

Insula of the Old World Monkey. I: Architectonics in the Insulo-orbito- temporal Component of the Paralimbic Brain

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ABSTRACT

The insula of the rhesus monkey has a surface area of approximately 160 mm² and can be divided into three architectonic sectors. The agranular sector is coextensive with prepiriform allocortex and is characterized by three agranular cellular strata, a zonal layer of myelinated fibers, and a high level of intracortical acetylcholinesterase (AChE). The dysgranular sector adjoins the agranular sector and shows first the emergence of a granular L4 and then a gradual differentiation of L2. Cortical myelin is low and mostly within deep layers; the AChE level is less than in the agranular sector. The third and granular sector covers the posterior aspect of the insula and contains granular L4 and L2, incipient sublamination of L3, increased cortical myelin with an emergent outer line of Baillarger, and a very low density of AChE. These observations indicate that AChE histochemistry can be used for the architectonic analysis of cortex.

The lateral orbital cortex and the temporal pole can also be subdivided into agranular, dysgranular, and granular regions. In the insula as well as in lateral orbital and temporopolar areas, the agranular sector is directly contiguous with prepiriform cortex. When these three brain regions are considered jointly, they are seen to be organized in the form of increasingly more differentiated agranular, dysgranular, granular, and hypergranular sectors arranged concentrically around prepiriform allocortex.

The term paralimbic is suggested as a generic term for all regions where such transitions occur from allocortex to granular isocortex. The insula, lateral orbital surface, and temporal pole are paralimbic areas with an olfactory allocortical focus. The parahippocampal, retrosplenial, cingulate, and subcallosal regions constitute a second group of paralimbic areas with a hippocampal-induseal focus. In the most general sense, the functional specializations of paralimbic areas are predominantly for behaviors which require an integration between extrapersonal stimuli and the internal milieu.

The human insula has a plan of organization virtually identical to that in the rhesus monkey. In the human, the insulo-orbito-temporopolar component of the paralimbic brain may become involved in conditions which range from epilepsy to psychosomatic disease.

The insula is a major component of the limbic brain (Yakovlev, '59). In the human, it is a common site for focal epileptic discharges, stroke, and tumor. However, there are virtually no neurological deficits which can be used as indicators of underlying insular damage since information

on the functional specializations and anatomical connections of this region is presently incomplete.

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The first systematic description of the insular region was offered by Johann Christian Reil (1809), whose name is now permanently associated with the Sylvian insula. One of the earliest architectonic descriptions of this area was published in 1877 by H.C. Major. Despite these initial achievements, subsequent advances in understanding the insula were particularly slow to develop. Even at a time when many other regions of the brain appeared on the verge of yielding their secrets, Bonin and Bailey ('47) singled out the insula: "Buried in the depth of the lateral fissure lies the enigmatic island of Reil whose functions and affinities are totally unknown."

Since then, considerable progress has occurred in our understanding of the insula. With respect to structure, it is now accepted that the insula of the human as well as that of the monkey contains several sectors ranging in architecture from agranular to granular (Bonin and Bailey, '47; Economo and Koskinas, '25; Jones and Burton, '76; Roberts and Akert, '63; Sanides, '68). With respect to behavior, the insula appears to participate in gustatory, autonomic, skeletomotor, auditory, and somesthetic functions (Bagshaw and Pribram, '53; Penfield and Faulk, '55; Sudakov et al., '71; Sugar et al., '48). The available information indicates that the connections of the insula parallel this diversity of structural plan and functional organization. Investigations by strychnine neuronography indicated connections between the insula and adjacent orbital, opercular, temporopolar, and medial temporal areas (Pribram et al., '50; Pribram and MacLean, '53). More recent studies with degeneration and transport methods concentrated on subcortical projections and demonstrated connectivity with virtually every subnucleus of the amygdala as well as with, ventrolateral, ventroposterior, supragenulate and intralaminar nuclei of the thalamus (Aggleton et al., '80; Burton and Jones, '76; Mufson et al., '81; Roberts and Akert, '63; Wirth, '73). The cortical connections of the insula, on the other hand, have not been investigated systematically with modern tracing methods.

In the present set of three reports, we will present observations on the architectonic composition and cortical connections of the insula in the old world monkey. Part I focuses on the perikaryal, myelin, and acetylcholinesterase architecture of the insula and the relationship of this region to olfactory, orbitofrontal, and temporopolar structures. Part II (Mufson and Mesulam, '82) will discuss the distribution of afferent cortical input in order to determine the type of information which reaches the insula. Part III (Mesulam and Mufson, '82) will focus on the organization of insular efferents in order to delineate those cortical regions which are under the neural influence of the insula.

Cytoarchitectonic maps of the insula and surrounding regions have been prepared for the old world monkey by Roberts and Akert ('63) and by Jones and Burton ('76). Each map subdivides the insula into three major sectors: an anterior agranular component which lacks inner or outer granular layers; a posterior six-layered granular moiety which has many features of homotypical isocortex; and an intercalated dysgranular component which displays incipient granularization. A somewhat different schema, based on the distribution not only of perikarya but also of myelin, was proposed by Sanides ('68). He described an anterior peripaleocortical component containing two agranular cortical strata. This peripaleocortical sector is followed by three proisocortical components which display progressively greater degrees of granularization.

Our own architectonic observations which will be described in this paper provide information to support and supplement each of these three maps. Furthermore, we have noted very close parallels between the organization of the insula and that of lateral orbitofrontal and temporopolar regions. These parallels are so striking that it becomes desirable to approach the insulo-orbital-temporopolar region collectively and as a single entity.

METHODS

The observations reported in this paper are derived from 15 male rhesus monkeys (*Macaca mulatta*) in the adolescent-adult age range and one human brain from a 25-year-old male. Three macaque specimens were embedded in celloidin and cut serially at 35 μm thickness, two in the coronal and one in the horizontal plane. Series of sections (every sixth in one coronally cut specimen, and every 20th in the other two brains) were stained with cresyl violet for Nissl substance, with the Loyez method for myelin, and with the Klüver-Barrera method for the simultaneous visualization of myelin and perikarya. The Loyez stain and the luxol fast blue component of the Klüver-Barrera stain were underdifferentiated in order to accentuate intracortical myelin. Additional cytoarchitectonic observations were made on six macaque brains embedded in paraffin, cut at 10 μm , and stained with cresyl violet. Another brain was embedded in gelatin-albumin, cut at 27 μm , and stained with cresyl violet. These specimens made it possible to correlate the architecture of perikarya with that of myelin and to examine specimens cut at different thicknesses and in more than one plane of section. The importance of variables such as tissue thickness and plane of cutting has been stressed by other investigators (Bonin and Bailey, '47; Sanides, '70; Walker, '40). Each one of these ten specimens was removed from the skull after transcardial perfusion with physiological saline and 10% formaldehyde.

The distribution of acetylcholinesterase (AChE) was determined in five specimens perfused with a solution of 1% paraformaldehyde-1.25% glutaraldehyde and cut at 40 μm with a freezing microtome. The sections were processed for AChE histochemistry as described elsewhere (Mesulam, '82; Appendix VII). Ethopropazine was used as an inhibitor of non-acetyl cholinesterases. In each of these brains, alternate sections were stained with cresyl violet, methylene blue, or neutral red so that the AChE distribution could be correlated with cytoarchitectonics. In two of these brains, the same section was concurrently stained for AChE and with neutral red.

The human specimen belonged to a 25-year-old male with no previous neurological disease who died after a protracted period of heart failure. The brain was fixed by immersion in 10% formalin and cut coronally into 35 μm sections. Alternative sections were stained with cresyl violet or with the Loyez stain.

The analysis of architectonic information was based on microscopic examination and on macrophotographs of relevant areas. In preparing our cytoarchitectonic map of the insula and surrounding regions, a series of coronally cut, 35 μm thick sections stained with cresyl violet was examined microscopically at $\times 40$ -200 magnification and charted with $\times 8$ magnification onto graph paper with the aid of an X-Y recorder electronically coupled to the mechanical stage of a Nikon compound microscope. Architectonic boundaries were introduced directly on the charting through the X-Y recorder. These tracings were used

to construct a planar map. On the map, the rostrocaudal distances were calculated according to section thickness and serial number. Dorsoventral distances were measured directly and drawn to scale. We also assumed a shrinkage factor of 20–25% from the fresh specimen to the microscopic sections (Cipolloni et al., '75). The scale of the map reflects the actual dimensions that would have been expected in the live brain. Although minor, there were definite interanimal variations in the distribution of perikarya, myelin, and AChE. Only those features encountered in two or more specimens influenced the conclusions.

RESULTS

The term insula is used as a topographic designation for the cortex which covers the medial wall of the Sylvian cistern. Superior and inferior limiting sulci in the Sylvian cistern form upper and lower boundaries for the insula. Anterior to the limen insulae, the superior limiting sulcus continues to provide a dorsal boundary for the insula. The ventral limiting sulcus does not continue anterior to the limen so that the ventral orbito-insular boundary is difficult to identify. The external shape of the insula approximates that of an ellipse. In the unfixed specimen from rhesus monkeys, the long axis of the insula varies from 18 to 21 mm and the short axis is about 10 mm. Assuming an elliptical shape, the calculated surface area for the insula is approximately 160 mm².

CYTOARCHITECTONICS

Terminology

Many terms are currently in use for describing cytoarchitectonic properties of cortical areas. Some terms such as "koniocortical" or "agranular" are merely descriptive of appearance, others such as "periallocortical" focus on topographical arrangement, and still some others such as "archicortical" or "proisocortical" contain assumptions about the development of cortex. We decided to rely exclusively on descriptive and topographic terms such as periallocortical, agranular, dysgranular, and granular.

The term periallocortex will be used to designate cortical areas which are immediately adjacent to olfactory and hippocampal allocortex. The term granular cortex will be used to designate five or six layered regions where layers 2 and 4 are *both* granular and clearly demarcated from adjacent laminae.¹ In the context of this paper, the term agranular will be used for regions that lack discernible concentrations of granule cells into laminae or into clusters and which also have a simple organization into two or three cellular strata. Dysgranular cortex offers intermediate stages between agranular and granular types: there may be up to five or six layers but only an incipient, rudimentary granularity in layers 2 and 4. In some portions of dysgranular cortex layer 4 may contain clusters of granules without full laminar demarcation while layer 2 may lack granularity altogether. In other portions, layer 4 may be relatively well developed but layer 2 may remain rudimentary. We reserve the term granular only for those areas where layers 2 and 4 are *both* clearly developed.

Regions anterior to the limen insulae

Rostral to the emergence of insular cortex, the lateral orbital sulcus is surrounded by areas 11 and 13 medially and area 12 laterally (Walker, '40; Fig. 1B). At this level,

both regions can be described as granular (OFg) since they contain sparsely granular but moderately well-demarcated layers 2 and 4. More posteriorly, the orbital extension of the claustrum begins to cap the cortex in this region and the superior limiting sulcus makes its appearance. At that point several changes occur in the cortex surrounding the lateral orbitofrontal sulcus. First, the deep layers lose their sharp demarcation from underlying white matter and there are cellular bridges which appear continuous with the claustrum. Second, layer 4 becomes transformed into interrupted clusters of granules and layer 2 can no longer be demarcated from layer 3. This posterior extension of lateral orbital cortex has a dysgranular architecture and is designated as OFdg (Figs. 1A,2A). Still more posteriorly, this region assumes a distinctly agranular character (OFa-p), especially in the immediate vicinity of the anterior olfactory nucleus and prepiriform cortex (Figs. 1A,2B–D,3,4A). This OFa-p region lacks identifiable collections of granule cells. It is a simplified type of cortex which consists of an outer and inner stratum rather than the five- or six-layered plan of other isocortical areas. The neurons of the inner stratum are continuous with the claustrum and form tangential rows parallel to the surface of the brain. The outer stratum is directly continuous with the pyramidal layer of prepiriform cortex and the most superficial layer contains clusters of deeply staining cells similar in appearance to the hyperchromatic prepiriform pyramid. The claustrum, prepiriform cortex, and orbital cortex tend to merge with each other within this agranular sector (Fig. 4A). Toward the boundary with OFdg, an intermediate stratum of deeply stained pyramidal neurons appears in OFa-p (Fig. 4A). This intermediate stratum is continuous with L5 of adjacent OFdg cortex. Lateral orbitofrontal cortex (Areas 12 and 13 of Walker '40) thus changes from a granular to a dysgranular and then to an agranular-periallocortical arrangement along a rostrocaudal axis. The agranular-periallocortical part of the orbital surface has been designated "Allo" by Roberts and Akert ('63) and junctional cortex (J) by Jones and Burton ('76) (see Fig. 1D,E). Our observations indicate that this area is an extension of lateral orbital cortex.

The anterior insula makes its appearance with the emergence of the superior limiting sulcus (Fig. 3). This sulcus forms a boundary between the frontoparietal operculum and the insula. Rostral to the limen insulae, there is no specific boundary between the ventral insula and orbital cortex (Figs. 1A,2,3). A small orbito-insular sulcus often appears anterior to the limen but remains entirely within the topographical confines of the insula (Figs. 1A,2,3). On either side of this orbito-insular sulcus, the insula contains a dysgranular type of cortex (Idg). In this portion of Idg, there is a thin but identifiable granular layer 4 which contains clusters of granules interrupted by pyramidal neurons. A granular layer 2 is absent. Instead, layer 2 in this anterior portion of Idg contains clusters of darkly staining small pyramids which are similar in appearance to those in L2 of prepiriform cortex (Fig. 4A). This portion of the dysgranular insula is almost identical in appearance to and continuous with the dysgranular component of cau-

¹ Granule cells are small, round neurons which stain lightly with Nissl stains and which correspond to the star pyramids and star cells in Golgi preparations (Lorente de N6, '49).

Abbreviations

AS	Arcuate sulcus	OFO	Opercular cortex ¹
AI	First auditory area	OIS	Orbitoinsular sulcus
AII	Second auditory area	PA	Postauditory cortex ²
CL	Clastrum	PF	Anterior inferior parietal cortex ³
CS	Central sulcus	PI	Parainsular cortex ²
G	Gustatory area	POC	Prepiriform part of olfactory cortex
I	Insula	Prco	Precentral operculum ¹
Ia-p	Insula, agranular periallocortical	PS	Principal sulcus
Idg	Insula, dysgranular	PT	Putamen
Ig	Insula, granular	RI	Retroinsular cortex ²
ILS	Inferior limiting sulcus	SLS	Superior limiting sulcus
IPS	Intraparietal sulcus	STP	Supratemporal plane
L	Lateral limb of ILS	STPg	Supratemporal cortex, granular
LF	Lateral fissure	SI	First somatosensory cortex
LILS	Lateral limb of ILS	SII	Second somatosensory cortex
LOS	Lateral orbitofrontal sulcus	TO	Olfactory tract
M	Medial limb of ILS	TP	Temporopolar cortex
OF	Orbitofrontal cortex	TPa-p	Temporopolar cortex, agranular periallocortical
OFa-p	Orbitofrontal cortex, agranular periallocortical	TPdg	Temporopolar cortex, dysgranular
OFdg	Orbitofrontal cortex, dysgranular	3, 1-2	Areas 3, 1, 2 ⁴
OFg	Orbitofrontal cortex, granular	12, 13	Orbitofrontal cortex ⁵

¹According to Roberts and Akert ('63).²According to Jones and Burton ('76).³According to Bonin and Bailey ('47).⁴According to Brodmann ('05).⁵According to Walker ('40).

dal orbitofrontal cortex. Darkly staining medium-size pyramids in OFdg and in anterior Idg lend the infragranular layers their tinctorial prominence. These deep layers are incompletely demarcated from the white matter and cellular bridges often extend into the claustrum (Fig. 5). The supragranular layers lack sublaminar or distinct columnar arrangement.

It appears that Roberts and Akert ('63) as well as Jones and Burton ('76) would designate most of this anterior portion of the insula as agranular (Fig. 1D,E). We based our map on 35 μ m thick sections as compared to the 30 μ m thickness used by Roberts and Akert ('63) or the 20 μ m thickness used by Jones and Burton ('76). The thicker sections facilitated the recognition of granule cell clusters in L4 and prompted us to classify this sector as dysgranular. In fact, when we examined specimens cut at thickness of 10 μ m or 27 μ m, the incipient granularity of layer 4 in this region was more difficult to detect, giving this region a rather agranular appearance.

Insula at the limen

At the limen, the insula becomes continuous with the temporal lobe. At about this level, prepiriform cortex trifurcates. One limb remains in an orbital position, a second limb extends into the insula, and a third limb covers the medial aspect of the temporal pole (Figs. 1A,5). The insular extension of prepiriform cortex is continuous with agranular-periallocortical cortex (Ia-p). As in the agranular orbital cortex, the most superficial cell layer in the outer stratum of the agranular insula is directly contiguous with the pyramidal layer of prepiriform cortex. There is no identifiable granule cell layer. The inner stratum is continuous with neurons of the claustrum and possibly also with those of the deep layer in olfactory cortex (Fig. 4B). As was the case in orbital agranular-periallocortical cortex, the agranular insula, claustrum, and prepiriform cortex are

incompletely demarcated from each other at this level (Fig. 4A,B). Toward the boundary with the dysgranular sector of the insula an intermediate stratum of deeply staining pyramidal neurons, which appears continuous with the L5 of the more dorsal cortical mantle, inserts itself between the outer and inner strata of the agranular Ia-p sector (Figs. 4B,5). The agranular-periallocortical part of the orbitofrontal area and the corresponding sector of the insula have identical architecture and are in direct continuity with each other (Figs. 1A,2B-F).

More dorsally, the insula assumes a dysgranular structure (Idg) with the appearance of granule cell clusters in layer 4 (Figs. 2E,F,4B,5). Layer 2 lacks appreciable aggregates of granule cells and is difficult to demarcate from L3. Layer 3 lacks consistent substratification by cellular

Fig. 1. Architectonic maps of the insula and surrounding cortical regions. A. This map is based on our observations of 35- μ m-thick celloidin-embedded, coronally cut sections stained with cresyl violet. The solid lines indicate the fundus of sulci. Broken lines demarcate architectonic boundaries. The dotted lines indicate the outer limits of the charted region which were set at the point of origin for the Sylvian fissure. Therefore, this map includes only the inner face of the frontoparietal operculum, the supratemporal plane, the insula, and some immediately adjacent parts of the temporal pole and orbital area. The wavy lines are the borders of areas more medially situated than those depicted on the other portions of the map. The gray area represents the insula. There are no obvious boundaries between the anterior insula and orbitofrontal regions. The blackened area represents prepiriform olfactory cortex (POC). The orbital and temporopolar portions of POC are only partially shown in this map and extend further medially. Anterior to the LOS, a granular cortex which would be designated OFg makes its appearance but is not shown in the map. B. Cytoarchitectonic parcellation of orbitofrontal cortex by Walker ('40). In this map, FM corresponds to the lateral orbital sulcus (LOS) and OS to the medial orbital sulcus (MOS). C. Cyto- and myeloarchitectonic parcellation of the supratemporal plane by Sanides ('72). D. Cytoarchitectonic parcellation of insula and frontoparietal opercula by Roberts and Akert ('63). "tr" refers to transitional belts. E. Cytoarchitectonic parcellation of insula and surrounding regions by Jones and Burton ('76).

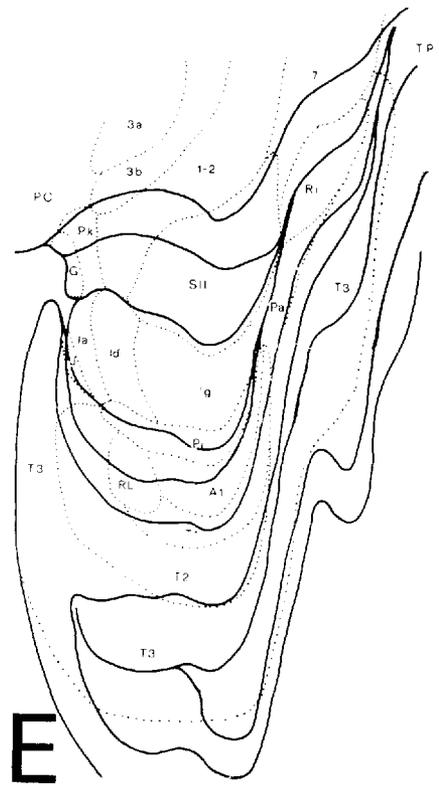
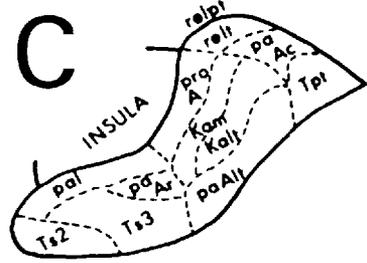
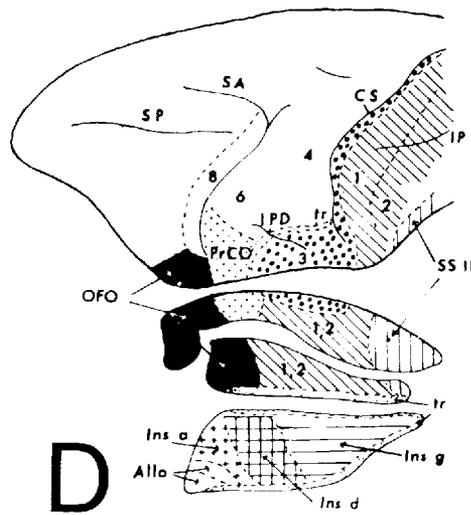
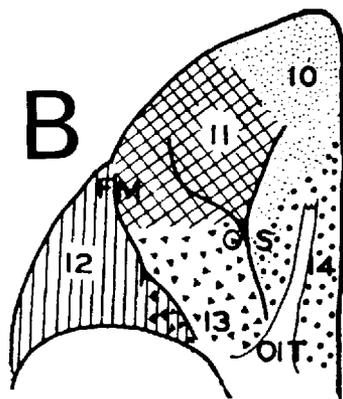
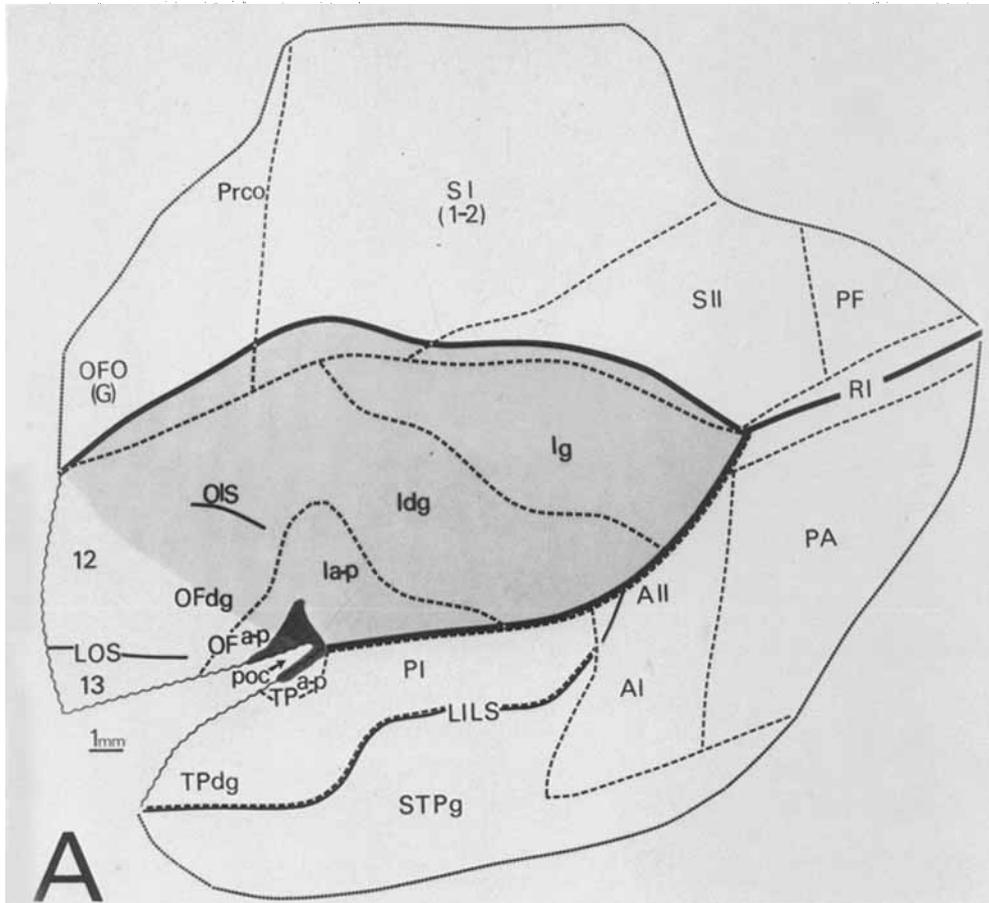


Figure 1

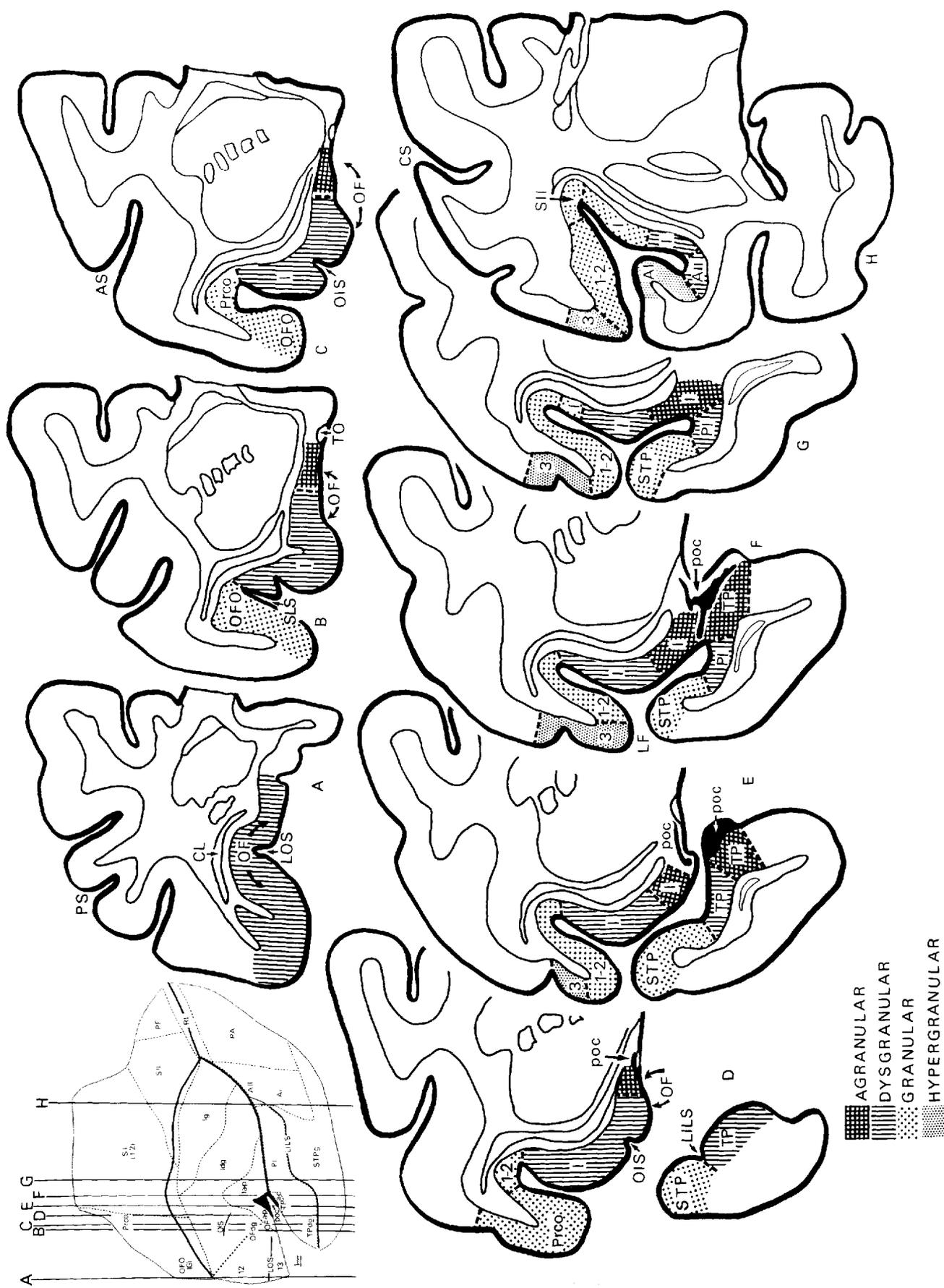


Fig. 2. Coronal cross sections show the organization of each architectonic subtype in the insular, orbital, and supratemporal regions.

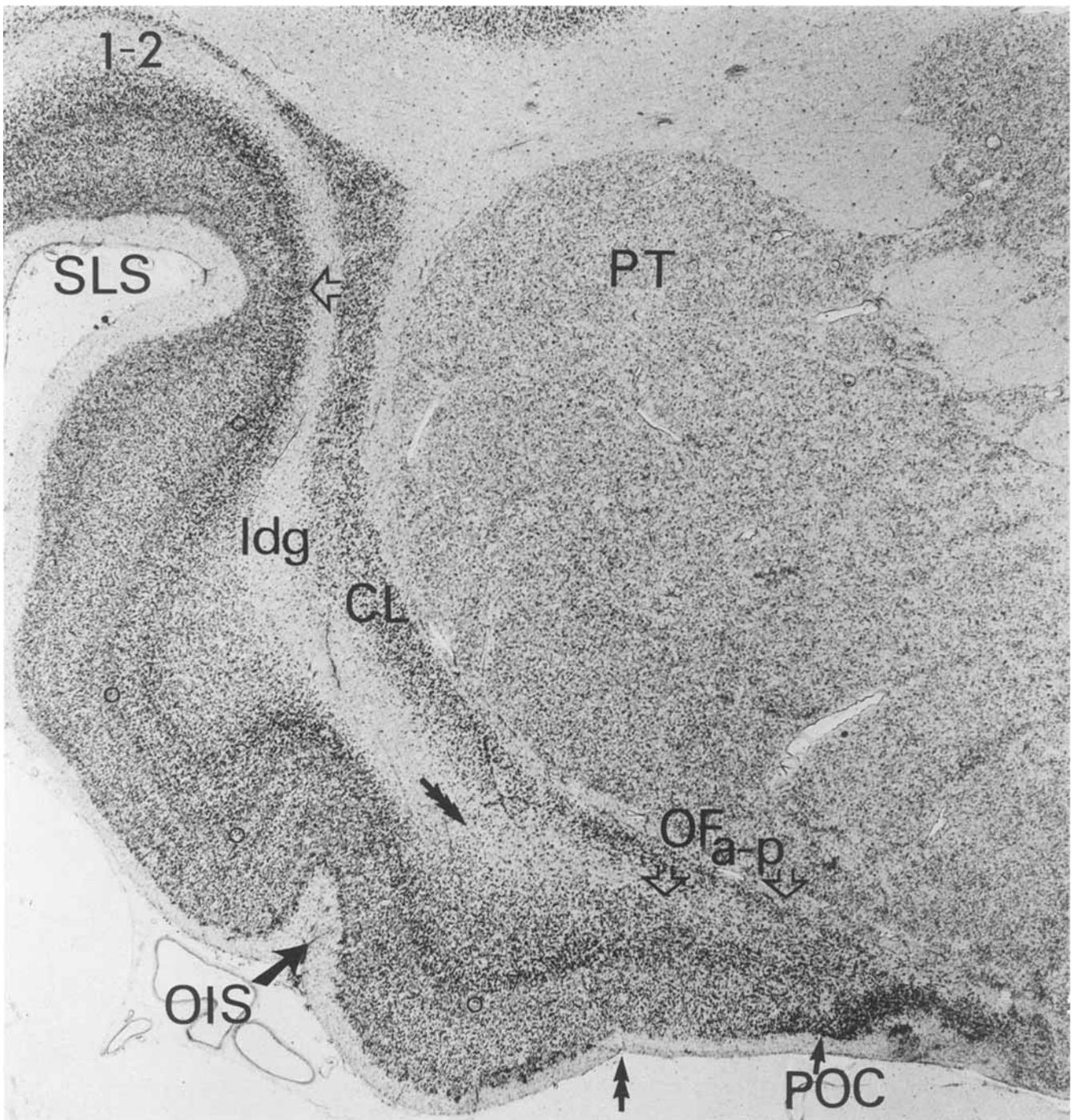


Fig. 3. Photomicrograph of section shown in Figure 2D. The open arrows point to architectonic boundaries. In OFa-p, the outer stratum is continuous with the pyramidal layer of POC, the inner stratum merges with the claustrum. Virtually no granule cells are present. More laterally the cortex takes on a dysgranular form as indicated by the appearance of clusters of granule cells. The double arrowhead points to the arbitrary division between orbitofrontal cortex medially and the insular region laterally. At this level there is only a thin sliver of OFdg, the rest of the dysgranular cortex is Idg. In the ventral part of Idg, L2 contains clusters

of deeply staining small pyramids which are similar to those seen in POC. The triple arrowhead points to neurons in the extreme capsule which form a bridge between the claustrum and Idg. The open circles in Idg indicate the position of a moderately well-granularized L4. The absence of a granular L2 makes this cortex dysgranular. Area 1-2 appears dorsally and can be identified by the presence of a more granular L2 and sublaminar in L3. These features become more easily discernible at more caudal levels (Figs. 6,7). $\times 18$.

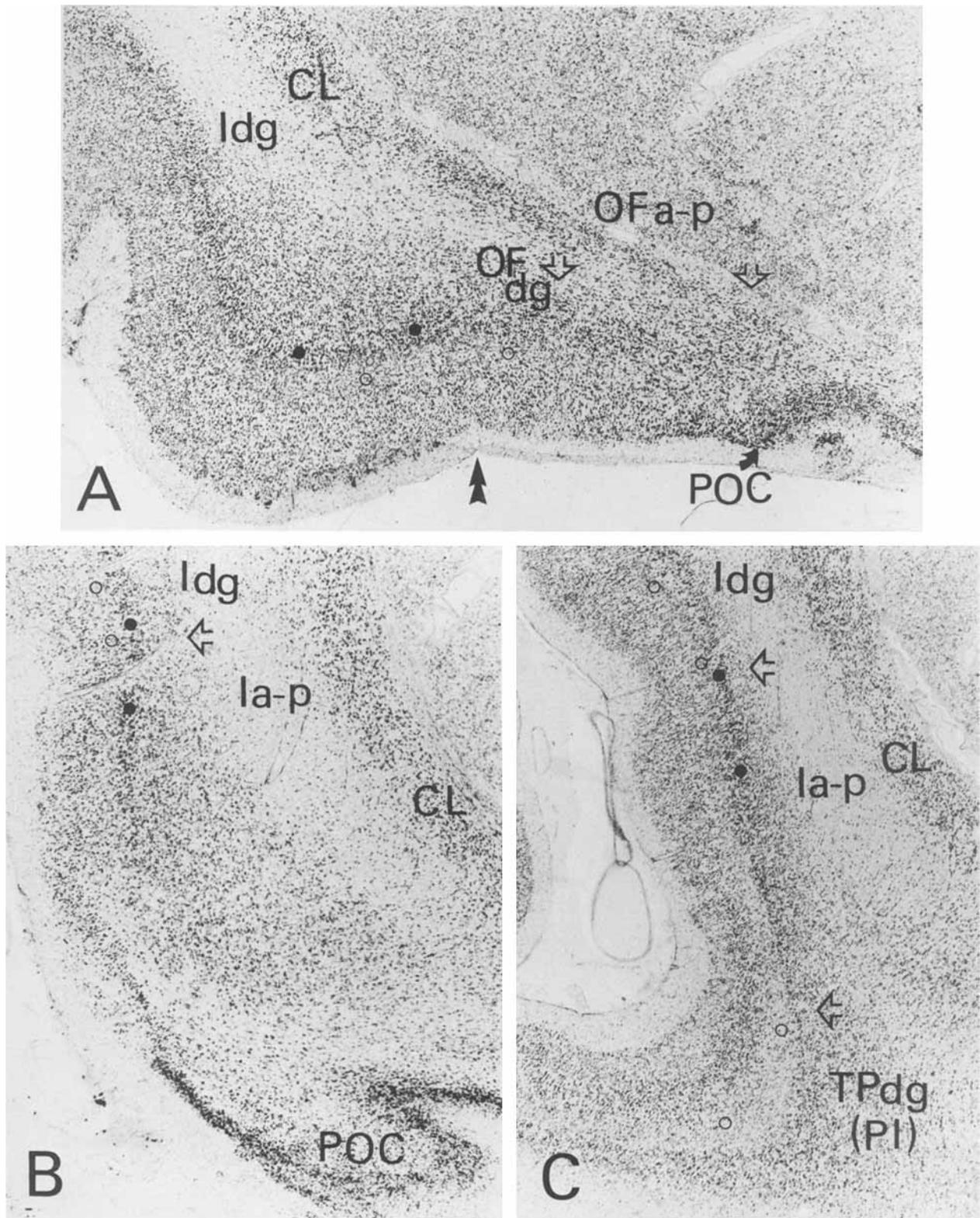


Fig. 4. A, B, and C show detail from Figures 3, 5, and 6, respectively. In each photomicrograph, the open circles indicate the position of L4 granules and the black circles the deeply staining infragranular pyramids. The double arrowhead in A indicates the division between orbital and insular cortex. The open arrows point toward architectonic boundaries. The agranular-periallocortical (a-p) segment in each photomicrograph is characterized by an inner stratum which is continuous with the claustrum (A, B, and C) and perhaps with deep layers of prepiriform cortex (B). The continuity of the outer stratum with the superficial pyramidal layer of POC can

be seen in A and B. An intermediate stratum of deeply staining pyramids (black circles) inserts itself between the other two strata. This intermediate stratum is continuous with L5 of the dysgranular sector. The agranular sector ends and the dysgranular begins when clusters of granules appear in L4 (open circles). There is no obvious distinction between OFdg and Idg (Fig. 4A). Idg in A and TPdg in C contain clusters of deeply staining small pyramid cells in L2. The lightly staining zone between the outer and intermediate strata of Ia-p in C contains virtually no granules. A, $\times 27$; B, $\times 53$; C, $\times 41$.

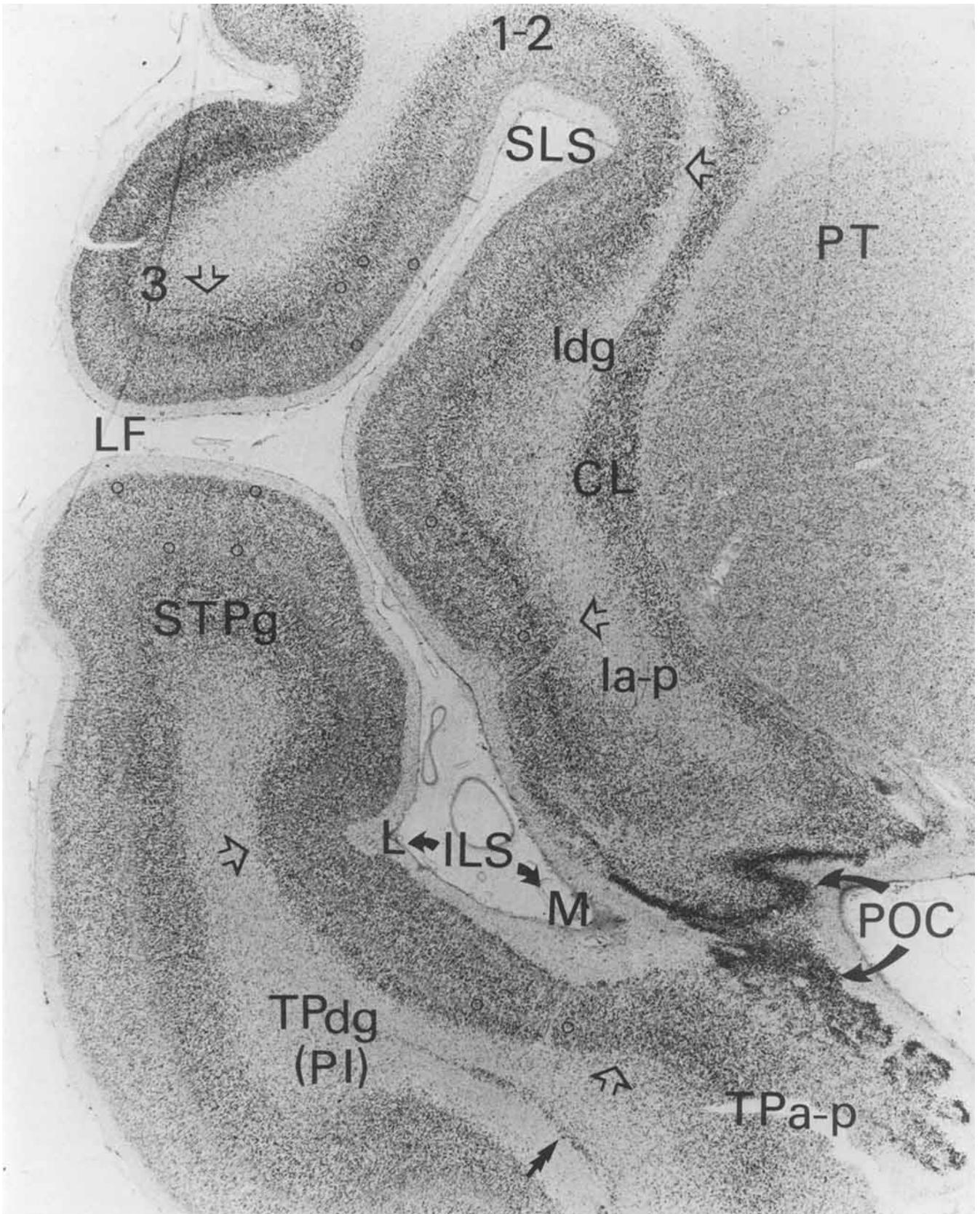


Fig. 5. Open arrows point toward architectonic boundaries. Open circles indicate the position of inner (L4) and outer (L2) granular layers. This section corresponds to Figure 2F and is at the level of the limen insulae. The trifurcation of POC occurs at this level. The insular extension of POC is continuous with Ia-p. The temporopolar extension of POC overlies TPa-p. The outer stratum of TPa-p is continuous with POC and the inner stratum is continuous with a subcortical cell area, which may correspond to a

temporal extension of the claustrum (double arrow). TPa-p does not have an intermediate stratum. TPdg begins with the appearance of granule cell clusters in L4 (open circles). At this level TPdg lacks a granular L2 but contains small deeply staining pyramids in that layer. STPg contains a differentiated granular layer not only in L4 but also in L2 (open circles). Idg begins with the appearance of L4 granule clusters (open circles). Some neurons continue to bridge the gap between insula and claustrum. Areas 1-2 contain granular layers 2 and 4 (open circles) and also sublamination in L3. Area 3 is hypergranular so that L4, 3, and 2 tend to merge. $\times 26$.

size or density and does not show columnar organization. Layer 5 stands out because of deeply staining pyramids (Fig. 5). The distinction between L5 and L6 is often blurred. Few neurons are scattered in the extreme capsule and bridge the gap between insula and claustrum. At the level of the limen, most of the insula is covered by this type of dysgranular cortex (Idg). This dysgranular cortex of the insula is identical in appearance to the dysgranular cortex of the orbitofrontal surface with which it is in direct continuity more anteriorly (Figs. 1A, 2A-F).

Insula posterior to the limen

Posterior to the limen, the medial limb of the inferior limiting sulcus provides a ventral boundary for the insula. For about another 5 mm posterior to the limen, Ia-p continues to cover the ventral part of the insula (Figs. 1A, 2G, 4C, 6). Dysgranular cortex also extends posterior from the limen. Initially, the cytoarchitecture in this part of Idg is identical to that described for the more rostral dysgranular insula. More posteriorly and dorsally, however, L4 of Idg becomes progressively more granularized and also more demarcated from adjacent laminae. A columnar organization appears in L3 but there is no consistent stratification into sublaminae. The tinctorial predominance of the infragranular layers is gradually lessened and the differentiation of L5 and L6 becomes more distinct (Figs. 6, 7). Even though the development of L4 may have led some observers to label this type of cortex granular, we continue to call it dysgranular because L2 shows only incipient granularity and is not demarcated from L3 (Figs. 1A, 2G, H, 6, 7).

The most caudal and dorsal third of the insula is covered by granular cortex (Ig). Layer 2 of Ig has a moderately advanced granularity which allows its demarcation from L3 (Fig. 7). There is an incipient stratification into L3A and L3B on the basis of cellular density rather than on the basis of a gradient in the size of the constituent neurons. Layer 4 is well granularized and almost fully demarcated. In contrast to dysgranular cortex, the infragranular layers of Ig are not prominent. Layers 5 and 6 are still not fully differentiated from each other but the demarcation from the underlying white matter is sharper (Fig. 7).

Temporal operculum

At the limen, the temporopolar extension of prepiriform cortex is also associated with an agranular-periallocortical sector (TPa-p). As in the case of orbital and insular agranular cortices, this agranular moiety also has a superficial stratum in virtual continuity with the overlying primary olfactory cortex and an internal stratum continuous with a subcortical group of neurons which may represent the temporopolar extension of the claustrum (Fig. 5). An intermediate pyramidal stratum is absent in TPa-p.

Immediately lateral to this agranular area lies a dysgranular type of cortex (TPdg) (Figs. 1A, 2D-G, 5). The second layer of TPdg lacks granularity and contains the small dark pyramids that are also found in layer 2 of the orbital and insular agranular-dysgranular regions. Layer 4 has incipient granularity. In contrast to orbital and insular dysgranular cortex, there is no tinctorial predominance of infragranular layers in TPdg. This dysgranular cortex extends beyond the limen insulae both anteriorly and posteriorly (Figs. 1, 2D, E). Posterior to the limen, this extension of TPdg on the supratemporal plane has been called

parainsular cortex (PI in Fig. 1A, C, E). Although L4 becomes gradually more granular in more posterior parts of PI, the lack of laminar demarcation or granularity in its L2 makes this cortex dysgranular in type (Figs. 5, 6). At the limen, the Ia-p can be differentiated from PI by the granularity of L4 in the latter. Caudal to the disappearance of the agranular insula, the dysgranular insula abuts on the dysgranular portion of the supratemporal plane (PI). At that level, the two types of dysgranular cortex are difficult to distinguish from each other.

Lateral to the supratemporal dysgranular cortex (PI), there is another longitudinal band of cortex with a granular cytoarchitecture (Figs. 1A, 2B-H, 5, 6). This supratemporal granular band (STPg) contains the Ts3 and paAlt of Sanides ('72) and T1 and T2 of Jones and Burton ('76) (Fig. 1A, C, E). These regions are characterized by granularity and laminar demarcation in both L2 and L4.

More posteriorly, the supratemporal plane contains the auditory cortex. Sanides ('72) has subdivided auditory cortex into proA (AII), Kam (medial AI), and Kalt (lateral AI). We have not drawn boundaries between AI and AII in our planar map (Fig. 1A). However, area AI can be identified by its hypergranular appearance, which causes layers 2, 3, and 4 to blend into an uninterrupted layer of superimposed granules. All six layers can be clearly identified in AII, which is less granular than AI. Posterior to the insula, the supratemporal plane contains granular homotypical association areas which have been designated as postauditory cortex (PA) by Jones and Burton ('76) and reIt, paAc, and Tpt by Sanides ('72). Compared to auditory cortex, especially AI, the group of areas in PA has a reduced overall granularity. Furthermore, the L3 pyramidal neurons which flank the outer edge of L4 are more conspicuous in PA than in auditory cortex.

Frontoparietal operculum

At the most anterior levels of the insula, the inner surface of the frontal operculum is covered by a cortical region which has been designated by Roberts and Akert ('63) as OFO anteriorly and Prco caudally. According to Sanides ('68, '70) and Jones and Burton ('76) OFO corresponds to a primary gustatory cortex (G). The cytoarchitectonic differences between OFO and Prco are minor and we have not drawn boundaries (Figs. 1A, D, E, 2B-D). The OFO and Prco regions contain a granular type of cortex with thinly populated but distinctly granular laminae 2 and 4. There is no sublamination in L3. Infragranular layers are more conspicuous than supragranular ones. The granularity in L2 allows this opercular cortex to be differentiated from the adjacent dysgranular insula (Idg).

Posterior to OFO-Prco, the inner face of the parietal operculum is covered by areas 1 and 2 of somatosensory cortex (SI). This is granular cortex with a densely cellular L4, moderately well-developed granularity in L2, and rather distinct demarcation of L5 from L6 and of L6 from the underlying white matter (Figs. 1A, 5-7). The distinction between SI and the more caudal SII is by no means obvious. SII tends to have a thicker layer 2, denser cellularity in L3A, and a somewhat less clear separation of L5 from L6. SI and SII both have a sublamination in L3 based on a size gradient so that the larger and deeper staining pyramids form a conspicuous L3B. This feature helps to differentiate SI from OFO-Prco and SI-SII from the insula (Fig. 7).

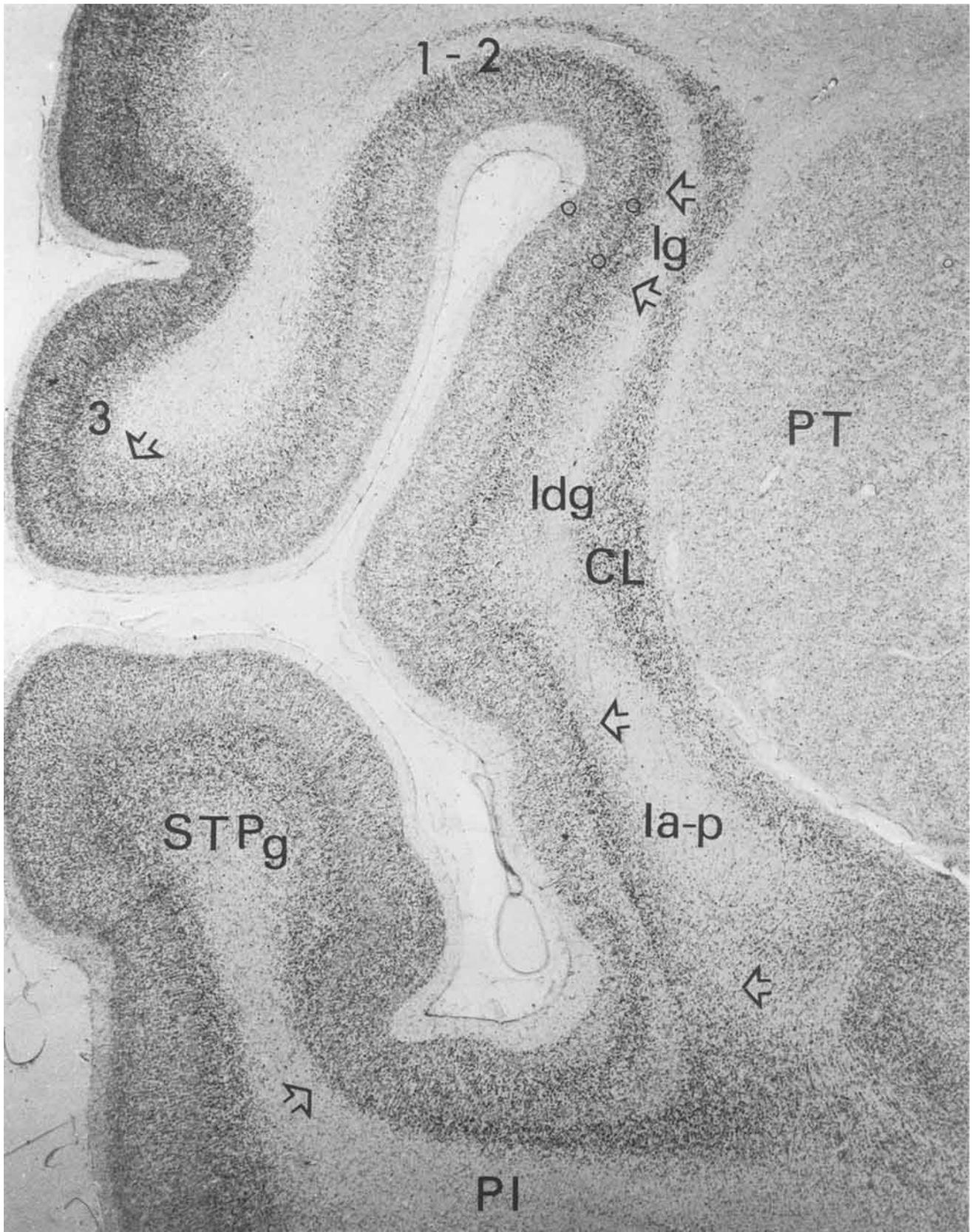


Fig. 6. This photomicrograph corresponds to Figure 2G. At this level Ig makes its appearance with the further differentiation of a granular L2 (open circles). Idg shows the tinctorial prominence of the infragranular

layer. This infragranular predominance is decreased in Ig and absent in PI. The presence of a marked L3 sublamination in 1-2 differentiates it from Ig. $\times 29$.

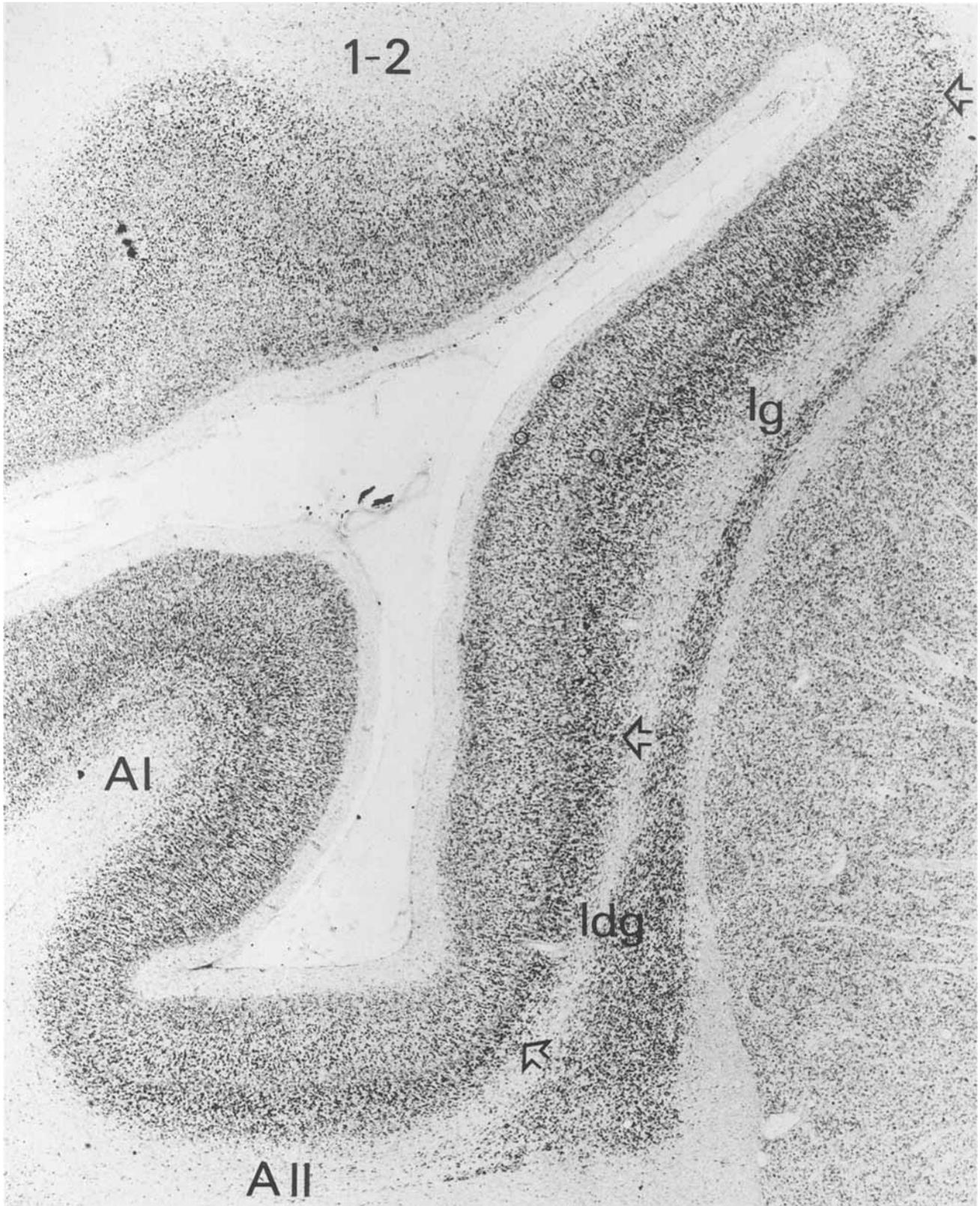


Fig. 7. This photomicrograph corresponds to Figure 2H. The granular Ig sector is now well established with a differentiated granular L2 and L4 (open circles). There is incipient sublamination in L3 but not as clearly as

in area 1-2. AII is characterized by the increased granularity of L2 when compared to Idg. AI is hypergranular cortex where the large number of granules cause layers 4, 3, and 2 to merge with each other. $\times 20$.

Behind SII, a sliver of PF cortex extends into the upper bank of the Sylvian fissure and can be distinguished from SII by the greater sublamination of its infragranular layers. Postinsular areas PA and PF are separated from each other by a thin band of retroinsular cortex (RI) which lines the depth of the caudal Sylvian fissure and which is distinguishable from PF and PA by the thinness of its infragranular layers.

The overall architectonic organization shown in Figure 1A was confirmed in the specimen cut in the horizontal plane of section.

MYELOARCHITECTONICS

The distribution of intracortical myelin in the insula shows differences from one cytoarchitectonic sector to another (Fig. 8). The agranular-periallocortical insula (Ia-p) is characterized by a conspicuous band of myelinated fibers arranged tangentially in L1 (Fig. 8B). This zonal layer of myelinated fibers is most conspicuous at the level of the limen and helps to differentiate the agranular insula from area PI (dysgranular supratemporal cortex) which does not contain the L1 band. The deeper stratum of the agranular insula contains few isolated myelinated fibers. A similar zonal band of myelin is also present in the agranular-periallocortical sector of the orbitofrontal area (OFa-p).

The dysgranular insula (Idg) contains a sparse population of myelinated radial fibers which extend from the extreme capsule to the inner half of layer 3 (Fig. 8C). In the more posterior part of the dysgranular sector, a faint outer line of Baillarger begins to appear in L4. This pattern is very similar to that of the dysgranular orbitofrontal region (OFdg) with which the insula is topographically continuous.

The granular insula (Ig) has a greater density of tangential fibers in the infragranular region. Furthermore, tangential fibers around L4 begin to form an insipient external line of Baillarger (Fig. 8A,D). A similar pattern is present in the granular portion of orbitofrontal areas 12 and 13 (OFg). The part of areas 1, 2, and SII which abut on the insula are characterized by considerably more intracortical myelin in the inner (L5) and outer (L4) tangential lines of Baillarger as well as along the deep radial fibers (Fig. 8A,E).

In the supratemporal plane, the higher myelin content along the outer line of Baillarger in STPg allows its differentiation from PI (Fig. 8A). Primary auditory cortex especially AI, has the highest overall myelin level in this region, especially in the form of radially oriented bundles which are so dense as to obscure the visibility of tangential layers of myelinated fibers. Postauditory cortex (PA) has fewer radial bundles and a relatively dense and conspicuous outer tangential layer in L4. This pattern of myelination in PA has been reported by Pandya and Sanides ('73).

In the frontoparietal operculum, OFO (G) is characterized by heavier myelination in L4 than the adjoining dysgranular orbitoinsular fields (Sanides, '70). SI contains even more intracortical myelinated fibers in L4 (outer layer of Baillarger) than OFO-Prco or SII.

These observations indicate that there is a gradual increase of intracortical myelin as one proceeds from the agranular to the granular sectors not only in the insula, but also in the caudal orbital region and in the rostral supratemporal plane. The individual intracortical myelin patterns of the orbital agranular, dysgranular, and gran-

ular sectors are virtually identical to the cytoarchitectonically corresponding sectors of the insula.

ACETYLCHOLINESTERASE CHEMOARCHITECTONICS

The insula and surrounding opercular regions contain AChE-rich fibers (Figs. 9-11). The agranular-periallocortical insula (Ia-p) has a dense plexus of thick AChE-rich fibers in the intermediate and inner strata (Fig. 10). The AChE content decreases in the outer layers. The immediately subpial region is virtually free of AChE. There is a loose AChE band among the superficial cells of the outer stratum. The rest of the outer stratum contains bundles of radially oriented AChE fibers which go as deep as the AChE-rich plate of the intermediate and inner strata (Fig. 10).

The AChE content is diminished in the dysgranular insula (Idg). In this region there is a wispy and loosely reticular pattern in layers 1 and 2 and then also in layers 5 and 6. Layers 3 and 4 have the least amount of the enzyme (Figs. 10,11). The granular insula (Ig) has even less AChE. The AChE gradually disappears from layers 1 and 2 and becomes confined to a loose reticulum in layers 5 and 6 of Ig (Fig. 11). In a small number of cases, on the other hand, the ventral portion of posterior Ig contained a dense band of AChE in L1.

The AChE pattern in the orbitofrontal region parallels that in the insula. The agranular-periallocortical orbital area (OFa-p) also has a very dense plate of AChE-rich fibers in the deep layers which is very similar to that in the agranular insula (Fig. 9). The dysgranular and granular orbitofrontal regions have AChE patterns which appear virtually identical to their cytoarchitectonic counterparts in the insula.

There is a different chemoarchitectonic pattern in the temporal operculum. The AChE in that area is heaviest in the most superficial layers (Figs. 10,11). This contrasts with the arrangement in the insula where the deeper layers always have higher AChE concentrations. Furthermore, PI can be distinguished from the adjacent agranular insula because the superficial AChE in PI begins immediately below the pia whereas in the insula there is a subpial zone free of AChE. Proceeding posteriorly within PI, the thickness of the superficial AChE band decreases (Figs. 10,11). A subpial AChE band is also present in STPg but is distinctly narrower than the one in PI (Figs. 10,11). Area AI can be distinguished from STPg on the basis of a light AChE band in the upper border of layer 4 in AI. As in insulo-orbital regions, the content of intracortical AChE diminishes from the agranular to the granular components of supratemporal regions.

This cortical pattern of reaction product is obtained when acetylthiocholine is used as the substrate for the histochemical reaction but not with butyrylthiocholine. This shows that the reaction product is being formed by true AChE activity rather than by other esterases.

COMPARISON WITH THE HUMAN BRAIN

The human insula is much more extensive than the one in the rhesus monkey and contains several sulci and at least two distinct gyri. However, the general architectonic plan in the two species are remarkably similar (Fig. 12). At the level of the limen insulae, there is an agranular Ia-p sector. The outer stratum of this sector is continuous with prepriiform cortex while the inner stratum is incom-

pletely separated from the underlying mass of the claustrum. An intermediate stratum appears dorsally in the agranular Ia-p sector. As in the rhesus monkey, intracortical myelin in Ia-p is concentrated in a zonal layer. More dorsally and posteriorly, the insula becomes covered by a dysgranular cortex where the infragranular layers show a tinctorial prominence. The granularity of L4 and L2 gradually becomes more extensive until both layers become sufficiently differentiated to give the posterior insula a granular appearance.

DISCUSSION

Architectonic plan in the insula of monkeys and humans

The insula of Reil in the old world monkey can be subdivided into three architectonic sectors (Jones and Burton, '76; Roberts and Akert, '63). A periallocortical-agranular sector (Ia-p) is continuous with the insular extension of prepiriform cortex. This sector lacks identifiable aggregates of granule cells and displays a relatively simple laminar arrangement consisting of three cellular strata. An outer stratum contains small pyramids and maintains direct continuity with the pyramidal layer of prepiriform cortex; an inner stratum of more polymorphic cells is in continuity with the underlying claustrum and perhaps also with the deep cellular layer of prepiriform cortex; an intermediate stratum of larger and more hyperchromic pyramids is in continuity with layer 5 of more dorsal dysgranular cortex. This agranular sector is characterized by a zonal layer of myelinated fibers in L1 but the overall level of cortical myelin is otherwise low. The density of cortical AChE in the insula reaches its peak in this agranular sector, especially along the intermediate and inner strata.

A dysgranular Idg sector containing five to six cortical layers abuts on the agranular-periallocortical insula. In the immediate vicinity of the agranular sector, the L2 of the dysgranular insula contains only scattered granule cells and cannot be demarcated from L3; L3 is sparsely populated and lacks a laminar or columnar suborganization; L4 contains granule cells arranged in clusters rather than in a continuous lamina; L5 is prominent because of its hyperchromic neurons; L6 is difficult to differentiate from L5 as well as from the underlying white matter. More dorsally and posteriorly, the dysgranular sector shows an incipient columnar arrangement in L3, a continuous lamination of granule cells in L4, and a decreased prominence of L5. However, L2 remains rudimentary. Intracortical myelin in Idg is low and mostly in the form of deep radial fibers. The lines of Baillarger are almost totally absent. In contrast to the agranular cortex, the zonal layer of myelin is quite inconspicuous in the dysgranular sector. Cortical AChE is less than in the agranular sector and remains concentrated mostly in the infragranular layers.

The granular Ig sector occupies a posterior-dorsal wedge of the insula. Layers 2 and 4 are both granular and fully demarcated from adjoining laminae; incipient sublamination occurs in L3; the infragranular layers are no longer prominent; and L6 can be demarcated more easily both from L5 as well as from the underlying white matter. Intracortical myelin in the insula reaches a peak in the granular sector where inner and outer lines of Baillarger appear in addition to radially oriented myelinated fibers.

Cortical AChE is further decreased and remains confined to a loose reticulum in the infragranular layers.

The human insula shows a remarkable similarity in overall plan and contains agranular, dysgranular, and granular sectors. There is a periallocortical sector which is agranular in character and which has continuity with prepiriform cortex through the outer stratum and the claustrum through the inner stratum. A zonal layer of myelin is also conspicuous in the agranular sector of the human insula. As in the monkey, there is increased laminar differentiation, granularization, and greater myelin content along a posterodorsal gradient.

A sequence of cortical divisions similar to those described in the insula can also be identified in supratemporal and lateral orbitofrontal regions. These two areas also contain an agranular sector which is in direct continuity with prepiriform cortex through the outer stratum and with a subcortical cell mass through the inner stratum. In contrast to orbitofrontal and insular dysgranular sectors, the supratemporal dysgranular area does not show the prominence of the infragranular pyramids and its adjoining agranular sector (TPa-p) lacks an intermediate stratum.

Within each of these three brain regions, cortical AChE is highest in the agranular sectors and shows a gradual decline in the dysgranular and then in the granular sectors. The laminar AChE distribution in the three lateral orbital sectors is virtually identical to that seen in the three corresponding sectors of the insula and shows a predilection for higher concentrations in inner cortical layers. In contrast, the most conspicuous band of AChE in the dysgranular and granular portions of the supratemporal plane occurs in the outer layers 1 and 2.

These observations indicate that the insula, lateral orbitofrontal cortex, and the dorsal temporopolar areas share many architectonic features.² In fact, the agranular, dysgranular, and granular sectors in the insula are so similar in cyto-, myelo-, and AChE architectonics to corresponding sectors of the lateral orbital region that the two could be considered as a single entity of insulo-orbital cortex. Sanides ('68) also stressed this continuity of orbitofrontal with insular fields in the new world monkey. It is conceivable that one unifying influence in the architectural plan of orbitoinsular cortex is the presence of the underlying claustrum.

² A more extensive description of temporopolar architectonics has been reported separately (Gower, '81; Gower and Mesulam, '82).

Fig. 8. Loyez stain for myelin. A. The open arrows point toward lines of cytoarchitectonic demarcation. These were determined by examining an immediately adjacent section stained with cresyl violet. The pattern of intracortical myelin shows regional changes which reflect cytoarchitectonic demarcations. Areas 3, 1, and 2 have the highest level of intracortical myelin. The outer line of Baillarger (double arrowhead) is quite conspicuous. Intracortical myelin decreases both in radial fibers and in the outer line of Baillarger in Ig. In Idg, myelin is confined to a few radial fibers in deep layers. Area PI (TPdg) contains virtually no intracortical myelin. STPg can be distinguished from PI by the increase of intracortical myelin and the appearance of the outer line of Baillarger. $\times 15$. B. The Ia-p showing the zonal layer of myelin in L1 and the low overall myelin. C. Myelin in the Idg sector. D. Myelin in Ig. An incipient outer layer of Baillarger appears in L4. E. Myelin in area 1-2. Intense intracortical myelin in radial fibers and especially in the outer line of Baillarger. B-E $\times 200$.

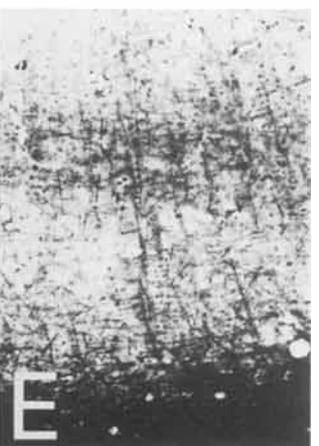
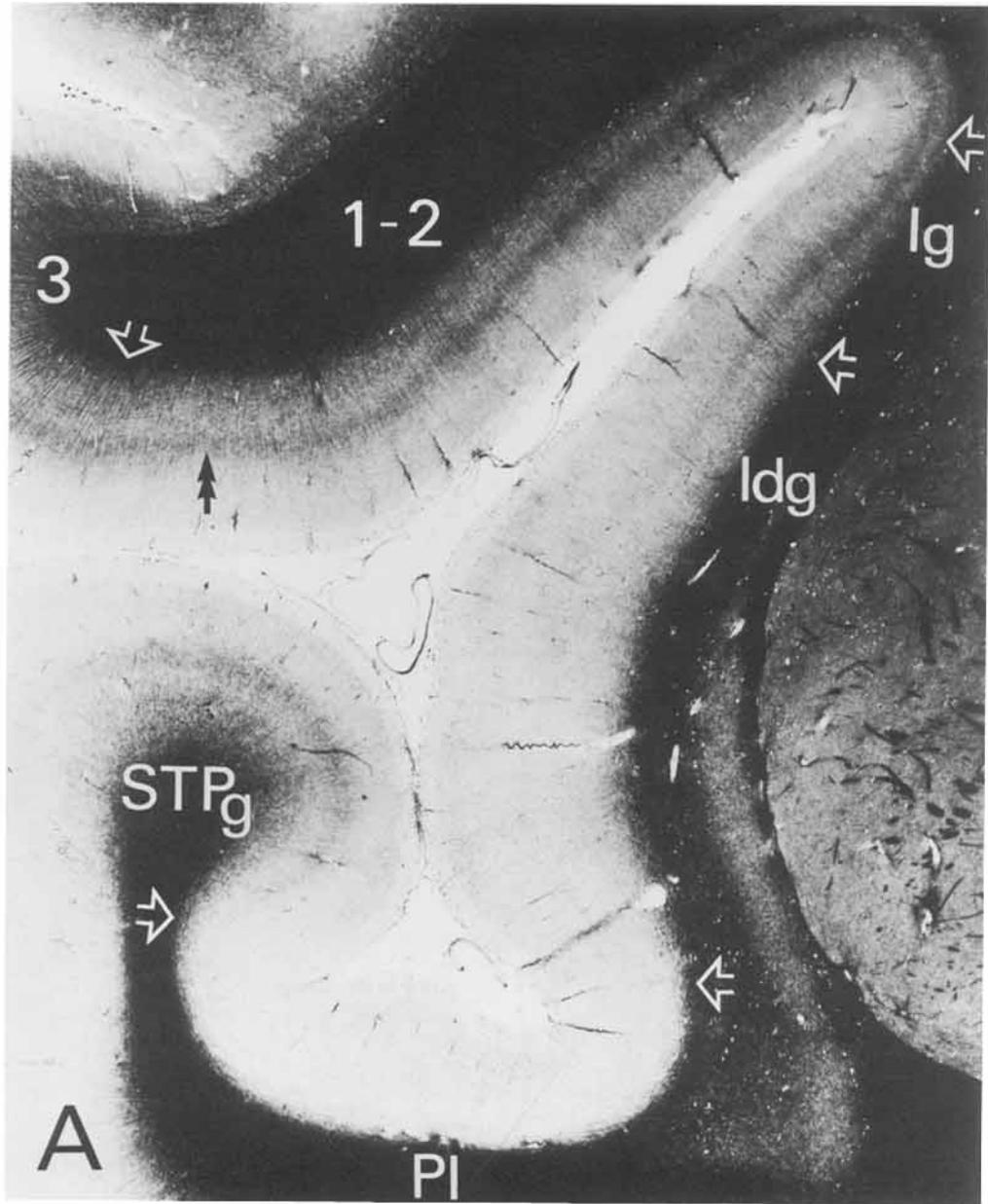


Figure 8

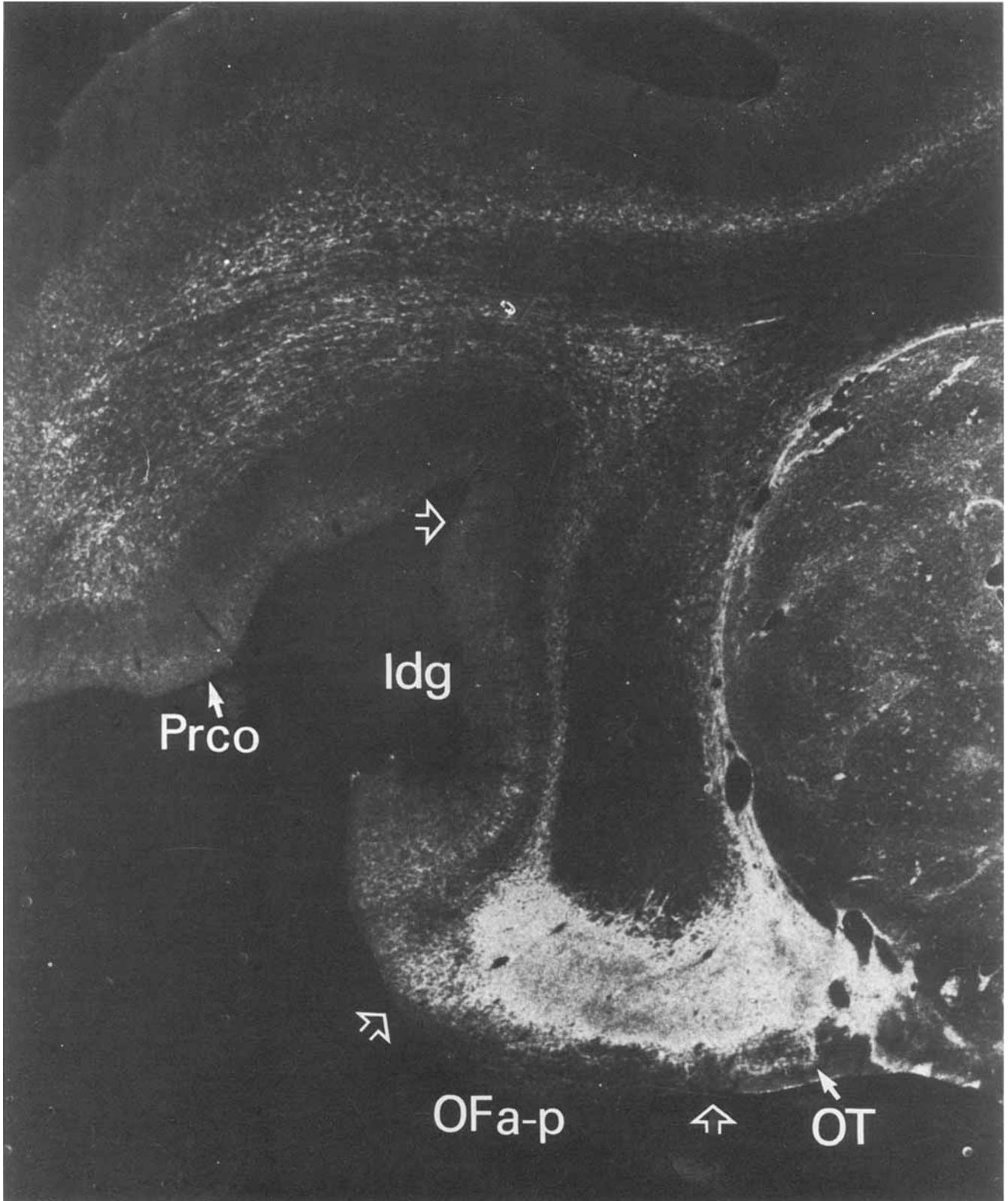


Fig. 9. Darkfield photography of intracortical AChE which appears as white against a dark background. Open arrows point to cytoarchitectonic subdivisions which were determined in matching sections stained with neutral red. OFa-p shows the highest degree of intracortical AChE, espe-

cially along the intermediate and inner strata. The AChE in Idg is much less. Its laminar distribution is difficult to determine at this level because the cortex is being cut in a tangential plane. The AChE in Prco is even lower and confined to a wispy reticulum in superficial layers. $\times 16$.

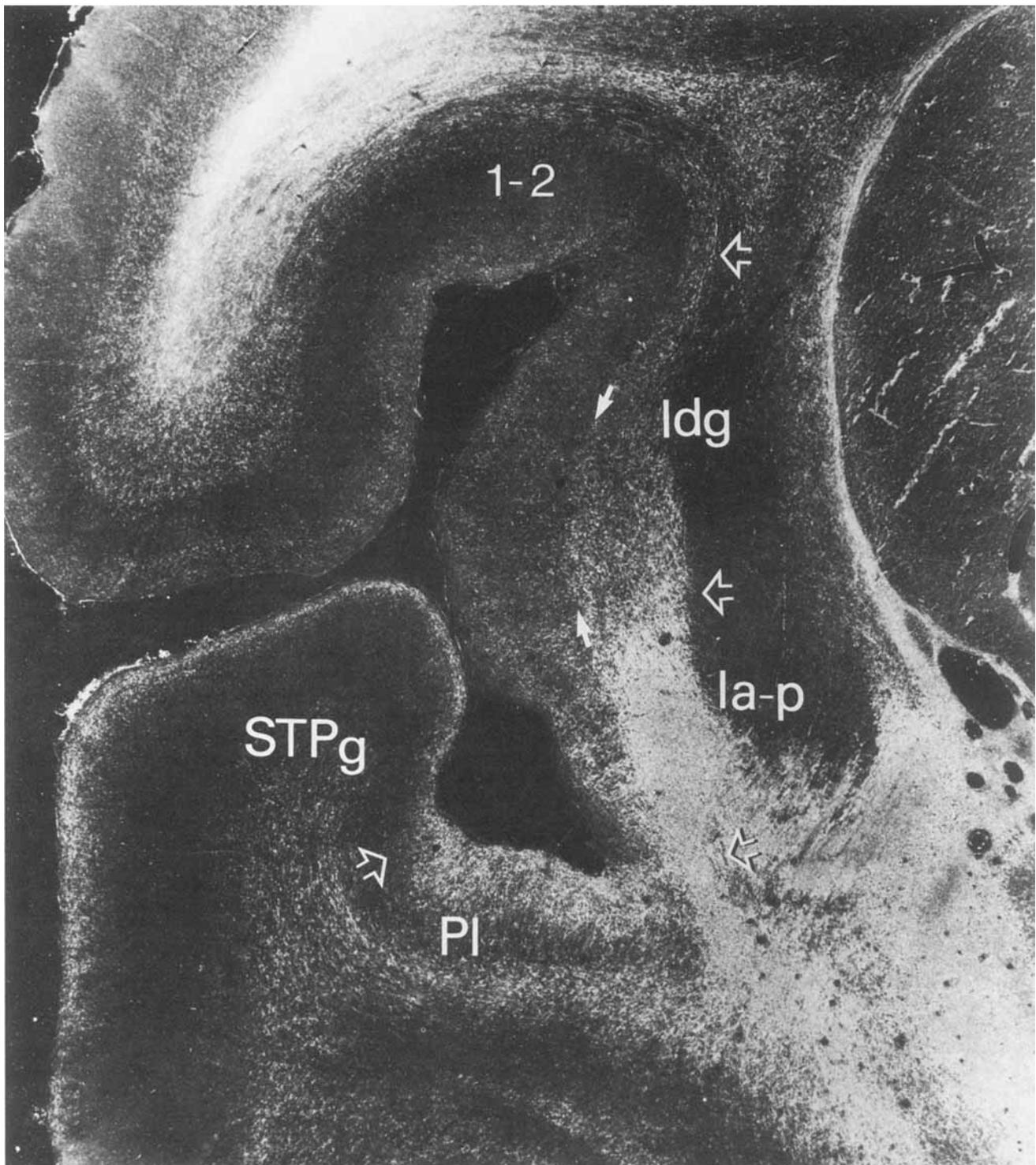


Fig. 10. Darkfield photography of intercortical AChE which appears white against a dark background. Open arrows point to cytoarchitectonic subdivisions which were determined in matching sections stained with neutral red. la-p has the greatest density of AChE, mostly in the intermediate and deep strata. A looser reticulum is also seen in the superficial stratum but the immediately subpial region is free of AChE. Idg has less AChE, mostly in the infragranular layers. The solid arrows point to the

position of L4. A loose wispy reticulum is seen in more superficial layers, especially 1 and 2. Areas 1-2 have the least AChE, confined to the most superficial layers. PI (TPdg) has a high level of AChE and most of it is in the superficial layers. The AChE in PI begins in the immediate subpial region. STPg has less AChE than PI. The most intense AChE in STPg is confined to a narrow band in layers 1 and 2. $\times 16$.

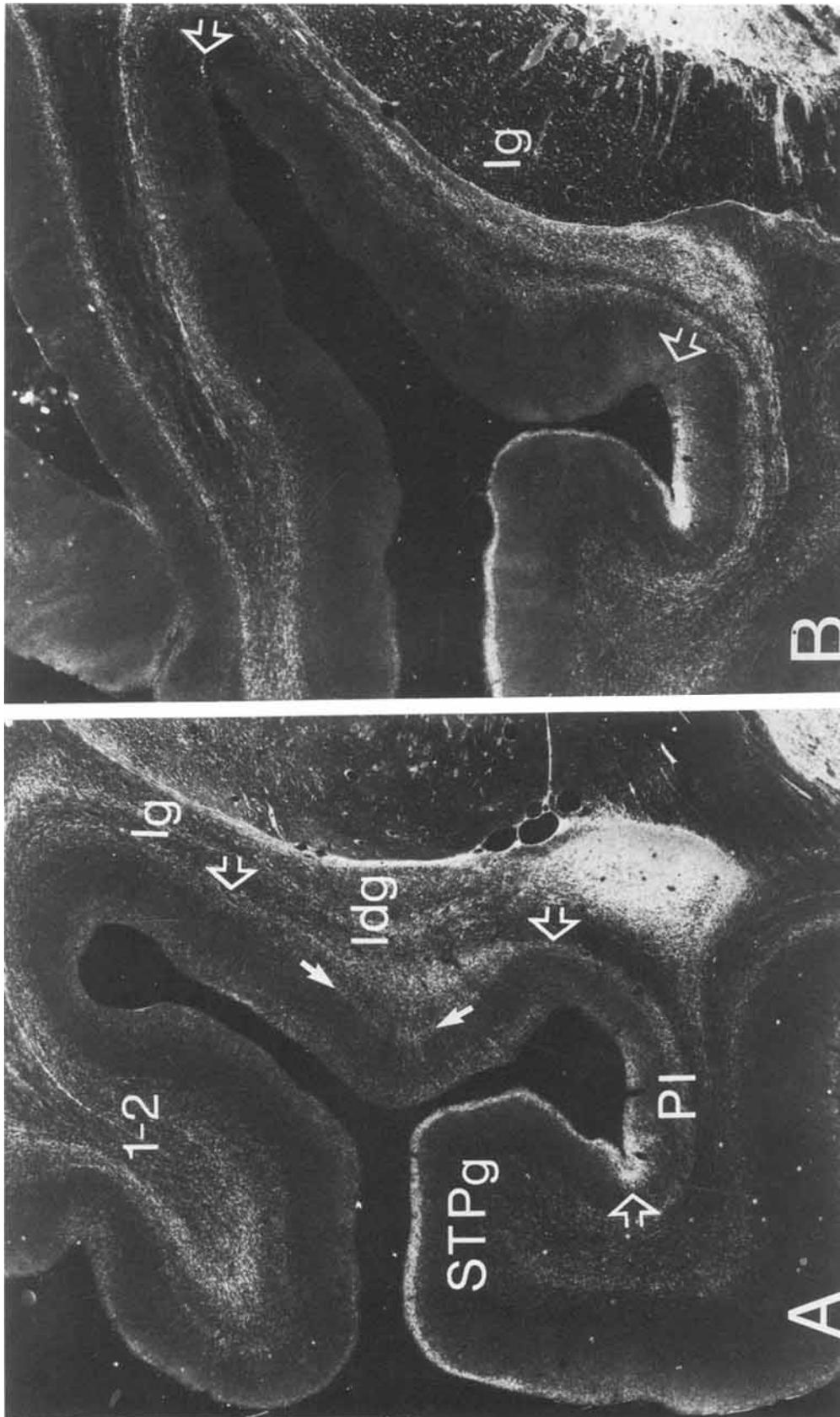


Fig. 11. Darkfield photography of intracortical AChE which appears white against a dark background. Open arrows point to cytoarchitectonic subdivisions which were determined in matching sections stained with neutral red. The solid white arrows point to the position of L4. A. The intracortical AChE in Ig is even less than in Idg. At this level, PI has less AChE than more anterior portions of PI (see Fig. 10). However the distribution of the AChE has a similar profile and is superficial in PI and STPg. $\times 11$. B. At this level, the entire insula is covered by Ig. The intracortical AChE is at its lowest level and has almost disappeared from the supra-granular layers. $\times 11$. In Figures 9-11 the underlying putamen has such a high content of AChE that the reaction product precipitates as a solid layer and does not give a darkfield effect.

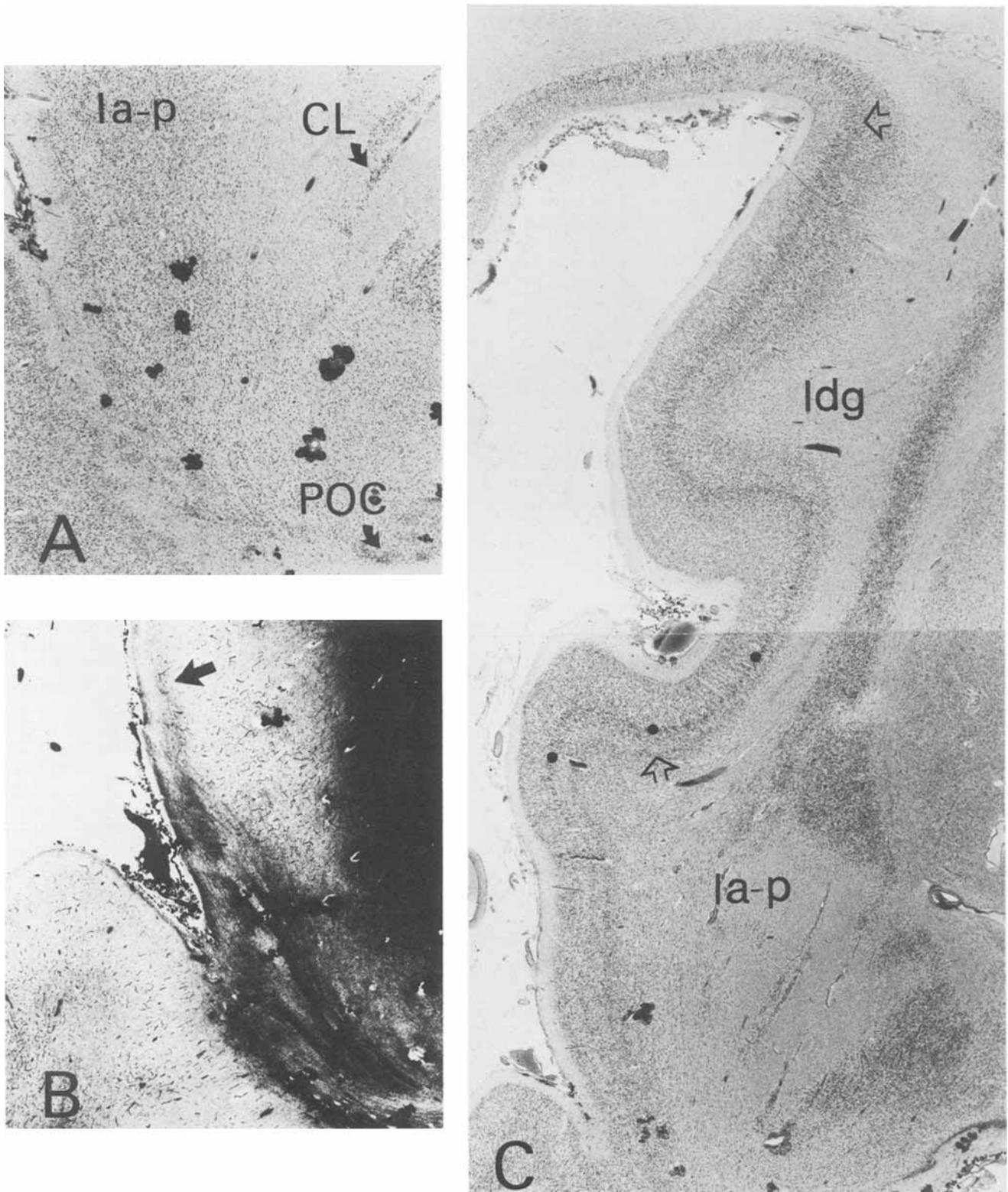


Fig. 12. Human Brain A. Cresyl violet stain of the agranular sector at the level of the limen insulae. There are no recognizable collections of granule cells. Cell bridges from the claustrum are continuous with the inner stratum of Ia-p while superficial POC cells are continuous with the outer stratum. $\times 10$. B. Immediately adjacent section stained for myelin shows the zonal band of myelin in Ia-p (arrow). $\times 7.5$. C. Photomicrograph

of the insula at a level slightly posterior to the limen. A stratum of deeply staining pyramids (black circles) is conspicuous in Idg and forms the intermediate stratum of Ia-p. The cell bridges with the claustrum are still present. Idg shows the tinctorial prominence of infragranular layers, an insipient granularity in L4, and very little granularity or differentiation in L2. $\times 9$.

The olfactory focus and concentric cortical fields: Architectural-functional features of the paralimbic brain

Prepiriform olfactory cortex is a pivotal focus when insular, lateral orbital, and temporopolar regions are considered collectively. The planar map in Figure 1A shows that around this allocortical core concentric rings of agranular, dysgranular, and granular cortex can be identified. The first periallocortical ring consists of the agranular sectors in orbital cortex (OFa-p), insula (Ia-p), and temporopolar cortex (TPa-p). The second intermediate belt consists of the orbital (OFdg), insular (Idg), and supratemporal (PI and TPdg) dysgranular areas. The third outer belt contains the granular portion of areas 12 and 13 (OFg), the granular frontoparietal operculum (OFO, 1,2, SII), the granular insula (Ig), and the granular supratemporal regions (STPg, AII, and PA). These granular sectors most closely fit the description of homotypical isocortex. It is possible to conceptualize a fourth, albeit incomplete, outermost hypergranular (koniocortical) belt in areas 3 and AI. Thus a concentric centrifugal gradient of granularization and laminar differentiation occurs around prepiriform cortex. A similar concentric plan of cortical organization has been described by both Yakovlev ('59) and Sanides ('68, '70), who concluded that this arrangement reflects the stages of cortical development in phylogeny and ontogeny.

In addition to sharing a common allocortical focus, the lateral orbital, insular, and temporopolar areas of the primate brain share common functional specializations in at least three realms: visceral-autonomic function, gustatory-olfactory sensation, and affiliative-motivational behavior. These common functions lend further validity to the need for approaching the orbital, insular, and temporopolar regions collectively. Electrical stimulation in several regions of the brain but particularly in the anterior insula, caudal orbital surface, and temporal pole yield consistent and marked changes in respiration, cardiac rate, blood pressure, and gastric motility (Hoffman and Rasmussen, '53; Kaada, '60; Kaada et al., '49; Showers and Lauer, '61; Sugar et al., '48; Wall and Davis, '51). Some of these effects can be quite dramatic and include inhibition of gastric peristalsis, respiratory arrest, and blood pressure changes up to 100 mm of mercury. Even multifocal cardiac necrosis can be obtained when monkeys with no intrinsic heart disease receive electrical stimulation in orbital cortex (Hall and Cornish, '77). Analogous effects have been obtained by stimulating equivalent regions in the human brain (Chapman et al., '50; Penfield and Faulk, '55). In particular, insular stimulation in the human gave rise to sensory experiences referred to the epigastrium and visceromotor phenomena such as borborygmus, belching, and vomiting (Penfield and Faulk, '55).

There is little doubt that the pacemakers and final common pathways for autonomic function are located in diencephalic and other brainstem nuclei. However, the insulo-orbito-temporal regions may provide a cortical system which also influences autonomic function, especially according to the prevailing mental state. For example, cognitive tasks and emotional states are associated with specific patterns of autonomic activity which reflect the difficulty of the cognitive task, the type of ongoing information processing, the nature of the emotion, and even the magnitude of its impact on the individual (Ax, '53; Fenz and Epstein, '67;

Kahneman et al., '69; Lacey, '67; Mesulam and Perry, '72). In clinical practice, psychological stress is known to increase blood pressure and even to induce potentially lethal cardiac arrhythmias in the absence of intrinsic cardiovascular disease (Lown et al., '76). A disturbance in the relationship between mental events and autonomic discharges is thought to be an underlying factor of psychosomatic disease (Alexander, '50). It is conceivable that associations between mental state and patterns of autonomic activation are modulated, at least in part, at the level of insulo-orbito-temporopolar cortex. This region may therefore provide a potential anatomical substrate for psychosomatic disease, essential hypertension, and perhaps even some types of heart disease. MacLean ('49) has reached similar conclusions and proposed the term "visceral brain" for these areas.

Another specialization common to these three cortical regions is olfactory-gustatory sensation. Bagshaw and Pribram ('53) concluded that the anterior insula and adjoining opercula in the rhesus monkey constituted a primary gustatory region while medial temporopolar areas were involved in more complex gustatory functions related to dietary preference. In the squirrel monkey, a locus in the anterior opercular-insular region responded to stimulation of peripheral gustatory nerves (Benjamin and Burton, '68). Subsequently, Sudakov et al. ('71) found that neurons in the anterior insula of squirrel monkeys responded to direct gustatory stimulation. In a human patient, stimulation of the anterior insula elicited olfactory sensations (Penfield and Faulk, '55). Tanabe et al. ('75a,b) showed that a region in caudal orbitofrontal cortex, probably corresponding to our OFdg and OFa-p, contained powerful evoked potentials to olfactory stimulation and that this same area was essential for odor discrimination.

A third group of functional specializations of this region occurs in motivational, mnemonic, and affiliative behavior. For example, caudal parts of area 13 (probably corresponding to our OFdg and OFa-p) sustain self-stimulation behavior in the rhesus monkey (Mora et al., '80). Lesions in areas 12 and 13 are known to cause learning deficits by impairing the ability to withhold response to unrewarded stimuli (Iversen and Mishkin, '70) and posterior insular lesions interfere with learning that depends on somesthetic discrimination (Murray et al., '80). Orbitofrontal and temporopolar areas are also important for regulating social interactions among conspecifics. Lesions in these regions decrease the effectiveness of aggressive encounters and result in social isolation and in a reduction of affiliative behaviors in monkeys (Franzen and Myers, '81; Kling and Steklis, '76; Raleigh and Steklis, '81; Raleigh et al., '79). Thus, in addition to a common architectonic organization, the insula, lateral orbital cortex, and temporal pole share many common patterns of behavioral specialization.

The orbital, insular, and temporopolar regions are not unique in containing architectonic transitions from allocortex to isocortex. Similar transitions occur in the parahippocampal region, in the retrosplenial area, in the cingulate gyrus, and in the subcallosal-paraolfactory region (Sanides, '70). In contrast to the insulo-orbito-temporopolar region where prepiriform cortex constitutes the allocortical focus, it is the hippocampal formation and its induseal rudiment which form an allocortical focus for this second group of regions. Zones of increasingly more differentiated cortex are related to this hippocampal-induseal core in a fashion which is analogous to the organization

centered around the primary olfactory core (Abbie, '42; Filimonoff, '47; Sanides, '68, '70; Yakovlev, '59). Whereas the olfactocentric organization of the insulo-orbito-temporopolar region culminates in auditory and somesthetic hypergranular koniocortex, the hippocampocentric axis of development may lead to visual koniocortex and perhaps even to the gigantopyramidal fields of motor cortex (Sanides, '70; Yakovlev, '59). The concentric organization of cortical areas is most conspicuous in the immediate vicinity of the relevant allocortical foci. However, even some of the more remote areas of the prefrontal and posterior parietotemporal regions may eventually yield to an analysis based on this dichotomous plan of cortical differentiation (Sanides, '70).

The term paralimbic could be used as a generic term to designate all cerebral regions where a transition occurs from allocortex to fully developed isocortex. Orbitofrontal cortex, the insula, the temporal pole, the parahippocampal area, the retrosplenial region, the cingulate gyrus, and the subcallosal-paraolfactory gyrus collectively constitute an uninterrupted paralimbic ring along the basal and medial boundaries of the cortical mantle.³ With respect to neural connectivity, the paralimbic areas could be conceptualized as neuronal bridges between association isocortex, on one hand, and core limbic structures on the other. The functional specializations attributed to paralimbic regions (e.g., memory, affiliative behavior, autonomic response to affective cues) parallel this organization in connectivity since they necessitate interactions between sensory input from the environment and inner motivational states. Despite individual differences, then, paralimbic areas share two general properties: They contain architectonic transitions from allocortex to isocortex and they provide a neural apparatus for mediating between the external environment and the internal milieu.

Cortical acetylcholinesterase

Neurons in the nucleus basalis of Meynert give rise to the principal cholinergic innervation of cortex and almost undoubtedly provide a major portion of the AChE-rich fibers within the insulo-orbito-temporal region (Levey et al., '82; Mesulam et al., '83; Mesulam and Van Hoesen, '76; Mesulam et al., '77; Mufson et al., '82). Our chemoarchitectonic observations indicate that the greatest concentration of AChE in the insula, temporal pole, and orbital cortex occurs within their agranular and dysgranular sectors. This suggests that a high AChE content and perhaps also substantial cholinergic innervation may be a characteristic of the nonisocortical components within paralimbic areas. It is conceivable that these regions receive a particularly intense cholinergic projection from the nucleus basalis.

Cortical cholinergic innervation recently attracted considerable attention when it was shown that one lesion in Alzheimer's disease consists of a depression in cortical AChE and choline acetyltransferase (Davies and Maloney, '76). It has also been shown that patients with Alzheimer's disease have a marked neuronal loss in the nucleus basalis when compared to age-matched controls (Whitehouse et al., '81). It is conceivable that the decline in cortical cholinergic markers in this disease reflects a degeneration in the corticopetal cholinergic projection from the basal forebrain. It is reasonable to assume that this decline in cortical cholinergic markers would be most extensive in areas with the highest intrinsic cholinergic innervation. Since

sectors within the insulo-orbito-temporal region have high AChE contents, these areas may well become highly relevant to investigations of Alzheimer's disease.

Another feature common to caudal orbitofrontal, insular, and temporopolar areas is the high frequency with which they become the source of partial epileptic discharges, a property which they share with the amygdala and hippocampus. This tendency may reflect an underlying similarity in the pharmacology of these areas. One pharmacological property which is common to caudal orbitofrontal, insular, and temporopolar areas as well as to the amygdala and hippocampus is that they each contain sectors with high AChE levels. This histochemical pattern may indicate the presence of substantial cholinergic innervation in these areas. This becomes of special relevance to the phenomenon of partial epilepsy since it has been shown that anticholinergic agents retard the development of kindled limbic seizures (Arnold et al., '73). It is therefore conceivable that the degree of intrinsic cholinergic innervation influences the susceptibility to the development of seizure foci and that AChE chemoarchitectonics may provide one means for identifying and investigating such regions.

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³ The term "limbic lobe" has also been used to designate the same areas. We prefer the term "paralimbic" in order to set them apart from core "limbic" structures such as the hippocampus, amygdala, etc. Parts of paralimbic regions have also been called mesocortex or proisocortex in other nomenclatures.

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