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Alzheimer's disease: areal and laminar pathology in the occipital isocortex*

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Summary. Sensitive and specific silver methods for demonstration of (1) amyloid and/or precursors of amyloid and (2) neurofibrillary changes were applied to examine the pathology revealed by the occipital isocortex in cases of Alzheimer's disease and age-matched controls. In general, amyloid and/or precursors of amyloid are encountered in plaque-like formations. Large numbers of amyloid plaques occur in layers that only occasionally harbor neuritic plaques. Amyloid deposits can be found in abundance in the occipital cortex of demented individuals exhibiting an only sparse number of neuritic plaques. In demented individuals the striate area contains almost as much amyloid as the parastriate area or the peristriate region. Neurofibrillary changes are encountered in neuritic plaques, neurofibrillary tangles, and neuropil threads. Neuritic plaques are predominantly found in layers II and III. Their density changes even within the boundaries of architectonic units. Large numbers of plaques are found in the cortex covering the depth of the sulci. The number of neurofibrillary tangles increases abruptly when passing the striate/parastriate and the parastriate/peristriate boundaries. The neuropil threads may densely fill a layer without the presence of neurofibrillary tangles (layer V of the striate area). Neuropil threads contribute a substantial part to the total amount of the intraneuronally deposited pathological material.

Key words: Alzheimer's disease – Amyloid – Neuritic plaques – Neurofibrillary tangles – Neuropil threads

The occipital isocortex consists of three major architectonic units, the visual core field (striate area, Brodmann area 17), the visual belt area (parastriate area, Brodmann area 18), and the visual association cortex (peristriate region, Brodmann area 19). The lamination pattern and connectivity of these areas, and the types of nerve cells residing within the individual laminae are well known in the brain of higher primates and man [3, 6, 7, 26, 30, 39–41].

In Alzheimer's disease numerous pathological changes can be recognized in isocortical areas [23, 27]. Closer examination reveals an area-specific, lamina-specific, and cell-type-specific distribution pattern of the pathology [25, 31, 35]. As the disease progresses increasing amounts of abnormal filaments are deposited in both extracellular and intraneuronal locations. The extracellular components are considered to be amyloid and/or precursors of amyloid [15, 16], while the intraneuronal components represent the neurofibrillary changes of the Alzheimer type [21, 46].

Highly sensitive and specific silver impregnation techniques are currently available for the demonstration of both the extracellular deposits and the intraneuronal pathology [14, 17]. The present study is aimed at examining the area-specific, lamina-specific, and cell-type-specific distribution pattern of both the extracellular deposits (amyloid) and the intraneuronal pathology (neurofibrillary changes) in the human occipital lobe.

Materials and methods

This study was performed on 18 brains obtained at autopsy and fixed by immersion in a 4% aqueous solution of formaldehyde. The brains nos. 1–12 were from patients with a definite history of presenile or senile dementia. On neuropathological evaluation, the brains exhibited sufficient numbers of neurofibrillary changes in multiple cortical regions to confirm the diagnosis of Alzheimer's disease [24]. Brains nos. 13–18 were from non-demented patients without known neurological disorder. None of the cases examined showed extended ischemic lesions (Table 1).

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Table 1. Sex, age, and neuropathological evaluation of the cases examined

No.	Sex	Age	Campbell	Gallyas
1.	f	59	+++	+++
2.	f	59	+++	+++
3.	f	60	+++	+++
4.	f	64	+++	+++
5.	f	58	+++	+++
6.	f	69	+++	+++
7.	m	64	+++	++
8.	f	71	+++	++
9.	m	72	+++	+
10.	m	71	+++	+
11.	f	71	+++	+++
12.	f	77	+++	+
13.	f	75	+	0
14.	f	62	0	0
15.	m	69	0	0
16.	m	74	+	0
17.	f	69	0	0
18.	f	65	+	0

The overall amount of unusual material in the occipital isocortex as seen in Campbell and Gallyas preparations is graded and labeled zero (0) with no discernible change, or (+) with slight, (++) with moderate, and (+++) with severe changes

Coronal slices running through the occipital lobe perpendicular to the intercommissural axis were cut with the aid of a macrotome. The blocks were embedded in polyethylene glycol (PEG 1000, Merck) and cut at 100 µm [38]. The first section of each block was processed with a silver technique demonstrating the amyloid [14]. These sections, if fully developed, also showed normal axons. The second section of each block was stained for neurofibrillary changes according to a technique proposed by Gallyas [17, 19] and others [12]. Both silver techniques take advantage of a physical development procedure [18]. The third section of each block was stained for lipofuscin pigment and Nissl material [6]. Architectonic units were identified in the pigment Nissl preparations according to the published characteristics [6, 13, 44].

Additional blocks (from the opposite hemisphere) were paraffin embedded, sectioned at 12 µm and stained with cresyl violet, congo red [32], and the silver techniques of Campbell et al. [14] and Gallyas [17]. Consecutive paraffin sections cut at 8 µm were used for comparison of immunocytochemical methods with the silver techniques under consideration. We analyzed several triplets of which the first section was treated with an antibody raised against synthetic A4 protein [28]. Immunostaining was performed to standard procedures using the avidin-biotin peroxidase complex system to label bound antibody and diaminobenzidine to visualize the reaction product. The immunostained section was then correlated to two succeeding sections having been treated either according to the Campbell method or the Gallyas technique (Fig. 1a–f). Other paraffin sections were immunostained with a polyclonal antibody raised against paired helical filaments soluble in sodium dodecylsulfate (antibody 89c: Grundke-Iqbal: personal communication) using 4-chloro-1-naphthol as chromogen. Following the photographic documentation of the immunoreactive structures the chromogen was de-stained in 70% ethanol. Subsequently, the sections were re-stained with the Gallyas silver technique and photographed again (Fig. 1g–k).

Results

General remarks

Preparations stained with the Campbell silver technique [14] show an abnormal material deposited in abundance in the occipital cortex of demented individuals (Figs. 2a, 3a, 4a,b, 5a,c). Just a sparse amount of this material can be seen – if at all – in non-demented individuals (Fig. 3c, Table 1). Closer examination reveals a fluffy material irregularly deposited in the neuropil. The distribution pattern of the material mimics that seen in preparations immunostained with an antibody raised against synthetic A4 protein (Fig. 1a, b, d, e). The silver-stained deposits of this material are here referred to as "amyloid plaques".

Preparations stained with the silver technique proposed by Gallyas [17] reveal accumulations of pathological filaments within both the somata and the processes of nerve cells. Considerable amounts of the Gallyas-positive material are only seen in the brains of demented individuals (Figs. 2b, 4c, 5b,d). Some demented individuals show a modest pathology (Fig. 3b, Table 1). With the exception of a few occasional deposits, the occipital areas of non-demented individuals remain devoid of neurofibrillary changes (Fig. 3d, Table 1, cases 13–18). The changes closely resemble those seen in preparations immunostained with an antibody raised against paired helical filaments (antibody 89c, Fig. 1g–k). The silver-stained material is referred to as the neurofibrillary change of the Alzheimer type.

Three kinds of lesions showing neurofibrillary changes can be distinguished, i.e., the neuritic plaques, the neurofibrillary tangles, and the neuropil threads. Only the plaques displaying argyrophilic processes filled with pathological filaments are referred to as "neuritic plaques" (Fig. 1c, f–h). In all architectonic units studied the neurofibrillary tangles have exclusively been found within the somata of pyramidal cells. The neuropil threads are pathologically changed processes of nerve cells scattered throughout the cortical gray (Fig. 1i,k).

In general, "neuritic plaques" also reveal the presence of amyloid (compare Fig. 1c, f with 1a, d), while "amyloid plaques" do not necessarily correspond to neuritic plaques. Amyloid plaques occur in large numbers in areas or layers that are devoid or almost devoid of neuritic plaques (compare Fig. 2a with 2b) and they are frequently found in the cortex of demented individuals showing only a few neuritic plaques (compare Fig. 3a with 3b).

The cortex covering the depth of the sulci generally shows a larger number of both amyloid and neuritic plaques in layers II and III than the cortex spreading over the crest of the gyri.

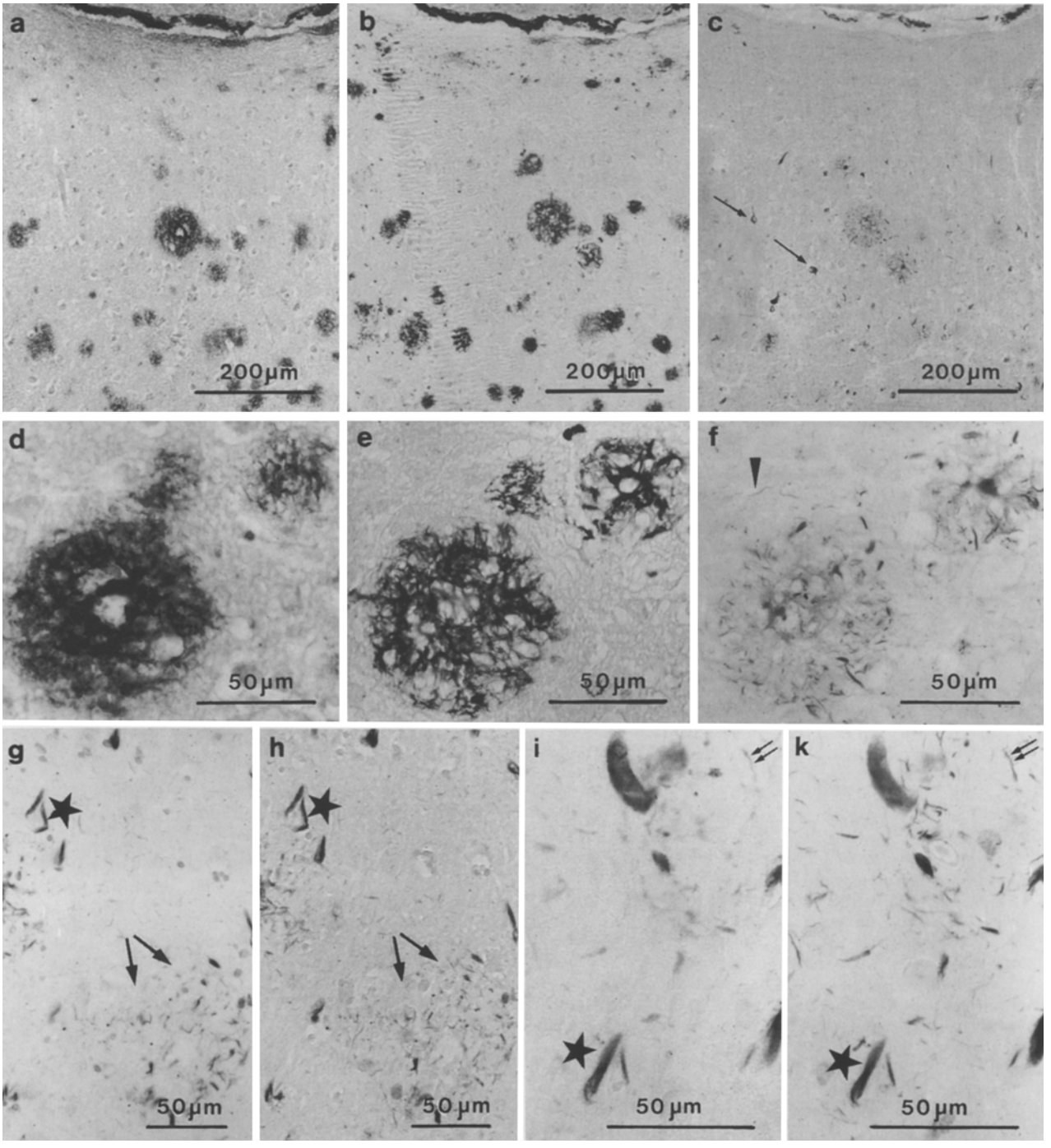

Fig. 1. a–f Three differently processed consecutive sections each showing the same portion of the cortex (peristriate region, 8-µm paraffin section, Alzheimer's disease). **a, d** Section for demonstration of anti-A4 (amyloid) immunoreactivity. **b, e** Section processed according to the method proposed by Campbell et al. [14]. **c, f** Section processed according to the method proposed by Gallyas [17] for neurofibrillary changes. The distribution pattern of the abnormal material marked in **a, d** closely resembles that in **b, e**. Neurofibrillary tangles as seen in **c** (*arrows*) remain unstained in **a** and **b**. The neuritic plaques as seen in **f** harbor a small number of distended argyrophilic processes. The same plaques appear marked by amyloid or precursors of amyloid in **d** and **e**. **g, i** Section for demonstration of paired helical filament immunoreactivity (peristriate region, 8-µm paraffin section, Alzheimer's disease). *Arrows* mark a neuritic plaque, stars indicate neurofibrillary tangles and *small arrows* point to a neuropil thread; **h, k** the same section decolorized and restained according to the method proposed by Gallyas for neurofibrillary changes. The distribution pattern of the neuritic plaques, the neurofibrillary tangles, and the neuropil threads marked in **g, i** closely resembles that seen in **h, k**

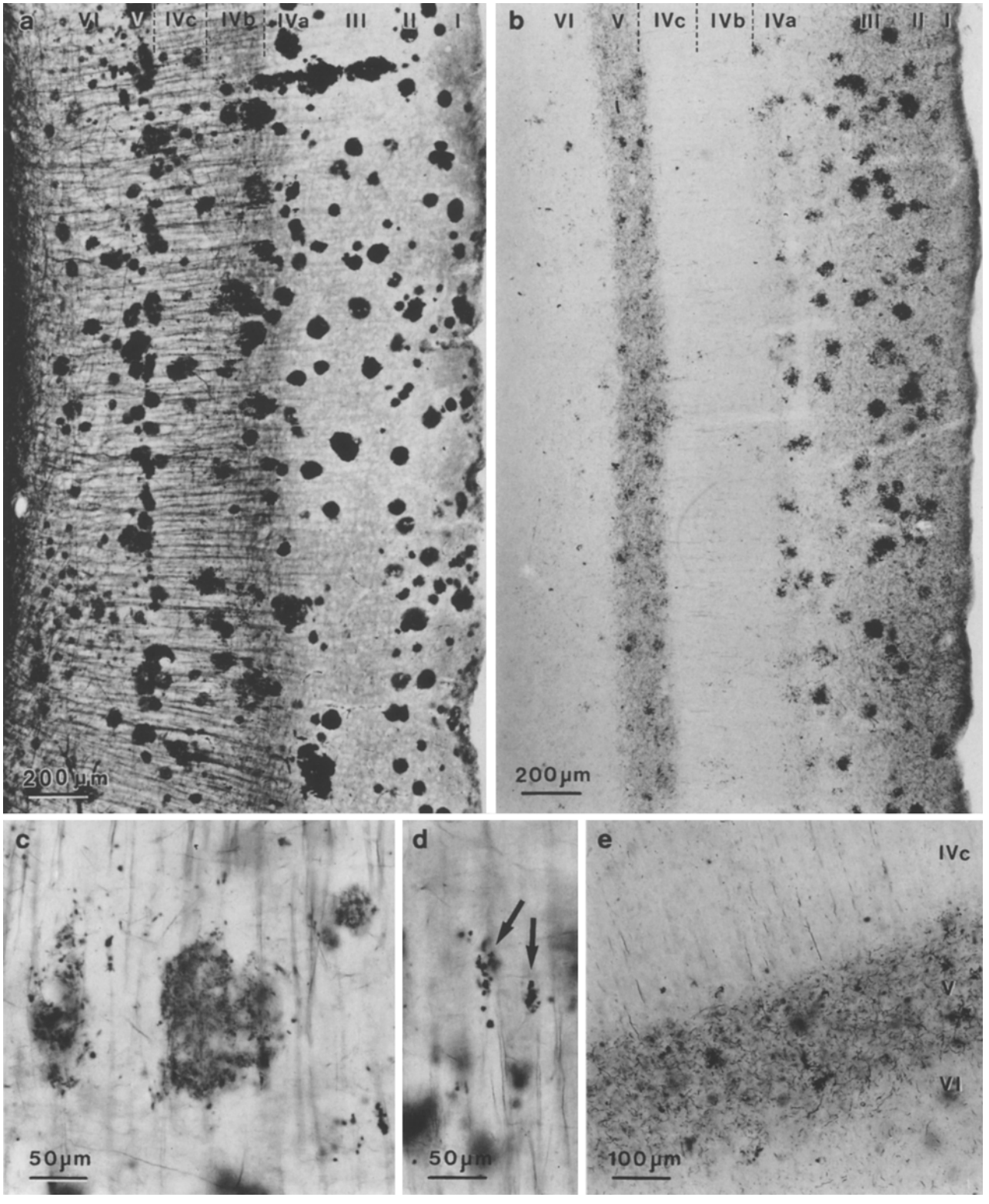

Fig. 2. Striate area. The laminar distribution pattern of amyloid plaques displayed by Campbell preparations (**a**) differs considerably from that of the neurofibrillary changes as seen in Gallyas preparations (**b**). The layers are indicated at the *upper margin*. **c, d** show portions of layer IVc with weakly tinged amyloid plaques (**c**) and intensely argyrophilic spots (**d**, *arrows*). The argyrophilic spots are a hallmark of the striate area and do not occur anywhere else in the isocortex. **e** shows the dense line of neuropil threads indicating the extent of layer V. Note the presence of neuritic plaques sparsely endowed with argyrophilic profiles and the radially aligned neuropil threads in layer IVc. Female, 60-year-old. Alzheimer's disease (case 3), 100-µm-thick sections, Campbell (**a, c, d**), Gallyas (**b, e**)

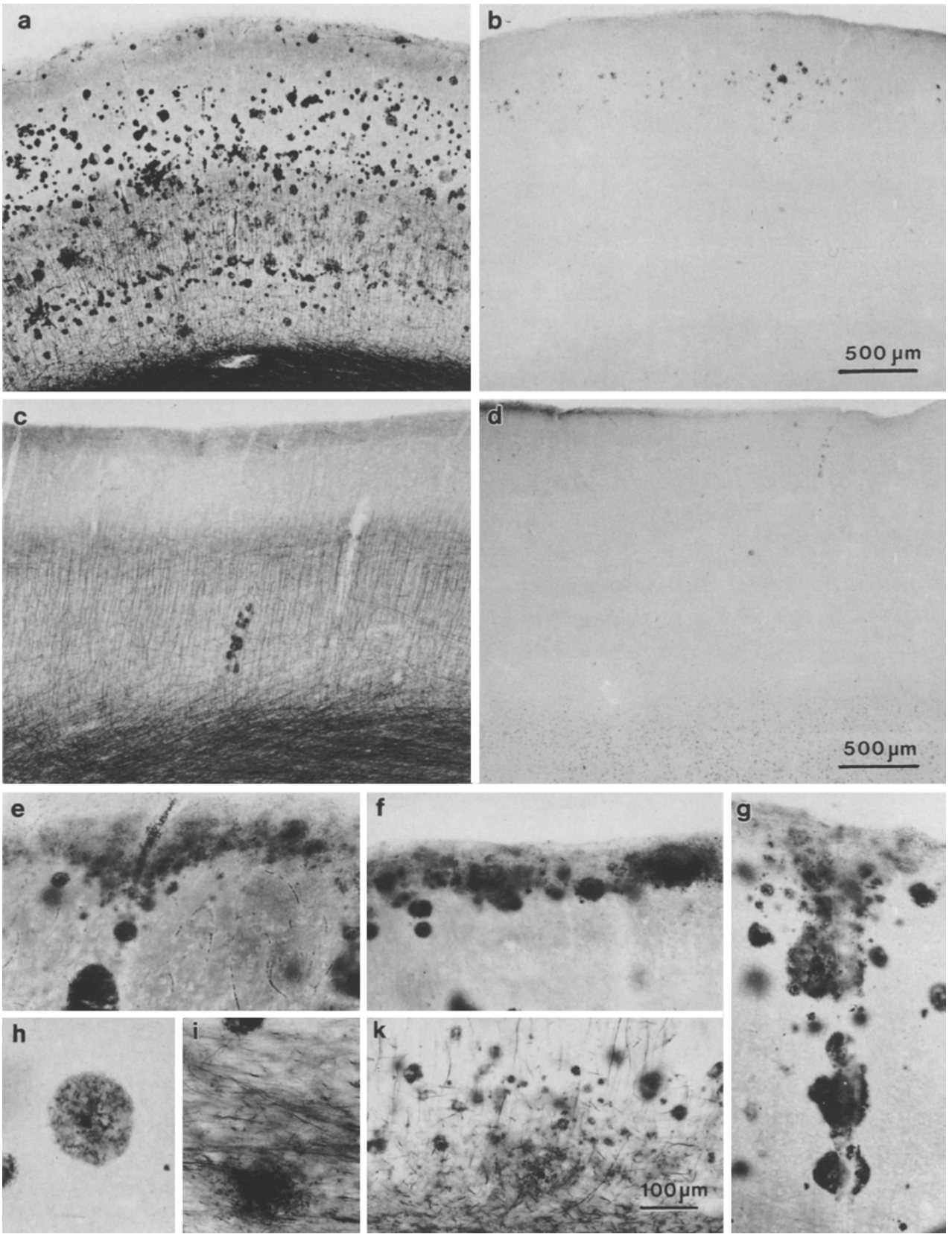

Fig. 3. Striate area. **a** Note the large number of amyloid plaques in characteristics laminar distribution in the striate area of a demented individual (71-year-old man, Alzheimer's disease, case 10). **b** Gallyas preparations in this case reveal an only small number of neuritic plaques in the layers II and III (compare with Fig. 2b). **c, d** The striate area of a non-demented individual (65-year-old female, case 18) is devoid or almost devoid of amyloid deposits (**c**) and neurofibrillary changes (**d**). Note a few amyloid plaques close to an intracortical vessel. **e–g** Amyloid deposits within layer I. **h** Amyloid plaque with a core, layer III. **i** Amyloid plaque as seen in the white matter subjacent the cortical gray matter. **k** Accumulations of weakly stained small amyloid deposits in the layer VI. A similar formation is seen in Fig. 2a close to the *lower left* corner. Sections 100-µm-thick, Campbell (**a, c, e–k**), Gallyas (**b, d**). Scale in **k** is also valid for **e–i**

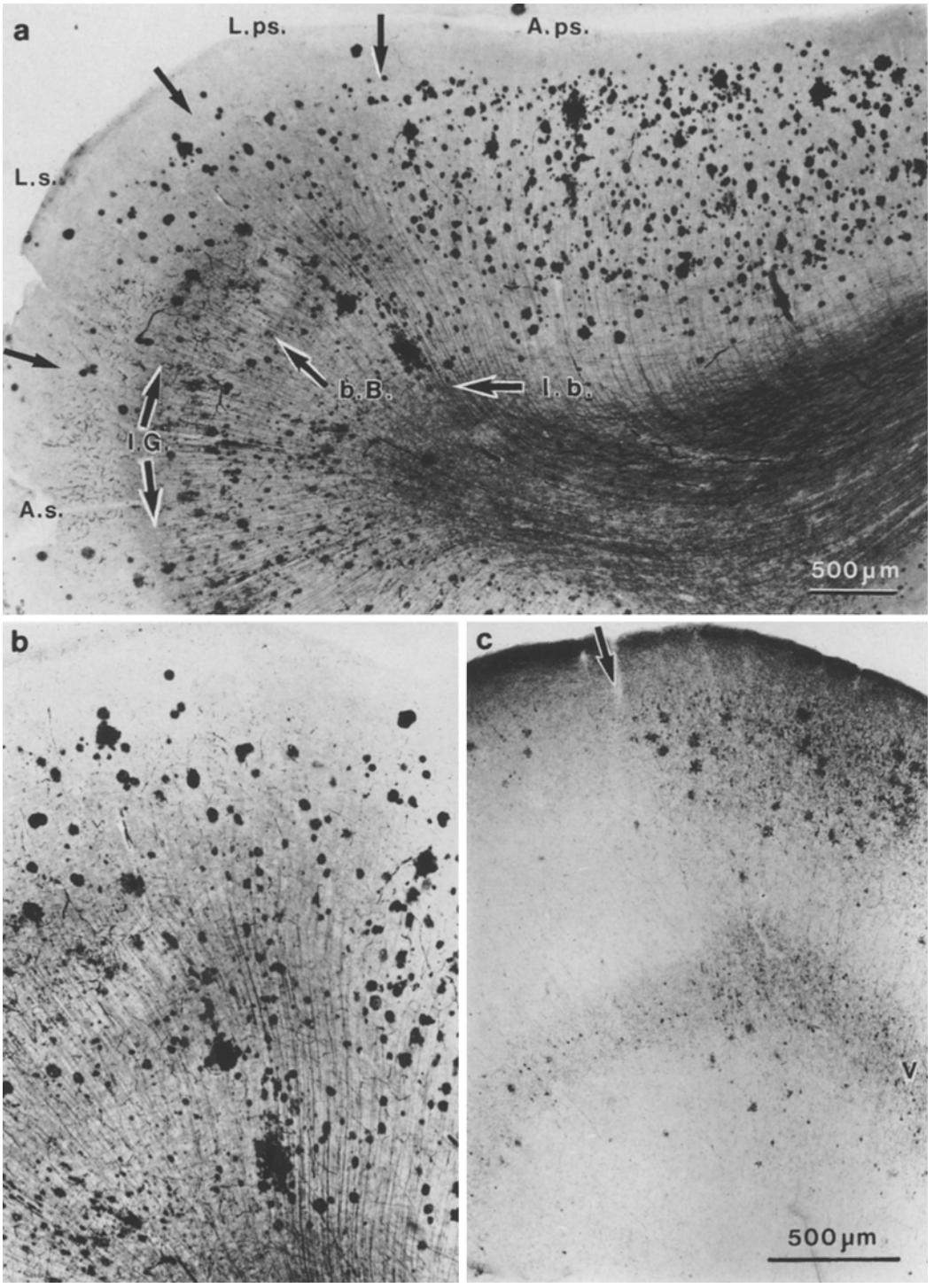

Fig. 4. a Border between the striate area (*A.s.*) and the parastriate area (*A.ps.*). *Arrows* indicate the extent of the two borderfields, limes striatus (*L.s.*) and limes parastriatus (*L.ps.*). The weak axon staining of the Campbell preparations permits recognition of the line of Gennari (*l.G.*), the bridging Baillarger (*b.B.*), and the limiting bundle (*l.b.*). Amyloid is sparsely distributed in the parastriate borderfield. A close-up of **a** is given in **b**. The adjacent section stained for neurofibrillary changes is seen in **c**. Note the sudden increase in the number of neuritic plaques when surpassing the striate/parastriate border (*arrow*). Large tangles in sublayer IIIc do not occur in the parastriate borderfield. Passing the striate/parastriate border layer V abruptly increases in breadth and in the density of tangles and neuropil threads. Female, 69-year-old, Alzheimer's disease (case 6). Sections 100-µm-thick, Campbell (**a, b**), Gallyas (**c**)

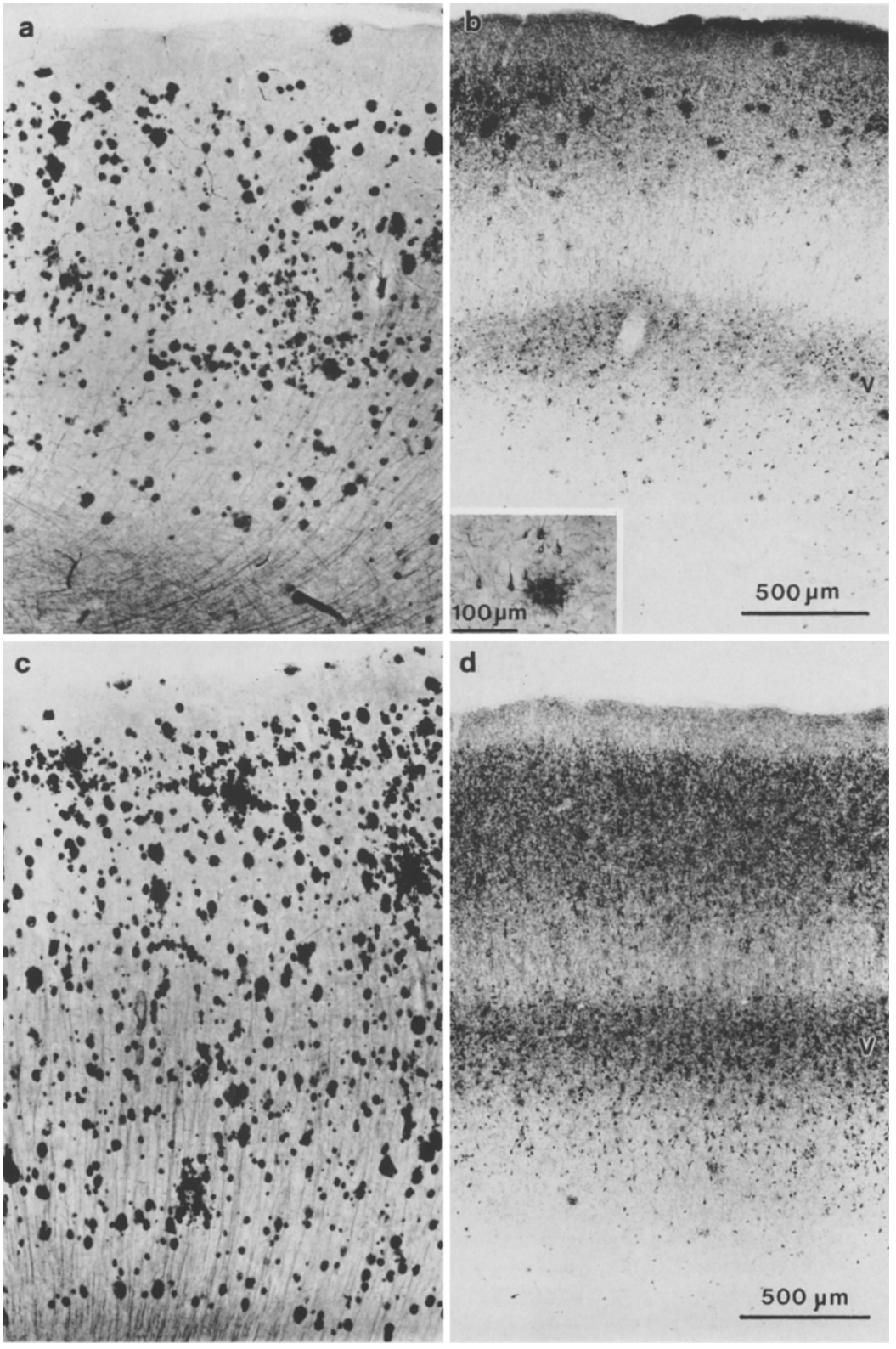

Fig. 5. Parastriate area (**a, b**) as compared to the peristriate region (**c, d**). The amyloid plaques are irregularly distributed in both territories without conspicuous differences in density. The neurofibrillary changes in contrast show area-specific features. The parastriate area is characterized by intensely argyrophilic neuritic plaques in sublayer IIIab. Sublayer IIIc is almost devoid of changes as is layer IV. Layer V contains a sparse population of tangle-bearing pyramidal cells (inset: neuritic plaques, neurofibrillary tangles, and neuropil threads in sublayer IIIab). The peristriate region in comparison is dominated by large numbers of tangles in layers II–III (in particular in layer IIIc) and V. Layer IV is smaller and less pallid than in the parastriate field. Sections 100-µm-thick, Campbell (**a, c**), Gallyas (**b, d**)

The striate area

Amyloid deposits (Campbell preparations). The external glial layer appears as an uninterrupted line devoid of amyloid. The remaining portions of layer I are filled with faintly tinged amyloid plaques gradually increasing in size from top to bottom. The superficially located deposits tend to agglomerate forming plates or clouds of variable size and shape (Fig. 3e, f). A core can only occasionally be encountered within this diffusely deposited material. The spherical plaques close to the border of layer II are usually provided with dense cores (Fig. 3e–g). Layers II and III contain a few intensely stained amyloid plaques (Figs. 2a, 3a, 6) often containing a core (Fig. 3h). Elongated ellipsoidal or pear-shaped plaques may also occur and these are with their long axis oriented perpendicular to the cortical surface. Layers II and III are almost devoid of the small and weakly stained areas encountered in layers I, IVb, IVc and VI. Often, plaques are seen close to vessel walls (Fig. 3g).

The broad layer IV is composed of a cell-dense IVa, a cell-sparse IVb harboring the line of Gennari, and a cell-dense IVc (Fig. 6). The plaques found in sublayer IVa resemble those seen in the layer III; in this respect sublayer IVa appears as a continuation of layer III. A few plaques can be encountered in sublayer IVb. The cell-dense sublayer IVc reveals deposits that do not occur anywhere else in the isocortex. Small and intensely argyrophilic spots clustered together stand out as a hallmark of both the layer and the area (Fig. 2d). Many of them show a ragged outline, while others are surrounded by thin and coiled fibers. Frequently, the spots are slightly elongated and oriented with their long axis perpendicular to the cortical surface. Weakly stained amyloid areas can be found close to the spots (Fig. 2c).

Within the reaches of layer V the usual type of intensely stained spherical plaques reappears, often arranged in a row resembling a string of beads (Fig. 2a). Layer VI shows close to the white substance a rich population of irregularly shaped and weakly tinged amyloid areas that have many features in common with those of the layer I (Fig. 3k). Scattered among them are medium-sized plaques with a dense core. Some core-bearing plaques can also be found in the white matter even at considerable distance to the cortex (Fig. 3i).

Neurofibrillary changes (Gallyas preparations). The external glial layer is devoid of Gallyas-positive material. The remaining portions of layer I are moderately filled with neuropil threads. Layer II harbors many intensely argyrophilic neuritic plaques and most of the neurofibrillary tangles found in the striate cortex. Due to the small size of the pyramidal cells the diameters of the tangles exceed only slightly those of the neuropil threads. In addition to plaques and tangles a dense accumulation of neuropil threads can be discerned (Fig. 2b). The changes seen in the layer III closely resemble those recognized in the layer II. The packing density of the plaques, the tangles, and the threads decreases as the layer is descended (Fig. 2b).

Sublayer IVa is sparsely provided with neuritic plaques and, if present at all, they are poor in argyrophilic profiles. Tangles are almost absent. In spite of all this, the layer can still be recognized on account of a small number of neuropil threads following a horizontal course (Fig. 2b). Sublayers IVb and IVc contain neuritic plaques that are provided with particularly few argyrophilic profiles (Fig. 2b). The solitary cells of Ramon y Cajal [33], the spiny stellate cells, and other neuronal types of IVb and IVc remain devoid of tangles. The hallmarks of both sublayers are radially oriented neuropil threads following a straight course (Fig. 2b, e). The thread density is a step higher in IVc than in IVb (Fig. 6).

The layer V contains neuritic plaques that are hardly recognizable due to the small number of argyrophilic profiles. Only a few tangles are encountered. Meynert cells are devoid of tangles. The hallmark of the layer is a dense network of neuropil threads. This is the reason why layer V appears as a clear-cut dark band in Gallyas preparations (Fig. 2b, e). When crossing the upper border of layer VI, the density of neuropil threads decreases abruptly. Layer VI contains a small number of neuritic plaques and a few scattered tangles. Occasionally, the white substance subjacent the cortex harbors some isolated tangle-bearing multipolar neurons that show long neuropil threads extending widely into the dendrites.

The parastriate area

Anatomical remarks. The parastriate area encompasses the visual core field throughout its entire circumference. The boundary between the core field and the belt area is characterized by the abrupt cessation of the line of Gennari. The inner line of Baillarger extends for a certain distance beyond the border of the parastriate area into striate area ("bridging stripe of Baillarger"). This borderline territory can, therefore, be distinguished from other portions of the striate area (Fig. 4a, Limes striatus). Adjoining parts of the parastriate area are also marked by special features. Unusually large layer IIIc pyramidal cells define the territory (Fig. 4a, Limes parastriatus) which, in addition, shows radially oriented fiber bundles of particular stoutness ("limiting bundles" [3, 4, 6, 36]).

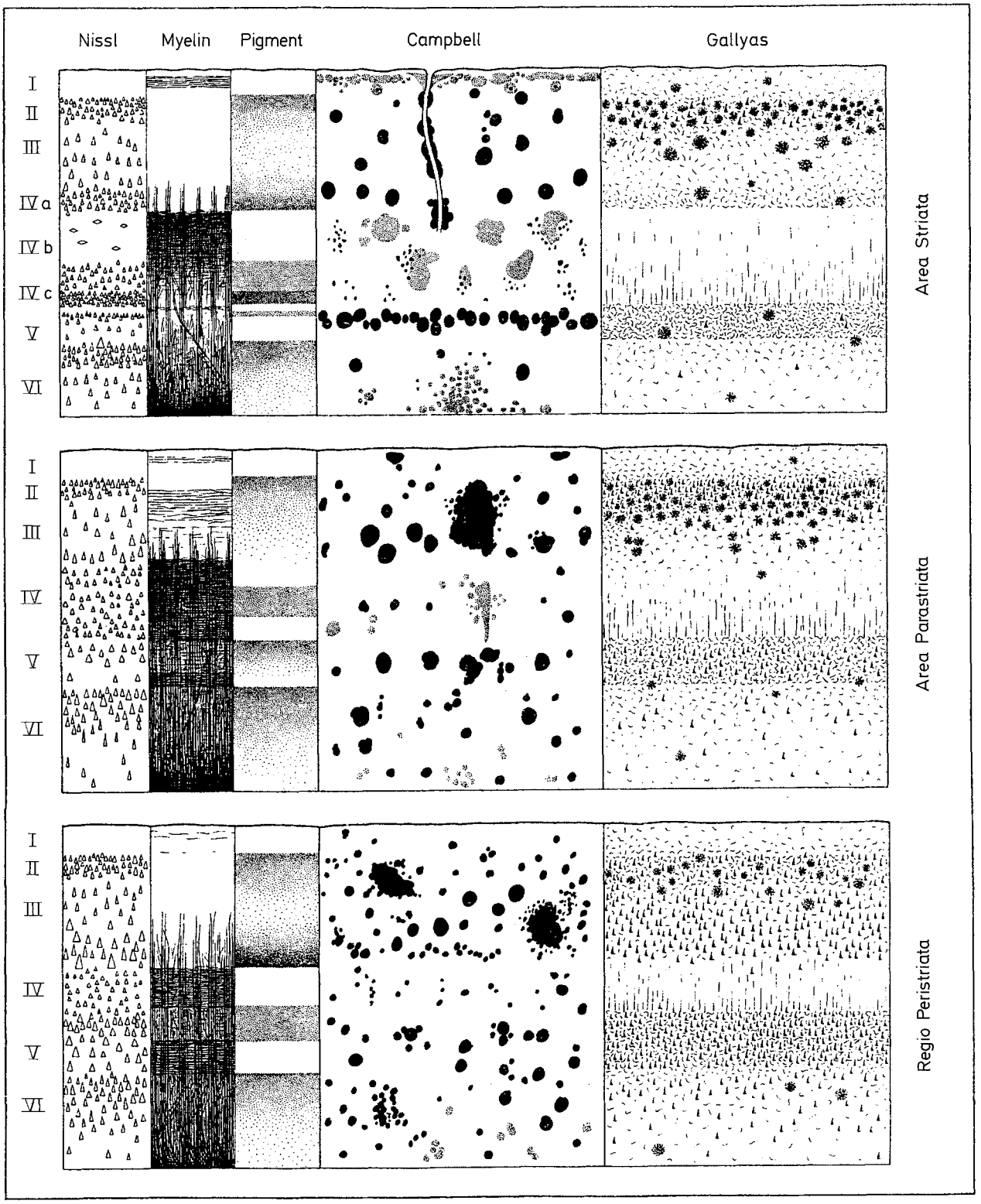

Fig. 6. Schematic lamination pattern of the architectonic units in the human occipital isocortex and the Alzheimer-related pathology as seen in Campbell and Gallyas preparations for demonstration of amyloid (*stippling* indicates weakly stained deposits) and neurofibrillary changes. At *left-hand* border a synopsis of the cyto-, myelo-, and pigmentoarchitectonic scheme is given of the striate area, the parastriate field, and the peristriate region

Amyloid deposits (Campbell preparations). The main characteristics in the laminar pattern of amyloid deposits resemble those recognized in the visual core field. The overall amount is roughly the same as in the striate area. Nevertheless, the plaques appear a step less orderly arranged in the parastriate area (Figs. 4a, b, 5a). Layer I contains a much smaller amount of amyloid. The spherical plaques in layers II and III usually are more intensely stained than those found in the striate cortex. Layers IV–VI harbor weakly tinged and irregularly outlined areas (Figs. 4a, b, 5a).

In general, the amyloid plaques are less densely packed in the parastriate borderfield even though a clear distinction of this subarea is not possible on account of the amyloid characteristics. Many Campbell preparations display a co-staining of normal axons (the myelin sheath remains unstained) and this allows one to draw the boundaries of both the striate and the parastriate borderfield (Fig. 4a, b).

Neurofibrillary changes (Gallyas preparations). The overall amount of Gallyas-positive material deposited in the parastriate area exceeds that found in the visual core field (Fig. 4c). Layers II and III contain numerous neuritic plaques decreasing in packing density as the layers are descended. Tangles are predominantly found in the second, as well as in the upper portions of the third layer. The network of neuropil threads in layer III is almost as thick as in layer II. Layer IV is characterized by radially oriented threads (Figs. 4c, 5b). Within layer V and VI the distribution pattern of the neuritic plaques and neuropil threads resembles that found in the core field even though there is an increase in the number of tangles. Some tangle-bearing white matter neurons can be observed as well.

The parastriate borderfield shows a pathology quite similar to other portions of the belt area (Fig. 4c). The large IIIc pyramidal cells distinguishing the field remain devoid of tangles.

The peristriate region

Anatomical remarks. The peristriate region surrounds the parastriate area and is composed of many fields closely related to each other. There is no considerable variation in pathology between the peristriate areas and, therefore, it appears sufficient to characterize the peristriate cortex as distinguished by a broad pyramidal layer with accentuation of sublayer IIIc and a narrow granular layer. In general, the boundary between the parastriate area and the peristriate region can be drawn using these criteria [5, 6].

Amyloid deposits (Campbell preparations). The overall amount and laminar pattern of the amyloid deposits is much the same as in the belt area. The spherical plaques in layers II and III are a step more densely packed (Fig. 5c). Layers V and VI contain weakly tinged amyloid deposits often in the vicinity of vessels.

Neurofibrillary changes (Gallyas preparations). The amount of Gallyas-positive material seen in the peristriate fields exceeds that found in the parastriate area. A distinguishing characteristic is the occurrence of large numbers of tangles in sublayer IIIc. In many cases it is possible to recognize the border between the parastriate area and the peristriate region due to the abrupt appearance of tangles in sublayer IIIc. The number of neuritic plaques in layers II and III appears to be slightly reduced. The narrow layer IV is more densely filled with radially oriented neuropil threads. Layers V and VI contain a larger number of tangles than in the belt area (Fig. 5d).

Discussion

Two silver impregnation techniques have been used in this study to demonstrate both the extracellular and the intraneuronal components of the pathology.

Amyloid deposits (Campbell preparations)

For the time being, the material delineated in Campbell preparations is considered to be amyloid and/or precursors of amyloid. This assumption is confirmed by the fact that the pathology closely resembles that seen in sections immunostained with an antibody raised against synthetic A4 protein (Fig. 1a–f [28]). Congo-red preparations of the same material appear almost unstained. Nevertheless, closer inspection reveals several congo-red-positive cores. The only subtle shading of the surrounding neuropil may be taken as a clue forshadowing the real extent of the amyloid plaques. Components of the material shown in Campbell preparations may, therefore, be regarded as precursors of the condensed fibrillary amyloid. Electron microscopical investigations are currently undertaken to study the differences between the material of the core and that of the periphery of amyloid plaques.

Most of the amyloid plaques remain devoid of nerve cell processes exhibiting neurofibrillary changes. It is unknown as yet whether and to which extent astrocytes and microglial cells contribute to their formation. Obviously, large numbers of amyloid plaques occur in layers that only occasionally show neuritic plaques (layers IV, V, and VI of the striate area for example, see Figs. 2a, b, 6). Furthermore, amyloid is deposited in layers I and IV, and the white substance subjacent the cortex, locations that usually are devoid of neuritic plaques. Hence, it appears to be inappropri-

ate to consider the amyloid plaques as structures inevitably transforming into neuritic plaques.

In general, amyloid plaques are far more irregularly distributed than neuritic plaques. The neuropil within the boundaries of amyloid plaques appears almost unchanged. Both findings suggest that amyloid plaques represent transient structures probably developed throughout a considerable period of time. Cortex rich in neurofibrillary changes and poor in amyloid has not been encountered. In several cases, in contrast, the cortex was rich in amyloid but poor in neurofibrillary changes suggesting that the deposition of amyloid precedes the development of neurofibrillary changes. It appears tempting to consider the intraneuronal pathology as secondarily induced by long lasting changes in the extracellular environment of the nerve cells.

Neurofibrillary changes (Gallyas preparations)

The pathology seen in Gallyas preparations closely resembles that seen in preparations immunostained with an antibody raised against paired helical filaments (antibody 89c, Fig. 1 g–k). It can, therefore, be considered to correspond to the neurofibrillary changes of the Alzheimer type. The Gallyas technique is far more specific than the classical methods usually applied for this purpose [1, 2, 43, 45]. It is well suited for application to routinely fixed autopsy material and shows the changes with almost no background staining [8, 17]. The pathological material is encountered in neuritic plaques, neurofibrillary tangles, and neuropil threads.

In the material studied most of the neuritic plaques are found in the parastriate area. It appears questionable whether there is a gradual increase in the number of neuritic plaques from the primary field through the belt area into the association cortex [29]. The density of neuritic plaques changes even within the same area and appears to be more related to the configuration of the sulci than to architectonic units. The fact that neuritic plaques are preferentially found in the depth of the sulci has been commented by several authors [20, 37, 42].

Neurofibrillary tangles develop in only a few neuronal types. In the occipital isocortex, tangles have been found in pyramidal cells only; interneurons remain devoid of the change [9]. Hence, we are unable to confirm the findings of Roberts et al. [34], who describe the occurrence of tangles in isocortical non-pyramidal cells. Also, no clustering of tangles [31] has been found. The density of tangles increases as one proceeds from the striate area via the parastriate field into the peristriate region [29]. In the striate area the majority of tangles is localized in layer II, in the parastriate area it is seen in layer III, and in the peristriate region a large proportion of the tangles is found in layer V. This shift into deeper positions has been pointed out [25] as coinciding with the pattern of pyramidal cells, establishing long cortico-cortical connections [22] and this class of pyramidal cells is considered to be particularly prone to develop tangles. In all probability the large layer IIIc pyramidal cells at the parastriate border establish a dense connection between both hemispheres [4]. In spite of this, the cells remain devoid of tangles. It remains an open question to what extent contralaterally projecting cells differ in their inclination to develop tangles from those establishing ipsilateral connections.

Neuropil threads [8, 10, 11, 17, 19] contribute a substantial part to the total amount of the pathological material. In many cortical layers and areas they represent the dominating change. The threads are known to occur within the dendrites of tangle-bearing pyramidal cells [10]. Isocortical non-pyramidal cells and glial cells remain devoid of neuropil threads. The present study shows that threads may even fill a layer without the presence of tangles. The formation of threads may in a number of places precede the development of tangles. Neuropil threads are thus important components of the Alzheimer-related pathology, making efforts to elucidate the conditions responsible for their development and pattern of distribution worthwhile.

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