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Pattern of brain destruction in Parkinson's and Alzheimer's diseases

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Summary. Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common age-related degenerative disorders of the human brain. Both diseases involve multiple neuronal systems and are the consequences of cytoskeletal abnormalities which gradually develop in only a small number of neuronal types. In AD, susceptible neurons produce neurofibrillary tangles (NFTs) and neuropil threads (NTs), while in PD, they develop Lewy bodies (LBs) and Lewy neurites (LNs). The specific lesional pattern of both illnesses accrues slowly over time and remains remarkably consistent across cases.

In AD, six developmental stages can be distinguished on account of the predictable manner in which the neurofibrillary changes spread across the cerebral cortex. The pathologic process commences in the transentorhinal region (clinically silent stages I and II), then proceeds into adjoining cortical and subcortical components of the limbic system (stages III and IV – incipient AD), and eventually extends into association areas of the neocortex (stages V and VI – fully developed AD).

During the course of PD, important components of the limbic system undergo specific lesions as well. The predilection sites include the entorhinal region, the CA2-sector of the hippocampal formation, the limbic nuclei of the thalamus, anterior cingulate areas, agranular insular cortex (layer VI), and – within the amygdala – the accessory cortical nucleus, the ventromedial divisions both of the basal and accessory basal nuclei, and the central nucleus. The amygdala not only generates important projections to the prefrontal association areas but also exerts influence upon all non-thalamic nuclei which in a non-specific manner project upon the cerebral cortex and upon the nuclei regulating endocrine and autonomic functions. All these amygdala-dependent structures themselves exhibit severe PD-specific lesions. In general, the extranigral destructions are in themselves not sufficient to produce overt

intellectual deterioration. Similarly, AD-related pathology up to stage III may be asymptomatic as well. Fully developed PD with concurring incipient AD, however, is likely to cause impaired cognition. Presently available data support the view that the occurrence of additional lesions in the form of AD stage III (or more) destruction is the most common cause of intellectual decline in PD.

Keywords: Alzheimer's disease, Parkinson's disease, limbic system, neurofibrillary changes, Lewy bodies, Lewy neurite.

Introduction

The two most common degenerative diseases of the ageing human brain, Alzheimer's disease (AD) and Parkinson's disease (PD), differ not only in their clinical symptoms, but also in the pathologic brain changes they cause. On closer inspection, however, it becomes obvious that the two disorders also share many features.

Both diseases are primarily disorders of the cytoskeleton of a few ageing nerve cell types. In AD, the cytoskeletal changes mainly consist of neurofibrillary tangles (NFTs) and neuropil threads (NTs), while in PD, they are comprised of Lewy bodies (LBs) and Lewy neurites (LNs) [for material and methods used for this review, see Braak and Braak (1991b), Braak E et al. (1994), Braak et al. (1994)]. Nerve cells containing NFTs/NTs or LBs/LNs eventually die, for reasons yet undiscovered. It is likewise unknown whether all of the neuronal loss occurring during the course of AD or PD is a result of the development of these specific cytoskeletal abnormalities. However, it is likely that NFTs/NTs or LBs/LNs play an important role in the pathogenesis of the two disorders (Lewy, 1923; Calne, 1983; Forno, 1986; Galloway et al., 1988; Gibb and Lees, 1988, 1989, 1991; Bancher et al., 1989; Gibb, 1989; Jellinger, 1989, 1991, 1994; Braak and Braak, 1991b, 1994; Gibb et al., 1991; Goedert 1993; Braak E et al., 1994; Braak et al., 1994, 1995; Fearnley and Lees, 1994; Iqbal et al., 1994; Lowe, 1994).

Both disorders involve more than a single neuronal system. Specific lesional patterns develop gradually during the course of the diseases. Many neuronal types, cortical areas, and subcortical nuclei remain unscathed, while others exhibit destruction. Probably, none of the subtle changes of a given area or nucleus seen in the initial phases of these illnesses is sufficient in itself to account for the appearance of the first clinical symptoms. Many of the involved nuclei and areas are tightly interconnected components of the limbic system. The inconspicuous but systematically distributed, bilateral lesions accumulate, until eventually clinical symptoms appear. The pathologic process underlying AD preferentially destroys "afferent" cortical structures such as the entorhinal region and the neocortical association areas. In PD, in contrast, the "efferent" subcortical structures such as the amygdala and the substantia nigra are the main targets of destruction.

Parkinson's disease

Most obvious in PD is the loss of specific subsets of melanin-laden projection cells of the substantia nigra (Mann, 1984; Braak and Braak, 1986; Hirsch et al.,

1988; Pearson et al., 1990; Gibb and Lees, 1991; Paulus and Jellinger, 1991; van Domburg and ten Donkelaar, 1991). However, characterizing PD as a loss of nigral dopaminergic neurons overemphasizes a single feature among the many facets of the disorder. Many dopaminergic neurons of the substantia nigra, the mesencephalic central gray, and the hypothalamus consistently escape destruction (Matzuk and Saper, 1985; Hirsch et al., 1988; Agid et al., 1993), while numerous non-dopaminergic neuronal types display severe changes. It is inaccurate to view PD as a disorder predominantly involving dopaminergic or neuromelanin-laden nerve cells. The pathologic process underlying PD affects many neuronal types, and locally, both the nigral and the extranigral changes may attain high densities (Jellinger, 1991; Braak et al., 1994, 1995).

Alzheimer's disease

AD is predominantly a disease of the cerebral cortex but involves a specific set of subcortical nuclei as well (Kemper, 1978; Hyman et al., 1984, 1990; van Hoesen and Hyman, 1990; Braak and Braak, 1985, 1992b, 1993a, 1994; Arnold et al., 1991; Price et al., 1991; van Hoesen et al., 1991). The magnocellular nuclei of the basal forebrain show particularly early and severe destruction. However, portraying AD as a loss of cholinergic basal forebrain neurons is inaccurate. The complex pattern of AD lesions develops gradually and more or less symmetrically in both hemispheres (Moossy et al., 1988). This predictable sequence of changes provides the basis for distinguishing six stages in the development of the neurofibrillary changes (Braak and Braak, 1991b). The pathologic process initially destroys a few projection cells in the transentorhinal region (clinically silent transentorhinal stages I and II), then proceeds into adjoining cortical and subcortical components of the limbic system (limbic stages III and IV), and eventually extends into the neocortex (neocortical stages V and VI). Stages III and IV are considered to represent incipient AD, while stages V and VI correspond to fully developed AD (Jellinger et al., 1991; Bancher et al., 1993; Braak et al., 1993; Braak and Braak, 1994).

Anatomical considerations and lesional pattern in Parkinson's and Alzheimer's diseases

Neocortex and limbic loop

The lesional patterns of PD and AD can be better understood if the main components of the limbic system are briefly described. The cerebral cortex is the chief controlling entity of the human nervous system. Most brain functions that distinguish man from other mammals depend on the complete maturation and the structural integrity of the cerebral cortex. Two fundamentally different types of gray matter – neocortex and allocortex – can be distinguished (Braak, 1980; Zilles, 1990). The more or less uniformly built neocortex (proneocortex and mature neocortex) predominates. The heterogeneously composed allocortex (periallocortex and allocortex) is small in comparison, and is located mainly in the anteromedial portions of the tempo-

ral lobe. It includes the hippocampal formation, the presubicular region, and the transentorhinal/entorhinal region. Closely related is the subcortical nuclear complex of the amygdala.

The parietal, occipital, and temporal neocortex is each comprised of a core field, a belt region, and extensive association areas (Braak, 1980). Somato-sensory, visual, and auditory data proceed through core and belt regions to a variety of association areas, and are then transported via long cortico-cortical projections to the frontal association fields (prefrontal cortex). From there, the information is transferred to the frontal core (primary motor field) via the

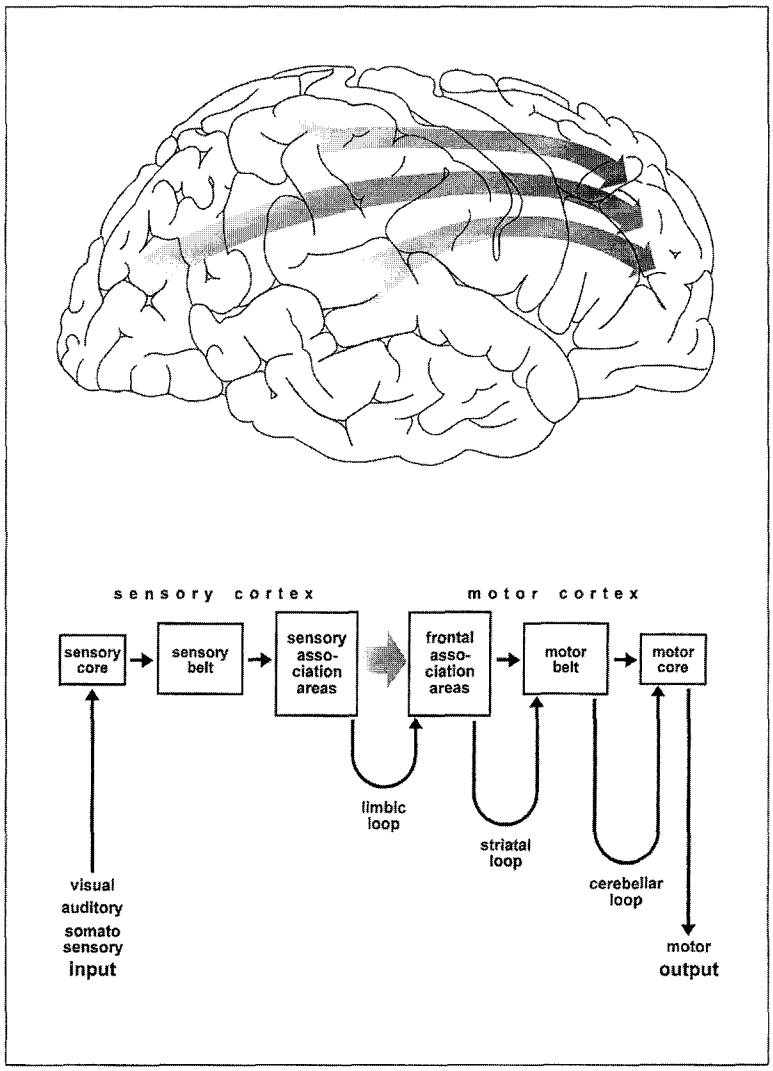

Fig. 1. Somato-sensory, visual, and auditory information proceeds through the respective core and belt fields of the neocortex to a variety of association areas. The data is transmitted to the prefrontal association areas via long cortico-cortical pathways. Tracts generated from this highest organisational level of the brain guide the data back via the frontal belt areas to the frontal core, the primary motor area. The striatal and cerebellar loops provide the major routes for this transport from the prefrontal cortex to the primary motor field (with permission from Braak et al., 1996)

frontal belt (premotor areas). The striatal and cerebellar loops provide the major routes for this transport to the primary motor field (Fig. 1). Major portions of the basal ganglia, many nuclei of the lower brain stem, and the cerebellum participate in the regulation of frontal output through these loops (Alexander et al., 1990; Alheid et al., 1990; Braak and Braak, 1993b).

Part of the main stream of data from the sensory association areas to the prefrontal cortex branches off and converges upon periallocortex, allocortex, and amygdala, i.e. the highest organisational level of the limbic system (Fig. 2)

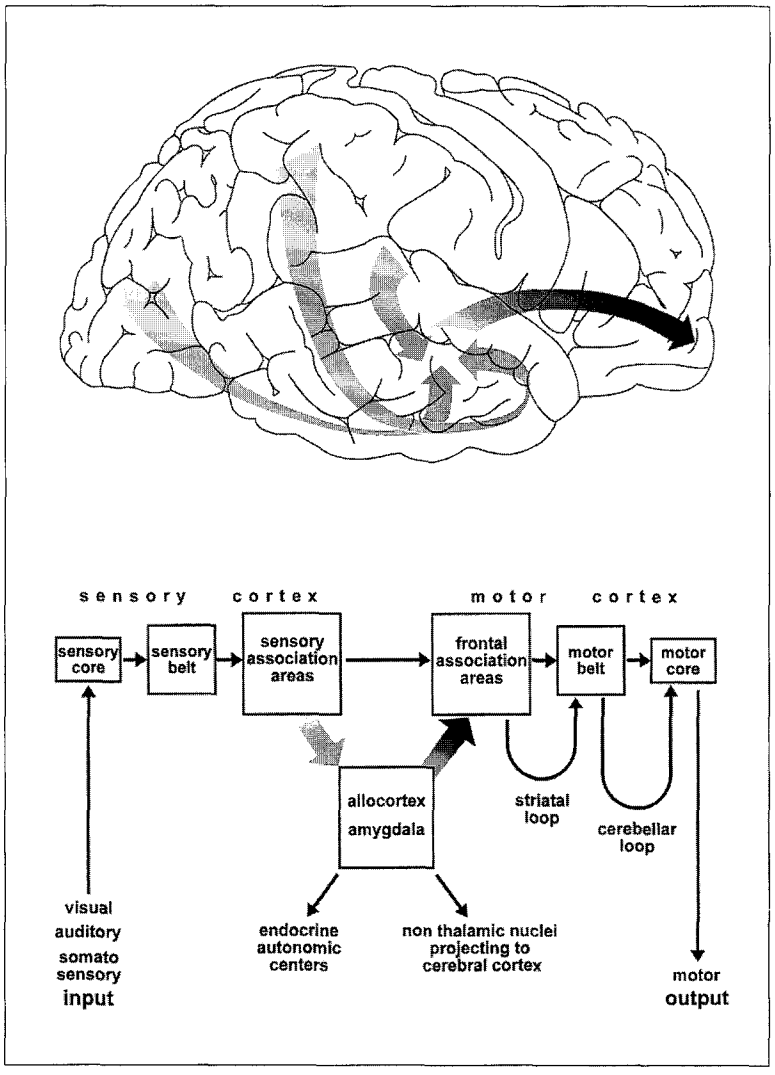

Fig. 2. Part of this stream of data from the sensory association areas to the prefrontal cortex branches off, to eventually converge upon the entorhinal region and the amygdala. These connections establish the afferent leg of the limbic loop. In the human brain, the stream of neocortical information thus provides the most important input to the limbic system. Projections from the entorhinal region, the amygdala, and the hippocampal formation contribute to the efferent leg of the limbic loop, which reaches the prefrontal cortex. The limbic system thus exerts important influence upon the prefrontal cortex (with permission from Braak et al., 1996)

(Felleman and van Essen, 1991). The transentorhinal region and the lateral nucleus of the amygdala serve as major gates of entrance for this highly processed neocortical information (Amaral, 1987), which is then distributed to a variety of related limbic structures via connections with the hippocampal formation (Fig. 3).

Projections from the hippocampal formation, the entorhinal region, and both the basal and accessory basal nuclei of the amygdala form the efferent leg of the limbic loop (Nauta, 1979, 1986; Heimer et al., 1982, 1991), which heads toward the prefrontal cortex (Figs. 1–3). Part of the hippocampal, entorhinal, and amygdalar efferents terminate in the ventral striatum ["limbic" subdivisions of the putamen and the accumbens nucleus; Heimer et al. (1982, 1991), Alheid et al. (1990)]. This input is supplemented by projections originating from the midline nuclei of the thalamus (Fig. 3). The data is then transferred via ventral pallidum and the magnocellular portion of the mediodorsal thalamic nucleus to the prefrontal cortex, particularly its medial and orbitofrontal portions (Pandya and Yeterian, 1985, 1990; Goldman-Rakic and Porrino, 1985; Goldman-Rakic, 1987; Markowitsch, 1982, 1995). The amygdala generates supplementary projections to the magnocellular portion of the mediodorsal thalamic nucleus and the mediofrontal and orbitofrontal

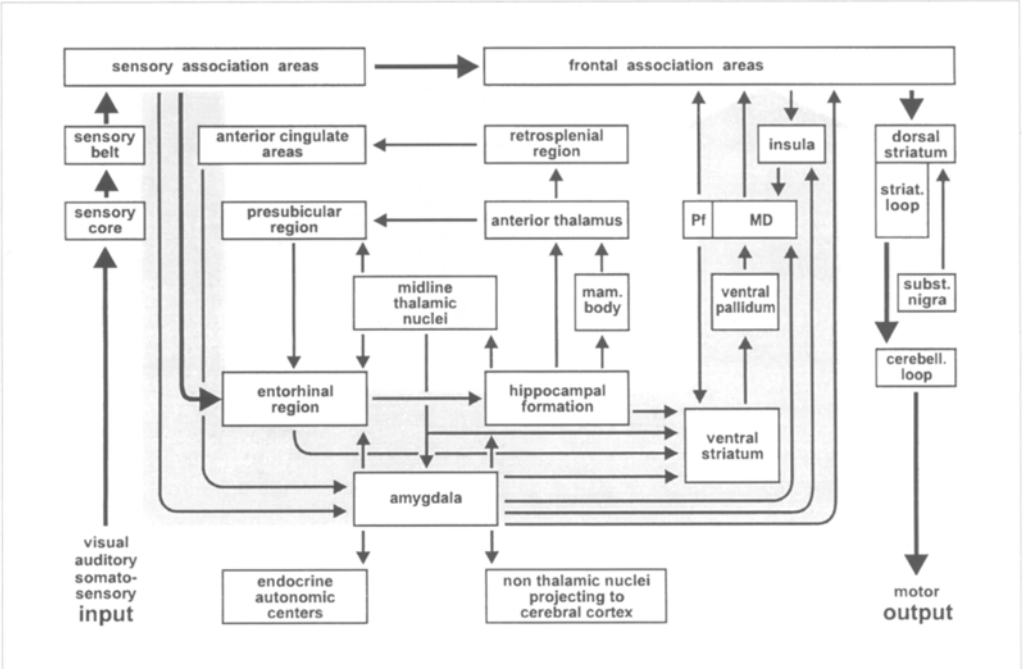

Fig. 3. The limbic loop is shown in greater detail. The grey arrow emphasizes the strategic position of the limbic loop between the neocortical sensory association areas and the prefrontal cortex. The hippocampal formation, the entorhinal region, and the amygdala are densely interconnected, and together the three represent the highest organisational level of the limbic system. *cerebell.loop* cerebellar loop; *mam.body* mamillary body; *MD* mediodorsal thalamic nucleus; *Pf* parafascicular nucleus; *striat. loop* striatal loop; *subst. nigra* substantia nigra (with permission from Braak et al., 1996)

cortical areas. Fronto-amygdalar projections reciprocate these connections (Amaral et al., 1992). The input from neocortical sensory areas, the processing within the limbic relay stations, and the output toward the prefrontal cortex are the essential features of the "limbic" loop (Figs. 1–3). It is important to note that this loop includes not only hippocampus, entorhinal cortex, and amygdala, but also portions of the basal ganglia and the thalamus. Its target is the prefrontal cortex, the highest controlling entity of the human brain (Fig. 3). The structural integrity of many of these components is a prerequisite for the maintenance of emotional stability, learning abilities, and memory functions (Mishkin, 1982; Amaral, 1987; Squire and Zola-Morgan, 1988, 1991; Hyman et al., 1990; Damasio and Damasio, 1991; Zola-Morgan and Squire, 1993; Markowitsch, 1995).

Entorhinal territory and anterior proneocortex

The transentorhinal and entorhinal regions extend over both the ambient gyrus and anterior portions of the parahippocampal gyrus (Fig. 4c). The transentorhinal region mediates between the entorhinal allocortex and the temporal pro-neocortex (perirhinal area). The lateral border of the territory is marked anteriorly by the rhinal sulcus and posteriorly by the collateral sulcus. Occasionally, the two sulci merge. The posterior pole is set off by an indentation into the parahippocampal gyrus caused by the anterior temporal artery (branch of the posterior cerebral artery) (Marinkovic et al., 1991). Wart-like elevations (verrucae hippocampi) on the free surface indicate the approximate position of the entorhinal region (Braak, 1980; Braak and Braak, 1985, 1992b; Amaral and Insausti, 1990; Insausti et al., 1995). The superficial entorhinal cellular layer (pre-α) consists mainly of large multipolar projection cells. These are unevenly distributed and join together to form cellular islands which underlie the verrucae hippocampi (Fig. 4a). Tangential sections display the pattern of the cellular islands (Braak, 1980; Braak and Braak, 1985, 1992b, 1995; van Hoesen and Solodkin, 1993). The right and left entorhinal regions of a given individual do not show marked differences as regards these patterns. However, there are interindividual differences in the total area occupied by the entorhinal region, as well as in the size and shape of the cellular islands (Fig. 4d,e). Specific features of the island pattern continue to develop postnatally. The ultimately achieved pattern is characteristic for each individual (Braak and Braak, 1995).

The entorhinal allocortex exhibits a complex layering and several architectonic subunits (Fig. 4b). Layers of the external main stratum, pre-α to pre-γ, give rise to the perforant path, which pierces the subiculum, crosses the obliterated hippocampal fissure, terminates in the first sector of the Ammon's horn (CA1) and within the molecular layer of the fascia dentata (Mizutani and Kasahara, 1995). Axons from a given point in the entorhinal cortex project to extensive portions of the hippocampus along its long axis (Witter, 1993). The transentorhinal region is, for the most part, hidden in the depths of the rhinal sulcus. Due to its hallmark, the gradual descent of the pre-α layer (see Fig. 7 AD stage III), it is one of the best defined areas of the cerebral

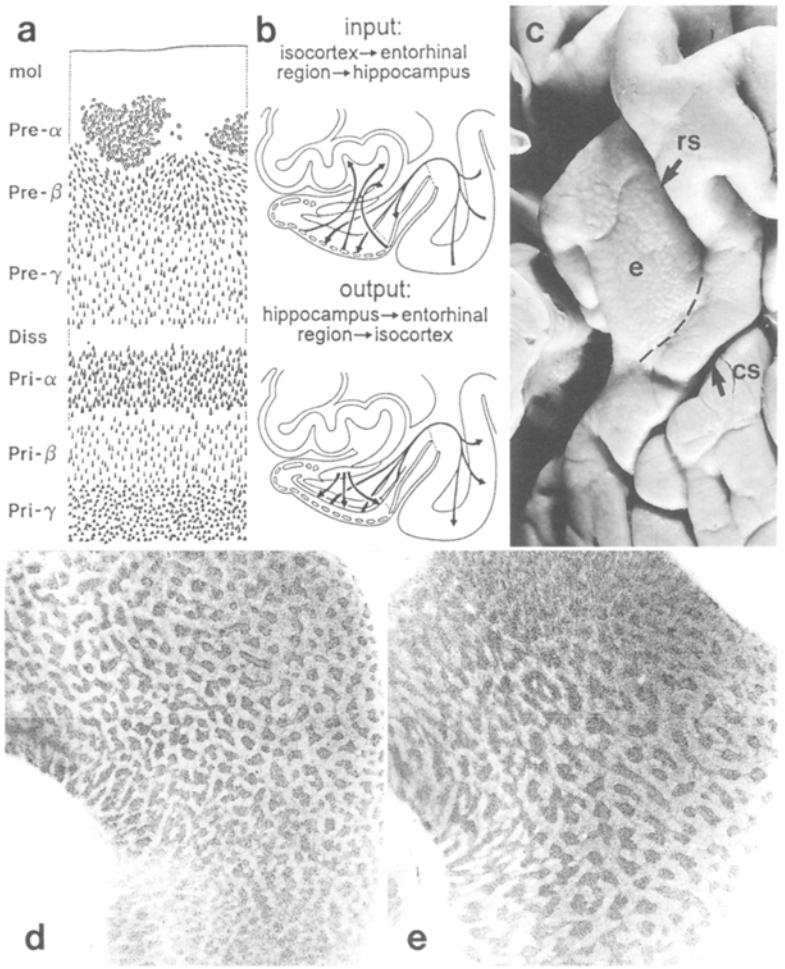

Fig. 4. a Schematic drawing of the lamination pattern of the entorhinal cortex (allocortex). *mol* molecular layer; *Pre-α*, *Pre-β*, *Pre-γ* – layers of the outer main stratum (stratum principale externum); *Diss* lamina dissecans; *Pri-α*, *Pri-β*, *Pri-γ* layers of the inner main stratum (stratum principale internum). Note the cellular islands of layer pre-α (with permission from Braak and Braak, 1992b). **b** Diagram of major entorhinal connections. Layer pre-α receives primarily neocortical data, along with additional input from limbic circuits, then transfers the information to the hippocampus. A dense feedback projection from the hippocampus terminates in the deep layer pri-α, from which the data is transferred back to the neocortex. The entorhinal region thus serves predominantly as an interface between the neocortex and the hippocampus (with permission from Braak and Braak, 1992b). **c** The entorhinal region (*e*) spreads over anteromedial portions of the temporal lobe. The surface exhibits small wart-like elevations. *cs* collateral sulcus; *rs* rhinal sulcus (with permission from Braak and Braak,1992b). **d** and **e** Tangential sections through layer pre-α of two individuals. The total area occupied by the entorhinal region, as well as the size and shape of individual cell islands, differ from one individual to another (with permission from Braak and Braak, 1995)

cortex (Braak, 1980; Braak and Braak, 1985, 1991b, 1992b). The region is most extensive in the human brain and decreases considerably in size going down the primate scale. The transentorhinal region probably serves as a port of entry for neocortical data (Fig. 5). Additional input to this region originates in the cholinergic nuclei of the basal forebrain (Mesulam and Geula, 1988; Mesulam et al., 1992; DeLacalle et al., 1994) and the basolateral amygdala. Direct afferents to the entorhinal region arise from the presubiculum, while

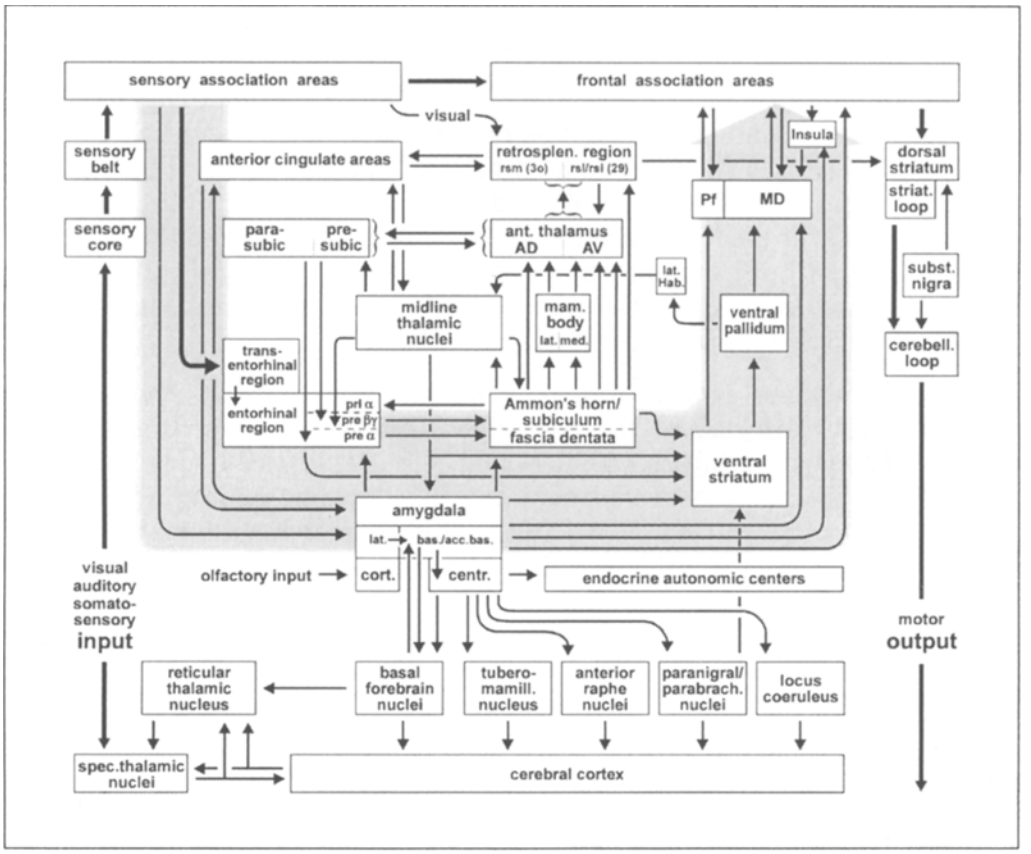

Fig. 5. This Figure illustrates the limbic loop and related structures in greater detail. The amygdala integrates exteroceptive sensory data with interoceptive stimuli from autonomic centers. A large number of amygdalar efferents terminate in nuclei regulating endocrine and autonomic functions. In addition, the amygdala generates efferent connections to all non-thalamic nuclei which project upon the cerebral cortex in a diffuse manner. *ant.thalamus AD AV* anterodorsal and anteroventral nuclei of the anterior thalamus; *cerebell.loop* cerebellar loop; *lat.Hab.* lateral habenula; *lat.bas./acc.bas.cort.centr.* lateral, basal, accessory-basal, cortical and central amygdalar nuclei; *mam.body lat. med.* lateral and medial nuclei of the mamillary body; *MD* mediodorsal thalamic nucleus; *paranigral/parabrach.* paranigral and pigmented parabrachial nuclei; *parasubic presubic* parasubiculum, presubiculum; *Pf* parafascicular nucleus; *Pri-α*, *Pre-β*, *Pre-γ*, *Pre-α* layers of the entorhinal region; *retrosplen.region rsm (30) rsl/rsi (29)* – medial retrosplenial area (Brodmann area 30), lateral and intermediate retrosplenial areas (Brodmann area 29); *spec. thalamic nuclei* specific projection nuclei of the thalamus; *striat. loop* striatal loop; *subst. nigra* substantia nigra; *tuberomamill.* tuberomamillary nucleus (with permission from Braak et al., 1996)

projections from olfactory areas are sparse and rudimentary. Both neocortical information and limbic circuit data are transported to the hippocampal formation via the perforant path. A dense feed-back projection from the subiculum terminates in the deep entorhinal layer pri-α, from which the data is transferred back to the neocortex (Amaral and Insausti, 1990; Hyman et al., 1990; van Hoesen and Hyman, 1990; van Hoesen et al., 1991). The entorhinal region thus serves predominately as an interface between the neocortex and the hippocampus. Bilateral damage of this region results in partial or total disconnection of the hippocampus from the neocortex (Kemper, 1978).

PD-related changes. In fully developed PD, cortical LBs can be observed in both the transentorhinal and the entorhinal regions. LB-containing pyramidal cells occur mainly in layer pri-α (Fig. 6b). Massive numbers of LBs are also encountered in layer VI of the adjoining temporal neocortex (Fig. 6c). Frequently, a band of LBs is seen to extend into anterior insular areas. A second predilection site is the lower portion of the molecular layer and the subjacent cellular layer of both the entorhinal region and the temporal proneocortex (Fig. 6a), in which many small punctate LNs develop. Occasionally, these structures display filiform appendages.

AD-related changes. The entorhinal territory exhibits the first changes and is most drastically affected by the AD-related lesions. In stage I there are no more than a few transentorhinal NFTs and NTs in layer pre-α (Fig. 6d), while stage II exhibits many NFTs at this location, supplemented by a few in the entorhinal layer pre-α (Fig. 7a,b). Stage III is characterized by severe affliction of the layer pre-α islands (Fig. 7c,d) supplemented, at stage IV, by destruction of layer pri-α (Fig. 7e,f). At this stage, the changes extend into the basal temporal and insular neocortex. The severity of involvement gradually diminishes as one proceeds from the entorhinal territory toward the first temporal gyrus. At stages V and VI, the entorhinal layers affected first may be completely denuded of nerve cells, with only ghost tangles to indicate the position of the former cellular layers (see also van Hoesen et al., 1991).

Hippocampal formation

The hippocampal formation is almost completely buried in the depths of the temporal lobe (Fig. 8). The club-shaped head of the hippocampus bends medially and approaches the amygdala. The posterior end ascends toward the splenium of the corpus callosum forming the supracallosal portion (Stephan, 1975; Braak, 1980; Amaral and Witter, 1989; Amaral and Insausti, 1990; Braak et al., 1996). Transverse sections through the hippocampal formation at the level of the lateral geniculate body reveal the boundaries of its major divisions: the fascia dentata, the four Ammon's horn sectors, and the subiculum (Fig. 8).

The glutamatergic perforant path provides the most important input to the fascia dentata and terminates preferentially within the outer two thirds of the molecular layer (Fig. 8). Additional input originates in the cholinergic nuclei of the basal forebrain, in particular the medial septal nucleus. These fibers, as

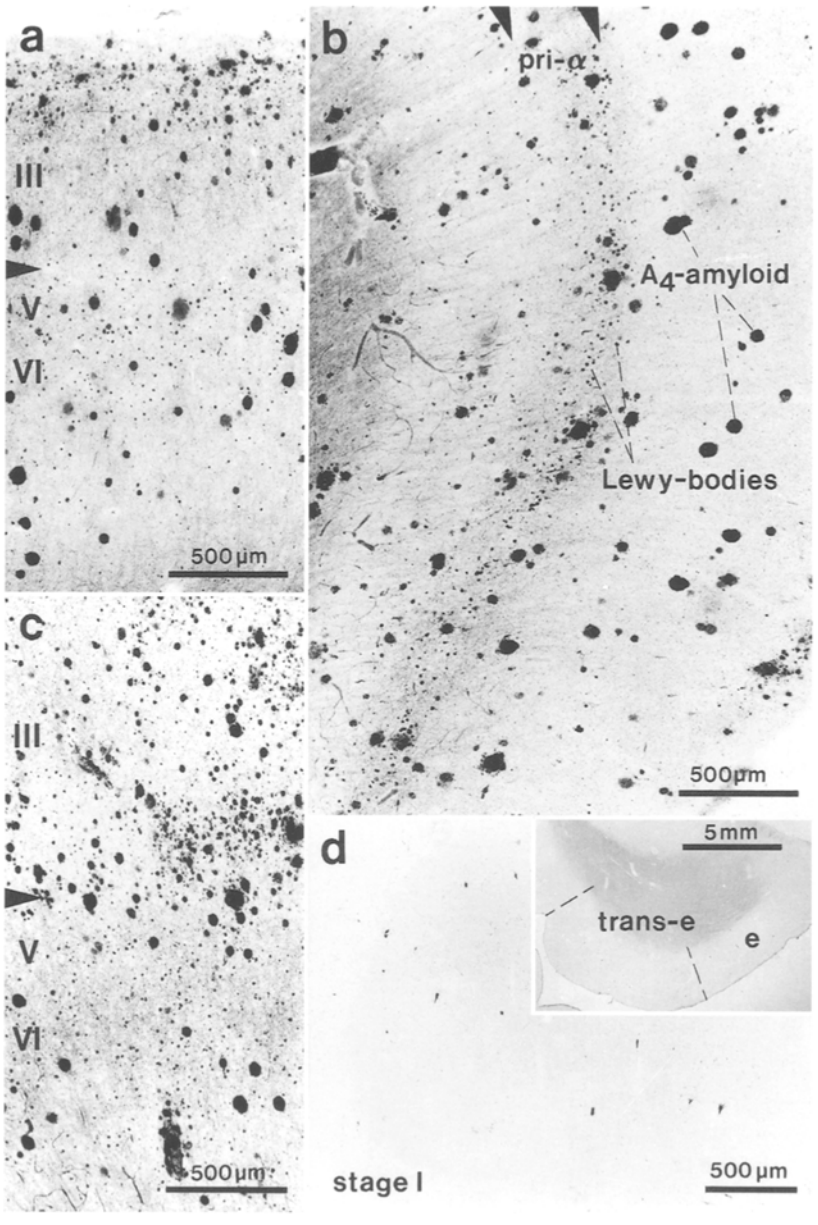

Fig. 6. a–c Micrographs of Parkinson-related lesions. The tiny dots represent cortical Lewy bodies, while the large ones indicate βA4 amyloid deposits (Campbell-Switzer silver impregnation, 100µm). **a** The anterior cingulate areas contain numerous Lewy bodies within layers V and VI. **b** The entorhinal region displays an abundance of Lewy bodies restricted to the deep layer pri-α. **c** The adjoining temporal neocortex shows Lewy bodies located predominantly in layers V and VI. **d** Micrograph of Alzheimer-related lesions at stage I: The transentorhinal region (inset: trans-e) mediates between the entorhinal region (e) and the temporal proneocortex. Initial neurofibrillary tangles are generally seen in layer pre-α of the transentorhinal region (Gallyas silver impregnation for neurofibrillary changes, 100µm)

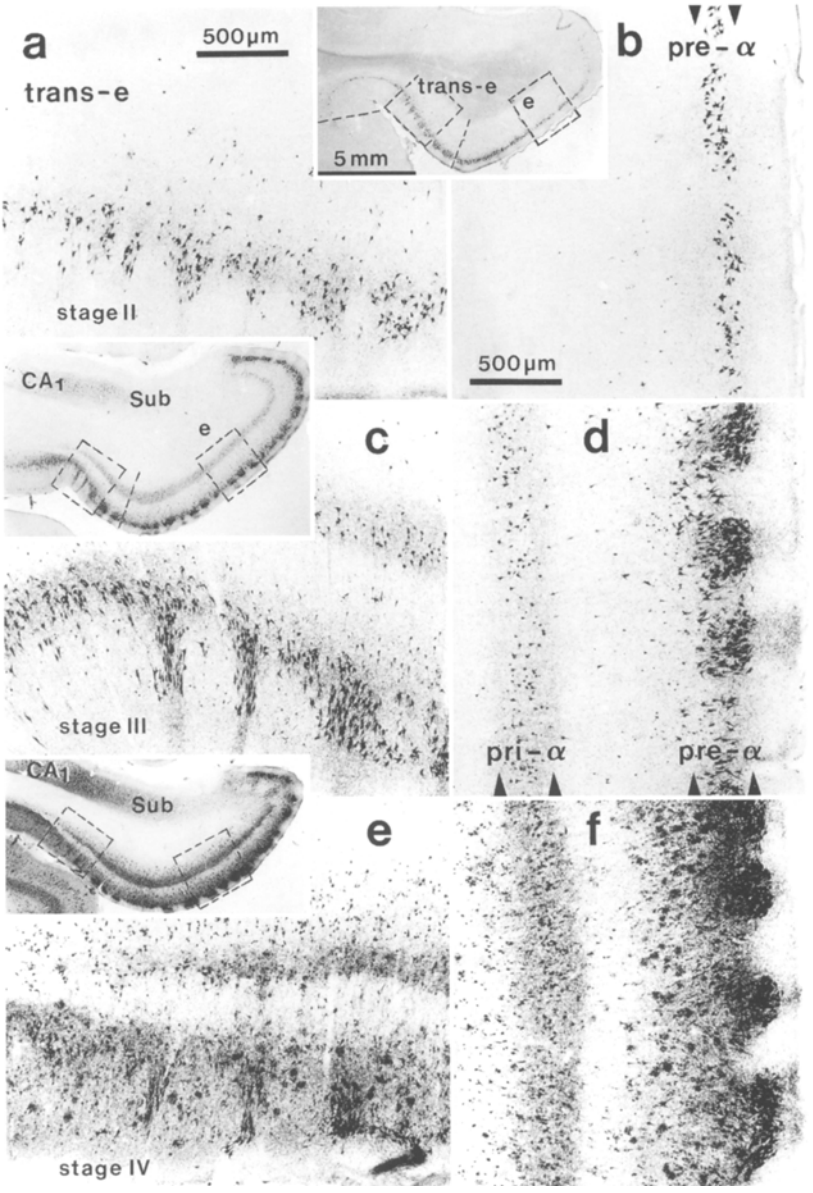

Fig. 7. a–f Gradual progress of entorhinal destruction occurring during the course of Alzheimer's disease. The insets provide an overview, with framed areas indicating the location of the photographs taken at higher magnification. On the left, portions of the transentorhinal region (trans-e) are shown with the pial surface oriented downwards. These are supplemented by portions of entorhinal cortex (*e*) with the pial surface toward right-hand border (Gallyas silver impregnation for neurofibrillary changes, 100µm). **a,b** Stage II: Neurofibrillary tangles are virtually restricted to layer pre-α; they are numerous in the transentorhinal region and less densely placed in the entorhinal region. **c,d** Stage III: Abundant neurofibrillary tangles mark the pre-α cellular islands in both the transentorhinal and entorhinal regions. Note the dense staining between the cellular islands and the pial surface caused by neuropil threads. Further neurofibrillary tangles mark the deep layer pri-α. **e,f** Stage IV: Both regions show a considerable increase in the number of neurofibrillary changes. At this stage, many new neurofibrillary tangles are formed in layer pre-β, and numerous neuritic plaques appear in pre-β and pri-β. *CA_1* first sector of the Ammon's horn; *sub* subiculum

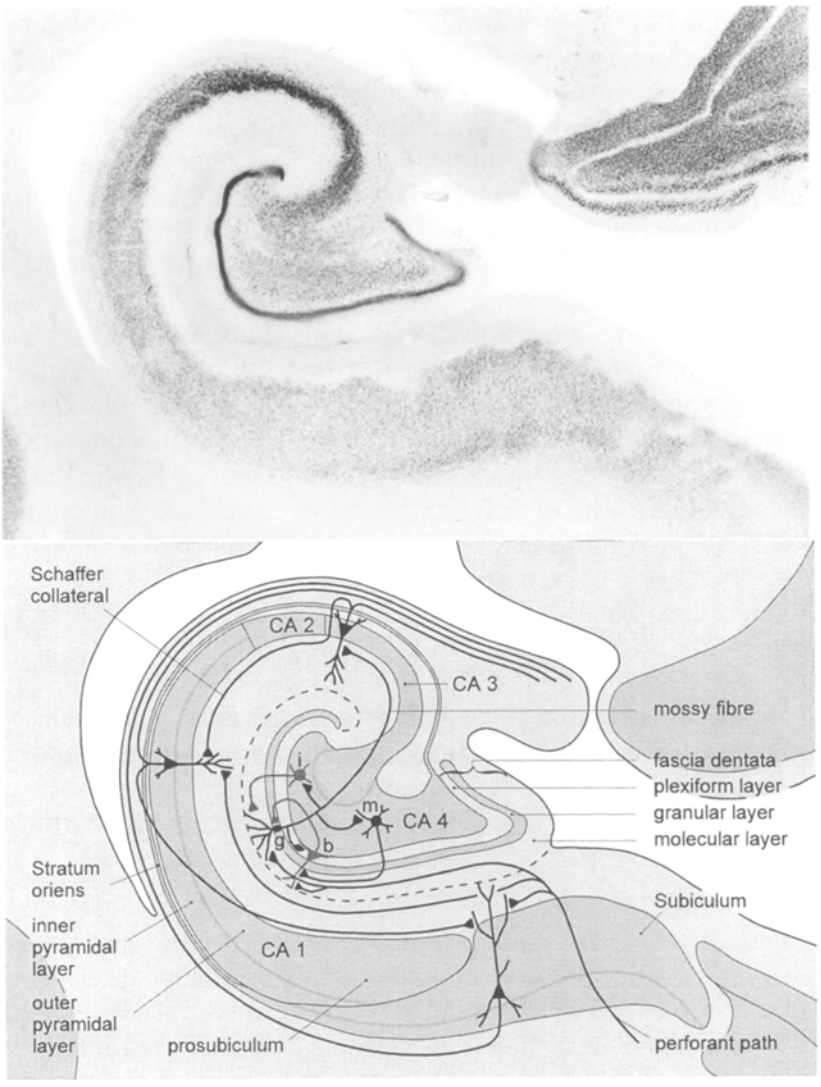

Fig. 8. *Above*: Micrograph of a frontal section through the hippocampus at the level of the lateral geniculate body (Aldehyde-fuchsin-Darrow red, 100 μm). *Below*: Drawing of the same section showing the layers and boundaries of the various hippocampal subdivisions. The boundaries have been intentionally omitted to enable the reader to draw independent conclusions about subdivisions within the hippocampus. Note the two pyramidal cell layers of CA1 (*CA1 to CA4* first to fourth sector of the cornu ammonis). The Ammon's horn is supplemented by the fascia dentata on the one side, and the subiculum on the other). The most important neuronal types and their characteristic connections are displayed as well. *b* basket cell (interneuron) of the fascia dentata; *g* granule cell (projection neuron) of the fascia dentata; *i* a large interneuron of CA4; *m* the mossy cell (CA4 projection neuron) (with permission from Braak et al., 1996)

well as association fibers from CA4-mossy cells, branch off within the inner third of the molecular layer. In contrast to the situation in small rodents, there is only sparse callosal input from the contralateral hippocampus. The hippocampal commissure, or psalterium, is rudimentary in the human brain (Rosene

and van Hoesen, 1987). The granule cells of the fascia dentata generate the mossy fibers, characterized by large synaptic boutons. These fibers branch profusely in the polymorph layer of the fascia dentata and terminate on microdendrites of CA4 and CA3 pyramidal cells. Sector CA4 fills the hilus of the fascia dentata with no discernible layering. This sector is closely related to, and in continuation with sector CA3. The glutamatergic multipolar projection cells of CA4 (mossy cells) generate association fibers which extend widely into other portions of the fascia dentata. The CA3 pyramidal cells furnish a similar association system within the boundaries of the sector. They also send collaterals to CA4-projection cells (mossy cells) and give rise to the Schaffer collaterals terminating in CA1 (Fig. 8). The CA1 pyramidal cells, in turn, project to the subiculum (Amaral and Insausti, 1990). The relative size of the CA1 sector increases considerably with ascent of the primate scale. In the human brain, the sector displays a superficial and a deep pyramidal cell layer. A wedge-shaped portion of CA1 partially overlaps the subiculum, and is referred to as the prosubiculum. The enigmatic sector CA2 is characterized by its densely packed and large pyramidal cells. On cross sections, the subiculum is wing-shaped, and consists of outer and inner pyramidal cell layers and a deep layer originating in the entorhinal cortex. The slender subicular pyramidal cells give rise to long apical dendrites which, in adults, contain spindle-shaped lipofuscin agglomerations. This feature readily identifies the borders of the subiculum (Braak, 1980). Hippocampal output is generated mainly in the subiculum (Fig. 5). Major projections lead to the septum, the entorhinal region, amygdala, mamillary nuclei, the midline and anterior nuclei of the thalamus, and the retrosplenial region (Amaral and Witter, 1989; Amaral and Insausti, 1990; van Hoesen and Hyman, 1990; Zilles, 1990).

PD-related changes. In fully developed PD, cortical LBs are usually seen in only superoanterior portions of the uncus. There, changes develop similar to those seen in the accessory cortical nucleus of the amygdala. The hippocampal CA2-sector exhibits a wealth of LNs, which frequently attain considerable length (Dickson et al., 1991). LNs are located preferably in the stratum oriens, from which they extend into the pyramidal layer. CA2-LNs are encountered in almost all cases of PD (Fig. 9) (Braak et al., 1995).

AD-related changes. The first NFT-bearing CA1 pyramidal cells appear at stage II. Later stages display numerous flame-shaped NFTs, particularly in the prosubicular portion of CA1. The outer pyramidal cell layer of CA1 is more heavily involved than the inner one. Flame-shaped NFTs are also seen in the supracallosal portion of the Ammon's horn. Two dense strips of NTs develop above and below the CA1 pyramidal cell layers. At stage III, large star-shaped CA4 nerve cells show NFTs which widely extend into the dendrites. These cells are different from the CA4-projection cells (mossy cells) which, at this stage, remain devoid of NFTs. At stage IV, NFTs develop within the subiculum and, gradually, a dense network of NTs fills the subicular pyramidal cell layers. At stages V and VI, the CA4-projection cells (mossy cells), the CA3-pyramidal cells, and eventually even the granule cells of the fascia dentata develop globose NFTs.

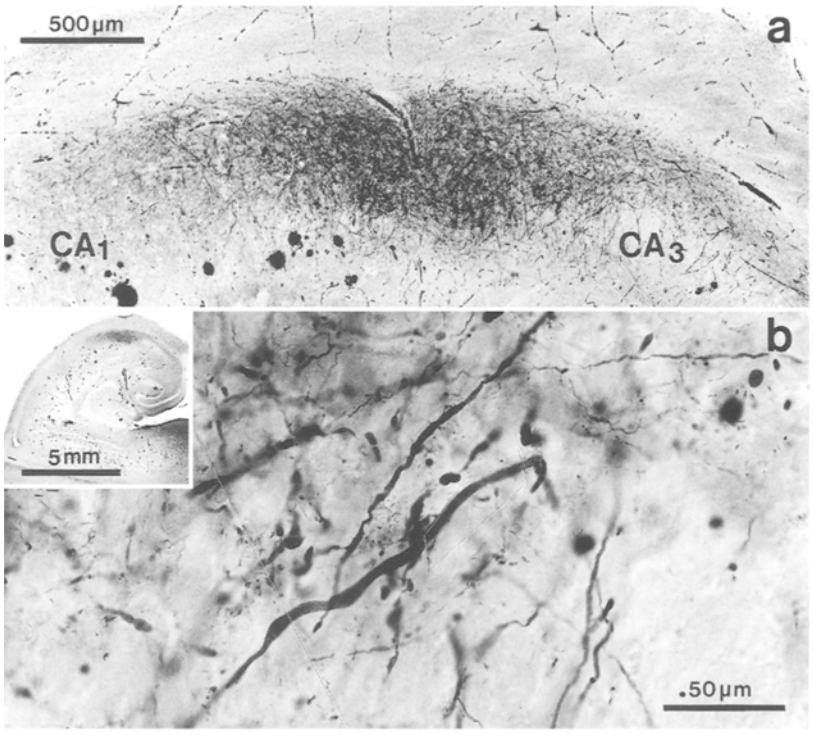

Fig. 9. A dense network of Lewy neurites typically occurring in Parkinson's disease in the CA2 sector of the Ammon's horn. For better orientation, the inset displays an overview of the hippocampal formation (Campbell-Switzer silver impregnation, 100 µm). **a** Note the accumulation of Lewy neurites between sectors CA1 and CA3 with a broad base in the stratum oriens and extensions into the pyramidal layer. **b** Higher magnification reveals the presence of particularly long and varicose Lewy neurites

Limbic circuits

Midline nuclei of the thalamus and reuniens circuit

The midline nuclei (medial portions of the central medial nucleus, the reuniens nucleus, and the thalamic paraventricular nucleus) establish short thalamo-allocortical circuits and generate important projections to the ventral striatum (Figs. 3, 5, 10a). The midline nuclei have ill-defined boundaries, are located within and around the interthalamic adhesion, and consist of heterogeneous populations of slender and mostly spindle-shaped nerve cells (Fig. 11). Their limbic input is derived mainly from subicular projections. In addition, they are bidirectionally connected with the anterior cingulate cortex and the basolateral amygdala. Further input comes from the magnocellular nuclei of the basal forebrain, the hypothalamic tuberomamillary nucleus, and the dopaminergic nuclei of the ventral tegmentum. The output of thalamic midline nuclei heads toward the CA1-sector, subiculum, the entorhinal cortex (molecular layer, layers pre-β and pre-γ), the presubiculum, parasubiculum, and amygdala (Jones, 1985). For sake of brevity, a portion of these connections is referred to as the "reuniens circuit" (Fig. 10).

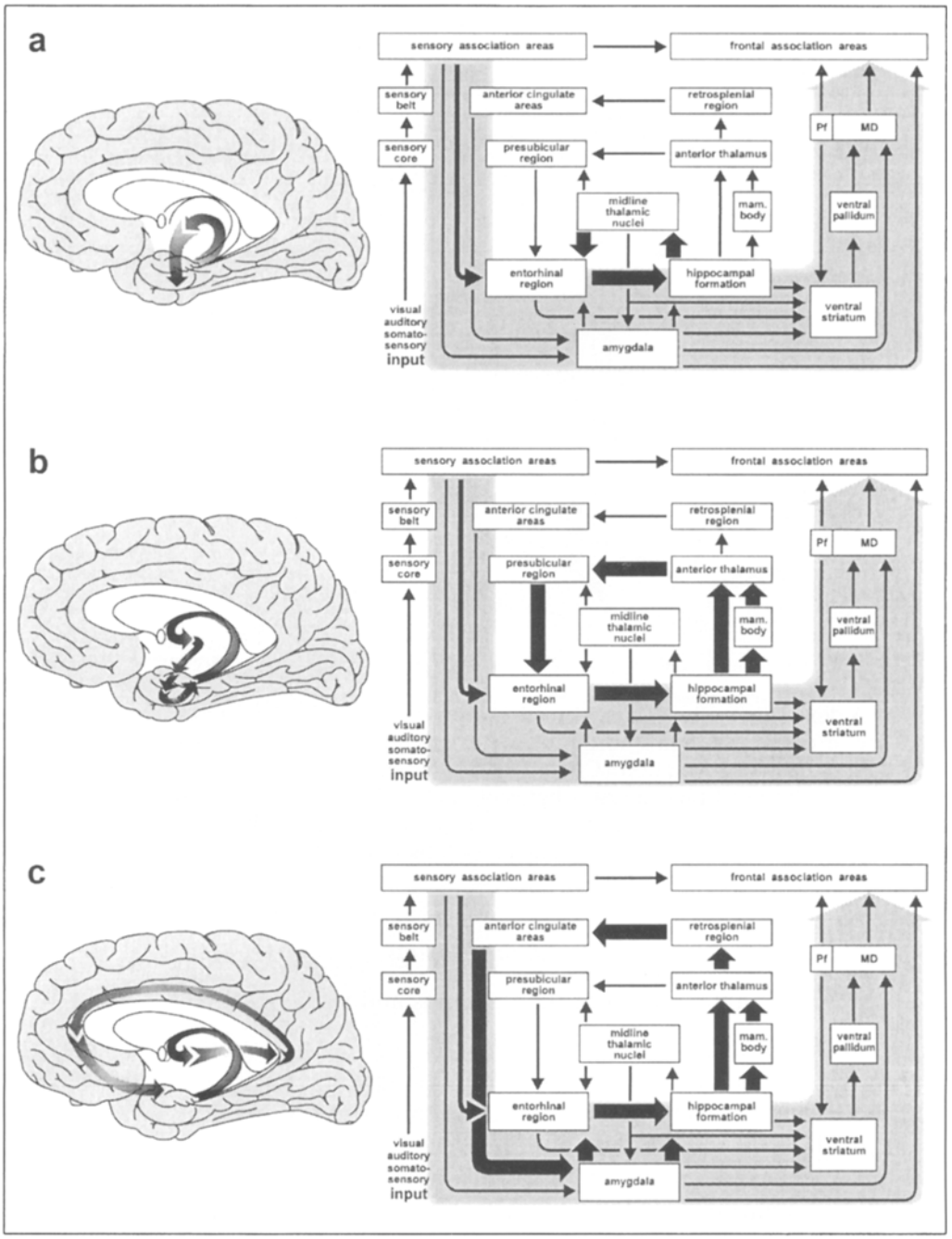

Fig. 10. Schematic representation of important limbic circuits. **a** "Reuniens circuit": Afferent and efferent projections of the midline thalamic nuclei establish short thalamo-allocortical circuits. **b** and **c** This circuit is supplemented by others, including the anterior thalamus. A relatively short circuit is formed by projections to the presubicular region (b), while a more extensive one includes the retrosplenial and anterogenual regions of the cingulate gyrus and the amygdala (c)

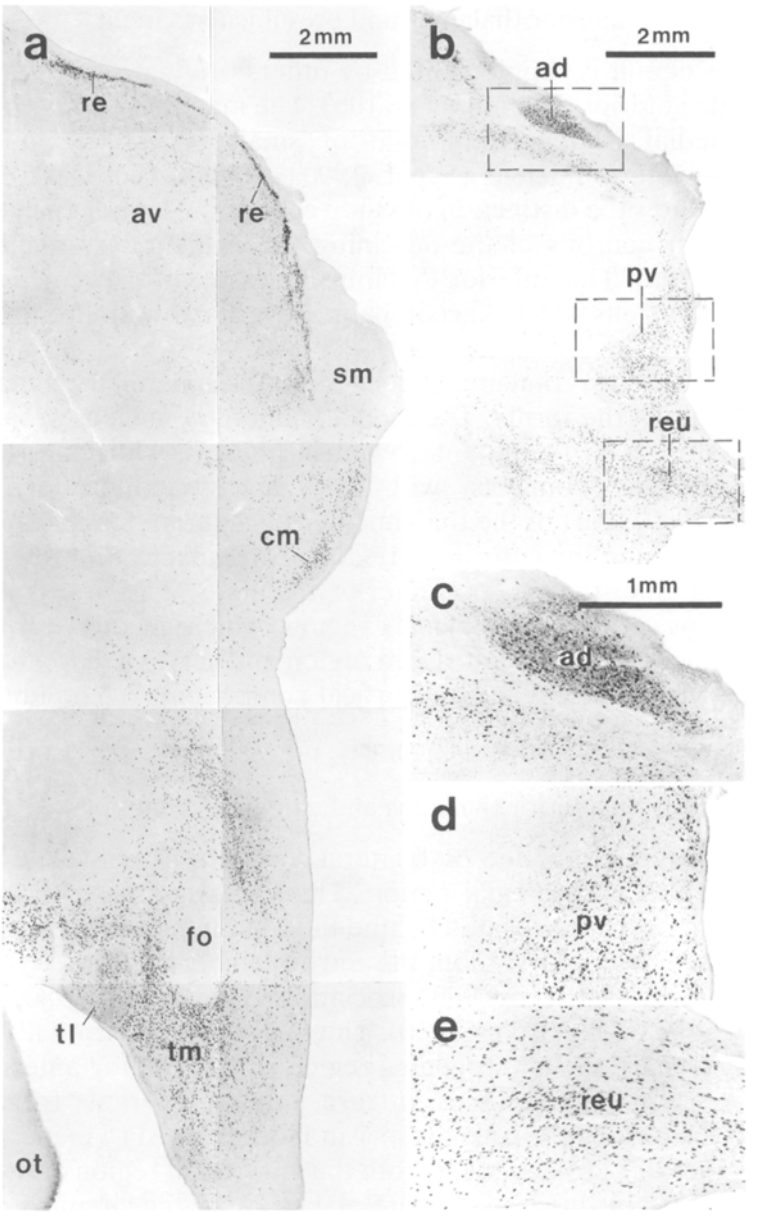

Fig. 11. Characteristic Alzheimer-related changes within the thalamus and hypothalamus at stage V (Gallyas silver impregnation for neurofibrillary changes, 100 μm). **a** Overview: Severe destruction is virtually restricted to the limbic nuclei of the thalamus and tuberomamillary (*tm*) and lateral tuberal nucleus (*tl*) of the hypothalamus. A dense accumulation of distended processes (*re*) is located between the anteroventral nucleus (*av*) and the ependymal lining. This network is continuous with a similar one found in anterior portions of the reticular nucleus. *cm* medial portions of the central medial nucleus; *fo* fornix; *ot* optic tract; *sm* stria medullaris. **b** A frontal section at the level of the interthalamic adhesion reveals severe involvement of the anterodorsal nucleus (*ad*), the paraventricular (*pv*) and the reuniens nucleus of the thalamus (*reu*). The framed areas in b are shown in greater detail in **c–e** (with permission from Braak and Braak, 1991a)

Anterior thalamus and presubicular circuit

The reuniens circuit is supplemented by others originating in the mamillary nuclei and the anterior thalamus (Fig. 10b). The mamillary body consists of an extensive medial nucleus composed of small nerve cells and a small magnocellular lateral nucleus (Saper, 1990a). The virtual lack of lipofuscin granules facilitates the distinction of nerve cells of the lateral nucleus from the lipofuscin-laden neurons of the adjoining tuberomamillary nucleus (Braak and Braak, 1992a). The anterior thalamus likewise consists chiefly of a large anteroventral nucleus which is accompanied by a narrow anterodorsal nucleus (Fig. 11).

Both the anterior thalamic nuclei and the mamillary nuclei receive subicular input via the fornix. The medial mamillary nucleus projects via the mamillothalamic tract to the anteroventral nucleus, while the small lateral mamillary nucleus connects with the narrow anterodorsal nucleus (Armstrong, 1990). Part of the thalamic nuclei generate feedback projections to the subiculum and the entorhinal region (Amaral and Insausti, 1990). Two limbic circuits emerge from the anterior thalamus. The first is initiated by short projections to the presubicular region, which, in turn, provides short efferent connections to the entorhinal region and serves predominantly as an interface between cortical and subcortical components of the limbic circuits (Fig. 10b) (Kalus et al., 1989).

Anterior thalamus and cingulate circuit

The second circuit is initiated by bilateral connections between the anterior thalamus and the retrosplenial region. This crescent-shaped portion of the cingulate proneocortex is located behind the splenium of the corpus callosum. In addition to limbic information, the retrosplenial region receives an abundance of visual data from occipital association areas (Braak, 1980; Vogt, 1985; Braak and Braak, 1993a; Zilles, 1990). The region is bidirectionally connected with its counterpart, the anterogenual region, and adjoining anterior areas of the cingulate gyrus. These fields, in turn, receive afferents from and send efferents to the basolateral amygdala (van Hoesen, 1981). As mentioned, the amygdala generates projections to both the entorhinal region and the hippocampal formation. In this way, a more elaborate limbic circuit is established supplementing the shorter ones (Fig. 10c). The anterior cingulate areas are, in addition, connected with the midline nuclei of the thalamus. Thus the reuniens circuit is tied into the circuits originating in the anterior thalamus. The retrosplenial region also projects upon the dorsal striatum and thereby exerts influence upon relay stations of the striatal loop (Figs. 1–3, 5).

Pathologic changes

PD-related changes. The midline nuclei of the thalamus show very severe PD-related changes. Abundant LBs occur in all these nuclei. The changes continue into the limitans nucleus of the pulvinar and into the mesencephalic central gray. The mamillary nuclei, as well as anterior nuclei of the thalamus,

the thalamic laterodorsal nucleus, and the retrosplenial region are almost spared of PD-specific changes while the anterior cingulate areas are severely afflicted in virtually every PD case. The pyramidal cells of the multiform layer are particularly prone to develop LBs. Since this layer generates the projections to the amygdala, it is possible that cells with amygdalar projections specifically develop the PD-related changes. Accumulations of cortical LBs are frequently seen in the deep layers of the insular and temporal proneocortex as well (Fig. 6a,c). Appearance of cortical LBs is an important aspect of the extranigral PD-related pathology (Braak et al., 1995; de Vos et al., 1995).

AD-related changes. In stages II–III, a marked AD-related destruction in midline nuclei of the thalamus occurs affecting medial portions of the central medial nucleus, the reuniens nucleus, the paraventricular nucleus, and the limitans nucleus (Fig. 11a–c). The nerve cells in these nuclei develop star-shaped NFTs with long extensions into the dendrites (Braak and Braak, 1991a, 1994). The medial mamillary nucleus is sparsely involved and the lateral nucleus usually free of AD-related changes. The anterior thalamus is affected in a different way. The projection cells of the anterior thalamic nuclei and of the laterodorsal nucleus develop globose NFTs which are confined to the soma and easily distinguishable from midline nuclei NFTs. Most heavily involved among the nuclei of the anterior thalamus is the anterodorsal nucleus. At early stages (II–III), this part of the thalamus is already infested with NFTs. Later stages display abundant ghost tangles and severe neuronal loss (Braak and Braak, 1991a, 1994). The retrosplenial region is afflicted in virtually every AD case and the capacity to develop dense networks of NTs is a distinguishing feature of this region (Braak and Braak, 1993a; Braak et al., 1992).

Amygdala

The amygdala is located deep in the temporal lobe, just in front of the uncal portion of the hippocamus. It consists of three divisions: the mediocentral nuclei, the cortical portions, and the basolateral complex. The latter is particularly voluminous in the human brain and is comprised of the lateral, the basal, and the accessory basal nuclei. Intercalated cell masses partially fill the space between the basolateral complex and the central nucleus. Less well-defined medial nuclei, the periamygdaloid cortex, and the accessory cortical nucleus extend out to the external surface of the brain (Fig. 12) (Braak and Braak, 1983).

The amygdala receives a broad range of afferents which function in integration of exteroceptive data (olfactory, somato-sensory, auditory, and in particular visual information) with interoceptive stimuli from a variety of autonomic centers. Accordingly, a large number of amygdalar efferents terminate in nuclei regulating endocrine and autonomic functions, while others are directed toward the neocortex (Figs. 2, 3). In this text, the connections with autonomic centers are mentioned only briefly. The nuclei of the basolateral complex maintain particularly strong interconnections with the prefrontal

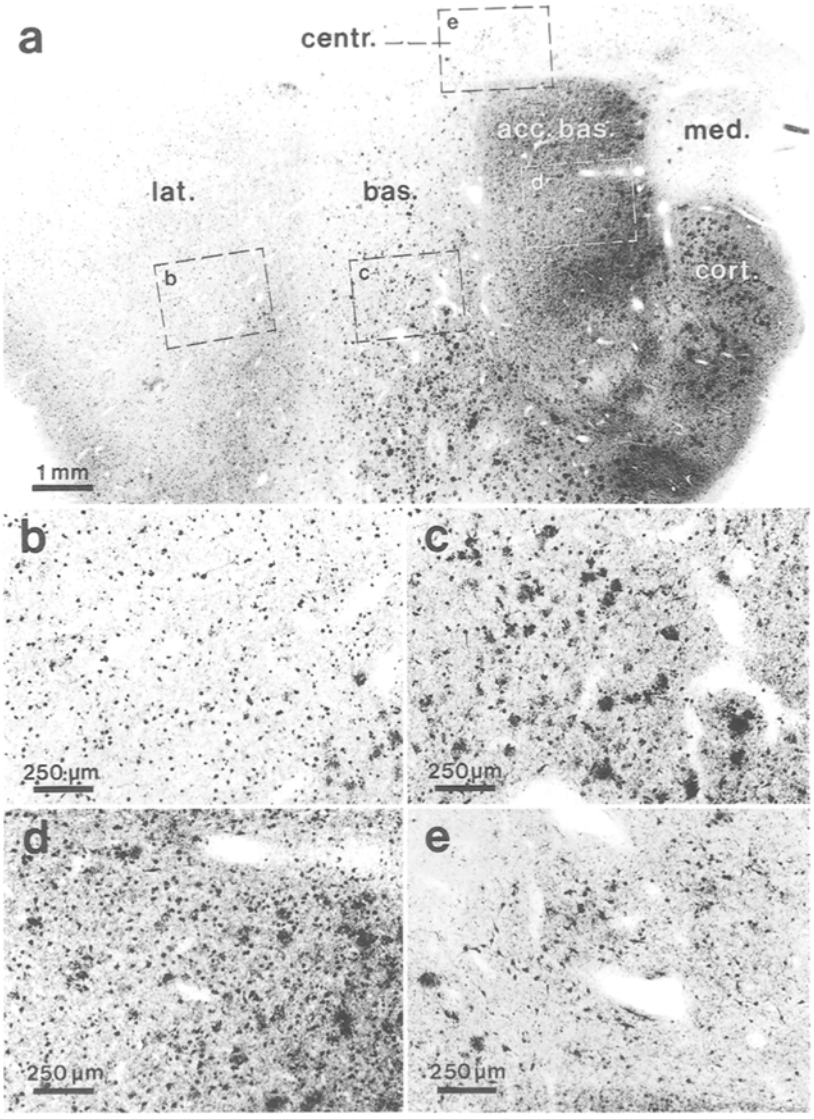

Fig. 12. Distribution pattern of Alzheimer-related neurofibrillary changes within the amygdala (Gallyas silver impregnation for neurofibrillary changes, 100 µm). **a** The overview reveals severe involvement of the cortical (*cort.*) and the accessory basal nucleus (*acc.bas.*). The basal nucleus (*bas.*) shows a less dense accumulation of neurofibrillary tangles and an abundance of neuritic plaques. The lateral nucleus (*lat.*) displays many early appearing neurofibrillary tangles and is virtually devoid of neuritic plaques. The central nucleus (*centr.*) develops characteristic star-shaped tangles in late stages of the disease. The framed areas are shown at higer magnification in **b–e**

cortex. They also generate projections to the ventral striatum and the dorsomedial nucleus of the thalamus (Fig. 12). Also of importance are connections with the neighbouring hippocampal formation and entorhinal cortex. Entorhinal afferents to the cortical nuclei and basolateral complex of the amygdala originate in the deep layer pri-α, while efferents from the accessory basal and the lateral nucleus of the amygdala terminate in layers pre-β and

pre-γ. The cortical nuclei and the basolateral complex maintain tight connections with the hippocampal formation. The central nucleus sends efferents to all non-thalamic nuclei diffusely projecting into the cerebral cortex, i.e. the cholinergic nuclei of the basal forebrain, the histaminergic tuberomamillary nucleus, the dopaminergic nuclei of the ventral tegmentum, the serotonergic anterior raphe nuclei, and the noradrenergic locus coeruleus. The cholinergic nuclei of the basal forebrain receive additional input from the basal nucleus and accessory basal nucleus (Figs. 5, 10c) (Saper, 1987b, 1990b; Braak et al., 1994). The amygdala thus is considered to be important in the regulation of emotion and social behavior, in the affect-related movement initiation, affect-related memory function, and in the regulation of endocrine and autonomic functions (Price et al., 1987; Alheid et al., 1990; de Olmos, 1990; Hyman et al., 1990; Amaral et al., 1992; Babinski et al., 1993).

PD-related changes. An abundance of LBs and LNs occur within the central nucleus and the accessory cortical nucleus. Less extensively involved are nuclei which abut upon the accessory cortical nucleus, such as the periamygdaloid cortex and the parvocellular portion of the basal and accessory basal nucleus. The intercalated cell masses and, in particular, the lateral nucleus generally remain free of Parkinson-specific destruction (Braak et al., 1994, 1995).

AD-related changes. The first neurofibrillary changes are seen in the basolateral complex of the amygdala (stages I–II). Substantial numbers of coarse and globular NFTs develop in the lateral nucleus, the basal nucleus, and the accessory basal nucleus (Fig. 12a). The latter two nuclei develop numerous neuritic plaques (Fig. 12c,d), while the lateral nucleus is virtually spared of this type of change (Fig. 12b) (Herzog and Kemper, 1980; Unger et al., 1988; Hyman et al., 1990; Kromer-Vogt et al., 1990). Severe neuronal loss and the relatively late development of star-shaped NFTs (stages V–VI) are features of the central nucleus (Fig. 12e) (Herzog and Kemper, 1980).

Non-thalamic nuclei with diffuse cortex projections

Magnocellular nuclei of the basal forebrain

The magnocellular nuclei of the basal forebrain lie in a line which commences anteromedially with the medial septal nucleus, then continues posterolaterally with the vertical limb, angular portion, and horizontal limb of the diagonal band and terminates with the basal nucleus of Meynert (Figs. 5, 10c). The cholinergic projection cells of these nuclei intermingle with cells synthesizing GABA (γ-amino-butyric acid) and various neuropeptides (Hedreen et al., 1984; Saper and Chelimsky, 1984; Saper et al., 1985; Saper, 1990b). The nuclei receive major input from cortical areas and subcortical nuclei of the limbic system (prefrontal neocortex, olfactory areas, hippocampus, amygdala, entorhinal region, and hypothalamus). Their efferent projections are the main source of cholinergic input to the amygdala, in particular to the basal nucleus, which, in turn, projects densely to the basal forebrain nuclei. Further projections head toward the midline nuclei of the thalamus

and magnocellular portions of the mediodorsal thalamic nucleus. Many cholinergic neurons generate axons extending through large territories of the neocortex, hippocampus, and the transentorhinal/entorhinal regions (Mesulam and Geula, 1988).

A dense cholinergic projection to the reticular nucleus of the thalamus deserves special consideration since the GABAergic projection cells of this nucleus generate fibers which terminate exclusively within thalamic relay nuclei. Collaterals from thalamocortical and corticothalamic fibers provide the specific input to the reticular nucleus, which is thereby capable of exerting tight control over the activity of the specific thalamocortical projections (Fig. 10c).

Tuberomamillary nucleus

The voluminous tuberomamillary nucleus extends throughout the lateral tuberal and the lateral mamillary region of the human hypothalamus and maintains close association with the medial forebrain bundle (Fig. 13). Large lipofuscin-laden projection cells predominate within the nucleus, and partly encircle the fornix, the lateral tuberal nucleus, and the mamillary nuclei (Saper, 1990a; Braak and Braak, 1992a; Swaab et al., 1992). The tuberomamillary projection cells synthesize histamin, GABA, and a variety of other substances (Panula et al., 1990; Airaksinen et al., 1991). This nucleus generates widespread projections to the cerebral cortex in approximately the same magnitude as those arising from the basal forebrain nuclei (Saper and German, 1987; Saper, 1990a). The nucleus probably sends projections to the CA2-sector of the Ammon's horn, and the ventral and dorsal striatum (Fig. 5).

Melanin-containing parabrachial and paranigral nuclei of the ventral tegmentum, anterior raphe nuclei, locus coeruleus, and pigmented subpeduncular nucleus

The paranigral nucleus and the pigmented parabrachial nucleus represent the dopaminergic nuclei of the ventral tegmentum. The paranigral nucleus lies next to medial portions of the substantia nigra and partially covers the interpeduncular nucleus. It is in continuation with the leaflike pigmented parabrachial nucleus which adjoins the linear nucleus of the anterior raphe complex near the midline. Constituents of both nuclei are melanin-laden neurons which provide dense projections to the hippocampal formation, the transentorhinal/entorhinal regions, and the prefrontal cortex (Fig. 5) (Pearson et al., 1990).

The serotonergic anterior raphe complex consists of a central, dorsal, and linear nucleus. The dorsal nucleus is well developed in the human brain, and exhibts a dome-shaped supratrochlear portion close to the motor nucleus of the trochlear nerve. Large lipofuscin-laden (probably serotonergic) neurons predominate. A number of cells similar in size and shape, but devoid of pigment, are found in this nucleus as well (Ohm et al., 1989). The ascending fibers of the anterior raphe nuclei generate projections to the hippocampal

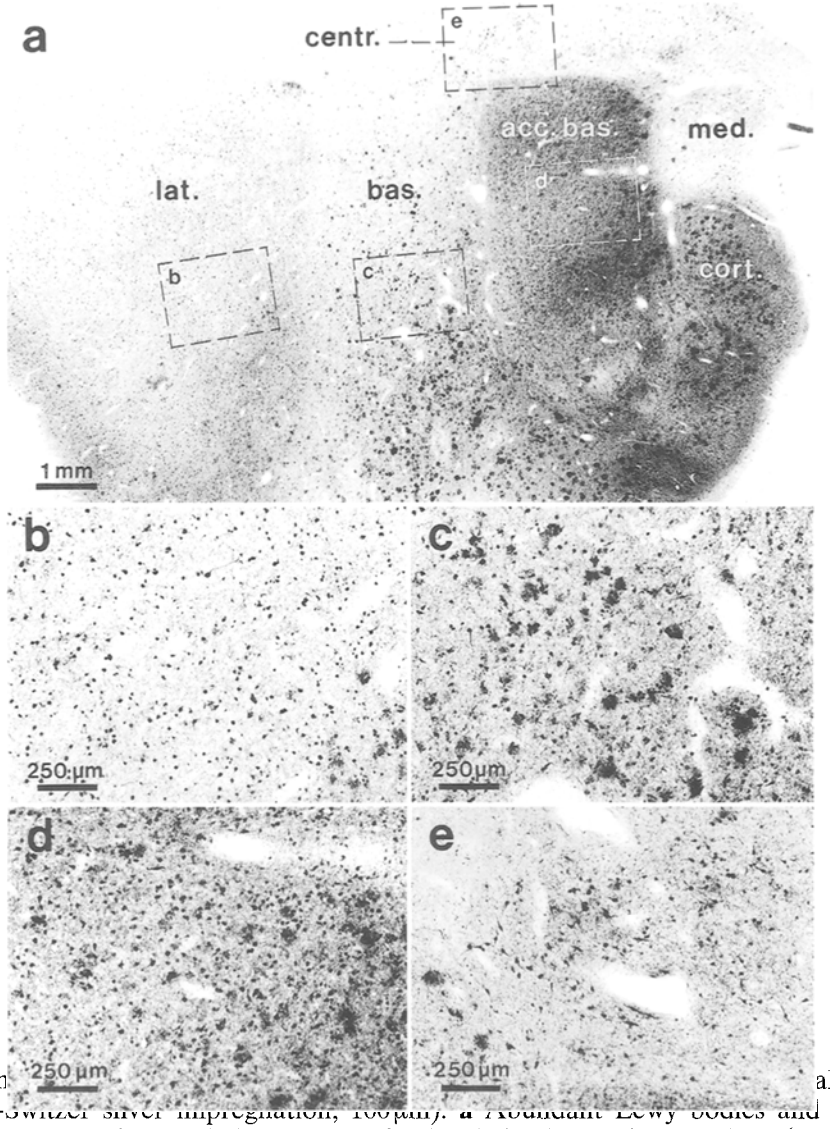

Fig. 13. Ch alamus (Campbell-Switzer silver impregnation, 100µm). **a** Abundant Lewy bodies and Lewy neurites of various sizes and shapes occur in the thalamic reuniens nucleus (reu) and within the interthalamic adhaesion (*mi* massa intermedia; *III* third ventricle). The framed area is shown in **b** at higher magnification. Similarly dense changes are seen in portions of the central medial and the paraventricular nucleus. **c** and **d** The extended hypothalamic tuberomamillary nucleus (*tm*) exhibits a large amount of Lewy bodies and Lewy neurites. *mb* mamillary body

formation, the entorhinal territory, and the neocortex (Törk and Hornung, 1990).

The noradrenergic locus coeruleus is situated in the lateral portions of the pontine tegmentum near the ependymal lining of the fourth ventricle. Predominant among its neuronal constituents are large neuromelanin-laden neurons, which give rise to long and frequently branching axons extending throughout large portions of the cerebral cortex, cerebellum, and spinal cord (van Dongen, 1981; Mann, 1984; Saper, 1987a; Manaye et al., 1995).

The pigmented subpeduncular nucleus is located within the pedunculolemniscal triangle, and accompanies the superior cerebellar peduncle (Fig. 15). A medium-sized spindle-shaped cell filled with small melanin granules represents the predominant neuronal type (Ohm and Braak, 1988). The connections of the nuclear gray are unknown.

Pathologic changes

PD-related changes. All of the nuclei mentioned above undergo marked destruction during the course of PD (Fig. 14). Abundant LBs/LNs are consistently encountered in the cholinergic nuclei of the basal forebrain and in the tuberomamillary nucleus (Lewy, 1923; Langston and Forno, 1978; Arendt et al., 1983; Whitehouse et al., 1983; Nakano and Hirano, 1984; Braak et al., 1994, 1995). The severe destruction of the tuberomamillary nucleus develops quite early and is often more pronounced than that of the magnocellular basal forebrain nuclei (Figs. 13, 14, 16). The raphe nuclei, the dopaminergic nuclei of the ventral tegmentum, and the locus coeruleus are slightly less severely

Fig. 14 and **15** (see page 480). Characteristic distribution pattern of Parkinson-related lesions (depicted in red, Fig. 14) and Alzheimer-related changes (depicted in blue, Fig. 15) in a series of sections cut perpendicular to Forels intercommissural axis (a–f), or respectively, to Meynerts brain stem axis (g-l). The Alzheimer changes are not portrayed as they appear in the end stage of the disease. They depict the relatively mild changes seen during the limbic stages III-IV. More severely involved areas generally correspond to areas which develop changes at earlier stages (depicted in dark blue). Less dense neurofibrillary changes developing during stages III and IV are light blue. *ab* accessory basal nucleus of amygdala, *ac* accessory cortical nucleus of amygdala, *ad* anterodorsal nucleus of thalamus, *am* anteromedial nucleus of thalamus, *an* abducens motor nucleus *ba* basal nucleus of amygdala, *bn* basal nucleus of Meynert *ca1* first Ammon's horn sector, *ca2* second Ammon's horn sector *ca* caudate nucleus, *cc* corpus callosum, *ce* central nuclei of amygdala, *cg* central grey of mesencephalon, *cl* claustrum, *co* cortical nuclei of amygdala, *cr* central nucleus of raphe, *db* nucleus of the diagonal band, *dm* dorsomedial hypothalamic nucleus, *dr* dorsal nucleus of raphe, *ds* decussation of superior cerebellar peduncles, *dv* dorsal nuclear complex of vagal nerve, *en* entorhinal region, *fn* facial motor nucleus, *fo* fornix, *gi* gigantocellular reticular nucleus, *gr* granular nucleus of amygdala, *hn* hypoglossal motor nucleus, *in* infundibular nucleus, *ir* intermediate reticular zone, *lc* locus coeruleus, *ld* laterodorsal nucleus of the thalamus, *lg* lateral geniculate body, *li* nucleus limitans thalami, *lt* lateral nuclei of the thalamus, *md* mediodorsal nuclei of thalamus, *me* medial nuclei of amygdala, *mf* medial longitudinal fasciculus, *mg* medial geniculate body, *ml* medial lemniscus, *mm* medial mamillary nucleus, *ms* medial septal nucleus, *mt* mamillothalamic tract, *mv* dorsal motor nucleus of vagal nerve, *oi* oliva inferior, *os* oliva superior, *ot* optic tract, *pe* external pallidum, *pf* parafascicular nucleus *ph* posterior hypothalamic nucleus, *pi* internal pallidum, *po* pontine grey, *pr* praepositus nucleus, *pu* putamen, *pv* paraventricular nucleus, *re* reticular nucleus of the thalamus, *rm* nucleus raphes magnus, *ru* nucleus ruber, *sb* subiculum, *sc* superior cerebellar peduncle, *sf* solitary fascicle, *so* supraoptic nucleus, *sn* substantia nigra, *sp* subpeduncular nucleus, *st* nucleus of the stria terminalis, *su* subthalamic nucleus, *te* transentorhinal region, *tl* lateral tuberal nucleus, *tm* tuberomamillary nucleus, *tp* tegmental pedunculopontine nucleus, *vl* ventrolateral nuclei of thalamus, *vm* ventromedial hypothalamic nucleus, *vn* vestibular nuclei, *vt* dopaminergic nuclei of ventral tegmentum (paranigral nucleus and pigmented parabrachial nucleus), *zi* zona incerta

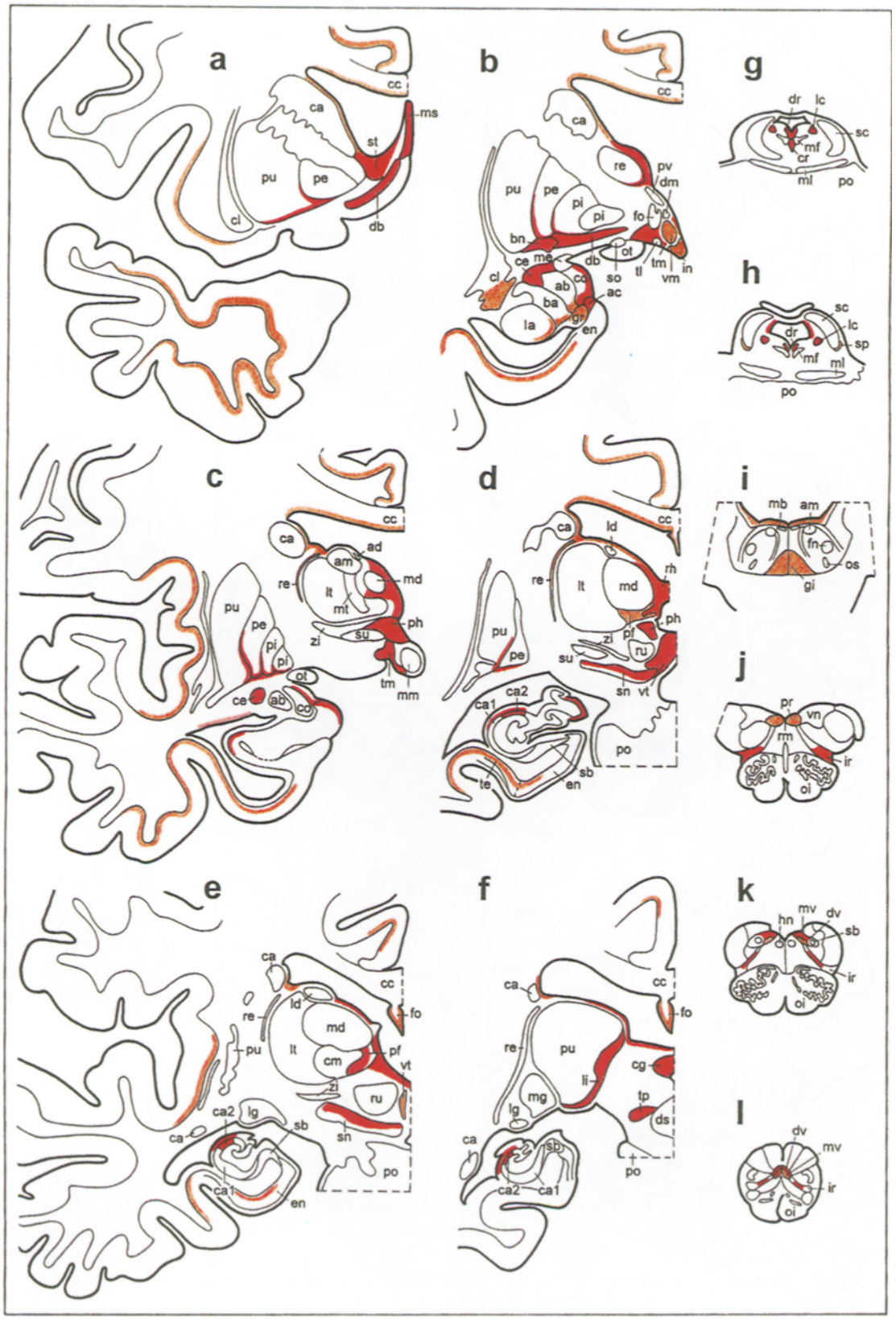
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Fig. 14

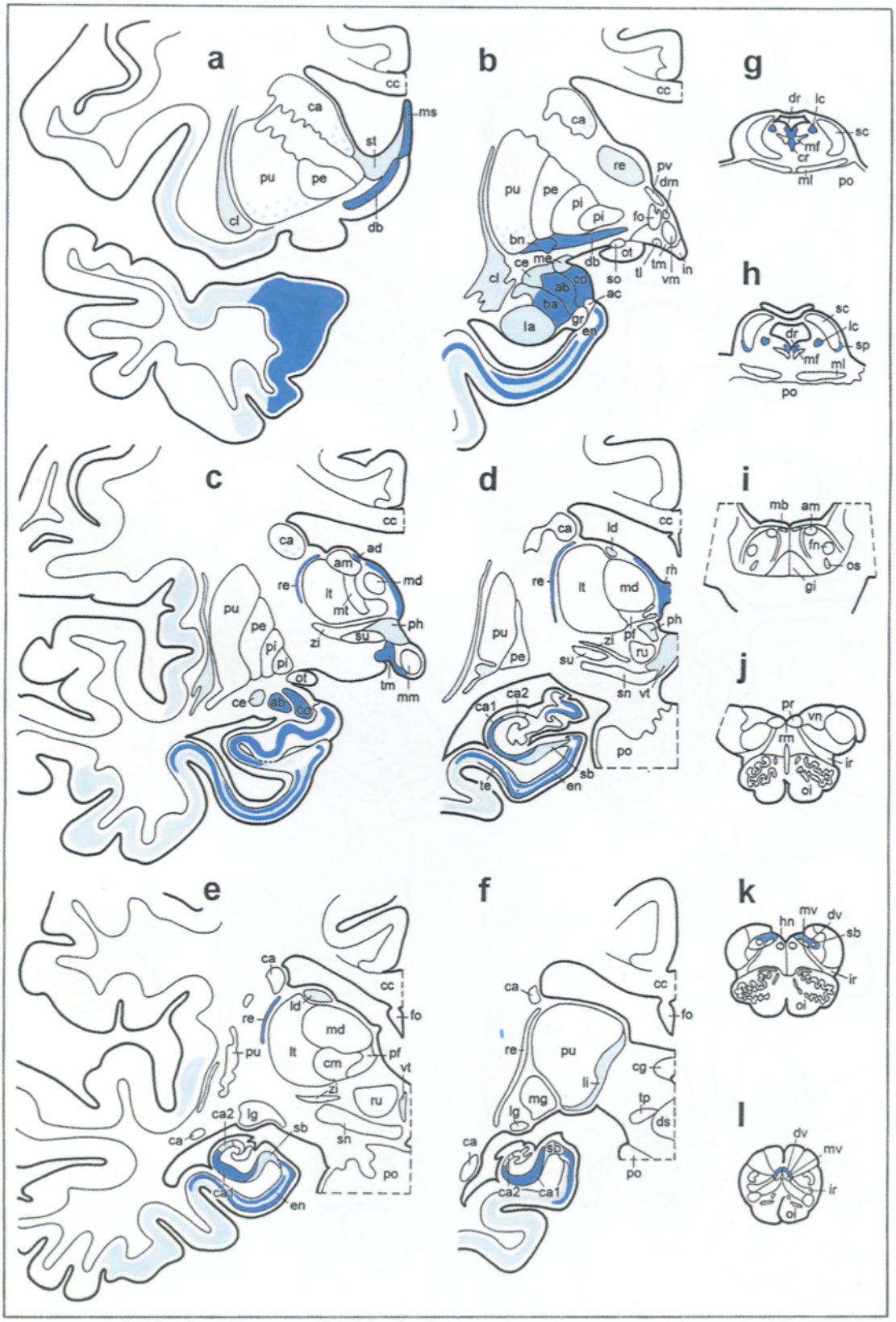
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Fig. 15

involved (Mann, 1984; Chan-Palay and Asan, 1989). All of the nuclei with diffuse cortex projections are subject to tight control from the central nucleus of the amygdala. Only the cholinergic nuclei receive additional input from the basolateral amygdala. The severe destruction of both the central nucleus and the nuclei with diffuse cortex projections greatly impairs the functioning of this system and reduces the input to the cerebral cortex (Fig. 16).

AD-related changes. All of the nuclei under consideration show AD-related changes restricted to those portions which generate projections to the cortex. Other portions of these nuclei with descending connections to the lower brain stem and spinal cord remain virtually unscathed (German et al., 1987). As in PD, the lesions result in a marked reduction of cortical input (Figs. 15, 17).

A further AD-related change deserves particular attention. It can be observed in anterior portions of the thalamic reticular nucleus. A dense network of club-shaped processes filled with AD-type abnormal material outlines the nucleus. This change may represent altered cholinergic terminal projections from basal forebrain nuclei. The position of this lesion predisposes it to interfere with the normal thalamocortical interactions (Fig. 11) (Tourtelotte et al., 1989; Xuereb et al., 1990; Braak and Braak, 1991a).

Functional consequences of the specific lesional patterns and of destruction resulting from co-occurrence of Parkinson's and Alzheimer's diseases

The lesional pattern which gradually develops during the course of PD involves many important components of the limbic system (Figs. 6a,b, 16, 17, 18). The pattern explains the gradual appearance of endocrine and autonomic dysregulation. In general, the lesions are not extensive enough to produce clinically overt intellectual impairment or personality changes, which might be expected to result from bilateral lesions of limbic system. It is tempting to suggest, however, that the PD-specific lesional pattern paves the way for the appearance of emotional disturbances, behavioral changes, and cognitive decline.

In AD, by contrast, impairment of memory appears early. As time passes, personality changes, speech disturbances, and eventually motor dysfunction in the form of a hypokinetic hypertonic syndrome supplement the initial symptoms. Only a few key areas of the limbic system are initially involved (Figs. 7, 10, 15, 17). Bilateral destruction just in entorhinal layer pre-α, however, results in a marked impairment of data transfer from the neocortex to the hippocampus. The additional involvement of a few related areas and nuclei leads to destruction of various limbic circuits at multiple sites (stages III and IV). The AD-specific lesional pattern thus, in all probability, contributes to the early appearance of memory impairment. Grave mental deterioration parallels the severe destruction of the neocortex (stages V and VI), and motor dysfunction eventually results from involvement of both the striatum (NFTs in cholinergic interneurons) and the substantia nigra (NFTs in dopaminergic projection cells).

The two diseases, PD and AD, frequently co-occur. Only a minority of

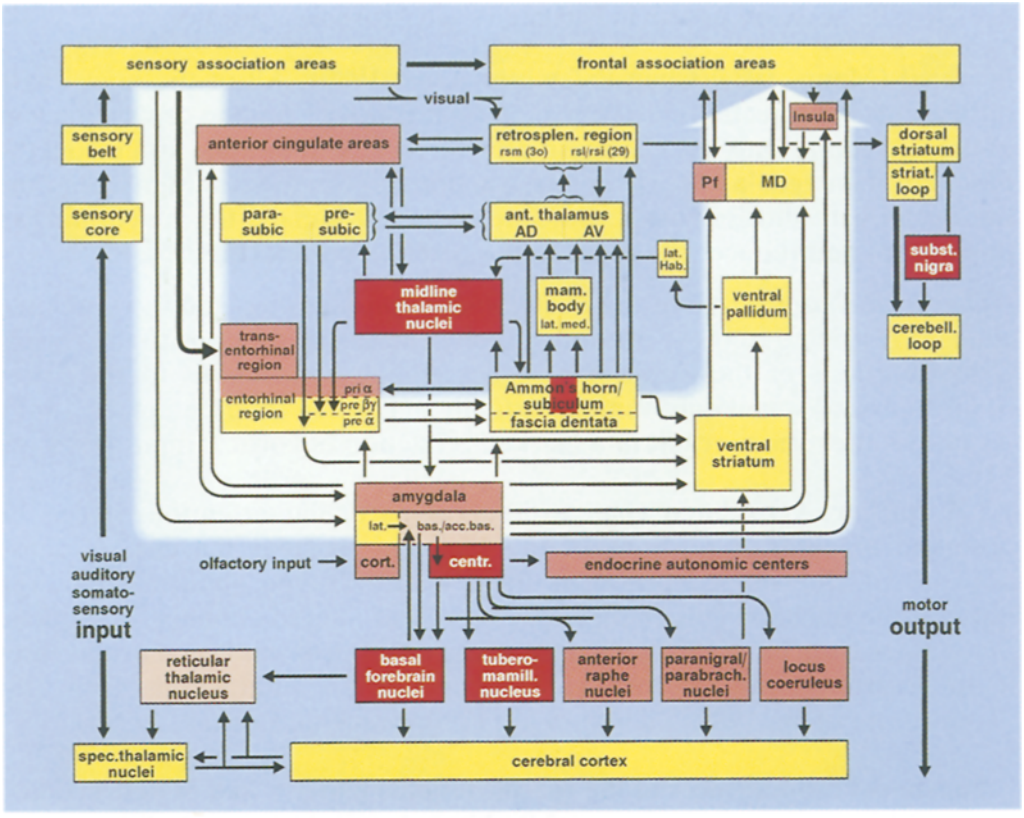

Fig. 16

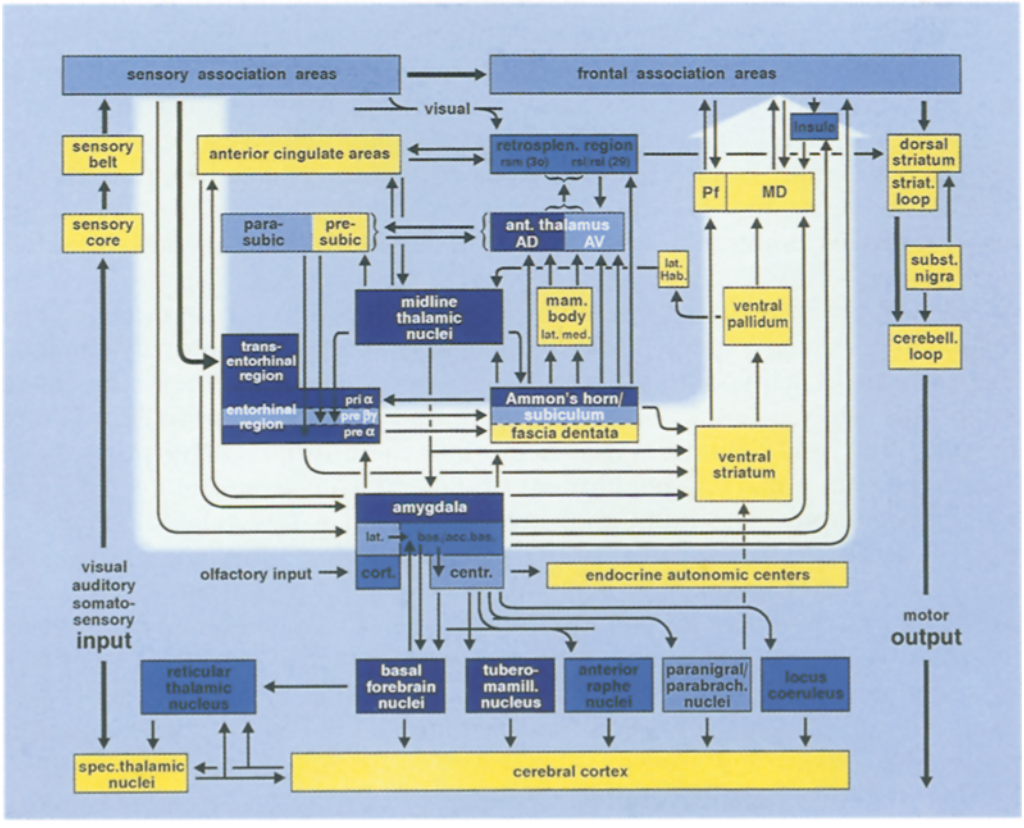

Fig. 17

Fig. 17

such cases show fully developed PD together with fully developed AD (stages V–VI). The majority include fully developed PD in the presence of relatively mild AD-related destruction corresponding to stage III or less. Both the PD- and the AD-related lesions maintain their characteristic distribution patterns. Many areas and nuclei show effects of changes caused by only one of the two diseases, while others display a combination of PD- and AD-related lesions (Fig. 18). Impairment of intellectual capabilities is frequently, though not consistently, observed in PD. Neuropathologic evaluation of many PD-cases with impaired cognition reveals concommitant AD at stage III (Braak and Braak, 1990). It is tempting to suggest that, in the Parkinsonian brain, the co-occurrence of even mild AD-related changes may be sufficient to produce mental deterioration, emotional instability, and personality changes. These symptoms do not usually occur in cases exhibiting solely PD-related lesions. It is important to note that many cases with purely AD-related stage III changes are also asymptomatic. However, a mild additional lesion to fully developed PD-related destruction may be enough to cause initial symptoms of cognitive impairment. The summary drawing (Fig. 18) shows the degree to which PD- and AD-specific lesions supplement each other and aggravate the destruction of the limbic system. Together, the two lesions probably have a potentiating effect sufficient to induce mental deterioration and changes in personality (Braak and Braak, 1990; Jellinger et al., 1991; Bancher et al., 1993; Jellinger and Bancher, 1995; Braak et al., 1995). This does not rule out the possibility that, in individual cases, other causes may be responsible for the appearance of dementia in PD (co-occurrence of argyrophilic grains (Braak and Braak,

Fig. 16. Schematic representation of the limbic loop and related structures. This Figure illustrates the nigral and the numerous extranigral changes seen in Parkinson's disease. Increasing intensity of red corresponds to increasing severity of Parkinson-related destruction. Among the extranigral lesions, the CA2 sector, the central amygdalar nucleus, midline thalamic nuclei, the basal forebrain nuclei and the tuberomamillary nucleus exhibit the most severe pathologic changes. *ant.thalamus AD AV* anterodorsal and anteroventral thalamic nuclei; *cerebell.loop* cerebellar loop; *lat.Hab.* lateral habenula; *lat.bas./acc.bas.cort.centr.* lateral, basal, accessory-basal, cortical and central amygdalar nuclei; *mam.body lat. med.* lateral and medial nuclei of the mamillary body; *MD* mediodorsal thalamic nucleus; *paranigral/parabrach.* paranigral and pigmented parabrachial nuclei; *parasubic presubic* parasubiculum, presubiculum; *Pf* parafascicular nucleus; *pri-α*, *pre-β*, *pre-γ*, *pre-α* layers of the entorhinal region; *retrosplen.region rsm (30) rsl/rsi (29)* medial retrosplenial area (Brodmann area 30), lateral and intermediate retrosplenial areas (Brodmann area 29); *spec. thalamic nuclei* specific projection nuclei of the thalamus; *striat. loop* striatal loop; *subst. nigra* substantia nigra; *tuberomamill.* tuberomamillary nucleus (with permission from Braak et al., 1996)

Fig. 17. Schematic representation of the Alzheimer-related neurofibrillary changes at intermediate limbic stages III–IV. In general, the more severely involved areas or nuclei are those which develop early changes (depicted in the most intense blue). More sparse neurofibrillary changes develop later in stages III and IV, and are marked in a lighter shade. At limbic stages, the transentorhinal/entorhinal regions, the anterodorsal thalamic nucleus, the limbic midline thalamic nuclei, several subnuclei of the amygdala, the basal forebrain nuclei and the tuberomamillary nucleus show the most severe changes. For abbreviations see Fig. 16

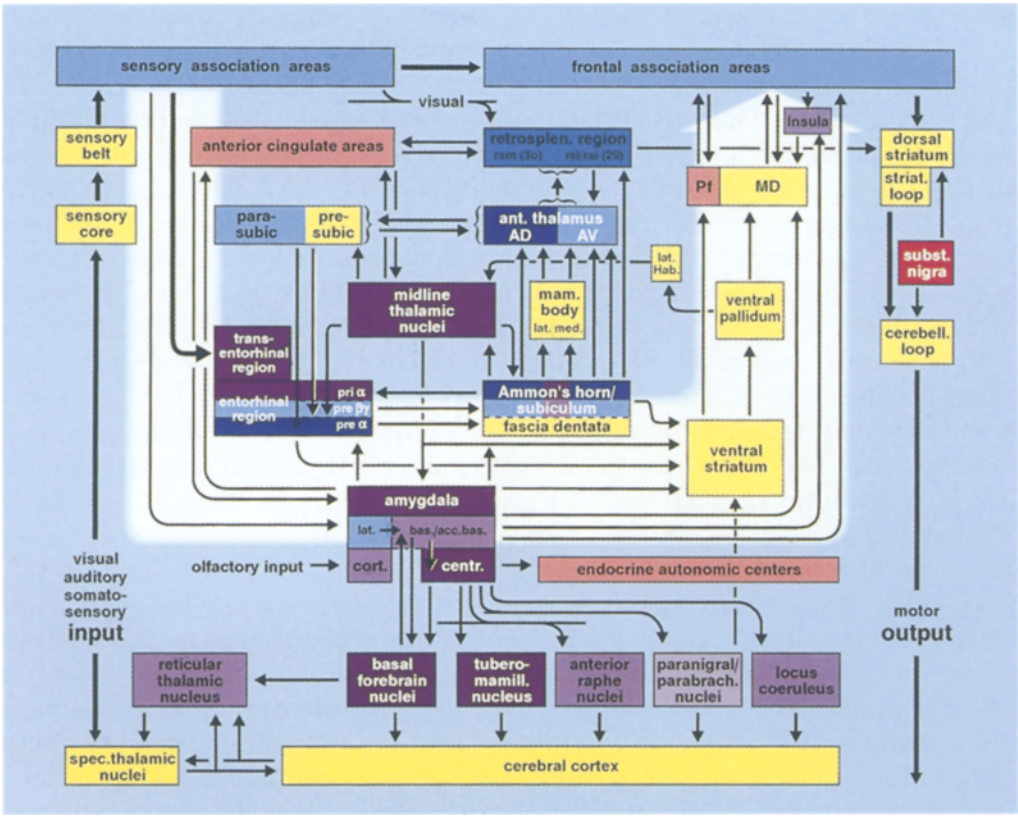

Fig. 18. Co-occurrence of fully developed Parkinson's disease and relatively mild Alzheimer-related changes corresponding to stage III or IV results in severe aggravation of limbic loop destruction. Some areas or nuclei show lesions caused by only one of the two diseases (depicted in either red or blue) while others display a combination of Parkinson- and Alzheimer-related destruction (displayed in violet). Together the two lesions lead to severe impairment of limbic loop functions. For abbreviations see Fig. 16

1989), multiple infarctions or other specific lesions). The concept that co-occurring AD-related brain destruction brings about most cases of intellectual decline in PD seems to be supported by the presently available data.

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