

THE DEVELOPMENT OF THE CORTEX AND THE FUNCTIONS OF ITS LAYERS.*

By C. U. ARIËNS KAPPERS, M.D.,

Director, Central Institution for Brain Research, Amsterdam.

THE functions of the different layers of the neocortex are a matter of great importance to the neurologist.

The character of the neocortex and the significance of its different layers are, however, most easily understood when compared with the older forms of cortex, the primary olfactory cortex, which I have called *palæocortex*, and the secondary olfactory cortex or *archicortex*.

In the frog, only the two latter regions may be distinguished, the dorso-lateral region being the *palæocortex*, and the dorso-mesial the *archicortex* or *primordium hippocampi*.

The former receives a large number of olfactory fibres from the *formatio bulbaris*, and, perhaps in addition, some fibres from the dorsal thalamus (Rubaschkin), but the cortical ending of these latter fibres is still doubtful, and certainly so insignificant in comparison to the former that we are fully justified in calling this cortex a primary olfactory or *palæocortex*.

Its cells show a very primitive arrangement, being mostly localized near the ventricular ependyma, as is also the case in the mammalian neocortex in an early stage of development.

Most of the dendrites of these cells extend to the lateral surface of the *palæopallium* (*cf.* P. Ramón y Cajal and others), to the olfactory tracts which are practically unmyelinated in frogs. The stimuli of these tracts cause their outgrowth in this direction (*neurobiotaxis*, Kuhlénbeck).

The *palæocortex* of frogs gradually continues into the *primordium hippocampi*, which is not yet differentiated into layers, but whose cells have migrated further away from the periventricular matrix than those of the *palæocortex*, a consequence of the larger number of fibres running in the superficial zone of the *archicortex* (tertiary olfactory largely), which fibres, moreover, are myelinated, thus showing a greater functional efficiency.

* A paper read before the Association, July 7, 1931. This paper also appeared in *Acta Psychiatr. et Neur.*, 1928, ii.

The cells of the archicortex are also larger than those of the palæocortex, especially the more peripheral ones.

In reptiles a further differentiation occurs. In serpents and lizards three cortical layers may be observed in the mid-region of the hemisphere, more or less joining each other in front and behind. These layers may topographically be called the lateral, dorsal, and medio-dorsal layer.

The lateral and dorsal layers consist of large pyramidal cells, but the medio-dorsal layer consists of small granular cells.

In the lateral layer, frontally, the olfactory tract ends. Its frontal part, consequently, is a primary olfactory cortex or palæocortex, a primitive homologue of the mammalian pre-piriform cortex in Brodmann's nomenclature.

Posteriorly it passes into what corresponds to piriform cortex (Elliott Smith) and there extends into the archistriatum (the piriform cortex extends into the amygdala in mammals).

Although the frontal part of this cortex is the primitive homologue of the pre-piriform cortex and the caudal part corresponds to the piriform cortex of mammals, it everywhere has approximately the same simple structure, in which no distinct layers may be recognized; thus showing a lower plan of organization than the pre-piriform and especially the piriform cortex of mammals.

The dorsal and medio-dorsal layers, though different in structure, belong together, establishing the archi- or hippocampal cortex, which, as in mammals, consists of two layers, for the most part adjoining each other, although the medio-dorsal cells lie somewhat nearer the surface.

The dorsal layer represents the ammon-pyramids, and the medio-dorsal or granular layer the fascia dentata (Adolf Meyer).

As in mammals, so in reptiles, the relation between the fascia dentata and the ammon-pyramids is such that the latter, only for a short distance, extend below the former as subgranular pyramids.*

Concerning these two strata of the archicortex, we know that the cells of the granular layer or fascia dentata generally have short axons (shorter than those of the ammon-pyramids), which moreover, mostly arborize in the neighbouring cortex (some extending into the septum).

We also know (P. Ramón y Cajal) that the dendrites of these granular cells all extend to the surface of the pallium, where the

* In lizards, in addition to these, some pyramid cells are found lying above the fascia dentata (really they are a part of the fascia dentata itself, which passes upward and changes its granular character into a pyramidal one).

ascending tertiary olfactory neurons run. From this it is apparent that this *granular layer or fascia dentata is predominantly a receptive or correlative layer*, transmitting the impulses to neighbouring structures.

Contrary to the latter, the cells of the dorsal layer, the ammon-pyramids, have large axons passing into the lining of the ventricle, and then leaving the hemisphere to enter either the hemisphere of the opposite side (commissural fibres) or run backward into the hypothalamus (fornix) and epithalamus (tr. cortico-habenularis). Consequently the *ammon-pyramids are cortico-fugal and commissural neurons*.*

Recapitulating the above, we may say that the archicortex of reptiles consists of two layers—a receptive (correlative) granular layer, and a cortifugal and commissural pyramidal layer, which partly extends under the granular layer.

This is the first clear example of a laminar differentiation. It is found again and in the same way in the hippocampus of mammals, and the functional division it shows is very instructive, as it gives us a key to the understanding of the lamination in the mammalian neocortex.

Before proceeding to the mammalian relations, I shall briefly discuss the question whether a neocortical primordium is already present in reptiles.

We immediately meet with the difficulty of recognizing it, since it is evident that in lizards we do not find any structure so complicated as the mammalian neocortex, *i.e.*, consisting of several (five or six) superimposed layers.

Yet there might be a primordium neopallii, as Elliot Smith called it—or “general cortex” (*cf.* Miss Crosby)—in an undifferentiated way.

In order to know if such a primordium neopallii is found in reptiles we must determine whether there are any fibres proceeding from the neothalamus which end in the cortex, since the typical feature of the neocortex is that it receives, not olfactory, but neothalamic projections (sensory, visual, etc.).

It is not impossible—it is even likely—that a few of such fibres occur.

As appears in Fig. 72 of my book on the *Evolution of the Nervous System*,† in reptiles a strong tract of fibres runs from

* Elliot Smith also found a lamination in *Lepidosiren* and an indication of it was found by Röthig in *Bufo*. But these laminations are by no means so distinct in their functional significance as those in reptiles.

† *The Evolution of the Nervous System in Invertebrates, Vertebrates and Man*, Erven F. Bohn, Haarlem, 1929.

the neothalamus to the forebrain, most of them ending in the neostriatum.

Some of these fibres, however, seem to continue their course frontally and laterally beyond the neostriatum and to the cortex. They end (some perhaps begin) in that part of it where the dorsal edge of the palæocortex stops, or where (in lower reptiles) it joins the ammon-pyramids.

Consequently this spot lies between the palæocortex and the ammon-pyramids of the archicortex.

This proves that, if there is a primordium neopallii, it is represented by cells connected with or arising at the dorsal edge of the palæocortex, in the latero-frontal region of the cortex.

This location is very interesting, since we know that the mammalian neocortex, too, develops frontally between the palæocortex and archicortex (or hippocampus), pushing the latter backwards in its later development.

Whereas, however, even in the lowest mammals (*cf.* Miss Obenchain's paper on *Cænolestes*) this neocortex is larger and much thicker than either of the other forms of cortex, in reptiles it is a mere vestige, only characterized by this fibre-connection and a slight increase of cortical cells just in front of the place where the neostriatum is in contact with it.

From the above it appears that if a vestige of a neocortex occurs in reptiles, it is only present in the latero-frontal part of the pallium, lying between the archicortex and palæocortex, and connected with the latter.

Proceeding to the cortex of mammals, I shall first discuss the fate of the palæo- and archicortex in these animals.

The neocortex of mammals being intercalated between the palæo- and the archi-cortex, its large development in mammals pushes the palæocortex ventrally, causing a limiting fissure between them—the *fissura rhinalis*.

The palæocortex or pre-piriform cortex of mammals, moreover, shows a higher stage of development, exhibiting two layers—a superficial granular and a deep pyramidal layer, the former being mainly receptive-correlative, the latter sending out large efferent tracts to various parts of the fore- and 'tween-brain. Apparently we are here dealing with a similar differentiation as in the archicortex, with the difference, however, that in this palæocortex the various layers lie on top of each other.

On the other hand, the dorsal and medial extension of the neocortex causes the adjacent pyramidal layer of the archicortex

to be lifted up and pushed medially, thus forming the semicircular curve so characteristic of the ammon-layer, the lower point of which remains underneath the hook-like fascia dentata.

This folding of the ammon-pyramid layer gives rise to the fissura hippocampi, which is not a limiting, but an axial furrow lying in the area of the ammon-pyramids (not limiting an area as the fiss. rhinalis does). The cytological difference between the mammalian and reptilian archicortex consists chiefly in a relative increase of ammon-pyramids at the expense of the granules of the fascia dentata, the cells of which apparently are partly embryonic or matrix cells. This corresponds with an increase of fibres of the psalterium or lyra and of the fornix.

The first development of the neocortex reminds us of the arrangement in the palæocortex and archicortex of the frog. All the cells are located in a ventricular matrix, as is the case in the palæocortex of the frog. Only later some of these matrix cells shift in the direction of the zonal layer,* as is also observed in the archicortex of amphibia. Still later the neocortex starts to develop into different laminæ. In this stage the neocortex is already much thicker than the palæo- and archicortex. In *Dasypus* at birth, in man already in a prenatal stage (Brodmann), it consists of five cell-layers,† showing a granular layer (IV) in the middle, and two layers of larger cells on either side of it (above and beneath). The supra-granular layer at birth is still small in man (Bolton).

These five cell-layers may, however, be classified in three groups: the supra-granular cells (layers II and III of Brodmann), the granular layer (IV of Brodmann), and the subgranular cells (V and VI of Brodmann).

We shall see that the relation of these three layers to the two layers of the older cortex forms is such that the granular layer (IV) of the neocortex is homologous with the granular layer of the archicortex (fascia dentata) and with the superficial granules of the palæocortex, while the large subgranular cells (V and VI) of the neocortex are homologous with the ammon-pyramids of the archicortex and with the deep pyramids of the palæocortex.

The supragranular pyramids of the neocortex, however, are a new development, typical of the mammalian neocortex. Though arising

* This occurs in the human embryo about the fourth to fifth month (Kuhlenbeck).

† Generally six cortical layers are distinguished: (I) Zonal layer (which is not a cellular layer); (II) layer of small pyramidal or stellate cells; (III) the supra-granular pyramids; (IV) the internal granular or granular layer "*tout court*"; then (V) the ganglionic layer; and finally (VI) the polymorphic layer. Campbell's division is very similar (differing slightly in nomenclature).

from the granular layer they have a more highly developed receptive-associative function than the granule-cells.

The laminar homology of the large subgranular cells of the neocortex with the ammon-pyramids is seen from the fact that the ammon-pyramids continue directly in the subgranular pyramids of the neocortex, as do also the deep pyramids of the pre-piriform cortex. From this also results the homology of the neocortical granular layer (IV) with the granules of the palæo- and archicortex, as in both cases the deep pyramids lie beneath these granules (in the archicortex partly under the fascia dentata).

The function of the granular layer (IV) and of the subgranular pyramids is also the same in the three forms of cortex; the granularis having a correlative-receptive function, the subgranular pyramids giving rise to efferent tracts and to commissural fibres. This is seen from the following facts:

The granular layer is strongly developed in those regions of the neocortex that have an exquisite sensory function—the post-central or sensory region, the frontal cortex (which receives fibres from the red nucleus, the auditory and visual cortex. In the area striata (visual cortex) afferent fibres running in the stria Gennarii and Vicq d'Azyr, end chiefly in the granular layer.* Only a few of the fibres end in other layers (Poljak).†

This does not mean that in the neocortex the granular layer is the only layer which receives afferent impulses. Afferent impulses, among which are those transmitted by the corpus callosum (van Valkenburg) also reach the supra-granular pyramids.

On the other hand, the prevailing efferent-commissural and corticofugal character of the subgranular pyramids is shown by the fact that section of the corpus callosum (v. Valkenburg, J. de Vries) or the centro-fugal tracts (Holmes and Nissl) causes a degeneration of subgranular pyramids, while lesions of the supra-granular pyramidal region give no cortico-fugal degenerations, although some of the callosum fibres may also originate here. So in the granular and subgranular layer of the neocortex we find a similar localization of functions as in the older cortical areas.

The specific neocortical character of the *supra*-granular pyramids, however, is evident, and appears from the fact that, in the palæo- and archicortex, no layer of pyramidal cells occurs on top of the granular layer (the few pyramidal cells in which the fascia dentata

* This granular layer is single in the lower mammals. In primates and man it is doubled.

† Poljak, "An Experimental Study of the Association, Callosal or Projection Fibres of the Cerebral Cortex of the Cat," *Journ. of Comp. Neur.*, 1927-28, xlv.

of lizards continues dorso-laterally, giving off fibres in the zonal layer, may be the only indication of such a process).

Besides, the more recent character of the supragranular layer of the neocortex appears from the fact that this layer is the last one to mature ontogenetically (Bolton, Brodmann).

That, however, the supragranular layer is chiefly a kind of extension of the granular layer (IV) is proved by van't Hoog, who showed that in the case of animals of the same sub-order, but differing in size (as cat and tiger, sheep and cow), in the larger animal the supra-granular cells are increased at the expense of the granular layer.

This is apparently due to the fact that in large animals sensory functions increase more than motor functions (Dubois), for the latter increase only with the bulk of the muscles, while the former increase both with the bulk of the muscles (proprioceptive sensibility) and with the surface area of the skin and sense-organs (exteroceptive sensibility).

That the supra-granular cells at the same time become larger than those of the granular layer may be the result of their axis cylinders (the area covered by it) growing out more in the larger brains, transmitting the received impulses over larger areas of the hemisphere. In addition to receptive they have associative functions, as appears also from the fact that the callosum fibres end here.

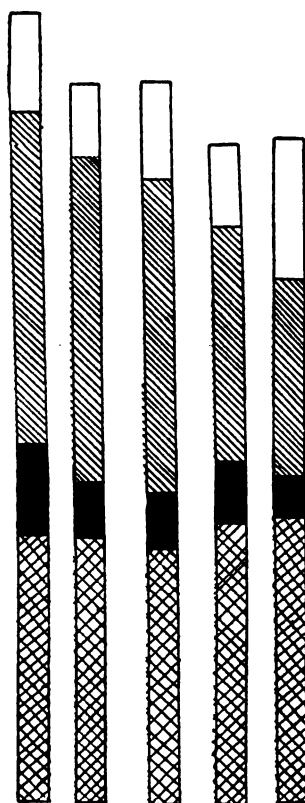
Finally the higher, associative character of the supra-granular layers appears from the fact, first observed by Mott, and confirmed by van't Hoog (see fig.) that in higher mammals this layer is much more developed than in lower ones.

Moreover Bolton observed that at birth this layer is still very small, and that in cases of extreme idiocy it may show a lack of development. A similar conclusion may be drawn from some of the cases described by Hammarberg.

The germinal character of the granularis explains why the degeneration of cells in dementia præcox chiefly occurs in that part of the supra-granular layer (III) that lies nearest to the granularis, and also in that part of the subgranular cells that lies nearest to the granularis (Sioli, Alzheimer, O. Vogt, Josephy, Naito, K. H. Bouman). This may be understood, as K. H. Bouman* pointed out, as a lack of vitality in the layers that lie nearest the germinal matrix (IV), the more so as Mott found a striking lack of basi-

* K. H. Bouman, "Die pathologische Anatomie des Zentralnervensystems bei Schizophrenie," *Psych. en Neur. Bladen*, Amsterdam, 1928.

chromatin in the nuclei of the granularis itself. Probably this involutive degeneration is an anatomical corollary of the dissociated thoughts and actions (K. H. Bouman).



Homo Troglodytes Lemur catta Felis leo Rusa hipp.

Relative development of the supra-granular and other layers in an ungulate, carnivore, lemur, chimpanzee, and in man. Granular layer black. Supra-granular cell layers striped obliquely, subgranular layers crossed. Post-central region. After van't Hoog.

SUMMARY.

Summarizing the facts, we may say that the primitive arrangement of the cortex as it appears in the palæo- and archipallium, shows two cell layers—the lamina granularis, which has mainly a

receptive-correlative function, and the deep pyramids, which have a cortico-fugal and commissural efferent function.

The principle of this lamination is kept up in the neocortex, with this difference, however, that the receptive-correlative granular layer has given rise to supra-granular cells, which again are subdivided into two sub-laminæ: the upper cells (II) still retain a smaller size, while the cells (III) lying nearer the granularis (IV) acquire a pyramidal form.

This differentiation of the supragranular cells does not seem very important. In some parts of the neocortex, in the regio retrosplenialis especially, the differentiation of the supragranular laminæ fails.

In this area, according to Brodmann, whose observations I can only confirm, the lamina zonalis is still very wide, the original granular layer (IV) still large, and the lamina supragranularis, between the zonal and granular layers, is only poorly developed and shows no subdivision.

As far as concerns the cause of the development of the supra-granular layer, Kuhlenbeck, and later, but independently of him, Faul, have given the following neurobiotactic explanation of this process, which is perfectly in accordance with the facts.

As in the palæocortex and in the archicortex the afferent cortical fibres, carrying corticopetal impulses, run in the zonal layer—a fact most fundamentally represented by the primary and secondary olfactory tracts—similarly in the neocortex, callosum fibres and part of the ascending thalamic fibres run in the more superficial parts of the cortex, between the surface and the granular layer.

Since therefore the space between the surface and the granular layer originally is an important region for corticopetal impulses, it is not strange that these impulses give rise to a much greater outgrowth of matrix cells of the granular layer in a superficial direction, and thus to the formation of supra-granular cell-layers, which, in maturing, at the same time acquire a larger size.

