labeling extended into the more caudal granular insula (Ig).

Parietal lobe. There were moderately heavy projections in the opercular portions of areas 3, 1, and 2 (Fig. 1, sections 6–8). More caudally, area PF (Bonin and Bailey, '47) in the inferior parietal lobule contained light labeling in its most anterior portion (Fig. 1, section 9). Area SII was virtually free of label.

Cingulate and surrounding regions. These areas contained light or moderate concentrations of label. The projection was limited to the anterior extent of the cingulate gyrus, especially to its dorsal and sulcal portion. A portion of the cingulate area which contained label corresponded to area 24 of Walker ('40). However, label was also seen in the deeper sulcal cortex in an area which appeared transitional between area 24 and the more dorsal area 6 (Fig. 1, sections 2 and 3).

Temporal lobe. In the dorsal region, there was moderate labeling in the agranular (TPa-p), dysgranular (TPdg), and granular (STPg) sectors of dorsal temporal cortex (Fig. 1, sections 5, 6). Ventrally, moderately heavy labeling was present in dysgranular polar cortex (Fig. 1, section 5). The

supratemporal plane contained moderately dense labeling in the parainsular (PI) area and more laterally in STPg (Fig. 1, sections 7–10). Principal auditory cortex (AI, AII) was virtually free of labeling. Moderate labeling was also present at the anterior tip of the superior temporal sulcus (STS) and in a portion of the inferior temporal gyrus which corresponds to TEM of Turner et al. ('80) (Fig. 1, sections 6–9). The anterior STS and TEM projections were located in cortex which can be classified as dysgranular because of a poorly differentiated second layer. The prorhinal and perirhinal areas along the banks of the rhinal fissure contained heavy to moderate labeling. Entorhinal cortex was not labeled (Fig. 1, sections 7–10).

Case B—TAA in posterior insula

Injection site. The injection site was almost entirely within Ig with a slight extension into the most caudal part of Idg and into the underlying claustrum (Fig. 3). Minor damage occurred to both banks of the lateral fissure at the level of the injection site.

Frontal lobe. In distinct contrast to Case A, this case had relatively few projections to the frontal lobe. In precentral granular cortex, light labeling was present in two

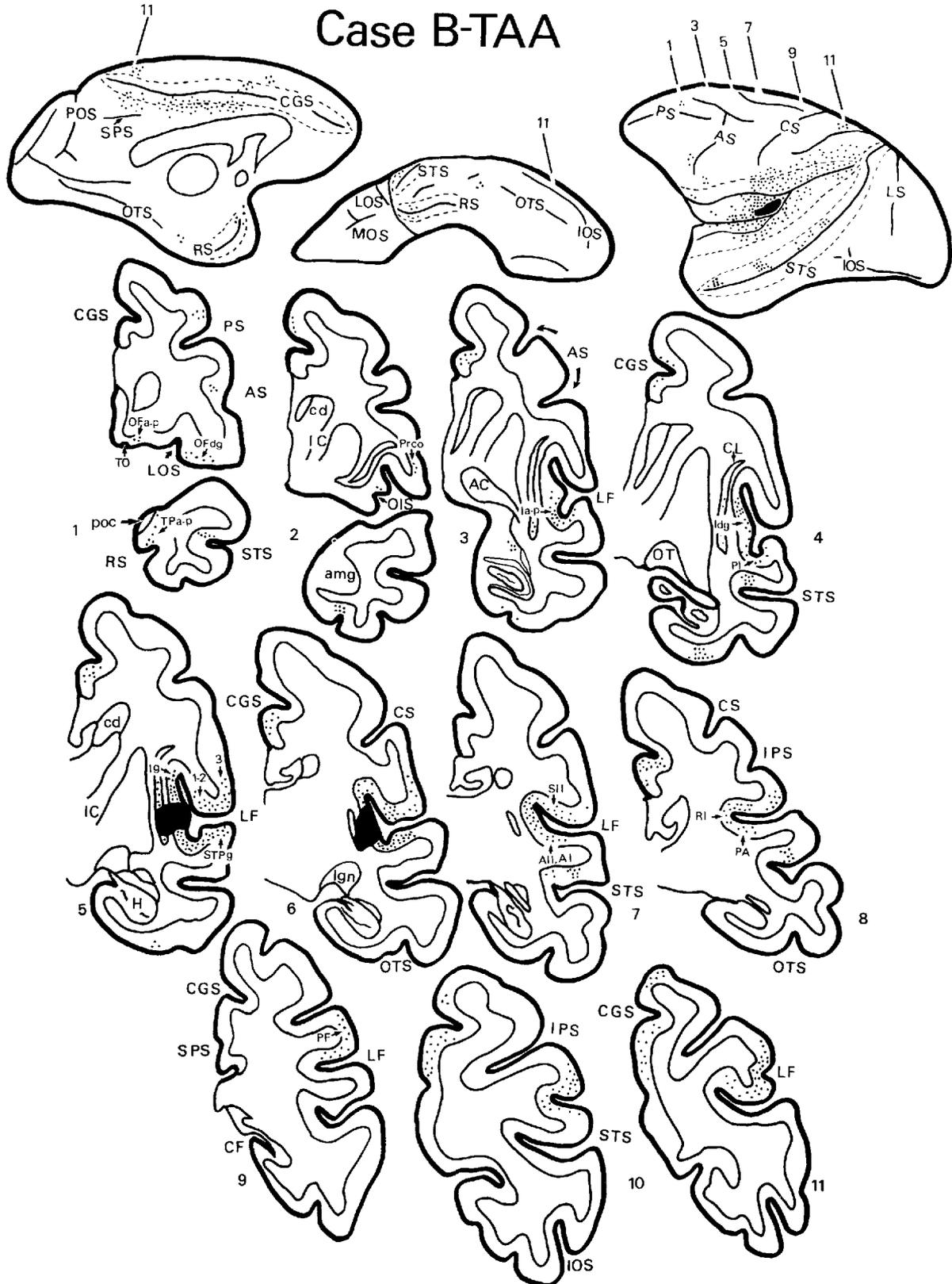


Fig. 3. Case B with TAA injected into the posterior insula. The injection site is shown as solid black. The labeled areas are indicated with black dots. At the top of the figure the medial, ventral, and lateral surfaces of the macaque brain are illustrated from left to right. The areas between dotted and solid lines represent cortex along the banks of sulci. The lateral

(Sylvian) fissure has been opened on the lateral view to show the inner face of the operculum, insula, parainsular belt, and supratemporal plane. The architectonic designations for intra-Sylvian regions containing label are included in the coronal sections and are based on Figure 1A of Mesulam and Mufson ('82).

small patches, one dorsal to the principal sulcus (area 46) and the other anterior to the lower limb of the arcuate sulcus (area 45) (Fig. 3, section 1). Projections to orbital cortex were limited to light labeling in OFa-p and in the portion of OFdg lateral to the LOS (Fig. 3, section 1). A small patch of Prco cortex contained light labeling (Fig. 3, section 2). Almost no labeling could be detected in area OFO.

Prepiriform olfactory cortex. In contrast to Case A, POC was free of labeling.

Insula. The anterior half of the insula (Idg and Ia-p) was relatively free of label. The more caudal parts of Ia-p, Idg, and the part of Ig remaining outside of the injection site were heavily labeled.

Parietal lobe. The parietal lobe labeling in this case was more extensive than in Case A. The portion of areas 3, 1, and 2 in the outer and inner faces of the operculum were heavily labeled as was area SII in the more caudal part of the parietal operculum (Fig. 3, sections 5-7). In the inferior parietal lobule, the granular isocortical area PF was heavily labeled (Fig. 3, section 9). It is conceivable that some of the labeling extended into adjacent parts of area PG. Granular cortex in the superior parietal lobule (area 5) was moderately labeled. This labeling extended into the medial parts of area 5 which is located around the subparietal sulcus (SPS) (Fig. 3, sections 10, 11). Areas SII and 5 which were extensively labeled in this case had remained free of label in Case A.

Cingulate and surrounding regions. There was extensive labeling of moderate intensity along the dorsal aspect of the mid- and posterior cingulate gyrus, including the sulcal banks. Some of the labeling was within areas 23 and 24 of Brodmann ('05) (Fig. 3, sections 2-6, 8, and 10). However, some of the projections reached the depths and upper banks of the sulcus. These richly pyramidal regions probably correspond to MII (Woolsey, '65).

Temporal lobe. The polar region had light labeling limited mostly to TPa-p (Fig. 3, section 1). The supratemporal plane contained heavy labeling in posterior parts of PI and STPg (Fig. 3, sections 3-5). In contrast to Case A, which lacked labeling of principal auditory cortex, this case showed moderate labeling in AII and AI (Fig. 3, section 7). In more caudal parts of the supratemporal plane, the granular postauditory (PA) and retroinsular (RI) areas were both moderately labeled (Fig. 3, section 8). The upper banks of STS contained multiple interrupted patches of moderately heavy labeling (Fig. 3, sections 1, 4, 7, and 8). The most anterior of these was in dysgranular cortex while the others were in granular cortex. As in Case A, moderate labeling was present in TEm and in the banks of the rhinal sulcus (Fig. 3, sections 2-5).

Case C—TAA in mid-insula

Injection site. The injection site was focused in the middle portion of Idg (Figs. 2B, 4). Minor extension of the injection site occurred into immediately adjacent portions of Ia-p, Ig and the underlying claustrum. With respect to insular topography, the injection site lay between those of the other two cases. The posterior extent of this injection site appeared to overlap with the injection site of Case B while some overlap may have occurred at its anterior portion with the injection site of Case A.

Frontal lobe. The projection pattern in the orbital cortex was virtually identical to Case A. There were patches of moderately heavy projections in OFg (within areas 11,

12 and 13), in OFdg (within area 12) and in OFa-p (Fig. 4, sections 1-3). Although reduced in extent, this case also had light labeling in prefrontal granular cortex below the principal sulcus (Fig. 4, section 3). Labeling in OFO which was heavy in Case A was virtually absent in this case and only light labeling existed in Prco. This suggests that these opercular projections may originate primarily from the anterior aspect of injection site A, especially in the case of the OFO projection. Light labeling was seen in the posterior bank of the ventral arcuate sulcus, in a cortical area which had architectonic features of area 6 (Fig. 4, section 5). This projection was not present in any of the other two cases, suggesting that it may originate from the central aspect of injection site C.

Prepiriform olfactory cortex. No POC labeling was detected in this case, suggesting that such projections originate predominantly in the most anterior part of injection site A.

Insula. All insular sectors showed labeling except for the most anterior part of Idg (Fig. 4, section 5-8).

Parietal cortex. The pattern of labeling was most similar to that in Case B. The opercular portions of SI, medial parietal cortex, areas SII, 5, and anterior PF were moderately or heavily labeled (Fig. 4, sections 6-10). In contrast to Case B, posterior PF remained unlabeled, suggesting that this projection arises primarily from the most posterior part of injection site B. Case C also had some light labeling in the most dorsal part of area 3, in regions that were not labeled in the other two cases.

Cingulate and surrounding regions. Moderate labeling was present in the dorsal part of areas 23 and 24 and also more dorsally in an area that may overlap with MII (Fig. 4, sections 3-5 and 8-10). This pattern is most similar to the one seen in Case B.

Temporal lobe. The pattern was virtually identical to that of case B and included light labeling in TPa-p and heavier labeling in PI, STPg, AI, AII, PA, RI, STS cortex, TEm, and the banks of the rhinal sulcus (Fig. 4, sections 3-11).

Cortical HRP injections

Case 1h—HRP in anterior STS. Retrogradely labeled perikarya were seen in Ia-p and in the anterior as well as posterior parts of Idg (Fig. 5). This is consistent with the observation that cases A, B, and C each had anterograde labeling in the anterior banks of the STS. The parainsular and more lateral supratemporal areas also contained retrograde labeling.

Case 2h—HRP in OFg-OFdg (areas 11, 12, and 13). Retrograde labeling occurred predominantly in Ig and posterior Idg. Less extensive perikaryal labeling was also present in anterior Idg (Fig. 5). The most posterior part of the insula was free of neuronal labeling. This is consistent with the virtual absence of anterograde labeling in this part of the orbital area in Case B. A similar projection from insula to the lateral orbital area was demonstrated with HRP histochemistry in the monkey by Potter and Nauta ('79). Other opercular areas in the frontoparietal operculum, supratemporal plane, and retroinsular region also contained labeled perikarya in this case.

Case 3h—HRP in mid-cingulate cortex. Labeled neurons were concentrated in posterior Idg and anterior Ig. The anterior Idg and Ia-p were free of labeling. This is consistent with the observation that Cases B and C but

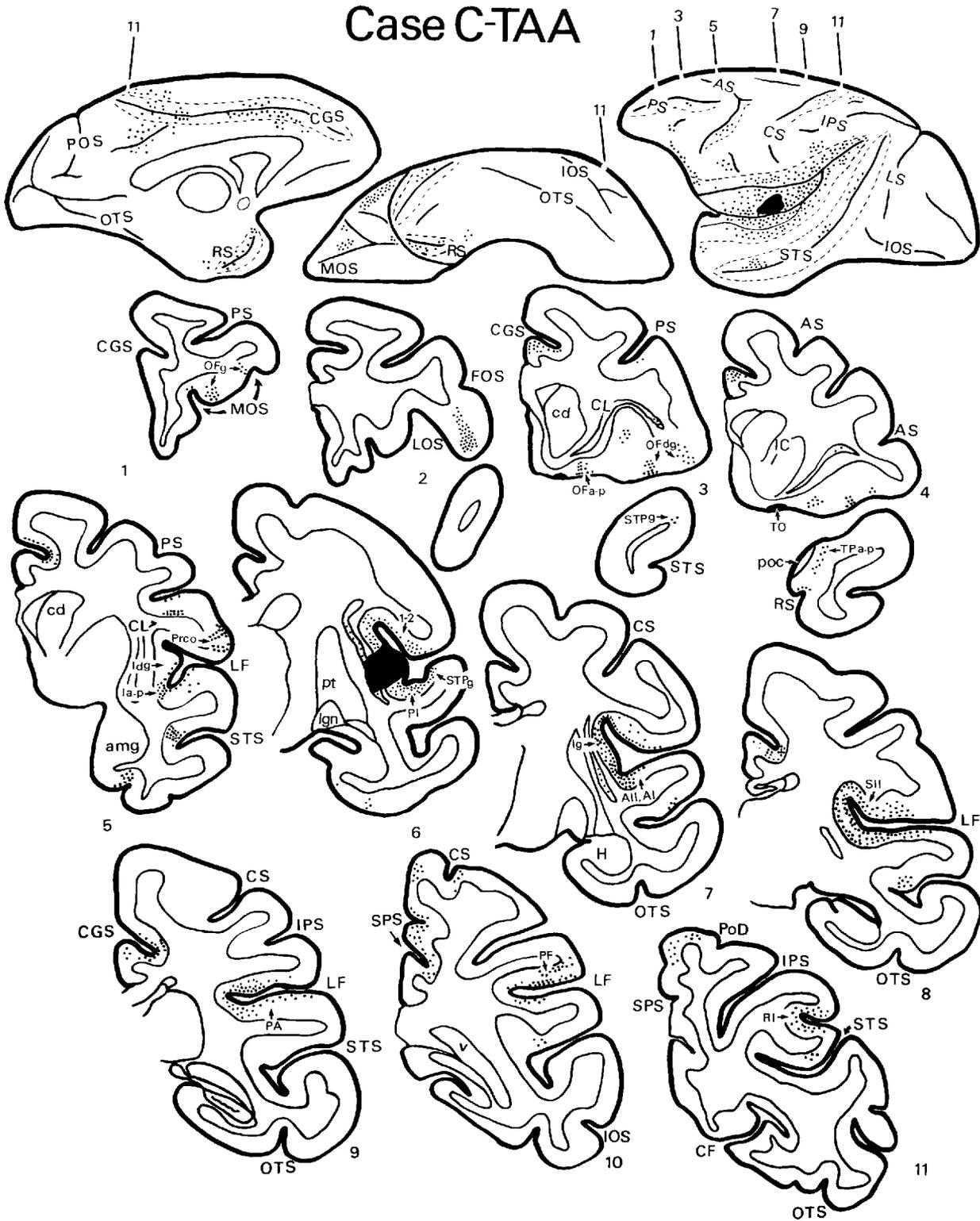


Fig. 4. Case C with TAA injected into the mid-insula. The injection site is shown as solid black. The labeled areas are indicated with black dots. At the top of the figure the medial, ventral, and lateral surfaces of the macaque brain are illustrated from left to right. The areas between dotted and solid lines represent cortex along the banks of sulci. The lateral (Syl-

vian) fissure has been opened on the lateral view to show the inner face of the operculum, insula, parainsular belt, and supratemporal plane. The architectonic designations for intra-Sylvian regions containing label are included in the coronal sections and are based on Figure 1A of Mesulam and Mufson ('82).

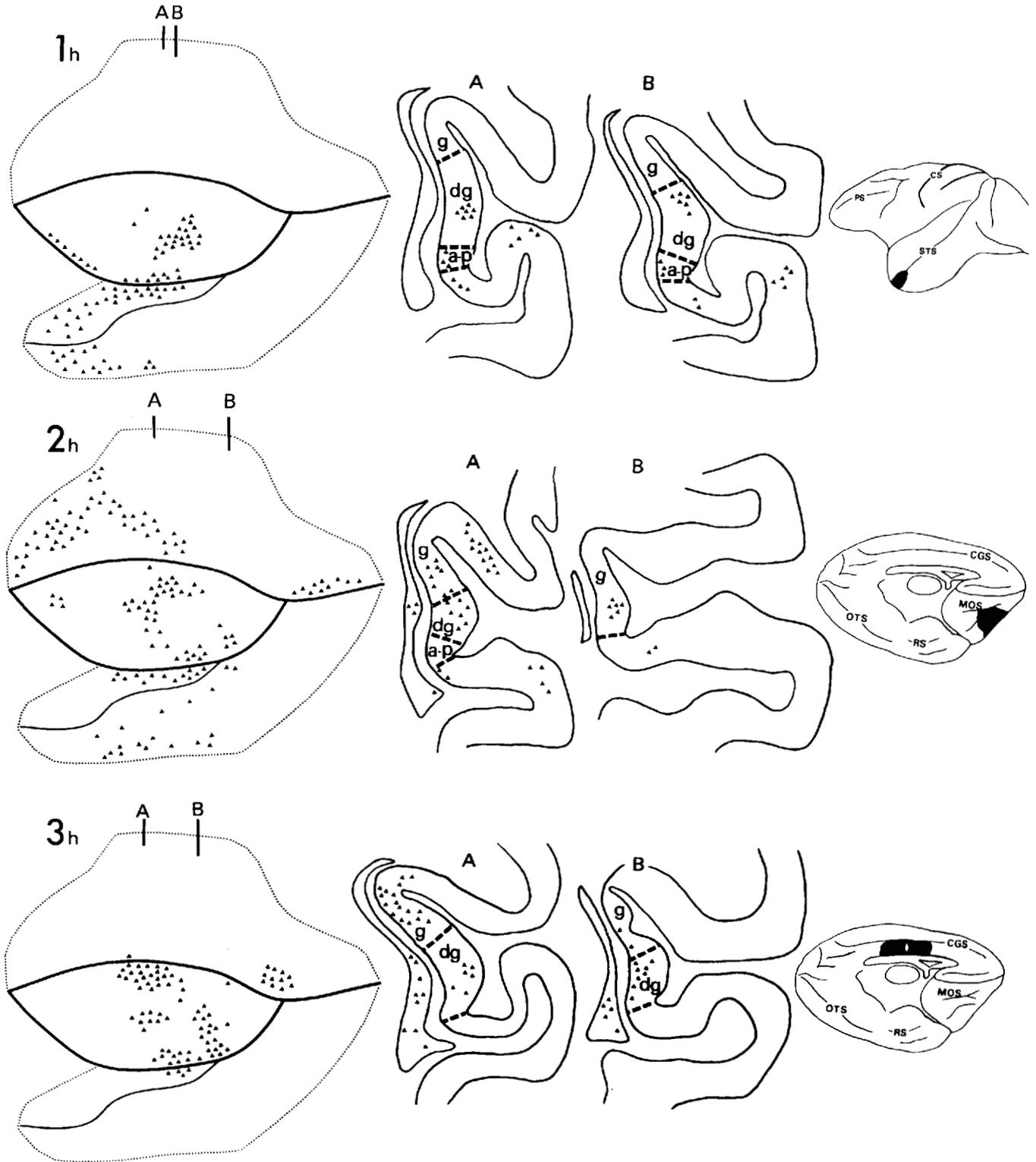


Fig. 5. In cases 1h, 2h, and 3h, the site of HRP injection is solid black. Arrows indicate extension of injection site into surrounding sulcal cortex. Perikaryal labeling in the intra-Sylvian region is indicated by black triangles. In the planar map on the left of each case, the central elliptical area represents the insula. Above the insula, the area bounded dorsally

by the dotted line corresponds to the inner face of the overlying operculum. The parainsular belt (PI) and the adjacent supratemporal plane are shown below the insula. The architectonic parcellation of these regions follows the map in Figure 1A of Mesulam and Mufson ('82).

not A had anterograde labeling in this part of the cingulate. The posterior parietal operculum and the parainsular belt also had retrograde labeling.

Case 4h—HRP in area 5 and adjacent regions of the superior parietal lobule. Retrograde labeling was concentrated in Ig with a minor extension into posterior Idg (Figs. 6, 7). This is consistent with the finding that only the more posterior TAA injections (Cases B and C) resulted in anterograde labeling in this region. Adjacent areas in the posterior parietal operculum and retroinsular area also contained labeled neurons.

Case 5h—HRP in Prco and area 6. Retrograde labeling was mostly posterior, in Idg and Ig (Fig. 6). However, Case A indicated that the most extensive Prco projection originated in the more anterior parts of the insula. The discrepancy between this observation and the pattern of anterograde labeling in Case A is probably due to the fact that the most ventral part of Prco which had the most anterograde labeling in Case A was not involved in this HRP injection site. Retrograde labeling was extensive in other parts of the frontal and parietal operculum.

Case 6h—HRP in ventral SI and anterior PF. Retrograde labeling was observed mostly in mid-Idg and anterior Ig. Additional retrograde labeling was present in parietal operculum (Fig. 6).

Case 7h—HRP in PF. Retrograde labeling in the insula was mainly confined to Ig in the posterior insula. This observation is consistent with the presence of anterograde PF labeling only in Cases B and C which had the more posterior TAA injection sites. The posterior parietal operculum also contained retrogradely labeled neurons.

Case 8h—HRP in prefrontal granular cortex. The anterior Ig contained retrogradely labeled neurons. This is consistent with the anterograde labeling in this region of prefrontal cortex which was observed in Case C. Additional labeled neurons were present in parietal operculum. A similar insulofrontal projection in the monkey has been shown with HRP histochemistry by Jacobson and Trojanowski ('77).

Retrograde labeling in the claustrum

It was difficult to detect a clear correspondence between the labeling of claustrum and insula. In cases such as 3h and 8h, labeling in the insula was associated with extensive retrograde labeling in the claustrum. In other cases such as 1h and 5h, however, equally intense insular labeling was associated with very little labeling in the claustrum. Topographical relationships were also difficult to discern. In case 8h, for example, where most of the insular labeling was found dorsally in Ig, the claustrum labeling was concentrated in the ventral blade (Fig. 8). Thus, there was no consistent relationship in the intensity and distribution of labeling when the insula was compared to the claustrum.

Laminar distribution of insular efferents

Considerable difficulties are encountered in determining the laminar termination of efferent projections with autoradiography. For example, a cortical region which receives terminal projections exclusively to superficial layers may also have substantial axonal labeling in the deeper

layers. Thus, the laminar specificity of the projection may not be discernible. Furthermore, local transynaptic transport may further prevent an accurate determination of laminar or columnar specificity. Perhaps as a consequence of these methodological limitations, columnar or laminar concentrations of label were observed in only very few of the cortical regions receiving insular projections. Columnar distribution of anterogradely transported TAA label was most consistently observed in OFg, TEm, Prco, and STS cortex. In these and all other projection sites, all cortical laminae contained label even though there was frequently a preponderance for supragranular layers, especially L1–L2, to contain intense labeling. In periallocortical areas such as TPa-p and OFa-p a greater concentration of label was also evident in the outer stratum. A columnar organization of retrograde labeling in the insula was present in some cases but not all (Fig. 7).

Cases 1h–8h showed that cortical efferents originated in all layers of the insula. Most of these neurons were found in L3, L5, and L6. However, when labeled perikarya were counted, the ratio of supragranular to infragranular labeling was found to vary greatly among individual cases. In cases 4h, 6h, and 7h this ratio was 0.46, 0.13, and 0.32, respectively, indicating the predominance of infragranular labeling. On the other hand, cases 1h, 2h, and 8h had ratios of 6.8, 2.72, and 2.8, respectively, indicating a predominance of supragranular labeling. The remaining two cases, 3h and 5h, had intermediate ratios of 0.96 and 0.95. In the cases with the lowest ratios, the projection was directed to parietal regions which included principal and association areas for the somesthetic modality. In the cases with the highest ratios, the projection was directed to higher-order association areas and paralimbic regions. We had previously observed that approximately 90% of the perikarya projecting to the amygdala are located in the supragranular layers of the insula (Mufson et al., '81). It is conceivable, therefore, that insular efferents to principal sensory and unimodal association areas may arise predominantly from infragranular perikarya whereas those to polymodal association, paralimbic, and limbic areas may arise preferentially from perikarya in supragranular laminae.

Concordance between the insula and orbital cortex

Architectonic observations had indicated that the insula and the lateral orbitofrontal areas share almost identical plans of organization (Mesulam and Mufson, '82). In order to see if these two areas also shared patterns of neural projections, we examined the orbital region in cases 3h, 4h, and 8h. In cases 3h and 4h where perikaryal labeling was restricted in the insula to Ig and Idg, retrograde labeling was also seen in OFg and OFdg. In case 8h, where insular labeling was limited to Ig, lateral orbital labeling was also present and was virtually confined to OFg. These preliminary observations and similar ones with respect to insular afferents (Mufson and Mesulam, '82) suggest that the two areas may share many parallel projection patterns.

DISCUSSION

This investigation of insular efferent output and a previous one on insular afferent input (Mufson and Mesulam, '82) show that virtually all cortical connections of the in-

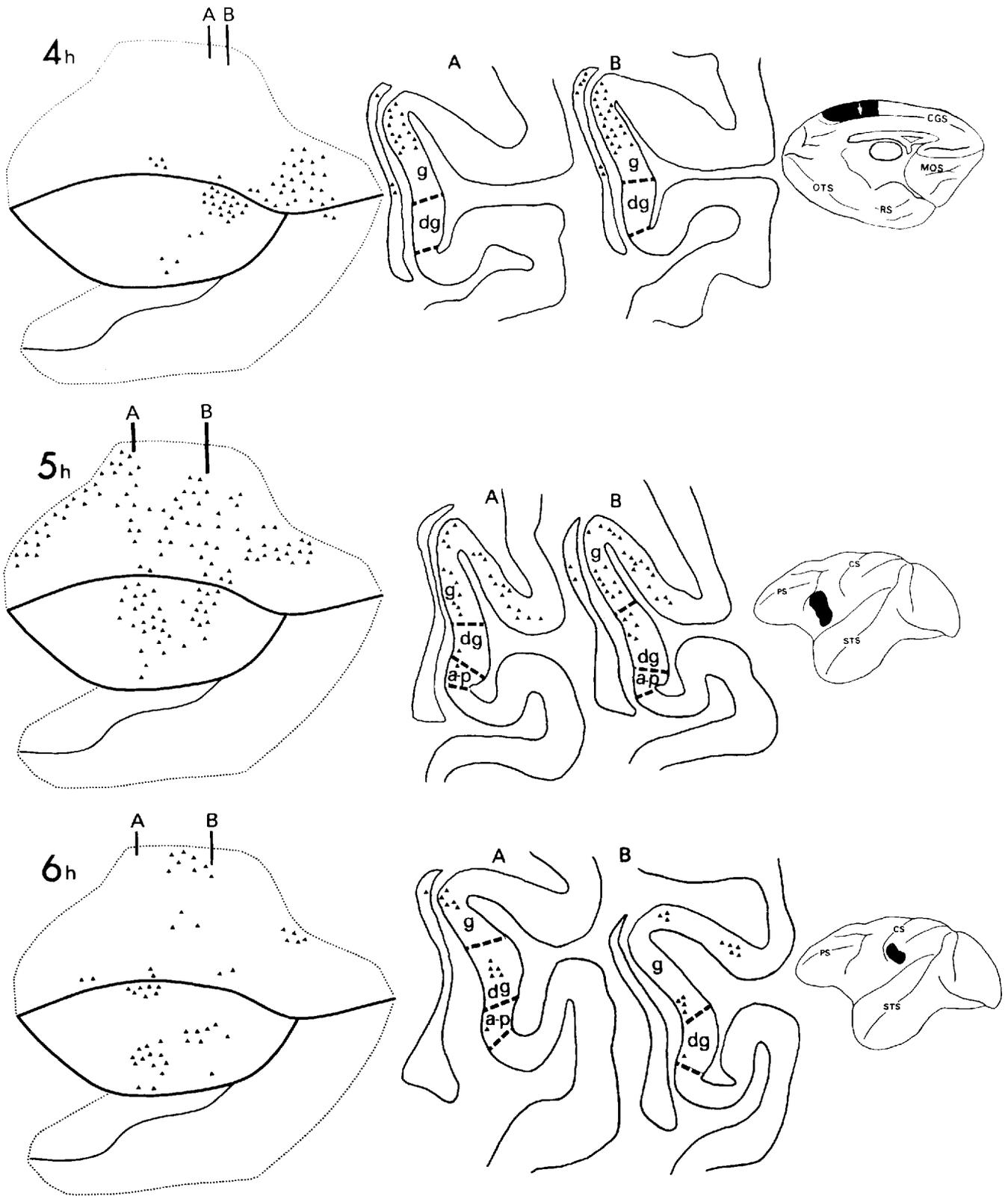


Fig. 6. In cases 4h, 5h, and 6h, the site of HRP injection is solid black. Arrows indicate extension of the injection site into surrounding sulcal cortex. Perikaryal labeling in the intra-Sylvian region is indicated by black triangles. In the planar map on the left of each case, the central elliptical area represents the insula. Above the insula, the area bounded dorsally

by the dotted line corresponds to the inner face of the overlying operculum. The parainsular belt (PI) and the adjacent supratemporal plane are shown below the insula. The architectonic parcellation of these regions follows the map in Figure 1A of Mesulam and Mufson ('82).

sula are reciprocal.¹ In view of this close concordance, the cortical afferents and efferents of the insula will be reviewed jointly in the following discussion.

Injections of HRP and TAA into the insula show that this region has connections with a wide range of cortical areas including prefrontal granular cortex, lateral orbitofrontal areas, frontal operculum, prepiriform olfactory cortex, gustatory cortex (OFO), SI, SII, areas 5 and PF, retroinsular cortex, supratemporal cortex, AI, AII, the temporal pole, the inferior temporal gyrus and cortex in the banks of the superior temporal, cingulate, and rhinal sulci. Among these connections, those with the temporal pole (TPdg), cingulate area, orbital cortex, rhinal cortex, olfactory cortex, frontal operculum, PF, area 5, precentral granular cortex, anterior STS, and SI have been confirmed by additional experiments with tracer injections outside the insula (cases 1a-9a in Mufson and Mesulam, '82, and 1h-8h in this study). Confirmatory cases are not yet available for the other connections. Therefore, the possibility may be entertained that they reflect, at least in part, the inclusion of the claustrum within the injection site or even the surreptitious spread of tracer through the microvasculature to neighboring areas. However, the intensity of these connections and their consistent demonstration by retrograde as well as by anterograde transport procedures suggests that they most probably represent connections of the insula itself.

Topographic and architectonic organization of insular connectivity

For purposes of topographic demarcation, the insula can be divided into an anteroventral and a posterodorsal division. The anteroventral division consists of la-p and the anterior portion of Idg. The posterodorsal portion consists of Ig and the posterior part of Idg. Some connections of the insula are distributed preferentially within the posterodorsal division of the insula. These include connections with area 45, the OFg-OFdg junction, MII, area 6, the outer opercular segment of SI, SII, PF, RI, area 5, PA, AI, AII, posterior STS cortex, and area 23. Other connections are predominantly distributed within the anteroventral division. This group includes connections with the OFa-p-OFdg junction, OFO, the most anterior portion of the cingulate region, POC, TPdg, ventral temporopolar cortex, and prrhinal-entorhinal cortex. A third group of connections appears widely distributed without any apparent preference for the anterior or posterior divisions. This group includes connections with TEm, TPa-p, STPg, PI, the inner opercular portion of SI, perirhinal cortex, anterior STS cortex, parts of prefrontal cortex, and Prco.

Cases 1a-9a in a previous study (Mufson and Mesulam, '82) and 1h-8h in this study allow some of these connections to be associated with specific architectonic sectors of the insula (Fig. 9). Connections that have been shown to originate and terminate in Ig include those with the outer opercular segment of SI, area 5, PF, prefrontal granular cortex, Prco, OFg-OFdg, and posterior cingulate cortex. It is interesting to note that virtually all of these connections of the granular insula occur with cortical areas that also have a granular architecture. On the other hand, the connections which can definitely be associated with the agranular insula (la-p) include those with TPdg, OFa-p, OFdg, prrhinal-entorhinal cortex, the anterior dysgranular part

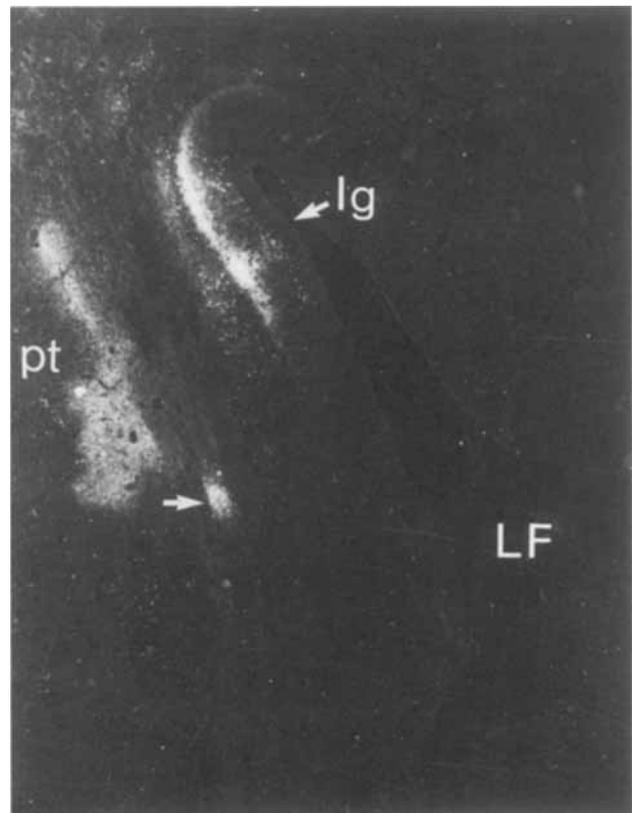


Fig. 7. Darkfield photomicrograph of HRP labeling in insula, claustrum, and putamen in case 4h. The intense labeling in layer 4 of Ig corresponds to anterograde transport from the injection site. Retrogradely labeled neurons are seen in the supragranular and infragranular layers. There is the suggestion of a columnar organization in the labeling. This case supports the presence of overlapping reciprocal connections between the insula and the superior parietal lobule. Furthermore, it is clear that the heaviest labeling occurs at different dorsoventral levels when the insula is compared to the claustrum. The HRP label in the claustrum (arrowhead) represents anterograde as well as retrograde transport. The putaminal labeling exclusively represents anterograde transport. $\times 15$.

¹By reciprocal we mean that the insula projects to the *same set* of areas from which it receives connections. In some cases the reciprocity is organized so that a projection to a certain area arises from exactly the same insular sector that receives input from the target region (Fig. 7). However, we do not know if this is true in all instances. Cases with TAA injections into the posterior insula contained anterogradely transported label in the principal auditory areas (AI and AII). However, parts of the medial supratemporal plane were almost always damaged in cases which had HRP injected into the insula (Mufson and Mesulam, '82). Consequently, we were unable to determine reliably if the principal auditory fields contained retrogradely labeled perikarya. This is the only major instance where the reciprocity of connections could not be established. However, the reciprocal nature of the other cortical projections makes it likely that the principal auditory area not only receives insular connections but that it also projects into the insula. In fact, Pandya et al. ('69) have shown that principal auditory fields do project to a posterior rim of insular cortex.

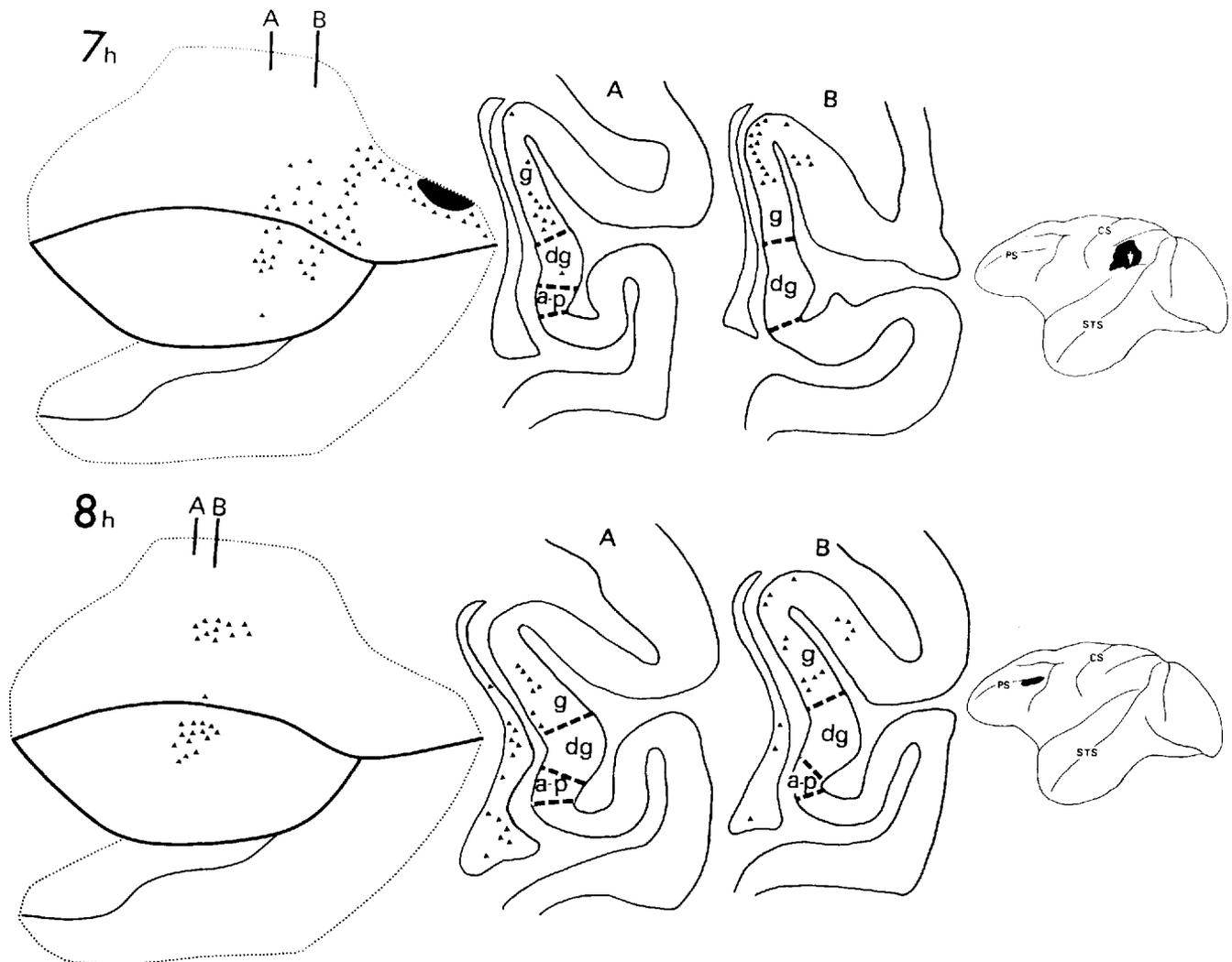


Fig. 8. In cases 7h and 8h, the site of HRP injection is solid black. Arrows indicate extension of the injection site into surrounding sulcal cortex. Perikaryal labeling in the intra-Sylvian region is indicated by black triangles. In the planar map on the left of each case, the central elliptical area represents the insula. Above the insula, the area bounded dorsally

by the dotted line corresponds to the inner face of the overlying operculum. The parainsular belt (PI) and the adjacent supratemporal plane are shown below the insula. The architectonic parcellation of these regions follows the map in Figure 1A of Mesulam and Mufson ('82).

of STS, and POC. In contrast to the areas that are connected with Ig, these areas have an allocortical, agranular, or dysgranular architecture.

The projections which can be shown to originate and terminate in the dysgranular (Idg) sector include those with PF, outer opercular SI, prefrontal granular cortex, OFg, OFdg, OFa-p, anterior (dysgranular) STS cortex, Prco, POC, cingulate cortex (23 and 24), TPdg, and pro-rhinal-entorhinal cortex. These cortical areas cover a wide spectrum of cellular architecture, ranging from allocortex to granular isocortex. This heterogeneous connectivity may well reflect the transitional architecture of Idg itself (Mesulam and Mufson, '82). The gradual changes in Idg occur in such a way that anteriorly its architecture is more similar to Ia-p whereas posteriorly similarities to Ig become apparent. These differences are reflected in the patterns of connectivity so that the posterior Idg has connectivity patterns that are similar to those of Ig whereas the connections of anterior Idg are more similar to those of Ia-p

(see Fig. 9). Thus, there is a considerable correspondence in the architectonic organization of insular sectors and the regions with which they are connected.

Functional organization of insular connectivity: The anterior insula

Our observations indicate that olfactory and gustatory connections are mostly confined to the anteroventral insula whereas auditory and somesthetic connections are concentrated within the posterodorsal insula. This pattern of connectivity provides an anatomical basis for previous physiological observation which revealed behavioral differences between the anterior and posterior parts of the insula. In a patient who underwent surgical exploration of the insula, olfactory sensations were reported only when the anterior insular cortex was stimulated (Penfield and Faulk, '55). Gustatory function also appears to be concentrated in the anterior insula. In the rhesus monkey, for

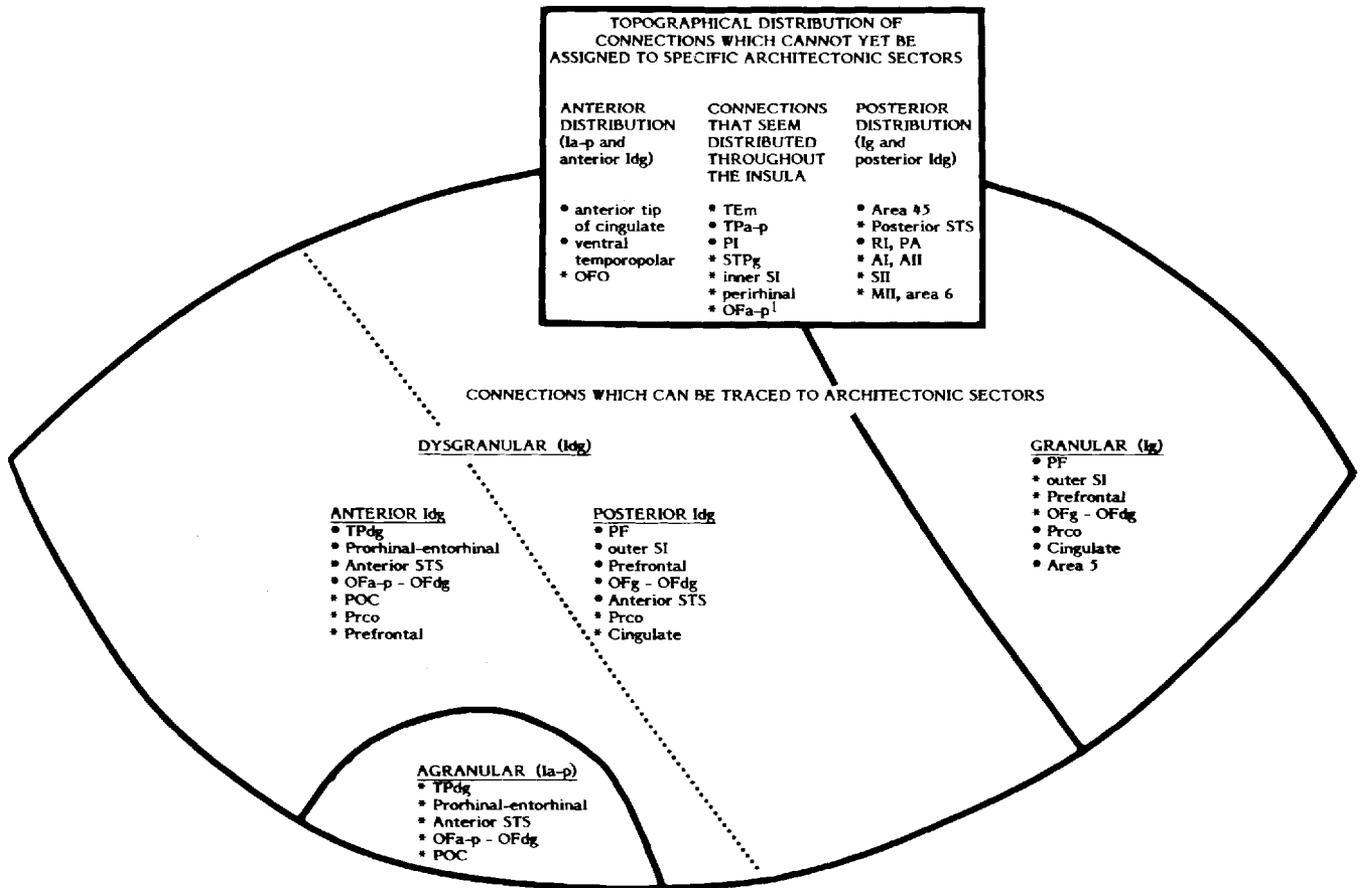


Fig. 9. Composite diagram of insular afferents and efferents. The dotted line arbitrarily bisects Idg into anterior and posterior divisions. The Ia-p and the anterior Idg collectively constitute an anteroventral subdivision of the insula. The Ig and posterior Idg together constitute the posterodorsal subdivision. The box on the upper part of the diagram lists the topographic distribution of connections. The additional connections listed below the box have also been traced to specific architectonic sectors on the basis of cases 1a-9a (Mufson and Mesulam, '82) and 1h-8h in this paper. The assignment of projections to various sectors reflects their predominant, but not necessarily exclusive, distribution within the insula. By "inner" and "outer" SI we mean to designate the part of SI on the inner and outer opercular faces, respectively. As discussed in the text, the reciprocal connectivity with prorhinal cortex is well established. However, the presence of an independent entorhinal projection is less certain.

example, gustatory function became impaired after ablations in the anterior insula (Bagshaw and Pribram, '53). Furthermore, electrical stimulation of taste nerves as well as direct gustatory stimulation of the tongue elicited responses that were most readily obtained in the anterior insula (Benjamin and Burton, '68; Sudakov et al., '71). Although the number of these relevant studies is small, they are consistent with the pattern of connectivity in suggesting a concentration of olfactory and gustatory function within the anterior insula.

The anterior insula may also contain the neural specialization for visceral sensation and autonomic responses. In humans, stimulation of the anterior insula elicits changes in gastrointestinal motility as well as reports of sensations associated with the digestive tract (Penfield and Faulk, '55). In rhesus monkeys, stimulation of the anterior but not of the posterior insula results in a great variety of cardiovascular, respiratory, salivatory, and gastrointestinal responses (Hoffman and Rasmussen, '53; Showers

¹In the case of OFa-p projections, information based on cases which had tracer injections into the insula indicates that this connection is widely distributed throughout the insula. However, case 4a (Mufson and Mesulam, '82), which contains a TAA injection in the OFdg-OFa-p junction shows anterograde labeling confined to anterior Idg and Ia-p. This discrepancy may arise from the fact that the injection in case 4a did not include all of OFa-p. Thus, the tentative conclusion is reached that the OFa-p connection is distributed widely within the insula even though the connection with the OFdg-OFa-p junction may be confined to the anteroventral subdivision of the insula.

and Lauer, '61). The first central synapse for visceral and gustatory afferent input occurs in the nucleus of the tractus solitarius (nTS). This nucleus also participates in many autonomic reflexes (see Kalia and Mesulam, '80a; '80b, for review). Since the anterior insula has a similar pattern of functional specializations, it may provide a cortical representation for the nTS. In fact, the VPMpc thalamic nucleus which receives most of the nTS afferents projects to the anterior insula and provides a relay between this region and the nTS (Beckstead et al., '80; Morse et al., '80). The anterior insula, VPMpc in the thalamus and the nTS may constitute components of a network that integrates olfactory, gustatory, and autonomic functions.

In addition to olfactory, gustatory, and autonomic function, the anterior insula is also characterized by extensive interactions with paralimbic cortical areas (Fig. 9). We also showed that the reciprocal connections between the amygdala and insula are more extensively concentrated within the anterior agranular-dysgranular insula (Mufson

et al., '81). The available anatomical and behavioral information thus leads to the conclusion that the anterior insula is specialized for olfactory, gustatory, and autonomic function and that this portion of the insula is also more closely associated with the limbic system. How this cluster of specializations relates to complex behavior is a matter for speculation. It is conceivable, for example, that the anterior insula may participate in a wide range of behaviors ranging from the modulation of complex ingestive behavior to the expression of autonomic patterns in response to affective tone.

Functional organization of insular connectivity: The posterior insula

In contrast to the anterior insula, the posterodorsal dysgranular-granular insula is characterized by connections with auditory (AI, AII), somesthetic (SII, PF, area 5), and paramotor (area 6 and perhaps MII) areas. Furthermore, neurons in the posterior but not in the anterior insula appear to have direct descending projections to medullary somatosensory nuclei (Catsman-Berrevoets and Kuypers, '76). Physiological observations are consistent with this distribution of connectivity within the insula. For example, Robinson and Burton ('80) showed that 76% of all sampled units in the Ig of rhesus monkeys responded to somesthetic stimulation. In the squirrel monkey, most of the units responsive to auditory and somesthetic stimulation are also concentrated in the posterior insula (Sudakov et al., '71). Furthermore, electrical stimulation of the posterior but not of the anterior insula in rhesus monkeys elicits skeletal movement (Showers and Lauer, '61). Thus, in contrast to the olfactory-gustatory-autonomic functions of the anterior insula, the posterior insula appears specialized for auditory-somesthetic-skeletomotor tasks.

The posterior insula has connections with AI and AII, on one hand, and with SI and SII, on the other (Mufson and Mesulam, '82; Pandya et al., '69). It is therefore possible that there is a convergence of somatosensory and auditory information in this portion of the insula. Such multimodal convergence is not unique to the insula and occurs elsewhere in the brain. However, in other instances, sensory information from principal sensory areas is processed in at least one intervening relay before reaching sites of potential multimodal convergence (Chavis and Pandya, '76; Mesulam, '81; Seltzer and Pandya, '78). In the insula, on the other hand, such multimodal convergence may occur more directly without intervening relays in modality-specific association areas. An analogous convergence of gustatory and olfactory inputs may occur in the anteroventral division of the insula. Intra-insular connections occur predominantly from the anterior to the posterior sectors. These posteriorly directed intra-insular connections provide a potential pathway for conveying olfactory and gustatory information into the posterior insula. Furthermore, the insula also receives visual input from area TEm. Thus, the posterior insula is in a unique position to receive information in all five sensory modalities: gustatory, olfactory, auditory, somesthetic and, to a lesser extent, visual.

The insula may also provide a neural relay for conveying sensory information into the limbic system. Connections between sensory areas and limbic structures are important for at least two reasons. First, they provide a means for interrelating events in the external world with relevant

motivational states. This may provide a fundamental anatomical substrate for learning and memory functions. Second, sensory-limbic connections may be necessary for associating sensory events with the appropriate emotional response. The insula may participate in both types of processes.

Several multisynaptic routes have been described for relaying auditory and visual information from association areas of the temporal lobe into the limbic system (Herzog and Van Hoesen, '76; Turner et al., '80; Van Hoesen, '81; Van Hoesen and Pandya, '75). However, equivalent pathways for the somesthetic modality have been difficult to identify. Our observations indicate that the insula may provide such a pathway. This conclusion is based on the fact that the posterior insula receives extensive somesthetic input and that it also projects into the amygdala (Mufson and Mesulam, '82; Mufson et al., '81). Perhaps, as Mishkin ('79) has suggested, SII is the principle source of the somesthetic information which is relayed by the insula into the amygdala. The insula may thus provide a major pathway for somesthetic-limbic interactions. Therefore, one consequence of damage to the posterior insula may be an impairment of learning based on somesthetic discrimination, a suggestion which is supported by the experiments of Murray et al. ('80). Another consequence of insular damage may be to alter the hedonic aspects of somatosensory experience. It is therefore interesting to note that at least one human case has been reported where lesions involving the insula and SII in the parietal operculum were associated with a dramatic loss of pain perception (Biemond, '56). This loss of pain sensation is often attributed to the involvement of SII, which is considered to provide a principal sensory area for pain perception. However, the cerebral damage in Biemond's ('56) case would also have produced a somesthetic-limbic disconnection by preventing somesthetic input from reaching the amygdala. Since the experience of pain undoubtedly has a strong limbic component, this somesthetic-limbic disconnection may explain, at least in part, the loss of pain sensation that occurs in patients with this type of insular and opercular stroke. In addition to somesthetic information, the posterior insula may also relay auditory input into the limbic system. The insula has its most direct projections into the limbic system through the amygdala (Aggleton et al., '80; Mufson et al., '81). However, the connections of the insula with cingulate and rhinal cortex also provide alternate but multisynaptic routes into the hippocampal component of the limbic system. Just as the posterior insula provides a pathway for conveying somesthetic and auditory inputs into limbic structures, the anterior part of the insula is in a similar position to relay visceral, olfactory, and gustatory sensations into the limbic system.

Insula as a paralimbic region

We identified three characteristics which are shared by components of the paralimbic brain (Mesulam and Mufson, '82). Architecturally, paralimbic areas contain transitions from allocortex to granular isocortex. Anatomically, they have connections, on one hand, with core limbic structures, and, on the other, with isocortical areas. Behaviorally, they are specialized for tasks that depend on interactions between the internal milieu and the extrapersonal space. All three of these characteristics clearly apply to the insula. Furthermore, there appears to be an internal polarization in that the anterior insula contains special-

izations related mostly to the internal milieu whereas those of the posterior insula are more heavily oriented toward the extrapersonal space.

Architectonic analysis indicates that insular, lateral orbital, and temporopolar areas share a common plan of cortical organization (Mesulam and Mufson, '82). For example, the agranular component in each of these three regions is directly continuous with prepiriform cortex. Furthermore, the agranular and dysgranular sectors in the insula are directly coextensive with the architectonically corresponding sectors of the lateral orbital region. Observations on connectivity patterns show that these three regions are also closely interconnected and that they share common patterns of cortical projections. For example, the insula is reciprocally interconnected with all architectonic sectors of the adjacent lateral orbital and temporopolar regions. Furthermore, many connections of the lateral orbital cortex with other nonparalimbic cortical areas are similar to those of the insula. Taken together, this information on architectonic organization and connectivity patterns strongly suggests that the insulo-orbito-temporal component of the paralimbic brain provides an integrated unit of cerebral organization. The behavioral implications of this suggestion remain to be elucidated.

ACKNOWLEDGMENTS

This research was supported in part by grants from the Essel Foundation and from NIH, NS 14625, NS 09211, and NS 07011. We are grateful to Dr. Deepak N. Pandya for providing some of the confirmatory cases. Dr. Irma Lessel participated in the initial stages of analysis. Mr. Rick Plourde and Ms. Susan Sasner provided expert technical and secretarial assistance.

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