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Review

Hierarchical Distribution of the Tau Cytoskeletal Pathology in the Thalamus of Alzheimer's Disease Patients

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Abstract. In spite of considerable progress in neuropathological research on Alzheimer's disease (AD), knowledge regarding the exact pathoanatomical distribution of the tau cytoskeletal pathology in the thalamus of AD patients in the advanced Braak and Braak AD stages V or VI of the cortical cytoskeletal pathology is still fragmentary. Investigation of serial 100 μm-thick brain tissue sections through the thalamus of clinically diagnosed AD patients with Braak and Braak AD stage V or VI cytoskeletal pathologies immunostained with the anti-tau AT8 antibody, along with the affection of the extraterritorial reticular nucleus of the thalamus, reveals a consistent and severe tau immunoreactive cytoskeletal pathology in the limbic nuclei of the thalamus (e.g., paraventricular, anterodorsal and laterodorsal nuclei, limitans-suprageniculate complex). The thalamic nuclei integrated into the associative networks of the human brain (e.g., ventral anterior and mediodorsal nuclei) are only mildly affected, while its motor precerebellar (ventral lateral nucleus) and sensory nuclei (e.g., lateral and medial geniculate bodies, ventral posterior medial and lateral nuclei, parvocellular part of the ventral posterior medial nucleus) are more or less spared. The highly stereotypical and characteristic thalamic distribution pattern of the AD-related tau cytoskeletal pathology represents an anatomical mirror of the hierarchical topographic distribution of the cytoskeletal pathology in the interconnected regions of the cerebral cortex of AD patients. These pathoanatomical parallels support the pathophysiological concept of a transneuronal spread of the disease process of AD along anatomical pathways. The AD-related tau cytoskeletal pathology in the thalamus most likely contributes substantially to the neuropsychiatric disease symptoms (e.g., dementia), attention deficits, oculomotor dysfunctions, altered non-discriminative aspects of pain experience of AD patients, and the disruption of their waking and sleeping patterns.

Keywords: Alzheimer's disease, cytoskeletal pathology, pathoanatomy, tau, thalamus

ALZHEIMER'S DISEASE-RELATED PATHOLOGIES

Alzheimer's disease (AD) is a relentlessly progressive neuropsychiatric disorder, represents the most frequent dementing disorder, and accounts for 60 to 70%

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of demented individuals worldwide [1–5]. AD thus constitutes a tremendous burden for the patients and their families and caregivers, as well as for the health systems and social economies [1, 2, 4–6].

The neuropathological hallmarks of AD include (1) severe neuronal loss in specific cortical and subcortical components of the limbic system (e.g., transentorhinal and entorhinal regions, hippocampus, amygdala, cholinergic nuclei of the basal forebrain, dopaminergic compact part of the substantia nigra, locus coeruleus, raphe nuclei) and (2) intraneuronal deposits of the hyperphosphorylated tau protein and extraneuronal deposits of the insoluble amyloid-β protein [4, 5, 7–16].

In demented AD patients, the extraneuronal neuropil depositions of the insoluble amyloid-β protein can be observed in all parts of the allo- and neocortex, amygdala, basal forebrain, striatum, hypothalamus, thalamus, in select brainstem nuclei, and in the cerebellum. The rostrocaudal distribution and extent of these cortical and subcortical amyloid-β protein depositions, however, displays a clear gradient in the brains of patients in the advanced clinical phase of AD. Their brain expansion begins already in the preclinical phase of AD, affects apparently healthy and neuropsychiatric unremarkable individuals, and ensures distinct temporal and topographical sequences in which the brain regions are hierarchically affected. According to Thal et al., this stereotypical sequence can be artificially subdivided into five developmental phases (i.e., phase 1: exclusive affection of the cerebral neocortex; phase 2: additional amyloid-β protein deposition in the cerebral allocortex; phase 3: additional amyloid-β protein deposits in the basal forebrain, hypothalamus, thalamus, and striatum; phase 4: additional affection of a few, select brainstem nuclei; phase 5: occasional affection of the cerebellum) [2, 4, 10, 17].

The sequential and hierarchical evolution of the AD-related brain β-amyloidosis correlates with the increasing severity of the AD-related tau cytoskeletal pathology in the cerebral cortex described and reflected by the Braak and Braak AD staging system (see next section). The development of the AD-related tau cytoskeletal pathology in most diseased brain regions precedes the onset of the AD-related brain β-amyloidosis, and contributes demonstrably more substantially to the pathogenesis of the clinical AD symptoms. The pathogenetic association of the evolution of the intraneuronal tau pathology and the extracellular neuropil deposits of the insoluble amyloid-β protein was specified many years ago in the 'amyloid cascade theory'. However, despite ongoing scientific efforts this association is still enigmatic. According to the cascade hypothesis, the increase in amyloid-β secretion in the diseased brain and the extraneuronal aggregation of amyloid-β may serve as inductors and triggers of a cascade of fatal changes, which sooner or later culminate in the development of the AD-related tau cytoskeletal pathology and eventually in neuronal death. However, the findings (1) that the progressive topographical spreads of the AD-related tau pathology and β-amyloidosis throughout the brain do not coincide and take different ways (also see next section), (2) that the AD-related tau cytoskeletal pathology in most affected brain regions develops in the absence of any brain amyloid-β deposits, and (3) that the final brain distribution patterns of the AD-related neuronal and extraneuronal protein pathologies are not identical call the validity of the 'amyloid cascade theory' into question and are in favor of the opinion that the accumulations of the amyloid-β protein do not represent the initial pathological AD-related alterations which secondarily provoke the evolution of the AD-related tau cytoskeletal pathology [2, 4–6, 10, 15, 17, 18].

Tau represents an axonal cytoskeletal and the major microtubule associated protein (MAP). In AD, tau undergoes pathological hyperphosphorylation owing to an imbalance of multiple protein kinases and phosphatases which leads to (1) a reduction of its affinity for microtubules, (2) ineffective microtubule polymerization, assembly, and stabilization, (3) loss of microtubule rails and impairments of intraaxonal transport mechanisms, and (4) to insolubility, self-aggregation, and deposition of the hyperphosphorylated tau protein in affected neurons [2, 4, 5, 10, 12–15, 19, 20]. These insoluble neuronal accumulations of the hyperphosphorylated tau protein ultimately acquire the form of paired helical filaments, which represent the ultrastructural basis of the AD-related cytoskeletal pathology and coalesce into argyrophilic neurofibrillary tangles (NFT) in neuronal perikarya and into dendritic neuropil threads (NT) [2, 4, 7–9, 13–15, 19, 20].

THE BRAAK AND BRAAK STAGING SYSTEM OF THE AD-RELATED CORTICAL TAU CYTOSKELETAL PATHOLOGY

Owing to the highly stereotypical, spatial, and chronological spread of the AD-related tau cytoskeletal pathology throughout the cerebral cortex, a

neuropathological staging procedure could be developed, which describes its progressive cortical spread, increasing severity and topographical distribution (i.e., Braak and Braak AD stages in the evolution of the AD-related cortical cytoskeletal pathology). The original version of this worldwide practiced six-point staging system was created nearly twenty-five years ago. It is based on the pathoanatomical investigation of Gallyas silver impregnated 100 μm thick brain tissue sections and the assessment of the cortical distribution of argyrophilic NFT and NT and represents a rapid, extremely time-consuming and reliable procedure for the postmortem assessment of the cortical distribution and degree of the AD-related tau pathology upon diagnostic neuropathological examination [2, 4, 5, 8, 10, 15, 21]. To enable its more uniform application, this diagnostic staging procedure was adapted nearly ten years ago to the needs of thin paraffin-embedded sections (5–15 μm) and robust immunoreactions with the monoclonal antibody AT8 raised against the hyperphosphorylated tau protein [2, 7]. Unfortunately, both the original and the recently adapted Braak and Braak staging procedures of the AD-related tau cytoskeletal pathology exclusively related to the distribution and progression of this pathology in the cerebral cortex and did not consider the AD-related subcortical tau cytoskeletal pathology in detail. The subcortical tau cytoskeletal pathology for a long time span has been regarded as a secondary pathological phenomenon that develops subsequent to the affection of the cerebral cortex [2, 7, 8, 10, 18, 21, 22].

The predictable temporal and spatial expansion of the AD-related cortical tau cytoskeletal pathology starts with initial cytoskeletal changes in the transentorhinal region of the mediobasal temporal lobe, then affects nerve cells in the immediately adjacent entorhinal region, penetrates the hippocampus, and ultimately extends into all portions of the cerebral neocortex. This reproducible and inter-individually consistent progression of the AD-related tau cytoskeletal pathology in the cerebral cortex also implies a long-lasting preclinical phase of approximately three to four decades and correlates closely with the progression of the clinical AD symptoms [1, 4, 5, 7, 8, 15, 22, 23].

The allocortical transentorhinal or entorhinal regions for a long time not only were considered as the starting point for the propagation of the AD-related tau cytoskeletal pathology in the cerebral cortex, but also were believed to represent the first brain targets of this pathology in Braak and Braak AD stage I [2, 4, 7, 8, 10, 15]. Recent cross-sectional studies, however, repeatedly showed that the extent and distribution of the AD-related subcortical tau cytoskeletal pathology has been considerably underestimated and the time point of its onset wrongly assessed in the past. They provided striking evidence that a subset of subcortical nuclei with projections to the allocortical transentorhinal and entorhinal regions including the limbic nuclei of the thalamus (e.g., central medial, cental lateral, paraventricular, and laterodorsal thalamic nuclei, limitans-suprageniculate complex) are already very early affected by the AD-related tau cytoskeletal pathology before initial changes become manifest in these allocortical regions [5] and indicated that the AD-related tau cytoskeletal pathology originates and is induced in one of these very early affected subcortical brain regions. These unexpected results reinforced the early 'outsider' concept that the AD-related tau cytoskeletal pathology has its starting point somewhere in subcortical regions and supported the widely held idea that the early occurring subcortical tau cytoskeletal pathology, including that in the thalamus, may play a crucial role in the cascades of the early pathological events of AD [5, 18, 21].

In view of its very early affection in the absence of any tau cytoskeletal changes in the allocortex (i.e., in Braak and Braak AD stage 0), the noradrenergic locus coeruleus of the pons has been recently suggested as the possible starting point of the AD-related brain tau cytoskeletal pathology. This appraisal led for the first time to the explicit consideration of subcortical cytoskeletal changes in the Braak and Braak AD staging system and resulted in its revision and in the introduction of a 'pre-cortical' phase in the evolution of the AD-related tau cytoskeletal pathology [2, 5]. In consideration, however, of the recently demonstrated widespread distribution of the very early subcortical tau cytoskeletal pathology in Braak and Braak AD stage 0 individuals and the controversial question regarding the exact starting point of the AD-related tau cytoskeletal pathology in the brain, it has been recommended to reconsider and to re-evaluate these recently modified neuropathological Braak and Braak AD stages [5, 8, 10, 18, 21].

THE HIERARCHICAL AFFECTION OF THE THALAMUS BY THE TAU CYTOSKELETAL PATHOLOGY IN AD AND ITS ASSOCIATION WITH THE THALAMIC β-AMYLOIDOSIS

Although it is well known that the thalamus is among the subcortical targets of and may be very early

affected by the AD-related tau cytoskeletal pathology [8–11, 24–30], knowledge regarding the exact anatomical distribution of this thalamic pathology in demented AD patients burdened by an advanced Braak and Braak AD stage V or VI cortical cytoskeletal pathology still is fragmentary and currently is only insufficiently described even in comprehensive monographs [2]. The elucidation of the essential principles and mechanisms of the highly ordered topographical and chronological brain spread and propagation of the AD-related tau cytoskeletal pathology and the search for and the generation of conclusive explanations for the high vulnerability of select brain regions for and the resistance of others against the development of the AD-related tau cytoskeletal pathology, however, requires holistic and metaanalytic considerations of the exact anatomical brain distribution pattern of this AD-related pathology. Therefore, detailed knowledge about the exact pathoanatomical distribution pattern of this pathology in all affected brains regions of AD patients, including the diencephalic thalamus, is mandatory.

In the present review, we provide a short overview of the hierarchical and anatomical distribution of the tau cytoskeletal pathology in the thalamus of AD patients (Fig. 1), the potential pathomechanisms of its evolution, and its possible relevance for the clinical picture of AD. This short pathoanatomical review is based (1) on previous reports about thalamic affection in AD patients, which were confined to select thalamic nuclei or regions and were predominantly based on the investigation of silver impregnated brain tissue sections, and (2) on the careful examination of AT8 immunostained, unconventional 100 μm thick serial tissue sections through the thalamus of seven clinically diagnosed and APOE-genotyped AD patients burdened by Braak and Braak AD stage V or VI cortical tau cytoskeletal pathologies [2, 7–11, 15, 18, 19, 24–30] and Thal phase 3, 4, or 5 brain β-amyloidosis [4, 17].

The main intention of our short review is to outline the precise pathoanatomical distribution of the tau cytoskeletal pathology in the thalamus of patients in the advanced clinical stages of AD. Although it was not designed to elucidate the enigmatic association between the evolution of the AD-related tau cytoskeletal pathology and β-amyloidosis, the review is complemented by a brief description of the topographical distribution of the thalamic β-amyloidosis as observed upon investigation of 100 μm thick serial thalamic tissue sections immunostained with the anti-amyloid-β antibody 4G8 [17].

Fig. 1. AT8-immunoreactive tau cytoskeletal pathology in thalamic nerve cells of an Alzheimer's disease (AD) patient. Pathological immunoreactive tau aggregations appearing as homogeneously distributed granules in the soma, dendrites, and proximal axon of an affected projection neuron of the thalamic anteroprincipal nucleus of an individual burdened by Braak and Braak AD stage VI cytoskeletal pathology (anti-tau immunostaining with the AT8 antibody; 100 μm PEG section).

The monoclonal anti-tau antibody AT8 is very sensitive in detecting the abnormal phosphorylated tau protein without showing cross-reactivity with normal tau epitopes. It recognizes phosphorylated tau epitopes at serine 202 and threonine 205 and reveals a robust, reliable, and consistent immunoreactivity for the hyperphosphorylated tau protein in human brain autopsy material regardless of the length of the fixation time in formaldehyde and/or the condition of the preserved brain tissue. The AT8 antibody highlights mature AD-related NFT with nearly identical clarity and sensitivity than the traditional silver staining techniques (e.g., Gallyas silver staining), but also facilitates the visualization of non-argyrophilic accumulations of the hyperphosphorylated tau protein (i.e., so-called pretangle material) in the somata, dendrites, and axons of affected nerve cells and prior to its transformation into argyrophilic, compact intraneuronal NFT, and/or NT (Fig. 1) [2, 5, 7, 10, 18, 19, 21].

Although some myths entwine around the neuroanatomy of the human thalamus and its functions, the architectonics of this large diencephalic nuclear complex can be encapsulated and depicted in a simplified fashion when condensing its essential components

according to subordinate topographical, connectional, and functional principles. Along with some fiber tracts (e.g., mamillothalamic tract, Vicq d'Azyr) and medullary laminae, the human thalamus harbors anatomically well-defined nuclei integrated into the limbic, associative, somatomotor, and sensory neural circuits of the human brain, represents the major anatomical link between its sensory systems and its cerebral cortex, and therefore is often designated as the 'gateway to consciousness'. The extra-territorially located reticular nucleus of the thalamus quasi acts as a control station, which actively regulates the entire thalamocortical and corticothalamic flow of neural information (Fig. 2) [31, 32].

In patients in the advanced clinical stages of AD and affected by Braak and Braak AD stage V or VI cortical cytoskeletal pathology, the thalamus shows a widespread affection by the AT8 immunoreactive tau cytoskeletal pathology. The pathological immunoreactive tau aggregations consistently appear as homogeneously distributed granules of various sizes in the somata, dendrites, and proximal axons of affected nerve cells (Figs. 1, 3, 4). The thalamic nuclei of AD patients, however, differ remarkably with respect to their predisposition to develop the tau immunoreactive cytoskeletal pathology and are affected by this pathology to differing degrees. This differential vulnerability ultimately results in a characteristic and inter-individually consistent hierarchical and nuclei-specific distribution pattern of the tau cytoskeletal pathology within the thalamus of AD patients. As with other affected cortical and other subcortical regions, the nuclei of the human thalamus assigned to and integrated into the limbic system are most severely affected by the AD-related cytoskeletal pathology and clearly dominate the distribution of the thalamic tau cytoskeletal pathology. The severity of the tau cytoskeletal pathology in these limbic thalamic nuclei followed by the marked affection of thalamic nuclei integrated into the associative networks of the human brain. In contrast, the motor and sensory nuclei of thalamus are at best slightly affected by the AT8 immunoreactive tau cytoskeletal pathology (Figs. 2–4) [5, 10, 11, 24–30; Udo Rüb personal, unpublished data].

The limbic nuclei of the human thalamus consistently affected by a severe AT8 immunoreactive tau cytoskeletal pathology include nuclei of the anterior (anterodorsal and laterodorsal nuclei), midline (paraventricular nucleus), rostral intralalaminar (central medial, paracentral, cucullar and central lateral nuclei) and caudal intralaminar groups (subparafascicular nucleus), the dorsomedial aspects of the medial pulvinar, and the limitans-suprageniculate complex at the thalamic border to the midbrain (Figs. 2–4) [5, 9, 11, 24; Udo Rüb personal, unpublished data]. A less severe, but marked tau cytoskeletal pathology is commonly present in the associative nuclei (fasciculosus, anteroprincipal, parataenial, mediodorsal, and parafascicular nuclei) (Figs. 1–4) [9, 24, 27; Udo Rüb personal, unpublished data]. The motor nuclei of the thalamus (ventral lateral thalamic nucleus, centromedian nucleus, lateral posterior nucleus), the somatosensory (ventral posterior medial and lateral nuclei), gustatory (ventral posterior medial nucleus, parvocellular part), primary (lateral geniculate body), and secondary visual nuclei (inferior and lateral pulvinar, pregeniculate nucleus), as well as the primary auditory medial geniculate body are either completely spared by the AD-related tau cytoskeletal pathology or may show not more than mild alterations [24, 26, 28; Udo Rüb personal, unpublished data]. The rostrally situated ventral anterior nucleus is integrated into the associative and motor circuits of the human brain and commonly is markedly affected by the tau cytoskeletal pathology (Figs. 2, 3) [Udo Rüb personal, unpublished data]. Finally, the extraterritorial reticular nucleus of the thalamus is consistently severely affected by the AD-related tau cytoskeletal pathology (Figs. 2–4) [29; Udo Rüb personal unpublished data].

As in numerous other diseased brain regions, the AD-related β-amyloidosis develops in the thalamus only a long time span after the onset of initial AD-related cytoskeletal changes. In addition, the ultimate topographical distribution of the amyloid-β deposits in the thalamus of demented AD patients admittedly overlaps, but does not entirely coincide with the hierarchical distribution of the tau cytoskeletal pathology [2, 4, 5, 10, 15]. Beginning with Thal phase 3 [17], the AD-related β-amyloidosis consistently affects all thalamic nuclei including the extraterritorial reticular nucleus (Fig. 5) [8, 9, 24–28; Udo Rüb personal, unpublished data]. The thalamic β-amyloidosis is less selective than the tau cytoskeletal pathology and commonly affects its paraventricular, fasciculosus, anteroprincipal, anterodorsal, central medial, paracentral, cucullar, parafascicular, ventral lateral, lateral posterior, central lateral, ventral posterior medial, ventral posterior lateral nuclei, the parvocellular part of the ventral posterior medial nucleus, the pulvinar, and medial geniculate body severely. In contrast, its ventral anterior, parataenial, centromedian, subparafascicular, pregeniculate, and reticular nuclei, as well as its limitans-suprageniculate complex and lateral geniculate body are markedly affected (Fig. 5).

POTENTIAL PATHOMECHANISMS OF THE HIERARCHICAL EVOLUTION OF THE THALAMIC TAU CYTOSKELETAL PATHOLOGY IN AD

The AD-related tau cytoskeletal pathology is distributed in the affected thalamus according to a hierarchical, nuclei-specific pattern, which represents an exact anatomical mirror of the differential and hierarchical affection of the interconnected and functionally related regions of the cerebral neo-and allocortex integrated into the limbic, associative, motor or sensory circuits of the human brain [2, 4, 5, 9–11, 15, 20, 24, 25].

Previous attempted explanations of the enigmatic phenomenon of the selective vulnerability of circumscribed brain regions for the AD-related tau cytoskeletal pathology were either based on their

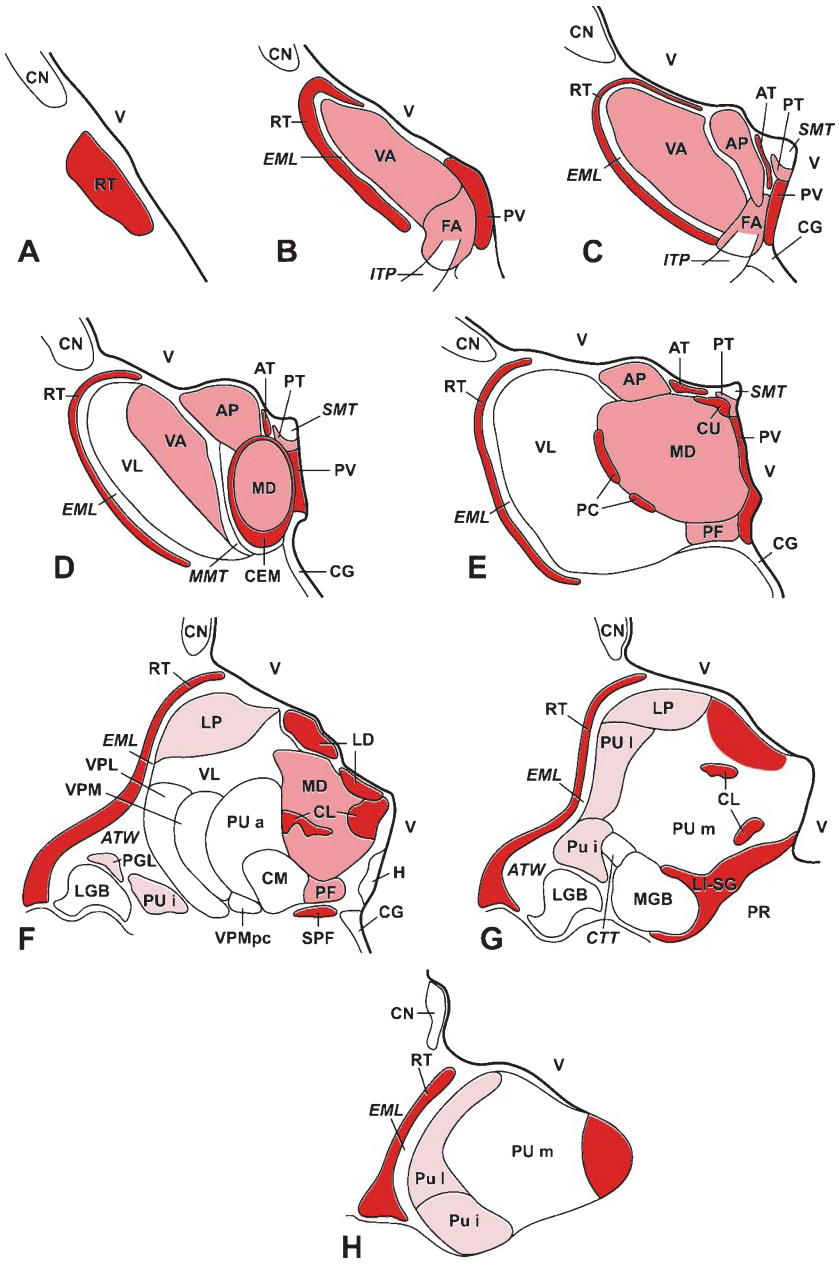

Fig. 2.

integration into the limbic brain system or specific brain neurotransmitter systems, on the specific molecular biochemical phenotypes or on the poorly developed myelin sheath of the long axons of diseased nerve cells [2, 5, 16, 19, 33]. Increasing evidence, however, points to the anatomical interconnectivities of a given brain region as a crucial factor accounting for its susceptibility for or resistance to the AD-related tau cytoskeletal pathology, and as the critical structural prerequisite for the strikingly well-ordered progressive brain expansion of the underlying pathological process and the resulting hierarchical brain distribution pattern of the AD-related tau cytoskeletal pathology [5, 10, 11, 16, 18, 20, 21, 33–36].

These close pathoanatomical parallels between the distribution patterns of the AD-related tau cytoskeletal pathology in the cerebral cortex and anatomically interconnected thalamic regions support the currently widely held pathophysiological concept that the anatomical interconnectivities of given brain regions establish their vulnerability for or resistance to this AD-related pathology. In addition, they are in agreement with the view that the pathological process of AD uses these anatomical pathways and interconnectivities for its predictable, inter-individually consistent, and chronologically and topographically highly ordered sequential transneuronal spread throughout the brain [5, 10, 11, 16, 18, 21, 33–36]. The high vulnerability of the limbic nuclei of the thalamus for the AD-related cytoskeletal pathology is not only reflected by their outstanding affection in the advanced neuropathological Braak and Braak AD stages V and VI, but is also documented by their very early affection during the evolution of the AD-related tau cytoskeletal pathology in the brain. According to recent cross-sectional studies the limbic nuclei of the thalamus are very early affected and already show initial tau cytoskeletal changes either in the absence or presence of at best mild alterations in the allocortical transentorhinal and/or entorhinal regions, which for a long time have been regarded as the first brain targets of the AD-related tau cytoskeletal pathology [2, 4, 5, 7–10, 15, 24].

The directed transneuronal spread and stereotypical brain propagating of the underlying disease process along anatomical pathways together with its begin in circumscribed brain regions are currently regarded to be among the neuropathological hallmarks of the human neurodegenerative ‘protein-conformational disorders’ assigned to the so-called ‘prion-like’ diseases [2, 5, 16, 34, 35]. The suggested begin of the pathological process associated with the occurrence of the initial AD-related tau cytoskeletal changes in

Fig. 2. Hierarchical anatomical distribution of the tau immunoreactive cytoskeletal pathology in the thalamus of Alzheimer’s disease patients. Schematized frontal sections cut perpendicularly to Forel’s intercommissural axis showing the rostrocaudal sequence of the nuclei of the human thalamus. A) Rostral pole of the thalamus with the extraterritorial reticular nucleus (RT). B) Rostral portion of the human thalamus with the reticular (RT), ventral anterior (VA), fasciculosus (FA), and paraventricular nuclei (PV). C) Rostral thalamic portion at the level of the anterodorsal nucleus (AT): Reticular (RT), anteroprincipal (AP), ventral anterior (VA), fasciculosus (FA), paraventricular (PV), and parataenial nuclei (PT). D) Rostral thalamus at the level of the mamillothalamic tract (Vicq d’Azyr): Reticular (RT), ventral lateral (VL), ventral anterior (VA), central medial (CEM), mediodorsal (MD), paraventricular (PV), parataenial (PT), anterodorsal (AT) and anteroprincipal nuclei (AP). E) Mid portion of the thalamus at the level of the rostral intralaminar cucullar nucleus (CU): Reticular (RT), ventral lateral (VL), mediodorsal (MD), paracentral (PC), parafascicular (PF), paraventricular (PV), parataenial (PT), anterodorsal (AT) and anteroprincipal nuclei (AP). F) Caudal portion of the thalamus at the level of the caudal intralaminar nuclei (centromedian nucleus, CM; parafascicular nucleus, PF; subparafascicular nucleus, SPF): Reticular nucleus (RT), lateral geniculate body (LGB), pregeniculate nucleus (PGL), inferior nucleus of the pulvinar (PU i), lateral posterior (LP), ventral lateral (VL), ventral posterior lateral (VPL) and ventral posterior medial nuclei (VPM), anterior nucleus of the pulvinar (PU a), ventral posterior medial nucleus, parvocellular part (VPMpc), central lateral (CL), mediodorsal (MD) and laterodorsal nuclei (LD). G) Caudal thalamus with the lateral (LGB) and medial geniculate bodies (MGB): Reticular (RT) and lateral posterior nuclei (LP), lateral (PU l) and inferior nuclei of the pulvinar (PU i), medial nucleus of the pulvinar (PU m), central lateral nucleus (CL), limitans-suprageniculate complex (LI-SG). H) Caudal pole of the thalamus with the reticular nucleus (RT), lateral (PU l), inferior (Pu i) and medial nuclei (PU m) of the pulvinar [31, 32]. Thalamic nuclei severely affected by the AD-related tau cytoskeletal pathology are colored in red. Markedly affected nuclei are colored in light red and slightly involved nuclei in light pink (Modified according to Rüb et al. Thalamic involvement in a spinocerebellar ataxia type 2 (SCA2) and a spinocerebellar ataxia type 3 (SCA3) patient, and its clinical relevance. Brain 2003, 126 : 2257-2272; Fig. 1, page 2260; with kind permission from Oxford University Press). AD, Alzheimer’s disease; AP, Anteroprinicipal thalamic nucleus; AT, Anterodorsal thalamic nucleus; ATW, Triangular area of Wernicke; CEM, Central medial thalamic nucleus; CG, Central grey; CL, Central lateral thalamic nucleus; CM, Centromedian thalamic nucleus; CN, Caudate nucleus; CTT, Corticotectal tract; CU, Cucullar thalamic nucleus; EML, External medullary lamina; FA, Fasciculosus thalamic nucleus; H, Habenular nuclei; ITP, Inferior thalamic peduncle; LD, Laterodorsal thalamic nucleus; LGB, Lateral geniculate body; LI-SG, Limitans-suprageniculate complex of the thalamus; LP, Lateral posterior thalamic nucleus; MD, Mediodorsal thalamic nucleus; MGB, Medial geniculate body; MMT, Mamillothalamic tract (Vicq d’Azyr); PC, Paracentral thalamic nucleus; PF, Parafascicular thalamic nucleus; PGL, Pregeniculate thalamic nucleus; PR, Pretectum; PT, Parataenial thalamic nucleus; PU a, Pulvinar of the thalamus, anterior nucleus; PU i, Pulvinar of the thalamus, inferior nucleus; PU l, Pulvinar of the thalamus, lateral nucleus; PU m, Pulvinar of the thalamus, medial nucleus; PV, Paraventricular thalamic nucleus; RT, Reticular thalamic nucleus; SMT, Stria medullaris thalami; SPF, Subparafascicular thalamic nucleus; V, Ventricle; VA, Ventral anterior thalamic nucleus; VL, Ventral lateral thalamic nucleus; VPL, Ventral posterior lateral thalamic nucleus; VPM, Ventral posterior medial thalamic nucleus; VPMpc, Ventral posterior medial thalamic nucleus, parvocellular part.

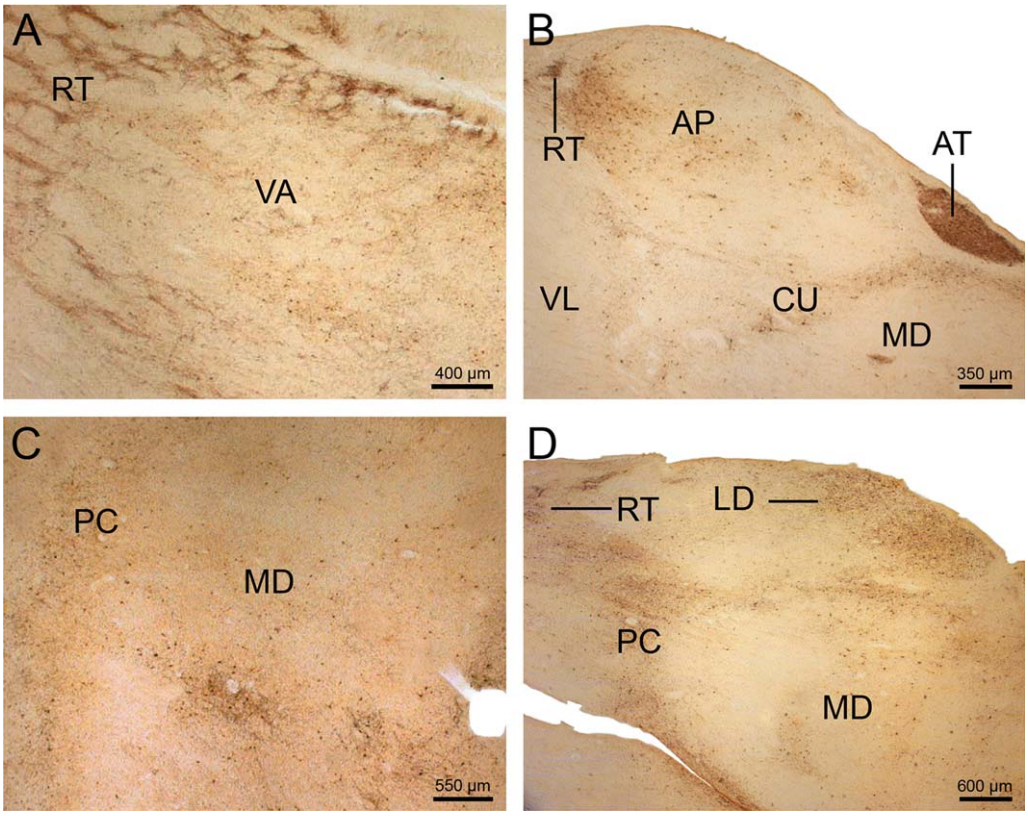

Fig. 3. AT8-immunoreactive tau cytoskeletal pathology in the thalamus of Alzheimer's disease patients. A) Severe AT8 tau cytoskeletal pathology in the extraterritorial reticular nucleus of the thalamus (RT) and markedly affected associative ventral anterior nucleus (VA) of an individual burdened by Braak and Braak AD stage V cytoskeletal pathology. B) Considerably affected extraterritorial reticular nucleus (RT), limbic anterodorsal (AT) and rostral intralaminar cucullar nuclei (CU). Marked tau cytoskeletal pathology in the associative anteroprincipal (AP) and mediodorsal nuclei (MD). Well preserved motor precerebellar ventral lateral nucleus (VL) of a patient with an advanced Braak and Braak AD stage V cytoskeletal pathology. C) Severely affected limbic and rostral intralaminar paracentral nucleus (PC) and marked tau cytoskeletal pathology in the associative mediodorsal nucleus (MD) a Braak and Braak AD stage VI patient. D) Severe tau cytoskeletal pathology in the reticular (RT), limbic laterodorsal (LD) and paracentral nuclei (PC). The adjacent mediodorsal nucleus (MD) is markedly affected (Braak and Braak AD stage V individual) (A–D: anti-tau immunostaining with the AT8 antibody; 100 µm PEG sections). AD, Alzheimer's disease; AP, Anteroprinicipal thalamic nucleus; AT, Anterodorsal thalamic nucleus; CU, Cucullar thalamic nucleus; LD, Laterodorsal thalamic nucleus; MD, Mediodorsal thalamic nucleus; PC, Paracentral thalamic nucleus; RT, Reticular thalamic nucleus; VA, Ventral anterior thalamic nucleus; VL, Ventral lateral thalamic nucleus

circumscribed subcortical brain regions (e.g., locus coeruleus or midbrain raphe nuclei) [2, 5, 18, 21], the presumed targeted transneuronal brain propagation of this process along anatomical pathways, are in favor of the currently popular idea of AD as a chronic prion-like neurodegenerative disorder [2, 5, 16, 34, 35]. Although, this idea is also supported by the findings of recent experimental studies, which pointed to a transsynaptically cell-to-cell propagation of hyperphosphorylated and misfolded tau protein aggregates in a progressive, prion-like manner [37–39], unequivocal empirical evidences from human studies are required to substantiate this outstanding scientific approach and to prove the suggested prion-like properties and behavior of the hyperphosphorylated tau protein in AD [2, 5, 16, 34, 35].

POTENTIAL CLINICAL RELEVANCE OF THE AFFECTION OF THE THALAMUS IN AD

AD patients affected by an advanced Braak and Braak AD stage V or VI tau cytoskeletal pathology along with a variety of other clinical symptoms commonly suffer from severe impairments of cognition and memory. Although various pathologies at different brain sites may be involved in the pathogenesis

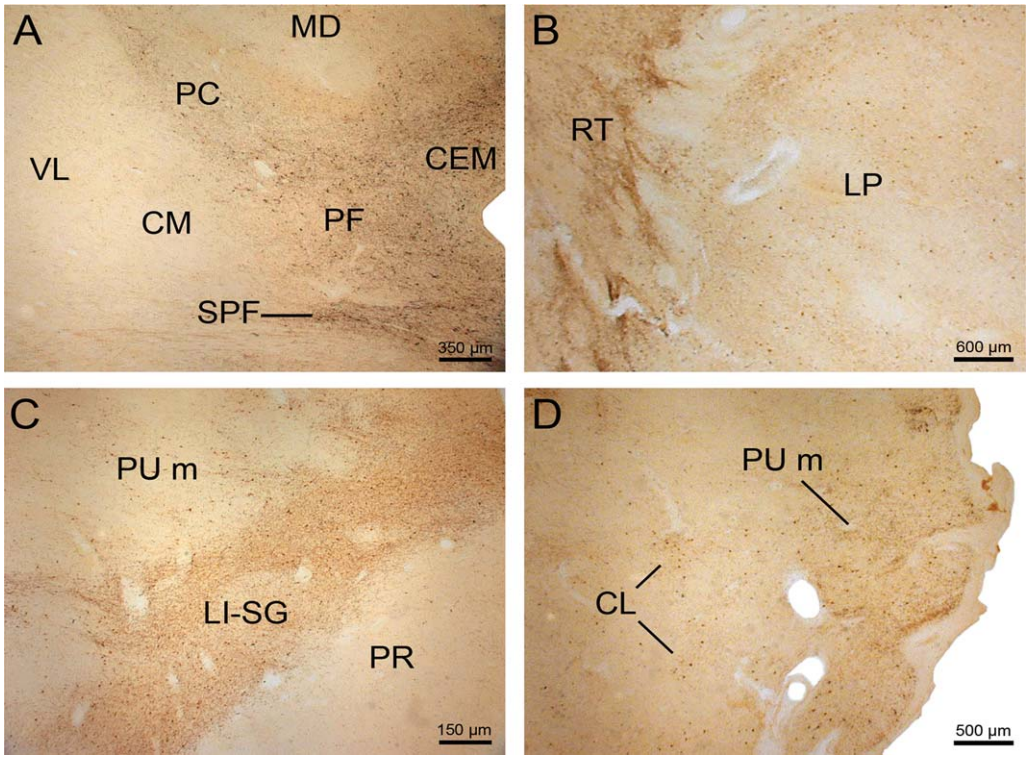

Fig. 4. AT8-immunoreactive tau cytoskeletal pathology in the thalamus of Alzheimer's disease patients. A) Hierarchical affection of the caudal intralaminar central complex with severe tau cytoskeletal pathology in the limbic subparafascicular nucleus (SPF), marked cytoskeletal changes in the associative parafascicular nucleus (PF) and spared motor centromedian nucleus (CM). Additional severe tau cytoskeletal pathology in the limbic central medial (CEM) and paracentral central nuclei (PC). Markedly affected mediodorsal nucleus (MD) and spared motor precerebellar ventral lateral nucleus (VL) (individual with Braak and Braak AD stage V cytoskeletal pathology). B) Severely affected extraterritorial reticular nucleus of the thalamus (RT) and markedly affected motor lateral posterior nucleus (LP) of a patient with Braak and Braak AD stage V cytoskeletal pathology. C) Severe tau cytoskeletal changes in the limbic limitans-supragenicular complex (LI-SG) of a Braak and Braak AD stage VI individual. D) Severe cytoskeletal pathology in the limbic dorsomedial aspect of the medial pulvinar (PU m) and in the islands of the limbic intralaminar central lateral nucleus (CL) (Braak and Braak AD stage V individual) (A-D: anti-tau immunostaining with the AT8 antibody; 100µm PEG sections). AD, Alzheimer's disease; CEM, Central medial thalamic nucleus; CL, Central lateral thalamic nucleus; CM, Centromedian thalamic nucleus; LI-SG, Limitans-supragenicular complex of the thalamus; LP, Lateral posterior thalamic nucleus; MD, Mediodorsal thalamic nucleus; PC, Paracentral thalamic nucleus; PF, Parafascicular thalamic nucleus; PR, Pretectum; PU m, Pulvinar of the thalamus, medial nucleus; RT, Reticular thalamic nucleus; SPF, Subparafascicular thalamic nucleus; VL, Ventral lateral thalamic nucleus

of these prominent clinical features of AD patients, it has been repeatedly shown that their manifestation and progress is correlated with loss of nerve cells, synaptic degeneration in the neocortex, and the topographical distribution of the tau cytoskeletal pathology in diseased brains. In view of the well-known essential role of the cortical and subcortical regions of the limbic system in the performance of normal cognitive and memory functions, the severe tau cytoskeletal pathology in the thalamic nuclei assigned to the limbic system most likely leads to impairments of neural processing in the circuits of the limbic system and thus contributes substantially to the manifestation of these guiding symptoms of AD patients [1, 2, 8, 9, 15, 18, 21, 24].

All of the rostral intralaminar thalamic nuclei (i.e., central medial, cucullar, paracentral, central lateral nuclei) are important components of the ascending activating reticular system of the human brain (ARAS), which via its diffuse projections influences the activity of the cerebral cortex and therefore is crucial for the modulation of attention and the level of arousal. Together with the parafascicular nucleus of the caudal intralaminar group, the rostral intralaminar nuclei of the thalamus are also integrated into the neural loops of the human brain, which are involved in the generation smooth pursuit eye movements and horizontal saccades. Accordingly, the severe tau cytoskeletal pathology in these thalamic nuclei may also be of substantial pathophysiological relevance for the

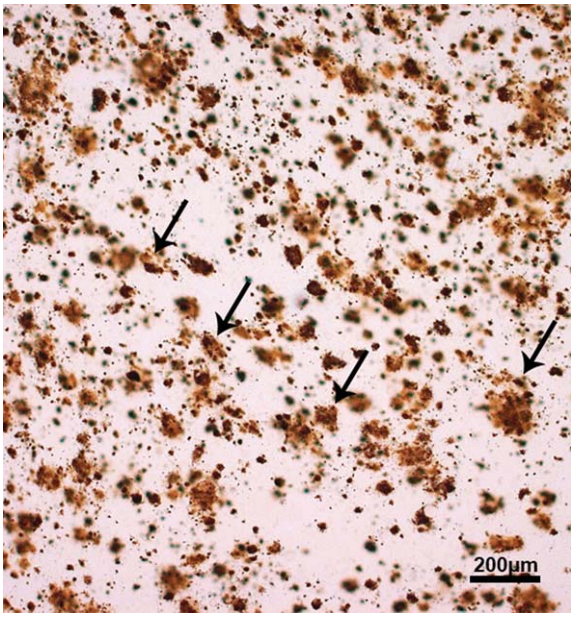

Fig. 5. Immunoreactive β-amyloidosis in the mediodorsal thalamic nucleus of an Alzheimer's disease patient. Severe immunoreactive β-amyloidosis in the mediodorsal nucleus of a clinically diagnosed AD patient burdened by Braak and Braak AD stage V cytoskeletal pathology and Thal phase 4 brain β-amyloidosis. Arrows point to immunoreactive amyloid-β deposits (anti-amyloid-β immunostaining with the 4G8 antibody; 100 µm PEG section).

development of attention deficits, dysfunctional smooth pursuit eye movements, and impaired saccades in AD patients [3, 24, 31].

In addition, the parafascicular and the rostral intralaminar nuclei, together with additional subcortical and cortical brain regions (i.e., anterior cingulate area, midbrain periaqueductal gray and pontine parabrachial nuclei) represent important building blocks within the so-called 'medial pain system', which mediates the non-discriminative aspects of pain experience (i.e., autonomic, emotional, and nocifensive reactions to painful stimuli). Therefore, it is likely that the tau cytoskeletal pathology in these components of the 'medial pain system' is responsible for the altered non-discriminative aspects of pain experience of AD patients (i.e., elevated pain tolerance, decrease in pain affect, altered autonomic reactions to sudden painful stimuli, reduced or extinct nocifensive reactions [2, 5, 10, 11, 24, 31].

Finally, owing to its paramount role in controlling and modulating the entire informational flow between the thalamus and the cerebral cortex, the thalamic reticular nucleus is crucial for the regulation of the sleep-wake cycle. Accordingly, its severe cytoskeletal pathology most likely is substantially involved in the pathogenesis of disrupted waking and sleeping patterns of AD patients [31, 40].

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