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Functional Architecture of Motor and Sensory Cortices in Primates in the Light of a New Concept of Neocortex Evolution*

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The Concept of Duality of the Neocortex

The dual structure of the neopallium—a parapiriform moiety and a parahippocampal moiety—was first conceived by Dart (1934) as a result of painstaking architectonic and stimulation studies on various South African reptiles. These studies were an outgrowth of the principal investigations of Johnston (1915), Crosby (1917), and Elliot Smith (1919) on the forebrain of reptiles. Dart already anticipated the principle of duality to be valid for the mammalian neocortex. Actually, it was Abbie who succeeded in presenting architectonic evidence of the duality of the neocortex, first in monotremes (1940) and later in marsupials (1942). In cytoarchitectonic terms Abbie subdivided the entire neocortex of echidna and platypus into two major components, one related to and adjacent to the hippocampus (archicortex), the other one to the piriform cortex (paleocortex). Both moieties show a differentiation into several stages. Within the parahippocampal neocortex Abbie distinguished four successive stages of differentiation and within the parapiriform neocortex three stages. This progressive differentiation takes place in both major components by thickening of the cortex, accentuation of the lamination, and eventually appearance of granular cells (granularization). In the marsupial *Perameles*, Abbie (1942) found the principle of the "dual nature of the neopallium" fully sustained. He concluded that the different architectonic fields represent successive waves of circumferential differentiation in evolution, commencing from the hippocampus and from the piriform cortex, respectively.

These important works of Abbie did not receive the attention they merit. Thus,

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20 years later, in 1962, on the basis of cytoarchitectonic and myeloarchitectonic data in the extensive human frontal lobe, we independently proposed the same principle: the dual origin of the neocortex. The combination of the cytoarchitectonic and myeloarchitectonic methods proved to be particularly valuable, not only in outlining the coinciding areas more reliably but also in tracing differential trends in several successive areas. The myeloarchitectonic method is advantageous because, operating at lower magnification, a series of architectonic areas can be surveyed simultaneously (Fig. 5).

Since our initial findings in the frontal lobe of man (1962a, b, 1964) we found the principle of a dual origin of neocortical differentiation confirmed in a series of primates (*Nycticebus*, *Saimiri*, *Macaca*, *Pan*), in Carnivora (cat, raccoon), in Rodentia (rat), in Insectivora (*Erinaceus*), and in Chiroptera (*Myotis lucifugus*).

A diagrammatic presentation of this principle is illustrated in the frontal lobes of man and monkey (Fig. 1). It is important to recall that the greatly expanded neocortical lobes of higher mammals still are bordered ventromedially and ventrolaterally by the old protocortices, the archicortex and the paleocortex. In the coronal sections of primates' frontal lobes (Fig. 1) the archicortex is represented by the supracallosal hyppocampus (vH, the vestigia hippocampi of Elliot Smith, 1919),

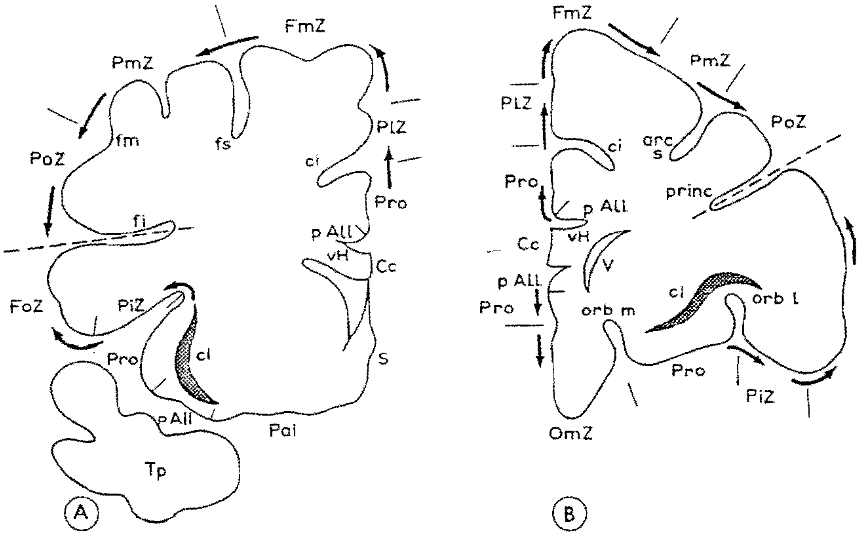

Figure 1. Coronal diagrams of frontal lobe of man (a) and monkey (b). The arrows indicate the differential trends from the cingular proisocortex (Pro) medially and the insular proisocortex laterally. Because of the lesser vault of the frontal lobe of the monkey the plane at the level of the sulcus principalis does not pass through the paleocortex (Pal)—the last source of insulolimbic differentiation—but only through the caudo-orbital claustrocortex (Pro). The paleocortex is present in the section through the human brain. The dashed line through sulcus frontalis inferior (fi) in man and sulcus principalis (princ) in monkey marks the basic medio/limbic borderline of the two prefrontal spheres. Sulci: arc, arcuatus superior; ci, cinguli; fm, frontalis medius; fs, frontalis superior; orbm, orbitalis medialis; orbl, orbitalis lateralis; Cc, corpus callosum. cl, claustrum; S, septum; V, ventricle; for further abbreviations see Table 1.

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whereas the bulk of the primate hippocampus is displaced by a sagittal rotation into the depth of the temporal lobe. The paleocortex, although reduced in the microsmatic simian primates, retains its original ventral position (Pal, Fig. 1a). Because the vault of the frontal lobe of the monkey is less than in man, a coronal section through the equivalent frontal regions of the convexity in the former does not include the paleocortex but rather the neocortical proisocortex. caudo-orbitally (Pro, Fig. 1b). (See Table I for abbreviations.)

It appears necessary to insert some remarks on the nomenclature of the cortical architecture. Most of the terms which we use were originally coined by Brodmann (1909) and C. and O. Vogt (1919). The neocortex, insofar as it passes through a six-laminated period during fetal life, is referred to as isogenetic cortex (isocortex). The older cortices—the medial archicortex (hippocampal formation of mammals) and the lateral paleocortex (olfactory cortex proper) which exhibit peculiar characteristics in addition to very limited lamination—are called the allogenetic cortex (allocortex). However, as we will see, two successive intermediate structural steps (Filimonoff, 1947; Sanides, 1962b; Stephan, 1963) are intercalated between the primitive allocortex and the mature isocortex, namely, the periallocortex (which is adjacent to the primitive allocortex) and the proisocortex (which is adjacent to the mature isocortex). The most primitive types of allocortex are also referred to as allocortex primitivus (Fig. 1).

The characteristic periallocortex and proisocortex show different regional and areal architectonic elaborations, in relationship to the bordering isocortical lobes. Medially, adjacent to the archicortex, they are bound to the limbic lobe, and ventrolaterally, adjacent to the paleocortex, they are bound to the insula Reilii, which was formerly called the stem lobe. Both these "lobes" are phylogenetically old structures. The insular cortex should be designated as part of the limbic cortex for ontogenetic and phylogenetic reasons (Yakovlev, 1959). The anterior cingulate gyrus and the anterior insular cortex exhibit basic architectonic resemblances.

It was Meynert (1872) who made the basic observation that looking at the freshly exposed brain we can distinguish two major components of cortex, that with a whitish surface and that with a greyish surface. The latter corresponds to the entire isocor-

TABLE 1. ***Explanation of Abbreviations***

A I	primary auditory area	Pal	paleocortex
A II	secondary auditory area	pAll	periallocortex
All	allocortex primitivus	parK	parakoniocortex
FmZ	frontomotor zone	parM	paramotor area
FoZ	frontopercular zone	PiZ	parinsular zone
FpZ	frontopolar zone	PlZ	paralimbic zone
G	gustatory area	PmZ	paramotor zone
Gig	area gigantopyramidalis	PoZ	paropercular zone
H	hippocampus	pre Fr	prefrontal cortex
Ism	intermediate sensorimotor area	preM	premotor area
Ka	auditory koniocortex	proM	promotor area
Ks	somatic koniocortex	proK	prokoniocortex
lam. diss.	lamina dissecans	Prt	parietal cortex
MpI	supplementary motor area	SmI	primary somatic area
MsI	primary motor area	SmII	secondary somatic area
OmZ	orbitomedial zone		

tex, and the former corresponds to the allocortex, including periallocortex. The whitish color reflects the fact that the cell-poor molecular or zonal layer possesses here particularly strong tangential fiber plexuses of which the striae olfactorii fibers are one example. This condition corresponds to the primitivity of the allocortex which does not yet depend exclusively on thalamic afferents.

In cytoarchitectonics we can disregard the first cell-poor layer. For example the so-called second layer of the isocortex forms the first real cellular layer. The periallocortex (the first architectonic step away from allocortex primitivus) is composed of two real cell strata, with emphasis on the inner one, and with a more or less discernible narrow layer devoid of cells in between. This blank layer is referred to as lamina dissecans (Figs. 3 and 16), since it cuts the cortical plate into the two cell strata. These strata are not comparable with the laminae of the isocortex. However, we will consider how the latter emerge from the former in the differential process of evolution.

The next step, *proisocortex*, is more laminated in that the inner stratum is differentiated into a pyramidal-celled layer V and spindle-celled layer VI. At the same time the outer stratum further differentiates into pyramidal-celled layer III adjacent to the relatively small-celled dense layer II. Actually there is a relative increase in emphasis of the outer stratum. In addition a fourth granular layer can make its first appearance in the level of the former lamina dissecans. Lamina IV belongs, in our classification as derived from comparative architectonic studies (Sanides and Krishnamurti, 1967), to the outer stratum. The proisocortex of the anterior cingulate gyrus is distinguishable from that of the anterior insula in that it is devoid of a lamina IV; i.e., it is agranular. The insular proisocortex has an incipiently granular to well-developed granular layer.

The limbic and insular proisocortices are adjacent to the paralimbic zone (PlZ) and a parinsular zone (PiZ), respectively (Fig. 1). By zones we mean belts of fields, each at a similar differential stage. Thus the numerous individual human architectonic areas of the frontal lobe can be organized into an array of consecutive zones. Commencing with the archicortical supracallosal hippocampus and its periarchicortex (pAll) is the sequence of proisocortex (Pro), paralimbic zone (PlZ), frontomotor zone (FmZ), paramotor zone (PmZ), and paropercular zone (PoZ). Commencing with the basal paleocortex and its ventroinsular peripaleocortex (pAll) is the sequence of the insular proisocortex (Pro), the parinsular zone, (PiZ), and the frontopercular zone (FoZ), which occupies the inferior frontal gyrus.

Thus the dividing line between predominantly archicortical limbic influences and predominantly paleocortical insular influences in the prefrontal cortex appears to be the inferior frontal sulcus (Fig. 1a). Moreover, in the dorsal part of the pars triangularis on the inferior frontal gyrus (corresponding to Vogt's area 58) and in the center of the orbital cortex [corresponding to Vogt's area 60, (Fig. 4)] bound to the transverse orbital sulcus are maximally differentiated areas within the prefrontal cortex of man which appear to be the product of an integration of medial limbic and insulolimbic influence (Sanides, 1962b, 1964, and Fig. 26).

As Figure 1b shows, essentially the same zonal array is valid for the frontal lobe of rhesus monkey. On the basis of combined cytoarchitectonic and myeloarchitectonic studies, the less elaborated frontal granular cortex can be shown to exhibit the same differential zones. The dividing line here between the medial limbic zone of influence and the insulolimbic zone of influence is the sulcus principalis, which is the equivalent to the inferior frontal sulcus of man (Sanides and Schiltz, 1967).

Concerning the sulcus principalis as being the limit between the medial limbic influenced moiety and the lateral insulolimbic influenced moiety of the rhesus monkey's frontal granular cortex, Nauta (1964) arrived at a remarkably similar conclusion, using quite another approach. He traced prefrontolimbic connections with his experimental silver technique. He refers to "a certain dualism in the prefrontolimbic associations" in that the dorsomedial part of the prefrontal cortex is projecting mainly on the cingulum bundle in the cingulate gyrus and from there backward to retrosplenial and parahippocampal regions. On the other hand, the ventrolateral part of the prefrontal cortex, including the orbital cortex, projects mainly, by the uncinate fascicle, onto the rostral temporal lobe, from where connections to the amygdala are projected. In addition, collaterals leave the uncinate fascicle, as it passes through the capsula extrema, and terminate in the claustrum. Such collaterals, according to the concept of Bishop (1959), may possibly be the evolutionarily older fiber connections. In this way Nauta also found the principal sulcus to be a fundamental borderline between both spheres of prefrontolimbic connections.

To demonstrate the main features of the differential trends from both limbic bordering regions, which we will refer to as "ur-trends,"* we begin with the cytoarchitectonics of the proisocortex of the anterior cingulate gyrus (Fig. 2). It exhibits as the most striking characteristic a bandlike fifth layer of dense medium-sized pyramidal cells, which was also described by Bailey and von Bonin (1951) as a "juxtallocortical" feature. Another conspicuous limbic feature of the anterior cingulate gyrus in man is the presence of large, extremely slender pyramidal and spindle cells, called rod cells, in its deep sublayer Vb. The latter are not present in the insular proisocortex, but the bandlike lamina V is the same there as in the cingulate gyrus. The limbic features undergo a diminution in the adjacent paralimbic (Fig. 1) and parinsular (PiZ) belts, respectively. At the same time new progressive characteristics emerge, for example, increase in overall cell size, and especially a relative increase of lamina III, which is still weak in Pro, particularly in the anterior cingular one. These are the two main cytoarchitectonic trends. It must be added that on the way to FmZ with its large efferent lamina V pyramidal cells, the PIZ is intermediate with regard to lamina V pyramidal cells which are larger and much less dense than in Pro with its band of smaller lamina V pyramidal cells, and on the other hand smaller and denser than those of FmZ.

After passing FmZ in the lateral direction a granular lamina IV makes its initial appearance in PmZ, marking the beginning of a stepwise granularization. At the same time the large efferent V pyramidal cells begin to decrease in size, step by step, and the pronounced increase in size of the lamina IIIc pyramidal cells bordering lamina IV continues. The differential trend from the insular Pro is basically similar. One main difference, however, is that the anterior insular Pro is, as mentioned above, not agranu-

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* In our German monograph on the frontal lobe we referred to the differential "trends" issuing from the archicortex medially and from the paleocortex laterally as "Ur-gradations," meaning, primeval or protogradations. We prefer now to speak of trends instead of gradations and propose the term "ur-trends" for both primeval trends. The old Germanic stem "ur" is preserved in the English in "ordeal."

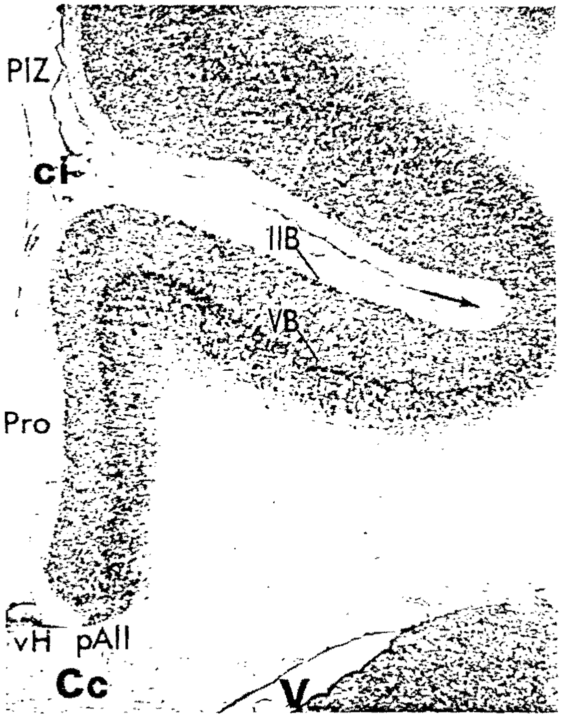

Figure 2. Proisocortex (Pro) of anterior cingulate gyrus of *Macaca*. PIZ, paralimbic zone. VB, bandlike V of dense pyramidal cells, which are larger and less dense in PIZ. IIB, accentuated II of Proisocortex. Cc, corpus callosum; ci, cingulate sulcus.

lar as is the anterior cingular Pro, but is dysgranular where it borders the precentral motor cortex. This means that there is a weak lamina IV which is still intermingled with lamina IIIc pyramidal cells. More rostrally the insular cortex has an even better demarcated lamina IV. In consequence the granularization proceeds faster from the insular cortex and culminates in the inferior frontal gyrus. The most remarkable fact is that even with the fundamental structural contrasts between the archicortex and paleocortex, there exists a striking similarity of the medial and lateral differential trends.

The cytoarchitectonic sequence of zones in man is illustrated in our frontal lobe monograph (Sanides, 1962b). As the frontal diagram (Fig. 1a) shows, the sequence occurs over a series of gyri. The fundamental relationships of architectonic areas to the sulcogyral configuration will be considered on page 149. We have, however, the unique possibility of demonstrating the main stages of the differential trend in an unconvoluted stretch of cortex without interference of surface indentations. This opportunity is offered by the Simian primates' gyrus rectus alongside the olfactory sulcus. The horizontal section through the gyrus rectus of the squirrel monkey (Fig. 3) demonstrates the range of differentiation from allocortex (All, precommissural hippocampus) successively through periallocortex (pAll), proisocortex (Pro), orbitomedial zone (OmZ) to the granular frontopolar zone (FpZ).

Before we discuss this differential trend in the squirrel monkey, it is necessary to clarify some aspects of comparative cytoarchitectonics. The major source of the difficulty encountered in comparing cortical areas and in examining homologies in mam-

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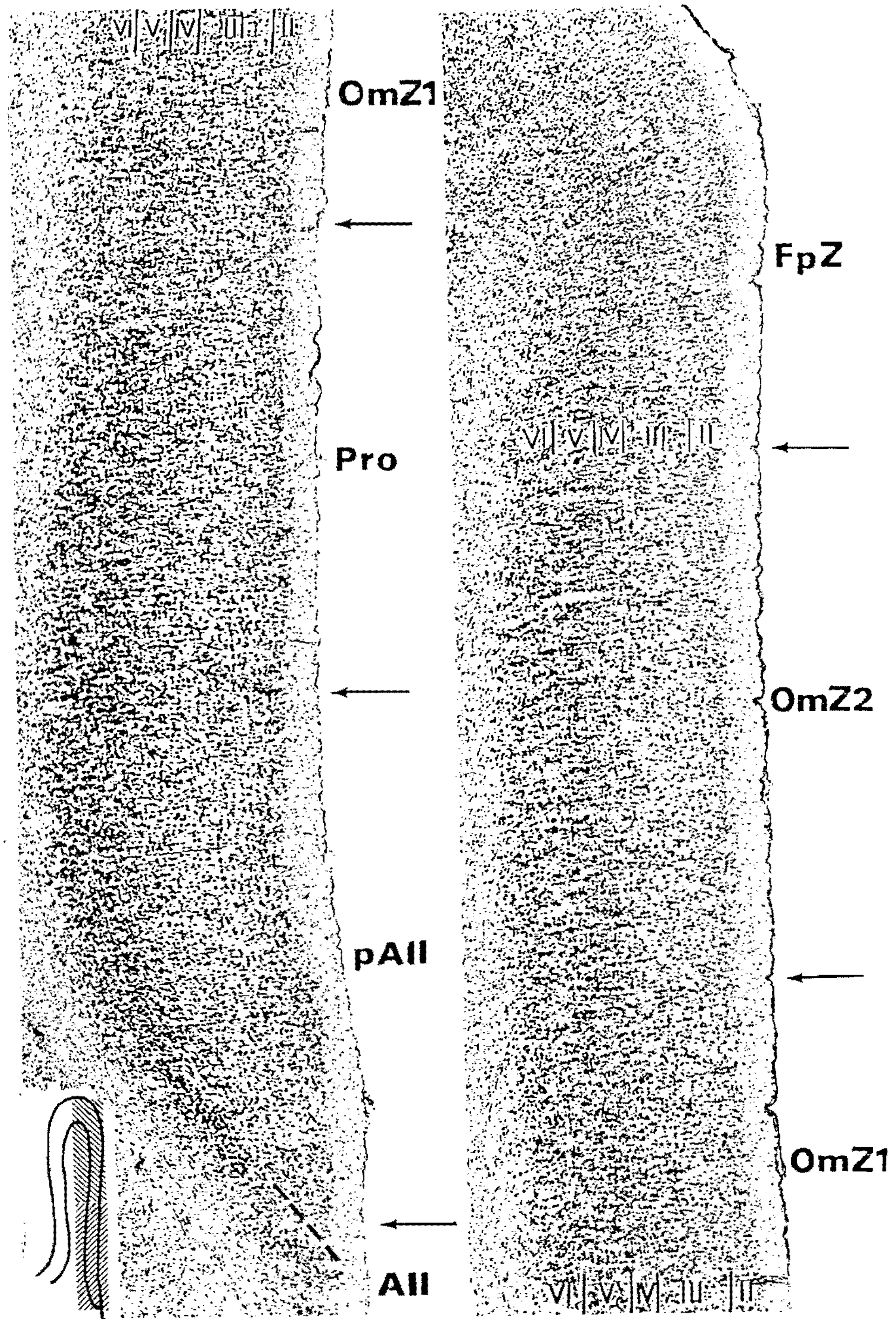

Figure 3. Horizontal section through gyrus rectus of *Saimari;* b is rostral to and continuous with a x 36 (See table 1 for abbreviations)

mals of different organization levels is the greater density of nerve cell bodies in lower mammals. The best characterization of this phenomenon is given by the grey-cell coefficient (von Economo and Koskinas, 1925), which is the ratio of the total volume of a nucleus or cortical area to the sum of the volumes of the perikarya (cell bodies) of the nerve cells contained within. Thus, it is virtually a measure of the interperikaryal space of an area. Ascending the scale of primates, this ratio increases markedly and is highest for man. Computed with modern methods in different series of mammals, the grey-cell coefficient is generally considered to be an indication of the level of organization of the cerebral cortex (Shariff, 1953; Haug, 1956). Moreover, there is also a correlation with brain size and weight (Cragg, 1967).

Thus, the cerebral cortex of the squirrel monkey has a cell density more than twice that of man, as does the cortex of the prosimian Nycticebus. This is expressed by the tendency of cell layers to fuse, at low magnification, a prerequisite for the evaluation of cell populations. In spite of this changing average cytoarchitectonic picture we can recognize and pursue the differential trends, first described in man, without difficulty.

As the insert of Figure 3 shows, we deal with a horizontal section through the whole length of the median cortex of the gyrus rectus representing the posterior half (left) and anterior half (right). Immediately caudal to the primitive cortex (All) is the nucleus of the diagonal band (DB). Irregular groupings of middle-sized dark staining cells without any lamination are found in this wedge-shaped cortical formation (All). This is the small remnant of allocortex primitivus of the precommissural hippocampus at this level. At its surface All becomes superposed by less darkly staining smaller pyramidal and multiform cells of the outer stratum. An indication of a lamina dissecans (dashed line) is present at the edge of the darker and denser celled inner stratum and the lighter and looser celled outer stratum. This is the two-strata-periallocortex (pAll). At the outer rim of the outer stratum is a condensation of darker, somewhat larger cells. These are forerunners of a layer II. Without any sharp edge the transition occurs into the better laminated Pro. The inner stratum exhibits an incipient differentiation in laminae V and VI, with the darker staining pyramidal cells in lamina V. At the same time within the outer stratum a third layer (III) with larger pyramidal cells in the deeper part emerges. Layer II is accentuated, continuing the cell condensations of pAll.

The transition to the next area, the first orbitomedial area (OmZ1), again without a sharp boundary, shows a further progress in lamination by the emergence of an incipient inner granular layer (IV). This is the dysgranular stage with granule cells still intermingled with small pyramidal cells. At the same time the inner stratum is less pronounced, and the narrow lamina V of rather dense middle-sized pyramidal cells is distinguishable from the looser lamina VI. The accentuation of lamina II tapers off 1 to 2 cm beyond the transition from the Pro. Lamina II is now composed of somewhat smaller cells.

The next area (OmZ2) is characterized by an increase in granularization; i.e., it has a clear-cut granular lamina IV. At the same time lamina II with denser, smaller pseudogranular cells is more demarcated from lamina III, which has a rim of larger pyramidal cells next to lamina IV. The inner stratum further is less pronounced, and a rather light lamina Vb is striking.

The final step to FpZ is characterized by a further enlargement of the granular lamina IV and by a decrease of the size of the lamina V pyramidal cells, which are now approximately matched by the deeper lamina III pyramidal cells. Lamina VI is now composed of smaller lighter-staining cells, so that the inner stratum has lost its predominance.

Much higher degrees of differentiation, with very large lamina IIIc pyramidal cells prevailing over lamina V pyramidal cells and with a high degree of granularization, are reached in the two differential maxima of the inferior frontal gyrus of man: Vogt's area 58 in the upper part of the pars triangularis, and Vogt's area 60 in the center of the orbital cortex, bound to the sulcus orbitalis transversus (Fig. 4). Both appear to be the product of a final integration of the medial and lateral ur-trends.

The differential trend in myeloarchitectonics is best demonstrated by the stepwise increase in myelin content.* Another factor concerns the appearance of the stripes of Baillarger and their increase in intensity. Particularly the inner stripe of Baillarger, which is composed of intracortical association fibers, shows a stepwise increase with the differential trends in the integration cortices. The most readily demonstrable trend of increase of the myelin content is seen in a coronal section through the midline cortex and paramotor zone of man's frontal lobe (Fig. 5) and in a coronal section through Saimiri's whole hemisphere at the level of the sensorimotor region (Fig. 6).

It is a general rule in myeloarchitectonics of the isocortex that the diameters of the projection fibers of an area are directly related to the average myelin content of that area (Hopf, 1956). Highly myelinated area (as the primary sensory and motor ones) also have the thickest projection fibers. This allows the application of the vast experience of Bishop in comparative neurology of the fiber tracts. After a "life among the axons" (Bishop, 1965) with systematic comparative studies of electrophysiological properties and diameter spectra of the axons of peripheral nerves, of ascending tracts of the spinal cord and brainstem, and of the immediately subcortical thalamic projection fibers, Bishop came to the conclusion that the finer myelinated fibers of related systems are basically older in evolution that the heavier myelinated ones. "Myelinization of small fibers and addition of successively larger fibers in the course of mammalian central nervous system evolution applies not only to *one* function structure, but relates to the acquisition, at the higher and more recently developed central structures, of a fiber spectrum similar to that prevalent in the periphery long before this central development in mammals" (Bishop and Smith, 1964). Thus, we may refer to a "*myelination trend in evolution*."

Figure 5 shows the example of this trend in man, particularly of the medial differential trend of limbic origin. On both sides of the interhemispheric fissure the very finely myelinated Pro of the cingulate gyri is seen. Two intermediate steps of the paralimbic zone on the left (47l and 47z) and one on the right (47l) grade to the maximum myelination of the convexity (areas 47) in the paramotor zone (nomenclature after Vogt, 1910, and Sanides, 1962b).

Concerning the myelination trend in *Saimiri* (Fig. 6), the overall myelination

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* The myeloarchitectonics of the cerebral cortex were developed by the Vogts (1919) as a useful method of cortical partitioning. They were particularly applied to the human isocortex by the Vogts and their disciples. Hopf (1966) recently developed a method of objective registration of the myeloarchitectonics of the isocortex by the use of an extinction writer. This method allowed Hopf (1968) to confirm the former qualitative results of the partitioning of the human cerebral cortex by a quantitative method.

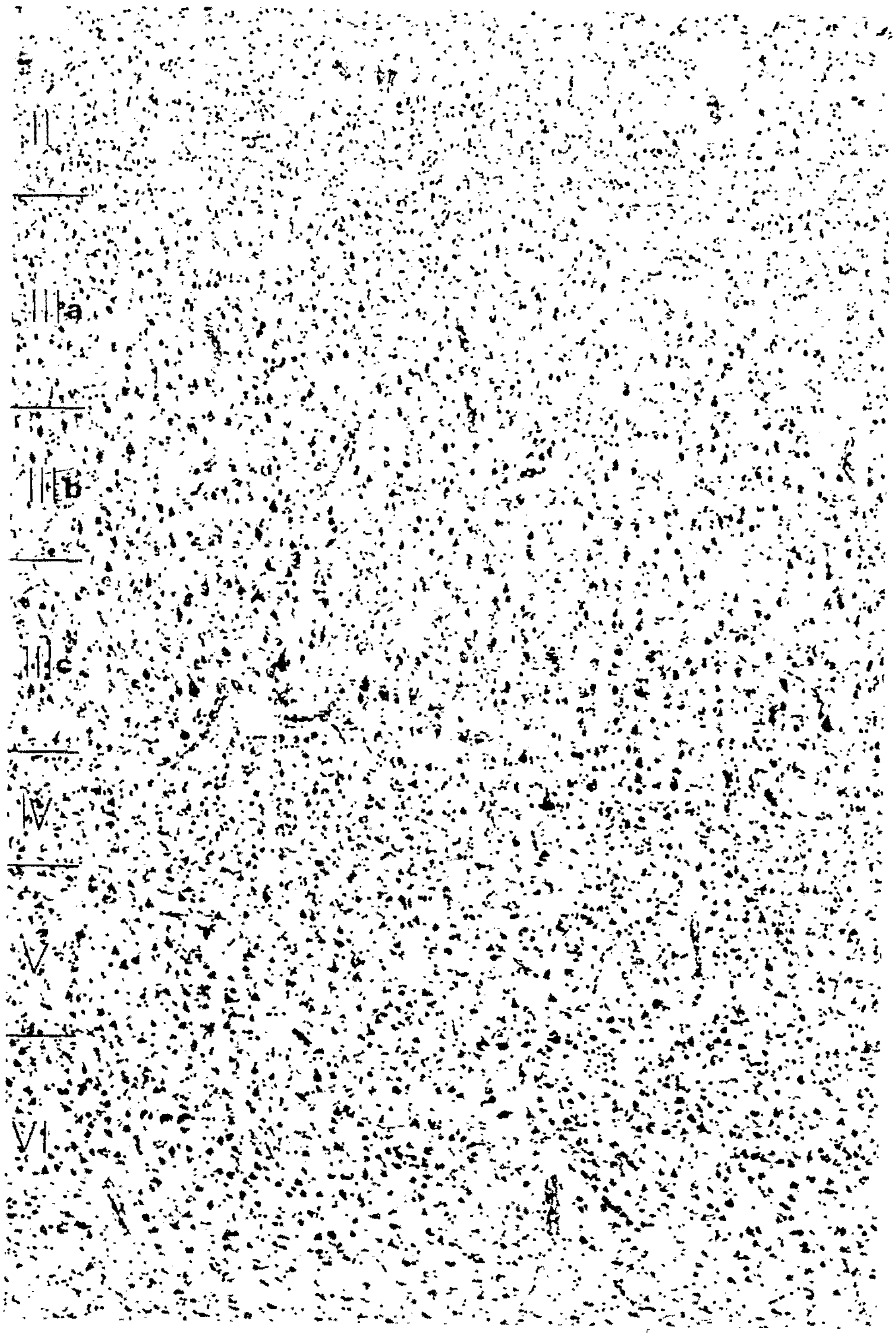

Figure 4. Central field of man's orbital cortex with maximum differentation x 80 (See max Fig. 26c). From Sanides. 1962b Monogr. Neurol. Psychiat., 98.

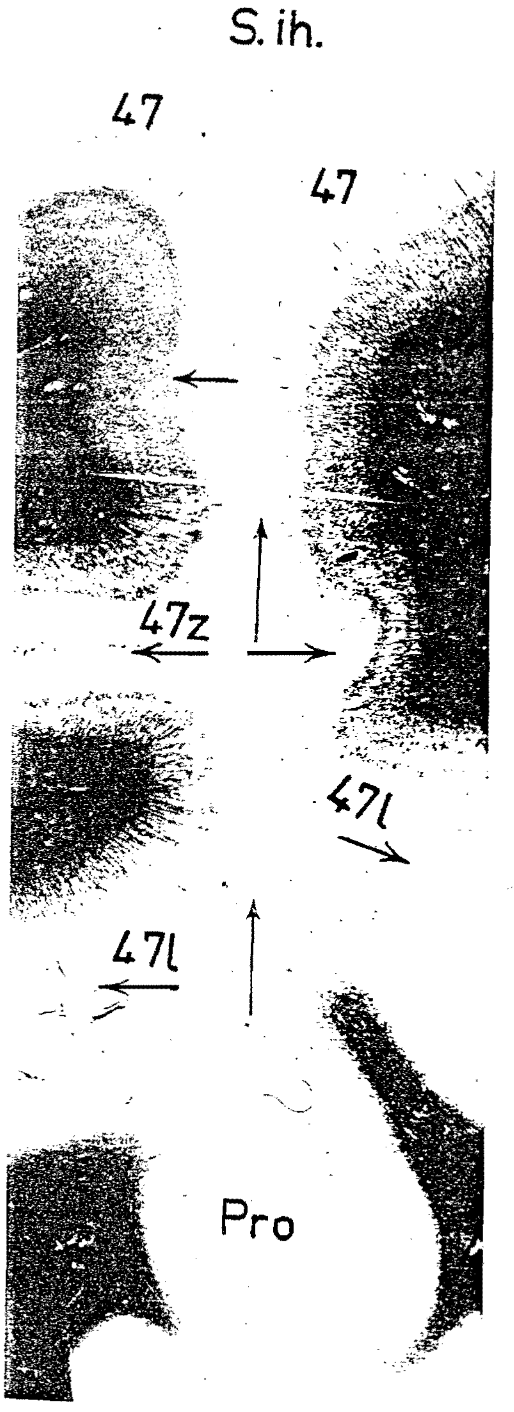

Figure 5. Coronal section through the interhemispheric fissure (S.ih.) of man's frontal lobe, demonstrating the myelination trend, x 5. From Sanides, 1962b. Monogr. Neurol. Psychiat., 98.

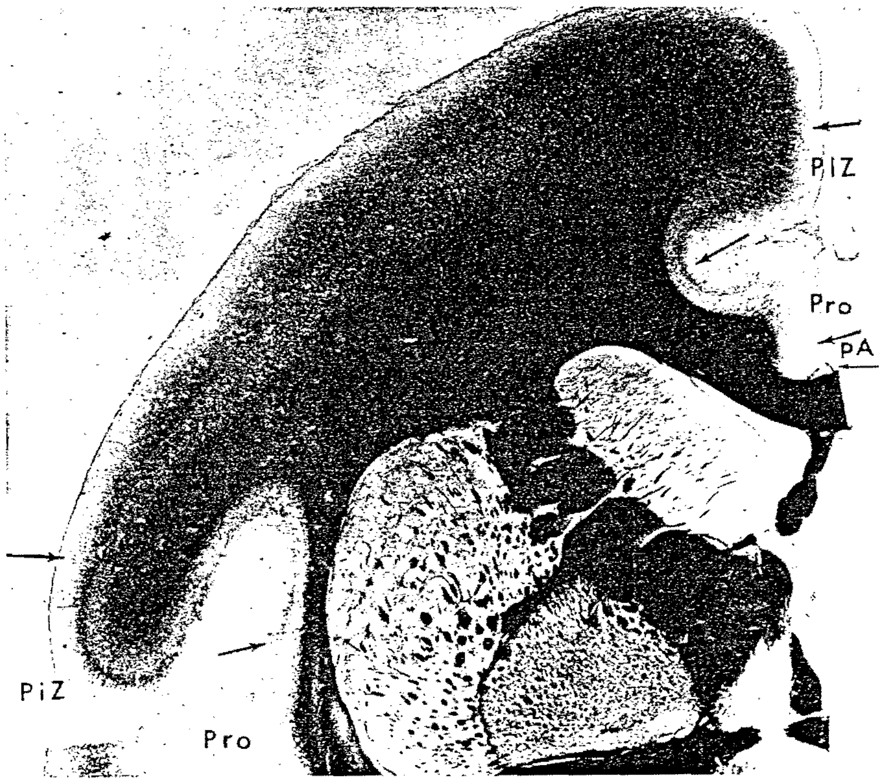

Figure 6. Coronal section through sensorimotor region of *Saimiri* demonstrating the myelination trends from medial to lateral, x 8. After Sanides. 1968. Brain Res., 8:97-124.

of its cortex is considerably less than in man. Therefore, a relatively overstained Heidenhain section was used to demonstrate the stepwise myelination from both limbic bordering cortices. On the convexity we find, as in other primates, the full expression of the classic sensorimotor regions with maximum myelination.

Pursuing the differential trend from the archicortex, we first note that the vestigia hippocampi (vH, induseum griseum) are still represented as gyrulus, covered by myelinated fibers (tenia tecta). Then a small section of pAll is present, with its faintly myelinated fibers demonstrable only at higher magnification. It also has relatively well developed tangential fibers in layer 1, a feature typical for all subdivisions of All. The adjacent cell stained section shows in pAll the typical two-cell-strata stage with a more pronounced inner one. The bulk of the cingulate gyrus is occupied by Pro, with its dense, fine radiate fibers, and an indication of an outer stripe of Baillarger. The transition to PIZ takes place in the bottom of the cingulate sulcus with a sharp increase in myelination of the outer stripe of Baillarger. The full expression of this area can be seen in the upper wall of the cingulate sulcus after cessation of the curvature influence (Sanides, 1962b). The transition into the area Gig (Fig. 6, arrow), halfway to the edge of the hemisphere, is marked by an increase in thickness of the radiate fibers and of the outer stripe of Baillarger. Thus we visualize after the

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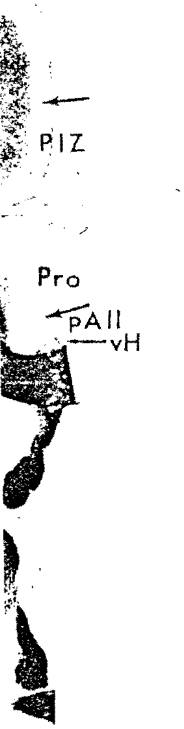

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initial stage of allocortex primitivus the stages of periallocortex, proisocortex, paralimbic zone, and finally classic motor region with increasing myelination.

On the lateral side we do not find the initial stage of paleocortex, that is allocortex primitivus, or the next stage, pAll, (both of which are more rostrally located in the base of the frontal lobe and the ventrolateral insula, respectively), but rather find the three subsequent stages of the myelination trend. Here we should note a peculiarity of Saimiri's cortical configuration, which is not present in Old World monkeys, that is, the large share of insula not underlaid by claustrum. This is an important point because the cortex superficial to the claustrum is more primitive in structure than the rest of the insular cortex. In Figure 6 note that, with the vanishing of the thin grey layer beneath the insular cortex (claustrum), a sudden increase in cortical myelination occurs. This is a similar transition as on the medial surface from Pro to PIZ, but here the transition is to the parinsular zone (PiZ). The latter was proved by Benjamin and Welker (1957) to contain the second sensorimotor representation (SmII). PiZ is, as in *Nycticebus* (Fig. 16), in cytoarchitectonic terms a prokoniocortex (proK) which exhibits here three subdivisions, corresponding to the three steps of myelination with gradual transitions in the bottom of the sulcus circularis and at the ventral tip of the operculum. The arrow (Fig. 6) on the outer side of the operculum marks the final transition to the koniocortex with its maximum myelination, particularly of the deeper horizontal fibers.

The Relationship of the Sulcal Pattern to Finer Cortical Organization and the Notion of Homology.

In the primate brain with the highest degree of gyrification, that of man, we demonstrated that the vast majority of the limits of architectonic fields are located in the bottoms of the sulci, fissurets, and dimples (Sanides, 1962b; 1964). In subhuman primates (Sanides and Krishnamurti, 1967; Sanides and Schiltz, 1967) and other mammals (Sanides and Hoffmann, 1969), the majority of the sulci and dimples also form architectonic field limits. However, since in lower mammals there are more field limits than indentations, only some are bound to the sulci. This relevance of the sulcal and gyral pattern to finer cortical organization was also a conclusion of Woolsey and his co-workers after two decades of comparative electrophysiological studies on localization of function in the mammalian cerebral cortex (Woolsey, 1959; Welker and Campos, 1963).

Thus sulci and gyri defined by architectonic and electrophysiological methods become more meaningful for comparative neurology. Within this context a reappraisal of the concept of homology as a tool of comparative neurology is presented.

At first we will follow a historical review by Starck (1950) on this subject. The origin of the concept "homology" goes back to the middle of the nineteenth century when it was introduced and defined by Owen (1848). He stated that homologous refers to the same organ in different animals under every variety of form and function. In this early definition, which is also called the typological one, the organ appears determined by the local relationships within the typus. After the general acceptance of the theory of evolution, the concept of homology was redefined by Haeckel: *Homol-*

ogy is the relation between two organs which have the same descent. In other words, organs are homologous in two different organisms if they derive from a common ancestral organ.

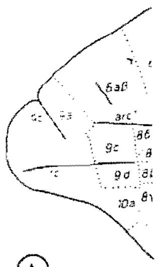
In the central nervous system, however, we cannot define homology by gross morphology only. For example, the cerebral cortex reveals its units only when we study its histology, that is, its architectonics as shown by specific staining techniques. On the other hand the common derivation of architectonic fields from ancestral forms is virtually impossible to prove. These are reasons which make the application of the notion homology questionable for the pattern of cortical units.

Our architectonic studies of the sensorimotor region in *Macaca* and *Saimiri* allow a test of the applicability of the notion of homology to the gyral pattern of New and Old World monkeys. The vast majority of the sulci of the mammalian cerebral cortex are "limiting sulci" rather than "axial sulci" (Elliot Smith, 1907). The latter are located well within a cortical field (e.g., calcarine fissure within the area striata). Thus we can characterize sulci in comparative neurology by the architectonic structure of the cortex of which they form the boundary.

Other than the Old World monkeys, the New World monkeys are unique in their wide range of brain differentiation from the small marmoset (*Hapale*) to the spider monkey (*Ateles*) with its fifth limb in the form of the highest developed prehensile tail. *Saimiri* occupies an intermediate position in this spectrum.

Both superfamiles of the primates (Old and New World monkeys) are known to have their common ancestors in presumably different prosimian stocks as far back as the early Tertiary period (Starck, 1953), i.e., prior to the elaboration of the present gyral pattern in the frontal lobe in the form of a central sulcus and a frontal arcuate sulcal complex. Yet both groups of monkeys reveal striking similarities in the formation of these sulci. Though this similarity is, by architectonic terms, far from identical, we are dealing here with one of the most astonishing examples of the phenomenon of parallel evolution, a phenomenon, which is intergraded with convergence. However, the comparative morphological phenomenon of convergence is by definition just contrary to homology, since it can be produced as a functional differentiation or even remodelling on different ancestral substrata or organs. For this reason, we prefer to come back to the term which the Vogts substituted for homology in the central nervous system, anatomical "equivalence." The equivalence of sulci, then, can safely be determined only be revealing the cortical architecture on both sides of the indentation.

The central sulcus of the primates usually is looked upon as a typical limiting sulcus between motor and somatic sensory areas. This, however, is an undue simplification because, technically, this is only true for the central sulcus of man. Even here we find in the bottom of the central sulcus a slight forward extension of area Ism (3a Vogts). In such apes as the chimpanzee (Strasburger, 1937) and Gibbon (Sanides, unpublished data) the somatic sensory cortex at the ventral end of the central sulcus extends a little farther rostral. In Old World monkeys, there is a definite protrusion of the somatic sensory fields at the ventral end of the central sulcus and a lesser one at the dorsal edge of the hemisphere (see Fig. 7, after the Vogts; confirmed in my cytomyeloarchitectonic studies on *Macaca*). The ventral protrusion beyond the central sulcus corresponds to part of the somatic face area. In the New World monkeys *Ateles* and *Cebus*, however, the rostral protrusion of the face area, investigated



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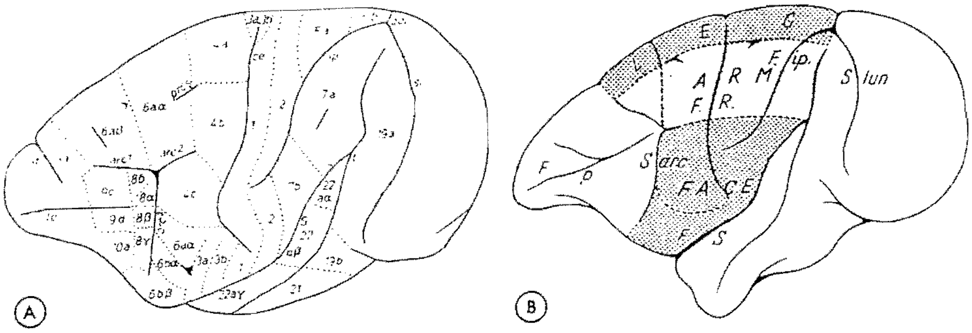

Figure 7. (a) Cytoarchitectonic map of *Cercopithecus* by, C. and O. Vogt (1919 J. Psychol. Neurol., 25:279-462.) Suffixes a-c and α-δ indicate subdivisions of Brodmann's map, the more detailed partitioning is based on stimulation experiments and architectonic control. (b) Somatotopic partitioning of the sensorimotor and parietal cortex of *Macaca mulatta* by the method of local strychninization from Dusser de Barenne (1941. J. Neurophysiol., 4:324-330.). arc, sulcus arcatus; arc 1, horizontal branch; arc 2, caudal spur; arc 3, vertical branch; ce, sulcus centralis; fp, sulcus principalis; ip, sulcus interparietalis; prcs, sulcus precentralis superior; S, fissura Sylvii; si, sulcus simialis, lun, sulcus lunatus.

electrophysiologically by Woolsey and co-workers, was much more extensive (Chang et al., 1947; Hirsch and Coxe, 1958). *Saimiri* also has a very pronounced rostral protrusion of the somatic face area (Benjamin and Welker, 1957), as is confirmed by our map (Figs. 8 & 9).

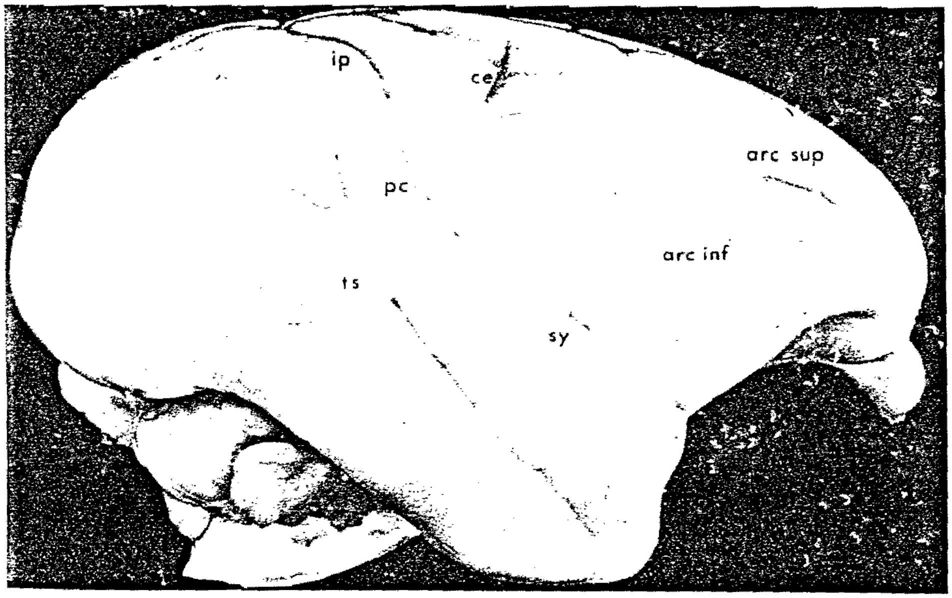

Figure 8. Lateral aspect of the cerebral hemisphere of *Saimiri.* arc inf, arc sup, sulcus arcuatus inferior and superior; ce, sulcus centralis; ip, sulcus intraparietalis; pc, sulcus postcentralis; sy, fissure Sylvii; ts, sulcus temporalis. From Sanides. 1968. Brain Res. 8:97-124.

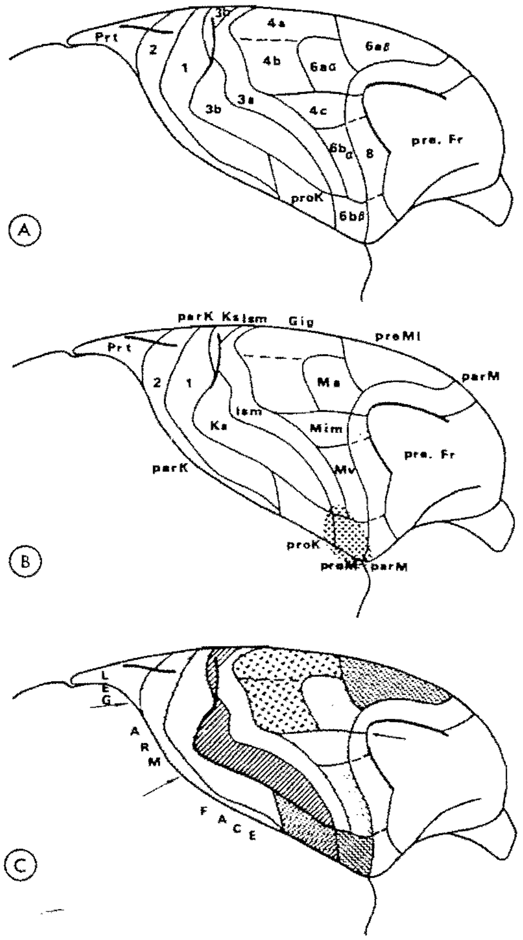

Figure 9. Architectonic map of *Saimiri's* frontal lobe. (a) Nomenclature after Brodmann-Vogt; (b) my nomenclature, see Table 1; deep taste area dotted; (c) areas in patterns. From Sanides. 1968. Brain Res., 8:97-124.

The relationships of the sensory and motor regions of *Saimiri* to the short central sulcus will be discussed (Figs. 8 and 9). A slight rostral protrusion of Ks is present at the dorsal end of the central sulcus similar to *Macaca*. In the dorsal half of the central sulcus Ks lies on the caudal wall and Ism on the rostral wall of the central sulcus. The latter is unknown for Old World monkeys. In the midlength of the sulcus there is a shift of Ks through the bottom of the sulcus to the rostral wall, so that at the ventral end of the sulcus the whole Ks is displaced to the rostral side. This shift from caudal to rostral occurs (based upon electrophysiological data) approximately at the level of the limit of leg and arm area (see arrows in Fig. 9c). We can conclude that in architectonic terms the equivalence of the central sulcus in Old and New World monkeys is incomplete. Rather one should speak here of a *regional* equivalence instead of an *areal* equivalence where the sulcus limits the same areas throughout. In terms of regional equivalence the central sulcus can be referred to as an axial sulcus of the primary sensorimotor region.

This common feature of New World monkeys can also be recognized in Vogts'

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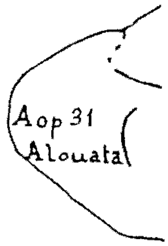

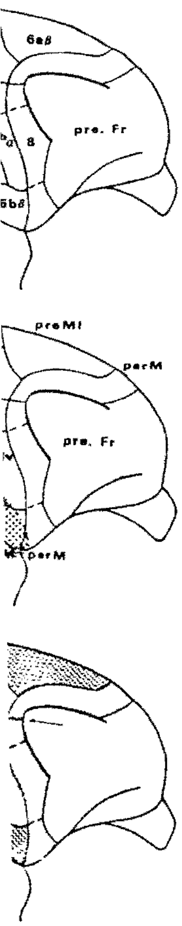

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map of *Alouatta's* motor cortex (Fig. 10) based on electrical stimulation experiments and cytoarchitectonics (C. and O. Vogt. 1907).

Sulcal Pattern in Evolution

Our cytoarchitectonic and microelectrode study on the sensorimotor region of a prosimian, *Nycticebus* (Sanides and Krishnamurti, 1967) demonstrated the delineating role of the sulci for architectonically and functionally defined cortical areas. Furthermore, we could trace the evolution of sulcal development and concluded that "we apparently enter a new phase of more thoroughgoing realization and interpretation of the different types of sulcal patterns and of their particular variants, relying on the cortical substratum itself, its electrophysiologic expression, and its architectonic structure." In the meantime two papers of Radinsky on extant and fossil brain fissuration (1968a, b) confirmed our prediction.

The value of paleoneurology was first demonstrated by Tilly Edinger (1948) in her great systematic study of the 55,000,000 years of brain evolution of the fossil *Equidae* up to extant horse. The fact that the leading structure in the mammalian brain as an end product of a long evolutionary process of rostralward migration of functions (v.Monakow 1911) settled as a "cortex," the cerebral cortex, at the utmost end of the forebrain, offers the unique opportunity to explore its expansion and even its sulcal and gyral pattern by endocranial casts of fossil skulls or by their own natural cast (Steinkern). A fundamental result of these studies on mammalian brain evolution is the growing pallium as such, and within the latter the increasing share of neopallium against the ventrolateral paleopallium. This is reflected in the steady downward movement of the rhinal fissure through the whole Tertiary period.

We will first consider general rules of the sulcal pattern in living mammals. Lower forms such as insectivores and the small specimens of all higher mammalian orders possess, with the exception of the rhinal fissure, a smooth cerebral surface; i.e., they are lissencephalic, whereas larger specimens have increasingly gyrencephalic brains. Gyrification, according to the law of Baillarger-Dareste (Ariens Kappers et al., 1936), is a function of brain size. This is basically geometric reasoning: The cortex, bound by its laminated structure, cannot increase proportionally in thickness with growing

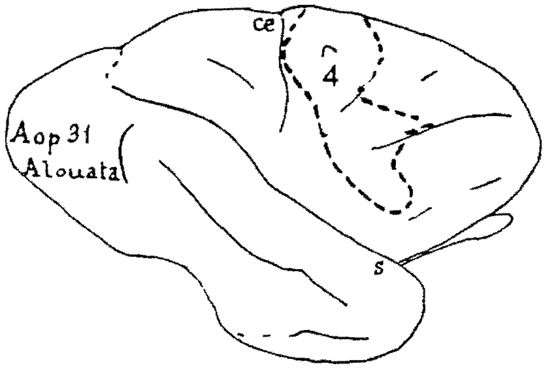

Figure 10. Motor cortex (area 4) of *Alouatta*. From C. and O. Vogt. 1907. J. Psychol. Neurol., 8:277-456.

brain size in evolution. Remaining a thin surface layer of the hemisphere it folds in order to compensate for the two-dimensional surface increase in contrast to the three-dimensional volume increase. In the largest primate brains, those of hominoids, the well-known enormous expansion of frontal and parieto-occipito-temporal integration cortices is added. It culminates in the extreme gyrification in man.

The first to develop further concepts on gyrus formation in phylogenesis was Le Gros Clark (1945). The starting point of his speculation on sulcal and gyral evolution is the statement that gyrus formation in phylogenesis and ontogenesis appears to proceed vertical to the lines of stress. The ventrolateral thickening of the hemisphere by the basal ganglia laterally and the formation of the corpus callosum medially are sites of counterpressure against the increasing distention of the hemisphere, causing prevailing lines of coronal stress. This effect is reinforced by the fact that our ur-trends of differentiation and growth of the neocortex course also in coronal direction. This leads to the original longitudinal cortical foldings* as they are found in such primitive mammals as the musk-deer, sloth, *Procavia* (hyrax), *Orycteropus* (aardvark), and *Galeopithecus*.

In the prosimians, except the smaller ones which are still semilissencephalic, the sagittal sulcal pattern prevails over the convexity. This, however, is combined in the posterior part of the hemisphere with the formation of a temporal lobe—a product of the sagittal rotation which is caused by the expansion of the parieto-occipito-temporal integration cortex with simultaneous fanlike deployment of the insular cortex.

With the increasing expansion of the frontal integration cortex and of the parieto-occipito-temporal integration cortex, as is characteristic in primate evolution, the sagittal growth stress is more and more brought into play. Thus, after some incomplete precursors in *Perodicticus* (Zuckerman and Fulton, 1941) and *Nycticebus* (Fig. 11; Sanides and Krishnamurti, 1967), the stress causes the definite simian coronal pattern of central, precentral, and postcentral sulci and lunate sulcus. The great spread of visual cortex contributes to the latter sulcus.

Thus, from the original sagittal sulcal pattern, one can trace a bifurcation (1) a sequence leading on the one hand to the carnivore and ungulate arcuate sulcal pattern by a kinking around the ventrolateral thickening of the hemisphere as a fixation point and (2) another sequence leading to the coronal pattern of simian primates with more or less pronounced vestiges of the sagittal sulci (see below). The basic structural difference can be recognized at the insular point of kinking or rotation. The rotation in primates, going hand-in-hand with a deployment of the insular cortex, is accompanied by the development of a flat laminar claustrum underlying that cortex. The kinking in the brains with an arcuate pattern does not coincide with a flat insula and is accompanied by the development of a relatively compact claustrum. Correspondingly we have in primate evolution a gradual overlapping of the insular stem lobe by the formation of frontal, parietal, and temporal opercula leading to the typical sylvian

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* The sulcus cinguli is a paradigm of a longitudinal sulcus from which Le Gros Clark developed his rule that sulci and gyri form vertical to lines of stress. This sulcus can be found running parallel to the corpus callosum in all eutherian mammals. The triad of lack of cingulate sulcus, presence of radiate sulci, and absence of a corpus callosum is found in marsupials and humans with congenital agenesis of the corpus callosum (Sanides, 1962b).

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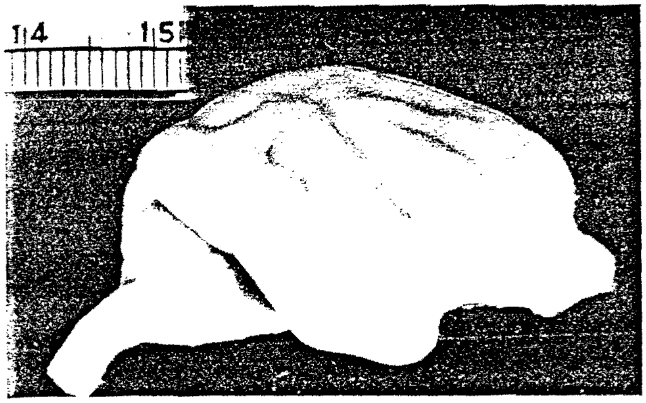

Figure 11. Lateral aspect of the cerebral hemisphere of *Nycticebus* showing the prevailing sagittal sulcal pattern.

fissure, whereas in the brain with the arcuate pattern the opercularization of part of the arcuate gyri leads to a pseudosylvian fissure.

So far we have followed Le Gros Clark's concept on sulcus and gyrus formation. We can go further by enclosing the fossil brains in this design and thus arrive at a pedigree of sulcal pattern in evolution (Fig. 12).

Actually, the fossil brains of carnivores (Radinsky. 1969) and ungulates in the early Tertiary period. i.e.. those orders which display the elaborate arcuate sulcal pattern. exhibit the sagittal pattern (Fig. 13). One reason this point has not yet been recognized may be that the transitions from sagittal to arcuate pattern in ungulates are gradual. whereas only the primate order unifies in itself the most striking contrasts from lissencephalic over sagittal to coronal pattern without substantial intermediate forms. Thus, Le Gros Clark as a primatologist was the first to conceive the sulcal pattern from a *developmental* point of view. Obviously, Edinger (1948) had no knowledge of his 1945 essay. Actually, Edinger compares the fossil brain of *Orohippus*, the second stage of equine evalution in middle Eocene, to that of *Procavia* (hyrax), one of Le Gros Clark's paradigms for the sagittal pattern brain. "In several important characters our *Orohippus* brain material resembles the slightly smaller brain of the much smaller hyrax." Then, however, she refers to the "long, arched suprasylvian sulcus" of *Procavia* which actually should be called lateral sagittal sulcus. A much shorter parasagittal sulcus, designated lateral sulcus, corresponds in our view to the medial sagittal sulcus. The *Orohippus* brains as illustrated were not complete enough to provide evidence of the sagittal pattern. The lower Eocene *Eohippus* brain (Fig. 13a) however, shows the two sagittal sulci beyond any doubt. Again the medial one was called lateral sulcus by analogy with the extant arcuate brain lateral sulcus, indeed equivalence with only the anterior part of the latter is to be suggested. The lateral sagittal sulcus of *Eohippus*, which was designated suprasylvian sulcus, shows a slightly lateral convex bending. It is in such an anterior position as to probably occupy the sensorimotor region of this primitive mammal. In other words what in the older paleoneurologic literature generally was called *lateral* and *suprasylvian* sulci in early Tertiary fossil brains actually should better be designated *medial* and *lateral* sagittal sulci, respectively.

In this context it appears that it was possible to solve the riddle of the meaning

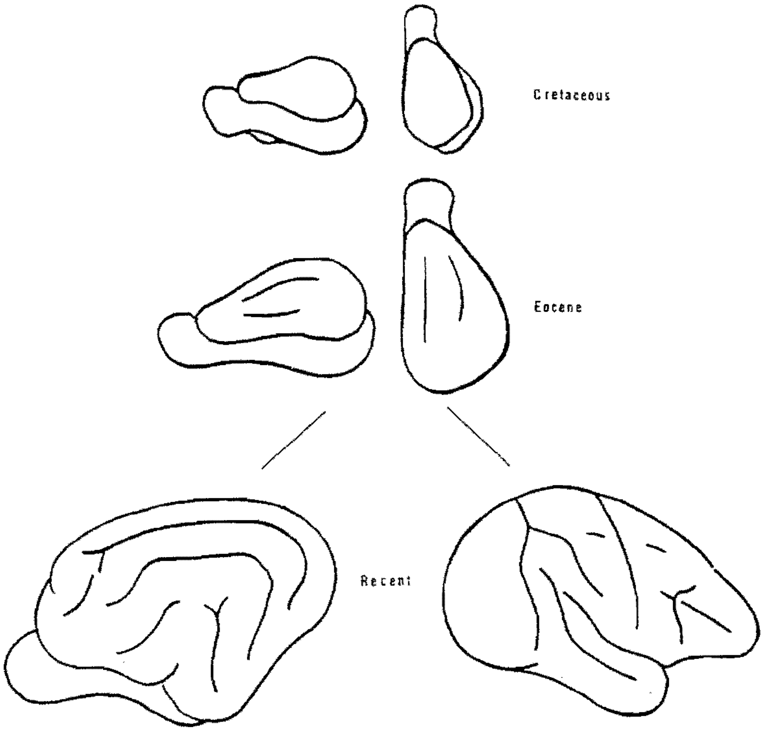

Figure 12. Pedigree of the sulcal pattern in evolution with final bifurcation into arcuate pattern and coronal pattern brains. Cretaceous: Lissencephalic brain of Protoinsectivora, compare with the recent *Erinaceus*. Eocene: Sagittal pattern brain of ancestors of Ungulata, Carnivora and Prostimiae, compare with the recent *Procavia*. Recent: Arcuate pattern brain (cat on left) and coronal pattern brain (*Macaca on right*). Note the steady downward movement of the rhinal sulcus (at the ventral border of the neopallium) which in the monkey has vanished from the lateral surface.

of the sagittal sulci of prosimians in *Nycticebus* (Fig. 11) by our combined approach with architectonic and electrophysiological methods. The main portion of these sulci lies within the sensorimotor region. They delimit the cortical representations of distinct body subdivisions. That is, the medial sagittal sulcus lies between the leg and arm representations, and the lateral one lies between the arm and head representations.

Further evidence that the riddle of the prosimian sagittal sulcal pattern finds its explanation by somatotopic subdivisions was found in the neurophysiological literature. The long sulcus rectus of lemurs, apparently equivalent to the lateral sagittal sulcus, was found by Vogt (1906) to separate motor hand and head areas. The same is the case with the shorter sulcus rectus of *Perodicticus* (Zuckerman and Fulton, 1941). To designate this kind of sulci adequately we introduced the term "somatotopic sulci."

We will now elucidate the factors which are involved in specific sulcus formation. Coronal or sagittal growth stress determines the general direction of developing sulci,

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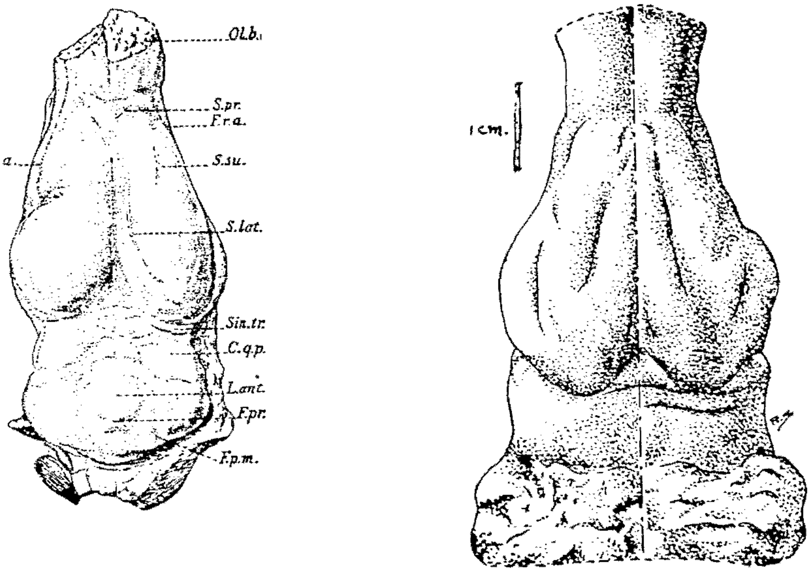

Figure 13. Sagittal pattern brains from Eocene. (a) *Eohippus* brain endocast. From Edinger. 1948. Geology Soc. Amer. Memoir, 25, x 177 pp. (b) *Arctocyon* brain endocast. From Edinger. 1964. Amer. Zool., 4:5-19.

that is, vertical to the lines of stress. The particular site where this stress is exerted requires another explanation, which was basically presented by Le Gros Clark. It is known, that if a beam of uneven dimension is subjected to lateral compression, there is a great concentration of stresses at the junctional zone where the material changes in thickness or consistency. Once a deformation at such a borderline has been initiated, the deflection of the lines of stress will increase the tendency still farther. Since similar conditions obtain at the junctional margins between cortical areas a plausible explanation is offered for the site of limiting sulci, e.g., of the cortical zones of the primate frontal lobe (Fig. 1).

There is also neurophysiological evidence that surface indentations, shallow and deeper ones, are the products of immediately adjacent evolving cortical areas (Welker and Seidenstein, 1959; Welker and Campos, 1963). In the raccoon an extensive behavioral use of the forepaws in manipulation and tactile exploration of the environment is correlated with a relatively large cortical hand representation. Within this region there is a discrete individual projection without any overlapping of single digits and palm pads, and nearly all individual parts are separated on a somatotopic basis by sulci, dimples, and spurs. The enlarged sensory somatic forepaw representation of the raccoon moreover is separated by an anterior limiting sulcus from the motor forelimb area, which implies that a partial equivalent of a central sulcus has developed which is not found elsewhere in the arcuate pattern brain.

Still further evidence for the relationship between development of limiting sulci and local elaboration of cortical areas in association with development of specializations of functions was presented by Woolsey (1959). A pertinent instance is the appearance of two short limiting sulci between the greatly enlarged motor and sensory representations for the prehensile tail of *Ateles* and the adjoining hindlimb representations in precentral Msl and postcentral Sml. There is no doubt that these two limiting sulci represent a new acquisition which occurred in connection with the very prominent enlargement of the sensorimotor areas for the prehensile tail in this genus.

Summarizing these particular examples of somatotopic sulci, we can formulate the rule: *In evolution fast-growing cortical areas exert growth pressure at their borderlines which, under conditions of counterpressure, brings limiting sulci into appearance.* Radinsky presented further convincing findings in extant prosimians (1968b) and fossil and extant carnivores (1968a). The author himself created a decisive prerequisite for the comparative study of endocranial casts by improving the latex casting technique, so that preparation of such casts can be done without damaging the skulls. Another precondition is that the "faithfulness of reproduction of external brain morphology appears to hold true for endocranial casts of all genera of mammals except for the largest brained ones, such as cetaceans, elephants and large primates" (Radinsky, 1968b). His pilot study comprised all but one of the extant prosimian genera. Pertinent are the results on indriids vs. lemurids. The greater outbulging of the area between the anterior section of medial and lateral sagittal sulci in the former led the author, referring to our findings in *Nycticebus,* to the interpretation of a differential enlargement of motor hand area. It is telling that this coincides with a more advanced frontalization of the eyes in the indriids than in the lemurids, for the combination of skill of the hands with stereoscopic vision (by overlapping peripheral visual fields) is the most important trend in primate evolution. It is the integration of both functions which is bound to the steadily growing parietal integration cortex of primates, culminating in man.

In the other study Radinsky (1968a) deals with endocasts of living and fossil otters, revealing particular elaborations of the gyral pattern of the sensorimotor region, which can be correlated with somatic sensory specialization due to anatomical and behavioral observations. In particular Radinsky found that in those otter genera which have a great reduction or loss of the claws of the hand, a special elaboration of the cortical hand area has occurred. He could show by fossil endocasts that such specializations developed as far back as about 10 million years ago. This somatotopic cortical elaboration has its behavioral correlate in that these small-clawed and clawless otters feed mainly on crustaceans and molluscs rather than on fish and probably use their hands for feeling around in mud and under stones to locate food (Walker et al., 1964)—an amazing parallel to the conditions in the raccoon!

For the evaluation of the sulcal and gyral pattern of the otters Radinsky (1968a) refers to the electrophysiological localization studies of Woolsey and co-workers in carnivores (Woolsey, 1959, containing further references). The most important pertinent finding is the somatotopic character of the coronal sulcus, which in all genera investigated separates somatic sensory and motor hand areas from head areas. This proves that the coronal sulcus is equivalent to the lateral sagittal sulcus of prosimians.

Moreover, Woolsey (1959) demonstrated the somatotopic character of the short sagittal sulci or fissurets of simians' sensorimotor region. In Old and New World monkeys the caudal spur of the arcuate sulcus delimits the motor head from motor hand areas, and in chimpanzee this somatotopic limit on the precentral gyrus is continuous with the inferior frontal sulcus. In other words there is obvious equivalence

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between the lateral sagittal sulcus of prosimians and this posterior spur of the monkey's arcuate sulcus as it is with the coronal sulcus of carnivores.

There are, however, in simian primates further obvious relics of the ancient prosimian sagittal pattern. The superior precentral and postcentral sulci, both short fissurets in New and Old World monkeys and chimpanzee, delimit hindlimb from forelimb areas. These are obviously relics of the medial sagittal sulcus of prosimians. The somatotopic significance of these relics of the ancient sagittal sulci in monkeys is moreover confirmed by Dusser de Barenne's strychnine neuronographic studies (1941, see Fig. 7b).

There are apparently relics of the ancient sagittal sulci even in the increasingly expanding integration cortices of higher primates, including man. Since this appears puzzling in such highly differentiated cortical areas, we will discuss our view based on comparative neurology, of the frontal and parieto-occipito-temporal integration cortices.

Because of the overwhelming growth of these integration cortices in higher primates and particularly in man, and because of the difficulty in delineating these limited areas of lower mammals (beside the motor and sensory areas), the idea had been put forward that the integration areas were principally later elaborations in evolution than motor and sensory areas. Thus the latter were referred to as primary regions and the former as secondary regions (Kuhlenbeck, 1928). The results of Flechsig's myelogenetic investigation (1920) of the human cerebral cortex favor this concept. Indeed, the motor and sensory areas are the first to differentiate in the perinatal gradual maturation process of myelination of immediate subcortical projection fibers. However, the Vogts (1919) had already stated the remarkable fact that it is the areas with the heaviest definitive myelin content which begin to myelinate first. This is just the case with these primary sensory and motor areas. Obviously this is a general ontogenetic counterrule which interferes with the biogenetic rule of Haeckel. This counterrule appears to signify that such tissues or histological elements which present a particularly high level of differentiation in the mature stage begin to differentiate irrespectively earlier in fetal life.* This leads to sequence dislocations of the ontogenetic maturation process compared with the pertinent phylogenetic periods.

We can also refer to Bishop's findings which we summarized as "myelination trend in evolution," that is, the finer myelinated fibers of related systems are basically older in evolution than the heavier myelinated ones. This conclusion, of course, is contradictory to the assumption that the primary sensory and motor areas are primary in evolution. On the contrary, from this ensues that the koniocortices, which are the heaviest myelinated cortical areas within the sensory regions, represent the most recent stage in sensory cortex evolution and that the area gigantopyramidalis, which is the heaviest myelinated motor area, represents the most recent stage in motor cortex evolution, an inference which is likewise suggested by the highest architectonic specialization of these areas and is parallelled by the highest functional specialization.

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* Yakovlev and Lecours (1967), studying the whole myelogenetic cycles of the brain, came to similar conclusions. "Those systems with special functional importance to a given species generally appear earlier, but have longer cycles of myelination than those systems with more universal and less specific functions which differentiate later, but have shorter cycles of myelination."

Moreover, we were able to trace the initial existence of the anterior and posterior integration cortices in the neocortex of the European hedgehog (Erinaceus europaeus). This most primitive insectivore exhibits, together with the neocortex of representatives of Chiroptera, the most primitive neocortex of placental mammals so far investigated.

Thus, what had been recognized as a main feature of neocortical evolution—the appearance and immense growth of the integration cortices, particularly in the primate series up to man—was actually not understood. Overwhelmed by this vast expansion of apparently functionally silent regions, that is, the integration cortices, and preoccupied with their neuropathologic and psychopathologic analysis, or had overlooked the fact that we are dealing with a typical feature of primates—*the most generalized neocortical structure is bound to become the enormously prevailing one, with the widest scope of further differentiation during life.*

In this view, the presence of apparent relics of the ancient sagittal sulci in the integration cortices, even of higher primates, can be expected. In the monkey's frontal lobe it is the sulcus principalis which, after a short interruption by the paramotor areas (Brodmann's 8) inside the arcuate sulcus, continues the direction of the motor region relic of the lateral sagittal sulcus, that is, the posterior spur of the arcuate sulcus (Fig. 7). In apes and man we found, as already discussed, the inferior frontal sulcus to be equivalent to the sulcus principalis. This assumption derived from the fact that both sulci delimit the dorsomedial zone of the frontal granular cortex, marked by the prevailing mediolimbic architectonic influence, from the ventrolateral zone, marked by the prevailing insulolimbic influence. The mediolimbic and insulolimbic directions of differentiation could, however, also be traced within the precentral motor cortex of man in the form of subdivisions (Sanides, 1962b). This showed that the basic borderline through the precentral gyrus is located at the same level as in the prefontal cortex, in continuation with the inferior frontal sulcus. In the somatotopic partitioning of the human motor cortex this level corresponds to the limit between head and hand representations. This is the case with the posterior spur of the arcuate sulcus of the *Macaca*, and the same level is valid for the chimpanzee (Fig. 14).

The superior frontal sulcus corresponds to the level of the limit between leg and arm areas of the precentral gyrus and thus appears to correspond to the medial sagittal sulcus of *Nycticebus*. A corresponding sulcus does not exist in the prefrontal granular cortex of monkeys.

The result of these considerations is that the inferior and superior frontal sulci of man and apes are part-equivalents of the lateral and medial sagittal sulci of prosimians, the somatotopic significance of which we have clarified. This sounds as if somatotopic partitioning also determines the character of the frontal integration cortex.* Indeed, that this is so in architectonic terms could be shown in the parietal integration cortex of *Nycticebus*. The somatic koniocortex (Ks=3b Vogts) exhibits a clear-cut cytoarchitectonic tripartitioning into subdivisions corresponding to hindlimb, forelimb, architectonic tripartitioning into subdivisions corresponding to hindlimb, forelimb, and head areas, separated by the two sagittal sulci. These subdivisions distinguish themselves prevalently by the size of the few efferent lamina V pyramidal cells within

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* An application of this view of the primate prefrontal cortex is to be found in a paper based on delayed response testing ablation experiments of rhesus monkeys (Sanides and Schlitz, 1967).

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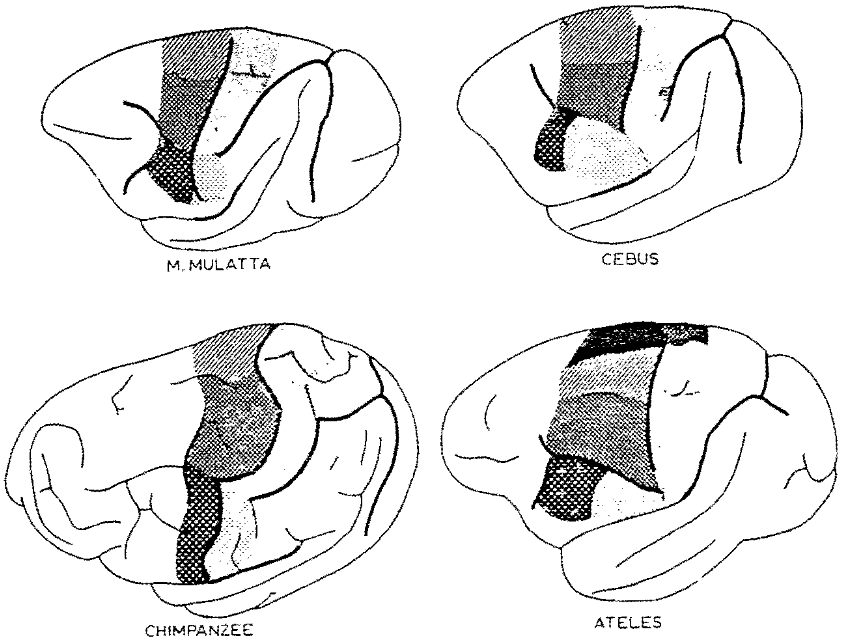

Figure 14. Brains of four primates (left, Old World; right, New World) showing corresponding somatopic sensorimotor subdivisions of MsI, and SmI into head, forelimb, and hindlimb areas. Note enlarged tail areas (black) in *Ateles*. For limiting sulci see text. From Woolsey, 1959. *In* Structure and Function of the Cerebral Cortex. Elsevier.

the otherwise light lamina V of area Ks. The largest are to be found in the hindlimb area, intermediate ones in the forelimb area, and smaller ones in the face area. This corresponds to the general experience in higher primates of a decrease in size of the giant pyramidal cells in the area Gig from leg to arm area and an absence of such giant pyramidal cells at all in the face area.

Corresponding architectonic subdivisions, somatotopically correlated and separated by the two sagittal sulci, were found also in the somatic parakoniocortex (parK = 1 Brodmann). Here the large lamina V pyramidal cells which are even more numerous than in Ks show the same size differences between medial and lateral subdivisions, as they are separated by the medial sagittal sulcus. A lateral subdivision was not found in *Nycticebus*, since the parK fuses at this level with proK. In the cat, however, all three subdivisions of parK corresponding to leg, arm, and head area with the same gradation of size of the V lamina pyramidal cells as in Ks could be demonstrated. In both *Nycticebus* and cat in the caudally contiguous parietal integration cortex corresponding architectonic subdivisions could be traced. The somewhat smaller and denser lamina V pyramidal cells of these areas show the same gradation in size between medially, intermedially, and laterally.

It is important that the sulcus intraparietalis which plays the limiting role between the apparent leg subdivision and the apparent arm subdivision of the parietal integration cortex is located at the level of the medial sagittal sulcus. And that in some of the slow loris specimens investigated (Krishnamurti, 1966) it is a direct caudal continuation of the medial sagittal sulcus. The intraparietal sulcus of higher primates, in the corresponding location, then, appears to be equivalent to this part of the medial sagittal sulcus. Even in man, the similar cytoarchitectonic findings of the parietal integration areas are known and are parallelled by the myelin content, which decreases with the diminution of the average cell size ventrally from the intraparietal sulcus (Hopf and Vitzthum, 1957). From the neuropathologic point of view, Schaltenbrand (1950) even designated the superior parietal lobule as part of his "leg brain" and the inferior parietal lobule as part of his "arm brain" with the intraparietal limiting sulcus separating them.

The evidence of the equivalence of the prosimian somatotopic sagittal sulci in higher primates and in extant carnivores is based not only on gross morphology but also on architectonics and electrophysiological results. For evaluation of the gyral pattern of fossil brains we will of course always depend on extrapolations concerning the functional character of area delimited by certain sulci.

After our presentation of Le Gros Clark's theoretical deductions of the development of the sulcal pattern and after our generalizations based on the interdisciplinary approach to the prosimian sagittal pattern, it may be justified to interpret the three early Tertiary fossil brains which are paradigms of our pedigree of the sulcal pattern in evolution, *Eohippus* (Fig. 13a), Notostylops, and *Arctocyon* (Fig. 13b), as marked by the same type of somatotopic sagittal sulci as the prosimians (Fig. 11).

Concerning the endocranial cast of the notoungulate Notostylops of Lower Eocene age, Edinger (1948) gives the following account of the configuration of the hemisphere: "The small neopallium had only two, more or less distinct longitudinal sulci and possibly a Sylvian fissure." The endocranial cast of *Arctocyon* of Upper Paleocene displays the same pattern, and Arctocyanidae were ancestral to all later Carnivora, as *Eohippus* was to Equidae.*

To secure the general validity of the somatotopic character of the sagittal sulci in fossil brains ancestral to extant arcuate pattern brains it appears important to examine the same in nonprosimians, that is, in the few recent aberrant primitive mammals mentioned above, using electrophysiological and/or cytoarchitectonic methods.

Organization Of The Sensorimotor, Gustatory, And Visual Areas

THE SENSORIMOTOR AREAS

Since the discovery of the secondary sensory and motor representations, the classic scheme of the motor, somatic sensory, auditory, and visual cortical areas has been fundamentally shaken. A new array including the additional representations has, in spite of the increasing amount of detailed knowledge on the sensory input areas, not

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* In a recent publication on "Outlines of canid and felid brain evolution" (Ann. N.Y. Acad. Sci. 167:277-288, 1969) Radinsky illustrated the endocast of Mesperocyon, the oldest known specimen of the canid family of Carnivora from the Middle Oligocene. This fossil brain still shows the two sagittal sulci pattern with only incipient arching of the lateral one.

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yet been found. This state of affairs appears not too much changed since Bucy's opening remarks to the second edition of the great monograph *The Precentral Motor Cortex* (1949) which he edited:

> "The discovery of the second motor and sensory centers by Adrian (1941), Woolsey (1943, 1944) Woolsey and Wang (1945), and Sugar, Chusid, and French (1948) is one of the most intriguing new developments. As yet, however, our understanding of these is not sufficient to allow us to correlate their activity with the activity of other cortical and subcortical centers."

Our cytoarchitectonic and myeloarchitectonic studies of the sensorimotor region in several primates which in the prosimian *Nycticebus* were correlated with a microelectrode recording study, as well as our cytoarchitectonic and myeloarchitectonic studies on the taste areas in *Saimiri* and *Macaca* which were correlated with Benjamin and co-worker's systematic electrophysiological studies, provide a basis for new discussion of the pertinent data of the literature. These will be confronted with our concept of neocortex evolution.

Considering our ur-trends of differentiation in evolution from archicortex via the cingulate gyrus medially and from paleocortex via the insula laterally, it was conceived that the supplementary motor (Mpl) representation (fig. 19), lying in the medial phylogenetic trend, is an earlier stage of motor control, and the second somatic sensory (SmII) representation lying in the lateral phylogenetic trend is an earlier stage of *sensory* control than the respective classic representations.

As we stated in 1962b, Mpl, as discovered by Penfield and Rasmussen in man (1952), actually lies mainly in the paralimbic zone (PlZ, Figs. 1 and 26) of our human map, that is, in an intermediate stage of architectonic differentiation between anterior cingular Pro and FmZ. SmII corresponds in its location to a parinsular zone (PiZ) on the inside of the central operculum, which in architectonic terms is intermediate between the insular Pro and the postcentral SmI.

When we, in our frontal lobe monograph (1962b) formulated the hypothesis for the additional sensorimotor representations we had no knowledge of the important paper about the somatic areas I and II of Woolsey and Fairman (1946) who, on electrophysiological grounds concerning SmII and AII, came to a similar assumption as we did:

> "Duality, therefore, appears to be a general principle of cortical organization. The position of somatic and auditory areas II between the rhinencephalon and insula on the one hand and the more highly differentiated areas I on the other suggests that the 'second' areas may be phylogenetically more ancient and primitive."

The microelectrode recording study of *Nycticebus*' somatic sensory cortex (Figs. 11 and 15) revealed a fundamental correlation between morphologic and cytoarchitectonic features and projection patterns from peripheral receptive fields. Thus we actually succeeded in outlining architectonically a parinsular area, proK, representing SmII. As a particular feature we found this area partly responsive to auditory stimuli, another indication of the limited specialization compared with the so-called

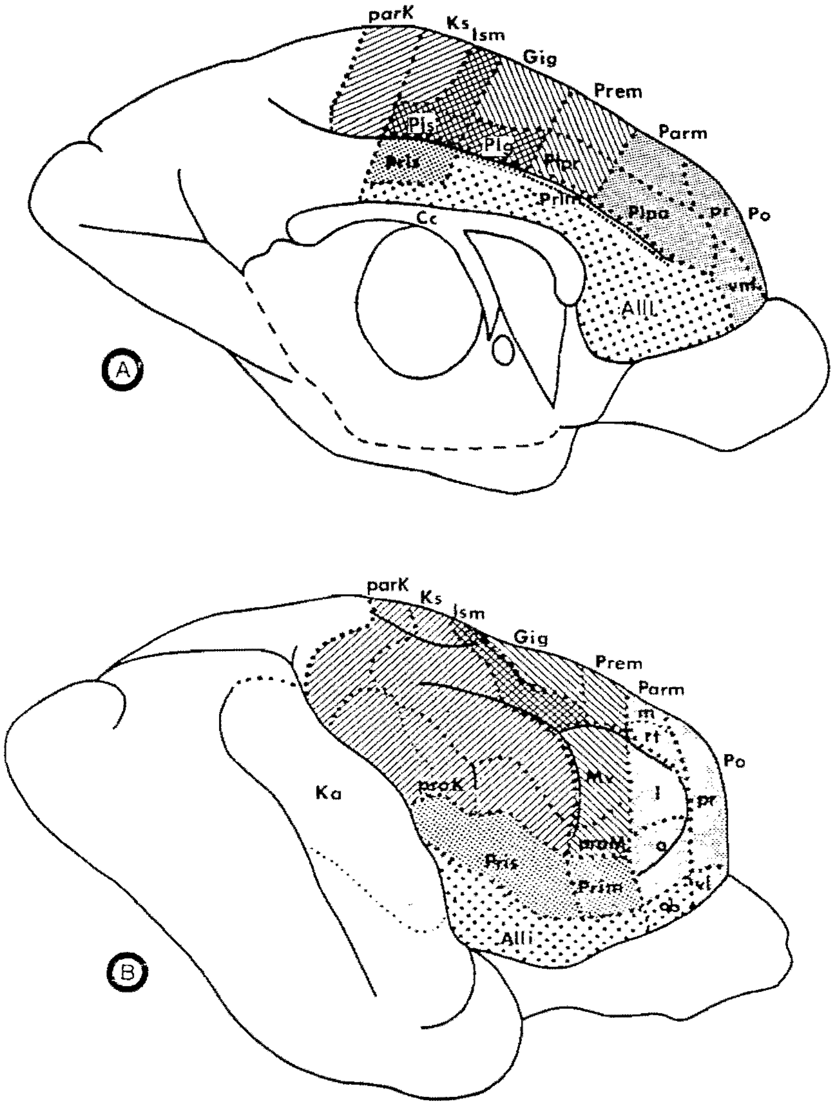

Figure 15. Cytoarchitectonic map of sensorimotor, insular, limbic, and prefrontal regions of *Nycticebus*. See Table 1 for abbreviations and Figure 9 for equivalent areas in Brodmann's nomenclature. From Sanides and Krishnamurti. 1967. J. Hirnforsch., 9:225-252.

primary areas. This overlapping of somatic and auditory receptive units in SmII previously has been systematically explored in the cat by Berman (1961a, b).

Since *Nycticebus* still possesses an exposed insular cortex (better designated claustrocortex, after Brockhaus, 1940), with the exception of a caudal fringe covered by a small temporal operculum, it offers the unique opportunity of studying the lateral ur-trend, within which Sm II lies, without interference of sulci or opercula, up to the somatic koniocortex of the head area (Fig. 16). Beginning at the anterior

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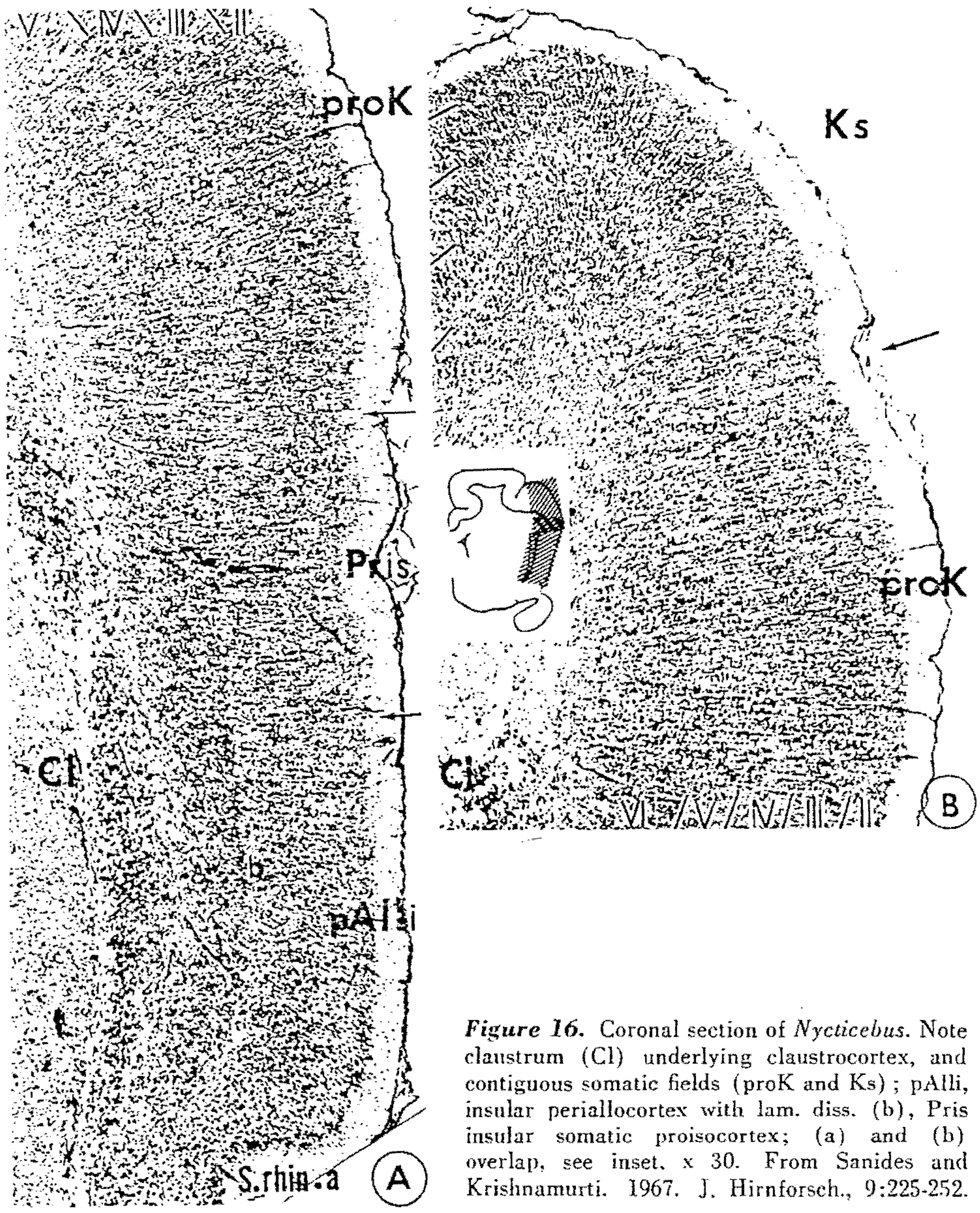

Figure 16. Coronal section of *Nycticebus.* Note claustrum (Cl) underlying claustrocortex, and contiguous somatic fields (proK and Ks); pAlli, insular periallocortex with lam. diss. (b), Pris insular somatic proisocortex; (a) and (b) overlap, see inset, x 30. From Sanides and Krishnamurti. 1967. J. Hirnforsch., 9:225-252.

rhinal sulcus, the borderline to the paleocortex (allocortex primitivus), we find as a first step the insular pAll which is composed essentially of two-cell-strata with a more prominent inner one and a rather inconspicuous lamina dissecans (b') in between. Both strata show a cell condensation externally. The outer lamina can be traced to the dense cell band of the paleocortex beyond the rhinal sulcus. In pAll this cell band is in the position of a second layer, though composed of densely packed multiform cells which are larger than granule cells. These cell condensations fade out towards the area limit to the proisocortex (Pris). Nevertheless, in Pris the layer II cells remain coarser than in contiguous proK.

In addition Pris is somewhat less prominent on the inner stratum, and instead of the lamina dissecans an incipient granular lamina IV appears. At the area limit of proK (i.e., SmII) the emphasis switches to the outer stratum where laminae II, III, and IV are almost fused. Laminae II and IV are composed partly of small pyramidal cells and partly of granule cells. Lamina V exhibts medium-sized pyramidal cells on a lighter background. Lamina VI is again denser and composed of medium-sized cells.

We can summarize the prevailing trends as a shift of emphasis from inner to outer stratum and a stepwise granularization. This also holds true for the transition of proK to Ks. Here the granularization reaches its maximum with almost complete fusion of laminae II, III, and IV, resulting in the dense outer stratum. Lamina V is light since it has less pyramidal cells than proK. The dense lamina VI is composed of smaller cells.

Thus we recognize proK, the area of the SmII representation, to be an intermediate step between insular proisocortex (Pris) and Ks; i.e., it is, compared with Ks, preliminary in granularization, preliminary in the density of the outer stratum (laminae II, III, and IV), and preliminary in the lightening of lamina V. In all these features we note proK as an area of much lesser specialization than Ks. Hence we referred to it as a "prokoniocortex" (proK), occupying part of the parinsular zone.

Similarly a paralimbic zone (Fig. 15) is delineated with intermediate areas (Pls, Plg, Plpr, Plpa) between Pro of the cingulate gyrus (Prlm and Prls) and the pertinent convexity areas. This zone probably contains Mpl, although this has not yet been established in *Nycticebus*. The intermediate stage of this zone can be recognized in Figure 17 in its location within the medial ur-trend. In the lower left we see the dorsal part of the cingulate gyrus with pAll and limbic motor proisocortex (Prlm). Adjacent to pAll ventrally would be the vestigia hippocampi. The periallocortex is, as the insular one, composed of two cell strata with a more prominent inner one. There is no lamina dissecans. As in the insular cortex, a bandlike condensation of cells appears at the surface. It is composed of densely packed small multiform cells, which are larger than granule cells. This cell band can be easily traced through the proisocortex (Prlm) to the bottom of the cingulate sulcus where it disappears at the transition with the paralimbic Plpr. Area Prlm exhibits, as does the anterior cingulate gyrus in higher primates, a particularly light lamina III. Its dense medium-sized V pyramidal cells fuse with the dense VI. In Plpr the dense V is composed of somewhat larger pyramidal cells standing out against a lighter VI. Lamina III increases considerably in its width and in the size of its pyramidal cells. The increase of the size of lamina V and lamina III pyramidal cells continues, as in higher primates, into area Gig.

Before we discuss further data of the combined architectonic—electrophysiological approach to the somatic sensory region of *Nycticebus*, a comment is included on our nomenclature as it is used in our maps (Figs. 9, 15). The sequence of the numbers used to name Brodmann's well-known areas was determined by the order of the appearance of each architectonic area in the horizontal serial sections of the human brain arranged from the crown to the base. The numbers have, as such, no reference er II cells remain

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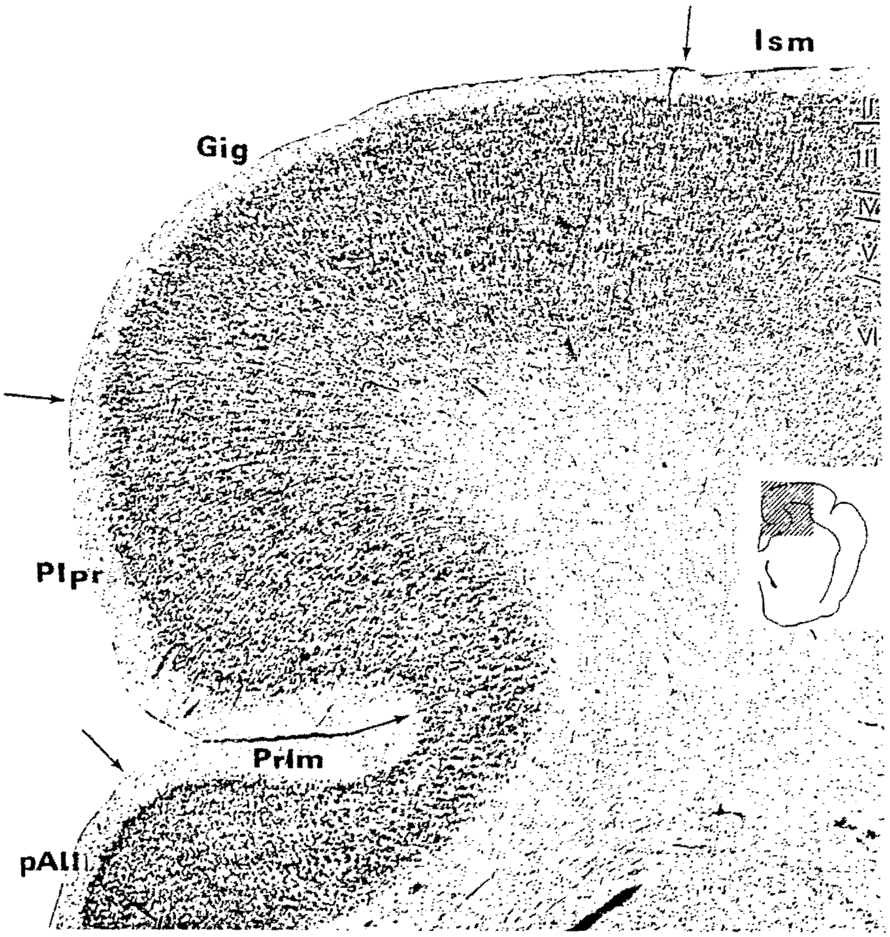

Figure 17. Coronal section of *Nycticebus* through anterior cingulate gyrus and adjacent motor cortex, pAll 1, limbic periallocortex; Prlm, limbic motor proisocortex; Plpr, paralimbic premotor area, x 28. From Sanides and Krishnamurti. 1967. J. Hirnforsch., 9:225-252.

to architectonic or functional qualities of the fields. Also, the paralimbic and parinsular areas were not yet detected by Brodmann, since emphasis was still laid on the convexity areas.

C. and O. Vogt (1919), by combining stimulation experiments in *Macaca* with architectonic controls, subdivided some of Brodmann's fields which have become well established, e.g., area 6bα, the mastication field at the base of the precentral motor cortex. However, the adding of a suffix to an area gives the impression that it is only a subarea of a major area. The dorsal parts of Brodmann's area 6, that is, 6aα and 6aβ have quite a different character functionally and architectonically. They are agranular and serve complex movements, whereas 6bα is dysgranular. Thus Brodmann's area 6 breaks up into incommensurable units.

Considering these fallacies in the current inadequate nomenclature we introduced our own nomenclature utilizing pertinent architectonic features, topology of the areas, and as far as possible functional correlates. In *Saimiri* almost all subdivisions as outlined by the Vogts in *Macaca* (Fig. 7a) could be found again, and both nomenclatures are included in Figure 9.

Of significance is the partitioning by the Vogts of Brodmann's somatic area 3 into 3a and 3b. We refer to 3b as somatic koniocortex, Ks, since it forms the hypergranular core of the somatic sensory region. Such a hypergranular core is also typical for the visual regions, i.e., visual koniocortex, Kv, and for the auditory region, i.e., auditory koniocortex, Ka. Area 3a shows rather intermediary character between Ks and Gig; that is, it exhibits more V pyramidal cells than Ks but is less granular than Ks. Therefore we designated this area intersensorimotor area, Ism, suggesting also its double function. With its less specialized sensory character Ism resembles the posterior somatic belt which we call parakoniocortex (parK). In *Saimiri* as in all simian primates so far investigated there are two fields in this belt, Brodmann's area 1 and 2, whereas in parK in *Nycticebus* only one clear-cut area was differentiated which exhibted at its caudal border a small magnocellular rim suggestive of an area parK$_2$ "in statu nascendi." The term koniocortex also refers to a general field bordering a koniocortex; it is distinguished by its conspicuously large pyramidal cells in lamina IIIc (Sanides and Hoffman, 1969).

We have now to consider some details of the electrophysiological results in *Nycticebus* and their relationship to the somatic sensory partitioning. For evaluation of the cortical points responsive to the peripheral tactile stimulus the relative size of the receptive field, the modality, and the ability to drive clusters of units were decisive. Maximal responses of this type were confined to the core of the somatic sensory region, i.e., Ks. Somatic sensory responses were also found in penetrations in the areas which border Ks rostrally and caudally, that is, in area Ism and parK (Fig. 18), respectively; here, however, light mechanical stimulation was ineffective, relatively strong mechanical stimulation was required to elicit activity. An evoked surface positive wave was found in these areas as in Ks, but units here were not so reliably driven as in Ks, and their peripheral receptive fields were larger. Thus the highest architectonic specialization, i.e., the koniocortex, was correlated with the highest functional specialization, providing the largest sensory discriminative power.

To complete the description of *Nycticebus*' somatic sensory region we have to mention the small paralimbic field Pls (Fig. 15) which resembles the intermediate field Ism but has more densely packed lamina Va pyramidal cells, which can be considered a characteristic of the anterior limbic lobe. A common feature of area Pls and area Ism is the occurrence of single unusually slender large pyramdial cells in lamina Vb which strongly resemble the conspicuous rod cells of the anterior limbic region in man.

Thus somatic koniocortex appears surrounded by four related granular fields (Fig 15). Three of them—the parinsular prokoniocortex (proK), the caudal parakoniocortex (parK), and the oral intermediate area (Ism)—have somatic input, while the paralimbic one (Pls) is possibly a part of the supplementary sensory representation of Penfield and Rasmussen (1952). This is similar to the architectoni-

cally and physiologically based concept of the auditory region of the cat (Rose and Woolsey, 1949). Rose and Woolsey proposed a fourfold partitioning such that the central koniocortical field AI is surrounded by three fringe areas which are architectonic transitions to the neighboring areas and are known also to receive auditory input. One of these is the parinsular AII which we classify as prokoniocortex. The fringe areas have, apart from the direct auditory input, corticocortical connections with the central primary field.

According to our findings in man, which will be discussed later, such a ringlike organization around a core koniocortex holds true also for the visual region. In this region, there are two concentric fringe areas (18 and 19 Brodmann's) for which direct visual input and corticocortical connections from the striate area have been demonstrated. To these can be added a visual prokoniocortex, designated prostriate area, which we found in a parasplenial location. Rostrally, it completes the ring around the striate area.

The uniqueness of the somatic sensory and of the precentral motor regions lies in the fact that they are based on both sides on proisocortex, i.e., the dorsal claustrocortex and the anterior limbic cortex, to which they are linked by parinsular fields laterally and paralimbic fields medially. This suggests a differentiation from *both* ur-trends. Another peculiarity is that these two regions possess a common fringe area in the intermediate field Ism.

The auditory and visual regions, on the other hand, with their respective parinsular (AII) and paralimbic (prostriata) links appear differentiated from *one* focus of origin only—the auditory region from caudoinsular cortex, the visual region from caudolimbic cortex.

The ringlike arrangements of the mammalian neocortical somatic sensory, motor, auditory, and visual regions and their relation to the ur-trends of neocortex differentiation will be discussed below.

Now we have to consider our pertinent findings in the New World monkey *Saimiri* which will be compared with findings in the Old World rhesus monkey. The ringlike organization of the somatic sensory and of the motor region holds true for both animals. In spite of the special New World monkey configuration with rostral protruding of the face representations, the somatic and motor fields exhibit similar architectonics in both monkeys. In the fringe of the premotor fields which surround area Gig in *Saimiri* (Fig. 9) the most rostral agranular field, preMl, will be discussed. As in other primates we distinguished at the medial surface in *Saimiri* a paralimbic field, plM, with very dense, smaller lamina V pyramidal cells. Area preMl, contiguous to the latter following the limbic ur-trend, exhibits somewhat larger and looser lamina V pyramidal cells. However, their great density as a limbic feature as compared with the other motor fields has prompted us to give the area the suffix l. For the equivalent field $6a\beta$ in *Macaca* the Vogts noted particularly adversive movements which were elicited at the lowest thresholds, whereas in the caudally adjacent area $6a\alpha$ these movements could be elicited only at a higher threshold. The Mpl representation, as described by Penfield and Rasmussen in man (1952), corresponds grossly to our paralimbic zone. In *Macaca*, Woolsey (1958) found the same location of Mpl on the medial surface, with little encroachment upon the convexity (Fig. 19). Here, too, it corresponds mainly

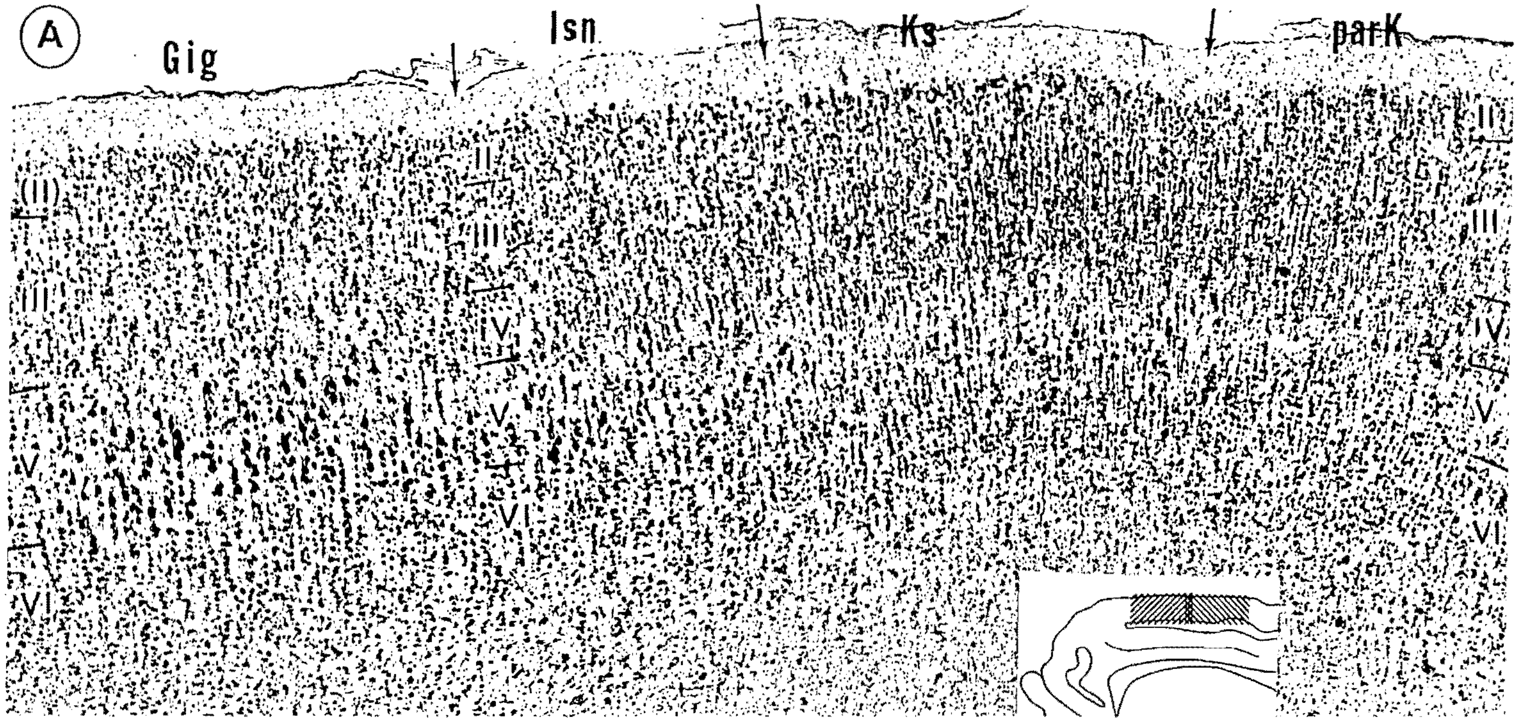

Figure 18. Parasagittal section of *Nycticebus*, illustrating the somatic fields parK, Ks, Ism; the motor fields Gig, Prem; the prefrontal field Parm; (a) rostral to and contiguous with (b), see inset. x 54. From Sanides and Krishnamurti. 1967. J. Hirnforsch., 9:225-252.

Figure 18. Parasagittal section of *Nycticebus*, illustrating the somatic fields parK, Ks, Ism; the motor fields Gig, Prem; the prefrontal field Parm; (a) rostral to and contiguous with (b), see insel. x 54. From Sanides and Krishnamurti. 1967. J. Hirnforsch., 9:225-252.

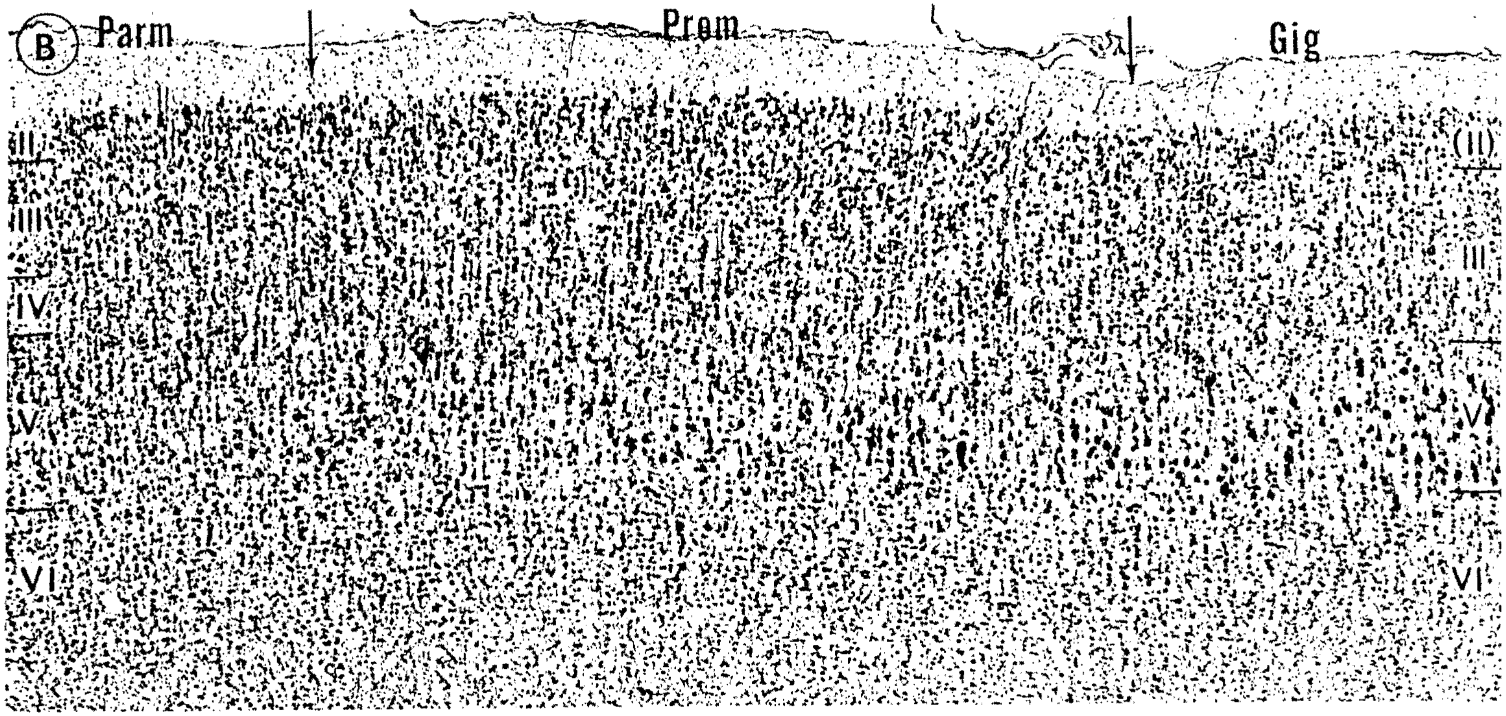

Figure 18. Parasagittal section of *Nycticebus*, illustrating the somatic fields parK, Ks, Ism; the motor fields Gig, Prem; the prefrontal field Parm; (a) rostral to and contiguous with (b), see insel. x 54. From Sanides and Krishnamurti. 1967. J. Hirnforsch., 9:225-252.

Figure 19. Diagram of neurophysiologic mapping of the sensorimotor regions in *Macaca.* MI and SI, classic precentral and postcentral sensorimotor representations. SII, parinsular somatic; MII, paralimbic motor representations. From Woolsey, C. N. *In* Schaltenbrand and Woolsey eds., "Cerebral Localization and Organization. (Madison, The University of Wisconsin Press 1964, pp. 17-32.)

to our paralimbic field and encroaches, particularly with the peripheral parts of the arm representation, upon 6aβ. Thus only Mpl in *Saimiri* appears to encroach so far upon the surface to cover the whole of preMl.

In our concept, plM and preMl are parts of the motor belt surrounding the highest specialized motor core, area Gig, plM remaining in a paralimbic stage and preMl being differentiated further. The conflicting physiologic findings raise the question whether the so-called adversive movements elicited by the convexity parts of 6aβ in *Macaca* by the Vogts (1919) correspond actually to the reactions elicited by the area designated as supplementary motor area at the same site in *Saimiri* (Benjamin and Welker, 1957).

The unsolved question of the cortical motor patterns can be attributed to the fact that the electrical excitation of motor responses is still the most unphysiologic method among the neurophysiologic techniques of investigating the cerebral cortex. From quite another approach, that of hodology of cortical fiber connections, a strong argument for the entity of the supplementary motor representation in a paralimbic site is provided by Pandya and Kuypers (1969) in *Macaca.* Using the Nauta technique, they found, after ablation of the second sensory area, numerous degenerating fibers projecting to the site of the ipsilateral Mpl at the medial wall of the hemisphere. We had already postulated such connections. In our view, the present stage of sensorimotor organization, with the classic precentral motor and postcentral somatic regions flanked medially by paralimbic supplementary motor and ventrolaterally by parinsular second sensorimotor areas, is preceded in evolution by a stage where the paralimbic and parinsular representations were still contiguous. Therefore interaction of both original motor and sensory areas by subcortical connections was strongly suggested. Thus in the results of Kuypers and Pandya, we can recognize a suggestion that the convexity cortex of the motor fringe areas are fundamentally different from the areas on the medial wall of the hemisphere. This is in line with our architectonic findings.

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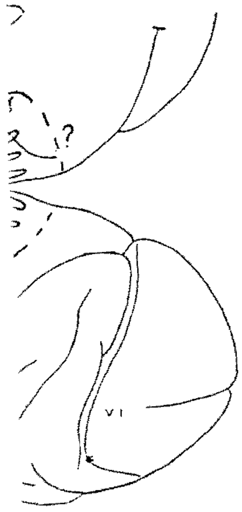

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THE CORTICAL TASTE NERVE AREAS

The taste projections to the cortex have been investigated by Benjamin and co-workers in a series of electrophysiological studies (Benjamin and Pfaffmann, 1955; Benjamin and Akert, 1959; Benjamin, 1963; Benjamin and Burton, 1968; Benjamin et al., 1968). Our architectonic studies are correlated with their findings in *Saimiri* (Sanides, 1968) and with unpublished data in *Macaca*. By courtesy of the authors we had occasion to study microscopically several of the experimental brains and to examine the two sites (1) the surface area and (2) the opercular/insular cortex which yielded positive responses to the stimulation of the taste nerves (chorda tympani and lingual-tonsillar branch of glossopharyngeus). In this way we identified the gustatory nerve projection areas on the convexity of the hemisphere as coinciding mainly with Ks, with the tongue representation. This and the deep gustatory nerve input area were revealed as a well-defined granular field at the anterior border of the insula (Figs. 9 and 20) occupying mainly the most rostral inner aspect of the frontal operculum. The relationship of these areas to the sensorimotor partitioning will be described in order to arrive at an evaluation of their differential stage in the context of our concept of neocortex evolution.

The deep pure taste area, G, turned out to be a rostral continuation of the parinsular belt (containing more caudally the somatic prokoniocortex, corresponding to SmII). We have first to pursue the course of the latter through insular and opercular cortex. In electrophysiological studies of the somatic sensory areas in *Saimiri*, Benjamin and Welker (1957) found the leg and trunk representation of SmII on the caudal half of the insular cortex in that section without an underlying claustrum. The architectonic particularity of this insular section against the ventral Pro is revealed strikingly in Figure 6 by its increase in myelin content. In cytoarchitectonics it exhibits its character as a prokoniocortex (in contrast to the ventral proisocortex) by an increase of granular lamina IV and decrease of the lamina V pyramidal cells. Some arm representation was found on the contiguous inside operculum, but for technical reasons it was not traced further forward. As far as face representation was found in the upper bank of the Sylvian fissure, it corresponds at this level to area parK2. Hence, it has to be designated, not as part of SmII (as was originally done), but as part of the outer somatic belt of SmI.

Microelectrode studies by Benjamin (personal communication) revealed that the tongue representation of SmII occupies the more rostral parts of the inside of the operculum, which are formed by proK. It is in this location that gustatory area G emerges at the level of Horsley-Clarke coordinate A13 to occupy about 3 mm length of the inside of the operculum rostrad up to A16. In its rostral half, area G encroaches within the insula into the region of the levelling off of the sulcus circularis and extends rostrally to the caudo-orbital cortex. At the upper lip of the Sylvian fissure area G is contiguous (1) with a subdivision of proK, (2) with proM (corresponding to caudal half of 6bβ Vogts), and (3) with parM, that is with the opercular subdivision of the slightly granular paramotor belt of the prefrontal cortex (Fig. 9).

The insular cortex, which abuts against area G in the depth of the sulcus circularis, corresponds to an anterior light granular section of the insular Pro which we could

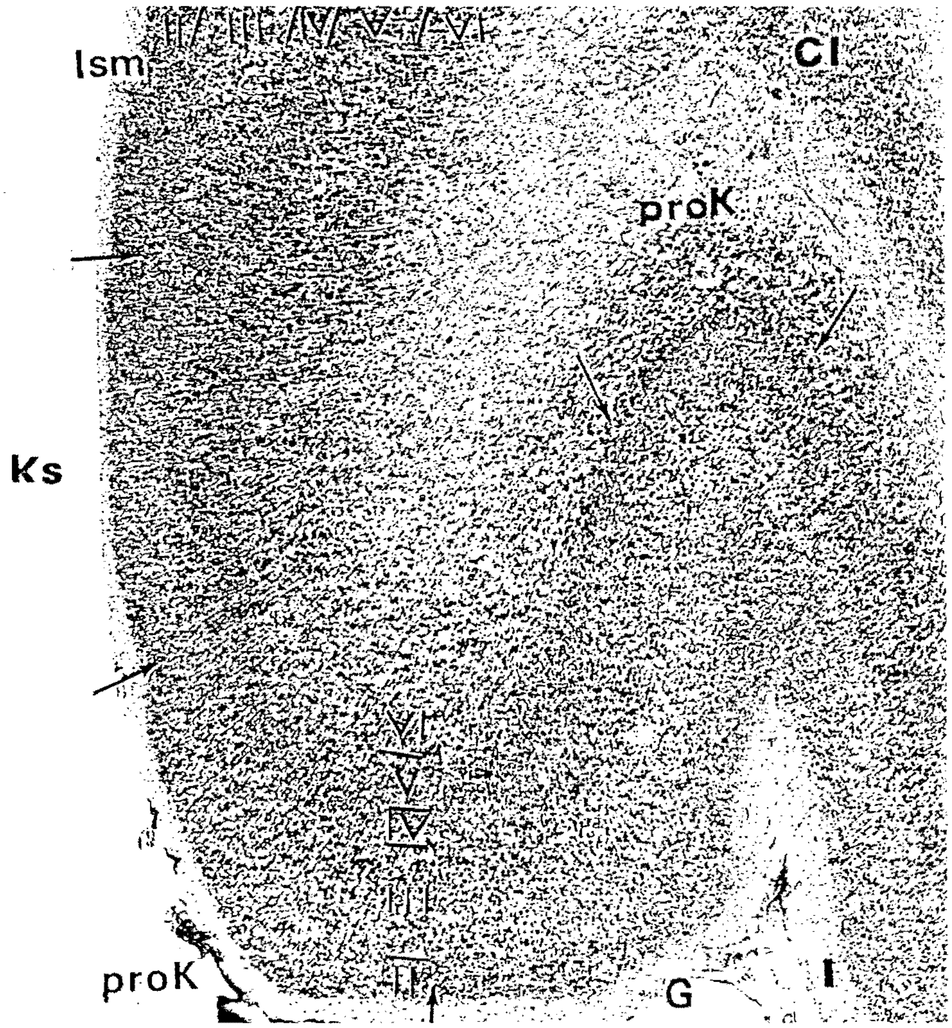

Figure 20. Coronal section of *Saimiri* through central operculum, adjacent insular cortex (I), showing gustatory area G, and somatic areas proK, Ks, Ism, x 37. From Sanides. 1968. Brain Res., 8:97-124.

also distinguish in *Macaca* from a dysgranular middle section with an accentuated dense lamina V which may be related to the precentral motor cortex.

Architectonically, area G is the rostral part of the parinsular belt (Fig. 20). It differs from proK by finer and lighter staining granules in lamina IV, smaller granuloid cells in lamina II, and a somewhat lighter lamina V. On the other hand, area G appears to be not as specialized as the somatic Ks. Rather it approaches the adjacent paramotor area of the prefrontal cortex and is best characterized as an intermediate step between the anterior light granular insular Pro and thus part of the prefrontal cortex.

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The basic tripartitioning of the insular proisocortex has been recognized previously only in man by Brockhaus (1940). It appears important that this tripartitioning is also valid for *Saimiri* and *Macaca.* This recalls an older general observation of the Vogts (1919) who noted that the different sections of the insula reflect in their architectonics the different adjacent convexity regions. This, however, is also basically true for the limbic lobe; this means that in the stage of proisocortex differentiation the areal architectonic partitioning of the adjacent neocortical belt is anticipated.

It is an intriguing result of these studies that the pure taste area G appears as one root of prefrontal cortex differentiation. To emphasize the remarkable fact that this is already anticipated in the insular proisocortex we designated this fine granular part of the insular cortex prefrontal insula.

In conclusion, the gustatory input has its main representation in the older parinsular belt rostral to SmII, whereas the gustatory surface projection onto the tactile tongue representation of SmI appears to be an associative function with the latter. Only tactile discrimination, audition, and vision—the sharper localizing and objectifying senses—are represented in recent mammals in so-called primary areas with highest specialized cores of koniocortex. The other chemical sense, olfaction, is represented in the paleocortex itself, which forms one base of the original telencephalon in early vertebrates.

Investigations of the pertinent regions of *Macaca* showed very similar relations to *Saimiri* (Fig. 21). Also here area G (1) encroaches partly upon the anterior fine granular insula, (2) occupies the broad depth of the sulcus circularis and (3) occupies the inside of the rostral operculum. By courtesy of Dr. Benjamin, who allowed an examination of an experimental brain with tracks of the deep gustatory nerve responses, we also could establish that these responsive loci were lying prevalently in area G, that is, particularly in the deeper parts around the bottom of the sulcus circularis. In the hemispheres of two monkeys we made a striking observation. Within area G in the depth of the opercular wall we found a koniocortex focus characterized by an accumulation of granule cells in laminae II and IV, a light lamina V, and a dense lamina VI (Fig. 21). This could be confirmed in adjacent myelin-stained sections in that this clear-cut focus shows a sharp increase in myelination compared with the otherwise faint myelination of area G in which it is lying. This requires further studies in other brains. However, we can regard it as a remarkable phenomenon that in area G, a subdivision of the parinsular stage of *Macaca's* neocortex, a premature koniocortex focus can be found.

A small koniocortex-like subdivision, 68gr in Vogts area 68, was described by Gerhardt (1938, 1940) in man and chimpanzee in the depth of the central operculum. Patton and Ruch (1946) referred to this as a possible taste area. This poorly myelinated area (Gerhardt, 1938) is located too far caudally to be equivalent to area G. The poor myelination would also be in contrast to our finding of a koniocortex focus in area G in *Macaca* and to the general observation of maximum myelination of koniocortices. von Bonin and Bailey (1947) show in their work on *Macaca* a corresponding spot to area 68 gr in the depth of the opercular wall adjacent to the insula. This possible koniocortex focus lies too far caudally, namely below the tip of the central sulcus, whereas area G also in *Macaca* has its caudal limit approximately in the level of the rostral limit of Ks.

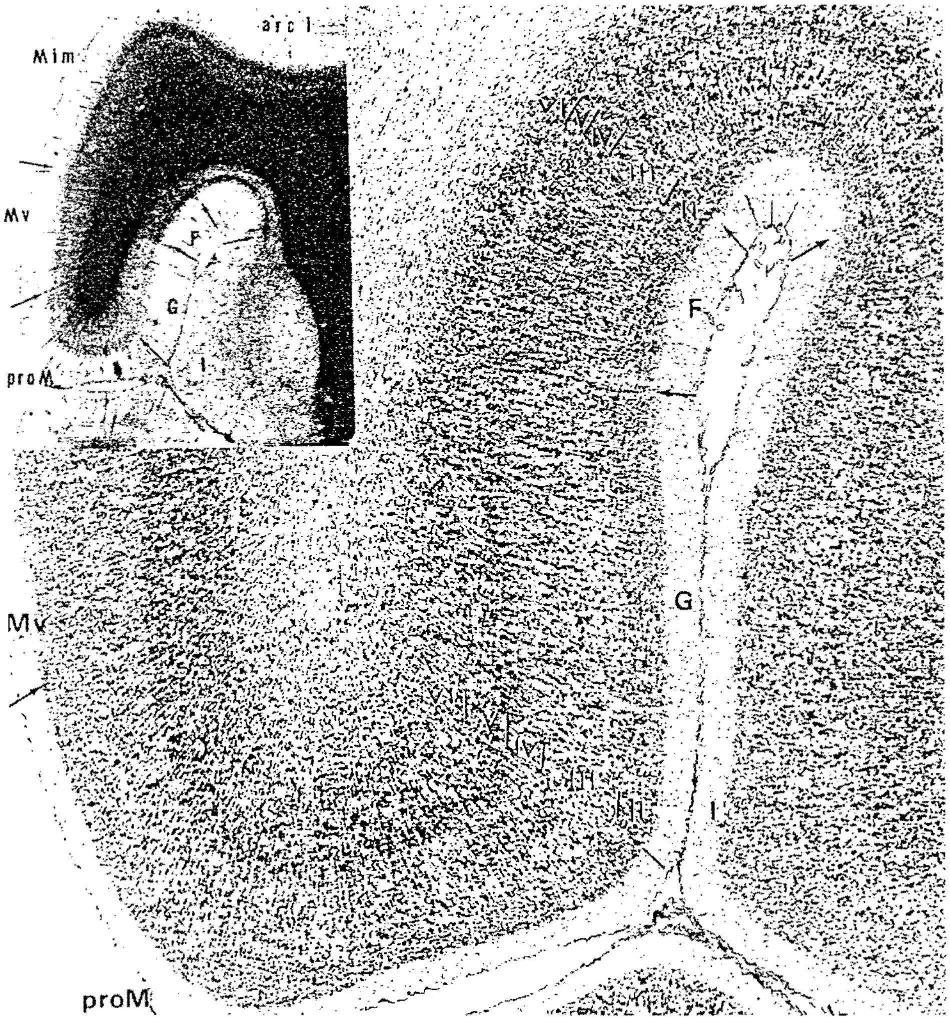

Figure 21. Coronal section of *Macaca* through central operculum and insular cortex (I), with gustatory area G, and motor areas proM, Mv, and Mim. Inset of adjacent myelin-stained (Heidenhain) section, showing the same areas in myeloarchitectonics. Note koniocortex focus F in the large picture, corresponding to heavily myelinated focus F in the inset; arc i, inf. arcuate sulcus, x 27.

Among the previous investigators of the cytoarchitectonics of the sensorimotor region in *Macaca* only Roberts and Akert (1963) included the inside of the opercular cortex in their studies. Their area Ofo on the rostral inside of the frontal operculum corresponds mainly to our taste area G. Their Plate I shows a good agreement with our outlines. In more rostral levels Roberts and Akert included within area Ofo the external opercular paramotor area. This first prefrontal area corresponds to the anterior half of 6bβ Vogts and has some resemblance to area G because G is intermediate to parM in the differential trend from the prefrontal insula.

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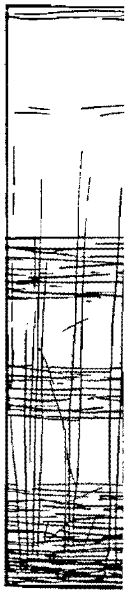

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This inclusion of opercular area parM is the reason why ablation of area Ofo resulted in retrograde degeneration of the ventral part of the paralamellar portion of the dorsomedial nucleus of the thalamus. Area G itself receives only sustaining input from the ventromedial complex (Benjamin and Burton, 1968).

Thus the pure gustatory area G in *Macaca* is also located beneath proM (caudal half of Vogt's 6bβ) and is contiguous orally with the paramotor belt of the prefrontal cortex. According to its location and architectonic character, area 68 of the Vogts with its hypergranular focus in man and chimpanzee (and the area described above in *Macaca*) appears to be the somatic prokoniocortex, corresponding to SmII.

THE VISUAL AREAS

The primates priority on vision can be recognized not only in the frontalization of the orbits in evolution almost up to a sagittal plane of the medial orbital wall in catarrhines, but also in the enormous expansion of the visual cortex, and in the highest specialized character of its koniocortex, the area striata. Only primates have such a striate area, marked by the strikingly myelinated Gennari's line, that is, an accentuated outer stripe of Baillarger which is not accompanied by an inner stripe of Baillarger (Fig. 22). In myeloarchitectonic nomenclature this type is referred to as singulostriate. The granularization reaches its maximum in the area striata with a particular elaboration of lamina IV.

A ringlike structure for the visual region in primates was already established by Brodmann (1909). After his maps one had the impression that the parastriate area 18 and the peristriate area 19 surround the striate area 17 as a complete double ring.

Figure 22. Diagram of main types of myeloarchitectonics of the isocortex. Left, bistriate; middle, singulostriate; right, unistriate.

Concerning the rostral end of the striate area, which is hidden in the depth of the common trunk of the calcarine fissure and parieto-occipital fissure, Brodmann was rather cautious in describing the ring by areas 18 and 19. The first to challenge this apparent closed ring of area 18 and 19 around 17 at the anterior, i.e., paralimbic, end of the striate area was Pfeifer, who depending on his excellent angioarchitectonic method prepared a complete atlas of the angioarchitectonics of the cerebral cortex in *Macaca* (1940). He could demonstrate that the striate area at the rostral end is actually contiguous with areas of limbic character and is not surrounded by areas 18 and 19.

Our comprehensive cytoarchitectonic and myeloarchitectonic studies on the visual region of man and preliminary studies in chimpanzee (Sanides and Vitzthum, 1965; Vitzthum and Sanides, 1966) led us to a similar conclusion. Contiguous to the anterior end of the striate area in the walls of the trunk of the calcarine fissure, which delimits the isthmus of the limbic lobe, neither areas 18 nor 19 are located but a limbic type area with slight myelination, accentuation of the lamina II, and single limbic cells (Figs. 23 and 24). On the other hand, this area belongs to the rare singulostriate type, of which the striate area is the extreme. For a limbic region this area which rostrally borders the striate area is at the same time rather granular and has a rather light lamina V. Thus it exhibits actually a combination of limbic and striata-like features. Seen in the context of the limbic ur-trend of differentiation is appears as an intermediate stage between the periarchicortex of the entorhinal region and the presubiculum anteriorly and the striate area posteriorly (Fig. 23).

This topology and the peculiar architectonics prompted us to designate this area "prostriata," suggesting that we are dealing here with a similar prokoniocortex as the parinsular second somatic and second auditory ones. This assumption proved to be in striking agreement with findings of MacLean and co-workers in microelectrode

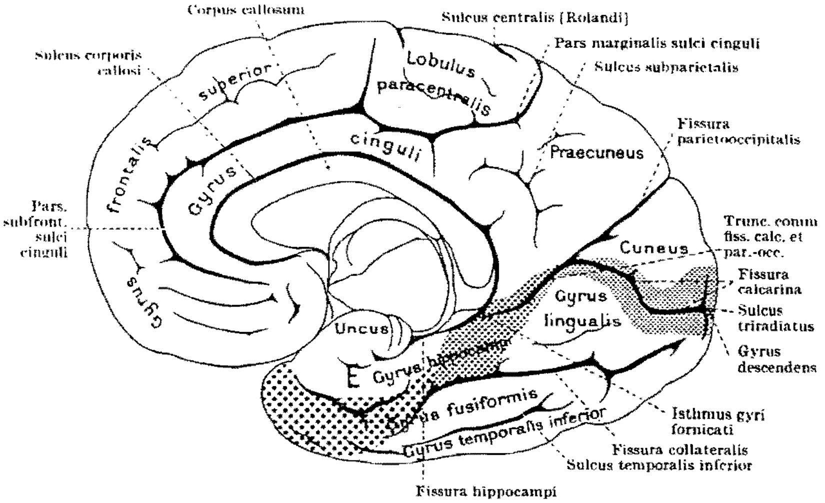

Figure 23. Diagram of the medial aspect of the human hemisphere with area striata (small dots) and two continuous singulostriate limbic areas surrounding the entorhinal region (E): prostriata (medium dotted), anterior V-accentuated area (large dotted). After Vitzthum and Sanides. 1966. *In* Evolution of the Forebrain. Thieme.

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studies in *Saimiri* with photic stimulation (Casey et al., 1965; Cuénod et al., 1965). Examining wider areas of the limbic lobe they found a short latency visual receiving area with a corresponding extension from the entorhinal region to the striate area, which is obviously equivalent to the prostriata as described by us in man and confirmed in chimpanzee. Thus it is a visual ProK, the prostriata, which closes the parastriate and peristriate ring around the area striata, the visual Ks. One peculiarity of the prostriata, compared with SmII, AII, and the supplementary motor and sensory representations, lies in the fact that we encounter here already in the stage of the proisocortex a prokoniocortex area which in general is located in the paralimbic/parinsular belts. That may be an indication of the close affiliation of the visual system with the limbic lobe, as conceived by MacLean (Gergen and MacLean, 1964).

We have also to think about the entorhinal region, which is extremely elaborate in higher primates, as an example of an older cortical structure with possibilities for further growth and differentiation or specialization. It is difficult to speculate when this intricate temporal addition to the periarchicortex has arisen. However, it is suggested that this occurred later than the development of the simple periarchicortical presubiculum. This could be the phylogenetic reason why we encounter a proK, the prostriata, at the entorhinal junction. The prostriata may be classified as part of the paralimbic/parinsular growth ring which contains also the other *prokoniocortices*.

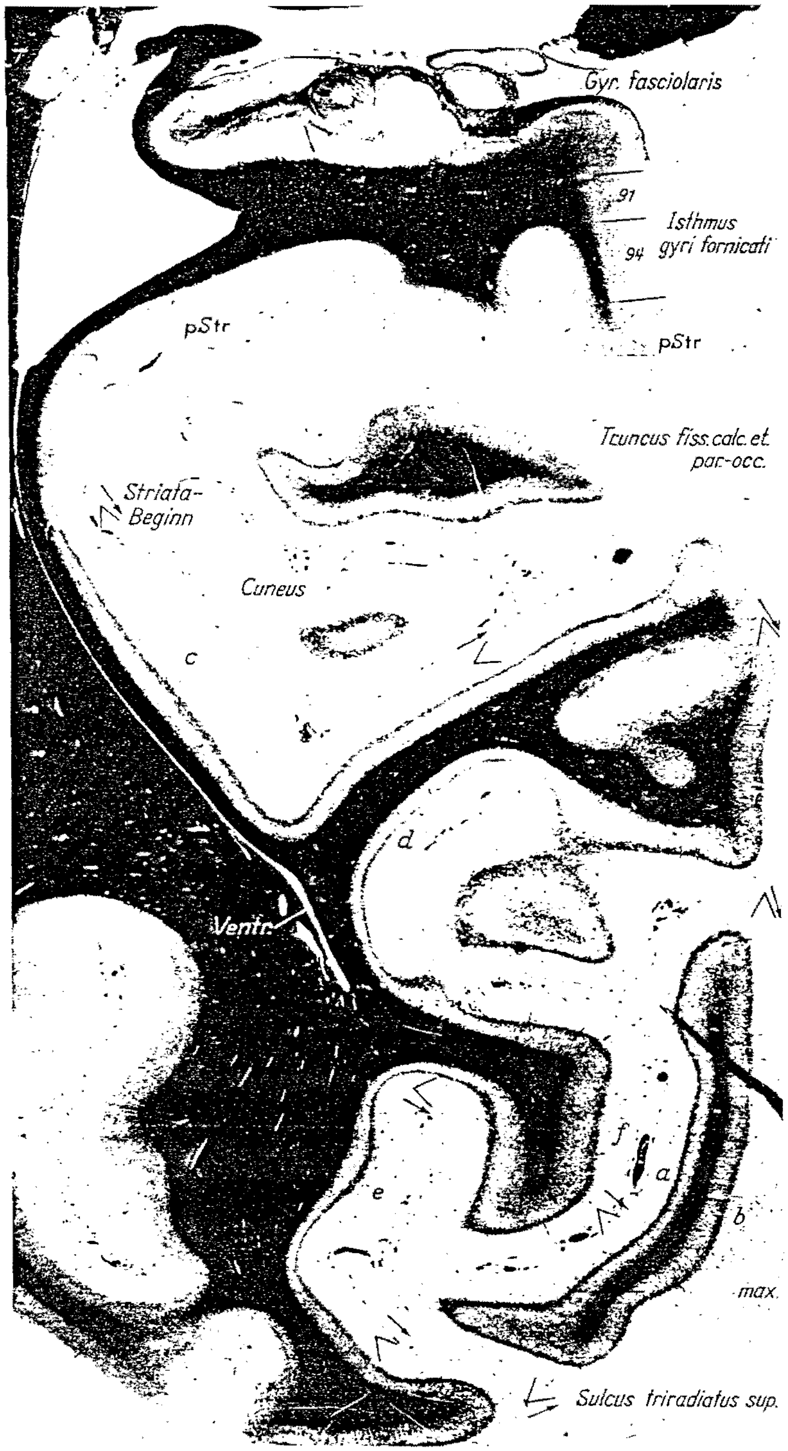
Finally we have to add that the area striata presents throughout its rostral to caudal range from its paralimbic border to the occipital pole several grades of myelination with a maximum in the *prepolar* site (Fig. 24). These grades are paralleled by a corresponding increase of cell size in the nongranular layers. The polar and prepolar area striata with their highest myelin content correspond to the central vision (macular region), which is phylogenetically most recently acquired. On the other hand the slightly myelinated oral part of the area striata corresponds to the temporal crescent which in the primates forms the remainder of phylogenetically ancient monocular vision; the middle sections of the area striata with medium myelination correspond to the binocular periphery of the fields of vision.

One can consider Fig. 24 to be an excellent example of the myelination trend in evolution, from the slightly myelinated prostriata through the heavily myelinated macular region of the striate area.

Growth Rings of the Neocortex

The data and ideas developed in the forgoing sections will be synthesized here to elaborate the concept of neocortex evolution. New pertinent material including Golgi studies of specimens of Insectivora, Chiroptera, and Rodentia will be presented, providing further support of this concept.

The new approach to the evolution and eventual definition of the mammalian neocortex resulted from a new combined application of cytoarchitectonics and myeloarchitectonics of the cerebral cortex as a tool for tracing differential trends of evolutionary significance in a series of primates and lower mammals. A pioneer in using the cytoarchitectonic method in such a sense was Abbie, who elaborating on Dart's concept of the duality of the neocortex, demonstrated in monotremes and marsupials



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differential trends from the archicortex and paleocortex, resulting in two different moieties of the cerebral neo-cortex. In his second article on this subject Abbie (1942) speaks very descriptively of "successive waves of circumferential differentiation" away from the hippocampus on the one hand and away from the paleocortex on the other. And this is exactly what we have demonstrated in a broad spectrum of *Eutheria*. and for what we would like to propose the term "growth rings of the neocortex."

THE PERIALLOCORTEX AS FIRST GROWTH RING OF THE NEOCORTEX

By now we can formulate the preconditions which neocortex has to fulfill compared to the older paleocortex and archicortex as they are revealed from the comparative neurological literature (Ariens Kappers et al., 1936). Neocortex is a laminated griseum which is located at the periphery of the endbrain between the medial archicortex and the lateral paleocortex and which is lying peripheral to its projection fibers including dorsal thalamic input. As we will see, these preconditions appear fulfilled already by the *periallocortex* which as the first intermediate stage rims the archicortex and paleocortex at the medial and ventrolateral borders of the isocortical lobes. The basic resemblance of this stage, whether it borders the archicortex or the paleocortex, is demonstrated in Figures 3, 16, and 17. It is defined as the two-cell-strata pAll with an inner large-celled stratum and an outer medium-celled stratum separated by a more or less well defined lamina dissecans (lam. diss.). From Golgi preparations of the periarchicortex it is known that the lam. diss. is the site of synaptic contact between basal dendrites of pyramids of the outer stratum and horizontal fibers (Lorente de Nó, 1938). This could occur without a clear-cut blank layer at the borderline between both strata so that the lam. diss. is not a necessary prerequisite for the basic organization of pAll. A common feature, however, of all forms of pAll—periarchicortical and peripaleocortical—is cell condensations of medium-sized polymorph cells at the surface of the outer stratum where it borders the zonal layer. This kind of cell condensation which can be traced to the site where they taper off into the next intermediate stage, Pro II, have quite another character than the lamina II of the isocortex which is made up of small mostly pyramidal cells. Although there are areal differences in the cell forms of the lamina II within the isocortex, it appears justified to refute the term "outer granular layer" for it, as done by Globus and Scheibel (1967), and to preserve the term "granular layer" for the lamina IV, which alone is composed predominantly of the star cells of the Golgi picture. As for the lamina II of the isocortex, one may rather refer to its granuloid character.

The significance of such a fine notional distinction is revealed by the progress in synaptology in electron microscopy, in particular by Gray's work in 1959 which proved the synaptic role of the dendritic spines. Pyramidal cell dendrites are more or less studded with spines, whereas true star cells, corresponding to the granule cells

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Figure 24. Subsplenial horizontal section of man's hemisphere through the isthmus of the limbic lobe and calcarine fissure up to occipital pole. Myelin staining (Heidenhain) showing the singulostriate character of the area striata with several grades of myelination and a prepolar maximum (max). The area striata is rostrally contiguous with the faintly myelinated singulostriate prostriata (pStr), x 3.3. After Sanides and Vitzthum. 1965. Deutsch. Z. Nervenheilk., 187:680-707.

of the isocortical lamina IV and dispersed also over the other isocortical layers, are characterized by their form, by the scarcity or total lack of spines, and by the beaded character of their dendrites.

In the Golgi picture pAll is characterized by the absence of a layer of true star cells, as it lacks in cytoarchitectonics a granular layer, which makes its first cortical appearance in Pro. Thus we could trace star cells in the level of layer IV in the insular Pro of the cat.

Since the true granular lamina IV in the isocortex is the site of the afferent axonal terminal plexus from the thalamus, there is the question, where do the thalamic fibers terminate in pAll.

The problem of thalamic projections to pAll and of their terminations was solved by a new approach to the thalamolimbic and reciprocal connections in the rat by Domesick (1969, and personal communication), who placed small lesions in different regions of the limbic cortex and anterior thalamus and traced the terminal degenerations with the Fink-Heimer technique. The pertinent findings are that the posterior cingulate pAll of the rat (Rose's area retrosplenialis granularis) * receives projections from the anteroventral nucleus thalami and sends reciprocal projections to this nucleus. The presubiculum, the simplest form of pAll receives a large thalamic projection which may originate from all the anterior nuclei (still under investigation). Thus these major parts of the periarchicortex fulfill all conditions of the neocortex definition.

Domesick (1969) presented clear evidence about the site of the thalamic terminations within the posterior cingular pAll. The terminations are in lamina I and in the so-called lamina III. The latter is that part of the outer stratum which lies deep to the external cell condensations. We will come back to these findings when we deal with our Golgi studies. At this point we may add only that the interesting findings of thalamic terminations in the zonal layer of the pAll is surprisingly paralleled by corresponding findings in the visual cortex of the opossum (Nauta, personal communication) and in the neocortex of the hedgehog (Ebner, personal communication). This of course does not exclude thalamic terminations in deeper layers.

Filimonoff (1947) united the peripaleocortex and the periarchicortex under the term "cortex intermedius" or pAll, recognizing the intermediary character of this complete rim around the allocortices sensu strictiori. Fascia dentata, cornu ammonis, subiculum, tenia tecta (induseum griseum corporis callosi) are the subdivisions of the hippocampal allocortex sensu strictiori. Tuberculum olfactorium, the diagonal region, the septum pellucidum, the periamygdalar region, and the prepiriform region are the subdivisions of the paleocortical allocortex sensu strictiori, to which he refers as semicortex or cortex semiseparatus. This emphasizes the fact that in the mature stage this cortex still shows an incomplete separation of the cortical plate from the periventricular cell masses. It is this fact which makes the paleocortex the most conservative mammalian cortical structure, still close to the amphibian stage of endbrain organization with only periventricular cell masses. One might therefore also refer to the paleocortex as a corticoid structure (Yakovlev, 1959). The archicortex on the other hand forms a separate cortical plate during ontogenesis, with some peculiarities, such as late migration and scarcity of cellular elements.

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From the borders of both these heterogenous cortices has arisen a new cortex, the pAll, which with both its moieties forms a *closed ring* around the next intermediate stage, Pro. How far this similarity extends between the organization of the peripaleocortex and periarchicortex was not recognized by Filimonoff. Our figures demonstrate, however, a lam. diss. between the outer and inner stratum of the peripaleocortex (Fig. 16), as they also show the accentuated superficial cell condensations.

It is true that in higher mammals, particularly in primates, the uniformity of this intermediate ring is somewhat obscured by the fact that the periarchicortex includes beside the simple presubiculum in the temporal lobe the highly specialized entorhinal region. This especially intricate region in higher primates appears to be a kind of integration cortex for olfactory and visual input at the level of pAll; it has preserved the basic structure of the periarchicortex including one or two lam. diss. and a particular elaboration of cell condensations—glomeruli—in the accentuated lamina II. Ramon y Cajal (1955) described the lamina II in the entorhinal region as composed of large stellate cells. His figures and those of Lorente de Nò show that these "star cells" are studded with spines, in contrast to the star cells of the isocortex. A layer of true star cells are not to be found in the entorhinal region, another confirmation of its pAll character.

An important difference in the relationships to the allocortices appears at the outer borderline of both moieties of pAll. The outer stratum of the peripaleocortex becomes continuous with the dense cell band of the paleocortex (Fig. 16), whereas the inner stratum of the periarchicortex becomes continuous with the cell band of the archicortex (Figs. 3 and 25). We are dealing here with the well-known superpositions at the limits of the primitive allocortices, which in our context suggest the common origin of both periallocortices in that the outer stratum appears derived from the paleocortex and the inner stratum appears derived from the archicortex.

Thus the pAll is recognized as the incipiently laminated neocortex with uniform main features throughout its periarchicortical and peripaleocortical extensions, which are adjacent to these dissimilar types of ancient cortex—the archicortex and the paleocortex. Hence the ring of pAll can best be understood as having evolved during phylogeny as a common derivation of both older cortices.

What now presents itself as a ringlike cortical structure, i.e. the first growth ring of the neocortex, must have been originally, in the extinct links between reptiles and mammals, a core of new cortex, built up from both, the paleocortex and the archicortex.

ORGANIZATION OF THE PROISOCORTICAL AND PARALIMBIC/PARINSULAR GROWTH RINGS

During the phylogeny of the neocortex, ever new waves of growth and differentiation evolved, and each time a new cortex developed as a new core, displacing the previous core to a ringlike structure. Thus a sequence of concentric growth rings has been formed by the effect of both differential ur-trends. The next stage is Pro, which is the last step prior to the mature isocortex. Progress in cellular lamination characterizes this step. A main feature is the incipient appearance of a granular lamina IV made up of true star cells, which in a sense fill the gap the lam. diss. had left between the two strata (Fig. 16). Now the new dorsal thalamic input enters this layer of

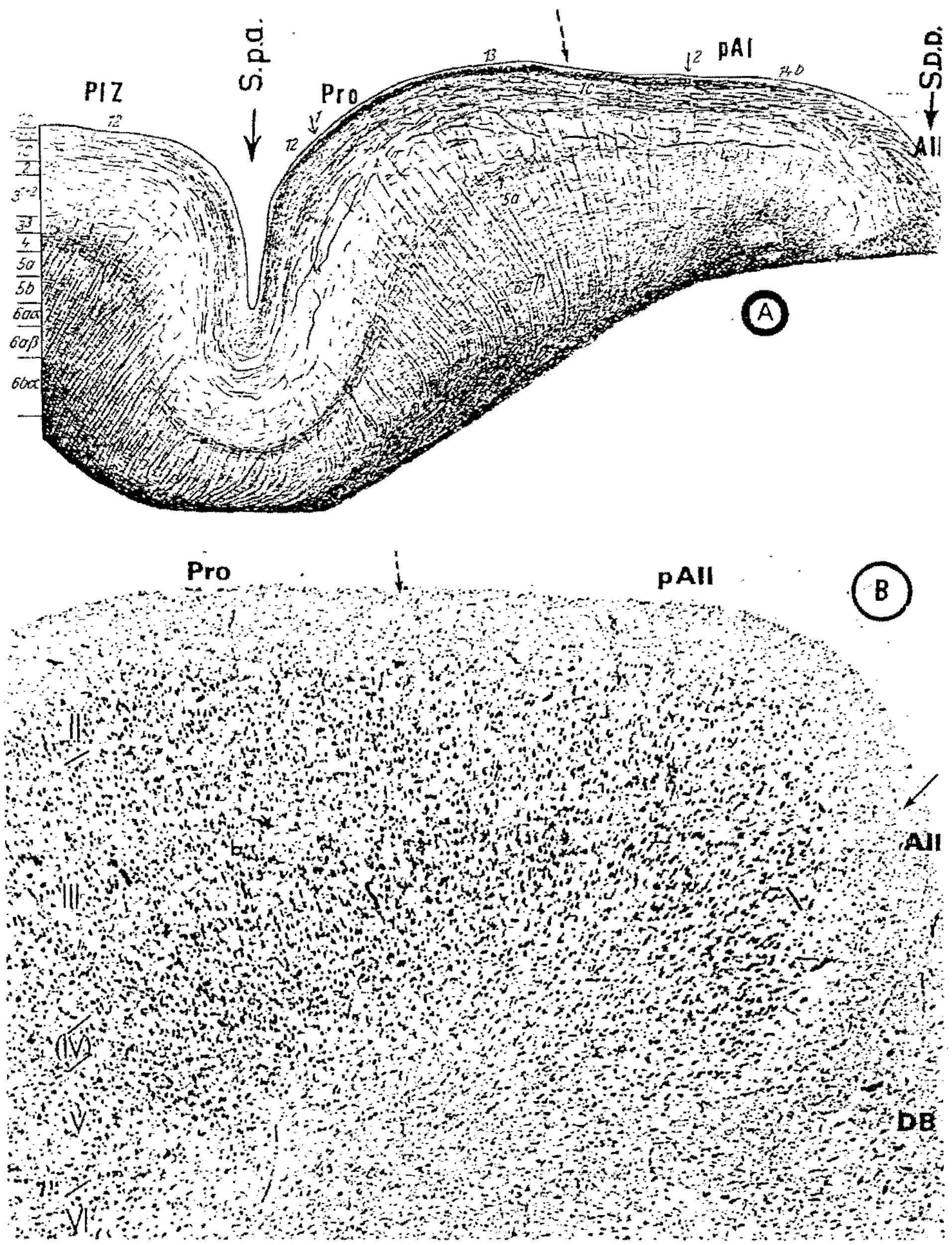

Figure 25. Horizontal sections through man's area adolfactoria (a) Myelin staining (Weigert-Kulschitzky). After C. and O. Vogt 1919. J. Psychol. Neurol., 25:279-462. (b) Nissl staining. x 32. After Sanides 1962b. Mongr. Neurol. Psychiat., 98. b, blank layer; DB, diagonal band; Spa and Spp, sulcus parolfactori anterior and posterior; (See Table 1 for abbreviations.)

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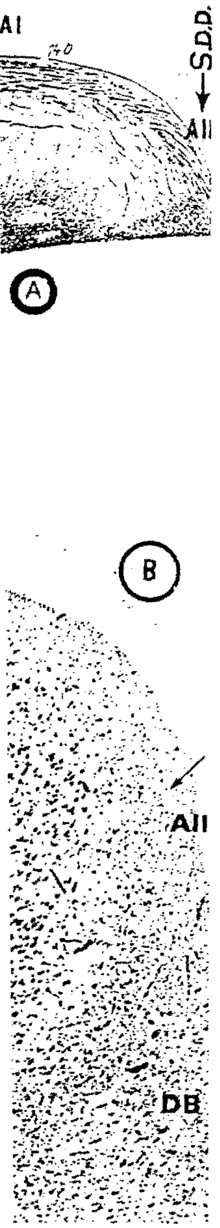

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star cells, forming the afferent plexus of the outer stripe of Baillarger and establishing a new kind of synaptic contact in the cortex.

As mentioned, there are already at the level of Pro such regional architectonic patterns which anticipate the architectonic areas of the next differential stage, the paralimbic/parinsular one, and even the next succeeding step with differentiation of koniocortex, which is the last in the sensory regions. We have already noted that the Pro of the anterior cingulate gyrus, which dorsally borders Mpl in the paralimbic zone, is cytoarchitectonically agranular as is the latter and the dorsally adjacent FmZ (Fig. 1).

We must emphasize that we cannot recognize whether any of the medium-sized perikarya are star cells in the poorly developed lamina III of the anterior cingulate Pro. So far we only know that the fine clear-cut granules of lamina IV of sensory and integration cortices correspond to the typical small star cells of the Golgi picture. But there are also larger star cells, which fulfill all pertinent criteria of star cells. They are not necessarily recognized in the Nissl picture. Therefore, it appears important that recent Golgi studies by Marin-Padilla (1969) demonstrated star cells in all layers of the human frontomotor zone, but predominantly in what would correspond to the level of lamina IV of granular cortex.

We now can demonstrate how this switch from zonal layer and outer stratum synaptic contact of the thalamic afferents in pAll to lamina IV synaptic contact in Pro and isocortex is reflected in cytoarchitectonics and myeloarchitectonics. For this purpose we refer to Vogt's graphic representation of a Weigert-Kulschitzky stained preparation—the most discretely working myelin method—of a horizontal section through man's area adolfactoria (Fig. 25a), and to compare it with a Nissl stained section in a corresponding plane (Fig. 25b).

The important role of the zonal layer in myeloarchitectonics of the older cortices is well known. Olfactory afferents of the paleocortex form the heavily myelinated outer part of the zonal layer of the prepiriform cortex. Tufted, lophodendritic cells of the cortical cell layer spread their dendrites into the olfactory fiber plexus. The pAll still possesses a much more pronounced fiber plexus in the zonal layer than the isocortex. Our figure allows survey of the gradual decrease of the archicortical strength of the zonal fiber plexus over pAll into Pro.

At the right of both figures is the sulcus parolfactorius posterior where cells of the diagonal band (DB) meet the wedgelike beginning of the primitive allocortex (rudimentary precommissural hippocampus). Here the entering tangential fibers of the medial stria olfactoria form almost the outer half of the cortex. This primitive allocortex, composed of thick spindle cells and lesser pyramidal cells is seen in Figure 25b to be continuous with the inner stratum of pAll at the area limit. The superposed outer stratum is composed of scattered cells of different sizes. Pronounced cell condensations are lacking at the surface of the stratum in this human material, but some typical agglomerations of medium-sized polymorph cells are present. Throughout pAll the emphasis is on the inner stratum, which also has typical limbic cell forms as rod cells and fork cells. A clearly-cut lam. diss. cannot be distinguished. In the myelin picture the strong tangential fibers of the zonal layer are gradually tapering off to a thinner subpial layer toward the area limit to Pro. However, the zonal fiber plexus is thinning and the outer stripe of Baillarger is gradually building up. This gradual increase continues into Pro. Thus we are dealing with a gradient of the architectonic changes and not with a gradation, i.e., stepwise change, as is the rule within the *isocortex.* The building up of the cytoarchitectonics of the proisocortex occurs gradually. There is a widening lamina III separated from a denser lamina II with medium-sized cells. A striking observation in such transitions is that before the dysgranular lamina IV emerges, a blank layer (b) between inner and outer stratum is discernible. Finally within this Pro the inner stratum differentiates into two layers: pyramidal-celled lamina V and more spindle-celled lamina VI. Beyond the sulcus parolfactorius anterior we find PlZ, with a thicker granular lamina IV and more pronounced lamination. The myeloarchitectonics in PlZ exhibit finer tangential fibers of the zonal layer and a stronger outer stripe of Baillarger coinciding with the granular lamina IV. At the same time thicker, deeper horizontal fibers of laminae V and VI begin to appear as they are known for their intracortical associative function. The radiate fibers are important in our context. Radiate fibers penetrate all layers up to lamina 1 in pAll and in the adjacent section of the Pro (supraradiate type Vogts). In Pro at the same time more radiate fiber bundles are ending at the outer stripe of Baillarger (infraradiate type Vogts), and in the paralimbic zone more heavily myelinated radiate fiber bundles are present which, as it is typical for the mature isocortex, pass the outer stripe of Baillarger and penetrate into the outer third of lamina 3 (euradiate type Vogts).

Concerning the described behavior of the tangential fibers of the zonal layer, the level of penetration of the radiate fibers, and the emergence of deeper horizontal fibers, bundling in the form of the stripes of Baillarger, principally similar changes take place in the *claustrocortex* of the *insula.* That is in the domain of the lateral ur-trend which is paleocortical in origin dependent in its initial stages on the *lateral* olfactory tract input.

The basic resemblance of the cytoarchitectonic and myeloarchitectonic changes in the respective spheres of both ur-trends has already been discussed previously. However, each ur-trend places its own architectonic marks. This seeming contradiction has to be elucidated: The basic resemblance of both ur-trends reveals itself in our view as an expression of the fact that each of the corresponding consecutive beltlike stages (rings) of both moieties was at the time of their original formation the integrate part of one new differentiated core. On the other hand, each moiety is subject to a prevailing, moulding influence from the pertinent spring territory, which may be thought to be exerted by means of the corticocortical fiber connections and the subcortical afferents and efferents.

Nauta's above quoted observation "on a certain dualism in the prefrontolimbic associations" can be regarded as an example of the persisting dependence of the higher differentiated moieties of the growth rings upon their respective territories of origin.

This moulding influence of the spring territories is also reflected in the functional architecture of the primate neocortex. Thus the frontal lobe, which is not only in its precentral motor cortex of a predominantly effector type (Sanides and Schiltz, 1967), is architectonically predetermined more by the hippocampal spring territory, which is an effector structure par excellence. Only the inferior frontal gyrus appears

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determined more by the paleocortical spring territory which is pure olfactory sensory. This is also reflected by the faster and greater granularization within the frontal lobe of the successive stages of the lateral ur-trend. That is even valid for the precentral motor cortex which includes Vogt's mastication field 6b. In all primates investigated this field is not agranular as the rest of the pyramidalized precentral motor cortex, but dysgranular. A slight granularization extends to the limit of head and arm representation.

In contrast, we came to the conclusion that in the sensory integration cortex of the parietal lobe the prevailing influence of the lateral ur-trend extends up to the intraparietal sulcus, including the arm brain.

The third neocortex growth ring is also formed by two moieties: the medial paralimbic zone and the lateral parinsular zone. This then is the site of the additional sensory and motor representations: AII, SmII, and the taste area G laterally and supplementary motor and sensory representations and prostriata medially. The lesser degree of functional differentiation of these representations is particularly evident for the sensorimotor areas. These show much less preference for the apices of the limbs and still include a major ipsilateral share of both features, quite in contrast to the primary areas. The intermediate architectonic character of those areas between insular Pro and pertinent koniocortex was discussed previously. Furthermore the intermediate architectonic character of the prostriata between the entorhinal region and the visual koniocortex was noted. To characterize this intermediate stage we introduced the term prokoniocortex.

LAST WAVE OF GROWTH AND DIFFERENTIATION OF THE NEOCORTEX

It is in the koniocortex that granularization reaches its culmination. It was Rose (1949) who pointed out how much the koniocortex in man (which resembles that of all higher primates) differs in appearance from that of other mammals e.g. the cat. Only simian primates appear to have granule cells with such clearly-demarcated small and rounded perikarya in their lamina IV. The prosimian *Nycticebus* (Fig. 16) has, instead of such clearly-demarcated granule cells, somewhat larger and irregularly shaped cells as has the cat (Sanides and Hoffmann, 1969). Nevertheless we could fashion a workable definition of the koniocortex first in *Nycticebus*, which, including the factor of cell density, appears to be the same in all mammals of the size range of monkeys, prosimians, cats, dogs, and smaller species. The relative cell density in these animals and the dispersion of small cells in the koniocortex result in a partial fusion of the cell layers of the outer stratum (II, III, and IV), with blurring of the lamination. This is accentuated in the layers of the inner stratum with its outstanding light lamina V and the dense lamina VI. Thus we have in the koniocortex a preponderance of the outer stratum which is more involved with afferent input and intracortical processing, as contrasted to the inner stratum which has predominantly an efferent function.

The high specialization of the koniocortex of higher primates is also revealed by the study of Cragg (1967), who showed that the cell density is much higher than in nonprimate brains of comparable weight. This is basically the product of the extreme granularization in higher primates. In the light of the new meaning of the star cells in synaptology compared to other small cells with dendritic spines, one can speak of stellarization as a trend in higher neocortex evolution.*

Our comparative studies in insectivores and bats suggest that the formation of the koniocortices as well as of the gigantopyramidalis i.e. the latest step in sensory and motor cortex evolution occurred in somewhat advanced mammals about 50 million years ago, in the *Eocene*, with the rise of modern orders and suborders of mammals, since *Erinaceus*, for example, also referred to as a survivor of the Paleocene when archaic mammals were dominant (Romer 1949), did not reach this stage.

With the primary motor and sensory areas of this last wave of growth and differentiation of the neocortex, we arrived at the convexity cortex of most recent mammals. The comparative architectonic and electrophysiological data of these areas indicate that the generalized design of these regions were derived from the prokoniocortices of the preceding growth ring. It will be much more difficult to indicate how the general design of the evolutionary pattern of the integration cortices was derived. Therefore, we will propose a tentative design only for the frontal cortex, about which we have collected much data in a wide range of primates (Fig. 26).

Once more we have to imagine that the paralimbic/parinsular growth ring originally occurred as a core within the Pro growth ring. The above quoted findings of Pandya and Kuypers (1969) of the corticocortical projections of *Macaca's* parinsular SmII to paralimbic supplementory motor area support this concept. The somatic, auditory, and visual koniocortices and the gigantopyramidalis are new growth cores which displaced the paralimbic and parinsular moieties to growth rings. In addition new emerging cores of the integration cortices were involved. Therefore in the paralimbic/parinsular stage we encounter components of separate growth rings for sensory, motor, and integration cortices with parts as the premotor areas and parakoniocortex areas crossing the hemisphere and no longer revealing their origin so easily in the coronal directions of differentiation of the ur-trends.

A ringlike structure was first described for the auditory region of the cat (Rose and Woolsey, 1949). Examining the cytoarchitectonics and myeloarchitectonics we arrived at the interpretation of AII as a proK intermediary between the insular Pro and AI, the area of the auditory koniocortex. The ringlike structure of the visual region was closed rostrally by the prostriata, the limbic visual proK intermediary to the area striata (the visual koniocortex). In the sensorimotor regions we encountered particular relations caused by the tight interlocking of tactile and motor functions, and because the somatomotor representations were primarily built up by the medial ur-trend, whereas the somatic sensory representations were primarily built up by the lateral ur-trend. Thus we find here a double sensorimotor ring with the common interconnecting fringe area, the intersensorimotor Ism (Vogts 3a) lying in the depth of simian primates' central sulcus.

Now we can resume our interpretations from a study of the sensory and motor

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* At this point a principal observation of Lorente de Nò appears relevant. Comparing his elaborate Golgi studies of the mouse neocortex as represented in his article in Fulton's textbook (1938) with the human neocortex, he states: "The reduction of the numbers of cells with short axons, without essential modification of the long links in the chains of cortical neurons, makes the cortex of the mouse the 'skeleton' for the human cortex."

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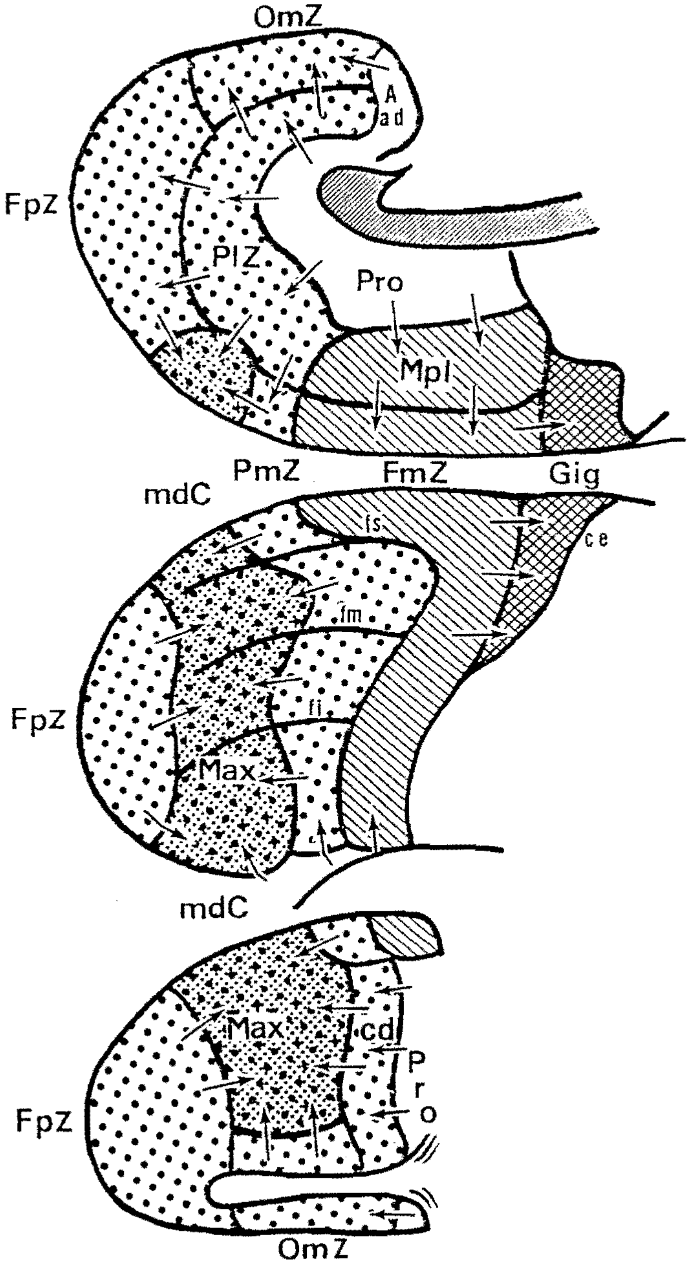

Figure 26. Architectonic map of man's frontal lobe with precentral motor cortex and prefrontal cortex: (a) medial, (b) lateral, (c) orbital aspects; frontomotor zone (FmZ) with highest specialized core, Gig. Prefrontal growth ring (dotted) and highest differentiated midfrontal core (mdC) with two differentiation maxima (Max); Aad, area adolfactoria; ce, sulcus centralis; fi, fm, fs, inferior, middle, superior frontal sulci.

regions of *Nycticebus* and *Saimiri* (Sandies, 1967). In the older paralimbic and parinsular representations, central foci have arisen with denser thalamic input and higher specialized structure, resulting in the most refined sensory and motor representations and relationships with peripheral sense organs and muscles. Prevailing in most recent mammals these sensory and motor fields were first detected and designated as primary fields. During later development the linking paralimbic and parinsular prokoniocortices and supplementary sensorimotor areas lagged behind; their representations at the periphery were less differentiated. The persisting original cortices became involved in associative sensory functions (parK); they retain connections with the respective koniocortex cores and with the adjacent integration cortices.

Approaching the problem of the growth rings of the frontal integration cortex (prefrontal cortex) in higher primates including man, we have first to consider that there are at the caudo-orbital and the insulo-opercular border of the frontal lobe the representations of the chemical senses, olfactory and gustatory, respectively. They are not intermediate to koniocortices. The olfactory paleocortex is rimmed by a caudo-orbital Pro (Fig. 26) of unknown function. Adjacent to this a particularly sudden differentiation in rostral direction takes place leading in man over a paralimbic belt and another intermediate area to the highest differentiated center of the orbital cortex (Vogts area 60; Fig. 4). The other chemical sense, taste, occupies the most rostral site in the parinsular belt, and it is intermediate between the prefrontal insula and the paramotor belt of the prefrontal cortex (Fig. 9).

In a way the amazing manifold architectonic partitioning of man's enormous frontal lobe, as revealed first by the Vogts with the myeloarchitectonic method (1910), then by Ngowyang with the cytoarchitectonic method (1934), and by us with the combined cytomyeloarchitectonic approach (1962b), was instrumental in finding and tracing main directions of architectonic differentiation. In their standard work the Vogts (1919) had described the phenomenon of architectonic gradations by the example of four frontal areas of *Macaca* which form a sagittal sequence: 4a, premotor 6aα, and 6aβ, and prefrontal 9. They explained that the extreme cytoarchitectonic differences of areas 4a and 9 are bridged by intermediate changes of the architectonic features in the areas 6aα and 6aβ. Thus the principle of architectonic sequences was detected and designated "areal gradations," emphasizing the stepwise change from area to area, as is the rule in the isocortex. Brockhaus (1940) was the first to elaborate this principle of architectonic differentiation for a whole region, the human insular cortex. Virtually he described what we later called lateral ur-gradation. However, he did not pursue this sequence to the operculum or make an evolutionary interpretation.

Instead of the term medial and lateral "ur-gradations" as used in our frontal lobe monograph (1962a) we now prefer to speak of medial and lateral ur-trends, since there is a minor difference if we deal with stepwise changes, i.e., gradations as dominant in the isocortex, or with gradual changes, i.e. gradiants as demonstrated in the area adolfactoria. The direction of differentiation is the constant and is better referred to as differential trend.

We described the differential sequences of man's frontal lobe and traced them back to the territories of origin, the concept of primary and secondary cortical regions as developed by Kuhlenbeck (1928) was still dominant, with seeming support from Flechsig's misunderstood myelogenesis (1920). The sensory and motor areas were

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looked upon as primary and the overlooked integration cortices of lower mammals as secondary. There is also a sequence of increasing granularization and reduction of lamina V pyramidal cells from the precentral motor cortex to the frontopolar zone (FpZ), that is, from so-called primary to so-called secondary regions. We referred to this sequence with some reluctance as "poleward gradation" and classified it as being more recent than the ur-gradations (ur-trends). The reluctance was caused by the fact that there was also a component of decrease of the average cell size and of the myelin content. Both factors have the effect of a higher resemblance of FpZ to adjacent PIZ, suggesting that it is the medial ur-trend which exerts the main influence. The basic evolutionary significance of the myelination trend as it is reflected in both ur-trends (Figs. 5 and 6) was derived later through Bishop's work. On the other hand the integration cortices have as a whole a somewhat finer myelination than the sensory and motor projection areas.

Finally the finding of small clear-cut anterior (frontal) and posterior integration areas in the European hedghog led us to a revision of the "poleward gradation." A poleward differential trend appears now only valid from the paramotor belt to a midfrontal cortical belt (Figs. 26a, b). Corresponding to the sensory and motor growth rings we again arrive at the assumption of an older growth ring and a more recent core. The ring of older prefrontal cortex exhibits incipient granularization in its paralimbic and paramotor zone and in a caudo-orbital paralimbic belt and persisting paralimbic features combined with somewhat higher granularization in OmZ and FpZ. The more recent midfrontal core appears then to be the product of concentric differentiation of this growth ring, as are the koniocortices within their fringe areas. This prefrontal core comprises (1) the two maxima of frontal differentiation (Max) in the convexity and orbital parts of the inferior frontal gyrus, (2) the middle section of the middle frontal gyrus, and (3) the adjacent part of the superior frontal gyrus. This core is highly granularized and possesses large lamina III pyramids and a relatively weak lamina V.

The paramotor belt was so named for its resemblance to the premotor areas, combined, however, with incipent granularization. It contains the frontal eye fields, Broca's area * in man, and in its ventral part an area from where respiration is influenced. The intermediate area from the prefrontal insula is formed by the gustatory area G.

For further substantiation of the prefrontal growth ring, detailed study of the thalamic dependencies appears promising, since there is some evidence that the thalamus exhibits a correlated concentric zonation within the mediodorsal nucleus (MD). The dorsal paralamellar part of MD projects to the motor eye fields of the paramotor belt (Scollo-Lavizzari and Akert, 1963). The ventral paralamellar part of MD projects to the ventral part of the paramotor belt (Roberts and Akert, 1963). FpZ and OmZ receive projections from the medial magnocellular portion of MD (Hassler, 1950). On the other hand, the midfrontal core (Fig. 26) receives projections from the central parvocellular portions of MD. According to Le Gros Clark (1930) it is this small-celled element which becomes progressively more conspicuous in higher

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* The frontomotor speech center could be a peculiar elaboration in man of an older primitive vocalization center in a comparable site.

primates. However, a complete parallelism between the growth and differentiation of the prefrontal cortex in higher primates up to man and that of the mediodorsal nucleus cannot be expected, since as a matter of fact the enormous expansion of human prefrontal cortex exceeds by far the rate of growth of MD.

CONFIRMATION OF THE EVOLUTIONARY STAGES OF THE NEOCORTEX IN PRIMITIVE EUTHERIA

In tracing the differential ur-trends in primates and describing growth rings of the neocortex we tried to extrapolate into the unknown of brain evolution. However, there is one group of recent mammals—the order of insectivores—which is known to be the most primitive among placentals. An architectonic and Golgi study of specimens of this group and the related Chiroptera was performed to validate our concept. Of course, a "survivor of the Paleocene" (*Erinaceus*) would not have survived if it would still represent completely the original stage of brain evolution. In some way, this species must have undergone further differentiation and specialization. If, however, one finds characteristics of their whole neocortex in common with those postulated older stages of neocortex differentiation of the bulk of placentals, this would be evidence for the correctness of the postulation.

This is exactly the case with specimens of Erinaceinae. *Erinaceus* and *Hemiechinus*, and of Chiroptera, *Myotis lucifugus*. Their neocortex exhibits no trace of koniocortex and gigantopyramidalis, which are typically found in such comparable-sized rodents as mouse and rat. Furthermore they share a specific characteristic of the whole neocortex with only limbic and insular cortices of other placentals. This is the accentuated lamina II, which is formed by darkly staining densely packed polymorph cells larger than granular cells: the peculiar character of which is revealed by the Golgi method. We drew the attention to this phenomenon in all our descriptions of the initial stages of the neocortex (Figs. 3, 16, and 17). In pAll we referred to it as cell condensations at the surface of the outer stratum. These cell condensations are continuous with an accentuated lamina II of Pro. We were able to trace this peculiar feature through several mammalian orders we investigated, including primates. At first we overlooked it in the insular and cingulate gyri of man. In the entorhinal region of man—this specialized, intriguing temporal periarchicortex—the emphasis on lamina II with formation of conspicuous glomeruli is best known. In man's insular cortex and cingulate gyrus we can now recognize this feature after our experience with lower mammals. It is much less pronounced because of the low general cell density.

In the rat's cerebral cortex (Fig. 27) we can demonstrate the conspicuous feature of the accentuated lamina II, surrounding the isocortex in a ringlike fashion in the limbic and insular boundary regions. It comprises the first (pAll) and second (Pro) neocortical stages. The peripaleocortex (pAll) begins near the rhinal sulcus. Its outer stratum with the superficial cell condensations is continuous with the dense band of the prepiriform cortex (Pal). The claustrum which is easily recognizable in the depth of Pal, fuses with the inner stratum of pAll and Pro and is almost indiscernible in these lower mammals. The inner stratum of pAll is formed by darkly staining

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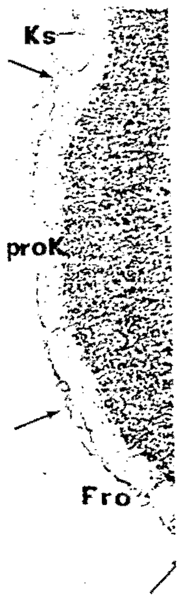

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larger pyramidal cells and is separated from the outer stratum by an indication of a lam. diss. (broken line). Within Pro the lamina II accentuation is less pronounced and tapers off toward the area limit of proK. More caudal sections show the lamina II accentuation ventrolaterally to be as pronounced as at the medial limbic boundary region of Figure 27.

Erinaceus (Fig. 28) with its small neocortical cap shows the accentuated lamina II all over the poorly laminated neocortex. It is continuous with Pal laterally. A careful scrutiny shows the precommissural hippocampus (H) to be continuous with the inner stratum of pAll. *Myotis* (Fig. 29) has a relatively larger neocortex over its reduced paleocortex (Stephan, personal communication). Again the entire poorly laminated neocortex exhibits an even sharper accentuated lamina II. The supracom-

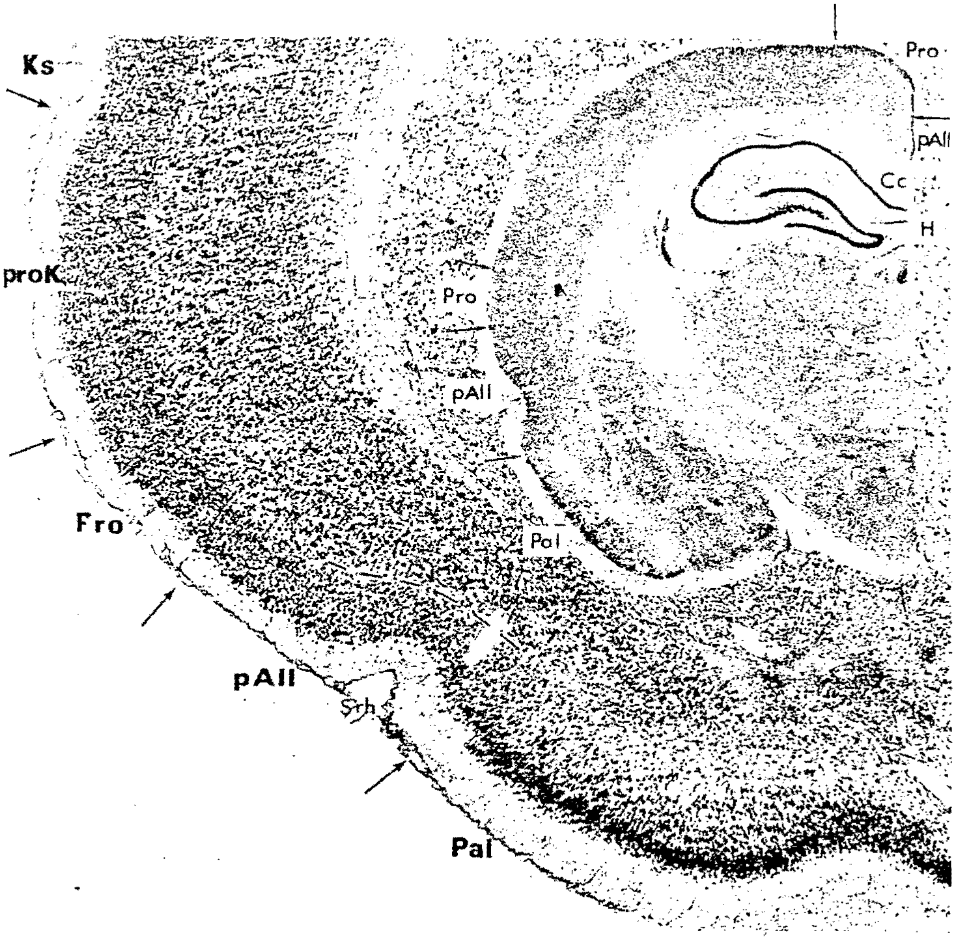

Figure 27. Coronal section through the hemisphere of the rat showing the sequence from paleocortex (Pal) to two-strata periallocortex (pAll, with indicated lam. diss., dashed line), to Pro, ProK, and Ks, x 40; inset shows a more candal section with periarchicortical pAll and Pro, and peripaleocortical pAll and Pro. Note the accentuated II in pAll and Pro. S.rh., rhinal sulcus.

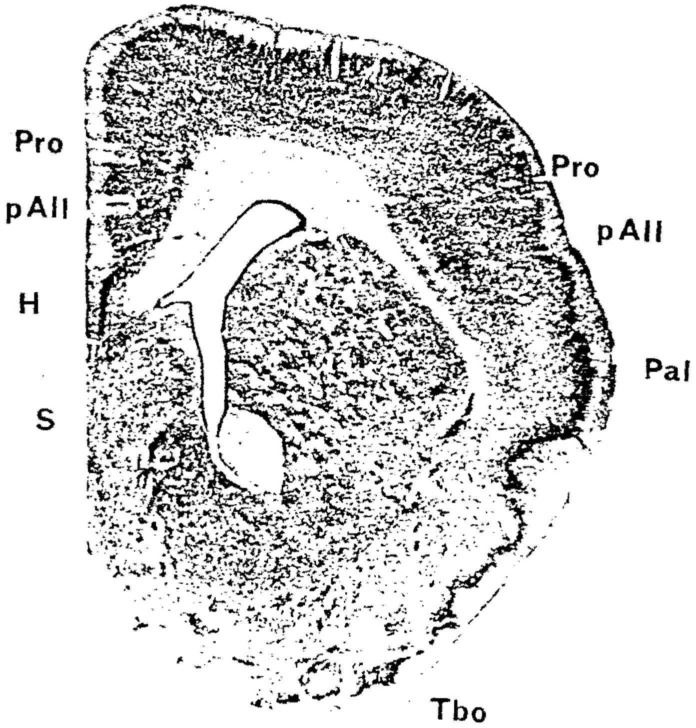

Figure 28. Coronal section through the hemisphere of *Erinaceus*. Ventrolateral is the large olfactory tubercle (Tbo). The small neocortical cap exhibits the lamina II accentuation all over the convexity. S, septum, x 10.

missural hippocampus (H), forming a gyrulus, is continuous with the inner stratum of pAll. Pal is continuous with the outer stratum of pAll. At this point we can add that in a recent work on the cytoarchitectonics of several Chiroptera (*Nyctalus noctula, Nyctalus leisleri, Vespertilio pipistrellus, Plecotus auritus*) Kurepina (1968) comes to the conclusion that "the cortex of the bat's brain is primitively developed, which corresponds to their low position in the phylogenetic scale." Kurepina's illustrations of the cytoarchitectonic structure of the bat's cortex reveal the lamina II accentuation over the convexity of the neocortex to be similar to our Figure 29. The author did not mention this as a particular characteristic. Comparative studies of another insectivore, the mole, and of *Tupaia* showed that the former also exhibits, though in a lesser degree, an accentuation of the lamina II, perhaps with the exception of the frontopolar region. In the mole, however, the convexity cortex already shows somewhat better lamination. Compared with the mole, the tree shrew (*Tupaia*) possesses far better lamination and typical koniocortices, the lamina II accentuation does not reach farther than that of the rat (Fig. 27).

Finally we have evidence for the existence of the lamina II accentuation in the

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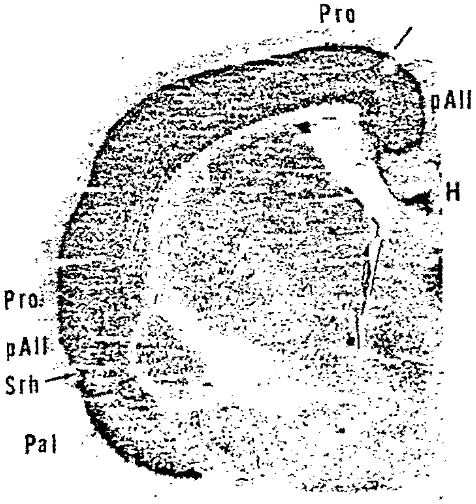

Figure 29. Coronal section through the hemisphere of *Myotis Lucifugus.* The small neocortical cap illustrates the lamina II accentuation all over the convexity. x 12.

convexity cortex of Metatheria and Prototheria. In an examination of a brain series of the American opossum, we found that the neocortex exhibits a relatively sharp accentuation of the lamina II. This, however, was combined with a fairly good lamination and granularization of the convexity cortex. Examining the figures of Abbie (1942) of a more primitive marsupial, *Perameles*, we found again a sharply accentuated lamina II over a laminated cortex, and a rather similar appearance can be discerned in Abbie's figures (1940) of the different areas of the monotremes *Echidna* and *Platypus*.

Summarizing our findings about the phenomenon of the accentuated lamina II we can say that it is a common characteristic of the more ancient neocortex growth rings in most of the recent placentals but is present all over the neocortex in some primitive mammals (insectivores * and bats). A similar condition of the II is found in the Metatheria so far investigated and in the Prototheria.

At lower magnification the future isocortex of a human fetus of about eight months shows approximately the same picture as the neocortex of the bat: a moderately differentiated cortex is covered by a sharp accentuated dense lamina II. Thus we recognize this peculiar feature persisting in a late ontogenetic stage. Of course the fate of these undifferentiated cells is quite different. Von Economo speculated about the possibility that at birth the dense lamina II is the source of nerve cells for the deeper layers. It is our impression that the consummation of the dense lamina II in other mammals may be rather protracted, since we have observed a relative density of lamina II in most mammals which were more or less immature. Corresponding

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* Reviewing illustrations of the cerebral cortex of insectivores by Stephan and Andy (1962) and Stephan and Spatz (1962) we could realize the accentuated lamina II in the following insectivores: Tenrec ecaudatus, Setifer setosus, Chlorotalpa stuhlmanni, Elephantulus fuscipes, and Potamogale velox.

observations can be made in photomicrographs of the cortex of immature monkeys (Powell and Mountcastle, 1959).

In conclusion we can say, the lack of koniocortex and gigantopyramidalis combined with poor lamination and granularization in the specimens of Erinaceiniae and Chiroptera indicate that the last stage of sensory and motor cortical differentiation has not been attained in these insectivores and "flying insectivores." This is obviously the paralimbic/parinsular stage of neocortical evolution. In most placentals the conspicuous lamina II accentuation does not extend beyond Pro limit. The fact that this peculiar feature is present all over the neocortex is indicative of an additional conservative character in these primitive placentals, combined even with the third stage of neocortex evolution.

In the marsupial virginian opossum, a more advanced neocortex shows the persistence of this peculiar accentuated lamina II. It is possibly an aberrant expression of neocortical evolution.

A cytoarchitectonic study (Gerebtzoff and Goffart, 1966) and a sensory projection study (Meulders et al., 1966), on the cerebral cortex of the sloth have produced significant data. The sloth, is one of the living primitive mammals with a sagittal sulcus pattern and a sharply accentuated lamina II all over its neocortex. It is composed of medium-sized darkly staining cells. This characteristic, combined with the poor lamination and poor granularization of the whole neocortex, suggested to these authors that this cortex was comparable to the juxta-allocortex of other mammals. In our view this cortex actually corresponds approximately to a predominant paralimbic/parinsular stage as demonstrated in the bat and hedgehog (Figs. 28 and 29). On the other hand the sagittal sulci would suggest that there exists SmI. The evoked potential study sustains this view and demonstrates that the two sagittal sulci delimit the forelimb area medially and laterally. The authors found, however, only a very limited area for the head. SmII on the other hand was completely overlapped by auditory input and lacked somatotopic partitioning. It is interesting that this aberrant primitive mammal evolved the sagittal sulcal pattern with the new coronal somatotopic representation but did not evolve a koniocortex.

A Golgi study (Tungsten modification of Golgi-Cox after Ramon-Moliner, 1958) was made of the brains of *Hemiechinus*, *Myotis lucifugus*, rat and cat. Slides counterstained with cresylviolet verified the relationships to the cytoarchitectonic layers. The general distribution of cortical neurons showed a predominance of pyramidal cells in all layers with typical apical and basal dendrites rich in spines. There were few typical star cells lying in middle and outer layers of the cortex, more so in the hedgehog than in the bat. Only the cells of the lamina II exhibited a well-developed dendritic pattern (Fig. 30), which is not found in the isocortical lamina II of the rat or cat. In the Golgi preparations of the latter animals, in lamina II typical or atypical pyramidal cells with short shaft or direct spreading of two bifurcating dendrites from the perikaryon into lamina I were found, as described by Globus and Scheibel (1967). We confirm the observation made by these authors that the apical bouquets and the basal dendrites of the pyramidal cells have the same horizontal spread. Thus the dendritic fields of the apical dendrites and the basal skirts together form a cylinder. Neurons of this type were not met in the densely packed lamina II of *Myotis lucifugus* and *Hemiechinus* but were already found at the inner border of

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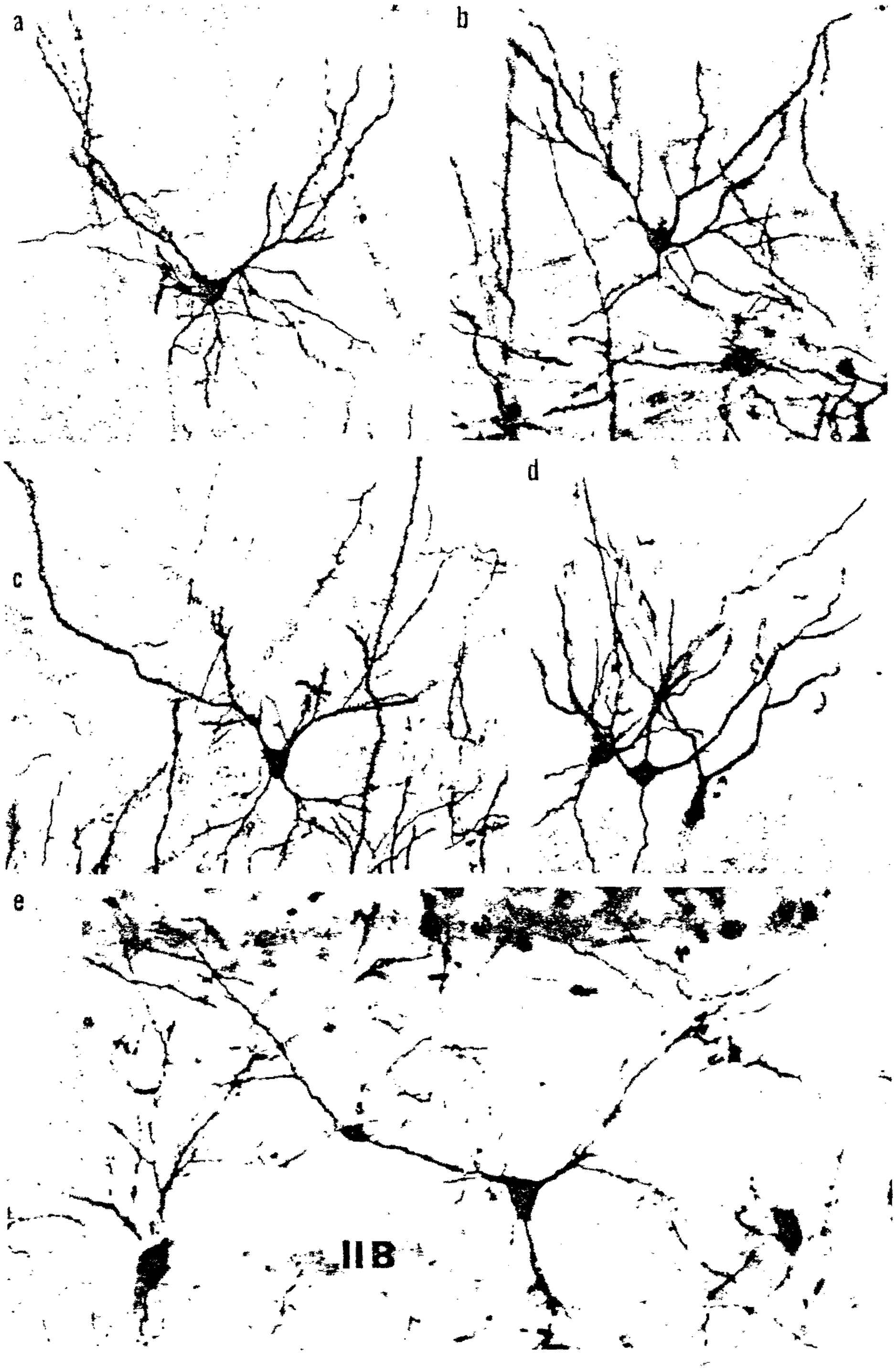

Figure 30. (a-d) Nerve cells of *Hemiechinus;* a-c, wide angle tufted cells of the bandlike accentuated lamina II of the convexity cortex; (d) tufted cell of the prepiriform cortex (Golgi method,) x 200; (e) wide angle tufted cell of the bandlike accentuated lamina II (IIB) of the convexity cortex of *Myotis Lucifugus;* (Golgi method, counterstained with cresylviolet,) x 300.

Figure 31. (a-c) Nerve cells of *Myotis Lucifugus;* (a) wide angle tufted cell of the bandlike accentuated lamina II of the convexity cortex; (b) similar cell type of the accentuated lamina II (IIB) of the entorhinal region; below and left of this cell a large starlike type; (c) immediately below the accentuated lamina II (IIB) of the convexity cortex usual atypical pyramidal cell; (Golgi method, (b) and (c) counterstained with cresylviolet,) x 300.

lamina II (Fig. 31c). The dendritic pattern of the accentuated lamina II neurons is shown in Figures 30e and 31a for the bat and Figure 30a-c for the hedgehog. These cells were the tufted type,* with particularly wide spreading of extraverted dendrites extending directly from the perikaryon without any shaft. The underdeveloped fine

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* It is a pleasure to acknowledge the valuable advice of Dr. Ramon-Moliner in these studies.

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basal dendrites did not reach the spread of the extraverted dendrites. Both types of dendrites were rich in spines with more spines on the outer dendrites.

Compared with other tufted neurons, for example those of the prepiriform cortex of *Hemiechinus* (Fig. 30d), the extreme wide spreading of the thick external dendrites was striking. The wider spread was common in the bat. These neurons have a similar dendritic pattern to the neurons of the frog endbrain (Fig. 32A; Ramon y Cajal, 1909). The axons of these neurons appear to terminate in deeper layers of the cortex. In essence the dendritic pattern of these neurons is characterized by an extensive overlapping of the external dendritic fields of the accentuated lamina II cells within the zonal layer. Although the neurons of lamina II of the hedgehog in general did not show such wide spreading apical bouquets, the incongruity between the very fine and shorter basal dendrites and the zonal layer dendritic spread was striking. Similar cell types were found in lamina II of the entorhinal region. Among those which Ramon y Cajal referred to as large star cells (Fig. 31b; compare also with Lorente de Nò, 1933, Fig. 3 of the entorhinal region of the mouse). However, the basal dendrites in both cases were relatively thick, the thicker external dendrites covering a wider dendritic field. As our Figure 32 from Ramon y Cajal demonstrates, this investigator traced the parallelism of the dendritic pattern of pallial neurons in phylogenesis and ontogenesis: A, B, C, and D representing major stages in phylogeny (amphibian, reptile, lower mammal, man), a, b, c, d, e, representing ontogenetic

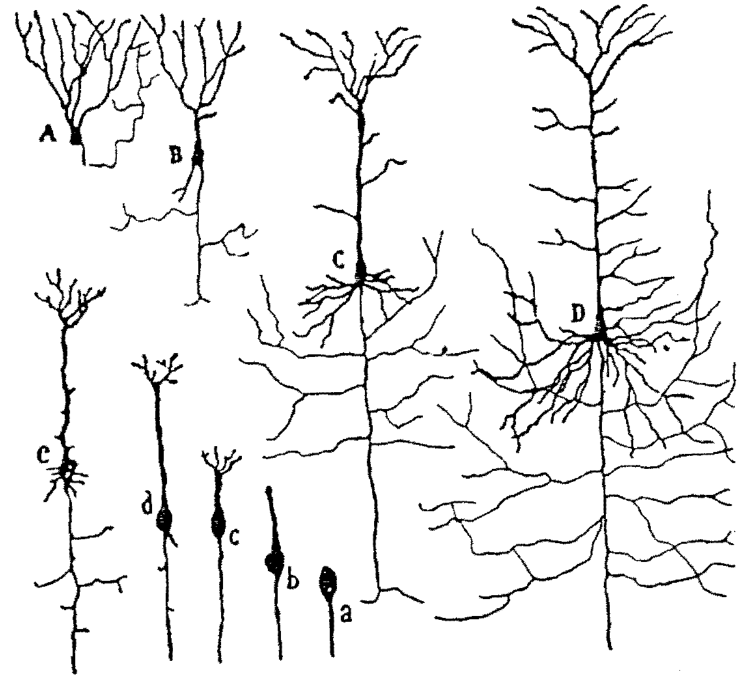

Figure 32. Diagram from Ramon y Cajal (1909. Histologie du Système Nerveux des Vertébrés, Maloine.) Showing phylogenesis of pallial neurons (A-D), parallelled by ontogenesis of a pyramidal cell of a mouse (a-e). A, frog; B, lizard; C, mouse; D, man.

stages of pyramidal cells of the mouse cortex. Thus the development of the lophodendritic cells towards pyramidal cells has been established, in the course of which basal dendrites appear in later stages than the apical ones.* A telling detail is that in contrast to Globus and Scheibel's rule, elaborated predominantly in rabbits, the basal skirt in man has a wider extent than that of the apical bouquet. We conclude that the apical bouquet is a conservative feature and that the basal skirt is a progressive feature in pallial neurons evolution.

The perikarya of the predominant cell type of the accentuated lamina II of hedgehog and bat appear to be shaped by the strong extraversion and wide dendritic spread into the zonal layer, in that they mostly had a broad base above and a tip or curve below. This peculiar type of extraverted cell is a specimen of the tufted cortical neurons, which have their extreme in mammals in the dentate fascia neurons without any basal dendrites. The extraversion of the related allocortical neurons is an expression of the fact that the zonal layer still represents in allocortex and periallocortex the main afferent and association plexus of the cortex.

In summary the dendritic pattern of our extraverted wide angle cells in the bat and the hedgehog neocortex indicates a conservative expression, which agrees with the observation in the hedgehog that the thalamic terminations reach the zonal layer. These terminals make synaptic contact with the extensively overlapping external dendrites. Such thalamic terminations in the zonal layers were described in the pAll of the rat, too.

The conclusion that the investigated specimens of Erinaceinae and Chiroptera did not reach the last stage of sensory and motor cortex evolution but persist at the paralimbic/parinsular stage and based on comparative cytoarchitectonics and myeloarchitectonics and Golgi studies. In neurophysiologic terms this would mean that in these animals the so-called primary sensory and motor areas are absent while, the so-called secondary ones (SmII, AII, supplementary motor and sensory areas, prostriata, and the gustatory area G) are present. The possibility of intermediate stages or aberrant development has also to be considered.

Microelectrode recording studies in the neocortex and thalamus of *Erinaceus* by Diamond and co-workers (1967), which we discussed recently (Sanides, 1968), lend support to our view that this "survivor of the Paleocene" did not yet reach the stage of the classic sensory and motor representations. The sensory relay nuclei of the thalamus should also reflect the neocortex stages as a kind of interdependent growth ring of the forebrain, as was indicated for the dorsomedial nucleus (noted above). Actually Diamond's (1967) and Bauchot's (1959) anatomical observations indicate that this mammal has the most primitive stage of thalamic differentiation among placentals. This corresponds to Diamond's electrophysiological results that the somesthetic nucleus (VP) and the auditory thalamic nucleus (medial geniculate body) are not yet "the exclusive target of one modality." Thus in the thalamus the specific relay nuclei may have differentiated during evolution as a core in a more generalized older ground area. An indication for such thalamic ground areas is the pulvinar-posterior system as presented by Rose and Woolsey (1958).

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* Noback and Purpura (1961), tracing the postnatal ontogenesis of neurons in cat neocortex confirmed this developmental sequence and discussed electrophysiological implications.

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The recording study of the sensory cortex (Diamond, 1967) is suggestive for nonclassic representations. The unusual large tactile receptive fields were found in the periphery, indicated a reduced discrimination power. Moreover, the predominance of sustaining input to the sensory cortex was found. This phenomenon, first revealed by Rose and Woolsey (1958), is characteristic for the sensory areas surrounding the koniocortex cores. The latter receives "essential" input (discussed in Sanides, 1968).

THE GROWTH RINGS OF THE NEOCORTEX AND THE RELATIONSHIP OF SMII AND MPL TO THE CLASSIC SENSORIMOTOR REPRESENTATIONS

We will now review the stages of forebrain evolution and present a tentative design of how the coronal somatotopic pattern of classic sensorimotor representations may have developed from the sagittal paralimbic and parinsular patterns of the secondary (secondarily detected!) representations. We demonstrated above that not only primates began their gyrification of the neocortex in evolution with a sagittal pattern, but also ungulates and carnivores, which represent the most successful groups with the arcuate patterned brain. The somatotopical significance of this sagittal pattern in terms of functional architecture was clarified and traced through recent carnivores and most advanced primates including man. The medial and lateral sagittal sulci which determine the sagittal patterned brain separate hindlimb, forelimb, and head areas not only in the classic sensorimotor regions but apparently also in the integration cortices. The question is whether we can find, looking backward from this point of departure, an explanation as to why and how the classic sensorimotor areas may have arisen following an earlier phylogenetic stage on which the so-called secondary representations of the paralimbic/parinsular zone "had done the job."

The principle of building of new nervous centers to meet new adaptive needs of an everchanging world during geological times is reflected in what von Monakow (1911) described as the rostralward migration of functions during brain evolution. This leads to the intricate sequential reorganization of the brain stem and diencephalon as seen in comparative neurology and ontogenesis. The rostralward migration terminated at the utmost end of the endbrain by forming the cerebral cortex and exploiting the new source of pial blood supply. Further waves of growth and differentiation making the adaptive responses to an everchanging environment (on land even more so than in the water) were now established as concentric growth rings of respective new cortices parallelled by corresponding waves of growth and differentiation of the interdependent thalamic nuclei, together with the differentiation of the affiliated peripheral sense organs. Thus we have traced in a series of mammals the sequence of four neocortex waves: Periallocortex, proisocortex, parinsular/paralimbic belt, and koniocortex plus gigantopyramidalis of the sensory and motor regions. Of course we can not easily determine the answer as to which requirements were fulfilled by the earliest growth ring, the pAll.

The raison d'etre of the next growth ring with its Pro is more easily surmised. We know that the insular Pro and cingular Pro are involved in a form of motor expression in the context of emotional and autonomic reactions (Showers, 1959; Showers and Lauer, 1961). The parinsular/paralimbic growth ring is composed of the prokoniocortices and supplementary motor areas, which may be functionally conceived as sensory and effector expressions which are largely emancipated from the realm of emotions and concommitant autonomic reactions. We can now focus on the sensorimotor areas which have assumed the central position in the cerebral hemispheres. Their somatotopic organization is expressed in the gyral pattern as well as in the architectonics. The basic problem is why were the sagittal paralimbic and parinsular representations of SmII and Mpl supplanted and displaced in the Tertiary by the coronal patterned new classic representations. In the large series of sensorimotor figurines of rodents, lagomorphs, primates, and carnivores as electrophysiologically elaborated by Woolsey and his co-workers, we find in such lower animals as the rat and rabbit the striking predominance of the head representations (especially muzzle!), and already here the forelimb area is about twice as large as the hindlimb area. This preference of the forelimb is growing in the carnivores leaving behind not only hindlimb, but head area, too. In prosimians, on the other hand, the hand and foot as prehensile limbs are developed correlating with large pertinent cortical areas.

We can conclude that preference for the representation of the forelimb in SmI and MsI compared with hindlimb is expressed in the original design of classic sensorimotor organization. This preference of the forelimb representation is not yet expressed in the older paralimbic and parinsular sensorimotor areas of non-primates. This indicates that these representations of the third neocortex growth ring serve a general tetrapod function.

The preference of the forelimb within the classic sensorimotor representations in the next growth ring is another expression related to the adaption to terrestial life. Thus the forelimb is partly released from the compulsory tetrapody to serve roles as a scouting function and as a weapon in attack and defense.

The significance of the new sensorimotor representation which expands and differentiates as a core between the paralimbic motor and parinsular sensory representations of the third growth ring could have evolved to serve this adaptive function of the forelimb. One can speculate that this new sensorimotor representation began with the development of the classic forelimb area and that this new expanding area between the older sagittal representations brought, under the counterpressure of the latter, its two sagittal sulci into appearance. (For example during evolution the growing prehensile motor tail representation of *Ateles* brought its limiting sulcus into appearance). Both sagittal sulci still delimit the classic hand area in recent prosimians, however against the complemented classic hindlimb area on the one hand (medial sagittal sulcus) and the classic head area on the other lateral sagittal sulcus.

THE DETERMINATION OF THE MAMMALIAN NEOCORTEX AND ITS PRECURSOR IN REPTILES

There appears to be a general agreement in relating the isocortex with neocortex, and the allocortex sensu ampliori (including periallocortex) with archicortex and paleocortex, (von Economo and Koskinas, 1925). This does not hold true for pAll, which we conceive as first growth ring of neocortex composed of a periarchicortex moiety and a peripaleocortex moiety.

This first wave of mammalian neocortex is a two-cell-strata cortex with emphasis on the larger celled inner stratum. Both strata are separated by a more or less clear-

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cut lam. diss. Another characteristic of this primary neocortex is the condensations of medium-sized tufted cells at the surface. Their dendritic tufts in the zonal layer receive synaptic contacts from the fibers of the surface-bound olfactory system and from the thalamic afferents. In the next wave of neocortex differentiation, Pro, the thalamic input switches from axodendritic synaptic contacts in the zonal layer and outer stratum to axosomatic synapses in the star-celled lamina IV. This is reflected in myeloarchitectonics as the decrease in the zonal afferent plexus and the development of the outer stripe of Baillarger afferent plexus (Fig. 5).

The latter organization of a multilaminar cortex is not reached in the reptiles. The question arises whether reptiles have somewhere, a general cortical organization equivalent to the primary neocortex—the two-cell-strata pAll of mammals. The dorsal or general cortex of reptiles which was once assumed to be the precursor of the mammalian neocortex (because of the lack of thalamic afferents) is now precluded (Kruger and Berkowitz, 1960). Rather it represents part of the hippocampal complex, as suggested by Rose (1923). Recall that the inner stratum of mammalian pAll is continuous with the hippocampal subiculum medially and that the outer stratum of pAll is continuous with the paleocortex laterally. There is an analogous condition in reptiles at the site where the dorsolateral component of the dorsal cortex underlies the lateral paleocortex. This occurs in the order Squamata (lizards and snakes) and in the order Chelonia (turtles). We note the wide divergence of the phyletic lines within the reptiles. The actual diversification of the forebrain structure of the reptilian orders has been recently traced thoroughly by Northcutt (1967). He concluded that the dorsolateral cortex underlying the paleocortex has a different character in the lizards and turtles. Only in turtles the efferent character in the form of pyramidal cells is preserved. It is functionally linked to the motor systems in the lateral forebrain bundle. In the group of reptiles which gave rise to birds—the saurapsid line which includes all living reptiles except the turtles—the dorsolateral component of the dorsal cortex has an associative role rather than a motor function.

In turtles, another requirement for the equivalence with the mammalian pAll is met. The dorsolateral component underlying part of the paleocortex receives thalamic afferents. Whether such afferents reach into the zonal layer of the superimposed paleocortex has not been established. This projection is suggested by the investigation of Orrego and Lisenby (1962) of the electrical activity in the turtle cortex. They concluded that there are sensory afferent paths terminating on apical dendrites of the general cortex.

The turtle cortex is divided into two strata—(1) an inner one, the dorsolateral cortex which is hippocampal in origin and efferent in character, and (2) an outer stratum, which is part of the paleocortex. This morphological organization appears to be the equivalent of the mammalian periallocortex. In turn, this is an expression of the primordium of a neocortex in evolution.

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