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Alzheimer Neuropathology and Limbic Circuits

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Neuropathological Changes in Alzheimer's Disease

The cerebral cortex represents the dominating structure of the human brain. It is divided into more or less uniform isocortex (proisocortex and isocortex sensu stricto) and heterogeneous allocortex (allocortex sensu stricto and periallocortex; Braak, 1980; Zilles, 1990). Isocortical fields account for about 95% of the total cortical surface area. Allocortex is small in comparison and comprises among other territories the hippocampal formation and the entorhinal region. Allocortical areas and nuclei of the mamillary body, a number of limbic thalamic nuclei, cingulate cortex, and the presubiculum are strongly interconnected and form limbic circuits that are of significance for maintaining mnemonic functions and establishing emotional aspects of personality (Papez, 1937; Gabriel et al., 1983; Squire and Zola-Morgan, 1988; Damasio and Damasio, 1989; Zola-Morgan et al., 1989; Hyman et al., 1990; Braak and Braak, 1992; Chapter 18 of this volume).

Alzheimer's disease is characterized by personality changes and a rapid decline of intellectual capabilities in a state of clear consciousness (Reisberg et al., 1985). Individuals suffering from this dementia develop a characteristic sequence of brain changes with particularly severe involvement of limbic territories (Hirano and Zimmerman, 1962; Hooper and Vogel, 1976; Brun and Gustafson, 1978; Kemper, 1978; Hyman et al., 1984, 1990; Braak and Braak, 1985, 1991a,c).

Most conspicuous among the changes is the progressive accumulation of fibrous material that normally does not occur in the human central nervous system. Extracellular deposits of amyloid can be distinguished from intraneuronal neurofibrillary changes. For still unknown reasons, the human brain is particularly prone to develop both changes. The deposition of the pathological material commences before initial symptoms can be observed clinically.

Amyloid Deposits

The extracellular deposits of A4-amyloid protein are among the first changes seen in the brains of nondemented and demented individuals of old age. Their predilection is for isocortical association areas but more advanced cases show amyloid deposits in allocortical areas and many subcortical territories as well. Most amyloid deposits do not correspond to and should carefully be distinguished from neuritic plaques. The question as to whether amyloid deposits

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interfere with normal brain functions is still a matter of debate (Castano and Frangione, 1988; Davies et al., 1988; Yamaguchi et al., 1988a,b, 1989; Braak et al., 1989a,b,c; Glenner and Murphy, 1989; Joachim and Selkoe, 1989; Kalus et al., 1989; Ogomori et al., 1989; Tabaton et al., 1989; Braak and Braak, 1990a, 1991c; Gambetti et al., 1990; Ikeda et al., 1990; Masliah et al., 1990).

Neurofibrillary Changes

Intraneuronal neurofibrillary changes are mainly composed of abnormally phosphorylated tau protein (Lee et al., 1991). Neurofibrillary changes occur in three kinds of lesions: neuritic plaques, neurofibrillary tangles, and neuropil threads.

Neuritic plaques are formed of spherical accumulations of nerve cell processes containing the pathological material. They, therefore, can easily be distinguished from diffuse amyloid deposits. Many neuritic plaques harbor, in addition, amyloid deposits. Cortical territories covering the depth of the sulci generally show a larger number of neuritic plaques than those located at the crest of the gyri (Fischer, 1910; Bielschowsky, 1911, Simchowicz, 1911; Grünthal 1930; von Braunmühl, 1957; Wilcock and Esiri, 1982; Gambetti et al., 1983, 1990; Probst et al., 1983, 1987; Tomlinson and Corsellis, 1984; Mann, 1985; Terry, 1985; Price, 1986; Braak et al., 1989b,c; Jellinger, 1989; Braak and Braak, 1992a).

Neurofibrillary tangles develop within the nerve cell soma and some types of tangles extend into the dendrites. The proximal axon, in contrast, remains free of neurofibrillary changes. Initial deposits of tangles are generally found close to the lipofuscin deposits. The amount of pathological material rapidly increases to the point of filling the cell body. Tangle-bearing neurons slowly decompose. After deterioration of the parent cell, the tangle becomes an extraneuronal structure ("ghost tangle") that is engulfed and slowly degraded by astrocytes. Astonishingly few types of human nerve cells are prone to develop tangles. Within proisocortex and isocortex, tangle-bearing neurons all belong to the class of pyramidal cells and, within this class, to only a few types of pyramidal cells. Isocortical interneurons do not form tangles. A similar situation is found in the thalamus, where only projection neurons of a few thalamic nuclei develop neurofibrillary tangles, while local circuit cells of the same nuclei remain devoid of these changes (Braak and Braak, 1991a).

Neuropil threads are another form of neurofibrillary change and resemble to a certain extent argyrophilic processes seen in neuritic plaques. However, in contrast to neuritic plaques they are scattered throughout the neuropil. In isocortex, they frequently occur in dendrites of tangle-bearing pyramidal cells. Interneurons and glial cells remain devoid of threads. Some areas and layers of the cortex, such as layer V of the striate area, exhibit a particularly high density of these changes. Neuropil threads contribute considerably to the total amount of the neurofibrillary changes in the cerebral cortex (Braak et al., 1986, 1989b; Braak and Braak, 1988, 1990a,b,c, 1991a,b,c; Tabaton et al., 1989; Gambetti et al., 1990; Yamaguchi et al., 1990; Perry et al., 1991). Finally, neurofibrillary tangles and neuropil threads show a consistent and highly characteristic area-specific, lamina-specific, and cell-type-specific pattern of distribution with only minor interindividual variations (Braak and Braak, 1991c).

The following review documents the patterns of deposition of amyloid and neurofibrillary changes in major relay stations of the limbic system in Alzheimer's disease. As a prelude to this analysis of each region there is a brief anatomical description of each region and some of its connections. Observations of changes in the brain of early and late stages of the disease are then synthesized into a probable sequence of events. These changes are conceptualized as six stages of a neuropathological process, and each set of changes may account for different aspects of the clinical expression of this dementia.

Hippocampal Formation

The hippocampal formation consists of three architectonic units, namely the fascia dentata hippocampi, Ammon's horn, and subiculum. The parvocellular fascia dentata represents an allocortical coniocortex and is particularly suited to receive afferents from different sources. Ammon's horn and the subiculum, in contrast, are dominated by large pyramidal cells giving rise to efferent projections. The subiculum, in particular, projects to the nuclei of the mamillary body, certain nuclei of the limbic thalamus, and lateral portions of the retrosplenial region (Stephan, 1975; Braak, 1980; Rosene and Van Hoesen, 1987; Amaral and Insausti, 1990; Zilles, 1990).

Amyloid Deposits

The hippocampal formation remains devoid of amyloid during the early stages of Alzheimer's disease. More severely affected brains show modest numbers of amyloid deposits within the pyramidal cell layers of the CA1 sector and the subiculum. There are also two rows of deposits. One is located in the molecular layer of the subiculum and in the upper half of CA1 stratum radiatum. The other row of deposits is located in outer portions of the molecular layer of the fascia dentata. Both rows roughly correspond to the termination fields of the perforant path (Hyman et al., 1988). Sectors CA2 to CA4 contain only a few deposits. There is also some fluffy material close to the free surface of the fascia dentata (Braak and Braak, 1991c).

Neurofibrillary Changes

Initial neurofibrillary changes are seen in the CA1 sector, in particular within its wedge-shaped prosubicular portion superimposing the subiculum. Advanced stages of Alzheimer's disease show large numbers of flame-shaped tangles in CA1. The outer pyramidal cell layer is more heavily involved than the inner one. The stratum oriens, in contrast, remains virtually devoid of tangles. Besides the sparse network of neuropil threads seen throughout the pyramidal cell layers, two bands of neuropil threads occur, one in the outer half of the stratum radiatum, the other within the stratum oriens. Neuritic plaques occur predominantly within the prosubicular portion but are also found in lower density in other sectors. Sector CA2 frequently does not contain neurofibrillary changes, but occasionally it shows an early and severe involvement. Neurofibrillary tangles in CA2 are coarse and have stout extensions into both apical and basal dendrites. They, therefore, can readily be differentiated from slender tangles in CA1 and CA3. During late stages of the disease, a few tangles develop in CA3 pyramidal cells and modified pyramidal cells of CA4. These are confined to the cell body. Large multipolar nerve cells close to and within the plexiform layer of the fascia dentata form tangles with far-reaching extensions into the dendrites. Only severely affected brains show involvement of the granule cells of the fascia dentata. The subiculum is consistently less heavily involved than the CA1 sector. Neurofibrillary tangles in subicular pyramidal cells have long and thin extensions into the apical dendrite and can, therefore, easily be distinguished from the short flame-shaped tangles in CA1. With increasing disease severity, the subiculum develops large numbers of neuropil threads (Braak and Braak, 1991c).

Mamillary Body

Considerable discrepancies exist in the nomenclature for the various mamillary nuclei (Table 21.1; Veazey et al., 1982a; Saper, 1990). The mamillary body is dominated by the voluminous medial mammillary nucleus that contains medium-sized and weakly basophilic nerve cells. The major portion of this nucleus is incompletely separated from a small lateral part by fornix fibers permitting subdivision of a medial and lateral subnu-

TABLE 21.1. Synopsis of nomenclature concerning mamillary nuclei and surrounding nuclear grays

Malone (1910):	Ganglion mediale corporis mamillaris		Intercalated nucleus	Mamilloinfundibular nucleus
Grünthal (1933):	Medial mamillary nucleus	Lateral mamillary nucleus	Intercalated nucleus	Mamilloinfundibular nucleus
LeGros Clark (1936):	Medial mamillary nucleus	Lateral mamillary nucleus	–	Intercalated nucleus
Hartwig and Wahren (1982):	Medial mamillary nucleus	Lateral mamillary nucleus	Intercalated nucleus	Tuberomamillary nucleus
Saper (1990):	Medial mamillary nucleus, medial subnucleus	Medial mamillary nucleus, lateral subnucleus	Lateral mamillary nucleus	Tuberomamillary nucleus

cleus (Saper, 1990). The magnocellular lateral mamillary nucleus is small in comparison to the medial one and is inserted between posterior extensions of the tuberomamillary nucleus and the medial mamillary nucleus. It can easily be distinguished from the latter by its large and intensely basophilic nerve cells. Difficulties arise when trying to differentiate the tuberomamillary from the lateral mamillary nucleus in Nissl preparations. Combined staining for lipofuscin deposits and Nissl substance permits a clear delineation, since the tuberomamillary neurons are laden with lipofuscin deposits while lateral mamillary neurons remain devoid of them (Braak and Braak, 1987, 1992a).

Studies in experimental animals have shown that the parvocellular medial mamillary nucleus projects to the anteroventral (AV) and anteromedial (AM) nuclei of the thalamus and the dorsal tegmental nucleus of Gudden. The magnocellular lateral nucleus sends fibers to the anterodorsal (AD) thalamic nucleus and ventral tegmental nucleus, thereby linking forebrain limbic areas with those of the midbrain (Cowan and Powell, 1954; Cruce, 1975; Veazey et al., 1982b; Hayakawa and Zyo, 1989; Saper, 1990).

Amyloid Deposits and Neurofibrillary Changes

Structural changes of the mamillary nuclei occur late during the course of Alzheimer's disease. Irregularly distributed deposits of amyloid occur in the medial mamillary nucleus. A zone close to the free surface of the brain consistently remains devoid of amyloid deposits. Only a few neurofibrillary tangles and neuropil threads are present within the medial mamillary nucleus. The magnocellular lateral nucleus does not develop neurofibrillary changes. This is in conspicuous contrast to the tuberomamillary nucleus, which is the most severely involved hypothalamic structure (Saper and German, 1987; Braak and Braak, 1991a,d). The tuberomamillary nucleus has many traits in common with the magnocellular nuclei of the basal forebrain. It sends fibers to the cerebral cortex, and this projection is of about the same magnitude as that of the basal forebrain nuclei (Saper, 1990). In concert with this, the severity of neurofibrillary tangle deposits in the tuberomamillary nucleus is comparable to the grade of involvement shown by the magnocellular nuclei of the basal forebrain.

Limbic Thalamus: Anterior, Laterodorsal, Central Medial, and Paraventricular Nuclei and Nucleus Reuniens

The anterior nuclear complex of the human thalamus is dominated by the pear-shaped anteroventral nucleus. Inferomedially, this nucleus blends into the adjoining AM nucleus. Sheets of myelinated fibers surround

the well-defined AD nucleus. The laterodorsal nucleus abuts the posterior extremity of the AV nucleus and can be considered a posterior elongation of the anterior nuclear complex (Hassler, 1959; Jones, 1985; Armstrong, 1986, 1990). All nuclei of the anterior complex and the laterodorsal (LD) nucleus are composed of multipolar projection cells with coarse lipofuscin granules and spindle-shaped local circuit neurons with finely granulated pigment (Braak and Braak, 1984; Braak and Weinel, 1985).

The anterior thalamic nuclei receive input from the subiculum both directly through the fornix and indirectly from the mamillary nuclei through the mamillothalamic tract. The voluminous medial mamillary nucleus projects to the similarly extended AV nucleus, while the small lateral mamillary nucleus sends fibers to the narrow AD nucleus (LeGros Clark, 1936; Armstrong, 1986). The AV nucleus projects back to the subiculum and additionally provides input to the entorhinal region (Amaral and Insausti, 1990). Both the AV and AD nuclei furnish dense projections to the retrosplenial region, which sends numerous fibers back to the AV nucleus but generates only a sparse projection to the AD nucleus (Robertson and Kaitz, 1981; Vogt, 1985; Vogt et al., 1987).

The central medial (CeM) nucleus of the thalamus consists of several subunits. Its superomedial portion has a homogeneous population of pigment-laden nerve cells corresponding to the cucullar nucleus of Hassler (1959). The thalamic paraventricular (Pv) nucleus is interposed between the ependyma and the CeM nucleus and consists of differently pigmented nerve cells. The nucleus reuniens (Re) is located close to the ependymal lining of the third ventricle and contributes to the massa intermedia. Similar to the Pv nucleus, it comprises slender nerve cells with varying lipofuscin pigment characteristics. The Re receives subicular input via the fornix and preferentially projects to layers I and III of the entorhinal region. In addition, the Re projects to CA1, the subiculum, presubiculum, parasubiculum, and the retrosplenial region, thereby forming a short allocorticothalamic circuit (Herkenham, 1978; Amaral and Cowan, 1980; Jones, 1985).

Amyloid Deposits

A fairly large number of amyloid deposits occur in almost all portions of the thalamus. Only a zone subjacent to the ependymal lining remains devoid of this material. Different types of deposits can be distinguished. Diffuse deposits prevail but, within the AV nucleus, quite a number of amyloid deposits with a dense core are also present (Braak and Braak, 1991a).

Neurofibrillary Changes

The thalamus is virtually devoid of neuritic plaques. Neurofibrillary tangles and neuropil threads occur in only a few nuclei of the limbic thalamus. Two types of tangles can be distinguished: compact tangles confined to the cell bodies and star-shaped tangles with extensions into the dendrites. Compact tangles occur in the anterior nuclei and the laterodorsal nucleus, while the star-shaped types are encountered in the cucullar portion of the CeM nucleus and in the Pv and Re, as shown in Figure 21.1. The density of neuropil threads roughly corresponds to that of neurofibrillary tangles.

In general, the AV, AM, and LD nuclei reveal only mild neurofibrillary changes. A slight increase in density of both neurofibrillary tangles and neuropil threads occurs close to the medial border of the nuclear grays. Most deposits in the limbic thalamus occur in the AD nucleus, which is infested with tangles and threads (Fig. 21.1). The neurofibrillary tangles are slightly larger than those found in the AV nucleus. During the course of Alzheimer's disease, the AD nucleus is one of the first subcortical nuclei showing neurofibrillary changes (Braak and Braak, 1991c). The cucullar portion of the CeM and Pv nuclei and the Re follow. In particular, the Re shows a significant number of neurofibrillary tangles and neuropil threads (Fig. 21.1).

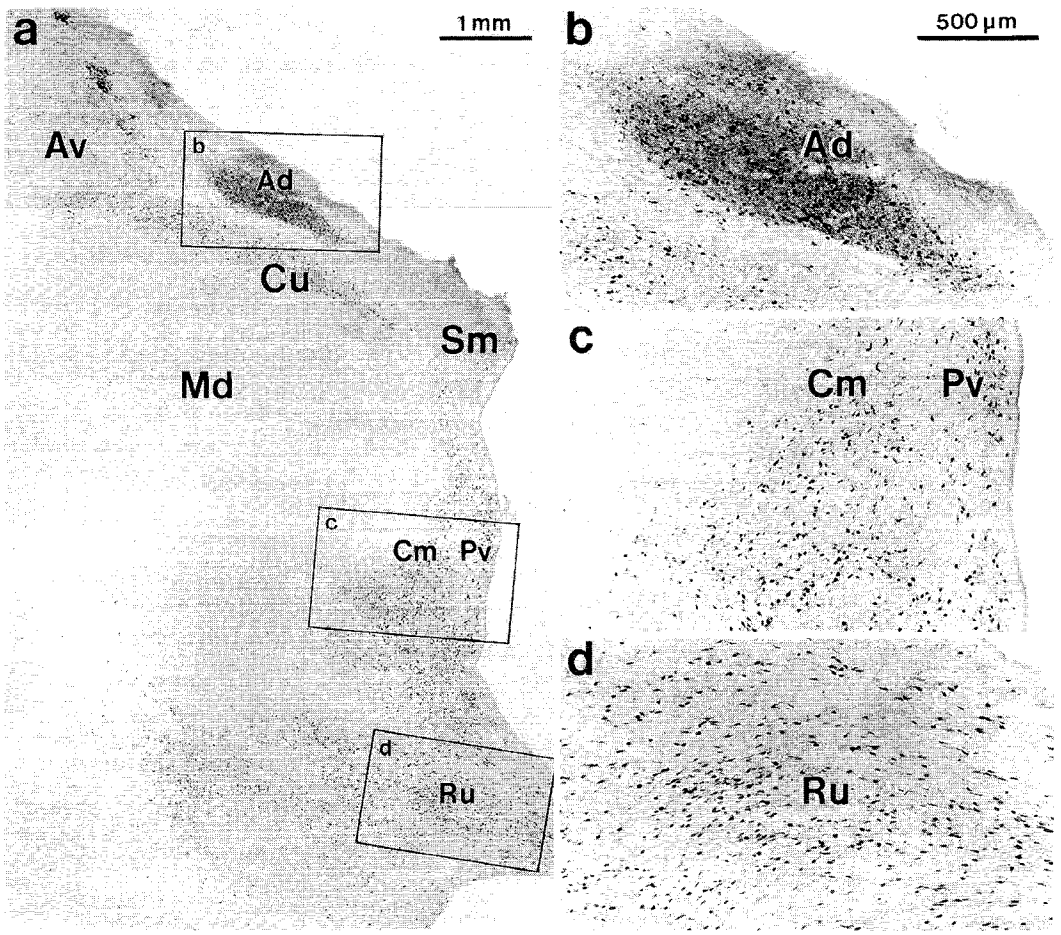
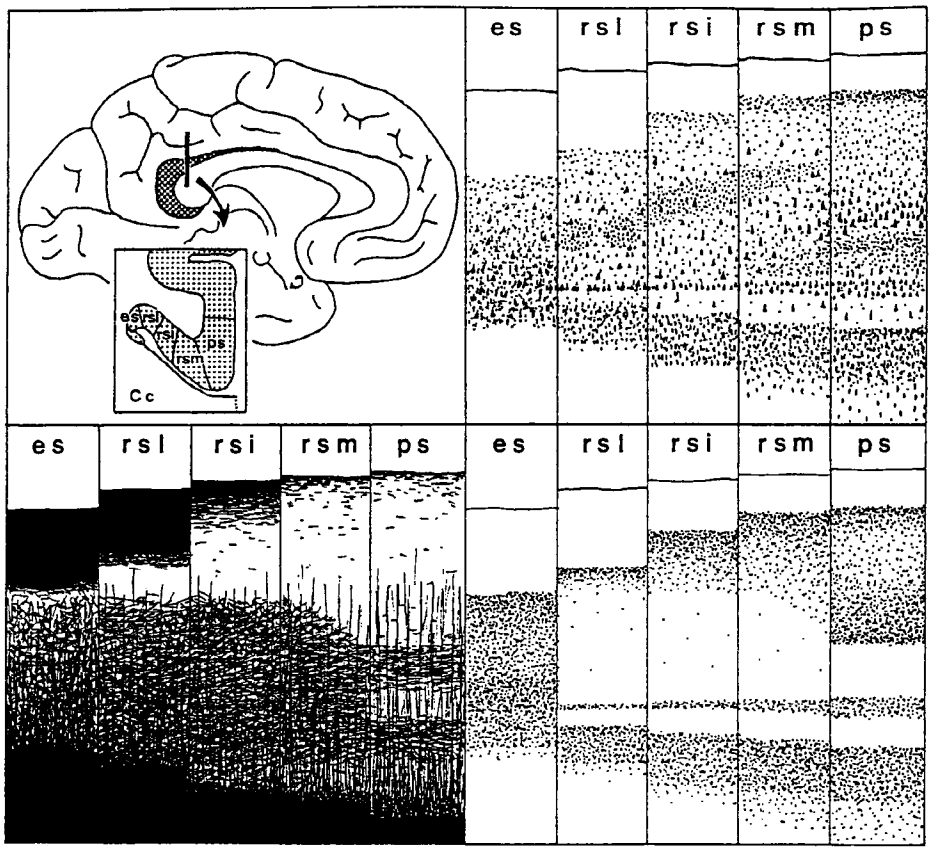


FIGURE 21.1. Distribution pattern of neurofibrillary changes in nuclei of the thalamus. *a*. Frontal, 100 µm thick section through the massa intermedia and displaying medial portions of the thalamus. The anterodorsal (Ad) nucleus bears the brunt of the Alzheimer-related pathology. The cucullar portion (Cu) of the centromedial (Cm) nucleus, the paraventricular (Pv) nucleus, and the nucleus reuniens (Ru) show large numbers of neurofibrillary tangles. Anteroventral (Av) nucleus; mediodorsal (Md) nucleus; stria medullaris, Sm. The position of *b* to *d* is indicated by frames in *a*. The scale bar in *b* applies to *c* and *d*. Silver technique for neurofibrillary changes (Gallyas, 1971). Reprinted with permission of Springer-Verlag from Braak and Braak (1991a).

Supracallosal Allocortex, Retrosplenial Region, and Adjoining Areas

The hippocampal formation gradually diminishes in size as it courses posterior and superior to join the ridge of the corpus callosum (Stephan, 1975). A poorly differentiated ectosplenial area is interposed between the supracallosal hippocampal formation and proisocortical areas forming the crescent-shaped, retrosplenial region. The retrosplenial areas are buried in the depth of the callosal sulcus as discussed in Chapter 1 of this volume. The adjoining parasplenial area is well developed in primates and extends on to the free surface of the cingulate gyrus, as shown in Figure 21.2. It exhibits the typical six-layered isocortical structure (Rose, 1928; Braak, 1979, 1980).

Supracallosal allocortex consists of a band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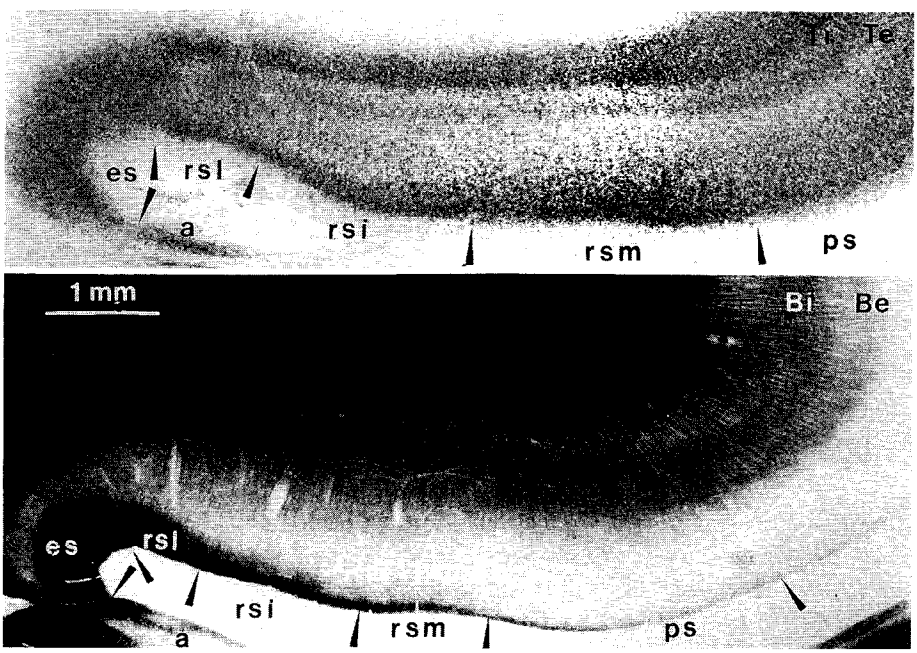
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of nerve cells termed the *indusium griseum* and fibers of the taenia tecta. The large pyramidal cells are oriented in various directions representing remnants of Ammon's horn and the subiculum. Bundles of myelinated fibers accompany supracallosal allocortex and adjoining structures. The molecular layer of cortex in the depths of the callosal sulcus is particularly rich in myelin, which is a characteristic of allocortical fields and adjoining areas. The myelin-rich zone gradually decreases in breadth between the ectosplenial area and the parasplenial field (Fig. 21.2). The ectosplenial area consists of only a single cellular layer and is formed of medium-sized to large-sized pyramidal cells, as shown in Figures 21.2 and 21.3.

Most authors subdivide the retrosplenial region into a granular field adjoining the ectosplenial area and an agranular or dysgranular area adjacent to isocortex (Brodmann, 1909; von Economo and Koskinas, 1925; von Economo, 1926; Rose, 1928, 1935; Stephan, 1975; Armstrong et al., 1986; Vogt, 1976, 1985; Zilles et al., 1986; Vogt et al., 1987; Zilles, 1990). The terms *granular* versus *agranular,* however, suggest extreme differences that do not exist between the two areas. Retrosplenial areas, in contrast, have many traits in common. They all lack a clearly defined layer IV and can, on this account, be characterized as "agranular" or "dysgranular" fields. All retrosplenial areas are parvocellular, richly myelinated, and poorly pigmented. A further trait they have in common is that the breadth of the outer main stratum considerably exceeds that of the inner main one (externocrassior type, Braak, 1980). It is because of these features that the retrosplenial region is similar to sensory core fields of isocortex—in particular, to the primary visual field. The nomenclature used in this text avoids the previously mentioned terms and accentuates the relative uniformity of the retrosplenial areas (Braak and Braak, 1992b). Table 21.2 provides a synopsis of the nomenclature used by different authors for designation of retrosplenial subunits and adjoining areas.

The border between the ectosplenial field and the lateral retrosplenial area is sharp, as shown in Figures 21.2 and 21.3. The breadth of the molecular layer decreases gradually from the lateral border of the retrosplenial region to the medial one. Layers II and III predominate. As in isocortex, layers II and IIIab form a superficial cellular stratum which is, in retrosplenial fields, followed by an uncommon sublayer of small and densely packed cells referred to as the parvocellular sublayer IIIpc. Flat islands of irregular size and shape represent sublayer IIIpc in the lateral retrosplenial field. The islands aggregate to form a continuous plate and by this define the border toward the intermediate field. The plate thins out and has blurred boundaries in the medial area and is lacking in adjoining parasplenial isocortex (Fig. 21.3). Sublayer IIIpc cannot be considered a normal isocortical component, because it does not occur anywhere else in the cerebral cortex. Tiny pyramidal cells almost devoid of lipofuscin deposits predominate in sublayer IIIpc. By this and other features, sublayer IIIpc is similar to sublayer IVc in striate cortex. The deep sublayer IIIc is

FIGURE 21.2. *Upper half:* Diagrammatic representation of the location of the retrosplenial region and parasplenial field. Key features of the various areas as seen in the Nissl (upper right quadrant), myelin, and pigment preparations (lower left and right quadrants).

Lower half: Frontal sections through the retrosplenial region. A pigment preparation (800 μm thick section) and a myelin preparation (100 μm thick section). The borders between the various areas are indicated by arrowheads. Supracallosal allocortex, a; outer and inner line of Baillarger, Be and Bi; corpus callosum, Cc; ectosplenial area, es; parasplenial area, ps; intermediate retrosplenial area, rsi; lateral retrosplenial area, rsl; medial retrosplenial area, rsm; outer and inner taenia, Te and Ti. Reprinted with permission of Springer-Verlag from Braak (1979).

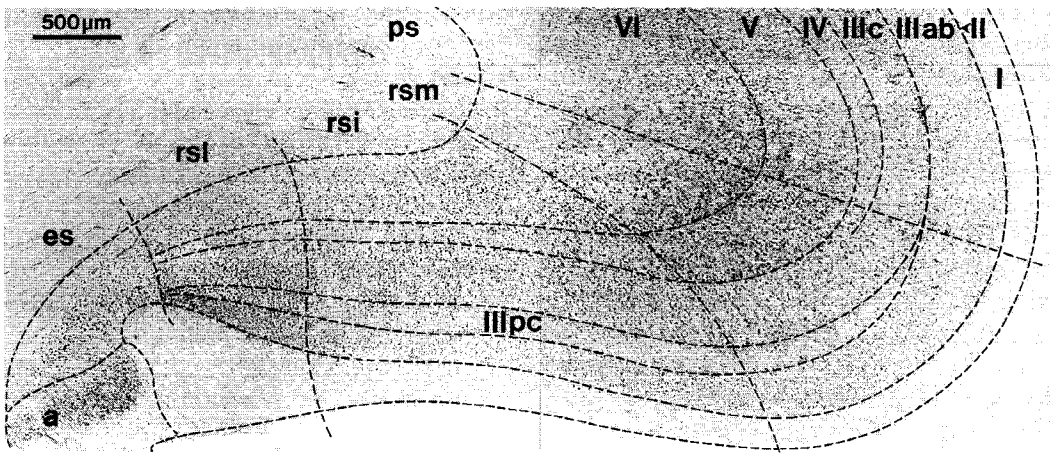


FIGURE 21.3. Retrosplenial region and adjoining areas. Pigment-Nissl preparation that is 100 µm thick. Areal and laminar boundaries are indicated by dashed lines. Supra callosal allocortex, a; Cortical layers, I–VI; ectosplenial area, es; parasplenial area, ps; parvocellular sublayer of layer III, IIIpc; intermediate retrosplenial area, rsi; lateral retrosplenial area, rsl; medial retrosplenial area, rsm. Reprinted with permission of Academic Press Inc. (London) Ltd. from Braak and Braak (1992b).

formed of medium-sized to large-sized, modestly pigmented pyramidal cells. Layer Va is a tenuous and sharply delimited band of pigmented pyramidal neurons (Fig. 21.2). Its breadth gradually increases from the ectosplenial to the parasplenial border. Layer Vb is a cell-sparse strip (Fig. 21.2, inner taenia). Layer VI has clearly defined upper and lower boundaries and increases in breadth from the ectosplenial to the parasplenial fields (Figs. 21.2 and 21.3; Braak and Braak, 1992b).

The retrosplenial region receives dense thalamic input from both the AV and AD nuclei. In primates, the thalamic terminals are located within the outer cellular layers (Vogt, 1985). It is tempting to speculate that in man these terminals preferentially distribute in the parvocellular sublayer IIIpc. In primates, the deep layers, in particular layer VI, project back to the AV thalamic nucleus and to a lesser extent to the AD nucleus. In addition, this region receives visual information from occipital association areas and is bidirectionally interconnected with anterior fields of the cingulate gyrus (Vogt et al., 1979, 1987; Mufson and Pandya, 1984; Vogt, 1985; van Groen and Wyss, 1990b; Zilles, 1990).

Amyloid Deposits

Supracallosal allocortex and the ectosplenial area usually have no more than a few isolated amyloid deposits in Alzheimer's disease; so too the hippocampal formation, which generally has sparse deposits of amyloid (Braak and Braak, 1991c). The pattern also underscores structural differences between ectosplenial cortex and the retrosplenial region, as shown in Figure 21.4.

Retrosplenial proisocortex in Alzheimer's disease is richly endowed with amyloid. Bands of amyloid deposits occur in the molecular layer. Even its densely myelinated portions are partially interspersed with amyloid deposits. A broad band almost devoid of amyloid includes the deep part of layer I and layers II–IIIab. The sublayer IIIpc and sublayer IIIc, in contrast, have tightly packed amyloid deposits of different sizes and shapes, which tend to agglomerate and form irregular plates. This pattern is similar to that found in the parvocellular layer of the presubiculum. The deep layers and the underlying white matter show the usual type of spherical deposits (Fig. 21.4; Braak and Braak, 1992b).

TABLE 21.2. Synopsis of nomenclature concerning the retrosplenial region and surrounding territories

Brodmann (1909):	Ectosplenial (26)	Retrolimbic granular (29)	Retrolimbic agranular (30)	Isocortex (23)
von Economo and Koskinas (1925):		Retrosplenial granular	Retrosplenial agranular	Isocortex
Rose (1928):		Retrosplenial granular medial (RSgα) Retrosplenial granular intermedia (RSgβ) Retrosplenial granular lateral (RSgγ)	Retrosplenial agranular (RSag)	Cingulate isocortex
Braak (1979, 1980):	Ectosplenial	Retrosplenial lateralis Retrosplenial intermedia	Retrosplenial medialis	Parasplenial

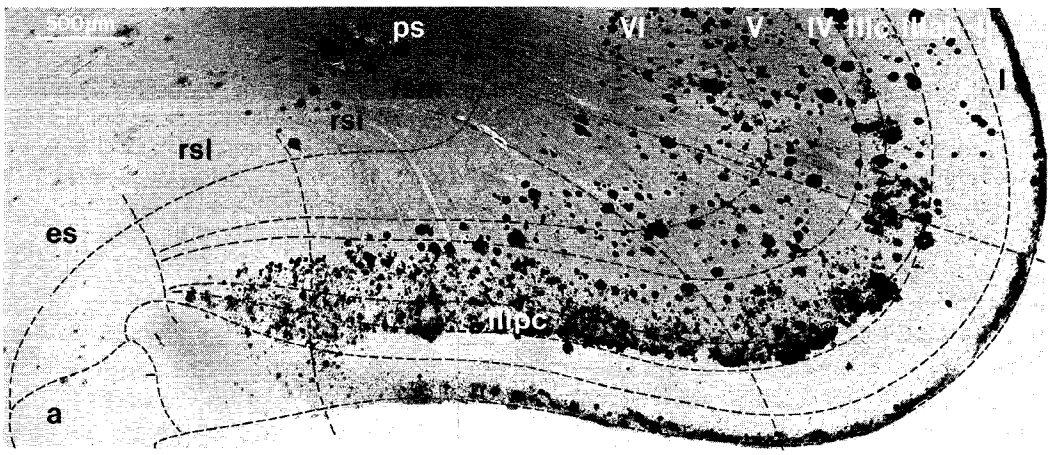


FIGURE 21.4. Retrosplenial region and adjoining areas. Section adjacent to the pigment-Nissl preparation in Figure 21.3 but silver-stained for amyloid deposits (PEG, 100 μm thick, Alzheimer's disease, Campbell et al., 1987). The net of dashed lines corresponds to the lamination pattern in Figure 21.3 and facilitates recognition of areas and layers. Note the presence of tightly agglomerated amyloid deposits in the sublayer IIIpc and in sublayer IIIc of retrosplenial areas. Supracallosal allocortex, a; cortical layers, I–VI; ectosplenial area, es; parasplenial area, ps; lateral retrosplenial area, rsl. Reprinted with permission of Academic Press Inc. (London) Ltd. from Braak and Braak (1992b).

Neurofibrillary Changes

Supracallosal allocortex exhibits numerous flame-shaped neurofibrillary tangles and many neuropil threads. The ectosplenial field contains only a few neuritic plaques, as shown in Figure 21.5. The most prominent feature of the retrosplenial region is its particular capacity to develop neuropil threads. Neuritic plaques are absent or occur in only small numbers close to the parasplenial border. In adjoining isocortex, neuritic plaques become a characteristic component of layers II and III (Fig. 21.5). The molecular layer of retrosplenial areas remains virtually devoid of changes. Few neurofibrillary tangles are found in layers II and III of the lateral and intermediate retrosplenial field and only a modest number of them are encountered in the medial field. The parasplenial area and adjoining cingulate isocortex, in contrast, are richly endowed with tangle-bearing su-

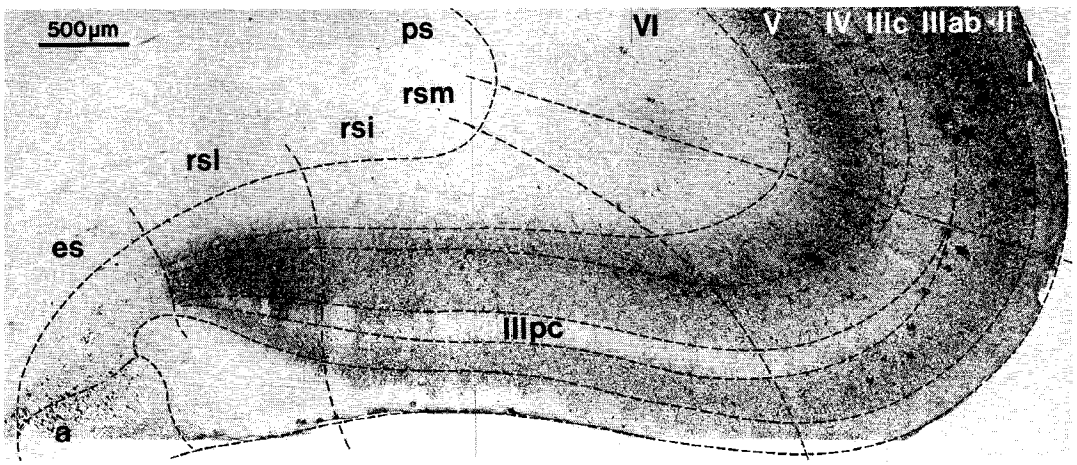


FIGURE 21.5. Retrosplenial region and adjoining areas. Section adjacent to the amyloid preparation in Figure 21.4 but silver-stained for neurofibrillary changes (PEG, 100 µm thick, Alzheimer's disease, Gallyas, 1971). The net of dashed lines corresponds to the lamination pattern in Figures 21.3 and 21.4. Note the virtual absence of neurofibrillary changes in the parvocellular sublayer IIIpc of retrosplenial areas. Supracallosal allocortex, a; cortical layers, I–VI; ectosplenial area, es; parasplenial area, ps; intermediate retrosplenial area, rsi; lateral retrosplenial area, rsl; medial retrosplenial area, rsm. Reprinted with permission of Academic Press Inc. (London) Ltd. from Braak and Braak (1992).

pragranular pyramidal cells. The retrosplenial layers II and III appear as dense feltworks of neuropil threads. This feltwork is interrupted by pallid islands corresponding to the parvocellular sublayer IIIpc, which is almost unaffected (Fig. 21.5). It is of interest to note that sublayer IVc of the striate area similarly does not form neurofibrillary tangles.

Neuropil threads also predominate in the deep layers. In cingulate isocortex, the fifth layer appears as a clear-cut band formed of a mixture of tangles and threads. This band can partially be followed into the retrosplenial region where it gradually decreases in breadth and tangle density. The sixth layer remains virtually unaffected in both cingulate isocortex and the retrosplenial region (Fig. 21.5).

Presubicular Region

The key feature of the human presubicular region is a voluminous parvopyramidal layer. The deep layers vary and represent continuations of adjoining allocortical or isocortical layers. Characteristics of the parvopyramidal layer and the pattern of the deep layers provide for a subdivision of the presubicular region in the presubiculum proper, the parasubiculum, and the transsubiculum. The presubiculum proper is located along the medial border of the subiculum and frequently shows parvopyramidal islands of varying size and shape. The parasubiculum adjoins the entorhinal region. The constituents of the parvopyramidal layer are slightly larger and more loosely packed than those of the presubiculum proper. Posteriorly, isocortical layers form the deep components and thus define the transsubiculum (Braak, 1978, 1980; Kalus et al., 1989).

Studies in experimental animals have shown that the presubicular region is bidirectionally interconnected with the anterior nuclei and the laterodorsal nucleus of the thalamus. In addition, the region receives fibers from the Re. Major efferents from the presubiculum course to the entorhinal region and predominantly terminate in pre-β/pre-γ, while those from the parasubiculum terminate in pre-α (Shipley, 1974; Shipley and Sorensen, 1975; Jones, 1985; van Groen and Wyss, 1990a).

Amyloid Deposits and Neurofibrillary Changes

In Alzheimer's disease, the parvopyramidal layers of both the presubiculum proper and the transsubiculum are filled with amyloid. The lower border of these amyloid islands is sharply delineated. The parasubicular parvopyramidal layer, in contrast, exhibits only a few amyloid deposits. Neuritic plaques are rare in all subdivisions. Neurofibrillary tangles and neuropil threads occur in modest to large numbers in the parvopyramidal layer of both the trans- and parasubiculum, while the parvopyramidal islands of the presubiculum proper are devoid of them. The deep layers contain neurofibrillary changes similar to those of the corresponding subicular, entorhinal, or isocortical layers (Kalus et al., 1989).

Entorhinal Territory

The entorhinal territory, including the entorhinal and transentorhinal regions, spreads over both the gyrus ambiens and anterior portions of the parahippocampal gyrus. Its posterior pole is frequently marked by a narrow sulcus indenting the parahippocampal gyrus. Small wartlike elevations with shallow grooves are encountered on the free surface of the anterior parahippocampal gyrus. These "verrucae hippocampi" indicate the macroscopic position of the entorhinal territory and even render its approximate delineation with the unaided eye possible.

The entorhinal region has a complex lamination pattern. This cortex comprises a broad molecular layer, an outer main stratum (lamina principalis externa = Pre), a cell-sparse zone (lamina dissecans), and an inner main stratum (lamina principalis interna = Pri; Rose, 1928, 1935). Nissl preparations permit easy recognition of only two outer cellular layers, while those counterstained for lipofuscin pigment enable distinction of three laminae (Pre-α, Pre-β, Pre-γ). The inner main stratum is poorly differentiated in Nissl sections, while additional staining for lipofuscin deposits reveals the existence of three laminae (Pri-α, Pri-β, Pri-γ; Braak, 1980; Braak and Braak, 1985). Discrepancies exist concerning the nomenclature of entorhinal layers (Table 21.3). It is important to note that none of the entorhinal layers corresponds to a layer of isocortex. To avoid confusion with isocortical layers, the terms of Rose are used throughout this text. The transentorhinal region is located along the lateral circumference of the entorhinal region and is largely buried in the depth of the rhinal sulcus. This region is between the entorhinal region and temporal isocortex. A characteristic feature is the conspicuous descent of layer Pre-α following an oblique course through the outer cortical layers (Braak, 1980; Braak and Braak, 1985).

Investigations in the primate brain have shown that the entorhinal region receives (via transentorhinal cortex) a dense input from association areas of isocortex, providing it with abundant somatomotor, somatosensory, acoustic, and visual information (Van Hoesen et al., 1972; Van Hoesen and Pandya, 1975; Seltzer and Pandya, 1976; Van Hoesen, 1982; Insausti et al., 1987). The outer cellular layers of the entorhinal region receive afferents from the presubiculum and Re (Pre-β and Pre-γ) and the parasubiculum (Pre-α). A dense projection from the subiculum terminates in the deep layer Pri-α (Sorensen and Shipley, 1979; van Groen et al., 1986). The perforant path arises primarily from layer Pre-α with fibers projecting to the molecular layer of the fascia dentata.

TABLE 21.3. Synopsis of nomenclature concerning entorhinal layers

Rose (1928, 1935):	Mol	Pre-α	Pre-β	Pre-γ	Diss	Pri-α	Pri-β	Pri-γ
Lorente de Nó (1933); Hyman et al. (1984):	I	II		III		IV	V	VI
Amaral and Insausti (1990):	1	2	3		4	5	6	

It is supplemented by fibers from Pre-β and Pre-γ, which terminate in sector CA1 (Steward and Scoville, 1976; Schwartz and Coleman, 1981; Witter et al., 1989).

Amyloid Deposits

The molecular layer and layer Pre-α remain devoid of amyloid in Alzheimer's disease. The deep layers of the outer main stratum (Pre-β and Pre-γ), in contrast, develop many tightly packed amyloid deposits that tend to aggregate. The lamina dissecans is spared, while the deep layers Pri-α and Pri-β show loosely arranged and voluminous deposits. Layer Pri-γ ultimately reveals faintly tinged amyloid strands with blurred boundaries. These tend to merge into each other generating drop like expansions from their tips (Braak and Braak, 1990b).

Neurofibrillary Changes

The projection cells of layer Pre-α are extremely susceptible to the development of neurofibrillary tangles. Those located within the transentorhinal region are among the first neurons in the brain to express this pathology. Cases exhibiting mild neurofibrillary changes consistently show a severe involvement of layer Pre-α in both the transentorhinal and entorhinal region as shown in Figure 21.6 (Braak and Braak, 1985, 1990b,c, 1991c). Eventually, all Pre-α projection cells contain a tangle (Hirano and Zimmerman, 1962; Kemper, 1978; Mann and Esiri, 1989). Additionally, the dendrites of these cells harbor numerous neuropil threads. Layer Pre-α is also the first component of cortex showing the presence of ghost tangles that remain following complete dissolution of the neuronal perikaryon. The next layer to be involved during the course of Alzheimer's disease is the deep layer Pri-α. Comparatively few tangles are encountered in layers Pre-β and Pre-γ, and these usually develop late in the course of the disorder (Braak and Braak, 1991c). The deep layers Pri-β and Pri-γ remain largely exempt from Alzheimer-related changes.

Six Stages in the Neuropathological Progress of Alzheimer's Disease

Amyloid Deposits

Low densities of amyloid deposits are first encountered in isocortex. This includes particularly the basal portions of the frontal, temporal, and occipital lobes. In such mildly affected cases, the hippocampal formation is almost devoid of amyloid, while the parvopyramidal layer of the presubiculum and entorhinal layers Pre-β and Pre-γ disclose typical bandlike deposits. Thereafter, isocortical association areas gradually become filled with amyloid deposits leaving only the primary areas of isocortex spared. In end stages of the disease even primary areas are laden with amyloid deposits. The pattern of amyloid deposition, however, is subject to considerable interindividual variations (Braak and Braak, 1991c). Figure 21.7*b* shows components of the limbic system that, in general, contain large amounts of amyloid in end stages of Alzheimer's disease.

Neurofibrillary Changes

The density of neuritic plaques varies not only within architectonic units but also from one individual to another. In contrast, the pattern of neurofibrillary tangles and neuropil threads exhibits a characteristic sequence of changes that uncovers six stages of the disease with increasing severity (Braak and Braak, 1991c). Stage I is characterized by neurofibrillary tangles and neuropil threads in only the transentorhinal layer Pre-α. Stage II has an additional involvement of the entorhinal layer Pre-α and the first sector of Ammon's horn, its prosubicular portion in particular. The main feature of stages I and II, however, is the pronounced and accentuated transentorhinal involvement (Fig. 21.7*c*). It may be speculated that stages I and II correspond to clinically silent periods of Alzheimer's disease.

Stage III is characterized by severe in-

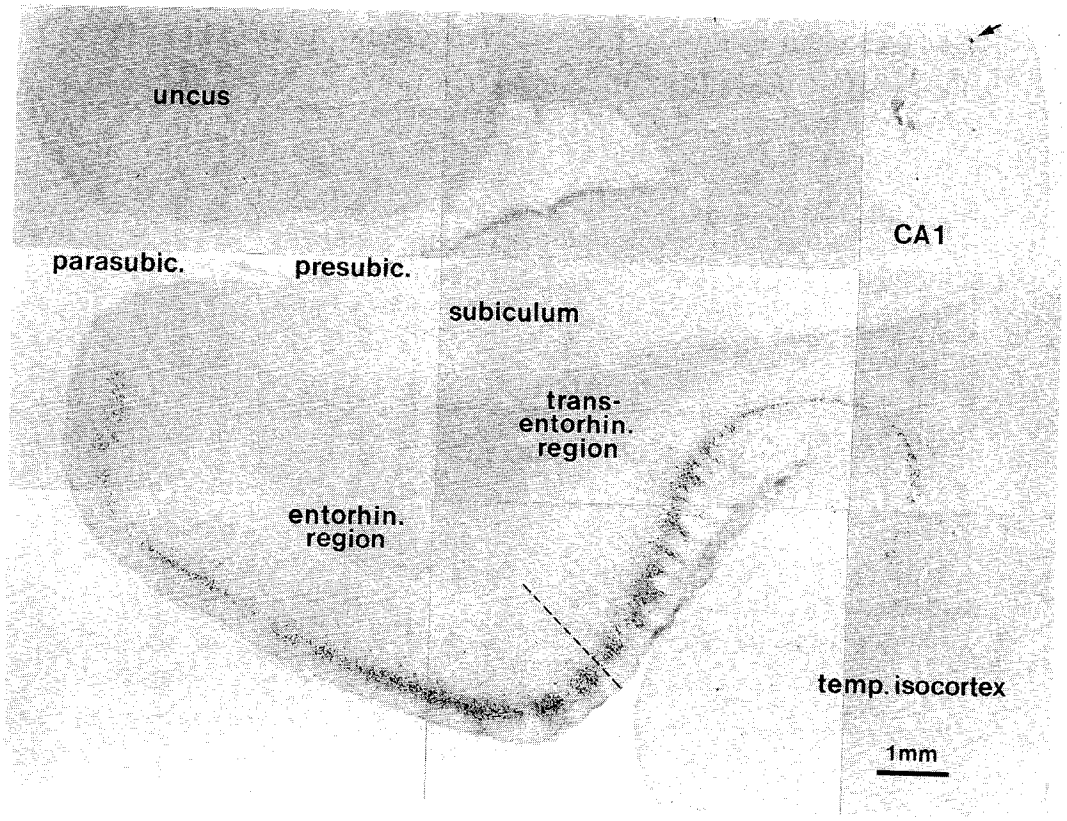
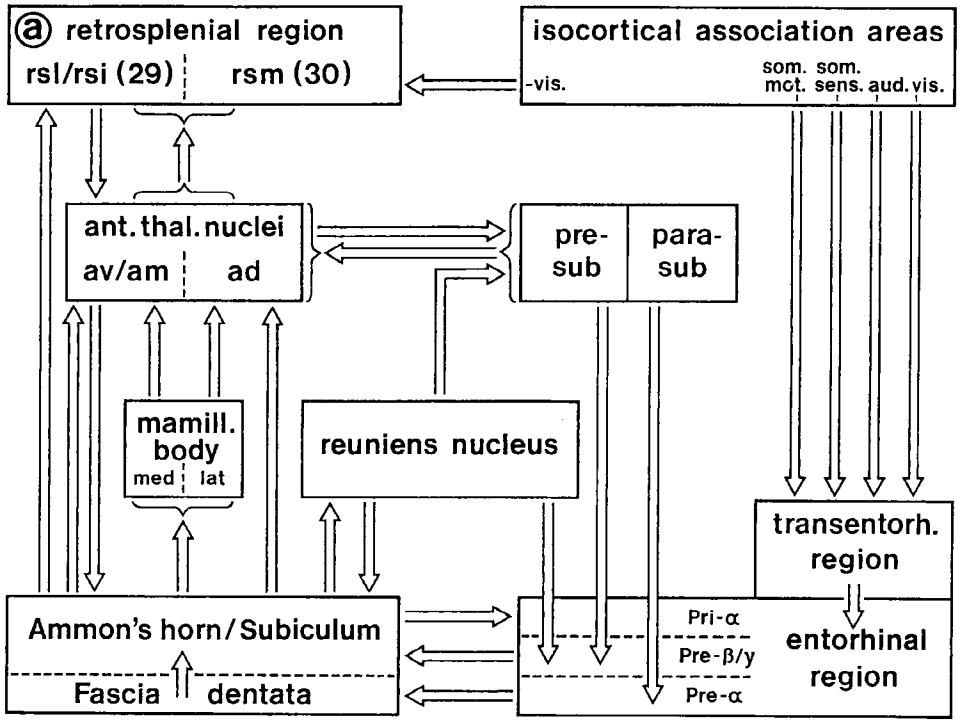
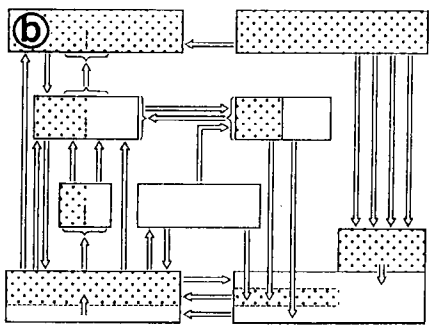


FIGURE 21.6. Frontal section through anterior portions of the parahippocampal gyrus and uncus showing a remarkably high density of neurofibrillary changes in layer Pre-α of both the entorhinal and transentorhinal region. Note the descent of Pre-α in the transentorhinal region. There is only very mild involvement of sector CA1 and temporal isocortex. First sector of the Ammon's horn, CA1; entorhinal, entorhin.; parasubiculum, parasubic.; presubiculum proper, presubic.; temporal, temp.; transentorhinal, transentorhin.; dotted line: border between entorhinal and transentorhinal region (PEG, 100 μm thick, Gallyas, 1971, silver technique for neurofibrillary changes). Reprinted from Braak H, Braak E (1991c).

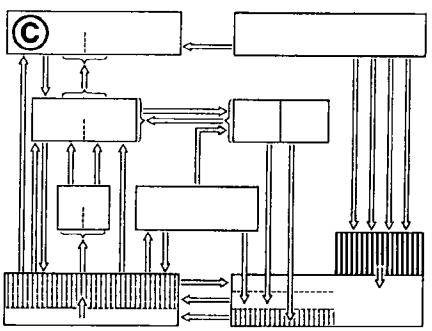
volvement of the transentorhinal and entorhinal layers Pre-α (Fig. 21.6). Ghost tangles first appear at this stage in layer Pre-α. Sector CA1 and the supracallosal allocortex display numerous neurofibrillary tangles. Modest-to-severe changes are encountered in the AD nucleus of the thalamus, the magnocellular nuclei of the basal forebrain, and the hypothalamic tuberomamillary nucleus. At stage IV, the deep entorhinal layer Pri-α, the Re of the thalamus, the retrosplenial region, and extended territories of temporal isocortex adjoining the allocortical core commence to show neurofibrillary changes. The key feature of stages III and IV is the conspicuous destruction of layer Pre-α in addition to severe changes in subcortical limbic nuclei (Fig. 21.7*d*). One may conjecture that these stages correspond to incipient Alzheimer's disease with mild clinical symptoms (Braak and Braak, 1990b,c, 1991c).

Stage V reveals entorhinal layers Pre-α, Pri-α, Pre-β, the first Ammon's horn sector, and the AD nucleus infested with neurofibrillary tangles and neuropil threads. Also, the retrosplenial areas are strongly involved. Severe changes are seen in the thalamic AV nucleus, the Re, and the parasubiculum. The leading feature, however, is the very strong involvement of all isocortical association

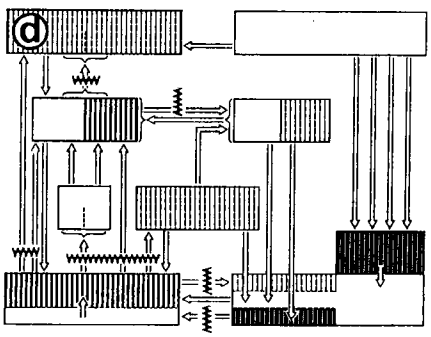




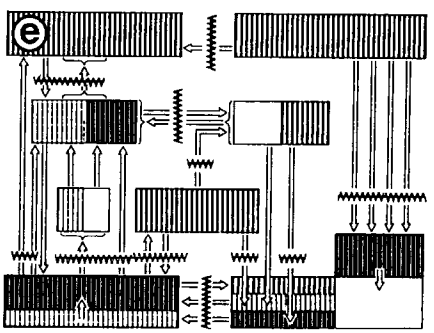
amyloid deposits



neurofibrillary changes: stage II



neurofibrillary changes: stage IV



neurofibrillary changes: stage VI

areas leaving only the primary motor and primary sensory areas uninvolved or mildly involved. At the final stage VI, however, numerous neurofibrillary changes are seen in primary areas as well. This final stage also reveals neurofibrillary tangles in granule cells of the fascia dentata, in large nerve cells of the striatum, and in melanin-containing neurons of the substantia nigra. The common hallmark of stages V and VI is the devastating involvement of isocortex (Fig. 21.7*e*). These stages meet the conventional criteria for neuropathological confirmation of the clinical diagnosis of Alzheimer's disease (i.e., they correlate to fully developed dementia of the Alzheimer type; Khachaturian, 1985).

Functional Consequences of the Morphological Changes

Initially, Alzheimer's disease affects only a small percentage of the total nerve cell number of the human brain. Individuals suffering from this disorder, however, show quite early impairment of cognition and changes in personality. A diffuse loss of small numbers of nerve cells most probably will not severely impair brain functions. The key characteristic of the pathological process underlying incipient Alzheimer's disease is, however, a bilateral and severe destruction of only a few areas, layers, and cell types. Most of the affected structures are tightly interconnected components of the limbic system, as diagrammed in Figure 21.7*a*. The functional significance of limbic circuits is still a matter of debate. Many morphological and clinical findings, however, support the assumption that limbic circuits are important for maintaining cognitive functions (Papez, 1937; Gabriel et al., 1983; Squire and Zola-Morgan, 1988; Zola-Morgan et al., 1989; Hyman et al., 1990; Chapter 18 of this volume).

It is because of the key position of the entorhinal region within the limbic system that bilateral involvement of only layer Pre-α already leads to severe functional disturbances (Fig. 21.6). In particular, the transfer of information from isocortical association areas to the hippocampal formation is likely hampered by this inconspicuous lesion (Figs. 21.7*d,e;* Kemper, 1978; Hyman et al., 1984, 1986, 1990; Braak and Braak, 1985, 1990b,c, 1991c; Van Hoesen and Hyman, 1990; Van Hoesen et al., 1991). The development of additional destruction in the AD nucleus, Re, and parasubiculum leads to disruption of limbic circuits at multiple sites. Circumscribed bilateral lesions of a few constantly affected components of the limbic system most likely contribute to the severe personality changes and early cognitive decline seen in individuals suffering from Alzheimer's disease.

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FIGURE 21.7. *a*. Schematic diagram of limbic relay stations and their connections. Predilection sites for amyloid deposits are displayed in *b* and those for neurofibrillary changes in *c* to *e*. These diagrams also show the spreading of neurofibrillary changes observed in cases with differing severities. Stage II is shown in *c*, that of stage IV in *d*, and that of stage VI in *e* (see Braak and Braak, 1991c). Note that the process leads to disruptions of limbic circuits at multiple sites. Anterior thalamus nuclei, ant. thal. nuclei, anterodorsal, ad, anteromedial, am, anteroventral, av; auditory, aud; parasubiculum, parasub.; presubiculum, presub.; intermediate retrosplenial area, rsi; lateral retrosplenial area, rsl; medial retrosplenial area, rsm; somatosensory, som. sens.; somatomotor, som. mot; transentorhinal, transentorh.; visual, vis.

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